Effective Health Care Program

Comparative Effectiveness Review
Number 155

Contrast-Induced Nephropathy: Comparative Effects of Different Contrast Media

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Prior to publication of the final evidence report, the EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Contrast-Induced Nephropathy: Comparative Effects of Different Contrast Media

Structured Abstract

Objectives. To evaluate the comparative effects of different types of contrast media with respect to the risk of developing contrast-induced nephropathy (CIN) by synthesizing the current literature.

Data sources. We searched for original studies in MEDLINE®, Embase®, and the Cochrane Library through October 1, 2014. We also searched for studies in ClinicalTrials.gov and the Scopus database.

Methods. Two reviewers independently reviewed each article to identify randomized controlled trials (RCTs) that reported on CIN-related outcomes in patients after receiving low-osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM). We included head-to-head comparisons of one LOCM versus another LOCM or of LOCM versus IOCM. (Only 1 IOCM is currently available in the United States.) For each study, one reviewer extracted the data and a second reviewer verified the accuracy. Both reviewers assessed the risk of bias for each study. Together, the reviewers graded the strength of evidence for the comparisons and outcomes of interest. We quantitatively pooled the results of studies that were sufficiently similar, using a 25-percent relative risk reduction as the threshold for a minimally important difference.

Results. We identified five RCTs that compared two or more LOCMs, including two studies of intra-arterial administration, two studies of intravenous administration, and one study examining both routes. We identified 25 RCTs that compared IOCM with LOCM, including 18 studies of intra-arterial administration and 7 studies of intravenous administration. No study comparing LOCMs reported a statistically significant or clinically important difference between study arms, and the overall analysis did not suggest that any one LOCM was superior to another. In a meta-analysis, we found a borderline significant reduction in short-term CIN risk with IOCM compared with a diverse group of LOCMs (pooled relative risk, 0.80; 95% confidence interval [CI], 0.65 to 0.99, p=0.045). When the analysis was stratified by route of administration, the aggregate pooled relative risk was 0.80 (95% CI, 0.64 to 1.01) for intra-arterial and 0.84 (95% CI, 0.42 to 1.71) for intravenous. In studies that investigated IOCM versus LOCM, the outcomes of mortality, cardiovascular outcomes, need for renal replacement therapy, and imaging quality or diagnostic accuracy showed no significant difference between groups. One study comparing different LOCMs investigated the outcomes of death and adverse events, and found no difference between groups.

Conclusions. We found low strength of evidence that the risk of CIN did not differ between LOCMs, and moderate strength of evidence that IOCM had a slightly lower risk of CIN than LOCM. The lower risk was not clinically important and just reached statistical significance.

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Executive Summary

Background

The administration of iodinated contrast media is an essential component of many diagnostic and therapeutic procedures that involve radiologic imaging. An important potential side effect of iodinated contrast administration is contrast-induced nephropathy (CIN), defined as 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.[1]

The precise mechanism of CIN is not entirely understood. The leading theories are that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of contrast media.[2,3] Alternatively, some experts have argued that acute kidney injury occurring after intravascular administration of contrast media is caused instead by coexisting risk factors and is only coincidentally related to the contrast media, especially if contrast media are administered intravenously.[4] Regardless of the precise etiology, however, the development of acute kidney injury after use of intravascular contrast media remains a major concern for clinicians.

Osmolality of contrast media is a key factor determining its tolerability.[5] Since the 1990s, low-osmolar contrast media (LOCM; 2–3 times plasma osmolality) has been the standard of care for intravascular injection. The newest class of intravascular contrast, iso-osmolar contrast media (IOCM), is isotonic to plasma. Iodixanol is currently the only IOCM available for intravascular injection. A preliminary literature search revealed conflicting reports about whether IOCM is associated with a reduction in CIN risk compared with LOCM.

In this systematic review, we sought to determine the comparative effects of different types of intravascular contrast media in patients receiving imaging studies or undergoing image-guided procedures. The preliminary search also revealed reports that intra-arterial administration may be associated with a greater CIN risk than intravenous administration, and therefore we also investigated whether the effects vary according to route of contrast administration.[4,6,7]

The populations of interest included patients of all ages and levels of risk for CIN. The interventions and comparisons of interest included contrast type (IOCM or LOCM) and administered dose or volume. The main outcome was the development of CIN. Secondary outcomes were also considered, such as need for renal replacement therapy (including dialysis or hemofiltration), cardiac outcomes, adverse events, mortality, imaging quality, and diagnostic accuracy. We sought evidence from both short- and long-term studies, and we considered both inpatient and outpatient settings.

Key Question

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)?

b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Data Sources

We searched the following databases for primary studies published through October 1, 2014: MEDLINE®, EMBASE®, and the Cochrane Library. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. We also searched ClinicalTrials.gov to identify ongoing studies. Additionally, we requested data from the manufacturers of contrast media, and searched the U.S. Food and Drug Administration Adverse Event Reporting System (AERS).

Study Eligibility Criteria, Participants, and Interventions

We followed the PICOTS framework (population, interventions, comparisons, outcomes, timing, and setting) in developing the criteria for including studies in the review, and we included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) in which the intervention group received intra-arterial or intravenous injection of IOCM or LOCM. We also reviewed applicable observational studies. Studies had to report on impairment of renal function before and after (up to 72 hours) contrast injection to be included in the report. For studies reporting on CIN (as defined above), we also extracted data on cardiac outcomes, need for renal replacement therapy, mortality, length of hospital stay, adverse events, imaging quality, and diagnostic accuracy.

Study Appraisal and Synthesis Methods

The titles and abstracts were screened independently by two reviewers. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team. At random intervals during screening, quality checks were performed to ensure that eligibility criteria were applied consistently.

We reviewed primary studies, as defined by our inclusion criteria, and we performed de novo meta-analyses of all studies on a given comparison if study heterogeneity was not important by clinical, qualitative, and statistical criteria. Pooled risks were calculated using a random-effects model using the DerSimonian and Laird method.[8]

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[9]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?

- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

When assessing the risk of bias in each study, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing. When applicable, we graded other outcomes independently.

The team graded the strength of evidence (SOE) on comparisons of interest for the key outcomes. We used the grading scheme recommended in the Agency for Healthcare Research and Quality "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[10] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.

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 risk-of-bias criteria. A body of evidence was assessed as having low study limitations if most (51% or greater) of the studies scored positive in all five domains. Bodies of evidence not meeting one of the above criteria were assessed as having medium study limitations.

Following the guidance of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group,[11] we rated evidence as precise if the total number of patients exceeded the optimum information size and the 95% confidence interval (CI) excluded a risk ratio of 1.0. 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 precise only if the 95% CI excluded the possibility of a clinically important benefit or harm (i.e., risk ratio less than 0.75 or greater than 1.25). For the main outcome of interest, CIN, we used an optimum information size of 2,000, based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25 percent. For less frequent adverse outcomes, we used an optimum information size of 10,000, based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25 percent. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the SOE pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Observational studies were considered in grading the strength of a body of evidence if the overall results of the observational studies were not similar to results of the RCTs applicable to the comparison.

Results

The literature search revealed 29 RCTs for summary and analysis and 10 observational studies. Five RCTs compared two or more LOCMs in 826 patients.[12-16] Twenty-five RCTs compared IOCM with one or more LOCMs in 5,053 patients.[12,17-40] Included in these RCTs was one study that reported data on both types of comparisons.[12] In the five RCTs comparing LOCM versus LOCM, four studies had a problem with one or more of the five risk-of-bias items that we assessed. In the 25 RCTs comparing IOCM versus LOCM, all studies had a problem with one or more of the five risk-of-bias items that we assessed. We did not find any studies that examined whether the benefits or harms of contrast media differed according to the type of strategy used to prevent CIN.

No study comparing one LOCM with another LOCM reported a statistically significant or clinically important difference between study arms in the incidence of CIN (or related measures of a change in renal function), and the overall analysis did not suggest that any one LOCM was superior to another (low SOE). RCTs comparing LOCM versus LOCM did not report outcomes similarly enough to be combined numerically. No studies indicated that a difference existed for a selected subgroup of patients or for a given dose of contrast media.

We found a borderline statistically significant reduction in short-term CIN risk (less than 7 days after administration of contrast) with IOCM compared with a diverse group of LOCMs (pooled relative risk, 0.80; 95% CI, 0.65 to 0.99, p=0.045; moderate SOE). However, the reduction was too small to be clinically important. When the analysis was stratified by route of administration, the pooled risk ratio was 0.80 (95% CI, 0.64 to 1.01) for intra-arterial and 0.85 (95% CI, 0.42 to 1.71) for intravenous, suggesting no difference in comparative CIN risk by route of administration. The SOE was low to support no clinically important difference between IOCM and LOCMs with regard to need for renal replacement therapy (5 studies), cardiovascular outcomes (7 studies), mortality (8 studies), adverse events (12 studies), or image and diagnostic quality (2 studies). We did not see any definitive evidence of a difference in CIN incidence between IOCM and LOCM that varied according to patient characteristics or contrast dose.

Results of the 10 observational studies in our review were similar to those reported in the RCTs. We did not make any changes in the SOE grading based on the observational studies.

Discussion

In this systematic review, the small number of trials comparing one LOCM with another LOCM reported no statistically significant or clinically important differences in the risk of CIN. For the trials comparing IOCM with LOCM, we found a slight reduction in CIN risk for IOCM that was of borderline statistical significance. However, the point estimate of this reduction did not exceed a minimally important relative risk difference of 25 percent.

Most trials in our review involved patients receiving intra-arterial contrast. In the few trials involving intravenous contrast, we saw no evidence that the relationship between contrast type and CIN risk differed from that observed in the intra-arterial trials.

We found no difference between LOCM types or between LOCM and IOCM in potential sequelae of CIN, such as cardiovascular events, mortality, need for renal replacement therapy, or other adverse events. Because we excluded studies that did not report data on CIN, we excluded studies that reported only nonrenal outcomes. However, a recent meta-analysis of RCTs comparing IOCM and LOCM that included such studies found no conclusive evidence that IOCM is superior to LOCM with respect to cardiovascular events.[41] This supports the findings from our dataset, which focused on renal outcomes.

Our results are similar to results of three published meta-analyses, which reported no statistically significant reduction of CIN with IOCM compared with LOCM.[42-44] Even though our review included six RCTs that have been published since those three meta-analyses, we obtained a similar estimate of the relative risk. Five other systematic reviews reported a lower incidence of CIN with IOCM than with LOCM, but all had important limitations and included different sets of studies than our review.[45-49] In one of these meta-analyses,[45] the two studies favoring IOCM the greatest[50,51] were excluded from our analysis because CIN was not adequately defined. Two other systematic reviews made indirect comparisons of contrast agents[46,47] and reported differences between IOCM and the LOCM iohexol, but not with other LOCMs. However, one of the indirect comparison studies was a network analysis that pooled all

outcomes (not just CIN),[46] and the other indirect comparison study included observational data (not just RCTs).[47] One of the reviews included only trials of IOCM that were sponsored by its manufacturer,[48] and another meta-analysis[49] included a large unpublished positive trial comparing IOCM with iopromide. Data for this trial are available only in a 2010 meeting abstract; to date, the study has not been published.

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. Some evidence exists from propensity-score–matched retrospective studies questioning the strength of the relationship between contrast administration and CIN.[4] This relationship is important for designing future research but does not affect the conclusions of this review regarding the comparative impact of contrast media type on observed CIN.[4,7,52]

Several limitations of the review should be noted. We generally considered LOCM agents together as a group even though seven different LOCM chemical compounds were used in the studies we reviewed. While direct comparisons of LOCMs are sparse, indirect evidence suggests that iohexol may differ from other LOCMs. The greatest CIN reduction with IOCM was reported in a study comparing it with iohexol.[37] Two indirect comparisons also suggested that differences existed between iohexol and other LOCMs.[46,47] These comparisons were not compelling. As mentioned above, one 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 IOCM versus LOCM comparison was a secondary analysis.

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, or other clinical details such as the severity of renal impairment. As a result, we were not able to assess whether the comparisons between types of contrast media depended on the indications for use of contrast media or baseline renal function. Furthermore, the studies frequently omitted details about total contrast volume, length of procedure, and contrast injection rates. These are potential sources of heterogeneity among the studies. Based on our inclusion criteria, we did not select studies based on these characteristics, so the results likely apply to a relatively diverse population of patients and procedures. We suggest that future research focus on identifying clinical factors that may be associated with a benefit of IOCM compared with LOCM.

Conclusions

In summary, we found low SOE to support no differences in CIN risk between LOCMs and moderate SOE that IOCM had a slightly lower risk of CIN than LOCM, but the lower risk was not clinically important and had only borderline statistical significance. No relationship was found between comparative CIN risk and route of administration. For clinicians, these findings suggest that the choice between IOCM and LOCMs will not have an important effect on the risk of CIN.

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Introduction

Background

The administration of iodinated contrast media is an essential component of a number of diagnostic and therapeutic procedures that involve radiologic imaging. One important potential side effect of iodinated contrast administration is contrast-induced nephropathy (CIN, see Appendix A for a list of acronyms), defined as 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[1] This definition of CIN, or variations of it, is the one most commonly used in past studies examining the risk, prevention, and treatment of 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. Although some guidelines have employed the term "contrast-induced acute kidney injury" (CI-AKI) instead of CIN, the vast majority of the literature has used the older term, CIN, so we will use the older term in our report.

The precise mechanism of CIN is not entirely understood. The leading theories are that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of the contrast media.[4,5] Alternatively, some experts have argued that acute kidney injury occurring after intravascular administration of contrast media is caused instead by co-existing risk factors or medical conditions and is only coincidentally related to the contrast media, especially if contrast media are administered intravenously. In a meta-analysis, McDonald et al. (2013) concluded that the incidence of acute kidney injury was similar between patients receiving intravenous contrast media compared to patients receiving an imaging procedure without contrast media.[6] Regardless of the precise etiology, however, the development of acute kidney injury after use of intravascular contrast media remains a major concern for clinicians.[6]

Osmolality of the contrast media is thought to be a key factor determining its tolerability.[7] Since iodinated contrast media was first used in 1929,[8] developments in the chemistry of contrast media have steadily decreased the number of osmotically active moieties per iodine atom. In the 1990s, high-osmolar contrast media (HOCM, 5-8 times plasma osmolality) was largely replaced by low-osmolar contrast media (LOCM, 2-3 times plasma osmolality) because the latter was associated with fewer severe adverse reactions and less patient discomfort.

The next logical step was the development of contrast media that is isotonic to plasma. Iodixanol has been the only iso-osmolar contrast media (IOCM) available for intravascular injection. One other IOCM, iotrolan, was available in Europe and Japan but was temporarily taken off the market in 1996 after an unexpected number of delayed reactions were reported.[9] It eventually was discontinued for intravascular use.

Our preliminary search of both primary studies and systematic reviews revealed conflicting reports about whether IOCM is associated with a reduction in CIN risk compared with LOCM. The guidelines by Kidney Disease Improving Global Outcomes (KDIGO) mentioned the use of IOCM and LOCM, but did not make recommendations regarding the circumstances where one type should be administered instead of the other.[10] We therefore sought to gain an understanding of these conflicting results by undertaking a systematic review of the peer-reviewed literature comparing IOCM and/or LOCM. Although the question has been raised whether acute kidney injury that develops after iodinated contrast exposure is causally or coincidentally related (i.e., contrast associated and not induced), it is not necessary to answer this question in order to assess

the comparative effect of IOCM and LOCM on observed acute kidney injury following administration.

In reviewing this literature, we also sought to determine whether differences in CIN risk between contrast types are affected by the route of administration (intra-arterial versus intravenous), since there is some evidence that intra-arterial administration is associated with more risk than intravenous administration.[6,11,12] Theories for a potential difference in risk between intra-arterial and intravenous contrast administration include differences in the volume of contrast given, differences in hemodynamic stability of patients undergoing intra-arterial versus intravenous imaging, or confounding factors such as an increased risk of atheroemboli occurring with intra-arterial procedures.

Scope of the Review

We compared the effectiveness of two types of contrast media, IOCM and LOCM, for the prevention of CIN (Figure 1). We reviewed all randomized controlled trials (RCTs) that reported on short-term outcomes (less than 7 days) or long-term outcomes (at least 30 days) after receiving LOCM or IOCM. We compared the effects of the interventions on the incidence of CIN, and other potential harms and benefits.

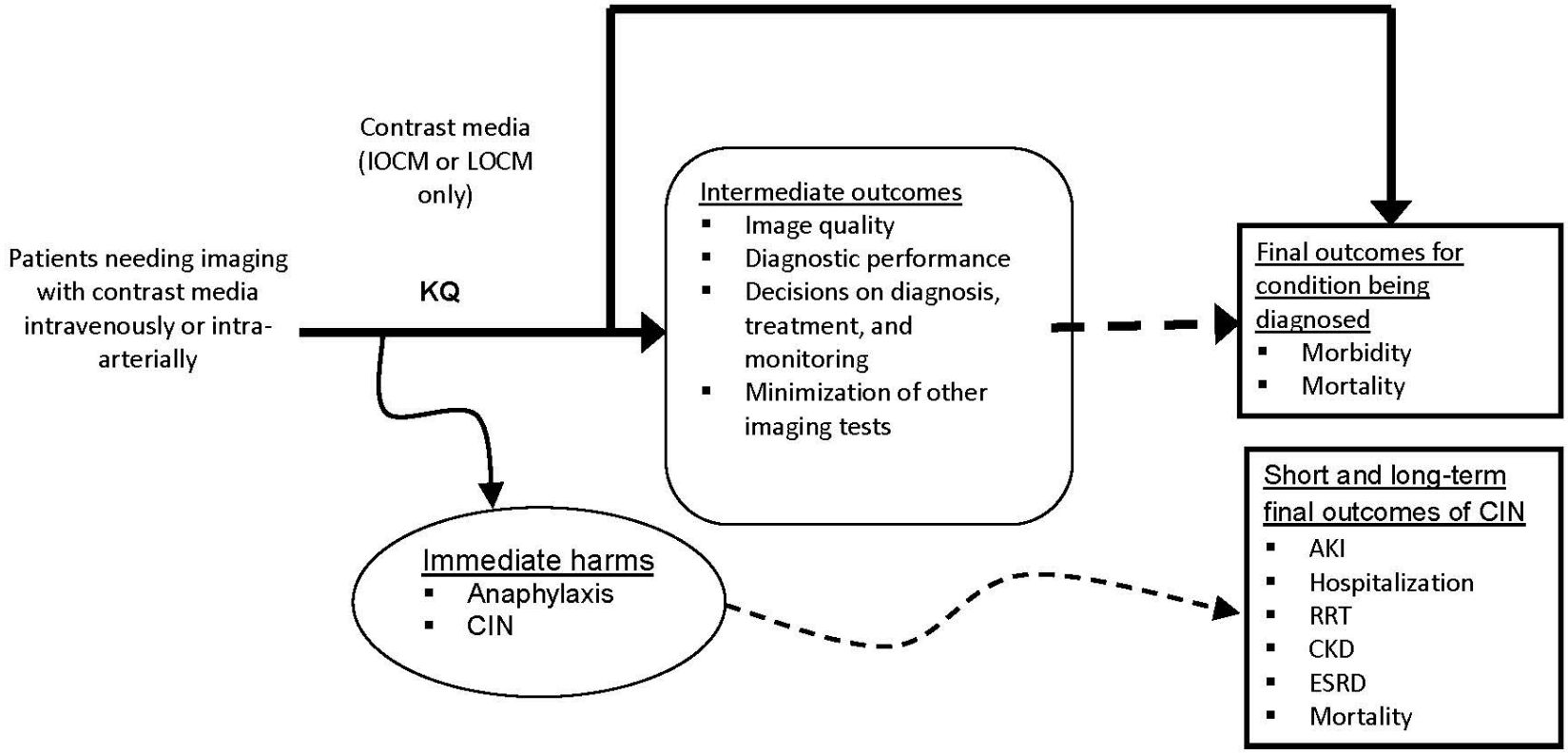
Key Question

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 (GFR), 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)?

b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Figure 1. Analytic framework: comparing benefits and harms of different contrast media



AKI = acute kidney injury; CIN = contrast induced nephropathy; CKD = chronic kidney disease; ESRD = end stage renal disease; IOCM = iso-osmolar contrast media; KQ = Key Question; RRT = renal replacement therapy; LOCM = low-osmolar contrast media

Methods

Topic Refinement and Protocol Review

We developed the Key Question with the input of a key informant panel that included: experts in nephrology, radiology, cardiology, and primary care; patient advocates; representatives from the Food and Drug Administration; and oversight by our Task Order Officer from the Agency for Health Care Research and Quality (AHRQ). We recruited a Technical Expert Panel that provided input to the Evidence-based Practice Center during our development of the protocol for the comparative effectiveness review. The protocol for our review is posted on the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/).

Literature Search Strategy

We searched the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Library through October 1, 2014 (see Appendix B for detailed search strategy). We did not add any date limits to the search. We developed a search strategy for MEDLINE, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. We reviewed the Scopus database and the reference lists of relevant review articles and related systematic reviews to identify articles that the database searches might have missed. We searched ClinicalTrials.gov to identify studies for which results have not yet been published. Scientific Information Packages (SIP) were requested from a number of industry representatives. We requested data from the manufacturers of contrast media and searched the U. S. Food and Drug Administration Adverse Event Reporting System (AERS).

We uploaded the articles into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

We followed the PICOTS (Table 1) framework in developing the criteria for inclusion of studies in the review. We included studies of patients of all ages having low, moderate, or high risk of developing CIN. We anticipated heterogeneity in the baseline risk assessment or stratification, and reported on the baseline assessment as it was defined by studies. To be included, studies had to report the incidence of CIN based on serum creatinine or GFR prior to and after (up to 72 hours) contrast media injection. The studies also had to have an intervention group receiving either IOCM or LOCM via intravenous or intra-arterial injection. The possible comparisons that we considered are listed in Table 1 and detailed in Table 2. We focused on RCTs that addressed the Key Question, but we also looked for relevant observational studies to see if their results were similar to the RCTs. Article inclusion was not restricted by publication date, language was only a restriction at the article screening level. We also evaluated existing systematic reviews on the topic to determine the extent to which they addressed our Key Question and PICOTS and whether they could be updated.

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review

PICOTS	Criteria
Populations	● All patients (including adults and children) undergoing procedures requiring the administration of contrast media. ● High or moderate risk patients (as defined by clinical or demographic risk factors such as age, cardiovascular and other comorbidities, creatinine level, etc.) vs. low risk or normal patients. ● Patients using contrast media for multiple imaging studies.
Interventions	● IOCM (including dose/volume and number of doses) ● LOCM (including dose/volume and number of doses)
Comparators	LOCM vs. LOCM LOCM vs. IOCM IOCM vs. IOCM (although only 1 IOCM is available for use)
Outcomes	**Short-term:** a. Renal function measures ● Development of CIN as defined by change in creatinine or change in GFR b. Renal disease-specific outcomes ● Need for RRT (dialysis or hemofiltration) c. Other clinical outcomes ● Mortality (in hospital or within 7 days) ● Cardiac outcomes ● Anaphylaxis d. Prolonged hospital stay e. Benefits of radiographic imaging with contrast media ● Intermediate outcomes – Image quality (resolution, contrast) – Diagnostic performance (test characteristics) ● Clinical benefits of image quality – Improved morbidity – Improved mortality – Minimization of other imaging tests and procedures **Long-term:** a. Renal function measures ● Development of CKD, including ESRD ● Rate of conversion to CKD at 3 and 6 months ● Chronic change in kidney function b. Renal disease-specific outcomes ● Need for RRT (dialysis, hemofiltration, or kidney transplant) c. Other clinical outcomes ● Cardiac outcomes ● Mortality in hospital or at 3 or 6 months ● Long-term clinical benefits of image quality ● Improved morbidity ● Improved mortality ● Minimization of other imaging tests
Timing	● Short-term: inpatient or within 7 days of procedure. ● Long-term: at least 30 days after procedure. For observational studies, the follow-up should be at least 2 years.
Setting	Inpatient and outpatient populations

CIN = contrast induced nephropathy; CKD = chronic kidney disease; ESRD = end stage renal disease; GFR = glomerular infiltration rate; IOCM = iso-osmolar contrast media; LOCM = low-osmolar contrast media; RRT = renal replacement therapy

Table 2. Low-osmolar and iso-osmolar contrast media

Name	Trade Name	Manufacturer	Classification
iohexol	Omnipaque	GE Healthcare	LOCM
iopamidol	Isovue	Bracco	LOCM
ioversol	Optiray	Mallinckrodt	LOCM
ioxaglate	Hexabrix	Guerbet	LOCM
iopromide	Ultravist	Bayer	LOCM
iobitridol	Xenetix	Guerbet	LOCM
iomeprol	Imeron	Bracco	LOCM
ioxilan	Oxilan	Guerbet	LOCM
iodixanol	Visipaque	GE Healthcare	IOCM

LOCM = low-osmolar contrast media, IOCM = iso-osmolar contrast media

Data Extraction

We screened titles first, then abstracts for relevance to the Key Question. Titles and abstracts were screened independently by two reviewers. Inclusion at the title screening level was liberal; if a single reviewer believed an article may contain relevant information, the article moved to the next level (abstract) for further screening. Abstracts were included for further review only if both reviewers agreed on inclusion. Disagreements that could not be resolved by the two reviewers were resolved by the internal experts (See Appendix C for screening forms.)

Full text articles included after the review of abstracts were reviewed independently by two reviewers and required agreement between the reviewers for either inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third member of the team. At random intervals during screening, quality checks by senior team members were performed to ensure that screening was consistent with inclusion/exclusion criteria.

Quality (Risk of Bias) Assessment of Individual Studies

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[13]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

Data Synthesis

For primary studies, as defined by our inclusion criteria and Key Question, we sought to perform de novo meta-analyses. Before conducting a meta-analysis, the review team discussed differences in the study design and reporting to identify characteristics that would limit the clinical meaningfulness of pooled results, such as variability in patient characteristics, contrast media used, or outcome definitions. Differences in these characteristics either prevented statistical pooling or were used to stratify the meta-analysis. Pooled risks were calculated using a random effects model using the method of DerSimonian and Laird.[14]

Statistical heterogeneity was assessed using the I-squared statistic.[15] When the I-squared value was greater than or equal to 50 percent, or the p-value was 0.2 or less, the clinicians were

asked to re-evaluate the studies for clinical heterogeneity and decide if the meta-analysis should be reported despite statistical heterogeneity. We did not plan to perform network meta-analyses because we anticipated a high degree of clinical heterogeneity among the studies.

We assessed both short- and long-term outcomes. We extracted data on short-term outcomes defined as within 7 days post-procedure. We also extracted data on long-term outcomes, looking particularly for outcomes at least 30 days post-procedure.

Minimally Important Difference

In comparing post-administration changes in numerical indicators of renal function between two contrast agents, we considered a minimally important difference to be approximately the coefficient of variation associated with the measurement. For serum creatinine, the short-term coefficient of variation within individuals has been reported to be 8 percent.[16] Assuming a normal serum creatinine of approximately 1.0 mg/dl, we assumed a minimally important difference of 0.1 mg/dl (approximately 8% of 1.0 mg/dl). For creatinine clearance, we assumed a minimally important difference of 20 percent, which is rounded from a reported estimate of 19 percent for the coefficient of variation within individuals.[17]

In comparing changes in risk of CIN, a binary outcome, we followed published guidelines for selecting a minimally important difference based on overall observed event rate in the studies.[18] 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 relative risk reduction of 25 percent would be clinically important, which is consistent with the guidance suggesting a relative risk reduction of 20 percent to 30 percent in determining optimal information size.

Strength of the Body of Evidence

The team graded the strength of evidence on comparisons of interest for the key outcomes. We used the grading scheme recommended in the Methods Guide[19] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[19]

Study limitations were determined for each comparison group for CIN and other reported outcomes. 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% 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.

Following the guidance of the GRADE Working Group[18], we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% confidence interval (CI) excluded a risk ratio of 1.0. 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 only rated the evidence as precise if the 95% CI excluded the possibility of a clinically important benefit or harm (i.e., risk ratio less than 0.75 or greater than 1.25). For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25 percent. For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25 percent. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the strength of evidence pertaining to each comparison into four category grades: high, moderate,

low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the strength of evidence could be upgraded.

Observational studies were considered in grading a comparison's overall strength of evidence if the overall results of the observational studies were not similar to the RCTs applicable to the comparison.

Applicability

We considered elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Question as recommended in the Methods Guide.[19] We considered important population characteristics, treatment characteristics, and settings that may cause heterogeneity of treatment effects and limit applicability of the findings.

Results

Results of the Literature Search

The literature search identified 11,768 unique citations. We excluded 9758 citations during title screening and excluded an additional 1568 during abstract screening. During article screening, we excluded an additional 400 (see Appendix D, List of excluded articles) articles that did not meet one or more of the inclusion criteria. We included 29 RCTs and 10 observational studies (Figure 2). We assessed the following outcomes: contrast-induced nephropathy (CIN), need for renal replacement therapy, cardiovascular outcomes, mortality, adverse events, image quality, and diagnostic accuracy. We did not find any studies that examined how the benefits or harms of contrast media differ according to the type of strategy used to prevent CIN.

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)?

b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Key Points

- No study comparing one LOCM to another LOCM reported a statistically significant or clinically important difference between study arms, and the overall analysis did not suggest that any one LOCM was superior to another (low strength of evidence).
- In our meta-analysis of RCTs comparing IOCM to a heterogeneous collection of LOCMs, we found a slight reduction in CIN risk for IOCM that just reached statistical significance; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25 percent and is unlikely to be clinically important. This finding was associated with moderate strength of evidence overall, moderate strength of evidence for intra-arterial administration, and low strength of evidence for intravenous administration.
- We found no evidence that the CIN incidence with IOCM or LOCM varies according to patient characteristics or contrast dose.
- For outcomes other than CIN (need for renal replacement therapy, cardiovascular outcomes, mortality, adverse events, image quality, or diagnostic accuracy), we found no difference between IOCM and LOCM. However, these secondary outcomes occurred uncommonly and/or were not reported for all studies; the strength of evidence of no difference was low. The strength of evidence was insufficient for determining whether outcomes other than CIN differed between LOCMs.

Overall Study Characteristics

We identified five trials that compared two or more LOCMs,[20-24] and 25 that compared IOCM with one or more LOCMs.[20,25-48] One trial, which compared IOCM to two LOCMs[20], was included in both groups. The individual components in the assessment for risk of bias in these 29 RCTs are shown in Appendix F.

No consistent definition of renal impairment was used among studies enrolling patients with chronic renal disease, so we did not attempt to refine the classification of renal impairment in these patient populations. Contrast concentration and administered volume were not consistently reported across studies, thereby precluding meaningful comparisons with respect to contrast dose. None of the studies formally examined the interaction between the primary outcomes and other factors such as demographic characteristics, comorbid conditions, or baseline renal function. The studies were inconsistent about reporting on any measures that may have been used to prevent CIN, and often did not provide any details.

In addition to the RCTs, we identified three observational studies with a total study population of 59,740 that compared two or more LOCMs.[49-51] We identified seven studies with a total study population of 108,119 that compared IOCM with one or more LOCMs.[52-58] All of the observation studies involved intra-arterial contrast administration except for one (Appendix E, Evidence Table E-12).[56]

Low-Osmolar Contrast Media Versus Low-Osmolar Contrast Media

Study Characteristics

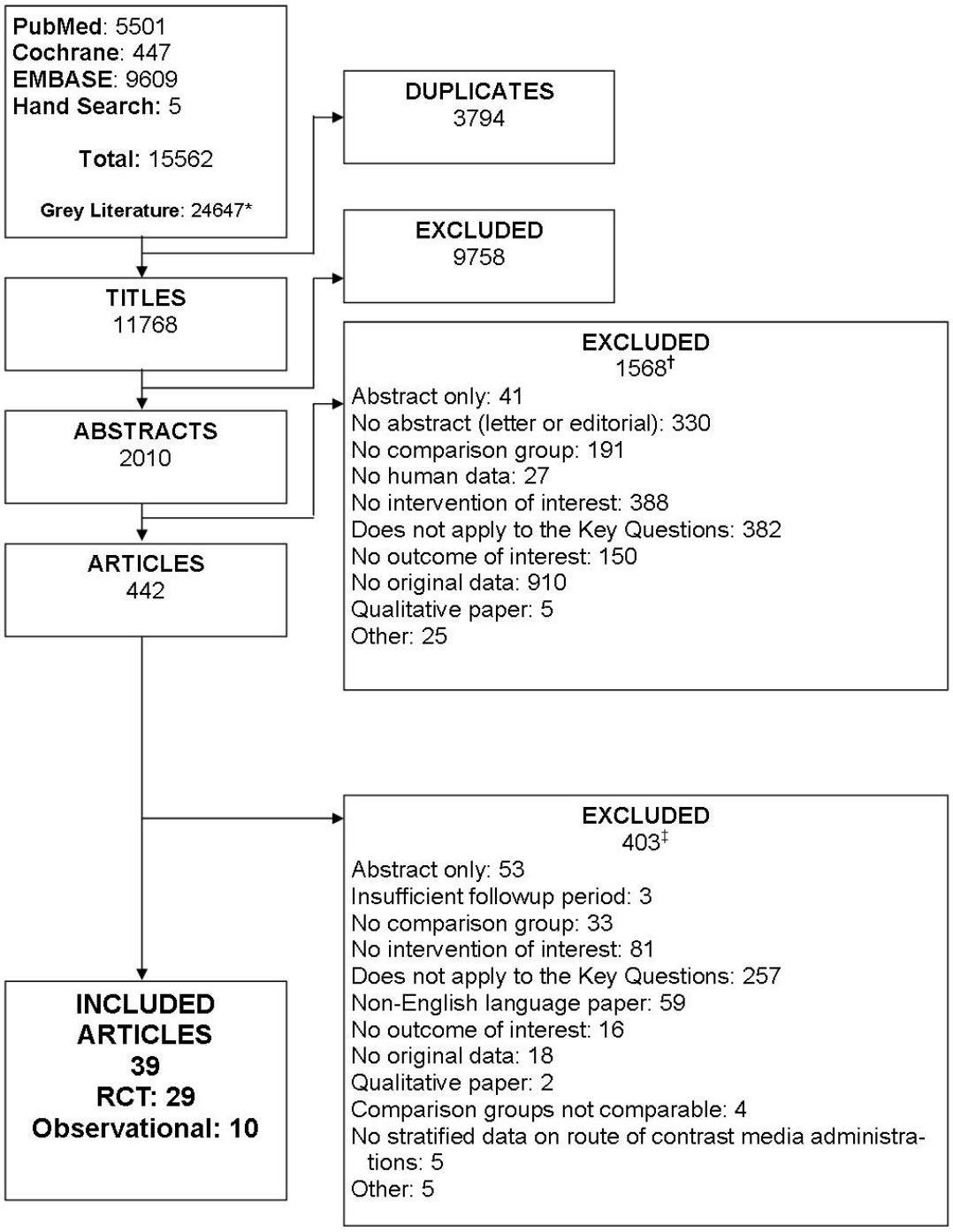
Of the five trials in the LOCM versus LOCM group (Appendix E, Evidence Tables E-1–E-4), two studies involved intra-arterial injections of the contrast media, and two studies involved intravenous injections. One study reported data on both intra-arterial and intravenous injections.[22] One study reported change in GFR as the primary outcome.[20] Only one study[21] included CIN incidence as a primary outcome. The other studies included changes in serum creatinine as a primary outcome. The five studies had a total of only 429 patients, well below the optimum information size for detecting a minimally important difference in the risk of CIN.

Contrast-Induced Nephropathy

In the LOCM versus LOCM group, none of the five studies addressing CIN found a statistically significant difference between the LOCMs that were compared.[20-24] Two studies reported serum creatinine or creatinine changes numerically for the entire study population.[20-22,24] These two studies reported the following point estimates for the difference in serum creatinine change between LOCMs: 0.02 mg/dl (intravenous),[21] 0.09 mg/dl (intravenous),[22] and 0.01 mg/dl (intra-arterial).[22] Corresponding CI's were not reported, but none of these point estimates exceeded the defined minimally important difference. These two studies were also the only ones in the group reporting outcomes that were defined similarly enough to be compared numerically (Appendix E, Evidence Tables E-5a and b). Therefore, we did not attempt further quantitative analysis. This group of studies included three intravenous administration studies and three intra-arterial administration studies (one study looked at both routes of administration). All of the intravenous studies had one or more problems with the risk of bias items included in our

assessment of study quality. All of the intra-arterial studies had problems with two or more of the items in our assessment of the risk of bias (Table 3; Appendix F, Appendix G).

Figure 2. Results of the literature search



RCT = randomized controlled trial
*Grey literature was not factored into the total number of studies for title screening.
†Sum of excluded abstracts exceeds 1,568 because reviewers were not required to agree on reasons for exclusion.
‡Sum of excluded articles exceeds 403 because reviewers were not required to agree on reasons for exclusion.

The risk of bias was high in these studies because the randomization was inadequately described and/or incomplete outcome data were not adequately addressed. The strength of evidence was low to support a conclusion that different LOCMs have equivalent effects on the incidence of CIN (Table 3; see Appendix G for study limitations). The strength of evidence was low mainly due to the small number of studies and low event rates, with heterogeneous reporting of renal outcomes. Given the small number of studies in this group and the low strength of evidence, it was not meaningful to stratify these results by route of administration.

The results of the 3 applicable observational studies[49-51] were similar to those reported in the RCTs; although these observational studies had a large number of patients, we did not upgrade the strength of evidence because of the high risk of bias in the observational studies on the comparison of LOCMs (Appendix E, Evidence Table E-12).

Mortality

One study[23] reported on mortality, where eight patients out of the total study population of 320 died between a few days and weeks of contrast administration. Contrast nephrotoxicity contributed to or caused three of these deaths (Appendix E, Evidence Table E-5b). The study had a high risk of bias because of inadequately described randomization and incomplete data were not adequately addressed. There was insufficient evidence to support a conclusion about the difference between LOCMs in their effects on mortality (Table 3; see Appendix G for study limitations).

Adverse Events

One study[23] reported on adverse events. Five percent of the total population of 320 had mild hypersensitivity reactions of nausea, vomiting, or hives (Ioxaglate arm: 20 participants, Iopamidol arm: 7 participants) (Appendix E, Evidence Table E-5b). There were no severe reactions. This study had a high risk of bias because of inadequately described randomization and incomplete data were not adequately addressed. There was insufficient evidence to support a conclusion about the difference between LOCMs in the incidence of adverse events (Table 3; see Appendix G for study limitations).

Image Quality and Diagnostic Accuracy

Our search did not identify any studies comparing LOCM to LOCM that reported on image quality or diagnostic accuracy.

Benefits or Harms by Patient Characteristics, Dose of Contrast Media, and Type of Preventive Strategy

No studies indicated that a difference existed for a selected subgroup of patients, or for a given dose of contrast media, or for use of a given type of strategy for preventing CIN.

Table 3. Summary of the strength of evidence: low-osmolar contrast media versus low-osmolar contrast media

Outcome	No. of RCTs (n)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence*	Summary of Key Outcomes
Development of CIN	5 (429)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence supporting no differences in CIN incidence between LOCMs.
Mortality	1 (320)	High	Direct	Unknown	Imprecise	Insufficient	Insufficient evidence that any one LOCM lowers the risk of death over another LOCM.
Adverse events	1 (320)	High	Direct	Unknown	Imprecise	Insufficient	Insufficient evidence that any one LOCM lowers the risk of adverse events over another LOCM.

CIN = contrast induced nephropathy; IOCM = iso-osmolar contrast medium; LOCM = low-osmolar contrast medium; NA = not assessed; RCT = randomized controlled trial; RRT = renal replacement therapy

*Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores, the more conservative study limitation designation was chosen.

Iso-Osmolar Contrast Media Versus Low-Osmolar Contrast Media

Study Characteristics

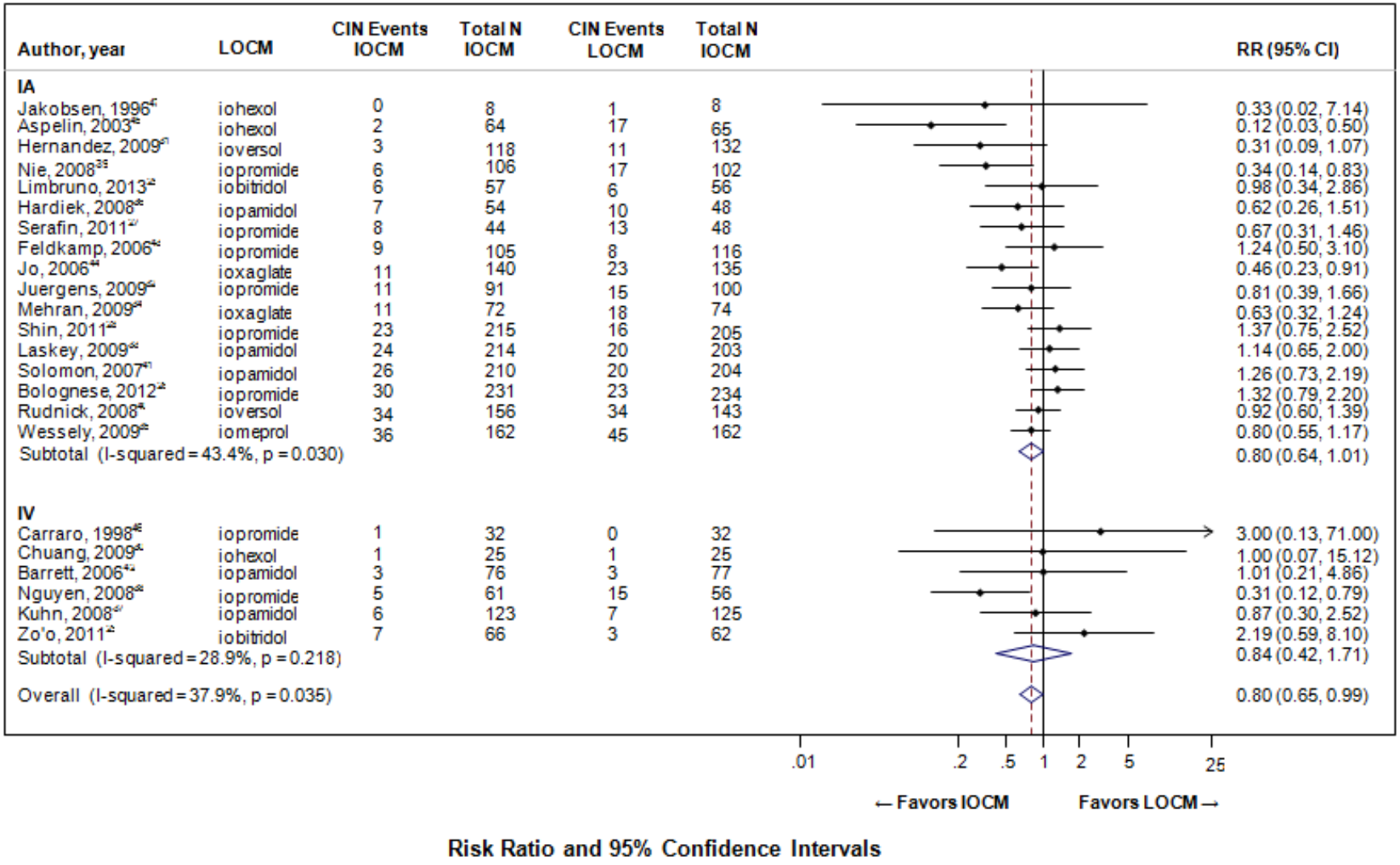
Of the 25 trials in the IOCM versus LOCM comparison (Appendix E, Evidence Table E-7), 18 studies involved intra-arterial contrast, and seven studies involved intravenous contrast. These studies involved seven LOCMs (in order of frequency): iopromide (9 studies), iopamidol (7 studies), iohexol (4 studies), iobitridol (2 studies), ioversol (2 studies), ioxaglate (2 studies), and iomeprol (1 study). All but one study[20] included CIN incidence or peak change in serum creatinine as a primary outcome. A substantial majority of these studies (19) involved patients with renal impairment and/or diabetes, and more than half (16) involved patients undergoing coronary catheterization. In studies reporting CIN as an outcome, nearly all defined CIN according to one or both of the following criteria: increase in serum creatinine greater than 25 percent or 0.5 mg/dl above baseline within 48-72 hours following contrast injection. Most studies also reported numerical changes in serum creatinine as either the mean or percent maximal difference between baseline and post-procedural values.

Contrast-Induced Nephropathy

Twenty-five studies addressed CIN as an outcome in the comparison of IOCM with LOCM.[20,25-48] These 25 studies randomized a total of 5097 patients (which is above the optimum information size that we specified) and reported an overall CIN rate of 11.0 percent (270/2449) for IOCM and 13.4 percent (326/2431) for LOCM. For these numbers of patients and event rates, we considered a relative risk difference of 25 percent to be a minimally important difference, that is, a relative risk outside the range from 0.75 to 1.25. Four of 25 studies reported reductions in CIN with IOCM compared to LOCM that were greater than a minimally important difference and statistically significant. Five studies reported reductions in CIN greater than a minimally important difference but not statistically significant. Four studies reported a greater incidence of CIN with IOCM that exceeded a minimally important difference but was not statistically significant. However, no study reported a statistically significant greater CIN incidence with IOCM compared to LOCM.

In meta-analyses including 23 of the IOCM studies reporting CIN incidence, there was a borderline significant reduction in the incidence of CIN with IOCM compared with a diverse group of LOCMs. The extent of reduction was consistent with or without stratification by route of administration (Figure 3). Statistical heterogeneity was relatively low, as indicated by the I-squared results displayed in Figure 3. The combined estimate of pooled relative risk was 0.80; (95% CI: 0.65 to 0.99), which corresponds to a number-needed-to-treat of 42 for the point estimate. The estimated relative risk did not exceed a minimally important difference. One study only reported on GFR and was not included in the meta-analysis. That study[20] did not report on a significant change in GFR between groups (Appendix E, Evidence Table E-8). Also excluded from the meta-analyses was one study[48] that reported no CIN in either comparison group but did not explicitly state the CIN criteria. Using Harbord's modified test for small study effects, we did not find evidence of asymmetry in results by study precision (bias coefficient of –0.44, standard error of 0.61, p=0.47).

Figure 3. Graphical summary of randomized controlled trials comparing iso-osmolar and low-osmolar contrast media with contrast-induced nephropathy as a primary outcome



CI = confidence interval; CIN = contrast induced nephropathy; IA = intra-arterial; IV = intravenous; IOCM = iso-osmolar contrast media; LOCM = low-osmolar contrast media; N = sample size; P = p-value; RR = risk ratio

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, although the statistical power was limited by the small number of studies.

When we considered study results by year of publication, we saw no trend over time in the results of studies comparing IOCM with LOCM for either route of administration.

When the meta-analysis was stratified by the two most studied LOCMs, the aggregate estimate of the pooled relative risk was 0.82 (95% CI: 0.53 to 1.25) for the eight studies comparing IOCM with iopromide (using either route of administration) and 1.05 (95% CI: 0.75 to 1.47) for the five studies comparing IOCM with iopamidol (using either route of administration). The results were similar when we included only studies using intra-arterial administration (6 for iopromide, and three for iopamidol). When we explored the differences in results between these trials, we found no apparent pattern associated with procedure type or study location.

The strength of the overall body of evidence included in the meta-analysis was moderate. For the studies including only intravenous administration of contrast media, the strength of evidence was low that IOCM had a slightly lower risk of CIN than LOCM that was not clinically important (with only borderline statistical significance), and for intra-arterial administration of contrast media, the strength of evidence was moderate that IOCM had a slightly lower risk of CIN than LOCM that was not clinically important (with only borderline statistical significance) (Table 4; see Appendix G for study limitations).

The results of the seven applicable observational studies[52-58] were similar to those reported in the RCTs. We did not make any changes in the grading of the overall strength of evidence based on the observational studies of the comparison of IOCM versus LOCM (Appendix E, Evidence Table E-12).

Need for Renal Replacement Therapy

Five studies reported on the need for hemodialysis or hemofiltration which ranged from 0 to 1.9 percent (Appendix E, Evidence Table E-9). Four involved intra-arterial administration[26,33,35,44] and one involved intravenous administration.[37] Differences between groups were either not reported or not statistically significant regardless of administration route. The studies reporting on the need for renal replacement therapy had a total of 1740 patients (well below the optimum information size we specified for this relatively rare event). Confidence intervals for relative risks were wide because of the low event rates in studies reporting need for renal replacement therapy. The strength of the overall body of evidence was low, based on the studies included in the overall meta-analysis (Table 4; see Appendix G for study limitations).

Cardiovascular Outcomes

Seven studies reporting on IOCM versus LOCM addressed cardiovascular outcomes. All involved intra-arterial administration (Appendix E, Evidence Table E-9). [26,28,32,34,35,39,41] All studies with the exception of one reported no statistically significant differences between groups (in Nie et al., the composite cardiovascular event rate (percent of sample size) was: IOCM arm = 0.1%, LOCM arm = 5.9%, p-value = 0.025).[39] This study[39] had a medium risk of bias, and we could find no explanation for why its results differed from the other six studies. The studies reporting on cardiovascular outcomes included a total of 2,258 patients (again below the optimum information size for this relatively rare type of adverse outcome). Confidence intervals

for relative risks were generally wide because of the low event rates. The strength of the overall body of evidence was low (Table 4; see Appendix G for study limitations).

Mortality

Eight studies reporting on IOCM versus LOCM addressed mortality as an outcome (Appendix E, Evidence Table E-9). Two reported on intravenous administration[37,38] and six reported on intra-arterial administration.[26,27,33-35,38,39] Differences between groups were either not reported or not statistically significant regardless of administration route. The studies reporting on mortality had a total of 2028 patients (below the optimum information size). Confidence intervals for relative risks were generally wide because of the low mortality rates, most of which ranged from 0 to 2.7 percent. One study reported a 9-percent mortality rate across the entire population with 4 percent dying in the LOCM group and 3 percent in the ICOM group (p=0.63).[26] The strength of the overall body of evidence was low (Table 4; see Appendix G for study limitations).

Adverse Events

Twelve studies reported on adverse events, with a total of 3363 patients, well below the optimum information size for rare events (Appendix E, Evidence Table E-9). Ten reported on intra-arterial administration [26,28,32-36,39,41,44] and two reported on intravenous administration.[29,30] Differences between groups were either not reported or not statistically significant regardless of administration route. The overall strength of evidence on adverse events was low (Table 4; see Appendix G for study limitations).

Image Quality and Diagnostic Accuracy

Two studies reporting on IOCM versus LOCM addressed imaging quality as an outcome (Appendix E, Evidence Table E-9).[29,39] One reported using intra-arterial administration of contrast and reported on image quality,[39] while the other study used intravenous contrast administration and reported on diagnostic efficacy.[29] Differences between groups were not statistically significant regardless of outcome measure in either study. The intra-arterial administration study had medium risk of bias. The intravenous administration study had low risk of bias. We were unable to grade the body of evidence on image quality due to the differences in the contrast media administration and the difference in outcomes reported.

Benefits or Harms by Patient Characteristics, Dose of Contrast Media, and Type of Preventive Strategy

Few studies reported on how differences in outcomes between contrast media varied according to selected study population characteristics such as age, baseline renal function, and presence or absence of diabetes mellitus. Six studies reported outcomes based on subgroups. Rudnick et al. (2008)[40] reported that there was no significant difference in outcomes between patients with and without diabetes mellitus and co-administration of N-acetylcysteine. Jo et al. (2006)[44] found the incidence of CIN was higher in patients with severe baseline renal impairment. Hernandez et al. (2009)[31] reported that baseline GFR and contrast media acted as independent predictors of CIN. Limbruno et al. (2014)[25] reported a dose-dependent effect of contrast media on renal function. Solomon et al. (2007)[41] showed no significant difference between groups with and without diabetes mellitus.

When we looked at how study populations varied between studies, we found that the vast majority of study populations had a mean age greater than 60 years, with only one done on a young population.[29] When we examined forest plots of results ordered by mean age of study patients, mean baseline renal function, or proportion of patients with diabetes mellitus, we did not see any notable trend in the results for groups receiving intravenous contrast media or intra-arterial contrast media. In the absence of any such trend, we did not include a meta-regression by any of these variables.

Table 4. Summary of the strength of evidence: iso-osmolar contrast media versus low-osmolar contrast media

Outcome	RCTs (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence*	Summary of Key Outcomes
Development of CIN	25 (5,097)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that IOCM had a slightly lower risk of CIN than LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Development of CIN (IV administration)	6 (790)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that IV IOCM had a slightly lower risk of CIN than IV LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Development of CIN (IA administration)	18 (4,194)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that IA IOCM had a slightly lower risk of CIN than IA LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Need for RRT	5 (1,740)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that the need for RRT does not differ between IOCM and LOCM.
Cardiovascular outcomes	7 (2,258)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that cardiovascular outcomes do not differ between IOCM and LOCM.
Mortality	8 (2,028)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that mortality does not differ between IOCM and LOCM.
Adverse events	12 (3,363)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that adverse event rates do not differ between IOCM and LOCM.

CIN = contrast induced nephropathy; IA = intra-arterial; IOCM = iso-osmolar contrast medium; IV = intravenous; LOCM = low-osmolar contrast medium; NA = not assessed; RCT = randomized controlled trial; RRT = renal replacement therapy

*Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores, the more conservative study limitation designation was chosen.

Discussion

In this systematic review of the comparative effects of different types of contrast media with respect to developing CIN, we found two types of RCTs: trials comparing two or more LOCMs to each other, and trials comparing IOCM to a LOCM. The small number of trials comparing LOCMs reported no statistically significant or clinically important differences for heterogeneously defined endpoints for CIN. The strength of evidence for the comparison of LOCMs was low, primarily due to the small number of available studies. For the trials comparing IOCM to LOCMs, we found a slight reduction in CIN risk for IOCM that was of borderline statistical significance, with a 95% CI: 0.65 to 0.99 for the relative risk. However, the point estimate of the pooled relative risk reduction (0.80) did not exceed a minimally important relative risk difference of 25 percent. The strength of evidence for the comparison of IOCM to LOCMs was moderate rather than high because most studies of this comparison had either medium or high study limitations despite exceeding the optimum information size.

The majority of trials in our review involved patients receiving intra-arterial administration of contrast. In the small number of trials involving intravenous administration, we saw no evidence that the relationship between contrast type and CIN risk differed from that observed in the intra-arterial trials. It should be noted that this finding represents the lack of an association between route of administration and the comparative risk between contrast types. This is not the same as the simpler relationship between route of administration and absolute CIN risk, which was not encompassed by our systematic review. Narrative reviews of the CIN literature have suggested that intravenous administration is safer than intra-arterial,[59] but we did not find evidence that the comparative CIN risk of different types of contrast media varies by route of administration.

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. A recent meta-analysis of RCTs compared IOCM and LOCM with cardiovascular events as a reported outcome,[60] and found no conclusive evidence that IOCM is superior to LOCM with respect to cardiovascular events. Our review likewise found no conclusive evidence for a difference with respect to cardiovascular events, mortality, subsequent need for renal replacement therapy, or other adverse events. It is important to note, however, that our review of the differences between types of contrast media was part of a comprehensive review that focused primarily on assessing the comparative effectiveness of interventions for preventing CIN.[61] Thus, our inclusion criteria targeted trials that were designed to examine the effects of interventions and types of contrast media on the risk of CIN. Therefore, our review may not have included some studies that focused on the effects of different types of contrast media on clinical outcomes other than the risk of CIN. For example, the recent meta-analysis of cardiovascular events by Zhang[60] included four RCTs (out of 11) which did not report outcomes directly related to CIN. The evidence grades we assigned to outcomes other than CIN apply only to evidence from studies reporting CIN and do not necessarily apply to all studies reporting these non-renal outcomes.

Our results and summary relative risks are similar to three published meta-analyses which reported no statistically significant reduction of CIN with IOCM compared to LOCM.[62-64] Even though our review included six RCTs that have been published since those three meta-analyses, we obtained a similar summary relative risk and 95% CI. This similarity enhances our

confidence in concluding that IOCM does confer a small reduction in CIN that is not clinically important.

Although five previously published systematic reviews examining trials comparing IOCM against LOCM have reported statistically significant results favoring IOCM, we identified reasons for the discrepancy from our results. In the case of one of those meta-analyses,[65] the two studies favoring IOCM the greatest[66,67] were excluded from our analysis because CIN was not adequately defined in the two studies. Two other systematic reviews did not strictly evaluate direct comparisons, but employed analytical methods that allowed indirect comparisons of contrast agents across individual studies.[68,69] Those two reviews reported differences specifically between IOCM and the LOCM iohexol, but not with other LOCMs. In our meta-analysis, as shown in Figure 3, the two studies that compared iohexol to IOCM were the two oldest studies and were among the four studies reporting the greatest difference favoring IOCM. One of the reviews involved a broadly defined outcome and included studies with outcomes other than CIN.[68] The other review pooled data from observational studies with data from RCTs.[69] Two other meta-analyses which reported differences between IOCM and LOCMs[70,71] may have been affected by inclusion criteria that were different than those used in our review. One of those meta-analyses included only trials of IOCM that were sponsored by its manufacturer.[70] The other meta-analysis[71] included a large unpublished positive trial comparing IOCM with iopromide in 1656 patients that comprised 28 percent of the subjects in the review. Data for this trial are only available in a 2010 meeting abstract; to date, the study has not been published.

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. Some evidence exists from propensity-score matched, retrospective studies questioning the strength of the relationship between contrast administration and CIN.[6] This relationship is very important for designing future research, but does not affect the conclusions of this review regarding the comparative impact of contrast media type on observed CIN.[6,12,72]

Limitations of the Evidence

Limitations of the published evidence should be noted. One of the biggest limitations is that the body of evidence is limited by the relatively small size of the available studies, making it difficult to derive precise estimates of any potential differences. Another limitation of the evidence is that few studies in our review reported on clinical outcomes other than the incidence of CIN. Diagnostic and therapeutic procedures involving iodinated contrast media are generally safe, so it is expected that major adverse events would be rare relative to CIN. Therefore, clinical trials may only have sufficient power to detect large differences in the incidence of major adverse events. While CIN was the primary outcome of interest, we collected data on other associated outcomes, such as cardiovascular events, mortality, adverse events, and image quality. Despite their clinical importance, we found these associated outcomes were inconsistently reported or omitted in the literature that we reviewed.

We found that studies examining CIN generally included patients based on referral for a diagnostic or therapeutic procedure and provided little detail about the distribution of specific clinical indications for the procedures or other details related to the clinical setting such as referral patterns, procedure urgency, severity of renal impairment, and other potential risk factors for CIN. Furthermore, details concerning the procedures themselves were commonly omitted, such as total contrast volume, length of procedure, and contrast injection rates, even though these

details are considered important elements of the procedures and are commonly recorded. 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 or other relevant clinical details such as the severity of renal impairment. These are all potential sources of unexplained heterogeneity among the studies in our review. Our inclusion criteria did not select studies based on any of these characteristics, so the results likely apply to a relatively diverse population of patients and procedures.

Limitations of the Review

One limitation of the review is that we generally considered LOCM together as a group even though there were seven chemically different LOCMs in the evidence we reviewed. While direct comparisons of LOCMs are sparse, there is some indirect evidence of heterogeneity involving iohexol. The greatest CIN reduction with IOCM was reported in a study comparing it to iohexol.[45] As mentioned previously, two indirect comparisons also concluded that differences existed between iohexol and other LOCMs.[68,69]

The relatively large number of trials comparing IOCM to a LOCM, in theory, provides indirect information about comparisons between LOCMs. 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 IOCM severely limits the reliability of such an analysis.[73] For this reason, a network meta-analysis was not performed in our review of the evidence.

Future Research

Since we are unable to draw definitive conclusions on how differences in CIN risk associated with contrast type are modified by demographic characteristics, comorbid conditions, baseline renal function, or use of interventions to prevent CIN, there is a need for additional research in this area. These interactions were either not examined in the reviewed studies, or the factors were inconsistently defined or reported. It makes sense to give highest priority to factors most likely to be associated with a high risk of CIN, such as baseline renal dysfunction or comorbid conditions associated with a high risk of kidney disease.

Additional RCTs comparing IOCM and LOCMs with respect to CIN risk would increase the strength of evidence and precision of pooled effect estimates associated with these comparisons. However, since we found that the CIN risk reduction associated with IOCM is relatively small and unlikely to be clinically important, the necessity for increased precision must be justified prior to conducting additional RCTs.

Conclusions

In summary, RCTs comparing LOCMs with each other are relatively sparse, but none reported a statistically significant or clinically important difference with respect to CIN. This absence of a difference is associated with a low strength of evidence. A larger number of trials compared IOCM to LOCM with respect to CIN. In aggregate, these trials demonstrated moderate strength of evidence for a slight CIN reduction associated with IOCM compared to a diverse group of LOCMs. However, this reduction had only borderline statistical significance and is

unlikely to be clinically important. No relationship was found between comparative CIN risk and route of administration.

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Appendix A. Acronyms

AHRQ	Agency for Healthcare Research and Quality
AKI	Acute kidney injury
CI	Confidence Interval
CIN	Contrast induced nephropathy
CKD	Chronic kidney disease
CV	Cardiovascular
EPC	Evidence-based Practice Center
ESRD	End stage renal disease
GFR	Glomular filtration rate
HD	Hemodialysis
HF	Heart failure
HOCM	High osmolar contrast media
IA	Intra-arterial
IOCM	Iso-osmolar contrast media
ITT	Intention to treat
IV	Intravenous
IVU	Intravenous urography
KDIGO	Kidney Disease: Improving Global Outcomes
KQ	Key Questions
LOCM	Low osmolar contrast media
MACE	Major adverse cardiac events
MeSH	Medical subject heading
MI	Myocardial infarction
NA	Not applicable
NR	Not reported
NS	Not significant
PCI	Percutaneous coronary intervention
PICOTS	Population, interventions, comparators, outcomes, timing, setting
PP	Protocol population
RCT	Randomized controlled trial
RRT	Renal replacement therapy
SOE	Strength of evidence
SIP	Scientific information package
TOO	Task Order Officer

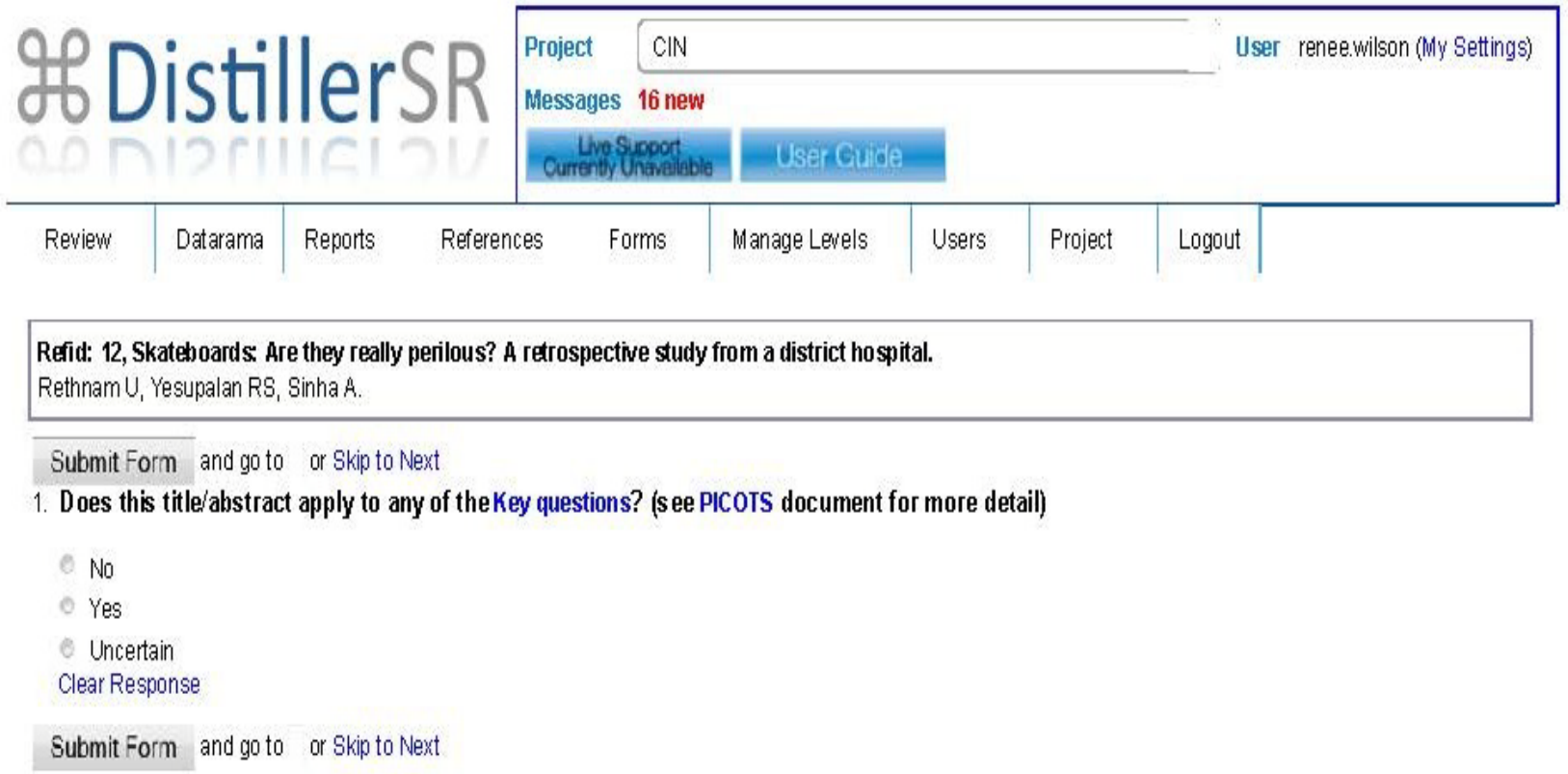
Appendix B. Detailed Search Strategy

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])	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)	8952	12151 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 Search #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	Other reviews: 52 Trials: 368 Technology assessments: 4 Economic evaluations: 5
Total		14,689	

Appendix C. Screening and Data Abstraction Forms

Title

DistillerSR https://systematic-review.ca/Submit/RenderForm.php?id=1&hide_abstract=1



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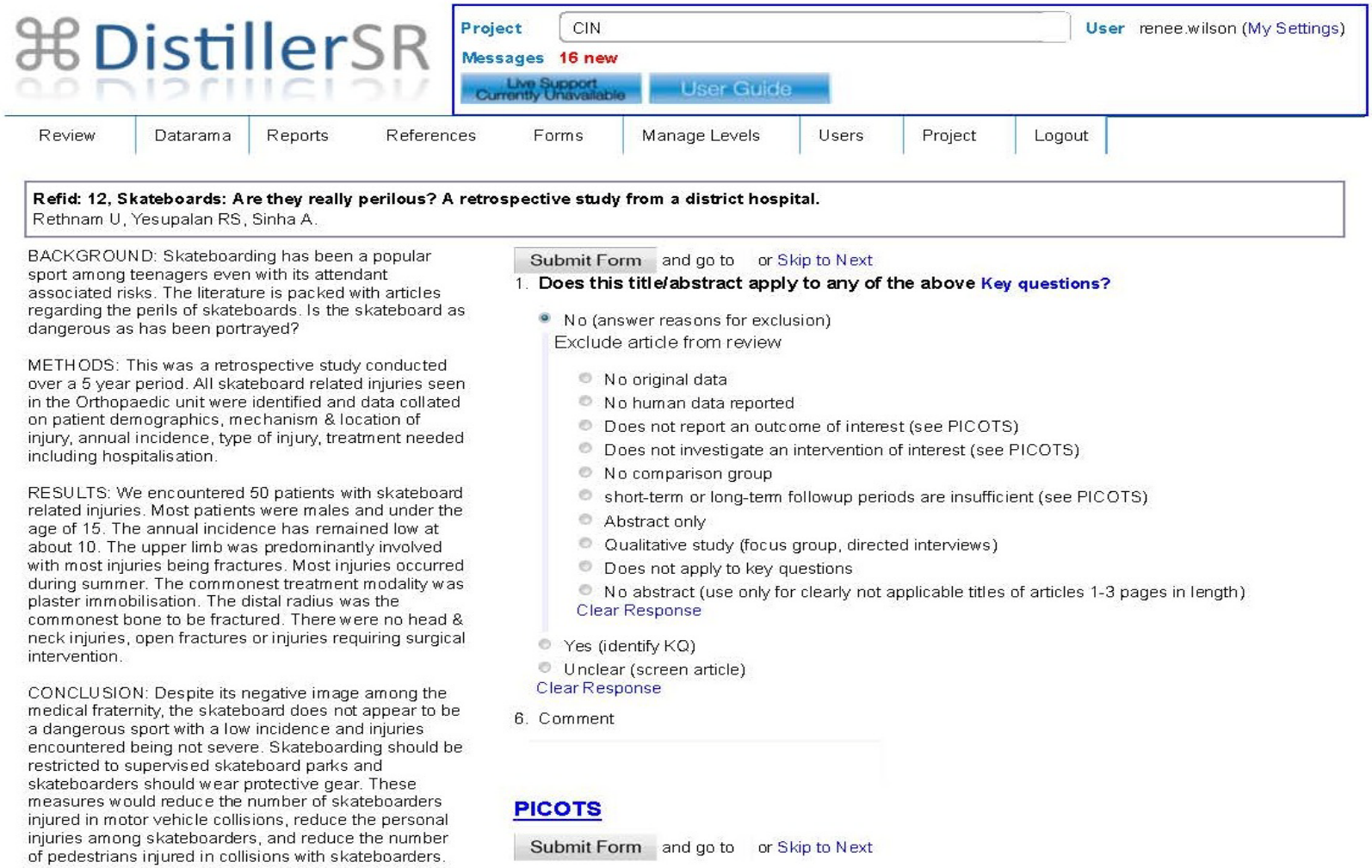

Abstract Screening – YES

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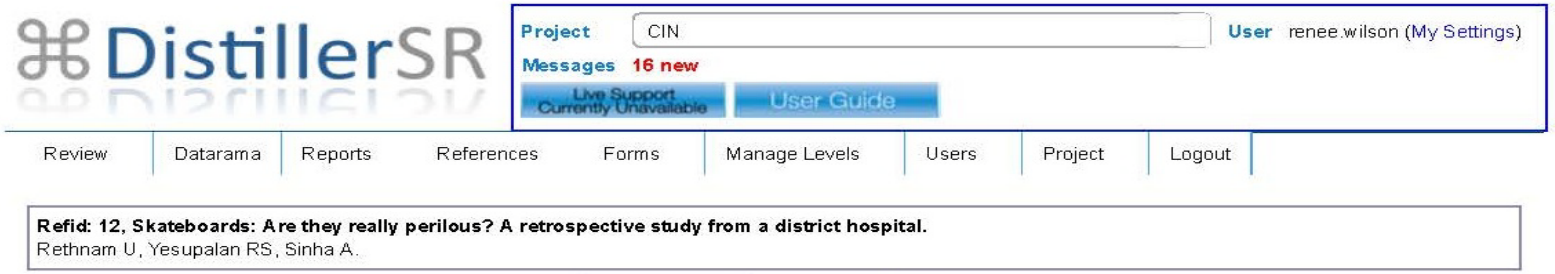

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

1. **Does this title/abstract apply to any of the above Key questions?**

- ○ No (answer reasons for exclusion)
- ◉ Yes (identify KQ)

Include article for review

- ☐ KQ1: IV contrast media (comparative effectiveness of interventions to prevent CIN)
- ☐ KQ2: IA contrast media (comparative effectiveness of interventions to prevent CIN)
- ☐ KQ3: IV contrast media--comparative benefits and harms of the media
- ☐ KQ4: IA contrast media--comparative benefits and harms of the media

- ○ Unclear (screen article)

Clear Response

6. Comment

PICOTS

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Abstract Screening – Unclear

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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

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Submit Form and go to or Skip to Next

1. **Does this title/abstract apply to any of the above Key questions?**

- ○ No (answer reasons for exclusion)
- ○ Yes (identify KQ)
- ◉ Unclear (screen article)
  - ○ No abstract available; title appears applicable
  - ○ Other reason

  Clear Response

Clear Response

6. Comment

PICOTS

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Article Screening – NO

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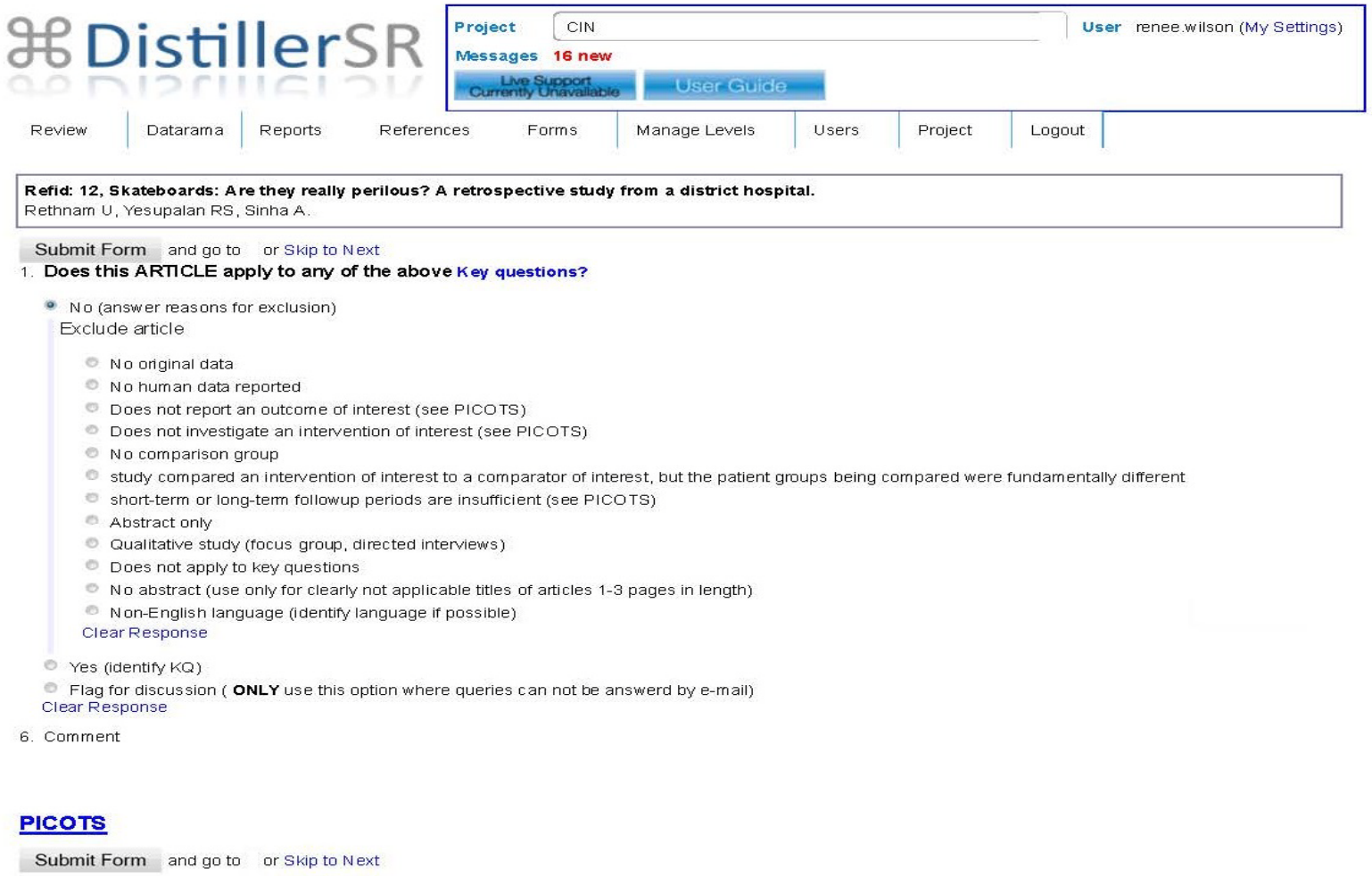

Article Screening – YES

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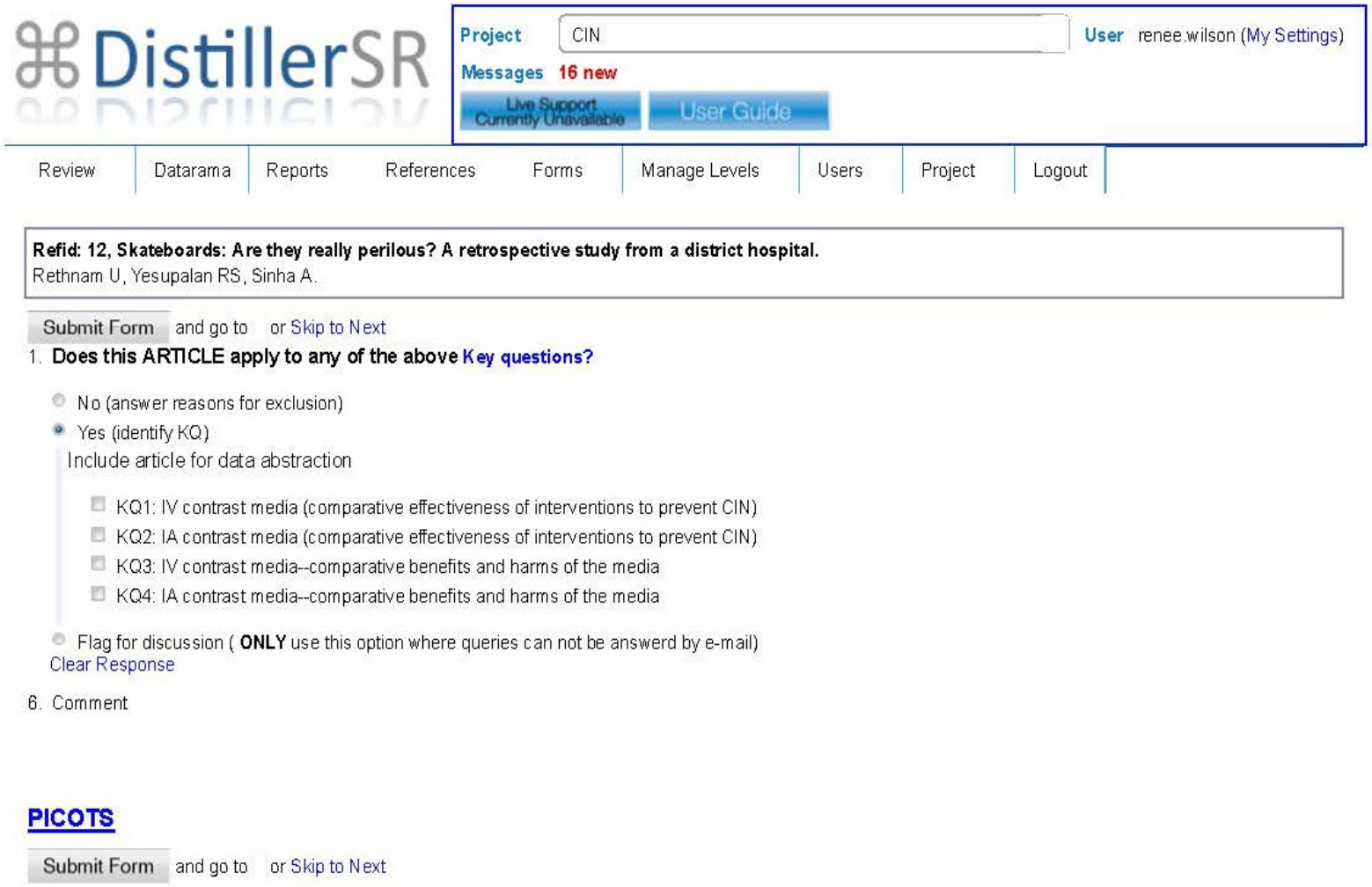

Participant Characteristics

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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Participant Characteristics at Baseline

1. Does the study report baseline characteristics for subgroups seperately?
(e.g., IV administration and IA administration)

- Yes
- No

Clear Response

2. Identify group for baseline characteristics
(You can submit this form multiple time)

Select an Answer

Arm 1 (control/usual care)	Arm 2	Arm 3	Arm 4	Arm 5
3.	4.	5.	6.	7.

8. N at baseline

- Total N
- Arm 1 (control/usual care) n
- Arm 2
- Arm 3
- Arm 4
- Arm 5
- Not reported

	Follow-up	Mean, median, max/min...	Units
9. Not reported Clear Response	10.	11. Select an Answer	12. Select an Answer

13. Sex

- reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5

14.	15.	16.	17.	18.	19.
☐ women, n ☐ women, %	☐ women, n ☐ women, %	☐ women, n ☐ women, %	☐ women, n ☐ women, %	☐ women, n ☐ women, %	☐ women, n ☐ women, %

○ not reported

20. Age

◉ reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
21. ☐ mean ☐ Median ☐ Range	22. ☐ mean ☐ Median ☐ Range	23. ☐ mean ☐ Median ☐ Range	24. ☐ mean ☐ Median ☐ Range	25. ☐ mean ☐ median ☐ range	26. ☐ mean ☐ median ☐ range

○ not reported

27. Race/ethnicity

◉ Reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
White, non-Hispanic	28. ☐ n ☐ %	29. ☐ n ☐ %	30. ☐ n ☐ %	31. ☐ n ☐ %	32. ☐ n ☐ %	33. ☐ n ☐ %
Black, non-Hispanic	34. ☐ n ☐ %	35. ☐ n ☐ %	36. ☐ n ☐ %	37. ☐ n ☐ %	38. ☐ n ☐ %	39. ☐ n ☐ %
Latino/Hispanic	40. ☐ n ☐ %	41. ☐ n ☐ %	42. ☐ n ☐ %	43. ☐ n ☐ %	44. ☐ n ☐ %	45. ☐ n ☐ %
Asian/Pacific Islander	46. ☐ n ☐ %	47. ☐ n ☐ %	48. ☐ n ☐ %	49. ☐ n ☐ %	50. ☐ n ☐ %	51. ☐ n ☐ %
American Indian/Alaska Native	52. ☐ n ☐ %	53. ☐ n ☐ %	54. ☐ n ☐ %	55. ☐ n ☐ %	56. ☐ n ☐ %	57. ☐ n ☐ %
58. Other	59. ☐ n ☐ %	60. ☐ n ☐ %	61. ☐ n ☐ %	62. ☐ n ☐ %	63. ☐ n ☐ %	64. ☐ n ☐ %

65. Other	66. n %	67. n %	68. n %	69. n %	70. n %	71. n %
72. Other	73. n %	74. n %	75. n %	76. n %	77. 2n %	78. 2n %

not reported

79. Education

Reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
< High School	80. n %	81. n %	82. n %	83. n %	84. n %	85. n %
Completed High School	86. n %	87. n %	88. n %	89. n %	90. n %	91. n %
College Degree	92. n %	93. n %	94. n %	95. n %	96. n %	97. n %
Post-graduate Degree	98. n %	99. n %	100. n %	101. n %	102. n %	103. n %
Years of education	104. mean median min max	105. mean median min max	106. mean median min max	107. mean median min max	108. mean median min max	109. mean median min max
110. Other	111. n %	112. n %	113. n %	114. n %	115. n %	116. n %
117. Other	118. n %	119. n %	120. n %	121. n %	122. n %	123. n %

124. Other	125. ☐ n ☐ %	126. ☐ n ☐ %	127. ☐ n ☐ %	128. ☐ n ☐ %	129. ☐ n ☐ %	130. ☐ n ☐ %

○ not reported

131. Smoking

◉ reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Current	132. ☐ n ☐ %	133. ☐ n ☐ %	134. ☐ n ☐ %	135. ☐ n ☐ %	136. ☐ n ☐ %	137. ☐ n ☐ %
Former	138. ☐ n ☐ %	139. ☐ n ☐ %	140. ☐ n ☐ %	141. ☐ n ☐ %	142. ☐ n ☐ %	143. ☐ n ☐ %
Ever	144. ☐ n ☐ %	145. ☐ n ☐ %	146. ☐ n ☐ %	147. ☐ n ☐ %	148. ☐ n ☐ %	149. ☐ n ☐ %
Never	150. ☐ n ☐ %	151. ☐ n ☐ %	152. ☐ n ☐ %	153. ☐ n ☐ %	154. ☐ n ☐ %	155. ☐ n ☐ %

○ not reported

156. Is the entire study population a subgroup (all particiupants have a specific disease or condition)?

◉ Yes

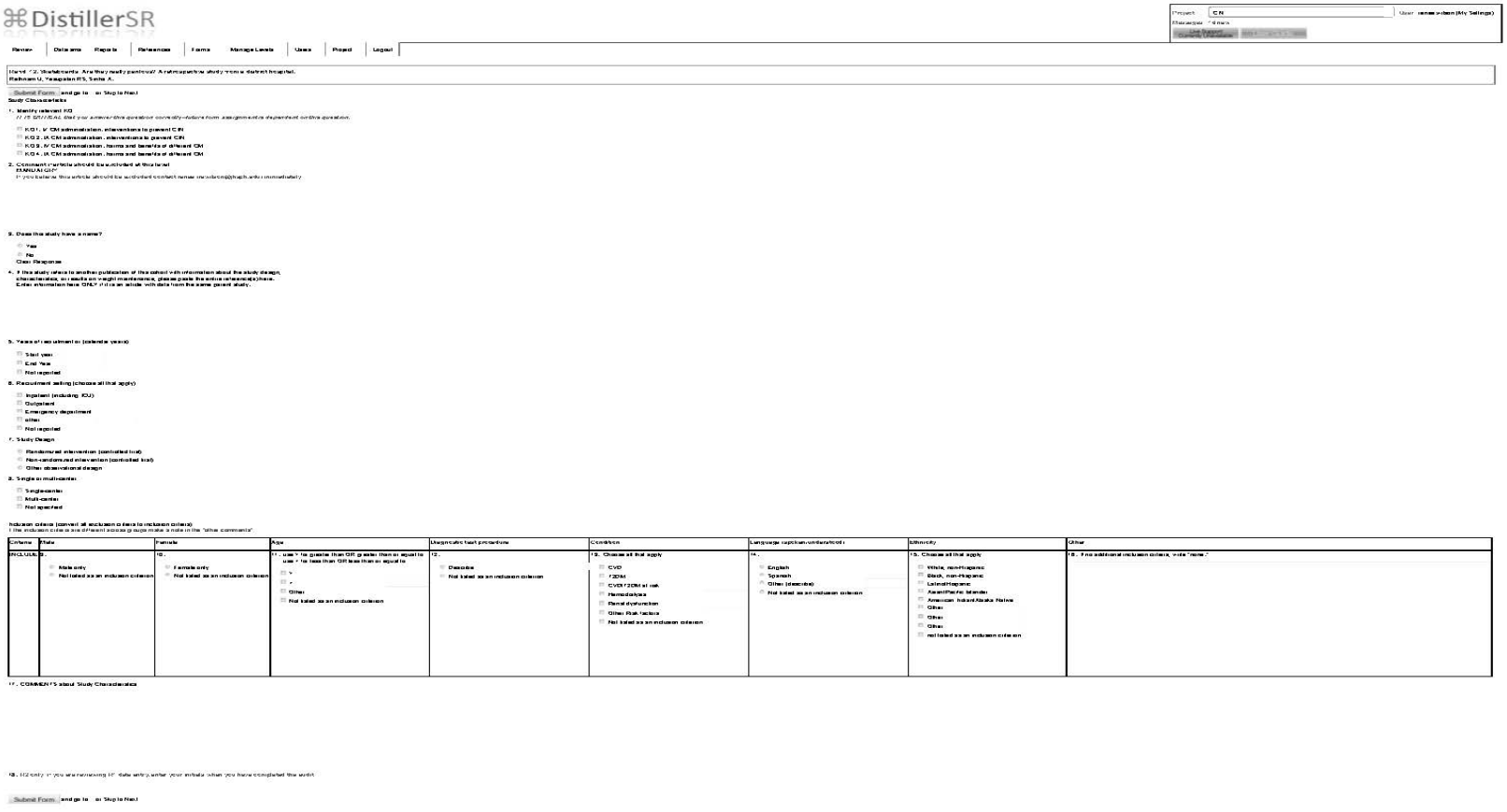
Condition	Define
Renal insufficiency (included CKD)	157.
Diabetes	158.
On Dialysis	159.
160. Other	161.
162. Other	163.

166. Other Comments

167. **R2 only: if you are reviewing R1 data entry, enter your initials when you have completed the audit**

Submit Form and go to or Skip to Next

Study Characteristics



Intervention Description*

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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Intervention Description
Key Questions 3_4

The following questions are in place to identify and describe contrast media (CM) only.
Use Arm 1 EXCLUSIVELY for the control or standard care intervention. If there is no control, leave those columns blank under Arm 1
NOTE: the Arms below should match the Arms described in the participant characteristics form

1. Does the study report Interventions for subgroups seperately?
(e.g., IV administration and IA administration)

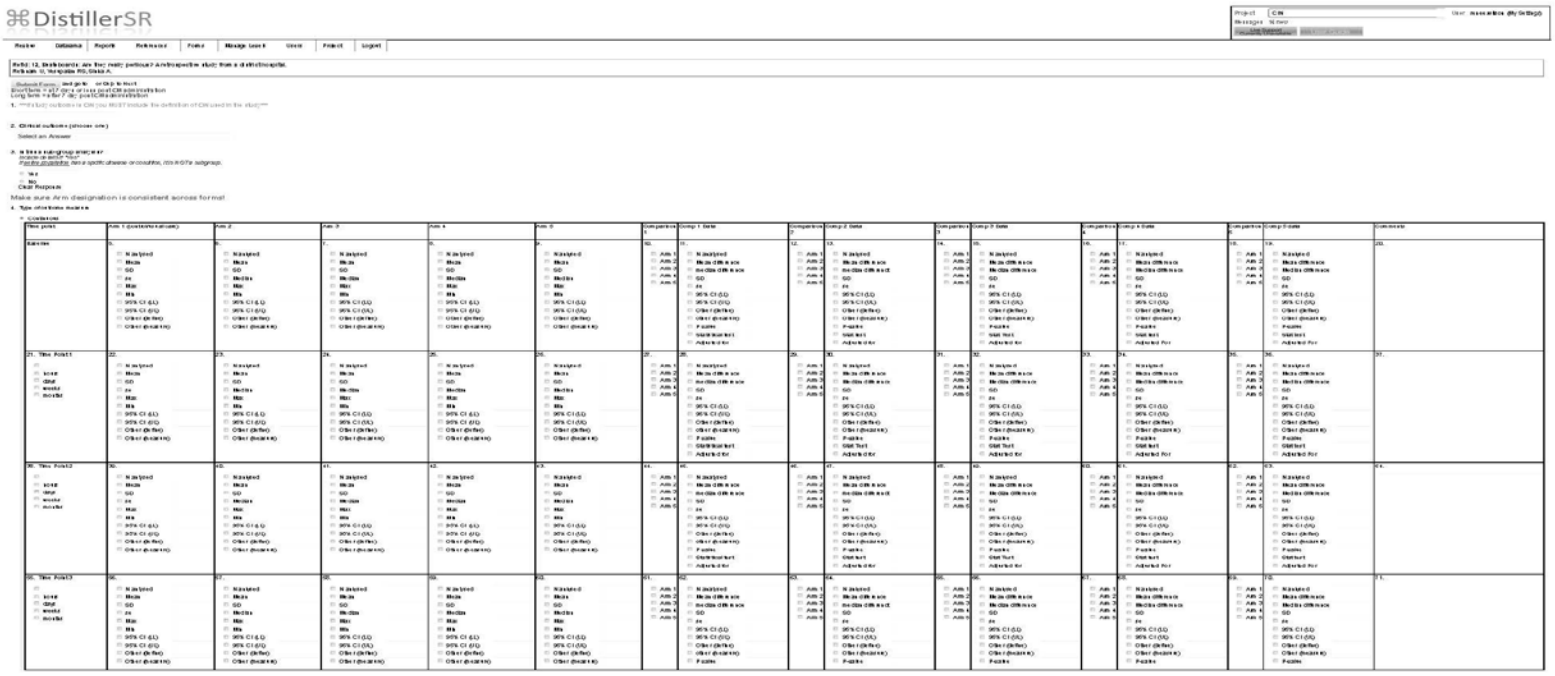
- Yes
  2. Identify group for baseline characteristics
  (You can submit this form multiple time)
  Select an Answer
- No

Clear Response

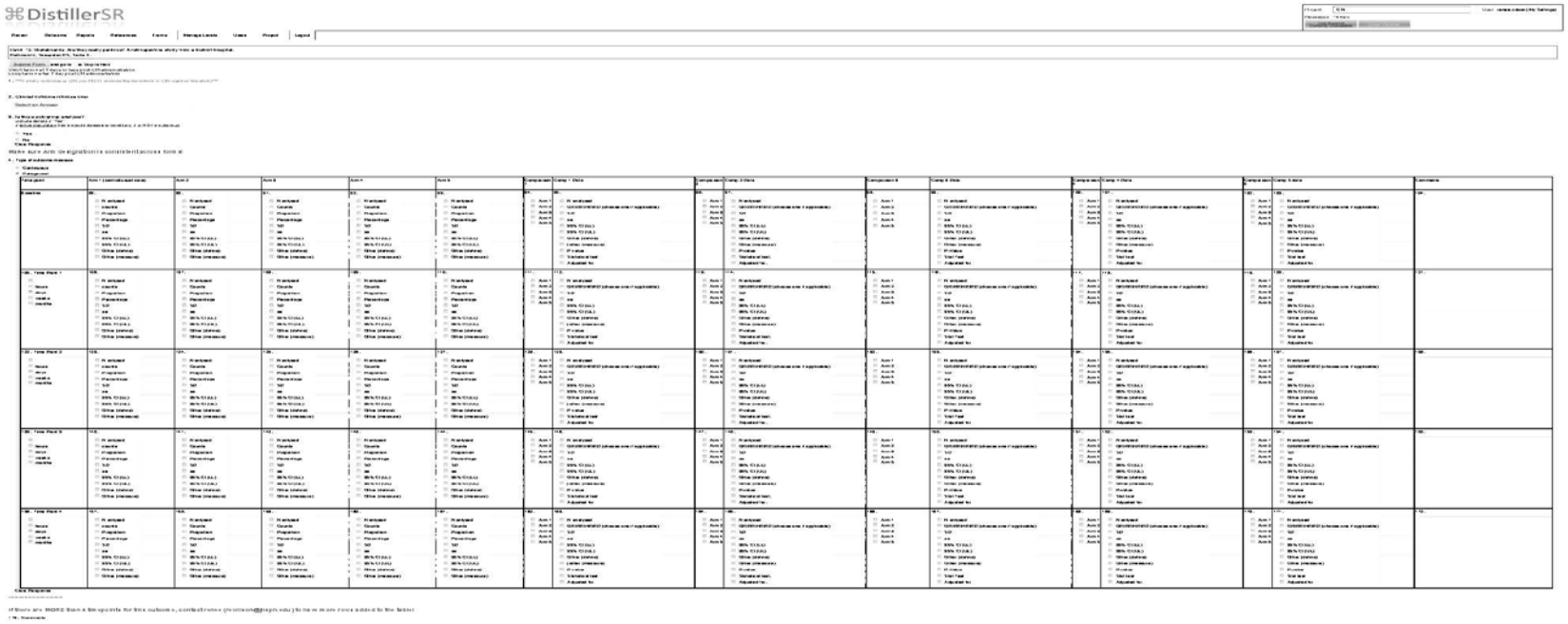
	Arm 1 (control/usual care)	Arm 2	Arm 3	Arm 4	Arm 5
Contrast Medium (Media) used	3. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	4. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	5. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	6. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	7. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description
Administration route	8. **NO CONTROL OR USUAL CARE** IV IA Not reported Other	9. IV IA Not reported Other	10. IV IA Not reported Other	11. IV IA Not reported Other	12. IV IA Not reported Other

*Forms were developed prior to the Key Questions (3 and 4) being combined—the same form was used for all.

Clinical Outcomes, Continuous

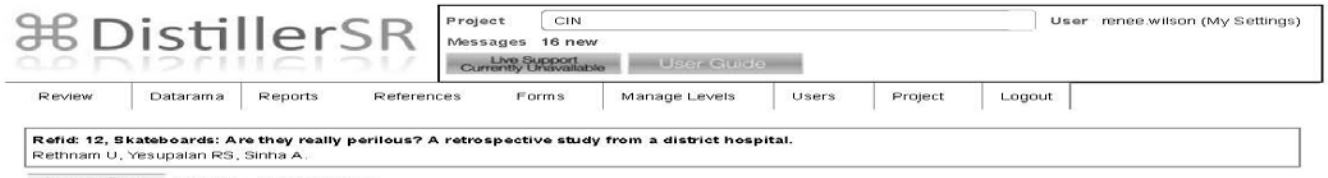


Clinical Outcomes, Categorical



DistillerSR https://systematic-review.ca/Submit/RenderForm.php?id=18&hide_abstract=1

Adverse Events



Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Adverse events

1. Did this study report adverse events?

Yes (inclueds a explicite report of no adverse events)

Harm	Describe
Imaging delay	2.
Need for additional imaging	3.
Fluid overload	4.
Heart failure	5.
Anaphalaxis	6.
7. Other	8.

Cochrane Risk of Bias

DistillerSR

Project CIN User renee.wilson (My Settings)

Messages 16 new

Live Support Currently Unavailable | User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Risk of Bias

1. Choose primary outcome (if study has more than 1 primary/main outcome, this form will need to be filled out multiple times).

Select an Answer

The full Cochrane Riskl of Bias tool can be accessed here: http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20assessment%20tool.pdf

Please refer to the link above while performing RoB assessments

Domain	Desription	Review Author's Judgement ...does the study:
Sequence Generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	2. Was the allocation sequence adequately generated? Select an Answer
Allocation Concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during enrollment.	3. Was allocation adequately concealed? Select an Answer
Blinding of Participants, Personnel, ad Outcome Assessors *Assessments should be made for each main outcome or class of*	Describe all measures used, if any to blind study personnel and participants from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	4. Was knowledge of the allocated intervention adequately prevented during the srudy? Select an Answer

outcomes		
Incomplete Outcome Data *Assessments should be made for each main outcome or class of outcomes*	Describe the completeness of outcome data for each main outcome, including attrition and exclusion from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compare with total randomized participants), reason for attrition/exclusions where reported, and any re-inclusions in analyses performed by teh review authors.	5. Were incomplete oucome data adequately addressed? Select an Answer
Selective Outcome Reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	6. Are reports of the study free of suggestion of selective outcome reporting? Select an Answer
Other Sources of Bias	State any important concerns about bias not addresses in the other domains in the tool.	7. Was the study apparently free of other problems that could put it at a high risk of biase? Select an Answer

8. Comments

9. **R2 only: if you are reviewing R1 data entry, enter your initials when you have completed the audit**

Submit Form and go to or Skip to Next

Appendix D. Excluded Studies

Exclusion: Abstract Only

M. R. Gandhi, P. Brown, C. A. Romanowski, S. K. Morcos, S. Campbell, A. M. el Nahas and T. A. Gray. The use of theophylline, an adenosine antagonist in the prevention of contrast media induced nephrotoxicity. Br J Radiol. 1992. 65:838

M. S. Davenport, S. Khalatbari, N. R. Dunnick, J. R. Dillman and J. H. Ellis. Contrast-induced nephrotoxicity: Risk of intravenous low osmolality iodinated contrast material stratified by estimated glomerular filtration rate. Abdominal Imaging. 2013. 38:628

J. Sugioka, M. Inagaki, S. Fukuzawa, A. Ikeda, S. Okino, J. Maekawa, S. Maekawa, S. Ichikawa, N. Kuroiwa and S. Okamoto. Risk prediction of contrast-induced nephropathy in diabetic patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Cardiology (Switzerland). 2013. 125:164

M. Fujimoto, K. Waseda, H. Takashima, K. Maeda, K. Asai, Y. Kuroda, T. Kosaka, A. Kurita, Y. Kuhara, H. Ando, S. Sakurai, D. Kato, A. Suzuki, Y. Nakano, T. Niwa, K. Mukai, S. Sato, T. Mizuno and T. Amano. Effect of oral hydration on renal function after coronary catheterization. American Journal of Cardiology. 2013. 111:89B

M. Habib, A. Hillis and A. Hamad. The role of ascorbic acid or n-acetylcysteine or combination in prevention of contrast-induced nephropathy in high-risk patients with ischemic heart disease. International Journal of Cardiology. 2013. 163:S64

M. Habib, A. Hillis and A. Hamad. Low dose of N-acetylcysteine plus ascorbic acid versus hydration with (saline 0.9%) for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. International Journal of Cardiology. 2013. 163:S81

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J. Samide, N. Saad, T. Abraham and E. Balmir. A retrospective evaluation on the usage of iodinated contrast media in an Urban hospital setting. Critical Care Medicine. 2012. 40:265

J. Kooiman, Y. W. Sijpkens, H. C. Brulez, J. P. P. De Vries, J. F. Hamming, A. J. Van Der Molen, N. J. Aarts, S. C. Cannegieter, T. J. Rabelink and M. V. Huisman. Randomized study of short prehydration with sodium bicarbonate versus standard pre- and posthydration with sodium chloride to prevent contrast induced acute kidney injury: The Salina trial. Circulation. 2012. 126:#pages#

A. M. Fayed. Human albumin versus isotonic sodium bicarbonate in prevention of contrast induced nephropathy in critically ill patients. Intensive Care Medicine. 2012. 38:S243-S244

X. Qun and L. Shijuan. Protection of n-acetylcysteine for patients with contrast induced nephropathy after percutaneous coronary intervention treatment. Heart. 2012. 98:E214

R. Li and H. Chen. Prevention of contrast-induced nephropathy with ascorbic acid. Heart. 2012. 98:E211

J. Juch, J. Le Noble and N. Foudraine. Incidence and prevention of contrast induced nephropathy (CIN) in the ICU: Preventive administration of Na+ bicarbonate is not effective. Single dose amino-glycoside is a major risk factor. Intensive Care Medicine. 2012. 38:S46

G. Deray, L. Marti-Bonmati, O. Rouviere, L. Bacigalupo, B. Maes, T. Hannedouche, F. Vrtovsnik, C. Rigothier, J. Billiouw and P. Campioni. Renal safety evaluation after Gd-DOTA-enhanced-MRI compared with non-enhanced-MRI in patients at high risk of developing contrast medium induced nephropathy. Journal of Medical Imaging and Radiation Oncology. 2012. 56:90

M. Erturk, E. Akbay, G. Kurtulus, N. Isiksacan, M. Gul, I. F. Akturk, O. Surgit, F. Uzun, A. Yildirim and N. Uslu. Effect of iv or oral N-acetylcysteine in the prevention of contrast-induced nephropathy in patients with moderate to severe renal insufficiency. European Heart Journal. 2012. 33:77

A. K. Singh and J. A. Kari. 24-hour isotonic sodium choloride was better than 7-hour sodium bicarbonate for preventing CIN. Annals of Internal Medicine. 2012. 157:JC1-9

V. Brulotte, F. A. Leblond, S. Elkouri, E. Therasse, V. Pichette and P. Beaulieu. Impact of sodium bicarbonate administration and N-acetylcysteine on the prevention of contrast media-induced nephropathy in endovascular aortic aneurysm

repair. European Journal of Anaesthesiology. 2012. 29:66

G. Gu, R. Lu, W. Cui, F. Liu, Y. Zhang and X. Yang. Low-dose furosemide administered with adequate hydration prevents contrast-induced nephropathy in patients undergoing coronary angiography. Circulation. 2012. 125:e868

K. Chatani, M. Abdel-Wahab, R. Toelg, V. Geist, M. Marwan, A. E. Mostafa and G. Richardt. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced acute kidney injury in unselected patients undergoing TAVI. EuroIntervention. 2012. 8:N160

A. Lacquaniti, V. Donato, M. Rosaria Fazio, S. Lucisano, V. Cernaro, R. Lupica and M. Buemi. Contrast media, nephrotoxicity and neutrophil-gelatinase associated lipocalin: Between doubts and certainties. Nephrology Dialysis Transplantation. 2012. 27:ii354-ii355

S. Traub, A. Mitchell, A. E. Jones, A. Tang, J. O'Connor, J. Kellum and N. Shapiro. A randomized trial of N-acetyl cysteine and saline versus normal saline alone to prevent contrast nephropathy in emergency department patients undergoing contrast enhanced computed tomography. Academic Emergency Medicine. 2012. 19:S22

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S. Ebisawa, T. Saigusa, K. Odagiri, S. Aso, K. Aizawa, M. Koshikawa, H. Kasai, A. Izawa, T. Tomita, Y. Miyashita, S. Kumazaki, T. Yaguchi, H. Hioki, J. Koyama, U. Ikeda, T. Kurita, M. Kimura and T. Suzuki. Impact of minimum contrast media on percutaneous coronary intervention for preventing contrast induced nephropathy in patients with coronary artery disease. Circulation. 2011. 124:#pages#

N. Mayaud, K. Isaaz, C. Mariat, A. Cerisier, M. Lamaud, L. Richard and A. Da. Contrast induced nephropathy in patients with normal renal function undergoing complex PCI with high dose of contrast media: Predictive value of Cystatin C. Journal of the American College of Cardiology. 2011. 58:B138

M. Elshawadfy, M. A. Oraby, H. M. Ismail and F. A. Maklady. Effectiveness of theophylline in prevention of contrast-induced nephropathy in risky Egyptian patients undergoing elective coronary angiography or percutaneous intervention: A randomized controlled trial. Journal of the American College of Cardiology. 2011. 58:B136

M. Menozzi, P. Magnavacchi, E. Puggioni, M. Valgimigli, L. Vignali, V. Guiducci, G. Pignatelli, P. Giacometti and A. Manari. Contrast induced acute kidney injury in patients undergoing primary angioplasty for acute myocardial infarction. a randomized trial on hydration with saline or bicarbonate. Journal of the American College of Cardiology. 2011. 58:B137-B138

A. Momeni, A. Ebrahimi and A. Khaledi. Comparison of three methods of contrast nephropathy prophylaxis in azotemic patients. Iranian Journal of Kidney Diseases. 2011. 5:10

S. Bajaj, M. Sharma, R. Parikh, S. Patel, N. Gupta, C. Chandran, A. Hamdan, F. Shamoon and M. Bikkina. Contrast induced nephropathy in patients with chronic kidney disease undergoing coronary angiography. Chest. 2011. 140:#pages#

W. Li, D. Li, T. Xu, Y. Zhang, H. Zhu and F. Han. Prevention of contrast-induced acute kidney injury with ascorbic acid and prostaglandin e1 in high risk factors patients undergoing PCI. Heart. 2011. 97:A151

Y. Miao and Z. Yu-Jie. Efficacy of short-term high-dose atorvastatin for prevention of contrastinduced nephropathy in patients with st segment elevation myocardial infarction undergoing percutaneous coronary intervention. Heart. 2011. 97:A229

X. Hou, Y. J. Wang, Q. X. Yin, J. L. Miao and H. Jiang. Prevention of contrast-induced nephropathy comparison of two hydration regimens in elderly patients undergoing percutaneous coronary intervention. Heart. 2011. 97:A230

L. Bertelli, F. A. Sgura, M. Manicardi, A. Campioli, G. Spadafora, C. Leuzzi, R. Rossi, G. Biondi Zoccai, G. M. Sangiorgi and M. G. Modena. Mid-term outcomes of iodixanol versus iomeprol contrast medium after primary angioplasty for st elevation myocardial infarction. European Heart Journal. 2011. 32:881

M. Brueck, H. Cengiz and A. Boening. Comparison of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced nephropathy in patients with renal insufficiency undergoing elective cardiac catheterization. European Heart Journal. 2011. 32:261-262

M. Mockel, M. J. Dumichen, K. Friedrich, Y. Kuhnle, J. O. Vollert, J. Searle, V. Combe, C. Schwenke and M. Schroder. Invasive renal

hemodynamics after left ventricular and coronary angiography with randomised use of different contrast media. EuroIntervention. 2011. 7:M15

X. Li, Y. Wang, N. Fu, R. Zhao, J. Xiao, Z. Li and H. Cong. Atorvastatin combining probucol can reduce the renal impairment induced with contrast-medium. EuroIntervention. 2011. 7:M17

Y. Chen, S. Hu, Y. Liu, L. Wang, G. Fu and Q. He. A randomised, double-blinded comparison of lopromide and lodixanol in renally impaired patients undergoing cardiac catheterisation (DIRECT study). EuroIntervention. 2011. 7:M11

J. Min, A. Ryan and J. Spalding. Renal morbidity, mortality, and costs in individuals undergoing invasive cardiac catheterization procedures with low-osmolar contrast media: A large retrospective database analysis. Value in Health. 2010. 13:A351

Y. Han, S. Wang, X. Wang, F. Li, X. Zhao and Q. Jing. Contrast-induced nephropathy following coronary intervention in elderly, renally impaired patients: A randomised comparison of the renal safety of iodixanol and iopromide. EuroIntervention. 2010. 6:#pages#

S. Rastelli, L. Zanoli, C. Marcantoni, J. Blanco, C. Tamburino and P. Castellino. Contrast media related risk of contrast induced nephropathy. NDT Plus. 2010. 3:iii56

H. El-Fishawy, N. Shaheen and A. Soliman. Ascorbic acid and acetylcysteine for prevention of acute deterioration of renal function following elective aorto-iliac and coronary angioplasty. NDT Plus. 2010. 3:iii300

S. S. Brar, A.-J. Shen, M. B. Jorgensen, V. J. Aharonian, V. Koshkaryan and A. I. Shah. A randomized controlled trial for the prevention of contrast induced nephropathy with sodium bicarbonate vs. sodium chloride in patients undergoing coronary angiography: 2-year results from the MEENA Trial. #journal#. 2010. #volume#:B77

J. G. Lavenberg and C. A. Umscheid. Prevention of contrast-induced nephropathy: acetylcysteine, sodium bicarbonate, or saline (Structured abstract). #journal#. 2011. #volume#:#pages#

Exclusion: Followup Less Than 1 Year

E. A. McGillicuddy, K. M. Schuster, L. J. Kaplan, A. A. Maung, F. Y. Lui, L. L. Maerz, D. C. Johnson and K. A. Davis. Contrast-induced nephropathy in elderly trauma patients. J Trauma. 2010. 68:294-7

T. Nozue, I. Michishita, T. Iwaki, I. Mizuguchi and M. Miura. Contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy developing after elective percutaneous coronary intervention. J Cardiol. 2009. 54:214-20

S. Khanal, N. Attallah, D. E. Smith, E. Kline-Rogers, D. Share, M. J. O'Donnell and M. Moscucci. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. Am J Med. 2005. 118:843-9

Exclusion: Unobtainable

M. M. Rahman, S. S. Haque, B. Rokeya, M. A. Siddique, S. K. Banerjee, S. A. Ahsan, F. Rahman, M. Mahmood, K. Ahmed, M. M. Bhuiyan, A. I. Joarder and R. C. Debnath. Trimetazidine in the prevention of contrast induced nephropathy after coronary angiogram. Mymensingh Med J. 2012. 21:292-9

Exclusion: No Comparison Group of Interest

D. Abe, A. Sato, T. Hoshi, Y. Kakefuda, H. Watabe, E. Ojima, D. Hiraya, T. Harunari, N. Takeyasu and K. Aonuma. Clinical Predictors of Contrast-Induced Acute Kidney Injury in Patients Undergoing Emergency Versus Elective Percutaneous Coronary Intervention. Circ J. 2013. #volume#:#pages#

N. Tan, Y. Liu, J. Y. Chen, Y. L. Zhou, X. Li, L. W. Li, D. Q. Yu, Z. J. Chen, X. Q. Liu and S. J. Huang. Use of the contrast volume or grams of iodine-to-creatinine clearance ratio to predict mortality after percutaneous coronary intervention. Am Heart J. 2013. 165:600-8

P. Burchardt, P. Guzik, P. Tabaczewski, T. Synowiec, M. Bogdan, P. Faner, A. Chmielarz-Sobocinska and A. Palasz. Early renal dysfunction after contrast media administration despite prophylactic hydration. Int J Cardiovasc Imaging. 2013. 29:959-66

S. Raposeiras-Roubin, E. Abu-Assi, R. Ocaranza-Sanchez, B. Alvarez-Alvarez, C. Cambeiro-Gonzalez, R. Fandino-Vaquero, A. Garcia-Castelo, J. M. Garcia-Acuna and J. R. Gonzalez-Juanatey. Dosing of iodinated contrast volume: A new simple algorithm to stratify the risk of contrast-induced nephropathy in patients with acute coronary syndrome: A New Simple Algorithm to Stratify the Risk of Contrast-Induced Nephropathy in Patients With Acute Coronary Syndrome. Catheter Cardiovasc Interv. 2013. #volume#:#pages#

S. Morabito, V. Pistolesi, G. Benedetti, A. Di Roma, R. Colantonio, M. Mancone, G. Sardella, L. Cibelli, M. Ambrosino, F. Polistena and A. Pierucci. Incidence of contrast-induced acute kidney injury associated with diagnostic or interventional coronary angiography. J Nephrol. 2012. 25:1098-107

Y. Kanei, K. Ayabe, J. Ratcliffe, L. Vales, N. Nakra, P. Friedman and J. Fox. The impact of iso-osmolar contrast use in emergent percutaneous coronary intervention for ST-segment elevation myocardial infarction. J Invasive Cardiol. 2011. 23:448-50

H. S. Gurm, S. R. Dixon, D. E. Smith, D. Share, T. Lalonde, A. Greenbaum and M. Moscucci. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2011. 58:907-14

H. J. Yoon and S. H. Hur. Determination of safe contrast media dosage to estimated glomerular filtration rate ratios to avoid contrast-induced nephropathy after elective percutaneous coronary intervention. Korean Circ J. 2011. 41:265-71

X. C. Wang, X. H. Fu, Y. B. Wang, X. W. Jia, W. L. Wu, X. S. Gu, J. Zhang, J. L. Su, G. Z. Hao, Y. F. Jiang, W. Z. Fan and S. Q. Li. Prediction of contrast-induced nephropathy in diabetics undergoing elective percutaneous coronary intervention: role of the ratio of contrast medium volume to estimated glomerular filtration rate. Chin Med J (Engl). 2011. 124:892-6

Y. Liu, N. Tan, Y. L. Zhou, P. C. He, J. F. Luo and J. Y. Chen. The contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy after primary percutaneous coronary intervention. Int Urol Nephrol. 2012. 44:221-9

F. Ribichini, M. Graziani, G. Gambaro, P. Pasoli, M. Pighi, G. Pesarini, C. Abaterusso, T. Yabarek, S. Brunelleschi, P. Rizzotti, A. Lupo and C. Vassanelli. Early creatinine shifts predict contrast-induced nephropathy and persistent renal damage after angiography. Am J Med. 2010. 123:755-63

H. Trivedi and W. D. Foley. Contrast-induced nephropathy after a second contrast exposure. Ren Fail. 2010. 32:796-801

J. R. Brown, J. F. Robb, C. A. Block, A. C. Schoolwerth, A. V. Kaplan, G. T. O'Connor, R. J. Solomon and D. J. Malenka. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury?. Circ Cardiovasc Interv. 2010. 3:346-50

S. Worasuwannarak and S. Pornratanarangsi. Prediction of contrast-induced nephropathy in diabetic patients undergoing elective cardiac catheterization or PCI: role of volume-to-creatinine clearance ratio and iodine dose-to-creatinine clearance ratio. J Med Assoc Thai. 2010. 93 Suppl 1:S29-34

E. A. McGillicuddy, K. M. Schuster, L. J. Kaplan, A. A. Maung, F. Y. Lui, L. L. Maerz, D. C. Johnson and K. A. Davis. Contrast-induced nephropathy in elderly trauma patients. J Trauma. 2010. 68:294-7

S. M. Kim, R. H. Cha, J. P. Lee, D. K. Kim, K. H. Oh, K. W. Joo, C. S. Lim, S. Kim and Y. S. Kim. Incidence and outcomes of contrast-induced nephropathy after computed tomography in patients with CKD: a quality improvement report. Am J Kidney Dis. 2010. 55:1018-25

D. Kiski, W. Stepper, E. Brand, G. Breithardt and H. Reinecke. Impact of renin-angiotensin-aldosterone blockade by angiotensin-converting enzyme inhibitors or AT-1 blockers on frequency of contrast medium-induced nephropathy: a post-hoc analysis from the Dialysis-versus-Diuresis (DVD) trial. Nephrol Dial Transplant. 2010. 25:759-64

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E. Chong, K. K. Poh, L. Shen, P. Chai and H. C. Tan. Diabetic patients with normal baseline renal function are at increased risk of developing contrast-induced nephropathy post-percutaneous

coronary intervention. Singapore Med J. 2009. 50:250-4

A. M. From, B. J. Bartholmai, A. W. Williams, S. S. Cha and F. S. McDonald. Mortality associated with nephropathy after radiographic contrast exposure. Mayo Clin Proc. 2008. 83:1095-100

G. La Manna, L. Pancaldi, V. Dalmastri, V. Cuna, A. Capecchi, G. Comai, E. Persici, G. Bacchi, G. Cianciolo, A. Lombardi, C. Marrozzini, L. Coli and S. Stefoni. Post-coronarography application of continuous veno-venous hemofiltration in the prevention of contrast nephropathy in patients with complex multisystem deficiency. In Vivo. 2008. 22:123-9

W. Huber, B. Jeschke, M. Page, W. Weiss, H. Salmhofer, U. Schweigart, K. Ilgmann, J. Reichenberger, B. Neu and M. Classen. Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. Intensive Care Med. 2001. 27:1200-9

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R. Mikkonen, T. Kontkanen and L. Kivisaari. Acute and late adverse reactions to low-osmolal contrast media. Acta Radiol. 1995. 36:72-6

C. J. Davidson, M. Hlatky, K. G. Morris, K. Pieper, T. N. Skelton, S. J. Schwab and T. M. Bashore. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann Intern Med. 1989. 110:119-24

W. K. Laskey, C. Jenkins, F. Selzer, O. C. Marroquin, R. L. Wilensky, R. Glaser, H. A. Cohen and D. R. Holmes Jr. Volume-to-Creatinine Clearance Ratio. A Pharmacokinetically Based Risk Factor for Prediction of Early Creatinine Increase After Percutaneous Coronary Intervention. Journal of the American College of Cardiology. 2007. 50:584-590

D. Drobnie-Kovac, A. Cerne, I. Kranjec and M. Globokar-Zajec. Effects of nonionic radiographic contrast media on renal function after cardiac catheterisation. Radiology and Oncology. 1996. 30:95-99

R. E. Katholi, G. J. Taylor, W. T. Woods, K. A. Womack, C. R. Katholi, W. P. McCann, H. W. Moses, J. T. Dove, F. L. Mikell, R. C. Woodruff, B. D. Miller and J. A. Schneider. Nephrotoxicity of nonionic low-osmolality versus ionic high-osmolality contrast media: A prospective double-blind randomized comparison in human beings. Radiology. 1993. 186:183-187

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Exclusion: No Intervention of Interest

M. M. Rahman, S. S. Haque, B. Rokeya, M. A. Siddique, S. K. Banerjee, S. A. Ahsan, F. Rahman, M. Mahmood, K. Ahmed, M. M. Bhuiyan, A. I. Joarder and R. C. Debnath. Trimetazidine in the prevention of contrast induced nephropathy after coronary angiogram. Mymensingh Med J. 2012. 21:292-9

R. H. Xu, G. Z. Ma, Z. X. Cai, P. Chen, Z. D. Zhu and W. L. Wang. Combined use of hydration and alprostadil for preventing contrast-induced nephropathy following percutaneous coronary intervention in elderly patients. Exp Ther Med. 2013. 6:863-867

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Appendix E. Evidence Tables

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Alexopoulos, 2010[1]	SrCr ≥1.2 mg/dL (106umol/L)	Total		231	2-5 days	17 (7.7)	65	NR	NR	NR	
		2	IOCM: Iodixanol	144		11 (7.6)	65	NR	NR	NR	
		3	Non-ionic LOCM	78		6 (7.7)	67	NR	NR	NR	Includes Iomeprol, Iobitridol, Iopentol,
		4	Ionic LOCM: Ioxaglate	9		NR	NR	NR	NR	NR	
Aspelin, 2003[2]	Diabetics with mild to moderate renal insufficiency (serum creatinins 1.5 to 3.5 mg/dl)	Total		129	7 days	53 (41)		NR	NR	NR	
Barrett, 2006[3]	General	Total		166	48-72 Hours	48(31.4)	67	NR	NR	NR	
		2	Iodixanol	82		25	67	White: 43(56.6) Black: 4(5.3) Asian/Pac: 29(38.2) Other: 0(0)	NR	NR	
		3	Iopamidol	84		23	67.3	White: 42(54.6) Black: 8(10.4) Asian/Pac: 24(31.2) Other: 3(3.9)	NR	NR	
Becker, 2013[4]	General	Total		113	72 Hours	61(54)	52	White: 22 Black: 23 Latino: 30 Asian/Pac: 38	NR	NR	
		1	Iopamidol	32		NR	NR	NR	NR	NR	
		2	Iohexol	35		NR	NR	NR	NR	NR	
		3	Iopromide	21		NR	NR	NR	NR	NR	
		4	Iodixanol	25		NR	NR	NR	NR	NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Bolognese, 2012[5]	STEMI	Total		475	72 Hours	110(23)	66	NR	NR	Current: 173	
		1	Iopromide	239		53	65	NR	NR	Current: 85	
		2	Iodixanol	236		57	66	NR	NR	Current: 88	
Campbell, 1990[6]	General	Total		478	NR	213	57.8	NR	NR	NR	Arm 1 is actually not the control/usual care, but just one of the treatment arms. 252 arterial and 226 IV injections of contrast
		1	Ioxaglate (Hexabrix 320)	161		NR	NR	NR	NR	NR	
		2	Iohexol (Omnipaque 350)	158		NR	NR	NR	NR	NR	
		3	Iopamidol (Isovue 370)	159		NR	NR	NR	NR	NR	
Carraro, 1998[7]	Mild to moderate renal insufficiency (serum cr 135 to 265 micromol/L within the previous 2 weeks)	Total		64	7 Days	9(14.1)	68	NR	NR	NR	
		2	Iodixanol	32		4	67	NR	NR	NR	
		3	Iopromide	32		5	69	NR	NR	NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Chuang, 2009[8]	General	Total		50	7 Days	16(32)	58	NR	NR	NR	
		2	Iodixanol	25		7(28)	62.9	NR		NR	
		3	Iohexol	25		9(36)	53.0	NR		NR	
Dillman, 2012[9]	General	Total		389	3 Days	204(52.4)	NR	NR	NR	NR	
		2	Iopamidol	199		99(49.7)	56.7	Black: 12(6.0) Other: 187(94)	NR	NR	
		3	Iohexol	190		105(55.3)	56.1	Black: 12(6.3) Other: 178(93.7)	NR	NR	
Feldkamp, 2006[10]	General	Total		83	48 Hours	54(24.4)	62	NR	NR	NR	
		2	Iodixanol	42		15	60.5	NR	NR	NR	
		3	Iopromid	41		12	62.7	NR	NR	NR	
Hardiek, 2008[11]	History of diabetes	Total		106	7 Days	85(83.3)	66	NR	NR	NR	
		2	Iodixanol	54		52	65 (36-83)	White: (98) Black: (2)	NR	NR	
		3	Iopamidol	48		33	66 (46-84)	White: (100) Black: (0)	NR	NR	
Hernandez, 2009[12]	Diabetic Patients	Total		250	72 Hours	92(36.8)	70	NR	NR	NR	
		2	Ioversol	132		47(33.6)	70.1	NR	NR	NR	
		3	Iodixanol	118		45(38.1)	69.1	NR	NR	NR	
Jakobsen, 1996[13]	Severe but stable pre-dialytic renal failure	Total		16	120 Hours	4(25)	55	NR	NR	NR	
		2	Iodixanol	8		1	55 (33-70)	NR	NR	NR	
		3	Iohexol	8		3	58 (33-72)	NR	NR	NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Jevnikar, 1988[14]	General	Total		23	20 Hours	4	56.1	NR	NR	NR	
		2	Ioxaglate	8		NR	NR	NR	NR	NR	
		3	Iohexol	8		NR	NR	NR	NR	NR	
		4	Diatrizoate	7		NR	NR	NR	NR	NR	
Jo, 2006[15]	General	Total		275	1 Month	121(43.6)	67	NR	NR	NR	
		2	Iodixanol	140		61	66.1	NR	NR	NR	
		3	Ioxaglate	135		60	68.7	NR	NR	NR	
Juergens, 2009[16]	Cr>130 - CrCl<60	Total		191	7 Days	46(24.1)	70	NR	NR	NR	
		2	Iopromide	100		27(27)	69.4	NR	NR	NR	
		3	Iodixanol	91		19(21)	70.2	NR	NR	NR	
Koutsikos, 1992[17]	Non-diabetics with satisfactory renal function (serum cr < 130 micromol/L) with perphieral or renal arterial vascular disease	Total		24	24 Hours	8(33.3)	NR	NR	NR	NR	
		2	Diatrizoate	8		1	41.6 (30-51)	NR		NR	
		3	Ioxaglate	8		1	48.33 (37-66)	NR		NR	
		4	Iohexol	8		6	37.61 (16-58)	NR		NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Kuhn, 2008[18]	Moderate to severe chronic kidney disease (estimated glomerular filtration rate [GFR] = 20–59 mL/ min/1.73 m2), Type 1 or 2 diabetes	Total		248	72 Hours	132(53.2)	69	NR	NR	NR	
		2	Iopamidol 370	125		54	69.5	NR		NR	
		3	Iodixanol 320	123		62	68.3	NR		NR	
Laskey, 2009[19]	CKD of non-acute etiology, type 1 or 2	Total		418	7 Days	148(35)	69.6 (41-87)	White: 307(73) Black: 22(5) Asian/Pac: 76(18) Other: 13(3)	NR	NR	
		2	Iodixanol	215		76(35)	69.6 (42-87)	White: 156(73) Black: 16(7) Asian/Pac: 39(18) Other: 4(2)		NR	
		3	Iopamidol	203		72(35)	69.7 (41-87)	White: 151(74) Black: 6(3) Asian/Pac: 37(18) Other: 9(4)		NR	
Limbruno, 2013[20]	General	Total		113	5 Days	49(43.4)	7	NR	NR	NR	
		2	Iodixanol	57		29(51)	77	NR		NR	
		3	Iobitridol	56		20(36)	76	NR		NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Mehran, 2009[21]	Renal impairment scheduled for coronary angio having 2 consecutive stable serum creatinine levels (>1.5 mg/dl and </=3.0 mg/dl) with most recent obtained within 24 hours before angiography	Total		NR	30 Days	18(12.3)	71	NR	NR	NR	
		2	Iodixanol	72		(12.5)	71.6	NR	NR	NR	
		3	Ioxaglate	74		(12.2)	71.3	NR	NR	NR	
Millward, 1996[22]	General	Total		48	NR	12(25.0)	63	NR	NR	NR	
		2	Ioxaglate	14		3	Median: 62 (51-79)	NR	NR	NR	
		3	Ioversol	34		9	Median: 62 (25-78)	NR	NR	NR	
Nguyen, 2008[23]	CKD Cr <1.5	Total		117	90 Days	34(29.1)	64	NR	NR	NR	
		2	Iodixanol	61		16	63	NR	NR	NR	
		3	Iopromide	56		18	65.8	NR	NR	NR	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Nie, 2008[24]	CrCl <60 ml/min	Total		208	3-7 Days	66(31.7)	61	NR	NR	NR	
		2	Iodixanol	106		33(31.2)	61	NR	NR	Current: 38(35.8)	
		3	Iopromide	102		33(32.4)	60	NR	NR	Current: 33(33.7)	
Rudnick, 2008[25]	SCr ≥ 1.7 mg/dL for men and ≥ 1.5 mg/dL for women	Total		299	72 Hours	87(41)	72	NR	NR	NR	
		2	Iodixanol	156		(31.8)	71.1	NR	NR	NR	
		3	Ioversol	143		(27.4)	72.6	NR	NR	NR	
Semerci, 2014[26]		Total		38	12 months	12 (31.6)	NR	NR	NR	NR	Current: 21 (55.3)
		2	Iopamidol	19		9 (47.4)	60 (38-75)	NR	NR	NR	Current: 8 (42.1)
		3	Iodixanol	19		3 (15.8)	56 (40-70)	NR	NR	NR	Current: 13 (68.4)
Serafin, 2011[27]	Neurosurgical patients	Total		92	72 Hours	67(72.8)	50	NR	NR	NR	
		2	Iopromide	48		35	49.6	NR	NR	NR	
		3	Iodixanol	44		32	49.6	NR	NR	NR	
Shin, 2011[28]	Impaired renal function; creatinine clearance (CrCl) <60 ml/min	Total		420	1 Month	194(46)	72	NR	NR	All: 199(47)	
		2	Iodixanol	215		105(49)	71.1	NR	NR	Current: 98(46)	
		3	Iopromide	205		89(43)	71.9	NR	NR	Current: 101(49)	

Evidence Table E-1. Participant characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, n female (%)	Age, mean unless otherwise specified(Range)	Race, n (%)	Education	Smoking status, n (%)	Comments
Solomon, 2007[29]	General	Total		414	120 Hours	149(36.0)	71	NR	NR	NR	
		2	Iopamidol-370	204		66	72.4	NR	NR	NR	
		3	Iodixanol-320	210		83	70.5	NR	NR	NR	
Solomon, 2009[30]	General	Total		294	Range: 12+ Months	108(37)	NR	NR	NR	NR	This population is the long term follow-up data from another randomized, double blind study of prevention CIN strategies (iopamidol vs. iodixanol) Age reported as n in two groups: 18 to 64 and >/= 65
		1	Iodixanol	149		44	NR	NR	NR	NR	
		2	Iopamidol	145		29	NR	NR	NR	NR	
Wessely, 2009[31]	General	Total		324	6 Months	89(31.3)	74	NR	NR	NR	
		2	Iodixanol	162		43(27)	75.0	NR	NR	NR	
		3	Iomeprol	162		46(28)	73.2	NR	NR	NR	
Zo'o, 2011[32]	General	Total		145	10 Days	59(40.7)	8	NR	NR	NR	
		2	Iobitridol	74		31(41.9)	8.7 (1-16)	NR	NR	NR	
		3	Iodixanol	71		28(39.4)	8.1 (0-16)	NR	NR	NR	

CIN=Contrast Induced Nephropathy; CKD=Chronic Kidney Disease; Cr=Creatinine; CrCl=Creatinine Clearance; GFR=Glomerular Filtration Rate; IV=Intravenous; Mg/dl=Milligrams per decliter; Micromol/L=Micromoles per liter; Ml/min/1.73m^2=milliliter per minute per 1.73 meters squared; NR=Not Reported; SCr=Serum Creatinine; STEMI=ST Elevation Myocardial Infarction

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Alexopoulos, 2010[1]	4	Non-RCT	Yes	NR	NR	NR	Undergoing nonemergent coronary angiography; SrCr ≥1.2 mg/dL (106umol/L); No known acute renal failure or end-stage renal disease requiring dialysis; had not received an intravascular administration of contrast medium within the previous 6 days or for whom readministration of contrast medium within the following 6 days was anticipated; had not ingested vitamin C supplements on a daily basis during the week before the procedure.	
Aspelin, 2003[2]	4	RCT/ Controlled		1999-2001	NR	Multi-center	Diabetic, serum creatinine 1.5-3.5 mg/dl 3 months prior to procedure,. Not pregnant or lactating, no IV administration of iodinated contrast media within 7 days of the study, no treatment with metformin or non-steroidal anti-inflammatory drugs, no nephrotoxic drugs within 7 days, no serious reaction to iodinated contrast media, no newly discovered unstable diabetes, no renal transplantation, no serious concomitant disease, no end stage renal disease necessitation dialysis.	
Barrett, 2006[3]	3	RCT/ Controlled	Yes	2004 to 2005	Outpatient	Multi-center	>18 years, CE-MDCT imaging of the liver or MDCT angiography of the lower-extremity vasculature, CVD; NYHA 1-2, moderate to severe Cr.>1.5, not received an investigational drug within 30 days before admission to the study, not undergone or were scheduled to undergo any other radiologic procedure using radiographic contrast media from 72 hours before to 7 days after the administration of the study agent. No New York Heart Association Class III or IV congestive heart failure or other medical conditions or circumstances which would have substantially decreased the chances of obtaining reliable data (eg, hypersensitivity to iodine-containing compounds, hyperthyroidism or thyroid malignancies, uncontrolled diabetes, unstable renal function, drug dependence, psychiatric disorders, dementia). Not nursing or pregnant patients, not scheduled to receive any medication to prevent CIN (eg, N-acetylcysteine, theophylline, fenoldopam or other drug).	
Becker, 2013[4]	3	RCT/ Controlled		NR	NR	NR	CT; Serum creatinine < or = 1.4 mg/dl	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

(continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Bolognese, 2012[5]	4	RCT/ Controlled	Yes	2009 to 2010	Inpatient (including ICU)	Multi-center	PCI; Other Risk factors, excluded those who had investigational drug within previous 30 days, IV or IA admin of iodinated contrast from 7 days to 72 hours before, nephrotoxic medications from 24 hours before or after its admitted with STEMI who underwent primary PCI <12 hours (18 hours in cardiogenic shock cases). Not pregnant, not lactating, no administration of any investigational drug within the previous 30 days, no intra-arterial or intravenous administration of iodinated contrast media from 7 days before to 72 hours after the administration of the study agents, no intake of nephrotoxic medications from 24 hours before to 24 hours after the administration of the study agents, no previous participation in this study, and an ability to give informed consent to participate in the study	
Campbell, 1990[6]	3,4	RCT/ Controlled	No	1989 to 1989	Inpatient (including ICU) Outpatient	Single-center	Non-pregnant patients	
Carraro, 1998[7]	3	RCT/ Controlled trial	No	1995 to 1996	NR	Single-center	>18 years; Intravenous Urography; Other Risk factors,The indications for IVU included: nephrolithiasis, hematuria, urinary tract neoplasms, voiding disorders, genital tract disorders, renal TB. They cannot be pregnant or lactating, or have received iodinated contrast media within 5 days of the study, or have a history of serious reactions to iodinated contrast media, or have severe concomitant disease. They also cannot be taking potentially nephrotoxic drugs; no pregnancy or lactation, no iodinated contrast media administration within 5 days of the study, no history of serious reactions to iodinated contrast media, no severe concomitant disease, and no current assumption of potentially nephrotoxic drugs	
Chuang, 2009[8]	3	RCT/ Controlled	No	2005 to 2006	Inpatient (including ICU)	Single-center	Intravenous pyelography; T2DM; diabetes with or without renal insufficiency; renal insufficiency with or without diabetes, no pregnancy, no volume depletion or fluid overload, no IV-iodinated CM within seven days, no treatment with metformin or NSAID within 48 hours, and nephrotoxic drugs within seven days.	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Dillman, 2012[9]	3	RCT/ Controlled	No	2008 to 2010	NR	Single-center	>18years, CT; <1.5, no pregnant patients; no patients with a most recent scr measurement of > 1.5 mg/dl (if no scr measurement was available, patients received contrast material according to departmental guidelines); no patients undergoing therapy with agents purported to reduce the risk of contrast-induced nephropathy (such as N-acetylcysteine or IV hydration); no patients undergoing CT who were administered contrast material with a lower or higher concentration of iodine (for example, 370 mg I/ml contrast material used for CT angiography in our department); no patients who had experienced any prior allergic like reaction to iodinated contrast material; no patients in whom soft-tissue extravasation of contrast material of more than 5 ml occurred (so that it was not possible to determine how much contrast material the patient received as a direct IV injection); no patients who were participating in other investigational drug, contrast material, or device trial	
Feldkamp, 2006[10]	4	RCT/ Controlled	No	NR	NR	NR	>18years, elective coronary angiography; no chronic kidney disease (GFR of 50 ml/min or less assessed by the MDRD formula), acute kidney injury before coronary angiography (assessed by serum creatinine), No pregnancy, myocardial infarction in the last three weeks, decompensated heart failure, mechanical ventilation, and patients with cardiogenic shock	
Hardiek, 2008[11]	4	RCT/ Controlled	No	2001 to 2002	NR	NR	>18 years, undergoing diagnostic or interventional angiography ; Other Risk factors, History of diabetes, Stable serum creatinine levels of <2mg/dl. No hypersensitivity to iodine or contrast media. No urinary obstruction or evidence of dehydration. No dialysis, pregnancy or administration of contrast, theophylline or NAC within 24 hours of procedure.	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Hernandez, 2009[12]	3	Non-RCT	No	2005 to 2007	Inpatient (including ICU) Outpatient	Single-center	Coronary angiography, with or without PCI, T2DM; being treated with insulin and/ or oral hypoglycemic agents, no emergency procedure (eg, primary angioplasty) that did not allow for adequate patient hydration; no cardiogenic shock; no previous heart or kidney transplantation or current use of immunosuppressive agents; no renal disease requiring dialysis; no administration of CM within the previous 7 days; no lack of baseline or 72-hour postprocedure scr measurement	Patients enrolled during the first 7 months of the study received ioversol and those enrolled during the following 11 months received iodixanol
Jakobsen, 1996[13]	3,4	RCT/ Controlled	No	NR	NR	NR	Predialytic chronic renal failure, Non-diabetic	
Jevnikar, 1988[14]	4	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	Coronary catheterization, CVD; controlled CHF; Cr >120umol, normal glucose levels, without prior contrast medium reaction	
Jo, 2006[15]	4	RCT/ Controlled	Yes	2004 to 2004	NR	Single-center	>19 years, Other Risk factors, Creatinine Clearance <60ml/min (using Cockscroft-Gault formula), Not pregnant or lactating. Have not received contrast media within 7 days of study entry. No emergent coronary angiography, acute renal failure, end stage renal disease requiring dialysis, hypersensitivity reaction to contrast, cardiogenic shock, pulmonary edema, multiple myeloma, mechanical ventilation, parenteral use of diuretics, use of NAC, use metformin or nonsteroidal anti-inflammatoery drugs within 48 hours of procedure.	
Juergens, 2009[16]	4	RCT/ Controlled	No	2003 to 2006	NR	Multi-center	>18 years coronary angiography or PCI,; Cr >130umol-crcl<60, Exclusion criteria were pregnancy, history of anaphylactic reaction to iodinated contrast medium, treatment with contrast agents within 7 days, known allergies to NAC, cardiogenic shock, current dialysis, conditions or circumstances that precluded adequate hydration or planned post contrast dialysis	
Koutsikos, 1992[17]	3,4	RCT/ Controlled	No	NR	NR	NR	Digital vascular imaging; Other Risk factors, Peripheral or renal arterial vascular disease, non-diabetic, well-hydrated patients with satisfactory renal function (serum creatinine < 130 micromol/l) (and with peripheral or renal arterial vascular disease, as mentioned in the other question)	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Kuhn, 2008[18]	3	RCT/ Controlled	Yes	2006 to 2007	Inpatient (including ICU)	Multi-center	>18 years, CT angiography or CT of the brain, head and neck, thorax, abdomen, or pelvis, CVD; NYHA I-III, stable moderate to severe chronic kidney disease (estimated glomerular filtration rate [GFR] = 20–59 ml/ min/1.73 m2), Other Risk factors, controlled Diabetes type 1 or 2, no pregnant or lactating patient, no hypersensitivity to iodine containing compounds, no hyperthyroidism, not received any iodinated contrast agent within 7 days before the administration of the investigational product, not scheduled to receive an iodinated contrast agent within 72 hours after administration of the investigational product, not received any nephrotoxic medication (chemotherapeutic agents, non-steroidal anti-inflammatory drugs other than acetylsalicylic acid up to 325 mg/d) within 24 hours before to 24 hours after the administration of the study agent, no medical condition or circumstances that would have substantially decreased the chances of obtaining reliable data	
Laskey, 2009[19]	3,4	RCT/ Controlled	No	2005 to 2007	Inpatient (including ICU)	Multi-center	>18 years, coronary angiography with or without percutaneous coronary intervention, excluded; CKD of non-acute etiology scr measurement not older than 6 m ≥150 µmol/L (1.7 mg/dl) for men and ≥133 µmol/L (1.5 mg/dl) for women or a creatinine clearance ≤50 ml/min, Other Risk factors, DM I or II, treated with insulin or oral antiglycemics for at least 1 year, non childbearig potential or if of childbearing potential the results of a serum or urine human chorionic gonadotropin pregnancy test, performed at screening, with the result known before contrast media administration, was negative, the subject was not planned to undergo major surgery (coronary artery bypass graft, carotid endarterectomy, vascular surgery) within 3 days after the contrast media administration, the subject was not planned to undergo selective renal angiography, no history of serious hypersensitivity reaction to iodinated contrast media, no history of severe liver or hematologic disease, multiple myeloma, or manifest thyrotoxicosis, severe	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Laskey, 2009[19] (cntinued)							heart failure requiring intravenous therapy with diuretics, inotropes, and/or vasodilators, the subject was not planned to receive an intravenous diuretic or intravenous mannitol in connection to the contrast media administration, not hemodynamically unstable prestudy (ie, inability to sustain systolic blood pressure 90 mm Hg within 48 hours before contrast media administration without pressor or balloon support), not on hemodialysis or peritoneal dialysis, and/or was not in acute renal failure, the subject had not undergone kidney transplantation, the subject had not received or would not receive any of the following potentially nephroprotective drugs within 3 days before or 3 days after contrast media administration; N-acetylcysteine, fenoldopam, dopamine or hydration with sodium bicarbonate (Potentially nephroprotective drugs such as Ca-channel blockers, theophylline, etc, were allowed provided they were used for treatment of the subject's chronic underlying disease), the subject had not received or was not planning to receive any of the following nephrotoxic drugs within 7 d before or 3 d after contrast media administration; aminoglycosides, vancomycin, amphotericin B, cyclosporin, methotrexate, cisplatin, the subject had not received or was not planning to receive nonsteroidal anti-inflammatory drugs within 3 d before or 3 d after contrast media administration, with the exception of low doses of acetyl salicylic acid (up to 325 mg/d, and at a single occasion in connection with percutaneous coronary intervention up to 500 mg). However, subjects who were on a stable non-steroidal regimen could be enrolled, the subject had not or was not planning to have the initiation, discontinuation, or change in dose within 3 d before or 3 d after contrast media administration of any of the following: trimethoprim, cimetidine, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers, the subject was not on metformin (eg, Glucophage, Bristol-Meyers- Squibb, New York, NY) at the time of coronary angiography/ intervention. Metformin had to be discontinued according to local guidelines, and stopped no later than the time of CM administration, withheld for at least 48 h, until the subject's scr had been evaluated and it was deemed safe to resume metformin.	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Limbruno, 2013[20]	4	RCT/ Controlled	No	NR	NR	NR	Undergoing coronary angiography and/or PCI; Creatinine clearance < or equal to 60ml/min. No allergies to iodinated contrast media. No prior contrast administration 1 month prior. Not currently using non-steroidal anti-inflammatory drugs. No acute ST-elevation myocardial infarction or cardiogenic shock.	
Mehran, 2009[21]	4	RCT/ Controlled	No	2000 to 2002	Inpatient (including ICU)	Single-center	150 consecutive imaging with min 100ml of parenteral CM (both IV and IA; Not pregnant. No contradictions to theophylline or acetylcysteine. Stable renal function with 2day fluctuation below 0.4 mg/dl. No previous examinations within 4 days of procedure.	
Millward, 1996[22]	3,4	Non-RCT	No	1993 to 1993	NR	NR	>18<80 years. Abdominal aortography- abdominal aortography, renal arteriography- iv ctap- aortography, carotid arteriography. Excluded: non pregnant and non-lactating women.	
Nguyen, 2008[23]	3	RCT/ Controlled	No	2004 to 2006	Inpatient (including ICU)	Single-center	>18 years Clinically indicated Contrast enhanced CT; excluded, Cr >1.5 -GFR <60, No pregnancy; no lactation; no administration of iodinated contrast media within 7 days prior to study entry; no history of anaphylaxis to iodinated contrast medium; no acute renal failure; no heart or kidney transplant or otherwise treated with cyclosporine or tacrolimus; no patients receiving other potentially nephrotoxic drugs; no administration of dopamine, mannitol, or theophylline 24 hours prior to enrollment; and no administration of non-steroidal anti-inflammatory drugs other than aspirin within 48 hours prior to enrollment.	
Nie, 2008[24]	4	RCT/ Controlled	No	NR	Outpatient	Single-center	Elective coronary, carotid or peripheral angiography and/or PTCA and stenting,; serum creatinine concentrations ≥0.13 mmol/l, No allergy to the study medication, absence of unstable renal function (creatinine rising by ≥0.04 mmol/(l day),patients not on dialysis, No uncontrolled asthma, pregnant or breastfeeding.	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Rudnick, 2008[25]	4	RCT/ Controlled	Yes	2001 to 2004	NR	Multi-center	>18 years, Cardiac angiography with or without PCI; no end-stage renal disease requiring dialysis or organ transplantation; CKD (≥ 1.7 mg/dl for men and ≥ 1.5 mg/dl for women), Exclusion criteria included acute cause(s) for the elevated serum creatinine (Scr) value or a Scr value unstable by >0.5 mg/dl within 10 days of study entry; hemodynamic instability prestudy; pregnancy; lactation; intravascular administration of iodinated CM within 7 days before study entry; a requirement for additional intravascular iodinated CM for any purpose between 8 and 72 hours after initial CM administration; the scheduling of a major surgical intervention within 72 hours after the study procedure; the administration of theophylline, fenoldopam, or mannitol within 7 days before or 72 hours after contrast administration; the initiation, discontinuation, or change in dose of any of the following — trimethoprim, cimetidine, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker —within 72 hours before study entry; initiation of nephrotoxic agents, or non-steroidal anti-inflammatory drugs within 72 hours of study entry; current use of metformin; severe liver or hematologic disease; severe heart failure or a history of serious reaction to intravascular iodinated CM	
Semerci, 2014[26]	4	RCT/ Controlled	No	NR	NR	Single-center	>20 years of age; undergoing coronary angiography; No acute myocardial infarction, no unstable SCr levels, renal insufficiency, no history of percutaneous transluminal coronary angioplasty or coronary bypass surgery,no congestive heart failure or ejection fraction <45%, no current pregnancy,or other medical conditions that would decrease the chance of obtaining reliable data (eg, uncontrolled hypertension, cardiomyopathy or cardiac valve disease, systemic inflammatory disease, decompensated renal, hepatic, cardiac, endocrine disorders, clinical laboratory evidence of infection, recent exposure to contrast media within 2 days of study entry, and administration of dopamine, mannitol, or diuretics).	

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Serafin, 2011[27]	3	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	>18 years, cerebral angiography or angiography with endovascular embolization egfr>30 ml / min / 1.73 m^2 no history of adverse reactions to any previously administrated iodinated CM, not suspected of hyperthyroidism, not pregnant, no contrast-enhanced imaging within 7 days of the study	
Shin, 2011[28]	4	RCT/ Controlled	No	2000 to 2001	NR	Single-center	>18 years, cardiac angiography; baseline serum creatinine > 1.7 mg/dl.; no patient unable to provide informed consent, no evidence of active atheroembolic disease, including but not limited to blue toes, livedo reticularis or eosinophilia, no known prior insensitivity to acetylcysteine, no severe asthma, no breast feeding women, no severe peptic ulcer disease, or respiratory depression, no women off contraception, no patients with serum creatinine measurements varied by more than 15% in the three days before angiography	
Solomon, 2007[29]	4	RCT/ Controlled	Yes	2005 to 2006	NR	Multi-center	>18 years, diagnostic cardiac angiography or percutaneous coronary interventions, moderate to severe CKD, Criteria for exclusion were pregnancy, lactation, administration of any investigational drug within the previous 30 days, intraarterial or intravenous administration of iodinated CM from 7 days before to 72 hours after the administration of the study agents, medical conditions or circumstances that would have substantially decreased the chances to obtain reliable data (New York Heart Association class IV congestive heart failure, hyper-sensitivity to iodine-containing compounds, hyperthyroidism or thyroid malignancies, uncontrolled diabetes mellitus, unstable renal function, drug dependence, psychiatric disorders, dementia), administration of any medication to prevent CIN other than N-acetylcysteine (NAC), or intake of nephrotoxic medications from 24 hours before to 24 hours after the administration of the study agent.	
Solomon, 2009[30]	4	RCT/ Controlled	Yes	2006 to 2008	Reported in CARE study	Multi-center	All listed in CARE	Same protocol as CARE, just after 12 months. All data is the same. The only new data is AEs

Evidence Table E-2. Study characteristics for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Wessely, 2009[31]	4	RCT/ Controlled	Yes	2006 to 2007	NR	NR	>18years, coronary angiography with a possibility of bypass graft or percutaneous intervention, Serum creatinine >1.5mg/dl measured 24 hours before procedure, Not pregnant, not lactating, no intravascular administration of iodine containing contrast within 7 days, no renal transplant, no cardiogenic shock, no end-stage renal disease necessitating hemodialysis, and an ability to give informed consent, not taking nephrotoxic drugs.	
Zo'o, 2011[32]	3	RCT/ Controlled	No	2004 to 2006	NR	Single-center	>18years, coronary angiography; serum creatinine ≥ 1.2 mg/dl or a creatinine clearance < 50 ml/min, no acute inflammatory disease, no medication with NSAID or metformin up to 3 days before entering study, no abnormal findings in physical examinations, e.g. Signs of dehydration or inflammation	

AE=Adverse Events; Ca=Calcium; CARE= Cardiac Angiography in Renally Impaired Patients; CE-MDCT; CHF=Congestive Heart Failure; CIN=Contrast Induced Nephropathy; CKD=Chronic Kidney Disease; CM=Contrast Media; Cr=Creatinine; CT= Computerized Tomography; CVD=Cardiovascular Disease; D=Days; DM=Diabetes Mellitus; eGFR=Estimated Glomerular Filtration Rate; GFR=Glomerular Filtration Rate; H=hours; IA=Intrarterial; ICU=Intensive Care Unit; IV=Intravenous; IVU=Intravenous Urogram; MDCT; MDRD=Modification of Diet in Renal Diseases; Mg/dl=Milligrams per Deciliter; Mg=Milligrams; Micromol/L=Micromoles per liter; Ml/min/1.73m^2=milliliter per minute per 1.73 meters squared; NAC=N-acetylcysteine; NSAID=Non-steroidal Anti-inflammatory Drug; NYHA=New York Heart Association; PCI=Percutaneous Coronary Intervention; PTCA=Percutaneous transluminal Coronary Angioplasty; RCT=Randomized Controlled Trial; SCr=Serum Creatinine; STEMI=ST Elevated Myocardial Infarction; T2DM=Type 2 Diabetes Mellitus; TB=Tuberculosis

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Alexopoulos, 2010[1]	2	IOCM: Iodixanol	IA	Average Volume: IOCM: 279 ml (SD 138)	
	3	Non-ionic LOCM	IA	Average Volume: LOCM: 259 ml (SD 140)	
	4	Ionic LOCM: Ioxaglate	IA	NR	Limited information on Ioxaglate arm
Aspelin, 2003[2]	1	Iodixanol	IA	Varied and not standardized	All patients well hydrated prior to procedure. Recommended: 500ml hydration orally, and 500ml saline IV before angiography followed by 1 L 0.9 percent saline
	2	Iohexol	IA	Varied and not standardized	
Barrett 2006 [3]	2	Iodixanol	IV	40+/-1.3 gI - 0.6 +/-0.1 gI/kg	
	3	Iopamidol	IV	40+/-1.3 gI - 0.6 +/-0.1 gI/kg	
Becker, 2013 [4]	1	Iopamidol	IV	NR	
	2	Iohexol	IV	NR	
	3	Iopromide	IV	NR	
	4	Iodixanol	IV	NR	
Bolognese, 2012 [5]	1	Iopromide	IA	"as necessary for each patient", N-acetylcysteine used in all pts: 1200 mg IV diluted with 100 ml 5% glucose during procedure and 1,00 mg orally twice daily for next 48 hours after PC; all its underwent hydration with IV isotonic saline (0.9%) at rate of 1 ml/kg/hr for 12 hours or 0.5 ml/kg/hr for 12 hours in cases of overt heart failure	IA balloons, inotropic drugs, abciximab, beta-blockers, ACE inhibitors, diuretics at discretion of interventional and CCU cardiologists
	2	Iodixanol	IA	"as necessary for each patient", N-acetylcysteine used in all pts: 1200 mg IV diluted with 100 ml 5% glucose during procedure and 1,00 mg orally twice daily for next 48 hours after PC; all its underwent hydration with IV isotonic saline (0.9%) at rate of 1 ml/kg/hr for 12 hours or 0.5 ml/kg/hr for 12 hours in cases of overt heart failure	

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Campbell, 1990 [6]	1	Ioxaglate	IV, IA	NR	CM given EITHER IV OR IA PER PATIENT. Clinical Outcomes reported only for IA but AEs reported for both (the articles says that the patients were randomized to be given one of the three agents "for a variety of arterial and central and peripheral studies'. ARM 1 is not actually a "control" group. All three arms are treatment groups.
	2	Iohexol	IV, IA	NR	
	3	Iopamidol	IV, IA	NR	
Carraro, 1998 [7]	2	Iodixanol	IV	600 mgI/kg b. w, preheated to 37 degrees	
	3	Iopromide	IV	600 mgI/kg b. w, preheated to 37 degrees	
Chuang, 2009 [8]	2	Iodixanol	IV	About 0.8 mL/kg for each IVP procedure	All patients were hydrated with 0.9% saline 1 mL/kg/hr 8–12 hours before and after IVP
	3	Iohexol	IV	about 0.8 mL/kg f r each IVP procedure	
Dillman 2012 [9]	2	Iopamidol	IA	100-150 ml	
	3	Iohexol	IV	100-150 ml	
Feldkamp 2006 [10]	2	Iodixanol	NR	CM: 320 mg iodine/ ml. All patients received normal saline IV hydration before, during and after procedure	
	3	Iopromide	NR	CM: 320 mg iodine/ ml. All patients received normal saline IV hydration before, during anf after procedure	
Hardiek 2008 [11]	2	Iodixanol	IA	320mg/ml, mean total iodine 46g (SD 20)	
	3	Iopamidol	IA	320mg/ml, mean total iodine 46g (SD 20)	
Hernandez 2009 [12]	2	Ioversol	NR	195.5mls+/-92.1	Prophylactic volume expansion with 1000 mL intravenous normal saline was administered for 6 to 12 hours before the procedure (100 to 150 mL/h) and an oral dose of 1200 mg N-acetylcysteine (NAC) (Fluimucil®, Zambon, Milan, Italy) was administered 6 hours before and 6 hours after the procedure
	3	Iodixanol	NR	195.5mls+/-92.1	

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Jakobsen 1996 [13]	2	Iodixanol	NR	Mean: 0.34 g I/kg b.w. (Range: 0.25-0.48)	
	3	Iohexol	NR	Mean: 0.34 g I/kg b.w. (Range: 0.25-0.48)	
Jevnikar 1988 [14]	2	Ioxaglate	IA	0.70+/-0.05 g Iodine/kg/body weight, total iodine 61.5+/-3.2	
	3	Iohexol	IA	0.70+/-0.05 g Iodine/kg/body weight, total iodine 61.5+/-3.2	
	4	Diatrizoate	IA	0.70+/-0.05 g Iodine/kg/body weight, total iodine 61.5+/-3.2	
Jo 2006 [15]	2	Iodixanol	IA	Mean dose: 204.6ml (SD 159.2)	Contrast media dose not set through protocol. Only given mean dosage.
	3	Ioxaglate	IA	Mean dose: 204.6ml (SD 159.2)	
Juergens 2009 [16]	2	Iopromide	IA	Iodine concentration: 370 mg/ml, Four doses of NAC were given orally(600 mg b.i.d.),starting the day before contrast administration. Saline (0.9%) was given intravenously so that patients received at least 500 mL before the procedure. atientsalsoreceived130 mL/h for at least 3 h post procedure in addition to liberal oral fluid intake	
	3	Iodixanol	IA	iodine concentration: 370 mg/ml, Four doses of NAC were given orally(600 mg b.i.d.),starting the day before contrast administration. Saline (0.9%) was given intravenously so that patients received at least 500 mL before the procedure. atientsalsoreceived130 mL/h for at least 3 h post-procedure in addition to liberal oral fluid intake	
Koutsikos, 1992 [17]	2	diatrizoate (also known as Urografin 76%)	IA	103.33+/-45.09 mL (mean iodine content 38.75 +/- 16.91 g)	
	3	Ioxaglate	IA	133.33+/-61.1 mL (mean iodine content 42.66 +/- 19.55 g)	
	4	Iohexol	IA	132.69+/-56.88 mL (mean iodine content 39.81 +/- 17.06 g)	
Kuhn 2008 [18]	2	Iopamidol	IV	mean=106.5 mL, range = 66–185 mL	all patients at risk (deemed clinically necessary or desirable) received prophylaxis for CIN via hydration before, during, or after contrast administration
	3	Iopamidol	IV	mean=106.5 mL, range = 66–185 mL	
Laskey 2009 [19]	2	Iodixanol	IA	NR	
	3	Iopamidol	IA	NR	
Limbruno 2013 [20]	2	Iodixanol	IA	320 mg/ml	All patients given 0.9% saline at 1 ml/kg/h, for 12 hours before and for 12 hours after procedure.
	3	Iobitridol	IA	320 mg/ml	

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Mehran 2009 [21]	2	Iodixanol	IA	Mean: 48.1 min (SD 35.5)	Patients received diphenydramine 25 mg IV before procedure as well as intravenous one-half isotonic saline at 100 ml/h for at least 3 to 5 h before the index procedure, throughout the angiographic interventional procedure, and for at least 12 h after CM administration.
	3	Ioxaglate	IA	NR	
Millward 1996 [22]	2	Ioxaglate	IV, IA	NR	
	3	Ioversol	IV, IA	NR	
Nguyen 2008 [23]	2	Iodixanol	IV	115ml	
	3	Iodixanol	IV	115ml	
Nie 2008 [24]	2	Iodixanol	IA	320 mg I/mL, Patients received prophylactic volume expansion with 1,000 mL intravenous normal saline at a rate of 1.0 to 1.5 mL/kg/hr for 4 hr before and continuing for 6 hr after the procedure	All patients received clopidogrel (300 mg) before the intervention. Clopidogrel (75 mg/day) was continued for 2 weeks in patients who did not undergo PCI, whereas patients who underwent PCI received clopidogrel (75 mg/day) and aspirin (100 to 300 mg/day)for 9 months
	3	Iopromide	IA	370 mg I/mL, patients received prophylactic volume expansion with 1,000 mL intravenous normal saline at a rate of 1.0 to 1.5 mL/kg/hr for 4 hr before and continuing for 6 hr after the procedure	
Rudnick 2008 [25]	2	Iodixanol	IA	320 mg-I/ml, sodium chloride solution (0.9%) was infused intravenously at 125 mL/h for at least 2 hours before and at least 6 hours after CM administration. Oral fluid intake was encouraged ad libitum. Use of NAC was left to the investigator's discretion	
	3	ioversol	IA	320 mg-I/ml, sodium chloride solution (0.9%) was infused intravenously at 125 mL/h for at least 2 hours before and at least 6 hours after CM administration. Oral fluid intake was encouraged ad libitum. Use of NAC was left to the investigator's discretion	

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Semerci, 2014[26]	2	Iopamidol	IA	Mean: 52ml,	All the diabetic patients received isotonic (0.9%) saline intravenously at a rate of 1 mL/kg per h for 6 to 12 hours before and after the angiography with combination of oral N-acetylcysteine (NAC) 600 mg administration twice daily.
	3	Iodixanol	IA	Mean: 52ml	All the diabetic patients received isotonic (0.9%) saline intravenously at a rate of 1 mL/kg per h for 6 to 12 hours before and after the angiography with combination of oral N-acetylcysteine (NAC) 600 mg administration twice daily.
Serafin 2011 [27]	2	Iopromide	IA	151.2 +/- 52.1 mL	
	3	Iodixanol	IA	151.2 +/- 52.1 mL	
Shin 2011 [28]	2	Iodixanol	IA	Mean: 179.0 +/- 127.2	Patients received intravenous normal saline at a rate of 1 ml/kg/hour >/= 8 hours before and after CAG. The use of N-acetylcysteine was allowed at the attending physician's discretion.
	3	Iopromide	IA	Mean: 179.0 +/- 127.2	

Evidence Table E-3. Interventions for studies comparing contrast media for the prevention of contrast-induced nephropathy (continued)

Author, year	ARM	Description	Administration route	Dose, duration, other details	Comment
Solomon 2007 [29]	2	Iopamidol	IA	796 mOsm/kg, all patients received prophylactic volume expansion with isotonic sodium bicarbonate solution, administered at 3 mL/kg per hr for 1 hour before angiography, and at 1 mL/kg per hr during angiography and for 6 hours after angiography. Each site chose whether they would administer a prophylactic NAC regimen to all of its patients, a regimen that consisted of an oral dose of 1200 mg twice per day administered on the day before and the day of the study procedure	
	3	Iodixanol	IA	796 mOsm/kg, all patients received prophylactic volume expansion with isotonic sodium bicarbonate solution, administered at 3 mL/kg per hr for 1 hour before angiography, and at 1 mL/kg per hr during angiography and for 6 hours after angiography. Each site chose whether they would administer a prophylactic NAC regimen to all of its patients, a regimen that consisted of an oral dose of 1200 mg twice per day administered on the day before and the day of the study procedure	
Solomon 2009 [30]	1	Iodixanol	IA	NR	
	2	Iodixanol	IA	NR	
	3	Iopamidol	IA	NR	
Zo'o 2011 [32]	2	Iobitridol	IV	2 ml/kg body weight, maximum 100 ml	
	3	Iodixanol	IV	2 ml/kg body weight, maximum 100 ml	

ACE=Angiotensin Converting Enzyme; AE=Adverse Events; b.i.d=Bi-daily; b.w=Bi-weekly; CAG=Coronary angiogram; CCU=Coronary Care Unit; CM=Contrast Media; hr=Hour; IA=Intrarterial; IV=Intravenous; IVP=Intravenous Pyelogram; kg=kilogram; Kg=kilograms; Mg=milligrams; ml=milliliter; mOsm/kg=milliosmoles per kilogram; NAC=N-acetylcysteine; NR=Not Reported; PC=Post Cibum; PCI=Percutaneous Coronary Intervention; Pts=parts; SD=Standard Deviation

Evidence Table E-4. Summary of randomized controlled trials comparing low-osmolar contrast media with contrast-induced nephropathy as an outcome

Author, year	Location	LOCM	Route	N	Population	Procedure	Mean age, y	Females, %	Primary outcome	Risk of bias
Campbell, 1990[6]	N. America	Iohexol, Ioxaglate, Iopamidol	IA	252	General	Peripheral arterio-graphy	58	45	Change in serum creatinine within 72 hours for those with detectable increase	H
Jevnikar, 1988[14]	N. America	Iohexol, Ioxaglate	IA	16	No renal impairment	Coronary	56	17	Change in serum creatinine after 20 hours	H
Koutsikos, 1992[17]	Europe	Iohexol, Ioxaglate	IA	40	No renal impairment	Renal	56	20	Change in serum creatinine after 24 hours	H
Becker, 2013[4]	N. America	Iohexol, Iopamidol, Iopromide	IV	113	No renal impairment	CT	52	54	Change in GFR within 72 hours	M
Dillman, 2012[9]	N. America	Iohexol, Iopamidol	IV	389	No renal impairment	CT	56	52	Development of CIN. Change in serum creatine >0.5mg/dl from baseline in 2 days	L

CT=computerized tomography; GFR=glomerular filtration rate; H=high risk of bias; IA=intra-arterial; IV=intravenous; L=low risk of bias; LOCM=low-osomolar contrast media; M=medium risk of bias; N. America=North America; N=sample size; Y=year

Evidence Table E-5a. Comparison between low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data)

Author, year	Outcome	Measure	Subgroup (not a subgroup is column is left blank)	Intervention	ARM	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlayzed	n (%) with outcome at time-point 2	Com-parison statistics at time point 2
Dillman, 2012[9]	Development of CIN (change in Creatinine or GFR--specify)--short term	Change in serum creatine >0.5mg/dl from baseline in 2 days		Iopamidol	2	2 or 3 days	199	1 (1)	p=0.62				
Dillman, 2012[9]	Development of CIN (change in Creatinine or GFR--specify)--short term	Change in serum creatine >0.5mg/dl from baseline in 2 days		Iohexol	3		190	1 (2)					
Campbell, 1990[6]	Change in Serum creatinine--short term	any rise in serum cr (yes or no) and mean change in serum cr (micromol/L)		Ioxaglate	1	72 hours	161	109					
Campbell, 1990[6]	Change in Serum creatinine--short term	any rise in serum cr (yes or no) and mean change in serum cr (micromol/L)		Iohexol	2		158	96					
Campbell, 1990[6]	Change in Serum creatinine--short term	any rise in serum cr (yes or no) and mean change in serum cr (micromol/L)		Iopamidol	3		159	103					
Campbell, 1990[6]	Change in Serum creatinine--short term	any increase in serum cr (umol/L) (yes or no) and the mean change in serum cr (micromol/L)	intra-arterial injection	Ioxaglate	1	72 hours	95	67 (71)	All arms P >=0.05				

Evidence Table E-5a. Comparison between low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Subgroup (not a subgroup is column is left blank)	Intervention	ARM	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at time-point 2	Com-parison statistics at time point 2
Campbell, 1990[6]	Change in Serum creatinine--short term	any increase in serum cr (umol/L) (yes or no) and the mean change in serum cr (micromol/L)	intra-arterial injection	Iohexol	2		67	47 (70)					
Campbell, 1990[6]	Change in Serum creatinine--short term	any increase in serum cr (umol/L) (yes or no) and the mean change in serum cr (micromol/L)	intra-arterial injection	Iopamidol	3		90	68 (76)					

%=percent; CIN=contrast induced nephropathy; Cr=creatinine; GFR=glomerular filtration rate; Mg/dl=milligram per decliter; Micromole/L=micromole per liter; n=number of events; N=sample size; P=p-value; Umol/l=micromole per liter

Evidence Table E-5b. Comparison between low-osmolar contrast media reporting on other outcomes

Author, year	Comparison	Mortality N/n (%)	Adverse events N/n (%)
Campbell, 1990[6]	Arm 2: Iohexol Arm 3: Iopamidol	Death (within a few weeks): Both arms" 320/8 (2.5) P=NR	Hypersensitivity, nausea, vomiting, hives: Arm 2 161/20 (8) Arm 3:159/7 (4.4) P=NR

n=number of events; N=total sample size; NR=not reported; P=p-value

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Change in Serum Creatinine																		
Chuang, 2009[8]	Change in Serum creatinine--short term	>10% rise in creatinine		Iodixanol	2	within 7 days of contrast administration	25	8	p=0.529									
	Change in Serum creatinine--short term	>10% rise in creatinine		Iohexol	3		25	6										
Development of CIN																		
Alexopoulos, 2010[1]	Development of CIN (change in Creatinine or GFR--specify)--short term	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure		IOCM: Iodixanol	2	2-5 days	144	21 (14.6)	Arm2 vs Arm3: p=1.00 Arm2 vs Arm3: OR: 1.37 (95% CI: 0.53-3.4) p=0.52									

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Alexopoulos, 2010[1]	Developm ent of CIN (change in Creatinine or GFR--specify)--short term	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure		Non-ionic LOCM	3		78	11 (14.1)										CIN incidence for individual non-ionic LOCM: Iomeprol: 4/40 (10) Iobitridol: 3/30 (10) Iopentol: 4/8 (50)
Alexopoulos, 2010[1]	Developm ent of CIN (change in Creatinine or GFR--specify)--short term	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure		Ionic LOCM: Ioxaglate	4		9	2 (22)										Comparis on NR for ioxaglate arm
Alexopoulos, 2010[1]	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	Given placebo + IV normal saline	IOCM: Iodixanol	2	2-5 days	75	16 (21)	p=NR									

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Alexopoulos, 2010[1]	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	Given placebo + IV normal saline	Non-ionic LOCM	3		34	7 (21)										
Alexopoulos, 2010[1]	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	Given IV Normal Saline + Oral Ascorbic Acid	IOCM: Iodixanol	2	2-5 days	69	5 (7)	p=NR									
Alexopoulos, 2010[1]	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	0.5mg/dl or 25% increase in serum Cr above baseline at 2-5 days after procedure	Given LOCM	Non-ionic LOCM	3		44	4 (9)										
Barrett, 2006[3]	Development of CIN (change in Creatinine or GFR--specify)--short term	a relative increase in SCr 25% from baseline to 48–72 +/-6 hours after contrast		Iodixanol	2	48-72 hrs	76	3 (4)	p=0.4									

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Barrett, 2006[3]	Developm ent of CIN (change in Creatinine or GFR--specify)--short term	a relative increase in SCr 25% from baseline to 48–72 +/-6 hours after contrast r		Iopamidol	3		77	3										
Barrett, 2006[3]	Developm ent of CIN (change in Creatinine or GFR--specify)--short term	absolute increase 0.5 mg/dL from baseline to 48–72 +/-6 hours after contrast		Iodixanol	2	48-72 hrs	76	2(2.6)	p=0.3									
Barrett, 2006[3]	Developm ent of CIN (change in Creatinine or GFR--specify)--short term	absolute increase 0.5 mg/dL from baseline to 48–72 +/-6 hours after contrast		Iopamidol	3		77	0										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Bolognese, 2012[5]	Development of CIN (change in Creatinine or GFR--specify)--short term	increase in serum creatinine >/= 25% from baseline to 72 hours after procedure	ClCr =/< 60ml/min	Iopromide	1	72	73	(17)	p=0.51									
Bolognese, 2012[5]	Development of CIN (change in Creatinine or GFR--specify)--short term	increase in serum creatinine >/= 25% from baseline to 72 hours after procedure	ClCr =/< 60ml/min	Iodixanol	2		60	(23)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Bolognese, 2012[5]	Development of CIN (change in Creatinine or GFR--specify)--short term	increase in serum creatinine >/= 25% from baseline to 72 hours after procedure	ClCr >/=60ml/min	Iopromide	1	72 hours	161	(6.2)	p=0.41									
Bolognese, 2012[5]	Development of CIN (change in Creatinine or GFR--specify)--short term	increase in serum creatinine >/= 25% from baseline to 72 hours after procedure	ClCr >/=60ml/min	Iodixanol	2		171	(9.2)										
Feldkamp, 2006[10]	Development of CIN (change in Creatinine or GFR--specify)--short term	decrease of 20% of the creatinine clearance 48 hrs after coronary angiography	Diabetes mellitus	Iodixanol	2	48 hours	42	(24)	p=0.73									
Feldkamp, 2006[10]	Development of CIN (change in Creatinine or GFR--specify)--short term	decrease of 20% of the creatinine clearance 48 hrs after coronary angiography	Diabetes mellitus	Iopromide	3		41	(28.6)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Feldkamp, 2006[10]	Development of CIN (change in Creatinine or GFR--specify)--short term	decrease of 20% of the creatinine clearance 48 hrs after coronary angiography		Iodixanol	2	48 hours	105	(19.7)	p=0.80									
Feldkamp, 2006[10]	Development of CIN (change in Creatinine or GFR--specify)--short term	decrease of 20% of the creatinine clearance 48 hrs after coronary angiography		Iopromide	3		116	(22.2)										
Hardiek, 2008[11]	Development of CIN (change in Creatinine or GFR--specify)--short term	Serum creatinine >25% over baseline		Iodixanol	2	1 days	51	1 (4)	p=NR	3 days	54	5 (9)	P=nr				P=nr	
Hardiek, 2008[11]	Development of CIN (change in Creatinine or GFR--specify)--short term	Serum creatinine >25% over baseline		Iopamidol	3		48	2 (2)			48	6 (12)						

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Hernandez, 2009[12]	Development of CIN (change in Creatinine or GFR--specify)--short term	absolute increase in SCr from baseline of >0.5 mg/dL or a relative increase of >25% at 72 hours following exposure to CM		Ioversol	2	72 hours	132	11 (8.3)	OR 0.255 (95% CI: 0.068 to 0.952)					1-6 months	189	2 (1.1)		
Hernandez, 2009[12]	Development of CIN (change in Creatinine or GFR--specify)--short term	absolute increase in SCr from baseline of >0.5 mg/dL or a relative increase of >25% at 72 hours following exposure to CM		Iodixanol	3		118	3 (2.5)						6 months	189	2 (1.1)		

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Age <75 years old	Iodixanol	2	2 days	115	9 (7.8)	p=0.035									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Age <75 years old	Ioxaglate	3		105	18 (17.1)										
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Age >75 years old	Iodixanol	2	2 days	25	2 (8)	p=0.436									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Age >75 years old	Ioxaglate	3		30	5 (16.7)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Creatinine clearance <30ml/min	Iodixanol	2	2 days	16	2 (12.5)	p=0.023									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Creatinine clearance <30ml/min	Ioxaglate	3		15	8 (53.3)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Creatinine clearance > 30ml/min		1	2 days			p=0.169						193	6 (3.1)		
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Creatinine clearance > 30ml/min	Iodixanol	2		124	9 (7.3)										
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Creatinine clearance > 30ml/min	Ioxaglate	3		120	15 (12.5)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Diabetes	Iodixanol	2	2 days	48	5 (10.4)	p=0.041						193	3 (1.6)		
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Diabetes	Ioxaglate	3		49	13 (26.5)										
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Dose of contrast media <140ml	Iodixanol	2	2 days	46	2 (4.3)	p=0.410									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Dose of contrast media <140ml	Ioxaglate	3		40	4 (10.0)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Dose of contrast media > 140ml	Iodixanol	2	2 days	82	8 (9.8)	p=0.038									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Dose of contrast media > 140ml	Ioxaglate	3		89	19 (21.3)										
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Left ventricular ejection fraction <40%	Iodixanol	2	2 days	21	5 (23.8)	p=1.0									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Left ventricular ejection fraction <40%	Ioxaglate	3		20	5 (25.0)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Left ventricular ejection fraction >40%	Iodixanol	2	2 days	115	6 (5.2)	p=0.014									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	Left ventricular ejection fraction >40%	Ioxaglate	3		113	17 (15.0)										
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	No diabetes	Iodixanol	2	2 days	92	6 (6.5)	p=0.234									
Jo, 2006[15]	Development of CIN (change in Creatinine or GFR--specify)--short term	Increased serum creatinine > 25% over baseline or an absolute increase of >0.5mg/dl	No diabetes	Ioxaglate	3		86	10 (11.6)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Juergens, 2009[16]	Development of CIN (change in Creatinine or GFR--specify)--short term	bsolute increase in the serum creatinine concentration of at least 44 umol/L (0.5 mg/dL) or by a relative increase of at least 25% from the baseline value on day 2		Iopromide	2	2 days	100	15 (15)	p=0.56	7 days	100	8 (8)	P=0.11					
Juergens, 2009[16]	Development of CIN (change in Creatinine or GFR--specify)--short term	bsolute increase in the serum creatinine concentration of at least 44 umol/L (0.5 mg/dL) or by a relative increase of at least 25% from the baseline value on day 2		Iodixanol	3		91	11 (12)			91	14 (15)						

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Limbruno, 2013[20]	Development of CIN (change in Creatinine or GFR--specify)--short term	CIN risk score		Iodixanol	2			72 hours	57	9 (5)	p=0.80							
Limbruno, 2013[20]	Development of CIN (change in Creatinine or GFR--specify)--short term	CIN risk score		Iobitridol	3				56	9 (4)								

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Limbruno, 2013[20]	Development of CIN (change in Creatinine or GFR--specify)--short term	postprocedural increase in serum creatinine more than 25% from baseline to 72 h after study contrast agent administration		Iodixanol	2	72 hours	57	6 (11)	p=0.97									
Limbruno, 2013[20]	Development of CIN (change in Creatinine or GFR--specify)--short term	postprocedural increase in serum creatinine more than 25% from baseline to 72 h after study contrast agent administration		Iobitridol	3		56	6 (11)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nguyen, 2008[23]	Change in Serum creatinine--short term	increase in SCr levels from baseline of 0.5 mg/dL or more and 1.0 mg/dL or more	Diabetics	Iodixanol	2	3 days	23	0	p=.041									
Nguyen, 2008[23]	Change in Serum creatinine--short term	increase in SCr levels from baseline of 0.5 mg/dL or more and 1.0 mg/dL or more	Diabetics	Iodixanol	3		10	3										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nie, 2008[24]	Development of CIN (change in Creatinine or GFR--specify)--short term	relative increase in serum creatinine (SCr) from baseline of 25% or an absoluteincrease of 0.5 mg/ dL (44 l mol/L) up to day 3		Iodixanol	2	3 days	106	6 (5.7)										
Nie, 2008[24]	Development of CIN (change in Creatinine or GFR--specify)--short term	relative increase in serum creatinine (SCr) from baseline of 25% or an absoluteincrease of 0.5 mg/ dL (44 l mol/L) up to day 3		Iopromide	3		102	17 (16.7)	p=0.011									

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Rudnick, 2008[25]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined as an increase in Scr from baseline of ≥ 0.5 mg/dL up to 72 hours post – contrast administration		Iodixanol	2	72 hours	156	34	rate diff, 1.98% (95% CI: -7.5 to 11.5),									
Rudnick, 2008[25]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined as an increase in Scr from baseline of ≥ 0.5 mg/dL up to 72 hours post – contrast administration		ioversol	3		143	34										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistics at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistics at time point 3	Comment
Rudnick, 2008[25]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined as an increase in Scr from baseline of ≥ 0.5 mg/dL up to 72 hours post – contrast administration	Diabetes	Iodixanol	2	72 hours	82	18 (21.9)	p=0.57									
Rudnick, 2008[25]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined as an increase in Scr from baseline of ≥ 0.5 mg/dL up to 72 hours post – contrast administration	Diabetes	ioversol	3		72	19 (26.4)										
Semerci, 2014[26]	Development of CIN (change in Creatinine or GFR--specify)--short term	NR		Iopamidol	2	6 hours	19	0 (0)	p=NR	12 months	19	0 (0)	p=NR					
Semerci, 2014[26]	Development of CIN (change in Creatinine or GFR--specify)--short term	NR		Iodixanol	3		19	0 (0)			19	0 (0)						

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Serafin, 2011[27]	Development of CIN (change in Creatinine or GFR--specify)--short term	post-contrast increase in SCr level of > 0.5 mg / dL (or 44 m mol / L) or >= 25% above the baseline value		Iopromide	2	1 days	48	7 (15)		3 days	48	5 (10)						
Serafin, 2011[27]	Development of CIN (change in Creatinine or GFR--specify)--short term	post-contrast increase in SCr level of > 0.5 mg / dL (or 44 m mol / L) or >= 25% above the baseline value		Iodixanol	3		44	6 (14)			44	7 (16)						
Shin, 2011[28]	Development of CIN (change in Creatinine or GFR--specify)--short term	a relative increase of >/= 25% after CAG compared to baseline SCr		Iodixanol	2	2 days	215	22 (10.2)	p=>.05									
Shin, 2011[28]	Development of CIN (change in Creatinine or GFR--specify)--short term	a relative increase of >/= 25% after CAG compared to baseline SCr		Iopromide	3		205	14 (6.8)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Wessely, 2009[31]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined by a increase in creatinine >0.5 mg/dL or 25% of the initial value	Participants receiving solely diagnostic cardangiography	Iodixanol	2	NR	315	29 (9.2)										
Wessely, 2009[31]	Development of CIN (change in Creatinine or GFR--specify)--short term	defined by a increase in creatinine >0.5 mg/dL or 25% of the initial value	Participants receiving solely diagnostic cardangiography	Iomeprol	3		336	27 (8.0)										
Wessely, 2009[31]	Development of CIN (change in Creatinine or GFR--specify)--short term	an increase of S-creatinine by >1 mg/dL and/or dialysis	Participants receiving solely diagnostic cardangiography	Iodixanol	2	NR	315	3 (1.0)	p=0.77									
Wessely, 2009[31]	Development of CIN (change in Creatinine or GFR--specify)--short term	an increase of S-creatinine by >1 mg/dL and/or dialysis	Participants receiving solely diagnostic cardangiography	Iomeprol	3		336	4 (1.2)										

Evidence Table E-6a. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (categorical data) (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Zo'o, 2011[32]	Development of CIN (change in Creatinine or GFR--specify)--short term	more than 25% reduction in creatinine clearance	intention to treat population	Iobitridol	2	3 days	62	3 (4.8)	p=0.72									
Zo'o, 2011[32]	Development of CIN (change in Creatinine or GFR--specify)--short term	more than 25% reduction in creatinine clearance	intention to treat population	Iodixanol	3		66	7 (10.6)										
Zo'o, 2011[32]	Development of CIN (change in Creatinine or GFR--specify)--short term	more than 25% reduction in creatinine clearance	per protocol population	Iobitridol	2		29	0 (0)	p=0.68									
Zo'o, 2011[32]	Development of CIN (change in Creatinine or GFR--specify)--short term	more than 25% reduction in creatinine clearance	per protocol population	Iodixanol	3	3 days	39	4 (10.3)										

%=Percentage, CAG=Coronary angiogram, CI=Confidence Interval, CIN=Contrast Induced Nephropathy, ClCr=Clearance Creatinine, GFR=Glomerular Filtration Rate, Hrs=Hours, Mg/dl=milligram per deciliter, Ml=milliliter, Mmol/L=millimol per liter, Mol/L=mole per liter, N=Sample Size, NR=Not Reported, OR=Odds Ratio, P=P-value, SCr=Serum Creatinine

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Change in GFR																								
Becker, 2013[1]	Change in GFR (eGFR)--short term	%		Iopamidol	1			3 hours		median=+5		72 hours		median=-5	p=>0.18									
	Change in GFR (eGFR)--short term	%		Iohexol	2					median=+1				median=-2.5										
	Change in GFR (eGFR)--short term	%		Iopromide	3					median, +5				median, +10										
	Change in GFR (eGFR)--short term	%		Iodixanol	4					median,				median, +9										

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Ti-me Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Juergens, 2009[2]	Change in Serum creatinine--short term	umol/L		Iopromide	2			2 days	100	13.1 (24.1)	p=0.54	2 or 7 days	100	18.4 (24.2)	p=0.33									
	Change in Serum creatinine--short term	umol/L		Iodixanol	3				91	11.2 (19.3)			91	21.9 (24.2)										
Nguyen, 2008[3]	Change in GFR (eGFR)--short term	Change in gfr from baseline to days 1,2 and 3		Iodixanol	2	61	51.8 (16.58)	1 days	65	55.48 (23.19)		2 days	65	55.11 (23.31)		3 days	65	55.51 (21.68)						
	Change in GFR (eGFR)--short term	Change in gfr from baseline to days 1,2 and 3		Iopromide	3	56	52.98 (26.02)		61	49.54 (19.82)			61	48.65 (25.60)			61	50.17 (24.68)						

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Rudnick, 2008[4]	Change in Serum creatinine--short term			Iodixanol	2			72 hours	156	14.7 (19.5)	p=0.06													
	Change in Serum creatinine--short term			ioversol	3				143	20.0 (17.8)														
Solomon, 2007[5]	Change in GFR (eGFR)--short term			Iopamidol 370	2			45-120 hours	204	-2.16 (7.86)	p=0.038													
	Change in GFR (eGFR)--short term			Iodixanol 320	3				210	-4.02 (8.10)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Change in serum creatinine																								
Alexopoulos, 2010[1]	Change in Serum creatinine--short term	Absolute change in SrCr, mg/dl		IOCM: Iodixanol	2	144		2-5 days	144	0.09 (0.23)	Arm2 vs Arm3: p=0.70													
Alexopoulos, 2010[1]	Change in Serum creatinine--short term	Absolute change in SrCr, mg/dl		Non-ionic LOCM	3	78			78	0.11 (0.42														
Alexopoulos, 2010[1]	Change in Serum creatinine--short term	Absolute change in SrCr, mg/dl		Ionic LOCM: Ioxaglate	4	9			9	NR	NR													
Aspelin, 2003[6]	Peak increase in serum creatinine	Change in serum creatinine		Iodixanol	2	64		3 days	64	0.13 mg/dl	P=0.0001													
Aspelin, 2003[6]				Iopamidol	3	65			65	0.55 mg/dl														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Aspelin, 2003[6]	Change in Serum creatinine--short term	within 24hrs		Iodixanol	2	32	150.3 micromol/L (26)	24 hours	32	146.7 micromol/L	NR													
Aspelin, 2003[6]	Change in Serum creatinine--short term	within 24hrs		Iopromide	3	32	149.4 micromol/L (18)		32	135.3 micromol/L														
Barrett, 2006[8]	Change in Serum creatinine--short term	mg/dl		Iodixanol	2			48-72 hours	76	0.04 (0.24)	arm 1 - arm2, -0.04 (95% CI: -0.11 to 0.02)													
Barrett, 2006[8]	Change in Serum creatinine--short term	mg/dl		Iopamidol	3				77	0.00 (0.16)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Bolognese, 2012[9]	Serum creatinine--short term	mean relative sCR change from baseline to maximum <72 hours		Iopromide	1			72 hours	236	10%	p=0.88													
Bolognese, 2012[9]	Serum creatinine--short term	mean relative sCR change from baseline to maximum <72 hours		Iodixanol	2				239	10%														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Hardiek, 2008[10]	Change in Serum creatinine--short term	Mean change in serum creatinine (mg/dl)		Iodixanol	2			1 days	51	-0.041 (0.1)	Difference, -0.02 (95% CI: -0.11 to 0.07)	3 days	54	0.028 (0.16)	Difference, 0.003 (95% CI: -0.06 to 0.07), p=NR	7 days	53	0.013 (0.16)	Difference, -0.04 (95% CI: -0.12 to 0.04), p=NR					
Hardiek, 2008[10]	Change in Serum creatinine--short term	Mean change in serum creatinine (mg/dl)		Iopamidol	3				48	0.0042 (0.15)			48	0.025 (0.17)			47	0.049 (0.24)						
Hernandez, 2009[11]	Change in Serum creatinine--short term		eGFR >60 mL/min/1.73m2	Ioversol	2	97	0.85 (0.18)	72 hours	97	0.89 (0.23)														
Hernandez, 2009[11]	Change in Serum creatinine--short term		eGFR >60 mL/min/1.73m2	Iodixanol	3	77	0.86 (0.20)		77	0.91 (0.29)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Hernandez, 2009[11]	Change in Serum creatinine--short term		No PCI	Ioversol	2	80	1.03 (.4)	??	80	1.05 (.46)														
Hernandez, 2009[11]	Change in Serum creatinine--short term		No PCI	Iodixanol	3	68	1.12 (.5)		68	1.11 (.5)														
Hernandez, 2009[11]	Change in Serum creatinine--short term		eGFR >60 mL/min/1.73 m2	Ioversol	2	97	0.85 (0.18)	72 hours	97	0.89 (0.23)														
Hernandez, 2009[11]	Change in Serum creatinine--short term		eGFR >60 mL/min/1.73 m2	Iodixanol	3	77	0.86 (0.20)		77	0.91 (0.29)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Hernandez, 2009[11]	Change in Serum creatinine--short term		No PCI	Ioversol	2	80	1.03 (.4)	??	80	1.05 (.46)														
Hernandez, 2009[11]	Change in Serum creatinine--short term		No PCI	Iodixanol	3	68	1.12 (.5)		68	1.11 (.5)														
Laskey, 2009[12]	Change in Serum creatinine--short term	Change over 7 days after procedure	Per protocol population	Iodixanol	2	215	1.63 (0.51)	72 hours	215	+.14 (0.38/ 0.1)	p=.28													
Laskey, 2009[12]	Change in Serum creatinine--short term	Change over 7 days after procedure	Per protocol population	Iopamidol	3	203	1.64 (0.56)		203	+.09 (0.26/ 0.09)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Mehran, 2009[13]	Serum creatinine--short term	change in serum creatinine		Iodixanol	2			3 days	72	0.12 (0.40)														
Mehran, 2009[13]	Serum creatinine--short term	change in serum creatinine		Ioxaglate	3				74	0.31 (0.78)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Nguyen, 2008[3]	Change in Serum creatinine--short term	change in the SCr concentration between baseline and the subsequent maximum SCr attained on day 1, 2, or 3 mg/dl		Iodixanol	2	61	1.77 (.24)	1 days	65	1.65 (0.35)	p=0.48	2 days	65	1.73 (0.53)	P=ns	3 days	65	1.73 (0.55)	P=ns					
Nguyen, 2008[3]	Change in Serum creatinine--short term	change in the SCr concentration between baseline and the subsequent maximum SCr attained on day 1, 2, or 3 mg/dl		Iopromide	3	56	1.75 (.32)		61	1.80 (0.42)			61	1.77 (0.49)			61	1.77 (0.62)						

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Solomon, 2007[5]	Change in GFR (eGFR)--short term		Diabetes mellitus	Iopamidol	2			45-120 hours	78	-2.05 (8.9)	p=0.016													
Solomon, 2007[5]	Change in GFR (eGFR)--short term		Diabetes mellitus	Iodixanol	3				92	-4.97 (7.65)														
Solomon, 2007[5]	Change in Serum creatinine--short term	mg/dl	Diabetes mellitus	Iopamidol	2			45-120 hours	78	0.07 (0.26)	p=0.013													
Solomon, 2007[5]	Change in Serum creatinine--short term	mg/dl	Diabetes mellitus	Iodixanol	3				92	0.16 (0.27)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Wessely, 2009[14]	Change in Serum creatinine--short term	Maximal rise in serum creatinine from baseline, mg/dl	Participants receiving solely diagnostic angiography	Iodixanol	2			NS	315	0.08 (0.29)	p=0.47													
Wessely, 2009[14]	Change in Serum creatinine--short term	Maximal rise in serum creatinine from baseline, mg/dl	Participants receiving solely diagnostic angiography	Iomeprol	3				336	0.06 (0.27)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Wessely, 2009[14]	Change in Serum creatinine--short term	Maximal rise in serum creatinine, percent of baseline value	Participants receiving solely diagnostic cardangiography	Iodixanol	2			NS	315	5.0 (15.9)	p=0.95													
Wessely, 2009[14]	Change in Serum creatinine--short term	Maximal rise in serum creatinine, percent of baseline value	Participants receiving solely diagnostic cardangiography	Iomeprol	3				336	4.9 (17.9)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Serum creatine short term																								
Alexopoulos, 2010[1]	Serum creatinine--short term	mg/dl		IOCM: Iodixanol	2	144	1.39 (0.58)	2-5 days	144	1.48 (0.60)	Arm2 vs Arm3: p=0.42													
Alexopoulos, 2010	Serum creatinine--short term	mg/dl		Non-ionic LOCM	3	78	1.44 (0.38)		78	1.54 (0.55)														
Alexopoulos, 2010	Serum creatinine--short term	mg/dl		Ionic LOCM: Ioxaglate	4	9	NR		9	NR	NR													
Barrett, 2006[8]	Serum creatinine--short term	mg/dl		Iodixanol	2	76	1.5 (0.5)	48-72 hours	76	1.6 (0.5)	P=0.9													
Barrett, 2006[8]	Serum creatinine--short term	mg/dl		Iopamidol	3	77	1.6 (0.4)		77	1.6 (0.4)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Chuang, 2009[15]	Serum creatinine--short term	mg/dl		Iodixanol	2	25	1.36 (.42)	2 days	25	1.36 (.44)	p=.429	3 days	25	1.37 (.48)	p=.422	7 days	25	1.33 (.39)	p=.450					
Chuang, 2009[15]	Serum creatinine--short term	mg/dl		Iohexol	3	25	1.34 (.45)		25	1.28 (.37)			25	1.30 (.39)			25	1.28 (.41)						
Jakobsen, 1996[16]	Serum creatinine--short term	Serum creatinine levels, umol/l		Iodixanol	2	8	560 (Range:451 to 669)	24 hours	8	565, (Max: 672 Min: 458)	p=ns	48 hours	8	589 (Max: 695; Min: 483)	P<0.05	72 hours	8	578 (Max: 682; Min: 475)	P<0.05	120 hours	N anlysed	557 (Max: 661; Mon: 453	p=ns	
Jakobsen, 1996[16]	Serum creatinine--short term	Serum creatinine levels, umol/l		Iohexol	3	8	689 ()Median: 860		8	736 (Max: 936, Min: 537)			8	785 (Max: 992; Min: 578)			8	782 (Max: 990; Min: 573)			N anlysed	776 (Max: 990; Mon: 561		
Nie, 2008[17]	Serum creatinine--short term	mg/dl		Iodixanol	2	106	1.48 (0.59)	3 days	106	1.5 (0.62)														
Nie, 2008[17]	Serum creatinine--short term	mg/dl		Iopromide	3	102	1.49 (0.49)		102	1.59 (0.61)														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Time Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Semerci, 2014[26]	Serum creatinine--short term	mg/dL		Iopamidol	2	19	Median: 0.71 Range: 0.57-1.40	6 hours	19	Median:0.79 Range: 0.66-1.53	p=0.826													
Semerci, 2014[26]	Serum creatinine--short term	mg/dL		Iodixanol	3	19	Median: 0.77 Range: 0.50-1.00		19	Median: 0.82 Range: 0.54-1.03														

EvidenceTable E-6b. Comparison between iso- and low-osmolar contrast media: prevention of contrast-induced nephropathy (continuous data) (continued)

Author, year	Out-come	Measure	Sub-group	Inter-vention	ARM	Base-line N anal-yzed	Mean (SD)*	Time Point 1	Time point 1 N analyzed	Mean (SD)*	Com-parison stat-istics at time point 1†	Time Point 2	Time point 2 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 2†	Ti-me Point 3	Time point 3 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 3	Time Point 4	Time point 4 N anal-yzed	Mean (SD)*	Com-parison stat-istics at time point 4	Com-ments
Wessely, 2009[14]	Serum creatinine--short term	Serum creatinine levels, mg/dl	Patients receiving solely diagnostic angiography	Iodixanol	2	162	1.36 (0.51	NR	162	1.55 (0.58)	P=0.51													
Wessely, 2009[14]	Serum creatinine--short term	Serum creatinine levels, mg/dl	Patients receiving solely diagnostic angiography	Iomeprol	3	162	1.37 (0.33)	NR	162	1.59 (0.48)														

%=Percentage, CI=Confidence Interval, eGFR=Estimated Glomerular Filtration Rate, GFR=Glomerular Filtration Rate, Mg/dl=milligram per deciliter, Micromole/L=micromole per liter, Ml/min/1.73m^2=milliliter per minute per 1.73 meter squared, N=Sample Size, NR=Not Reported, NS=Not Significant, p=P-value, PCI=Percutaneous Coronary Intervention, SCr=Serum Creatinine, SD=Standard Deviation, Umol/L=micromole per liter

Evidence Table E-7. Comparison between iso- and low-osmolar contrast media: need for renal replacement therapy

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Need for RRT, short term																		
Bolognese, 2012[9]	Need for RRT--short term	In-hospitaly dialysis		Iodixanol	2	In-hospital	236	0 (0)	0.49									
Bolognese, 2012[9]				Iopromide	3		239	2 (0.8)										
Jo, 2006[18]	Need for RRT—short term	Acute renal failure requiring hemodialysis		Iodixanol	2	NR	140	1 (0.7)	NR									
Jo, 2006[18]				Ioglaxate	3		135	1 (0.7)										
Kuhn, 2008[19]	Need for RRT--short term	Dialysis		Iopamidol	2	72 hours	125	0	NR									
Kuhn, 2008[19]				Iopamidol	3		123	0										
Laskey, 2009[12]	Need for RRT--short term	Hemodialysis or hemofiltration		Iodixanol and Iopamidol	2 and 3	NR	417	3 (0.7)	NR									
Semerci, 2014[26]	Need for RRT--short term	Require hemodialysis		Iopamidol	2	8 months	19	0 (0)	p=NR									
Semerci, 2014[26]	Need for RRT--short term	Require hemodialysis		Iodixanol	3		19	1 (5.3)										

Evidence Table E-7. Comparison between iso- and low-osmolar contrast media: need for renal replacement therapy (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Wessely, 2009[14]	Need for RRT--short term	Need for hemodialysis	Participants receiving solely diagnostic cardangiography	Iodixanol	2	NR	315	0 (0)	p=NR									
Wessely, 2009[14]			Participants receiving solely diagnostic cardangiography	Iomeprol	3		336	0 (0)										

%=Percentage, N=Sample Size, NR=Not Reported, P=P-value, RRT=Renal Replacement Therapy

Evidence Table E-8. Comparison between iso- and low-osmolar contrast media: cardiovascular outcomes

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Cardiac Events																		
Bolognese, 2012[9]	Cardiac events (define)--long term	cardiac death		Iopromide	1	30 days	239	11 (5)	p=0.5001									
Bolognese, 2012[9]		cardiac death		Iodixanol	2		236	8 (3)										
Juergens[2]	Cardiac events	Arrhythmia		Iodixanol	2	NS	191	3	--									
Juergens[2]				Iopromide	3													
Juergens[2]		Peri-pro-cedural MI				NS	191	4	--									
Juergens[2]																		
Mehran, 2009[13]	Cardiac events (define)--long term	Myocardial Infarction		Iodixanol	2	30 days	70	0 (0)	P=1.00									
Mehran, 2009[13]		Myocardial Infarction		Ioxaglate	3		74	1 (1.4)										
Nie[17]	Cardiac events-	Emergent PCI		Iodixanol	2	In hospital	106	0	0.24									
Nie[17]				Iopromide	3		102	2										
Nie[17]		Abrupt vessel closure		Iodixanol	2	In hospital	106	1	0.61									
Nie[17]				Iopromide	3		102	2										
Nie[17]		Cardiac death		Iodixanol	2	In hospital	106	0	--									
Nie[17]				Iopromide	3		102	0										
Nie[17]		Nonfatal MI		Iodixanol	2	In hospital	106		0.49									
Nie[17]				Iopromide	3		102	0										

Evidence Table E-8. Comparison between iso- and low-osmolar contrast media: cardiovascular outcomes (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nie[17] (continued)		CABG		Iodixanol	2	In hospital	106	0	--									
Nie[17]				Iopromide	3		102	0										
Shin[20]	Cardiac events—long term	Major adverse CV events		Iodixanol	2	30 days	215	5	NR									
Shin[20]				Iopromide	3		205	4										
Solomon[5]	Cardiac events	Serious cardio-vascular events		Iodixanol	2	NR	210	0	--									
Solomon[5]				Iopamidol	3		204	0										
Wessely, 2009[14]	Cardiac events (define)--long term	Incidence of myocardial infarction	Participants receiving solely diagnostic cardangiography	Iodixanol	2			1		6 months	315	1 (0.3)	p=0.30					
Wessely, 2009[14]		Incidence of myocardial infarction	Participants receiving solely diagnostic cardangiography	Iomeprol	3						336	0 (0.0)						

%=Percentage, CABG= Coronary Artery Bypass Grafting, CV=Cardiovascular, MI=Myocardial Infarction, N=Sample Size, NR=Not Reported, NS=Not Significant, P=P-value, PCI=Percutaneous Coronary Intervention

Evidence Table E-9. Comparison between iso- and low-osmolar contrast media: mortality

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Mortality, long term																		
Bolognese, 2012[9]	Cardiac events (define)--long term	cardiac death		Iopromide	1	30 days	239	11 (5)	p=0.5001									
Bolognese, 2012[9]	Cardiac events (define)--long term	cardiac death		Iodixanol	2		236	8 (3)										
Kuhn[19]	Death			Both groups			None reported											
Laskey, 2009[19]	Mortality--in hospital (short term)			Iodixanol	2													
Laskey, 2009[19]	Mortality--in hospital (short term)			Iopamidol	3													
Mehran, 2009[13]	Mortality--in hospital (short term)			Iodixanol	2	3 days	72	2 (2.8)	p=0.24									
Mehran, 2009[13]	Mortality--in hospital (short term)			Ioxaglate	3		74	0 (0)										

Evidence Table E-9. Comparison between iso- and low-osmolar contrast media: mortality (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nguyen, 2008[3]	Mortality--in hospital (short term)			Iodixanol	2	30 days	61	3										
Nguyen, 2008[3]	Mortality--in hospital (short term)			Iopromide	3		56	2										
Nie, 2008[17]	Mortality--in hospital (short term)			Iodixanol	2	30 days post discharge	106	0 ()	NR									
Nie, 2008[17]	Mortality--in hospital (short term)			Iopromide	3		102	0 ()										
Serafin, 2011[21]	Mortality--in hospital (short term)			Both groups		In hospital	92	2 (2)	NR									
Wessely, 2009[14]	Mortality at 3 or 6 months--long term	Death	Participants receiving solely diagnostic cardangiography	Iodixanol	2					6 months	315	18 (5.7)	p=0.59					
Wessely, 2009[14]	Mortality at 3 or 6 months--long term	Death	Participants receiving solely diagnostic cardangiography	Iomeprol	3						336	16 (4.8)						

%=Percentage, N=Sample Size, NR=Not Reported, P=P-value

Evidence Table E-10. Comparison between iso- and low-osmolar contrast media: adverse events

Author year	Location	LOCM	Route	N	Population	Procedure	Mean age y	Fe-males %	Adverse event	IOCM group	LOCM group	P value	Follow-up	Primary result	Risk of bias
Bolognese[9]	Europe	iopromide	IA	475	myocardial infarction	coronary	66	23	Major cardiac adverse events Cardiac death Reinfarction Hospitalization for heart failure In-hospital death In-hospital dialysis	18/236 8/236 6/236 1/236 7/236 0/236	13/239 11/239 5239 2/239 9/239 2/239	0.37 0.50 0.77 1.00 0.62 0.49	30 d 30 d 30 d 30 d < 24 hr <24 hr	NS*	L
Chuang[15]	Asia	iohexol	IV	50	renal impairment or diabetes	IVU	58	32	Total allergic reactions Early reaction Burning in throat Dizziness Late reactions Skin rash	2/25 0/25 0/25 0/25 2/25 2/25	6/25 3/25 1/25 2/25 3/25 3/25	0.24 0.23 1 1 1 1	< 1 h to 7 d < 1 hr < 1 h to 7 d < 1 h to 7 d >1hr to 7 d < 1 h to 7 d	NS	H
Hardiek[10]	N. America	iopamidol	IA	106	diabetes	coronary	66	83	Nausea Fever Rash ARF	2/54 0/54 4/54 0/54	2/48 2/54 1/54 1/54	NR NR 5-7 d NR	NR NR NR NR	NR	L
Jo[18]	Asia	ioxaglate	IA	275	renal impairment	coronary	67	44	Composite†	3/140	3/135	NR	NR	NR	M
Juergens[2]	Australia	iopromide	IA	382	renal impairment	coronary	70	24	Multiple AEs	NR	NR	NS	NR	NS	L
Laskey[12]‡	Europe Asia	iopamidol	IA	418	renal impairment and diabetes	coronary	70	35		NR	NR	NR	NR	NR	M
Mehran[13]	N. America	ioxaglate	IA	146	renal impairment	coronary	71	12	Adverse events§	0/72	4/74	0.12	Up to 30 d	NS	M

Evidence Table E-10. Comparison between iso- and low-osmolar contrast media: adverse events (continued)

Author year	Location	LOCM	Route	N	Population	Procedure	Mean age y	Fe-males %	Adverse event	IOCM group	LOCM group	P value	Follow-up	Primary result	Risk of bias
Nie[17]	Asia	iopromide	IA	208	renal impairment	coronary	61	32	Composite¶ Emergent PCI Abrupt vessel closure Stroke Thombosis Cardiac death Nonfatal MI CABG	2/106 0/106 1/106 0/106 1/106 0/106 0/106 0/106	9/102 2/102 2/102 1/102 3/102 0/102 1/102 0/102	0.025 0.24 0.61 0.49 0.36 -- 0.49 --	30 d In hosp In hosp In hosp In hosp In hosp In hosp In hosp	pos	M
Semerci, 2014[26]	Asia	Iopamidol	IA	38	no renal impairment	Coronary	56	32	NR	NR	NR	NR	NR	NS	
Shin[20]	Asia	iopromide	IA	420	renal impairment	coronary	72	46	Major adverse cardiac events	5/215	4/205	NR	30 d	NS	L
Solomon[5]‖	N. America	iopamidol	IA	414	renal impairment	coronary	71	36						NR	M
Wessely[14]	Europe	iomeprol	IA	324	renal impairment	coronary	74	31	MI and death**	NR	NR	NS	6m	NR	M
Zo'o[22]	Europe	iobitridol	IV	145	children	CT	8	41	Pts with at least 1 AE Serious AEs	17/71 4/71	16/74 5/74	NR NR	10 d	NR	L

CIN = contrast-induced nephropathy; CT=computerized tomography; CV=cardiovascular; H=High risk of bias; HF=heart failure; IA = intra-arterial; IOCM-iso-osmolar contrast media; ITT=intention to treat; IV = intravenous; IVU = intravenous urography; L=low risk of bias; LOCM = low-osmolar contrast media; MI=myocardial infarction; M-moderate risk of bias; NA = not applicable; NR = not reported; NS = not significant; PCI=percutaneous coronary intervention; PP=protocol population; Pts=patients; RRT = renal replacement therapy

*Treatment groups were pooled to assess the effect of CI-AKI on major cardiac events. The incidence of major cardiac events was significantly different between paitients with and without CI-AKI (p=0.001)
‡death, myocardial infarction, revascularization, cerebral infarction, dialysis. Adverse events were reported but not stratified by CM but by ITT or PP study groups. No conclusions can be made
§Nodifference between groups for death, myocardial infarction and repeat revascularization
¶Composite of CVevents in-hospital and 30 days post discharge and diagnostic image quality.
‖ Most AEs were non-serious and resolved themselves—no statistics provided
** rates reported as similar

Evidence Table E-11. Comparison between iso- and low-osmolar contrast media: Image quality and diagnostic accuracy

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Image quality (resolution/contrast)																		
Nie, 2008[17]	Image quality (resolution /contrast)	Grade 1 is optimal, providing optimal informa- tion for making an unequivocal radiological diagnosis		Iodixanol	2	during proce dure	106	75 (70.8)	p=NR									
Nie, 2008[17]	Image quality (resolution /contrast)	Grade 1 is optimal, providing optimal informa- tion for making an unequivocal radiological diagnosis		Iopromide	3		102	81 (79.4)										

Evidence Table E-11. Comparison between iso- and low-osmolar contrast media: Image quality and diagnostic accuracy (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nie, 2008[17]	Image quality (resolution /contrast)	Grade 2 is suboptimal, providing less than optimal in-formation for making a diagnosis (this category was used if the diagnostic quality was less than optimal in any aspect, even if a diagnosis could be made);		Iodixanol	2	during proce dure	106	21 (19.8)	p=0.353									

Evidence Table E-11. Comparison between iso- and low-osmolar contrast media: Image quality and diagnostic accuracy (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nie, 2008[17] (continued)	Image quality (resolution /contrast)	Grade 2 is suboptimal, providing less than optimal in-formation for making a diagnosis (this category was used if the diagnostic quality was less than optimal in any aspect, even if a diagnosis could be made);		Iopromide	3		102	14 (13.7)										
Nie, 2008[17]	Image quality (resolution /contrast)	Grade 3 is not diagnostic, providing insufficient information to make a radiological diagnosis		Iodixanol	2	during proce dure	106	10 (9.4)	p=NR									

Evidence Table E-11. Comparison between iso- and low-osmolar contrast media: Image quality and diagnostic accuracy (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Nie, 2008[17] (continued)	Image quality (resolution /contrast)	Grade 3 is not diagnostic, providing insufficient information to make a radiological diagnosis		Iopromide	3		102	7 (6.9)										
Zo'o, 2011[22]	Image quality (resolution /contrast)	"Good"		Iodixanol	2		66	59 (89.4)	P=0.73									For both groups image quality was judged poor or moderate in patients with a high BMI or who did not receive sufficient dose of contrast media
Zo'o, 2011[22]				Iobitridol	3		62	52 (83/9)										

Evidence Table E-11. Comparison between iso- and low-osmolar contrast media: Image quality and diagnostic accuracy (continued)

Author, year	Outcome	Measure	Sub-group (not a subgroup is column is left blank)	Interven-tion	ARM	Time Point 1	Time point 1 N anal-yzed	n (%) with out-come at time point 1	Comp-arison statistic s at time point 1	Time Point 2	Time point 2 N analyzed	N(%) with out-come at time point 2	Com-parison statistics at time point 2	Time Point 3	Time point 3 N anal-yzed	n (%) with out-come at time point 3	Com-parison statistic s at time point 3	Comment
Diagnostic efficacy																		
Zo'o, 2011[22]	Diagnostic efficacy	"easy"		Iodixanol			66	65 (98.5)	P=0.58									
Zo'o, 2011[22]				Iobitridol			62	56 (90.2)										

%=percent, AE=Adverse Events, CI=Confidence Interval, CIN=Contrast Induced Nephropathy, ClCr=Creatinine Clearance, cr=Creatinine, eGFR=estimated Glomerular Filtration Rate, ESRD=End Stage Renal Diseasem, H=Hours, Hrs=Hours, IA=Intra-arterial, Mg/dl=milligrams per deciliter, MI=Myocardial Infarction, Ml=milliliter, N=Sample size, NR=Not Reported, NR=Not reported, Ns=Not significant, P=p-value, PCI=percutaneous coronary intervention, SCr=Serum Creatinine, Umol/L=micromole per liter

Evidence Table E-12. Summary of observational studies comparing contrast media for the prevention of contrast-induced nephropathy

Author, year	Comparison	N	Population	Age, range of mean§	CM Route*	Mean follow up	Definition of CIN*	Incidence of CIN, n/N (%)	Other Outcomes, n/N (%)
Ajami, 2010[33]	Iopromide vs Iohexol	80	Pediatric patients	8.7	IA	48 hours	Increased creatinine x 1.5 or GFR decrease >25% at 48 hours	Iopromide: 5/40 (12.5) Iohexol: 3/40 (7.5) p=0.0001	NR
Briguori, 2005[34]	Iobitridol vs Iodixanol	225	SrCr >1.5mg/dl or GFR <60ml/min/1.73m^2	67	IA	48 hours	>0.5 mg/dl of SrCr	Iobitridol: 4/115 (3.5) Iodixanol: 3/110 (2.7) p=1.00	Requiring dialysis At 48 hours Iobitridol: 0 (0) Iodixanol: 0 (0) p=NR
Donadio, 2001[35]	Iopromide vs Ioversol vs Ioxaglate	45	Cardiac patients	62-64	IA	72 hours	NR	NR	GFR <50% of baseline At 48 hours 0 participants in all arms, p=NR
From, 2008[36]	Iodixanol vs Iohexol	794	General	69	IV	2 years	>25% or >0.5 mg/dl of SrCr	At 7 days Iodixanol: 54/397 (10.7) Iohexol: 52/397 (10.3) p=0.84	Requiring dialysis Iodixanol: 1/397 (0.3) Iohexol: 0/397 (0) p=NR Mortality Average time to event: 1.2 years Iodixanol: 87/397 (22) Iohexol: 103/397 (26) p=0.18
Hsieh, 2006[37]	Iodixanol vs Iopromide	54	SrCr >2.5mg/dl	71-73	IA	6 months	NR	NR	change inSrCr (%) At 6 months Iopromide: +47 Iodixanol: -10 p<0.001 Requiring dialysis At 1 year Iopromide: 1/27 (4%) Iodixanol: 4/27 (15) p=NS

Evidence Table E-12. Summary of observational studies comparing contrast media for the prevention of contrast induced nephropathy (continued)

Author, year	Comparison	N	Population	Age, range of mean[§]	CM Route*	Mean follow up	Definition of CIN*	Incidence of CIN, n/N (%)	Other Outcomes, n/N (%)
Kanei, 2011[38]	Iodixanol vs Iopamidol	212	STEMI	59.6	IA	72 hours	>25% or >0.5 mg/dl of SrCr	At 72 hours Iodixanol: 20/121 (17) Iopamidol: 13/91 (14) p=0.80	Composite of adverse cardiac events (death, AMI and target vessel revascularization) At 72 hours Iodixanol: 6/121 (5.0) Iopamidol: 2/91 (2.2) p=0.47 Length of hospital stay (days) Iodixanol: 9.4 Iopamidol: 6.9 p=0.08
Karlsberg, 2010[39]	Iodixanol vs LOCM	275	General	64	IA	24 hours	>25% of SrCr	At 24 hours Iodixanol: 8/147 (5.4) LOCM: 14/103 (13.6) p=0.025	Heart Failure At 24 hours Iodixanol: 1/147 (0.68) LOCM: 1/103 (0.97) p=NR
LaBounty, 2012[40]	Iohexol vs Iopamidol vs Ioversol	107,994	General	45% >65 years	IA	30 days	NR	Re-admission for CIN At 30 days Iohexol: (0.1) Iopamidol: (0.1) Ioversol: (0.1) p=0.77	In-hospital mortality Iohexol: (0.6) Iopamidol: (0.7) Ioversol: (0.7) p=0.17 In-hospital hemodialysis Iohexol: (0.34) Iopamidol: (0.48) Ioversol: (0.49) p=0.02 Hospital length of stay (days) Iohexol: 2.8 Iopamidol: 3.0 Ioversol: 2.9 p<0.001
Liss, 2006[41]	Iodixanol vs Ioxaglate	57,925	General	65	IA	3 months	NR	Renal failure diagnosis At 3 months Iodixanol: 141/45485 (0.3) Ioxaglate: 10/12440 (0.1) p<0.001	Started dialysis At 3 months Iodixanol: 79/45485 (0.2) Ioxiglate: 9/12440 (0.1) p=0.010

Evidence Table E-12. Summary of observational studies comparing contrast media for the prevention of contrast induced nephropathy (continued)

Author, year	Comparison	N	Population	Age, range of mean[§]	CM Route*	Mean follow up	Definition of CIN*	Incidence of CIN, n/N (%)	Other Outcomes, n/N (%)
Valente, 2006[42]	Iodixanol vs Iopromide	194	STEMI	73-78	IA	1 month	>0.5 mg/dl of SrCr	At 72 hours Iodixanol: 15/67 (22.3) Iopromide: 6/127 (4.7) p<0.05	Mortality At 1 month 4 deaths total (2.31%), all developed CIN Chronic renal failure At 1 month 1 developed renal failure from all arms

%=percent; AMI=acute myocardial infarction; CIN=contrast induced nephropathy; CM=contrast media; GFR=glomerular filtration rate; IA=intra-arterial; LOCM=low-osmolar contrast media; mg/dl=milligram per deciliter; ml/min/1.73m^2=millimeter per minute per 1.73 meter squared; n=number of events; N=total sample size; NR=not reported; NS=not significant; p=p-value; SrCr=serum creatinine; STEMI= ST-elevated myocardial infarction

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Appendix F. Study Limitations

Table F-1. Study limitations

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the srudy?	Were incomplete oucome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Alexopoulos, 2010[1]	Yes	No	No	Yes	Yes
Barrett, 2006[2]	Yes	Yes	Yes	Yes	Yes
Becker, 2013[3]	Yes	No	No	Yes	Yes
Bolognese, 2012[4]	Yes	Yes	Yes	Yes	Yes
Campbell, 1990[5]	Unclear	Unclear	Yes	No	Unclear
Carraro, 1998[6]	Unclear	Unclear	Yes	Unclear	Unclear
Chuang, 2009[7]	Unclear	Unclear	Unclear	Yes	Yes
Dillman, 2012[8]	Yes	Yes	Yes	Yes	Yes
Feldkamp, 2006[9]	Unclear	Unclear	Unclear	Yes	Yes
Hardiek, 2008[10]	Yes	Yes	Yes	Yes	Yes
Hernandez, 2009[11]	No	No	No	Yes	Yes
Jakobsen, 1996[12]	Unclear	Unclear	Yes	Yes	Yes
Jevnikar, 1988[13]	Unclear	Unclear	Yes	No	Yes
Jo, 2006[14]	Unclear	Unclear	Yes	Yes	Yes
Juergens, 2009[15]	Yes	Yes	Yes	Yes	Yes
Koutsikos, 1992[16]	Unclear	Unclear	Unclear	Yes	Yes
Kuhn,2008[17]	Unclear	Unclear	Unclear	Yes	Yes
Laskey, 2009[18]	Unclear	Yes	Yes	Yes	Yes
Limbruno, 2013[19]	Unclear	Unclear	Unclear	Unclear	Yes
Mehran, 2009[20]	Yes	Yes	Yes	Yes	Unclear
Nguyen, 2008[21]	Yes	Unclear	Yes	Yes	No
Nie, 2008[22]	Yes	Unclear	Yes	Yes	Yes
Rudnick, 2008[23]	Yes	Yes	Yes	Yes	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the srudy?	Were incomplete oucome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Semerci, 2014[24]	No	No	No	Yes	Yes
Serafin, 2011[25]	Yes	Unclear	Yes	Yes	Yes
Shin, 2011[26]	Yes	Yes	Yes	Yes	Yes
Solomon, 2007[27]	Yes	Unclear	Yes	Yes	Yes
Solomon, 2009[28]	Unclear	Unclear	Unclear	Yes	Yes
Wessely, 2009[29]	Unclear	Unclear	Yes	Yes	Yes
Zo'o, 2011[30]	Yes	Yes	Yes	Yes	Yes

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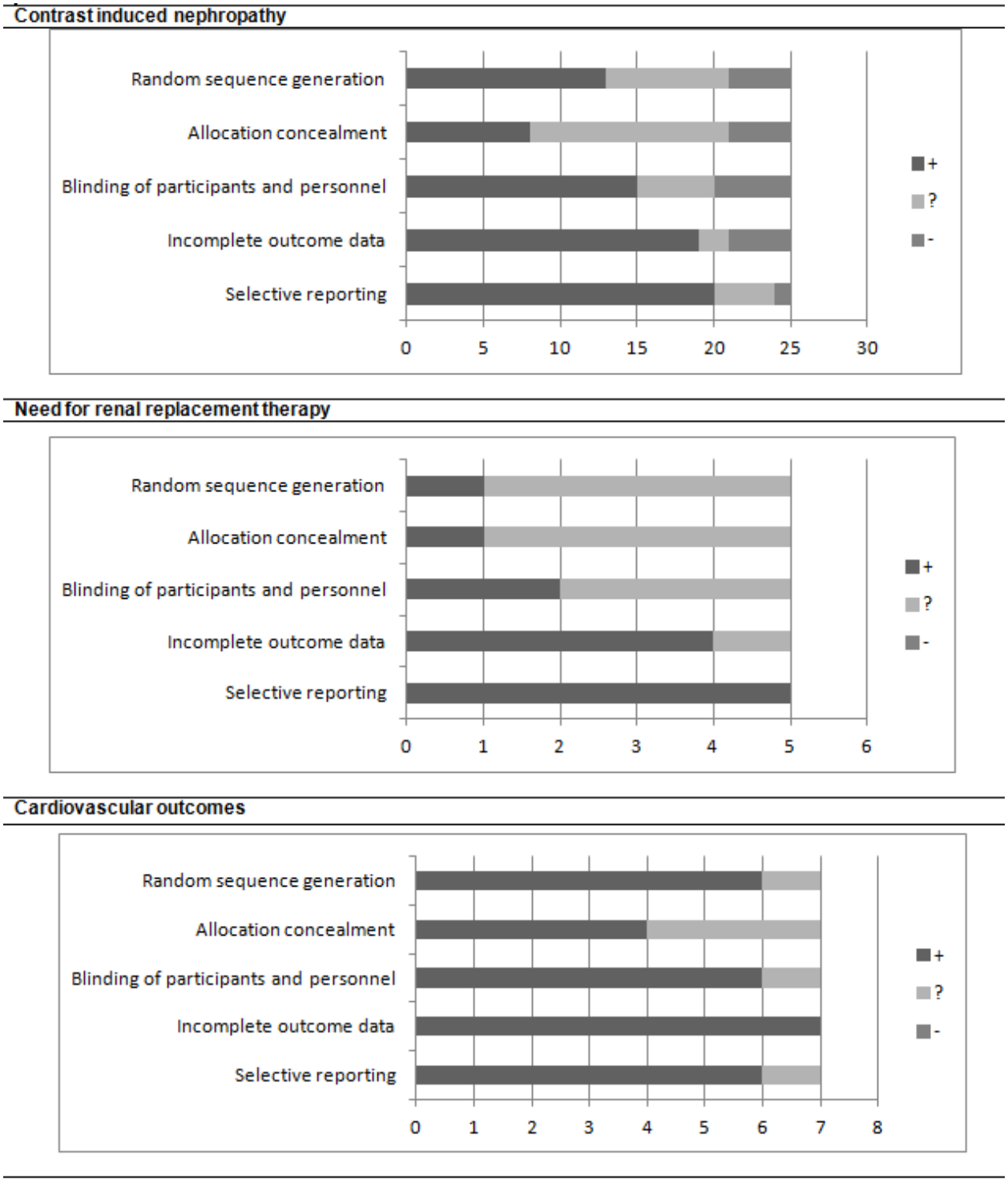
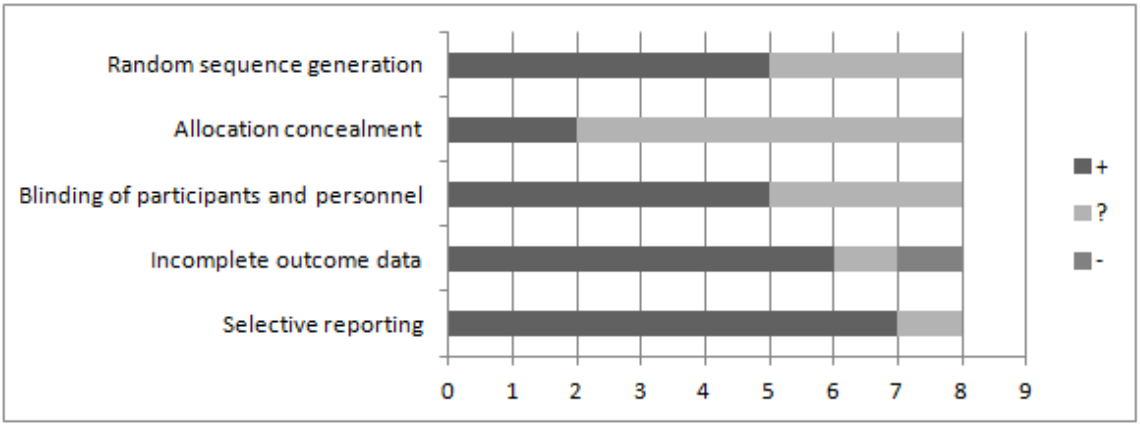
Appendix G. Study Limitation Figures

Figure G-1. IOCM versus LOCM study limitations



Mortality


Random sequence generation
Allocation concealment
Blinding of participants and personnel
Incomplete outcome data
Selective reporting
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