Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis

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Abstract

Background: To simultaneously evaluate the relative efficacy of multiple pharmacological strategies for preventing contrast-induced acute kidney injury (CI-AKI).

Study Design: Systematic review containing a Bayesian network meta-analysis of randomized controlled trials (RCTs)

Setting & Population: Participants undergoing diagnostic and/or interventional procedures with contrast media.

Selection Criteria for Studies: RCTs comparing the active drug treatments with each other or with hydration alone.

Intervention: Any of the following drugs in combination with hydration: N-acetylcysteine (NAC), theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), tocopherol (vitamin E), alpha lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide.

Outcomes: The occurrence of CI-AKI

Results: The trial network included 150 trials with 31,631 participants and 4,182 CI-AKI events assessing 12 different interventions. Compared with hydration, the odds ratios (ORs) for CI-AKI were 0.31 (95% credible interval 0.14 to 0.60) for high-dose statin plus NAC, 0.37 (0.19 to 0.64) for high-dose statins alone, 0.37 (0.17 to 0.72) for prostaglandins, 0.48 (0.26 to 0.82) for theophylline, 0.62 (0.40 to 0.88) for bicarbonate sodium plus NAC, 0.67 (0.54 to 0.81) for NAC alone, 0.64 (0.41 to 0.95)

for vitamins and its analogues, 0.70 (0.29 to 1.37) for natriuretic peptides, 0.69 (0.31 to 1.37) for fenoldopam, 0.78 (0.59 to 1.01) for bicarbonate sodium, and 0.98 (0.41 to 2.07) for low dose statin. High-dose statin plus NAC or high-dose statin alone were likely to be ranked the best or the second best for preventing CI-AKI. The overall results were not materially changed in meta-regressions, subgroup and sensitivity analyses.

Limitations: Patient-level data was unavailable. Unable to include some treatment agents, low event rates, and imbalanced distribution of participants among treatment strategies.

Conclusions: High-dose statins plus hydration with or without NAC might be the preferred treatment strategy to prevent CI-AKI in patients undergoing diagnostic and/or interventional procedures requiring contrast media.

Index Words:

contrast-induced acute kidney injury (CI-AKI), contrast media, kidney disease, acute kidney failure, statins, hydroxymethylglutaryl-CoA reductaseinhibitor, atorvastatin, rosuvastatin, simvastatin, serum creatinine, cardiovascular events, systematic review.

Introduction

With the steady increase in the rates of diagnostic and/or interventional procedures with contrast media (CM), contrast-induced acute kidney injury (CI-AKI) has become the third most common cause of AKI in hospitalized patients.[1] CI-AKI leads to prolonged hospitalization, increased costs, and increased morbidity and mortality.[2] Factors associated with the risk of CI-AKI include pre-existing renal functional impairment, diabetes, hypertension, chronic heart failure, advanced age, volume depletion, haemodynamic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of CM.[3,4]

Minimization of the CM dose and the use of iso-osmolar or low-osmolar CM are recommended as non-pharmacological precautions, and numerous pharmacological strategies for preventing CI-AKI have been evaluated. In 2008, a comprehensive meta-analysis of randomized controlled trials (RCTs) concluded that *N acetylcysteine* (NAC) in combination with hydration was more effective than hydration alone.[5] However, due to the lack of head-to-head comparisons between treatment agents, traditional pairwise meta-analyses could not be used to simultaneously synthesize all evidence and generate clear hierarchies for the efficacy of different treatments.[5-8] Therefore, the choice of the best treatment in practice is generally based on subjective judgement, and objective information regarding the relative efficacy of different interventions would help the development of clinical practice guidelines for preventing CI-AKI.

Bayesian network meta-analysis, also known as mixed treatment comparison,

enables indirect comparison using a common comparator, and combines direct and indirect comparisons to synchronously assess multiple treatments.[9-11] The usefulness of this method has been demonstrated in many studies on various medical conditions and interventions.[12-14] This systematic review and network meta-analysis therefore aims to compare the relative efficacy of different pharmacological interventions for preventing CI-AKI by means of network meta-analysis within a Bayesian framework.

Methods

Data Sources and Searches

This systematic review was performed according to a pre-specified protocol (**Item S1**) and the reporting was in line with PRISMA guidelines.[15] We searched MEDLINE via Ovid (from 1946 to May 2016), Embase (from 1966 to May 2016), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; before May 2016) for RCTs of CI-AKI prevention, without any language restrictions (see **Item S1** for full search terms). The ClinicalTrials.gov website was also searched for RCTs that were registered as completed but not yet published.

Study Selection

We included RCTs that evaluated any of the following drugs in combination with hydration: NAC, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), vitamin E or its analogues (tocopherol), alpha

lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide. RCTs comparing the above active drug treatments with each other or with hydration were eligible. We excluded studies that contained only one or none of the above treatments. Eligible participants were those who underwent diagnostic and/or interventional procedures with CM, such as diagnostic coronary or peripheral arterial angiography or percutaneous intervention, ventriculography, enhanced CT, intravenous pyelography, and other relevant procedures.

The treatment groups were classified into 12 categories according to the drug species and/or dose: 1. atrial natriuretic peptide, B-type natriuretic peptide and carperitide were classified into natriuretic peptide; 2. ascorbic acid (vitamin C, tocopherol and alpha-lipoic acid were classified into vitamins and its analogues; 3. simvastatin 40-80 mg, rosuvastatin 20-40 mg and atorvastatin 40-80 mg were known as high-dose statin; 4. low-dose statin included simvastatin 10-20 mg, rosuvastatin 10 mg and atorvastatin 10-20 mg; 5. iloprost, alprostadil, misoprostol and prostaglandin E1 were categorized into prostaglandin. The other seven treatments included: 6. theophylline (aminophylline); 7. NAC; 8. fenoldopam; 9. bicarbonate sodium; 10. bicarbonate sodium plus NAC; 11. high-dose statin plus NAC; 12. hydration

Data Extraction and Quality Assessment

Study selection, data extraction, and quality assessment were performed independently by two investigators (XL.S and XF.X) according to the pre-specified study protocol (**Item S1**). The two investigators screened the titles and abstracts of the records identified by the search strategies for eligibility. Disagreements were resolved

by discussion with a third reviewer (LJ.L). Data on pre-specified variables from the included studies were extracted into a computerized spreadsheet.

The outcome used was the development of CI-AKI, defined as an absolute increase in the baseline serum creatinine level of greater than 44.2 μmol/L (0.5 mg/dL) or a relative increase of greater than 25%, typically within 48-72 h after contrast injection.[16,17] If data was not available for the first 48-72 h after the treatment, we used data obtained within the first 5 days of treatment (the data point closest to 48-72 h was given preference).[18] If different measurement index (eg. eGFR, Ccr) or standard was applied, we extracted data according to one defined by authors of the included studies.

We assessed sources of bias using the Cochrane Collaboration risk-of-bias tool,[19] including an assessment of financial conflicts of interest.[20] We developed operational definitions for high, low, and unclear risk of bias for each of the eight validity domains (**Item S2**).

Data Synthesis and Analysis

We used odds ratio (OR) and its 95% credible intervals (CrIs) to measure the relative effect of different treatments on CI-AKI outcome. Before conducting network meta-analysis, we conducted conventional pairwise meta-analyses for treatments that were directly compared in RCTs. We used fully Bayesian method (FB), assuming a binomial likelihood on the log-odds scale, in pairwise meta-analyses through WinBUGS 1.4.3.[21,22] To investigate heterogeneity in conventional pairwise meta-analysis, we used STATA 12.0 to conduct meta-regression of direct comparisons

based on empirical Bayes method, and estimated I^2, tau^2 and Q value.

Network meta-analysis was conducted by using random-effects model within a Bayesian framework, assuming a binomial likelihood and using WinBUGS 1.4.3 and R2WinBUGS package of R software 3.1.1 according to a pre-defined protocol (**Item S1**). We used non-informative priors with vague normal (mean, 0; variance, 100,000) and uniform (0 to 5) prior distributions for parameters such as means and standard deviations, respectively.[11] For each analysis, we generated 200,000 simulations for each of the two sets of different initial values, and discarded the first 80,000 simulations as the burn-in period. Convergence was reached when Rhat, the potential scale reduction factor is close to 1 for each of the parameters using the Brooks–Gelman–Rubin statistic.[23] We used the surface under the cumulative ranking (SUCRA) probabilities to rank the treatments.[24]

Inconsistency refers to differences in effect estimates between direct and indirect comparisons, which could be assessed when three treatments are connected within a loop.[25,26] For each closed loop, we estimated the absolute difference between the direct and indirect comparisons, which is termed inconsistency factor. Inconsistent loops were identified by a significant disagreement (inconsistency factor and its 95% CI that excludes 0) between direct and indirect evidence.[25,27,28] As a whole, inconsistency was also assessed by the comparison between the consistency model and inconsistency model of the network meta-analysis using deviance information criterion (DIC). A lower value of the DIC suggests a more parsimonious model. If the trade-off between model fit and complexity favours the model with assumes

inconsistency, then the assumption of consistency is likely to be violated.[12,29]

We carried out the following pre-specified sensitivity analyses: exclusion of trials with sample sizes less than 50 in order to reduce small study effect and publication bias; exclusion of trials with high-osmolar and unspecified CM types; and exclusion of data from patients with non-DM (**Item S1**). Other analyses were post-hoc: exclusion of trials evaluating only patients with normal kidney function, published before 2004, with oral hydration and unspecified hydration agent.

Pre-specified multiple-treatments meta-regression and subgroup analyses were conducted by several major covariates, such as mean CM dose, mean age, baseline serum creatinine concentration, different CI-AKI definitions, and different radiologic procedures with CM (**Item S1**). Post-hoc subgroup analysis was conducted by types of CM and different hydration agents.

The models used, the WinBUGS codes, and R routines for all results are presented in detail and exemplified in http://www.mtm.uoi.gr. and http://www.nicedsu.org.uk. A short summary is supplied in **Item S3**.

Results

The literature search yielded 4144 articles. We assessed the full text of 396 of these articles for eligibility, and eventually included 150 RCTs in the network meta-analysis (**Figure 1**, see details of included studies in **Table S1)**. CI-AKI was measured according to the difference between the baseline serum creatinine level and the level within 48 h-72h in 120 studies. In 30 trials, CI-AKI was defined according to different

points in time and measurements (eg. eGFR, Ccr), or the determination method was not specified. Of the included RCTs, 104 trials included patients with impaired renal function, 37 trials included patients with normal or impaired renal function, and 9 trials included only patients with normal renal function. Participants were recruited at an average age of 67 years, and male participants accounted for 68% of the total population. A total of 11 types of CM were used, including iso-osmolar, low-osmolar, and high-osmolar media. The dosing regimens and types of CM used in the included trials are detailed in **Table S1**.

The methodological quality of the included trials was not high overall and varied substantially (**Item S2, Figure S1, S2**). The proportion of trials with a low risk of bias was 53% in terms of random sequence generation, 54% in terms of allocation concealment, 49% in terms of blinding of both participants and health care professionals, 59% in terms of blinding of outcome assessors, 48% in terms of attrition, and 35% in terms of reporting bias. With respect to conflicts of interest, about 50% of RCTs were funded by pharmaceutical industry and 51% reported author-industry financial relationships. In order to investigate reporting/published bias, we searched and found 21 protocols for 396 full-text reviewed articles. In studies without reporting the outcome of interest, we didn't find any pre-planned CI-AKI outcome.

A total of 4,182 CI-AKI events were reported in 150 trials with 31,631 participants. **Figure 2** shows all comparisons that were analysed in the network meta-analysis. The results of available direct comparisons are shown in **Figure 3** and **Table S2**, and the

results of testing heterogeneity (I^2, tau^2 and Q) within treatment strategies were showed in **Table S2**. We summarized the results of random-effects consistency network meta-analysis in **Figure 3**. The effects of individual treatment strategies compared with hydration on preventing CI-AKI are presented in **Figure 4.** Compared with hydration alone, high-dose statin plus NAC, high-dose statin, prostaglandin, theophylline, bicarbonate sodium plus NAC, vitamins and their analogues and NAC alone (all in combination with hydration) statistically significantly reduced the risk of CI-AKI (**Figure 3** and **Figure 4**). In addition, high-dose statins were significantly more effective than low-dose statins (OR: 0.42; 95% CrI: 0.19 to 0.79), NAC (OR: 0.51; 95% CrI: 0.29 to 0.98) and bicarbonate sodium(OR: 0.49; 95% CrI: 0.23 to 0.86). Prostaglandin was significantly more effective than bicarbonate sodium (OR: 0.49; 95% CrI: 0.22 to 0.98). High-dose statin combined with NAC was statistically more effective than NAC (OR: 0.41; 95% CrI: 0.22 to 0.86), low-dose statins (OR: 0.28; 95% CrI: 0.12 to 0.99), bicarbonate sodium plus NAC (OR: 0.51; 95% CrI: 0.24 to 0.99) and bicarbonate sodium alone (OR: 0.35; 95% CrI: 0.18 to 0.79).

High-dose statin plus NAC (SUCRA: 0.90) and high-dose statin (SUCRA: 0.83) were most likely to be ranked the best or second best (**Figure S3**). They were followed by prostaglandins (SUCRA: 0.82) and theophyllines (SUCRA: 0.70). SUCRAs (range: 0.41 to 0.49) and rankings were similar for bicarbonate sodium plus NAC, vitamins and its analogues, natriuretic peptides, fenoldopam and NAC. Hydration alone was ranked as the least effective treatment.

The DIC value was lowest in the random consistency model than in the other three

models, which indicated that the former was the preferred model with a better trade-off between model fit and complexity (**Table S3**). However, significant discrepancy between the direct and indirect comparisons was identified in two of the 13 loops (**Figure S4**). The two inconsistent loops consisted of (1) vitamins and its analogues *vs.* bicarbonate sodium plus NAC *vs.* hydration; and (2) vitamins and its analogues *vs.* bicarbonate sodium plus NAC *vs*. NAC. Further investigation was performed, but we were unable to identify possible sources of inconsistency. As the number of relevant studies in the inconsistent loops was small, the extent of inconsistency was not substantial enough to affect the overall results.

Treatments with high-dose statin plus NAC or high-dose statin were consistently associated with the lowest or second lowest incidence of CI-AKI in sensitivity analyses, meta-regression, and subgroup analyses (**Table S4** and **S5**). A notable exception is that the effects of vitamins and its analogues became statistically non-significant compared with hydration in some sensitivity and subgroup analyses.. When the analysis included only DM participants (38 trials, 7984 patients and 826 events), credible intervals were wide and all ORs were no longer statistically significant due to the reduced sample size, although high-dose statin plus NAC and high-dose statin remained the first and the second ranking among all treatment strategies. None of the other sensitivity, meta-regression, or subgroup analyses led to important changes in the overall results (**Table S4** and **S5**).

Discussion

Our study included 150 trials with more than 30,000 participants and a total of 4,182 CI-AKI events. The mixed treatment comparison of 12 treatment strategies for preventing CI-AKI confirmed that treatment with a high-dose statin alone or in combination with NAC (both in combination with hydration) during CM administration significantly reduced the risk of CI-AKI compared with hydration alone. Compared with other protective regimens, oral administration of high-dose statins is simple and convenient. These results indicate an opportunity to potentially simplify prevention strategies for CI-AKI. Our analysis also found a number of other strategies that appeared to be superior to hydration alone, including prostaglandins, theophylline, bicarbonate sodium plus NAC, vitamins and their analogues and NAC.

A recent comprehensive pairwise meta-analysis reported that the greatest reduction in CI-AKI was seen with NAC plus hydration and with statins plus NAC plus hydration in patients receiving CM.[30] Our study simultaneously compared multiple treatment strategies using Bayesian network meta-analysis method, and found that patients using CM were most likely to benefit from high-dose statin. The results of the current study were similar to findings from previous primary studies[31–34] and meta-analyses,[6,35–37] which suggested that short-term prophylaxis with high-dose statins led to a significant reduction in the risk of CI-AKI. In contrast, the meta-analysis by Zhang T et al.[38] found no significant reduction in the incidence of CI-AKI with statins treatment, as determined using the pooled estimate of the included trials. However, it should be noted that the meta-analysis by Zhang T et al incompletely include relevant randomized trials.[39,40]

Pre-existing renal dysfunction is an independent predictor of CI-AKI.[41] Findings from some previous pairwise meta-analyses[35,36] suggested that the use of statins may not be effective for patients with pre-existing chronic kidney disease (CKD). Our meta-regression analyses found that baseline serum creatinine concentration as a continuous covariate was not a statistically significant effect-modifier (regression coefficient: 0.09; 95% CrI: -1.86 to 1.90). Consistent with our results, the TRACK-D study involving almost 3,000 DM participants with mild-to-moderate CKD demonstrated a significant reduction in the relative risk of CI-AKI with rosuvastatin therapy.[40]

Although the pathogenesis of CI-AKI is not completely understood, multiple mechanisms are probably involved, including direct toxicity of CM on the renal tubular epithelium, inflammatory reactions, oxidative stress, ischemic injury, and renal tubular obstruction.[42] Statins may have multiple non-lipid-lowering effects, such as enhancement of endothelial nitric oxide production,[43–45] anti-inflammatory and anti-oxidative actions,[46,47] and apoptosis prevention.[34] These pleiotropic effects of statins could mediate the reduction of CI-AKI risk after iodinated contrast administration. Furthermore, use of antioxidants (eg, vitamins and its analogues, NAC) might be an effective strategy to prevent CI-AKI, considering their roles in attenuating the oxidative damage from radiocontrast.

Apart from high-dose statins and high-dose statins plus NAC, prostaglandins had better effects than other treatment strategies, based on evidence from five trials that included a total of 943 participants and evaluated four classes of prostaglandins.

Adequate renal prostaglandin levels may counteract contrast-induced renal vasoconstriction and selective renal tubular epithelial cell toxicity.[48]

As a non-selective adenosine receptor antagonist, theophylline may help attenuate the vasoconstrictive tendencies observed after CM administration.[49,50] A previous pairwise meta-analysis also showed that theophylline administration reduced the incidence of CI-AKI compared with the control group.[51] Although pre-interventional theophylline administration might be helpful in patients with CM, the possibility of cardiovascular side-effects and the interactions with numerous drugs associated with theophylline should be recognized.[52,53]

Many but not all studies reported that NAC has a protective effect on CI-AKI when administered before the onset of renal insult. Of the 11 previous meta-analyses published on this subject, seven found a net benefit of NAC in CI-AKI prevention. However, due to statistically significant heterogeneity and possible publication bias, the benefit of NAC might have been overestimated.[54] With low the strength of evidence, Kidney Disease Improving Global Outcomes Clinical Practice Guideline for CI-AKI suggests the use of oral *N*-acetylcysteine plus hydration. Another meta-analysis found that a combination of NAC and sodium bicarbonate substantially reduced CI-AKI risk compared with NAC alone.[55] However, we found that both sodium bicarbonate plus NAC and vitamins and their analogues were involved in significant inconsistent loops, and results for vitamins and their analogues were not robust in sensitivity and subgroup analyses.

This network meta-analysis provides a most comprehensive picture of the

likelihood of a range of treatments to prevent CI-AKI, and reports the results of mixed comparisons of multiple treatments that have been rarely compared in head to head trials. We also report the ranking probability for all 12 treatment agents. However, treatment rankings derived from network meta-analyses may have a substantial degree of imprecision,[56] and the results in terms of treatment ranking should be interpreted with caution.

Our study has several limitations. First, the trial network could not include some treatment agents, such as Na/K citrate,[57] allopurinol,[58] statin plus alsprostadil,[59] that may be efficacious but were evaluated in only one or two small trials without a connection with other commonly used treatments. For many specific treatments, the number of patients and events in the available trials may not be sufficient to form a well-connected network for meta-analysis. We therefore combined drugs with the same types and similar mechanism of action and evaluated treatment effects of major drug classes. Second, many of the included studies showed low CI-AKI event rates or no events at all in one or both trial arms, and there was an imbalance in the distribution of participants among some of the treatment strategies. Consequently, the uncertainty in the analyses was increased, resulting in wide CrIs for several treatment comparisons. Third, the absence of patient-specific data, varying quality and design of the included studies are limitations common to all meta-analyses. To at least partly nullify the latter factors, we included only RCTs. Furthermore, the meta-regression based on trial-level covariates rather than individual patient data might bring the ecological fallacy.[60] Fourth, we included only published studies in this analysis, and

reporting bias could not be ruled out because not all studies reported CI-AKI outcome, especially when CI-AKI events were not primary end points.

Further studies with head-to-head comparisons of statins at both high and low doses were needed to illuminate whether important differences exist in their abilities to reduce CI-AKI risk and whether dose matters. Prospective randomized trials should focus on relatively homogeneous patient populations, such as DM, or whether patients with different stages of CKD would benefit similarly or differently from peri-procedural statin therapy. Future studies are also needed to test effects of combinations of different strategies shown to be beneficial in this analysis, and to uncover possible mechanisms.

Our Bayesian network meta-analysis indicates the effects and superiority of using a high-dose statin plus hydration with or without NAC in patients undergoing diagnostic and/or interventional procedures requiring CM. The results should be interpreted with caution due to important data and methodological limitations.

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Figure 1: Summary of trial identification and selection

Figure 2: Network of treatment comparisons for the Bayesian network meta-analysis

The size of the nodes is proportional to the number of patients randomized to receive the treatment. Directly comparable treatments are linked with a line, the width of which is proportional to the number of trials comparing the connected treatments.

NAC, *N*-acetylcysteine.

Figure 3: Summary of the results from NMA (on the lower triangle) **and traditional pairwise meta-analysis** (on the upper triangle) On the lower triangle, the column-defining treatment is compared with the row-defining treatment, and odds ratios (ORs) lower than 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared with the column-defining treatment, and ORs lower than 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. The direct comparisons within two inconsistent loops are underlined.

BIC, Bicarbonate sodium; BIC+NAC, Bicarbonate sodium plus NAC; FEN, Fenoldopam; HST, High-dose statin; HST+NAC, High-dose statin plus NAC; HYD, Hydration; LST, Low-dose statin; NAC, *N*-acetylcysteine; NAP, Natriuretic peptide; PRO, Prostaglandin; THE, Theophylline; VIT, Vitamins and its analogues.

Figure 4: Forest plot for efficacy of 11 active drugs compared with hydration

Treatments are ranked according to their OR values(*vs.*hydration).

CrI, credible interval. SUCRA, surface under the cumulative ranking curve measure. NAC, N-acetylcysteine. OR, odds ratio.

Supplemental Material

Table S1: Description of included studies

ALA, alpha-lipoic acid; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CI-AKI, contrast-induced acute kidney injury; Crcl, Creatinine clearance rate; eGFR, estimated glomerular filtration rate; NA, no available; NAC, *N*-acetylcysteine; $NaHCO_3$, bicarbonate sodium; Scr, Serum creatinine.

Table S2: Meta-analytic results of traditional pairwise meta-analysis

Abbreviations: CI, confidence interval; N, number of trials; n, number of patients; NA, no available; NAC, *N*-acetylcysteine; OR, odds ratio, *vs.*, versus.

[a] τ^2 represents between-study heterogeneity characterized by standard deviation.

[b] the meta-regression based on empirical Bayes method was used to calculate ORs and 95CIs. ORs are lower than 1 favor the former treatment of every comparison.

Table S3: Evaluation of the model fit

For a binomial likelihood each trial arm contributes 1 independent **data point**.

Dbar is considered as an absolute measure of fit, and is used to check formally whether a model's fit is satisfactory. This is the posterior mean of the deviance under the current model minus the deviance for the saturated mode. We can then compare the value of *Dbar* to the number of independent data points to check if the model fit can be improved.

Leverage (P_D) is considered an appropriate measure of the complexity of a model that reasonably describes the data. P_D also is termed the effective number of parameters, and is calculated as the posterior mean of the residual deviance minus the deviance at the posterior mean of the fitted values.

Deviance Information Criterion (DIC) is the sum of the posterior mean of the residual deviance and the P_D , and provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model. The DIC is particularly useful for comparing different parameter models for the same likelihood and data, for example fixed and random effects models or fixed effect models with and without covariates. As shown in above table, the random consistency model is clearly more parsimonious than the other three models.

Table S4: Results of sensitivity analyses

Data are odds ratio (95% CrI). All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, τ^2. Significant results are in bold.

CM, contrast media; CrI, credible interval; DM, Diabetes mellitus; SUCRA, surface under the cumulative ranking curve measure; NAC, *N*-acetylcysteine.

Table S5: Results of meta-regression and subgroup analyses

Data are odds ratio (95% CrI) after adjusting covariates: a. continuous variables include "Mean CM dose", "Baseline scr concentration", and "Mean age years"; b. categorical variables include "CM type (iso-, low- or high-osmolar)", "Isotonic (0.9%) or hypotonic (0.45%) saline hydration", "Different CI-AKI definitions (48h,72h or 120h)", "Cardiovascular diagnostic/interventional procedures or enhanced CT or not specified radiologic procedure with CM". All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, τ^2. Significant results are in bold.

CM, contrast media CrI, credible interval; CT, computed tomography; Scr, Serum creatinine; NAC, *N*-acetylcysteine.

Figure S1: Risk of bias summary: judgements from each study

The green symbols represent low risk of bias, the yellow symbols represent unclear risk of bias, and the red symbols represent high risk of bias. The figure was generated using Review Manager Version 5.0.16.

Figure S2: Risk of bias graph of included clinical trials

Each methodological quality item is presented as percentages across all included studies. The figure was generated using Review Manager Version 5.0.16.

Figure S3: Cumulative and non-cumulative SUCRA ranking curves

Treatment is ranked according to SUCRA. The SUCRA would be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst. Higher rank indicates greater benefit probability of preventing CI-AKI.

SUCRA, surface under the cumulative ranking curve measure; NAC, *N*-acetylcysteine.

Figure S4: Assessment of inconsistency

We estimated inconsistency as the difference between direct and indirect estimates (called inconsistency factor, IF) and the corresponding 95% confidence intervals (CI) for IF in each closed loop. The following graphs show all closed triangular loops (loops formed by three treatments) in CI-AKI outcome network. Inconsistent loops are those that present IF with 95% CIs incompatible with zero.

There are two inconsistent loops (1–11–9 = Vitamins and its analogues – Bicarbonate sodium plus NAC – Hydration; 1–11–3 = Vitamins and its analogues – Bicarbonate sodium plus NAC – NAC) out of 13 loops.

1 = Vitamins and its analogues, 2 = Natriuretic peptide, 3 = NAC, 4 = Prostaglandin, 5 = High-dose statin, 6 = Low-dose statin, 7 = Theophylline, 8 = Bicarbonate sodium, 9 = Hydration, 10 = Fenoldopam, 11 = Bicarbonate sodium plus NAC, 12 = High-dose statin plus NAC.

Item S1: Study protocol

Item S2: Statistical method

Item S3: Assessment domains of risk of bias

Item S4: PRISMA checklist

Table S1 Description of included studies

Study	Year	Number of patients	Men (%)	Mean age	CM	Type of CM	Mean volume of CM(mL)	Inclusion criteria of kidney function	Drug 1	New cases of CI-AKI/total	Drug 2	New cases of CI-AKI/total	Drug 3	New cases of CI-AKI/total	Drug 4	New cases of CI-AKI/total	Funding Source
Gurkowski[1]	1995	125	98	63	diatrizoate melamine	high-osmolar	100	Scr<2mg/dl	misoprostol+hydration	1/63	placebo+hydration	0/62					Non-industry
Kurnik[2]	1998	247	83	60	NA	NA	100	Scr>1.8mg/dl	ANP+hydration	44/187	placebo+hydration	11/60					NA
Abizaid[3]	1999	40	68	75	hexabrix	low-osmolar	190	Scr≥1.5mg/dl	aminophylline+hydration	6/20	hydration	7/20					NA
Erley[4]	1999	64	78	64	iopromide	low-osmolar	114	Scr>1.5mg/dl	theophylline+hydration	2/35	placebo+hydration	1/29					NA
Koch[5]	2000	117	66	67	NA	low- or iso- or high-osmolar	159	Scr>1.5mg/dl	prostaglandin E1+hydration	24/88	placebo+hydration	15/29					NA
Tepel[6]	2000	83	57	66	iopromide	low-osmolar	75	Scr>1.2mg/dl	NAC+hydration	1/41	placebo+hydration	9/42					NA
Allapaband[7]	2002	123	58	71	NA	low-osmolar	122	Scr≥1.6mg/dl	NAC+hydration	8/45	Fenoldopam+hydration	6/38	placebo+hydration	6/40			NA
Briguori[8]	2002	183	86	64	iopromide	low-osmolar	124	Scr>1.2mg/dl	NAC+hydration	6/92	hydration	10/91					NA
APART[9]	2002	54	80	73	ioxilan	low-osmolar	47	Scr≥1.4mg/dl	NAC+hydration	2/25	placebo+hydration	13/29					NA
Durham[10]	2002	79	66	70	Iohexol	low-osmolar	81	Scr≥1.7mg/dl	NAC+hydration	10/38	placebo+hydration	9/41					NA
Huber[11]	2002	100	9	NA	iomeprol	low-osmolar	207	Scr>1.2mg/dl	theophylline+hydration	2/50	placebo+hydration	8/50					NA
Kramer[12]	2002	56	75	60	NA	low-osmolar	NA	Scr<1.3mg/dl	theophylline+hydration	3/28	placebo+hydration	4/28					Non-industry
Shyu[13]	2002	121	68	70	iopamidol	low-osmolar	117	Scr 2-6mg/dl	NAC+hydration	2/60	placebo+hydration	15/61					Non-industry
Tumlin[14]	2002	45	76	63	NA	low- or iso-osmolar	88	Scr 2-5mg/dl	fenoldopam+hydration	5/23	placebo+hydration	9/22					Non-industry with drug supplied by industry
RAPPID[15]	2003	80	88	69	iodixanol	iso-osmolar	229	Scr>1.36mg/dl	NAC+hydration	2/41	placebo+hydration	8/39					Non-industry
Boccalandro[16]	2003	179	60	66	iodixanol	iso-osmolar	192	Scr>1.2mg/dl	NAC+hydration	10/73	placebo+hydration	13/106					NA
Efrati[17]	2003	49	90	67	Iopromide	low-osmolar	140	Scr>1.2mg/dl	NAC+hydration	0/24	placebo+hydration	2/25					Non-industry
Mahmoud[18]	2003	120	NA	NA	NA	NA	NA	Scr>1.36mg/dl	NAC+hydration	3/60	placebo+hydration	2/60					NA

Huber[19]	2003	100	83	69	iomeprol	low-osmolar	207	Scr≥1.4mg/dl	theophylline+hydration	2/50	placebo+hydration	10/50					NA
Kay[20]	2003	200	62	69	iopamidol	low-osmolar	125	Scr>1.2mg/dl	NAC+hydration	4/102	placebo+hydration	12/98					Non-industry
Kefer[21]	2003	104	75	63	iopromide or iohexol	low-osmolar	199	no limited kidney function	NAC+hydration	2/53	placebo+hydration	3/51					NA
MacNeill[22]	2003	43	86	73	iopromide or ioxilan	low-osmolar	110	Scr≥1.4mg/dl	NAC+hydration	1/21	placebo+hydration	7/22					NA
Oldemeyer[23]	2003	96	55	76	iopamidol	low-osmolar	NA	Scr>1.2mg/dl	NAC+hydration	4/49	placebo+hydration	3/47					NA
Stone[24]	2003	283	66	69	NA	low-osmolar	158	CrCl<60ml/min	fenoldopam+hydration	46/137	placebo+hydration	44/146					Industry
Agrawal[25]	2004	25	68	64	iohexol	low-osmolar	NA	Scr≥1.5mg/dl	NAC+hydration	2/11	placebo+hydration	2/14					NA
Balderramo[26]	2004	61	NA	NA	NA	NA	NA	CRF	NAC+hydration	1/33	placebo+hydration	2/28					NA
Briguori[27]	2004	192	85	69	iodixanol	iso-osmolar	164	Scr≥1.5mg/dl	NAC+hydration	4/97	fenoldopan+hydration	13/95					NA
Fung[28]	2004	91	70	68	iopromide	low-osmolar	128	Scr 1.7-4.5mg/dl	NAC+hydration	8/46	hydration	6/45					NA
Goldenberg[29]	2004	80	83	70	iodamidol	low-osmolar	116	Scr≥1.5mg/dl	NAC+hydration	4/41	placebo+hydration	3/39					NA
Merten[30]	2004	119	45	68	iodamidol	low-osmolar	132	Scr≥1.1mg/dl	$NaHCO_3$+hydration	1/60	hydration	8/59					Non-industry
Miner[31]	2004	180	74	70	iohexol	low-osmolar	347	Scr>1.2mg/dl or DM	NAC+hydration	9/95	placebo+hydration	19/85					NA
Ochoa[32]	2004	80	58	72	iodixanol/iohexol/ioxaglate/diatrizoate	low- or iso- or high-osmolar	144	Scr>1.8mg/dl (male) Scr>1.6mg/dl (female)	NAC+hydration	3/36	placebo+hydration	11/44					Non-industry
Rashid[33]	2004	94	64	71	NA	NA	143	Scr<1.3mg/dl	NAC+hydration	3/46	placebo+hydration	3/48					No funding supported
Spargias[34]	2004	231	92	66	NA	low- or iso-osmolar	274	Scr≥1.2mg/dl	ascorbic acid+hydration	11/118	placebo+hydration	23/113					NA
Webb[35]	2004	447	61	70	ioversol	low-osmolar	120	eGFR<50ml/min	NAC+hydration	25/220	placebo+hydration	24/227					Non-industry
Azmus[36]	2005	397	NA	NA	NA	NA	NA	Scr≥1.3mg/dl	NAC+hydration	14/196	placebo+hydration	17/201					NA
Gomes[37]	2005	156	59	65	ioxaglate	low-osmolar	103	Scr≥1.2mg/dl	NAC+hydration	8/77	placebo+hydration	8/79					NA
Gulel[38]	2005	50	76	61	ioxaglate	low-osmolar	NA	Scr>1.3mg/dl	NAC+hydration	3/25	hydration	2/25					NA
Kotlyar[39]	2005	60	83	67	iopromide	low-osmolar	87	Scr≥1.5mg/dl	NAC+hydration	0/41	placebo+hydration	0/19					Non-industry with drug supplied by

																	industry
Coyle[40]	2006	134	65	65	NA	low- or iso- or high-osmolar	93	no limited kidney function	NAC+hydration	6/65	hydration	1/69					NA
Dussol[41]	2006	233	73	64	NA	low-osmolar	123	CrCl 15-60ml/min	theophylline+hydration	6/80	hydration	9/153					No funding supported
Khalili[42]	2006	70	60	58	iohexol	low-osmolar	140	Scr≥1.2mg/dl	NAC+hydration	5/35	hydration	12/35					NA
Marenzi[43]	2006	354	95	63	iohexol	low-osmolar	266	no dialysis	NAC+hydration	27/235	placebo+hydration	39/119					Non-industry
CAFCIN[44]	2006	84	75	68	NA	low- or iso-osmolar	168	Scr≥1.2mg/dl	NAC+hydration	5/44	fenoldopan+hydration	8/40					NA
Boscheri[45]	2007	143	47	71	iodixanol	iso-osmolar	106	Scr>1.4mg/dl	ascorbic acid+hydration	5/74	placebo+hydration	3/69					NA
REMEDIAL[46]	2007	326	90	70	iodixanol	iso-osmolar	174	Scr 2-8mg/dl	NAC+hydration	12/111	NAC+$NaHCO_3$	2/108	ascorbic acid+NAC+hydration	12/107			NA
Carbonell[47]	2007	216	76	62	iopromide	low-osmolar	188	Scr<1.4mg/dl	NAC+hydration	11/107	placebo+hydration	11/109					NA
Hobikoglu[48]	2007	81	72	62	NA	NA	NA	Scr 1.4-2mg/dl	NAC+hydration	2/40	placebo+hydration	4/41					NA
Hsu[49]	2007	20	NA	NA	iohexol	low-osmolar	NA	Scr>1.6mg/dl	NAC+hydration	0/11	placebo+hydration	5/9					NA
Lawlor[50]	2007	78	69	NA	NA	NA	162	Scr>1.6mg/dl	NAC+hydration	4/53	placebo+hydration	2/25					Non-industry
Masuda[51]	2007	65	61	76	iopamidol	low-osmolar	116	Scr>1.1mg/dl	$NaHCO_3$+hydration	2/30	placebo+hydration	10/35					NA
Ozcan[52]	2007	264	69	75	ioxaglate	low-osmolar	110	Scr>1.2mg/dl	NAC+hydration	11/88	$NaHCO_3$	4/88	hydration	12/88			NA
RENO[53]	2007	111	69	65	iomeprol	low-osmolar	285	no limited kidney function	NAC+$NaHCO_3$	1/56	NAC+hydration	17/55					NA
DVD[54]	2007	229	75	67	iopromide	low-osmolar	134	Scr 1.3-3.5mg/dl	NAC+hydration	6/114	hydration	7/115					Non-industry
Rajamalar[55]	2007	40	65	76	iohexol	low-osmolar	141	Scr>1.4mg/dl (male) Scr>1.3mg/dl (female)	NAC+hydration	1/20	placebo+hydration	2/20					NA
REINFORCE[56]	2008	145	78	72	iodixanol	iso-osmolar	140	Scr>1.2mg/dl	$NaHCO_3$	3/71	hydration	2/74					NA
Brar[57]	2008	323	36	71	ioxilan	low-osmolar	132	eGFR<60ml/min	$NaHCO_3$	30/165	hydration	26/158					Non-industry

Heng[58]	2008	60	78	73	iomeprol or iodixanol	low- or iso-osmolar	203	eGFR<56ml/min	NAC+$NaHCO_3$	1/28	$NaHCO_3$	2/32					Non-industry
Mohamed[59]	2008	100	84	57	iohexol	low-osmolar	132	CrCl 40-90ml/min	NAC+hydration	2/49	placebo+hydration	6/51					Non-industry
PROMISS[60]	2008	236	72	66	iodixanol	iso-osmolar	182	Scr>1.1mg/dl	simvastatin 40mg+hydration	3/118	placebo+hydration	4/118					Non-industry
Kimmel[61]	2008	36	75	69	iomeprol	low-osmolar	193	Scr≥1.2mg/dl	NAC+hydration	2/17	placebo+hydration	1/19					No funding supported
Maioli[62]	2008	502	59	74	iodixanol	iso-osmolar	165	CrCl<60ml/min	NAC+hydration	52/252	NAC+$NaHCO_3$	38/250					NA
Masuda[63]	2008	59	61	76	iopamidol	low-osmolar	116	Scr>1.1mg/dl	$NaHCO_3$	2/30	hydration	10/29					Non-industry
Wang[64]	2008	46	59	67	iopromide	low-osmolar	93	no dialysis	NAC+hydration	0/23	hydration	0/23					NA
Amini[65]	2008	90	60	64	iohexol or iodixanol	low- or iso-osmolar	120	Scr>1.5mg/dl (male) Scr>1.4mg/dl (female)	NAC+hydration	5/45	placebo+hydration	6/45					No funding supported
Baskurt[66]	2009	145	60	68	ioversol	low-osmolar	120	eGFR 30-60ml/min	NAC+hydration	5/72	placebo+hydration	7/73					No funding supported
Ferrario[67]	2009	200	65	75	iodixanol	iso-osmolar	174	CrCl<55ml/min	NAC+hydration	8/99	placebo+hydration	6/101					No funding supported
Kim[68]	2009	108	NA	NA	iodixanol	iso-osmolar	NA	CrCl<60ml/min	ALA+hydration	2/53	placebo+hydration	2/55					NA
NASPI[69]	2009	174	78	65	iodixanol	iso-osmolar	210	Scr≥1.1mg/dl	NAC+hydration	1/83	ascorbic acid+hydration	4/91					Non-industry
Marikawa[70]	2009	254	72	74	iomeprol	low-osmolar	140	Scr≥1.3mg/dl	ANP+hydration	4/126	hydration	15/128					NA
Pakfetrat[71]	2009	192	61	58	iodixanol	iso-osmolar	63	no dialysis	$NaHCO_3$	4/96	hydration	12/96					Non-industry
Ratcliffe[72]	2009	78	60	66	iodixanol	iso-osmolar	150	Scr>1.5mg/dl (male) Scr>1.3mg/dl (female)	hydration	1/15	NAC+hydration	1/21	$NaHCO_3$	2/19	NAC+$NaHCO_3$	1/23	NA
Spargias[73]	2009	208	89	71	NA	low- or iso-osmolar	203	Scr≥1.4mg/dl	iloprost+hydration	8/103	placebo+hydration	23/105					Industry
Tamura[74]	2009	144	88	73	iohexol	low-osmolar	85	Scr 1.1-2mg/dl	$NaHCO_3$+hydration	1/72	hydration	9/72					NA
Tasanatong[75]	2009	103	74	67	iopromide	low-osmolar	141	Scr≥1.2mg/dl	alpha tocopherol+hydration	12/52	placebo+hydration	3/51					NA
Farahani[76]	2009	265	83	64	iohexol	low-osmolar	114	Scr≥1.5mg/dl	$NaHCO_3$+hydration	8/130	hydration	11/135					Non-industry

Jia[77]	2009	228	36	66	iohexol or iodixanol	low- or iso-osmolar	NA	no dialysis	simvastatin 20mg+hydration	18/113	simvastatin 80mg+hydration	6/115					NA
Zhou[78]	2009	100	59	60	iopamidol	low-osmolar	116	Scr<1.7mg/dl	atorvastatin 80mg+hydration	0/50	atorvastatin 10mg+hydration	3/50					NA
Hakan[79]	2010	60	70	61	iobitridol	low-osmolar	NA	no limited kidney function	NAC+hydration	1/30	hydration	1/30					No funding supported
Carbonell[80]	2010	81	80	70	iopromide	low-osmolar	160	Scr≥1.4mg/dl	NAC+hydration	2/39	placebo+hydration	10/42					NA
Castini[81]	2010	156	88	72	iodixanol	iso-osmolar	195	Scr≥1.2mg/dl	NAC+hydration	9/53	$NaHCO_3$	7/52	hydration	7/51			NA
ENABLE[82]	2010	166	73	62	iodixanol or iopamidol or iobitridol	low- or iso-osmolar	209	Scr<1.4mg/dl (male) Scr<1.2mg/dl (female)	NAC+hydration	3/80	hydration	7/86					NA
Kinbara[83]	2010	45	62	70	iopamidol	low-osmolar	143	no dialysis	NAC+hydration	0/15	aminophylline	0/15	hydration	0/15			No funding supported
Malhis[84]	2010	280	60	50	iohexol or iopamidol	low-osmolar	141	no dialysis	theophylline+hydration	2/128	$NaHCO_3$	12/152					NA
Matejka[85]	2010	56	61	75	iodixanol	iso-osmolar	95	Scr≥1.5mg/dl	theophylline+hydration	3/31	placebo+hydration	0/25					Non-industry
Hakan[86]	2010	130	41	55	iopamidol	low-osmolar	95	Scr≤1.5mg/dl	atorvastatin 80mg+hydration+NAC	2/60	NAC+hydration	7/70					No funding supported
Rohani[87]	2010	60	NA	62	iohexol	low-osmolar	205	Scr>1.3mg/dl	aminophylline+hydration	4/30	placebo+hydration	6/30					NA
Sar[88]	2010	45	53	57	iohexol	low-osmolar	NA	Scr<1.2mg/dl	NAC+hydration	0/25	hydration	2/20					No funding supported
LIPSIA[89]	2010	249	68	68	iopromide	low-osmolar	170	no dialysis	NAC+hydration	18/126	placebo+hydration	25/123					NA
Toso[90]	2010	304	64	76	iodixanol	iso-osmolar	158	CrCl<60ml/min	atorvastatin 80mg+hydration+NAC	15/152	NAC+hydration	16/152					NA
Farahani[91]	2010	72	79	62	iohexol	low-osmolar	118	Scr>1.5mg/dl	$NaHCO_3$+hydration	2/36	hydration	2/36					Non-industry
Zhang[92]	2010	149	70	64	iohexol or iodixanol	low- or iso-osmolar	186	no limited kidney function	BNP+hydration	12/74	placebo+hydration	24/75					Non-industry
ACT[93]	2010	2272	61	68	NA	low- or iso- or high-osmolar	100	Scr>1.5mg/dl	NAC+hydration	147/1153	placebo+hydration	142/1119					Non-industry
Kim[94]	2011	191	NA	NA	iodixanol	iso-osmolar	NA	NA	atorvastatin80mg+hydratio	5/92	hydration	4/99					NA

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PREVENT[95]	2011	375	71	68	iodixanol	iso-osmolar	117	Scr≥1.1mg/dl	NAC+hydration	10/187	$NaHCO_3$+NAC	17/188					Non-industry
Maioli[96]	2011	300	74	65	iodixanol	iso-osmolar	216	no dialysis	$NaHCO_3$	18/150	hydration	34/150					No funding supported
Motohiro[97]	2011	155	70	73	iopamidol	low-osmolar	135	eGFR<60ml/min	$NaHCO_3$+hydration	2/78	hydration	10/77					NA
ARMYDA[98]	2011	241	78	66	iobitridol	low-osmolar	211	Scr<3mg/dl	atorvastatin80mg+hydration	6/120	placebo+hydration	16/121					NA
Sadat[99]	2011	40	NA	72	iopamidol	low-osmolar	73	no dialysis	NAC+hydration	1/21	hydration	3/19					No funding supported
Tanaka[100]	2011	76	82	62	iopamidol	low-osmolar	211	no dialysis	NAC+hydration	2/38	hydration	5/38					NA
Ueda[101]	2011	59	78	76	iopamidol or iohexol	low-osmolar	110	Scr≥1.1mg/dl	$NaHCO_3$	1/30	hydration	8/29					NA
Aslanger[102]	2012	312	77	56	ioxaglate	low-osmolar	200	no dialysis	NAC+hydration	51/213	placebo+hydration	23/99					No funding supported
Bilasy[103]	2012	60	60	57	iopamidol	low-osmolar	117	no dialysis	theophylline+hydration+NAC	0/30	NAC+hydration	6/30					No funding supported
Cao[104]	2012	180	57	63	NA	NA	161	no dialysis	atorvastatin40mg+hydration	6/90	atorvastatin20mg+hydration	18/90					Non-industry
Gomes[105]	2012	301	72	64	ioxaglate	low-osmolar	125	Scr≥1.1mg/dl	$NaHCO_3$	9/150	hydration	9/151					No funding supported
Gunebakmaz[106]	2012	80	68	66	iopromide	low-osmolar	63	Scr≥1.2mg/dl	NAC+hydration	9/40	hydration	11/40					No funding supported
Hafiz[107]	2012	320	57	74	iodixanol or iopamidol or ioversol	low- or iso-osmolar	105	eGFR<50ml/min	hydration	11/80	NAC+hydration	8/81	$NaHCO_3$	6/79	$NaHCO_3$+NAC	8/80	No funding supported
Jaffery[108]	2012	398	61	65	iodixanol	iso-osmolar	167	no dialysis	NAC+hydration	33/206	placebo+hydration	25/192					No funding supported
Kitzler[109]	2012	30	57	75	iopromide	low-osmolar	NA	Scr>1.3mg/dl (male) Scr>1.1mg/dl (female)	NAC+hydration	0/10	vitamin E+hydration	0/10	placebo+hydration	0/10			Non-industry
Klima[110]	2012	258	64	77	NA	NA	100	Scr>1.3mg/dl (male) Scr>1.1mg/dl (female)	$NaHCO_3$	16/169	hydration	1/89					Non-industry
CASIS[111]	2012	220	78	64	iohexol	low-osmolar	127	Scr≥1.1mg/dl	NAC+hydration	2/80	hydration	19/140					NA
Li[112]	2012	161	76	66	iohexol	low-osmolar	102	normal kidney function	atorvastatin80mg+hydratio	2/78	placebo+hydration	13/83					NA

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Okumura[113]	2012	112	68	74	iohexol	low-osmolar	66	eGFR<60ml/min	carperitide+hydration	5/59	hydration	3/53					No funding supported
NAPLE II[114]	2012	410	54	70	iodixanol	iso-osmolar	181	no limited kidney function	atorvastatin80mg+hydration+NAC	7/202	$NaHCO_3$+NAC	12/208					Non-industry
Zhou[115]	2012	156	84	71	NA	NA	135	Scr≥1.1mg/dl	ascorbic acid+hydration	6/82	placebo+hydration	4/74					No funding supported
Albabtain[116]	2013	185	73	61	ioxaglate	low-osmolar	88	Scr≥1.3mg/dl	ascorbic acid+hydration	2/57	NAC+hydration	5/62	placebo+hydration	5/66			NA
Boucek[117]	2013	120	75	65	NA	low-osmolar	110	Scr≥1.1mg/dl	$NaHCO_3$	7/61	hydration	5/59					No funding supported
Brueck[118]	2013	483	64	75	iopromide	low-osmolar	112	Scr≥1.3mg/dl	ascorbic acid+hydration	24/98	NAC+hydration	53/192	placebo+hydration	62/193			No funding supported
Cicek[119]	2013	78	60	65	iohexol	low-osmolar	78	Scr<1.5mg/dl	ALA+hydration	3/39	hydration	3/39					No funding supported
Drorsak[120]	2013	81	73	71	iopamidol	low-osmolar	138	Scr≥1.2mg/dl	ascorbic acid+hydration	2/40	placebo+hydration	3/41					No funding supported
Ricardo[121]	2013	123	72	66	ioversol	low-osmolar	192	Scr≥1.2mg/dl	$NaHCO_3$	15/42	NAC+$NaHCO_3$	3/43	NAC+hydration	6/38			No funding supported
Hui[122]	2013	182	NA	NA	NA	NA	NA	NA	NAC+hydration	4/92	placebo+hydration	10/90					NA
ALIVE[123]	2013	202	50	72	iodixanol or iopromide or iobitridol	low- or iso-osmolar	170	CrCl≤60ml/min	ALA+hydration	3/100	hydration	7/102					Non-industry
Koc[124]	2013	195	52	62	NA	NA	90	Scr<3mg/dl	$NaHCO_3$	15/94	hydration	6/101					NA
Maaz[125]	2013	160	NA	NA	NA	NA	NA	NA	atorvastatin80mg+NAC+hydration	2/80	NAC+hydration	9/80					NA
Miao[126]	2013	330	77	79	iohexol	low-osmolar	NA	Scr<3mg/dl	alprostadil+hydration	14/154	placebo+hydration	39/176					Non-industry
Poletti[127]	2013	110	50	78	iohexol	low-osmolar	118	CrCl≤60ml/min	NAC+hydration	8/52	placebo+hydration	10/58					NA
Tasanarong[128]	2013	305	72	67	iopromide	low-osmolar	135	eGFR≤60ml/min	tocopherol+hydration	11/204	placebo+hydration	15/101					Non-industry
Stephen[129]	2013	357	41	61	iodixanol or iopamidol or ioversol	low- or iso-osmolar	123	Scr>1.4mg/dl	NAC+hydration	14/185	placebo+hydration	12/172					Non-industry

Erturk[130]	2014	307	64	66	iopromide	low-osmolar	126	eGFR<60ml/min	NAC+hydration	27/204	placebo+hydration	7/103					No funding supported
Han[131]	2014	2998	39	61	iodixanol	iso-osmolar	115	CKD stage 2-3 and DM	rosuvastatin10mg+hydration	34/1498	hydration	58/1500					NA
Antonto[132]	2014	500	61	59	ioxitalamate	high-osmolar	91	no limited kidney function	NAC+hydration	49/126	$NaHCO_3$+hydration	75/125	$NaHCO_3$+NAC	72/124	hydration	61/125	Non-industry
Kama[133]	2014	107	55	71	iohexol	low-osmolar	NA	no limited kidney function	NAC+hydration	7/36	$NaHCO_3$+hydration	4/36	hydration	5/35			No funding supported
PRATO-ACS[134]	2014	504	66	66	iodixanol	iso-osmolar	144	no dialysis	rosuvastatin20-40mg+hydration+NAC	17/252	NAC+hydration	38/252					Non-industry
Li[135]	2014	163	67	64	iohexol	low-osmolar	170	eGFR≥30ml/min	Prostaglandin E1+hydration	3/82	hydration	9/81					Non-industry
Manari[136]	2014	592	75	65	iodixanol	iso-osmolar	198	no dialysis	$NaHCO_3$	56/293	hydration	51/299					NA
PROMEC[137]	2014	231	55	60	iohexol	low-osmolar	100	Scr>1.2mg/dl	$NaHCO_3$	12/111	hydration	8/120					No funding supported
Thayssen[138]	2014	715	77	63	iodixanol	iso-osmolar	140	no dialysis	hydration	43/181	NAC+hydration	32/176	$NaHCO_3$+hydration	33/181	$NaHCO_3$+NAC	33/177	Non-industry
Yang[139]	2014	527	45	59	iohexol	low-osmolar	127	eGFR≥30ml/min	hydration	5/161	NAC+hydration	7/157	$NaHCO_3$	8/159	$NaHCO_3$+NAC	8/150	No funding supported
Fahmy[140]	2014	200	NA	NA	NA	NA	NA	NA	Rosuvastatin 20mg+hydration	15/100	placebo+hydration	38/100					NA
Yeganehkhah[141]	2014	78	78	59	iohexol	low-osmolar	44	Scr≤4mg/dl	NaHCO3+hydration	7/50	NAC+hydration	6/50	hydration	7/50			Non-industry
Abaci[142]	2015	208	71	68	ioversol	low-osmolar	129	eGFR 30-60ml/min	Rosuvastatin 40mg+hydration	6/103	hydration	9/105					No funding supported
Arabmomeni[143]	2015	62	43	62	iodixanol	low-osmolar	136	normal kidney function	theophylline+hydration	6/30	NAC+hydration	7/32					Non-industry
Bidram[144]	2015	200	91	60	iodixanol	iso-osmolar	35	eGFR≥60ml/min	atorvastatin 80mg+hydration	1/100	placebo+hydration	2/100					NA
CONTRAST[145]	2015	453	76	68	iohexol or iopamidol or ioversol or iopromide	low-osmolar	116	eGFR 15-60ml/min	NAC+hydration	10/153	NaHCO3	19/149	NAC+NaHCO3	16/151			No funding supported
Galal[146]	2015	80	64	56	NA	low-osmolar	241	eGFR 60-90ml/min	Atorvastatin80mg+hydration	5/40	Atorvastatin10mg+hydration	7/40					No funding supported

Jo[147]	2015	218	85	59	NA	NA	NA	no limited kidney function	Atorvastatin80mg+hydration	6/110	Atorvastatin10mg+hydration	11/108					Non-industry
Shehata[148]	2015	130	62	56	iopromide	low-osmolar	276	eGFR 30-90ml/min	atorvastatin 80mg+hydration+NAC	5/65	NAC+hydration	13/65					No funding supported
BOSS[149]	2015	391	58	72	NA	NA	107	eGFR<45ml/min	NaHCO3	26/195	hydration	18/196					Non-industry
Rezaei[150]	2016	298	69	67	iodixanol	low-osmolar	50	eGFR<60ml/min	Vitamin E+hydration	10/149	placebo+hydration	21/149					Non-industry

ALA, alpha-lipoic acid; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CI-AKI, contrast-induced acute kidney injury; Crcl, Creatinine clearance rate; eGFR, estimated glomerular filtration rate; NA, no available; NAC, *N*-acetylcysteine; $NaHCO_3$, bicarbonate sodium; Scr, Serum creatinine.

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Table S2. Meta-analytic results of traditional pairwise meta-analysis

Comparisons	N	n	τ^{2a}	I^2% (95%CI)	Q	OR (95%CI)[b] from traditional pairwise meta-analysis
Vitamins and its analogues *vs.* hydration	13	2149	0	0(0,58)	10.19	0.49(0.33,0.70)
Vitamins and its analogues *vs.* NAC	5	821	0	0(0,85)	2.58	0.80(0.17,2.29)
Vitamins and its analogues *vs.* bicarbonate sodium+NAC	1	215	NA	NA	NA	6.70(1.46,30.68)
Natriuretic peptide *vs.* hydration	4	762	0.5	68(6,89)	9.3	0.60(0.07,4.78)
NAC *vs.* theophylline	3	152	0.67	29(0,93)	2.83	1.05(0.003,252)
NAC *vs.* bicarbonate sodium	11	1959	0.26	53(8,76)	21.45	0.77(0.47,1.22)
NAC *vs.* hydration	70	12128	0.17	36(14,52)	104.68	0.74(0.62,0.88)
NAC *vs.* fenoldopam	2	276	0	0[c]	0.55	0.32(0.006,147.8)
NAC *vs.* bicarbonate sodium+NAC	12	2792	0.63	65(35,81)	31.53	1.19(0.61,2.14)
NAC *vs.* high-dose statin+NAC	6	1228	0.06	23(0,68)	5.21	2.57(0.94,4.87)
Prostaglandin *vs.* hydration	5	943	0	0(0,79)	1.87	0.35(0.17,0.65)
High-dose statin *vs.* low-dose statin	5	806	0	0(0,79)	2.21	0.69(0.08,0.78)
High-dose statin *vs.* hydration	7	1437	0.1	21(0,64)	7.59	0.38(0.18,0.71)
Low-dose statin *vs.* hydration	1	2998	NA	NA	NA	0.58(0.38,0.89)
Theophylline *vs.* bicarbonate sodium	1	280	NA	NA	NA	0.19(0.04,0.85)
Theophylline *vs.* hydration	9	739	0.39	32(0,69)	11.73	0.55(0.18,1.21)
Bicarbonate sodium *vs.* hydration	28	5561	0.66	60(40,74)	68.35	0.68(0.46,0.95)
Bicarbonate sodium *vs.* bicarbonate sodium+NAC	8	1598	0.13	25(0,66)	9.28	1.21(0.70,2.04)
Fenoldopam *vs.* hydration	2	328	0.32	55[c]	2.26	0.76(0.009,516.7)
Bicarbonate sodium+ NAC *vs.* hydration	6	1194	0.06	1(0,75)	5.07	1.21(0.70,2.04)
High-dose statin+NAC *vs.* bicarbonate sodium+NAC	1	410	NA	NA	NA	0.45(0.20,1.23)

Abbreviations: CI, confidence interval; N, number of trials; n, number of patients; NA, no available; NAC, *N*-acetylcysteine; OR, odds ratio, *vs.*, versus.

[a] τ^2 represents between-study heterogeneity characterized by standard deviation.

[b] the meta-regression based on empirical Bayes method was used to caculate ORs and 95CIs. ORs are lower than 1 favor the former treatment of every comparison.

Table S3. Evaluation of the model fit

Model assumption	*Dbar*	*Pd*	# of data points	*DIC*
Random consistency	338	232	322	**570**
Random inconsistency	343	236	322	579
Fixed consistency	629	156	322	785
Fixed inconsistency	502	168	322	630

For a binomial likelihood each trial arm contributes 1 independent **data point**.

Dbar is considered as an absolute measure of fit, and is used to check formally whether a model's fit is satisfactory. This is the posterior mean of the deviance under the current model minus the deviance for the saturated mode. We can then compare the value of *Dbar* to the number of independent data points to check if the model fit can be improved.

Leverage (P_D) is considered an appropriate measure of the complexity of a model that reasonably describes the data. P_D also is termed the effective number of parameters, and is calculated as the posterior mean of the residual deviance minus the deviance at the posterior mean of the fitted values.

Deviance Information Criterion (DIC) is the sum of the posterior mean of the residual deviance and the P_D , and provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model. The DIC is particularly useful for comparing different parameter models for the same likelihood and data, for example fixed and random effects models or fixed effect models with and without covariates. As shown in above table, the random consistency model is clearly more parsimonious than the other three models.

Table S4. **Results of sensitivity analyses**

Treatment strategies	Standard analysis	Excluding 13 trials with sample size less than 50	Excluding 18 trials with high-osmolar and unspecified CM type	Excluding 14 trials with oral hydration and unspecified hydration agent	Excluding 9 trials evaluated only patients with normal kidney function	Excluding data for non-DM patients	Excluding 24 trials published before 2004
High-dose statin+NAC	**0.31(0.14,0.60)**	**0.32(0.15,0.58)**	**0.32(0.14,0.64)**	**0.38(0.15,0.83)**	**0.32(0.14,0.66)**	0.24(0.07,1.27)	**0.33(0.16,0.60)**
High-dose statin	**0.37(0.19,0.64)**	**0.38(0.21,0.64)**	**0.39(0.21,0.68)**	**0.35(0.17,0.62)**	**0.42(0.20,0.72)**	0.47(0.11,1.33)	**0.38(0.21,0.62)**
Prostaglandin	**0.37(0.17,0.72)**	**0.37(0.17,0.68)**	**0.43(0.16,0.86)**	**0.40(0.17,0.74)**	**0.45(0.21,0.87)**	-	**0.42(0.16,0.88)**
Theophylline	**0.48(0.26,0.82)**	**0.46(0.24,0.82)**	**0.46(0.26,0.75)**	**0.55(0.29,0.93)**	**0.48(0.23,0.85)**	0.77(0.01,4.69)	0.60(0.27,1.14)
Bicarbonate sodium+NAC	**0.62(0.40,0.88)**	**0.57(0.38,0.80)**	**0.47(0.30,0.69)**	**0.54(0.36,0.77)**	**0.55(0.37,0.79)**	1.14(0.46,2.42)	**0.56(0.37,0.82)**
Vitamins and its analogues	**0.64(0.41,0.95)**	**0.64(0.42,0.96)**	**0.58(0.38,0.87)**	**0.63(0.41,0.95)**	**0.62(0.38,0.93)**	0.87(0.43,1.57)	0.75(0.48,1.13)
NAC	**0.67(0.54,0.81)**	**0.71(0.58,0.87)**	**0.64(0.52,0.77)**	**0.67(0.54,0.81)**	**0.66(0.54,0.81)**	0.81(0.54,1.14)	**0.73(0.59,0.88)**
Natriuretic peptide	0.69(0.31,1.37)	0.71(0.31,1.40)	0.70(0.32,1.34)	0.71(0.30,1.31)	0.71(0.31,1.35)	1.91(0.45,5.71)	0.62(0.27,1.30)
Fenoldopam	0.70(0.32,1.36)	1.69(0.68,3.44)	1.22(0.54,2.48)	1.26(0.57,2.44)	1.26(0.55,2.52)	0.95(0.41,1.85)	2.53(0.69,7.05)
Bicarbonate sodium	0.78(0.59,1.01)	0.79(0.60,1.00)	**0.66(0.49,0.84)**	**0.77(0.58,0.99)**	**0.78(0.59,1.01)**	1.31(0.67,2.38)	**0.78(0.59,0.99)**
Low-dose statin	0.98(0.41,2.07)	0.96(0.44,1.90)	0.89(0.39,1.72)	0.74(0.30,1.52)	1.04(0.41,2.11)	0.65(0.20,1.52)	0.95(0.42,1.85)
Hydration	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Heterogeneity	0.33(0.21,0.54)	0.35(0.19,0.56)	0.30(0.16,0.49)	0.34(0.19,0.55)	0.35(0.19,0.54)	0.15(0.00,0.71)	0.29(0.15,0.50)
DIC	570	521	500	522	541	142	480
Number of trials	150	137	132	125	141	38	126
Heterogeneity change		rise 6%	drop 9%	rise 3%	rise 6%	drop 55%	drop 12%

Data are odds ratio (95% CrI). All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, τ^2. Significant results are in bold. CM, contrast media; CrI, credible interval; DM, Diabetes mellitus; SUCRA, surface under the cumulative ranking curve measure; NAC, *N*-acetylcysteine;

Table S5. **Results of meta-regression and subgroup analyses**

Treatment strategies	Standard analysis	Mean CM dose	Baseline Scr concentration	Mean age years	CM type (iso-, low- or high-osmolar)	Isotonic (0.9%) or hypotonic (0.45%) saline hydration	Different CI-AKI definitions(48h ,72h or 120h)	Cardiovascular diagnostic/ interventional procedures or enhanced CT or not specified radiologic procedure with CM
High-dose statin+NAC	**0.31(0.14,0.60)**	**0.35(0.14,0.69)**	**0.29(0.13,0.55)**	**0.35(0.15,0.72)**	**0.33(0.14,0.65)**	**0.40(0.15,0.86)**	**0.33(0.14,0.66)**	**0.29(0.13,0.54)**
High-dose statin	**0.37(0.19,0.64)**	**0.36(0.15.0.76)**	**0.34(0.16,0.64)**	**0.35(0.17,0.68)**	**0.44(0.21,0.80)**	**0.39(0.17,0.75)**	**0.36(0.17,0.68)**	**0.33(0.17,0.58)**
Prostaglandin	**0.37(0.17,0.72)**	**0.40(0.14,0.89)**	**0.38(0.17,0.74)**	**0.37(0.17,0.76)**	**0.37(0.14,0.70)**	**0.43(0.19,0.82)**	**0.35(0.15,0.68)**	**0.47(0.20,0.92)**
Theophylline	**0.48(0.26,0.82)**	**0.46(0.24,0.84)**	**0.47(0.25,0.79)**	**0.52(0.28,0.90)**	**0.48(0.25,0.84)**	**0.59(0.31,0.99)**	**0.45(0.24,0.77)**	**0.46(0.25,0.77)**
Bicarbonate sodium+NAC	**0.62(0.40,0.88)**	**0.54(0.35,0.80)**	**0.51(0.33,0.73)**	**0.55(0.37,0.79)**	**0.52(0.34,0.75)**	**0.57(0.36,0.84)**	**0.45(0.29,0.69)**	**0.52(0.34,0.75)**
Vitamins and its analogues	**0.64(0.41,0.95)**	**0.62(0.39,0.97)**	**0.63(0.39,0.96)**	**0.57(0.32,0.90)**	0.88(0.41,1.67)	**0.66(0.43,0.97)**	0.70(0.45,1.03)	0.72(0.48,1.02)
NAC	**0.67(0.54,0.81)**	**0.66(0.52,0.81)**	**0.66(0.52,0.82)**	**0.67(0.54,0.83)**	**0.65(0.53,0.79)**	**0.70(0.56,0.89)**	**0.67(0.53,0.82)**	**0.64(0.51,0.77)**
Natriuretic peptide	0.69(0.31,1.37)	0.71(0.30,1.40)	0.71(0.31,1.35)	0.71(0.33,1.42)	0.70(0.30,1.45)	0.75(0.33,1.51)	0.91(0.33,1.88)	0.66(0.30,1.27)
Fenoldopam	0.70(0.32,1.36)	1.25(0.47,2.47)	1.25(0.54,2.47)	1.27(0.56,2.49)	1.25(0.53,2.39)	1.43(0.57,2.94)	1.21(0.52,2.35)	1.18(0.52,2.35)
Bicarbonate sodium	0.78(0.59,1.01)	0.78(0.59,1.02)	**0.77(0.58,0.99)**	0.78(0.60,1.01)	**0.67(0.49,0.88)**	0.79(0.59,1.04)	0.75(0.55,1.04)	**0.74(0.55,0.96)**
Low-dose statin	0.98(0.41,2.07)	0.92(0.33,2.10)	0.91(0.37,1.92)	0.94(0.32,2.18)	1.00(0.38,2.50)	0.79(0.31,1.65)	0.91(0.36,1.90)	0.83(0.34,1.68)
Hydration	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Heterogeneity	0.33(0.21,0.54)	0.38(0.21,0.60)	0.34(0.19,0.56)	0.33(0.19,0.54)	0.30(0.18,0.52)	0.33(0.20,0.55)	0.33(0.19,0.58)	0.33(0.20,0.55)
B coefficient		0.001(-0.008,0.007)	-0.27(-2.04,1.48)	-0.05(-0.17,0.07)	0.45(-0.21,1.18)	-0.21(-0.58,0.19)	0.09(-0.19,0.35)	0.09(-0.10,0.28)
DIC	570	502	534	530	519	517	501	571
Heterogeneity change		rise 15%	rise 3%	0%	drop 9%	0%	0%	0%

Data are odds ratio (95% CrI) after adjusting covariates: a. continuous variables include “Mean CM dose”, “Baseline scr concentration”, and “Mean age years”; b. categorical variables include “CM type (iso-, low- or high-osmolar)”, “Isotonic (0.9%) or hypotonic (0.45%) saline hydration”, “Different CI-AKI definitions (48h,72h or 120h)”, “Cardiovascular diagnostic/interventional procedures or enhanced CT or not specified radiologic procedure with CM”. All odds ratios use

hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, τ^2. Significant results are in bold. CM, contrast media CrI, credible interval; CT, computed tomography; Scr, Serum creatinine; NAC, *N*-acetylcysteine.

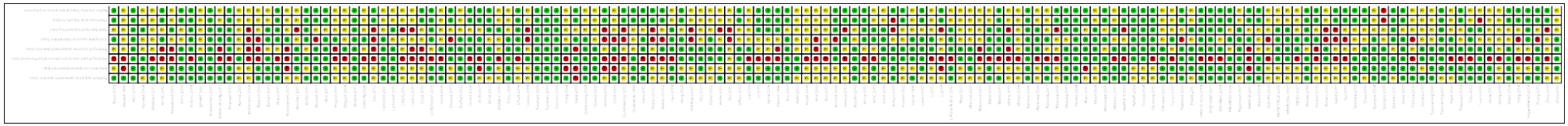

Figure S2

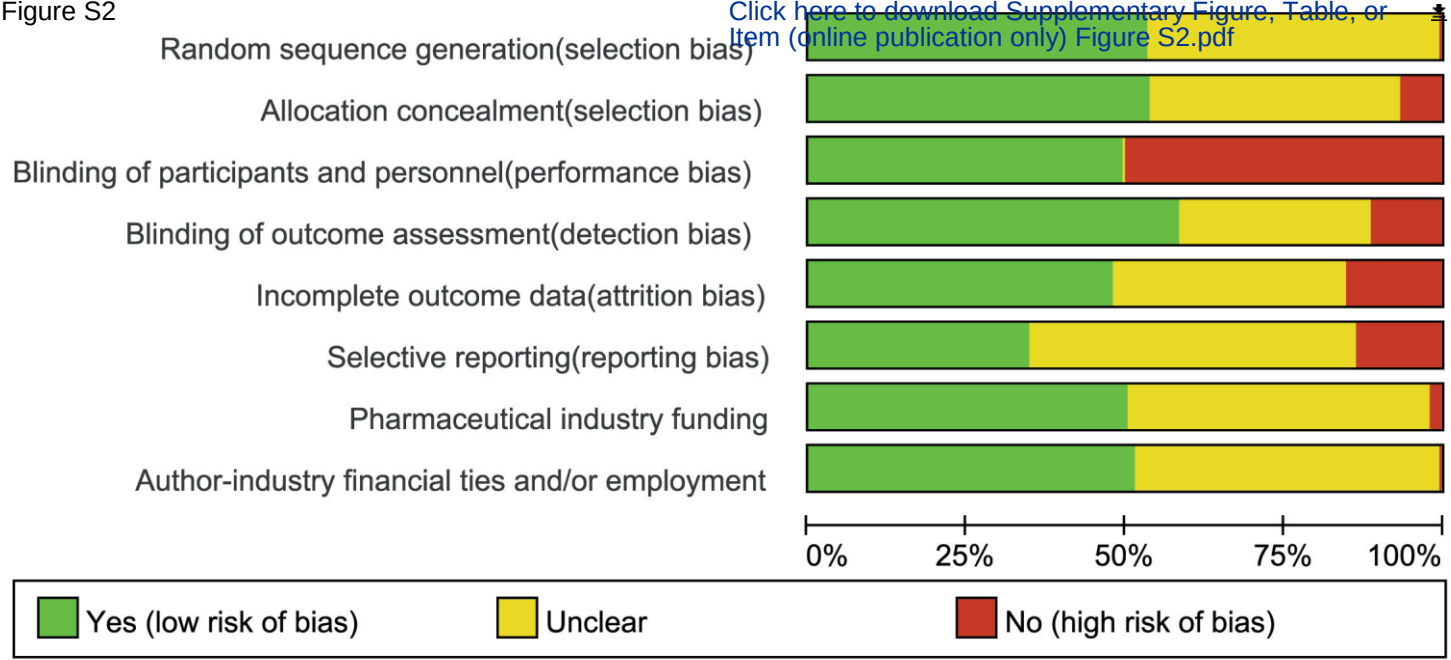

Figure S3

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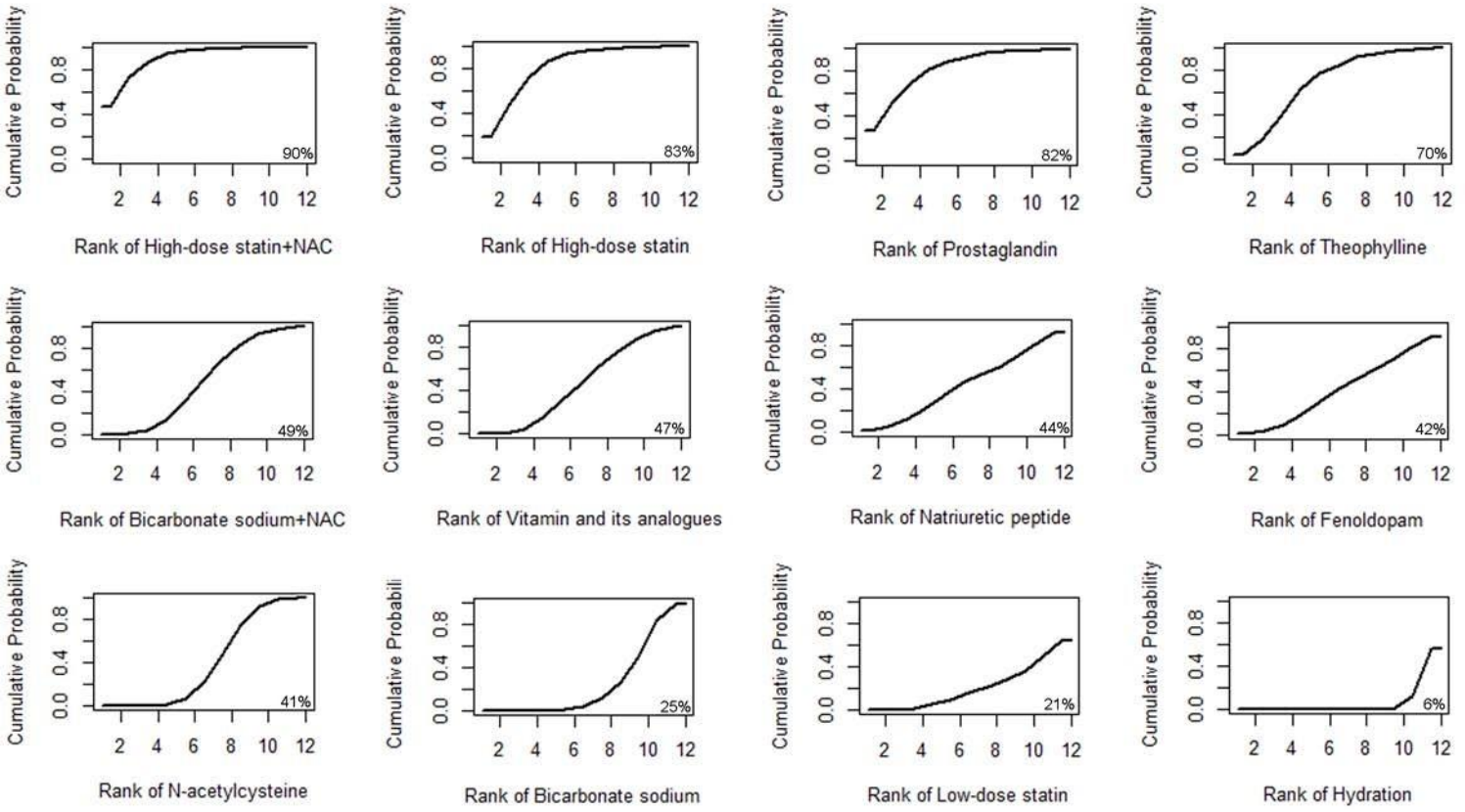
Cumulative SUCRA ranking curves



Non-cumulative ranking curves

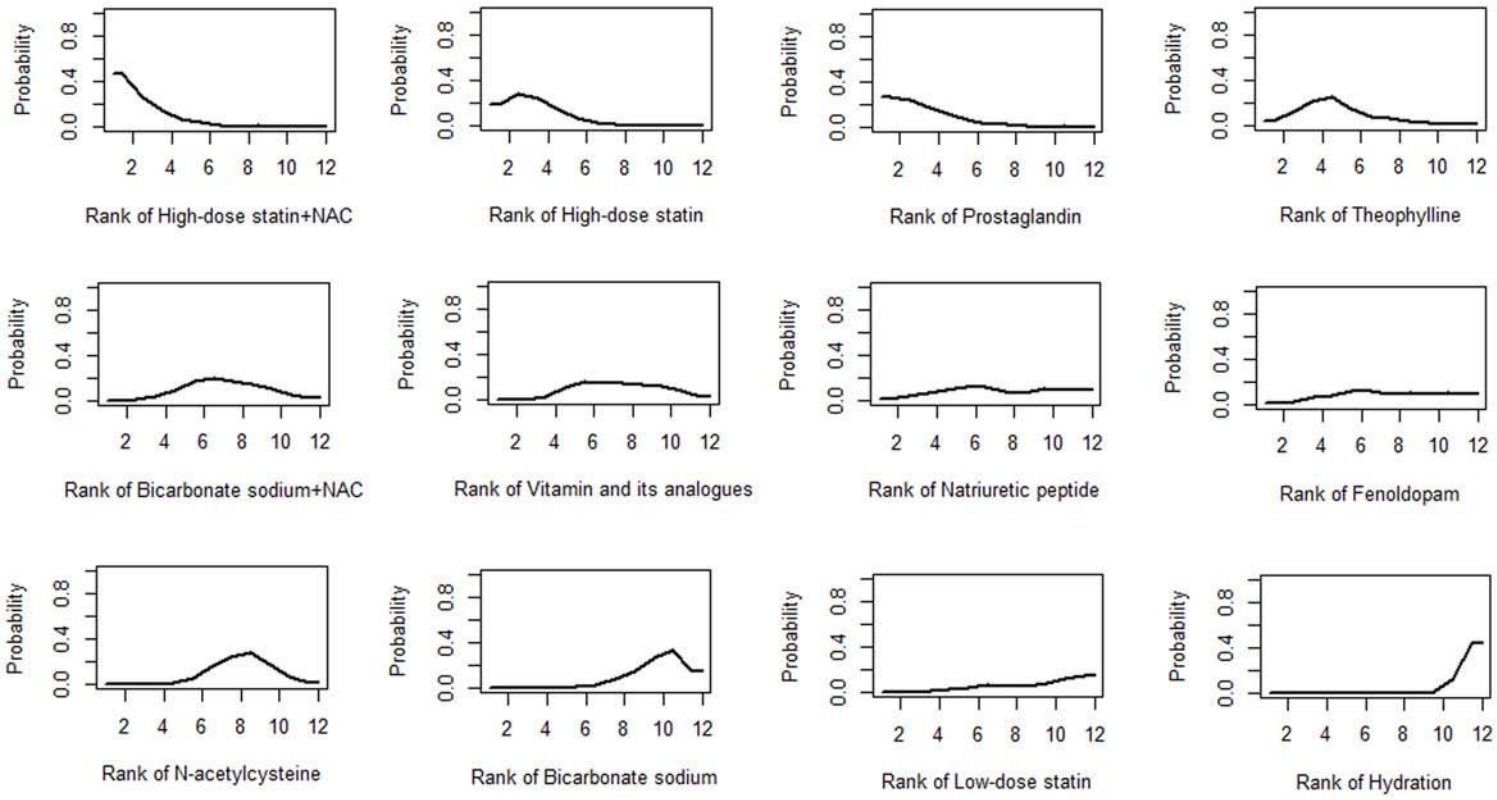


Figure S4

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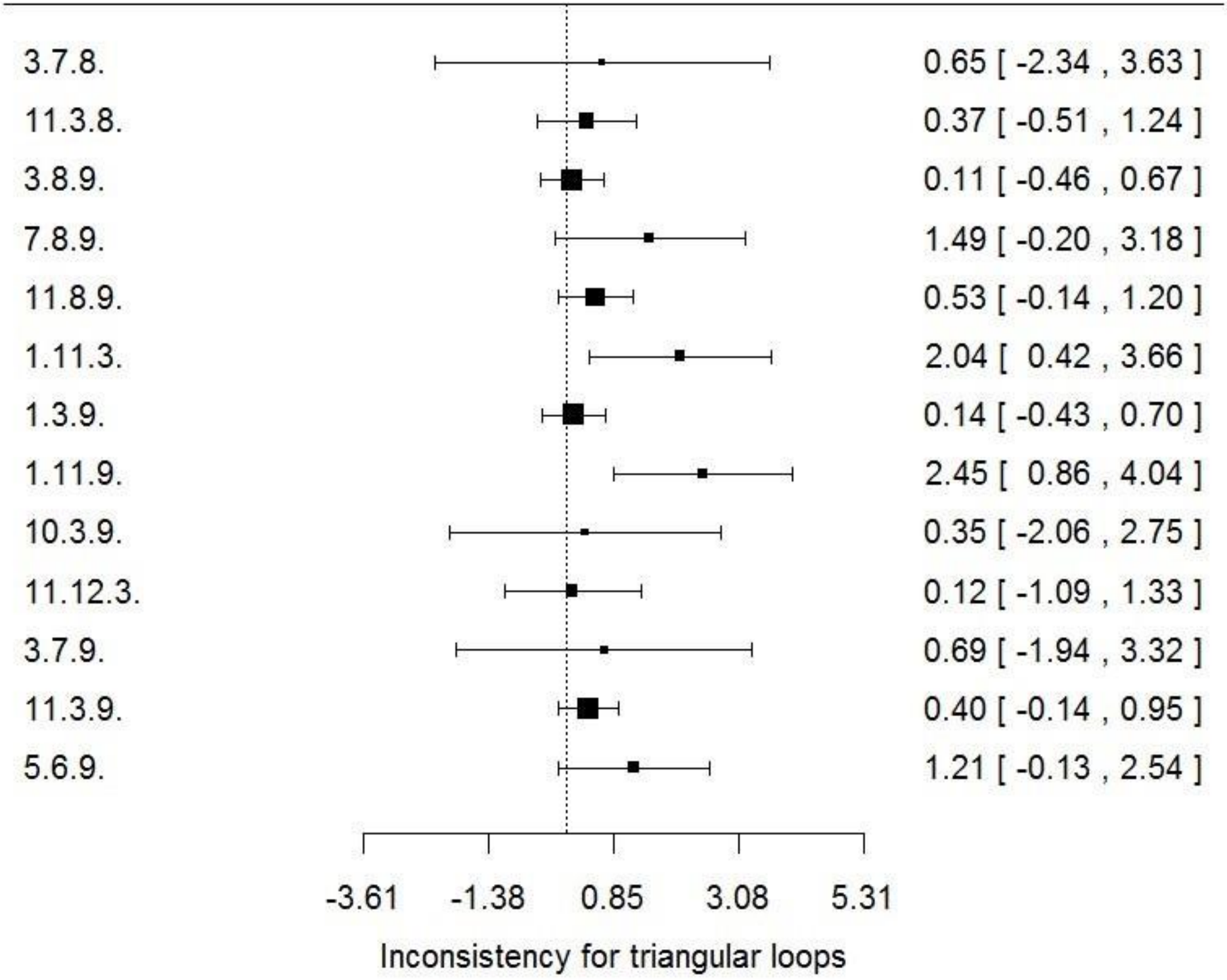

Item S1. Study protocol:

PROTOCOL

First drafted in October 2014
Modified in January 2015

Comparative Effectiveness of 12 Treatment Strategies in Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis

Xiaole Su, Xinfang Xie, Lijun Liu, Jicheng Lv, Fujian Song, Perkovic Vlado and Hong Zhang

Objectives:

Integrate the available evidence to compare various types of pharmacological strategies when used in patients undergoing diagnostic and/or interventional procedures with contrast media(CM) and create hierarchies of the comparative efficacy of active drug treatments on preventing contrast-induced acute kidney injury (CI-AKI).

Background

Acute injure in renal function induced by CM is generally mild and transient but can result in lasting renal dysfunction and the need for renal replacement therapy. CI-AKI is a leading cause of new onset kidney injury in hospitalized patients (1, 2). It is associated with significantly increased in-hospital morbidity and mortality, acceleration of chronic kidney disease, and increased costs of medical care (3). There have been a large number of pharmacological strategies to prevent CI-AKI so far, such as *N*-acetylcysteine (NAC), theophylline, fenoldopam, dopamine, iloprost, statins, bicarbonate sodium, ascorbic acid (vitamin C), vitamin E and. The question of which treatment strategies should be preferred for the prevention of CI-AKI is controversial, and traditional meta-analyses are hindered by heterogeneity across trials and the lack of trials direct comparing different treatment agents. We will undertake a network meta-analysis, which accounts for both direct and indirect comparisons to assess the efficacy of treatments on preventing CI-AKI.

Research Plan:

A) Methods of the Review

We will conduct a Bayesian-framework, multiple-treatments meta-analysis (which uses

both direct and indirect comparisons) of randomized controlled trials (RCTs) (4).

B) Data Sources:

Relevant RCTs will be identified by computerized searches from the following data sources without language restriction:

1) MEDLINE OVID SP (from 1947 through October 2014);
2) EMBASE (from 1966 through October 2014);
3) The Cochrane Central Register of Controlled Trials (no date restriction);
4) Reference lists in nephrology textbooks, review articles, and relevant trials were also searched.

C) Study Selection:

Types of Studies:

· Inclusion criteria:

We will include RCTs compared two or more of treatment groups received: NAC, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid, vitamin E, tocopherol, alpha-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, carperitide and hydration or placebo plus hydration. All above active drug treatments were based on hydration. All participants underwent diagnostic and/or interventional procedures with CM.

· Exclusion criteria:

Trials contained only one or none of the above strategies.

Types of Participants:

· Inclusion criteria:

Adult patients (age≥18 years) underwent diagnostic and/or interventional procedures with CM.

· Exclusion criteria: None

Type of Intervention:

· Treatment groups:

N-acetylcysteine, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid, vitamin E or its analogues (tocopherol), alpha-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, carperitide and hydration or placebo plus hydration;

· Compared two or more of the above mentioned treatment agents;

· All above active drug treatments were based on hydration.

Type of Outcome Measures*:*

· Primary Outcome

The occurrence of CI-AKI, defined as an absolute increase in baseline serum creatinine greater than 44.2 μmol/L (0.5 mg/dL) or a relative increase greater than 25% within typically 48-72 h after contrast injection. If 48-72 h data were not available, we used data within 5 days (the data point closest to 48-72 h was given preference).

· Secondary Outcome

None

D) Assess Study Quality:

We will use the Cochrane risk of bias method to appraise study quality on the seven domains (low, unclear, or high bias for sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) (5).

E) Statistical analysis

We will use Stata 12.0 to perform the traditional pairwise meta-analysis. Bayesian network meta-analysis will be done with WinBUGS version 1.4.3 and the R2WinBUGS package of R software 3.1.1. Clinical outcome analyses were compared by odds ratios (ORs) and 95% credible intervals (CrIs) using a Bayesian hierarchical random-effects model. Model fit will be assessed by comparing deviance information criterion (DIC). We will use the surface under the cumulative ranking (SUCRA) probabilities to rank the treatments (6). We will estimate the absolute difference between direct and indirect estimates in each closed loop. A significant (95% CrI that excludes 0) disagreement between direct and indirect evidence will indicate Inconsistent loops (7,8).

We will do multiple-treatments meta-regression with the following covariates: mean age, mean CM dose, and baseline serum creatinine concentration (7). Subgroup analyses will be performed by comparing with trials using with different CI-AKI definitions, and comparing with trials of cardiovascular diagnostic/interventional procedures and CT examination (7). Sensitivity analyses will be conducted by only including of trials of DM patients and by excluding of trials with small sample size and trails of high-osmolar CM used.

F) The Search Strategy:

1) MEDLINE OVID SP

1. exp Acute Kidney Injury/

2. exp renal failure/

3. (kidney disease* or renal disease* or renal failure or kidney failure or acute kidney or acute renal or nephrotoxic or nephropathy).mp.

4. (impair or injury or damage or reduce).mp. and (renal or kidney).mp.

5. 1 or 2 or 3 or 4

6. (contrast-induced or contrast-associated).mp.

7. (contrast or radiocontrast or iopamidol or iodine or ioxaglic acid or iodine compounds) .mp.

8. (iohexol or urography or tomography or X ray computed or diatrizoate).mp.

9. 6 or 7 or 8

10. randomized controlled trial .pt.

11. controlled clinical trial.pt.

12. randomized.ab.

13. placebo. ab.

14. clinical trials as topic.sh

15. randomly.ab.

16. trial.ti.

17. 10 or 11 or 12 or 13 or 14 or 15 or 16

18. animals.sh. not (humans.sh. and animals.sh.)

19. 17 not 18

20. 5 and 9 and 19

2) EMBASE

#1 ' Acute Kidney Injury'/exp

#2 ' renal failure'/exp

#3 ‘kidney disease$’ or ‘renal disease$’ or ‘renal failure’ or ‘kidney failure’ or ‘acute kidney’ or ‘acute renal’ or nephrotoxic or nephropathy

#4 (impair or injury or damage or reduce) and (renal or kidney)

#5 #1 OR #2 OR #3 OR #4

#6 ‘contrast-induced’ or ‘contrast-associated’

#7 contrast or radiocontrast or iopamidol or iodine or ‘ioxaglic acid’ or ‘iodine compound$’

#8 iohexol or urography or tomography or ‘X ray computed’ or diatrizoate

#9 #6 OR #7 OR #8

#10 random$ OR blind$ OR placebo OR 'meta analysis'

#11 #5 AND #9 AND #10

3) CENTRAL

#1 MeSH descriptor: [Acute Kidney Injury] explode all trees

#2 MeSH descriptor: [renal failure] explode all trees

#3 kidney disease* or renal disease* or renal failure or kidney failure or acute kidney or acute renal or nephrotoxic or nephropathy

#4 (impair or injury or damage or reduce) and (renal or kidney)

#5 #1 or #2 or #3 or #4

#6 contrast-induced or contrast-associated

#7 contrast or radiocontrast or iopamidol or iodine or ioxaglic acid or iodine compound*

#8 iohexol or urography or tomography or X ray computed or diatrizoate

#9 #6 or #7 or #8

#10 #5 and #9

4) Reference lists of nephrology textbooks, review articles, and relevant trials were also searched.

Reference

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983; 74(2): 243-8.

2. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA. 1996; 275(19): 1489-94.

3. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002; 105(19): 2259-64.

4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339: b2700.

5. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928.

6. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011; 64(2): 163-71.

7. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment report by the decision support unit. September 2011 (last updated April 2012). http://www.nicedsu.org.uk/TSD3%20 Heterogeneity.final%20report.08.05.12.pdf (accessed Feb 12, 2015).

8. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials report by the decision support unit. May 2011(last updated April 2014). http://www.nicedsu.org.uk/ TSD4%20Inconsistency.final.15April2014.pdf (accessed Feb 12, 2015).

Item S2. Assessment domains of risk of bias

We assessed risk of bias for sequence generation, allocation concealment, blinding, selective reporting, incomplete outcome data and other sources of bias, and determined overall risk of bias based on predefined rules, utilizing the Cochrane Collaboration risk of bias tool.[1]

Sequence generation (Selection bias)

• Low risk of bias, if randomization was generated by a computer, or a table of random numbers.

• High risk of bias, if method of randomization was inadequate (i.e. "quasi-randomized").

• Unclear risk of bias, if method of randomization was not described.

Allocation concealment (Selection bias)

• Low risk of bias, if the method of allocation involved a central independent unit or consecutively numbered sealed envelopes.

• High risk of bias, if allocation sequence was known to the investigators or conducted with an inadequate method.

• Unclear risk of bias, if the method of allocation concealment was not described.

Blinding of participants and personnel (Performance bias)

• Low risk of bias, if the study was of a double-blind design.

• High risk of bias, if the study was open-label.

• Unclear risk of bias, if there was insufficient information to determine whether the study was double-blind or open-label.

Blinding of outcome assessment (Detection bias)

• Low risk of bias, if the outcome assessment was blind.

• High risk of bias, if the outcome assessment was open.

• Unclear risk of bias, if there was insufficient information to determine whether the outcome assessment was blind or open.

Selective outcome reporting (Detection bias)

• Low risk of bias, if the specific outcome was reported adequately for all treatment arms.

• High risk of bias, if the specific outcome was reported with inadequate detail for the data to be included in a meta-analysis or if it was reported only for a subset of the randomized population.

• Unclear risk of bias, if there was insufficient information to assess whether the risk of bias of selective outcome reporting was present.

Incomplete outcome data (Attrition bias)

• Low risk of bias, if

1. attrition rate was balanced between treatment arms and relatively low (below 20%), and

2. reasons for discontinuation were described, and

3. an intention-to-treat analysis was performed, and

4. an appropriate method of imputation of missing outcome data was applied.

• High risk of bias, if

1. withdrawal rates were unbalanced between treatment arms or more than 20%, or

2. reasons for drop-outs were not clearly described, or

3. an inappropriate analysis was performed (i.e. per protocol analysis), or

4. an inappropriate imputation method (i.e. last observation carried forward method) was used to handle missing data.

• Unclear risk of bias, if it is not clear whether there were any drop-outs, or reasons for these withdrawals are not clear, or no method of imputation of missing data is mentioned.

Pharmaceutical industry funding (Sponsor bias)[2]

• Low risk of bias, if the trial was not funded by a drug manufacturer.

• High risk of bias, if the trial was funded by a drug manufacturer.

• Unclear risk of bias, if the source of funding was unclear.

Author-industry financial ties and/or employment (Other bias)[2]

• Low risk of bias, if any authors did not disclose financial ties and/or employment by the pharmaceutical industry.

• High risk of bias, if any authors disclose financial ties and/or employment by the pharmaceutical industry.

• Unclear risk of bias, if author-industry financial ties or affiliation were not reported.

Reference

1. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane Collaboration's tool for assessing risk of bias in randomised

trials. BMJ. 2011;343:d5928.

2. Roseman M, Milette K, Bero LA, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA*. 2011;305(10):1008-1017.

Item S3 Statistical method

(A short summary, see details http://www.mtm.uoi.gr. and http://www.nicedsu.org.uk.)

1. Bayesian approach and Credible intervals (CrI)

The Bayesian approach utilizes both sample data and prior knowledge in estimating validity and weights each in proportion to its information value. The sample information is combined with the prior distribution to produce a posterior distribution, the mean of which is then taken as the estimate of the parameter of interest, in this case, test validity. Confidence intervals—called credible intervals by Bayesians—can be placed around this mean[1].

Confidence intervals (*CI*) usually is used in conventional non-Bayesian statistical analysis to indicate the precision of an estimate (for example, estimate of effect size).

Credible intervals (*CrI*) in Bayesian statistics could be considered as analogous to confidence interval (CI) in non-Bayesian (or frequentist) statistical analysis, reflecting the precision of an estimate. A 95% credible interval can be interpreted as the following: there is 95% probability that the true treatment effect lies in a 95% credible interval.[2,3]

2. Model interpretation

Defining r_{ik} as the number of events (occurrence of CI-AKI), out of the total number of patients in each arm, n_{ik}, for arm k of trial i, we assume that the data generation process follows a Binomial likelihood i.e.

$$r_{ik} \sim Binomial(p_{ik}, n_{ik})$$

where p_{ik} represents the probability of an event in arm k of trial i (i=1,2…139; k=1,2,3,4). p_{ik} can only take values between 0 and 1. We model the probabilities of

events p_{ik} on the logit scale as

$$logit(p_{ik}) = \mu_i + \delta_{i,jk} I_{\{k \neq 1\}} \quad (1)$$

where

$I_{\{u\}}$=1 if u is true

$I_{\{u\}}$=0 otherwise

In this setup, μ_i are trial-specific baselines, representing the log-odds of the outcome in the 'control' treatment, $\delta_{i,jk}$ are the trial-specific log-odds ratios of events on the treatment group k compared to j.

Parameterization of the model:

The probabilities of event in the arms of a study p_{ik} can be parameterized in terms of the log-odds ratios *(OR)*. The underlying trial-specific effect are defined as $\theta_{i,jk}$; the *log(OR)* of treatment k relative to j in study i.

Random effects model:

For a random effects model the trial-specific log-odds ratios come from a common distribution:

$$\delta_{i,jk} \sim N(d_{jk}, \sigma^2)$$

where d_{jk} is the multiple-treatments meta-analysis estimate of the relative effect of treatment j relative to k and σ is the heterogeneity standard deviation assumed common across comparisons.

Fixed effect model:

For a fixed effect model we replace equation (1) with

$$logit(p_{ik}) = \mu_i + d_{ik} I_{\{k \neq 1\}}$$

which is equivalent to setting the between-trial heterogeneity σ^2 to zero thus assuming homogeneity of the underlying true treatment effects.

Consistency model:

Assuming consistency, the means of the random effects distribution are related. Selecting *T*-1 basic parameters μ_{Ak}, all means are related via $\mu_{jk}=\mu_{Ak}-\mu_{Aj}$.

Inconsistency model:

In a random effects inconsistency model, no association between the μ_{Ak}s are assumed, so the model is a series of independent comparison-specific meta-analyses which however share the same heterogeneity parameter σ^2.

In a fixed effects inconsistency model no shared variance parameter needs to be considered. The inconsistency model is then equivalent to performing completely separate pairwise meta-analysis of the data.

Meta-regression and subgroup model:

The model specification considered is to assume that all *treatment by covariate* interactions (for all treatments vs the common control comparator) are identical; that is, the same regression coefficient (β) is assumed regardless of treatment (excluding control) implying the same covariate effect for each treatment relative to control. A prior distribution is given for the common regression coefficient.

$$\delta_{jbk} \sim \begin{cases} \text{Normal}(d_{Ak}+\beta X_j, \sigma^2) \sim \text{Normal}(d_{Ak}-d_{AA}+\beta X_j, \sigma^2) & \text{if } b=A \\ \text{Normal}(d_{bk}, \sigma^2) \sim \text{Normal}(d_{Ak}-d_{Ab}, \sigma^2) & \text{if } b\neq A \end{cases}$$

$$r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk}) \quad \text{for trial } j, \text{ treatment } k$$

$$\text{logit}(p_{jk}) = \begin{cases} \mu_{jb} & b = A, B, C, \ldots. \quad \text{if } k = b \\ \mu_{jb} + \delta_{jkb} & \text{if } k \text{ alphabetically after } b \end{cases}$$

μ_{jb} is the log odds of an event in trial j on 'baseline' treatment b, δ_{jbk} is the trial-specific log odds ratio of treatment k relative to treatment b in trial j. The pooled log odds ratios, d_{bk}, are identified by expressing them in terms of the reference treatment A, $d_{Ak} - d_{Ab}$, where d_{AA} is set equal to zero. The between-study variance σ^2 is assumed constant for all treatment comparisons.[4]

SUCRA

The treatments can be ranked according to their effectiveness. The order of treatment in every MCMC circle is calculated as

$$order_k = \sum_{j=1}^{nt} I(d_j \leq d_k)$$

where $I(d_j \leq d_k)$=1 if $d_j \leq d_k$ and 0 otherwise. The probability of treatment k to be at the j order is estimated from the quantity $effectiveness_{k,j}$ and the cumulative probabilities by $cum.effectiveness_{k,j}$. Then the surface under the cumulative ranking curve (*SUCRA*) for the treatment is

$$SUCRA_k = \frac{\sum_{j=1}^{nt-1} cum.effectiveness_{k,j}}{nt - 1}$$

3. Model fit

We checked whether a model's fit is satisfactory using the deviance information criterion (*DIC*). *DIC* is the sum of *Dbar* (the posterior mean residual deviance) and the leverage, *Pd* (also termed the effective number of parameters). The model fits the data

adequately when *Dbar* is approximative with the number of data points. *Pd* provides a measure of model complexity. Then the *DIC* means a measure of model fit that penalizes model complexity – lower values of the *DIC* suggest a more parsimonious model.

In order to assess whether the model provided adequate fit, we calculated *DIC*s of four models, including random consistency, random inconsistency, fixed consistency, fixed inconsistency model within a Bayesian framework using the WinBUGS and R software.

4. Assessment of inconsistency

A "direct" estimate of the C vs. B effect, $\hat{d}_{BC}^{dir}$, is to be compared to an "indirect" estimate, $\hat{d}_{BC}^{ind}$, formed from the AB and AC direct evidence

$$\hat{d}_{BC}^{ind} = \hat{d}_{AC}^{dir} - \hat{d}_{AB}^{dir}$$

$$Var(\hat{d}_{BC}^{ind}) = Var(\hat{d}_{AC}^{dir}) + Var(\hat{d}_{AB}^{dir})$$

We assume that the direct estimates can either be estimates from individual trials. An estimate of the inconsistency, ω, can be formed by simply subtracting the direct and indirect estimates:

$$\hat{\omega}_{BC} = \hat{d}_{BC}^{dir} - \hat{d}_{BC}^{ind}$$

$$Var(\hat{\omega}_{BC}) = Var(\hat{d}_{BC}^{dir}) + Var(\hat{d}_{BC}^{ind}) = Var(\hat{d}_{BC}^{dir}) + Var(\hat{d}_{AB}^{dir}) + Var(\hat{d}_{AC}^{dir})$$

An approximate test of the null hypothesis that there is no inconsistency can be obtained by referring $Z_{BC} = \frac{\hat{\omega}_{BC}}{\sqrt{Var(\hat{\omega}_{BC})}}$ to the standard normal distribution. the method can only be applied to 3 independent sources of data. Obviously, the method can only be applied to 3 independent sources of data. This idea can be extended to all loops formed in the

network and plot the ω together with its 95% confidence interval. In the presence of consistency within a loop all intervals should be compatible with zero.

Another way to infer about consistency in the network as a whole is to compare the DICs between the consistency and inconsistency model. If the DIC assuming inconsistency is lower than the DIC assuming consistency by three or more units, then the assumption of consistency is likely to be violated.

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