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Preventive Strategies for Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Procedures

Evidence From a Hierarchical Bayesian Network Meta-Analysis of 124 Trials and 28 240 Patients

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Background—The effectiveness of currently available effective preventive strategies for contrast-induced acute kidney injury (CIAKI) is a matter of debate.

Methods and Results—We performed a Bayesian random-effects network meta-analysis of 124 trials (28 240 patients) comparing a total of 10 strategies: saline, statin, N-acetylcysteine (NAC), sodium bicarbonate ($NaHCO_3$), NAC+$NaHCO_3$, ascorbic acid, xanthine, dopaminergic agent, peripheral ischemic preconditioning, and natriuretic peptide. Compared with saline, the risk of CIAKI was reduced by using statin (odds ratio [OR], 0.42; 95% credible interval [CrI], 0.26–0.67), xanthine (OR, 0.32; 95% CrI, 0.17–0.57), ischemic preconditioning (OR, 0.48; 95% CrI, 0.26–0.87), NAC+$NaHCO_3$ (OR, 0.50; 95% CrI, 0.33–0.76), NAC (OR, 0.68; 95% CrI, 0.55–0.84), and $NaHCO_3$ (OR, 0.66; 95% CrI, 0.47–0.90). The benefit of statin therapy was consistent across multiple sensitivity analyses, whereas the efficacy of all the other strategies was questioned by restricting the analysis to high-quality trials. Overall, high heterogeneity was observed for comparisons involving xanthine and ischemic preconditioning, although the impact of NAC and xanthine was probably influenced by publication bias/small-study effect. Hydration alone was the least effective preventive strategy for CIAKI. Meta-regressions did not reveal significant associations with baseline creatinine and contrast volume. In patients with diabetes mellitus, no strategy was found to reduce the incidence of CIAKI.

Conclusions—In patients undergoing percutaneous coronary procedures, statin administration is associated with a marked and consistent reduction in the risk of CIAKI compared with saline. Although xanthine, NAC, $NaHCO_3$, NAC+$NaHCO_3$, ischemic preconditioning, and natriuretic peptide may have nephroprotective effects, these results were not consistent across multiple sensitivity analyses. **(*Circ Cardiovasc Interv*. 2017;10:e004383. DOI: 10.1161/CIRCINTERVENTIONS.116.004383.)**

Key Words: acetylcysteine ■ acute kidney injury ■ chronic kidney disease ■ contrast media ■ creatinine ■ meta-analysis ■ percutaneous coronary intervention

Over the past 25 years, the number of percutaneous procedures requiring contrast media administration has increased exponentially.[1] Contrast-induced acute kidney injury (CIAKI) is not an infrequent complication of coronary angiography and percutaneous coronary intervention and has been associated with increased mortality and cardiovascular events.[2,3]

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The optimal CIAKI prevention strategy for patients with suspected or confirmed coronary artery disease undergoing percutaneous coronary procedures is unknown. A wide array of medications and hydration regimens have been investigated in recent years.[4–6] Indeed, the large variety of available

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WHAT IS KNOWN

- CIAKI is a relatively common complication of percutaneous coronary procedures, which has been associated with increased mortality and cardiovascular events.
- True effectiveness of several preventive strategies for CIAKI continues to be matter of debate as consequence of the extreme heterogeneity of available evidence.

WHAT THE STUDY ADDS

- This Bayesian network meta-analysis of 124 randomized clinical trials and 28 240 patients simultaneously compares the 10 most representative CIAKI preventive strategies tested in the past 25 years.
- When compared with saline hydration alone, periprocedural administration of a statin was associated with a significant CIAKI risk reduction with consistent results across multiple analyses, whereas the notable benefit of xanthine seemed to be significantly influenced by between-trial heterogeneity and disappeared after pooling only of patients with moderate-to-severe chronic kidney disease and trials with highest quality.
- NAC, $NaHCO_3$, NAC+$NaHCO_3$, and ischemic preconditioning reduced the risk of CIAKI when compared with saline hydration alone, but results were highly inconsistent across sensitivity analyses; hydration with saline was found to be the least effective strategy without significant variations after pooling only of trials ensuring an intense and prolonged infusion.

comparative trials provided extremely contradictory conclusions that has made it difficult to ascertain the best strategy for CIAKI prevention in clinical practice. Moreover, differences in the baseline clinical and procedural characteristics that are responsible for the interindividual susceptibility to CIAKI (ie, chronic kidney disease, diabetes mellitus, and contrast media volume) have significantly confounded the results of these studies.[7,8]

Network meta-analyses are extensions of standard pairwise meta-analyses that allow for simultaneous pooling of data related to multiple interventions, combination of direct and indirect components of the evidence in a single estimate, and comparison of treatments without a direct connection on the basis of indirect information.[9,10] We performed a comprehensive network meta-analysis of randomized clinical trials comparing preventative strategies for CIAKI in patients with suspected or confirmed coronary artery disease undergoing contrast media administration in the setting of a percutaneous coronary procedure.

Methods

This study was conducted in keeping with the PRISMA consensus (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols)[11] (PRISMA checklist, Appendix in the Data Supplement), the PRISMA extension statement for network meta-analyses,[12] and the Cochrane Collaboration recommendations.[13]

Search Strategy and Selection Criteria

PubMed, Embase, Scopus, Cochrane Library, and Web of Knowledge databases were searched for randomized clinical trials investigating the effects of preventive strategies for CIAKI, from the date of database inception to November 15, 2016. Additional specifications are reported in the Methods in the Data Supplement.

Inclusion and Exclusion Criteria

Studies were considered for inclusion only if they were randomized controlled trials of patients undergoing percutaneous coronary procedures (ie, coronary angiography with or without intervention) comparing ≥2 preventive strategies for CIAKI. Conference proceedings, unpublished reports, and trials with unclear treatments posology and CIAKI definition were excluded. Screening and data extraction are reported in the Methods in the Data Supplement.

End Points

The end point of interest was CIAKI, defined according to the most common definition as a relative ≥25% or an absolute ≥0.5 mg/dL serum creatinine increase within 48 to 72 hours from the procedure.[3,7] In some studies, CIAKI was defined as either a relative ≥25% or an absolute ≥0.5 mg/dL serum creatinine increase from baseline to 48 to 72 hours from the procedure. Some studies used definitions with time ≤1 week from the procedure. The rare studies (n=6) using only an AKIN (Acute Kidney Injury Network)/RIFLE-derived (Risk, Injury, Failure, Loss of Function, End Stage Renal Disease) definition of CIAKI were retained only in the main analysis. Trials using CIAKI definitions other than those listed above, mostly including definitions based on alternative biomarkers (ie, cystatin C, neutrophil gelatinase–associated lipocalin, urine creatinine, etc), were excluded.

Statistical Analyses

We performed a hierarchical Bayesian network meta-analysis using random-effects consistency models and noninformative priors.[14–16] After arm-level data imputation, the models were computed by Markov chain Monte Carlo simulations using 3 chains with overdispersed initial values, and Gibbs sampling was based on 100 000 iterations following discard of 50 000 (burn-in). Convergence was appraised according to Brooks and Gelman.[17] Posterior inference was summarized as odds ratio (OR) and 95% credible interval (CrI). Treatments were ranked to define the probability associated to each one to be the best strategy.[18] Inconsistency was assessed by comparing the deviance information criterion of consistency and inconsistency models and by contrasting direct and indirect evidence from the network (node-split).[15] Direct estimations represent the summary effects of Bayesian meta-analyses of trials comparing 2 strategies. Heterogeneity was graded based on I^2 statistics with values <25%, 25% to 50%, and >50%, representing mild, moderate, and severe heterogeneity, respectively.[19] All analyses were performed using R (version 3.1.1), WinBUGS (version 1.4), and STATA (version 12.1).

Sensitivity Analyses

Several sensitivity analyses according to different CIAKI definitions, moderate-to-advanced chronic kidney disease, diabetes mellitus, methodological characteristics of included trials (sample size, global qualitative assessment, blinding, and independent event adjudication), imputation of patients lost at follow-up, trial design, and treatment posology were run to investigate the robustness of the results and explore potential sources of inconsistency. Two network sensitivity analyses were also performed: (1) detachment of complex nodes of the primary network to the individual components and (2) selection of a network including only consistent comparisons and nodes with acceptable balance. The full methodology relevant to all these sensitivity analyses is more extensively described in the Methods in the Data Supplement.

Meta-Regression

The results of the main analysis were adjusted for baseline creatinine and contrast volume (see the Methods in the Data Supplement for further details).

Qualitative Assessment

Qualitative trial assessment was performed according to the 7-domain tool of the Cochrane Collaboration, whereas publication bias/small-study effect was inspected by comparison-adjusted funnel plot.[13] A description of qualitative assessment and comparison-adjusted funnel plot is provided in the Methods in the Data Supplement.

Results

Figure 1 illustrates the selection process and the geometry of the network. A total of 124 trials (n=28 240 patients) investigating 10 different preventive strategies (saline, statin, N-acetylcysteine [NAC], sodium bicarbonate [$NaHCO_3$], NAC+$NaHCO_3$, ascorbic acid, xanthine, dopaminergic agent, peripheral ischemic preconditioning, and natriuretic peptide) were finally selected (Figure I in the Data Supplement; Methods in the Data Supplement). References of the included trials and key trial–level methodological and clinical characteristics are reported in the Appendix in the Data Supplement (Trials List, Tables I and II in the Data Supplement). In about 95% of trials, CIAKI was reported according to the main definition or its 2 variants, although a 48 to 72 hours adjudication time was available in about 80%. Trial-level baseline creatinine and contrast volume values were significantly variable across trials.

Network Meta-Analysis

The incidence of CIAKI ranged from about 4% to 24% across strategies. Forest plots and rankograms of the network meta-analysis are illustrated in Figure 2. Compared with saline, the risk of CIAKI was reduced by statin (OR, 0.42; 95% CrI, 0.26–0.67), xanthine (OR, 0.32; 95% CrI, 0.17–0.57), ischemic preconditioning (OR, 0.48; 95% CrI, 0.26–0.87), NAC (OR, 0.68; 95% CrI, 0.55–0.84), $NaHCO_3$ (OR, 0.66; 95% CrI, 0.47–0.90), and NAC+$NaHCO_3$ (OR, 0.50; 95% CrI, 0.33–0.76). When comparing these strategies head to head, statin reduced the risk of CIAKI by 49% compared with NAC, whereas xanthine reduced the risk of CIAKI by 53%, 52%, 56%, and 59% compared with NAC, $NaHCO_3$, ascorbic acid, and dopaminergic agent, respectively (Figure 2). At treatments ranking, xanthine and statin emerged as the best strategies, whereas dopaminergic agent and saline were the worst.

Inconsistency Analysis, Node-Split, and Heterogeneity

The deviance information criterion was lower in the consistency model but to a small extent. Sources of inconsistency in specific segments of the network were inspected by node-split (Figure II in the Data Supplement). A significant inconsistency was detected only for the comparisons of NAC+$NaHCO_3$ versus saline (P=0.017) and xanthine versus NAC (P=0.039). Heterogeneity was extremely variable across comparisons, ranging from mild-to-extreme degree (Figure II in the Data Supplement). The comparison of statin versus saline presented a mild degree of heterogeneity (I^2=23.4%), whereas the comparison of xanthine versus saline showed a high degree of heterogeneity (I^2=66.0%). The comparisons of preconditioning versus saline and preconditioning versus NAC showed extreme heterogeneity.

Sensitivity Analyses

Figure 3 and Tables III through VI in the Data Supplement show the risk distribution of different strategies using saline

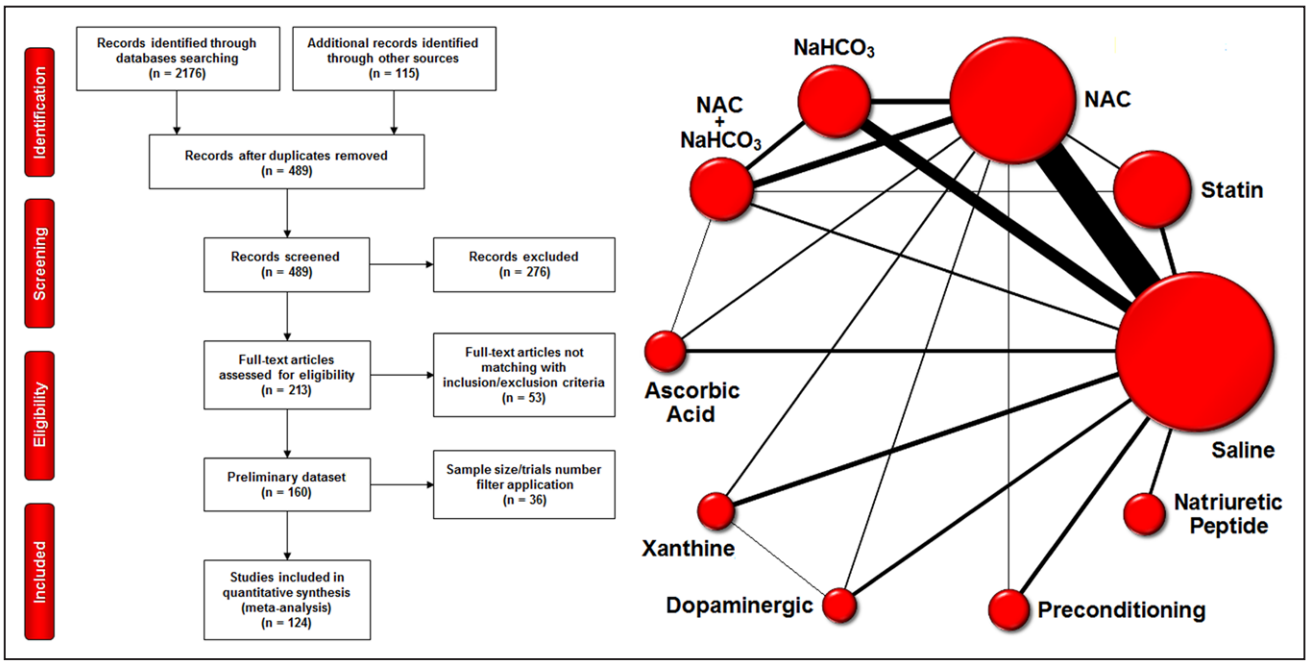

Figure 1. Flow diagram and network geometry**. Left**, The flow diagram describes the trials screening process. **Right**, Network of contrast-induced acute kidney injury preventive strategies. The node size is proportional to the number of patients included, and solid black lines define direct comparisons among strategies with thickness proportional to the number of trials involved. NAC indicates N-acetylcysteine; and $NaHCO_3$, sodium bicarbonate.

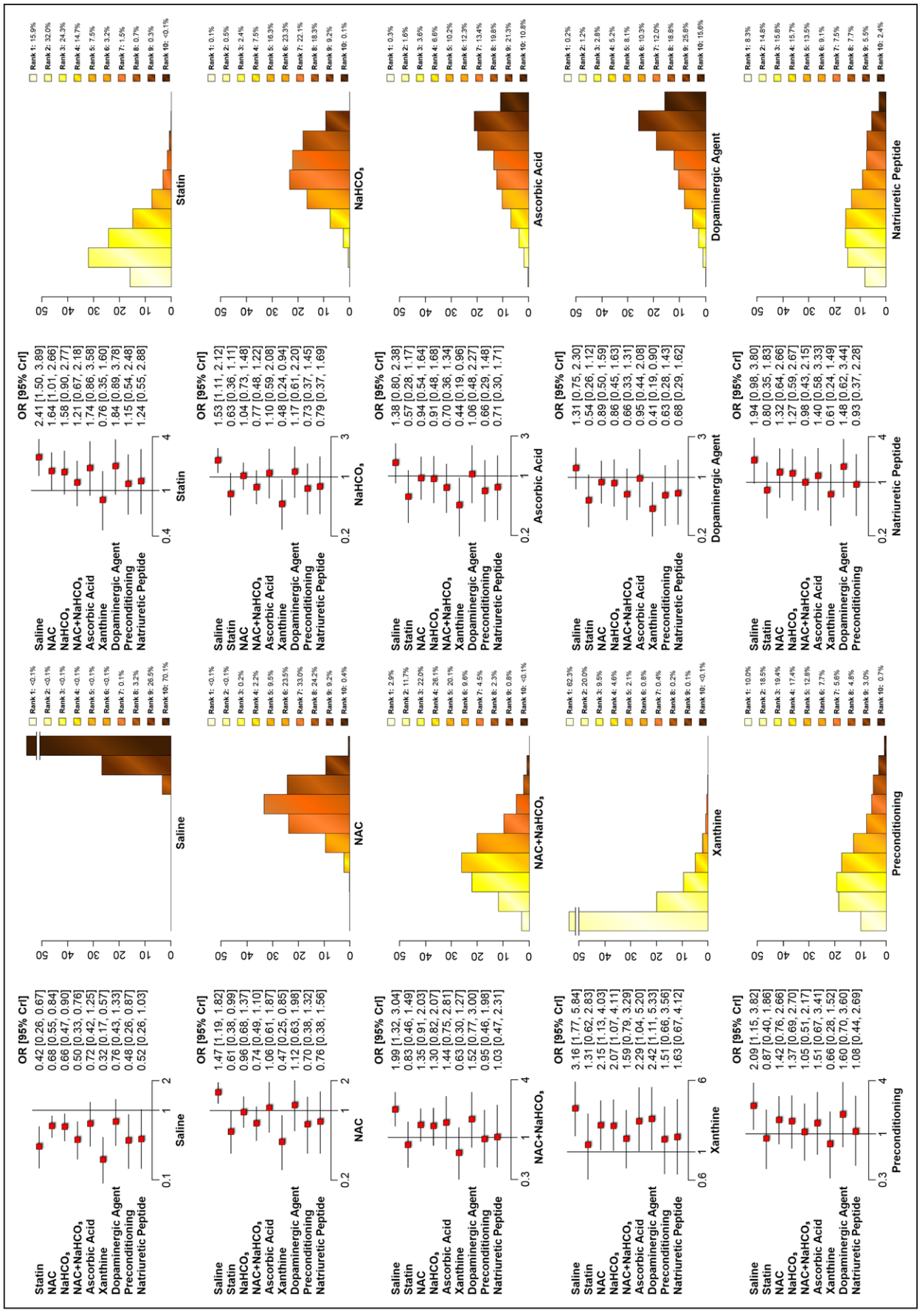

Figure 2. Continued

Figure 2 Continued. Main analysis**. Left**, The forest plots illustrate the risk distribution across the included strategy referred to a different common reference at a time. **Right**, Treatments are ranked according to the relative probability to be the first, the second, the third, etc., most effective. CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

as the common reference after stratification by type of CIAKI definition. In trials reporting CIAKI events using both relative (≥25%) and absolute (≥0.5 mg/dL) serum creatinine criteria and trials using only relative criteria, the benefit of xanthine was no longer observable. Many strategies, including statin, xanthine, NAC, $NaHCO_3$, and NAC+$NaHCO_3$, were not sensitive to the different definitions.

Figure 4 and Tables VII and VIII in the Data Supplement show the risk distribution of different strategies using saline as common reference in analyses restricted to patients with moderate-to-severe chronic kidney disease or diabetes mellitus. In patients with estimated glomerular filtration rate ≤60 mL/min per 1.73 m^2 (or, when not available, estimated creatinine clearance ≤60 mL/min) or serum creatinine ≥1.5 mg/dL, statin, NAC, and ischemic preconditioning were associated with a risk reduction. In patients with diabetes mellitus, none of the strategies were found to reduce the risk of CIAKI compared with saline.

Figure 5 and Tables IX through XII in the Data Supplement show the risk distribution according to study quality assessment. After exclusion of smaller trials, the benefit of NAC, $NaHCO_3$, and NAC+$NaHCO_3$ over saline was reduced but persisting, whereas the superiority of statin and xanthine remained unchanged. By contrast, in analysis restricted to higher-quality trials, the effect associated with xanthine compared with saline was comparable, whereas statin and NAC continued to reduce the risk of CIAKI. Although in this analysis ischemic preconditioning and natriuretic peptide were associated with a notable risk reduction, they were supported by few trials, and high heterogeneity was noticed for ischemic preconditioning. Xanthine was no longer beneficial in trials with patient blinding or independent event adjudication. Only the risk reduction associated with statin and ischemic preconditioning compared with saline resulted unchanged or enhanced after pooling of trials with independent event adjudication, and NAC, $NaHCO_3$, and NAC+$NaHCO_3$ showed similar efficacy compared with saline. No trials investigating natriuretic peptide effectiveness were available for this analysis. The results remained consistent after imputation of the number of patients lost to follow-up and exclusion of the 3- or 4-arm trials which theoretically could have lost the benefit of randomization after removal of 1 arm testing a treatment that was not of interest (6.5%) or combination of 2 arms investigating the same treatment with different posology (4.0%; Figure III in the Data Supplement; Table XIII in the Data Supplement). Pooling only trials with a more generous and prolonged periprocedural 0.9% saline hydration regime and a intermediate-to-intense posology for each strategy (Figure 6; Table XIV in the Data Supplement) showed that statin and xanthine were the only 2 strategies associated with a marked CIAKI risk reduction compared with saline. However, whereas no heterogeneity was detected for statin versus saline, the comparison of xanthine versus saline showed high heterogeneity (I^2=76.3%).

Overall, the heterogeneity across these analyses showed a distribution generally similar to that of the main analysis (Table III in the Data Supplement). Although comparisons involving preconditioning showed extreme I^2 values and the xanthine versus saline comparison showed moderate-to-high heterogeneity, only a mild-to-moderate degree of heterogeneity was detected for statin versus saline.

After detaching complex nodes of the primary network (Figure IV in the Data Supplement), statin—both alone and combined with NAC and $NaHCO_3$—consistently reduced the risk of CIAKI compared with saline. Among xanthines, only theophylline—alone and in combination with NAC—was associated with a risk reduction. However, comparisons involving theophylline+NAC were inconsistent (Figure IV in the Data Supplement). Excluding nodes affected by significant *P* values at node-split and applying a minimum number of studies per node/sample size filter, the risk of CIAKI was reduced only in patients receiving statin, NAC, and $NaHCO_3$ (Figure V in the Data Supplement; Table XV in the Data Supplement).

Meta-Regressions

Bayesian network meta-regressions using weighted trial–level mean values of baseline creatinine (mg/dL) and contrast volume (mL) did not reveal significant changes for all the strategies other than ischemic preconditioning which resulted more effective than saline (Figure VI in the Data Supplement).

Qualitative Assessment

Bias assessment is schematically illustrated in Figures VII and VIII in the Data Supplement. Approximately 50% of trials did not ensure any blinding, and approximately 55% did not properly describe the process of random sequence generation. In addition, significant concerns arose from the high proportion of trials with unclear performance of allocation concealment (about 60%–65%) and blinded events adjudication (about 80%). Although the comparison-adjusted funnel plot did not display an asymmetrical distribution of the estimates for most strategies (Figure IX in the Data Supplement), a moderate asymmetry favoring treatment efficacy compared with control and a possible small-study effect was observed for NAC and xanthine.

Discussion

The main findings of this network meta-analysis can be summarized as follows. First, treatment with statin, xanthine, and—to a lesser extent—NAC, $NaHCO_3$, and NAC+$NaHCO_3$ is associated with a significant reduction in the risk of CIAKI compared with saline. Second, in contrast to xanthine, the benefit of statin was robust and consistent in multiple sensitivity analyses. Third, diabetes mellitus may offset the benefit of preventive strategies for CIAKI. Fourth, although often promoted as the best strategy against CIAKI, periprocedural hydration alone resulted to be the least effective preventive treatment without significant variation after inclusion of only trials ensuring an intense and prolonged infusion. In aggregate, these findings underscore the prominent role of statin and the possible role of xanthine as the best treatment options

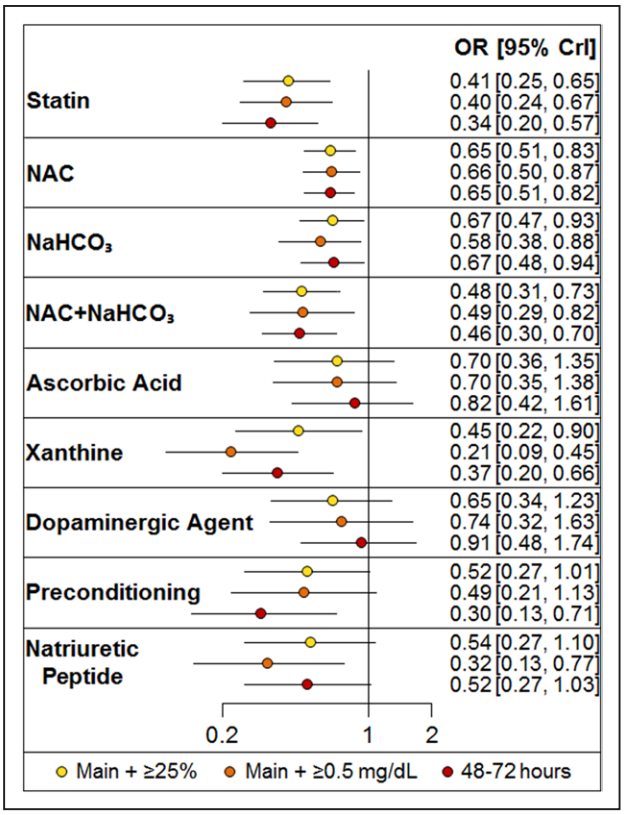

Figure 3. Subgroup analyses according to different contrast-induced acute kidney injury definitions. Trials and contrast-induced acute kidney injury events were pooled according to 3 different criteria: (1) main definition+contrast-induced acute kidney injury as serum creatinine increase ≥25%; (2) main definition+contrast-induced acute kidney injury as serum creatinine increase ≥0.5 mg/dL; and (3) events occurring between 48 and 72 h. CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

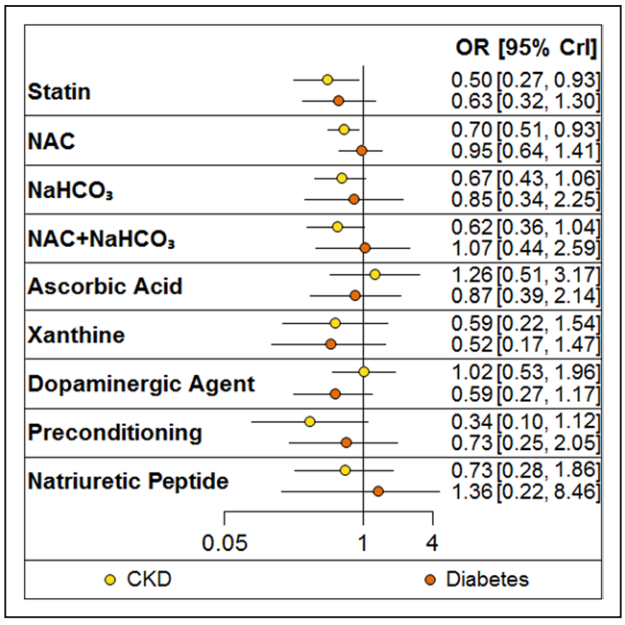

Figure 4. Subgroup analyses according to moderate-to-advanced chronic kidney disease and diabetes mellitus. In 2 different subgroup analyses, patients with advanced chronic kidney disease, defined as estimated glomerular filtration rate ≤60 mL/min per 1.73 m^2 (or, when not available, estimated creatinine clearance ≤60 mL/min) or serum creatinine ≥1.5 mg/mL and diabetes mellitus were pooled. CKD indicates chronic kidney disease; CrI, credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

for preventing CIAKI in patients undergoing percutaneous coronary procedures with contrast media administration.

Inflammation, oxidative stress, direct tubular injury, osmotic loading, and medullary hypoxia play a significant role in the pathogenesis of CIAKI.[20,21] Preventive strategies have been tested on the assumption of a significant effect on one or more of these mechanisms.[5,6] Statins have known pleiotropic effects that act by decreasing local and systemic inflammation, improving endothelial function, and modulating regulatory mechanisms of cell survival.[22–24] Statins may be particularly effective in CIAKI prevention if patients present with a high expression of inflammation biomarkers[25] but can also play a beneficial role downstream by counteracting one of the possible common final pathways of the CIAKI process, namely contrast-induced tubular cells apoptosis.[24,26] In a recent in vitro study, statins reduced the activation of apoptosis in human kidney cells, with a lower phosphorylation of JNK and p53 and a lower expression of caspase 3.[26] Results on rats were comparable.[27] Although these findings are preliminary, they are consistent with a biologically plausible mechanism. In our study, the renoprotective effects observed in patients receiving preprocedural statin administration were marked and consistent regardless of the different CIAKI definitions used across trials, the presence of baseline moderate-to-severe chronic kidney disease, and the quality of the studies analyzed. Because the methodological quality of trials included in a meta-analysis can significantly influence pooled estimate,[13] we inspected the consistency of results associated with statin after pooling only trials with larger sample size, blinding, independent adjudication of the events, and higher cumulative methodological quality as defined by the Cochrane Collaboration[13] without detecting any significant change. In addition, heterogeneity across analyses was overall acceptable, and no asymmetry in trial-level estimates distribution was observed. Finally, meta-regression analyses did not suggest significant associations with basal creatinine and contrast volume variations across trials.

Theophylline or aminophylline (theophylline–ethylenediamine) and pentoxifylline are nonselective A_1 and A_2 adenosine receptors antagonists that produce renal vasodilation by blocking A_1 adenosine receptor–mediated vasoconstriction and induce diuresis by reducing sodium reabsorption in the proximal tubules.[28,29] We found a marked risk reduction in CIAKI with xanthine when compared with saline. However, although not sensitive to the definition of CIAKI and variations in posology, this effect was significantly mitigated in critical subsets, such as advanced chronic kidney disease and diabetes mellitus, and in trials with higher quality, blinding, and independent event adjudication. In addition, results associated with xanthine were supported only by 11 small trials (nearly 600 patients), and inspection of local inconsistency of the network showed that direct evidence significantly contrasted with indirect evidence for the comparison of xanthine

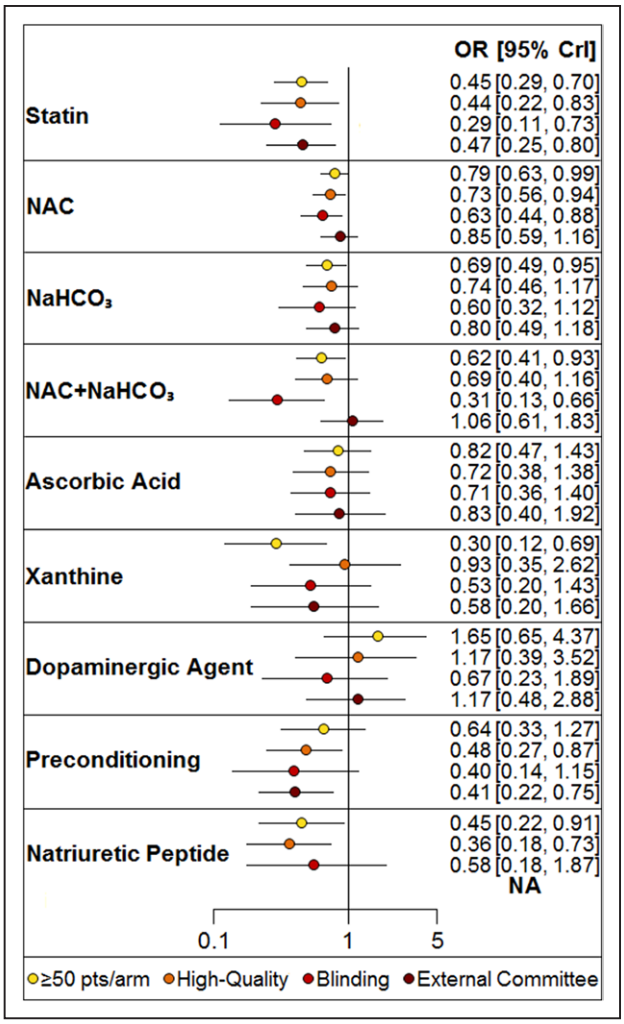

Figure 5. Subgroup analyses according to trials quality. Trials and contrast-induced acute kidney injury events were pooled according to 4 different methodological aspects: (1) trials with ≥50 patients per arm; (2) trials with high methodological quality, defined as a cumulative score ≥5.5 by combining components of the Cochrane Collaboration tool[13]; (3) trials planning at least patients blinding; and (4) trials having a blinded committee for contrast-induced acute kidney injury events adjudication. CrI indicates credible interval; NA, not available; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

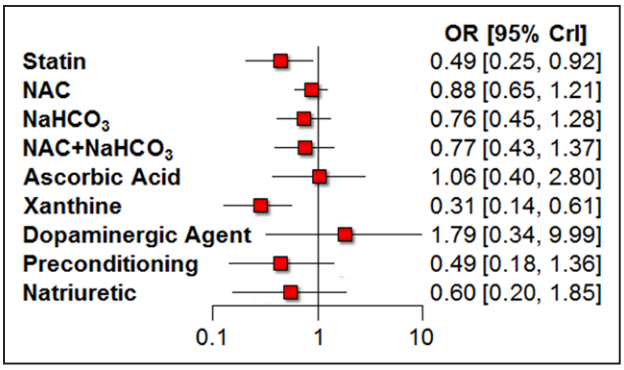

Figure 6. Sensitivity analysis of trials with intense posology. In this sensitivity analysis, only trials with systematic intense 0.9% (≥1 mL kg^{-1} h^{-1}) saline hydration regimens, from at least 6 h before to at least 6 h after the procedure, medium-to-high dose of medications, and reasonable periprocedural application (cycles for peripheral ischemic preconditioning) were considered. This sensitivity analysis sought to minimize the influence of trials including patients not hydrated or receiving saline solution with limited amount or duration. Secondary objective was to remove the influence of trials using low dose of medications, by including only trials using medium-to-high doses (ie, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥20 mg, etc). CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

versus NAC. After detachment of the network to individual strategies, we found that the benefit of xanthine is mostly attributable to theophylline and not pentoxifylline. Finally, concerns about the xanthine strategy arose from the high degree of heterogeneity detected across analyses, and funnel plot inspection showed a moderate asymmetry in the distribution of trial-level estimates likely with the presence of a small-study effect.

When compared with saline, we also observed a reduced risk of CIAKI with NAC, $NaHCO_3$, and NAC+$NaHCO_3$. The trials investigating these therapies included about 40% of patients included in the meta-analysis. The available data on the efficacy of NAC for CIAKI prevention, including several meta-analyses, provided contradictory conclusions.[5,30,31] Indeed, although NAC reduced CIAKI without significant variations across definitions, we found that these results could be influenced by trials with lower global quality and absence of independent event adjudication. These findings are in agreement with a systematic review appended to the ACT trial (Acetylcysteine for Contrast-Induced Nephropathy Trial),[31] in which deficiencies in allocation concealment and blinding provided partial explanation for the extreme variability in results across trials. In addition to these findings, low doses of NAC with or without inadequate hydration regimens may have introduced heterogeneity, and a publication bias/small-study effect amplifying NAC efficacy cannot be excluded. Interestingly, the removal of all trials with at least 1 arm, including <50 patients, produced a pooled effect comparable with saline.

Infusion of $NaHCO_3$ is another traditional strategy tested over time with mixed results.[32,33] $NaHCO_3$ was more effective than saline in the main analysis and was associated with efficacy similar to NAC. However, $NaHCO_3$ exhibited marked variations across subanalyses and was no longer effective in patients with moderate-to-severe chronic kidney disease or diabetes mellitus and trials of higher methodological quality. The exclusion of trials without systematic and adequate hydration regimens and medium-to-intense $NaHCO_3$ posology confuted the main analysis conclusions.

The combination of NAC+$NaHCO_3$ in a single strategy was explored in several trials in the attempt to amplify the effects of individual treatment components, but the results were not univocal.[34,35] In the main analysis, we observed a notable risk reduction associated with NAC+$NaHCO_3$ compared with saline, which had higher extent than the individual components of NAC+$NaHCO_3$ potentially indicating a cumulative effect. However, we revealed by network node-split a significant inconsistency for NAC+$NaHCO_3$ versus saline, with direct estimation reporting a similar effect of the 2 strategies. Finally, although the combination of statin with

NAC+$NaHCO_3$ was associated with the highest effect among statin-based strategies, this result was supported only by 1 trial,[26] which demands additional confirmation.

Ischemic preconditioning and natriuretic peptide showed a notable risk reduction when compared with saline in several analyses. Although these results are promising and deserve further attention in future, they should be considered with caution because, when compared with other strategies, the ischemic preconditioning and natriuretic peptide nodes included fewer patients and fewer trials. The limited data can explain the variable findings across analyses, where the selection of some trial having strong influence on pooled estimate could have driven the results. Moreover, some of the included trials investigating ischemic preconditioning were primarily conducted for other purpose. This consideration may explain the extreme heterogeneity constantly observed.

By node-split, we provided updated direct evidence estimates of different CIAKI prevention strategies (Figure II in the Data Supplement). Indeed, we are able to supplement considerably the latest frequentist meta-analyses of CIAKI[5,33,36–38] because in our study the direct component of evidence deriving from each available pair of preventive strategies is similar to a standard meta-analysis.

In aggregate, the results of our meta-analysis generate 2 additional considerations. First, although few studies have directly addressed volume expansion against CIAKI, intense hydration is commonly advocated as the cornerstone preventive strategy.[3,5–7] However, in our meta-analysis, hydration with saline solution alone was the least effective strategy, and the inclusion only of trials ensuring a more generous and prolonged periprocedural infusion did not modify this conclusion. On the one hand, our results do not contradict the central role of saline infusion, taking into consideration that all arms of included trials received a similar regimen, but on the other hand highlight the limitations of a preventive strategy based only on hydration. Second, comparisons between strategies other than saline tended to produce limited differences that can be only partially explained by the number of direct comparison in the network. The differential relative effectiveness across nonsaline-based strategies reflects the real magnitude of required advances against CIAKI.

Finally, in our study, we observed a significant negative impact of diabetes mellitus on the effectiveness of CIAKI preventive strategies, including statin and xanthine. Diabetes mellitus is an important cause of nephropathy and, although these conditions can be observed in the same patient, both can independently predispose to CIAKI.[2,3,7] However, on the one hand, according to our findings more information is needed to identify effective preventive strategies against CIAKI in diabetic patients, and on the other hand, the absence of individual patient data and event reporting in a significant proportion of trials limited our sample size.

Limitations

As with any meta-analysis, this study shares the limitations of the original trials included, and despite the multiple sensitivity analyses conducted, some remaining questions would only be addressed by individual patient data. More specifically, the results of our meta-analysis should be interpreted taking the following limitations into account. First, some of the included trials were heterogeneous, with differences in definitions, methods, and posology. Although our sensitivity analyses detected a modest influence of these variables, the influence of other unmeasured confounding factors cannot be ruled out. Moreover, as with any meta-analysis, the results of some restrictive analyses might be influenced by the reduction of included trials. Second, the estimation of a cutoff value to exclude underemployed strategies (ie, adding heterogeneity without producing any relevant additional finding) may imply a possible selection bias. However, as observable in the Figure I in the Data Supplement, this was necessary because about 50% of treatments identified before applying our ad hoc filter included <100 patients and as such would have been compared with strategies including several thousands of patients (ie, saline, statin, NAC, and $NaHCO_3$). Similarly, the exclusion of treatments investigated in <5 trials was empirical but preserved from the risk of considering strategies in which the evidence was supported only by a single large trial or unequally shared across few trials. As a matter of fact, the impact of this filter was not marked because it led to removal of only 1 strategy (ie, furosemide), and about 85% of patients treated with furosemide came only from a single medium-quality trial. A threshold for a minimum population size assigned to each identified treatment was also established using nonconservative parameters, which allowed for the inclusion of a large number of strategies, while excluding at the same time poorly represented and noninformative treatments. Third, analysis of treatment combinations implies per se a risk of bias (lumping). However, by detaching the network into the most elementary variants of strategies, the results remained unchanged and supported a similar effect within nodes, including similar treatments, with the exception of xanthine, as described earlier. Fourth, although our results apply to patients with suspected or confirmed coronary artery disease undergoing coronary diagnostics or procedures, about 10% of the trials enrolled a minor (<35%) proportion of patients who also underwent contrast administration for peripheral angiography or intervention sometimes performed in the same setting of the coronary procedures. Conversely, we deliberately excluded patients undergoing contrast media administration in the setting of computed tomographic diagnostics, transcatheter aortic valve replacement, and fully endovascular procedures because these procedures potentially entail different patient profiles and mechanisms of acute kidney injury. Fifth, the lack of specific trial-level outcomes did not enable exploring the influence of clinical presentation (ie, acute coronary syndrome, stable angina, silent angina, etc.) on the results of the meta-analysis. However, the posology subanalysis, including only trials requiring an intense hydration regimen for an adequate interval of time before the procedure, led to the exclusion of patients presenting with ST-segment–elevation myocardial infarction or undergoing emergency coronary procedure. Finally, detaching the statin node according to statin type (ie, atorvastatin, rosuvastatin, simvastatin, etc.) was not feasible. However, in 2 recent frequentist pairwise meta-analyses, no difference between statin types in terms of CIAKI risk reduction was observed.[36,38]

Conclusions

A preventive approach with statin was found to reduce the risk of CIAKI in patients undergoing coronary catheterization compared with saline. A xanthine-based strategy also proved effective compared with saline, but these results could be influenced by the presence of moderate-to-severe chronic kidney disease and the inclusion of lower-quality and small trials exaggerating the benefit of this strategy. NAC, $NaHCO_3$, and NAC+$NaHCO_3$ administration may be associated with a mild CIAKI risk reduction compared with saline, although the benefit of these strategies was attenuated in some sensitivity analyses. Ischemic preconditioning and natriuretic peptide may present a nephroprotective effect but larger and high-quality trials are required to draw conclusions. In patients with diabetes mellitus, none of the investigated strategies reduced the incidence of CIAKI.

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Disclosures

None.

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