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SYSTEMATIC REVIEW AND META-ANALYSIS

Tailored Versus Standard Hydration to Prevent Acute Kidney Injury After Percutaneous Coronary Intervention: Network Meta-Analysis

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BACKGROUND: Contrast-induced acute kidney injury (CI-AKI) is a serious complication after percutaneous coronary intervention. The mainstay of CI-AKI prevention is represented by intravenous hydration. Tailoring infusion rate to patient volume status has emerged as advantageous over fixed infusion-rate hydration strategies.

METHODS AND RESULTS: A systematic review and network meta-analysis with a frequentist approach were conducted. A total of 8 randomized controlled trials comprising 2312 patients comparing fixed versus tailored hydration strategies to prevent CI-AKI after percutaneous coronary intervention were included in the final analysis. Tailored hydration strategies included urine flow rate–guided, central venous pressure–guided, left ventricular end-diastolic pressure–guided, and bioimpedance vector analysis–guided hydration. Primary endpoint was CI-AKI incidence. Safety endpoint was incidence of pulmonary edema. Urine flow rate–guided and central venous pressure–guided hydration were associated with a lower incidence of CI-AKI compared with fixed-rate hydration (odds ratio [OR], 0.32 [95% CI, 0.19–0.54] and OR, 0.45 [95% CI, 0.21–0.97]). No significant difference in pulmonary edema incidence was observed between the different hydration strategies. *P* score analysis showed that urine flow rate–guided hydration is advantageous in terms of both CI-AKI prevention and pulmonary edema incidence when compared with other approaches.

CONCLUSIONS: Currently available hydration strategies tailored on patients' volume status appear to offer an advantage over guideline-supported fixed-rate hydration for CI-AKI prevention after percutaneous coronary intervention. Current evidence suggests that urine flow rate–guided hydration as the most convenient strategy in terms of effectiveness and safety.

Key Words: contrast-induced acute kidney injury ■ coronary angiography ■ hydration ■ percutaneous coronary intervention

Contrast-induced acute kidney injury (CI-AKI) complicates ≈7% of percutaneous coronary interventions (PCIs).[1] The development of CI-AKI is associated with a higher risk of dialysis, myocardial infarction, major bleeding, and death both during the hospital stay[1] and up to 1 year after discharge.[2] Hydration before, during, and after the procedure and limiting contrast volume administration are the most effective preventive measures against CI-AKI.[3] Traditionally, hydration regimens with fixed intravenous infusion rates of normal saline have been employed.[3] However, recent evidence suggests that tailoring the infusion rate to patient volume status, that is, by adjusting infusion rate according to central venous

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CLINICAL PERSPECTIVE

What Is New?

- Tailoring intravenous hydration on objective measurements of patient volume status appears to be more effective than the currently recommended one-size-fits-all hydration for the prevention of contrast-induced acute kidney injury in the setting of percutaneous coronary intervention.

What Are the Clinical Implications?

- If feasible, tailored hydration strategies may be considered over standard fixed-rate hydration for the prevention of contrast-induced acute kidney injury.

Nonstandard Abbreviations and Acronyms

BIVA	bioimpedance vector analysis
CI-AKI	contrast-induced acute kidney injury
CVP	central venous pressure
LVEDP	left ventricular end-diastolic pressure
UFR	urine flow rate

pressure (CVP), left ventricular end-diastolic pressure (LVEDP), bioimpedance vector analysis (BIVA), or urine flow rate (UFR), can lead to lower rates of CI-AKI compared with fixed hydration strategies.[3] Each of such tailored strategies has been directly compared with a fixed hydration regimen, but comparisons across different tailored hydration strategies are mostly lacking. We therefore performed a systematic review and network meta-analysis of randomized controlled trials of tailored versus fixed hydration strategies for CI-AKI prevention following coronary angiography and intervention.

METHODS

The authors declare that all supporting data are available within the article.

Literature Search

A total of 3 authors (F.M., L.B., and L.A.) independently searched MEDLINE, Embase, and Cochrane Central Database of Controlled Trial from inception until September 9, 2020, using a combination of key words including "contrast-induced acute kidney injury," "contrast-induced nephropathy," "hydration," and "percutaneous coronary intervention." No language restrictions were applied. Full queries are available in Table S1. Backward snowballing, that is, a review of references from the identified articles and relevant reviews, was also performed.[4] This network meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analysis.[5] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for the study selection process is shown in Figure S1, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for the present network meta-analysis is available in Data S1.

Data Selection

All published randomized controlled trials comparing different hydration strategies for the prevention of CI-AKI after PCI and including at least 1 tailored hydration arm (defined as adjusting hydration volume or rate to the patient volume status) were considered eligible for inclusion in the present network meta-analysis.

Outcome Measures

The prespecified efficacy end point was the occurrence of study-defined CI-AKI. The prespecified safety end point was the occurrence of study-defined pulmonary edema.

Data Identification and Extraction

A total of 2 investigators (F.M., L.B.) independently extracted data on patient characteristics, treatment strategies, and outcomes using a standardized data extraction form. Conflicts regarding inclusion and data extraction were discussed and resolved with a third senior investigator (L.A.). Data collection included authors, year of publication, inclusion and exclusion criteria, sample size, baseline clinical features of patients, hydration strategies, total hydration volume per treatment arm, and end point definitions. Data on complications were also collected when available.

Risk of Bias and Certainty Assessment

A total of 2 independent reviewers (F.M., L.A.) assessed the risk of bias (low, intermediate, or high) of the included studies using the Cochrane Collaboration Tool for Randomized Trials 2.0 for each outcome.[6] Publication bias and small study effect was assessed with outcome-specific comparison-adjusted funnel plots and subsequent regression analysis as previously described.[7] We graded the certainty of direct and network evidence using the Grading of Recommendations Assessment, Development, and Evaluation criteria for network meta-analysis.[8,9]

Statistical Analysis

Cumulative event rates for efficacy and safety end points were obtained and reported. Network meta-analysis was conducted based on a frequentist approach to compare treatments without direct pairwise comparisons.[10] We used a random effect model to allow for apparent heterogeneity between studies in treatment comparison effects. The network map for the analysis was built with nodes, representing interventions, of a size weighted by the overall number of subjects receiving the intervention, connected by edges having a thickness proportional to the number of studies available for that specific pairwise comparison (Figure 1).[11] A complete network geometry description was provided using specific network analysis statistics.[12] Treatment ranking was performed by means of *P* scores.[13] All outcomes of interest were binary and the treatment effects were reported in the odds ratio (OR) scale with 95% CI. The validity of the consistency assumption between direct and indirect sources of evidence was evaluated locally using the node-splitting approach,[14,15] involving only 3 treatments (ie, fixed-rate hydration, LVEDP-guided hydration, and UFR-guided hydration) where both the direct and indirect evidence were available. Meta-regression of the occurrence of CI-AKI and of pulmonary edema on mean total hydration volume per treatment arm was performed as previously described.[16,17] A network meta-analysis using a frequentist approach was subsequently performed to evaluate the differences in terms of mean hydration volume between treatments. Statistical analyses were conducted with STATA version 14.0 (StataCorp, College Station, TX) using the package "mvmeta," R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) using packages "meta" and "netmeta," and Comprehensive Meta-Analysis version 3 (Biostat, Engelwood, NJ).

Ethical Consideration

Considering the meta-analytic approach of the present study, which employed only published data in aggregated form, the requirement for ethics committee evaluation and institutional review board approval was not deemed necessary.

RESULTS

Data Selection

Literature search identified 783 studies. Among these, 772 were excluded during screening based on title and abstract. Of the 11 remaining studies, 3 were excluded at a second verification phase. Finally, 8 studies, for a total of 2312 patients, were included in the present network meta-analysis.[18–25] Details of the studies are provided in Tables S2 and S3. A total of 3 studies compared UFR-guided hydration with fixed hydration,[18,19,21] 2 studies compared LVEDP-guided hydration with fixed hydration,[20,24] and 1 study was available for BIVA-guided hydration versus fixed hydration,[23] CVP-guided hydration versus fixed hydration,[22] and LVEDP-guided hydration versus UFR-guided hydration, respectively.[25] One study comparing UFR-guided and fixed hydration did not report on in-hospital pulmonary edema[21] and was therefore excluded from the safety end point analysis. The distribution of baseline characteristics by treatment was generally balanced, except for Maioli et al,[23] who mainly included subjects at lower risk of CI-AKI (ie, very low proportion of baseline chronic kidney disease) and excluded urgent or emergent cases. Information on concomitant use of N-acetylcysteine inconsistently reported across the included studies and therefore was not reported in the present work.

Mixed Meta-Analysis for the Primary Outcomes

The network map involved 5 treatments. (Figure 1A shows the map for CI-AKI, whereas Figure 1B the map for pulmonary edema.) The number of studies for each direct comparison ranged from 1 to 3 in the case of CI-AKI and from 1 to 2 for pulmonary edema. Fixed-rate hydration was used as common comparator for both outcomes. Figure 2A presents the league tables for CI-AKI and pulmonary edema. Network meta-analysis showed that UFR-guided (OR, 0.32; 95% CI, 0.19–0.54) and CVP-guided (OR, 0.45; 95% CI, 0.21–0.97) hydration strategies were more efficacious than fixed hydration in preventing CI-AKI.

In terms of safety profile, the overall occurrence of pulmonary edema was low (incidence ranging from 0%[23,24] to 8.8%[19]). Network meta-analyses showed no differences across all possible comparisons. According to *P* scores, UFR-guided hydration ranked first for the prevention of CI-AKI and second to fixed hydration in terms of risk of pulmonary edema. Figure 2 shows *P* scores with respect to CI-AKI (Figure 2B) and pulmonary edema (Figure 2C).

Rates of Complications for Specific Hydration Strategies

To establish UFR-guided and CVP-guided hydration, the following additional invasive procedures are required: urinary catheter and a central venous line placement, respectively. Because these procedures inherently carry additional risks, such excess risk should be taken into account to inform appropriate decision making. Failure to place a central venous line was reported in 4/269 patients in the study by Qian and colleagues.[22] No major complications related to central

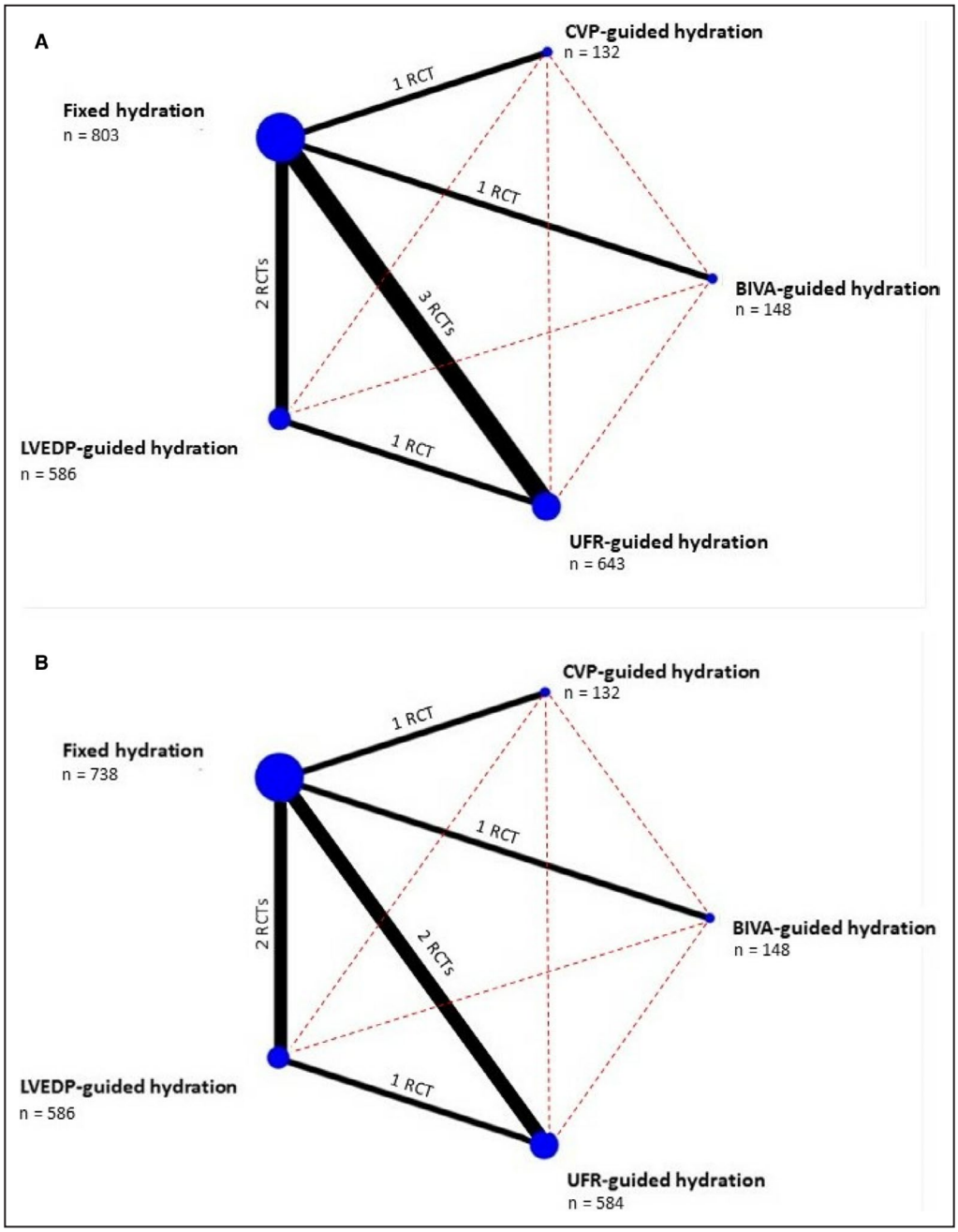
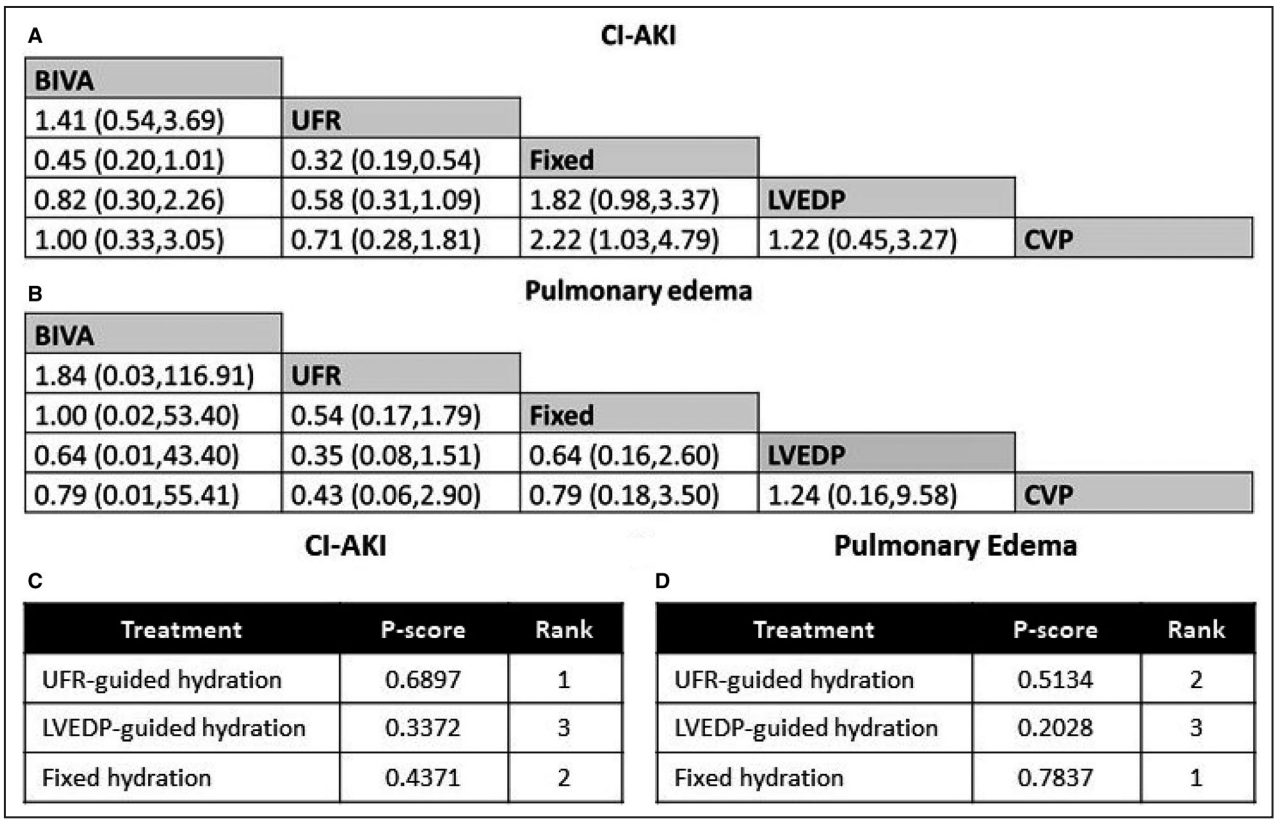


Figure 1. Network maps of study treatments: (A) contrast-induced acute kidney injury and (B) pulmonary edema.

Nodes represent each treatment; node size is proportional to the number receiving the corresponding treatment, which is indicated below treatment name. Solid edges represent direct comparisons available in the literature. The thickness of each edge is proportional to the number of available studies, which is indicated near the edge itself. Red-dashed edges represent indirect comparisons. BIVA indicates bioimpedance vectorial analysis; CVP, central venous pressure; LVEDP, left ventricular end-diastolic pressure; RCT, randomized controlled trial; and UFR, urine flow rate.

vein catheterization were reported. The total number of complications reported for Foley catheter insertion was 8/648, for a pooled event rate of 0.8% (95% CI, 0.0–1.7%).[18,19,21,25] In detail, 5 patients complained of pain or discomfort during micturition and 1 patient suffered hematuria, and in 2 cases a failure to place the catheter was reported. No major complication was reported. On top of the aforementioned complications, overall, 7 patients withdrew informed consent to participate in the studies because of concerns connected to urinary catheter positioning, for a pooled event rate of 0.6% (95% CI, 0.0–1.4%). The administration of furosemide



Treatment	P-score	Rank
UFR-guided hydration	0.6897	1
LVEDP-guided hydration	0.3372	3
Fixed hydration	0.4371	2

Treatment	P-score	Rank
UFR-guided hydration	0.5134	2
LVEDP-guided hydration	0.2028	3
Fixed hydration	0.7837	1

Figure 2. League of tables for CI-AKI (A) and pulmonary edema (B).
Each cell contains the odds ratio and 95% CI for the comparison of treatment reported in the column vs treatment reported in the row. Gray cells contain treatment name (**C** and **D**), *P* score, and ranking analysis. BIVA indicates bioimpedance vectorial analysis; CI-AKI, contrast-induced acute kidney injury; CVP, central venous pressure; LVEDP, left ventricular end-diastolic pressure; and UFR, urine flow rate.

during UFR-guided hydration raises the concern for the potential development of electrolyte imbalances. A total of 3 studies comparing UFR-guided hydration to a hydration strategy not requiring loop diuretic administration reported on the development of hypokalemia.[18,19,25] Hypokalemia occurred in 37/570 patients in the UFR-guided hydration group and in 20/568 controls, for a pooled OR of 1.62 (95% CI, 0.53–5.01; *P*=0.40). No cases of severe hypokalemia or arrhythmias were reported. A total of 2 studies reported on the development of hypernatremia.[18,25] Hypernatremia occurred in 4/483 patients undergoing UFR-guided hydration and in 4/483 controls, for a pooled OR of 1.00 (95% CI, 0.50–4.03; *P*=1.00). A single study reported an incidence of hypomagnesemia of 16/132 patients in the UFR-guided hydration group, whereas no cases were described among controls.[18] All patients with hypomagnesemia were asymptomatic, and no intervention was required.

Sensitivity Analysis

Although trial design was somewhat homogeneous across most included studies, the work by Maioli et al,[23] who compared BIVA-guided versus a fixed hydration strategy, differed significantly. Specifically, patient volume status was evaluated before randomization, and only subjects with low total body water (as assessed noninvasively with BIVA) were considered eligible to take part in the study and subsequently randomly assigned to receive a standard or a high-volume hydration regimen. Consequently, we performed a sensitivity analysis excluding this study. Effect estimates and surface under the cumulative ranking curve (SUCRA) values did not substantially change compared with the primary analysis: UFR-guided and CVP-guided hydration were still more efficacious in CI-AKI prevention than fixed hydration (OR, 0.32 [95% CI, 0.19–0.54] and OR, 0.45 [95% CI, 0.21–0.97], respectively). Similarly, no differences were found across any comparison in terms of pulmonary edema. Sensitivity analyses league tables are shown in Table S4.

Risk of Bias and Certainty of Evidence

Bias analysis is presented in Figures S2 and S3. We judged 1 study[23] to have a high risk of bias arising from

Patient population: patients undergoing coronary angiography or percutaneous coronary intervention.

Interventions: Urine Flow-Rate (UFR) guided hydration, Left Ventricular End-Diastolic Pressure (LVEDP) guided hydration, Central Venous Pressure (CVP) guided hydration, Bioimpedance Vector Analysis (BIVA) guided hydration.

Comparator (Reference): Fixed hydration.

Outcome: Incidence of Contrast-Induced Acute Kidney Injury (CI-AKI).

Setting: Inpatients.

Total Studies: 8 RCTs Total participants: 2312	OR 95% CI	Anticipated absolute effect (95% CI)			NNT	Certainty of evidence	P-score	Interpretation of findings
		No intervention	With intervention	Difference				
UFR-guided hydration (4 RCTs, 643 patients)	0.32 (0.19 – 0.54) Network estimate	202 per 1000	68 per 1000	134 per 1000 lower (from 100 lower to 168 lower)	8	⨁⨁⨁◯ Moderate*	0.6897	Probably superior
BIVA-guided hydration (1 RCT, 148 patients)	0.45 (0.20 – 1.01) Network estimate	202 per 1000	114 per 1000	88 per 1000 lower (from 29 lower to 146 lower)	12	⨁◯◯◯ Very low*†‡§	-	Very low certainty of evidence pointing at possible lower incidence of CI-AKI
CVP-guided hydration (1 RCT, 132 patients)	0.45 (0.21 – 0.97) Network estimate	202 per 1000	159 per 1000	43 per 1000 lower (from 24 higher to 112 lower)	24	⨁⨁◯◯ Low*‖	-	Low certainty of evidence pointing at possible lower incidence of CI-AKI
LVEDP-guided hydration (3 RCTs, 586 patients)	0.55 (0.30 – 1.02) Network estimate	202 per 1000	87 per 1000	115 per 1000 lower (from 79 lower to 152 lower)	9	⨁⨁⨁◯ Moderate‖	0.3372	Possibly superior
Fixed hydration (7 RCTs, 803 patients)	Reference comparator						0.4731	Reference Comparator

NMA SoF Table Definitions:

- OR: Odds Ratio;
- 95% CI: 95% confidence interval;
- Anticipated absolute effect: anticipated absolute effect compares two risks by calculating the difference of risk in the intervention group and the risk in the comparator group;
- NNT: number needed to treat;

GRADE Working Group grades of evidence (or of certainty of evidence):

High quality: we are confident that the true effect lies close to that of the estimate of effect.
Moderate quality: we are moderately confident in the effect estimates; the true effect is likely to be close to the estimate of effects, but there is the possibility for it to be substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes explanation:

*Downgrade for Publication Bias:

- UFR-guided hydration: skewed funnel plot for the direct comparison (smaller studies with larger effect);
- BIVA-guided hydration: single study with low event number and large effect;
- CVP-guided hydration: single study with low event number and large effect;

†Downgrade for Risk of Bias:

- BIVA-guided hydration: some risk of bias, see Supplementary Materials for Cochrane Risk of Bias 2 tool analysis;

‡Downgrade for Indirectness:

the present network meta-analysis, since patients were selected to have low total body fluids, hence would likely be affected differently by hydration with respect to other studies.

§Downgrade for Transitivity

- BIVA-guided hydration: patients were selected to have low total body fluid, hence control group could not fulfill entirely transitivity requirements (baseline difference likely to affect the effect of hydration on controls).

‖Downgrade for Imprecision:

- CVP-guided hydration: single study with small sample size and low number of events, leading to an anticipated absolute effect which crosses neutrality.
- LVDEP-guided hydration: direct effect estimate which has a large 95% CI, crossing neutrality and spanning from large protective effect to large detrimental effect (direct estimate OR 0,73 with 95% CI 0,14 – 3,76).

Figure 3. Summary of findings of the network meta-analysis: CI-AKI (efficacy outcome).
BIVA indicates bioimpedance vector analysis; CI-AKI, contrast-induced acute kidney injury; CVP, central venous pressure; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LVEDP, left ventricular end-diastolic pressure; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; and UFR, urine flow-rate.

Patient population: patients undergoing coronary angiography or percutaneous coronary intervention.

Interventions: Urine Flow-Rate (UFR) guided hydration, Left Ventricular End-Diastolic Pressure (LVEDP) guided hydration, Central Venous Pressure (CVP) guided hydration, Bioimpedance Vector Analysis (BIVA) guided hydration.

Comparator (Reference): Fixed hydration.

Outcome: Incidence of Pulmonary edema.

Setting: Inpatients

Total Studies: 7 RCTs Total participants: 2188	OR 95% CI	Anticipated absolute effect (95% CI)			NNT	Certainty of evidence	P-score	Interpretation of findings
		No intervention	With intervention	Difference				
UFR-guided hydration (3 RCTs, 584 patients)	0.54 (0.17 – 1.79) Network estimate	24 per 1000	15 per 1000	9 per 1000 lower (from 5 higher to 20 lower)	111	⨁◯◯◯ Very low*†‡	0.5134	Very low certainty of evidence pointing at marginal reduction in Pulmonary Edema incidence
BIVA-guided hydration (1 RCT, 148 patients)	1.00 (0.02 – 53.40) Network estimate	24 per 1000	0 per 1000	24 per 1000 lower (from 13 lower to 35 lower)	42	⨁◯◯◯ Very low*‡§‖	-	Very low certainty of evidence pointing at neutral effect
CVP-guided hydration (1 RCT, 132 patients)	1.26 (0.29 – 5.56) Network estimate	24 per 1000	37 per 1000	13 per 1000 higher (from 47 higher to 20 lower)	-#	⨁⨁◯◯ Low*	-	Low certainty of evidence pointing at an increase in the rate of Pulmonary Edema
LVEDP-guided hydration (3 RCTs, 586 patients)	1.56 (0.38 – 6.37) Network estimate	24 per 1000	17 per 1000	7 per 1000 lower (from 7 higher to 22 lower)	142	⨁⨁◯◯ Low*†	0.2028	Low certainty of evidence pointing at a reduction in Pulmonary Edema incidence
Fixed hydration (7 RCTs, 803 patients)	Reference comparator						0.7837	Reference Comparator

NMA SoF Table Definitions:

- OR: Odds Ratio;
- 95% CI: 95% confidence interval;
- Anticipated absolute effect: anticipated absolute effect compares two risks by calculating the difference of risk in the intervention group and the risk in the comparator group;
- NNT: number needed to treat;

GRADE Working Group grades of evidence (or of certainty of evidence):

High quality: we are confident that the true effect lies close to that of the estimate of effect.
Moderate quality: we are moderately confident in the effect estimates; the true effect is likely to be close to the estimate of effects, but there is the possibility for it to be substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes explanation:

*Downgrade for Imprecision:

- UFR-guided hydration: few events leading to large CI for the direct estimate, spanning from high reduction to high increase in outcome of interest (direct estimate OR 0,89 with 95% CI 0,15 – 5,49);
- BIVA-guided hydration: single study, no events in the BIVA group, which does not allow an adequate direct estimate calculation and severely affects indirect estimate confidence interval – very severe imprecision considering single study only;
- CVP-guided hydration: single study with low event number, leading to large CI direct estimate, spanning from high reduction to high increase in outcome of interest (direct estimate OR 1,26 with 95% CI 0,33 – 4,79) – very severe imprecision considering single study only;
- LVDEP-guided hydration: few events leading to large CI for the direct estimate, spanning from high reduction to high increase in outcome of interest (direct estimate OR 0,97 with 95% CI 0,19 – 4,85).

†Downgrade for Inconsistency:

- UFR-guided hydration: substantial heterogeneity in the direct estimate (I2=55%, $p_{heterogeneity}$=0,14);
- LVDEP-guided hydration: 95% CI not calculable for 1 out of 2 studies included in direct estimate (no events), leading to impossibility to evaluate CI overlapping hence heterogeneity.

‡Downgrade for Risk of Bias:

- UFR-guided hydration: one of the studies identified in the systematic search did not report on this outcome.

§Downgrade for Transitivity:

- BIVA-guided hydration: patients were selected to have low total body fluids, hence control group could not fulfill entirely transitivity requirements (baseline difference likely to affect the effect of hydration on controls).

‖Downgrade for Indirectness:

- BIVA-guided hydration: selection criteria of the study not fully respondent to original PICO (Population, Intervention, Comparator, Outcome) of the present network meta-analysis, since patients were selected to have low total body fluids, hence would likely be affected differently by hydration with respect to other studies.

Number needed to harm: 76.

Figure 4. Summary of findings of the network meta-analysis: Pulmonary Edema (safety outcome)
BIVA indicates bioimpedance vector analysis; CI-AKI, contrast-induced acute kidney injury; CVP, central venous pressure; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LVEDP, left ventricular end-diastolic pressure; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; and UFR, urine flow-rate.

the randomization process and selection of reported results. Of the trials, 4[18,19,21,24] had some concerns about the randomization process and deviation from the intended treatment, outcome measurement, and selective reporting of outcomes. Overall, a low risk of bias was detected. When we evaluated the consistency assumption, we found evidence of inconsistency for the comparison of 3 treatments (namely, fixed-rate hydration, UFR-guided hydration, and LVEDP-guided hydration) in both CI-AKI and pulmonary edema (Table S5 and Figure S4). CVP-guided and BIVA-guided hydration were excluded in the assessment of inconsistency because of the lack of direct evidence. Comparison-adjusted funnel plot analysis was consistent with a low risk of publication bias for both CI-AKI and pulmonary edema (Figure S5). The certainty of evidence of network estimates for the outcomes of interest are presented in Figures 3 and 4, which report certainty of evidence of treatment effect estimates according to the Grading of Recommendations Assessment, Development, and Evaluation criteria. Certainty was moderate or low/very low for most comparisons, mainly because of publication bias, risk of bias, indirectness, imprecision, inconsistency, and the possibility of intransitivity.

Hydration Volume and Study Outcomes

Five studies, for a total of 1610 patients, reported mean hydration volume per treatment arm and were subsequently included in this subanalysis.[19–22,25] A total of 2 studies compared UFR-guided hydration and fixed hydration,[19,21] 1 study compared CVP-guided hydration and fixed hydration,[22] 1 study compared LVEDP-guided hydration with fixed hydration,[20] and 1 study compared LVEDP-guided hydration with UFR-guided hydration.[25] Post hoc meta-regression shows evidence of an association between total hydration volume and treatment effect for the occurrence of CI-AKI, with larger volumes being associated with lower rates of CI-AKI, albeit with a small effect size (coefficient=−0.0005; 95% CI, −0.0009 to −0.0002; P=0.001; R^2=0.56; Figure 5A). On the other hand, no significant influence of hydration volume on pulmonary edema occurrence could be detected (coefficient=0.0001; 95% CI, −0.0007 to 0.0009; P=0.720; R^2<0.0001; Figure 5B). The network meta-analysis showed that UFR-guided hydration and LVEDP-guided hydration provided the highest infused volumes when compared with fixed hydration (LVEDP-guided hydration versus fixed hydration mean difference 1313 mL [95% CI, 1797–2284 mL] and UFR-guided hydration versus fixed hydration

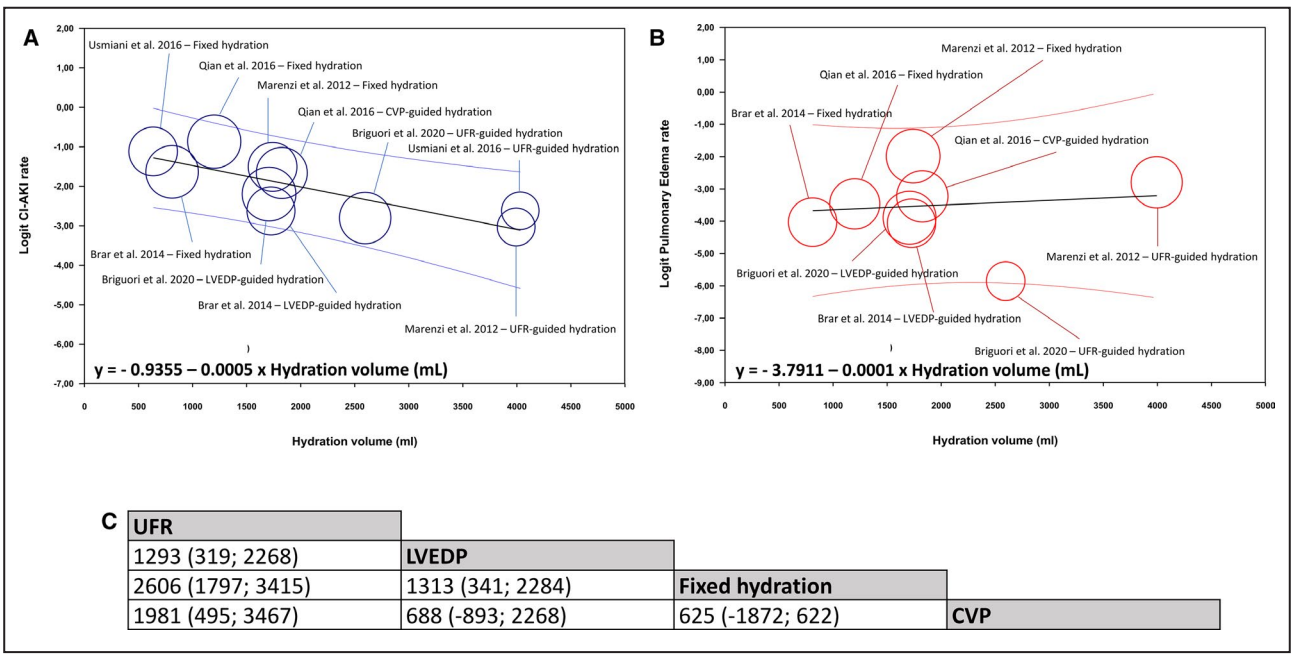


Figure 5. Hydration volume meta-analysis.
A, The bubble plot for the meta-regression of the logit event rate for CI-AKI over mean hydration volume for each treatment arm of the studies included (efficacy outcome). **B**, The bubble plot for the meta-regression of the logit event rate of pulmonary edema (safety outcome) over mean hydration volume. Bubbles represent each treatment arm, and bubble size is proportional to relative weight in the analysis. **C**, The league table for hydration volume differences. Each cell contains the effect size estimate for mean difference and 95% CI in hydration volume between the treatment reported in the column vs treatment reported in the row. All values are expressed in mL. A positive value means that mean hydration provided by the treatment indicated in the column is larger than the mean hydration provided by the treatment indicated in the row. Gray cells contain treatment name. CI-AKI indicates contrast-induced acute kidney injury; CVP, central venous pressure; LVEDP, left ventricular end-diastolic pressure; and UFR, urine flow rate.

mean difference 2606 mL [95% CI, 1797–3415 mL]), with UFR-guided hydration providing the highest overall mean hydration volumes (Figure 5C).

DISCUSSION

The main findings of the present systematic review and network meta-analysis are the following:

1. UFR-guided hydration is superior to guideline-supported fixed-rate hydration with respect to CI-AKI prevention with a moderate certainty of evidence.
2. UFR-guided hydration outperformed all other hydration strategies in terms of both CI-AKI prevention and risk of pulmonary edema.
3. Higher total hydration volumes were associated with lower rates of CI-AKI, whereas no impact of total hydration volume on pulmonary edema was detected. UFR-guided hydration was found to provide the highest total hydration volumes across different hydration strategies.

The incidence of CI-AKI following PCI greatly varies across published studies, and as such its incidence ranges between 3.3% and 14.5%.[26,27] Although in most cases CI-AKI is a self-limited event, with renal function returning to baseline within 3 weeks,[28] it has not uncommonly been associated with severe adverse outcomes, irreversible kidney injury, myocardial infarction, stroke, heart failure, or death as well as increased hospital stay and costs.[29] The pathophysiology of CI-AKI after PCI is complex. On one hand, contrast media alters kidney hemodynamics by inducing vasoconstriction and subsequent hypoperfusion. On the other hand, contrast media has a direct toxic effect on tubular cells and promotes the release of reactive oxygen species within the nephron.[3] Moreover, other procedural-related factors may contribute to the development of CI-AKI, such as embolization of atheromatous debris into the renal arteries induced by catheter manipulation and renal hypoperfusion secondary to periprocedural hypotension.[3] Because no effective treatment exists once CI-AKI has established, prevention is critical. Hydration before, during, and after the procedure is the cornerstone of CI-AKI prevention.[30] Current guidelines support a strategy of fixed-rate isotonic saline infusion to reduce the incidence of CI-AKI.[31] Hydration guarantees adequate intravascular volume (hence renal perfusion) and may reduce kidney exposure to contrast media by diluting contrast and favoring its rapid excretion.[3,32] Prophylactic intravenous hydration carries risks, the most severe of which is pulmonary edema secondary to volume overload (reported in up to 5.5% of cases), raising questions on the risk-to-benefit balance of hydration.[33] In our analysis, we observed an impact of total hydration volume on CI-AKI occurrence, with higher infused volumes being associated with lower CI-AKI rates. Of note, we did not detect an association between pulmonary edema and total volume infused. Indeed, tailoring hydration to patient volume status can optimize volume expansion while still identifying patients at risk for volume overload. Larger volumes are infused selectively in patients with lower volume status. Conversely, aggressive infusion therapy is selectively avoided in those patients with higher preloads and left ventricular filling pressures who are at higher risk of pulmonary edema. Indeed, it should be noted that in the face of higher mean total infused volumes, tailored hydration strategies have higher crude measures of dispersion, reflecting the wide range of volumes infused.

Our analyses confirmed the advantage of all tailored strategies compared with fixed hydration albeit in some cases with large confidence (BIVA-guided and LVEDP-guided regimens) intervals marginally crossing the neutrality line. This was achieved in the face of similar rates of pulmonary edema. The low number of studies available on this topic, as well as differences in terms of study populations, could have decreased the power of the present analysis to detect a significant effect. It should also be noted that some minor heterogeneity in the definition of CI-AKI adopted by different studies could have influenced our analysis.

A large reduction in term of CI-AKI was, however, detected for both UFR-guided and CVP-guided hydration strategies. Multiple measurements of the patient volume/hemodynamic conditions and subsequent dynamic adjustment of hydration inherent to these approaches (based on replenishment of urine output and optimization of CVP, respectively) may ensure an optimal venous filling. Venous congestion (as reflected by a high CVP) is a strong predictor of AKI, whereas low CVP is generally associated with volume depletion and kidney hypoperfusion.[32,34,35] Classical physiology experiments have demonstrated that raising renal vein pressure fosters renal sodium retention and reduces glomerular filtration rate, initiating a vicious cycle that eventually leads to volume overload and worsening of renal function.[36,37] This underlines how overzealous volume replacement may actually increase the incidence of CI-AKI before causing overt manifestations such as pulmonary edema. On the other hand, BIVA-guided and LVEDP-guided hydration regimens feature an initial single measurement of patient body water or hemodynamic conditions, respectively, which may not allow for the fine-tuning of hydration and dynamic volume optimization during and after the procedure, thus failing to take advantage of the full potential of a tailored hydration approach.

The use of furosemide in UFR-guided hydration represents 1 of the major differences that sets this approach apart from the others. Inhibition of active ionic transport in the loop of Henle by loop diuretics was

shown to reduce kidney energy expenditure, which could exert a protective cellular effect.[38] The renoprotective effect of furosemide could be undermined by volume depletion induced by forced diuresis, reinforcing the fundamental role of urine output replenishment provided in UFR-guided hydration.[39]

Despite the advantage in terms of efficacy and safety, some factors preventing the wider adoption of tailored hydration strategies have to be acknowledged. UFR-guided and BIVA-guided hydration require dedicated equipment, increasing procedural costs. UFR-guided hydration requires placement of urinary catheter, which could carry risks related to local traumatic or infectious complications and may negatively impact patient satisfaction and perception of received care quality. CVP-guided hydration requires placement of a central venous line, which has classically been associated with hematoma, arterial puncture, and pneumothorax (up to 13% in some series)[40] as well as catheter-related bloodstream infections.[41] Furosemide administration for UFR-guided hydration can induce electrolyte disturbances. UFR-guided hydration requires time to achieve an adequate urine flow (up to 55 minutes in 1 study[25]), which could adversely impact the workflow of a busy modern catheterization laboratory and makes it unsuitable for emergency situations. Table S6 summarizes the limitations of each strategy. These limitations and considerations notwithstanding, our data indicate that the UFR-guided approach, followed by the CVP-guided regimen, are the most effective strategies to provide tailored hydration and decrease the risk of CI-AKI in patients undergoing coronary angiography and intervention. A direct randomized comparison of these 2 strategies is eagerly awaited.

Limitations

Our study also presents several limitations. First, the quality of our analyses is limited by the inherent limitations of the individual included randomized controlled trials, which were overall small studies including a relatively exiguous number of patients. Second, individual patient data were not available, precluding sophisticated statistical adjustments. Third, although we showed full assessment of the risk of bias of all included trials (Figures S2 and S3), some studies did not report adequate information about allocation sequence concealment and blinding and provided incomplete data on outcomes, which weakens the present network meta-analysis. Fourth, it was not possible to estimate the effect of treatment duration for all hydration strategies because of multicollinearity and missing linkage. Moreover, the results of our meta-regression are weakened by the lack of individual patient data. In addition, a legacy treatment effect could not be explored because of the lack of long-term follow-up. Minor differences in fixed hydration strategies employed in control groups may have introduced minor bias; however, all different hydration strategies employed are considered clinically equivalent, hence transitivity assumptions are not violated in the analysis.[42,43] Finally, it has to be acknowledged that our work did not take into consideration other currently available prevention strategies, which were not the focus of the present meta-analysis. Indeed, hydration, despite being readily available and readily implementable, is not the sole strategy to reduce the risk of CI-AKI. The amount of contrast plays a major role as well as the type of contrast employed, with contrast osmolarity possibly playing a role.[44] In addition, adjunct treatment including periprocedural high-intensity statin therapy as well as vasodilator treatment were shown to be safe and effective in abating CI-AKI incidence.[42]

CONCLUSIONS

The present network meta-analysis of 8 randomized controlled trials represents an updated synthesis of currently available evidence on hydration strategies for the prevention of CI-AKI. Based on moderate certainty evidence, UFR-guided hydration was found to provide the greatest efficacy for CI-AKI prevention in patients undergoing coronary angiography and intervention. It was also found, albeit with very low certainty of evidence and modest effect size, to have a favorable safety profile with regard to pulmonary edema. On the other hand, standard-of-care fixed hydration regimens were shown to be the least effective in terms of CI-AKI prevention. Further studies directly comparing different tailored hydration strategies are awaited to establish the most effective, safe, and convenient approach to minimize the incidence of this important complication.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S6
Figures S1–S5

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Supplemental Material

Data S1.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis.

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Title Page (Page 1)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	Page 5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	Pages 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5-6

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 5-7 Supplemental Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5-7
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 5-7
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5 Supplemental Figure 3 and 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	Page 5-6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	Page 5-7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 5-7 Supplemental Table 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5-7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	Page 5-7

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6 Supplemental Figure 1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Figure 1***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***Page 8***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8 Supplemental Table 2 and 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Supplemental Figure 3 and 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Supplemental Tables 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 8-10, Figure 2, Supplemental Table 4 and Supplemental Figure 4
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 8-9 Supplemental Table 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Supplemental Figures 3 and 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	Page 10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Pages 12-15 Tables 1-2

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Page 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pages 16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Page 1

PICOS = population, intervention, comparators, outcomes, study design.

Table S1. Search strategies.

	Query for Embase
#1	'contrast induced acute kidney injury'/exp
#2	'contrast induced nephropathy'
#3	'CIN'
#4	'CI-AKI'
#5	contrast AND acute AND renal AND failure
#6	contrast AND nephropathy
#7	#1 OR #2 OR #3 OR #4 OR #5
#8	Hydration
#9	Fluid AND administration
#10	Volume AND expansion
#11	Intravenous AND sodium AND bicarbonate
#12	Saline AND infusion
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	Cardiac AND catheterization
#15	Coronary AND angiography
#16	Coronary AND intervention
#17	Percutaneous AND coronary AND intervention
#18	PCI
#19	Percutaneous AND transluminal AND coronary AND angioplasty
#20	PTCA
#21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	#7 AND #13 AND #21
	Query for MEDLINE
	((contrast-induced acute kidney injury OR contrast-induced nephropathy OR CIN OR CI-AKI OR contrast acute renal failure OR contrast nephropathy) AND (hydration OR fluid administration OR volume expansion OR intravenous sodium bicarbonate OR saline infusion)) AND (cardiac catheterization OR coronary angiography OR coronary intervention OR percutaneous coronary intervention OR PCI OR percutaneous transluminal coronary angioplasty OR PTCA)
	Query for Cochrane CENTRAL
#1	(contrast induced acute kidney injury):ti,ab,kw OR (contrast induced nephropathy):ti,ab,kw OR (CIN):ti,ab,kw OR (CI-AKI):ti,ab,kw OR (contrast acute renal failure):ti,ab,kw OR (contrast nephropathy):ti,ab,kw
#2	(hydration):ti,ab,kw OR (fluid administration):ti,ab,kw OR (volume expansion):ti,ab,kw OR (intravenous sodium bicarbonate):ti,ab,kw (saline infusion):ti,ab,kw
#3	(cardiac catheterization):ti,ab,kw OR (coronary angiography):ti,ab,kw OR (coronary intervention):ti,ab,kw OR (percutaneous coronary intervention):ti,ab,kw OR (PCI):ti,ab,kw OR (percutaneous transluminal coronary angioplasty):ti,ab,kw OR (PTCA):ti,ab,kw
#4	#1 AND #2 AND #3

Table S2. Description of the hydration protocols in the included studies.

Author, Year (Ref)	Protocol	Description	Total hydration per group (mL)
Briguori et al, 2011 (18)	UFR	250 mL of i.v. saline in 30 min as "priming" (reduced to 150 mL if LVEF≤30% on transthoracic echocardiography). After priming, a bolus of furosemide 0.25 mg/kg was administered i.v. to achieve a urine output of ≥300 mL/h. The procedure was initiated after achieving the target urine flow rate (mean 58±13 min). Subsequent hydration with saline was matched automatically to urine flow output using the RenalGuard system. Hydration was maintained for 4 hours after the end of the procedure.	2312 [1928-2999]
	Fixed	3 mL/kg per hour of 154 mEq/L of NaHCO3 in dextrose for 1 hour. Subsequent hydration was maintained at 1 mL/kg per hour during the procedure and 6 hours thereafter.	1438 [1390-1487]
Marenzi et al, 2012 (19)	UFR	250 mL of i.v. saline in 30 min as "priming". After priming, a bolus of furosemide 0.50 mg/kg was administered i.v. to achieve a urine output of ≥300 mL/h. The procedure was initiated after achieving the target urine flow rate (mean 48±16 min). Subsequent hydration with saline was matched automatically to urine flow output using the RenalGuard system. At the end of the procedure, a second dose of 0.20 mg/kg of i.v. furosemide was allowed if intraprocedural urine flow did not reach the target. Hydration was maintained for 4 hours after the end of the procedure.	3995±1401
	Fixed	1 mL/kg per hour of isotonic saline (0.5 mL/kg per hour if LVEF ≤40%) from 12 hours before to 12 hours after the procedure	1742±290
Brar et al, 2014 (20)	LVEDP	Initial bolus of normal saline 3 mL/kg in one hour. Subsequent infusion rate was set on the basis of LVEDP: if <13 mmHg infusion rate was set to 5 mL/kg per hour, 13 – 18 mmHg infusion rate was set to 3 mL/kg per hour, if >18 mmHg infusion rate was set to 1.5 mL/kg per hour. Hydration was continued during the procedure and for 4 hours thereafter.	1727±583
	Fixed	Initial bolus of normal saline 3 mL/kg in one hour. Subsequent fluid rate was set to 1.5 mL/kg per hour and was maintained throughout the procedure and 4 hours thereafter.	812±142
	UFR	250 mL of i.v. saline in 30 min as "priming". After priming, a bolus of furosemide 0.50 mg/kg was administered i.v. to achieve a urine output of ≥300 mL/h. The procedure was initiated after achieving the target urine	4033±1405

Usmiani et al, 2016 (21)		flow rate. Subsequent hydration with saline was matched automatically to urine flow output using the RenalGuard system. Additional furosemide boli were allowed at physician discretion to maintain target urine flow. Hydration was maintained for 4 hours after the end of the procedure.	
	Fixed	1000 mL 12 hours before the procedure at a flow rate adjusted for LVEF: 20 – 40 mL/h if LVEF <30%, 80 – 120 mL/h if LVEF 30 – 50%; 200 mL/h if LVEF >50%. Subsequent hydration was carried out with 1.4% sodium bicarbonate at 3 mL/kg per hour per 1 hour before the procedure. During and after the procedure, hydration was continued with 1.4% sodium bicarbonate at 1 mL/kg per hour. Hydration was terminated after 6 hours.	637±128
Qian et al, 2016 (22)	CVP	Hydration with normal saline was initiated 6 hours before and finished 12 hours after the procedure. Patients with a CVP <6 cmH_2O received normal saline at a rate of 3 mL/kg per hour, if CVP was 6 – 12 cmH_2O received normal saline at a rate of 1.5 mL/kg per hour, and if CVP was ≥13 cmH_2O the rate was set at 1 mL/kg per hour. Subsequent infusion rate was dynamically adjusted according to CVP variation.	1827±497
	Fixed	Hydration with normal saline was initiated 6 hours before and finished 12 hours after the procedure and maintained for 1.5 mL/kg per hour.	1202±247
Maioli et al, 2018 (23)	BIVA	Patients' hydration status was evaluated before inclusion in all patients using BIVA, and only patients with low volume status were included. In the experimental group, isotonic saline at 2 mL/kg per hour for 12 hours before and after the procedure. Infusion rate was halved if LVEF ≤40%.	3216 (2522–3600)
	Fixed	Patients' hydration status was evaluated before inclusion in all patients using BIVA, and only patients with low volume status were included. Isotonic saline at 1 mL/kg per hour for 12 hours before and after the procedure. Infusion rate was halved if LVEF ≤40%.	1476 (961–1680)
Marashizadeh et al, 2019 (24)	LVDEP	Normal saline at 1 mL/kg per hour procedure (0.5 mL/kg per hour if LVEF ≤40%) was administered for 12 hours before contrast administration and during the procedure. Hydration was subsequently adjusted for 4 hours after the procedure according to LVEDP: 5 mL/kg per hour if LVEDP ≤ 13 mmHg, 3 mL/kg per hour if LVEDP 13 – 18 mmHg and 1.5 mL/kg per hour if LVEDP ≥ 18 mmHg.	Not reported
	Fixed	Normal saline at 1 mL/kg per hour (0.5 mL/kg per hour if LVEF ≤40%) was administered from 12 hours before to 4 hours after the procedure.	Not reported

Briguori et al, 2020 (25)	UFR	250 mL of i.v. saline in 30 min as "priming" (reduced to 150 mL if LVEF≤30% or average E/e' >14 on transthoracic echocardiography). After priming, a bolus of furosemide 0.25 mg/kg was administered i.v. to achieve a urine output of ≥300 mL/h. The procedure was initiated upon obtainment of the target urine flow rate (mean 55±30 min). Subsequent hydration with saline was matched automatically to urine flow output using the RenalGuard system. Additional furosemide bolus of 0.25 mg/kg were administered 30' apart if urine flow rate dropped below 300 mL/h. Hydration was maintained for 4 hours after the end of the procedure.	2598±1349
	LVEDP	Hydration with normal saline was initiated 1 hour before the procedure was titrated on the basis of non-invasive estimates of LVEDP based on echocardiographic average E/e'. Saline flow rate was adjusted to 5 mL/kg per hour if E/e' <10, 3 mL/kg per hour if E/e' 10 – 14 and 1.5 mL/kg per hour if E/e' >14. Hydration rate was subsequently adjusted intraprocedurally according to invasive LVEDP: 5 mL/kg per hour if LVEDP was found to be low (<12 mmHg), 3 mL/kg per hour if LVEDP was intermediate (12 – 18 mmHg) or 1.5 mL/kg per hour if it was high (>18 mmHg). Hydration was continued for 4 hours after procedure. I.v. furosemide was allowed in case of pulmonary congestion of urine output <0.5 mL/kg per hour.	1709±1116

UFR: Urine flow rate; LVEDP: left ventricular end diastolic pressure; CVP: central venous pressure; BIVA: bio-impedance vector analysis; LVEF: left ventricular ejection fraction; i.v.: intravenous. Total hydration data are reported as Mean±Standard Error or Median [Interquartile Range] as appropriate.

Table S3. Characteristics of the included studies.

Authors, Year (ref)	n	Population included	Definition of high AKI risk	Treatment arms	CI-AKI definition	CI-AKI Rates	Pulmonary edema rates
Briguori et al, 2011 (18)*	292	Patients undergoing elective coronary angiography (38%), elective PCI (54%) or peripheral angiography/intervention (8%) with high AKI risk	eGFR (mMDRD) ≤30 ml/min 1.73 m^2 OR Mehran score ≥11	UFR-guided hydration (n=146) vs fixed hydration (n=146)	Serum creatinine increase from baseline ≥0.3 mg/dL 48h after procedure or new need for dialysis	UFR: 16/146 Fixed: 30/146	UFR: 3/146 Fixed: 1/146
Marenzi et al, 2012 (19)	170	Elective or urgent coronary angiography (49%) or coronary angiography plus PCI (51%) in subjects at risk for AKI. Urgent procedures constituted 41% of total	eGFR (mMDRD) ≤60 ml/min 1.73 m^2	UFR-guided hydration (n=87) vs fixed hydration (n=83)	Serum creatinine increase ≥25% or ≥0,5 mg/dL over baseline during the first 72h from procedure	UFR: 4/87 Fixed: 15/83	UFR 5/87 Fixed: 10/83
Brar et al, 2014 (20)	350	Elective or urgent cardiac catheterization in subjects at high risk of AKI. PCI was performed in 28% of cases. 42% of patients presented with ACS	eGFR (mMDRD) ≤60 ml/min 1.73 m^2 and one or more of: diabetes mellitus, history of CHF, HTN, ≥75 years of age.	LVEDP-guided hydration (n=178) vs fixed hydration (n=172)	Serum creatinine increase ≥25% or ≥0,5 mg/dL over baseline obtained during post-procedural days 1-4	LVEDP: 12/178 Fixed: 28/172	LVEDP: 3/178 Fixed: 3/172
Usmiani et al, 2016 (21)	124	Elective or urgent coronary angiography or PCI in subjects at high risk for AKI. PCI was performed in 47% of	eGFR (CKD-EPI) ≤60 ml/min 1.73 m^2	UFR-guided hydration (n=59) vs fixed	Serum creatinine increase ≥0,3 mg/dL or ≥50% over baseline over 48h or 7 days post-procedure respectively	UFR: 4/59 Fixed: 16/65	-

		cases. Urgent procedures represented 40% of cases.		hydration (n=65)			
Qian et al, 2016 (22)	264	Elective or urgent coronary angiography or PCI performed in subjects at high risk for AKI and a clinical history of CHF. PCI was performed in 88% of cases. 81% of patients presented with ACS; STEMI were excluded.	eGFR (mMDRD) ≤60 ml/min 1.73 m^2	CVP-guided hydration (n=132) vs Fixed hydration (n=132)	Serum creatinine increase ≥25% or ≥0,5 mg/dL over baseline during the first 72h after contrast administration	CVP: 21/132 Fixed: 39/132	CVP: 5/132 Fixed: 4/132
Maioli et al, 2018 (23)	296	Elective coronary angiography or PCI in subjects with low body fluid volume as assessed per bio-impedance vector analysis. PCI was performed in 59% of cases.	Not applicable	BIVA-guided hydration (n=148) vs fixed hydration (n=148)	Serum Cystatine C increase ≥10% over baseline within 24h after contrast administration	BIVA: 17/148 Fixed: 33/148	BIVA: 0/148 Fixed: 0/148
Marashizadeh et al, 2019 (24)	109	Elective coronary angiography or PCI in subjects with chronic coronary syndromes and high risk of AKI. PCI was performed in 42% of cases.	eGFR (mMDRD) between 15-60 ml/min 1.73 m^2	LVEDP-guided hydration (n=57) vs fixed hydration (n=52)	Serum creatinine increase ≥25% or ≥0,5 mg/dL over baseline during at 24h or 72h after contrast administration	LVEDP: 4/57 Fixed: 2/57	LVEDP: 0/57 Fixed: 0/57
Briguori et al, 2020 (25)*	702	Patients undergoing elective coronary angiography (36%), elective PCI (61%) or peripheral angiography/PTA (3%) with high AKI risk	eGFR (mMDRD) ≤45 ml/min 1.73 m^2 OR Mehran score ≥11 OR Gurm's score >7%	UFR-guided hydration (n=351) vs LVEDP-guided hydration (n=351)	Serum creatinine increase ≥25% or ≥0,5 mg/dL over baseline obtained during post-procedural days 1-4	UFR: 20/351 LVEDP: 35/351	UFR: 1/351 LVEDP: 5/351

eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention; PTA: percutaneous transluminal angioplasty; AKI: acute kidney injury; CI-AKI: contrast induced acute kidney injury; PE: pulmonary edema; ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; mMDRD: modified Modification of Diet in Renal Disease formula(45); CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration(46); UFR: Urine flow rate; LVEDP: left ventricular end diastolic pressure; CVP: central venous pressure; BIVA: bio-impedance vector analysis.
Mehran's and Gurm's score: see (47) and (48), respectively

*Studies (18) and (25) were included in the analysis despite including patients undergoing peripheral angiography/intervention since >90% of the study population consisted of coronary angiography and PCI patients, therefore minimizing the risk of bias connected to heterogeneous procedures.

Table S4. League Table for contrast-induced acute kidney injury (upper panels) and pulmonary edema (lower panels) in the sensitivity analysis. Each cell contains an odds ratio (OR) for the comparison of treatment reported in the column vs treatment reported in the line. Grey cells contain treatment name.

CI-AKI

UFR			
0.32 (0.19,0.54)	**Fixed Hydration**		
0.58 (0.31,1.09)	1.82 (0.98,3.37)	**LVEDP**	
0.71 (0.28,1.81)	2.22 (1.03,4.79)	1.22 (0.45,3.26)	**CVP**

Pulmonary Edema

UFR			
0.54 (0.17,1.79)	**Fixed Hydration**		
0.35 (0.08,1.51)	0.64 (0.16,2.60)	**LVEDP**	
0.43 (0.06,2.90)	0.79 (0.18,3.50)	1.24 (0.16,9.58)	**CVP**

CI-AKI: contrast induced acute kidney injury; UFR: urine flow rate; LVEDP: left ventricular end diastolic pressure; CVP: central venous pressure.

Table S5. Loop-specific inconsistency for contrast-induced acute kidney injury (CI-AKI – upper panel) and pulmonary edema (lower panel).

Comparison	K	Prop	NMA	Direct	Indirect	RoR	z	p
CI-AKI								
BIVA vs CVP	0	0	1.000	.	1.000	.	.	.
BIVA vs Fixed	1	1.00	0.4538	0.4538	.	.	.	.
BIVA vs LVEDP	0	0	0.8182	.	0.8182	.	.	.
BIVA vs UFR	0	0	1.4230	.	1.4230	.	.	.
CVP vs Fixed	1	1.00	0.4538	0.4538	.	.	.	.
CVP vs LVEDP	0	0	0.8182	.	0.8182	.	.	.
CVP vs UFR	0	0	1.4230	.	1.4230	.	.	.
Fixed vs LVEDP	2	0.61	1.8028	1.9097	1.6465	1.1599	0.22	0.8253
Fixed vs UFR	3	0.77	3.1355	3.0302	3.5147	0.8622	-0.22	0.8253
LVEDP vs UFR	1	0.62	1.7392	1.8404	1.5867	1.1599	0.22	0.8253
Pulmonary Edema								
CVP vs Fixed	1	1.00	1.2586	1.2586	.	.	.	.
CVP vs LVEDP	0	0	0.6963	.	0.6963	.	.	.
CVP vs UFR	0	0	2.0906	.	2.0906	.	.	.
Fixed vs LVEDP	1	0.65	0.5532	1.0305	0.1727	5.9650	0.95	0.3412
Fixed vs UFR	2	0.83	1.6610	1.2264	7.3155	0.1676	-0.95	0.3412
LVEDP vs UFR	1	0.52	3.0024	7.0993	1.1902	5.9650	0.95	0.3412

CI-AKI: contrast induced acute kidney injury; UFR: urine flow rate; LVEDP: left ventricular end diastolic pressure; CVP: central venous pressure; k: number of studies providing direct evidence; Prop: direct evidence proportion; NMA: estimated treatment effect from the network meta analysis; direct: estimated treatment effect from direct evidence; indirect: estimated treatment effect from indirect evidence; RoR: ratio of ratios (direct vs indirect); z: z-value for disagreement test; p: p-value of disagreement test.

Table S6. Limitations of currently available tailored hydration strategies. The + sign whether the tailored hydration strategy possesses the characteristic mentioned in the heading. Red color indicates potential drawback, green color potential advantage

	Requires dedicated equipment	Requires invasive procedures for set up	Requires electrolytes monitoring	Requires delaying PCI	Provides multiple measures to fine-tune hydration
UFR	+	+	+	+	+
CVP	-	+	-	-	-
BIVA	+	-	-	-	-
LVDEP	-	-	-	-	-

BIVA: bio-impedance vectorial analysis; UFR: urine flow rate; LVEDP: left ventricular end diastolic pressure; CVP: central venous pressure.

Figure S1. PRISMA diagram for study selection process.

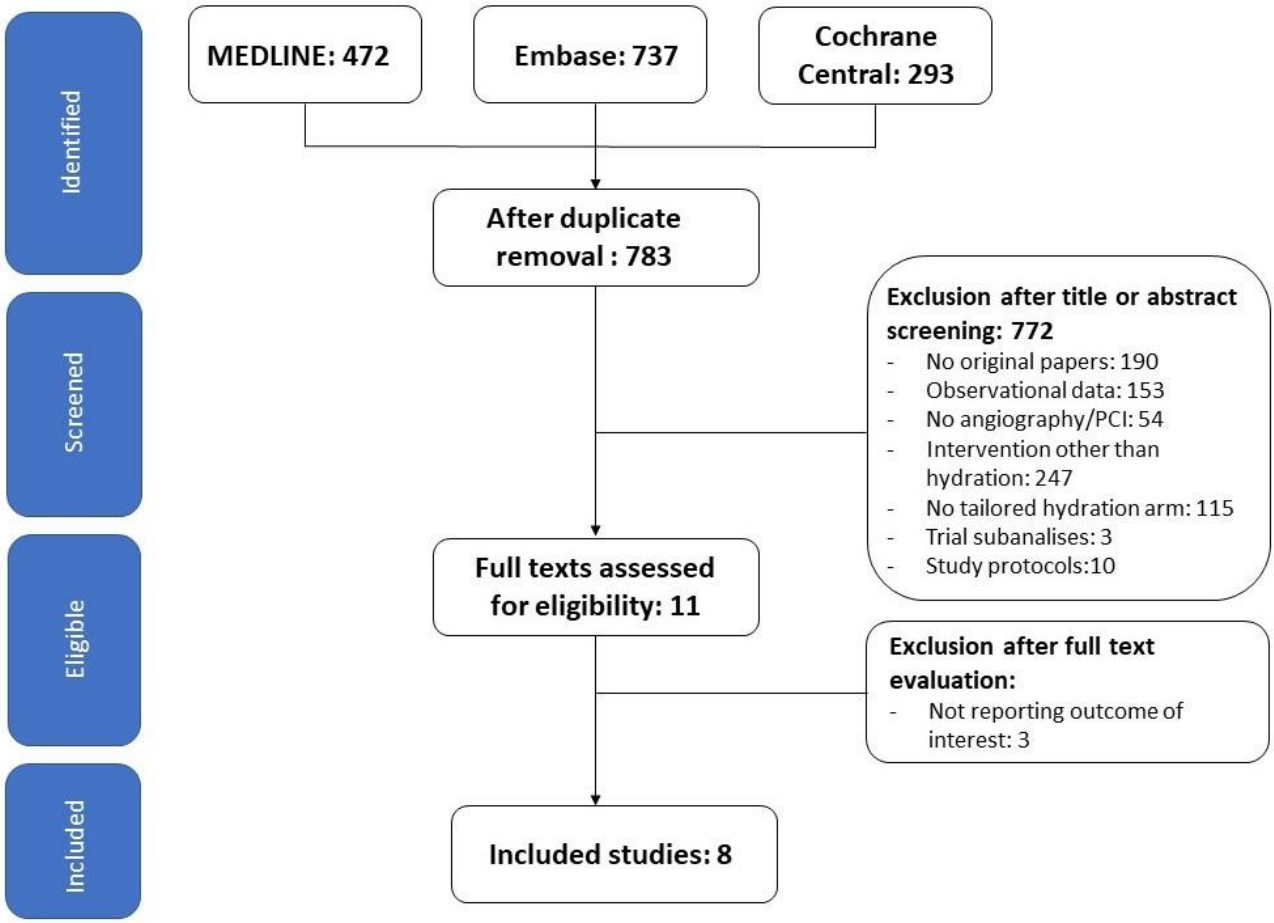


Figure S2. Risk of bias assessment for the primary efficacy outcome (contrast-induced acute kidney injury) according to the Revised Cochrane Risk of Bias assessment tool (RoB 2). (6)

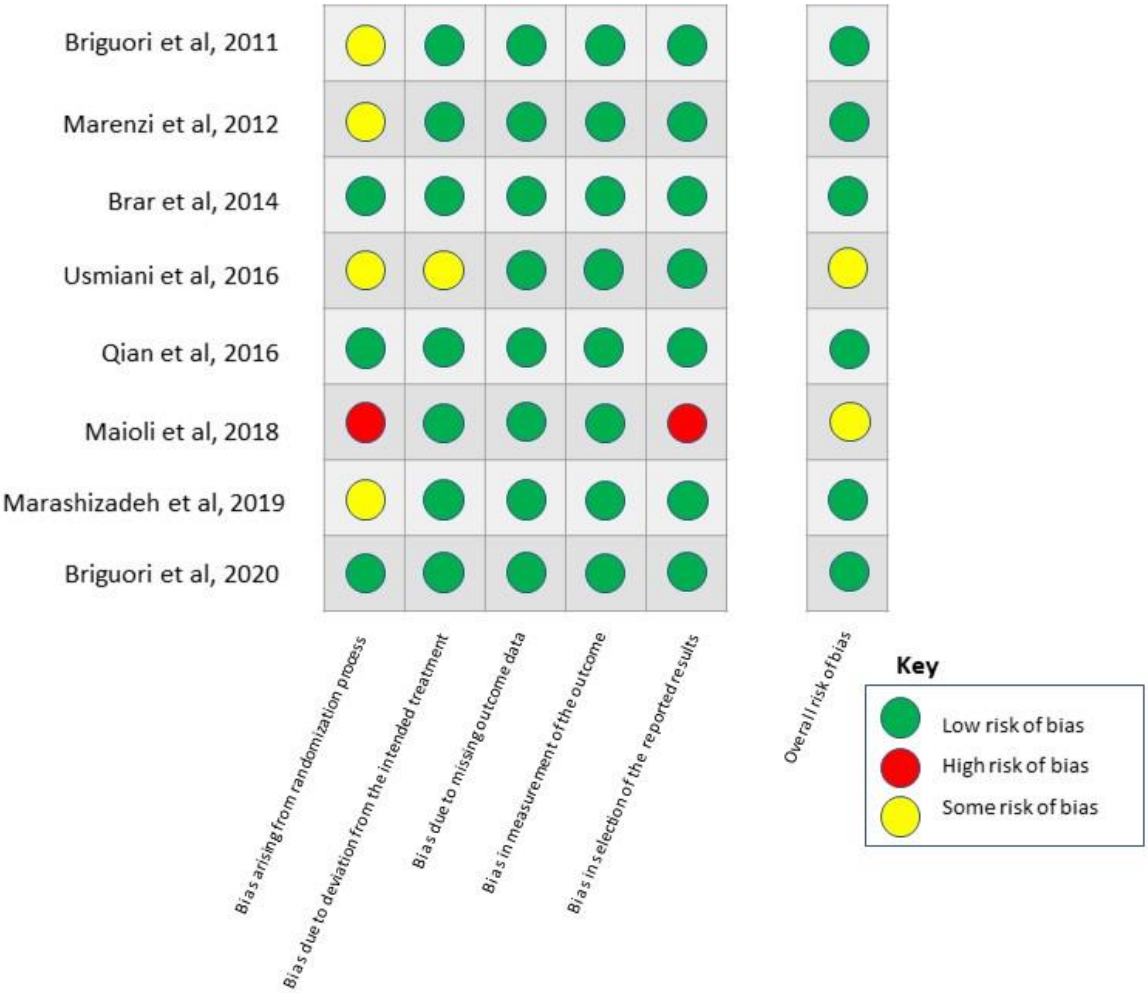


Figure S3. Risk of bias assessment for the primary safety outcome (acute pulmonary edema) according to the Revised Cochrane Risk of Bias assessment tool (RoB 2). (6)

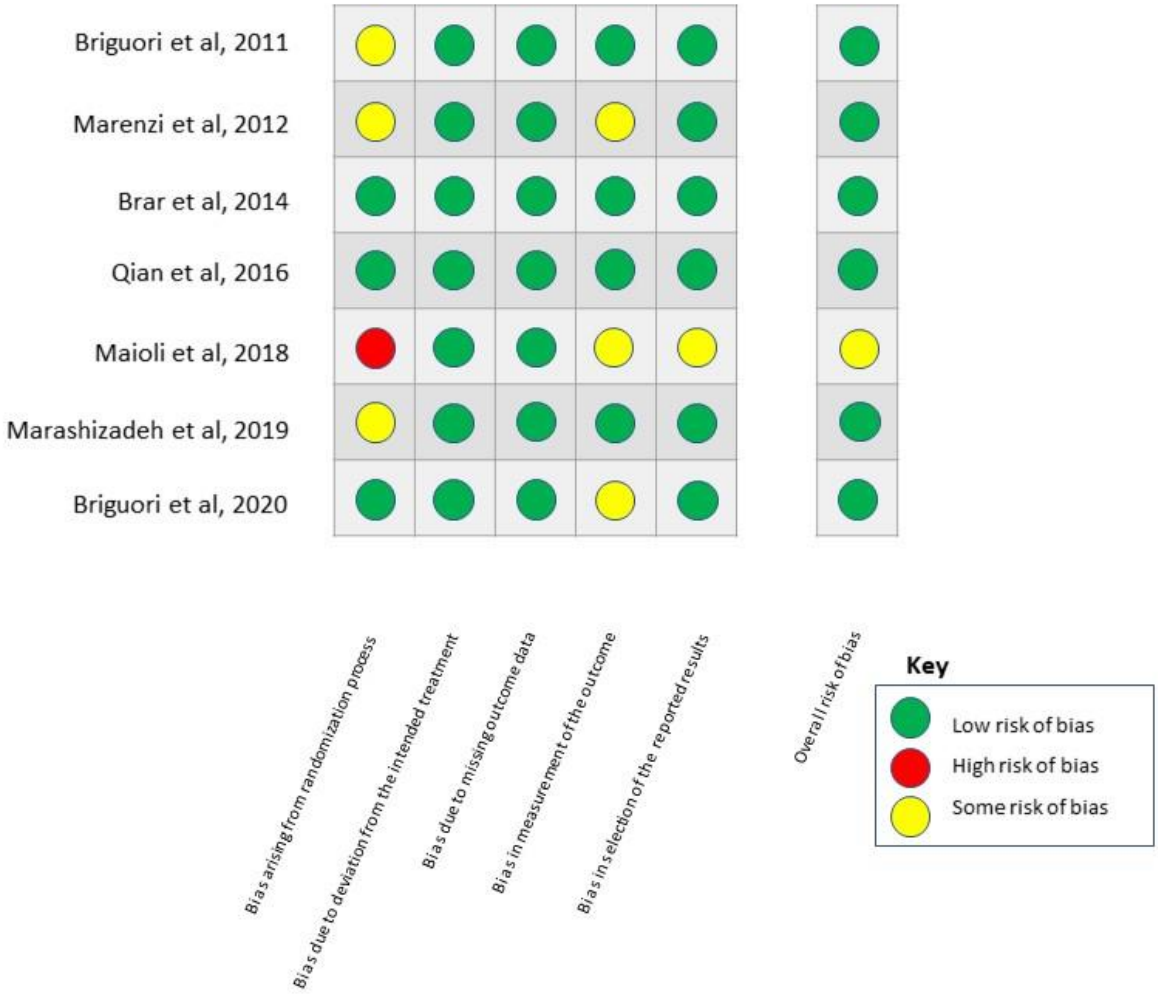
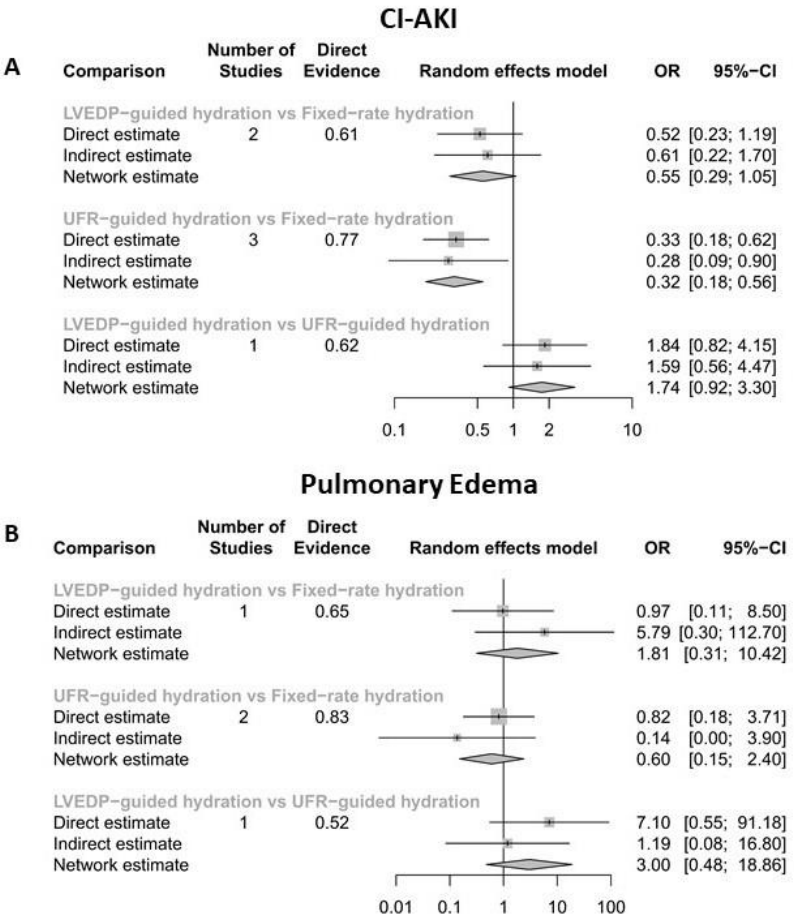
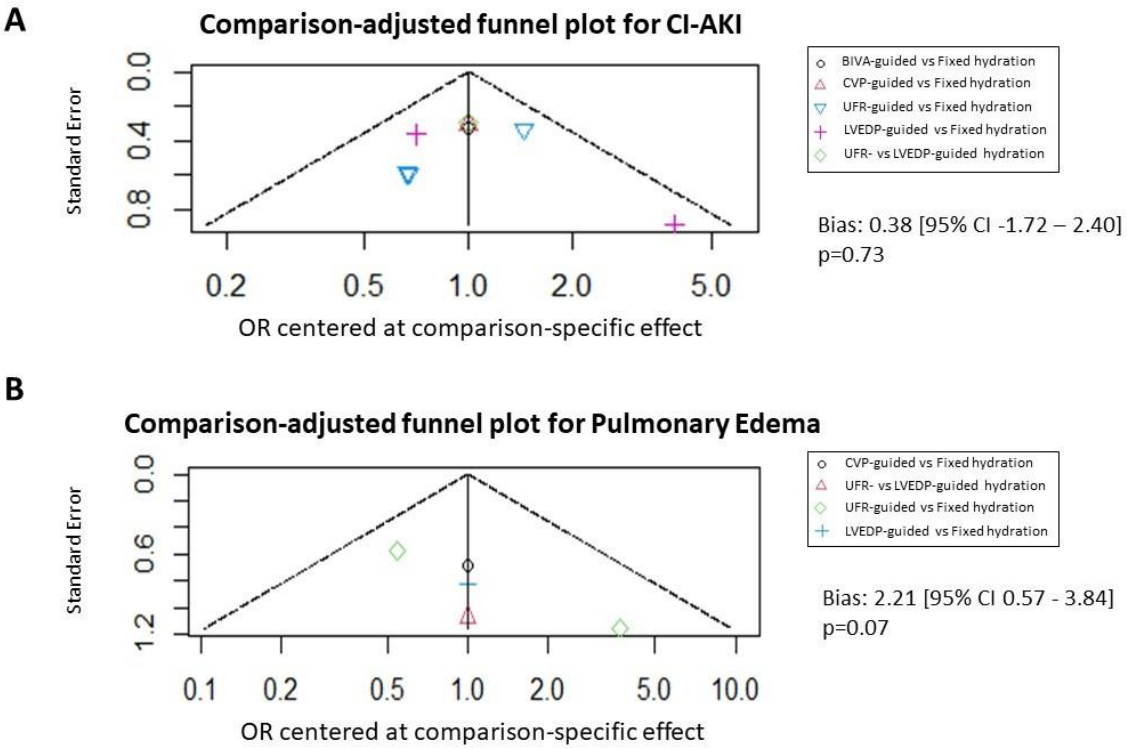


Figure S4. Forest plots of direct and indirect estimates of effect size obtained through node-splitting, separate indirect from direct evidence (SIDE) method.



Panel A shows the estimates for CI-AKI, while panel B shows the results for pulmonary edema. CI-AKI, contrast induced acute kidney injury; LVEDP, left ventricular end diastolic pressure; UFR, urinary flow rate.

Figure S5. Comparison-adjusted funnel plots.



Panel A shows the comparison adjusted funnel plot for contrast induced acute kidney injury (CI-AKI), while panel B shows the plot for pulmonary edema. Considering that 0 pulmonary edema events were reported in the study by Maioli et al reporting on bioimpedance vector analysis guided hydration,(23) the strategy could not be included in funnel plot analysis for the latter outcome. On the right side of the plots, bias with respective 95% confidence intervals and p-values are reported. Bias were calculated as previously described.(7)