Prevention of Contrast-Induced Acute Kidney Injury by Furosemide With Matched Hydration in Patients Undergoing Interventional Procedures

A Systematic Review and Meta-Analysis of Randomized Trials

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ABSTRACT

OBJECTIVES The objective of this meta-analysis of randomized trials was to evaluate if the administration of furosemide with matched hydration using the RenalGuard System reduces contrast-induced acute kidney injury (CI-AKI) in patients undergoing interventional procedures.

BACKGROUND CI-AKI is a serious complication following angiographic procedures and a powerful predictor of unfavorable early and long-term outcomes.

METHODS Online databases were searched up to October 1, 2016, for randomized controlled trials. The primary outcome was the incidence of CI-AKI, and the secondary outcomes were need for renal replacement therapy, mortality, stroke, and adverse events.

RESULTS A total of four trials (n = 698) published between 2011 and 2016 were included in the analysis and included patients undergoing percutaneous coronary procedures and transcatheter aortic valve replacement. RenalGuard therapy was associated with a lower incidence of CI-AKI compared with control treatment (27 of 348 [7.76%] patients vs. 75 of 350 [21.43%] patients; odds ratio [OR]: 0.31; 95% confidence interval [CI]: 0.19 to 0.50; $I^2 = 4\%$; p < 0.00001) and with a lower need for renal replacement therapy (2 of 346 [0.58%] patients vs. 12 of 348 [3.45%] patients; OR: 0.19; 95% CI: 0.05 to 0.76; $I^2 = 0\%$; p = 0.02). No major adverse events occurred in patients undergoing RenalGuard therapy.

CONCLUSIONS The main finding of this meta-analysis is that furosemide with matched hydration by the RenalGuard System may reduce the incidence of CI-AKI in high-risk patients undergoing percutaneous coronary intervention or transcatheter aortic valve replacement. However, further independent high-quality randomized trials should elucidate the effectiveness and safety of this prophylactic intervention in interventional cardiology. (J Am Coll Cardiol Intv 2017;10:355–63) © 2017 by the American College of Cardiology Foundation.

Contrast-induced acute kidney injury (CI-AKI), also known as contrast-induced nephropathy, is a frequent complication following angiographic procedures with significant impact on health care costs and a powerful predictor of unfavorable early and long-term outcomes (1–3).

Following contrast administration, CI-AKI is defined as a rise in serum creatinine (SCr) of 0.5 mg/dl (44.2 μmol/l) or a 25% relative rise in SCr within 72 h of contrast exposure in the absence of an alternative cause (3,4). Because accumulation of SCr is relatively slow, it requires 48 to 72 h to identify many cases of

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CI-AKI = contrast-induced acute kidney injury

GFR = glomerular filtration rate

GRADE = Grading of Recommendations Assessment, Development and Evaluation

OR = odds ratio

RRT = renal replacement therapy

SCr = serum creatinine

CI-AKI. Acute kidney injury up to 7 days post-contrast administration could be considered CI-AKI. A minority of patients may have symptoms such as anuria, electrolyte imbalance, hypotension, or hypertension and may need renal replacement therapy (RRT) (2). The incidence of CI-AKI is estimated to be 1% to 2% (5,6), but it may be significantly higher in patients with diabetes mellitus and pre-existing renal impairment (6) or in case of intra-arterial contrast administration (7); moreover, in patients with pre-existing renal impairment, the risk for CI-AKI can be as high as 50%. It is also procedure dependent, with 14.5% overall in patients undergoing percutaneous coronary interventions (8) compared with 1.6% to 2.3% for diagnostic intervention (9). In patients undergoing percutaneous coronary intervention, each 100 ml of contrast was associated with a 12% increased risk for CI-AKI (10).

The optimal treatment for preventing CI-AKI has not yet been defined (2): trials of *N*-acetylcysteine, diuretic agents, dopamine, calcium-channel blockers, atrial natriuretic peptides, aminophylline, statins, and endothelin antagonists have yielded contrasting results (2). Only periprocedural hydration is widely accepted to prevent contrast nephropathy (2,3,11).

Multiple kidney-protective strategies have been studied, but few have shown benefit in prospective randomized studies (12). Recently, a novel system aimed at reducing CI-AKI was introduced in the market. The RenalGuard System (PLC Medical Systems, Milford, Massachusetts) delivers intravenous fluids matched to urine output with a combination of hydration with normal saline at an initial dose bolus plus a low dose of furosemide and continuous monitoring for a urine output flow of >300 ml/h sustained for 6 h (12).

The aim of our systematic review and meta-analysis was to evaluate if furosemide with matched hydration using the RenalGuard System effectively decreases the incidence of CI-AKI in patients undergoing interventional procedures.

METHODS

The present study was conducted in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13); a complete checklist is provided in Online Table 1. We registered the study protocol on the PROSPERO database of systematic reviews (CRD42016036208).

SEARCH STRATEGY. Two trained investigators independently searched PubMed, Embase, and the Cochrane Central Register of Clinical Trials (last updated October 1, 2016) for appropriate reports. The full PubMed search strategy is available in the Online Appendix. The search strategy aimed to include any randomized study ever performed with furosemide with matched hydration with the RenalGuard System compared with any control group in adult humans in interventional cardiology settings. Abstracts from recent international conferences were searched for additional relevant studies. In addition, we hand-scanned the references of retrieved reports and pertinent reviews of the published research. No language restriction was enforced.
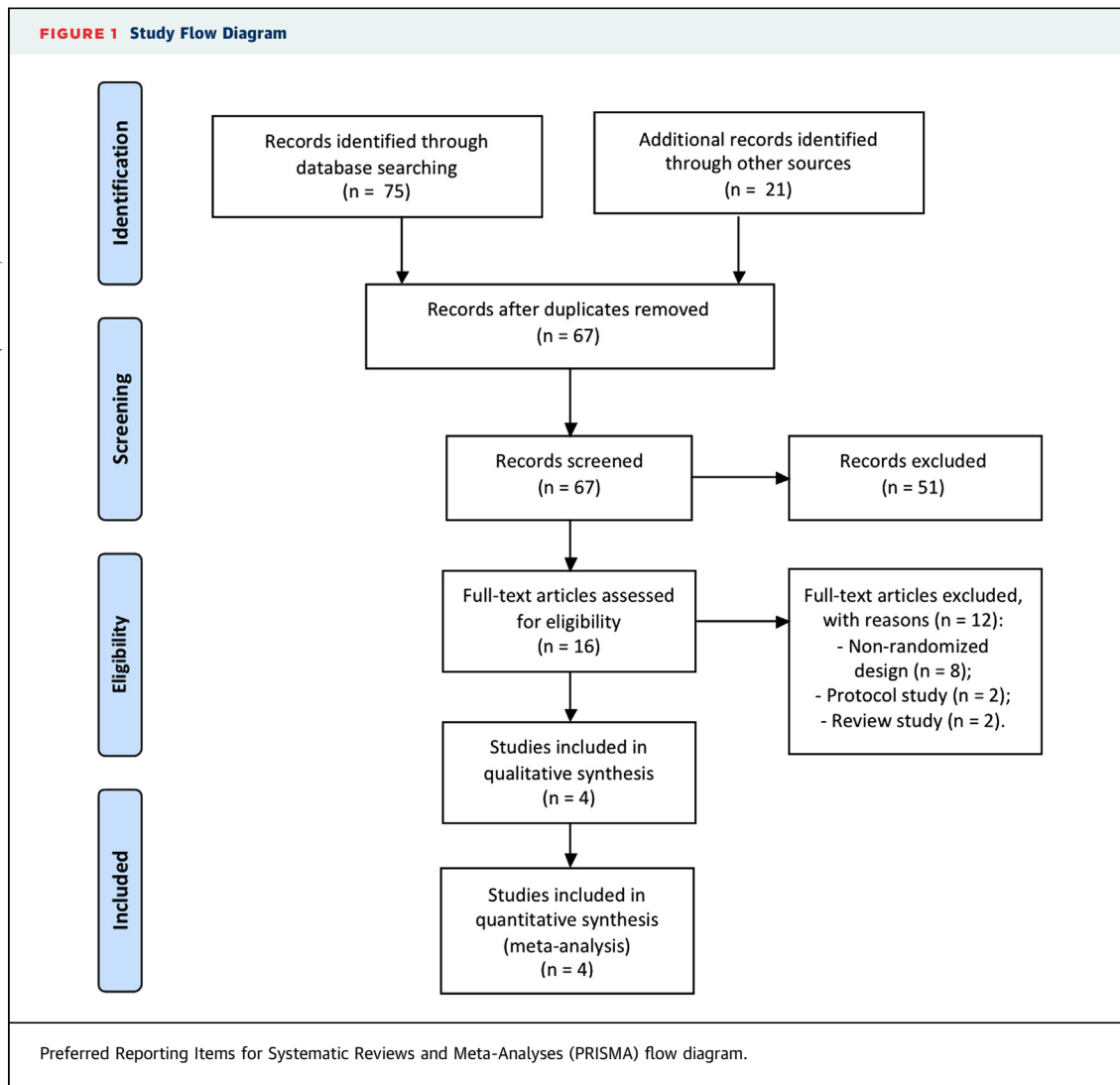
STUDY SELECTION. References obtained from searches were first independently examined at the abstract level by 2 investigators and then, if potentially relevant, collected as complete reports. Eligible studies met the following PICOS criteria: 1) population: adult hospitalized patients undergoing interventional procedures; 2) intervention: furosemide with matched hydration with the RenalGuard System; 3) comparison intervention: any type of control group; 4) outcome: incidence of CI-AKI; and 5) study design: randomized controlled trials. The exclusion criteria were overlapping populations and pediatric studies. Two investigators independently assessed selected studies for the final analysis, with eventual divergences finally resolved by consensus with a third investigator. If the report did not include primary data, the corresponding investigator was contacted for further data.

DATA ABSTRACTION AND STUDY CHARACTERISTICS. Two authors independently extracted data from studies and entered them into a pre-defined database. We collected potential sources of clinical heterogeneity, such as study design, clinical setting, inclusion and exclusion criteria, intervention regimen and length, control intervention, time point of outcome assessment, CI-AKI definition, and adverse events.

The primary outcome of the present review was the incidence of CI-AKI. The secondary outcomes were need for RRT, mortality at longest follow-up available, acute coronary syndromes, stroke or transient ischemic attack, and adverse events. The outcomes were reported as per-study definition.

We rated the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (14).

FIGURE 1 Study Flow Diagram

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Identification

Records identified through database searching (n = 75)

Additional records identified through other sources (n = 21)

Records after duplicates removed (n = 67)

Screening

Records screened (n = 67)

Records excluded (n = 51)

Eligibility

Full-text articles assessed for eligibility (n = 16)

Full-text articles excluded, with reasons (n = 12):
- Non-randomized design (n = 8);
- Protocol study (n = 2);
- Review study (n = 2).

Studies included in qualitative synthesis (n = 4)

Included

Studies included in quantitative synthesis (meta-analysis) (n = 4)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

RISK OF BIAS ASSESSMENT. Each trial included was evaluated for risk of bias according to a modified Jadad quality scale that assesses the adequacy of randomization, the concealment of treatment allocation, the similarity of treatment groups at randomization, investigator blinding, and the description of withdrawals and dropouts. Post hoc risk of bias analysis was performed according to Cochrane Collaboration methods (14).

DATA ANALYSIS AND SYNTHESIS. To analyze the binary outcome, we calculated odds ratio (OR) with 95% confidence interval (CI). We also calculated the number needed to treat in case of statistically significant results. To assess between-study heterogeneity, we used the Cochran Q statistic and the I^2 statistic. We pooled the study-specific estimate using a fixed-effect model in case of low statistical inconsistency ($I^2 \leq 25\%$) or with a random-effect model in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Publication bias was assessed by visually inspecting a funnel plot for the primary outcome. Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing.

To test the strength of the results, we performed sensitivity analysis removing 1 trial at a time and reanalyzing the remaining dataset. Further sensitivity analysis was performed by analyzing data with a fixed-effect versus random-effects model and to investigate whether choice of summary statistic changed the results of the meta-analysis (14). In case of possible or unreported conflicts of interests within the included trials, we performed a sensitivity analysis excluding them. We performed post hoc

TABLE 1 Characteristics of the Included Trials

First Author (Year) (Ref. #)	Number of Centers	Sample Size	Age (yrs)	Setting	Control	GFR* Inclusion Criteria	GFR* at Inclusion (ml/min/1.73 m²)	CI-AKI Definition	CI-AKI Assessment	Possible Conflicts of Interest
Barbanti (2015) (26)	Single center	112	81 ± 6	TAVR	Normal saline	Any GFR	63 ± 23	Increase in SCr ≥50% of baseline or ≥0.3 mg/dl (≥26.4 µmol/l)	72 h	NR
Briguori (2011) (29)	Multicenter	292	75 ± 9	Elective coronary angiography, elective PCI, elective peripheral angiography	Sodium bicarbonate and NAC	GFR ≤30 ml/min/1.73 m² or GFR ≤60 ml/min/1.73 m² with risk score >10†	32 ± 8	Increase in SCr ≥0.3 mg/dl (≥26.4 µmol/l) or need for dialysis	48 h	No
Marenzi (2012) (28)	Single center	170	73 ± 8	Elective coronary angiography, elective and urgent‡ PCI	Normal saline	GFR <60 ml/min/1.73 m²	40 ± 11	Increase in SCr ≥25% of baseline or ≥0.5 mg/dl (≥44.2 µmol/l)	72 h	No
Usmiani (2015) (27)	Single center	133	75 ± 9	Elective coronary angiography, elective PCI	Sodium bicarbonate, normal saline, NAC, and vitamin C	GFR <60 ml/min/1.73 m²	44 ± 12	Increase in SCr ≥0.3 mg/dl (≥26.4 µmol/l) within 48 h or ≥50% of baseline within 7 days	48 h and 7 days	No

*The MDRD (Modification of Diet in Renal Disease) or Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate GFR from SCr. †Risk score for predicting CI-AKI calculated according to the following algorithm (8): hypotension (integer score 5), intra-aortic balloon pump support (integer score 5), congestive heart failure (integer score 4), age 75 yrs (integer score 4), diabetes mellitus (integer score 3), GFR <60 ml/min/1.73 m² (integer score 2 to 6), pre-existing anemia (integer score 3), and contrast media volume (integer score 1 for each 100 cm³). ‡Urgent PCI defined as procedure within 24 h from hospital admission because of non-ST-segment elevation acute myocardial infarction.

CI-AKI = contrast-induced acute kidney injury; GFR = glomerular filtration rate; NAC = N-acetylcysteine; PCI = percutaneous coronary intervention; SCr = serum creatinine; TAVR = transcatheter aortic valve replacement.

subgroup analyses studying the effect of the intervention in different subsettings to evaluate possible subgroup effect. Post hoc metaregression was used to examine the possible influence of age and baseline glomerular filtration rate (GFR) on primary outcome.

Statistical analysis was performed using Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

CHARACTERISTICS OF INCLUDED STUDIES. The search strategy yielded 96 citations (**Figure 1**). Eighty references were excluded because they did not meet the inclusion criteria. Major exclusions were due to lack of a randomized design (n = 8) (12,15-21), protocol study (n = 2) (22,23), and review study (n = 2) (24,25) (**Figure 1**).

Four trials (26-29) (698 patients) met the inclusion criteria (**Table 1**, Online Table 2). The trials were published between 2011 and 2016. All trials but 1 (29) had a single-center design. All trials were performed in Italy.

All trials used the RenalGuard System for the prevention of CI-AKI in patients undergoing coronary artery procedures (27-29) or transcatheter aortic valve replacement (26). All trials administered specific treatments as control: isotonic saline (26,28), intravenous sodium bicarbonate plus *N*-acetylcysteine (29), or sodium bicarbonate plus isotonic saline plus *N*-acetylcysteine plus vitamin C (27). Interventions' regimens are reported in detail in Online Table 3.

Trials performed in the setting of coronary procedures enrolled patients with pre-operative kidney impairment, whereas transcatheter aortic valve replacement trials enrolled all patients regardless of their kidney function (**Table 1**). To estimate GFR from SCr, the Modification of Diet in Renal Disease (MDRD) equation was used in 3 trials and the Chronic Kidney Disease Epidemiology Collaboration equation in 1 trial (27). Different CI-AKI definitions were used (**Table 1**).

All trials scored 4 of 6 points in the modified Jadad/ Oxford quality scale and were judged to be at high risk of bias according to Cochrane methodology (Online Table 4). None of the trials was blinded, although the difficulty of blinding patients and personnel should be acknowledged given the nature of the intervention.

CI-AKI. Overall, RenalGuard therapy was associated with a lower incidence of CI-AKI compared with control treatment (27 of 348 [7.76%] vs. 75 of 350

FIGURE 2 Meta-Analysis Comparing the Effects of RenalGuard Therapy Versus Control Group on Post-Operative Contrast-Induced Acute Kidney Injury and Need for Renal Replacement Therapy
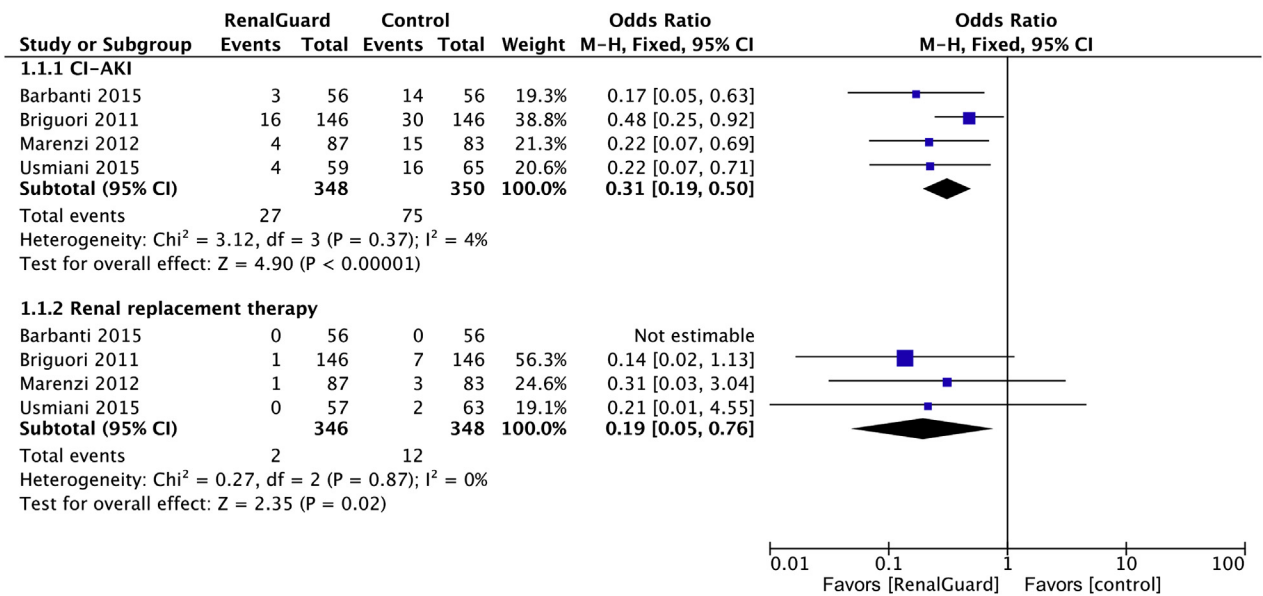
RenalGuard therapy was found to significantly decrease both contrast-induced acute kidney injury (CI-AKI) and renal replacement therapy. CI = confidence interval; M-H = Mantel-Haenszel.

[21.43%]; OR: 0.31; 95% CI: 0.19 to 0.50; p for heterogeneity = 0.37; I^2 = 4%; p < 0.00001; number needed to treat = 8) with all trials included (**Figure 2**). The level of evidence according to GRADE was moderate.

RenalGuard therapy was associated with a lower need for RRT (2 of 346 [0.58%] vs. 12 of 348 [3.45%] patients; OR: 0.19; 95% CI: 0.05 to 0.76; I^2 = 0%; p = 0.02) with all trials included (**Figure 2**). The level of evidence according to GRADE was low.

The efficacy of the RenalGuard system was confirmed when results were limited to patients with GFRs <60 ml/min at randomization who underwent elective coronary procedures (27-29) (n = 325; OR: 0.38; 95% CI: 0.22 to 0.65; p for heterogeneity = 0.43, I^2 = 0%; p = 0.0004) or urgent coronary procedures (28) for non–ST-segment elevation acute myocardial infarction (n = 60; OR: 0.11; 95% CI: 0.02 to 0.57; p = 0.008) (Online Table 4). Furosemide with matched hydration was associated with a lower incidence of acute kidney injury also in TAVR (112 patients; OR: 0.17; 95% CI: 0.05 to 0.63; p = 0.008) with 1 trial included (26) (Online Table 5).
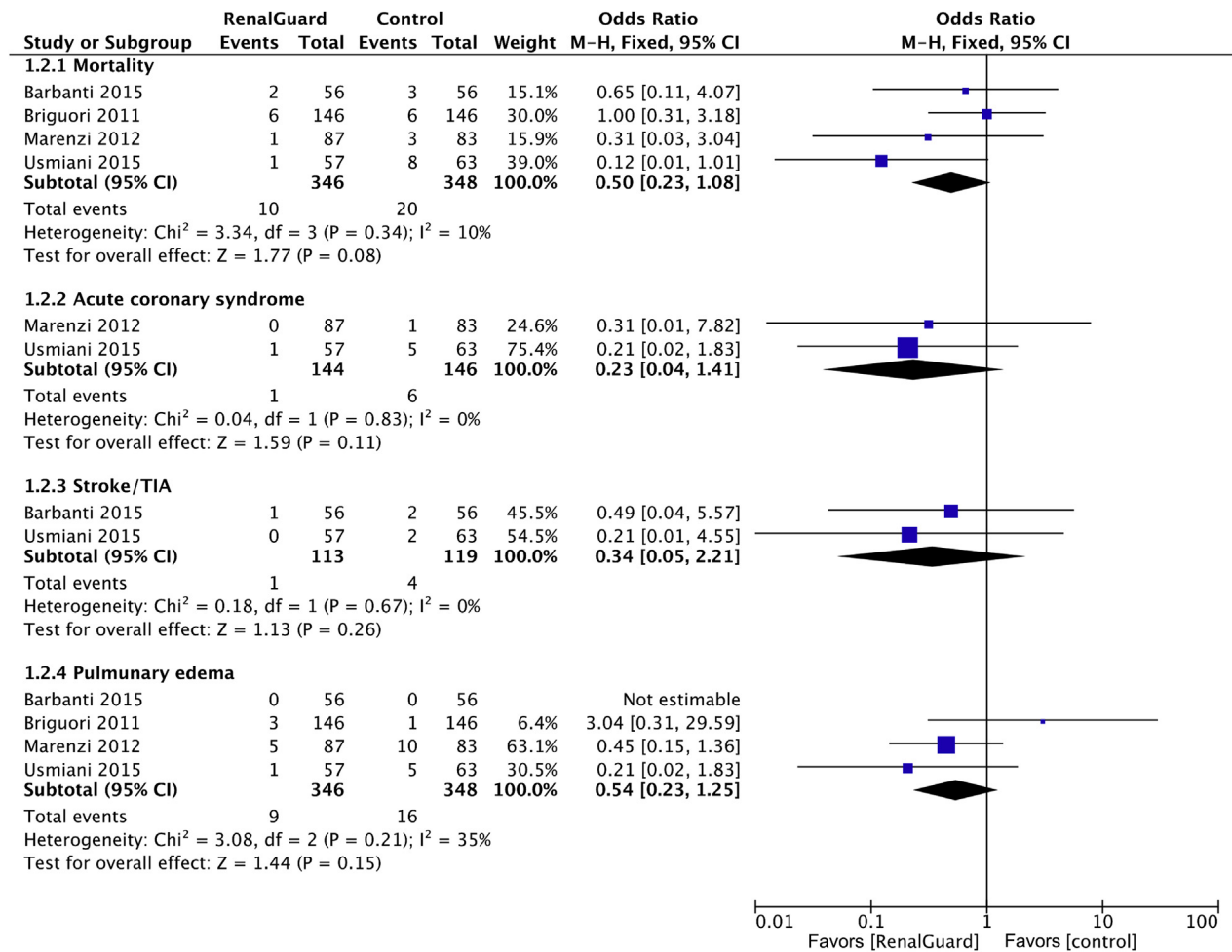
Meta-regression failed to find any significant correlation with age and GFR at randomization (Online Appendix). The sensitivity analyses of the primary outcome confirmed the results (Online Table 6) also when excluding trials with possible or unreported conflicts of interest (26), confirming the benefit of RenalGuard over control group (OR: 0.34; 95% CI: 0.21 to 0.57; p < 0.0001).

OTHER CLINICAL OUTCOMES. The RenalGuard was associated with a nonsignificant lower mortality rate compared with control group (OR: 0.50; 95% CI: 0.23 to 1.08; I^2 = 10%; p = 0.08) at the longest follow-up available (**Figure 3**). The longest follow-up available was 1-month mortality (26,29), in-hospital mortality (28), and 1-year mortality (27).

A nonsignificant lower incidence of post-operative acute coronary syndromes (OR: 0.23; 95% CI: 0.04 to 1.41; p = 0.11, with 2 trials included [27,28]) and stroke or transient ischemic attack (OR: 0.34; 95% CI: 0.05 to 2.21; p = 0.26, with 2 trials included [26,27]) was found in the case group (**Figure 3**).

SAFETY PROFILE AND ADVERSE EVENTS. No life-threatening adverse events were reported in patients undergoing RenalGuard therapy. Because of the nature of the intervention, perioperative pulmonary edema could be considered one of the worrying adverse events. However, the meta-analysis for

FIGURE 3   Meta-Analysis Comparing the Effects of RenalGuard Therapy Versus Control Group on Secondary Clinical Outcomes

Study or Subgroup	RenalGuard Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.1 Mortality						
Barbanti 2015	2	56	3	56	15.1%	0.65 [0.11, 4.07]
Briguori 2011	6	146	6	146	30.0%	1.00 [0.31, 3.18]
Marenzi 2012	1	87	3	83	15.9%	0.31 [0.03, 3.04]
Usmiani 2015	1	57	8	63	39.0%	0.12 [0.01, 1.01]
Subtotal (95% CI)		346		348	100.0%	0.50 [0.23, 1.08]
Total events	10		20			

Heterogeneity: Chi² = 3.34, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 1.77 (P = 0.08)

	RenalGuard Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.2 Acute coronary syndrome						
Marenzi 2012	0	87	1	83	24.6%	0.31 [0.01, 7.82]
Usmiani 2015	1	57	5	63	75.4%	0.21 [0.02, 1.83]
Subtotal (95% CI)		144		146	100.0%	0.23 [0.04, 1.41]
Total events	1		6			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)

	RenalGuard Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.3 Stroke/TIA						
Barbanti 2015	1	56	2	56	45.5%	0.49 [0.04, 5.57]
Usmiani 2015	0	57	2	63	54.5%	0.21 [0.01, 4.55]
Subtotal (95% CI)		113		119	100.0%	0.34 [0.05, 2.21]
Total events	1		4			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

	RenalGuard Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
1.2.4 Pulmunary edema						
Barbanti 2015	0	56	0	56		Not estimable
Briguori 2011	3	146	1	146	6.4%	3.04 [0.31, 29.59]
Marenzi 2012	5	87	10	83	63.1%	0.45 [0.15, 1.36]
Usmiani 2015	1	57	5	63	30.5%	0.21 [0.02, 1.83]
Subtotal (95% CI)		346		348	100.0%	0.54 [0.23, 1.25]
Total events	9		16			

Heterogeneity: Chi² = 3.08, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 1.44 (P = 0.15)

Odds Ratio M–H, Fixed, 95% CI

0.01   0.1   1   10   100
Favors [RenalGuard]   Favors [control]

A nonsignificant lower incidence of stroke, acute coronary syndromes, and pulmonary edema was found in the RenalGuard group compared with the control group. Abbreviations as in **Figure 2**.

perioperative pulmonary edema showed no difference between the RenalGuard and control groups (9 of 346 [2.60%] vs. 16 of 348 [4.60%] patients; OR: 0.54; 95% CI: 0.23 to 1.25; I² = 35%; p = 0.15, with all trials included) (**Figure 3**).

Other potential adverse effects include electrolyte imbalance due to the high volume of saline administered with furosemide forced diuresis and complications of Foley catheter placement. However, the trials reported no symptomatic electrolyte disorders. The meta-analysis of asymptomatic hypokalemic events did not find significant differences between RenalGuard and control group (34 of 202 [16.83%] vs. 26 of 202 [12.87%] patients; OR: 1.18; 95% CI: 0.67 to 2.09; I² = 0%; p = 0.56), with 2 trials included (26,29). Finally, 1 trial (29) reported that 4 patients

(2.7%) in the RenalGuard group experienced pain on micturition caused by the Foley catheter. Data regarding urinary retention, urinary tract infections, and other urinary tract complications were not reported by the trials.

Length of hospital stay was not different between groups (standardized mean difference, 0.22; 95% CI: −0.83 to 1.28; I² = 0%; p = 0.60), with 2 trials included (26,29).

DISCUSSION

The main finding of this meta-analysis is that furosemide with matched hydration by the RenalGuard System may reduce the incidence of CI-AKI in high-

risk patients undergoing interventional procedures, leading to a significantly lower need for RRT. The effect is confirmed even when considering the subgroups of patients with pre-existing renal impairment and is consistent throughout the 4 trials included, 3 of which were performed in patients undergoing coronary interventions and 1 percutaneous aortic valve replacement.

Contrast media have direct toxic effect on renal tubular cells, causing vacuolization and altered mitochondrial function. As a consequence, nitric oxide-mediated mechanism and prostaglandin-induced vasodilatation are inhibited, leading to vasoconstriction and consequently to ischemia of the vascular supply of kidney medulla (30,31). The mechanism of action of the RenalGuard is not yet fully elucidated, but one can postulate that the high urine output (>300 ml/h) maintained during the procedure has a direct protective effect on the tubular cells (32) and improves simultaneously renal medulla perfusion, thus counterbalancing the direct and the ischemic effects induced by the contrast media. However, there remains much to be learned about the mechanisms of possible effects of this system on renal function, and a class effect in patients with renal impairment cannot be ruled out.

One can also speculate that the lower although not significant rate of post-operative acute coronary syndromes and stroke may reflect an additional protective effect in the RenalGuard group at the cerebral and cardiac levels. Further data are needed to draw any conclusions, however.

Generally, CI-AKI follows a benign course, and persistent renal impairment and dialysis dependence are rare (33). In that regard, seldom is there considerable risk for RRT in CI-AKI, with need for dialysis in <1% of patients with CI-AKI (33) and in about 3% of patients undergoing primary PCI for acute coronary syndromes (34). In selected subgroups of patients, such as those with chronic kidney disease or diabetes mellitus, however, up to 7% require transient dialysis (35).

The lower rate of CI-AKI and especially the significant reduction of RRT could also have a positive economic impact. According to National Health Service Kidney Care, the cost of AKI to the National Health Service has been estimated to be between approximately $700 million and 1 billion per year, which is more than expenditures on breast cancer or lung and skin cancer combined (36,37). A recent analysis of the direct costs linked to CI-AKI showed that the associated economic burden is

high. The average in-hospital cost of CI-AKI is $10,345, and the 1-year cost of treatment for a patient with CI-AKI is $11,812 (38). The major driver of the increased economic burden is the longer initial hospitalization; however, further studies should systematically assess the impact of RenalGuard therapy on this outcome.

Another crucial point is RenalGuard's safety. According to randomized evidence, the RenalGuard showed a similar risk profile compared with conservative treatment, particularly for the systemic effect related to volume and diuretic agent administration (pulmonary congestion and electrolyte imbalance). Particular attention should be paid to the urological complications related to the Foley catheter, because urological problems might have potential serious consequences (39), particularly in men undergoing interventions with the use of antithrombotic drugs.

STUDY LIMITATIONS. Notably, this is the first meta-analysis performed on the topic, and we assessed one of the most important clinical outcomes, CI-AKI, associated with patients' morbidity and mortality. We performed a systematic review of several databases, aiming to reduce the possibility of missing minor publications. However, our meta-analysis included only 4 studies with high risk of bias, and control regimens were not identical among trials. Traditional limitations of aggregate patient data meta-analyses are present, and we recognized that only individual patient data permit full exploration of and adjustment for patient characteristics. These statements suggest that our results are only exploratory and hypothesis generating.

In the near future, new trials are warranted, in particular comparing furosemide with matched hydration with and without the RenalGuard System and to elucidate its possible efficacy also in other medical procedures, such as in diagnostic radiology, endovascular procedures, and maybe during therapy with nephrotoxic chemotherapeutic agents (e.g., cisplatin, methotrexate). Future studies of the comparative effectiveness of interventions for preventing CI-AKI should stratify patients according to baseline risk for CI-AKI, especially because detecting a treatment effect in low-risk patients may be difficult. Finally, future studies should be performed independently, without any industrial support and systematically report side and adverse events (e.g., pulmonary edema, electrolyte disorders, Foley catheter complications).

According to our results, large randomized trials are now needed to confirm or reject the potential

beneficial effect of RenalGuard therapy. Two randomized studies, including 326 and 220 patients, are currently running in the United States and Israel, respectively, and recruitment is expected to be completed in 2018 (NCT01456013 and NCT01866800).

CONCLUSIONS

The main findings of this meta-analysis is that furosemide with matched hydration by the RenalGuard System seems to reduce the incidence of CI-AKI and RRT in high-risk patients undergoing interventional procedures. Further independent high-quality multicenter randomized trials should elucidate the effectiveness and safety of the RenalGuard System in this population.

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PERSPECTIVES

WHAT IS KNOWN? CI-AKI is an uncommon but serious complication in patients undergoing interventional procedures, particularly in those presenting with pre-existing renal failure. The optimal prevention strategy has not yet been defined, and previous small randomized trials demonstrated a potential beneficial effect of RenalGuard therapy.

WHAT IS NEW? Our meta-analysis including 4 randomized controlled trials enrolling 698 patients showed a significantly lower incidence of CI-AKI and a lower need for RRT in high-risk patients treated with RenalGuard therapy compared with control treatment.

WHAT IS NEXT? Larger randomized controlled trials are needed to confirm our findings and to further evaluate the safety and efficacy of RenalGuard therapy for preventing CI-AKI in patients undergoing interventional procedures with contrast medium exposure.

REFERENCES

1. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2008;51:1419–28.

2. Solomon RJ, Mehran R, Natarajan MK, et al. Contrast-induced nephropathy and long-term adverse events: cause and effect? Clin J Am Soc Nephrol 2009;4:1162–9.

3. Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. Heart 2016;102:638–48.

4. Kitajima K, Maeda T, Watanabe S, Sugimura K. Recent issues in contrast-induced nephropathy. Int J Urol 2011;18:686–90.

5. Stacul F, Adam A, Becker CR, et al. Strategies to reduce the risk of contrast-induced nephropathy. Am J Cardiol 2006;98:59–77.

6. Finn WF. The clinical and renal consequences of contrast-induced nephropathy. Nephrol Dial Transplant 2006;21:i2–10.

7. Dong M, Jiao Z, Liu T, Guo F, Li G. Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. J Nephrol 2012;25:290–301.

8. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. J Am Coll Cardiol 2004;44: 1393–9.

9. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention. Am J Med 1997;103:368–75.

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

11. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. J Am Soc Nephrol 2000;11:177–82.

12. Dorval J-F, Dixon SR, Zelman RB, Davidson CJ, Rudko R, Resnic FS. Feasibility study of the RenalGuardTM balanced hydration system: a novel strategy for the prevention of contrast-induced nephropathy in high risk patients. Int J Cardiol 2013;166:482–6.

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

14. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5. Copenhagen, Denmark: The Cochrane Collaboration, 2011.

15. Bertelli L, Politi L, Roversi S, et al. Comparison of RenalGuard System, continuous venovenous hemofiltration and hydration in high-risk patients for contrast-induced nephropathy. J Am Coll Cardiol 2012;59:E96.

16. Ben-Assa E, Arbel Y, Rofe M, et al. CRT-155 Forced diuresis with matched hydration using the RenalGuard® System for the prevention of contrast induced acute kidney injury—a single center experience. J Am Coll Cardiol Intv 2014;7: S25.

17. Briguori C, Visconti G, Donahue M, et al. RenalGuard system in high-risk patients for contrast-induced acute kidney injury. Am Heart J 2016;173:67–76.

18. Visconti G, Focaccio A, Donahue M, et al. RenalGuard System for the prevention of acute kidney injury in patients undergoing transcatheter aortic valve implantation. EuroIntervention 2016; 11:e1658–61.

19. Wassef N, Ehtisham J, Shaukat N. Value of the RenalGuard System in coronary interventions. EuroIntervention. Available at: http://www.pcronline.com/eurointervention/AbstractsEuroPCR2016_issue/abstracts-europcr-2016/Euro16A-POS0574/value-of-the-renalguard-system-in-coronary-interventions.html. Accessed November 12, 2016.

20. Gritti V, Crimi G, Favoccia C, et al. RenalGuard to prevent acute kidney injury in high risk patients undergoing coronary interventions. Eur Hear J 2016;37 Suppl 1:985–1393.

21. Lopez Otero D, Gonzalez Ferreiro R, Trillo Nouche R, et al. Prevention of contrast-induced nephropathy with RenalGuard system in patients at high and very-high risk, undergoing transcatheter aortic valve implantation. Eur Heart J 2016;37 Suppl 1:985–1393.

22. Briguori C, Visconti G, Ricciardelli B, Condorelli G, for the REMEDIAL II Investigators. Renal insufficiency following contrast media administration trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury: rationale and design. EuroIntervention 2011;6:1117–22.

23. Arbel Y, Ben-Assa E, Halkin A, et al. Forced diuresis with matched hydration in reducing acute kidney injury during transcatheter aortic valve implantation (REDUCE-AKI): study protocol for a

randomized sham-controlled trial. Trials 2014;15:262.

24. Briguori C, McCullough PA, Tumlin J, et al. RenalGuard System: a dedicated device to prevent contrast-induced acute kidney injury. Int J Cardiol 2013;168:643–4.

25. Solomon R. Forced diuresis with the Renal-Guard System: impact on contrast induced acute kidney injury. J Cardiol 2014;63:9–13.

26. Barbanti M, Gulino S, Capranzano P, et al. Acute kidney injury with the RenalGuard System in patients undergoing transcatheter aortic valve replacement: the PROTECT-TAVI trial (Prophylactic Effect of Furosemide-Induced Diuresis With Matched Isotonic Intravenous Hydration in Transcatheter Aortic Valve Implantation). J Am Coll Cardiol Intv 2015;8:1595–604.

27. Usmiani T, Andreis A, Budano C, et al. AKI-GUARD (Acute Kidney Injury Guarding Device) trial: in-hospital and one-year outcomes. J Cardiovasc Med (Hagerstown) 2016;17:530–7.

28. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. J Am Coll Cardiol Intv 2012;5:90–7.

29. Briguori C, Visconti G, Focaccio A, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): Renal-Guard System in high-risk patients for contrast-induced acute kidney injury. Circulation 2011;124:1260–9.

30. Sendeski MM. Pathophysiology of renal tissue damage by iodinated contrast media. Clin Exp Pharmacol Physiol 2011;38:292–9.

31. Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. Biomed Res Int 2014;2014:741018.

32. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. Kidney Int 1992;41:1008–15.

33. Freeman RV, O'Donnell M, Share D, et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. Am J Cardiol 2002;90:1068–73.

34. Marenzi G, Lauri G, Assanelli E, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2004;44:1780–5.

35. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000;36:1542–8.

36. Calculating the cost. Interview with Marion Kerr. Health Serv J 2011; Suppl 1:3.

37. Sadat U, Usman A, Boyle Jr, Hayes PD, Solomon RJ. Contrast medium-induced acute kidney injury. Cardiorenal Med 2015;5:219–28.

38. Subramanian S, Tumlin J, Bapat B, Zyczynski T. Economic burden of contrast-induced nephropathy: implications for prevention strategies. J Med Econ 2007;10:119–34.

39. Davis NF, Quinlan MR, Bhatt NR, et al. Incidence, cost, complications and clinical outcomes of iatrogenic urethral catheterization injuries: a prospective multi-institutional study. J Urol 2016;196:1473–7.

KEY WORDS contrast-induced acute kidney injury, interventional procedures, invasive cardiology, meta-analysis, randomized trials

APPENDIX For supplemental material and tables, please see the online version of this article.