RenalGuard system in high-risk patients for contrast-induced acute kidney injury

Carlo Briguori, MD, PhD,[a] Gabriella Visconti, MD,[a] Michael Donahue, MD,[a] Francesca De Micco, PhD,[a] Amelia Focaccio, MD,[a] Bruno Golia, MD,[a] Giuseppe Signoriello, PhD,[b] Carmine Ciardiello, PhD,[c] Elvira Donnarumma, PhD,[d] and Gerolama Condorelli, MD, PhD[e] *Naples, Italy*

Background High urine flow rate (UFR) has been suggested as a target for effective prevention of contrast-induced acute kidney injury (CI-AKI). The RenalGuard therapy (saline infusion plus furosemide controlled by the RenalGuard system) facilitates the achievement of this target.

Methods Four hundred consecutive patients with an estimated glomerular filtration rate ≤30 mL/min per 1.73 m^2 and/or a high predicted risk (according to the Mehran score ≥11 and/or the Gurm score >7%) treated by the RenalGuard therapy were analyzed. The primary end points were (1) the relationship between CI-AKI and UFR during preprocedural, intraprocedural, and postprocedural phases of the RenalGuard therapy and (2) the rate of acute pulmonary edema and impairment in electrolytes balance.

Results Urine flow rate was significantly lower in the patients with CI-AKI in the preprocedural phase (208 ± 117 vs 283 ± 160 mL/h, $P < .001$) and in the intraprocedural phase (389 ± 198 vs 483 ± 225 mL/h, $P = .009$). The best threshold for CI-AKI prevention was a mean intraprocedural phase UFR ≥450 mL/h (area under curve 0.62, $P = .009$, sensitivity 80%, specificity 46%). Performance of percutaneous coronary intervention (hazard ratio [HR] 4.13, 95% CI 1.81-9.10, $P < .001$), the intraprocedural phase UFR <450 mL/h (HR 2.27, 95% CI 1.05-2.01, $P = .012$), and total furosemide dose >0.32 mg/kg (HR 5.03, 95% CI 2.33-10.87, $P < .001$) were independent predictors of CI-AKI. Pulmonary edema occurred in 4 patients (1%). Potassium replacement was required in 16 patients (4%). No patients developed severe hypomagnesemia, hyponatremia, or hypernatremia.

Conclusions RenalGuard therapy is safe and effective in reaching high UFR. Mean intraprocedural UFR ≥450 mL/h should be the target for optimal CI-AKI prevention. (Am Heart J 2016;173:67-76.)

Contrast-induced acute kidney injury (CI-AKI) is a powerful predictor of unfavorable early and late outcomes.[1-3] The RenalGuard therapy (hydration with saline plus furosemide controlled by the RenalGuard system) is superior to the conventional hydration regimens in preventing CI-AKI in high-risk patients.[4,5] It has been reported, indeed, that most patients treated with the RenalGuard therapy reaches the target urine flow rate (UFR) ≥300 mL/h, with a limited furosemide dose and without significant impairment in electrolytes balance.[4,5] This high UFR, maintained during and until 4 hours after contrast media (CM) exposure, has been suggested as the target for an effective kidney protection.[6] At present, however, it is unclear whether this cutoff (1) is effective in high-risk patients; (2) should be maintained during all the 3 phases (preprocedural, intraprocedural, and postprocedural) of the RenalGuard therapy or, on the contrary, mostly in the intraprocedural phase; and (3) should be considered as absolute value or normalized to the baseline kidney function. The only 2 clinical trials that assessed the effectiveness of RenalGuard therapy in preventing CI-AKI, indeed, did not clarify these issues.[4,5] Furthermore, concerns have been raised on the risk of both pulmonary edema and hypovolemia and impairment in electrolyte balance during RenalGuard therapy.

The current registry reports the performance of the RenalGuard therapy in a large cohort of high-risk patients, to (1) clarify the relationship between UFR and CI-AKI and (2) report potential side effects.

From the [a]Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, Naples, Italy, [b]Department of Mental Health and Preventive Medicine, Second University of Naples, Naples, Italy, [c]HT MED, Pozzuoli, Naples, Italy, [d]IRCCS SDN, Naples, Italy, and [e]Department of Cellular and Molecular Biology and Pathology, "Federico II" University of Naples, Naples, Italy.

Submitted July 17, 2015; accepted December 4, 2015.

Reprint requests: Carlo Briguori, MD, PhD, Interventional Cardiology, Clinica Mediterranea, Via Orazio, 2, I-80121 Naples, Italy.
E-mail: carlobriguori@clinicamediterranea.it

0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.12.005

Methods

Patient population

This is a single-center (Clinica Mediterranea, Naples, Italy), prospective, observational registry assessing the effectiveness of the RenalGuard therapy in preventing CI-AKI in patients at high risk. All patients scheduled for coronary and/or peripheral angiography/angioplasty from January 2011 to September 2014 and treated with the RenalGuard therapy were included into the present registry. Criteria for using the RenalGuard therapy for CI-AKI prevention were (1) an estimated glomerular filtration rate (eGFR) ≤30 mL/min per 1.73 m^2 and/or (2) an high predicted risk according to the Mehran risk score ≥11 and/or the Gurm score >7%.[7,8] Exclusion criteria were age <18 years; acute myocardial infarction; acute pulmonary edema; cardiogenic shock; dialysis; multiple myeloma; administration of other compounds or drugs with potential impact on CI-AKI, including sodium bicarbonate, theophylline, dopamine, mannitol, and/or fenoldopam; recent (≤48 hours) administration of iodinated CM; and current enrollment in any other study that would involve deviation from either protocol. All patients who met the inclusion/exclusion criteria and signed an informed consent were included into the study. The eGFR was calculated by applying the Levey modified Modification of Diet in Renal Disease formula: (186.3 × serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × (0.742 if female).[9] *Chronic kidney disease* (CKD) was defined as an eGFR <60 mL/min per 1.73 m^2. Iodixanol (Visipaque, GE, a nonionic, iso-osmolar [290 mOsm/kg mOsm per kilogram of water]) CM was used in all patients. To identify patients receiving a high-contrast load, the following weight- and creatinine-adjusted maximum contrast dose formula was used: 5 × kilograms of body weight divided by serum creatinine (milligrams per deciliter).[10] This limit was converted to a dichotomous variable by dividing the actual amount of contrast received by the calculated maximum contrast dose to determine the "contrast ratio." If the ratio was >1, then the maximum contrast dose was considered exceeded.[10]

All patients were treated by hydration with normal saline plus NAC (1500 mg in each 1 liter of saline administered) controlled by the RenalGuard system (PLC Medical Systems, Inc, Franklin, MA). The characteristics of this system have been previously reported.[6] Briefly, the RenalGuard system includes (*a*) a closed loop fluid management system, (*b*) a high-volume fluid pump, (*c*) a high accuracy dual weight measuring system, (*d*) motion detection artifact reduction, (*e*) a single-use intravenous set and urine collection system that interfaces with a standard Foley catheter, (*f*) real-time display of urine and replacement fluid volume, (*g*) a timely alerts to drain the urine bag or to replace the hydration fluid bag, and (*h*) safety features such as automatic air and occlusion detection. An initial bolus ("priming") of 250 mL was infused over 30 minutes (preprocedural phase). The priming was reduced to (*a*) 150 mL in the presence of left ventricular (LV) ejection fraction ≤30% (as assessed by 2-dimensional echocardiography) or (*b*) 50 to 100 mL in the presence of LV ejection fraction ≤30% and high LV end diastolic pressure (estimated by the transmitral flow velocity to annular velocity ratio [E/E′ index]), assessed by tissue Doppler imaging. After the priming, furosemide (0.25 mg/kg) was administered intravenously to achieve the recommended UFR ≥300 mL/h. As soon as the UFR reached the target value, the patient was moved into the catheterization laboratory, and the procedure was started (procedural phase). Controlled hydration by the RenalGuard system continued during the procedure and for 4 hours after the procedure (postprocedural phase). Urine flow rate was monitored and maintained at the target value throughout the procedure and during the following 4 hours. Additional furosemide doses (in increment of 0.25 mg/kg every 30 minutes) were allowed in instances of (*a*) lack of achievement of the target UFR and (*b*) a decrease in UFR below the target value during the RenalGuard therapy. At the end of the RenalGuard therapy, intravenous saline infusion (0.5-1 mL/kg/h according to the hemodynamic conditions) was continued for at least 6 hours, unless contraindicated by the clinical status.

Biomarkers of kidney function

Serum creatinine (sCr), cystatin C (sCyC), and blood urea nitrogen were measured the day before the procedure and at 24 hours, 48 hours, and 1 week after administration of the CM. Additional measurements were performed in all instances of renal function deterioration. Serum sodium, potassium, and magnesium were measured the day before the procedure; just before starting RenalGuard therapy, after the procedure (as soon as the patients returned in the regular floor or in the intensive coronary care unit); at the end of the RenalGuard therapy; and at 12, 24, and 48 hours after CM administration.

Study end points

The primary outcome measures are (1) the relationship between CI-AKI (defined as ≥0.5 mg/dL or ≥25% sCr increase above the baseline value at 48 hours after administration of CM) and the UFR during the RenalGuard therapy and (2) the rate of acute pulmonary edema and impairment in electrolytes balance. Secondary end points are (1) the development of CI-AKI, defined according to different proposed cutoffs (that is ≥0.3 mg/dL, ≥0.5 mg/dL ≥25%, and ≥50% sCr increase above the baseline value at 48 hours after administration of CM)[11]; (2) the severity of acute kidney injury (AKI) assessed according to the Acute Kidney Injury Network criteria: stage 1, an sCr increase ≥0.3 mg/dL or ≥1.5 to 1.9 times from baseline; stage 2, an sCr increase ≥2.0 to 2.9 times from baseline; and stage 3, an sCr increase ≥3.0 times from

Table I. Clinical characteristics of the global population and of patients with versus those without CI-AKI

	Global population (n = 400)	CI-AKI group (n = 34)	No CI-AKI group (n = 366)	*P*
Age (y)	75 ± 9	77 ± 7	75 ± 8	.11
Male	247 (62%)	23 (68%)	224 (62%)	.46
Weight (kg)	76 ± 13	75 ± 9	76 ± 10	.54
Height (m)	1.65 ± 0.8	1.66 ± 0.7	1.65 ± 087	.25
Body mass index (kg/m^2)	28 ± 6	28 ± 3	27 ± 5	.91
Blood pressure (mm Hg)				
Systolic	156 ± 32	153 ± 28	156 ± 30	.71
Diastolic	79 ± 12	79 ± 14	79 ± 12	.81
Mean	104 ± 16	103 ± 16	105 ± 16	.25
LV ejection fraction (%)	46 ± 10	45 ± 9	46 ± 10	.53
≤30	48 (12%)	3 (9%)	45 (12%)	.78
Systemic hypertension	348 (87%)	30 (88%)	318 (87%)	1.00
Diabetes mellitus	240 (60%)	21 (62%)	219 (60%)	.83
Peripheral chronic artery disease	32 (8%)	5 (16%)	28 (8%)	.11
Drugs				
ACE inhibitor	220 (55%)	14 (41%)	206 (56%)	.10
Calcium-channel blocker	128 (32%)	11 (33%)	117 (32%)	.69
Angiotensin II receptor inhibitor	112 (28%)	12 (37.5%)	100 (27%)	.44
Diuretics	308 (77%)	29 (84%)	279 (76%)	.68
β-Blockers	304 (76%)	26 (78%)	278 (76%)	.68
Statins	336 (84%)	30 (88.5%)	306 (83%)	1.00
Procedure performed				
Coronary angiography	180 (45%)	14 (41%)	166 (45%)	.72
PCI	188 (47%)	15 (44%)	174 (47.5%)	.72
Coronary angiography and ad hoc PCI	18 (4.5%)	3 (9%)	14 (4%)	.17
Peripheral procedure	14 (3.5%)	2 (6%)	12 (3.5%)	.33
Volume of contrast media (mL)	109 ± 75	130 ± 98	107 ± 72	.08
Contrast ratio >1	80 (20%)	22 (64%)	58 (16%)	<.001

Abbreviations: *ACE*, Angiotensin-converting enzyme; *PCI*, percutaneous coronary intervention.

Table II. Clinical characteristics of the global population and of patients with versus those without CI-AKI

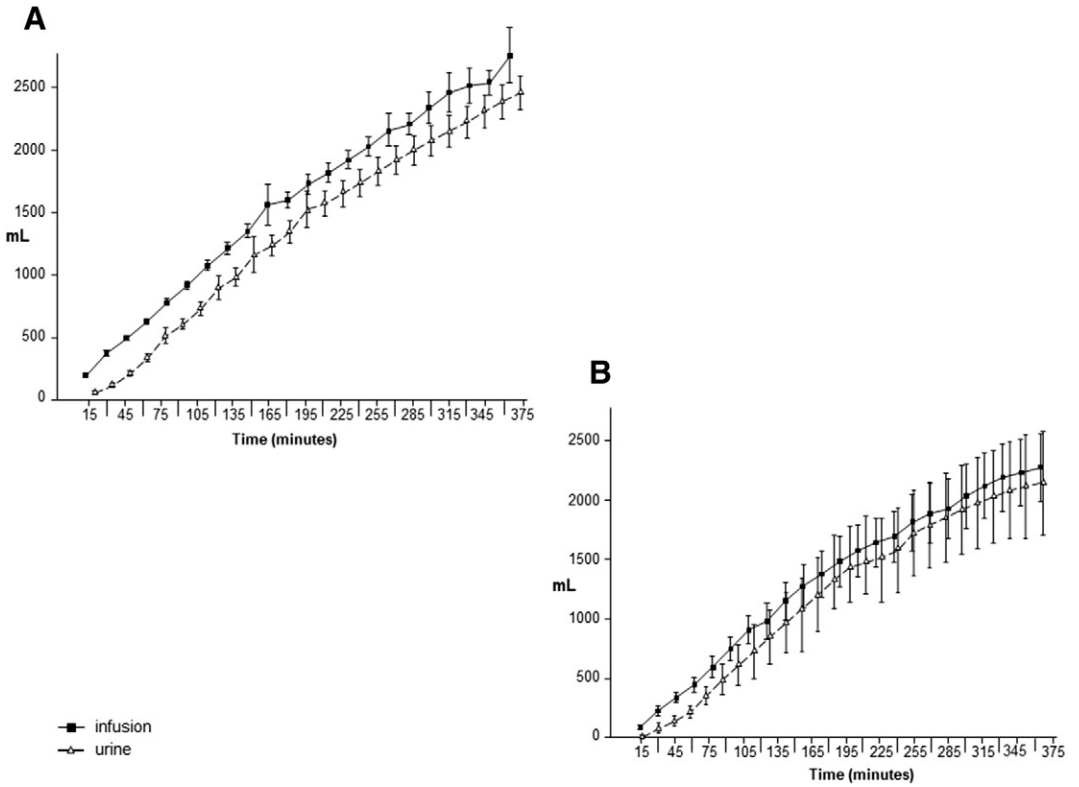
	Global population (n = 400)	CI-AKI group (n = 34)	No CI-AKI group (n = 366)	*P*
sCr (mg/dL), median (Q1-Q3)	2.09 (0.6-5.3)	2.08 (1.50-4.20)	2.08 (1.00-5.30)	.20
sCyC (mg/dL), median (Q1-Q3)	1.94 (1.0-4.3)	2.27 (1.28-3.80)	1.92 (0.6-4.24)	.008
eGFR (mL/min/1.73 m^2)	30 ± 9	26 ± 7	30 ± 10	.045
Contrast nephropathy risk score				
Mehran et al	12 ± 3	13 ± 5	12 ± 3	.41
CI-AKI (%)	21 ± 4	22 ± 9	20 ± 15	.45
Dialysis (%)	2.5 ± 4.1	2.7 ± 2.5	2.2 ± 4.3	.21
Gurm et al				
CI-AKI (%)	13 ± 6	14 ± 8	13 ± 6	.55
Dialysis (%)	1.7 ± 0.9	1.7 ± 1.0	1.7 ± 0.9	.93
Serum urea nitrogen (mg/dL)				
Baseline	87 ± 33	91 ± 36	86 ± 36	.44
After 48 h	86 ± 40	92 ± 36	86 ± 40	.36
Serum sodium (mEq/L)				
Baseline	139 ± 3	139 ± 3	139 ± 3	.38
After 48 h	140 ± 7	139 ± 3	140 ± 4	.77
Serum potassium (mEq/L)				
Baseline	4.5 ± 0.6	4.4 ± 0.7	4.5 ± 0.6	.51
After 48 h	4.0 ± 0.5	4.0 ± 0.6	4.0 ± 0.5	.79
Serum magnesium (mg/dL)				
Baseline	1.92 ± 0.4	1.93 ± 0.2	1.92 ± 0.4	.65
After 48 h	1.86 ± 0.4	1.86 ± 0.4	1.85 ± 0.6	.75

baseline or the need for dialysis[11]; (3) changes in the sCyC concentration at 24 and 48 hours after CM exposure; (4) the rate of acute renal failure requiring dialysis (defined as a decrease in renal function necessitating acute hemodialysis, ultrafiltration, or peritoneal dialysis within the first 5 days postintervention); and (5) the rate of in-hospital and 1-month major adverse events (MAEs, including death, renal failure requiring dialysis, and acute pulmonary edema).

Statistical analysis

Continuous variables are given as mean ± 1 SD or median and first and third quartiles (Q1-Q3), when appropriate. The Student *t* test and the nonparametric Mann-Whitney *U* tests were used to determine differences between mean values for normally and, respectively, not normally distributed variables. Categorical variables were reported as percentage and were analyzed by either χ^2 or Fisher exact test, as appropriate. Correlations between eGFR, UFR, and furosemide dose were assessed by Pearson test. To assess the impact UFR on rate of CI-AKI, we used repeated-measures analysis of variance models. Urine flow rate was analyzed as absolute value (milliliter per hour) and also normalized to baseline glomerular filtration rate (GFR) (UFR/GFR ratio). Receiver operating characteristic (ROC) curve was generated, and the area under curve (AUC) was calculated to evaluate the threshold of UFR below which patients developed AKI. Cox regression analysis was performed to identify independent predictors of CI-AKI; variables included into the model were selected according to the study hypothesis (UFR), literature, and significance ($P < .1$) at univariate analysis. Variance inflation factor analysis was implemented to exclude collinearity. Hosmer-Lemeshow goodness-of-fit test was assessed. Probability level <0.05 was considered significant throughout the analysis. Data were analyzed with SPSS 20 (Chicago, IL) for Windows.

Figure 1



Cumulative fluid balance during treatment by using the RenalGuard system in the global population (**A**) and in the subgroup with LV ejection fraction ≤30% (**B**). Continuous line indicates infusion; dashed line, urine.

Results

Patient population

Four hundred patients are included into the present study. The clinical and biochemical characteristics of the global population are summarized in the Tables I and II. Diabetes mellitus was present in 60% of patients, and the baseline mean eGFR was 30 ± 9 mL/min per 1.73 m^2.

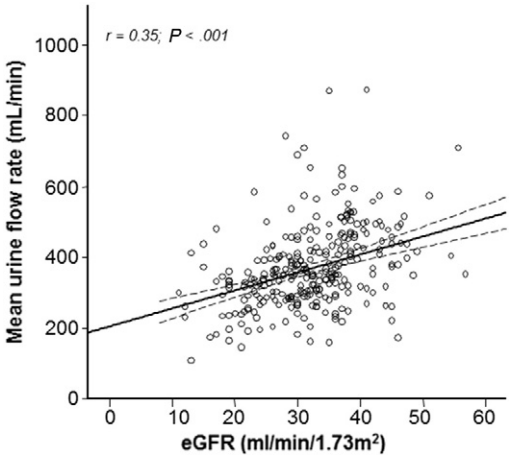
RenalGuard therapy

The total volume of intravenous hydration was 2,228 mL (Q1-Q3 1809-2756 mL). The priming volume was 250 mL (Q1-Q3 200-250 mL): in the 48 patients (12%) with LV ejection fraction ≤30% and/or high LV end-diastolic pressure, the priming volume was 150 mL (Q1-Q3 50-250 mL). We observed highly accurate, temporally matched fluid replacement during the treatment both in the global population (Figure 1A) and in the subgroups with LV ejection fraction ≤30% (Figure 1B). The mean UFR (assessed from the beginning to the end of RenalGuard therapy) was 335 ± 119 mL/h. The proposed UFR target (≥300 mL/h) was reached in the 91.5% of patients (mean value during the all 3 phases of RenalGuard therapy 364 ± 126 mL/h), whereas in the remaining 8.5% (34/400) of patients, it was constantly below the target (172 ± 56 mL/h). A significant correlation was observed between mean UFR and eGFR (r = 0.35, P < .001) (Figure 2). Indeed, in the subgroup of patients who did not reach the proposed UFR target, mean eGFR was significantly lower (23 ± 6 vs 30 ± 10, P = .001). On the contrary, we did not find any significant difference in the mean UFR in patients with versus those without LV ejection fraction ≤30% (339 ± 107 mL/h vs 361 ± 137 mL/h, P = .34). Total furosemide dose was 22 ± 25 mg (10-275 mg). The furosemide dose to reach the target UFR was 14 ± 9 mg (0-60 mg); in 69 patients (17%), indeed, the target UFR was reached after the priming, without furosemide administration. No significant correlation was observed between total furosemide dose and eGFR (r = 0.05, P = .38).

Urine flow rate and CI-AKI

The trend of UFR during the 3 phases of the RenalGuard therapy in patients with and without CI-AKI is represented in the Figure 3. Urine flow rate was significantly lower in patients who developed CI-AKI. In details, UFR (1) was

Figure 2



Correlation between UFR and eGFR.

significantly lower in the CI-AKI group in the preprocedural (208 ± 117 vs 283 ± 160 mL/h, $P < .001$) and intraprocedural phases (389 ± 198 vs 483 ± 225 mL/h, $P = .009$), whereas it was similar in the 2 groups in the postprocedural phase (312 ± 111 vs 338 ± 143 mL/h, $P = .25$) and (2) remained constantly below the proposed target (300 mL/h) during the treatment more often in the CI-AKI group 9/34 [26.5%] vs 25/366 [7%], $P = .009$. Mean UFR/GFR ratio was similar in the 2 groups (10 ± 4 vs 11 ± 5, $P = .36$), whereas the intraprocedural phase UFR/GFR ratio was lower in the CI-AKI group (14 ± 6 vs 17 ± 8, $P = .044$). By ROC analysis, we identified a mean intraprocedural phase UFR ≥450 mL/h as the best threshold for CI-AKI prevention (AUC 0.62 [0.57-0.67], $P = .009$, sensitivity 80%, specificity 46%) (Table III, Figure 4).

The priming volume was similar the 2 groups (CI-AKI group: 250 mL [Q1-Q3 50-250 mL], non–CI-AKI group: 250 mL [Q1-Q3 100-300 mL], $P = .13$). The total intravenous hydration volume during RenalGuard therapy was also similar in CI-AKI group and non–CI-AKI group (2141 ± 748 mL vs 2344 ± 809 mL, $P = .18$). Furthermore, total NAC dose was also similar in CI-AKI group and non–CI-AKI group (3508 ± 1215 vs 3279 ± 111 mg, $P = .32$). Total furosemide dose (to reach and maintain the target UFR) was significantly higher in the CI-AKI group (33 ± 24 vs 21 ± 25 mg, $P = .014$). By ROC analysis, we identified a furosemide dose >0.32 mg/kg as the threshold for increased rate of CI-AKI (AUC 0.65 [0.60-0.70], sensitivity 71%, specificity 65%, $P < .002$).

Cox regression analysis was performed to identify independent predictors of CI-AKI. Variables included into the model were age, gender, LV ejection fraction ≤30%, type of procedure (coronary intervention versus angiography alone), contrast ratio >1, eGFR, total furosemide dose >0.32 mg/kg, and mean intraprocedural phase UFR <450 mL/h. Type of procedure (hazard ratio [HR] 4.13, 95% CI 1.81-9.40, $P < .001$), the intraprocedural phase UFR <450 mL/h (HR 2.27, 95% CI 1.05-2.01, $P = .012$), and total furosemide dose >0.32 mg/kg (HR 5.03, 95% CI 2.33-10.87, $P < .001$) were independent predictors of CI-AKI (Table IV).

Side effects

Pulmonary edema occurred in 4 patients (1%): 3/366 (0.8%) in the non–CI-AKI group versus 1/34 (2.9%) in the CI-AKI group ($P = .30$). In all instances, pulmonary edema occurred after a percutaneous coronary intervention. In all these patients, the matched hydration by RenalGuard was prematurely withdrawn, to obtain a negative fluid volume. The characteristics of these 4 patients are depicted in Table V: of note, none of these 4 patients had LV ejection fraction ≤30%. Ten patients (2.5%) experienced pain on micturation due to the Foley catheter; in 1 patient, it was necessary to prematurely interrupt the RenalGuard therapy at 2.5 hours after the procedure. Asymptomatic hypokalemia (serum potassium <3.5 mEq/L) occurred in 30 patients (7.5%). Potassium replacement was required in 16 patients (4%). Hypomagnesemia (serum magnesium <1.7 mg/dL) occurred in 44 patients (11%): none of them, however, had severe (<1.0 mg/dL) hypomagnesemia. No patients developed hyponatremia or hypernatremia.

In-hospital and 1-month MAE

Contrast-induced acute kidney injury rate according to the different cutoffs of sCr and sCyC increase is reported in the Table VI. Most patients who developed CI-AKI had a mild (stage 1) AKI (31/34 patients [91%]); more severe (stages 2 and 3) damage occurred in only 3 (9%) of 34 patients. In-hospital renal failure requiring dialysis occurred in 3 patients (0.8%). Length of in-hospital stay (from admission to discharge) was longer in patients who developed CI-AKI (10 ± 6 vs 7 ± 5 days, $P = .007$). Major adverse event at 1 month occurred in 25 patients (6.2%) and more often in the CI-AKI group (7/36 [19.5%] vs 18/366 [5%], $P = .001$) (Table VII).

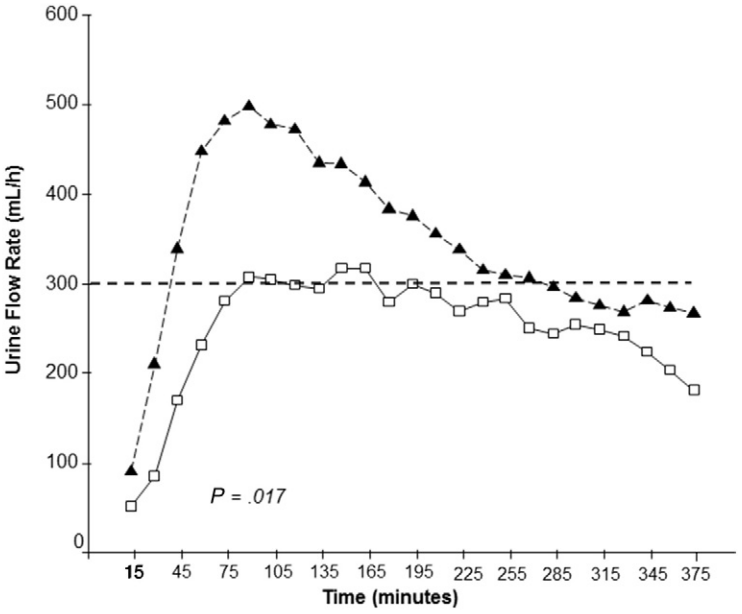
Discussion

The main results of the current study are (1) the RenalGuard therapy is safe and effective in reaching high UFR and (2) mean intraprocedural UFR ≥450 mL/h should be the target for optimal CI-AKI prevention.

Urine flow rate and CI-AKI

In the current study, we confirmed the significant interaction between UFR and development of CI-AKI. In details, UFR was significantly lower in the CI-AKI group in the preprocedural and intraprocedural phases. Normalization of the mean UFR to the baseline kidney function (UFR/GFR ratio) did not add significantly to the assessment of the absolute UFR. The best threshold for

Figure 3



	Pre-CM phase	CM phase	Post-CM phase
CIAKI group □	61±19 min	55 ±40 min	245 ±3 min
No CIAKI group ▲	60 ±23 min	51 ±30 min	243 ±5 min

Mean UFR in patients with and without CI-AKI. Non–CI-AKI group: dashed line, closed symbol; CI-AKI group: continuous line, open symbol ($P = .017$; $F = 4.97$ by repeated-measures analysis of variance). Pre-CM phase, pre–contrast media exposure or preprocedural time; CM phase, contrast media exposure or intraprocedural time; and post-CM phase, postcontrast media or postprocedural time. In the table underneath the figure, we reported the duration (in minutes) of each phase of the RenalGuard therapy.

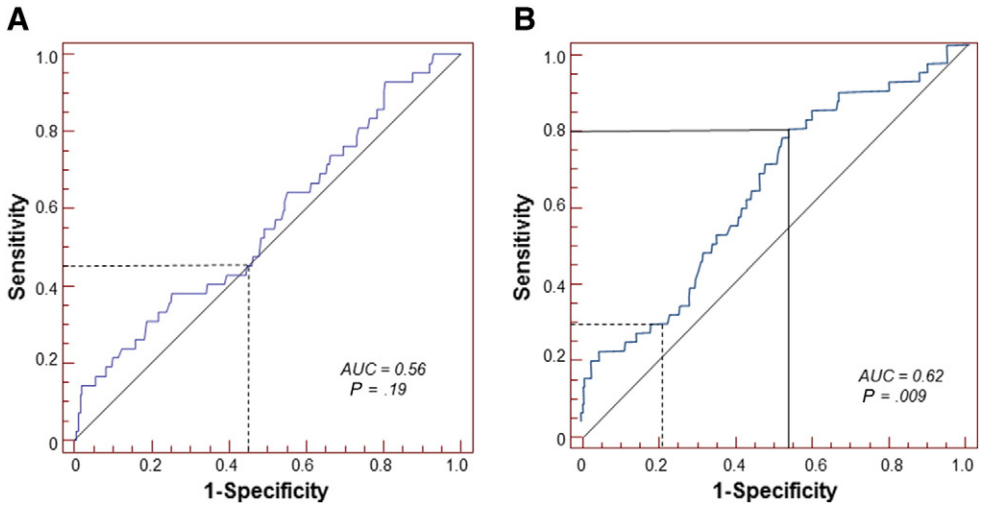
Table III. Absolute and eGFR-adjusted UFR cutoff values for the prediction of CI-AKI

RenalGuard therapy phase	Threshold (mL/h)	AUC (95% CI)	Sensitivity (%)	Specificity (%)	LR+/LR–
Preprocedural phase					
UFR	≤222	0.57 (0.52-0.62)	78	38	1.26/0.58
UFR/eGFR	≤1.37	0.54 (0.48-0.59)	23	89	1.98/0.87
Intraprocedural phase					
UFR	≤450	0.62 (0.57-0.67)	80	46	1.45/0.47
	<300	0.62 (0.57-0.67)	29	79	1.17/0.95
UFR/eGFR	≤15	0.58 (0.53-0.63)	63	54	1.38/0.68
Postprocedural phase					
UFR	≤193	0.51 (0.46-0.57)	21	88	1.85/0.89
UFR/eGFR	≤10	0.53 (0.48-0.59)	68	43	1.19/0.74
Mean value through all phases					
UFR	≤380	0.59 (0.55-0.65)	87	29	1.25/0.40
	<300	0.59 (0.55-0.65)	45	55	1.20/0.83
UFR/eGFR	≤10	0.55 (0.50-0.61)	53	62	1.37/0.77

Abbreviation: *LR*, likelihood ratio.

CI-AKI prevention was a mean intraprocedural phase UFR ≥450 mL/h. On the contrary, the proposed UFR threshold ≥300 mL/h showed lower performance when analyzed both as mean value during all the 3 phases of the therapy or only in the intraprocedural phase. This cutoff has been adopted from the Prevention of Radiocontrast

Figure 4



A, Receiver operating characteristic curves of mean UFR during all phases of the RenalGuard therapy. The proposed 300 mL/h threshold (dashed line) showed a 45% sensitivity and 55% specificity. **B**, Receiver operating characteristic curves of the intraprocedural mean UFR. The best threshold was 450 mL/h (continuous line) with an 80% sensitivity and 46% specificity, whereas the proposed 300 ml/h threshold (dashed line) showed a 26% sensitivity and 78% specificity.

Table IV. Independent predictors of CI-AKI

	Univariate model			Multivariate model		
Variable	OR	CI (95%)	*P*	OR	CI (95%)	*P*
PCI vs coronary angiography alone	3.19	1.51-6.72	.001	4.13	1.81-9.40	<.001
Intraprocedural UFR <450 mL/h	2.69	1.28-5.65	<.006	2.27	1.05-5.01	.012
Total furosemide dose >0.32 mg/kg	4.63	2.28-9.39	<.001	5.03	2.33-10.87	<.001
Contrast ratio >1*	2.19	1.13-4.24	.022			
LVEF <50%	1.85	0.94-3.62	.068	1.63	0.80-3.30	.17
Priming <250 mL*	1.75	0.89-3.41	.10			
Age	1.03	0.99-1.07	.11	1.04	0.52-2.10	.89
GFR	1.63	0.80-3.30	.18			

* In the multivariable model, contrast ratio >1 and priming <250 mL were excluded due to collinearity with percutaneous coronary intervention and, respectively, intraprocedural UFR <450 mL/h. Hosmer-Lemeshow goodness-of-fit test, *P* = .45.

Induced Nephropathy Clinical Evaluation study, which suggest that increasing the UFR ≥150 mL/h reduces the toxic effect of CM,[12] but was never directly confirmed in the clinical practice. The observed prevalent importance of the mean intraprocedural UFR emphasizes its crucial role in the CI-AKI prevention. A strong time dependence of contrast-induced renal cell cytotoxicity has been reported.[13] In an experimental model, the percentage of apoptotic cells was significantly increased within 15 minutes after exposure to CM and continued to rise progressively up to the maximum studied period of 3 hours.[13] This time dependency highlights the importance of strategies limiting the kidneys' exposure to CM by generating high UFR in patients at risk, especially when the CM is actually injected. The high UFR may reduce the incidence of CI-AKI via a combination of its known physiological effects,[14,15] including (*a*) a lower concentration of CM in the kidneys, (*b*) a more rapid transit of CM through the kidneys, (*c*) a less overall exposure to toxic CM, (*d*) a potential reduction of oxygen consumption in the medulla, and (*e*) reduction in sludging and precipitation of CM in tubular cells.[16] However, we can argue whether UFR is itself protective or simply a marker of an inherent vulnerability of the kidney to injury. Indeed, the achievement of high UFR was less likely in patients with more advanced CKD. This issue is closely linked to the finding that furosemide dose was an independent predictor of AKI. These data give rise to a number of interpretations: (1) The administration of higher doses of furosemide would just be a marker, rather than a mechanism, for poor outcome. As kidney function decreases, higher doses of diuretics are in demand to have similar diuretic effect.[17] In patients with CKD, an increased diuretic dose must be given to ensure delivery of tubular fluid sufficient to elicit diuretic response[18]. (2) Furosemide may induce a shunting of blood flow from medulla to cortex. Furosemide, indeed, decreases medullary blood flow approximately 3 times more than the cortical blood flow.[19] The decrease in medullary blood

Table V. Characteristics of patients who developed acute pulmonary edema

Patient	Age	Sex	LVEF	GFR	SBP	Mehran risk score	Gurm risk score	Total saline volume	Total urine output	Furosemide dose	Contrast volume	Contrast ratio >1	LAD lesion	CI-AKI
1	72	M	51	19	110	19	21	784	786	250	450	Yes	Yes	Yes
2	70	M	60	35	120	15	12	2123	1980	275	150	No	No	No
3	80	M	40	31	130	12	10	2838	2784	75	150	No	No	No
4	78	F	38	35	120	13	8	3420	3271	95	250	No	Yes	No

Total saline volume, total urine output, and contrast volume are expressed in milliliters. Furosemide dose is expressed in milligrams. Abbreviations: *LVEF*, left ventricular ejection fraction; *SBP*, systolic blood pressure before procedure (millimeters of mercury); *M*, male; *F*, female; *LAD*, left anterior descending artery.

Table VI. Distribution of the changes in serum creatinine and cystatin C levels in the global population

	N = 400
Changes in creatinine at 48 h	
Increase ≥25%	31 (7.7%)
Increase ≥50%	11 (2.8%)
Increase ≥0.5 mg/dL	34 (8.5%)
Increase ≥0.3 mg/dL	47 (11.8%)
Changes in cystatin C at 24 h	
Increase ≥0.3 mg/dL	25 (6.6%)
Increase ≥10%	45 (11.9%)
Increase ≥15%	29 (7.7%)
Increase ≥25%	14 (3.7%)
Changes in cystatin C a 48 h	
Increase ≥0.3 mg/dL	35 (9.5%)
Increase ≥10%	53 (14.1%)
Increase ≥15%	42 (11.2%)
Increase ≥25%	21 (5.7%)

Table VII. Major adverse events at 1 month of the global population and in patients with versus those without CI-AKI

	Global population (n = 400)	CI-AKI group (n = 34)	No CI-AKI group (n = 366)	*P*
Cumulative MAEs	25 (6.2%)	7 (19.5%)	18 (5%)	.001
Death	23 (5.7%)	6 (16.6%)	17 (4.6%)	.004
Dialysis	5 (1.2%)	5 (13.9%)	0	.001
Acute pulmonary edema	4 (1%)	1 (2.9%)	3 (0.8%)	.30

flow would lead to ischemia and, therefore, AKI.[20] However, this shunting effect seems to be dose independent, being present already at low furosemide dose,[19] and the data in humans are also difficult to interpret because most of it is done in patients with normal kidney function and not in CKD patients undergoing coronary procedures, such as those included into the present study. (3) Increasing furosemide dose in the absence of diuresis may not be particularly beneficial. Furosemide administration has actually been shown to be deleterious and to increase the rates of CI-AKI.[21] It has been suggested that the deleterious effect observed is a result of a negative fluid balance.[22] The negative fluid balance probably stimulated sympathetic and renin angiotensin leading to enhanced vasoconstriction within the renal circulation. However, negative fluid balance was not documented in the present study, thanks to the highly accurate, temporally matched fluid replacement obtained by the RenalGuard therapy. (4) Even in the absence of negative fluid balance, furosemide may inhibit glomerulotubular feedback resulting in reduction in renal blood flow due to increased generation of angiotensin within the kidney.[23] Finally, evidence exists that furosemide may also protect the kidney by reducing the outer medullary hypoxia caused by CM by blocking the Na-K-2Cl transporter in the medullary thick ascending limb.[24]

Side effects

Pulmonary edema occurred in 1% of patients. The reported rate of pulmonary edema in patients treated by saline infusion for the prevention of CI-AKI ranges from 0% to 11%; the highest rate has been reported in high risk patients,[25] as those enrolled in the present trial. In the recent POSEIDON trial (supporting the strategy of "dosing" the hydration regimen according to the baseline LV end-diastolic pressure), the reported rate of pulmonary edema was 1.5%, although the enrolled patients had a lower risk than those included in our study.[26] We observed a perfect temporally matched fluid replacement even in the 4 patients who developed acute pulmonary edema. All these 4 patients were at high risk for CI-AKI according to both Mehran's and Gurm's scores. Interestingly, all patients experienced clinical signs of pulmonary edema after the coronary intervention, suggesting a potential role of the CM volume and the myocardial damage induced by the percutaneous coronary intervention.[4] Our approach of reducing the priming in patients with LV ejection fraction ≤30% and/or high LV end-diastolic pressure may have played an important role in the observed rate of pulmonary edema. On the other hand, however, this strategy may limit the chance to reach the UFR target in this high-risk subgroup of patients.

The high UFR obtained with the RenalGuard system have raised concerns regarding the potential hazards of hypovolemia and impairment in electrolyte balance.

However, no clinically significant changes in electrolyte balance were documented, and the highly accurate, temporally matched fluid replacement observed reduced the risk of hypovolemia.

Study limitations

The optimal UFR threshold resulted from the same patient population: further prospective studies are needed to validate this UFR cutoff. The results of the current study refer to patients with an eGFR ≤30 mL/min per 1.73 m^2 and/or high risk score. This subset represents approximately 30% of all patients with CKD.[4] In this subgroup of patients, the effectiveness of hemofiltration has been reported.[25] However, the applicability of this approach to current clinical practice is unclear.[27] Finally, the need of a Foley catheter may be a practical issue, especially in patients at lower risk than those included into the present study.

Conclusions

RenalGuard therapy is safe and effective in reaching high UFR. Mean intraprocedural UFR ≥450 mL/h should be selected as the target for optimal CI-AKI prevention with the RenalGuard therapy.

Acknowledgements

This work was partially supported by funds from Associazione Italiana Ricerca sul Cancro (grant no. 10620) to G.C., MERIT (RBNE08E8CZ_002) to G.C., and PON01_02342 to C.B.

Disclosures

None. All authors have approved the final article.

References

1. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2008;51(15):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(7):1162-9.
3. Briguori C, Visconti G, Rivera NV, et al. Cystatin C and contrast-induced acute kidney injury. Circulation;121(19):2117–2122.
4. Briguori C, Visconti G, Focaccio A, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. Circulation 2011;124(11):1260-9.
5. 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. JACC Cardiovasc Interv 2012;5(1):90-7.
6. Dorval JF, Dixon SR, Zelman RB, et al. Feasibility study of the RenalGuard balanced hydration system: a novel strategy for the prevention of contrast-induced nephropathy in high risk patients. Int J Cardiol 2013;166(2):482-6.
7. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004;44(7):1393-9.
8. Gurm HS, Seth M, Kooiman J, et al. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2013;61(22): 2242-8.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-S266.
10. Cigarroa RG, Lange RA, Williams RH, et al. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989;86(6 Pt 1):649-52.
11. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.
12. Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J Am Coll Cardiol 1999;33(2):403-11.
13. Romano G, Briguori C, Quintavalle C, et al. Contrast agents and renal cell apoptosis. Eur Heart J 2008;29(20):2569-76.
14. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium–induced nephropathy. Kidney Int 2005;68(1):14-22.
15. Tumlin J, Stacul F, Adam A, et al. Pathophysiology of contrast-induced nephropathy. Am J Cardiol 2006;98(6A):14K-20K.
16. Wang JH, Lin WC, Wei CJ, et al. Diagnostic value of unenhanced computerized tomography urography in the evaluation of acute renal colic. Kaohsiung J Med Sci 2003;19(10):503-9.
17. Brater DC, Anderson SA, Brown-Cartwright D. Response to furosemide in chronic renal insufficiency: rationale for limited doses. Clin Pharmacol Ther 1986;40(2):134-9.
18. Sica DA. Diuretic use in renal disease. Nat Rev Nephrol 2012;8(2): 100-9.
19. Dobrowolski L, B dzyńska B, Sadowski J. Differential effect of frusemide on renal medullary and cortical blood flow in the anaesthetised rat. Exp Physiol 2000;85(6):783-9.
20. Kennedy-Lydon TM, Crawford C, Wildman SS, et al. Renal pericytes: regulators of medullary blood flow. Acta Physiol (Oxf) 2013;207(2): 212-25.
21. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331(21): 1416-20.
22. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron 1992;62(4): 413-5.
23. Oppermann M, Hansen PB, Castrop H, et al. Vasodilatation of afferent arterioles and paradoxical increase of renal vascular resistance by furosemide in mice. Am J Physiol Renal Physiol 2007;293(1):F279-87.
24. Liss P, Nygren A, Ulfendahl HR, et al. Effect of furosemide or mannitol before injection of a non-ionic contrast medium on intrarenal oxygen tension. Adv Exp Med Biol 1999;471:353-9.
25. Marenzi G, Marana I, Lauri G, et al. The prevention of radio-contrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003;349(14):1333-40.

26. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet 2014;383(9931):1814-23.

27. Klarenbach SW, Pannu N, Tonelli MA, et al. Cost-effectiveness of hemofiltration to prevent contrast nephropathy in patients with chronic kidney disease. Crit Care Med 2006;34(4): 1044-51.