

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

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Objectives This study investigated the effect of furosemide-forced diuresis and intravenous saline infusion matched with urine output, using a novel dedicated device designed for contrast-induced nephropathy (CIN) prevention.

Background CIN is a frequent cause of acute kidney injury associated with increased morbidity and mortality.

Methods A total of 170 consecutive patients with chronic kidney disease (CKD) undergoing coronary procedures were randomized to either furosemide with matched hydration (FMH group, $n = 87$) or to standard intravenous isotonic saline hydration (control group; $n = 83$). The FMH group received an initial 250-ml intravenous bolus of normal saline over 30 min followed by an intravenous bolus (0.5 mg/kg) of furosemide. Hydration infusion rate was automatically adjusted to precisely replace the patient's urine output. When a urine output rate >300 ml/h was obtained, patients underwent the coronary procedure. Matched fluid replacement was maintained during the procedure and for 4 h post-treatment. The definition of CIN was a $\geq 25\%$ or ≥ 0.5 mg/dl rise in serum creatinine over baseline.

Results In the FMH group, no device- or therapy-related complications were observed. Four (4.6%) patients in the FMH group developed CIN versus 15 (18%) controls ($p = 0.005$). A lower incidence of cumulative in-hospital clinical complications was also observed in FMH-treated patients than in controls (8% vs. 18%; $p = 0.052$).

Conclusions In patients with CKD undergoing coronary procedures, furosemide-induced high urine output with matched hydration significantly reduces the risk of CIN and may be associated with improved in-hospital outcome. (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention [MYTHOS]; NCT00702728) (J Am Coll Cardiol Intv 2012;5:90–7) © 2012 by the American College of Cardiology Foundation

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Contrast-induced nephropathy (CIN) is a frequent complication of coronary diagnostic and interventional procedures, and is associated with significantly unfavorable outcomes, including major cardiovascular events, prolonged hospitalization, and early death (1,2). Chronic kidney disease (CKD) and reduced effective circulating volume are well-recognized risk factors for CIN (3). Preventive intravenous hydration with isotonic saline solution protects against CIN (4,5). In patients with CKD, however, hydration is usually performed at a rate significantly lower than that shown to provide protection because of the fear of overhydration and pulmonary edema, particularly in patients with impaired left ventricular function. In previous studies, diuretics have been combined with hydration therapy to increase urine output and prevent overhydration (6-8). In addition to increasing urine flow, resulting in greater contrast dilution within the renal tubules and reduced direct kidney toxicity, loop diuretics may protect against medullary ischemia, a potential mechanism of CIN (9,10). In these studies, however, furosemide was associated with deleterious effects that were likely the result of vasoconstriction induced by intravascular volume depletion, further exacerbating that produced by contrast itself (6-8). Interestingly, the PRINCE (Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation) study showed that forced diuresis, achieved with a single dose of diuretic in combination with intravenous fluid replacement matched to urine output, prevented dehydration and provided a modest protective effect against CIN (11). More importantly, this study showed that CIN requiring dialysis did not develop in any patient with a mean urine flow rate above 150 ml/h. Thus, furosemide-induced high-volume diuresis with concurrent maintenance of intravascular volume through matched hydration may be an alternative strategy for CIN prevention in high-risk patients. Based on these data, we sought to assess the safety and efficacy of a new system capable of delivering intravenous fluid in an amount exactly matched to the volume of urine produced by the patient and precisely weighed by the system. This may prevent both fluid overload in response to intravenous hydration and hypovolemia as a result of high-volume diuresis induced by furosemide administration.

We performed a prospective, randomized trial to investigate the role of combined furosemide-induced high-volume diuresis and automated matched hydration, compared with standard saline hydration, for the prevention of CIN in CKD patients undergoing coronary procedures.

Methods

Study Population. We enrolled consecutive patients with CKD scheduled for coronary angiography at our hospital

between September 1, 2008, and February 28, 2011. Inclusion criteria were age ≥ 18 years and ≤ 85 years, and elective or urgent (within 24 h from hospital admission because of non-ST-segment elevation [acute] myocardial infarction [NSTEMI]) coronary angiography and, when indicated, percutaneous coronary intervention (PCI). The day before the procedure (at hospital admission in NSTEMI patients), the estimated glomerular filtration rate (eGFR) was assessed using the modified formula of Levey et al. (12); CKD was defined as an eGFR < 60 ml/min/1.73 m², based on the recommendations of the National Kidney Foundation (13). Exclusion criteria were primary or rescue PCI and angiography procedures requiring a direct renal injection of contrast, cardiogenic shock, overt congestive heart failure, acute respiratory insufficiency, recent acute kidney injury, chronic peritoneal or hemodialysis treatment, known furosemide hypersensitivity, receipt of intravenous contrast within 10 days before the procedure or another planned contrast-enhanced procedure in the following 72 h, and contraindications to placement of a Foley catheter in the bladder. Renoprotective drugs were not administered, and a non-ionic, low-osmolality contrast agent (iomeprol) was used. The ethical committee of our institution approved the protocol. All patients provided written informed consent.

Study Protocol. Patients were randomized, in a 1:1 ratio, to receive either furosemide with matched hydration (FMH group) or hydration with isotonic saline (control group) based on computer-generated random numbers. Randomization was stratified for elective or urgent coronary angiography.

The control group received a continuous intravenous infusion of isotonic saline at a rate of 1 ml/kg/h (0.5 ml/kg/h in case of left ventricular ejection fraction $< 40\%$) for at least 12 h before and 12 h after the procedure.

In the FMH group, a standard 18-gauge catheter was inserted into a peripheral vein of the arm. The catheter was connected with the extracorporeal circuit of the RenalGuard System (PLC Medical Systems, Milford, Massachusetts) for fluid infusion, and a standard Foley catheter was positioned in the bladder for urine collection. The RenalGuard System is capable of delivering sterile replacement solution to a patient in an amount matched to the volume of urine produced by the patient, avoiding hypovolemia and fluid overload.

Abbreviations and Acronyms

CI = confidence interval

CIN = contrast-induced nephropathy

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

FMH = furosemide with matched hydration

IV = intravenous

NSTEMI = non-ST-segment elevation (acute) myocardial infarction

PCI = percutaneous coronary intervention

RR = relative risk

Approximately 90 min before the coronary procedure, FMH treatment was started with an initial intravenous bolus (250 ml) of normal saline solution over 30 min. Furosemide was then administered as a single intravenous bolus of 0.5 mg/kg (up to a maximum of 50 mg) (Fig. 1). Urine output was calculated continuously by the system, and when a urine output rate >300 ml/h was achieved, patients were brought to the catheterization laboratory and underwent coronary angiography. Matched hydration was continued throughout the catheterization procedure and for 4 h after the last contrast dose. At this time, therapy was discontinued. Additional doses of furosemide (up to a maximal cumulative dose of 2.0 mg/kg) were given in cases where the urine output was below 300 ml/h during treatment. The Foley catheter was removed 24 h after the procedure.

Blood urea nitrogen, serum creatinine, and serum electrolytes were evaluated at baseline, the day of coronary angiography, each day for the following 3 days, and at hospital discharge. Periprocedural medical therapy, PCI technique, and contrast dose were left to the discretion of the cardiologist responsible for the patient and the interventional cardiologist, on the basis of current guidelines. During hospitalization, medications were changed as required by the clinical situation.

Study Endpoints. The primary endpoint was CIN occurrence, defined as a $\geq 25\%$ or ≥ 0.5 mg/dl rise in serum creatinine over baseline during the first 72 h post-procedure (14). Secondary endpoints were as follows: 1) serious complications secondary to CIN prophylactic therapy; and 2) major post-procedure in-hospital adverse clinical events, including acute pulmonary edema, cardiogenic shock, CIN requiring renal replacement therapy (hemofiltration or hemodiafiltration), clinically significant arrhythmias, and death.

Statistical Analysis. For the calculation of the sample size, we assumed a CIN rate of 20% in controls based on the

following assumptions: 1) inclusion of approximately 50% of CKD patients with NSTEMI, with an anticipated CIN incidence of more than 25% (15); and 2) an anticipated CIN rate of approximately 15% in CKD patients undergoing elective procedures (16). Therefore, averaging the 25% and 15% CIN rates, the overall rate of CIN was expected to be 20% in control patients. Moreover, we assumed a CIN incidence of 5% in the FMH group (15% absolute and 75% relative reduction) (17). Using a 2-sided chi-square test with a significance level of 0.05 and 80% power, 80 subjects in each group and a total sample size of 160 are required to demonstrate the expected difference in the incidence of CIN between groups.

Continuous variables are presented as mean \pm SD and were compared using the *t* test for independent samples. Variables not normally distributed are presented as median and interquartile range, and compared with the Wilcoxon rank sum test. Categorical data are presented as percentages and were compared using the chi-square test or the Fisher exact test, as appropriate. Multivariable log-binomial regression models were developed to adjust for indication to coronary angiography (elective or urgent) and the Mehran risk score (18). Relative risks (RR) are reported with 95% confidence intervals (CIs). Spearman correlation analysis was used for the evaluation of 2 continuous variables. Primary and secondary endpoints were also analyzed according to the intention-to-treat principle. All tests were 2-tailed, and a *p* value of <0.05 was required for statistical significance. All calculations were computed with the aid of the SAS software package (version 9.13, SAS Institute, Cary, North Carolina).

Results

A total of 174 consecutive patients (mean age: 73 ± 7 years, 136 men) with CKD (mean eGFR: 39 ± 10 ml/min/1.73

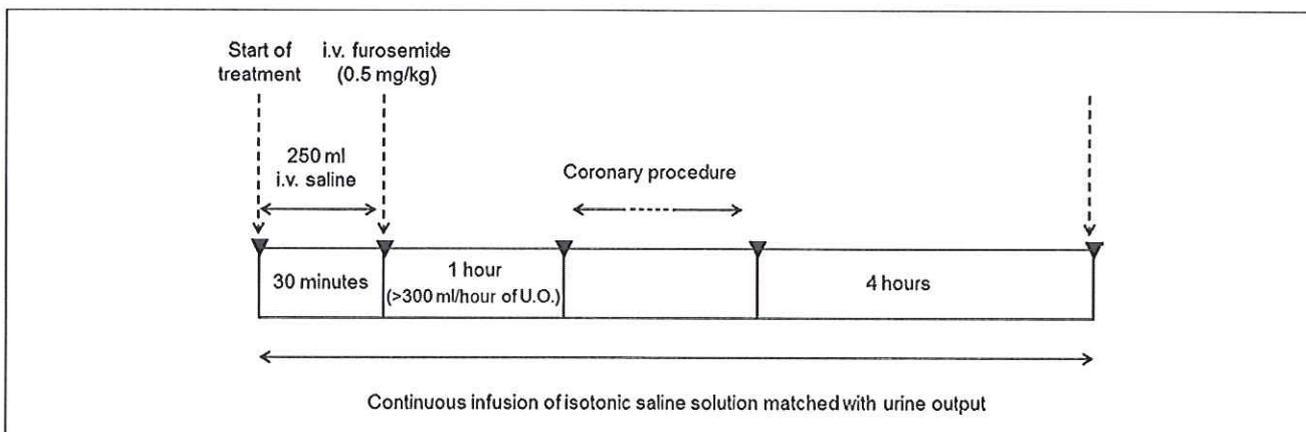
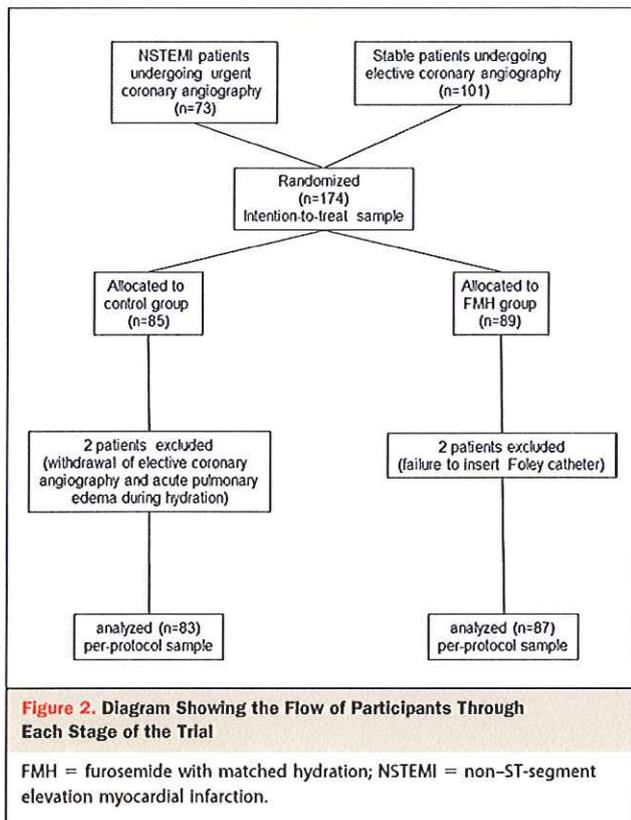


Figure 1. Protocol Diagram of Furosemide-Induced Diuresis With Matched Hydration Treatment

i.v. = intravenous; U.O. = urine output.



m²) were included in the study. Of them, 101 underwent elective procedures and 73 underwent urgent angiography because of NSTEMI. Eighty-nine patients were randomized to the FMH group and 85 to the control group. Two patients in the FMH group and 2 in the control group were excluded, and 170 patients completed the study (Fig. 2). One FMH patient with NSTEMI developed acute pulmonary edema during urgent PCI; FMH treatment was interrupted in order to achieve negative fluid balance and clinical recovery. This patient was included in the final analysis.

Baseline characteristics of the 2 groups were comparable, except for a lower serum potassium concentration in the FMH group (Table 1). All patients had moderate or severe CKD. The frequency of additional CIN risk factors and calculated risk score (18) were also similar. Baseline characteristics were also similar in the 2 groups, when patients undergoing elective angiography and those undergoing urgent angiography were analyzed separately.

In all FMH patients, urine output increased above 300 ml/h within 48 ± 16 min after intravenous furosemide, and remained high during treatment (median: 760 ml/h; interquartile range: 560 to 1,119 ml/h). In 18 (21%) cases, an additional 0.5 mg/kg intravenous bolus of furosemide was required during treatment to maintain urine output above the 300 ml/h threshold. Two additional furosemide boluses

were required in 3 (3.4%) cases. Overall, the duration of the FMH treatment was 6 ± 1 h. The cumulative intravenous (IV) saline hydration volume during the 6-h treatment period was 3,995 ± 1,401 ml. Urine output, by definition,

Table 1. Baseline Characteristics of the Study Patients (per Protocol Analysis)

	FMH Group (n = 87)	Control Group (n = 83)	p Value
Baseline clinical characteristics			
Age, yrs	73 ± 7	74 ± 8	0.27
Men	68 (78%)	65 (78%)	0.98
Weight, kg	76 ± 14	73 ± 12	0.09
Height, cm	167 ± 8	167 ± 8	0.97
Smokers	4 (7%)	7 (13%)	0.26*
Diabetes mellitus	38 (44%)	29 (35%)	0.24
Hypertension	72 (83%)	69 (83%)	0.94
Dyslipidemia	62 (71%)	56 (68%)	0.59
Prior myocardial infarction	42 (48%)	34 (41%)	0.37
Prior CABG	28 (32%)	21 (25%)	0.32
Prior PCI	46 (53%)	34 (41%)	0.12
Elective procedure	48 (55%)	52 (63%)	0.32
Urgent procedure	39 (45%)	31 (37%)	0.32
Mean LVEF, %	51 ± 13	52 ± 13	0.58
CIN risk score (18)	9.3 ± 4.6	10.3 ± 3.5	0.08
Stage 3 CKD	65 (75%)	69 (83%)	0.18
Stage 4 CKD	22 (25%)	14 (17%)	0.18
Medications			
ACE inhibitors	54 (63%)	56 (67%)	0.52
Aspirin	74 (86%)	76 (92%)	0.25
Diuretics	47 (55%)	48 (58%)	0.68
Calcium-channel blockers	35 (41%)	28 (34%)	0.34
Beta-blockers	53 (62%)	51 (61%)	0.98
Insulin	15 (17%)	11 (13%)	0.45
Oral hypoglycemic agents	20 (24%)	17 (20%)	0.63
Baseline laboratory measures			
Serum creatinine, mg/dl†	1.8 ± 0.6	1.7 ± 0.5	0.12
eGFR, ml/min/1.73 m ²	38 ± 11	41 ± 10	0.17
BUN, mg/dl‡	69 ± 34	73 ± 30	0.34
Serum Na ⁺ , mEq/l	140 ± 2	139 ± 3	0.34
Serum K ⁺ , mEq/l	4.1 ± 0.7	4.4 ± 0.6	0.02
Hemoglobin, g/dl	12.4 ± 1.9	12.2 ± 1.7	0.57
Procedural data			
Coronary angiography	87 (100%)	83 (100%)	1.0
PCI	50 (57%)	54 (65%)	0.31
Contrast volume, ml	181 ± 104	158 ± 109	0.17
Contrast ratio >1§	26 (30%)	31 (37%)	0.30
Major peri-PCI bleedings	4 (5%)	1 (1.2%)	0.19*

Values are mean ± SD or n (%). *By Fisher exact test. †To convert from mg/dl to μmol/l, multiply by 88.4. ‡To convert from mg/dl to mmol/l, multiply by 0.357. §The contrast ratio was defined as the ratio between the contrast volume effectively administered and that calculated according to the following formula: (5 × kg)/serum creatinine.

ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; CIN = contrast-induced nephropathy; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FMH = furosemide with matched hydration; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

was exactly matched to the infusion rate (minus the initial 250-ml saline bolus). The duration of IV saline hydration in the control group was 25 ± 2 h. During this period, the cumulative IV saline hydration was $1,742 \pm 290$ ml. No significant differences, in terms of IV hydration duration (25 ± 1.9 h and 25 ± 1.5 h, respectively; $p = 1.0$), and cumulative IV fluid administration ($1,757 \pm 302$ ml and $1,718 \pm 271$ ml, respectively; $p = 0.55$) were observed between control patients undergoing elective or urgent angiography. Urine output during IV hydration in the control group was $3,117 \pm 876$ ml, with no difference between patients undergoing elective or urgent angiography ($3,021 \pm 655$ ml and $3,169 \pm 982$ ml, respectively; $p = 0.41$). Thus, a 2-fold higher IV hydration rate and a slightly higher urine output were obtained in a 4-fold shorter time in FMH-treated patients when compared with controls.

No significant FMH-associated complications were observed. Four patients developed asymptomatic hypokalemia that was corrected with potassium supplementation.

After the procedure, 4 (4.6%) of the FMH patients developed CIN compared with 15 (18%) of the control group ($p = 0.005$). The FMH treatment was particularly effective in patients with NSTEMI undergoing urgent PCI (Fig. 3). Overall, the incidence of CIN was 4.5% ($n = 3$) in patients undergoing coronary angiography only, whereas it was 15% ($n = 16$) in those undergoing coronary angiography and PCI.

Figure 4 shows the relationship between maximal hourly urine output in response to furosemide and changes in maximal serum creatinine concentration in the FMH group. A significant relationship was found between maximal urine output and baseline eGFR in this group ($r = 0.40$; $p = 0.0001$).

Table 2 shows post-procedure complications. Cumulative in-hospital morbidity was lower in FMH patients.

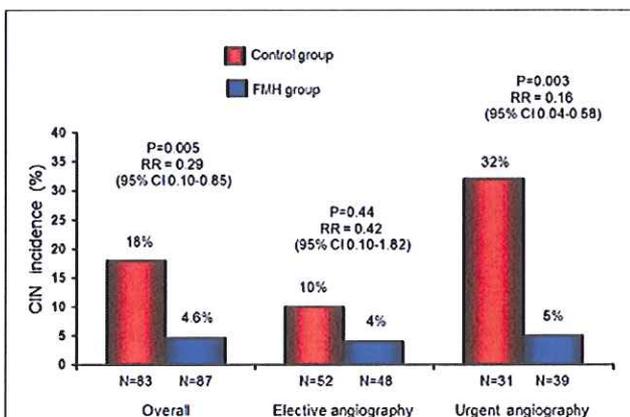


Figure 3. Incidence of CIN in All Study Patients and in Those Undergoing Elective or Urgent Coronary Angiography

CI = confidence interval; CIN = contrast-induced nephropathy; FMH = furosemide with matched hydration; RR = relative risk (unadjusted).

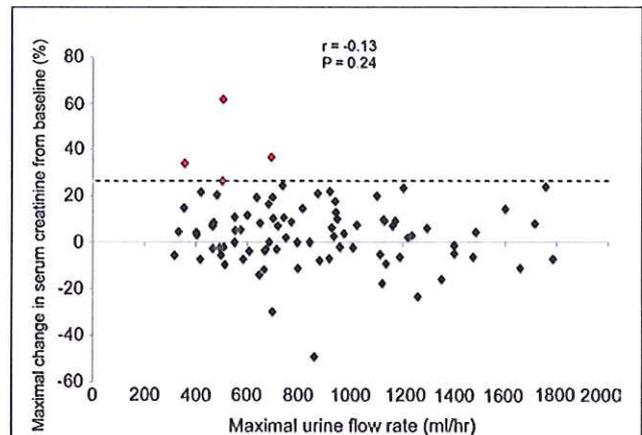


Figure 4. Relationship Between Percent Maximal Creatinine Change and Maximal Urine Flow Rate in Patients Undergoing Furosemide With Matched Hydration

Red symbols indicate patients who developed contrast-induced nephropathy. The dotted line indicates the $\geq 25\%$ threshold of serum creatinine increase used for the definition of contrast-induced nephropathy.

In the per-protocol analysis, the overall RR for CIN of the FMH group versus control, adjusted for baseline CIN risk score, was 0.29 (95% CI: 0.1 to 0.83; $p = 0.023$). After adjustment also for coronary angiography indication (elective vs. urgent), RR was 0.31 (95% CI: 0.11 to 0.89; $p = 0.03$). In the 2 groups, the combined incidence of CIN and major adverse clinical events was 13% and 40%, respectively ($p < 0.001$). The net clinical benefit, in terms of adjusted RR of this combined endpoint, was 0.32 (95% CI: 0.15 to 0.67; $p = 0.003$) in the per-protocol analysis and 0.31 (95% CI: 0.16 to 0.63; $p = 0.0014$) in the intention-to-treat analysis.

	FMH Group (n = 87)	Control Group (n = 83)	p Value
CIN requiring RRT	1 (1.1%)	3 (4%)	0.29*
Acute myocardial infarction	0 (0%)	1 (1.2%)	0.30*
AF/VT	1 (1.1%)	2 (2.4%)	0.53*
Emergency CABG	0 (0%)	0 (0%)	—
Acute pulmonary edema	5 (6%)	10 (12%)	0.15*
Hypotension/shock	0 (0%)	0 (0%)	—
In-hospital death	1 (1.1%)	3 (4%)	0.29*
Patients with ≥ 2 events	1 (1.1%)	3 (4%)	0.29*
All clinical events (per protocol)	7 (8%)	15 (18%)	0.052
All clinical events (intention-to-treat)	7 (8%)	17 (20%)	0.02

Values are n (%). *By Fisher exact test.
AF = atrial fibrillation; CIN = contrast-induced nephropathy; RRT = renal replacement therapy; VT = ventricular tachycardia; other abbreviations as in Table 1.

Discussion

The main finding of our study is that a prophylactic intravenous loading dose of 250-ml normal saline solution combined with furosemide-induced high-volume diuresis and maintenance of intravascular volume through automatic matched hydration is an effective and safe strategy for the prevention of CIN in high-risk patients undergoing both elective or urgent coronary procedures. Moreover, in-hospital clinical outcome was improved as compared with controls.

Hydration remains the cornerstone of CIN prevention. It produces expansion of plasma volume with concomitant suppression of the renin-angiotensin-aldosterone system, down-regulation of tubuloglomerular feedback, dilution of contrast media, and thus, prevention of renal vasoconstriction and tubular obstruction (4,5). Furosemide administration may have some positive effects when associated with hydration. First, it enhances contrast dilution in the renal tubule through increased urine flow. Second, it blocks tubular sodium reabsorption in the medulla and, as a consequence, reduces tubular workload and concomitant oxygen requirement at a time when contrast is expected to decrease medullary oxygen delivery. Moreover, furosemide may reduce renal vascular resistance, increasing renal blood flow (19), and produce some degree of metabolic alkalosis (20). The latter effect has been associated with a renal protective effect against CIN (21). Finally, it prevents fluid overload, reducing the risk of heart failure. On the other hand, these positive actions may be thwarted by furosemide-induced reduction of the effective circulating volume, prostaglandin-mediated venodilation, and dehydration as a result of increased urine output (22). These phenomena may cause activation of the renin-angiotensin-aldosterone axis and vasoconstriction, in addition to that induced by contrast administration, with consequent reduction in renal blood flow and GFR (23). Indeed, previous clinical studies demonstrated that the net effect of prophylactic furosemide seems to be an increased CIN rate (7,8).

In the PRINCE study, a protective effect against CIN was observed when a mean urine flow rate above 150 ml/h was achieved with a single dose of diuretic and matched intravenous fluid replacement (11). However, in this trial, fluid administration matched to urine output started after the catheterization procedure. Thus, it is possible that some patients who did not show any benefit had intravascular volume reduction before receiving prophylactic treatment. This may be overcome by the RenalGuard system, which is capable of fluid delivery in an amount precisely and timely matched to the urine volume, thus preventing hypovolemia and, at the same time, fluid overload. Our study further confirms that urine

output increase and dehydration prevention have a protective effect against CIN in high-risk patients. However, the results of the recent Majumdar *et al.* study (24) are not in agreement with this concept. These authors investigated the CIN preventive effect of forced diuresis obtained with mannitol and furosemide combined with intravenous infusion of a hypotonic saline volume manually matched to urine output in 92 CKD patients undergoing coronary angiography. A higher (50%) CIN rate was observed in forced diuresis patients than in those who received saline infusion only (28%; $p = 0.03$). The discrepancy between these results and the present study may be explained by the significant differences between the 2 treatment protocols. In particular, delayed and unmatched versus instantaneous and matched urine output replacement, administration of hypotonic versus isotonic saline solution, continuous infusion versus intravenous bolus of furosemide, and significantly lower urine output (150 ml/h vs. ~ 800 ml/h) resulting in a reduced hydration rate significantly differentiate the 2 studies. Finally, patients in the Majumdar *et al.* study had more severe CKD (average eGFR: 27 ml/min/1.73 m²). Thus, it is likely that a more powerful preventive strategy, such as hemofiltration, may be needed for such patients (17). It is remarkable that the RenalGuard System reproduced some characteristics of hemofiltration treatment. Indeed, with hemofiltration, the priming saline solution contained within the extracorporeal circuit and administered to the patient is similar to the initial fluid load used with this novel treatment. Moreover, the hourly hydration volume is also similar (1,000 ml with hemofiltration and 800 ml with FMH treatment). Thus, a new concept is emerging for CIN prevention: hydration volume should be commensurate to patient risk, and high-risk patients likely require a high-volume (~ 1 l/h) of controlled hydration. This goal can be achieved either by exactly matching fluid removal to high-volume intravenous hydration to prevent fluid overload (hemofiltration) or by exactly matching intravenous hydration to forced urine output to avoid hypovolemia (FMH treatment).

Our study also emphasizes the close relationship between CIN and poor clinical outcome, and the benefit of preventing this complication. Indeed, in the FMH group, the 3-fold reduction in CIN was associated with a lower incidence of post-procedural major adverse clinical events as compared with controls. However, this study was not powered to detect differences in clinical outcome. Thus, this result should be considered preliminary, and the impact of this strategy on meaningful clinical endpoints requires confirmation in larger and multicenter trials.

It is noteworthy that the positive results of our study were mostly driven by the effect of FMH in NSTEMI patients undergoing urgent angiography. This is a high-risk subgroup of patients who are less likely to receive CIN

prophylaxis, and in whom several factors, such as hemodynamic instability, periprocedural bleedings, acute hyperglycemia, and nephrotoxic drugs, may further increase the risk of renal injury (15,25). It is possible that these patients may benefit the most from this strategy, not only in terms of contrast toxicity prevention, but also in terms of overall kidney protection from acute injury. Although we observed an important (almost 60%) reduction in the incidence of CIN in elective angiography patients who were treated with FMH, when compared with controls, this difference did not reach statistical significance, likely because the sample size was underpowered. Therefore, the cost-benefit ratio of FMH in patients undergoing elective angiography needs further investigation, and this prophylactic approach may be more well founded in patients with a more severe CIN risk profile.

Study limitations. In interpreting these data, some limitations should be considered. First, this was a single-center study. Second, the study was unblinded, which may have influenced our results. Third, the treatment protocol used in the FMH group in terms of overall duration, furosemide dosage, and urine output target was arbitrarily predetermined. Therefore, it is possible that the potential benefit of this strategy may be further improved with a greater urine output increase and/or a longer treatment period. Indeed, CIN was not observed among patients whose urine output exceeded the median value (760 ml/h) of the entire treated population, suggesting that a higher urine output target than that used in our study may increase FMH efficacy. Further investigation is needed to determine whether a higher urine output threshold may provide greater renal protection and a higher furosemide dose may be beneficial in patients with more compromised baseline renal function. This is suggested by the direct relationship between baseline eGFR and hourly urine output, indicating that a higher furosemide dose is likely needed in patients with stage IV CKD to reach and maintain the target diuresis.

Conclusions

This study indicates that furosemide-induced diuresis with maintenance of intravascular volume through matched hydration can be safely and effectively obtained with the RenalGuard system and reduces the risk of CIN in high-risk patients undergoing coronary procedures.

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REFERENCES

- 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.
- Best PJM, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002;39:1113-9.
- McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997;103:368-75.
- Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract* 2003;93:C29-34.
- Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;162:329-36.
- Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron* 1992;62:413-5.
- Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;331:1416-20.
- Dussol B, Morange S, Loundoun A, Auquier P, Berland Y. A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients. *Nephrol Dial Transplant* 2006;21:2120-6.
- Brezis M, Rosen S. Hypoxia of the renal medulla: its implications for disease. *N Engl J Med* 1995;332:647-55.
- Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2006;68:1422-8.
- 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. *J Am Coll Cardiol* 1999;33:403-11.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, for the Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39 Suppl 1:S1-246.
- Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006;354:379-86.
- Recio-Mayoral A, Chaparro M, Prado B, et al. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO study. *J Am Coll Cardiol* 2007;49:1283-8.
- McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 2003;4 Suppl 5:S3-9.
- Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003;349:1333-40.
- 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;44:1393-9.
- Hook JB, Bailie MD. Release of vasoactive materials from the kidneys by diuretics. *J Clin Pharmacol* 1977;17:673-80.
- Hropot M, Fowler N, Karlmark B, Giebisch G. Tubular action of diuretics: distal effects on electrolyte transport and acidification. *Kidney Int* 1985;28:477-89.
- Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004;291:2328-34.
- Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973;288:1087-90.

23. Gottlieb SS, Brater DC, Thomas I, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 2002;19:1348-53.
24. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis* 2009;54:602-9.
25. Marenzi G, De Metrio M, Rubino M, et al. Acute hyperglycemia and contrast-induced nephropathy in primary percutaneous coronary intervention. *Am Heart J* 2010;160:1170-7.

Key Words: contrast-induced nephropathy ■ furosemide ■ high urine output ■ hydration ■ percutaneous coronary intervention.