Effects of Hydration in Contrast-Induced Acute Kidney Injury After Primary Angioplasty
A Randomized, Controlled Trial

Mauro Maioli, MD; Anna Toso, MD; Mario Leoncini, MD; Carlo Micheletti, RN; Francesco Bellandi, MD

Background—Intravascular volume expansion represents a beneficial measure against contrast-induced acute kidney injury (CI-AKI) in patients undergoing elective angiographic procedures. However, the efficacy of this preventive strategy has not yet been established for patients with ST-elevation–myocardial infarction (STEMI), who are at higher risk of this complication after primary percutaneous coronary intervention (PCI). In this randomized study we investigated the possible beneficial role of periprocedural intravenous volume expansion and we compared the efficacy of 2 different hydration strategies in patients with STEMI undergoing primary PCI.

Methods and Results—We randomly assigned 450 STEMI patients to receive (1) preprocedure and postprocedure hydration of sodium bicarbonate (early hydration group), (2) postprocedure hydration of isotonic saline (late hydration group), or (3) no hydration (control group). The primary end point was the development of CI-AKI, defined as an increase in serum creatinine of ≥25% or 0.5 mg/dL over the baseline value within 3 days after administration of the contrast medium. Moreover, we evaluated a possible relationship between the occurrence of CI-AKI and total hydration volume administered. There were no significant differences in baseline clinical, biochemical, and procedural characteristics in the 3 groups. Overall, CI-AKI occurred in 93 patients (20.6%): the incidence was significantly lower in the early hydration group (12%) with respect to both the late hydration group (22.7%) and the control group (27.3%) (P for trend=0.001). In hydrated patients (early and late hydration groups), lower infused volumes were associated with a significant increase in CI-AKI incidence, and the optimal cutoff point of hydration volume that best discriminates patients at higher risk was ≤960 mL.

Conclusions—Adequate intravenous volume expansion may prevent CI-AKI in patients undergoing primary PCI. A regimen of preprocedure and postprocedure hydration therapy with sodium bicarbonate appears to be more efficacious than postprocedure hydration only with isotonic saline.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00770614.

Key Words: acute myocardial infarction ■ contrast media ■ acute kidney injury ■ catheter based coronary intervention

Contrast-induced acute kidney injury (CI-AKI) is a significant cause of iatrogenic renal dysfunction, contributing to morbidity, prolonged hospitalization, mortality, and increased costs of health care.1–4

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Patients treated with primary percutaneous coronary intervention (PCI) for ST-segment elevation–myocardial infarction (STEMI) are at greater risk for CI-AKI, which is associated with higher rates of early clinical complications and mortality.5–7 At present, since a feasible, effective therapeutic strategy has not yet been identified, certain preventive measures against CI-AKI can be adopted in a timely manner in patients with STEMI who are submitted to primary PCI, to improve renal and cardiac outcome.

In elective PCI, the main preventive strategies lie in preprocedural intravenous volume expansion with isotonic saline or sodium bicarbonate,1,8–10 antioxidant therapy with oral N-acetylcysteine (NAC)11,12 or ascorbic acid,13 and use of low- or iso-osmolality contrast agents.14–16

Early administration of NAC has recently been proposed for CI-AKI prevention also in patients submitted to urgent PCI,7 but the role of hydration in primary PCI has not yet been clarified. In particular, the agents, timing, quantity, and velocity for hydration of these latter patients have not been investigated.

The aims of this prospective, randomized, 3-arm study were to evaluate the possible beneficial role of periprocedural intravenous volume expansion and to compare 2 different hydration strategies in patients with STEMI who are undergoing primary PCI.
WHAT IS KNOWN

- Contrast-induced acute kidney injury (CI-AKI) is a significant cause of iatrogenic renal dysfunction, contributing to morbidity, prolonged hospitalization, mortality, and increased costs of health care.
- The routine use of hydration protocol before contrast exposure is an established preventive measure, recommended in the guidelines against CI-AKI in all elective angiographic procedures involving administration of iodine contrast medium. However, the efficacy of this preventive strategy has not yet been established for patients with ST-elevation–myocardial infarction who are at higher risk of this complication after primary percutaneous coronary intervention.

WHAT THE STUDY ADDS

- This prospective, randomized study shows that among patients with acute myocardial infarction treated with primary percutaneous coronary intervention, intravenous volume expansion is beneficial against CI-AKI development. In particular, the regimen of early hydration with sodium bicarbonate significantly reduces the rate of CI-AKI compared with a regimen of only late hydration with saline or no hydration treatment.
- Early infusion guarantees a larger quantity of fluids than postprocedural hydration, and the amount of fluids administered plays an important role in this setting: multivariate analysis identifies a total hydration volume of \( \geq 960 \text{ mL} \) as one of the independent predictors of CI-AKI.
- Our findings suggest that routine procedure for patients with ST-elevation–myocardial infarction candidates to primary percutaneous coronary intervention should include standard pharmacological treatment associated with early hydration protocol, dosed according to patient weight and baseline ejection fraction, and started in the emergency room whenever feasible.

Methods

Population and Study Protocol

From July 2004 to December 2008, all consecutive patients with STEMI who were candidates for primary PCI at our institution were considered for enrollment in the present study. Initial exclusion criteria were contrast medium administration within the previous 10 days, end-stage renal failure requiring dialysis, and refusal to give informed consent. Eligible patients were randomly assigned in a 1:1:1 ratio to receive preprocedure and postprocedure hydration (early hydration group), postprocedure hydration (late hydration group), or no hydration (control group). Computer-generated, open-label randomization block was used (Plan Procedure of SAS, version 8.2, SAS Institute, Cary, NC).

Patients assigned to early hydration were administered a bolus of 3 mL/kg of sodium bicarbonate solution (154 mEq/L in dextrose and water) in 1 hour, starting in the emergency room, followed by infusion of 1 mL/kg per hour for 12 hours after PCI. Patients assigned to late hydration received isotonic saline (1 mL/kg per hour 0.9% sodium chloride) for 12 hours immediately after PCI.

Echocardiographic evaluation of left ventricular function was performed in all patients in the emergency room immediately before the acquisition of informed consents for both primary PCI and enrollment in the study. Hydration rate was reduced to 0.5 mL/kg per hour in patients with left ventricular ejection fraction (EF) \( \leq 40\% \) or New York Heart Association class III–IV in both groups. In all cases, we used Iodixanol (Visipaque, GE Healthcare Ltd, Amersham, UK), a nonionic, dimeric iso-osmolar contrast medium.

Serum creatinine concentration was assessed at the time of hospital admission and on days 1, 2, 3, 5, and 10 after the procedure. All tests were performed in the hospital laboratory with consistent methodology. Data were recorded in a dedicated database. The study was approved by the hospital ethics committee, and all patients gave informed consent.

Primary PCI

Primary PCI was performed by a 24-hour, on-call interventional team, according to standard clinical practice, and the recommended intervention was coronary stenting. In no case was the procedure delayed to allow completion of preprocedural hydration bolus in the early hydration group. All patients received a bolus of 500 mg aspirin, 600 mg clopidogrel 300 mg loading dose, and 60 U heparin/kg body weight (up to a maximum of 5000 U) in the emergency room. In patients without contraindication, the glycoprotein IIb/IIIa inhibitor abciximab was administered periprocedurally with an intravenous bolus of 0.5 mg/kg body weight followed by a continuous infusion of 0.125 \( \mu \text{g/kg} \) per minute (up to a maximum of 10 \( \mu \text{g/min} \) for 12 hours. Eventual supportive mechanical and pharmacological therapies were left to the discretion of the interventional cardiologist. The Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade was evaluated after PCI in all patients and used as angiographic index of reperfusion.

End Points and Clinical Definitions

The primary end point of the study was the development of CI-AKI, defined as an increase in serum creatinine of \( \geq 25\% \) or 0.5 mg/dL over the baseline value within 3 days after administration of the contrast medium. Additional end points were (1) the reduction of estimated glomerular filtration rate (eGFR) \( \geq 25\% \) at 72 hours and (2) the development of CI-AKI in patients who received preprocedural hydration (early hydration and late hydration groups) in relation to total hydration volume administered.

GFR was estimated by applying the level-modified Modification of Diet in Renal Disease formula. Renal function was categorized according to the stages set by the National Kidney Foundation (USA), with eGFR \( \geq 90 \text{ mL/min considered normal}, 60 \text{ to } 89 \text{ mL/min mildly impaired}, 30 \text{ to } 59 \text{ mL/min moderately impaired}, <30 \text{ mL/min severely impaired}. \) The nephropathy risk score was calculated as specified by Mehran et al. The administered contrast volume-to-eGFR ratio was calculated by using the Laskey method. Major and minor bleedings were defined according to the TIMI criteria. Major adverse cardiovascular events included death, recurrent myocardial infarction, repeated urgent revascularization, stroke, and major bleeding. Recurrent myocardial infarction was defined as a new increase in creatinine kinase MB fraction of more than 3 times the upper limit of normal, associated with chest pain and/or electrocardiographic changes. Urgent revascularization was defined as a repeated coronary revascularization performed within 48 hours after the index revascularization procedure.

Statistical Analysis

We calculated the sample size on the basis of a power analysis that assumed a reduction in the average rate of the primary end point of CI-AKI from 25% in the control group to 12.5% in the hydration groups. The inclusion of 130 patients in each group allowed for a statistical power of 80%, with a type 1 error of 0.05. Our protocol required that each original group comprise at least 150 patients to allow for dropouts and/or incomplete data.

Categorical variables were reported as absolute values and percentages and were analyzed by \( \chi^2 \) analysis or Fisher exact test.
Multiplicity issues resulting from the pairwise comparisons were approached with the Bonferroni adjustment (yielding a significance threshold of 0.016).

Normal distributions of continuous data were tested using a Kolmogorov-Smirnov test, and variables are represented as mean±SD or as medians (interquartile range). One-way ANOVA test and the Kruskal-Wallis test were used to determine differences between normal and nonnormally distributed continuous variables, respectively. The ANOVA for repeated measures was used to compare the time course of creatinine values between the groups. In hydrated patients, receiver operating characteristic (ROC) curve analysis was performed to establish the cutoff values of continuous variables (volume of hydration, left ventricular EF, volume-to-creatinine clearance ratio, and others) most predictive of CI-AKI. Multivariate logistic regression analysis was also performed in hydrated patients, using all potentially relevant variables to identify independent predictors of CI-AKI. In hydrated patients, incidence of CI-AKI was compared among tertiles, based on hydration volume by the Mantel-Haenszel linear-by-linear association $\chi^2$ test for trend.

All analyses were performed with SPSS statistical software, version 17.0 (SPSS Inc, Chicago, IL). All probability values are 2-tailed, and statistical significance was defined as $P<0.05$.

Results

Clinical Characteristics

Of the 481 consecutive patients with STEMI who were considered eligible for the present study, 20 were excluded. Thus, a total 461 patients were randomly assigned. After random assignment, another 11 patients were excluded (2 patients required emergency bypass grafting and 9 patients did not undergo PCI because of spontaneous recanalization of the culprit vessel). Thus, 450 patients were included in the trial, 150 patients per group. Figure 1 shows the enrollment criteria and the trial flow.

All patients completed the assigned hydration protocol, and there were no cases of fluid overload or acute pulmonary edema that required premature termination of the infusion. There were no significant differences in baseline clinical, biochemical, and procedural characteristics among the 3 groups (Table 1). In particular, patients $\geq$75 years of age and those with diabetes mellitus, moderate-to-severe renal dysfunction, anterior myocardial infarction, Killip class $\geq 1$, and reduced EF were evenly distributed in the 3 groups. The amount of contrast medium administered and the ratio between contrast volume and GFR were also similar in the 3 groups. As expected, the fluid volume administered was significantly lower in the late hydration group than in the early hydration group.

CI-AKI and Hydration

The overall incidence of CI-AKI was 20.6% (93/450); the incidence was significantly lower in the early hydration group than in both the late hydration group and the control group (Table 2 top). Also the decrease in eGFR $\geq 25\%$ at 72 hours showed a significant positive trend with early hydration (Table 2, top).

Patients receiving intravenous fluids (before and after or only after the procedure) showed a significantly lower incidence of CI-AKI when compared with nonhydrated control subjects (17.3 versus 27.3%, $P=0.004$). The time course of mean creatinine values in hydrated patients and in nonhydrated patients is shown in Figure 2: in the control group, creatinine values (circles) rose consistently up to day 5, whereas in hydrated patients, creatinine values (squares) showed an immediate reduction in the first 24 hours and a slight increase thereafter (ANOVA for repeated measures between groups, $P=0.011$).

As mentioned, the patients at higher risk for CI-AKI were equally divided among the 3 study groups. Noticeably, there was a lower incidence of CI-AKI in high-risk patients randomly assigned in the early hydration group than in the
960 mL was identified as the optimal cutoff point to predict risk for CI-AKI occurrence.

The ROC curve analysis showed that administered volumes (linear-by-linear association) of 0.65 (95% confidence interval, 0.57–0.73; *P*<0.001) significantly discriminates between patients with and without CI-AKI, with an area under the curve of 0.65 (95% confidence interval, 0.57–0.73; *P*=0.001). A hydration volume of ≥960 mL was identified as the optimal cutoff point to predict risk for CI-AKI occurrence.

Multivariate analysis evidenced that the incidence of CI-AKI was independently related to total hydration volume ≥960 mL, suboptimal index of myocardial perfusion after PCI (TIMI perfusion grade ≤2), depressed left ventricular function at baseline (EF ≤40%), and nephropathy risk score (odds ratio for every 1-point increase; Table 3).

**In-Hospital Clinical Outcome**

The overall mortality rate was 3.5% (16 patients); as expected, the rate was higher in patients who had CI-AKI than in those who did not have it (12.9% versus 1.1%, *P*<0.001). Similarly, patients with CI-AKI had a higher incidence of major in-hospital adverse events (Table 4). The incidence of major adverse cardiovascular events in the 3 different hydration groups was not statistically significant (Table 2, bottom), although the trend was toward a minor incidence with larger quantity and earlier administration of fluids.

**Discussion**

This prospective, randomized study shows that also among patients with acute myocardial infarction treated with primary...
PCI, intravenous volume expansion is beneficial against CI-AKI development. In particular, the regimen of early hydration with sodium bicarbonate significantly reduces the rate of CI-AKI compared with a regimen of only late hydration with saline or no hydration treatment.

In patients treated with primary PCI, acute renal injury occurs in 20% to 30% of cases and is a strong predictor of in-hospital morbidity and mortality. In fact, patients with CI-AKI have a more prolonged and complicated clinical course and strikingly higher in-hospital mortality rates (up to 30%). Moreover, the risk of CI-AKI after primary PCI regards not only patients with chronic kidney disease but also those with normal baseline renal function. In an era in which primary PCI is the preferred reperfusion treatment for patients with STEMI, prophylactic interventions against CI-AKI are warranted.

Table 2. End Points of the Study, Incidence of CI-AKI in High-Risk Patients, and In-Hospital Outcomes in the 3 Study Groups

<table>
<thead>
<tr>
<th>Primary and secondary end points</th>
<th>Control Group (n=150)</th>
<th>Late Hydration Group (n=150)</th>
<th>Early Hydration Group (n=150)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine increase by ≥0.5 mg/dL and/ or by ≥25% within 72 h, n (%)</td>
<td>41 (27.3)*</td>
<td>34 (22.7)†</td>
<td>18 (12.0)‡</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR decrease by &gt;25% at 72 h, n (%)</td>
<td>23 (15.6)</td>
<td>15 (10.3)</td>
<td>9 (6.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Incidence of CI-AKI in high-risk patients

| High to very high contrast nephropathy risk score (≥11) (%) | 18/52 (34.6) | 14/46 (30.4) | 11/45 (24.4) | 0.28 |
| eGFR <60 mL/min (%) | 10/34 (29.4) | 12/46 (26.1) | 6/40 (15.0) | 0.14 |
| Age ≥75 y (%) | 11/29 (37.9) | 15/36 (41.7) | 8/38 (21.1) | 0.12 |
| Diabetes mellitus (%) | 10/34 (29.4) | 11/31 (35.5) | 5/31 (16.1) | 0.24 |
| Anterior myocardial infarction (%) | 22/65 (33.8) | 16/63 (25.4) | 12/61 (19.7) | 0.07 |
| Left ventricular ejection fraction ≤40% (%) | 24/61 (39.3) | 20/58 (34.5) | 12/56 (21.4) | 0.04 |
| Volume contrast media-to-eGFR ratio ≥3.7 (%) | 15/50 (30.0) | 15/55 (27.3) | 9/48 (18.8) | 0.20 |

In-hospital outcome

| Hemofiltration, n (%) | 1 (0.7) | 1 (0.7) | 2 (1.3) | 0.54 |
| In-hospital death, n (%) | 8 (5.3) | 5 (3.3) | 3 (2.0) | 0.12 |
| Cardiogenic shock, n (%) | 8 (5.3) | 9 (6.0) | 6 (4.0) | 0.60 |
| Recurrent myocardial infarction, n (%) | 5 (3.3) | 6 (4.0) | 2 (1.3) | 0.30 |
| Repeated urgent PCI, n (%) | 2 (1.3) | 5 (3.3) | 1 (0.7) | 0.66 |
| Stroke, n (%) | 2 (1.3) | 2 (1.3) | 2 (1.3) | 1.0 |
| Major bleeding, n (%) | 8 (5.3) | 12 (8.0) | 6 (4.0) | 0.62 |
| MACE, n (%) | 15 (10.0) | 19 (12.7) | 11 (7.3) | 0.44 |

CI-AKI indicates contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; and MACE, major adverse cardiovascular events (death, recurrent myocardial infarction, repeated urgent PCI, stroke, and major bleeding).

Data are presented as n (%) of patients.

*Early hydration versus control group, P=0.001 (Bonferroni correction).
†Early versus late hydration group, P=0.015 (Bonferroni correction).

Figure 2. The time course of mean creatinine values in hydrated patients (squares) and in nonhydrated patients (circles) (ANOVA for repeated measures between groups, P=0.011). Bars give SD for each measurement.
The routine use of hydration protocol before contrast exposure is an established preventive measure, recommended in the guidelines against CI-AKI in all elective angiographic procedures involving administration of iodine contrast medium.18 To date, the current guidelines have not still suggested definite recommendations about the preferred hydration protocol (saline or sodium bicarbonate). The results of 2 recent meta-analyses do not clarify this issue.23,24 It would seem that earlier and smaller studies have probably overestimated the magnitude of sodium bicarbonate benefit,23,25 whereas larger, more recent trials have had neutral results.26,27

To our knowledge, to date, there have been no controlled studies regarding routine periprocedural hydration or evaluation of optimal hydration volume in primary PCI. Marenzi et al reported the use of periprocedural hydration with saline solution in STEMI patients treated with primary PCI.6,7 Rapid preprocedural infusion of sodium bicarbonate, first used, successfully, by Merten et al in elective PCI,17 was later used in emergency procedures in 2 small studies.28,29 In the present study, which involves a larger and clinically homogeneous (only STEMI) population—as well as a control group, intravascular volume expansion confers protection against the development of CI-AKI after primary PCI. As specified above, early, rapid hydration with bicarbonate, dosed according to patient weight and baseline EF, is significantly more effective than both no hydration and postprocedural hydration only. Intravenous volume expansion, obtained immediately before primary PCI, although moderate (3 mL/kg in 1 hour), could partially compensate for reduced cardiac output and hypotension secondary to myocardial infarction and contribute to patient hemodynamic equilibrium. Moreover, in patients with depletion of intravascular volume caused by vomiting, diaphoresis, or decreased oral intake, correction of hypovolemia can maintain renal perfusion and have nephroprotective action. In addition, intravenous volume expansion may lead to dilution of contrast medium and all the neurotransmitters, liberal radicals, cell necrosis factors, and so forth, that are released in acute conditions and that may exert a renal toxic effect.

Early infusion guarantees a larger quantity of fluids than postprocedural hydration only within the first 12 hours after PCI. The amount of fluids administered plays an important role in the development of CI-AKI: ROC analysis indicates that the smaller the quantity of periprocedurally infused fluids (before and after PCI or only after PCI) the higher the CI-AKI incidence. Moreover, multivariate analysis identifies a total hydration volume of ≥960 mL as one of the independent predictors of CI-AKI.

In the present study, patients with acute MI who had CI-AKI had higher incidence of in-hospital adverse clinical outcomes. No significant differences were found in the occurrence of death or major clinical complications among the 3 groups. We cannot draw conclusions regarding these findings because our study was designed primarily to evaluate

**Table 3. Multivariate Logistic Regression Model of CI-AKI Predictors**

<table>
<thead>
<tr>
<th>Significant Variables</th>
<th>Parameter Estimates</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration volume ≥960 mL</td>
<td>1.14</td>
<td>3.1</td>
<td>1.4–6.8</td>
<td>0.004</td>
</tr>
<tr>
<td>TIMI myocardial perfusion grade 0–2</td>
<td>0.94</td>
<td>2.6</td>
<td>1.1–5.9</td>
<td>0.028</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≤40%</td>
<td>0.91</td>
<td>2.5</td>
<td>1.1–5.6</td>
<td>0.028</td>
</tr>
<tr>
<td>Nephropathy risk score</td>
<td>0.11</td>
<td>1.1</td>
<td>1.0–1.2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI-AKI indicates contrast-induced acute kidney injury; CI, confidence interval; TIMI, Thrombolysis In Myocardial Infarction; Nephropathy risk score, odds ratio for every 1-point increase.
ate the incidence of CI-AKI and not statistically powered to assess differences in morbidity and mortality.

Study Limitations
The main limitation of this study is the use of 2 different hydration agents in the 2 hydrated groups (sodium bicarbonate in the early group and saline solution in the late group). We decided to adopt 2 strategies previously experienced in emergency conditions: sodium bicarbonate has been used for rapid infusion and saline solution for slow infusion. Therefore, the design of the present study makes impossible to define which solution is to be preferred in the setting of STEMI. The antioxidant action of sodium bicarbonate can possibly play a role in the prevention of CI-AKI, eventually contributing to the better results obtained in the early hydration group. Another limitation is related to the randomization procedure that followed an open-label assignment. Finally, the GFR was estimated by applying the level-modified Modification of Diet in Renal Disease formula, but the use of standard formulas can be overridden by the acute conditions in which there is a fluctuation in the creatinine values.

Conclusions
In patients with STEMI treated with primary PCI, the incidence of CI-AKI is significantly reduced by intravenous volume expansion with preprocedural and postprocedural infusion of sodium bicarbonate. Our findings suggest that routine procedure expansion with preprocedural and postprocedural infusion of sodium bicarbonate plus N-acetylcysteine in patients undergoing primary PCI should define which solution is to be preferred in the setting of STEMI. The antioxidant action of sodium bicarbonate can possibly play a role in the prevention of CI-AKI, eventually contributing to the better results obtained in the early hydration group. Another limitation is related to the randomization procedure that followed an open-label assignment. Finally, the GFR was estimated by applying the level-modified Modification of Diet in Renal Disease formula, but the use of standard formulas can be overridden by the acute conditions in which there is a fluctuation in the creatinine values.

Disclosures
None.

References
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