Renal Function–Adjusted Contrast Volume Redefines the Baseline Estimation of Contrast-Induced Acute Kidney Injury Risk in Patients Undergoing Primary Percutaneous Coronary Intervention

Giuseppe Andò, MD, PhD; Cesare de Gregorio, MD; Gaetano Morabito, MD; Olimpia Trio, MD, PhD; Francesco Saporito, MD; Giuseppe Oreto, MD

Background—Age, estimated glomerular renal function (eGFR), and ejection fraction are preprocedural predictors of contrast-induced acute kidney injury (CI-AKI) after primary percutaneous coronary intervention. The effect of renal function–adjusted contrast volume (CV) remains not totally explored, and a threshold has not yet been established.

Methods and Results—Logistic regression and receiver-operating characteristic curve analyses were used to assess whether CV/eGFR was an independent predictor of CI-AKI. The increased discriminative value of CV/eGFR over the preprocedural model based on age, eGFR, and ejection fraction was examined using the net reclassification improvement analysis. Of 470 patients enrolled, we observed 25 (5.3%) cases of CI-AKI. Patients with CI-AKI had received a higher renal function–adjusted CV (CV/eGFR 3.62 versus 1.96; \(P<0.001\)), and CI-AKI incidence was higher (15%; \(P<0.001\)) in patients in the highest quartile of CV/eGFR, corresponding to the cutoff indicated by the receiver-operating characteristic curve (>2.5; area under the curve, 0.77). At multivariable analysis, CV/eGFR above the cutoff (odds ratio, 5.57; \(P=0.002\)) remained an independent predictor of CI-AKI. The model with CV/eGFR demonstrated a statistically significantly net reclassification improvement of 0.23 (\(P=0.021\)) over the baseline preprocedural model, largely driven by a correct decrease in risk estimates for patients not experiencing CI-AKI, with a likelihood ratio \(\chi^2\) of 5.973 (\(P=0.029\)).

Conclusions—CV remains a key risk factor for CI-AKI after primary percutaneous coronary intervention and our study supports the need for minimizing CV, independently from baseline preprocedural risk. A CV restricted to no more than twice and a half the baseline eGFR might be valuable in reducing the risk of CI-AKI. (Circ Cardiovasc Interv. 2014;7:00-00.)

Key Words: acute kidney injury ■ balloon coronary angioplasty ■ contrast media adverse effects ■ myocardial infarction

Contrast-induced acute kidney injury (CI-AKI) is an important complication of iodinated contrast media administration. Although the pathogenesis is not completely understood, there is increasing evidence that CI-AKI occurs as a combination of oxidative stress, ischemic injury, direct toxicity, and obstruction of the renal tubular epithelium. It particularly occurs after coronary procedures; the reported incidence of CI-AKI may be as high as 50%, depending on patient population, baseline risk factors, and definition used. In patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment–elevation myocardial infarction (STEMI), CI-AKI is an established predictor of mortality. Left ventricular dysfunction and hemodynamic instability resulting in impaired systemic perfusion and the impossibility to implement renal prophylactic measures before exposure to contrast medium are key contributing factors to CI-AKI development in this setting. Apart from increasing mortality, CI-AKI is also associated with other in-hospital adverse events, such as bleeding and vascular complications, and late cardiovascular events. Finally, CI-AKI results in prolonged hospitalizations and additional costs.

To estimate the preprocedural risk of CI-AKI in interventional cardiology is of crucial importance, especially in patients with STEMI, whose renal function cannot yet be assessed accurately at the time of clinical presentation. Identifying patients at risk has a direct effect in targeting prophylactic interventions. These include hydration with normal saline and minimization of contrast volume (CV); the latter issue remains controversial and, despite European Society of Cardiology recommendations for patients undergoing percutaneous revascularization, it cannot totally be addressed in the setting of primary PCI for patients with

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WHAT IS KNOWN

• To identify patients at risk of contrast-induced acute kidney injury after percutaneous coronary intervention has a direct effect in targeting prophylactic measures.
• A 3-variable risk score based on clinical data that are known before the procedure (age, estimated glomerular filtration rate, and ejection fraction) predicts the occurrence of contrast-induced acute kidney injury in patients undergoing primary percutaneous coronary intervention.

WHAT THE STUDY ADDS

• Renal function–adjusted contrast volume is a key risk factor for contrast-induced acute kidney injury in patients undergoing primary percutaneous coronary intervention on top of risk estimation based on clinical presentation and increases the 3-variable risk score specificity.
• A total amount of contrast media restricted to no more than twice and a half the baseline estimated glomerular filtration rate is a reasonable threshold not to be overcome during primary percutaneous coronary intervention.

Study Protocol
Primary PCI was performed by a 24-hour on-call interventional team, using femoral approach and according to standard clinical practice. Pharmacological therapy, as well as the indication to intra-aortic balloon pump support, was left to the discretion of the attending cardiologists. The protocol followed to prevent CI-AKI did not include any intervention other than hydration. The hydration was initiated during the diagnostic procedure and was continued for ≥48 hours. Saline solution (0.9%) was given intravenously at a rate of 1 mL/kg per hour; hydration rate was reduced to 0.5 mL/kg per hour in patients with severe left ventricular dysfunction or overt heart failure. Nonionic low-osmolar contrast media (iopromide: Ultravist 370 mg iodine/mL or iomeprol: Iomeron 400 mg iodine/mL) were used in all cases depending on internal availability.

Blood samples were collected for measurement of serum creatinine concentration on hospital admission, 6 hours after the procedure, every day for the following 3 days, and at discharge from the coronary care unit. Baseline estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation. The study was planned according to the ethical standards detailed in the Declaration of Helsinki and was approved by the institutional review board. Informed consent was obtained from all patients.

Renal Function–Adjusted Contrast Dose
The maximum accepted contrast dose was calculated according to the Cigarroa formula. The ratio of CV:creatinine clearance have been proposed to calculate the eGFR, based on modification of diet in renal disease equation, as the best estimate of creatinine clearance (CV/eGFR).

Definitions and Study End Points
Renal dysfunction was defined as stage 3 or higher chronic kidney disease (ie, an eGFR <60 mL/min per 1.73 m²), in accordance to National Kidney Foundation Practice Guidelines.

The primary end point of the study was the occurrence of CI-AKI, defined as an absolute increase in serum creatinine concentration ≥25% from baseline within 72 hours after the administration of contrast medium, without any other plausible cause. In-hospital mortality rate was also computed as secondary end point.

Statistical Analysis
Continuous variables are expressed as mean±SD and compared with t test; categorical variables are expressed as absolute counts and percentages and compared by Fisher exact test or χ² test, as appropriate.

A multivariable analysis was performed to assess the independent predictors of CI-AKI. First, univariate analysis was performed to assess the association of CI-AKI with several demographic, clinical, humoral, preprocedural, and procedural variables. Variables associated with CI-AKI development with P<0.1 were then entered into a stepwise multivariable regression model to determine their significance as independent predictors of CI-AKI. The odds ratio (OR) and 95% confidence interval (CI) are presented. Receiver-operating characteristic (ROC) curve analysis was performed to establish cutoff values for variables independently associated with CI-AKI, with the area under the curve (AUC) as a measurement of accuracy. Sensitivity and specificity were calculated, and the best cutoff value was identified at the point where the sum of sensitivity and specificity was the highest according to the Youden index [(sensitivity+specificity)-1].

The increased discriminative value of CV/eGFR over the model based on the only AGES score was examined using the net reclassification improvement (NRI). The NRI is influenced by the requirement of a prespecified definition of risk categories and considers the changes in risk category associated with the introduction of the new covariate. For this purpose, 2 logistic regression models were fitted to the database, each with the occurrence of CI-AKI as the outcome: model 1 included AGES score as the only covariate, whereas model 2 included AGES score and CV/eGFR. First, the accuracy of each model was assessed in terms of discrimination and calibration: ROC

Methods

Patient Population
Inclusion and exclusion criteria have been described in detail elsewhere. Briefly, we consecutively enrolled all patients referred to the Intensive and Interventional Cardiology Department of the University Hospital of Messina during a 3-year period (2009–2011) for primary PCI. We present hereafter the analysis performed in all patients whose data set, including total CV, was available.
curves analysis was performed to assess discrimination, as measured by the AUC or C statistic, and ROC curves were compared pairwise. Calibration of each model was assessed by the Hosmer–Lemeshow $\chi^2$ statistic, and likelihood ratio test was performed for comparing model 2 to model 1. Then, the occurrence of CI-AKI for models 1 and 2 was adjusted to 4 a priori clinically meaningful categories of risk (0%–2%, 3%–5%, 6%–25%, and >25%), as demonstrated by Pencina.20 The effects of reclassification using model 2 when compared with model 1 were assessed: the prediction model for each individual was re-estimated with the information for the new covariate (CV/eGFR) included in the estimate.

We validated model 2 in 126 additional, nonconsecutive patients undergoing primary PCI between 2012 and 2013 and not enrolled in the randomized Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX) trial (ClinicalTrials.gov Identifier: NCT01433627).21 A 2-tailed $P<0.05$ was always requested for statistical significance. All calculations were performed using Statistical Package for Social Sciences, version 20.

**Results**

During the study period, 535 patients with STEMI underwent primary PCI. Of these, 65 were excluded from the study: 4 patients on chronic hemodialysis, 17 patients who died within 2 days after the procedure, 8 patients who were transferred soon after the procedure to undergo emergency cardiac surgery, and 36 patients were also excluded because their data set was incomplete to assess the occurrence of CI-AKI. The final study population consisted of 470 patients.

Demographic characteristics and procedural data are summarized in Table 1. Briefly, mean age was 62±12 years. Seventy-three percent percent were men, 43% were current smokers, 30% were diabetic, 60% had a history of hypertension, and 58% of dyslipidemia. Mean eGFR was 91±32 mL/min per 1.73 m².

We observed 25 (5.3%) cases of CI-AKI. These patients (Table 1) were older, had a more severe impairment of global hemodynamic status, as expressed by the Killip class (Killip=I in 32% versus 12%; $P<0.001$), and worse basal renal function, as expressed by eGFR on admission. In addition, patients with CI-AKI had a higher troponin at clinical presentation and a higher prevalence of hypertension and diabetes mellitus.

From the procedural standpoint, patients with CI-AKI had a poorer postprocedural thrombolysis in myocardial infarction flow (on average 2.6±0.9 versus 2.9±0.4; $P<0.001$) and were more likely to have received an intra-aortic balloon pump. They had, on average, a 2-day longer hospitalization. Moreover, 4 of the 25 patients (16%) who developed CI-AKI died in hospital when compared with 6 of 445 (1.3%) who did not. Despite global in-hospital mortality of the study population was as low as 2%, CI-AKI was associated with a 14-fold increase in the odds of death (OR, 13.9; 95% CI, 3.65–53.04; $P<0.001$).

Mean procedural CV was 164±63 mL; 83 patients (18%) received ≥200 mL and only 14 patients (3%) received ≥300 mL of dye. The incidence of CI-AKI was not higher in these subgroups receiving higher CV or across different quartiles of contrast media (data not shown) and, notably, no patient exceeded the maximum accepted contrast dose.14,22

Despite patients developing CI-AKI had not been given a higher total CV (Table 1), they received a much higher adjusted dose (CV/eGFR 3.62 versus 1.96; $P<0.001$). Conversely, the difference in maximum accepted contrast dose14 was not significant (0.52 versus 0.40; $P=0.07$). Using ROC curve analysis for CI-AKI risk according to CV/eGFR, the AUC was 0.77 (95% CI, 0.66–0.87; $P<0.001$), with the best cutoff value set at 2.5 (sensitivity was 72.0% and specificity was 78.2%, positive and negative predictive values were 15.7% and 98%, respectively). Of note, CI-AKI incidence was much higher (15%; $P<0.001$) in patients in the highest quartile of CV/eGFR ratio, which corresponds to the threshold (CV>2.5) indicated by the ROC curve.

### Table 1. Clinical and Procedural Variables in Patients With and Without CI-AKI in the Development Series

<table>
<thead>
<tr>
<th></th>
<th>CI-AKI</th>
<th>No CI-AKI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>25 (5.3)</td>
<td>445 (94.7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Age, y</td>
<td>73±10</td>
<td>61±12</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Men (%)</td>
<td>18 (72)</td>
<td>237 (73)</td>
<td>0.51</td>
</tr>
<tr>
<td>Familiar history of coronary artery disease (%)</td>
<td>13 (52)</td>
<td>244 (55)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>5 (20)</td>
<td>199 (45)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21 (84)</td>
<td>259 (58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>13 (52)</td>
<td>129 (29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>14 (56)</td>
<td>260 (58)</td>
<td>0.48</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>9 (36)</td>
<td>116 (26)</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous acute myocardial infarction (%)</td>
<td>5 (20)</td>
<td>74 (17)</td>
<td>0.43</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>39±14</td>
<td>48±11</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>sCr, mg/dL</td>
<td>1.49±0.62</td>
<td>0.91±0.31</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>52±19</td>
<td>94±32</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>eGFR&gt;60 mL/min per 1.73 m² (n=70)</td>
<td>17 (68%)</td>
<td>53 (12%)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>95±35</td>
<td>111±45</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.9±2.1</td>
<td>13.9±1.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Troponin, ng/mL</td>
<td>22±68</td>
<td>8±22</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>86±23</td>
<td>79±18</td>
<td>0.07</td>
</tr>
<tr>
<td>Preprocedural Killip class</td>
<td>1.4±0.7</td>
<td>1.1±0.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Grade 0 (%)</td>
<td>2 (8)</td>
<td>3 (0.7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Grade 1 (%)</td>
<td>3 (12)</td>
<td>9 (2)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (%)</td>
<td>1 (4)</td>
<td>28 (6)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>19 (76)</td>
<td>406 (91)</td>
<td></td>
</tr>
<tr>
<td>Total CV, mL</td>
<td>165±79</td>
<td>164±62</td>
<td>0.94</td>
</tr>
<tr>
<td>Total CV&gt;200 mL</td>
<td>3 (12%)</td>
<td>80 (18%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total CV&gt;300 mL</td>
<td>1 (4%)</td>
<td>13 (3%)</td>
<td>0.54</td>
</tr>
<tr>
<td>MACD (Cigarroa formula)</td>
<td>0.51±0.25</td>
<td>0.40±0.22</td>
<td>0.07</td>
</tr>
<tr>
<td>CV/eGFR</td>
<td>3.62±2.6</td>
<td>1.96±1.05</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>In-hospital stay, d</td>
<td>9±5</td>
<td>7±3</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>4 (16)</td>
<td>6 (1.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

AGEF indicates age, estimated glomerular filtration rate and ejection fraction; CI-AKI, contrast-induced acute kidney injury; CV, contrast volume; eGFR, estimated glomerular renal function; IABP, intra-aortic balloon pump; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MACD, maximum accepted contrast dose; sCr, serum creatinine concentration; and TIMI, thrombolysis in myocardial infarction.
At univariate analysis, 11 variables were associated with the occurrence of CI-AKI: age, left ventricular ejection fraction, heart rate, troponin, low-density lipoprotein-cholesterol, hemoglobin and Killip class at admission, history of hypertension, diabetes mellitus or cigarette smoking, and CV/eGFR. At stepwise multivariable analysis, however (Table 2), only age (OR, 1.08; \(P=0.004\)), left ventricular ejection fraction (OR, 0.94; \(P=0.004\)), and troponin at admission (OR, 1.01; \(P=0.043\)) and CV/eGFR ratio above the threshold or in the highest quartile (OR, 5.57; \(P=0.002\)) remained independent predictors of CI-AKI.

Both model 1 and model 2 had good discriminative power and calibration as predictors of CI-AKI. AUC was 0.88 (95% CI, 0.83–0.93) and Hosmer–Lemeshow \(\chi^2\) was 5.39 (\(P=0.72\)) for model 1. AUC improved to 0.91 (95% CI, 0.86–0.95) with model 2, whereas Hosmer–Lemeshow \(\chi^2\) was 8.93 (\(P=0.35\)). The likelihood ratio test for comparing model 2 to model 1 was \(\chi^2=5.973\) (\(P=0.029\)). The difference between AUCs (Figure) was not significant at pairwise comparison of ROC curves (\(P=0.27\)), as expected when the improvement in discrimination for a model containing a new covariate is simply defined as the difference in AUCs calculated using 2 models, with and without the covariate of interest.

On the contrary, the addition (Tables 3 and 4) of the procedural factor (CV/eGFR+AGEF, model 2) to the model based on the preprocedural variables (AGEF, model 1) improved classification in 5 and worsened in 1 of 25 patients who experienced CI-AKI, with a net gain in reclassification in 4 of 25 (16%) patients (\(P=0.1\)). In the 445 patients who did not experience CI-AKI, model 2 reclassified 45 downward and 14 upward, with a net gain in reclassification in 31 of 445 (7%) patients (\(P<0.001\)). The global NRI for model 2 over model 1 was, therefore, estimated to be 0.23 (\(P=0.021\)), and it was largely driven by the significant improvement in classification of patients not experiencing CI-AKI. In other words, model 2 added significant information to decrease the risk estimates of patients not having CI-AKI correctly, thus definitely improving the specificity of preprocedural approach with model 1.

Our model 2 confirmed a good discriminative power to predict CI-AKI in the validation series of 126 patients (Table 5): AUC was 0.86 (95% CI, 0.80–0.92) although the model was not as well calibrated (Hosmer–Lemeshow \(\chi^2\) 59.9, \(P<0.001\)) as in the derivation series because of the smaller sample size. The choice of the vascular access site (60 patients femoral and 66 patients radial) for these patients had remained at operator’s discretion.

### Table 2. Predictors of CI-AKI at Multivariable Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV/eGFR&gt;2.5</td>
<td>5.57</td>
<td>1.90–15.37</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.02–1.14</td>
<td>0.004</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.94</td>
<td>0.90–0.98</td>
<td>0.004</td>
</tr>
<tr>
<td>Troponin</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.043</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CI-AKI, contrast-induced acute kidney injury; CV, contrast volume; eGFR, estimated glomerular renal function; and LVEF, left ventricular ejection fraction.

### Discussion
To evaluate the risk of CI-AKI in patients undergoing primary PCI for STEMI is a crucial issue in clinical practice, and several predictive algorithms have been proposed to estimate the risk of CI-AKI in interventional cardiology to date. The Mehran Risk Score is a comprehensive predictor of CI-AKI in patients undergoing PCI based on a nonlinear model, \(^24\) which has been recently validated even for primary PCI. \(^25\) However, the procedure-related variables of the Mehran Risk Score cannot be assessed at baseline. More recently, Gurm et al \(^26\) have proposed an accurate computational tool for the risk of AKI, which is based only on clinical and preprocedural variables and may guide bedside clinical decision making. We had demonstrated that a simpler 3-variable risk score, based on those preprocedural variables that were independently associated with CI-AKI, may be valid as well in predicting the development...
of CI-AKI after primary PCI although with low specificity and positive predictive value. The low positive predictive value is inherent to models where the prevalence of a disease is low. Indeed, the overall incidence of CI-AKI in our consecutive population of patients with STEMI undergoing primary PCI remained as low as 5%. As expected, elderly patients and those with a higher infarct size at admission had a higher risk.

The results of the present analysis add further to the possibility of estimating the risk of CI-AKI before primary PCI in patients with STEMI. The renal function–adjusted CV remains a strong independent predictor of CI-AKI and may overcome the limited specificity inherent in the simple consideration of age, left ventricular ejection fraction, and baseline renal function. The use of a total CV not higher twice and a half the CV/eGFR ratio may serve as a general and simple protective measure for CI-AKI after primary PCI: for instance, biplane angiography and intravascular ultrasound guidance together with careful procedural planning are crucial steps to CV restriction. In addition, because nonevent NRI was in any case larger than event NRI, the addition of CV/eGFR to the AGEF score helps decrease predicted risk for those without CI-AKI (catch nonevents) to a larger degree than it does increase predicted risk for those who experienced CI-AKI (catch events). In simpler and practical words, to maintain CV as low as reasonably possible has a positive effect in reducing the occurrence of CI-AKI on top of the baseline risk assessed with AGEF score and might be a clue to avoid postprocedural overtreatment in those patients with moderate to high risk.

These results corroborate and extend other previous reports aimed to identify a renal function–adjusted CV not to be overcome, provided the strong pharmacodynamical background and the relationship with clinical outcomes. Laskey et al elegantly demonstrated that a CV/eGFR of 3.7 was an independent predictor of early postprocedural creatinine increase. Our lower cutoff of 2.5 is in line with the results of the larger database by Gurm et al, showing that a CV adjusted on the estimated renal function, with a planned CV restricted accordingly to twice-to-thrice the eGFR, may reduce the risk of CI-AKI. Differently than in those studies, our population consisted only of patients with STEMI and, therefore, it is wise to underline the issue of more stringent CV minimization toward a lower cutoff in this subset because of the higher clinical and hemodynamic instability of patients with STEMI.

Taken all together, these data indicate that the most important predictor of acute kidney injury (AKI), after contrast media exposure, is the contrast load every individual can tolerate in terms of clearance, rather than the renal function itself, at least in patients without pre-existing renal dysfunction. Indeed, in our relatively small subgroup of patients with eGFR<60 mL/min per 1.73 m², CV/eGFR did not remain an independent predictor of CI-AKI (data not shown). It is likely that for such high-risk subset with overt renal impairment, baseline renal function and clinical characteristics become as much important as to remain untied from total CV and outlining the need of more demanding prophylactic interventions. Accordingly, in our patients with established renal

### Table 3. Reclassification Table for the Addition of CV/eGFR (Model 2) to the Baseline Risk Model Based on the AGEF Score (Model 1): Patients With CI-AKI

<table>
<thead>
<tr>
<th>Model 2 (AGEF+CV/eGFR)</th>
<th>≤2% (CI-AKI)</th>
<th>3%–5% (CI-AKI)</th>
<th>5%–25% (CI-AKI)</th>
<th>≥26% (CI-AKI)</th>
<th>Upward</th>
<th>Downward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (AGEF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2% (CI-AKI)</td>
<td>1</td>
<td>0*</td>
<td>1*</td>
<td>0*</td>
<td>1*</td>
<td>...</td>
</tr>
<tr>
<td>3%–5% (CI-AKI)</td>
<td>0†</td>
<td>2</td>
<td>1*</td>
<td>0*</td>
<td>1*</td>
<td>...</td>
</tr>
<tr>
<td>5%–25% (CI-AKI)</td>
<td>0†</td>
<td>0†</td>
<td>9</td>
<td>3*</td>
<td>3*</td>
<td>...</td>
</tr>
<tr>
<td>≥26% (CI-AKI)</td>
<td>0†</td>
<td>0†</td>
<td>1†</td>
<td>7</td>
<td>...</td>
<td>1†</td>
</tr>
</tbody>
</table>

* and † Cases correctly and incorrectly, respectively, reclassified with model 2. Model 2 allowed 5 patients having CI-AKI to be correctly reclassified in the higher risk category and only 1 patient to be incorrectly reclassified in the lower risk category. AGEF indicates age, estimated glomerular filtration rate and ejection fraction; CI-AKI, contrast-induced acute kidney injury; CV, contrast volume; and eGFR, estimated glomerular renal function.

### Table 4. Reclassification Table for the Addition of CV/eGFR (Model 2) to the Baseline Risk Model Based on the AGEF Score (Model 1): Patients Without CI-AKI

<table>
<thead>
<tr>
<th>Model 2 (AGEF+CV/eGFR)</th>
<th>≤2% (No CI-AKI)</th>
<th>3%–5% (No CI-AKI)</th>
<th>5%–25% (No CI-AKI)</th>
<th>≥26% (No CI-AKI)</th>
<th>Upward</th>
<th>Downward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (AGEF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2% (no CI-AKI)</td>
<td>285</td>
<td>8*</td>
<td>0*</td>
<td>0*</td>
<td>8*</td>
<td>...</td>
</tr>
<tr>
<td>3%–5% (no CI-AKI)</td>
<td>28†</td>
<td>28</td>
<td>3*</td>
<td>0*</td>
<td>3*</td>
<td>28†</td>
</tr>
<tr>
<td>5%–25% (no CI-AKI)</td>
<td>0†</td>
<td>17†</td>
<td>62</td>
<td>3*</td>
<td>3*</td>
<td>17†</td>
</tr>
<tr>
<td>≥26% (no CI-AKI)</td>
<td>0†</td>
<td>0†</td>
<td>2†</td>
<td>9</td>
<td>...</td>
<td>2†</td>
</tr>
</tbody>
</table>

* and † Cases incorrectly and correctly, respectively, reclassified with model 2. Forty-five patients not having CI-AKI were correctly reclassified downward and 14 patients not having CI-AKI were incorrectly reclassified upward. AGEF indicates age, estimated glomerular filtration rate and ejection fraction; CI-AKI, contrast-induced acute kidney injury; CV, contrast volume; and eGFR, estimated glomerular renal function.
The actual incidence of CI-AKI remains strictly related to the definition used. Small postprocedural creatinine increases in patients with basally preserved renal function are likely to have minimal, if any, prognostic effect. We have chosen the most widely used and accepted definition in the current literature. Anyway, a standardized definition of AKI is needed to evaluate any strategy for prevention and early diagnosis correctly. For this purpose, the 2013 KDIGO Clinical Practice Guideline for AKI, which were released after the beginning of our study, now encompass both more stringent criteria of serum creatinine concentration increase and the issue of urine output decline (which we did not measure in our study) and will likely become the standard reference for defining both occurrence and severity of AKI. Of note, in our population CI-AKI would have risen to 9.8% (46 of 470 patients) if we had classified as having CI-AKI, according to KDIGO guidelines for AKI, any patient with an increase in serum creatinine concentration by ≥0.3 mg/dL within 48 hours.

The pathophysiology of AKI after PCI is only partially understood, but there seem to be several modifiable factors beyond contrast media that remained unexplored in our study. Retrospective data indicate a reduced incidence of AKI after transradial PCI and in the small validation series of this study there was a nonsignificant trend toward CI-AKI reduction with radial access (OR, 0.27; 95% CI, 0.07–1.05; P=0.06). The putative mechanisms for a protective role of radial access include reduced bleeding-related hemodynamic compromise, reduced cholesterol embolization into the renal circulation, or a combination of both. Because all procedures in the development series of this study were performed from the femoral approach, we think that the issue of vascular access did not represent a bias in fitting our models to the database. Of note, operator’s experience in radial access is crucial in reducing CV in more challenging cases and, in other words, radial procedures performed by operators at the beginning of the learning curve might not be roughly associated with a reduction of CV and overall better outcomes.

The integrated discrimination improvement (IDI) is considered a more robust method to evaluate reclassification when compared with NRI because it assumes the changes in estimated prediction probabilities as a continuous variable and evaluates the changes between 2 models, 1 without and 1 with the new covariate of interest, in this case CV/eGFR. Changes of probability in the right direction are obtained when the new model assigns a case subject a higher probability than the others. The IDI can thus be estimated as the difference between the mean of changes in predicted probabilities in the right direction and the mean of changes in the wrong direction. An IDI near 0 shows that the new indicator apparently adds no relevant information. In our population, the IDI was 0.21 (1 tailed, P=0.25). The choice of the most useful improvement metric, either the NRI or the IDI, should take into account the question to be answered: for example, if falling above or below a given cutoff is the primary basis for the choice of care, the NRI might be the best choice. However, if no established risk cutoffs exist, the above might be of little use and the IDI might be preferred. Because CI-AKI is an event for which baseline estimation of risk and cutoffs may
be meaningfully drawn from a large body of evidences,\textsuperscript{2,24} we are convinced that NRI rather than IDI may demonstrate the validity of our approach.\textsuperscript{20}

Conclusions

CV remains a key risk factor for CI-AKI in patients undergoing primary PCI, at least in patients without overt renal dysfunction. This study supports the need for minimizing CV, beyond baseline preprocedural estimation of risk based on clinical presentation. A CV restricted to no more than twice and a half the baseline eGFR might be valuable in reducing the risk of CI-AKI.

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Disclosures

None.

References


Renal Function–Adjusted Contrast Volume Redefines the Baseline Estimation of Contrast-Induced Acute Kidney Injury Risk in Patients Undergoing Primary Percutaneous Coronary Intervention

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