ORIGINAL RESEARCH

Acute Kidney Injury in Diabetic Patients With Acute Myocardial Infarction: Role of Acute and Chronic Glycemia

Giancarlo Marenzi, MD; Nicola Cosentino, MD; Valentina Milazzo, MD; Monica De Metrio, MD; Mara Rubino, MD; Jeness Campodonico, MD; Marco Moltrasio, MD; Ivana Marana, MD; Marco Grazi, MD; Gianfranco Lauri, MD; Alice Bonomi, MSc; Simone Barbieri, MSc; Emilio Assanelli, MD; Alessia Dalla Cia, MD; Roberto Manfrini, MD; Roberto Ceriani, MD; Antonio Bartorelli, MD

***Background*—**In acute myocardial infarction, acute hyperglycemia is a predictor of acute kidney injury (AKI), particularly in patients without diabetes mellitus. This emphasizes the importance of an acute glycemic rise rather than glycemia level at admission. We investigated whether, in diabetic patients with acute myocardial infarction, the combined evaluation of acute and chronic glycemic levels may have better prognostic value for AKI than admission glycemia.

***Methods and Results*—**At admission, we prospectively measured glycemia and estimated average chronic glucose levels (mg/dL) using glycosylated hemoglobin (HbA_{1c}), according to the following formula: $28.7 \times HbA_{1c}$ (%)-46.7. We evaluated the association with AKI of the acute/chronic glycemic ratio and of the difference between acute and chronic glycemia (Δ_{A-C}). We enrolled 474 diabetic patients with acute myocardial infarction. Of them, 77 (16%) experienced AKI. The incidence of AKI increased in parallel with the acute/chronic glycemic ratio (12%, 14%, 22%; P=0.02 for trend) and Δ_{A-C} (13%, 13%, 23%; P=0.01) but not with admission glycemic tertiles (P=0.22). At receiver operating characteristic analysis, the acute/chronic glycemic ratio (area under the curve: 0.62 [95% confidence interval, 0.55–0.69]; P=0.001) and Δ_{A-C} (area under the curve: 0.62 [95% confidence interval, 0.54–0.69]; P=0.002) accurately predicted AKI, without difference in the area under the curve between them (P=0.53). At reclassification analysis, the addition of the acute/chronic glycemic ratio and Δ_{A-C} to acute glycemia allowed proper AKI risk prediction in 16% of patients.

***Conclusions*—**In diabetic patients with acute myocardial infarction, AKI is better predicted by the combined evaluation of acute and chronic glycemic values than by assessment of admission glycemia alone. **(*J Am Heart Assoc*. 2018;7:e008122. DOI: 10.1161/JAHA.117.008122.)**

Key Words: acute hyperglycemia • acute kidney injury • acute myocardial infarction • diabetes mellitus • glycosylated hemoglobin

Acute kidney injury (AKI) is a frequent complication of acute myocardial infarction (AMI) treated with percutaneous coronary intervention (PCI) that critically affects in-hospital and long-term outcome.[1,2] In-hospital mortality has been shown to be 20 times higher in AMI patients who experience AKI compared with those without this complication.[3] Moreover, a close association has been established between AKI development during AMI and increased long-term morbidity and mortality, persistent loss of kidney function, and risk of progression to end-stage renal disease.[4,5]

In patients with AMI undergoing PCI, both diabetes mellitus (DM) and elevated levels of plasma glucose at hospital admission (acute hyperglycemia) have been recognized as independent clinical predictors of AKI.[6–10] However, the interplay between DM and acute hyperglycemia in AMI is still unclear because the relationship between the latter and AKI risk is markedly different among patients with and without DM.[11] On one hand, high admission glycemic levels are closely associated with a significant increase of AKI risk among non-DM patients. On the other hand, a similar robust association has not been reported in patients with DM, who experience a high AKI rate regardless their admission glucose levels. These observations suggest that an acute glucose-level rise, rather than chronic elevation, may be a predisposing

From the Centro Cardiologico Monzino, IRCCS, Milan, Italy (G.M., N.C., V.M., M.D.M., M.R., J.C., M.M., I.M., M.G., G.L., A. Bonomi, S.B., E.A., A.D.C., R.M., R.C., A. Bartorelli); Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Italy (A. Bartorelli).

Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/7/8/e008122/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Giancarlo Marenzi, MD, Centro Cardiologico Monzino, Via Parea 4, 20138 Milan, Italy. E-mail: giancarlo.marenzi@ccfm.it

Received November 15, 2017; accepted February 5, 2018.

Clinical Perspective

What Is New?

- The ability of admission glycemia to predict acute kidney injury in diabetic patients with acute myocardial infarction, who are treated with percutaneous coronary intervention, improves significantly if average chronic glucose, as estimated by glycosylated hemoglobin, is also taken into account.
- Our findings highlight that an acute glucose-level rise, unlike chronic elevation, is an important predisposing factor for acute kidney injury.

What Are the Clinical Implications?

- Assessment of acute and chronic glycemia in diabetic patients with acute myocardial infarction and high admission glycemic levels may help physicians identify true stress hyperglycemia and discern high-risk patients who may benefit from renal preventive strategies.

factor for AKI in the setting of AMI. In DM patients with AMI, elevated glucose levels at admission do not necessarily indicate stress hyperglycemia. Stress hyperglycemia might be better reflected by the combined assessment of acute and chronic glycemic values. Of note, average chronic glycemic levels can be estimated by the glycosylated hemoglobin (HbA_{1c}) value.[12] Consequently, we hypothesized that in DM patients, the combination of acute (measured at hospital admission) and chronic (estimated by HbA_{1c}) glycemia may predict AKI risk with greater accuracy than admission glycemia alone.

In this study, we assessed the relationship between acute and chronic glycemia and the risk of AKI in an unselected cohort of DM patients with AMI.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. This material can be made available by the corresponding author on reasonable request.

Patient Population

This study was prospective and observational. We enrolled 474 consecutive DM patients with AMI, both ST-segment–elevation myocardial infarction (STEMI) undergoing primary PCI and non-STEMI undergoing early (within 24 hours) PCI, who were admitted to the intensive cardiac care unit (ICCU) of the Centro Cardiologico Monzino in Milan between April 1, 2011, and April 30, 2017. Diabetic patients experiencing AMI as a complication of elective PCI (type 4a AMI; n=21), those with a history of hemoglobinopathy (n=1), and those with severe anemia (hemoglobin <8 g/dL; n=4) were excluded. The study complied with the Declaration of Helsinki, and the ethics committee of our center approved the research protocol (no. R520-CCM549). Written informed consent was obtained from all participants.

Study Protocol

Blood glucose and HbA_{1c} levels were measured in all patients at hospital admission. A diagnosis of DM was made if this disease and/or antidiabetic treatment, including oral agents or insulin, were recorded in the admission history. A diagnosis of unknown DM was made when patients had ≥6.5% (48 mmol/mol) HbA_{1c} despite no previous history of the disease.[13] Acute hyperglycemia was defined as a blood glucose level at admission >198 mg/dL (>11 mmol/L), according to the definition used in previous studies focusing on AMI patients.[11,14–16] Average chronic glucose levels were estimated by HbA_{1c}, expressed as percentage value, according to the following validated formula[12,13,17]:

$$\text{Estimated chronic glucose levels}\,(\text{mg/dL}) = 28.7 \times \text{HbA}_{1c}(\%) - 46.7$$

In all patients, we measured blood glucose at admission (acute glycemia) and estimated chronic glucose levels to calculate (1) the acute/chronic (A/C) glycemic ratio and (2) the absolute difference between acute and chronic glycemia (Δ_{A-C}).

Serum creatinine was measured at hospital admission and each day during intensive cardiac care unit stay. Glomerular filtration rate was estimated using the abbreviated MDRD (Modification of Diet in Renal Disease) equation.[18] AKI was defined applying the Acute Kidney Injury Network classification, according to the maximum serum creatinine increase recorded between baseline (hospital admission) and the first 72 hours.[19]

Study patients received standard medical treatment and coronary revascularization (primary or early PCI), according to the current standards of care recommended by published guidelines.[20,21] In all patients with DM, antidiabetic medications were withheld at hospital admission. In patients with acute hyperglycemia (>198 mg/dL), insulin was administered with a glucose-level target range of 140 to 180 mg/dL.[22] Nonionic, low-osmolality contrast agents were used in all patients. In non-STEMI patients, isotonic (0.9%) saline was given intravenously at a rate of 1 mL/kg per hour for 12 hours before and after contrast exposure; in STEMI patients, hydration was given for 12 hours after PCI. In patients with left ventricular ejection fraction <40% or overt

heart failure, the hydration rate was reduced to 0.5 mL/kg per hour.

Demographic, clinical, biochemical, and echocardiographic data were obtained. Left ventricular ejection fraction was measured with echocardiography in all patients within 24 hours of hospital admission.

The primary end point of the study was the incidence of AKI. Major in-hospital adverse clinical events, including death, were evaluated as secondary end points of the study.

Statistical Analyses

A sample size of 450 patients was calculated under the following assumptions: 13% overall incidence of the primary end point,[11] with an expected 10% and 20% incidence in patients with the first 2 tertiles pooled together and the highest A/C glycemic ratio and Δ_{A-C} tertiles, respectively. This sample size allowed 82% statistical power in assessing a significant difference (α error of 0.05) of the primary end point between tertiles.

Continuous variables are presented as mean±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 were compared using the χ^2 test or the Fisher exact test, as appropriate. Trends of AKI incidence across acute glycemia, A/C glycemic ratio, and Δ_{A-C} tertiles were assessed by Mantel–Haenszel χ^2 test.

Receiver operating characteristic curves were calculated, and the areas under the receiver operating characteristic curves (AUCs) with 95% confidence intervals (CIs) were used to measure the ability of the considered variables to predict AKI. AUCs were compared as recommended by DeLong et al.[23] Youden's index was used to calculate cutoff values for the A/C glycemic ratio and for Δ_{A-C}, which were able to maximize the sensitivity and specificity of predicting a case.

Net reclassification improvement was used to identify the possible additional prognostic value of A/C glycemic ratio and Δ_{A-C} when added to acute glycemia, both according to their absolute and cutoff values. In the absence of widely recognized cutoffs for defining low-, medium- and high-risk categories, we used the tertiles of the predicted event probability.

The associations between acute hyperglycemia, A/C glycemic ratio, and Δ_{A-C} and AKI were assessed by logistic regression analysis. Analyses were also adjusted for variables recorded at hospital admission and found to be associated ($P<0.05$) with AKI at univariate analysis. The following parameters remained significantly associated with AKI at multivariable analysis: age, serum creatinine, left ventricular ejection fraction, troponin I, and high-sensitivity C-reactive protein assessed at hospital admission and cardiogenic shock. Results are presented as odds ratios with 95% CIs.

Table 1. Baseline Characteristics and In-Hospital Outcomes of Study Patients With and Without AKI

	No AKI (n=397)	AKI (n=77)	*P* Value
Age, y	69±11	73±10	0.001
Men, n (%)	311 (78)	56 (73)	0.28
Body weight, kg	79±15	76±14	0.11
STEMI, n (%)	171 (43)	38 (49)	0.30
Hypertension, n (%)	310 (78)	65 (84)	0.21
Smoker, n (%)	211 (53)	27 (35)	0.004
Hyperlipidemia, n (%)	254 (64)	46 (60)	0.48
Prior myocardial infarction, n (%)	138 (35)	30 (39)	0.43
Prior CABG, n (%)	79 (20)	17 (22)	0.62
Prior PCI, n (%)	150 (38)	29 (38)	0.95
LVEF, %	50±11	42±14	<0.001
Contrast volume, mL	187±82	206±91	0.07
Laboratory values at hospital admission			
Blood glucose, mg/dL	200±77	231±105	0.002
HbA_{1c}, %	7.4±1.6	7.1±1.4	0.17
Average chronic glycemia, mg/dL	166±45	158±39	0.17
A/C glycemic ratio	1.22±0.4	1.47±0.6	<0.001
Δ_{A-C}, mg/dL	35±66	74±92	<0.001
Serum creatinine, mg/dL	1.1±0.5	1.5±0.8	<0.001
eGFR, mL/min/1.73 m^2	77±26	57±26	<0.001
Hemoglobin, g/dL	13.3±1.9	12.8±2.1	0.04
Troponin I, ng/mL, median (IQR)	0.44 (0.09–1.64)	1.34 (0.15–5.6)	0.002
hs-CRP, mg/dL, median (IQR)	4.6 (1.7–15.5)	12.8 (4.0–50.4)	<0.001
Total cholesterol, mg/dL	166±43	156±49	0.07
HDL, mg/dL	41±13	37±10	0.02
LDL, mg/dL	98±36	94±44	0.44
Triglycerides, mg/dL	138±89	124±80	0.25
Medication before myocardial infarction, n (%)			
Statin	204 (52)	37 (48)	0.54
Aspirin	211 (53)	53 (69)	0.01
ACEI/ARB	204 (51)	36 (47)	0.46
Beta blocker	203 (51)	39 (51)	0.93
Oral antidiabetic	199 (50)	33 (43)	0.24
Insulin	65 (16)	19 (25)	0.08
Oral antidiabetic and insulin	18 (5)	5 (6)	0.46

Data are shown as mean±SD unless otherwise noted. A/C indicates acute/chronic; ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

All tests were 2-tailed, and $P<0.05$ was required for statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute). Reclassification statistics were assessed with the SAS macros published by Cook and Ridker.[24]

Results

A total of 474 consecutive DM patients with AMI (209 STEMI and 265 non-STEMI, mean age 70±11 years, 367 men) were included in the study. Of them, 206 (43%) had acute hyperglycemia. Mean acute glucose level at hospital admission was 205±83 mg/dL, and estimated chronic glucose level was 164±44 mg/dL.

AKI occurred in 77 patients (16%). The frequency of AKI stage 1 and stages 2 and 3 was 70% (n=54) and 30% (n=23), respectively. Table 1 shows the baseline characteristics of patients with and without AKI. Patients with AKI were older; had lower hemoglobin and left ventricular ejection fraction; and higher serum creatinine, troponin I, and high-sensitivity C-reactive protein levels. Notably, no difference was found between the 2 groups in prior use of statins and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Patients with AKI also had a more complicated and prolonged intensive cardiac care unit clinical course, with significantly higher mortality (Table 2).

Figure 1 shows AKI incidence in the entire population stratified according to acute glycemia, A/C glycemic ratio, and Δ_{A-C} tertiles. At receiver operating characteristic analysis, A/C glycemic ratio (AUC: 0.62 [95% CI, 0.55–0.69]; $P=0.001$) and Δ_{A-C} (AUC: 0.62 [95% CI, 0.54–0.69]; $P=0.002$) showed greater accuracy than acute glycemia (AUC: 0.57 [95% CI, 0.49–0.64]; $P=0.08$) in terms of capacity to predict AKI ($P=0.02$ and $P=0.01$ for comparison versus acute glycemia, respectively). No difference in the AUC was observed between the A/C glycemic ratio and Δ_{A-C} ($P=0.53$). In the entire population, the A/C glycemic ratio and Δ_{A-C} cutoff values that were able to jointly maximize sensitivity and specificity for prediction of AKI were 1.5 and 106 mg/dL, respectively. When these cutoffs were considered, patients with values above them had significantly higher incidence of AKI than those with values below these thresholds (Figure 2).

Figure 3 shows the distribution of study patients with AKI according to their acute and chronic glycemic values, with 77% of them located above the continuous identity line.

At reclassification analysis, the addition of A/C glycemic ratio and of Δ_{A-C} to acute glycemia allowed proper reclassification of 16% of patients; similarly, when their cutoff values were considered, almost 20% of patients were reclassified (Table 3 and Tables S1 through S4).

Table 4 shows the unadjusted and adjusted odds ratios for AKI of acute glycemia, A/C glycemic ratio, and Δ_{A-C} in the overall study population and in patients with known and unknown DM. In patients with known DM, AKI risk was significantly higher when the A/C glycemic ratio and Δ_{A-C} were considered, compared with that associated with acute glycemia. No interaction was found between acute and chronic glycemia ($P=0.65$).

Discussion

The primary finding of the study is that the ability of glycemia at admission to predict AKI in DM patients with AMI treated with PCI significantly improves when the average chronic

Table 2. In-Hospital Complications, Troponin I, and Serum Creatinine Peak Values, and ICCU Length of Stay in Patients With and Without AKI

	No AKI (n=397)	AKI Stage 1 (n=54)	AKI Stages 2–3 (n=23)	*P* for Trend
Death, n (%)	1 (0.25)	4 (7.4)	6 (26.1)	<0.001
APE, n (%)	34 (9)	23 (43)	10 (44)	<0.001
Cardiogenic shock, n (%)	11 (3)	13 (24)	8 (35)	<0.001
MV, n (%)	8 (2)	7 (13)	9 (39)	<0.001
Atrial fibrillation, n (%)	52 (13)	11 (20)	12 (52)	<0.001
VT/VF, n (%)	14 (4)	2 (4)	5 (22)	0.004
AV block, n (%)	14 (4)	5 (9)	2 (9)	0.05
Blood transfusion, n (%)	15 (4)	6 (11)	10 (43)	<0.001
Troponin I peak, ng/mL, median (IQR)	5.64 (1.34–32.0)	13.8 (3.8–72.2)	21.7 (3.8–58.1)	<0.001
Creatinine peak, mg/dL, mean±SD	1.13±0.5	1.87±0.7	3.90±1.4	<0.001
ICCU length of stay, d, mean±SD	4±2	5±2	10±10	<0.001

AKI indicates acute kidney injury; APE, acute pulmonary edema; AV, atrioventricular; ICCU, intensive cardiac care unit; IQR, interquartile range; MV, mechanical ventilation; VT/VF, ventricular tachycardia/ventricular fibrillation.

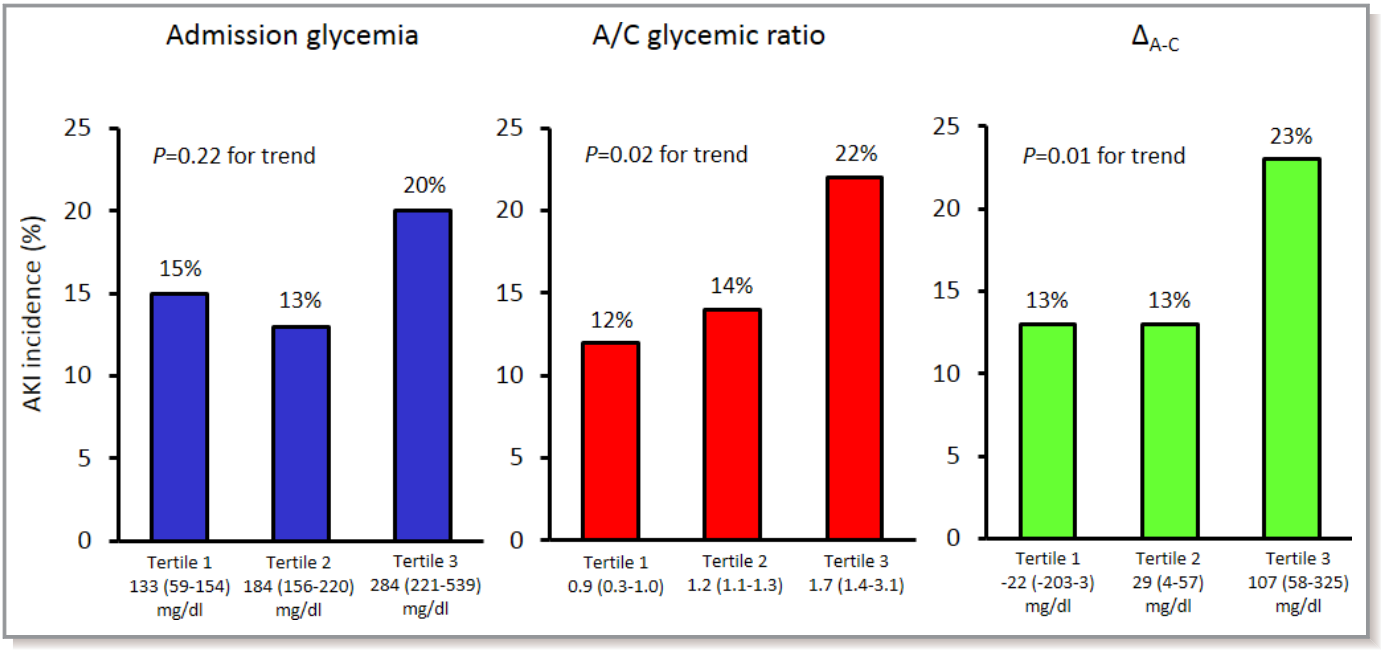

Figure 1. Acute kidney injury (AKI) incidence stratified according to tertiles of acute glycemia, acute/chronic (A/C) glycemic ratio, and the difference between acute and chronic glycemia (Δ_{A-C}).

glucose, as estimated by HbA_{1c}, is also taken into account. In particular, we found that both the A/C glycemic ratio and Δ_{A-C} perform better, in terms of AKI prognostication, than acute glycemia, even after adjustment for baseline major confounders.

Acute hyperglycemia is common in AMI and a strong predictor of mortality and increased risk of in-hospital complications in patients with and without DM.[6–10] Although a near-linear relationship between higher admission glucose levels and worse outcome has been reported consistently in AMI patients without DM,[25,26] such an association has not been clearly established in DM patients.[15,27,28] Moreover, although HbA_{1c} is a useful tool in assessing average glucose control in the outpatient setting, it has limited prognostic value in predicting in-hospital mortality rates in AMI patients.[29,30]

A strong association among acute hyperglycemia, AKI occurrence, and poor prognosis has also been described in AMI.[6–10] Again, the relationship between acute hyperglycemia and AKI risk has been reported to be markedly different among patients with and without DM, with non-DM patients showing higher relative risk of AKI at each given blood glucose

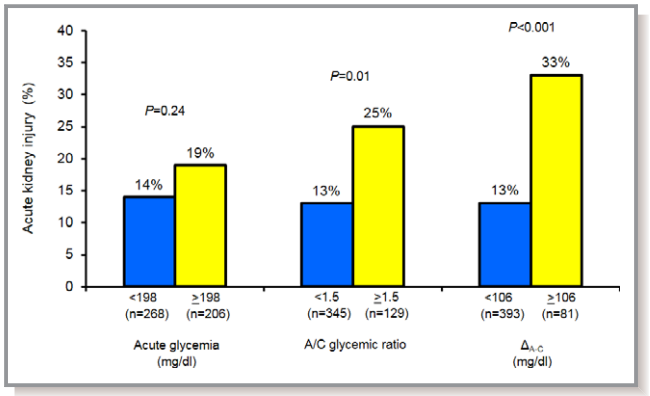

Figure 2. Acute kidney injury (AKI) incidence according to acute hyperglycemia (<198 and ≥198 mg/dL), acute/chronic (A/C) glycemic ratio (<1.5 and ≥1.5), and the difference between acute and chronic glycemia (Δ_{A-C}; <106 and ≥106 mg/dL).

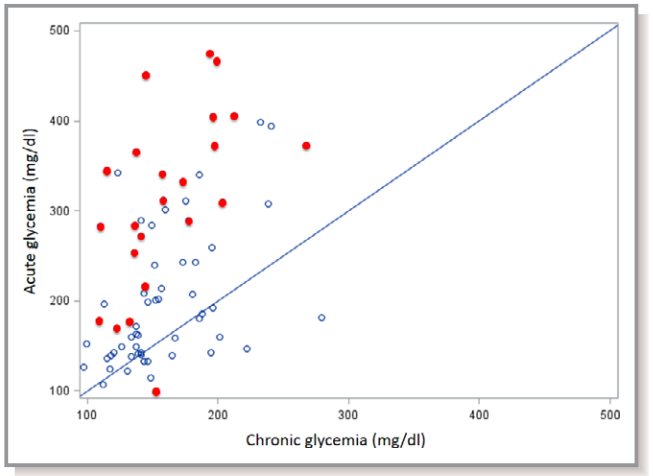

Figure 3. Scatter plot showing the distribution of study patients with acute kidney injury (AKI; n=77) according to acute and chronic glycemia. Blue empty dots refer to patients with AKI stage 1. Red full dots refer to patients with AKI stages 2 and 3.

Table 3. Reclassification Statistic Comparisons of A/C Glycemic Ratio and Δ_{A-C} Added to Acute Glycemia for the Prediction of AKI

Model	NRI (%)	95% CI	*P* Value
Acute glycemia vs acute glycemia plus A/C glycemic ratio	16	2–30	0.03
Acute glycemia vs acute glycemia plus Δ_{A-C}	16	0–32	0.05
Acute hyperglycemia (≥198 mg/dL) vs acute glycemia plus A/C glycemic ratio ≥1.5	19	5–31	0.006
Acute hyperglycemia (≥198 mg/dL) vs acute glycemia plus Δ_{A-C} ≥106 mg/dL	20	0–39	0.05

Δ_{A-C} indicates difference between acute and chronic glycemia; A/C indicates acute/chronic; AKI, acute kidney injury; CI, confidence interval; NRI, net reclassification improvement.

level.[11] Consequently, a knowledge gap still exists regarding the connection between elevated glucose levels and AKI risk in DM patients with AMI. A possible explanation could be that in DM patients, a high glycemia level at admission does not allow discrimination between high chronic levels and acute hyperglycemia; therefore, the combined assessment of acute and chronic glycemia may help physicians reveal "true" stress hyperglycemia in DM patients with AMI.

In our selected population, we observed that the risk of AKI was not associated with acute hyperglycemia, as typically defined by a glycemic value >198 mg/dL.[11,14–16] Indeed, the AKI rate was similar in DM patients with and without acute hyperglycemia. Conversely, we found a significant increase in AKI incidence that tallied with the A/C glycemic ratio and Δ_{A-C} increase. At receiver operating characteristic analysis, only these 2 variables predicted AKI and, at reclassification analysis, they allowed reclassification of ≈20% of patients compared with acute glycemia alone. Moreover, 2- to 3-fold higher AKI risk was demonstrated in patients with an A/C glycemic ratio and Δ_{A-C} above the identified cutoff values, and these relationships remained significant even after adjustment for baseline clinical confounders.

Our findings indicate that an acute glucose level rise, unlike chronic elevation, may be an important predisposing factor in AKI occurrence (Figure 3). True acute hyperglycemia in DM patients can be better unveiled by combining chronic and acute glycemic values. Although Δ_{A-C} reflects absolute acute

Table 4. AKI Unadjusted and Adjusted ORs of Acute Glycemia, A/C Glycemic Ratio, and Δ_{A-C}

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
Overall study population (n=474)				
Acute glycemia (every 10-mg/dL increase)	1.04 (1.01–1.07)†	0.003	1.03 (0.99–1.06)	0.11
Chronic glycemia (every 10-mg/dL increase)	0.96 (0.90–1.02)†	0.17	0.97 (0.89–1.04)	0.40
A/C glycemic ratio (every 0.1 increase)	1.12 (1.06–1.18)	<0.001	1.07 (1.01–1.14)	0.03
Δ_{A-C} (every 10-mg/dL increase)	1.07 (1.04–1.11)	<0.001	1.05 (1.01–1.09)	0.02
Acute hyperglycemia ≥198 mg/dL	1.41 (0.87–2.30)	0.17	1.12 (0.60–2.06)	0.72
A/C glycemic ratio ≥1.5	2.61 (1.55–4.39)	<0.001	1.94 (1.04–3.62)	0.04
Δ_{A-C} ≥106 mg/dL	3.43 (1.98–5.94)	<0.001	2.42 (1.21–4.86)	0.01
Patients with unknown DM (n=135)				
Acute glycemia (every 10 mg/dL increase)	1.04 (0.98–1.11)	0.16	1.02 (0.94–1.09)	0.66
Chronic glycemia (every 10 mg/dL increase)	0.98 (0.85–1.09)	0.74	0.94 (0.77–1.08)	0.43
A/C glycemic ratio (every 0.1 increase)	1.11 (0.98–1.26)	0.09	1.06 (0.92–1.23)	0.39
Δ_{A-C} (every 10 mg/dL increase)	1.07 (0.99–1.15)	0.08	1.04 (0.96–1.13)	0.34
Patients with known DM (n=339)				
Acute glycemia (every 10-mg/dL increase)	1.04 (1.04–1.07)	0.01	1.04 (0.99–1.08)	0.09
Chronic glycemia (every 10-mg/dL increase)	0.95 (0.88–1.02)	0.16	0.98 (0.89–1.07)	0.70
A/C glycemic ratio (every 0.1 increase)	1.12 (1.06–1.19)	<0.001	1.08 (1.01–1.16)	0.03
Δ_{A-C} (every 10-mg/dL increase)	1.07 (1.03–1.11)	<0.001	1.05 (1.01–1.11)	0.03

Δ_{A-C} indicates difference between acute and chronic glycemia; A/C indicates acute/chronic; AKI, acute kidney injury; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.
*ORs were adjusted for age, serum creatinine concentration, left ventricular ejection fraction, troponin I, and high-sensitivity C-reactive protein assessed at hospital admission and for cardiogenic shock.
†Acute glycemia adjusted for chronic glycemia: OR: 1.07 (95% CI, 1.04–1.10); *P*<0.001; chronic glycemia adjusted for acute glycemia: OR: 0.89 (95% CI, 0.82–0.95); *P*=0.04.

glycemic changes and does not take into account the patient chronic glycometabolic profile, the A/C glycemic ratio considers acute glycemic variation and DM status. Consequently, patients with similar absolute acute glycemic rise (Δ_{A-C}) may have different A/C glycemic ratios, according to their chronic values.[31,32] A patient with Δ_{A-C} of 200 mg/dL, for example, may have an A/C glycemic ratio of 2 in case of an admission value of 400 mg/dL and a chronic glycemic value of 200 mg/dL. Conversely, another patient with a similar Δ_{A-C} of 200 mg/dL may have an A/C glycemic ratio of 3 if admission glycemia is 300 mg/dL and chronic glycemia is 100 mg/dL. Despite this premise, we found that both A/C glycemic ratio and Δ_{A-C} had similar accuracy for predicting AKI. The fact that we detected similar chronic glycemia in patients with and without AKI may explain this finding, at least in part. Our data indicate that estimation of chronic glycemia is essential to reveal true acute glycemic rise in DM patients; however, we were unable to identify which combination of acute and chronic glycemia is more closely associated with AKI risk. Aside from the aforementioned combination, our observations are in agreement with previous experimental and clinical studies on AKI demonstrating that acute glycemic changes have a more detrimental effect on renal function compared with absolute high levels at admission.[33–35]

To our knowledge, this study is the first in DM patients with AMI to explore the relationship between the combination of acute and chronic glycemia and AKI. It is unclear whether an acute rise of glucose level directly contributes to renal injury or is only a marker of disease severity. Nevertheless, we can infer that a causal link between acute glycemic rise and AKI may exist, as this relationship remained significant even after adjustment for major clinical confounders. In agreement with this hypothesis, experimental and clinical evidence has shown that an acute increase of plasma glucose suppresses flow-mediated vasodilatation, likely through increased production of oxygen-derived free radicals, and increases oxidative stress[34,35] that may exacerbate the deleterious effects of contrast agents on the kidney. Moreover, acute hyperglycemia may induce osmotic diuresis, resulting in volume depletion and dehydration and further increasing AKI risk and severity.

The results of the present report may have some potential clinical implications. Assessment of acute and chronic glycemia in DM patients with AMI and high glycemic levels at hospital admission may help physicians more accurately discern those at high risk for AKI, who may benefit from preventive therapeutic strategies and closer monitoring of renal function. Moreover, assessment may be used to customize glucose control. The detrimental effects of glycemic disorder are not limited to stress hyperglycemia; they also include fluctuations of glycemic values, with acute glucose changes in both directions.[35] Accordingly, it has been shown that intensive lowering of glycemia may have a detrimental effect in patients with high glycemic values at admission but without stress hyperglycemia.[36,37] In view of the close association between stress hyperglycemia and AKI risk, future studies should investigate whether tight control of hyperglycemia, based on the combined evaluation of acute and chronic glycemia, will prevent AKI and improve overall prognosis in AMI.

The strengths of the current study include its prospective design, a well-characterized population with DM, adjustment for a variety of risk factors, and a special focus on AKI. Some limitations warrant mention. First, we evaluated a population admitted to a single center and treated with PCI. Because this therapeutic strategy may have influenced the results of our study, the overall applicability of our findings to patients not undergoing coronary revascularization needs to be clarified. Second, because this study was observational, a cause–effect relationship between plasma glucose and AKI cannot be established. Third, the impact on AKI of in-hospital glycemic fluctuations, therapeutic management of acute hyperglycemia, glycemic target choice, and DM type (1 versus 2) was not investigated and should be taken into account as a possible bias. Finally, the A/C glycemic ratio and Δ_{A-C} were calculated using the average chronic glycemic value estimated from HbA_{1c}. Consequently, we cannot exclude the possibility that the calculated variables do not fully reflect acute glycemic changes occurring during the index event, as suggested by the AUCs found in our study; however, the combined assessment of acute and chronic glycemia represents a clear advance over the evaluation of the glucose value at admission only. Future research is needed in DM patients with AMI, focusing on novel, more specific biomarkers of stress hyperglycemia, to improve AKI risk stratification.

In conclusion, we demonstrated that, in DM patients with AMI treated with PCI, the combined evaluation of acute and chronic glycemic values is more closely associated with AKI than admission glycemia alone. If confirmed in larger studies, our results might support early identification of patients at high risk of AKI who will benefit from intensive glucose lowering and/or from renal-protective strategies.

Acknowledgments

We thank Eleonora Ecca for her help with data collection.

Disclosures

None.

References

1. Marenzi G, Cosentino N, Bartorelli AL. Acute kidney injury in patients with acute coronary syndromes. *Heart*. 2015;101:1778–1785.
2. Giacoppo D, Madhavan MV, Baber U, Warren J, Bansilal S, Witzenbichler B, Dangas GD, Kirtane AJ, Xu K, Kornowski R, Brener SJ, Généreux P, Stone GW,

Mehran R. Impact of contrast-induced acute kidney injury after percutaneous coronary intervention on short- and long-term outcomes: pooled analysis from the HORIZONS-AMI and ACUITY Trials. *Circ Cardiovasc Interv*. 2015;8:e002475.

3. Marenzi G, Cabiati A, Bertoli SV, Assanelli E, Marana I, De Metrio M, Rubino M, Moltrasio M, Grazi M, Campodonico J, Milazzo V, Veglia F, Lauri G, Bartorelli AL. Incidence and relevance of acute kidney injury in patients hospitalized with acute coronary syndromes. *Am J Cardiol*. 2013;111:816–822.
4. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, Pannu N, Manns BJ, Klarenbach SW, Hemmelgarn BR; Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation*. 2011;123:409–416.
5. Nemoto N, Iwasaki M, Nakanishi M, Araki T, Utsunomiya M, Hori M, Ikeda N, Makino K, Itaya H, Iijima R, Hara H, Takagi T, Joki N, Sugi K, Nakamura M. Impact of continuous deterioration of kidney function 6 to 8 months after percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol*. 2014;113:1647–1651.
6. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773–778.
7. Patschan D, Müller GA. Acute kidney injury in diabetes mellitus. *Int J Nephrol*. 2016;2016:6232909.
8. Stolker JM, McCullough PA, Rao S, Inzucchi SE, Spertus JA, Maddox TM, Masoudi FA, Xiao L, Kosiborod M. Pre-procedural glucose levels and the risk for contrast-induced acute kidney injury in patients undergoing coronary angiography. *J Am Coll Cardiol*. 2010;55:1433–1440.
9. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449–461.
10. Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek EP, Krumholz HM. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005;111:3078–3086.
11. Marenzi G, De Metrio M, Rubino M, Lauri G, Cavallero A, Assanelli E, Grazi M, Moltrasio M, Marana I, Campodonico J, Discacciati A, Veglia F, Bartorelli AL. Acute hyperglycemia and contrast-induced nephropathy in primary percutaneous coronary intervention. *Am Heart J*. 2010;160:1170–1177.
12. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31:1473–1478.
13. Executive summary: standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S5–S13.
14. Nakamura T, Ako J, Kadowaki T, Funayama H, Sugawara Y, Kubo N, Momomura S. Impact of acute hyperglycemia during primary stent implantation in patients with ST-elevation myocardial infarction. *J Cardiol*. 2009;53:272–277.
15. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL; ICONS Investigators. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol*. 2002;40:1748–1754.
16. Ishihara M, Kojima S, Sakamoto T, Asada Y, Tei C, Kimura K, Miyazaki S, Sonoda M, Tsuchihashi K, Yamagishi M, Ikeda Y, Shirai M, Hiraoka H, Inoue T, Saito F, Ogawa H; Japanese Acute Coronary Syndrome Study Investigators. Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era. *Am Heart J*. 2005;150:814–820.
17. Consensus: Committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. *Diabetes Care*. 2007;30:2399–2400.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; 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;130:461–470.
19. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
20. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
21. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
22. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract*. 2009;15:353–369.
23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
24. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med*. 2009;150:795–802.
25. Foo K, Cooper J, Deaner A, Knight C, Suliman A, Ranjadayalan K, Timmis AD. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart*. 2003;89:512–516.
26. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, Masoudi FA, Marso SP, Spertus JA. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117:1018–1027.
27. Ishihara M. Acute hyperglycemia in patients with acute myocardial infarction. *Circ J*. 2012;76:563–571.
28. Stranders I, Diamant M, van Gelder RE, Spruijt HJ, Twisk JW, Heine RJ, Visser FC. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med*. 2004;164:982–988.
29. Hadjadj S, Coisne D, Mauco G, Ragot S, Duengler F, Sosner P, Torremocha F, Herpin D, Marechaud R. Prognostic value of admission plasma glucose and HbA in acute myocardial infarction. *Diabet Med*. 2004;21:305–310.
30. Cao JJ, Hudson M, Jankowski M, Whitehouse F, Weaver WD. Relation of chronic and acute glycemic control on mortality in acute myocardial infarction with diabetes mellitus. *Am J Cardiol*. 2005;96:183–186.
31. Roberts GW, Quinn SJ, Valentine N, Alhawassi T, O'Dea H, Stranks SN, Burt MG, Doogue MP. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. *J Clin Endocrinol Metab*. 2015;100:4490–4497.
32. Liao WI, Wang JC, Chang WC, Hsu CW, Chu CM, Tsai SH. Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. *Medicine (Baltimore)*. 2015;94:e1525.
33. Yang Z, Laubach VE, French BA, Kron IL. Acute hyperglycemia enhances oxidative stress and exacerbates myocardial infarction by activating nicotinamide adenine dinucleotide phosphate oxidase during reperfusion. *J Thorac Cardiovasc Surg*. 2009;137:723–729.
34. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, Kugiyama K, Ogawa H, Yasue H. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol*. 1999;34:146–154.
35. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295:1681–1687.
36. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
37. Krinsley JS, Preiser JC, Hirsch IB. Safety and efficacy of personalized glycemic control in critically ill patients: a 2-year before and after interventional trial. *Endocr Pract*. 2017;23:318–330.

SUPPLEMENTAL MATERIAL

Table S1. Observed risk and risk reclassification according to acute glycemia vs. acute on chronic (A/C) glycemic ratio added to acute glycemia**.**

Acute glycemia	**A/C glycemic ratio + acute glycemia**			**% reclassified into new risk category**	
				Lower	**Higher**
	<0.13	**0.13-0.16**	**> 0.16**		
<0.13					
n (%)	120 (82)	24 (16)	3 (2)	-	18
Observed risk	0.13	0.29	0.33		
n events	15	7	1		
0.13-0.16					
n (%)	52 (34)	52 (34)	47 (32)	34	31
Observed-risk	0.58	0.58	0.85		
n events	30	30	40		
>0.16					
n (%)	21 (12)	27 (15)	128 (73)	27	-
Observed risk	-	0.15	0.23		
n events	-	4	30		

A/C=acute on chronic.

Table S2. Observed risk and risk reclassification according to acute glycemia vs. the difference between acute and chronic glycemia ($_{\Delta A\text{-}C}$) added to acute glycemia.

Acute glycemia	**$\Delta_{A\text{-}C}$ + acute glycemia**			**% reclassified into new risk category**	
				Lower	**Higher**
	<0.13	**0.13-0.16**	**> 0.16**		
<0.13					
n (%)	99 (67)	33 (23)	15 (10)	-	32
Observed risk	0.12	0.18	0.33		
n events	12	6	5		
0.13-0.16					
n (%)	55 (36)	40 (26)	56 (36)	36	37
Observed-risk	0.13	0.08	0.18		
n events	7	3	10		
>0.16					
n (%)	33 (19)	17 (10)	126 (71)	28	-
Observed risk	0.03	0.18	0.24		
n events	1	3	30		

$\Delta_{A\text{-}C}$=difference between acute and chronic glycemia.

Table S3. Observed risk and risk reclassification according to acute hyperglycemia (≥198 mg/dl) vs. acute on chronic (A/C) glycemic ratio ≥1.5 added to acute glycemia.

Acute hyperglycemia (>198 mg/dl)	**A/C glycemic ratio ≥1.5 + acute glycemia**			**% reclassified into new risk category**	
				Lower	**Higher**
	<0.13	**0.13-0.16**	**> 0.16**		
<0.13					
n (%)	147 (100)	-	-	-	0
Observed risk	0.16				
n events	23	-	-		
0.13-0.16					
n (%)	97 (64)	44 (29)	10 (7)	64	7
Observed-risk	0.11	0.14	0.30		
n events	11	6	3		
>0.16					
n (%)	-	71 (40)	105 (60)	40	-
Observed risk		0.08	0.27		
n events	-	6	28		

A/C=acute on chronic.

Table S4. Observed risk and risk reclassification according to acute hyperglycemia (≥198 mg/dl) vs. the difference between acute and chronic glycemia (Δ_{A-C}) ≥106 mg/dl added to acute glycemia.

Acute hyperglycemia (≥198 mg/dl)	**Δ_{A-C} ≥106 mg/dl + acute glycemia**			**% reclassified into new risk category**	
				Lower	**Higher**
	<0.13	**0.13-0.16**	**> 0.16**		
<0.13					
n (%)	22 (15)	125 (85)	-	-	85
Observed risk	0.14	0.16			
n events	3	20	-		
0.13-0.16					
n (%)	151 (100)	-	-	100	-
Observed-risk	0.13				
n events	20	-	-		
>0.16					
n (%)	95 (54)	-	81 (46)	54	-
Observed risk	0.07		0.33		
n events	7	-	27		

Δ_{A-C}=difference between acute and chronic glycemia.