Glycemic Variability Is a Powerful Independent Predictive Factor of Midterm Major Adverse Cardiac Events in Patients With Diabetes With Acute Coronary Syndrome

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OBJECTIVE

Acute glucose fluctuations are associated with hypoglycemia and are emerging risk factors for cardiovascular outcomes. However, the relationship between glycemic variability (GV) and the occurrence of midterm major cardiovascular events (MACE) in patients with diabetes remains unclear. This study investigated the prognostic value of GV in patients with diabetes and acute coronary syndrome (ACS).

RESEARCH DESIGN AND METHODS

This study included consecutive patients with diabetes and ACS between January 2015 and November 2016. GV was assessed using SD during initial hospitalization. MACE, including new-onset myocardial infarction, acute heart failure, and cardiac death, were recorded. The predictive effects of GV on patient outcomes were analyzed with respect to baseline characteristics and cardiac status.

RESULTS

A total of 327 patients with diabetes and ACS were enrolled. MACE occurred in 89 patients (27.2%) during a mean follow-up of 16.9 months. During follow-up, 24 patients (7.3%) died of cardiac causes, 35 (10.7%) had new-onset myocardial infarction, and 30 (9.2%) were hospitalized for acute heart failure. Multivariable logistic regression analysis showed that GV >2.70 mmol/L, a Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score >34, and reduced left ventricular ejection fraction of <40% were independent predictors of MACE, with odds ratios (ORs) of 2.21 (95% CI 1.64–2.98; *P* < 0.001), 1.88 (1.26–2.82; *P* = 0.002), and 1.71 (1.14–2.54; *P* = 0.009), respectively, whereas a Global Registry of Acute Coronary Events (GRACE) risk score >140 was not (OR 1.07 [0.77–1.49]; *P* = 0.69).

CONCLUSIONS

A GV cutoff value of >2.70 mmol/L was the strongest independent predictive factor for midterm MACE in patients with diabetes and ACS.

Diabetes is known to be one of the major cardiovascular risk factors (1,2). In the setting of acute myocardial infarction (AMI), many factors related to diabetes, such as admission blood glucose (3,4), fasting blood glucose, hyperglycemia (5), and glycosylated hemoglobin (HbA_{1c}) are associated with adverse cardiovascular events or cardiovascular death (6). Conversely, the prognostic implications of

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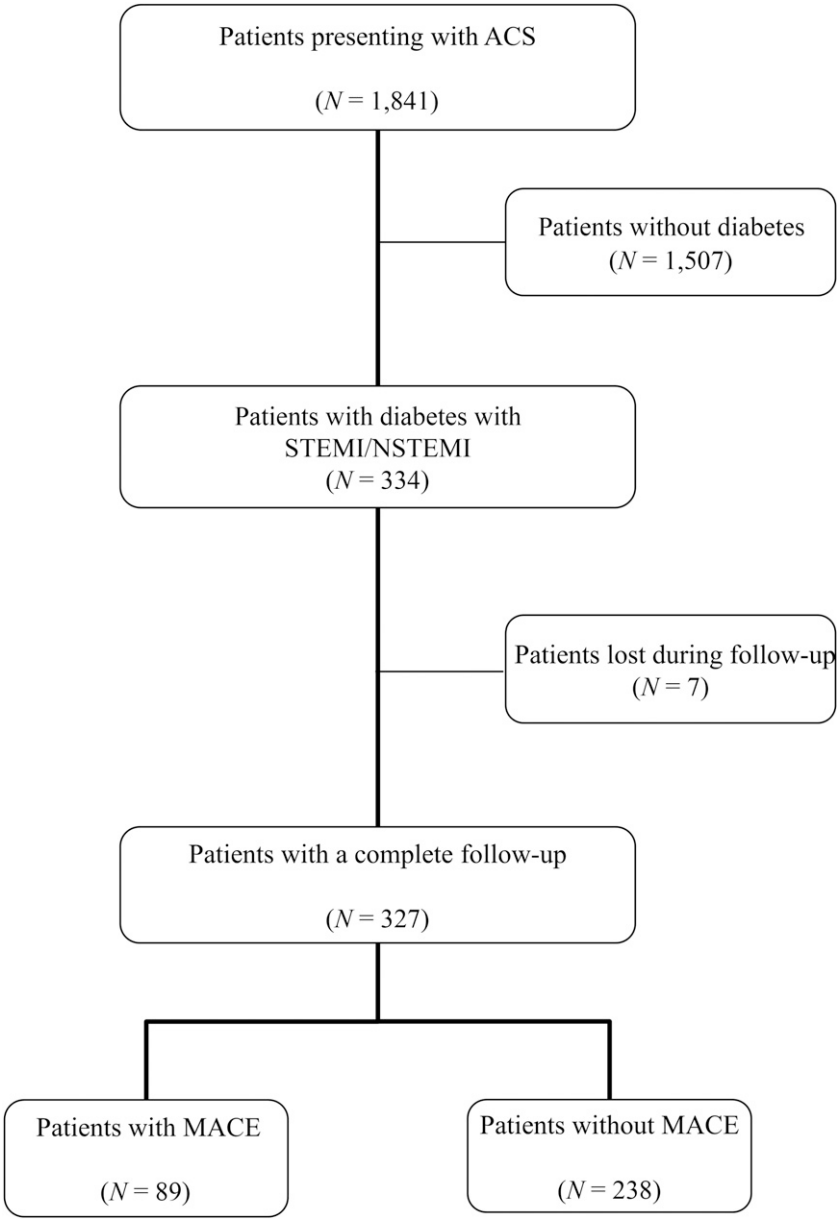

Figure 1—Flowchart of the study. NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

hypoglycemic episodes are still unclear (6,7). Previous studies have struggled to prove that correcting these factors in the acute phase improves the prognosis of patients with diabetes (8,9). Glycemic variability (GV) is one component of dysglycemia (10). GV corresponds to swings in blood glucose levels in the same individual within-day, day-to-day, or even over longer periods of time (11). Increasing GV may contribute to diabetes-related complications, including retinopathy, nephropathy, and cardiovascular events (12–14). In the context of AMI, Su et al. (15) described an association between high GV (measured by continuous glucose monitoring) and 1-year occurrence of major adverse cardiac events (MACE) in patients with or without diabetes (53.6% of the study population study had diabetes). However, a study dedicated to patients with diabetes assessing the association between GV and midterm MACE occurrence is lacking. The aim of this study was to evaluate the association between GV and midterm MACE in patients with diabetes and acute coronary syndrome (ACS).

RESEARCH DESIGN AND METHODS

Study Population

A total of 1,841 consecutive patients with diabetes and ACS were admitted to the intensive cardiovascular care unit (ICCU) of Bordeaux University Hospital between January 2015 and November 2016. Patients for the study were selected using the following inclusion criteria: *1*) confirmed diagnosis of ACS; *2*) admission glucose <16.7 mmol/L; and *3*) confirmed diagnosis of type 1 or type 2 diabetes. Exclusion criteria were *1*) diabetic ketosis or nonketotic hyperosmolar coma at admission or *2*) acute transient stress hyperglycemia during hospitalization. A patient could only be included once. Complete data, including previous history of coronary artery disease (CAD), clinical examination, biological data, extent of CAD (on invasive coronary angiography), and therapy strategies for diabetes, were recorded in the hospital.

ACS was defined and managed according to the European Society of Cardiology guidelines (16,17). Type 1 or type 2 diabetes was diagnosed according to American Diabetes Association criteria or the previous use of insulin or glucose-lowering medication before admission and/or if the HbA_{1c} value at admission was ≥6.5% (18,19). Stress hyperglycemia was defined as a transient elevation of blood glucose of >11 mmol/L due to the stress of illness. On coronary angiography, significant vessel disease was defined as ≥50% narrowing of the diameter of at least one major (≥2.5-mm diameter) epicardial vessel. Vessel diameter and degree of lumen narrowing were calculated by quantitative coronary angiography. CAD severity was determined as no significant stenosis, one diseased vessel, two diseased vessels, or left main and/or three-vessel disease. The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (SS) was also calculated by two experienced interventional cardiologists (E.G., P.C.) on the website http://www.syntaxscore.com according to the SYNTAX trial (20). Echocardiography was performed during hospitalization to determine the left ventricular ejection fraction (LVEF). The Global Registry of Acute Coronary Events (GRACE) risk score was calculated on the website http://gracescore.org/ according to previous studies (21).

The study protocol was approved by the Bordeaux University Hospital Medical Ethics Committee, and the procedures followed were in accordance with institutional guidelines. The study complied with the Declaration of Helsinki, and informed consent was obtained from all patients.

Measurement of Glycemia

Blood glucose measurements were performed using the Accu-Chek Inform II system (Roche Diagnostics GmbH, Mannheim, Germany), allowing point-of-care measurement of all capillary blood glucose values. These were collected during all stays in the hospital, including the ICCU and conventional cardiology unit. All glucometers were identified and connected to the central middleware cobas IT 1000, with results automatically repatriated in the patient file. Devices that were verified before their distribution in care services (linearity and repeatability tests) were set up so that daily quality controls were performed in the care services. The laboratory point-of-care team monitored the analytical performances, the results of quality controls, and the empowerments of health care operators whose access to devices was nominative.

Measurement of Glycemic Variability

Because of the discontinuous monitoring of glycemia and the possible application of this method to everyday life, we arbitrarily chose to use the SD of glycemia (mmol/L) instead of mean amplitude of glycemic excursions (MAGE) to evaluate GV for each patient. In a first analysis, receiver operating characteristic (ROC) curves differentiated two groups according to GV level ($\leq$2.70 or $>$2.70 mmol/L). Three groups per tertile of GV were also defined.

Management of Diabetes During Hospital Stay

During the ICCU stay, intravenous insulin therapy was used if necessary to achieve the glycemic target according to French Society of Cardiology guidelines (22). Continuous insulin administration was initiated when blood glucose on admission was $\geq$10.0 mmol/L and/or when premeal glycemia was $\geq$7.7 mmol/L during the ICCU stay. All other antidiabetic treatments were stopped during the ICCU stay. The

Table 1—Baseline characteristics of the study population (N = 327)

Baseline characteristics	Value
Age (years)	69 ± 11.9
Male sex	252 (77.1)
Smoking status	
Nonsmoker	159 (48.6)
Former smoker	101 (30.9)
Current smoker	67 (20.5)
Hypertension*	253 (77.4)
Type of diabetes	
Type 1	18 (5.5)
Type 2	307 (93.9)
Secondary (chronic pancreatitis)	2 (0.6)
HbA_{1c} (%)	7.55 ± 1.44
Cholesterol	
Total (mmol/L)	4.55 ± 1.40
LDL (mmol/L)	2.72 ± 1.19
HDL (mmol/L)	1.06 ± 0.51
Hypertriglyceridemia (mmol/L)	4.56 ± 3.96
BMI (kg/m^2)	28.5 ± 4.7
Family history of CAD	40 (12.2)
Personal history of CAD	126 (38.5)
eGFR ($mL/min/1.73\ m^2$)	77.6 ± 25.0
STEMI presentation	100 (30.6)
Nonreperfused STEMI†	31 (9.5)
PCI-related delay (ECG to needle) (min)	240 (170–500)
Extent of CAD	
No invasive angiography	7 (2.2)
No significant stenosis	10 (3.1)
One-vessel disease	75 (22.9)
Two-vessel disease	91 (27.8)
Left main and/or three-vessel disease	144 (44.0)
SS	19.5 ± 12.0
TIMI grade flow	
0	10 (3.2)
1	2 (0.2)
2	25 (7.8)
3	290 (88.8)
Revascularization strategy	
PCI	250 (76.5)
CABG	22 (6.7)
Hybrid strategy	5 (1.5)
Medical treatment only‡	50 (15.3)
LVEF (%)	51.7 ± 10.9
Killip score	
1	247 (75.6)
2	46 (14.1)
3	30 (9.1)
4	4 (1.2)
Brain natriuretic peptide (pg/mL)	427 ± 697
Peak troponin I (ng/mL) (normal $<$0.04)	22.6 ± 56.8
Acute kidney failure§	107 (32.7)
CKD with RRT	7 (2.1)
GRACE score	135 ± 32
GRACE score $>$140	95 (29)
Vasopressor/inotropic agent‖	15 (4.6)
Treatment at hospital discharge	
Antithrombotic treatment	
Single APT	24 (7.3)
DAPT	239 (73.1)

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Table 1—Continued

Baseline characteristics	Value
OAC monotherapy	4 (1.2)
Dual therapy (OAC + SAPT)	14 (4.3)
Triple therapy (OAC + DAPT)	46 (14.1)
RAASI	252 (77.1)
β-Blocker	277 (84.7)
Statin	307 (93.8)
Oral hypoglycemic agents	196 (59.9)
Insulin therapy	153 (46.8)
Glycemic status	
Glycemia assays per patient (*n*)	25 (11–42.5)
Glycemia assays per patient per day (*n*)	5 (3–8)
Admission glycemia (mmol/L)	11.2 ± 5.8
Glycemia (mmol/L)	8.9 ± 1.8
Hypoglycemia, %¶	0.6
Patients with hypoglycemia	45 (13.8)
Hypoglycemia events per patient (*n*)	2 (1–2)
Hyperglycemia, %#	31.7
Patients with hyperglycemia	290 (88.7)
GV (SD, mmol/L)	2.5 ± 1.2

Data shown are *n* (%), median (25th-75th percentiles), or mean ± SD, unless otherwise indicated. APT, antiplatelet therapy; CABG, coronary artery bypass graft surgery; CKD with RRT, chronic kidney disease with renal replacement therapy; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulation therapy; PCI, percutaneous coronary intervention; RAASI, renin-angiotensin-aldosterone system inhibitors; SAPT, single antiplatelet therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction. *Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with oral antihypertensive drugs. †Nonreperfused STEMI was defined as STEMI patients presenting with a delay between initial symptoms and hospitalization >24 h. ‡Decision for medical treatment or failure of revascularization. §Acute kidney failure defined according to Kidney Disease: Improving Global Outcomes (KDIGO) staging of acute kidney injury (stage ≥1: elevation of creatinine 1.5–1.9 times baseline or ≥0.3 mg/dL [≥26.5 μmol/L]). ‖Vasopressor/inotropic agents used during initial hospitalization in ICCU. ¶Detection of glucose concentration <3 mmol/L among all measurements obtained in all patients at any time during hospitalization. #Detection of glucose concentration ≥10 mmol/L among all measurements obtained in all patients at any time during hospitalization.

glycemic target was between 7.7 and 10 mmol/L. During the hospital stay on nonintensive care wards, diabetes was managed medically following European Society of Cardiology guidelines with specialist advice if necessary (19).

Outcomes

The follow-up period was defined as the time elapsed between May and August 2017. The incidence of MACE was recorded, including new-onset myocardial infarction, acute heart failure, and cardiac death. The primary outcome and health status of all patients were collected using the medical records available in our center or by contacting the patients' general practitioners, cardiologists, or other hospitals. In some rare cases, patients were contacted themselves. All MACE data were adjudicated by an experienced cardiovascular physician blinded to clinical details and outcomes.

Statistical Analysis

Data are presented as frequencies or percentages for categorical variables, median for abnormally distributed parameters, and mean ± SD for continuous variables, unless otherwise indicated. The distribution of the data was tested for normality to determine the use of parametric or nonparametric tests. Categorical variables were compared using a χ^2 test with Yates correction. The relationships between GV and other variables were investigated using a linear regression analysis. A Pearson correlation coefficient of 0.40–0.69 indicates strong positive relationship and an *r* value of 0.30–0.39 indicates moderate positive relationship. HbA_{1c}, LVEF, and GV were also included as continuous and categorized variables (HbA_{1c}: <6.5% [48 mmol/mol] and ≥6.5% [48 mmol/mol]; LVEF: <40% and ≥40%). ROC curve analyses were conducted to determine the optimal cutoff values for GV, admission glycemia, mean glycemia, and the SS to predict MACE. Thus, the best cutoff values were used to binarize each variable for further multivariate analysis. Two groups were obtained according to the level of GV (≤2.70 or >2.70 mmol/L). All SS binarized data (≤34 or >34) were also included in the multivariate analysis.

Univariate analysis was performed initially. Kaplan-Meier survival curves were used to represent the proportional risk of MACE for GV, and the log-rank test was performed to assess differences between high levels and low levels of GV. To ascertain the independent contribution of GV, hypoglycemia, admission glycemia, and mean glycemia to MACE, and because these parameters were correlated, multivariate logistic regression analysis was performed using several models, including predefined and more relevant variables with a significance level of $P < 0.15$ in univariate analysis. To avoid bias due to too-small number of events per variable in proportional hazards analysis (23), a number of events per variable of <10 was chosen. Odds ratios (ORs) and 95% CIs were calculated. A *P* value of <0.05 was considered statistically significant.

All statistical analyses were performed using NCSS 2001 software (NCSS Statistical Software, Kaysville, UT), and Kaplan-Meier event-free survival curves were constructed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 1,841 patients with ACS were admitted to the Bordeaux University Hospital ICCU between January 2015 and November 2016, and 334 patients fulfilled the inclusion criteria. Seven patients were lost during follow-up, which was conducted between January 2015 and August 2017. The final analysis included 327 patients with complete data (Fig. 1). Table 1 reports the baseline characteristics of the enrolled patients. The median duration of hospitalization was 4 days (first quartile 3 days, third quartile 8 days, interquartile range 5 days).

Intravenous insulin therapy was administered to 269 patients (82.3%) in the ICCU, targeting a blood glucose level between 140 and 180 mg/dL (7.77 and 10.0 mmol/L). During hospitalization, 22 patients (6.7%) were maintained

Table 2—Univariate logistic regression analysis for MACE

Variables	OR	95% CI	*P* value
Age (years)	1.03	1.01–1.06	**0.003**
Male sex	1.72	0.99–2.99	0.053
Current smoker status	2.56	1.16–5.55	**0.02**
Hypertension	0.68	0.37–1.26	0.22
Diabetes type	1.79	0.50–6.39	0.37
HbA_{1c} ≥6.5%	1.14	0.80–1.62	0.47
Cholesterol (mmol/L)			
Total	2.08	1.22–3.57	**0.007**
LDL	2.33	1.24–4.35	**0.009**
HDL	1.69	0.04–7.66	0.69
Hypertriglyceridemia (mmol/L)	0.90	0.73–1.11	0.33
BMI (kg/m^2)	1.04	0.98–1.10	0.17
eGFR ($mL/min/1.73\ m^2$)	1.03	1.01–1.05	**<0.001**
Family history of CAD	0.89	0.45–1.75	0.74
Personal history of CAD	2.28	1.37–3.70	**0.001**
STEMI presentation (compared with NSTEMI)	1.06	0.63–1.79	0.84
Nonreperfused STEMI	0.55	0.22–1.39	0.21
PCI-related delay (ECG to needle) (min)	0.99	0.80–1.21	0.89
Extent of CAD			
One-vessel disease	0.61	0.36–1.04	0.92
Two-vessel disease	0.82	0.35–1.93	0.66
Left main and/or three-vessel disease	1.65	1.28–2.12	**<0.001**
SS	1.03	1.01–1.05	**0.003**
Initial TIMI 3 flow (compared with TIMI ≤2)	0.91	0.62–1.34	0.64
Revascularization strategy			
PCI	1.08	0.61–1.93	0.79
CABG	1.41	0.59–3.40	0.70
Hybrid strategy	1.22	0.22–6.66	0.83
Medical treatment only	1.02	0.48–2.17	0.95
LVEF <40% (compared with LVEF ≥40%)	1.82	1.37–2.44	**<0.001**
Killip score ≥2 (compared with Killip <2)	2.15	1.55–2.97	**<0.001**
Brain natriuretic peptide at admission (pg/mL)	1.00	1.00–1.01	**<0.001**
Peak troponin (ng/mL)	1.00	0.99–1.01	0.16
Acute kidney failure during hospitalization	2.94	1.75–4.90	**<0.001**
CKD with RRT	3.56	0.81–15.6	0.09
GRACE score	1.01	1.00–1.02	**0.001**
GRACE score >140	1.81	1.07–3.13	**0.023**
Vasopressor/inotropic agents	4.35	1.52–12.5	**0.007**
Admission glucose level (mmol/L)	1.00	1.00–1.01	**0.03**
Mean glycemia (mmol/L)	1.01	1.00–1.02	**0.002**
Hypoglycemia (%)	1.11	1.00–1.24	**0.042**
Hyperglycemia (%)	1.01	1.00–1.03	**0.005**
GV (SD, mmol/L)	1.04	1.02–1.05	**<0.001**
GV >2.70 (SD, mmol/L)	2.31	1.78–3.01	**<0.001**
GV tertiles			
First	0.83	0.57–1.19	0.31
Second	1.38	0.70–2.75	**0.006**
Third	3.00	1.69–5.35	**<0.001**

P values in boldface type indicate numbers that are significant at the 95% confidence limit. CABG, coronary artery bypass graft surgery; CKD with RRT, chronic kidney disease to renal replacement therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

between the two target blood glucose values of 7.7 and 10 mmol/L. Among all glycemia measurements obtained in all patients during hospitalization (*n* = 12,318), glycemia values were <3 mmol/L 78 times (0.6%), between 3 and 7.7 mmol/L 4,158 times (33.8%), between 7.7 and 10 mmol/L 4,177 times (33.9%), and ≥10 mmol/L 3,905 times (31.7%). Ten patients (3.1%) had newly diagnosed diabetes. Diabetes was well-controlled in most patients (mean HbA_{1c} 7.55%) as was dyslipidemia (mean LDL cholesterol 2.72 mmol/L). Concerning GV (SD), mean and tertiles were 2.5 mmol/L (SD), <1.79 mmol/L, 1.79–2.87 mmol/L, and >2.87 mmol/L, respectively. The correlations of GV with admission glucose and HbA_{1c} were significant (Pearson correlation coefficient $r = 0.505$ and $r = 0.427$, respectively; all $P < 0.001$). The correlation of GV with hypoglycemia encountered at any time during the hospitalization per individual patient was significant (Pearson correlation coefficient $r = 0.366$; $P < 0.001$).

Incidence of MACE

In our cohort, the mean follow-up time was 16.9 ± 7.1 months. MACE occurred in 89 patients (27.2%): 24 patients (7.3%) died of cardiac causes, 35 (10.7%) had new-onset myocardial infarction, and 30 (9.2%) were admitted to the hospital with acute heart failure.

Univariate Regression Analysis

In univariate analysis, the criteria associated with MACE occurrence were age, current smoker status, total cholesterol, LDL cholesterol, personal history of CAD, left main and/or three-vessel disease, SS, LVEF <40%, Killip stage ≥2, brain natriuretic peptide value, estimated glomerular filtration rate (eGFR), acute kidney failure during hospitalization, GRACE score, use of vasopressor/inotropic agents during hospitalization, admission glucose level, mean glycemia, percentages of hypoglycemia and hyperglycemia, and GV (SD) values, except for the first GV (SD) tertile (Table 2).

Multivariate Regression Analysis

The qualitative variables included were personal history of CAD, SS >34, LVEF <40%, GRACE score >140, use of vasopressor/inotropic agents during hospitalization, and GV (SD) >2.70 mmol/L. Multivariate proportional Cox regression analysis (Table 3) showed that GV >2.70 mmol/L, SS >34, LVEF <40%, and personal history of CAD significantly increased the risk of MACE by 2.21 (95% CI 1.64–2.98; $P < 0.001$), 1.88 (1.26–2.82; $P = 0.002$), 1.71 (1.14–2.54; $P = 0.009$), and 1.42 (1.05–1.91; $P = 0.03$), respectively. ACS patients with diabetes with a

Table 3—Multivariate logistical regression analysis of predictive factors for MACE

Variables	OR	95% CI	*P* value
Personal history of CAD	1.42	1.05–1.91	**0.03**
SS >34 (compared with SS ≤34)	1.88	1.26–2.82	**0.002**
LVEF <40% (compared with LVEF ≥40%)	1.71	1.14–2.54	**0.009**
GRACE score >140	1.07	0.77–1.49	0.69
Vasopressor/inotropic agents	1.73	0.87–3.44	0.12
GV (SD) >2.70 mmol/L	2.21	1.64–2.98	**<0.001**

P values in boldface type indicate numbers that are significant at the 95% confidence limit.

higher GV level (>2.70 mmol/L) had a significantly higher incidence of MACE: cardiac mortality ($P = 0.003$), new-onset myocardial infarction ($P < 0.001$), hospitalization for acute heart failure ($P < 0.001$), and combined MACE ($P < 0.001$). Interestingly, ACS patients with an SS >34 had a significantly higher incidence of cardiac mortality ($P = 0.007$), new-onset myocardial infarction ($P = 0.001$), and all combined MACE ($P = 0.003$).

Concerning hospitalization for acute heart failure, there was no significant difference in adverse cardiovascular event rates between the two study groups ($P = 0.55$). Patients with an LVEF <40% had a significantly higher incidence of cardiac death ($P < 0.001$), of hospitalization for acute heart failure ($P = 0.014$), and of all combined MACE ($P = 0.004$). Concerning new-onset myocardial infarction, there was no significant difference in adverse cardiovascular event rates between the two study groups ($P = 0.20$). Kaplan-Meier event-free survival curves for freedom from MACE in the two patient groups according to admission GV level are shown in Supplementary Fig. 1.

When the qualitative variable "GV >2.70 mmol/L" was replaced by hypoglycemia in the multivariate analysis, hypoglycemia, an SS >34, reduced LVEF (<40%), and personal history of CAD were independent predictors of MACE, with ORs of 1.89 (95% CI 1.30–2.75; $P < 0.001$), 1.84 (1.25–2.71; $P = 0.002$), 1.65 (1.11–2.43; $P = 0.012$), and 1.51 (1.13–2.01; $P = 0.006$), respectively, whereas a GRACE risk score >140 was not (OR 1.03 [0.75–1.43]; $P = 0.84$). An ROC curve analysis was conducted to determine the optimal cutoff value for admission glycemia to predict MACE. Thus, two groups were obtained according to the level of the admission glycemia (≤12.7 or >12.7 mmol/L).

When the qualitative variable "GV >2.70 mmol/L" was replaced by "admission glycemia >12.7 mmol/L" in the multivariate analysis, an SS >34, admission glycemia >12.7 mmol/L, personal history of CAD, and reduced LVEF (<40%) were independent predictors of MACE, with ORs of 2.21 (95% CI 1.30–3.78; $P = 0.004$), 1.99 (1.33–2.98; $P = 0.001$), 1.85 (1.25–2.75; $P = 0.002$), and 1.58 (0.95–2.61; $P = 0.04$), respectively, whereas a GRACE risk score >140 was not (OR 0.99 [0.63–1.54]; $P = 0.96$). An ROC curve analysis was conducted to determine the optimal cutoff value for mean glycemia to predict MACE. Thus, two groups were obtained according to the level of the mean glycemia (≤9.8 or >9.8 mmol/L).

When the qualitative variable "GV >2.70 mmol/L" was replaced by "mean glycemia >9.8 mmol/L" in the multivariate analysis, an SS >34, reduced LVEF (<40%), personal history of CAD, and mean glycemia >9.8 mmol/L were independent predictors of MACE, with ORs of 1.76 (95% CI 1.20–2.58; $P = 0.004$), 1.66 (1.14–2.44; $P = 0.009$), 1.56 (1.17–2.08; $P = 0.002$), and 1.49 (1.12–2.00; $P = 0.007$), respectively, whereas a GRACE risk score >140 was not (OR 1.10 [0.80–1.51]; $P = 0.56$).

CONCLUSIONS

This study investigated the association between GV, well-known cardiovascular risk factors, and established cardiac parameters and midterm MACE in patients with diabetes and ACS. Our results demonstrate that elevated GV (SD) (>2.70 mmol/L) was the strongest independent predictor of increased risk of midterm MACE in this population. Furthermore, an increased SS >34 and reduced LVEF <40% were also independent predictive factors for MACE.

Our study focused on a specific population of patients with diabetes. Su et al. (15) reported an association between high GV (measured by continuous glucose monitoring) and 1-year occurrence of MACE in patients. Only 53.6% of their population had diabetes, however, and tests to detect diabetes were not performed systematically; thus, some cases of diabetes may have been missed. The results of our study seem to be convincing because the patients were treated effectively for common cardiovascular risk factors (mean LDL cholesterol 2.72 mmol/L, mean HbA_{1c} 7.55%) before hospital admission; moreover, medical treatment at hospital discharge was optimal. Furthermore, our pilot study reflects a "real-life" population because it included all consecutive patients with diabetes hospitalized with ACS during the study period.

Interestingly, the OR for GV >2.70 mmol/L was superior to that for increased SS and reduced LVEF, two well-known cardiovascular parameters associated with the occurrence of MACE (24,25). GV also appears to be a better predictive factor of midterm MACE than the GRACE score in patients with diabetes and ACS, whereas this classical score system is frequently used for risk stratification in ACS (21,26).

There is still extensive debate about GV as a predictive risk factor for cardiovascular complications. In the face of growing interest in this variable, some authors have reported a connection between GV and not only microvascular diabetes complications (27) but also macrovascular complications such as CAD severity (28). Other groups have found an interesting association between GV and coronary plaque vulnerability (29) or left ventricular remodelling (30). Conversely, some previous studies failed to find a significant association between GV and MACE (31,32). Siegelaar et al. (31) reanalyzed data of the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes (HEART2D) study, which showed that targeting postprandial glucose/decreased intraday GV would not reduce MACE in patients with AMI. However, that study was not designed to determine the predictive value of GV for MACE risk. To the best of our knowledge, only one well-conducted and dedicated trial, by Mellbin et al. (32), failed to find an association between GV and

prognosis in patients with AMI and type 2 diabetes treated with insulin infusions. However, three other different measures of GV (i.e., root mean square error, range, and slope) were used in their study.

To quantify GV, many methods have been proposed for measuring short- (acute glucose fluctuations) and long-term GV, but there is no universally accepted gold standard. MAGE and SD are among the most widely used and seem to be relevant (11). For short-term (24-h) GV, the best estimate is provided by the coefficient of variation for glucose (%CV), defined as the SD adjusted to the 24-h mean glucose concentration. A cutoff value of 36% was recently validated by the International Consensus on the Use of Continuous Glucose Monitoring to separate stable glucose levels from unstable glucose levels (33). In our study, using discontinuous glucose monitoring and defining the %CV cutoff value as the SD cutoff value (2.70 mmol/L) adjusted to the mean glucose concentration (8.9 mmol/L) during hospitalization, we obtained a %CV cutoff value of 30%. Regarding glycemic measurement, point-of-care measurement of all blood glucose levels, on connected devices rigorously followed by the laboratory, avoids input errors. Furthermore, discontinuous glucose monitoring is useful because it is applicable to everyday life even though it is less efficient to estimate the real GV.

At present, current guidelines concerning the management of glycemia in ACS (22) propose that insulin-based glycemic control should be considered in cases of hyperglycemia ($>$10 mmol/L or $>$180 mg/dL) with the target adapted to possible comorbidities, but exact targets are still to be defined. Many large trials have not found a benefit of strict control of blood glucose in the acute phase of myocardial infarction (34,35). However, short-term GV will perhaps become the target for diabetes management in the acute phase. Recently, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (36) showed a reduction in occurrence of MACE with the use of liraglutide (a glucagon-like peptide analog) versus placebo in patients with type 2 diabetes with a high cardiovascular risk. However, to the best of our knowledge, no study has attempted to evaluate the effect of reducing short-term GV in the acute phase of myocardial infarction.

Study Limitations

We acknowledge that patients with more pronounced changes and frequent changes in glucose levels are probably the ones with increased comorbidities and/or more exposed to cardiovascular risk in general. To provide a risk score for the general risk, including cardiovascular risk, would be very helpful. Unfortunately, to the best of our knowledge, such a universally accepted general risk score currently does not exist. The use of SD (which reflects more dispersion than variability) is debatable (37). However, some authors have shown that the random sampling errors in SD are significantly and consistently smaller than in other variables such as MAGE (38,39). SD is useful and probably sufficient to assess GV and its evolution in routine practice (38). Its use could also be extended to assess ambulatory GV with self-monitoring of blood glucose (40). Continuous glucose monitoring (CGM) was not used after admission. However, to equip all consecutive ACS patients ($>$1,800 patients during this study) with an implantable system is difficult in an emergency setting. Furthermore, possible changes in subcutaneous glucose recovery due to hemodynamic alterations (i.e., hypotension, shock, vasoactive drugs, bleeding consecutive to dual-antiplatelet therapy associated with anticoagulation) could alter the CGM signal. Moreover, a real-time CGM device is not approved in Europe and the U.S. to make clinical adjustments of insulin therapy. Finally, it would have been interesting to know the evolution of GV and common cardiovascular risk factors during follow-up, but unfortunately, these data were not available.

Clinical Implications

A GV cutoff value of $>$2.70 mmol/L emerged as the strongest independent predictive factor for midterm MACE in patients with diabetes and ACS. A high GV must at least alert physicians in charge of patients to their potential cardiovascular risk. Other prospective trials are needed to consider short-term GV as an independent risk factor for diabetic complications. Whether correction of high short-term GV can reduce the occurrence of MACE is still an unresolved question. However, this study emphasizes that a high GV should probably be avoided in patients with diabetes and ACS.

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