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THÈSE POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Glycemic variability: a cardiovascular risk factor?
La variabilité glycémique: un facteur de risque cardiovasculaire?

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Abstract

Objective

Glycemic variability (GV) seems to be related to the occurrence of complications in patients with diabetes. However, the relationship between GV level and the occurrence of mid-term major cardiovascular event in patients with diabetes remains unclear. We evaluated the association between GV and the mid-term occurrence of major adverse cardiac event (MACE) in diabetic patients presenting with acute coronary syndrome (ACS).

Research design and Methods

This retrospective analysis included a cohort of 339 consecutive diabetic patients presenting with ACS between January 2015 and November 2016. A discontinuous glucose monitoring was performed during the hospital stay. GV was assessed by using standard deviation (SD). Two analysis were carried out, one using a cut-off of 50mg/dl (SD) to determine two groups: high GV [$>50\text{mg/dl(SD)}$] and low GV [$<50\text{mg/dl(SD)}$], and the other one using three groups per tertile of GV.

Results

Type 2 diabetes was largely predominant (93.5%). There was 8 (2.7%) newly diagnosed diabetes. Mean HbA1C measured during hospitalization was 7.55%. With a mean follow-up of 16.1 months, 87 patients (29.6%) presented at least one MACE. Female gender, age, known cardiovascular risk factors (smoking status, LDL-C value), previous coronary artery disease (CAD), a three-vessel disease, Killip class ≥ 2 , left ventricular ejection fraction (LVEF), BNP value, the occurrence of acute kidney failure, vasopressor/inotropic agents use, insulin therapy at hospital discharge, high level of hyperglycemia during hospitalization and elevation of GV [$>50\text{mg/dl(SD)}$ and 3rd tertile] were associated with the occurrence of MACE ($p < 0.05$) in the univariate analysis. Multivariate analysis, including variables with a significance level of $p < 0.2$ in univariate analysis, showed that Killip class ≥ 2 , high GV by using the cut-off of 50 mg/dl(SD) and the 3rd GV tertile were strongly associated with the occurrence of MACE ($p = 0,006$, $p = 0.014$ and $p = 0.04$ respectively).

Conclusions

GV in diabetic patients presenting with ACS is a powerful independent predictive factor of mid-term MACE.

Keywords

diabetes - ACS - glycemic variability - glucose monitoring - MACE

Résumé

But

La variabilité glycémique (VG) semble être associée à la survenue de complications chez le patient diabétique. Cependant, la relation entre VG et survenue d'événements cardiovasculaires majeurs (ECVM) chez les patients diabétiques reste incertaine. Nous avons donc évalué l'association entre VG et survenue d'ECVM à moyen terme chez une population de patients diabétiques ayant présenté un syndrome coronarien aigu.

Design de l'étude et Méthodes

Cette étude rétrospective a concerné une cohorte de 339 patients diabétiques ayant présenté un syndrome coronarien aigu. Ceux-ci ont été inclus consécutivement entre Janvier 2015 et Novembre 2016. Un monitoring discontinu de la glycémie a été réalisé durant l'hospitalisation pour l'infarctus du myocarde. La VG a été évaluée en utilisant la déviation standard (DS). Ensuite, deux analyses ont été réalisées, l'une utilisant un cut-off de 50mg/dl(DS) pour déterminer deux groupes : haute VG [$>50\text{mg/dl(DS)}$] et faible VG [$<50\text{mg/dl(DS)}$] et l'autre établissant trois groupes par tertile de VG.

Résultats

Le diabète de type 2 était largement prédominant (93.5%). Il y a eu 8 (2.7%) découvertes de diabète. L'HbA1C moyenne mesurée pendant l'hospitalisation était de 7.55%. Avec un suivi moyen de 16,1 mois, 87 patients (29.6%) ont présenté au moins un ECVM. Le sexe féminin, l'âge, les facteurs de risque cardiovasculaire connus (tabagisme, taux de LDL-C), un antécédent coronarien, une coronaropathie tritonculaire, un score Killip ≥ 2 , la fraction d'éjection ventriculaire gauche, le taux de BNP, la survenue d'une insuffisance rénale aiguë durant l'hospitalisation, l'utilisation d'amines, une insulinothérapie à la sortie d'hospitalisation, un nombre élevé d'hyperglycémies durant le séjour et une importante VG [$>50\text{mg/dl(DS)}$ et le 3^{ème} tertile] étaient associés à la survenue d'ECVM ($p < 0.05$) en analyse univariée. L'analyse multivariée incluant les variables avec un niveau de significativité $p < 0.2$ en analyse univariée montrait qu'un score Killip ≥ 2 , une VG importante en utilisant le cut-off de 50mg/dl(DS) et le 3^{ème} tertile étaient fortement associés à la survenue d'ECVM (respectivement $p = 0.006$, $p = 0.014$ et $p = 0.04$).

Conclusions

La VG chez des patients diabétiques présentant un syndrome coronarien aigu est un puissant facteur prédictif indépendant de survenue d'ECVM à moyen terme.

Mots-clés

diabète - syndrome coronarien aigu - variabilité glycémique - monitoring glycémique - événement cardiovasculaire majeur

Abbreviations and acronyms

ACS: acute coronary syndrome

AMI: acute myocardial infarction

APT: antiplatelet therapy

BMI: body mass index

BNP: brain natriuretic peptide

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CKD: chronic kidney disease

CKD-EPI: chronic kidney disease-epidemiology collaboration

DAT: dual antiplatelet therapy

GV: glycemic variability

HbA1C: glycosylated hemoglobin

HDL-C: high-density lipoprotein cholesterol

ICCU: intensive cardiovascular care unit

ICU: intensive care unit

KDIGO: kidney disease improving global outcomes

LDL-C: low-density lipoprotein cholesterol

LVEF: left ventricular ejection fraction

OAC: oral anticoagulant

OAD: oral antidiabetic drug

PCI: primary coronary intervention

RAASI: renin-angiotensin-aldosterone system inhibitor

RRT: renal replacement therapy

STEMI: ST-segment elevation myocardial infarction

TC: total cholesterol

TG: triglyceride

TIMI: thrombolysis in myocardial infarction

Introduction

Diabetes mellitus has long been known as one of the major cardiovascular risk factors (1–4). Among patients with type 1 and type 2 diabetes, cardiovascular disease remains the most common cause of death (3,5,6). Many previous studies demonstrated an association between coronary artery disease, cardiovascular mortality (3), and hyperglycemia (1,7), long term glycemic level by using HbA1C (2,8,9), hypoglycemia (10,11). In the same way, effective diabetes control dramatically reduces cardiovascular complications (2,8,9) and mortality (9). However too strict control does not reduce macrovascular complications (seems to be effective on microvascular ones) (12–14) and may even lead to hypoglycemia and be deleterious (13–15).

Those complications can be explained at the cellular scale by multiple and complex mechanisms at the origin of an endothelial dysfunction, inflammation, thrombosis, oxidative stress (10,18) which promote atherosclerosis (19), coronary plaque vulnerability, the occurrence of no-reflow phenomenon (20), might increase myocardial infarction size (21,22) induce arrhythmias (23,24).

In the setting of acute myocardial infarction (AMI), many factors related to diabetes such as admission blood glucose (25,26), fasting blood glucose, hyperglycemia (27,28), HbA1C are associated with adverse cardiovascular event or mortality (29). At the opposite, prognostic implications of hypoglycemic episodes still debated (29,30). Thus, previous studies are often struggling to prove that correcting these factors in the acute phase improves the prognosis of patients with diabetes (31,32). Kosiborod et al.(33) is one of the few to report (31) that glucose normalization after an AMI was associated with better survival in hyperglycemic patients.

An other marker reflecting diabetes instability appears more and more in the literature: the glycemic variability (GV). GV (34) seems to be related to the occurrence of complications in patients with diabetes (35–37). This is explained by the impact of GV on the previously mentioned pathophysiological mechanisms: oxidative stress (38), endothelial dysfunction (39), inflammation (40), fibrosis (41), atherogenesis (42). Furthermore the development and the availability of continuous glucose monitoring systems encourage its evaluation (43).

To quantify GV, lots of methods are available but there is no universally accepted "gold standard" (41). Mean amplitude glycemic excursion (MAGE) and standard deviation (SD) are among the most used and seem to be relevant (41,44).

In the face of the growing interest aroused by this variable, some authors raise the question of the impact of this factor on the prognosis of diabetic patients and the expected benefit of orienting therapeutics on the reduction of GV. Some studies report a connection between GV and microvascular diabetes complications (45), predictive cardiovascular risk (46), but also

macrovascular complications such as coronary artery disease (47). Several Japanese teams found an interesting association with the coronary plaque progression (48) and vulnerability (49,50), left ventricular remodeling (51).

At the opposite, previous studies did not find a significant association between GV and the occurrence of MACE (52–55).

In the context of AMI, Su et al. describe an association between an important GV (measured by continuous glucose monitoring) and 1-year MACE in patients with or without diabetes (56,57). Other studies reported similar results (58–60).

However, the association between GV level and the occurrence of mid-term major cardiac event in patients with diabetes remains unclear (35). Thus, the aim of this study was to evaluate the association between GV and the mid-term occurrence of major adverse cardiac event (MACE) in diabetic patients presenting with acute coronary syndrome (ACS).

Research Design and Methods

Study population

1841 patients presenting with ACS were hospitalized in the intensive cardiovascular care unit (ICCU) of the Bordeaux University Hospital between January 2015 and November 2016. This retrospective analysis of a cohort of 339 consecutive diabetic patients presenting with ACS was conducted between January 2015 and August 2017. Clinical data of all these diabetic patients were collected.

First 339 patients were eligible. Among those patients, 45 patients (13.3%) were excluded from the analysis because they died of a non-CV cause before the point date ($n=11$) or their date of last view was anterior to the minimum follow-up of 8 months ($n=34$) (*Figure 1*).

Despite the patients excluded from the analysis the initial and the final cohorts remain comparable (*Table 1*).

Inclusion criteria

A patient was considered diabetic if he was known diabetic and/or if he received an antidiabetic treatment and/or if his HbA1C at admission was $\geq 6.5\%$ (61,62). We did not use venous glucose level to exclude patients with stress hyperglycemia.

ACS was defined according the European Society of Cardiology Guidelines (63,64).

Measurement of glycemia

All blood glucose measurements were collected by using the *ACCU-CHEK Inform II*® system allowing the point-of-care measurement of all the glycemia values. They were collected during the all stay in our hospital including the ICCU and the conventional cardiology unit stay.

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 SD of glycemia instead of MAGE or coefficient of variation to evaluate the glycemic variability of each patient (41,44,65,66). In a first analysis two groups were obtained according to the degree of GV ($<$ or $>$ 50mg/dl). Then three groups per tertile of GV were defined.

Management of diabetes during the hospitalization

During the ICCU stay, intravenous insulin therapy was used if necessary to achieve the glycemic target according to the ESC guidelines (62). Diabetes during traditional cardiology unit stay was medically managed following ESC guidelines (62) with the possibility of specialized advice if necessary.

Outcomes

The follow-up period was defined as the time elapsed between May and August 2017. The primary endpoint and health status of all the patients were collected by using all medical reviews available in our center or by contacting general practitioners, patients' cardiologists or peripheral hospitals. In some rare cases, we needed to contact patients themselves.

Primary outcome was defined as MACE including myocardial infarction, hospitalization for acute heart failure and cardiovascular death.

Statistical analysis

Data are presented as frequencies and percentages for categorical variables, median for abnormal distributed parameters and mean \pm SD for continuous distributed variables, unless otherwise indicated. Continuous variables were expressed as mean \pm SD or median (25th, 75th percentiles), while categorical variables were compared using a Chi² test with a Yates correction. Differences between two groups were assessed by using the Chi square, Mann-Whitney rank analysis and unpaired t-tests. First, a univariate analysis was performed. To ascertain the independent contribution of GV to MACE, a multivariate logistical regression analysis was carried out including the variables with a significance level of $p < 0.20$ in univariate analysis. Variables adjusted in the model were: female gender, age, smoking status, LDL-C value, a previous coronary artery disease (CAD), a three-vessel disease, left ventricular ejection fraction (LVEF), a Killip stage ≥ 2 , elevation of cardiac biomarkers (BNP, troponin I), the occurrence of acute kidney failure during hospitalization, elevation of creatinine clearance level (CKD-EPI), the use of vasopressor/inotropic agents, presence of an insulin therapy, a renin-angiotensin-aldosterone system inhibitor (RAASI), a beta-blocker and an oral antidiabetic drug (OAD) at hospital discharge and elevation of GV (group with GV > 50mg/dl, 3rd tertile). A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed by using R v3.4.2.

Results

In our study, patients were mostly male (77.9%), average age was 68.2 years old. Type 2 diabetes was largely predominant (93.5%) which may explain the metabolic patients profile (78.8% of hypertension, mean BMI 28.9kg/m²). There were 8 patients (2.7%) newly diagnosed diabetes. Most patients were relatively well treated concerning diabetes (mean HbA1C = 7.55%) and dyslipidemia (mean LDL-C = 1.06g/l); thus among them 38.1% had previous CAD. Concerning ACS, 30.1% of them were STEMI; 136 patients (46.3%) had a three-vessel disease. Acute kidney failure (defined as \geq stage 1 of KDIGO classification (67)) occurred in approximately one third of patients (34.1%). 232 patients (78.9%) underwent primary coronary intervention (PCI), 15 patients (5,1%) were treated using coronary artery bypass grafting (CABG) and 47 patients (16%) were medically managed. At hospital discharge, the majority of patients received optimal medical treatment (beta-blocker: 88,4%, RAASI: 80%, statin: 95,4%). 133 patients (46.8%) received insulin therapy and 177 patients (62.3%) received OAD. Regarding to glycemic measurement, there were a median of 25 glycemia per patient and a mean of 5,1 glycemia per patient per day. Due to the high proportion of type 2 diabetes, hypoglycemic episodes were rare (0.6%) whereas hyperglycemic ones were really common (31.2%).

Concerning the GV, mean value was 46mg/dl(SD). When applying the cut-off of 50 mg/dl(SD), 190 patients (64.6%) had a low GV and 104 (35.4%) a high one (*Table 2*).

In our cohort, the mean follow-up was 16,1 months. A MACE occurred in 87 patients (29,6%) (*Figure 1*): 38 (12,9%) hospitalization for acute heart failure, 35 (11.9%) AMI and 24 (8.2%) CV-death (*Table 2*).

Univariate regression analysis

In univariate analysis, following criteria are associated with the occurrence of MACE ($p < 0.05$): female gender (68), age, known cardiovascular risk factors (smoking status, LDL-C, TG, TC), a previous CAD, a three-vessel disease, LVEF, a Killip class ≥ 2 , BNP value, the occurrence of acute kidney failure during hospitalization, the use of vasopressor/inotropic agents, an insulin therapy at hospital discharge, high level of hyperglycemia during hospital stay and elevation of GV (group with GV>50mg/dl, 3rd tertile). At the opposite, the following factors were protective: presence of an RAASI, a beta blocker and an OAD at hospital discharge, elevation of creatinine clearance level (CKD-EPI).

Type of diabetes, level of HbA1C ($p = 0.57$), admission glycemia ($p = 0.05$), number of hypoglycemia ($p = 0.06$), HTA ($p = 0.07$), type of AMI ($p = 0,7$) are not associated with the

occurrence of MACE. Neither the presence of statin at discharge ($p = 0.93$) (probably because of the low statistical power generated by the small number of untreated patients).

Multivariate regression analysis

In the multivariate proportional Cox regression analysis (*Table 3*), only two variables still to be strongly associated with the occurrence of MACE: a Killip class ≥ 2 ($p = 0.004$) and GV.

This important relation between GV and MACE was valid with the cut-off value of 50mg/dl ($p = 0.014$) and with the 3rd tertile group ($p = 0.04$).

The rate of MACE in high GV group (SD>50mg/dl) was 46.2% vs. 20.5% in the low one (SD<50mg/dl). The rate of MACE by GV (SD) tertile (>51.47mg/dl, 34.66-51.47mg/dl, <34.66) was respectively 44.9% vs. 24.5% vs. 19.4%.

Conclusions

Our study shows the association between GV after an ACS in the specific population of diabetic patients and the occurrence of mid-term MACE. This pilot study demonstrates a major association between GV and MACE and therefore the importance to be interested in this variable in the management of patients with diabetes in the acute phase of myocardial infarction and in secondary prevention.

The strength of this study lies in the adjustment to several different factors known to be associated with the occurrence of MACE such as cardiovascular risk factors and parameters related to severity criteria of ACS. It also includes the variables linked to the prognosis in ICCU. The results of this study seem to be convincing as the study population before hospital admission was well-treated concerning common cardiovascular risk factors (mean LDL-C=1.06g/l, mean HbA1C=7.55%) and medical treatment at hospital discharge was quite optimal.

Our pilot study reflect the “real world” population in that it includes all consecutive diabetic patients hospitalized with AMI during the study period. Regarding the glycemic measurement, the point-of-care measurement of all blood glucose levels avoids input errors. Discontinuous glucose monitoring is very interesting because it is applicable to everyday life but is less efficient to estimate the real GV.

Study limitations

The use of SD (which reflects more dispersion than variability) can be objectionable (69) but some authors have shown that the random sampling errors in the SD (65) are significantly and consistently smaller than the use of other variables such as MAGE (65,66). SD is usefull and sufficient to assess GV and its evolution in patients in clinical routine practice (41,65). Its use could also be extended to assess ambulatory GV with self monitoring blood glucose (70).

The evolution of GV and common cardiovascular risk factor during follow-up could have been a valuable indication but is missing too in our study.

Clinical implications

Regarding specific population of patients with type 1 diabetes who were a minority in our study (5.8%), previous studies did not show any association between short term GV and diabetes complications (35). However, it seems difficult to definitely conclude in this population.

In the literature, some studies whose methodologies are open to criticism because of a low number of glycemias (54) or because authors re-analyse databases that are not built to answer the initial

question of influence of GV (52), do not find any connection between GV and MACE. To our knowledge, only one well-conducted trial lead by Mellbin et al. (55) did not outline any association between GV and diabetic patients prognosis after an AMI but he used other variables to evaluate GV.

At present, guidelines concerning management of glycemia in ACS (62) propose that an insulin-based glycemetic control should be considered in case of hyperglycemia (>10 mmol/L or >180 mg/dL) with the target adapted to possible comorbidities but exact targets are still to be defined. As a reminder, many large trials do not find a benefit to a strict control of blood glucose in the acute phase of myocardial infarction (71–73).

At this time, more and more authors have investigated GV as a target for the management of diabetes (74).

In the current therapeutic arsenal of type 2 diabetes, molecules like dipeptidyl peptidase-IV inhibitors (75,76), glucagon-like peptide-1 analogues (77–79) but also the accessibility and the development of continuous glucose monitoring systems allow to significantly reduce GV (80). This finding is all the more relevant as the recent LEADER trial (81) shows a reduction in the occurrence of MACE with the use of liraglutide (a glucagon-like peptide analogue) vs. placebo in patients with type 2 diabetes with high cardiovascular risk. But to our knowledge, no study has attempted to evaluate the impact of reducing GV in the acute phase of myocardial infarction.

Other prospective trials are needed to assess whether GV is an independent cardiovascular risk factor and whether correction of high GV can reduce the occurrence of cardiovascular events.

GV after an AMI in patients with diabetes is a powerful independent predictive factor of mid-term cardiovascular risk. A high GV must at least alert to the patient's cardiovascular risk.

Tables and Figures

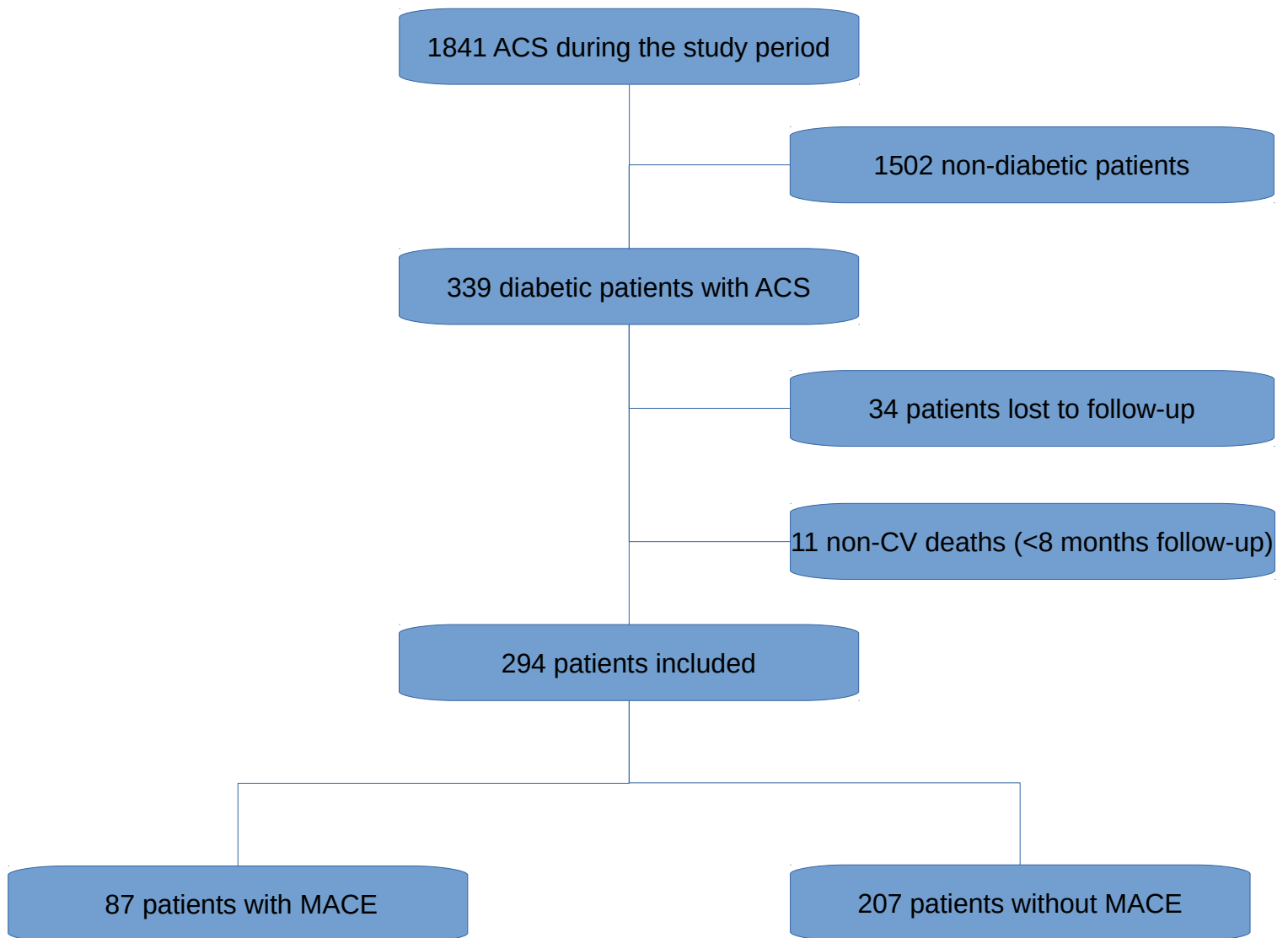


Figure 1. Flow chart of study population

Variables	Eligible Patients (n=339)	Final Cohort (n=294)	p-value
Male gender [n(%)]	261 (77)	229 (77.9)	0.86
Age [years;mean(SD)]	69 (11.9)	68.2 (11.7)	0.41
Smoking status [n(%)]			0.91
Non-smoker	164 (48.4)	139 (47.3)	
Former smoker	106 (31.3)	91 (31)	
Current smoker	69 (20.4)	64 (21.8)	
Hypertension* [n(%)]	263 (77.5)	232 (78.8)	0.76
Type of diabetes [n(%)]			0.95
Type 1	18 (5.3)	17 (5.8)	
Type 2	319 (94.1)	275 (93.5)	
Secondary (chronic pancreatitis)	2 (0.6)	2 (0.7)	
HbA1C [%;mean(SD)]	7.55 (1.43)	7.55 (1.4)	0.98
TC [g/l;mean(SD)]	1.75 (0.54)	1.76 (0.55)	0.78
LDL-C [g/l;mean(SD)]	1.05 (0.46)	1.06 (0.46)	0.86
HDL-C [g/l;mean(SD)]	0.41 (0.1)	0.41 (0.1)	0.82
TG [g/l;mean(SD)]	1.76 (1.53)	1.76 (1.39)	0.99
BMI [kg/m ² ;mean(SD)]	28.8 (5)	28.9 (4.9)	0.75
LVEF [%;mean(SD)]	51.8 (10.9)	51.8 (11.2)	0.99
Family history of CAD [n(%)]	41 (12.1)	37 (12.6)	0.95
Previous CAD [n(%)]	133 (39.2)	112 (38.1)	0.83
STEMI [n(%)]	102 (30.4)	88 (30.2)	1
Extent of CAD [n(%)]			0.97
No invasive angiography	7 (2.1)	4 (1.4)	
No significant stenosis	7 (2.1)	6 (2)	
One-vessel	74 (21.8)	68 (23.1)	
Two-vessel	89 (26.3)	78 (26.5)	
Three-vessel	158 (46.6)	136 (46.3)	
Non-reperfused STEMI† [n(%)]	31 (9.1)	27 (9.2)	1
Delay to reperfusion (STEMI) [hours;mean(SD)]	4.5 (3.7)	4.3 (3.6)	0.78
TIMI Grade Flow [n(%)]			0.98
TIMI 0	11 (3.2)	11 (3.7)	
TIMI 1	2 (0.6)	2 (0.7)	
TIMI 2	3 (0.9)	3 (1)	
TIMI 3	280 (82.6)	243 (82.6)	
Killip score [n(%)]			0.99
Killip 1	251 (74)	216 (73.5)	
Killip 2	50 (14.7)	42 (14.3)	
Killip 3	31 (9.1)	29 (9.9)	
Killip 4	4 (1.2)	4 (1.4)	

Peak troponin I [ng/ml;mean(SD)]	22.2 (55.8)	22.2 (58.5)	1
BNP [pg/ml;mean(SD)]	426 (687)	435 (721)	0.89
Creatinine clearance (CKD-EPI) [μmol/l;mean(SD)]	77.6 (25.2)	77.9 (25.1)	0.88
Acute kidney failure‡ [n(%)]	112 (33.8)	98 (34.1)	1
CKD with RRT [n(%)]	7 (2,1)	6 (2)	1
Vasopressor/inotropic agent [n(%)]	15 (4.4)	12 (4.1)	0.99
Revascularization strategy			0.89
PCI [n(%)]	263 (77.6)	232 (78.9)	
CABG [n(%)]	20 (5.9)	15 (5.1)	
Medical treatment only§ [n(%)]	56 (16.5)	47 (16)	
Antithrombotic treatment [n(%)]			1
Single APT	23 (6.8)	18 (6.1)	
DAT with clopidogrel	48 (14.2)	40 (13.6)	
DAT with ticagrelor	151 (44.5)	132 (44.9)	
DAT with prasugrel	39 (11.5)	37 (12.6)	
OAC monotherapy	4 (1.2)	2 (0.7)	
Dual therapy (OAC+SAPT)	14 (4.1)	13 (4.4)	
Triple therapy (OAC+DAT)	50 (14.7)	44 (15)	
Treatment at hospital discharge			
RAASI [n(%)]	259 (79)	228 (80)	0.83
Beta blocker [n(%)]	283 (86.3)	252 (88.4)	0.5
Statin [n(%)]	313 (95.4)	272 (95.4)	1
Insulin therapy [n(%)]	155 (47.3)	133 (46.8)	0.98
OAD [n(%)]	199 (60.9)	177 (62.3)	0.77
Nb of glycemia per patient (median)	25	25	
Nb of glycemia per patient per day (mean)	5.1	5.1	
Admission glycemia [mg/dl;mean(SD)]	204 (105)	203 (106)	0.89
Mean glycemia [mg/dl;mean(SD)]	162 (33)	162 (34)	0.93
Hypoglycemia (%)	0.6	0.6	0.93
Number of patients with hypoG [n(%)]	45 (13.3)	36 (12.2)	0.79
Hyperglycemia¶ (%)	31.5	31.2	0.85
Number of patients with hyperG [n(%)]	290 (85.5)	250 (85)	0.95
Glycemic variability [mg/dl;mean(SD)]	46 (22)	46 (22)	0.95

Table 1. Baseline characteristics of the study population

* Hypertension = antihypertensive treatment at admission

† Non-reperfused STEMI: persistence of ST-segment elevation on ECG due to failure of revascularization or delay between initial symptom and hospitalization > 24h

‡ Acute kidney failure defined according to KDIGO staging of acute kidney injury (≥ stage 1: elevation of creatinine 1.5 times baseline or ≥ 26,5 μmol/l increase)

§ decision of medical treatment or failure of revascularization

|| Hypoglycemia = glycemia ≤ 60 mg/dl

¶ Hyperglycemia = glycemia ≥ 180 mg/dl [recommended glycemic target in ICU(31)]

Variables	Final Cohort (n=294)
Glycemic variability [mg/dl;mean(SD)]	46 (22)
Low GV [SD<50mg/dl;n(%)]	190 (64,6)
High GV [SD>50mg/dl;n(%)]	104 (35,4)
Duration of follow-up [months;mean(SD)]	16,1 (7,2)
Non CV death [n(%)]	7 (2,4)
CV death [n(%)]	24 (8,2)
Hospitalization for acute heart failure [n(%)]	38 (12,9)
AMI [n(%)]	35 (11,9)
Total MACE [n(%)]	87 (29,6)

Table 2. Level of glycemic variability and MACE

Variables	Multivariate analysis			
	GV>50mg/dl (SD)		GV 3 rd tertile (SD)	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Male gender	0.68 (0.22-2.08)	0.495	0.74 (0.24-2.32)	0.597
Age (years)	0.99 (0.94-1.04)	0.691	0.99 (0.94-1.04)	0.703
Smoking status				
Former smoker	2.75 (0.98-8.19)	0.06	2.87 (1.01-8.72)	0.053
Current smoker	2.23 (0.52-9.84)	0.28	2.54 (0.58-11.58)	0.217
Hypertension	0.60 (0.19-2.01)	0.4	0.65 (0.2-2.18)	0.475
LDL-C (g/l)	0.42 (0.12-1.38)	0.164	0.43 (0.12-1.42)	0.178
TG (g/l)	0.82 (0.46-1.28)	0.438	0.79 (0.44-1.24)	0.366
LVEF	0.99 (0.95-1.04)	0.7	0.99 (0.95-1.04)	0.709
Previous CAD	1.44 (0.54-3.79)	0.459	1.3 (0.48-3.46)	0.6
Killip score ≥ 2	3.76 (1.48-10)	0.006	3.72 (1.45-10.07)	0.007
Peak troponin I (ng/ml)	0.99 (0.96-1)	0.175	0.99 (0.96-1)	0.191
BNP (pg/ml)	1 (1-1)	0.174	1 (1-1)	0.165
Creatinine clearance (CKD-EPI) (μmol/l)	0.98 (0.96-1)	0.084	0.98 (0.96-1)	0.072
Acute kidney failure	1.51 (0.52-4.39)	0.441	1.44 (0.49-4.22)	0.501
Vasopressor/inotropic agent	3.63 (0.22-74.81)	0.37	4.91 (0.25-120.12)	0.306
RAASI	1.4 (0.46-4.64)	0.37	1.39 (0.46-4.63)	0.575
Beta blocker	0.29 (0.08-1.07)	0.063	0.31 (0.08-1.2)	0.087
Insulin therapy	2.34 (0.66-8.38)	0.185	2.3 (0.65-8.28)	0.197
OAD	0.83 (0.27-2.55)	0.737	0.75 (0.25-2.32)	0.617
GV>50mg/dl (SD)	3.33 (1.29-8.89)	0.014		
GV [mg/dl;tertile;(SD)]				
1 st tertile				
2 nd tertile			1.05 (3.33-3.42)	0.934
3 rd tertile			3.53 (1.08-12.32)	0.04

Table 3. Multivariate logistical regression analysis including the variables with a significance level of $p < 0.20$ in univariate analysis

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