Original Research

Distinct Association of Admission Hyperglycemia with One-Year Adverse Outcome in Diabetic and Non-Diabetic Patients with Acute ST-Elevation Myocardial Infarction

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Introduction: Both admission hyperglycemia (AH) and diabetes mellitus adversely affect the prognosis in acute coronary syndromes. We prospectively assessed the predictive role of AH in patients with acute ST-segment elevation myocardial infarction (STEMI).

Methods: Three hundred-one consecutive patients hospitalized for STEMI were enrolled. Patients were stratified into four groups based on their history of diabetes and the presence of AH (plasma glucose level >11.0 mmol/l or 200 mg/dl). The pre-specified endpoint was the composite of all-cause mortality, non-fatal MI and stroke after one year follow up.

Results: The incidence of the endpoint was 19.6% (35 all-cause deaths, 21 non-fatal MIs, and 3 strokes). Non-diabetic patients with AH exhibited a significantly higher incidence of the composite endpoint compared to those with neither diabetes nor AH (50% vs. 15.3%, log rank p<0.001) and diabetics with or without AH (50% vs. 17.2% vs. 19.3%, log rank p<0.05 for both). Ejection fraction (HR 0.946, p=0.007), treatment with primary percutaneous coronary intervention (HR=0.488, p=0.041), and AH in the absence of known diabetes (HR 2.207, p=0.043) were the only independent predictors of the endpoint.

Conclusions: AH in non-diabetic STEMI patients is accompanied by a worse long-term prognosis compared to diabetics (with or without AH) or normoglycemic patients and constitutes a potent predictor of an adverse outcome.

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An increase in plasma glucose concentration is often observed during the early hours of acute myocardial infarction (AMI).[1] Certain studies have demonstrated that admission plasma glucose is a strong predictor of short- and long-term mortality in AMI patients with and without diabetes mellitus (DM), independently from glycated hemoglobin levels.[2-10] It has been emphasized that in patients without a history of DM, the relationship between admission glucose levels and in-hospital mortality seems to be linear, whereas a U-shape relation was observed in diabetic patients.[11]

Increased plasma glucose on admission in patients without a history of DM defines admission hyperglycemia (AH). It has been reported that both AH and DM are independently associated with adverse outcomes after both ST-segment elevation MI (STEMI) and non-STEMI, regardless of treatment modality (fibrinolysis or primary percutaneous coronary intervention – PCI).[2-9] However, definitions of AH are inconsistent, ranging from 6 to 11 mmol/L.[3] Regarding the role of AH in short- and long-term mortality in AMI patients with and without diabetes, the existing data are rather equivocal. In one

study, non-diabetic patients with AH had a higher short-term (30-day) mortality risk than hyperglycemic patients with known diabetes, although late mortality (beyond 30 days) was higher in diabetics with AH.[12] In another investigation, however, during a 6-month follow-up period the worst outcomes occurred in non-diabetic hyperglycemic patients.[13] In the present study we sought to assess the predictive value of AH for 1-year adverse outcomes in diabetic and non-diabetic patients with acute STEMI.

Methods

Study population

We prospectively collected in-hospital data from 340 consecutive patients hospitalized for acute STEMI in our institution within 12 hours of symptom onset, as previously described.[14] The AMI diagnosis was established according to current guidelines.[15] In particular, STEMI was diagnosed in patients with new ST-segment elevation ≥2 mm in ≥2 contiguous precordial leads, or ≥1 mm in ≥2 continuous limb leads, or when new left bundle branch block in the presence of compatible symptoms was found on the qualifying electrocardiogram. Patients with active infection or chronic inflammatory disease, any significant systemic disease (n=2), hepatic or overt renal dysfunction (serum creatinine >2.5 mg/dl) (n=3), malignancy (n=2), or major surgery in the previous month (n=1) were not included. Patients who presented with cardiogenic shock or died during the first 48 hours of their hospital stay (n=6) or during revascularization (n=3) were also excluded from the study. During the study period, 323 patients who fulfilled the above criteria were finally enrolled.

The present study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of our institution. Each patient gave written consent before enrollment.

Data collection and biochemical assays

The patients' baseline characteristics, together with in-hospital and follow-up data, were recorded in predesigned case report forms. In all patients a detailed medical history was obtained, including the presence and management of hypertension, hypercholesterolemia, DM, any family medical history of coronary artery disease, and smoking status.

On admission, venous blood samples were obtained before administration of any medication. Total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, plasma glucose and creatinine were measured in all participants by a colorimetric enzymatic method, using a Technicon automatic analyzer RA-1000 (Dade-Behring Marburg GmbH, Marburg, Germany). The abbreviated Modification of Diet in Renal Disease Study Group equation was used to estimate glomerular filtration rate (GFR) (ml/min/1.73 m^2).[16] In addition, admission blood analyses included hemoglobin and white blood cell count, as well as troponin I (TnI), B-type natriuretic peptide (BNP), and C-reactive protein (CRP). AH was defined as a venous plasma glucose level >11.0 mmol/l (or >200 mg/dl) on admission.[17] DM was considered to be present if a patient had been informed of this diagnosis and/or was on prescribed treatment for diabetes. Patients were stratified into four groups, based on their history of DM and the presence of AH (i.e. diabetics with or without AH, non-diabetics with AH, and normoglycemic patients).

Patients with acute STEMI were normally treated with primary PCI (n=170). However, as the PCI facility was not available 24 hours a day during the first year of the study, fibrinolytic therapy was alternatively applied in a number of STEMI patients (n=116), unless contraindicated (n=15). In those patients who received fibrinolysis coronary angiography was performed 3-24 hours after successful fibrinolytic therapy, or immediately in cases of suspected fibrinolysis failure 60 min after its administration (n=10).[18] Accordingly, the extent of the coronary artery disease (as expressed by the number of vessels with an obstruction >70% of the lumen diameter) as well as any left anterior descending artery involvement were recorded. It is important to note that primary PCI in patients with STEMI and multivessel disease was limited to the culprit vessel, according to the guidelines.[15]

Left ventricular ejection fraction was assessed on admission by two-dimensional echocardiography, applying the modified Simpson's rule, using a Hewlett Packard 5500 Sonos Ultrasound Machine with a multifrequency transducer (2-5 MHz).

After the patients' discharge, information concerning the incidence of the pre-specified endpoint was obtained on an outpatient basis or by interview. Death verification was obtained by reviewing the relevant certificates, hospital records, or after contact with the familial environment and/or the attending physicians. The composite of all-cause mortality, nonfatal MI and stroke after one year of follow up was selected as the endpoint of this investigation.

Statistical analysis

Continuous variables are presented as either means (±SD) or medians (with interquartile ranges), and categorical variables as numbers and percentages. Natural logarithmic transformation was used for CRP, BNP and TnI analyses because of their skewed distribution. Baseline characteristics of the groups (patients with and without DM and AH) were compared using one-way ANOVA with Bonferroni's post test for continuous variables and the χ^2 statistic for categorical variables. A logistic regression analysis was performed to determine the independent predictors of AH in non-diabetic patients.

Event-free survival was estimated by the Kaplan–Meier method, and curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazard analyses were used to assess the relationship between the study variables and the composite endpoint. Only variables with $p<0.2$ in the univariate logistic regression analyses were used in the multiple logistic regression analysis. Differences were considered statistically significant at the 2-sided $p<0.05$ level. All statistical analyses were performed using the SPSS version 18.0 statistical software (SPSS Inc, Texas, IL, USA).

Results

After a 1-year follow-up period, complete data were available for 301 patients (93.2%), who were included in all analyses, while the remaining 22 patients (6.8%) were lost to follow up. No difference was observed between patients lost to follow up and the final study population as regards demographics and all baseline clinical and laboratory characteristics examined, thus excluding any possible bias in analysis. DM without AH was present in 31 patients (10.3%) while 35 (11.6%) were diabetics with AH. AH was present in 32 non-diabetic patients (10.6%) (Figure 1). Left anterior descending involvement was detected in 74.8% of the STEMI patients, whereas multivessel coronary artery disease was observed in 43.1%.

The baseline clinical and demographic characteristics and the laboratory findings of the study population according to DM status and the presence of AH are presented in Tables 1 and 2.

Non-diabetic patients with AH were treated with primary PCI less frequently compared to non-diabetics with AH (by 18.3%, p=0.048) and had significantly lower diastolic blood pressure at admission (by 8.3 mmHg, p=0.012), lower ejection fraction (by 5.5%, p=0.018), and hemoglobin levels (by 1.4 g/dl, p<0.001), as well as higher peak levels of TnI (by 56.5 ng/ml, p=0.048) and plasma glucose (by 154.5 mg/dl, p<0.001). The prevalence of hypertension was significantly lower in non-diabetic patients with AH compared to diabetics (either with AH or not), while glucose levels were higher in diabetics with AH compared to non-diabetics with AH (by 44.7 mg/dl, p=0.003).

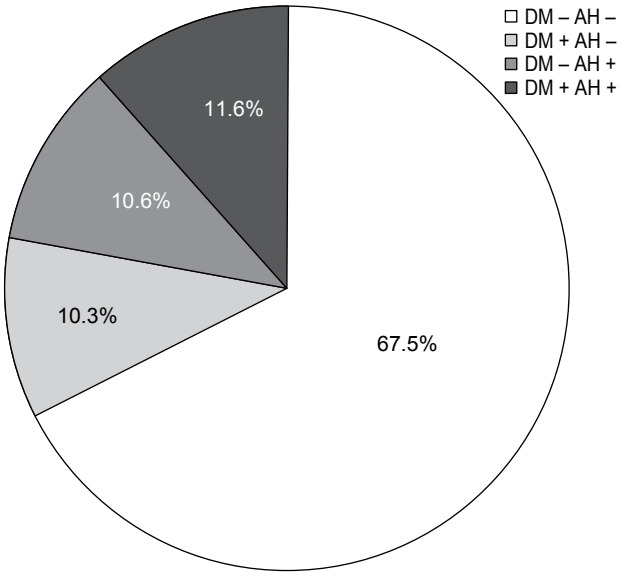

Figure 1. Patients' distribution according to admission hyperglycemia (AH) and diabetes mellitus (DM).

Compared to those with neither DM nor AH, patients with DM and AH were older (by 9 years, p<0.001), were treated with primary PCI less frequently (by 22.1%, p=0.014), exhibited a higher prevalence of left anterior descending involvement (by 18.2%, p=0.025), and had higher levels of plasma glucose (by 198.2 mg/dl, p<0.001), admission BNP (by 146.5 pg/ml, p=0.01) and admission TnI (by 4.03 ng/ml, p=0.011). No difference was observed between STEMI subgroups regarding the presence of multivessel disease and, accordingly, incomplete revascularization (p=NS for all).

The incidence of the composite endpoint during 1-year follow-up was 19.6% (35 all cause deaths, 21 non fatal MIs and 3 strokes). Non-diabetic patients with AH exhibited a significantly higher incidence of the composite endpoint compared to those with neither DM nor AH (50% vs. 15.3%, log rank p<0.001) and diabetics with and without AH (50% vs. 17.2%, log rank p=0.019 and 50% vs. 19.3%, log rank p=0.027, respectively), whereas no difference was detected between other study sub-groups (p=NS).

Table 1. Baseline clinical and demographic characteristics according to hyperglycemia and DM status.

Characteristics	Patients with DM (-) AH (-) (n=203)	Patients with DM (+) AH (-) (n=31)	Patients with DM (-) AH (+) (n=32)	Patients with DM (+) AH (+) (n=35)	p
Age, y	58.3 ± 12†	65.4 ± 10*	64.0 ± 11	67.3 ± 12*	<0.001
Males (%)	86.2	93.5	71.9	82.9	0.091
Hypertension (%)	49.8	77.4*‡	46.9†	80*‡	<0.001
Dyslipidemia (%)	59.1	71	53.1	65.7	0.438
Smokers (%)	69	58.1	46.9*	62.9	0.081
Family history of CAD	26.6	22.6	21.9	20	0.799
LAD involvement (%)	70.4	80.6	81.3	88.6*	0.078
Complete revascularization (%)	58.3	58.1	51.6	55.9	0.913
Primary PCI (%)	62.1	51.6	43.8*	40*	0.031
Systolic BP (mmHg)	133.1 ± 26	136.6 ± 29	122.0 ± 35	132.6 ± 37	0.186
Diastolic BP (mmHg)	78 ± 13	77.6 ± 12	69.7 ± 17*	74.7 ± 16	0.015
Ejection fraction (%)	42.4 ± 9	42.1 ± 10	36.9 ± 11*	38.6 ± 11	0.007

DM – diabetes mellitus; AH – admission hyperglycemia; CAD – coronary artery disease; LAD – left anterior descending artery; BP – blood pressure. * p<0.05 vs. DM (-) AH (-); † p<0.05 vs. DM (+) AH (-); ‡ p<0.05 vs. DM (-) AH (+).

Table 2. Baseline laboratory characteristics according to hyperglycemia and DM status.

Characteristics	Patients with DM (-) AH (-) (n=203)	Patients with DM (+) AH (-) (n=31)	Patients with DM (-) AH (+) (n=32)	Patients with DM (+) AH (+) (n=35)	p
Plasma glucose (mg/dl)	125.8 ± 27‡	147.3 ± 34‡	279.3 ± 89*†‡	324 ± 101*†	<0.001
Admission Cr (mg/dl)	1.08 ± 0.32	1.20 ± 0.36	1.11 ± 0.23	1.16 ± 0.28	0.125
GFR	81.7 ± 22	71.4 ± 24	74.4 ± 17	71.2 ± 19	0.007
Total cholesterol (mg/dl)	211.3 ± 52†	176.9 ± 37*	192.5 ± 53	203.3 ± 49	0.002
HDL cholesterol (mg/dl)	39.5 ± 10	35.1 ± 8	38.1 ± 10	36.2 ± 8	0.050
LDL cholesterol (mg/dl)	143 ± 45†	109.5 ± 31*	124 ± 48	143 ± 44†	<0.001
Triglycerides (mg/dl)	140 ± 86	153 ± 89	134 ± 90	140 ± 89	0.837
Hemoglobin (g/dl)	14.1 ± 1.6‡	13.5 ± 1.4	12.7 ± 1.8*	13.7 ± 2	<0.001
White blood cell count	11885 ± 3735	11869 ± 4182	12615 ± 3187	13472 ± 4464	0.124
CRP	15.3 (6.3-61.2)	11.6 (3.1-24.9)	26.5 (8.3-97.1)	22.8 (8.7-70.7)	0.254
BNP	90.5 (36.3-267)	136 (46-376)	161.5 (41-365)	237 (102-605)*	0.012
Admission TnI	0.47 (0.03-9.19)	0.48 (0.04-6.89)	0.42 (0.06-5.4)	4.5 (0.8-15.5)*	0.019
Peak TnI	38.3 (18-89.2)‡	39.6 (14.2-120)	94.8 (31-198)*	34 (16.3-110)	0.079

DM – diabetes mellitus; AH – admission hyperglycemia; GFR – glomerular filtration rate; Cr – creatinine; HDL & LDL – high and low density lipoprotein; CRP – C-reactive protein, BNP – brain natriuretic peptide; TnI – troponin. * p<0.05 vs. DM (-) AH (-); † p<0.05 vs. DM (+) AH (-); ‡ p<0.05 vs. DM (-) AH (+).

Univariate Cox regression analysis revealed that age (hazard ratio, HR 1.053, p<0.001), female gender (HR 2.174, p=0.012), left anterior descending artery involvement (HR 6.155, p=0.002), multivessel disease (HR 2.89, p<0.001), treatment with primary PCI (HR 0.422, p=0.003), ejection fraction (HR 0.923, p<0.001), admission diastolic blood pressure (HR 0.979, p=0.039), GFR (HR 0.988, p=0.039), BNP (HR 2.662, p<0.001), peak TnI levels (1.873, p=0.018), and AH (HR 3.597, p<0.001) were associated with the incidence of the composite endpoint. Multivariate Cox regression analysis revealed that AH in the absence of known DM (HR 2.207, p=0.043) was an adverse independent predictor of the composite endpoint, while ejection fraction (HR 0.946, p=0.007) and treatment with primary PCI (HR=0.488, p=0.041) turned out to have an independent protective role regarding the composite endpoint (Table 3). Life–table analysis of the composite endpoint according to the presence of AH and DM after adjustment for age, ejection fraction and application of primary PCI is plotted in Figure 2.

Discussion

This was a prospective single-centre study in which the impact of AH on 1-year outcomes in diabetic

Table 3. Predictors of the composite endpoint by logistic regression analysis.

	Univariate			Multivariate		
	HR	(95% CI)	p	HR	(95% CI)	p
Age, years	1.053	(1.029–1.077)	<0.001	1.029	(0.999–1.060)	0.061
Female gender	2.174	(1.182–3.996)	0.012	1.202	(0.564–2.563)	0.634
Hypertension	1.098	(0.638–1.889)	0.736			
Diabetes mellitus	0.973	(0.512–1.848)	0.993			
Dyslipidemia	0.810	(0.474–1.386)	0.443			
Smoking	0.917	(0.528–1.593)	0.758			
AH	3.597	(1.921–6.737)	<0.001	2.207	(1.027–4.743)	0.043*
LAD involvement	6.155	(1.921–19.722)	0.002	3.640	(0.84–15.681)	0.083
Incomplete revascularization	2.890	(1.612–5.181)	<0.001	1.65	(0.874–3.115)	0.122
Primary PCI	0.422	(0.240–0.742)	0.003	0.488	(0.245–0.970)	0.041*
Ejection fraction (%)	0.923	(0.898–0.948)	<0.001	0.946	(0.908–0.985)	0.007*
Systolic BP (mmHg)	0.995	(0.986–1.005)	0.351			
Diastolic BP (mmHg)	0.979	(0.960–0.999)	0.039	0.992	(0.972–1.012)	0.416
Adm. BNP (lg10)	2.662	(1.706–4.152)	<0.001	1.221	(0.677–2.201)	0.507
Adm. troponin I (lg10)	1.172	(0.968–1.419)	0.103			0.929
Peak troponin I (lg10)	1.873	(1.113–3.152)	0.018	1.505	(0.856–2.647)	0.155
Admission CRP (lg10)	1.507	(0.982–2.311)	0.060	1.005	(0.631–1.600)	0.984
White blood cell count (Kl)	1.049	(0.985–1.117)	0.137	1.025	(0.945–1.112)	0.552
Hemoglobin (g/dl)	0.896	(0.773–1.037)	0.142			0.333
GFR (ml/min/1.73 m^2)	0.988	(0.976–0.999)	0.039	1.002	(0.988–1.016)	0.751

AH – admission hyperglycemia; LAD – left anterior descending; BP – blood pressure; BNP – B type natriuretic peptide; CRP – C-reactive protein; GFR – glomerular filtration rate. *statistically significant predictors.

and non-diabetic patients with acute STEMI was assessed. It is interesting (and rather unexpected) that, during a 1-year follow-up, non-diabetic patients with AH (i.e. plasma glucose levels ≥11 mmol/dl) exhibited a significantly higher incidence of the composite endpoint (50%) compared to those with DM (with or without AH). Importantly, AH along with other well-established prognostic factors, such as low ejection fraction and treatment with primary PCI rather than fibrinolysis, or no reperfusion, were independent predictors of the composite endpoint, while the presence of DM was not. The inclusion of all consecutive unselected STEMI patients strengthens our results, since this study reflects "real world" patient care.

Previous studies have shown that AH affects mortality in patients with AMI.[3,10] In a systematic review performed by Capes, it was reported that the prevalence of stress hyperglycemia in patients without DM ranged from 5% to 71%. The overall pooled prevalence was 13.7% when patients with AMI were considered. However, we should take into consideration that the AH definition varied from 6.1 to 10 mmol/L in the assessed studies.[3] In the present study, AH was defined as admission plasma glucose ≥11 mmol/dl, according to the ADA recommendations for DM diagnosis, although this criterion cannot ascertain diabetes in the setting of AMI.[17]

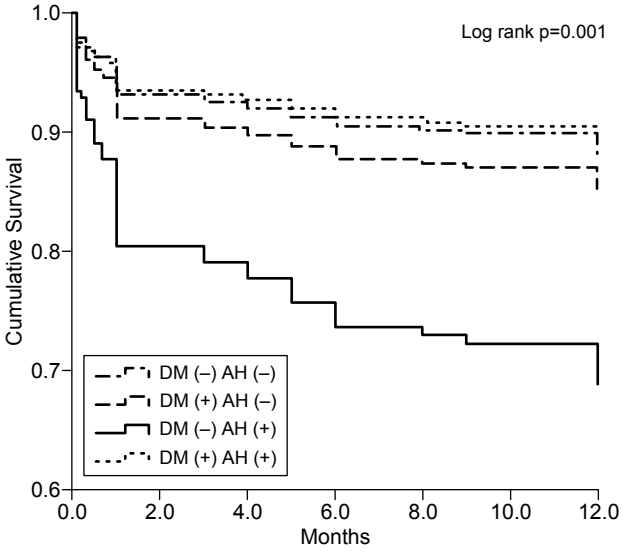

Figure 2. Life table analysis of the composite endpoint based on the presence of admission hyperglycemia (AH) and diabetes mellitus (DM) after adjustment for age, ejection fraction, and treatment with primary percutaneous coronary intervention.

Regarding those studies that dealt with AH in AMI patients and had a long follow up, when AH was defined as a glucose level >7.7 mmol/l, 1-year mortality risk in non-diabetics was similar to that of patients with DM, even when the risk score and use of guide-

lines-recommended treatment were controlled for.[7] Notably, non-diabetic AMI patients with hyperglycemia (glucose level >11 mmol/l) had the worst outcomes in a 6-month follow-up period, even when compared to diabetic patients with AH.[13] In line with the above findings, in this investigation we highlighted the adverse prognostic impact of AH in non-diabetic STEMI patients compared not only to those without AH, but particularly to those with DM and AH. In the absence of diabetes, AH turned out to be an independent predictor of the composite endpoint, even after adjustment for well established confounders, such as the severity and extension of underlying coronary artery disease, use of fibrinolysis (or no reperfusion) instead of primary PCI, as well as neurohormonal and inflammatory activation. Overall, these findings are in accordance with the observation that the relation between admission glucose and in-hospital mortality differs between non-diabetic and diabetic patients.[11]

Several underlying mechanisms have been proposed to explain the association between AH and adverse prognosis in non-diabetic STEMI patients. It has been suggested that non-diabetic patients with AH may have longstanding undiagnosed and untreated DM and consequently run a higher risk of cardiovascular disease than normoglycemic patients.[19] However, acute phase hyperglycemia may result not only from unrecognized diabetes. Excessive secretion of catecholamines during the first hours of an acute infarction augments hepatic glycogenolysis and leads to partial inhibition of the pancreatic β-cell release of insulin, with increased cortisol and glucagon levels, leading to impaired glucose tolerance and elevated glucose levels.[20]

Regardless of the mechanism of AH in acute myocardial infarction, experimental studies have shown that the acute glucose fluctuations observed in non-diabetics with AH increase oxidative stress and inactivate both nitric oxide and prostacyclin, which are potent vasodilators and anti-aggregants.[21] Consequently, AH aggravates platelet-dependent thrombosis, activates the inflammatory immune process, attenuates endothelium-dependent vasodilation, and reduces collateral blood flow by adversely affecting nitric oxide availability.[22-26] These unfavorable changes in microvascular function may be responsible for the higher incidence of the no-reflow phenomenon in AH patients with successful reperfusion, and consequently for the greater infarct size and more severe left ventricular dysfunction.[8,27-29] In accordance with these plausible underlying mechanisms that link AH to a worse prognosis, our data reveal an increase in cardiac necrosis markers (peak TnI) and a decrease in left ventricular ejection fraction in non-diabetic patients with AH compared to those without AH. Besides the above indirect association of AH with cardiac damage, it has also been demonstrated that AH increases interstitial fibrosis and myocyte apoptosis, promoting left ventricular remodeling.[30] Furthermore, hyperglycemic STEMI patients without known diabetes are much less likely to be treated with insulin than those with diabetes, even when glucose levels are markedly elevated. Given the possible beneficial effects of insulin-mediated normoglycemia in a setting of myocardial ischemia, this therapeutic difference may account in part for the disparity in outcomes.[10]

Study limitations

Measurement of glycated hemoglobin levels was not included in our pre-specified protocol. Accordingly, some diabetic patients may have been missed. However, the measurement of glycated hemoglobin is not universally accepted as a marker for the diagnosis of DM. Moreover, for all patients categorized as non-diabetics with AH, recent blood tests (within the previous 6 months) disclosing normal glycose levels were available. We also acknowledge that 6.8% of our study population was lost to follow up, although no difference in baseline characteristics was observed between those patients and the final study population. As this was a prospective study, the number of patients in each subgroup was rather small, and larger studies are certainly needed to confirm our findings. Nevertheless, even with this sample size we achieved statistically significant results. Finally, since in the present study only single-centre data were used, this could potentially have lead to selection bias. However, the inclusion of all consecutive unselected STEMI patients strengthens our results, since our study reflects "real world" patient care.

Conclusions

In the present investigation, conducted in a clinical practice setting, we have highlighted the unfavorable independent prognostic role of AH in non-diabetic patients with STEMI, regardless of AMI severity, extension, and treatment. The acute rather than the chronic pre-existing glycometabolic state seems to account for the prognosis after AMI, since AH has an unfavorable impact only in non-diabetic patients. Moreover, our findings gain particular importance as they were derived from an unselected STEMI population treated according to current clinical practice, taking into account in the analysis most of the estab-

lished clinical and laboratory AMI-related prognostic parameters. High admission glucose serum levels (>11 mmol/l or 200 mg/dl) in non-diabetic STEMI patients should not be underscored and simply interpreted as a non-specific stress status. In contrast, these patients should be closely followed up as half of them will exhibit a late major adverse event.

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