The prognostic impact of glycated hemoglobin in diabetic ST-elevation myocardial infarction

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The prognostic impact of glycated hemoglobin in diabetic ST-elevation myocardial infarction☆

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Despite widespread recognition of the importance of long-term glycemic control, it has been recently reported that only a low percentage (about 1/2) of patients with diabetes (DM) had their glycated hemoglobin (HbA1c) values known or measured when hospitalized for acute myocardial infarction (AMI) [1].

Data on the prognostic role of HbA1c in AMI patients are still controversial [1–6] since studies mainly differ for patients' selection criteria, therapy (thrombolysis vs mechanical revascularization) and number consistency.

We aimed at assessing the prognostic role of HbA1c for mortality at short and long terms in 195 consecutive diabetic with ST-elevation myocardial infarction (STEMI), all submitted to mechanical revascularization and consecutively admitted to our Intensive Cardiac Care Unit (ICCU) from 1st January 2008 to 30th June 2010 [7–12].

On ICCU admission, after PCI, in a fasting blood sample the following parameters were measured: glucose (mg/dl), insulin values (UI/l), C-peptide (ng/ml), Hb A1c(%) troponin I (ng/ml), insulin (mU/l), uric acid (mg/dl), C-reactive protein (mg/dl) (normal values<9), alanine amino-transferase (ALT, UI/l), aspartate amino transferase (AST, UI/l) [13], gamma-glutamyl transferase (GGT, UI/l) [14] NT-pro Brain Natriuretic Peptide (NT-pro BNP) (pg/ml) [11] total cholesterol (mg/dl), triglycerides (mg/dl), HDL, LDL, and fibrinogen (mg/dl). Creatinine (mg/dl) was also measured in order to calculate glomerular filtration rate (eGFR, ml/min/1.73 m^2) [15]. Nadir eGFR was also recorded. Glucose, Tn I were measured three times a day during ICCU stay and peak values for each variable were considered. Acute insulin resistance was measured by means of the Homeostatic Model Assessment (HOMA) index, as previously described [10,16–18].

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained in all patients before enrollment.

Data are reported as frequencies (percentages) and medians (95% Confidence Interval — CI) and analyzed by means of χ^2 (or Fisher's exact text, when predicted counts in almost one cell were less than 5) for categorical variables and Mann–Whitney *U*-test for continuous variables (that, at Kolmogorov–Smirnov normality test, resulted almost all non-normally distributed), respectively. Multivariable logistic regression analyses were carried out considering as outcome intra-ICCU mortality. Models' calibration was assessed by means of Hosmer–Lemeshow goodness-of-fit tests as well as plotting the area under the Receiver Operating Characteristic (ROC) curve (AUC); Nagelkerke R squares are also reported. Long time survival was explored, after proportionality of risk assessment, with Cox regression analysis, both with HbA1c as the sole candidate variable and in a multivariable manner. In all multivariable analyses candidate variables were chosen as those considered clinically relevant or that showed a univariate relationship with outcome; nonsignificant ones were dropped by means of backward selection. HbA1c was forced into the analyses. (SPSS 13.0 statistical package, SPSS Inc, Chicago, IL). A p value<0.05 was considered statistically significant.

Males were prevalent (67.2%) and hypertension was detectable in the 75.4%. Anterior myocardial infarction was the most frequently observed (53.8%). In-hospital mortality rate was 3.1%.

Hb A1c≥6.5 was detectable in the 55.9% (Table 1). Patients with Hb A1c≥6.5 showed higher values of admission and peak glucose ($p<0.001$ and $p<0.001$, respectively), of insulin ($p<0.001$) and incidence of HOMA positivity ($p<0.001$). Higher values of ALT, AST ($p<0.001$ and $p=0.05$, respectively) and ESR ($p=0.049$) were observed in patients with Hb A1c≥6.5. No difference was observed in in-hospital mortality rate between the two subgroups.

At multivariable analysis eGFR was independently associated with in-hospital death [eGFR(1 ml/min/1.73 m^2 increase): O.R. 1.96: 95%CI 0.92 to 0.99, $p<0.014$]. HbA1c≥6.5% (O.R. 2.28: 95%CI 0.31 to 11.53, $p=0.495$). Hosmer and Lemeshow test $\chi^2=2.92$, $p=0.940$; Nagelkerke R square = 0.22; area under the ROC curve 0.88 (95%CI 0.80 to 0.96, $p=0.002$).

At Cox regression analysis, the following variables were independently associated with long-term mortality: Age (1 year step) (H.R. 1.08: 95%CI 1.05 to 1.11, $p<0.001$); LVEF at discharge (1% step)

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Table 1
Comparison between STEMI patients with HbA1c ≥ 6.5 and those without.

	Hb A1c < 6.5 n = 86 (44.1%)	Hb A1c ≥ 6.5 n = 109 (55.9%)	p value
Males/Females	64/22 (74.4/25.6%)	67/42 (61.5/38.5%)	0.056
Age (years), mean ± SD	71.4 ± 11.4	69.1 ± 10.1	0.149
BMI (kg/m^2), mean ± SD	26.1 ± 3.8	26.6 ± 4.2	0.334
Estimated GFR (ml/min/1.73 m^2), mean ± SD	78.0 ± 38.0	81.3 ± 40.6	0.564
Estimated GFR at nadir (ml/min/1.73 m^2), mean ± SD	63.0 ± 29.7	66.7 ± 26.5	0.362
AMI anterior, n (%)	40 (46.5%)	65 (59.6%)	0.116
Killip class n (%)			0.694
I–II	74 (85.7%)	91 (84.3%)	
III–IV	12 (14.3%)	18 (15.8%)	
LVEF (%), mean ± SD	42.5 ± 11.5	41.6 ± 8.9	0.528
PCI failure, n (%)	8 (9.5%)	5 (4.6%)	0.175
Admission glucose (mg/dl), mean ± SD	158 ± 61	227 ± 76	<0.001
Peak glucose (g/l), mean ± SD	157 ± 58	252 ± 71	<0.001
Insulinemia (mU/L), median (IQR)	8.0 (5.0 to 16.3)	19.7 (8.3 to 40.3)	<0.001
HOMA index positivity, n (%)	8 (11.4%)	40/(50.0%)	<0.001
AST, median (IQR)	41 (26 to 68)	84 (38 to 166)	<0.001
ALT, median (IQR)	46 (30 to 138)	39 (25 to 76)	0.051
GGT, median (IQR)	28 (20 to 44)	29 (19 to 45)	0.550
Peak Tn I (ng/ml), median (IQR)	87.4 (42.1 to 239.7)	110.0 (49.1 to 241.0)	0.403
NT-proBNP (pg/ml), median (IQR)	2210 (798 to 7369)	1676 (671 to 5712)	0.443
Uric acid (mg/dl), mean ± SD	5.9 ± 1.8	5.7 ± 1.8	0.293
ESR (mm/h), median (IQR)	24 (12 to 39)	31 (15 to 51)	0.049
Positive CRP, n (%)	50 (60.2%)	47 (46.5%)	0.064
Leucocytes (*10^3/μl), mean ± SD	11.4 ± 4.3	12.0 ± 3.7	0.289
Fibrinogen (mg/dl), mean ± SD	454 ± 125	453 ± 114	0.953
Total cholesterol (mg/dl), mean ± SD	171 ± 43	178 ± 41	0.390
HDL cholesterol (mg/dl), mean ± SD	39 ± 9	39 ± 10	0.944
LDL cholesterol (mg/dl), mean ± SD	108 ± 36	111 ± 31	0.513
Triglycerides (mg/dl), mean ± SD	116 ± 57	122 ± 61	0.533
In-hospital mortality, n (%)	4 (4.7%)	2 (1.8%)	0.408*

BMI: body mass index; AMI: acute myocardial infarction; EF: ejection fraction; PCI: percutaneous coronary intervention; GFR: glomerular filtration rate; HOMA: homeostatic model assessment; AST: aspartate transferase; ALT: alanine transferase; GGT: gamma glutamyl transferase.

(H.R. 0.94 95%CI 0.91 to 0.98, p = 0.002). HbA1c ≥ 6.5% (H.R. 1.79 95%CI 0.88 to 3.64, p = 0.107).

The main finding of our investigation performed in consecutive diabetic STEMI patients submitted to mechanical revascularization, is that HbA1c values are not related to mortality, both at short and long term.

Data on this topic are so far scarce and controversial.

In AMI patients with diabetes, the two Diabetes Insulin Glucose in Acute Myocardial Infarction studies both showed that increasing HbA1c levels increased mortality in diabetic patients with MI [2,3]. Conversely [5], in OPTIMAAL trial (including patients with myocardial infarction complicated by heart failure) the level of HbA1c had no impact on mortality among the patients with well-known diabetes. In consecutive diabetic patients undergoing PCI [19], HbA1C was not a predictor of cardiac events at one-year follow-up.

In our investigation, which includes the largest series of consecutive STEMI patients with known diabetes submitted to mechanical revascularization, we observed that HbA1c was not associated with mortality both at short and at long term. Nevertheless, higher HbA1c values (which are detectable in about half of the entire population) helps in identifying a subset of patients who, in the early phase of STEMI, show an abnormal glucose response to stress as indicated by higher values of glucose, a worse glycemic control during ICCU stay (as inferred by peak glycemia) and a higher incidence of acute insulin resistance (as indicated by HOMA index). This subset of patients may deserve a more aggressive treatment for glucose management. Previous studies performed by others [20] and us [7,8,11,16,21] showed that admission glycemia and peak glycemia, are independent predictors for in-hospital mortality in STEMI patients.

According to our results, in consecutive diabetic STEMI patients HbA1c values helps in identifying patients who, in the early phase, develop an abnormal glucose response to acute ischemia as indicated by higher admission and worse in-hospital glucose control (as inferred by peak glycemia), though it is not associated with increased mortality at short and long term. Further studies are needed to confirm the role of glycated hemoglobin in the risk stratification of STEMI patients both at short and long terms.

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Takotsubo syndrome associated with seizures: The visible part of the iceberg?

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We thank Stollberger and colleagues for their interest in our paper. Takotsubo syndrome associated with seizure (TSAS) is now a well established entity, and its relation with sudden unexpected deaths in epilepsy seems very likely. Stollberger's case control study adds interesting epidemiological information on the subject.

According to this study, patients with TSAS are younger, more frequently males and have a higher rate of cardiogenic shock than in Takotsubo syndrome (TS) associated with other triggers. More important and more prolonged catecholamine surge release during seizure may explain these findings. However, in these cases, TS is often diagnosed because of complications unrelated to epilepsy such as heart failure, hypotension… which leads to cardiological investigations. Therefore these reports probably represent only the most severe cases, and we can easily imagine that numerous "mild" TSAS are not diagnosed partly because chest pain is rarely reported due to impaired consciousness, and because ECG is not systematically performed in these situations. Furthermore, epileptic patients, especially those suffering from recurrent seizures, may be discharged without any complication since TS has favourable outcome in most instances.

Stöllberger et al. [1] also pointed out the higher rate of recurrence in patients suffering from TSAS. Epileptic patients with a history of TS may be at higher risk of sudden death or other serious complications. The question of a specific preventive treatment in this population is of paramount importance.

Larger scale prospective studies would reveal true incidence of TSAS. They would also specify patient's profile, identify those at high risk of TSAS, and those who present high risk of recurrence.

On one hand, as reminded by Stollberger et al., localization of the epileptic focus may matter. Precise electroencephalogram description, morphological and functional MRI would be therefore of great relevance. On the other hand, TSAS should be diagnosed cautiously. A patent acute or chronic cardiac disease should not be attributed to TS. For instance, some acute coronary syndromes may induce ventricular arrhythmia with subsequent prolonged syncope and jerky movements.

For all the above-mentioned reasons, studies must be conducted by multidisciplinary teams of cardiologist and neurologist. The expertise of both specialties is required to go further in the understanding of this disease that could affect the management of seizures in general.

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