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Original Citation:

The prognostic impact of glycated hemoglobin in diabetic ST-elevation myocardial infarction / C.Lazzeri; S.Valente; M.Chiostrì; C.Picariello; P.Attanà; G.F.Gensini. - In: INTERNATIONAL JOURNAL OF CARDIOLOGY. - ISSN 0167-5273. - STAMPA. - 151:(2011), pp. 250-252.

Availability:

The webpage <https://hdl.handle.net/2158/592650> of the repository was last updated on

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References

- [1] Lavie P, Lavie L. Cardiovascular morbidity and mortality in obstructive sleep apnea. *Curr Pharm Des* 2008;14:3466–73.
- [2] Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale Chest 1993;103:30–6.
- [3] Chica-Urzola HL, Escobar-Córdoba F, Eslava-Schmalbach J. Validating the Epworth sleepiness scale. *Rev Salud Publica* 2007;9:558–67.
- [4] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of sleep medicine task force, 22. *Sleep*; 1999. p. 667–89.

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doi:10.1016/j.ijcard.2011.06.076

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

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ARTICLE INFO

Article history:

Received 12 June 2011
Accepted 14 June 2011
Available online 1 July 2011

Keywords:

STEMI
Diabetes
Prognosis
Hyperglycemia
Insulin resistance

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), HbA1c(%) 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 m²) [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 test, 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%.

HbA1c ≥ 6.5 was detectable in the 55.9% (Table 1). Patients with HbA1c ≥ 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 HbA1c ≥ 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 m² 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 χ^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)

[☆] No conflict of interest.

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

	Hb A1c<6.5 n = 86 (44.1%)	Hb A1c \geq 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 \pm SD	71.4 \pm 11.4	69.1 \pm 10.1	0.149
BMI (kg/m ²), mean \pm SD	26.1 \pm 3.8	26.6 \pm 4.2	0.334
Estimated GFR (ml/min/1.73 m ²), mean \pm SD	78.0 \pm 38.0	81.3 \pm 40.6	0.564
Estimated GFR at nadir (ml/min/1.73 m ²), mean \pm SD	63.0 \pm 29.7	66.7 \pm 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 \pm SD	42.5 \pm 11.5	41.6 \pm 8.9	0.528
PCI failure, n (%)	8 (9.5%)	5 (4.6%)	0.175
Admission glucose (mg/dl), mean \pm SD	158 \pm 61	227 \pm 76	<0.001
Peak glucose (g/l), mean \pm SD	157 \pm 58	252 \pm 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 \pm SD	5.9 \pm 1.8	5.7 \pm 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 ($\times 10^3/\mu$ l), mean \pm SD	11.4 \pm 4.3	12.0 \pm 3.7	0.289
Fibrinogen (mg/dl), mean \pm SD	454 \pm 125	453 \pm 114	0.953
Total cholesterol (mg/dl), mean \pm SD	171 \pm 43	178 \pm 41	0.390
HDL cholesterol (mg/dl), mean \pm SD	39 \pm 9	39 \pm 10	0.944
LDL cholesterol (mg/dl), mean \pm SD	108 \pm 36	111 \pm 31	0.513
Triglycerides (mg/dl), mean \pm SD	116 \pm 57	122 \pm 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 \geq 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.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

References

- [1] Stolker JM, Sun D, Conaway DG, et al. Importance of measuring glycosylated hemoglobin in patients with myocardial infarction and known diabetes mellitus. *Am J Cardiol* 2010;105(8):1090–4.
- [2] Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650–61.
- [3] Malmberg K, Norhammar A, Wedel H, et al. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;99:2626–32.
- [4] Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;151:91.
- [5] Gustafsson I, Kistorp CN, James MK, Faber JO, Dickstein K, Hildebrandt PR. OPTIMAAL Study Group. Unrecognized glycometabolic disturbance as measured by hemoglobin A1c is associated with a poor outcome after acute myocardial infarction. *Am Heart J* 2007;154:47026.
- [6] Cakmak M, Cakmak N, Cetemen S, et al. The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. *Can J Cardiol* 2008;24(5):375–8.
- [7] Lazzeri C, Chiostrì M, Sori A, Valente S, Gensini GF. Postprocedural hyperglycemia in ST elevation myocardial infarction submitted to percutaneous coronary intervention: a prognostic indicator and a marker of metabolic derangement. *J Cardiovasc Med (Hagerstown)* 2010;11(1):7–13.
- [8] Lazzeri C, Valente S, Chiostrì M, Picariello C, Gensini GF. Predictors of the early outcome in elderly patients with ST elevation myocardial infarction treated with primary angioplasty: a single center experience. *Intern Emerg Med* 2011 Feb;6(1):41–6.
- [9] Valente S, Lazzeri C, Chiostrì M, Sori A, Giglioli C, Gensini GF. Prior and new onset anemia in ST-elevation myocardial infarction: a different prognostic role? *Intern Emerg Med* 2010 Dec 8.
- [10] Lazzeri C, Sori A, Chiostrì M, Picariello C, Gensini GF, Valente S. Prognostic role of insulin resistance as assessed by homeostatic model assessment index in the acute phase of myocardial infarction in nondiabetic patients submitted to percutaneous coronary intervention. *Eur J Anaesthesiol* 2009;26(10):856–62.
- [11] Valente S, Lazzeri C, Chiostrì M, et al. NT-proBNP on admission for early risk stratification in STEMI patients submitted to PCI. Relation with extension of STEMI and inflammatory markers. *Int J Cardiol* 2009;132(1):84–9.
- [12] Valente S, Lazzeri C, Saletti E, Chiostrì M, Gensini GF. Primary percutaneous coronary intervention in comatose survivors of cardiac arrest with ST-elevation acute myocardial infarction: a single-center experience in Florence. *J Cardiovasc Med (Hagerstown)* 2008;9(11):1083–7.
- [13] Lazzeri C, Valente S, Tarquini R, Chiostrì M, Picariello C, Gensini GF. Prognostic values of admission transaminases in ST-elevation myocardial infarction submitted to primary angioplasty. *Med Sci Monit* 2010;16(12):CR567–74.
- [14] Lazzeri C, Valente S, Tarquini R, Chiostrì M, Picariello C, Gensini GF. The prognostic role of gamma-glutamyltransferase activity in non-diabetic ST-elevation myocardial infarction. *Intern Emerg Med* 2011 Jun;6(3):213–9.
- [15] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604–12.
- [16] Lazzeri C, Valente S, Chiostrì M, Picariello C, Gensini GF. Acute glucose dysmetabolism in the early phase of ST-elevation myocardial infarction: the age response. *MDDiabetes Vasc Dis Res* 2010;7(2):131–7.
- [17] Balkau B, Charles M, for the European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO Consultation. *Diabet Med* 1999;16:442–3.
- [18] Lazzeri C, Valente S, Chiostrì M, Picariello C, Gensini GF. Correlates of acute insulin resistance in the early phase of non-diabetic ST-elevation myocardial infarction. *Diab Vasc Dis Res* 2011 Jan;8(1):35–42.

- [19] Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of hemoglobin A1C levels in patients with diabetes mellitus undergoing percutaneous coronary intervention with stent implantation. *Am J Cardiol* 2009;104(1):41–5.
- [20] Deedwania P, Kosiborod M, Barrett E, et al. American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the

- American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008;117(12):1610–9.
- [21] Lazzeri C, Valente S, Chiostrì M, Picariello C, Gensini GF. In-hospital peak glycemia and prognosis in STEMI patients without previously known diabetes. *Eur J Card Prevention and Rehabil* 2010;17(4):419–23.

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doi:10.1016/j.ijcard.2011.06.077

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

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ARTICLE INFO

Article history:

Received 10 June 2011

Accepted 14 June 2011

Available online 7 July 2011

Keywords:

Takotsubo cardiomyopathy

Stress cardiomyopathy

Seizure

Sudden death in epilepsy

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.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

References

- [1] Stöllberger C, Wegner C, Finsterer J. Seizure-induced Takotsubo syndrome is more frequent than reported. *Int J Cardiol* 2011;150:359–60.

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