Hyperglycemia Drives Stent Restenosis in STEMI Patients

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ST-elevation myocardial infarction (STEMI) is one of the leading causes of death and hospitalization worldwide (1). Hyperglycemia (HG) has been shown to adversely affect STEMI clinical outcomes, leading to higher mortality and severe complications (1,2).

The aim of our study was to investigate the impact of HG at hospital admission on the risk of restenosis after primary percutaneous coronary intervention (PCI) for STEMI, comparing normoglycemic subjects (NG group), patients without diabetes mellitus (DM) but with HG (HG-non-DM group), and patients with both HG and DM (HG-DM group). HG was defined by glycemia >140 mg/dL, according to the guidelines of the American Diabetes Association (3). We evaluated STEMI patients referred to the Division of Cardiology of "Antonio Cardarelli" Hospital from February 2008 to February 2016. Inclusion criteria were age >18 years and first STEMI. Exclusion criteria were left ventricular ejection fraction <25% and prior coronary artery bypass grafting. Routine blood analysis, including HbA_{1c}, was obtained at admission. The STEMI culprit lesion was identified and treated via primary PCI, crossed with an angioplasty guidewire followed by stent implantation. All patients were contacted 1 year after the procedure. The sample size was calculated via GPower software. Research was carried out according to the Declaration of Helsinki, and every patient signed an informed consent; the Institutional Review Board of the University of Campania approved the protocol.

The three groups (NG, HG-non-DM, and HG-DM) were matched using a propensity score-matching algorithm developed according to the predictive probabilities of a multivariable logistic regression model. We calculated Kaplan-Meier product limit estimates and compared curves, from admission to 365 days, using the log-rank test. Furthermore, we performed a multivariate Cox regression analysis to calculate hazard ratio, CI, and *P* value, evaluating whether age, systolic and diastolic blood pressure, heart rate, glycemia, BMI, total and LDL cholesterol, creatinine, use of statins, and HbA_{1c} could affect the risk of restenosis. Rehospitalization for restenosis was defined as readmission to the hospital for acute coronary syndrome, which was confirmed to be due to restenosis of a previously successfully treated lesion, as determined by quantitative coronary angiography (2). All calculations were computed using SPSS 26.

A total of 336 propensity score-matched patients were included in the study: 112 NG, 112 HG-non-DM, and 112 HG-DM. We used bare metal stents or 2nd-generation drug-eluting stents (DES), detecting no significant differences among our three groups in terms of the type of stent implanted (percentage of 2nd-generation DES: NG 76.8%, HG-non-DM 76%, HG-DM 77%).

At 1 year follow-up, 6.5% of NG, 14.0% of HG-non-DM, and 18.5% of HG-DM patients had been rehospitalized for restenosis; Kaplan-Meier curves ($P = 0.009$) are depicted in Fig. 1*A*.

Interestingly, the significant association between restenosis and glycemia at hospital admission in HG-non-DM patients was confirmed in a Cox proportional hazards regression model after adjusting for other potential risk factors for restenosis, including cholesterol (total and LDL), creatinine, BMI, systolic and diastolic blood pressure, heart rate, age, use of statins, and HbA_{1c} values (Fig. 1*B*).

HG triggers endothelial dysfunction, an established mechanism underlying restenosis (4), leading to vascular damage and microvascular obstruction(s), and is also known to increase oxidative stress, inflammation, and platelet aggregation (1,4). Of note, HG may also be a marker for disease severity (5). During the year following the PCI, other factors, including blood pressure control, HbA_{1c}, and lipid levels, all could have affected the risk of restenosis (6); however, in our regression analysis the association between restenosis and glycemia in HG-non-DM patients remained significant even after accounting for an expanded set of potential risk factors.

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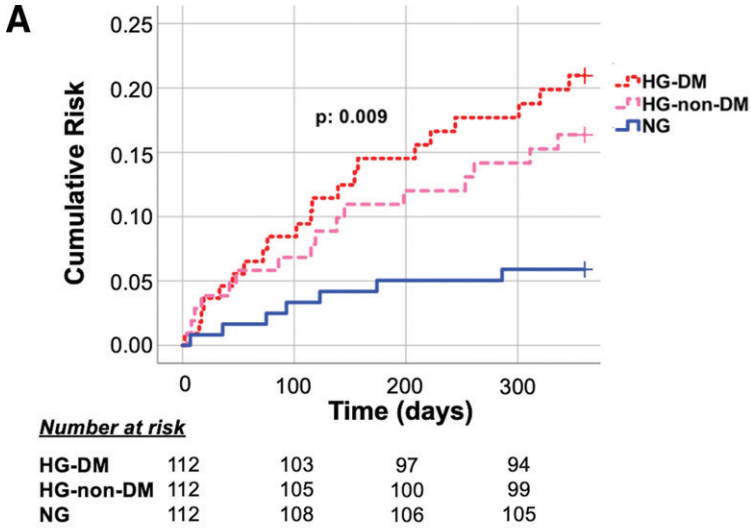

B

	HR	95% CI for HR		*p*
		Lower bound	Upper bound	
Glycemia	1.026	1.008	1.045	*0.005*
Total Cholesterol	0.973	0.951	0.996	*0.019*
LDL Cholesterol	1.089	1.049	1.111	*0.009*
Creatinine	0.924	0.838	1.071	*0.291*
BMI	0.844	0.458	1.556	*0.588*
SBP	0.983	0.946	1.022	*0.392*
DBP	0.946	0.833	1.074	*0.390*
Heart rate	0.996	0.966	1.026	*0.779*
Age	0.945	0.887	1.007	*0.079*
Statins	0.979	0.849	1.174	*0.091*
HbA1c	2.787	0.938	5.379	*0.055*

Figure 1–*A*: Kaplan-Meier curves assessing the cumulative risk of restenosis in patients with ST-elevation myocardial infarction (STEMI) from hospital admission to 365 days; patients were subdivided into three groups: normoglycemic (NG) subjects, patients without diabetes mellitus (DM) but with hyperglycemia HG (HG-non-DM), and patients with both HG and DM (HG-DM). *B*: Multivariate Cox regression analysis in STEMI HG-non-DM patients. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure.

To the best of our knowledge, the impact of HG on restenosis has not been assessed in patients without DM. The current study is the first to evaluate the effects of HG on the risk of restenosis in STEMI patients without DM, comparing the results to both HG-DM and NG subjects. Taken together, our data indicate that HG is associated with adverse outcomes in STEMI patients independent of DM.

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References

1. Zarich SW, Nesto RW. Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. Circulation 2007; 115:e436–e439

2. Marfella R, Sasso FC, Siniscalchi M, et al. Peri-procedural tight glycemic control during early percutaneous coronary intervention is associated with a lower rate of in-stent restenosis in patients with acute ST-elevation myocardial infarction. J Clin Endocrinol Metab 2012;97:2862–2871

3. American Diabetes Association. 15. Diabetes care in the hospital: *Standards of Medical Care in Diabetes–2021*. Diabetes Care 2021;44(Suppl. 1):S211–S220

4. Santulli G, Wronska A, Uryu K, et al. A selective microRNA-based strategy inhibits restenosis while preserving endothelial function. J Clin Invest 2014;124:4102–4114

5. Roberts GW, Quinn SJ, Valentine N, et al. Relative hyperglycemia, a marker of critical illness: Introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 2015;100:4490–4497

6. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. J Am Coll Cardiol 2004;43:8–14