International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The stress hyperglycemia ratio, an index of relative hyperglycemia, as a predictor of clinical outcomes after percutaneous coronary intervention☆

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ARTICLE INFO

Article history:
Received 27 January 2017
Accepted 19 February 2017
Available online xxxx

Keywords:
Coronary artery disease
Diabetes
Major adverse cardiovascular and cerebrovascular events
Percutaneous coronary intervention
Stress hyperglycemia ratio

ABSTRACT

Background: We aimed to investigate the outcome-predicting value of a novel index of stress hyperglycemia in coronary artery disease (CAD) patients who underwent percutaneous coronary intervention (PCI).
Methods: This was a retrospective observational study. Four-thousand-three-hundred-sixty-two subjects from the COACT registry were used to estimate the risk of major adverse cardiovascular and cerebrovascular events (MACCE), which are defined as composites of all-cause death, non-fatal myocardial infarction (MI) and non-fatal stroke. The stress hyperglycemia ratio (SHR) was calculated by dividing the random serum glucose at admission with the estimated average glucose derived from HbA1c.
Results: Over a median follow-up of 2.5 years, 344 (7.9%), 43 (1.0%), and 89 (2.0%) cases of death, non-fatal MI, and non-fatal stroke occurred, respectively. Compared with the subjects in the lower three quartiles of SHR, the HR (95% CI) for the highest SHR quartile (Q4) group for MACCE was 1.31 (1.05, 1.64) in the total population and 1.45 (1.02, 2.06) in the non-diabetic population after adjusting for potential covariables. The risk of MACCE in the SHR Q4 group was significantly higher in patients presenting with ST-elevation MI (STEMI), which was not the case for patients presenting with other CAD types. The prognostic impact of SHR was more prominent for the 30-day MACCE. Similar results were observed in another cohort consisting of patients who only presented with acute MI.
Conclusions: SHR is a useful predictive marker of MACCE after PCI, especially in non-diabetic patients with STEMI, which could be utilized to identify high-risk patients for adverse outcomes.

1. Introduction

The association between chronic hyperglycemia and poor outcomes in patients with diabetes has been well demonstrated. When patients suffer from an acute illness, acute hyperglycemia can be a response to physiological stress, even in the absence of preexisting diabetes. Stress hyperglycemia has also been demonstrated to be associated with a higher risk of mortality and morbidity in critically ill patients [1–5]. Recent studies have shown this correlation irrespective of the previous diabetes status, and it is sometimes even stronger in subjects without diabetes [1–3]. This finding suggests that different mechanisms affect the adverse outcomes between chronic hyperglycemia and stress hyperglycemia. However, most previous studies have relied on glucose concentrations at admission to identify the degree of stress hyperglycemia. Although participants are categorized by their past history of diabetes, the glucose concentrations at admission could result from acute physiological stress, chronic high baseline glucose levels or both [6]. This prompts a search for a more refined marker that reflects the stress hyperglycemia intensity.

Recently, a novel index of relative hyperglycemia (stress hyperglycemia ratio [SHR]) was suggested by Roberts et al. [7]. This value is defined as the admission glucose divided by the estimated average glucose calculated with the glycosylated hemoglobin (HbA1c). By adjusting the chronic

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2017.02.065
0167-5273/

glycemic status from the previous 2–3 months, the SHR could more accurately identify and quantify stress hyperglycemia. Roberts et al. showed that SHR is a better predictive marker of critical illness (in-hospital death or critical care) than the absolute hyperglycemia in hospitalized patients with any acute illness [7]. However, this result could be the combined effect of the heterogeneous population of acute-ill patients. Therefore, further studies are needed to validate this association in specific conditions.

In this study, we aimed to clarify whether the relative hyperglycemia (SHR) could predict the adverse outcomes in patients who have undergone percutaneous coronary intervention (PCI) to treat coronary artery disease (CAD) in two large cohorts. In addition, we analyzed the major adverse cardiovascular and cerebrovascular events (MACCE) according to the length of follow-up with the goal of determining the time-dependent prognostic impact of the SHR.

2. Methods

2.1. Study population

Between January 2004 and December 2009, a total of 9292 patients were enrolled in the CathOlic University of Korea percutAneous Coronary inTervention (COACT) registry from eight university-affiliated hospitals [8,9]. This large, observational registry included clinical, echocardiographic, angiographic and long-term outcome data in consecutive all-comer patients. Patients with missing laboratory data for the HbA1c ($n = 4277$), serum glucose ($n = 80$) and serum creatinine ($n = 4$) were excluded. Patients with conditions affecting the HbA1c levels were also excluded; these conditions included overt renal failure [$n = 233$] with a serum creatinine level higher than 2.0 mg/dL, receiving hemodialysis or peritoneal dialysis, kidney transplantation recipients, and anemia defined as hemoglobin <10 g/dL [$n = 171$]). Ultimately, a total of 4362 patients comprised the study population.

To verify the study results, we also performed similar analysis using data from another registry, the COnvergent REgistry of cAtholic and Chonnam University for Acute Myocardial Infarction (COREA-AMI), which was designed to evaluate real-world outcomes in consecutive all-comers with acute MI at nine major cardiovascular centers in Korea. Of the 4748 enrolled patients, 2523 remained for analysis after excluding subjects with missing data ($n = 1726$), renal failure ($n = 135$) and anemia ($n = 312$). Detailed information on this registry is described elsewhere [10]. One thousand and ninety-eight subjects were included in both cohorts.

Written informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki, as reflected in a priori approval by the institutional review board at each participating center.

2.2. PCI procedure and medical treatment

All patients underwent PCI within 48 h after admission without fibrinolysis. Coronary angiography and primary PCI were performed according to the current standard guidelines. Significant CAD was defined by angiographic stenosis ≥70% in the epicardial coronary arteries and ≥50% in the left main coronary artery. 4181 patients were implanted with drug-eluting stent and 181 patients were implanted with bare-metal stent. Antiplatelet therapy and periprocedural anticoagulation were administered according to standard regimens. Patients were prescribed aspirin (loading dose of 200 mg) plus clopidogrel (loading dose of 300 or 600 mg) before or during PCI. After the procedure, aspirin (100–200 mg/day) was continued indefinitely, and clopidogrel (75 mg/day) for at least 1 year. Post-intervention medications included aspirin, clopidogrel, statins, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and β-blockers. Patients received these medications within the first 24 h, unless such treatment was contraindicated, and these medications were continued after discharge. The strategies of multivessel intervention, pre-dilation, direct stenting, post-adjunct balloon inflation, and the administration of glycoprotein IIb/IIIa receptor blockers were decided at the discretion of individual physicians.

2.3. Follow-up

Each patient was followed up at outpatient clinics or with a telephone questionnaire at 1, 6, and 12 months. Patients were then followed annually thereafter. Information about death was obtained from hospital records or from the patient's guardians via telephone contact. The death data were matched with records from the National Population Registry of the Korea National Statistical Office, and a unique personal identification number was used to validate mortality follow-up data. All clinical outcomes of interest were confirmed by source documents and were centrally adjudicated by a local events committee at the Cardiovascular Center of Seoul St. Mary's Hospital and by an independent group of clinicians unaware of the patient status.

2.4. Definitions

SHR was defined as the first-measured random serum glucose divided by the average glucose: [glucose (mg/dL) / 18]/[(1.59 × HbA1c) − 2.59] [7]. Subjects who had a prior history of diabetes, were taking antidiabetic medications, or had a HbA1c level higher than 6.5% were considered to have diabetes. Acute MI was diagnosed when there were characteristic clinical symptoms of ischemia, electrocardiographic findings consistent with myocardial ischemia/infarction, imaging evidence with new loss of viable myocardium or new regional wall motion abnormalities and increased cardiac enzyme values that meet the universal definition of MI [11]. In all patients, we confirmed the diagnosis by coronary angiography. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging studies. The primary observational outcome of this study was MACCE (a composite of all-cause death, nonfatal recurrent MI or nonfatal stroke) after the index PCI. The secondary observational outcomes were each component of the primary outcome and revascularization after index PCI.

2.5. Statistical analysis

Differences between groups of continuous variables were evaluated with an independent sample t-test or Mann–Whitney U test, and they were expressed as the means ± SD or median (25–75%). Differences between groups of discrete variables were analyzed with a χ^2 or Fisher's exact test, as appropriate, and are expressed as percentages. We constructed Kaplan–Meier curves for the MACCE for patients according to the quartile groups of the SHR and presence of diabetes. Differences between groups were assessed with the log-rank test. Multivariable Cox proportional hazards regression analysis was performed to adjust for potential confounders and to compute the hazard ratio (HR) [95% confidence interval (CI)] as estimates for each end point. The variables that were considered potentially relevant were the age (≥65 yrs), gender, body mass index (≥25 kg/m^2), hypertension, diabetes, hypercholesterolemia, current smoking, MDRD-GFR (<60 mL/min/1.73 m^2), previous MI, previous PCI, previous cerebrovascular accident (CVA), left ventricular ejection fraction (LVEF) < 45%, anemia (male < 13 g/dL, female < 12 g/dL), presence of multivessel disease and initial diagnosis. Diabetes was excluded in a set of covariates when analyzing non-diabetic population. Subgroup analysis was conducted by the stratification of diabetic status and initial diagnosis. To assess events occurring in the first 30 days and between 30 days and 5 years, a landmark analysis was performed [12,13]. All analyses were two-tailed, and clinical significance was defined as $P < 0.05$. Statistical analyses were performed with statistical package SPSS V.20.0 (SPSS Inc., Chicago, Illinois, USA) and MedCalc V.12.7 (MedCalc Software, Mariakerke, Belgium).

Please cite this article as: Y. Yang, et al., The stress hyperglycemia ratio, an index of relative hyperglycemia, as a predictor of clinical outcomes after percutaneous coronar..., Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.02.065