COMMENT ON GERBAUD ET AL.

Glycemic Variability Is a Powerful Independent Predictive Factor of Midterm Major Adverse Cardiac Events in Patients With Diabetes With Acute Coronary Syndrome. Diabetes Care 2019;42:674–681

You Yang and Yunzhao Hu

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In their recently published article in *Diabetes Care*, Gerbaud et al. (1) reported that in a total of 327 patients with diabetes and acute coronary syndrome (ACS), glycemic variability (GV) defined as SD >2.70 mmol/L during initial hospitalization was the strongest independent predictive factor for midterm major cardiovascular events (MACE). This study was interesting and further supported the opinion that GV should be regarded as a risk factor for cardiovascular disease (2). However, there are several views that should be discussed.

First, the authors reported that the multivariate logistic regression analysis was performed to ascertain the contributions of GV for MACE and that the odds ratios were calculated. It should be noted that odds ratios are commonly used in cross-sectional or case-control studies but not in cohort studies, as this would lead to overestimation of the real risks. According to the prospective design of the study by Gerbaud et al., hazard ratios should be calculated.

Second, many different metrics of GV, including SD, coefficient of variation, variability independent of mean, average successive variability, etc., had been defined in prior studies. While there is no agreement on which is the "best" GV metric, currently the preferred GV metric for research work is the coefficient of variation (defined as SD/mean of the observation), which is the least influenced by mean glucose level (3). It should be noted that SD does not consider mean levels of glycemia, which are particularly important in a study with intensive antihyperglycemic treatment. In the study by Gerbaud et al., multiple glycemia parameters, including admission glycemia and mean glycemia, were correlated with SD, and these parameters were analyzed in separate statistical models. This method failed to demonstrate whether the increased risks were independently caused by the fluctuation of blood glucose ("variability") or mediated by mean glycemia levels and, again, would lead to overestimation of real risk for GV.

Third, continuous insulin administration was initiated when blood glucose on admission was ≥10.0 mmol/L and/or when premeal glycemia was ≥7.7 mmol/L in the study by Gerbaud et al. However, it is still controversial as to whether intensive insulin administration is beneficial in patients with ACS; one of the most important considerations is that such treatment may cause severe hypoglycemia, which has been documented as an independent risk factor for cardiovascular mortality (4). Therefore, to assess whether severe hypoglycemia may account for the effects of GV on prognosis of ACS, the relative risks should adjust for status of hypoglycemia in multivariable adjusted models (5). Although only 0.6% of glycemic values detected were <3 mmol/L, and considering that glycemia status was not detected by continuous monitoring, the incidence of hypoglycemia may be underestimated in the study by Gerbaud et al.

In conclusion, the study by Gerbaud et al. is interesting and has important clinical implications (1). This study emphasizes that efforts for glucose control in patients with diabetes and ACS may need to consider how these strategies influence the glucose fluctuation. However, due to the limitations of unsuited statistical analysis, unadjusted factors such as mean glycemia levels, and undetected hypoglycemia, the results should be interpreted with caution and the question is still open.

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Department of Cardiology, The Affiliated Chencun Hospital of Shunde Hospital, Southern Medical University, Foshan, China

Corresponding author: Yunzhao Hu, huyunzhao4406@163.com

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