Association between glucose variability and adverse in-hospital outcomes for Chinese patients with acute coronary syndrome

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ABSTRACT

الأهداف: التحقق من العلاقة الموجودة بين معدل سكر الغلوكوز وتباين الغلوكوز في الدم من جهة والنتائج السلبية المترتبة خلال فترة المكوث في المستشفى وذلك بين المرضى الذين يعانون من متلازمة الشريان التاجي الحادة.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في مستشفيين من الدرجة الثانية، بكين، الصين، حيث قمنا بمراجعة سجلات المرضى المصابين بمتلازمة الشريان التاجي الحادة والذين دخلوا إلى المستشفى خلال الفترة من يناير 2003م إلى ديسمبر 2006م. لقد أسفرت نتائج معامل تباين الغلوكوز ومعدل سكر الغلوكوز عن ارتباط فرط سكر الدم ببعض الاضطرابات السريرية (مثل الاضطرابات القلبية الوعائية الشديدة، والموت في المستشفى). قُسم المشاركين في الدراسة إلى أربع مجموعات وذلك اعتماداً على الأرباع أو المستويات التي يتراوح ما بينها معامل تباين الغلوكوز والأرباع التي يتراوح ما بينها معدل الغلوكوز في الدم ومن ثم عُزلت المجموعات الفرعية التي تشمل المرضى المصابين بالسكري والغير مصابين بالسكري وتم تحليلها. واستخدم تحليل الانحدار اللوجستي متعدد المتغيرات من أجل تقييم العوامل المستقلة التي تزيد من خطر الوفاة أثناء فترة المكوث في المستشفى.

النتائج: شملت هذه الدراسة 1756 حالة، ولقد كان انتشار النتائج السلبية أكثر بين المرضى الذين يعانون من ارتفاع معامل تباين الغلوكوز أو معدل الغلوكوز بالمقارنة مع المرضى الآخرين وذلك في المجموع الكلي أو مجموع المرضى الغير مصابين بالسكري (p for trend <0.001)، وفيما يخص مرضى السكري المُصابين بمتلازمة الشريان التاجي الحادة فقد كانت الاضطرابات القلبية الوعائية الشديدة منتشرةً أكثر في المستويات العالية من أرباع معامل تباين الغلوكوز وأرباع معدل الغلوكوز بالمقارنة مع الأرباع الأخرى (p for trend <0.001). وزادت نسبة الوفيات داخل المستشفى بين أرباع معدل الغلوكوز في الدم (p for trend <0.001) وكذلك أرباع معامل تباين الغلوكوز (p for trend=0.004). أظهر تحليل الانحدار اللوجستي متعدد المتغيرات بأن ارتباط معامل تباين الغلوكوز بارتفاع نسبة الوفيات داخل المستشفى (OR: 1.29) كان أقوى من ارتباط معدل الغلوكوز بنسبة الوفيات (OR: 1.20).

خاتمة: أشارت الدراسة إلى أن معامل تباين الغلوكوز له تأثير قوي على زيادة نسبة الوفيات داخل المستشفى وذلك أكثر من معدل الغلوكوز في المرضى المصابين بمتلازمة الشريان التاجي الحادة.

Objectives: To investigate the association between mean blood glucose (MBG) and glucose variability (GV) during hospitalization, and adverse in-hospital outcomes for patients with acute coronary syndrome (ACS).

Methods: This is a retrospective cohort study and conducted in 2 tertiary hospitals in Beijing, China. All data were collected from the medical records concerning ACS patients admitted to the hospital between January 2003 to December 2006. Hyperglycemia was related to clinical outcomes (including major adverse cardiovascular events [MACEs] and in-hospital death) using coefficient of variation of blood glucose (GluCV) or mean blood glucose (MBG). Total cohort was stratified by GluCV or MBG quartiles. Diabetic and non-diabetic subgroups were then separately analyzed. Multivariate logistic regression analysis was performed to evaluate the independent risk factor of in-hospital death.

Results: A total of 1756 cases were enrolled in this study. For total cohort or non-diabetic cohort, prevalence of adverse outcomes was higher in patients with higher MBG or GluCV (*p* for trend <0.001). For diabetic ACS patients, MACEs were found more common in MBG or GluCV quartiles (*p* for trend <0.001), in-hospital mortality increased across MBG (*p* for trend <0.001), or GluCV quartiles (*p* for trend=0.004). Multivariate logistic regression analysis showed that GluCV (odds ratio: 1.29) was a stronger predictor of in-hospital death than MBG (odds ratios: 1.20).

Conclusions: The GluCV is a better discriminator of in-hospital mortality than MBG in ACS patients.

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It is known that hyperglycemia on admission is associated with adverse outcomes for acute coronary syndrome (ACS) patients with and without diabetes.[1-5] Meanwhile, Kosiborod et al[6] found that mean blood glucose (MBG) over the course of hospitalization is a more effective predictor of death than just simple on-admission glucose levels in acute myocardial infarction (AMI) patients. Goyal et al[7] found that the glucose variability (GV) within the first 24 hours could assist in predicting mortality in non-diabetic AMI patients. All these studies suggested that glucose control might be an important part of improving prognosis of ACS patients. However, findings concerning the effect on mortality in ACS and other critically ill patients of intensive insulin therapy (IIT) have been conflicting.[8-12] The reason for the discrepancy in the results is not clear. The Leuven investigators recently found that during IIT, GV increases and is associated with increased mortality.[13] Recently, several studies have shown that GV was a powerful predictor of mortality independent of MBG in critically ill patients.[14-16] We performed this retrospective study for a better understanding of the relationship between persistent hyperglycemia during hospitalization and in-hospital mortality in ACS patients, and to clarify the possible significance of GV on adverse outcomes in these patients.

Methods. *Study population.* The current study was conducted as a retrospective observational study at China-Japan Friendship Hospital and Chinese PLA General Hospital, which are tertiary public hospitals in Beijing, China. There were 2316 hospital admissions with a diagnosis of ACS between January 2003 to December 2006. We excluded 348 patients with diabetes ketosis, hyperthyroidism, acromegaly, and liver or renal dysfunction. A total of 212 patients with <10 glucose measurements during hospitalization, or <3 days hospital stay were also excluded, leaving 1756 patients for our analyses. Patients in this study were partly treated with strict glycemic control, and there was no uniform glycemic management protocol. Plasma glucose was measured with the use of a hexokinase enzymatic method by automatic biochemical analyzer. The Ethics Committee of Chinese Medical Association, Beijing, China approved the study protocol. Pre-established criteria for the diagnosis of AMI, including ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) were adopted in these 2 hospitals to help diagnose ACS.[17] We assessed demographic characteristics, medical history, biochemical and electrocardiographic findings, treatment practices and adverse in-hospital outcomes. The primary outcome referred to all causes of death in the hospital, the secondary outcome referred

to major adverse cardiovascular events (MACEs), including serious cardiac arrhythmias, heart failure (above Killip class 3), and cardiogenic shock. Serious cardiac arrhythmias were defined by premature ventricular complex (above LOWN class 4), Morbiz type, and complete atrioventricular block, sinus arrest, ventricular tachycardia, and ventricular fibrillation. The Global Registry of Acute Coronary Events (GRACE) risk score was evaluated as a measure for severity of the disease.[18,19] Information on glycosylated hemoglobin was not included due to the large numbers of subjects with missing data.

Clinical data collection. All data were collected retrospectively from the medical records by trained chart abstractors. We chose to examine GV and MBG, as they are 2 important aspects that can reflect the overall blood glucose status during hospitalization, not only the severity of hyperglycemia, but also the range of blood glucose fluctuation. Coefficient of variation of blood glucose concentration (GluCV) during hospitalization was calculated as a marker of GV.[20] The total cohort was divided into 4 groups according to quartiles of MBG or GluCV. Diabetic (n=596) and non-diabetic (n=1160) subgroups were then separately analyzed (diabetic and non-diabetic subgroups referred to ACS cohort with or without pre-existing diabetes mellitus [DM]).

Statistical analysis. Results are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the distribution of the data. Categorical data among GluCV quartiles were compared by Chi-square test, and continuous data among GluCV quartiles were compared by one-way analysis of variance (ANOVA). The area under the receiver operator characteristics (ROC) curves was calculated for MBG and GluCV. Linear Chi-square trend test was used to check the statistical association between GluCV quartiles and adverse in-hospital outcomes and the trend of incidence rate of adverse in-hospital outcomes among GluCV or MBG quartiles. Using multivariate logistic regression analysis, we calculated odds ratios (ORs) for in-hospital mortality for MBG and GluCV, and corrected for clinical relevant confounders: gender, age, current smoking, body mass index (BMI), history of DM, history of hypertension, history of dyslipidemia, ACS type, clinical management (thrombolytics, percutaneous coronary intervention, coronary artery bypass graft entered the regression models as dummy variable), length of hospital stay, severe hypoglycemia (glucose ≤2.8 mmol/L), and GRACE risk scores. A backward stepwise elimination process was then used to remove covariates. We assessed the calibration of the model with Hosmer-Lemeshow test. All statistical analysis was performed using the Statistical Package for

Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was set at $p<0.05$.

Results. *Clinical characteristics of the study population.* Baseline demographic and clinical characteristics of the studied cohort according to GluCV are listed in **Table 1**. Of the total cohort, the mean age was 61.4 ± 9.3 years, and 27.6% were female; 33.9% had a history of diabetes and 9.3% died during hospitalization. The median duration of hospitalization was 14 days (IQR: 6-35 days). The total number of glucose measurements of all patients during hospitalization was 21,852 with a median of 15 glucose measurements per patient (IQR: 10-42). For the entire cohort, the median MBG was 6.68 mmol/L (IQR: 5.66-8.43 mmol/L), and the median GluCV was 24.1% (IQR; 13.3-34.8%). Age ($p=0.000$) and gender distribution ($p=0.000$), BMI ($p=0.044$), and GRACE risk score ($p=0.000$) among quartiles of GluCV were significantly different. Patients with higher GluCV had higher prevalence of DM ($p=0.000$), dyslipidemia ($p=0.000$), and hypertension ($p=0.000$). Smoking, length of hospital stay and the rates of severe hypoglycemia during hospitalization did not seem to be associated with GluCV. The rates of thrombolytics and revascularization were similar among quartiles of GluCV. The rates of STEMI were similar among quartiles of GluCV ($p=0.434$) however, unstable angina ($p=0.012$) and NSTEMI was significantly different among quartiles of GluCV ($p=0.047$).

Association between glucose index and adverse in-hospital outcomes in ACS patients with and without pre-existing DM. The ranges of GluCV quartiles and MBG quartiles of total cohort with incidence rate of MACEs or in-hospital death are shown in **Figure 1**. The incidence rate of MACEs and in-hospital death are higher in higher MBG or GluCV quartiles (p for trend =0.000). The highest incidence rate of MACEs and in-hospital death were seen in the highest MBG quartile (50.0% and 21.4%, respectively), or in the highest GluCV quartile (35% and 14.5%, respectively) (**Figure 1**). **Table 2** shows the relation between GluCV and MBG and adverse in-hospital outcomes in diabetic and non-diabetic ACS patients. In the subgroup of non-diabetic ACS patients, the incidence rate of MACEs and in-hospital death increased across quartiles of MBG or GluCV (p for trend =0.000). We also noticed that among MBG quartile, the lowest death rate was in the third quartile (range from 6.12 - 6.97 mmol/L) however, it could not cover up the general variation

Table 1 - Clinical characteristics of ACS patients stratified by GluCV.

Characteristics	GluCV quartiles (%)				*P*-value
	<13.3 (n=440)	13.4-24.1 (n=438)	24.2-34.8 (n=438)	>34.9 (n=440)	
Age, years (mean ± SD)	61.87 ± 11.66	63.11 ± 11.79	63.9 ± 12.42	65.18 ± 12.31	0.000
Female, n (%)	152 (34.5)	94 (21.5)	110 (25.1)	130 (29.5)	0.000
Body mass index, mean ± SD	25.6 ± 3.1	25.2 ± 3.5	25.7 ± 3.3	25.2 ± 3.5	0.044
Current smoker	194 (44.1)	218 (49.7)	184 (42.0)	210 (47.7)	0.09
Previous agina pectoris	120 (27.2)	124 (28.3)	128 (29.2)	131 (29.7)	0.855
Previous myocardial infraction	142 (32.3)	138 (31.5)	146 (33.3)	171 (38.8)	0.088
Previous stroke	42 (9.5)	56 (12.8)	68 (15.5)	6 (14.1)	0.055
History of diabetes mellitus	84 (19.1)	118 (26.9)	170 (38.8)	222 (50.5)	0.000
History of hypertension	226 (51.4)	270 (61.6)	284 (64.8)	272 (61.8)	0.000
History of dyslipidemia	274 (62.3)	338 (77.2)	368 (84.0)	358 (81.4)	0.000
Peripheral vascular diseases	45 (10.3)	49 (11.2)	52 (11.9)	55 (12.5)	0.744
ACS type					
STEMI	150 (34.1)	142 (32.4)	136 (31.1)	128 (29.1)	0.434
NSTEMI	240 (54.5)	214 (48.9)	240 (54.8)	256 (58.2)	0.047
Unstable angina pectoris	50 (11.4)	82 (18.7)	62 (14.2)	56 (12.7)	0. 012
Management					
Thrombolytics	19 (4.3)	17 (3.9)	21 (4.8)	23 (5.1)	0.794
Percutaneous coronary intervention	218 (49.5)	212 (48.2)	225 (51.3)	232 (52.7)	0.585
Coronary artery bypass graft	38 (8.6)	42 (9.6)	45 (10.3)	52 (11.8)	0.455
Length of hospital stay, days	15 (8-35)	13 (6-22)	12 (16-21)	16 (7-31)	0.543
GRACE risk score, mean ± SD	89 ± 14	96 ± 17	113 ± 27	129 ± 31	0.000
Severe hypoglycemia, %	4 (0.9)	5 (1.1)	4 (0.9)	6 (1.3)	0.901

ACS - acute coronary syndrome, GluCV - coefficient of variation of blood glucose, NSTEMI - non-ST-segment elevation myocardial infraction, STEMI - ST-segment elevation myocardial infraction, CABG - coronary artery bypass graft, GRACE risk score - Global Registry of Acute Coronary Events risk score
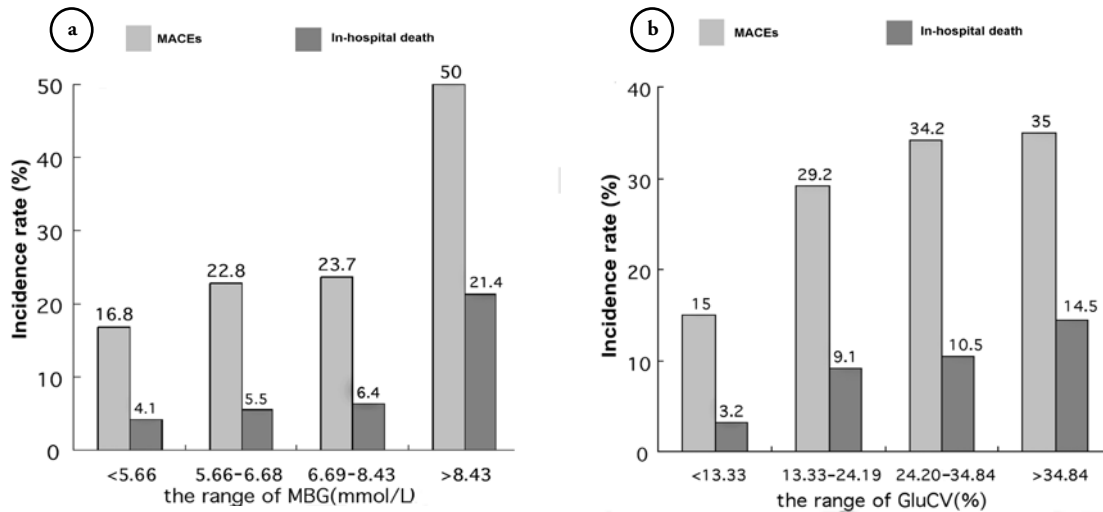
Figure 1 - Relation between mean blood glucose (MBG) and in-hospital mortality in the total cohort; **a**) relation between coefficient of variation of blood glucose concentration (GluCV), and **b**) in-hospital mortality in the total cohort.

Table 2 - Relation between GluCV, MBG, and in-hospital mortality in diabetic and non-diabetic ACS patients.

Variables	MBG quartiles (mmol/L)				P trend value	GluCV quartiles (%)				P trend value
Non-diabetic ACS										
Range of each quartile, (n=290)	<5.28	5.28 – 6.11	6.12 – 6.97	>6.97		<10.47	10.47 – 19.99	20.00 – 29.98	>29.98	
MACEs, n (%)	48 (16.5)	62 (21.4)	70 (24.1)	98 (33.8)	0.000	32 (11.0)	56 (19.3)	94 (32.4)	96 (33.1)	0.000
Death, n (%)	14 (4.8)	24 (8.3)	6 (2.1)	44 (15.2)	0.000	6 (2.1)	14 (4.8)	32 (11.0)	36 (12.4)	0.000
Diabetic ACS										
Range of each quartile	<6.97 (n=150)	6.97 – 8.69 (n=148)	8.70 – 11.01 (n=148)	>11.01 (n=150)		<19.29 (n=150)	19.29 – 30.16 (n=148)	30.17 – 40.24 (n=148)	>40.24 (n=150)	
MACEs, n (%)	36 (24.0)	38 (25.7)	56 (37.8)	90 (60.0)	0.000	38 (25.3)	50 (33.8)	62 (41.9)	70 (46.7)	0.000
Death, n (%)	6 (4.0)	12 (8.1)	20 (13.5)	38 (25.3)	0.000	12 (8.0)	14 (9.5)	24 (16.2)	26 (17.3)	0.004

ACS - acute coronary syndrome, GluCV - coefficient of variation of blood glucose, MBG - mean blood glucose,
MACEs - major adverse cardiovascular events

Table 3 - Estimate the independent risk factor of in-hospital mortality through multivariant logistic regression analysis.

Variables	Odds ratio	95% confidence interval	P-value
GRACE risk score (per 1)	1.22	1.09-1.43	0.000
GluCV (per 1 percent)	1.29	1.14-1.55	0.000
MBG (per 1 mmol/L)	1.20	1.12-1.31	0.000
History of diabetes	1.79	1.28-2.12	0.000
STEMI	1.85	1.49-2.23	0.002

GRACE risk score - Global Registry of Acute Coronary Events risk score, GluCV - coefficient of variation of blood glucose, MBG - mean blood glucose, STEMI - ST-segment elevation myocardial infraction

trend. In the subgroup of diabetic ACS patients, the incidence rate of MACEs increased across MBG or GluCV quartiles (*p* for trend 0.000), and in-hospital mortality also increased across MBG (*p* for trend 0.000) or GluCV quartiles (*p* for trend 0.004) The GluCV

was significantly stronger associated with in-hospital death compared with the MBG in univariate analysis, a difference in the area under the ROC of 4.9% (95% confidence interval [CI], 2.8-7.1; *p*=0.000).

Multivariate logistic regression analysis showed that independent predictors of in-hospital mortality for total cohort were GRACE risk score, GluCV, MBG, history of diabetes and STEMI. The odds ratios for in-hospital mortality were 1.20, 1.29 per each millimolar change in MBG, and per each percent change in GluCV. For this model, the Hosmer-Lemeshow goodness-of-fit statistic was 13.8 (*p*=0.097) (**Table 3**).

Discussion. Several studies have documented the association between hyperglycemia and increased death rates in ACS patients, however, hyperglycemia remains under appreciated as a risk factor, and it is frequently untreated in ACS patients since data are limited according to glucose management in these patients.

We found that both MBG and GluCV over the course of hospitalization were significantly associated with adverse in-hospital outcomes among ACS patients with and without pre-existing DM, and both of them were significant independent predictors of in-hospital mortality. We also found that in non-diabetic patients, the lowest death rate was in the third MBG quartile, which is concordant with other investigators who demonstrated that a J-shaped mortality exists between average glucose and mortality in patients with AMI.[21] Furthermore, we found that variability of glucose concentration was a stronger predictor of in-hospital mortality than mean glucose concentration. These observations support the hypothesis that variability of glucose control might be a more important dimension of patient care than mean glucose in ACS patients. The GluCV and MBG are both expression of the severity of hyperglycemia. They[21] described different aspects of glucose control, and that variability could be detrimental both when glucose control is apparently "good" (low MBG), and when it is "poor" (high MBG). In this respect, GV might be more reliable than MBG in prognosing in-hospital mortality.[21]

Our findings are in accordance with previous studies that have investigated the relationship between GV and mortality. In the studies of Egi[15] and Krinsley,[16] GV in the intensive care unit (ICU) was a predictor of mortality independent of MBG. A recent study performed by Hermanides et al[22] confirmed that GV is associated with ICU mortality and hospital mortality, and GV is a stronger predictor of ICU and hospital mortality than MBG. These findings are more than simple theoretical concerns as if decreasing glucose variability was a major biologic mechanism behind the benefits of glucose control, it might not be necessary for doctors to pursue lower glucose levels with the attendant risks of hypoglycemia. The results of the NICE-SUGAR study[23] suggests that the benefit of tight glucose control might be covered by the risk that come from severe hypoglycemia due to too strict target range of glucose control.

The GV reflected by GluCV change is a causative harmful phenomenon, or whether it is an epiphenomenon resulting from metabolic deterioration during severe illness and dying, is not clear.[24] The results of several studies suggested a causal relationship from pathophysiological viewpoints: in vitro - glucose fluctuations enhance cell apoptosis;[25] in rats - high blood glucose concentrations following hypoglycemic coma can initiate neuronal death; in healthy volunteers - oscillating glucose is more harmful to endothelial function than mean glucose.[22,26,27] It might be that the adaptive cell mechanisms triggered by constant hyperglycemia are ineffective facing oscillating glucose,

explaining the toxicity of GV,[22,28] also maybe that in humans, GV exerts a deleterious effect on various tissues, thereby contributing to fatal events need further research.

There are limitations in this study. First, this is a retrospective study with all the inherent limitations of such studies. To better understand the significance of variability control, more prospective, randomized, and controlled studies should be followed up. Second, lack of information on the combined use of medication (insulin or other hypoglycemic drugs, catecholamine, corticosteroids and nutritional support) is an important limitation; with different treatment these findings might be different. Third, the variability of blood glucose concentration as presented, did not consider its time distribution, which might have affected our findings.[29] However, time-related effects on the distribution of values should have affected both variables equivalently and assessment of changes in GluCV over time indicates little time-related effect. More importantly, GluCV showed a significantly greater area under the ROC curve than MBG. These factors might modulate the predictive ability of glucose indices and future studies should focus on their impact. Finally, we note that MBG and GluCV are not useful prognostic variables since they can only be measured after hospital discharge. We did not try to find new prognostic indices in this study, instead we were tried to find out whether an evidence exists to support the hypothesis that GV may be a more reliable indicator of glucose control, and a predictor of in-hospital outcome than mean glucose alone.

In conclusion, GluCV is a better predicator of in-hospital mortality than MBG during hospitalization in ACS patients. The GV might be an important part of glucose management, and a possible mechanism underlying the beneficial effects of IIT. However, it still needs to be proven in prospective randomized trials in the future.

References

1. Meier JJ, Deifuss S, Klamann A, Launhardt V, Schmiegel WH, Nauck MA. Plasma glucose at hospital admission and previous metabolic control determine myocardial infarct size and survival in patients with and without type 2 diabetes: the Langendreer Myocardial Infarction and Blood Glucose in Diabetic Patients Assessment (LAMBDA). *Diab Care* 2005; 28: 2551-2553.

2. Vivas D, García-Rubira JC, González-Ferrer JJ, Núñez-Gil I, del Prado N, Fernández-Ortiz A, et al. [Prognostic value of first fasting glucose measurement compared with admission glucose level in patients with acute coronary syndrome] *Rev Esp Cardiol* 2008; 61: 458-464. Spanish.

3. Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, et al. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. *Circulation* 2005; 111: 754-760.

4. Cao JJ, Hudson M, Jankowski M, Whitehouse F, Weaver WD. Relation of chronic and acute glycemic control on mortality in acute myocardial infarction with diabetes mellitus. *Am J Cardiol* 2005; 96: 183-186.

5. Otten R, Kline-Rogers E, Meier DJ, Dumasia R, Fang J, May N, et al. Impact of pre-diabetic state on clinical outcomes in patients with acute coronary syndrome. *Heart* 2005; 91: 1466-1468.

6. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation* 2008; 117: 1018-1027.

7. Goyal A, Mahaffey KW, Garg J, Nicolau JC, Hochman JS, Weaver WD, et al. Prognostic significance of the change in glucose level in the first 24 hours after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J* 2006; 27: 1289-1297.

8. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, 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: 650-661.

9. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 2006; 29: 765-770.

10. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359-1367.

11. Coester A, Neumann CR, Schmidt MI. Intensive insulin therapy in severe traumatic brain injury: a randomized trial. *J Trauma* 2010; 68: 904-911.

12. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006; 55: 3151-3159.

13. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med* 2010; 38: 1021-1029.

14. Ali NA, O'Brien JM Jr, Dungan K, Phillips G, Marsh CB, Lemeshow S, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med* 2008; 36: 2316-2321.

15. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105: 244-252.

16. Krinsley JS. Glycemic variability in critically ill patients: impact of diabetes. *J Diab Sci Tech* 2009; 3: 1292-1301.

17. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001; 141: 190-199.

18. Yan AT, Yan RT, Tan M, Eagle KA, Granger CB, Dabbous OH, et al. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. *Am J Cardiol* 2005; 96: 913-916.

19. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; 163: 2345-2353.

20. Muggeo M, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. *Diabetes Care* 2000; 23: 45-50.

21. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et,al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation* 2008; 117: 1018-1027.

22. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med* 2010; 38: 838-842.

23. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-1297.

24. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab* 2001; 15: 533-551.

25. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes* 2003; 52: 2795-2804.

26. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest* 2007; 117: 910-918.

27. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; 57: 1349-1354.

28. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 2005; 19: 178-181.

29. van der Horst IC, Gans RO, Nijsten MW, Ligtenberg JJ. Beneficial effect of glucose-insulin-potassium infusion in noncritically ill patients has to be proven. *J Intern Med* 2003; 254: 513-514.