Association of Hyperglycemia and Final TIMI Flow with One-Year Mortality of Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary PCI

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Int J Angiol 2019;28:182–187.

Abstract

The association of hyperglycemia at admission and final thrombolysis in myocardial infarction (TIMI) flow with 1-year mortality of patient with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) has not much been explored. We evaluated the association of hyperglycemia and final TIMI flow with 1-year mortality in patients with acute STEMI who underwent primary PCI.

We retrospectively analyzed 856 patients with STEMI who underwent primary PCI in a tertiary care academic center between January 2014 and July 2016. Based on the receiver operating characteristics curve, the cutoff used for hyperglycemia in this study was greater than or equal to 169 mg/dL. Cox proportional hazard model was used to determine the association of hyperglycemia and TIMI flow with 1-year mortality.

Compared with patients with lower blood glucose level ($<$169 mg/dL; $n = 549$), a greater proportion of patients who presented with hyperglycemia ($\geq$169 mg/dL; $n = 307$) had final TIMI flow 0 to 1 (3.3 vs. 0.5%; adjusted odds ratio = 5.58, 95% confidence interval [CI] 1.30–23.9, $p = 0.02$). Hyperglycemia was associated with an increased risk for 1-year mortality (adjusted hazard ratio [HR]= 2.0, 95% CI: 1.13–3.53, $p = 0.017$). Multivariable Cox regression showed that the interaction of hyperglycemia and final TIMI flow 0 to 1 was associated with an elevated risk for 1-year mortality (adjusted HR= 9.4, 95% CI: 2.34–37.81, $p = 0.002$).

A higher proportion of patients with acute STEMI who presented with hyperglycemia had final TIMI flow 0 to 1 after primary PCI. The interaction of hyperglycemia and final TIMI flow 0 to 1 was associated with an increased risk for 1-year mortality. This study suggests that aggressive control of hyperglycemia prior to primary PCI may facilitate better angiographic and clinical outcomes after primary PCI.

Clinical Trial Registration Clinicaltrials.gov Identifier number: NCT02319473.

Keywords
- STEMI
- hyperglycemia
- final TIMI flow
- 1-year mortality

published online
June 17, 2019

DOI https://doi.org/10.1055/s-0039-1691811.
ISSN 1061-1711.

Despite recent advances in the treatment of patient with acute ST-segment elevation myocardial infarction (STEMI) such as implementation of regional STEMI network, wide adoption of primary percutaneous coronary intervention (PCI), shorter reperfusion time, and use of newer antiplatelet therapy,[1,2] hyperglycemia at admission remains a challenging situation in an acute phase of acute myocardial infarction (AMI) and was found to be an independent predictor of short- and long-term mortality of patients with AMI.[3–5] Studies have also found that hyperglycemia is associated with microvascular obstruction[6] and a worse thrombolysis in myocardial infarction (TIMI) flow after primary PCI.[7] Whether the interaction of hyperglycemia and final TIMI flow after primary PCI contributes to a higher long-term mortality of patients with STEMI undergoing primary PCI has not been explored in detail.

Accordingly, we investigated the association of hyperglycemia at admission and final TIMI flow with 1-year mortality of patients with acute STEMI undergoing primary PCI.

Materials and Methods

A retrospective analysis of the Jakarta Acute Coronary Syndrome (JAC) registry was performed. All patients with STEMI ($n = 2285$) admitted to the emergency department (ED) of our hospital between 2nd January 2014 and 31st July 2016 were recorded. Of these, 1185 patients underwent primary PCI. Final analysis was performed in 856 patients. Selection of the study sample is shown in ►**Fig. 1**.

JAC Registry

The JAC registry has been set-up in the hospital since 2007 and currently is being used as the main source of data for measuring the performance of STEMI care in the region as part of the STEMI network program (Jakarta Cardiovascular Care Unit Network System).[8–11] All consecutive patients with acute coronary syndrome including STEMI were recorded in the database. The dataset consists of demographic and clinical characteristics, laboratory and primary PCI variables. Data quality was maintained by a routine verification by the primary investigator of the JAC registry (SD). This study was approved by the institutional review board of the hospital.

Study Outcome

The primary outcome of this study was all-cause mortality at 1 year.

Clinical Follow-Up

One-year clinical follow-up was performed by medical record studies and/or phone calls by trained personnel that were blinded to the study objectives.

Blood Glucose Measurement

Blood glucose measurement was performed in each patient at the ED of the PCI center before primary PCI. There were two methods used for measuring the blood glucose: (1) Glucometer (FreeStyle Optium, Abbott, IL); and (2) Automated clinical chemistry analyzer (Architect ci4100, Abbott, IL). The measurement was performed by laboratory personnel and blinded to the clinical characteristics of the patients. Blood glucose data were recorded from the database.

Definition of Variables

The diagnosis of STEMI was confirmed by the presence of ST-segment elevation in two or more contiguous leads, a new left bundle branch block, or a true posterior myocardial infarction confirmed by ST-segment elevation in posterior leads. Final TIMI flow grade was classified into 0, 1, 2, or 3 (TIMI flow 0: absent of antegrade flow, TIMI flow grade 1: partial contrast penetration beyond an occlusion with incomplete distal filling; TIMI flow grade 2: patent epicardial artery with opacification of the entire distal artery but contrast filling or washout is delayed; TIMI flow grade 3: patent epicardial artery with normal flow).[12]

Hyperglycemia was defined as patient having blood glucose level at admission $\geq$ 169 mg/dL.

Statistical Analysis

Patients were grouped on the basis of the hyperglycemia status. Continuous data are presented as mean $\pm$ standard deviation or median (interquartile range) and compared by Student's *t*-test or Mann–Whitney U-test as appropriate. Categorical data are presented as percentages and differences were compared by the chi-square test or Fischer's exact test as appropriate. Comparisons between groups were performed by Student's *t*-test or Mann–Whitney U-test for continuous data and the chi-square test or the Fisher's exact test for categorical data. TIMI flow was grouped into TIMI flow 0 to 1 and 2 to 3. Logistic regression analysis was performed to find independent predictors of TIMI flow after primary PCI. Cox proportional hazard model was used to determine the association of hyperglycemia and TIMI flow with 1-year mortality after accounting for potential confounders (age, sex, diabetes mellitus, smoking, hypertension, anterior wall MI, TIMI risk score, Killip classification, and baseline renal function).

Kaplan–Meier method was used to evaluate the cumulative survival between patients with hyperglycemia and without hyperglycemia, and compared with log-rank test. The cutoff of hyperglycemia ($\geq$169 mg/dL) for the optimal prediction of the mortality was calculated using the receiver operating characteristics (ROC) curve [a sensitivity of 63%, a specificity of 66%, and an area under the curve of 0.68 (95% CI: 0.59–0.77)].

A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using a statistical package (SPSS version 17, SPSS Inc. Chicago, IL).

Results

Characteristics of Patients

Three hundred seven patients were found to have hyperglycemia. Patients with hyperglycemia at admission were older, less frequently male, more often had TIMI risk score >4 and Killip classification >1 on presentation, and more often had a baseline creatinine level $\geq$1.3 mg/dL as compared with patients with lower blood glucose level. The baseline TIMI

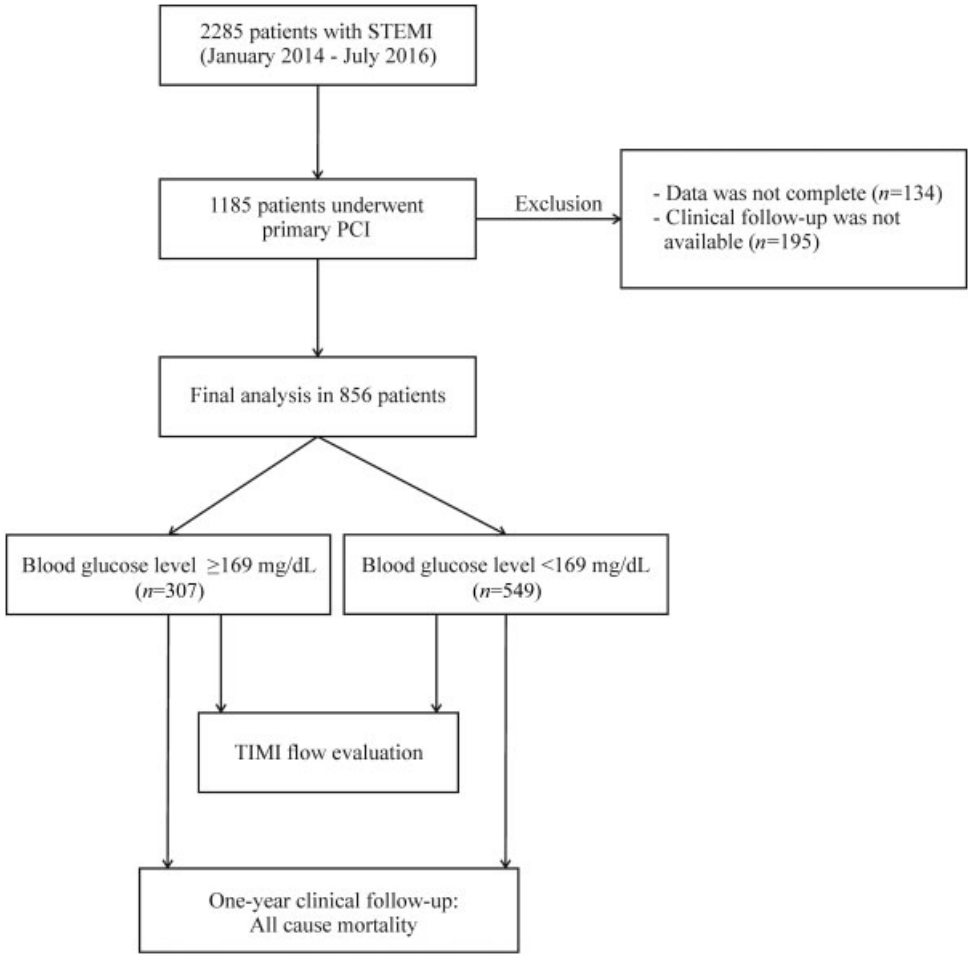

Fig. 1 Study flowchart. PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

flow during primary PCI was similar between the two groups (►**Table 1**).

Study Outcome

Association of Blood Glucose and TIMI Flow

Compared with patients with lower blood glucose level, a greater proportion of patients who presented with hyperglycemia had final TIMI flow 0 to 1 (3.3 vs. 0.5%; adjusted odds ratio [OR] = 5.58, 95% confidence interval [CI] 1.30–23.9, $p = 0.02$) and associated with an increased risk of 1-year mortality (16.3 vs. 6%; adjusted hazard ratio [HR]= 2.0, 95% CI: 1.13–3.53, $p = 0.01$) as compared with patients with lower blood glucose level (►**Tables 1–3**).

Interaction of Blood Glucose and Final TIMI Flow

The interaction of hyperglycemia and final TIMI flow was associated with an elevated risk for 1-year mortality (adjusted HR= 9.4, 95% CI: 2.34–37.81, $p = 0.002$) (►**Table 4**).

Survival Analysis

The cumulative survival at 1 year was significantly lower in patients with hyperglycemia as compared with patients with lower blood glucose level (log-rank test, $p < 0.001$) (►**Fig. 2**).

Discussion

The main findings from this study were: (1) hyperglycemia strongly associated with final TIMI flow 0 to 1 after primary PCI (OR= 5.58, $p = 0.01$); (2) the multivariate analysis from this study showed that the highest risk for 1-year mortality in the cohort was found in patients with both hyperglycemia and final TIMI flow 0 to 1 (OR= 9.4, $p = 0.002$).

A previous study showed that admission hyperglycemia is associated with increased mortality even in nondiabetic STEMI patients.[3] However, studies that found the association between hyperglycemia and mortality did not analyze the underlying pathologic mechanism related with the hyperglycemia condition.

The exact mechanism of how hyperglycemia affects the TIMI flow during primary PCI remains unclear. Several theories have been postulated to explain the pathologic mechanisms related with hyperglycemia such as increased oxidative stress,[13] tissue factor (TF)[14] and circulating adhesion molecules,[15] enhanced thrombin formation, platelet activation,[16] and fibrinolytic resistant.[16,17] In details, acute hyperglycemia induces an increase in plasma interleukin-6, tumor necrosis factor-α, and interleukin-18 concentrations, and suggests that an oxidative mechanism mediates the

Table 1 Patient characteristics

	Patients with hyperglycemia ($n = 307$)	Patients without hyperglycemia ($n = 549$)	*p*-Value
Age, years	57 (51–63)	55 (48–62)	00.002
Male gender	251 (82)	500 (91)	<0.001
CAD risk factor			
Smoking	184 (60)	374 (68)	00.01
Hypertension	191 (62)	283 (51)	00.003
Diabetes mellitus	175 (57)	56 (10)	<0.001
Dyslipidemia	103 (33)	160 (29)	00.18
Family history	38 (12)	94 (17)	00.06
Symptom onset >6 h	116 (38)	241 (44)	00.08
Anterior wall MI	152 (49)	286 (52)	00.46
TIMI risk score >4	142 (46)	185 (34)	<0.001
Killip classification >1	100 (33)	139 (25)	00.02
Creatinine level ≥1.3 mg/dL	123 (40)	115 (21)	<0.001
Baseline TIMI flow			
0–1	260 (85)	444 (81)	00.16
2–3	47 (15)	105 (19)	
Final TIMI flow			
0–1	10 (3.3)	3 (0.5)	00.003
2–3	297 (96)	546 (99)	
Mortality			
In-hospital	29 (9.4)	17 (3.1)	<0.001
One year	50 (16.3)	33 (6.0)	<0.001

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction, TIMI, thrombolysis in myocardial infarction.

effect of hyperglycemia.[13] Furthermore, hyperglycemia increased circulating TF procoagulant activity[14] and adhesion molecules.[15] It is hypothesized that all these mechanisms create a prothrombotic state and contribute to no reflow phenomena leading to a worse TIMI flow after primary PCI.

Our study did not evaluate the pathologic mechanism related with hyperglycemia, and therefore, further

Table 2 Multivariate predictors of final TIMI flow 0–1 (logistic regression)

Variable	OR (95% CI)	*p*-Value
Hyperglycemia	5.58 (1.3–23.9)	0.02
Age >65 years	0.28 (0.03–2.33)	0.24
Male	0.87 (0.18–4.20)	0.87
Diabetes mellitus	0.78 (0.21–2.83)	0.70
Hypertension	1.17 (0.35–3.97)	0.79
Smoking	0.48 (0.13–1.75)	0.27
Anterior MI	1.15 (0.35–3.80)	0.81
Creatinine ≥ 1.3 mg/dL	0.85 (0.25–3.02)	0.84
TIMI risk score >4	2.11 (0.50–8.81)	0.30
Killip classification >1	2.79 (0.73–10.67)	0.13

Abbreviations: CI, confidence interval; MI, myocardial infarction; OR, odds ratio; TIMI, thrombolysis in myocardial infarction.

Table 3 Multivariate predictors of 1-year mortality

	HR (95% CI)	*p*-Value
Hyperglycemia	2.0 (1.13–3.53)	0.01
Age >65 years	1.16 (0.61–2.19)	0.63
Male	0.91 (0.41–2.03)	0.83
Diabetes mellitus	1.29 (0.72–2.31)	0.39
Hypertension	0.64 (0.38–1.07)	0.09
Smoking	1.06 (0.59–1.88)	0.83
Anterior wall MI	0.96 (0.58–1.60)	0.9
Creatinine ≥1.3 mg/dL	2.29 (1.37–3.83)	0.002
TIMI risk score >4	2.8 (1.54–5.07)	0.001
Killip classification >1	2.03 (1.18–3.50)	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Table 4 Multivariate predictors of 1-year mortality using the interaction of hyperglycemia and final TIMI flow 0–1 as the reference (Cox regression)

	HR (95% CI)	*p*-Value
Hyperglycemia and final TIMI flow 0–1	9.40 (2.34–37.81)	0.002
Age >65 years	0.78 (0.41–1.47)	0.45
Male	0.91 (0.41–2.04)	0.83
Diabetes mellitus	1.79 (1.06–3.02)	0.02
Hypertension	0.60 (0.36–1.01)	0.05
Smoking	1.08 (0.60–1.93)	0.78
Anterior MI	0.95 (0.57–1.58)	0.84
Creatinine ≥1.3 mg/dL	2.55 (1.54–4.25)	<0.001
TIMI risk score >4	2.77 (1.52–5.05)	0.001
Killip classification >1	1.97 (1.14–3.42)	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

experimental studies are needed to find the pathologic mechanism of hyperglycemia affects the TIMI flow.

Our study showed an association of hyperglycemia and a worse final TIMI flow after primary PCI. However, a previous study showed an association of hyperglycemia with a worse baseline TIMI flow before primary PCI,[7] suggesting that hyperglycemia plays an important role to determine the coronary perfusion before and after primary PCI. The procoagulant and prothrombotic state related to hyperglycemia are probably the reasons for a worse TIMI flow during primary PCI.

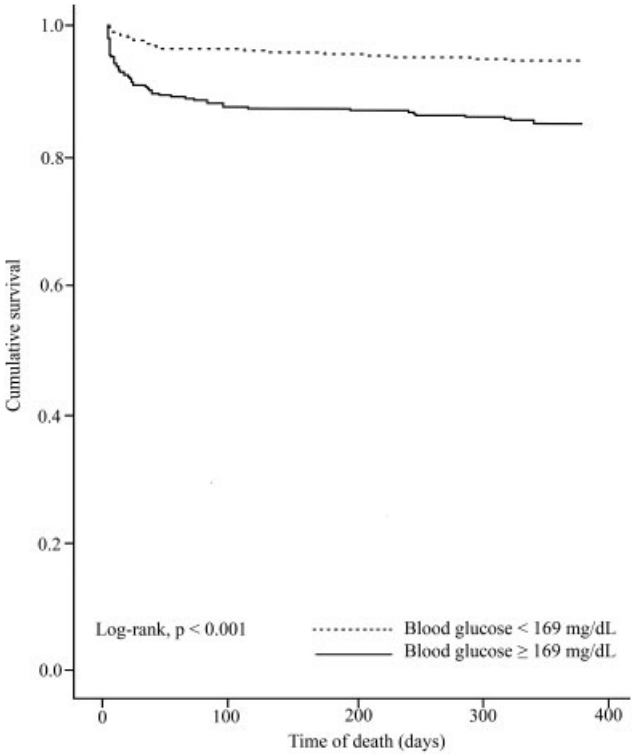

Fig. 2 Kaplan–Meier cumulative survival estimates at 365 days in patients with blood glucose ≥169 mg/dL and <169 mg/dL.

Clinical Implication

The results of this study may help clinicians with early risk stratification of patients with STEMI undergoing primary PCI who are at higher risk of mortality.

The interaction of hyperglycemia and TIMI flow found in this study suggests that achieving a better final TIMI flow after primary PCI may be facilitated by an aggressive control of the blood glucose before primary PCI. Aggressive blood glucose control using insulin infusion has been associated with a better long-term clinical outcome than standard treatment in patients with AMI.[18–20] However, not all study showed the benefit of an intensive insulin-based glucose control in patients with AMI.[21] Importantly, the effort of controlling the blood glucose before primary PCI should not delay the reperfusion therapy and thereby should not prolong the door-to-device time of the PCI center.

The targeted blood glucose level during the acute phase of STEMI has not been standardized yet. Several studies used different cutoff to define hyperglycemia such as ≥180 mg/dL[22,23] or ≥140 mg/dL.[7] Although all studies showed different cutoff values to define hyperglycemia, all the studies suggest benefits of reducing hyperglycemia in patients presented with AMI.[7,22,23]

In addition, this study found that patients with hyperglycemia were patients with high-risk profile as shown by more patients presented with TIMI risk score >4, Killip classification II to IV at presentation and baseline creatinine level ≥1.3 mg/dL than patients with lower blood glucose level (►**Table 1**). The high-risk profile may contribute to the lower cumulative survival at 1 year of patients with hyperglycemia as compared with patients with lower blood glucose level (►**Fig. 2**).

Study Limitation

In this study, we did not evaluate the direct mechanism of hyperglycemia on coronary artery flow after primary PCI. The association of hyperglycemia and TIMI flow was evaluated on the basis of the statistical interaction. Moreover, this study was a retrospective analysis and data were collected from a registry.

Conclusion

A higher proportion of patients with acute STEMI who presented with hyperglycemia had final TIMI flow 0 to 1 after primary PCI. The interaction of hyperglycemia and final TIMI flow 0 to 1 was associated with an increased risk for 1-year mortality. This study suggests that aggressive control of hyperglycemia prior to primary PCI may facilitate better angiographic and clinical outcomes after primary PCI.

Source of Funding
No external funding support.

Disclosures
None.

Funding
There is no funding to support this study and this study has no relationship with any industrial company. All authors have no conflict of interest to declare.

Conflict of Interest
None declared.

Acknowledgments
The authors thank all the nurses and physicians at the emergency department and the catheterization laboratory of the hospital for their excellent support.

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