Long-term prognostic value of admission haemoglobin A_{1c} (HbA_{1c}) levels in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract

Introduction: Many studies have reported the diagnostic and prognostic value of haemoglobin A_{1c} (HbA_{1c}) levels in patients with acute coronary syndrome. However, the short- and long-term prognostic value of HbA_{1c} level in patients with ST elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) is controversial.

Aim: To investigate whether admission HbA_{1c} level has a prognostic value for in-hospital, short-, and long-term cardiovascular (CV) mortality and major adverse cardiovascular events in patients with STEMI undergoing primary PCI.

Material and methods: This prospective study included 443 consecutive patients with STEMI who underwent primary PCI between September 2010 and July 2012. The patients were divided into three groups based on admission HbA_{1c} levels: group I ($HbA_{1c} \leq 5.6\%$), group II (HbA_{1c} 5.7–6.4%), and group III ($HbA_{1c} \geq 6.5\%$). The in-hospital, 1-month, and 1-year CV events of all 3 patient groups were followed up.

Results: A significant association was found between HbA_{1c} level and 1-year primary clinical outcomes, including CV mortality, non-fatal reinfarction, and stroke ($p = 0.037$). In addition, age, Killip class > 1, and left ventricular ejection fraction were found to be independent predictors of long-term CV mortality in multivariate analysis (hazard ratios (95% confidence interval) 1.081 (1.020–1.146), 4.182 (1.171–14.935), and 0.832 (0.752–0.920); $p = 0.009$, $p = 0.028$, and $p < 0.001$, respectively).

Conclusions: In this study, we demonstrated that increased admission HbA_{1c} levels were associated with higher rates of major adverse CV events, including mortality, non-fatal reinfarction, and stroke, in patients with STEMI who underwent primary PCI.

Key words: haemoglobin A_{1c}, prognosis, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention.

Introduction

Primary percutaneous coronary intervention (PCI) provides significant protection against cardiovascular (CV) mortality or reinfarction within 6 months of acute myocardial infarction (AMI) [1]. The AMI is still associated with a high risk for short – and long-term CV mortality. The stratification and differentiation of high-risk patients are very important to ameliorate prognosis. It is well known that diabetes mellitus (DM) is associated with increased rates of cardiovascular disease and mortality. This risk, which starts prior to impaired glucose tolerance, increases in both postprandial hyperglycaemia and non-diabetic conditions [2]. Haemoglobin A_{1c} (HbA_{1c}), which is a stable marker of long-term blood glucose control, reflects the average blood glucose concentrations over the previous 8–12 weeks [3]. Many meta-analyses and clinical studies in the literature have shown the diagnostic and prognostic value of glycated HbA_{1c} level in patients with DM and pre-DM [3–5]. Tenez *et al*. reported the predictive value of HbA_{1c} for long-term CV mortality and morbidity in post-myocardial infarction (MI) non-diabetic subjects [4], and a recent meta-analysis reported that a 0.9% decline in HbA_{1c} level led to a 17% decrease in major adverse cardiovascular events (MACE) during acute coronary syndrome in patients with DM [5].

The main pathophysiological mechanisms underlying this association between HbA_{1c} level and ST elevation myocardial infarction (STEMI) is unknown. Although the predictive value of HbA_{1c} was reported in patients with AMI in some previous studies, the short- and long-term

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prognostic value of this marker in STEMI patients who underwent primary PCI is controversial. While Cicek *et al*. showed the predictive role of HbA_{1c} for short-term CV mortality, Titan *et al*. did not support this finding [6, 7]. Moreover, both Timmer *et al*. and Singla *et al*. found controversial results regarding the prognostic value of HbA_{1c} for long-term CV mortality in this setting [8, 9]. There are few studies in the literature regarding the association of HbA_{1c} levels with in-hospital, short-, and long-term CV mortality and morbidity in patients with STEMI who underwent PCI, and those that exist have reported controversial results.

Aim

Therefore, we aimed to investigate whether admission HbA_{1c} level has a prognostic value for in-hospital, short-, and long-term CV mortality and MACE in patients with STEMI undergoing primary PCI. As expected, the main hypotheses of the present study were the occurrence of several acute or chronic CV events, including mortality, after STEMI due to the adverse effects of DM on the coronary vasculature and the strong independent prognostic value of HbA_{1c} level in predicting these events.

Material and methods

Patient population

In this prospective observational study, we included 530 consecutive patients admitted to a large-volume tertiary training and research hospital with a diagnosis of STEMI who underwent primary PCI between September 2010 and July 2012. The inclusion criterion was electrocardiography (ECG) revealing STEMI, which was defined as > 30 min of continuous typical chest pain and ST-segment elevation ≥ 2 mm in two contiguous ECG leads within 12 h of symptom onset or for up to 18 h if there was evidence of continuing ischaemia or haemodynamic instability. We excluded patients from our analysis who had no indication for PCI (n = 15), had no suitable coronary anatomy for PCI (n = 15), or had missing or unavailable data about admission HbA_{1c} levels (n = 57). Therefore, the final study population consisted of 443 patients. Using new American Diabetes Association (ADA) criteria, the patients were divided into three groups based on admission HbA_{1c} levels: group I ($HbA_{1c} \leq 5.6\%$, n = 103), group II (HbA_{1c} 5.7–6.4%, n = 211), and group III ($HbA_{1c} \geq 6.5\%$, n = 129) [3]. All primary PCI procedures were performed in a single, high-volume tertiary care centre (> 3000 PCI/year) by expert operators who perform an average of > 75 PCIs per year.

Eligible patients were between 18 and 80 years of age and all were able to provide written informed consent, which was a prerequisite for enrolment. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee.

Analysis of patient data

Baseline characteristics of the patients, including demographic data, previous history of disease, vital signs on admission, laboratory results, reperfusion and door-to-balloon times, and details of the MI were recorded. The drugs administered to each patient during the hospital stay were also recorded. Primary and secondary clinical outcomes were followed up in-hospital and after 1 month and 1 year of the index event.

On admission, venous blood samples were obtained from all patients. Blood samples for HbA_{1c} were obtained in the first 24 h after admission. The admission HbA_{1c} level was assayed using an automated, high-performance, liquid chromatography analyser (Trinity Biotech, Jamestown, NY, USA). A 12-lead ECG was recorded for each patient just after hospital admission; the MI type was obtained from the ECG. Twenty-four to 72 h after revascularisation, a transthoracic echocardiographic examination was performed using a Vivid S5 3S-RS probe(GE Healthcare, WI, USA) with a 1.7/3.4-MHz phased array transducer. The left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method [10], the glomerular filtration rate (GFR) was calculated using the measured plasma creatinine levels, and the Modification of Diet in Renal Disease (MDRD) formula was used to estimate renal function [11].

Coronary angiography and primary percutaneous coronary intervention

Chewable acetylsalicylic acid (300 mg) and a loading dose of clopidogrel (600 mg) were prescribed to all patients without contraindications. Primary PCI was initiated using standard techniques. The access approach was either transfemoral or transradial. During the procedure, non-ionic, low-osmolality contrast media were used and the coronary artery was confirmed to be clinically significant if its stenosis was more than 50%. Angiographic data of the patients were evaluated from catheter laboratory records. The artery that was presumed to be unobstructed was injected first. Blood flow in the infarct-related artery (IRA) was graded according to the Thrombolysis in Myocardial Infarction classification [12]. Heparin (100 IU/kg) was administered when the coronary anatomy was first defined. After visualising the left and right coronary arteries, 2.5 µg of nitrate was selectively injected into the IRA to rule out a possible coronary spasm. An angiographic evaluation was made by visual assessment. Primary angioplasty (including balloon angioplasty and/or stent implantation) was performed only on the IRA, according to lesion type. For each procedure, interventional success at the acute phase was defined as a reduction to 30% of obstruction and stenosis of the IRA with Thrombolysis in Myocardial Infarction 3 flow just after primary angioplasty. After the PCI procedure, 300 mg of acetylsalicylic acid was administered for 3 days, after which a persistent low-

dose regimen (100 mg) in conjunction with clopidogrel was continued in all patients. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

Definitions

Reperfusion time was defined as the time from onset of symptoms until coronary reperfusion was obtained with balloon inflation. The door-to-balloon time was defined as the time between hospital admission and balloon inflation. Acute clinical status was determined according to the Killip classification [13]. Advanced heart failure was defined as New York Heart Association classification ≥ 3. Anaemia was set as a baseline haemoglobin concentration < 13 mg/dl in males and < 12 mg/dl in females. Renal failure was defined as a GFR < 60 ml/min per 1.73 m², which was calculated by the MDRD formula [11]. The DM was defined as a history of DM or the use of insulin or any other anti-diabetic drug to control blood glucose. In accordance with the 2012 revised ADA criteria, prediabetes was defined as an HbA_{1c} of 5.7–6.4% in non-diabetic patients [3]. Cardiovascular mortality was defined as unexplained sudden death due to acute STEMI, acute heart failure, or haemodynamically significant arrhythmia. We set the repeat target vessel revascularisation (TVR) as the need for PCI or coronary artery bypass surgery because of restenosis or reocclusion of the IRA. Reinfarction was defined according to the third universal definition of MI guidelines [14]. We determined the occurrence of definite or probable stent thrombosis based on Academic Research Consortium criteria [15].

Follow-up

Follow-up data of the study patients were obtained from hospital records or by interviewing (in person or by telephone) the patients, their families, or their personal physicians. Primary clinical outcomes consisted of the sum of CV mortality, non-fatal reinfarction, and stroke. Secondary clinical outcomes were CV mortality, non-fatal reinfarction, TVR, stroke, and advanced heart failure.

Statistical analysis

Quantitative variables are presented as mean ± SD, and qualitative variables are expressed as number and rate. For stratification analysis, the study population was divided into three groups according to admission HbA_{1c} levels. Baseline characteristics of the study groups were compared using Pearson's χ^2 test for qualitative variables and univariate analysis of variance test for quantitative variables. A backward stepwise multivariate Cox regression analysis, which included variables with *p*-values < 0.1, was performed to identify independent predictors of long-term CV mortality. The cumulative survival curve for 1-year CV mortality was constructed using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was indicated when a two-sided *p*-value was < 0.05. All statistical analyses were carried out using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

Baseline demographic, clinical, and laboratory characteristics of the study groups are summarised in Table I. The mean HbA_{1c} level of the study population was 6.50 ±1.47% (range: 4.60–13.60). Group III was older and had more reperfusion time than the other groups; the prevalence of DM was also found to be higher in the highest HbA_{1c} group. The body mass index (BMI) of group III was significantly higher than that of group I, but it was not significantly higher than that of group II. In addition, the prevalence of hyperlipidaemia was higher in group III than in group I or II. The other baseline clinical characteristics of the patients were similar among the three groups.

Laboratory findings

Comparison of the laboratory characteristics of the study groups are reported in Table II. Higher glucose and lower haematocrit levels were observed in group III at admission ($p < 0.001$ and $p < 0.001$, respectively). Peak troponin T level was found to be higher in group II than in group I ($p = 0.001$), but there was no statistically significant difference between groups II and III. There were no statistically significant differences in baseline creatinine, total cholesterol, LDL cholesterol, or HDL cholesterol levels or white blood cell counts among the groups.

Angiographic and procedural characteristics

Comparisons of the angiographic and procedural characteristics of the study groups are shown in Table III. Culprit lesions were similar in the three groups; however, the patients in group III had three-vessel disease more often than those in the other groups ($p < 0.02$). The rates of unsuccessful procedure and stent implantation were not statistically different among the three groups ($p > 0.05$).

Medical therapy at discharge

At the time of discharge from the hospital, insulin was prescribed significantly more often in group III than in the other groups ($p < 0.001$). Duration of dual antiplatelet therapy after PCI and prevalence of use of other medications were similar among the three groups (Table III).

In-hospital outcomes

The in-hospital outcomes of the patient groups after primary PCI are shown in Table IV. The primary clinical outcomes, including CV mortality, were found to be similar among the groups ($p = 0.311$). The rate of stroke was higher in the lowest HbA_{1c} group ($p = 0.036$). While

Table I. Baseline demographic, clinical, and laboratory characteristics of the study groups

Parameter	$HbA_{1c} \leq 5.6$ (*n* = 103)	$5.7 \leq HbA_{1c} \leq 6.4$ (*n* = 211)	$HbA_{1c} \geq 6.5$ (*n* = 129)	Value of *p*
Age [years] (SD)	51 ±12	55 ±12	57 ±12	**< 0.01**
Male gender, *n* (%)	89 (86.4)	168 (79.6)	105 (77.5)	0.209
BMI [kg/m²] (SD)	22.1 ±3.0	23.3 ±4	24 ±4	**0.003**
Smoking, *n* (%)	83 (80.6)	161 (76.3)	87 (67.4)	0.56
DM, *n* (%)	1 (1.9)	8 (3.8)	73 (56.6)	**< 0.001**
Hypertension, *n* (%)	31 (30.1)	64 (30.3)	58 (45)	**0.013**
Hyperlipidaemia, *n* (%)	5 (4.98)	36 (17.1)	35 (25.6)	**< 0.001**
By-pass history, *n* (%)	0	5 (2.4)	5 (3.9)	0.144
PCI history, *n* (%)	11 (10.7)	27 (12.9)	21 (16.3)	0.444
MI history, *n* (%)	11 (10.7)	30 (14.2)	28 (21.7)	0.53
Stroke history, *n* (%)	2 (1.9)	7 (3.3)	6 (4.7)	0.524
Anterior MI, *n* (%)	49 (47.6)	92 (43.6)	52 (40.3)	0.541
Killip class > 1, *n* (%)	4 (3.9)	14 (6.6)	10 (7.8)	0.469
RV MI, *n* (%)	22 (21.4)	35 (16.6)	24 (18.6)	0.586
SBP [mm Hg] (SD)	130 ±33	134 ±32	137 ±33	0.189
DBP [mm Hg] (SD)	80 ±17	83 ±19	82 ±21	0.503
Heart rate [bpm] (SD)	77 ±18	77 ±18	81 ±19	0.139
Reperfusion time [min] (SD)	200 ±115	250 ±141	277 ±149	**< 0.001**
Door-to-balloon time [min] (SD)	41 ±14	42 ±15	45 ±16	0.190

SD – standard deviation, DM – diabetes mellitus, PCI – percutaneous coronary intervention, RV – right ventricular, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MI – myocardial infarction

Table II. Comparison of laboratory characteristics among haemoglobin A_{1c} (HbA_{1c}) groups

Parameter	$HbA_{1c} \leq 5.6$ (*n* = 103)	$5.7 \leq HbA_{1c} \leq 6.4$ (*n* = 211)	$HbA_{1c} \geq 6.5$ (*n* = 129)	Value of *p*
Creatinine [mg/dl] (SD)	0.93 ±0.57	0.95 ±0.35	0.95 ±0.39	0.911
GFR [ml/min/1.73 m²] (SD)	110 ±30	104 ±37	107 ±35	0.347
Peak CK-MB [IU/l] (SD)	116.6 ±111.6	160.4 ±146.5	131.7 ±140.5	**0.024**
Peak troponin-T [ng/ml] (SD)	7.6 ±8.6	12.9 ±12.2	10.8 ±11.9	**0.001**
Total-cholesterol [mg/dl] (SD)	195.4 ±43.9	201.7 ±42.9	196.6 ±55.9	0.455
LDL-cholesterol [mg/dl] (SD)	130.3 ±34	138.1 ±34.8	128.6 ±40.7	**0.045**
HDL-cholesterol [mg/dl] (SD)	40.2 ±9.3	41.8 ±11.1	41.1 ±9.6	0.430
Triglycerides [mg/dl] (SD)	111.6 ±80.5	129.7 ±86.9	134.1 ±162.5	0.492
Glucose [mg/dl] (SD)	135.6 ±41.6	144.8 ±50.7	224.4 ±16.6	**< 0.001**
WBC [10³/l] (SD)	12.2 ±3.9	12.5 ±8.5	12.0 ±3.8	0.753
Neutrophil [10³/l] (SD)	8.8 ±4.2	9.1 ±3.7	9.6 ±4.2	0.519
Haematocrit [g/dl] (SD)	43.9 ±5.3	42.6 ±5.5	40.6 ±6.7	**< 0.001**
Platelet [10³/l] (SD)	255.5 ±66.1	257.7 ±71.8	257.8 ±74.6	0.960
LVEF (SD)	48.9 ±8.5	47.7 ±8.5	47.0 ±8.9	0.248

SD – standard deviation, CK-MB – creatinine kinase MB, LDL – low-density lipoprotein, HDL – high-density lipoprotein, WBC – white blood cell, GFR – glomerular filtration rate, LVEF – left ventricular ejection fraction

no-reflow phenomenon was found significantly more frequently in group III than in group I ($p = 0.016$), there was no statistically significant difference between group III and II. Atrial fibrillation was significantly more prevalent in group II than in group I and III ($p = 0.035$). The other in-hospital patient outcomes were similar among the three groups (Figure 1).

One-month outcomes

The 1-month outcomes of the patients are reported in Table V. There were no differences between the three groups in terms of primary clinical outcomes ($p > 0.219$). The rate of TVR was found to be significantly more frequent in group III than in group I ($p = 0.045$), but it was not statistically different between group III and II

Table III. Comparison of angiographic and procedural characteristics among haemoglobin A_{1c} (HbA_{1c}) groups

Parameter	$HbA_{1c} \leq 5.6$ (*n* = 103)	$5.7 \leq HbA_{1c} \leq 6.4$ (*n* = 211)	$HbA_{1c} \geq 6.5$ (*n* = 129)	Value of *p*
Culprit lesion, *n* (%):				0.604
LAD	49 (48)	97 (46.6)	50 (39.4)	
LCX	12 (11.8)	24 (11.5)	12 (9.4)	
RCA	41 (40.2)	85 (40.9)	64 (50.4)	
Others	0	2 (1)	1 (0.8)	
Number vessel, *n* (%):				**0.020**
One-vessel disease	54 (52.9)	95 (45.7)	48 (37.8)	
Two-vessel disease	30 (29.4)	76 (33.7)	36 (28.3)	
Three-vessel disease	18 (17.6)	43 (20.7)	43 (33.9)	
Unsuccessful procedure	2 (2)	17 (8.2)	6 (4.7)	0.071
Stent use, *n* (%)	1.07 ±0.41	1.12 ±0.44	1.11 ±0.50	0.616
Stent length [mm] (SD)	23.3 ±8.4	23.7 ±10	22.8 ±10.9	0.755
Stent diameter [mm] (SD)	3.54 ±2.87	3.22 ±0.4	3.37 ±1.93	0.340
Procedure type, *n* (%):				0.310
PTCA	10 (9.9)	16 (7.7)	16 (12.6)	
Stent	30 (29.7)	46 (22.1)	29 (22.8)	
PTCA + stent	61 (60.4)	146 (70.2)	82 (64.6)	
DES use	4 (4.3)	2 (1)	4 (3.6)	0.179
Acetylsalicylic acid, *n* (%)	101 (98.1)	209 (99.1)	127 (98.4)	0.754
Clopidogrel, *n* (%)	101 (98.1)	209 (99.1)	127 (98.4)	0.754
β-Blocker, *n* (%)	86 (83.5)	179 (84.8)	108 (83.7)	0.940
ACEI/ARB, *n* (%)	79 (76.7)	169 (80.1)	102 (79.1)	0.786
Statin, *n* (%)	81 (78.6)	182 (86.3)	108 (83.7)	0.229
Insulin, *n* (%)	0	1 (0.5)	8 (6.2)	**< 0.001**

ACEI/ARB – angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, LCX – left circumflex artery, LAD – left anterior descending artery, RCA – right coronary artery, PTCA – percutaneous transluminal coronary angioplasty, DES – drug eluting stent

Table IV. Comparison of in-hospital adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

Parameter	$HbA_{1c} \leq 5.6$	$5.7 \leq HbA_{1c} \leq 6.4$	$HbA_{1c} \geq 6.5$	Value of *p*
Primary outcomes, *n* (%)	6 (5.8)	15 (7.1)	14 (10.8)	0.311
Secondary outcomes, *n* (%):				
CV mortality	3 (2.9)	6 (2.8)	5 (3.99)	0.858
Non-fatal reinfarction	2 (1.9)	10 (4.7)	10 (7.8)	0.126
TVR	2 (1.9)	11 (5.2)	9 (7)	0.209
Stroke	2 (1.9)	0	0	**0.036**
Advanced heart failure	7 (6.8)	13 (6.2)	11 (8.5)	0.706
CPR	5 (4.9)	8 (3.8)	6 (4.7)	0.882
VT	3 (2.9)	9 (4.3)	3 (2.3)	0.603
VF	3 (2.9)	10 (4.79)	3 (2.3)	0.466
Use of inotropes	5 (4.9)	14 (6.6)	7 (5.4)	0.794
Cardiogenic shock	4 (3.9)	8 (3.8)	5 (3.9)	0.999
IABP usage	3 (2.9)	10 (4.7)	3 (2.3)	0.466
Atrial fibrillation	0	6 (2.9)	0	**0.035**
Acute thrombosis	2 (1.9)	11 (5.2)	8 (6.2)	0.286
Subacute thrombosis	0	0	1 (0.8)	0.296
Blood transfusion	0	0	2 (1.6)	0.087
No-reflow phenomenon	11 (10.9)	40 (19)	33 (26)	**0.016**
Use of tirofiban	37 (41.6)	73 (37.2)	36 (33.3)	0.492

Primary outcomes – the sum of cardiovascular mortality, non-fatal reinfarction, and stroke. Secondary outcomes – cardiovascular mortality, non-fatal reinfarction, TVR, stroke, and advanced heart failure. IABB – intra-aortic balloon pump, VT – ventricular tachycardia, VF – ventricular fibrillation, TVR – target-vessel revascularisation

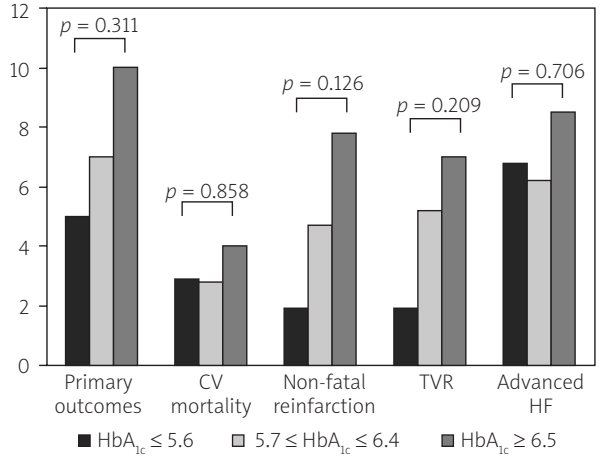

Figure 1. Comparison of in-hospital adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

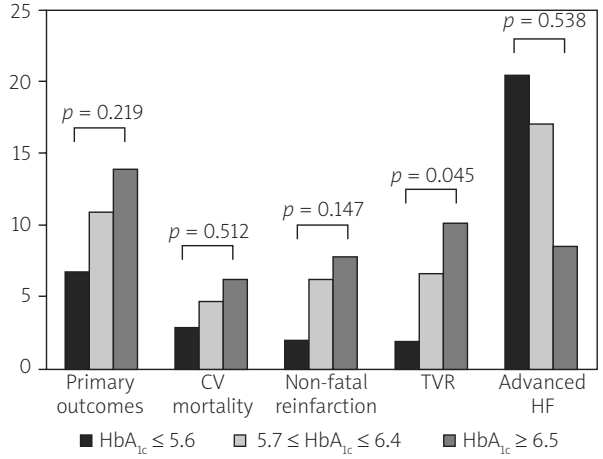

Figure 2. Comparison of 1-month adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

Table V. Comparison of 1-month adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

Parameter	$HbA_{1c} \leq 5.6$	$5.7 \leq HbA_{1c} \leq 6.4$	$HbA_{1c} \geq 6.5$	Value of *p*
Primary outcomes, *n* (%)	7 (6.7)	23 (10.9)	18 (13.9)	0.219
Secondary outcomes, *n* (%):				
Cardiovascular mortality	3 (2.9)	10 (4.7)	8 (6.2)	0.512
Non-fatal reinfarction	2 (1.9)	13 (6.2)	10 (7.8)	0.147
TVR	2 (1.9)	14 (6.6)	13 (10.1)	**0.045**
Stroke	2 (1.9)	0	0	**0.036**
Advanced heart failure	21 (20.4)	36 (17.1)	28 (21.7)	0.538

Primary outcomes – the sum of cardiovascular mortality, non-fatal reinfarction, and stroke. Secondary outcomes – cardiovascular mortality, non-fatal reinfarction, TVR, stroke, and advanced heart failure. TVR – target-vessel revascularisation

Table VI. Comparison of 1-year adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

Parameter	$HbA_{1c} \leq 5.6$	$5.7 \leq HbA_{1c} \leq 6.4$	$HbA_{1c} \geq 6.5$	Value of *p*
Primary outcomes, *n* (%)	13 (12.6)	27 (12.7)	29 (22.4)	**0.037**
Secondary outcomes, *n* (%):				
Cardiovascular mortality	5 (4.9)	12 (5.7)	10 (7.8)	0.620
Non-fatal reinfarction	4 (3.9)	14 (6.6)	17 (13.2)	**0.021**
TVR	8 (7.8)	23 (10.9)	20 (15.5)	0.173
Stroke	4 (3.9)	1 (0.5)	4 (3.1)	0.079
Advanced heart failure	15 (14.7)	35 (16.6)	22 (17.2)	0.871

Primary outcomes – the sum of cardiovascular mortality, non-fatal reinfarction, and stroke. Secondary outcomes – cardiovascular mortality, non-fatal reinfarction, TVR, stroke, and advanced heart failure. TVR – target-vessel revascularisation

(Figure 5). However, the rate of stroke was higher in the lowest HbA_{1c} group ($p = 0.036$) (Figure 2).

One-year outcomes

The 1-year outcomes of the study groups are presented in Table VI. The primary outcomes were found to be significantly higher in group III compared to group I and II ($p = 0.037$). In addition, while the rate of non-fatal reinfarction was more frequent in group III than in group I ($p = 0.021$), it was not statistically different between group III and II. No significant differences were observed among the three groups in terms of CV mortality, TVR, advanced heart failure, or stroke when they were investigated individually ($p > 0.05$) (Figure 3).

A Kaplan-Meier survival plot for 1-year CV mortality in all groups is presented in Figure 4. The independent predictors of CV mortality, such as age, male gender, BMI, DM, hypertension, history of MI, Killip class, GFR, peak troponin, LVEF, and HbA_{1c}, were included in a Cox regression model and analysed in a stepwise fashion. Age, Killip class > 1, and LVEF were found to be independent predictors for 1-year CV mortality after adjustment for other

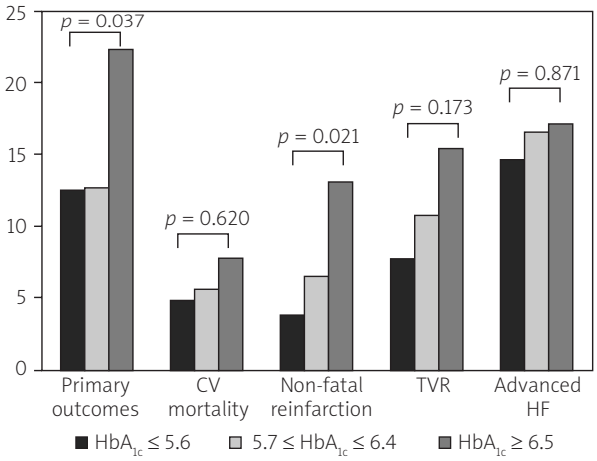

Figure 3. Comparison of 1-year adverse cardiovascular events among haemoglobin A_{1c} (HbA_{1c}) groups

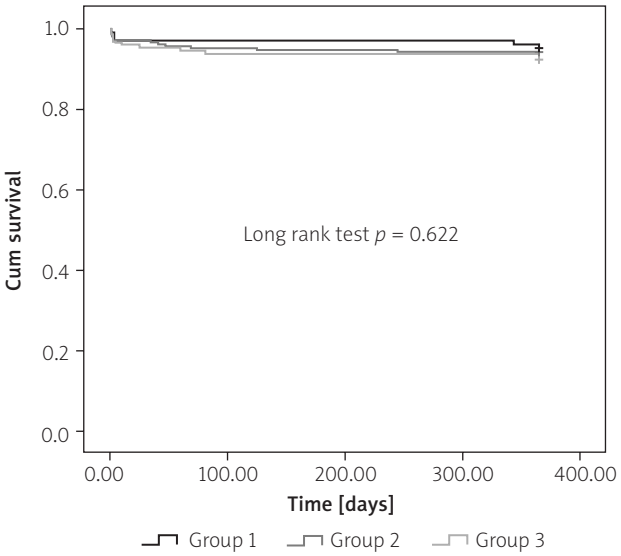

Figure 4. Kaplan-Meier survival plot for 1-year CV mortality in all groups

Table VII. Univariate and multivariate analyses for predictors of 1-year cardiovascular mortality

Parameter	Univariate		Value of *p*	Multivariate		Value of *p*
	OR	95% CI		OR	95% CI	
Age [years]	1.112	1.078–1.142	**< 0.001**	1.081	1.020–1.146	**0.009**
Gender, male	2.557	1.171–5.584	**0.019**			
BMI	0.865	0.755–0.991	**0.037**			
DM	3.121	1.448–6.725	**0.004**			
Hypertension	2.082	0.979–4.430	0.057			
MI history	1.675	0.614–4.571	0.314			
Killip class > 1	10.364	4.739–22.670	**< 0.001**	4.182	1.171–14.935	**0.028**
GFR [ml/min/1.73 m²]	0.966	0.953–0.979	**< 0.001**			
Peak troponin [ng/ml]	1.047	1.020–1.075	**0.001**			
LVEF	0.836	0.822–0.891	**< 0.001**	0.832	0.752–0.920	**< 0.001**
HbA_{1c}	1.132	0.913–1.402	0.258			

OR – odds ratio, CI – confidence interval, DM – diabetes mellitus, LVEF – left ventricular ejection fraction, BMI – body mass index, MI – myocardial infarction, GFR – glomerular filtration rate

risk factors (Table VII). However, admission HbA_{1c} level was not found to be associated with 1-year CV mortality in patients with STEMI who underwent primary PCI.

Discussion

The main findings of the present study were as follows. 1) The long-term primary clinical outcomes, which consisted of the sum of CV mortality, non-fatal reinfarction, and stroke, were found to be significantly increased in the highest HbA_{1c} tertile, while there was no difference among the three groups in terms of in-hospital and 1-month CV events. 2) The long-term rate of non-fatal reinfarction was higher in the upper HbA_{1c} groups. 3) Age, LVEF, and Killip class were found to be independent predictors of long-term CV mortality. Although some previous studies reported that HbA_{1c} had separate in-hospital, short-, and long-term predictive roles for CV mortality and MACE in STEMI, the present study found that HbA_{1c} had a concurrent in-hospital, short-, and long-term prognostic role in STEMI patients who underwent primary PCI.

Haemoglobin A_{1c} reflects the three-month blood glucose level, and it is not affected by acute metabolic changes [3]. There are controversial study results showing the association of HgA1c with higher in-hospital mortality and MACE rates in acute MI cases. Britton et al. reported no association of HgA1c with in-hospital mortality in their registry study; their subgroup analysis revealed this relationship only in diabetic STEMI patients [16]. However, in the retrospective study of Timmer et al., no association was found between HgA1c and 1-month mortality in diabetic STEMI patients who underwent PCI [8]. Moreover, Tian et al. reported no relationship between HgA1c and 1-month

mortality and MACE (all causes of mortality, cardiogenic shock, and reinfarction) in their prospective study [7]. Consistent with some previous studies, we found no relationship between HgA1c level and in-hospital and 1-month CV mortality in our study. However, in contrast to the Tian et al. study, we found increased rates of no-reflow phenomenon, TVR, and non-fatal reinfarction in the two higher HbA1c groups. These findings might be due to different baseline patient characteristics. While age, BMI, hypertension, DM, hyperlipidaemia, and three-vessel disease were found to be higher in the highest HbA1c group in our study, Tian et al. reported no differences between study groups in terms of baseline patient characteristics. The increased rate of primary and secondary clinical outcomes in the highest HbA1c group might be due to the occurrence of additional CV risks leading to these events. In contrast to our study, Cicek et al. reported that HbA1c level was related to in-hospital mortality in STEMI patients who underwent PCI [6]. In that study, LVEF was found to be significantly lower in the higher HbA1c group, which is different from the results of our study. In addition, their rate of in-hospital mortality was higher than that of our study (11% vs. 3.9%). The contradictory results between the two studies might be explained by different patient characteristics. The short- and long-term mortality of patients with STEMI might be related to reperfusion time, infarcted area, and/or other short-term complications. In our study, LVEF, age, and high Killip class were found to be associated with long-term CV mortality. It is possible that the highest HbA1c group included a more diffuse atherosclerotic involvement of epicardial vessels, a higher propensity for developing restenosis after PCI, and unremitting atherosclerotic progression causing de novo stenosis [17]. All of these factors might explain the high rate of MACE that is encountered in diabetic patients. In our study, the incidence of patients with three-vessel disease and the rate of 1-year non-fatal reinfarction were found to be higher in the highest HbA1c group, as was the rate of 1-month TVR.

In a previous observational study of 4176 non-diabetic STEMI patients treated with primary PCI, it was found that admission levels of HbA_{1c} were independently associated with long-term mortality after adjusting for other risk factors [8]. However, Singla *et al*. reported no association between HbA_{1c} levels and CV mortality at 12 months in patients with acute coronary syndrome who underwent successful stent implantation procedures [9]. In a retrospective, longitudinal, cohort study conducted by Kauffman *et al*., it was reported that HbA_{1c} level was not an independent predictor of CV events, even with aggressive treatment of secondary risk factors [18]. Similar to the Kauffman and Singla *et al*. studies, we did not demonstrate any significant relationship between admission HbA_{1c} level and long-term CV mortality in our study when it was assessed individually. However, we found a significant association between HbA_{1c} and long-term major adverse CV events, which consisted of the sum of CV mortality, non-fatal reinfarction, and stroke.

Long-term use of high-dose dual antiplatelet agents concomitant with the use of a statin, a β-blocker, and an ACE inhibitor for secondary prevention post-MI might produce a decrease in the adverse effects of chronic hyperglycaemia on CV mortality. This development in treatment strategies for STEMI, including primary PCI and coronary stenting, might explain the different results reported in recent studies [19, 20].

The main limitations of the present study include a short follow-up period and a low number of encountered clinical endpoints. Because HbA_{1c} levels were measured only once during admission, we could not evaluate changes in HbA_{1c} levels in response to aggressive treatment.

Conclusions

In this study, we demonstrated that increased admission HbA_{1c} levels were associated with higher rates of major adverse CV events, including mortality, non-fatal reinfarction, and stroke, in patients with STEMI who underwent primary PCI. Even after adjusting for various risk factors, age, LVEF, and Killip class were found to be independent predictors of long-term CV mortality in STEMI patients. HbA_{1c}, which reflects average blood glucose concentrations over the previous 8–12 weeks, is an inexpensive and readily available biomarker that provides an additional level of risk stratification, beyond that provided by conventional risk scores, in predicting long-term major adverse CV events in STEMI cases.

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