Influence of preoperative hemoglobin A1c on early outcomes in patients with diabetes mellitus undergoing off-pump coronary artery bypass surgery

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ABSTRACT

Objective: There seem to be modifiable components of diabetes in terms of glycemic control to improve surgical outcome. The aim of the study was to evaluate impact of preoperative glycated hemoglobin (HbA1c) level in patients with diabetes mellitus undergoing off-pump coronary bypass (OPCAB) on perioperative glycemic variability and short-term outcome.

Methods: Medical records of 703 patients with diabetes mellitus who underwent OPCAB from 2005 to 2017 were reviewed. The perioperative goal of glycemic control was <180 mg/dL. Patients were divided into 2 groups according to HbA1c level ($<7.0\%$ or $\geq 7.0\%$). Glycemic variability during surgery and up to 24 hours after surgery was assessed by coefficient of variation (CV). Primary outcome was defined as composite of postoperative permanent stroke, prolonged ventilation, deep sternal wound infection, renal failure, reoperation, and 30-day mortality.

Results: Incidence of composite of postoperative morbidity and mortality endpoints was greater in patients with HbA1c $\geq 7.0\%$ (21% vs 15%, $P = .041$). Perioperative time-weighted average glucose concentration was also greater in patients with HbA1c $\geq 7.0\%$, whereas the CV did not show any difference. Multivariable logistic regression analysis revealed that congestive heart failure, chronic kidney disease, moderate mitral regurgitation or greater, preoperative hemoglobin level, and preoperative HbA1c $\geq 7.0\%$ were independently associated with composite of postoperative morbidity and mortality, but perioperative CV and time-weighted average glucose ≥ 200 mg/dL were not.

Conclusions: Increased preoperative HbA1c ($\geq 7.0\%$) level reflecting long-term glycemic control seems to exert an adverse influence on outcome, whereas the influence of perioperative glycemic variables appear to be abrogated using a target glucose level of <180 mg/dL in patients with diabetes mellitus undergoing OPCAB. (J Thorac Cardiovasc Surg 2020;159:568-76)

DM and chronic and acute glycemic control have a mutual effect on postoperative outcome.

Central Message

Preoperative HbA1c of $\geq 7\%$ is a risk factor for increasing short-term postoperative composite morbidity/mortality in patients with diabetes undergoing off-pump coronary artery bypass.

Perspective

In patients with DM undergoing OPCAB, increased preoperative HbA1c ($\geq 7.0\%$) level has potential influence on short-term postoperative adverse outcome, whereas perioperative glycemic variables including CV have low prognostic significance at target glucose level of <180 mg/dL. A prospective trial is required to determine whether postponing the surgery to lower HbA1c level would yield improved outcomes.

See Commentary on page 577.

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Diabetes mellitus (DM) is a prevalent comorbidity among patients undergoing coronary artery bypass graft surgery (CABG) that is known to worsen outcome.^{1,2} Nonetheless, not all patients with DM undergoing cardiac surgery are at an increased risk of poor outcome. Several studies focused on influencing factors for increased risk, especially glycemic control, which has potential as a modifiable factor, have reported conflicting results.^{1,3,4}

Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CI	= confidence interval
CKD	= chronic kidney disease
CMM	= composite of postoperative morbidity and mortality
CPB	= cardiopulmonary bypass
CV	= coefficient of variation
DM	= diabetes mellitus
DSWI	= deep sternal wound infection
HbA1c	= glycated hemoglobin
ICU	= intensive care unit
OPCAB	= off-pump coronary artery bypass
SD	= standard deviation
TWAG	= time-weighted average glucose

Glycated hemoglobin (HbA1c) level, a well-known index measure of long-term glycemic control of recent 3 to 4 months, has been reported to be related to microvascular dysfunction, inducing organ damage.⁵ The relationship between elevated HbA1c level and detrimental outcome has been investigated in various subsets of surgical patients.⁶⁻⁸ From the perspective of short-term glycemic control, perioperative hyperglycemia as well as increased glycemic variability were closely associated with adverse outcome in patients undergoing cardiac surgeries.¹⁻³

Perioperative glycemic control is affected by preoperative HbA1c level and degree of surgical stress.⁷ Impact of HbA1c on perioperative glycemic control was influenced by severity of surgical stimulation such that at a greater level of stimulus, there was less effect of HbA1c on glycemic control.³ Thus, under cardiac surgery requiring cardiopulmonary bypass (CPB), a significant factor causing glucose dyshomeostasis,⁹ postoperative outcome might be less influenced by HbA1c level.¹⁰ In addition, DM was reported to alter the relationship between perioperative glycemic control and prognosis^{1,11} and weaken the influence of perioperative glycemic control on postoperative outcome.¹²

Off-pump coronary artery bypass surgery (OPCAB) without need for CPB results in less glucose dyshomeostasis than its on-pump counterpart⁹ and has been shown to be beneficial in certain groups of high-risk patients.^{13,14} Although DM has been recognized as a risk factor for adverse outcome in patients undergoing OPCAB, no comprehensive data have been reported on the distinguished impact of HbA1c level on perioperative glycemic control and prognosis. In this retrospective study, we aimed to investigate the effect of preoperative HbA1c level on perioperative glycemic variability and

short-term postoperative outcome in patients with DM undergoing OPCAB.

METHODS

Our institutional review board approved this study (no. 4-2018-0221), and the need for informed consent was waived. Data from electronic medical records were retrospectively collected from patients who underwent OPCAB from December 2005 to November 2017. Data of patients aged ≥ 20 years with history of preoperative DM and available results of HbA1c test within 3 months before surgery were included. Data of patients who had a history of previous CABG or whose surgery plan was changed to surgery through CPB were excluded.

Blood glucose levels were recorded before, during, and up to 24 hours after surgery in the intensive care unit (ICU). Intraoperative and postoperative glucose control and measurements were conducted under standard institutional guidelines. In the operating room, target blood glucose control in patients with DM was set to <180 mg/dL¹⁵ and was measured using arterial blood gas test at 30-, 60-, or 120-minute intervals as necessary, and hyperglycemia was controlled by intermittent regular insulin (Humulin; Eli Lilly and Company, Indianapolis, Ind) injection. In the ICU, target blood glucose level was <180 mg/dL, and arterial blood glucose level was checked every 2 to 4 hours for the 12-hour postoperative period and every 4 to 8 hours thereafter; in cases with blood glucose level >180 mg/dL for 2 consecutive measurements, insulin was injected per standard guideline (insulin protocol) of our institution. Per protocol, glucose concentration was checked at an interval of 2 hours until the target level was attained. The percent of hypoglycemia (blood glucose <60 mg/dL) and hyperglycemia (blood glucose >200 mg/dL) for each patient's readings that were examined was investigated. With regard to blood glycemic variability, standard deviation (SD) and coefficient of variation (CV) of blood glucose were evaluated during the perioperative period including intraoperative period and up to 24 hours postoperatively, and CV defined as the SD divided by the average was regarded as major variable.³ In addition, perioperative mean blood glucose concentration and time-weighted average glucose (TWAG) concentrations were calculated:

$$\text{TWAG} = \{[(X_1 + X_2)(T_2 - T_1) + (X_2 + X_3)(T_3 - T_2) + \dots + (X_{n-1} + X_n)(T_n - T_{n-1})]/[2 \times (T_n - T_1)]\}$$

where T_n is n th time point and X_n is the blood sugar concentration at T_n .

TWAG is the average value between 2 consecutive measurements weighted by the time interval in which the measurement was made. Because intra- and postoperative TWAG ≥ 200 mg/dL were known to adversely affect the outcome,¹ perioperative TWAG ≥ 200 mg/dL was also recorded for each patient.

Baseline patient demographic data were obtained including age, sex, presence of emergency operation, body surface area (m^2), euroSCORE, and history of hypertension, hyperlipidemia, cerebrovascular disease, congestive heart failure, unstable angina, myocardial infarction within 1 week before surgery, chronic kidney disease (CKD), chronic lung disease, peripheral arterial disease, and previous percutaneous coronary intervention. CKD was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 with the Chronic Kidney Disease Epidemiology Collaboration equation from serum creatinine.¹⁶ The Society of Thoracic Surgeons definitions were used for "cerebrovascular disease," "chronic lung disease," "peripheral arterial disease," and "prior percutaneous coronary intervention."¹⁷ Preoperative hemoglobin, creatinine, and albumin levels and estimated glomerular filtration rate calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation from serum creatinine¹⁶ were evaluated. Moderate or higher mitral regurgitation grades on the preoperative echocardiography were recorded. Administered preoperative medications including aspirin, clopidogrel, beta blockers, calcium channel blockers, renin-angiotensin system antagonists, insulin, oral hypoglycemic agents, and β -hydroxy β -methylglutaryl-CoA reductase inhibitors were recorded. All oral hypoglycemic agents were discontinued at the morning of

surgery, whereas other medications were all continued except clopidogrel, which was discontinued 3 to 5 days before surgery at the discretion of the attending physicians.

Assessment of intraoperative and postoperative data involved the number of grafts anastomosed, duration of operation, fluid and transfusion requirement, and urine output. During perioperative period, norepinephrine was used as first-line vasopressor, and vasopressin was administered in case of non-maintenance of target mean arterial pressure (65–80 mm Hg) under increasing dose of norepinephrine (up to $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; first quartile). Intraoperatively, patients who had mixed venous oxygen saturation of $<60\%$ for more than 10 minutes or new mitral regurgitation of grade ≥ 3 and mean pulmonary arterial pressure >30 mm Hg received milrinone. In the ICU, in cases with cardiac index $>2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or in whom mixed venous oxygen saturation $>60\%$ could not be maintained despite adequate preload and hematocrit level, milrinone was used as primary inotrope. Chest tube drainage for 24 hours postoperatively, use of vasopressor and inotrope for 48 hours postoperatively, and perioperative use of insulin were recorded. Days of ICU and hospital stay after surgery and major complications and death after surgery were recorded.

The primary goal of the study was to investigate the effect of preoperative HbA1c level on the composite of postoperative morbidity and mortality (CMM) endpoints within 30 days after surgery. The secondary goals were to investigate the effect of preoperative HbA1c level on perioperative glycemic variability and effect of short-term glycemic variability on CMM endpoints. Outcome variables were per definition of the Society of Thoracic Surgeons version 2.81 adult cardiac surgery database.¹⁷ These included permanent stroke (any confirmed neurologic deficit of abrupt onset caused by disturbance in blood supply to the brain), renal failure (serum creatinine level up to ≥ 4.0 mg/dL with increase of ≥ 0.5 mg/dL or $3\times$ most recent preoperative creatinine level; new requirement for dialysis postoperatively), prolonged ventilation (>24 hours), deep sternal wound infection (DSWI), and reoperation. The definition of operative mortality was all deaths, regardless of cause, that occurred during hospitalization in which operation was performed or before the end of postoperative day 30.

Statistical Analysis

In this study, enrolled patients were divided into 2 groups according to HbA1c level ($<7.0\%$ or $\geq 7.0\%$). HbA1c 7.0% is the reference point for predicting the occurrence of complications and mortality in studies including patients with DM.^{6,18} The American Diabetes Association recommends maintaining target HbA1c $<7.0\%$ in nonpregnant adults with DM.¹⁹ Postoperative complications, mortality, and perioperative glycemic variability were compared between patients with HbA1c $\geq 7.0\%$ and $<7.0\%$. Continuous variables were analyzed by independent *t* test or Mann–Whitney *U* test according to results from Shapiro–Wilk test for normality. Categorical variables were analyzed by the χ^2 test or Fisher exact test. All analyses were performed through Statistical Package for the Social Sciences (SPSS) version 23 software (IBM Corp, Armonk, NY), R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS (version 9.4; SAS Inc, Cary, NC).

“Age,” “sex,” and variables of interest “HbA1c $\geq 7.0\%$,” “perioperative CV” (as our main glycemic variables), “TWAG ≥ 200 mg/dL,” and clinically significant factors among preoperative characteristics that might affect postoperative outcome were entered into a multivariable logistic model for assessment of their impact on CMM. For satisfying the rule of 10, the variables with a *P* value of less than .05 in the univariable analysis were included preferentially. After that, the remaining variables that increase the predictive power of the model were also included within the range of the rule of 10. Statistical significance was set as *P* $< .05$.

RESULTS

Overall, 703 patients were included (Figure 1), and there were no missing data for validating our hypothesis.

Preoperative HbA1c was $<7\%$ in 287 patients (41%, normal HbA1c group) and $\geq 7.0\%$ in 416 patients (59%, high HbA1c group). Patients in the high HbA1c group were younger, with greater preoperative serum glucose levels (151 [114–211] mg/dL vs 128 [104–153] mg/dL, *P* $< .001$) and more frequent history of preoperative insulin use (16% vs 6%, *P* $< .001$) (Table 1). Remaining characteristics including comorbidities were similar between the groups.

In all patients, during perioperative period, arterial glucose measurements were conducted at least 6 times. Perioperative mean serum glucose concentration (183 [167–202] mg/dL vs 160 [147–178] mg/dL, *P* $< .001$), SD of glucose (37 [27–51] mg/dL vs 32 [23–41] mg/dL, *P* $< .001$), and patients with TWAG ≥ 200 mg/dL (11% vs 35%, *P* $< .001$) were significantly greater in the high HbA1c group than in the normal HbA1c group, whereas the CV showed no significant intergroup difference. Frequency of insulin use (89% vs 69%, *P* $< .001$) and hyperglycemic event (33.3% vs 11.1%, *P* $< .001$) were significantly greater in the high HbA1c group than in the normal HbA1c group (Table 2).

Operative data showed no statistically significant differences between the 2 groups (Table 3). Amount of postoperative bleeding (770 [580–981] mL vs 710 [541–890] mL, *P* = .012) and transfusion requirement of packed erythrocytes (37% vs 29%, *P* = .029) were significantly greater in the normal HbA1c group than in the high HbA1c group (Table 3).

Incidence of CMM endpoints was significantly greater in the high HbA1c group than in the normal HbA1c group (21% vs 15%, *P* = .041). DSWI was significantly more frequent (6% vs 2%, *P* = .019), whereas the high HbA1c group had a clinically meaningful greater incidence of renal failure, but this result did not reach statistical significance (5% vs 2%, *P* = .062) in the high HbA1c group than in the normal HbA1c group (Table 4). Mortality was not significantly different between the 2 groups.

In univariable analysis, congestive heart failure, CKD, previous percutaneous coronary intervention, moderate mitral regurgitation or greater, preoperative hemoglobin level, and preoperative HbA1c $\geq 7.0\%$ were positively associated with increased CMM endpoints. Perioperative glycemic variables were not significantly associated with CMM. In multivariable logistic regression analysis, congestive heart failure, CKD, moderate mitral regurgitation or greater, preoperative hemoglobin level, and preoperative HbA1c $\geq 7.0\%$ were independently associated with the CMM endpoints, but perioperative CV and TWAG ≥ 200 mg/dL were not (Table 5). When introducing the HbA1c as a continuous variable (excluding categorical HbA1c variable) to the multivariable model, it was not identified as an independent risk factor for adverse outcome (odds ratio, 1.126, 95% confidence interval [CI], 0.987–

FIGURE 1. Flowchart of the patients' enrollment. Among the 2491 patients who underwent off-pump coronary artery bypass surgery from December 2005 to November 2017 in the institution, 1108 (44.5%) patients were diagnosed with diabetes mellitus before surgery. Of the 1108 patients with diabetes mellitus, 394 did not meet the inclusion criteria. Among the remaining 714 patients, 9 patients who received redo off-pump coronary artery bypass surgery and 2 patients who were converted to an emergent on-pump surgery were excluded. Finally, 703 patients were divided into 2 groups based on a preoperative HbA1c level of 7.0%. *OPCAB*, Off-pump coronary artery bypass; *DM*, diabetes mellitus; *CPB*, cardiopulmonary bypass; *HbA1c*, glycated hemoglobin.

1.285, $P = .078$), whereas the significance of other variables did not change. Receiver operator-characteristic curve analysis revealed HbA1c 7.85% as the optimal threshold for CMM endpoints (area under the curve; 0.556, 95% CI, 0.501-0.611, $P = .048$) and DSWI (area under the curve: 0.661; 95% CI, 0.565-0.757, $P = .002$).

The mortality (β : -0.038 , $P = .528$) and morbidity (β : 0.428 , $P = .228$) rates did not vary over the study period (12 years). Thus, dividing the time frame was not considered.

DISCUSSION

In the current study, preoperative HbA1c of $\geq 7\%$ was determined as an independent risk factor for short-term adverse outcome in patients with DM undergoing OPCAB. Preoperative HbA1c of $\geq 7\%$ adversely affected perioperative glycemic variables, including the SD, mean, and TWAG, but not the CV of glucose. None of the glycemic variables except HbA1c $\geq 7\%$ was associated with unfavorable prognosis.

DM,³ HbA1c,^{6,8} and perioperative glycemic control^{1,20} are closely interlinked variables, either independent or interrelated, that have been shown to exert adverse

influence on outcome after cardiac surgery through the following underlying mechanisms (Figure 2). DM is known to worsen endothelial function and increase oxidative stress and inflammation; chronic hyperglycemia, reflected by increased HbA1C level, has been shown to further aggravate cell damage.²¹ A representative study investigating the role of HbA1c in outcome after cardiac surgery showed that hospital mortality, cerebrovascular accident, renal failure, and DSWI were significantly increased in patients with HbA1c $\geq 7\%$, regardless of the presence of DM.⁶ Interestingly, the prognostic role of increased HbA1c was limited to fewer complications in patients with DM. In another study including patients with and without DM undergoing CABG, HbA1c was identified as an independent risk factor for respiratory complication and sternal wound infection in patients with DM, whereas its adverse influence disappeared in patients without DM.²²

These controversies are also present in studies focusing on perioperative glycemic control. Perioperative hyperglycemia is known to reduce leucocyte activity, activate coagulation, and delay recovery.²³ In addition, acute glucose fluctuation causes oxidative stress²⁴ and endothelial dysfunction.²⁵ Indeed, with regard to increased glycemic variability, both

TABLE 1. Preoperative characteristics of patients

Variable	HbA1c <7% n = 287	HbA1c ≥7% n = 416	P value
Patient			
Age, y	67 ± 8	65 ± 8	.014
Female sex	79 (28%)	125 (30%)	.469
Emergency	2 (1%)	8 (2%)	.212
Body surface area, m ²	1.70 ± 0.16	1.72 ± 0.38	.561
Hypertension	235 (82%)	326 (78%)	.254
Cerebrovascular accident	51 (18%)	58 (14%)	.168
Congestive heart failure	51 (18%)	62 (15%)	.309
Chronic kidney disease	36 (13%)	57 (14%)	.656
Chronic lung disease	21 (7%)	22 (5%)	.270
Peripheral arterial disease	21 (7%)	45 (11%)	.118
Previous percutaneous coronary intervention	85 (30%)	110 (26%)	.355
Moderate mitral regurgitation or greater	7 (2.4%)	15 (3.6%)	.384
Unstable angina	105 (37%)	142 (34%)	.503
Myocardial infarction within 1 wk	22 (8%)	48 (12%)	.092
Left main >50% stenosis	87 (31%)	105 (26%)	.224
Triple coronary artery disease	247 (86%)	375 (90%)	.096
Preoperative medications			
Aspirin	236 (82%)	348 (84%)	.621
Clopidogrel	186 (65%)	247 (59%)	.145
Beta blocker	168 (59%)	250 (60%)	.679
Calcium channel blocker	144 (50%)	180 (43%)	.071
RAS inhibitor	174 (61%)	245 (59%)	.645
Statins	211 (74%)	305 (73%)	.953
Oral hypoglycemic agents	253 (88%)	361 (87%)	.590
Insulin	16 (6%)	68 (16%)	<.001
euroSCORE	4 [3-6]	4 [3-6]	.654
Laboratory data			
Serum glucose level, mg/dL	128 [104-153]	151 [114-211]	<.001
Hemoglobin level, g/dL	12.6 ± 1.8	12.6 ± 1.9	.993
Serum albumin level, g/dL	4.1 [3.8-4.4]	4.1 [3.7-4.4]	.076

Values are mean ± standard deviation, median [first quartile-third quartile], or the number of patients (percent). *HbA1c*, Glycated hemoglobin; *RAS*, renin-angiotensin system; *euroSCORE*, European System for Cardiac Operative Risk Evaluation.

the CV and hyperglycemia (>200 mg/dL) have been reported to be predictors of poor prognosis in patients undergoing cardiac surgery¹; however, intraoperative glycemic control to near normoglycemic level was not associated with reduced risk in the same study. In some cases, the presence of DM

may regulate negative influence of poor perioperative glycemic control on outcome, with consequent less net influence. In critically ill patients, interaction between hyperglycemia and/or glycemic variability and mortality was reported to be much stronger in patients without DM.^{26,27} The optimal

TABLE 2. Glycemic variables during operation and 24 hours postoperatively

Variable	HbA1c <7% n = 287	HbA1c ≥7% n = 416	P value
Mean glucose, mg/dL	160 [47-178]	183 [167-202]	<.001
TWAG, mg/dL	164 [145-182]	185 [164-208]	<.001
TWAG >200, mg/dL	31 (11%)	144 (35%)	<.001
SD of glucose, mg/dL	32 [23-41]	37 [27-51]	<.001
CV of glucose, %	20.0 [14.6-25.3]	20.8 [15.1-28.1]	.094
Perioperative use of insulin	198 (69%)	372 (89%)	<.001
Hyperglycemic event, %	11.1 [0.0-25.0]	33.3 [12.5-50.0]	<.001
Hypoglycemic event, %	0.0 [0.0-0.0]	0.0 [0.0-0.0]	.691

Values are median [first quartile-third quartile] or the number of patients (percent). *HbA1c*, Glycated hemoglobin; *TWAG*, time-weighted average glucose; *SD*, standard deviation; *CV*, coefficient of variation.

TABLE 3. Intraoperative and postoperative data

Variable	HbA1c <7% n = 287	HbA1c ≥7% n = 416	P value
Intraoperative			
Graft number	3 [3-4]	3 [3-4]	.262
Duration of anesthesia, min	300 [275-330]	300 [275-330]	.717
Crystalloids, mL	1900 [1350-2500]	1800 [1350-2500]	.872
Colloids, mL	500 [500-1000]	500 [500-1000]	.227
Urine output, mL	380 [220-630]	365 [210-603]	.497
Number of patients transfused	101 (35%)	139 (33%)	.625
Salvaged blood, mL	200 [120-250]	173 [120-240]	.066
Postoperative			
Crystalloid for 24 h, mL	3298 [2866-3945]	3461 [3033-3865]	.228
Colloid for 24 h, mL	250 [0-500]	235 [0-500]	.304
Urine output for 24 h, mL	2955 [2425-3420]	2930 [2370-3460]	.557
Bleeding for 24 h	770 [580-981]	710 [541-890]	.012
Patients transfused with RBC	106 (37%)	121 (29%)	.029
Vasopressor use for 48 h	208 (73%)	283 (68%)	.207
Inotrope use for 48 h	45 (16%)	68 (16%)	.813

Values are median [first quartile-third quartile] or the number of patients (percent). HbA1c, Glycated hemoglobin; RBC, red blood cell.

target of glycemic control in patients with DM, especially those with high HbA1c levels, is not clear, as due to cellular adaptation to the high-glucose milieu, mild-to-moderate hyperglycemia may be beneficial to these patients.^{28,29} In addition to the complex interrelationship among DM, HbA1c, and perioperative glycemic control, inconsistencies regarding their influence on outcome after cardiac surgery may be attributed to the use of CPB. CPB inevitably provokes glucose dyshomeostasis, which is expected to significantly alter the interrelationship among DM and glycemic variables, as well as their prognostic value.

OPCAB is an important technique of surgical revascularization, which has been shown to be beneficial compared with on-pump CABG in certain high-risk patient groups, such as those with advanced age or acute coronary syndrome.^{13,14} By eliminating the requirement of CPB, perioperative glucose homeostasis is significantly less altered as compared to that with on-pump CABG.⁹ Although interaction among DM, HbA1c, and perioperative

glycemic control as well as their prognostic role are expected to differ in patients undergoing OPCAB, supportive evidence is limited. Certainly, not all patients with DM share the same risk of adverse outcome, and analysis of the impact of DM-related variables as potential modifiable risk factors is of clinical significance.

Our data indicated that high HbA1c (≥7.0%) level alone, and not the variables related to perioperative glycemic control, was independently associated with adverse outcome in patients with DM undergoing OPCAB, although high HbA1c levels contributed to greater perioperative glycemic variability. The high HbA1c group showed an increased risk of poor prognosis despite presence of younger age, lower level of blood loss, and less transfusion requirement compared with the normal HbA1c group. Insulin, which itself exerts a beneficial effect on inflammation and metabolism,³⁰ was more frequently administered in the high HbA1c group than in the normal HbA1c group. Nevertheless, adverse outcome was more prevalent in the high

TABLE 4. Comparison of postoperative outcomes

Variable	HbA1c <7% n = 287	HbA1c ≥7% n = 416	P value
Composite morbidity/mortality	42 (15%)	86 (21%)	.041
Renal failure	7 (2%)	22 (5%)	.062
Permanent stroke	2 (1%)	6 (1%)	.483
Hemostatic reoperation	5 (2%)	5 (1%)	.748
Deep sternal infection	7 (2%)	26 (6%)	.019
Prolonged ventilation	28 (10%)	41 (10%)	.965
Mortality	5 (2%)	5 (1%)	.748
Duration of intensive care unit stay, d	2 [2-3]	2 [2-3]	.645
Duration of hospitalization, d	9 [7-11]	9 [8-12]	.163

Values are median [first quartile-third quartile], or the number of patients (percent). HbA1c, Glycated hemoglobin.

TABLE 5. Risk factors for the composite of morbidity and mortality end points

Variable	Multivariable OR (CI)	P value
Age, y	1.01 (0.98-1.03)	.740
Female sex	1.07 (0.67-1.71)	.767
Congestive heart failure	1.64 (1.00-2.70)	.050
Chronic kidney disease	2.00 (1.16-3.46)	.013
Peripheral arterial disease	1.24 (0.65-2.37)	.513
Previous percutaneous coronary intervention	1.52 (0.99-2.34)	.059
Moderate mitral regurgitation or greater	4.47 (1.77-11.30)	.002
Preoperative hemoglobin, g/dL	0.80 (0.70-0.91)	.001
Hemoglobin A1c $\geq 7\%$	1.60 (1.03-2.50)	.038
Perioperative CV of glucose, %	0.98 (0.96-1.01)	.133
Perioperative TWAG ≥ 200 mg/dL	1.05 (0.64-1.71)	.848

Values are presented as the OR (95% CI). OR, Odds ratio; CI, confidence interval; CV, coefficient of variation; TWAG, time-weighted average glucose.

HbA1c group, supporting the important role of increased HbA1c as a prognostic marker in patients with DM undergoing OPCAB.

These findings contrast with the results of the only 2 previous studies performed in patients with DM undergoing OPCAB that reported no relationship between HbA1c level and postoperative outcome.^{31,32} Moreover, another study including patient groups with and without DM reported that occurrence of atrial fibrillation after CABG was significantly less frequent in patients with greater HbA1c levels.³³ These inconsistencies might be due to the following: Both previous studies on patients with DM undergoing OPCAB included small sample sizes (306 and 101 patients, respectively), which could result in a type II statistical error, and cut-off values of HbA1c ranging from 6.5% to 7.5%, as compared with that of 7.0% for poor preoperative long-term glycemic control in the present study. In our study, selection of the cut-off value was based on its prognostic importance in patients undergoing cardiac surgery^{6,18} and the guideline of the American Diabetes Association.¹⁹ Both previous studies did not clarify predefined glycemic control guidelines and perioperative glycemic variables, whereas in the current study, perioperative glycemic control was done per protocol,¹⁵ and perioperative glycemic control data consisted of at least 6 repeated glucose measurements per patient. Thus, the strength of our study lies in that it is the first of its kind to concomitantly address the influence of preoperative long-term glycemic control (HbA1c) and acute perioperative glycemic control (CV and TWAG) on outcome in a fairly large number of patients with DM undergoing OPCAB using a comprehensive data set of glycemic variables.

FIGURE 2. Diabetes mellitus and chronic and acute glycemic control are closely interlinked and exert adverse influence on patient's outcome after cardiac surgery, either independently or interrelatedly. In addition to the complex interrelationship among diabetes mellitus, preoperative chronic hyperglycemia, and perioperative acute glucose fluctuation, inconsistencies regarding their influence on outcome after cardiac surgery may occur depending on the strength of the surgical stimulus.

In our study, all perioperative glycemic variables except the CV were significantly greater in the high HbA1c group. The rate of perioperative hyperglycemic event and use of insulin were significantly more frequent in the high HbA1c group, whereas the incidence of hypoglycemia was similar in both groups. In patients with elevated HbA1c levels, lower vulnerability to hyperglycemia through adaptive response to chronic hyperglycemia could have contributed to the observed lack of impact of perioperative glycemic control on poor prognosis.¹² Nonetheless, mean glucose values, including TWAG, were only slightly above the target value (<180 mg/dL), even in the high HbA1c group, with a mere mean intergroup difference of 21 mg/dL. Moreover, CV of glucose was less than previously reported values in patients undergoing on-pump CABG,³ without any intergroup difference due to a slightly greater SD of glucose concentration in the high HbA1c group. In studies reporting adverse relationship between glycemic control and short-term outcome,^{1,2} TWAG or CV was greater, indicating large fluctuations in glycemic control under CPB. Thus, our findings clearly indicate the importance of preoperative long-term glycemic control on outcome over the perioperative glycemic control in patients with DM undergoing OPCAB under standardized glycemic control protocol (<180 mg/dL) without considerable swings in glycemic control.

With regard to evaluated morbidity endpoints, DSWI showed significantly lower frequency of occurrence, and renal failure showed a trend of lower incidence in the normal HbA1c group. Patients with infection and acute kidney injury were reported to be more vulnerable to chronic hyperglycemia due to reduced humoral and cell immunity

and defense action mechanism,³⁴ as well as increased apoptosis and caspase activity, which collectively enhances tissue injury.³⁵

The limitations of the present study are as follows. The study had a retrospective design with an inherent limitation with respect to validating causality. Furthermore, dichotomization of a continuous variable (HbA1c) that may show a nonlinear relationship with outcome for ease of clinical applicability results in reduced statistical power and incomplete correction for confounders. More intriguingly, HbA1c as a continuous variable only showed a statistical trend toward being an independent risk factor of adverse outcome, possibly indicating a reduced statistical power as well. Similarly, receiver operator-characteristic curve analysis revealed HbA1c 7.85% as the optimal threshold for CMM (area under the curve: 0.556, $P = .048$) and DSWI (area under the curve: 0.661, $P = .002$), showing small areas under the curve despite being statistically significant. Yet, our analyses are intended as hypothesis-generating results for future prospective studies with sufficient power to appropriately examine whether postponing the surgery to lower HbA1c level would actually yield improved outcome.

In conclusion, the current study provides novel evidence that increased preoperative HbA1c ($\geq 7.0\%$) levels showed potential as an important influencing factor on patients' adverse outcome, whereas at a target glucose level of <180 mg/dL, perioperative glycemic variables were not associated with poor prognosis in patients with DM undergoing OPCAB.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: off-pump coronary artery bypass surgery, hemoglobin A1c, glycemic variability, morbidity, mortality, diabetes