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Long-term effects of the mean hemoglobin A1c levels after percutaneous coronary intervention in patients with diabetes

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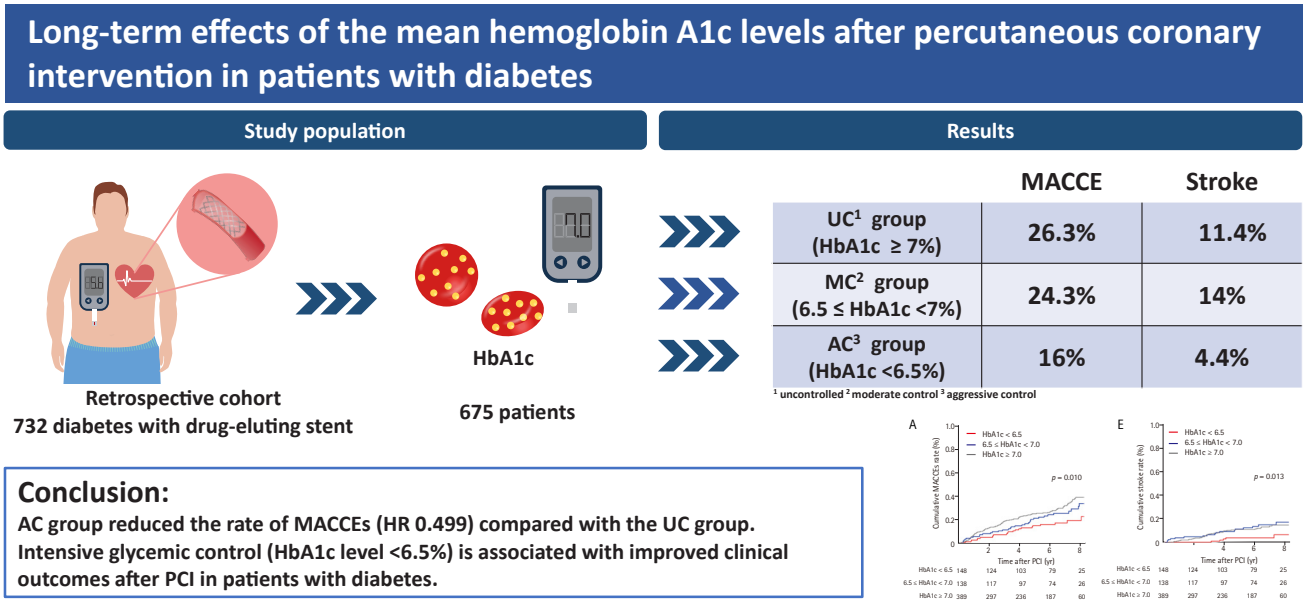

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Background/Aims: The clinical benefit of strict blood glucose-lowering therapy for patients with coronary artery disease (CAD) is still debated. We aimed to evaluate the long-term outcomes of patients with diabetes who underwent percutaneous coronary intervention (PCI), according to the mean hemoglobin A1c (HbA1c) level after PCI.
Methods: We evaluated 675 diabetes patients with CAD treated with PCI. We categorized the study population into three groups based on the mean observed HbA1c levels during the follow-up duration, as follows: aggressive control (AC) group (HbA1c level < 6.5%, n = 148), moderate control (MC) group (HbA1c level ≥ 6.5% and < 7.0%, n = 138), and uncontrolled (UC) group (HbA1c level ≥ 7.0%, n = 389). The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCEs), defined as cardiac death, myocardial infarction, repeat target vessel revascularization, and stroke.
Results: The mean HbA1c level of the AC group was significantly lower than that of the MC and UC groups (6.04% ± 0.36% vs. 6.74% ± 0.14% vs. 8.39% ± 1.20%, $p < 0.001$). The incidence of MACCEs was significantly lower in the AC group than in the MC and UC groups (16.0% vs. 24.3% vs. 26.3%, $p = 0.010$), mostly driven by the incidence of stroke (4.4% vs. 14.0% vs. 11.4%, $p = 0.013$). Multivariate Cox regression analysis showed that only the AC group was associated with a reduced rate of MACCEs (hazard ratio, 0.499; 95% confidence interval, 0.316 to 0.786; $p = 0.004$) compared with the UC group.
Conclusions: Our study showed that intensive glycemic control (HbA1c level < 6.5%) is associated with improved clinical outcomes after PCI in patients with diabetes.

Keywords: Coronary artery disease; Diabetes mellitus; Percutaneous coronary intervention; Glycated hemoglobin A; Treatment outcome

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for atherosclerotic cardiovascular disease, including coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease. Furthermore, cardiovascular disease is a leading cause of morbidity and mortality in patients with T2DM [1]. Although intensive blood glucose-lowering strategies for patients with T2DM are consistently reported to be associated with a lower incidence of microvascular complications, limited evidence of their effect with respect to reducing macrovascular complications is provided in previous randomized controlled trials [2-4]. Furthermore, according to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a target hemoglobin A1c (HbA1c) level of < 6.0% may be associated with increased mortality [4]. On the basis of these findings, the American guidelines suggest an HbA1c target level between 7% and 8% for glycemic control [5]. However, in Korea, where the prevalence of T2DM is high, the guidelines suggest a stricter target, HbA1c level < 6.5%, for glycemic control to prevent the onset and progression of microvascular complications [6]. For patients with established cardiovascular disease, especially CAD, the clinical benefit of secondary prevention with a strict blood glucose-lowering therapy is still debated [7-10]. We aimed to evaluate the long-term clinical outcomes of patients with diabetes who underwent percutaneous coronary intervention (PCI), according to the mean HbA1c levels.

METHODS

Study population and data collection

We investigated the clinical data of 732 diabetes patients with CAD who underwent PCI from January 2010 to December 2013, from the medical database of the Yeungnam University Medical Center PCI registry. After excluding 57 patients (10 patients with in-hospital mortality and 47 patients with no available HbA1c data), a total of 675 patients were included in the final analysis. We categorized the study population into three groups based on the mean observed HbA1c levels during the follow-up period: aggressive control (AC) group (HbA1c level < 6.5%, n = 148), moderate control (MC) group (HbA1c level ≥ 6.5% and < 7.0%, n = 138), and uncontrolled (UC) group (HbA1c level ≥ 7.0%, n = 389). Fig. 1 outlines the selection

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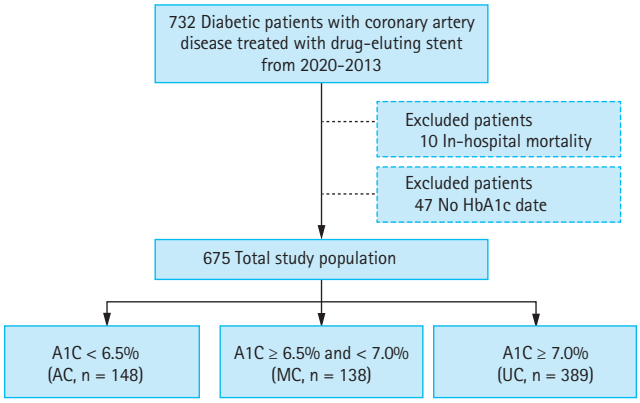

Figure 1. Selection process for the study population. HbA1c, hemoglobin A1c; AC, aggressive control; MC, moderate control; UC, uncontrolled.

process for the study population.

The data on the baseline medical history, medications, revascularization procedure and immediate and late outcomes were collected from the patients' electronic medical records. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board of Yeungnam University Medical Center approved this study (reference no. 2019-10-007) and waived the requirement of obtaining informed consent from the patients because of the retrospective nature of the analysis.

Angioplasty procedure and clinical follow-up

The decision to perform PCI was made on the basis of angiographic findings of ≥ 70% or ≥ 50% diameter stenosis with evidence of myocardial ischemia, such as ischemic symptoms or a positive stress test. All study patients were administered at least 100 mg aspirin and a total of 300 mg clopidogrel as a loading dose at least 12 hours before PCI. For patients with acute coronary syndrome, ticagrelor was administered at a loading dose of 180 mg, followed by 90 mg twice daily. Most of the patients were advised to stop metformin 48 hours before angiography and to restart metformin 48 hours after the procedure. An intra-arterial bolus of 5,000 IU heparin was injected after sheath placement, and heparin was additionally administered to maintain an activated clotting time of > 250 seconds. The PCI procedures were performed using the following current conventional technique: after predilation with a plain balloon, drug-eluting stent (DES) implantation, and adjuvant dilation with a noncompliant balloon if significant residual stenosis was noted. The selection of the type of DES was at the discretion of the attending physicians.

After a successful PCI, cardiovascular medications including beta antagonists, renin–angiotensin–aldosterone antagonists, and lipid-lowering drugs were administered unless contraindicated. The HbA1c level was monitored for at least 6 months after the procedure in all study patients. Particularly in patients with poor glycemic control, close monitoring of the HbA1c level with 3 months follow-up was performed, according to the guidelines [6]. The selection of oral hypoglycemic agents or insulin was based on physician preference and clinical practice guidelines for T2DM [5,6].

Study endpoints and definitions

The objectives of the present study were, as follows: (1) to evaluate macrovascular complications in a real-world population of patients with established cardiovascular disease who underwent PCI and (2) to investigate the long-term clinical effect of aggressive glycemic control (HbA1c level < 6.5%). With respect to the definition of T2DM, we adopted the diagnostic criteria of the Committee of Clinical Practice Guidelines, Korean Diabetes Association. T2DM was defined on the basis of the plasma glucose level (either the fasting plasma glucose level or the 2-hour plasma glucose level during a 75-g oral glucose tolerance test) or HbA1c level ≥ 6.5% [6]. We also included patients already diagnosed with T2DM who were taking oral hypoglycemic agents or insulin.

The primary endpoint of this study was major adverse cardiovascular and cerebrovascular events (MACCEs), defined as cardiac death, nonfatal myocardial infarction (MI), repeat target vessel revascularization (TVR), and stroke, based on the guidelines of the Academic Research Consortium [11]. Death without an explainable noncardiac cause was considered cardiac death. MI was defined based on the third universal definition of MI [12]. TVR was defined as any repeat PCI for the target vessel or bypass surgery of the target vessel performed for restenosis or other complications of the target vessel. All repeat revascularizations were considered clinically indicated if angiography at follow-up showed a percent diameter stenosis of ≥ 70% or ≥ 50%, as assessed with quantitative coronary angiographic analysis, with either

ischemic symptoms or a positive stress test. Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and did not develop owing to another identifiable cause. Brain imaging (computed tomography or magnetic resonance imaging) was recommended for all patients with suspected stroke. The secondary endpoints were each component of the primary endpoint and all-cause mortality. All endpoint events were identified by two analysts who were blinded to both the clinical and angiographic information.

Statistical methods

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range [IQR]). Continuous variables were compared using analysis of variance followed by Scheffe's *post hoc* test for pairwise comparisons, and categorical data were compared using chi-square statistics or Fisher's exact test. Event-free survival was analyzed using Kaplan–Meier survival curves, and differences between event-free survival curves were compared using the log-rank test. Age, sex, hypertension, chronic kidney disease, cerebrovascular disease, and multivessel disease presented with a p value of < 0.10 in the univariate analysis and were entered in the multivariate analysis model. After adjusting for these variables, the hazard ratios (HRs), were computed using Cox regression hazard models. The adjusted HRs for each clinical endpoint in the AC and MC groups were calculated with the UC group as the reference. Statistical analyses were performed using SPSS version 20.0.0 (IBM, Armonk, NY, USA) and R Statistical Software version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). A p value of < 0.05 was considered statistically significant.

RESULTS

Baseline and angiographic characteristics

The baseline characteristics of the study population are summarized in Table 1. The mean age was 63.9 ± 10.6 years, and 68.7% of the patients were men. The rate of poor glycemic control (UC group) was 57.6%. Patients in the UC group were younger than those in the AC group (62.9 ± 10.4 years vs. 66.2 ± 10.0 years, p < 0.001). The other baseline clinical variables including atrial fibrillation were similar among the three groups, except for the prevalence of hypertension. The duration of diabetes in the UC group was significantly longer than that in the AC/MC group. Laboratory findings showed that the mean observed HbA1c level during the follow-up duration was significantly different among the three groups (6.04% ± 0.36% vs. 6.74% ± 0.14% vs. 8.39% ± 1.20%, p < 0.001). Due to close monitoring of the HbA1c level performed in patients with poor glycemic control, the mean HbA1c level follow-up duration in the UC group was significantly shorter than that in the AC or MC group. Although the level of low-density lipoprotein cholesterol showed no statistical differences, the levels of high-density lipoprotein cholesterol and triglycerides were significantly different among the three groups. The rate of oral hypoglycemic agents and insulin treatment was significantly higher in the UC group than in the other groups. The antidiabetic drugs used in the study population are summarized in Supplementary Table 1. Cardiovascular medications including antiplatelet agents were similarly used among the three groups.

The angiographic and procedural characteristics are summarized in Table 2. The angiographic findings were similar, but lesion length showed a trend toward being longer in the UC group than in the AC group. The procedural findings were also similar among all study patients except for the total stent length. The total stent length of the UC group was longer than that of the AC and MC groups (35.7 ± 24.2 mm vs. 30.1 ± 16.7 mm vs. 34.7 ± 22.4 mm, p = 0.037).

Clinical outcomes

The median follow-up duration after the index procedure was 74.1 months (IQR, 32.6 to 85.0). The long-term clinical outcomes according to the mean observed HbA1c level are summarized in Table 3. The MACCE rate at 74.1 months was significantly lower in the AC group than in the MC and UC groups (16.0% vs. 24.3% vs. 26.3%, p = 0.010) (Fig. 2). The difference in the MACCE rates among the three groups was driven by stroke (4.4% vs. 14.0% vs. 11.4%, p = 0.013) (Fig. 2). However, the incidence of the other clinical outcomes, such as cardiac death, nonfatal MI, and TVR, was similar. The all-cause mortality rate was also similar among all study patients.

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Table 1. Baseline characteristics

Variable	AC (n = 148)	MC (n = 138)	UC (n = 389)	*p* value	*p* value[a]	*p* value[b]	*p* value[c]
Age, yr	66.2 ± 10.0	64.4 ± 11.3	62.9 ± 10.4	0.004	0.135	< 0.001	0.149
Female sex	47 (31.8)	43 (31.2)	121 (31.1)	0.989	0.913	0.884	0.991
Hypertension	85 (57.4)	99 (71.7)	240 (61.7)	0.034	0.012	0.366	0.034
Duration of diabetes, mo	47.5 ± 69.7	56.1 ± 89.2	107.0 ± 100.8	< 0.001	0.440	< 0.001	< 0.001
Dyslipidemia	95 (64.2)	92 (66.7)	271 (69.7)	0.453	0.660	0.224	0.513
Chronic kidney disease	2 (1.4)	6 (4.3)	15 (3.9)	0.732	0.125	0.139	0.800
Smoking	88 (59.5)	84 (60.9)	245 (63.0)	0.732	0.808	0.452	0.660
Previous PCI	9 (6.1)	10 (7.2)	31 (8.0)	0.582	0.693	0.457	0.785
Atrial fibrillation	16 (10.8)	14 (10.1)	27 (6.9)	0.256	0.854	0.140	0.227
Old CVA	13 (8.8)	25 (18.1)	47 (12.1)	0.053	0.020	0.278	0.076
Clinical presentation				0.343	0.640	0.271	0.251
Stable angina	69 (46.6)	53 (38.4)	176 (45.2)				
Unstable angina	15 (10.2)	22 (15.9)	61 (15.7)				
STEMI	35 (23.6)	39 (28.3)	74 (19.0)				
NSTEMI	29 (19.6)	24 (17.4)	78 (20.1)				
LVEF, %	54.4 ± 12.0	55.5 ± 9.8	53.9 ± 12.0	0.413	0.457	0.657	0.185
Laboratory finding							
Mean observed HbA1c, %	6.04 ± 0.36	6.74 ± 0.14	8.39 ± 1.20	< 0.001	< 0.001	< 0.001	< 0.001
Total cholesterol, mg/dL	177.7 ± 47.6	182.9 ± 51.7	181.9 ± 48.3	0.616	0.377	0.382	0.838
LDL-C, mg/dL	101.5 ± 46.1	115.3 ± 100.0	100.8 ± 41.9	0.051	0.059	0.909	0.017
HDL-C, mg/dL	46.8 ± 25.0	42.6 ± 11.6	42.4 ± 12.2	0.018	0.028	0.006	0.937
Triglyceride, mg/dL	149.6 ± 114.4	164.0 ± 123.6	193.7 ± 164.6	0.006	0.426	0.003	0.049
Mean HbA1c level follow-up duration, mo	7.35 ± 2.63	6.63 ± 2.19	6.04 ± 2.53	< 0.001	0.015	< 0.001	0.018
Diabetes drugs				< 0.001	0.001	< 0.001	< 0.001
OHA	85 (57.4)	100 (72.5)	278 (71.5)				
Insulin	4 (2.7)	10 (7.2)	72 (18.5)				
Cardiovascular medication							
Aspirin	146 (98.6)	135 (97.8)	382 (98.2)	0.870	0.596	0.718	0.782
Clopidogrel	146 (98.6)	137 (99.3)	384 (98.7)	0.853	0.603	0.952	0.594
Statin	129 (87.2)	124 (89.9)	325 (83.5)	0.161	0.476	0.301	0.073
Beta blocker	77 (52.0)	81 (58.7)	201 (51.7)	0.346	0.257	0.941	0.155
RAS blocker	82 (54.8)	76 (55.1)	219 (962)	0.962	0.955	0.852	0.803
Calcium channel blocker	29 (19.6)	20 (14.5)	71 (18.3)	0.493	0.253	0.721	0.315
Diuretics	8 (5.4)	9 (6.5)	31 (8.0)	0.560	0.690	0.306	0.581

Values are presented as mean ± standard deviation or number (%).

AC, aggressive control; MC, moderate control; UC, uncontrolled; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; OHA, oral hypoglycemic agent; RAS, renin-angiotensin system.

[a]AC (HbA1c level < 6.5%) versus MC (HbA1c level ≥ 6.5% and < 7.0%).

[b]AC (HbA1c < 6.5%) versus UC (HbA1c level ≥ 7.0%).

[c]MC (HbA1c level ≥ 6.5% and < 7.0%) versus UC (HbA1c level ≥ 7.0%).

Table 2. Angiographic and procedural characteristics

Variable	AC (n = 148)	MC (n = 138)	UC (n = 389)	*p* value	*p* value[a]	*p* value[b]	*p* value[c]
Target vessel							
LM	7 (4.7)	5 (3.6)	15 (3.9)	0.871	0.641	0.648	0.902
LAD	76 (51.4)	67 (48.6)	225 (57.8)	0.116	0.636	0.176	0.059
LCX	40 (27.0)	40 (29.0)	116 (29.8)	0.816	0.712	0.524	0.854
RCA	55 (37.2)	55 (39.9)	145 (37.3)	0.853	0.640	0.981	0.592
Involved vessel				0.577	0.698	0.677	0.392
One-vessel	81 (54.7)	78 (56.5)	197 (50.6)				
Two-vessel	46 (31.1)	45 (32.6)	135 (34.7)				
Three-vessel	21 (14.2)	15 (10.9)	57 (14.7)				
Multivessel disease	67 (45.3)	60 (43.5)	192 (49.4)	0.465	0.761	0.397	0.235
Stent type				0.146	0.475	0.069	0.297
1st generation DES	5 (3.4)	7 (5.1)	30 (7.7)				
2nd generation DES	143 (96.6)	131 (94.9)	359 (92.3)				
Reference vessel diameter, mm	3.08 ± 0.44	3.00 ± 0.47	2.99 ± 0.48	0.099	0.145	0.033	0.733
Minimal lumen diameter, mm	0.24 ± 0.23	0.21 ± 0.21	0.22 ± 0.19	0.481	0.231	0.399	0.544
Diameter stenosis %	88.3 ± 10.3	89.1 ± 10.6	87.8 ± 10.7	0.456	0.575	0.565	0.220
Lesion length, mm	19.6 ± 9.6	22.3 ± 11.3	22.3 ± 12.1	0.089	0.114	0.058	0.981
Acute gain, mm	2.913 ± 0.451	2.914 ± 0.446	2.86 ± 0.484	0.323	0.986	0.229	0.233
Chronic total occlusion	6 (4.5)	8 (6.2)	24 (6.8)	0.632	0.543	0.338	0.795
Bifurcation lesion				0.825	0.676	0.840	0.506
Single stent	22 (14.9)	26 (18.8)	74 (19.0)				
Two stents	2 (1.4)	2 (1.4)	9 (2.3)				
ACC/AHA lesion description				0.249	0.306	0.095	0.643
Type A or B	108 (80.6)	98 (75.4)	258 (73.3)				
Type C	26 (19.4)	32 (24.6)	94 (26.7)				
In-stent restenosis	4 (3.0)	7 (5.4)	18 (5.1)	0.563	0.329	0.313	0.905
Total stent number	1.37 ± 0.65	1.47 ± 0.76	1.53 ± 0.84	0.143	0.318	0.050	0.417
Stent diameter, mm	3.18 ± 0.44	3.12 ± 0.45	3.09 ± 0.42	0.219	0.312	0.081	0.621
Total stent length, mm	30.14 ± 16.67	34.71 ± 22.41	35.69 ± 24.23	0.037	0.085	0.011	0.660

Values are presented as number (%) or mean ± standard deviation.
AC, aggressive control; MC, moderate control; UC, uncontrolled; LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; ACC, American College of Cardiology; AHA, American Heart Association.
[a]AC (hemoglobin A1c level < 6.5%) versus MC (hemoglobin A1c level ≥ 6.5% and < 7.0%).
[b]AC (hemoglobin A1c level < 6.5%) versus UC (hemoglobin A1c level ≥ 7.0%).
[c]MC (hemoglobin A1c level ≥ 6.5% and < 7.0%) versus UC (hemoglobin A1c level ≥ 7.0%).

Predictors of MACCEs

The following clinical variables were associated with an increased risk for MACCEs in the univariate Cox proportional hazard regression analysis (Table 4): age, female sex, hypertension, chronic kidney disease, atrial fibrillation, old cerebrovascular accident, multivessel disease, and AC (HR, 0.507; 95% confidence interval [CI], 0.323 to 0.794; $p = 0.003$). However, MC was not associated with

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Table 3. Clinical outcomes

Variable	AC (n = 148)	MC (n = 138)	UC (n = 389)	*p* value	*p* value[a]	*p* value[b]	*p* value[c]
MACCE	20 (16.0)	29 (24.3)	88 (26.3)	0.010	0.060	0.002	0.418
Cardiac death	3 (2.2)	3 (2.7)	14 (4.5)	0.371	0.670	0.202	0.412
Non-fatal MI	5 (4.8)	8 (7.3)	13 (4.6)	0.539	0.265	0.363	0.715
TVR	10 (8.7)	10 (8.9)	32 (10.3)	0.490	0.888	0.363	0.336
Stroke	5 (4.4)	16 (14.0)	34 (11.4)	0.013	0.006	0.009	0.365
All-cause mortality	7 (5.4)	9 (8.3)	27 (8.9)	0.618	0.739	0.356	0.593

Values are presented as number (%).
AC, aggressive control; MC, moderate control; UC, uncontrolled; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; TVR, target vessel revascularization.
[a]AC (HbA1c level < 6.5%) versus MC (HbA1c level ≥ 6.5% and < 7.0%).
[b]AC (HbA1c < 6.5%) versus UC (HbA1c level ≥ 7.0%).
[c]MC (HbA1c level ≥ 6.5% and < 7.0%) versus UC (HbA1c level ≥ 7.0%).

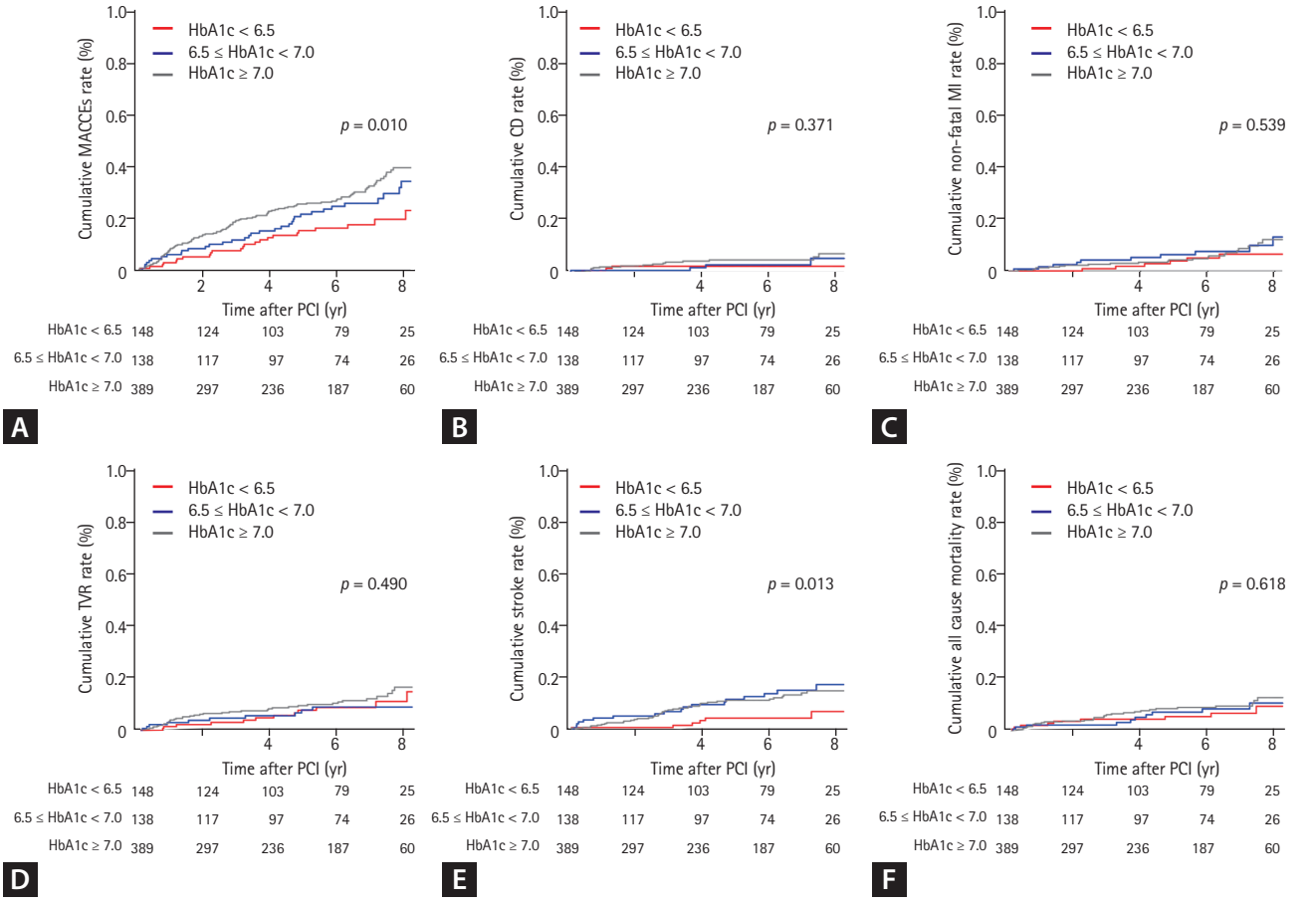

Figure 2. Kaplan–Meier survival curves. (A) Major adverse cardiovascular and cerebrovascular events (MACCEs) according to the mean observed hemoglobin A1c (HbA1c) level during the follow-up period, (B) cardiac death (CD), (C) nonfatal myocardial infarction (MI), (D) target vessel revascularization (TVR), (E) stroke, and (F) all-cause mortality. PCI, percutaneous coronary intervention.

Table 4. Predictors of major adverse cardiovascular and cerebrovascular events

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	1.032 (1.017–1.048)	< 0.001	1.026 (1.008–1.045)	0.005
Female	1.429 (1.059–1.927)	0.019	1.093 (0.754–1.583)	0.639
Hypertension	1.465 (1.076–1.995)	0.015	1.135 (0.792–1.627)	0.490
Dyslipidemia	0.828 (0.610–1.124)	0.225		
Previous MI	0.845 (0.443–1.614)	0.610		
CKD	2.471 (1.304–4.682)	0.006	2.257 (1.000–5.092)	0.050
Atrial fibrillation	2.211 (1.456–3.358)	< 0.001	1.620 (0.942–2.787)	0.081
Old CVA	1.652 (1.117–2.445)	0.012	1.487 (0.908–2.436)	0.115
Multivessel disease	1.459 (1.205–1.766)	< 0.001	1.551 (1.096–2.197)	0.013
ACS presentation	0.796 (0.596–1.064)	0.124		
AC group[a]	0.507 (0.323–0.794)	0.003	0.499 (0.316–0.786)	0.003
MC group[b]	0.859 (0.594–1.242)	0.419		

CI, confidence interval; MI, myocardial infarction; CKD, chronic kidney disease; CVA, cerebrovascular accident; ACS, acute coronary syndrome; AC, aggressive control; MC, moderate control.
[a]Uncontrolled (UC) group as the reference.
[b]UC group as the reference.

Table 5. Hazard ratios of the aggressive control and moderate control groups compared with the uncontrolled group

Variable	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
AC (reference UC)				
MACCE	0.507 (0.323–0.794)	0.003	0.499 (0.316–0.786)	0.003
Cardiac death	0.456 (0.133–1.566)	0.212	0.522 (0.150–1.823)	0.309
Non-fatal MI	0.658 (0.267–1.623)	0.363	0.719 (0.287–1.802)	0.482
TVR	0.747 (0.391–1.426)	0.376	0.802 (0.415–1.549)	0.511
Stroke	0.346 (0.147–0.816)	0.015	0.375 (0.158–0.894)	0.027
All-cause mortality	0.705 (0.336–1.481)	0.356	0.966 (0.461–2.025)	0.927
MC (reference UC)				
MACCE	0.859 (0.594–1.242)	0.419	0.812 (0.556–1.184)	0.279
Cardiac death	0.638 (0.213–1.909)	0.422	0.711 (0.235–2.148)	0.545
Non-fatal MI	1.149 (0.544–2.428)	0.715	1.414 (0.656–3.047)	0.376
TVR	0.716 (0.367–1.399)	0.329	0.729 (0.370–1.434)	0.360
Stroke	1.264 (0.747–2.139)	0.382	1.13 (0.645–1.920)	0.700
All-cause mortality	0.825 (0.404–1.683)	0.597	0.892 (0.432–1.844)	0.759

HR, hazard ratio; CI, confidence interval; AC, aggressive control (hemoglobin A1c level < 6.5%); UC, uncontrolled (hemoglobin A1c level ≥ 7.0%); MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; TVR, target vessel revascularization; MC, moderate control (hemoglobin A1c level ≥ 6.5% and < 7.0%).

MACCE occurrence in the univariate analysis. None of the antidiabetic drugs showed a significant correlation with an increased risk of MACCEs in univariate analysis (Supplementary Table 2). In the multivariate analysis, AC was an independent predictor of reduced MACCEs (HR, 0.499; 95% CI, 0.316 to 0.786; $p = 0.003$), along with

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age, chronic kidney disease, and multivessel disease.

The adjusted HRs of the AC and MC groups compared with those of the UC group are described in Table 5. Even after adjusting for the risk factors, AC was significantly associated with reduced rates of MACCEs (HR, 0.499; 95% CI, 0.316 to 0.786; $p = 0.003$) and stroke (HR, 0.375; 95% CI, 0.158 to 0.894; $p = 0.027$) compared with UC. However, MC was not related to MACCEs and each component of the primary endpoint.

DISCUSSION

In this study, we evaluated the long-term clinical outcomes according to the glycemic control status in diabetes patients with established cardiovascular disease who underwent PCI. Although diabetes patients with established CAD are at a high risk for future cardiovascular events, almost 60% of the patients were categorized in the UC group. The major study findings were, as follows: (1) the incidence of MACCEs was lower in the AC group (HbA1c level < 6.5%) than in the MC and UC groups; (2) the difference in the MACCE incidence was driven by stroke; and (3) AC was an independent predictor of reduced rates of MACCEs and stroke.

The association between glycemic control and clinical outcomes after PCI in patients with diabetes has been evaluated. Several studies have suggested that the effect of dysglycemia at the time of admission or before PCI can be related to poor prognosis after PCI in diabetes patients with acute coronary syndrome [13-16]. However, the glycemic status before PCI cannot reflect the long-term effects of glycemic control because catecholamine surge induced in response to acute coronary events may be associated with dysglycemia. Therefore, we categorized the study population based on the mean observed HbA1c level during the follow-up period, which reflects the glycemic control status after PCI.

With respect to PCI performed before the DES implantation era, prospective registry data suggested that optimal glycemic control (HbA1c level ≤ 7%) was associated with a lower rate of TVR [17]. However, in the era of first-generation DES implantation, the PCI registry data showed that the preprocedural HbA1c level was not associated with future adverse outcomes, as noted by the absence of a benefit of strict glycemic control in preventing macrovascular complications [18]. Other studies on the HbA1c level and PCI outcomes in patients with diabetes showed that glycemic control status was not associated with the incidence of major adverse cardiovascular events, defined as death, MI, and target vessel failure [9,19]. Our study also reported that the incidence of cardiac death, nonfatal MI, TVR, and all-cause mortality was similar among the three groups. However, our study defined the primary endpoint as the incidence of MACCEs, which included stroke events, and the AC group showed a significantly reduced rate of MACCEs, compared with the MC and UC groups, driven by stroke events. Our median follow-up duration was > 6 years; therefore, the long-term effect of the glycemic control status is reflected more effectively in our study than in the previous studies. The data on the glycemic control status after PCI in diabetes patients from another registry showed that HbA1c levels ≤ 7% measured at 2 years after PCI were associated with a reduced rate of MACCEs, mostly driven by target lesion revascularization [10]. However, the HbA1c level measured at 2 years after PCI cannot accurately reflect the glycemic control status. To reflect the accurate glycemic control status after the index procedure, we evaluated the mean observed HbA1c level during the follow-up period. Furthermore, a strength of our study is that the clinical effect of aggressive glycemic control (HbA1c level < 6.5%) was investigated, and an association between aggressive glycemic control and reduced rates of MACCEs and stroke was noted.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial investigated the effects of intensive glucose control on the vascular outcomes and found that the rate of the combined outcome of major macrovascular and microvascular events decreased [3]. However, the reduced rate of the primary outcome was mainly owing to the reduced rates of microvascular events and not of macrovascular events. Another large-scale randomized trial, the ACCORD study, reported that despite a non-significant decrease in the rate of ischemic events in patients with intensive glycemic control, higher rates of all-cause mortality were observed [4]. The Veterans Affairs Diabetes Trial on the effects of intensive and standard glucose control on cardiovascular events also reported that intensive glucose control had no significant

effect on the incidence of major cardiovascular events [20]. Previous randomized trials have shown that intensive glycemic control is associated with an increased rate of hypoglycemic events. Hypoglycemia may be a major contributor towards adverse cardiovascular events in patients with a high cardiovascular risk [21]. Our study showed that a mean observed HbA1c level of < 6.5% was significantly associated with a reduced rate of MACCEs, mainly driven by stroke. Recently, many effective oral hypoglycemic agents, such as dipeptidyl peptidase 4 inhibitors or sodium glucose co-transporter 2 (SGLT2) inhibitors, associated with a low risk for hypoglycemia, have been administered in patients with cardiovascular disease. Large-scale randomized trials on intensive glycemic control with such drugs are needed.

The data from the U.K. Prospective Diabetes Study showed that a higher HbA1c level was associated with an increased rate of nonfatal MI and stroke [22]. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study evaluated the clinical effect of glycemic control in patients with T2DM and a history of macrovascular disease [23]. In this trial, an HbA1c level ≥ 7.5% was a strong positive predictor of a stroke event, and aggressive glycemic control with pioglitazone was associated with a reduced rate of stroke [23]. Traditionally, stroke is associated with macrovascular complications in patients with T2DM. However, in patients with T2DM, stroke due to cerebral small-vessel disease from fibrinoid necrosis, usually lacunar stroke, is more commonly encountered [24]. Our study also showed that a mean observed HbA1c level of < 6.5% was associated with a lower incidence of stroke, similar to that reported previously. However, the other components of the primary endpoint showed similar incidences among the three groups. It is possible that intensive glycemic control in patients with T2DM is mainly driven by reduced microvascular complications, including stroke due to small-vessel disease. Although the patients in the AC group were older than those in the UC group, the incidence of stroke was lower in the AC group than in the UC group (HR, 0.373; 95% CI, 0.157 to 0.886; p = 0.025). Therefore, in diabetes patients with established coronary heart disease, the glycemic control status is an important factor for predicting future adverse events, especially stroke.

There are several limitations of this study. First, our study was based on single-center PCI registry data, and the intrinsic limitations related to the retrospective study design cannot be disregarded. For this reason, there were significant differences in baseline characteristics, including patient age and lack of data about detailed microvascular complications, such as diabetic retinopathy or peripheral neuropathy. To reduce the impact of differences in baseline characteristics among the three groups, we adjusted for meaningful variables in the univariate analysis. In this regard, AC of the HbA1c levels does not indicate aggressive glycemic management. To evaluate the clinical outcomes of strict glycemic control in diabetes patients with CAD, large-scale prospective randomized studies should be required. However, our study aimed to evaluate the long-term outcomes according to the mean observed HbA1c level in a relatively large real-world population of diabetes patients with CAD. Future prospective studies on the long-term clinical outcomes according to glycemic control with current oral hypoglycemic agents should be conducted, on the basis of our study results. Second, as our data were based on the patients' electronic medical records, it was difficult to acquire data regarding the hypoglycemic events. However, to the best of our knowledge, serious hypoglycemic events leading to lethal arrhythmias, cardiovascular events, and mortality did not occur. Third, SGLT2 inhibitors were not prescribed during the study period. Recently, several large-scale randomized trials have reported that SGLT2 inhibitors reduce the rates of adverse cardiovascular outcomes [25,26]. Our study findings strongly suggest that further large-scale randomized studies should be conducted for evaluating strict glycemic control with SGLT2 inhibitors in diabetes patients with CAD.

In conclusion, more intensive glycemic control (HbA1c level < 6.5%) was associated with improved clinical outcomes, mainly driven by stroke in diabetes patients with CAD treated with PCI. For these patients, measurement of the HbA1c level is important for predicting major adverse cardiovascular events. Large-scale randomized trials evaluating the long-term clinical outcomes according to the glycemic control strategy in diabetes patients with established CAD are warranted.

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KEY MESSAGE

1. Although diabetes patients with established coronary artery disease (CAD) are at a high risk for future cardiovascular events, 57.6% of the patients were categorized in the uncontrolled group (mean hemoglobin A1c [HbA1c] level ≥ 7.0%).
2. More intensive glycemic control (HbA1c level < 6.5%) was associated with lower incidence of major adverse cardiovascular and cerebrovascular events, mainly driven by stroke in diabetes patients with CAD treated with percutaneous coronary intervention.
3. Future large-scale randomized trials on the long-term clinical outcomes according to glycemic control strategy in diabetes patients with established CAD should be required.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Antidiabetic agents' prescription

Variable	AC (n = 148)	MC (n = 138)	UC (n = 389)	*p* value	*p* value[a]	*p* value[b]	*p* value[c]
Metformin	44 (29.7)	80(58.0)	231 (59.4)	< 0.001	< 0.001	< 0.001	0.772
Sulfonylurea	35 (23.6)	34 (24.6)	179 (46.0)	< 0.001	0.845	< 0.001	< 0.001
α-Glucosidase inhibitor	11 (7.4)	5 (3.6)	31 (8.0)	0.219	0.161	0.836	0.082
Thiazolidinedione	0	1 (0.7)	10 (2.6)	0.070	0.300	0.049	0.192
DPP-4 inhibitor	20 (13.5)	28 (20.3)	80 (20.6)	0.160	0.125	0.061	0.945
SGLT2 inhibitor	0	2 (1.4)	15 (3.9)	0.026	0.142	0.015	0.169
Insulin	4 (2.7)	10 (7.2)	72 (18.5)	< 0.001	0.075	< 0.001	0.002

Values are presented as number (%).

AC, aggressive control; MC, moderate control; UC, uncontrolled; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium glucose co-transporter 2.

[a]AC (hemoglobin A1c [HbA1c] level < 6.5%) versus MC (HbA1c level ≥ 6.5% and < 7.0%).

[b]AC (HbA1c < 6.5%) versus UC (HbA1c level ≥ 7.0%).

[c]MC (HbA1c level ≥ 6.5% and < 7.0%) versus UC (HbA1c level ≥ 7.0%).

Supplementary Table 2. Hazard ratio of antidiabetic agents for MACCEs

Variable	Univariate analysis	
	Hazard ratio (95% CI)	*p* value
Metformin	0.793 (0.592–1.061)	0.118
Sulfonylurea	1.049 (0.777–1.417)	0.755
α-Glucosidase inhibitor	0.892 (0.497–1.602)	0.702
Thiazolidinedione	1.540 (0.572–4.152)	0.393
DPP-4 inhibitor	0.818 (0.550–1.216)	0.320
SGLT2 inhibitor	0.697 (0.259–1.879)	0.476
Insulin	1.132 (0.747–1.715)	0.558

MACCE, major adverse cardiovascular and cerebrovascular event; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium glucose co-transporter 2.

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