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

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Abstract

Background: There is controversy regarding the long-term effect of glycemic control on the clinical outcomes after percutaneous coronary intervention (PCI) in diabetes patients with coronary artery disease (CAD). We aimed to evaluate the long-term outcomes of patients with diabetes who underwent PCI, according to the mean hemoglobin A1c (HbA1c) level after PCI.

Methods: We retrospectively evaluated 675 diabetes patients with CAD treated with PCI from 2010 to 2013. 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. The median follow-up duration was 74.1 (32.6–85.0) months.

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). Patients in the AC group were older than those in the MC and UC groups (66.2±10.0 vs. 64.4±11.3 vs. 62.9±10.4 years, p=0.004); however, the other clinical characteristics were similar among the groups. 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. 11.0%, p=0.013). Multivariate Cox regression analysis showed that only the AC group was associated with a reduced rate of MACCEs (hazard ratio 0.513, 95% confidence interval 0.326–0.808, p=0.004) compared with the UC group.

Conclusion: Our study showed that intensive glycemic control (HbA1c level <6.5%) is associated with improved clinical outcomes after PCI in patients with diabetes.

Background

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). Figure 1 outlines the selection 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 at our institute 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 h 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 h before angiography and to restart metformin 48 h after the procedure. An intra-arterial bolus of 5000 IU heparin was injected after sheath placement, and heparin was additionally administered to maintain an activated clotting time of >250 s. 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-h 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 h 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 vs. 66.2±10.0 years, p<0.001). The other baseline clinical variables were similar among the three groups, except for the prevalence of hypertension. 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). 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 insulin treatment was significantly higher in the UC group than in the other 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 vs. 30.1±16.7 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, 32.6–85.0 months). The long-term clinical outcomes according to the mean observed HbA1c level are summarized in Additional file 1. 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; Figure 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; Figure 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.

Predictors of MACCEs

The following clinical variables were associated with an increased risk for MACCEs in the univariate Cox proportional hazard regression analysis (Table 3): age, female sex, hypertension, chronic kidney disease, old cerebrovascular accident, multivessel disease, and AC (HR, 0.507; 95% confidence interval [CI] 0.323–0.794; p=0.003). However, MC was not associated with MACCE occurrence in the univariate analysis. In the multivariate analysis, AC was an independent predictor of reduced MACCEs (HR, 0.513; 95% CI 0.326–0.808; p=0.004), along with age, chronic kidney disease, and multivessel disease.

Table 3. Predictors of major adverse cardiovascular and cerebrovascular events
|                          | 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               | 1.032 (1.015-1.049)  | <0.001               |
| Female                   | 1.429 (1.059-1.927)  | 0.019                | 1.085 (0.786-1.499)  | 0.619                |
| Hypertension             | 1.465 (1.076-1.995)  | 0.015                | 1.197 (0.858-1.670)  | 0.291                |
| 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                | 2.713 (1.351-5.447)  | 0.005                |
| Old CVA                  | 1.652 (1.117-2.445)  | 0.012                | 1.306 (0.852-2.000)  | 0.220                |
| Multivessel disease      | 1.459 (1.205-1.766)  | <0.001               | 1.376 (1.129-1.678)  | 0.002                |
| ACS presentation         | 0.796 (0.596-1.064)  | 0.124                |                       |                      |
| AC group                 | 0.507 (0.323-0.794)  | 0.003                | 0.513 (0.326-0.808)  | 0.004                |
| MC group†                | 0.859 (0.594-1.242)  | 0.419                |                       |                      |

* UC group as the reference.

† UC group as the reference.

CI, confidence interval; MI, myocardial infarction; CKD, chronic kidney disease; CVA, cerebrovascular accident; ACS, acute coronary syndrome

The adjusted HRs of the AC and MC groups compared with those of the UC group are described in Table 4. Even after adjusting for the risk factors, AC was significantly associated with reduced rates of MACCEs (HR, 0.513; 95% CI, 0.326–0.808; p=0.004) and stroke (HR, 0.373; 95% CI, 0.157–0.886; p=0.025) compared with UC. However, MC was not related to MACCEs and each component of the primary endpoint.

**Table 4. Hazard ratios of the aggressive control and moderate control groups compared with the uncontrolled group**
|                  | Unadjusted HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
|------------------|------------------------|---------|----------------------|---------|
| AC (reference UC)|                        |         |                      |         |
| MACCE            | 0.507 (0.323-0.794)     | 0.003   | 0.513 (0.326-0.808)   | 0.004   |
| Cardiac death    | 0.456 (0.133-1.566)     | 0.212   | 0.443 (0.128-1.538)   | 0.200   |
| Non-fatal MI     | 0.658 (0.267-1.623)     | 0.363   | 0.653 (0.262-1.629)   | 0.361   |
| TVR              | 0.747 (0.391-1.426)     | 0.376   | 0.759 (0.394-1.463)   | 0.410   |
| Stroke           | 0.346 (0.147-0.816)     | 0.015   | 0.373 (0.157-0.886)   | 0.025   |
| All-cause mortality | 0.705 (0.336-1.481)   | 0.356   | 0.731 (0.343-1.560)   | 0.418   |
| MC (reference UC)|                        |         |                      |         |
| MACCE            | 0.859 (0.594-1.242)     | 0.419   | 0.824 (0.567-1.199)   | 0.313   |
| Cardiac death    | 0.638 (0.213-1.909)     | 0.422   | 0.618 (0.203-1.883)   | 0.200   |
| Non-fatal MI     | 1.149 (0.544-2.428)     | 0.715   | 1.281 (0.596-2.751)   | 0.526   |
| TVR              | 0.716 (0.367-1.399)     | 0.329   | 0.726 (0.369-1.427)   | 0.353   |
| Stroke           | 1.264 (0.747-2.139)     | 0.382   | 1.086 (0.634-1.860)   | 0.763   |
| All-cause mortality | 0.825 (0.404-1.683)   | 0.597   | 0.793 (0.382-1.644)   | 0.532   |

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

**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 \( \leq 7\% \)) 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 \( \leq 7\% \) 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 nonsignificant 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 $\geq 7.5\%$ 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 0.157–0.886, $p = 0.025$). 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. Therefore, aggressive control 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.

**Conclusion**

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.

**Abbreviations**

AC, aggressive control; CAD, coronary artery disease; DES, drug-eluting stent; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction; MC, moderate control; PCI, percutaneous coronary intervention; SGLT2, sodium glucose co-transporter 2; T2DM, type 2 diabetes mellitus; TVR, target vessel revascularization; UC, uncontrolled

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the institutional review board of Yeungnam University Medical Center (reference no. 2019-10-007).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available owing to regulations regarding the release of patient information to the public but are available from the corresponding author on reasonable request, after anonymization.

**Competing interests**

The authors have no conflicts of interest to disclose.

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Not applicable.

**Authors’ contributions**

JB, JHY, HTK: data curation, formal analysis, and original draft preparation. JHL: conceptualization, data curation, investigation, methodology, software, writing, reviewing, and editing. JHN, CHL, JWS, UK, JSP, DGS: reviewing and editing. All authors read and approved the final manuscript.

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References

1. American Diabetes A: **Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020.** *Diabetes Care* 2020, 43(Suppl 1):S111-S134.

2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998, 352(9131):837-853.

3. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P *et al.*: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008, 358(24):2560-2572.

4. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F *et al.*: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008, 358(24):2545-2559.

5. Qaseem A, Wilt TJ, Kangasara D, Horwitch C, Barry MJ, Forciea MA, Clinical Guidelines Committee of the American College of P: *Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med* 2018, 168(8):569-576.

6. Kim MK, Ko SH, Kim BY, Kang ES, Noh J, Kim SK, Park SO, Hur KY, Chon S, Moon MK *et al.*: 2019 Clinical Practice Guidelines for Type 2 Diabetes Mellitus in Korea. *Diabetes Metab J* 2019, 43(4):398-406.

7. Singla A, Orshaw P, Boura J, Harjai KJ: Glycosylated hemoglobin and outcomes in diabetic patients with acute myocardial infarction after successful revascularization with stent placement: findings from the Guthrie health off-label stent (GHOST) investigators. *J Interv Cardiol* 2012, 25(3):262-269.

8. Sharma PK, Agarwal S, Ellis SG, Goel SS, Cho L, Tuzcu EM, Lincoff AM, Kapadia SR: Association of glycemic control with mortality in patients with diabetes mellitus undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2014, 7(4):503-509.

9. Ike A, Nishikawa H, Shirai K, Mori K, Kuwano T, Fukuda Y, Takamiya Y, Yanagi D, Kubota K, Tsuchiya Y *et al.*: Impact of glycemic control on the clinical outcome in diabetic patients with percutaneous coronary intervention—from the FU-registry. *Circ J* 2011, 75(4):791-799.

10. Hwang JK, Lee SH, Song YB, Ahn J, Carriere K, Jang MJ, Park TK, Choi SH, Yang JH, Choi JH *et al.*: Glycemic Control Status After Percutaneous Coronary Intervention and Long-Term Clinical Outcomes in Patients With Type 2 Diabetes Mellitus. *Circ Cardiovasc Interv* 2017, 10(4).

11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P *et al.*: Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007, 115(17):2344-2351.

12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESCAHAHWFHFTffUDoMI, Authors/Task Force Members C, Thygesen K, Alpert JS *et al.*: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012, 60(16):1581-1598.
13. Chung JW, Park YS, Seo JE, Son Y, Oh CW, Lee CH, Nam JH, Lee JH, Son JW, Kim U et al.: Clinical Impact of Dysglycemia in Patients with an Acute Myocardial Infarction. Diabetes Metab J 2020.

14. Kim EJ, Jeong MH, Kim JH, Ahn TH, Seung KB, Oh DJ, Kim HS, Gwon HC, Seong IW, Hwang KK et al.: Clinical impact of admission hyperglycemia on in-hospital mortality in acute myocardial infarction patients. Int J Cardiol 2017, 236:9-15.

15. Ishihara M, Kagawa E, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nakama Y, Maruhashi T, Ookawa K, Dai K et al.: Impact of admission hyperglycemia and diabetes mellitus on short- and long-term mortality after acute myocardial infarction in the coronary intervention era. Am J Cardiol 2007, 99(12):1674-1679.

16. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M: Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005, 26(13):1255-1261.

17. Corpus RA, George PB, House JA, Dixon SR, Ajluni SC, Devlin WH, Timmis GC, Balasubramaniam M, O’Neill WW: Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. J Am Coll Cardiol 2004, 43(1):8-14.

18. Lemesle G, Bonello L, de Labriolle A, Maluenda G, Syed Al, Collins SD, Ben-Dor I, Torguson R, Kaneshige K, Xue Z et al.: Prognostic value of hemoglobin A1C levels in patients with diabetes mellitus undergoing percutaneous coronary intervention with stent implantation. Am J Cardiol 2009, 104(1):41-45.

19. Kassaian SE, Goodarzynejad H, Boroumand MA, Salarifar M, Masoudkabir F, Mohajeri-Tehrani MR, Pourhoseini H, Sadeghian S, Ramezanpour N, Alidoosti M et al.: Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovasc Diabetol 2012, 11:82.

20. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R et al.: Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009, 360(2):129-139.

21. Hanefeld M, Frier BM, Pistrosch F: Hypoglycemia and Cardiovascular Risk: Is There a Major Link? Diabetes Care 2016, 39 Suppl 2:S205-209.

22. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR: Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care 2004, 27(1):201-207.

23. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J, Investigators PR: Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007, 38(3):865-873.

24. Rothwell PM: Prevention of stroke in patients with diabetes mellitus and the metabolic syndrome. Cerebrovasc Dis 2005, 20 Suppl 1:24-34.
25. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA et al: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019, 380(4):347-357.

26. Packer M, Anker SD, Butler J, Filippatos G, Pocock S, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M et al: Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020.

Tables

Table 1. Baseline characteristics
| Variables                        | AC     | MC     | UC     | p-value | p-value* | p-value† | p-value‡ |
|---------------------------------|--------|--------|--------|---------|---------|---------|---------|
| Age, years                      | 66.2±10.0 | 64.4±11.3 | 62.9±10.4 | 0.004   | 0.135   | <0.001  | 0.149   |
| Female, n (%)                   | 47 (31.8) | 43 (31.2) | 121 (31.1) | 0.989   | 0.913   | 0.884   | 0.991   |
| Hypertension, n (%)             | 85 (57.4) | 99 (71.7) | 240 (61.7) | 0.034   | 0.012   | 0.366   | 0.034   |
| Dyslipidemia, n (%)             | 95 (64.2) | 92 (66.7) | 271 (69.7) | 0.453   | 0.660   | 0.224   | 0.513   |
| Chronic kidney disease, n (%)   | 2 (1.4) | 6 (4.3) | 15 (3.9) | 0.732   | 0.125   | 0.139   | 0.800   |
| Smoking, n (%)                  | 88 (59.5) | 84 (60.9) | 245 (63.0) | 0.732   | 0.808   | 0.452   | 0.660   |
| Previous PCI, n (%)             | 9 (6.1) | 10 (7.2) | 31 (8.0) | 0.582   | 0.693   | 0.457   | 0.785   |
| Old CVA, n (%)                  | 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, n (%)            | 69 (46.6) | 53 (38.4) | 176 (45.2) |        |         |         |         |
| Unstable angina, n (%)          | 15 (10.2) | 22 (15.9) | 61 (15.7) |        |         |         |         |
| STEMI, n (%)                    | 35 (23.6) | 39 (28.3) | 74 (19.0) |        |         |         |         |
| NSTEMI, n (%)                   | 29 (19.6) | 24 (17.4) | 78 (20.1) |        |         |         |         |
| LVEF (%)                        | 59.1±55.28 | 55.5±9.78 | 53.9±11.96 | 0.266   | 0.304   | 0.069   | 0.579   |
| 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 cholesterol, mg/dL          | 101.5±46.1 | 115.3±100.0 | 100.8±41.9 | 0.051   | 0.059   | 0.909   | 0.017   |
| HbA1c level | AC (HbA1c <6.5%) | MC (HbA1c level ≥ 6.5% and <7.0%) | UC (HbA1c level ≥ 7.0%) |
|-------------|-----------------|----------------------------------|------------------------|
| OHA, n (%)  | 85 (57.4)       | 100 (72.5)                       | 278 (71.5)             |
| Insulin, n (%) | 4 (2.7)        | 10 (7.2)                          | 72 (18.5)              |

Data are presented as mean ± standard deviation or n (%).

* AC (HbA1c level <6.5%) versus MC (HbA1c level ≥ 6.5% and <7.0%).

† AC (HbA1c <6.5%) versus UC (HbA1c level ≥ 7.0%).

‡ MC (HbA1c level ≥ 6.5% and <7.0%) versus UC (HbA1c level ≥ 7.0%).

AC, aggressive control; MC, moderate control; UC, uncontrolled; PCI, percutaneous coronary intervention; MI, myocardial infarction; 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, low-density lipoprotein; HDL, high-density lipoprotein; OHA, oral hypoglycemic agent

Table 2. Angiographic and procedural characteristics
| Variables                          | AC (n=148) | MC (n=138) | UC (n=389) | p-value  | p-value* | p-value‡ | p-value‡‡ |
|-----------------------------------|------------|------------|------------|----------|----------|----------|----------|
| **Target vessel**                 |            |            |            |          |          |          |          |
| LM, n (%)                         | 7 (4.7)    | 5 (3.6)    | 15 (3.9)   | 0.871    | 0.641    | 0.648    | 0.902    |
| LAD, n (%)                        | 76 (51.4)  | 67 (48.6)  | 225 (57.8) | 0.116    | 0.636    | 0.176    | 0.059    |
| LCX, n (%)                        | 40 (27.0)  | 40 (29.0)  | 116 (29.8) | 0.816    | 0.712    | 0.524    | 0.854    |
| RCA, n (%)                        | 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, n (%)                 | 81 (54.7)  | 78 (56.5)  | 197 (50.6) |          |          |          |          |
| Two vessel, n (%)                 | 46 (31.1)  | 45 (32.6)  | 135 (34.7) |          |          |          |          |
| Three vessel, n (%)               | 21 (14.2)  | 15 (10.9)  | 57 (14.7)  |          |          |          |          |
| Multivessel disease, n (%)        | 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, n (%)         | 5 (3.4)    | 7 (5.1)    | 30 (7.7)   |          |          |          |          |
| 2nd generation DES, n (%)         | 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, n (%)    | 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, n                   | 22 (14.9)  | 26 (18.8)  | 74 (19.0)  |          |          |          |          |
| (%)                  | 2 (1.4) | 2 (1.4) | 9 (2.3) |
|---------------------|---------|---------|---------|
| Two stents, n (%)   |         |         |         |
| ACC/AHA lesion description | 0.249   | 0.306   | 0.095   | 0.643   |
| Type A or B, n (%)  | 108 (80.6) | 98 (75.4) | 258 (73.3) |
| Type C, n (%)       | 26 (19.4)  | 32 (24.6)  | 94 (26.7)  |
| In-stent restenosis, n (%) | 4 (3.0)   | 7 (5.4)    | 18 (5.1)    | 0.563   | 0.329   | 0.313   | 0.905   |
| Total stent number, n | 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   |

* AC (hemoglobin A1c level <6.5%) versus MC (hemoglobin A1c level ≥6.5% and <7.0%).

† AC (hemoglobin A1c level <6.5%) versus UC (hemoglobin A1c level ≥7.0%).

‡ MC (hemoglobin A1c level ≥6.5% and <7.0%) versus UC (hemoglobin A1c level ≥7.0%).

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

**Figures**
Figure 1

Selection process for the study population
Figure 1

Selection process for the study population
Figure 2

Kaplan–Meier survival curves (a) Major adverse cardiovascular and cerebrovascular events according to the mean observed HbA1c level during the follow-up period; (b) cardiac death; (c) nonfatal myocardial infarction; (d) target-vessel revascularization; (e) stroke; and (f) all-cause mortality. MACCE, major adverse cardiovascular and cerebrovascular event; PCI, percutaneous coronary intervention; HbA1c, hemoglobin A1c; CD, cardiac death; MI, myocardial infarction; TVR, target vessel revascularization
Figure 2

Kaplan–Meier survival curves (a) Major adverse cardiovascular and cerebrovascular events according to the mean observed HbA1c level during the follow-up period; (b) cardiac death; (c) nonfatal myocardial infarction; (d) target-vessel revascularization; (e) stroke; and (f) all-cause mortality. MACCE, major adverse cardiovascular and cerebrovascular event; PCI, percutaneous coronary intervention; HbA1c, hemoglobin A1c; CD, cardiac death; MI, myocardial infarction; TVR, target vessel revascularization

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