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ORIGINAL ARTICLE
Cardiovascular Intervention

Effect of Glycemic Control During Follow-up on Late Target Lesion Revascularization After Implantation of New-Generation Drug-Eluting Stents in Patients With Diabetes

— A Single-Center Observational Study —

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Background: Few studies have investigated the importance of glycemic control in patients with diabetes mellitus (DM) for reducing the incidence of late target lesion revascularization (TLR) after implantation of new-generation drug-eluting stents (DES).

Methods and Results: We retrospectively identified 1,568 patients who underwent new-generation DES implantation. Patients were divided into 3 groups based on diabetic status and glycemic control 1 year after the procedure: those without DM (non-DM group; n=1,058) and those with DM at follow-up with either good (HbA1c <7%; n=328) or poor (HbA1c ≥7%; n=182) control. The cumulative 5-year incidence of clinically driven late TLR after the index procedure was significantly higher in DM with poor control at follow-up than in those with good control at follow-up or non-DM (14%, 4.8%, and 2.9%, respectively; P<0.0001). Multivariate analysis revealed that poor control at follow-up was significantly associated with a higher risk of clinically driven late TLR compared with the non-DM group (hazard ratio [HR] 4.58, 95% confidence interval [CI] 2.50–8.16, P<0.0001). However, good control at follow-up group was not associated with a higher risk of clinically driven late TLR compared with the non-DM group (HR 1.35, 95% CI 0.68–2.56, P=0.38).

Conclusions: DM patients with poor glycemic control at follow-up had a significantly higher risk of clinically driven late TLR than non-DM patients.

Key Words: Diabetes mellitus; Drug-eluting stent; Restenosis; Percutaneous coronary intervention

New-generation drug-eluting stents (DES) have significantly decreased the rate of restenosis and target lesion revascularization (TLR) compared with first-generation DES.[1,2] Therefore, placement of a new-generation DES is currently the default strategy in percutaneous coronary intervention (PCI).[3] However, similar to first-generation DES, late TLR after implantation of new-generation DES cannot be ignored, because it continues to occur constantly without attenuation over a long period of time, in contrast with bare metal stents (BMS) restenosis, in which TLR beyond 1 year is reportedly uncommon.[4,5] In particular, patients with diabetes mellitus (DM) are at higher risk of restenosis and TLR.[5,6] However, the importance of glycemic control in the development of restenosis has not been adequately investigated.

There are conflicting data regarding the effects of glycemic control before PCI on cardiovascular outcomes.[7,8] The relationship between glycemic control after PCI and cardiovascular outcomes is also contentious.[9–11] These previous studies were mostly conducted in the era of BMS and first-generation DES.

In the present study we examined the association of glycemic control before and after PCI, as represented by HbA1c levels at baseline and at 1-year after PCI, with the incidence of late TLR over long-term follow-up in DM patients who underwent new-generation DES implantation.

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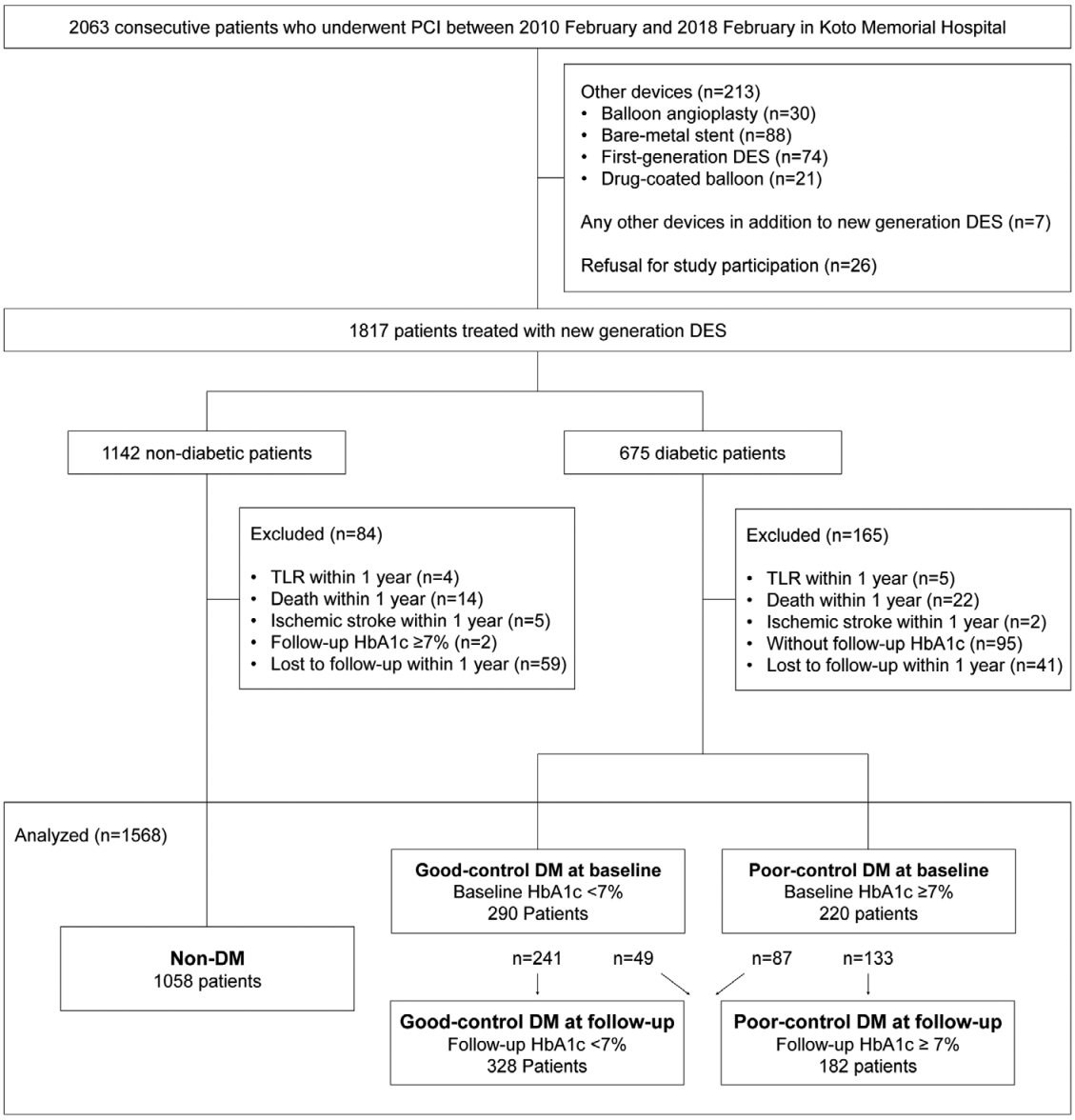


Figure 1. Study flow chart. DES, drug-eluting stent; DM, diabetes mellitus; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

Methods

Study Population

The present study was a retrospective cohort study among 2,063 consecutive patients who underwent PCI at Koto Memorial Hospital between February 2010 and February 2018. Only the first PCI for each patient during the study period was evaluated. Of the initial 2,063 consecutive patients, 213 patients treated without new-generation DES, 7 patients treated with any other devices in addition to new-generation DES, and 26 patients who refused to participate in the study were excluded. The remaining 1,817 patients underwent PCI exclusively with the use of new-generation DES.

In the present study, DM was defined as either HbA1c ≥6.5%, the use of antidiabetic medication, or being diagnosed as having DM by a primary care physician. The presence of DM and baseline HbA1c values were recorded in all patients by members of the cardiac catheterization team. Follow-up HbA1c values were obtained retrospectively from the electronic database. When several follow-up HbA1c values were available in a given patient, we used the measurement closest to 1-year after PCI. The HbA1c at 1-year after PCI was selected as follow-up data because it reflects glycemic control during the early phase after PCI, which may affect the incidence of late TLR.

There were 1,142 non-DM patients and 675 DM patients in this study. Of these patients, 9 patients who received TLR, 43 patients who died or had an ischemic stroke, and 100 patients who were lost to follow-up during the 1-year

after PCI were excluded from analysis. In addition, a further 95 DM patients whose follow-up HbA1c levels were not available and 2 non-DM patients whose follow-up HbA1c levels were ≥7% were excluded. Thus, the final study population consisted of 1,568 patients (non-DM patients, n=1,058; DM patients with HbA1c data available at both baseline and follow-up n=510; **Figure 1**).

Baseline characteristics and clinical outcomes beyond 1-year after PCI were compared among 3 groups: non-DM patients (n=1,058) and DM patients with either good (n=290) or poor (n=220) glycemic control at baseline. In addition, the 510 DM patients were divided into another 2 groups based on glycemic control at the 1-year follow-up (good [n=328] or poor [n=182]). Good glycemic control at baseline or the 1-year follow-up was defined as HbA1c <7%; poor glycemic control at baseline or the 1-year follow-up was defined as HbA1c ≥7%. Furthermore, the 510 DM patients were divided into 2 groups based on the difference in HbA1c between baseline and the 1-year follow-up, namely those with improved DM (follow-up HbA1c lower than baseline HbA1c; n=253) and those with no improvement in DM (follow-up HbA1c the same or higher than baseline HbA1c; n=257).

This study was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The need for written informed consent was waived because of the retrospective design of the study, although those patients who refused to participate in the study when contacted for follow-up were excluded. The research protocol, including the waiver for informed consent, was approved by the Institutional Ethics Committee of Koto Memorial Hospital (Shiga, Japan).

PCI

All interventions were performed according to standard clinical guidelines. The interventional strategy, devices, and periprocedural medication were at the discretion of the attending interventional cardiologists. The duration of dual antiplatelet therapy (DAPT) and other treatments after PCI was left to the discretion of each attending physician, although DAPT was generally recommended for at least 6 months.

Data Collection

Demographic, clinical, angiographic, procedural, and outcome data were obtained from hospital records and were entered prospectively into our electronic database. Lesion complexity was categorized based on American College of Cardiology (ACC)/American Heart Association (AHA) classification.[12] Follow-up information was primarily obtained from hospital charts. Additional follow-up information was obtained by telephone or mail contact with the patients, their relatives and/or referring physicians.

Outcome Measures and Definitions

The primary outcome measure was clinically driven late TLR, defined as repeat PCI or bypass surgery for the original target lesion beyond 1-year after the index PCI with either of the following: (1) angiographic diameter stenosis >50% with a positive history of recurrent angina symptoms or objective evidence of myocardial ischemia; and (2) angiographic diameter stenosis >70% regardless of

Table 1. Baseline Characteristics of the Study Patients Based on Glycemic Control at Baseline

	Non-DM (n=1,058)	DM patients		P-value
		Good control (n=290)	Poor control (n=220)	
Patient characteristics				
Age (years)	71.9±10.5	71.8±9.2	69.1±9.5	0.0009
Female sex	323 (31)	73 (25)	55 (25)	0.08
BMI (kg/m^2)	23.4±3.2	24.9±3.6	25.1±3.8	<0.0001
ACS	291 (28)	66 (23)	71 (32)	0.06
Triple vessel disease	168 (16)	72 (25)	64 (29)	<0.0001
Hypertension	732 (69)	227 (78)	168 (76)	0.003
Dyslipidemia	847 (80)	248 (86)	189 (86)	0.03
CKD	489 (46)	147 (51)	99 (45)	0.33
ESRD on hemodialysis	3 (0.3)	6 (2.1)	1 (0.5)	0.003
Current smoker	264 (25)	80 (28)	72 (33)	0.054
Previous MI	67 (6.3)	40 (14)	24 (11)	<0.0001
Previous CABG	11 (1.0)	9 (3.1)	0 (0)	0.004
Family history of IHD	138 (13)	32 (11)	19 (8.6)	0.16
Laboratory examination				
eGFR (mL/min/1.73 m^2)	62.0±15.9	59.7±16.8	62.3±17.8	0.10
BNP (pg/mL)	33.3 [15.0–79.5]	40.5 [18.8–102.9]	34.4 [13.2–106.4]	0.13
LDL-C (mg/dL)				
Baseline	114.3±31.4	106.1±30.7	110.0±31.6	0.0002
Follow-up	89.6±26.5	85.9±26.2	93.5±34.0	0.05
HbA1c (%)				
Baseline	5.66±0.37	6.37±0.37	7.96±1.13	<0.0001
Follow-up	5.75±0.37	6.50±0.57	7.41±1.27	<0.0001

(**Table 1** continued the next page.)

	Non-DM (n=1,058)	DM patients		P-value
		Good control (n=290)	Poor control (n=220)	
Lesion and procedure				
Lesion location				0.08
LMCA	51 (4.8)	20 (6.9)	17 (7.7)	
LAD	539 (51)	120 (41)	102 (46)	
LCx	212 (20)	69 (24)	49 (22)	
RCA	256 (24)	81 (28)	52 (24)	
Lesion type				
ACC/AHA Type B2/C	869 (82)	252 (87)	192 (87)	0.047
Restenotic	20 (1.9)	8 (2.8)	7 (3.2)	0.40
True bifurcation	373 (35)	102 (35)	98 (45)	0.03
Calcified	627 (59)	191 (66)	145 (66)	0.04
Use of IVUS	1,057 (99.9)	290 (100)	220 (100)	0.79
Stent type				0.96
Everolimus-eluting stents	919 (87)	252 (87)	187 (85)	
Biolimus-eluting stents	131 (12)	36 (12)	31 (14)	
Others	8 (0.8)	2 (0.7)	2 (0.9)	
Stent diameter (mm)	3.07±0.43	3.08±0.42	3.01±0.42	0.18
Stent length (mm)	23 [18–33]	24 [18–38]	24 [18–38]	0.02
Postdilatation	1,056 (99.8)	290 (100)	220 (100)	0.62
Minimum stent area (mm^2)	6.49±2.52	6.48±2.58	5.94±2.34	0.01
Medication at discharge				
Dual antiplatelet therapy	1,023 (96.7)	283 (97.6)	217 (98.6)	0.25
Statin	739 (70)	223 (77)	164 (75)	0.04
ACEI/ARBs	598 (57)	178 (61)	141 (64)	0.06
β-blockers	265 (25)	64 (22)	53 (24)	0.58
Insulin	0 (0)	12 (4.1)	39 (18)	<0.0001
TZDs	0 (0)	30 (10)	37 (17)	<0.0001
DPP4 inhibitors	0 (0)	101 (35)	131 (60)	<0.0001
SGLT2 inhibitors	0 (0)	3 (1.0)	8 (3.6)	<0.0001
Sulfonylurea	0 (0)	61 (21)	90 (41)	<0.0001
α-GIs	0 (0)	38 (13)	46 (21)	<0.0001
Biguanides	0 (0)	18 (6.2)	46 (21)	<0.0001

Data are given as the mean±SD, median [interquartile range], or number (%). Good glycemic control in diabetes mellitus (DM) patients was defined as HbA1c <7% at baseline, whereas poor control was defined as HbA1c ≥7% at baseline. ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHA, American Heart Association; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; α-GI, α-glucosidase inhibitor; ESRD, end-stage renal disease; IHD, ischemic heart disease; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL-C, low density lipoprotein cholesterol; LMCA, left main coronary artery; MI, myocardial infarction; RCA, right coronary artery; SGLT2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

symptoms or ischemia.

Secondary outcome measures included death, cardiac death, non-cardiac death, myocardial infarction (MI), stroke, any coronary revascularization, and a composite of all-cause death, non-fatal MI, or non-fatal stroke beyond 1-year after the index PCI.

Any coronary revascularization was defined as any PCI or bypass surgery.

Statistical Analysis

Continuous variables are expressed as the mean±SD or median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. The significance of differences across the 3 groups was assessed using analysis of variance or the Kruskal-Wallis test for continuous variables and the Chi-squared test for categorical variables. In the following survival analyses, the date after a 365-day period after the index PCI was set as Time 0. The cumulative incidence of clinical events was estimated using the Kaplan-Meier method and the significance of differences was assessed using the log-rank test. To evaluate the effects of good or poor glycemic control in DM patients relative to non-DM on clinically driven late TLR, a multivariable Cox proportional hazards model was constructed incorporating risk-adjusting variables such as age, sex, hemodialysis, insulin use, statin use, restenotic lesion, stent size ≤2.5 mm, and stent length >28 mm. Age was used as continuous variable. Proportional hazard assumptions for comparisons between non-DM patients and DM patients with good glycemic control, as well as between non-DM patients and DM patients with poor glycemic control, either at baseline or at follow-up, were assessed on plots of log(time) vs. log[−log(survival)] stratified by those groups, and the assumptions were verified to be acceptable. Results are

Table 2. Baseline Characteristics of Study Patients Based on Glycemic Control at Follow-up

	Non-DM (n=1,058)	DM patients		P-value
		Good control (n=328)	Poor control (n=182)	
Patient characteristics				
Age (years)	71.9±10.5	71.3±9.4	69.5±9.3	0.01
Female sex	323 (31)	80 (24)	48 (26)	0.07
BMI (kg/m^2)	23.4±3.2	24.9±3.7	25.1±3.8	<0.0001
ACS	291 (28)	91 (28)	46 (25)	0.81
Triple vessel disease	168 (16)	88 (27)	48 (26)	<0.0001
Hypertension	732 (69)	259 (79)	136 (75)	0.002
Dyslipidemia	847 (80)	283 (86)	154 (85)	0.02
CKD	489 (46)	165 (50)	81 (45)	0.34
ESRD on hemodialysis	3 (0.3)	6 (1.8)	1 (0.6)	0.009
Current smoker	264 (25)	92 (28)	60 (33)	0.06
Previous MI	67 (6.3)	34 (10)	30 (16)	<0.0001
Previous CABG	11 (1.0)	9 (2.7)	0 (0)	0.01
Family history of IHD	138 (13)	32 (10)	19 (10)	0.22
Laboratory examination				
eGFR (mL/min/1.73 m^2)	62.0±15.9	60.3±17.1	61.8±17.5	0.25
BNP (pg/mL)	33.3 [15.0–79.5]	36.9 [18.7–97.5]	38.8 [12.4–116.9]	0.26
LDL-C (mg/dL)				
Baseline	114.3±31.4	109.6±31.4	104.6±30.4	0.0001
Follow-up	89.6±26.5	85.9±26.8	95.2±34.5	0.02
HbA1c (%)				
Baseline	5.66±0.37	6.73±0.90	7.64±1.23	<0.0001
Follow-up	5.75±0.37	6.35±0.39	7.87±1.13	<0.0001
Lesion and procedure				
Lesion location				0.06
LMCA	51 (4.8)	21 (6.4)	16 (8.8)	
LAD	539 (51)	143 (44)	79 (43)	
LCx	212 (20)	73 (22)	45 (25)	
RCA	256 (24)	91 (28)	42 (23)	
Lesion type				
ACC/AHA type B2/C	869 (82)	287 (88)	157 (86)	0.04
Restenotic	20 (1.9)	6 (1.8)	9 (5.0)	0.03
True bifurcation	373 (35)	125 (38)	75 (41)	0.25
Calcified lesion	627 (59)	213 (65)	123 (68)	0.03
Use of IVUS	1,057 (99.9)	328 (100)	182 (100)	0.79
Stent type				0.67
Everolimus-eluting stents	919 (87)	287 (88)	152 (84)	
Biolimus-eluting stents	131 (12)	38 (12)	29 (16)	
Others	8 (0.8)	3 (0.9)	1 (0.6)	
Stent diameter (mm)	3.07±0.43	3.05±0.42	3.05±0.44	0.74
Stent length (mm)	23 [18–33]	24 [18–40]	24 [18–38]	0.02
Postdilatation	1,056 (99.8)	328 (100)	182 (100)	0.62
Minimum stent area (mm^2)	6.49±2.52	6.26±2.45	6.22±2.56	0.20
Medication at discharge				
Dual antiplatelet therapy	1,023 (96.7)	321 (97.9)	179 (98.4)	0.31
Statin	739 (70)	248 (76)	139 (76)	0.04
ACEI/ARBs	598 (57)	215 (66)	104 (57)	0.01
β-blockers	265 (25)	78 (24)	39 (21)	0.55
Insulin	0 (0)	15 (4.6)	36 (20)	<0.0001
TZDs	0 (0)	40 (12)	27 (15)	<0.0001
DPP4 inhibitors	0 (0)	123 (38)	109 (60)	<0.0001
SGLT2 inhibitors	0 (0)	6 (1.8)	5 (2.7)	<0.0001
Sulfonylurea	0 (0)	72 (22)	79 (43)	<0.0001
α-GIs	0 (0)	52 (16)	32 (18)	<0.0001
Biguanides	0 (0)	23 (7.0)	41 (23)	<0.0001

Data are given as the mean±SD, median [interquartile range], or number (%). In patients with DM, good glycemic control was defined as HbA1c <7% at follow-up, whereas poor control was defined as HbA1c ≥7% at follow-up. Abbreviations as in Table 1.

Table 3. Clinical Outcomes Based on Glycemic Control at Baseline

	No. patients with event (cumulative 5-year incidence [%])			P-value
	Non-DM (n=1,058)	DM patients		
		Good control (n=290)	Poor control (n=220)	
Clinically driven late TLR	30 (2.9)	16 (5.9)	19 (11)	0.0003
Death/non-fatal MI/non-fatal stroke	84 (8.3)	26 (8.6)	10 (3.6)	0.15
Death	64 (6.7)	21 (7.2)	7 (1.6)	0.14
Cardiac death	9 (1.0)	3 (0)	0 (0)	0.35
Non-cardiac death	55 (5.8)	18 (7.2)	7 (1.6)	0.28
MI	4 (0.2)	0 (0)	1 (0.5)	0.54
Stroke	28 (2.5)	7 (2.0)	4 (1.5)	0.69
Any coronary revascularization	270 (31)	109 (43)	104 (57)	<0.0001

The number of patients with the event was counted throughout the entire follow-up period, whereas the cumulative incidence was estimated at 5 years. P-values were calculated using the log-rank test. Good glycemic control in diabetes (DM) patients was defined as HbA1c <7% at baseline, whereas poor control was defined as HbA1c ≥7% at baseline. MI, myocardial infarction; TLR, target lesion revascularization.

Table 4. Clinical Outcomes Based on Glycemic Control at Follow-up

	No. patients with event (cumulative 5-year incidence [%])			P-value
	Non-DM (n=1,058)	DM patients		
		Good control (n=328)	Poor control (n=182)	
Clinically driven late TLR	30 (2.9)	13 (4.8)	22 (14)	<0.0001
Death/non-fatal MI/non-fatal stroke	84 (8.3)	24 (6.2)	12 (7.1)	0.70
Death	64 (6.7)	18 (4.9)	10 (4.7)	0.82
Cardiac death	9 (1.0)	3 (0)	0 (0)	0.43
Non-cardiac death	55 (5.8)	15 (4.9)	10 (4.7)	0.87
MI	4 (0.2)	0 (0)	1 (0.6)	0.48
Stroke	28 (2.5)	9 (1.8)	2 (1.9)	0.40
Any coronary revascularization	270 (31)	123 (45)	90 (56)	<0.0001

The number of patients with the event was counted throughout the entire follow-up period, whereas the cumulative incidence was estimated at 5 years. P-values were calculated using the log-rank test. Good glycemic control in DM patients was defined as HbA1c <7% at baseline, whereas poor control was defined as HbA1c ≥7% at baseline. Abbreviations as in Table 3.

expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

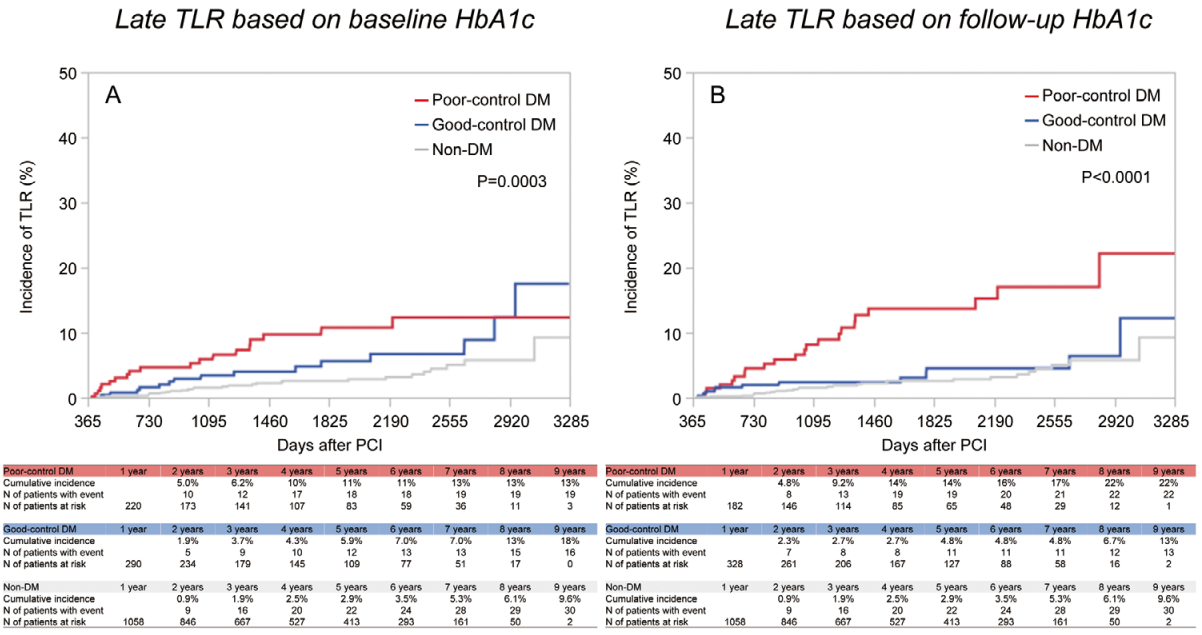
Two-tailed P<0.05 was considered significant. All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, NC, USA).

Results

The mean age of the entire study population was 71.5±10.2 years, 71% were male, and 33% had DM (142 treated with diet or exercise only, 317 treated with oral antidiabetic drugs [OADs], and 51 treated with insulin). Of the 510 DM patients, 290 (57%) and 220 (43%) were classified as have good and poor glycemic control at baseline, respectively; at the 1-year follow-up 328 (64%) and 182 (36%) patients were classified as have good and poor glycemic control, respectively. Follow-up HbA1c at 1 year was lower than baseline HbA1c in 253 DM patients (50%), and the same or higher in 257 DM patients (50%). Clinical presentation included stable angina in 1,140 patients (73%) and acute coronary syndrome in 428 patients (27%). Angiographic success was achieved in all patients (100%). Everolimus-eluting stents were used in 1,358 patients (87%) and biolimus-eluting stents were used 198 patients (13%). Other new-generation DESs were implanted in 12 patients (0.8%; sirolimus-eluting stents in 5, zotarolimus-eluting stents in 3, and a combination of different types of new-generation DESs in 4).

Tables 1 and **2** summarize baseline demographic, clinical, angiographic, and procedural characteristics across the 3 groups. Compared with non-DM patients, the prevalence of triple vessel disease, hypertension, and dyslipidemia was higher in DM patients. Moreover, complex lesions, such as true bifurcation lesions and calcified lesions, were more common in DM than non-DM patients. DM patients with poor glycemic control were more commonly treated with insulin and OADs than DM patients with good glycemic control. Data regarding the use of insulin and other diabetes medications at follow-up were not available.

The median follow-up after the index PCI was 1,505 days (IQR 849–2,311 days). Follow-up data from 2 to 9 years after the index PCI were available for 1,286/1,540



Poor-control DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		5.0%	6.2%	10%	11%	11%	13%	13%	13%
N of patients with event		10	12	17	18	18	19	19	19
N of patients at risk	220	173	141	107	83	59	36	11	3

Good-control DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		1.9%	3.7%	4.3%	5.9%	7.0%	7.0%	13%	18%
N of patients with event		5	9	10	12	13	13	15	16
N of patients at risk	290	234	179	145	109	77	51	17	0

Non-DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		0.9%	1.9%	2.5%	2.9%	3.5%	5.3%	6.1%	9.6%
N of patients with event		9	16	20	22	24	28	29	30
N of patients at risk	1058	846	667	527	413	293	161	50	2

Poor-control DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		4.8%	9.2%	14%	14%	16%	17%	22%	22%
N of patients with event		8	13	19	19	20	21	22	22
N of patients at risk	182	146	114	85	65	48	29	12	1

Good-control DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		2.3%	2.7%	2.7%	4.8%	4.8%	4.8%	6.7%	13%
N of patients with event		7	8	8	11	11	11	12	13
N of patients at risk	328	261	206	167	127	88	58	16	2

Non-DM	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Cumulative incidence		0.9%	1.9%	2.5%	2.9%	3.5%	5.3%	6.1%	9.6%
N of patients with event		9	16	20	22	24	28	29	30
N of patients at risk	1058	846	667	527	413	293	161	50	2

Figure 2. Kaplan-Meier curves for clinically driven late target lesion revascularization (TLR) based on (**A**) baseline and (**B**) follow-up HbA1c. Good-control DM, diabetic patients with HbA1c <7% either at baseline or follow-up; non-DM, patients without diabetes; poor-control DM, patients with HbA1c ≥7% at baseline or follow-up.

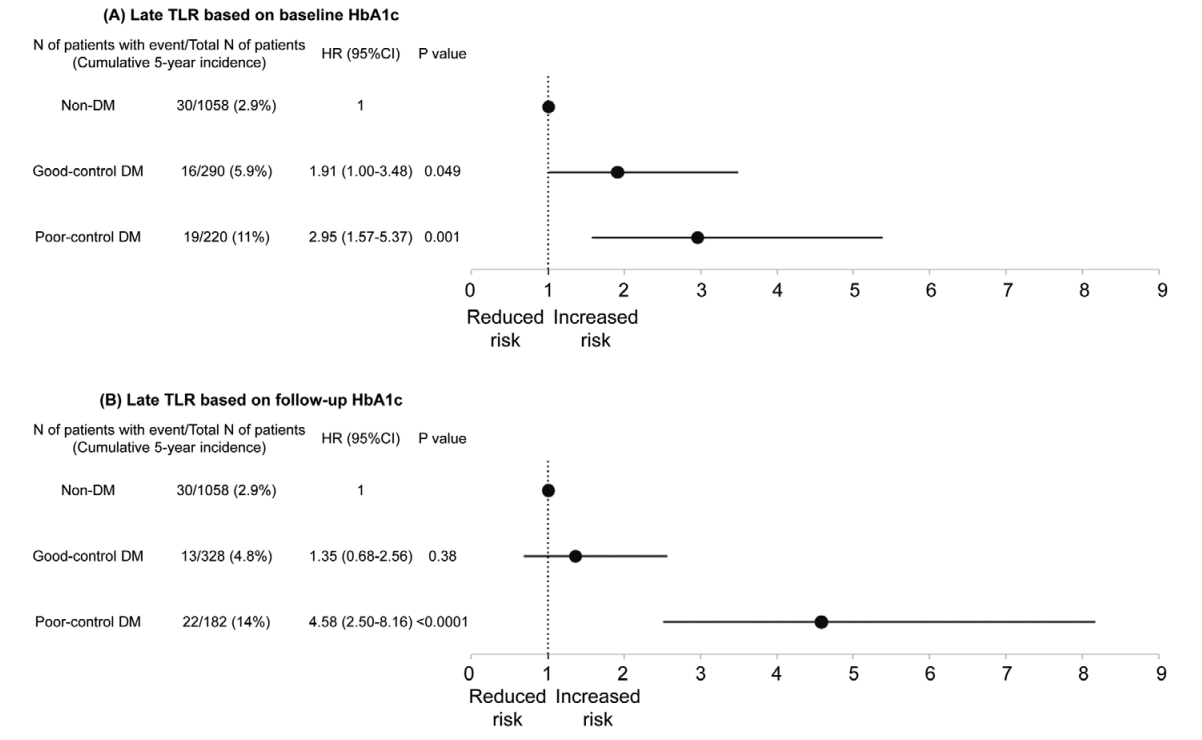


Figure 3. Forest plots for the effects of good and poor glycemic control in diabetic patients relative to patients without diabetes (non-DM) for clinically driven late target lesion revascularization (TLR) based on (**A**) baseline and (**B**) follow-up HbA1c, adjusted for age, sex, hemodialysis, insulin use, statin use, restenotic lesion, stent size ≤2.5 mm, and stent length >28 mm. The number of patients with the event (N) was counted throughout the entire follow-up period, whereas the cumulative incidence was estimated at 5 years. CI, confidence interval; good-control DM, diabetic patients with HbA1c <7% either at baseline or follow-up; HR, hazard ratio; poor-control DM, patients with HbA1c ≥7% at baseline or follow-up.

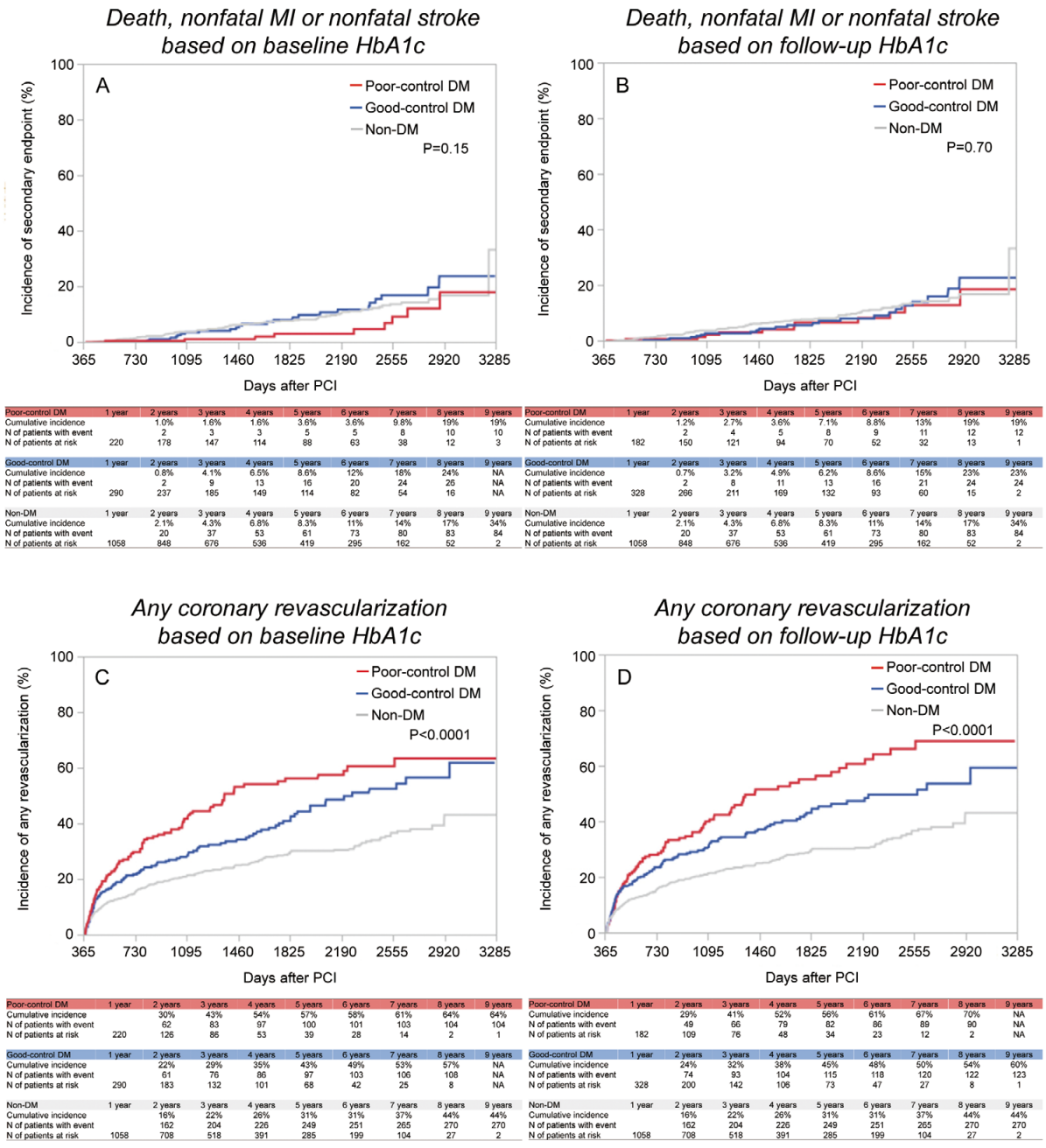


Figure 4. Kaplan-Meier curves for (**A**,**B**) death, non-fatal myocardial infarction (MI), or non-fatal stroke based on baseline (**A**) or follow-up (**B**) HbA1c and (**C**,**D**) any coronary revascularization based on baseline (**C**) or follow-up (**D**) HbA1c. Good-control DM, diabetic patients with HbA1c <7% either at baseline or follow-up; NA, not available; PCI, percutaneous coronary intervention; poor-control DM, patients with HbA1c ≥7% at baseline or follow-up.

(84%), 1,055/1,352 (78%), 864/1,119 (77%), 694/948 (73%), 525/748 (70%), 349/564 (62%), 174/396 (44%), and 97/217 (45%) eligible patients, respectively. Follow-up HbA1c values were available in DM patients at a median of 378 days after the procedure. Follow-up HbA1c values beyond 1 year in DM patients were very scarce. Follow-up low-density lipoprotein (LDL) data were available for 841 patients (54%) at a median of 375 days after the procedure.

Overall, follow-up angiography beyond 1-year after the index PCI was performed in 559 (36%) patients at a median of 486 days after the procedure. Of 1,009 (64%) patients who were not evaluated by follow-up angiography, 529 underwent follow-up coronary computed tomography angiography (CCTA) and 42 underwent myocardial perfusion scintigraphy (MPS) at a median of 506 days after the procedure.

Clinically driven late TLR was performed in 65 patients (stable angina: 55 patients; acute coronary syndrome: 10 patients). All TLRs were performed with PCI. The cumulative incidence of clinically driven late TLR was significantly higher in DM patients with poor glycemic control than in those with good glycemic control, and in the non-DM group based on glycemic control both at baseline and at follow-up (**Tables 3** and **4**; **Figure 2**). When groups were classified according to baseline HbA1c, the higher risk of clinically driven late TLR in those with good and poor glycemic control relative to the non-DM group remained significant (adjusted HR 1.91 [95% CI 1.00–3.48, P=0.049] and 2.95 [95% CI 1.57–5.37, P=0.001], respectively; **Figure 3**). When groups were classified according to follow-up HbA1c, the higher risk of clinically driven late TLR in the poor glycemic control group relative to the non-DM group remained significant (adjusted HR 4.58, 95% CI 2.50–8.16, P<0.0001), whereas the higher risk of clinically driven late TLR in the good glycemic control group relative to the non-DM group was no longer significant (adjusted HR 1.35, 95% CI 0.68–2.56, P=0.38; **Figure 3**). Kaplan-Meier curve analysis in which DM patients were divided according to differences in HbA1c between baseline and follow-up revealed that the cumulative incidence of clinically driven late TLR was significantly higher in both the improved and non-improved DM groups than in the non-DM group (**Supplementary Figure 1**). The higher risk of clinically driven late TLR in both the improved and non-improved DM groups relative to the non-DM group remained significant (adjusted HR 2.03 [95% CI 1.04–3.78, P=0.04] and 2.61 [95% CI 1.43–4.66, P=0.002], respectively; **Supplementary Figure 2**).

Statin was associated with a lower incidence of late TLR. However, neither baseline nor follow-up LDL <70 mg/dL was associated with a higher incidence of late TLR (**Supplementary Figure 3**).

Among the secondary endpoints, there were incremental increases in the rate of any coronary revascularization from the non-DM group to the DM group with good glycemic control and to the DM group with poor glycemic control using both glycemic control classifications based on baseline and follow-up HbA1c (**Figure 4**).

Discussion

In the present study we analyzed the association of glycemic control at baseline and at the 1-year follow-up with late TLR during long-term follow-up in DM patients who underwent new-generation DES implantation. DM patients with poor glycemic control, either at baseline or at 1-year follow-up, had a significantly higher risk for late TLR than non-DM patients. However, the higher risk of DM patients with good glycemic control at 1-year relative to non-DM patients was not significant for late TLR, although the higher risk of DM patients with good glycemic control at baseline relative to non-DM patients was marginally significant for late TLR. Furthermore, improvements in HbA1c were not associated with a lower incidence of late TLR. These observations may suggest the importance of glycemic control to achieve HbA1c <7% during the early phase after PCI in reducing late restenosis.

Clinical trials have already demonstrated the substantial benefits of intensive glycemic control to reduce microvascular outcomes in patients with diabetes.[13,14] However, the effect of tight glycemic control on cardiovascular end points remained unclear.[14–16] Therefore, current guidelines have provided weak recommendation for an HbA1c target of <7% for the prevention of cardiovascular events.[17] Those clinical trials evaluated MI as one of the outcome measures for cardiovascular events. In the case of patients who underwent PCI, restenosis is also an important problem due to its relatively high incidence, especially in patients with diabetes.[5] Restenosis is not a benign event, because it can occur as acute coronary syndrome and it may not infrequently result in recurrent restenosis.[18] Therefore, interventionists and physicians should strive to prevent restenosis after PCI. However, data are scarce regarding the association between glycemic control and restenosis.

The association between HbA1c before coronary intervention and restenosis is unclear. Although a previous prospective observational study showed that HbA1c <7% at the time of the procedure is associated with a lower rate of target vessel revascularization (TVR), another study showed no association between preprocedural HbA1c levels and TVR.[7,8] However, a more important question is whether optimal glycemic control after PCI can reduce restenosis. An observational study suggested that glycemic control started at PCI was not associated with an improvement in clinical outcome at approximately 300 days of follow-up.[9] In that study, patients were divided into those with good or poor glycemic control based on the difference between pre-PCI and follow-up HbA1c regardless of the follow-up HbA1c value itself. Another observational study showed that good glycemic control, as evidenced by mean HbA1c levels before and 1 and 6 months after elective coronary stenting, was associated with a lower rate of TVR at the 1-year follow-up.[10] However, these studies were conducted in the era of BMS and first-generation DES. Moreover, late restenosis is a clinically relevant issue for new-generation DES, although the use of these stents has substantially reduced stent thrombosis.[4] Nevertheless, the follow-up duration in these previous studies was too short to examine late restenosis. To the best of our knowledge, only a single study has explored the association between glycemic control after PCI and the long-term incidence of cardiovascular outcomes in 980 prospectively collected patients with diabetes, in which new-generation DES were used in nearly half of patients.[11] In that study, HbA1c <7% measured 2 years after PCI was associated with a reduced rate of cardiovascular outcomes, especially repeat revascularization including TLR.[11] The findings of the present study are in accordance with the previous study and encourage diabetic patients and their physicians to actively achieve good glycemic control.

The major mechanism of restenosis after coronary stenting is neointimal hyperplasia composed of smooth muscle cells and extracellular matrix. The findings of the present study are supported by the fact that chronic hyperglycemia is known to promote various restenosis processes, such as platelet activation, smooth muscle cell proliferation and migration, and extracellular matrix deposition.[19] DES suppress the restenosis processes by releasing antiproliferative drugs, but drug elution stops within months. In the present study, the increased risk of late TLR in DM patients with good glycemic control at baseline compared with the non-DM group was attenuated in those with good glycemic control at the 1-year follow-up, suggesting that optimal glycemic control during the early phase after PCI is more important than that before PCI in reducing late TLR. We think this is reasonable, because neointimal

proliferation begins after stenting. Moreover, the effect of glycemic control on restenosis may increase after the release of the antiproliferative drug from the DES finishes. Because HbA1c data beyond 1 year after PCI were scarce in the present study, we cannot discuss the importance of glycemic control beyond 1 year after PCI to reduce restenosis. A previous study reported that HbA1c <7% measured 2 years after PCI was associated with a reduced rate of TLR.[11] We think that optimal glycemic control for only 1 year after PCI is not sufficient, and indefinite control may be needed.

In addition to conventional neointimal hyperplasia noted above, in-stent neoatherosclerosis, characterized by the accumulation of lipid-laden foamy macrophages within the neointima with or without necrotic core formation and/or calcification, has emerged as another possible factor contributing to restenosis, especially after DES implantation.[20] The findings of the present study are also supported by an observational study that reported that high HbA1c levels in DM patients contributed to the development of neoatherosclerosis.[21] Although hyperinsulinemia also contributes to restenosis, the effect of insulin therapy on restenosis is inconclusive.[19] A previous observational study found an increased rate of TLR in insulin-treated DM (ITDM) compared with non-ITDM and non-DM patients.[22] However, a subanalysis of a randomized trial showed that the increased risk of adverse cardiovascular events in patients with ITDM compared with non-ITDM was attenuated in a propensity score-adjusted model that accounted for baseline risk facrors.[23] Furthermore, that study revealed that, compared with paclitaxel-eluting stents, the use of everolimus-eluting stents significantly reduced the rate of cardiovascular events, particularly TLR in ITDM. In the present study, follow-up HbA1c ≥7%, but not insulin therapy, was a significant predictor of late TLR. Furthermore, in addition to baseline characteristics, follow-up HbA1c values were available for patients in the present study, and new-generation DES were used in all patients, including 1,358 (87%) patients treated with everolimus-eluting stents, which may account for the absence of an association between insulin therapy and late TLR in the multivariate analysis. The results of the present study suggest that optimal glycemic control may be important in reducing restenosis, regardless of insulin therapy.

Study Limitations

First, we could not assess the restenosis rate because follow-up angiograms were not performed in all patients. However, 1,130 (72%) patients in all were evaluated with detailed examinations such as angiography, CCTA, or MPS in addition to clinical assessment. Second, 95 DM patients (14%) were excluded from the study because follow-up HbA1c levels were not available. None of those patients had undergone late TLR, because HbA1c is always measured when undergoing revascularization. Therefore, this selection bias may have resulted in overestimation of the incidence of late TLR. Third, we have no data regarding the type of diabetes (i.e., type 1 or type 2) and antidiabetic medication at follow-up, which may be confounding factors when assessing the effect of glycemic control on the incidence of outcomes. Fourth, insulin levels and insulin resistance, which may contribute to restenosis, were not assessed in this study. Finally, we do not have any data on the use of glucagon-like peptide-1 receptor agonists, which are currently recommended in patients with diabetes and cardiovascular disease.

Conclusions

DM patients with poor glycemic control at follow-up had a significantly higher risk of clinically driven late TLR than non-DM patients.

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Disclosures

The authors declare that they have no conflicts of interest.

IRB Information

This study was approved by the Institutional Ethics Committee of Koto Memorial Hospital (No. 2020-6).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-20-0065