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ORIGINAL ARTICLE

Effect of pioglitazone on cardiometabolic profiles and safety in patients with type 2 diabetes undergoing percutaneous coronary artery intervention: a prospective, multicenter, randomized trial

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Abstract
Pioglitazone has superior antiatherosclerotic effects compared with other classes of antidiabetic agents, and there is substantial evidence that pioglitazone improves cardiovascular (CV) outcomes. However, there is also a potential risk of worsening heart failure (HF). Therefore, it is clinically important to determine whether pioglitazone is safe in patients with type 2 diabetes mellitus (T2DM) who require treatment for secondary prevention of CV disease, since they have an intrinsically higher risk of HF. This prospective, multicenter, open-label, randomized study investigated the effects of pioglitazone on cardiometabolic profiles and CV safety in T2DM patients undergoing elective percutaneous coronary intervention (PCI) using bare-metal stents or first-generation drug-eluting stents. A total of 94 eligible patients were randomly assigned to either a pioglitazone or conventional (control) group, and pioglitazone was started the day before PCI. Cardiometabolic profiles were evaluated before PCI and at primary follow-up coronary angiography (5–8 months). Pioglitazone treatment reduced HbA1c levels to a similar degree as conventional treatment (pioglitazone group 6.5 to 6.0%, $P < 0.01$; control group 6.5 to 5.9%, $P < 0.001$), without body weight gain. Levels of high-molecular weight adiponectin increased more in the pioglitazone group than the control group ($P < 0.001$), and the changes were irrespective of baseline glycemic control. Furthermore, pioglitazone significantly reduced plasma levels of natriuretic peptides and preserved cardiac systolic and diastolic function (assessed by echocardiography) without incident hospitalization for worsening HF. The incidence of clinical adverse events was also comparable between the groups. These results indicate that pioglitazone treatment before and after elective PCI may be tolerable and clinically safe and may improve cardiometabolic profiles in T2DM patients.

Keywords Pioglitazone · Type 2 diabetes mellitus · Adiponectin · Cardiac function · Percutaneous coronary intervention

Introduction

Atherosclerotic cardiovascular (CV) complications are a major cause of mortality and morbidity in patients with type 2 diabetes mellitus (T2DM) [1, 2]. Despite a decreased risk of stent-related adverse events (in-stent restenosis (ISR) and thrombosis) due to recent technical progress in percutaneous coronary intervention (PCI) and the use of drug-eluting stents (DESs) rather than bare-metal stents (BMSs), T2DM is still a major determinant of short- and long-term adverse clinical outcomes in patients with T2DM who undergo coronary stent implantation [3–6].

Recent studies showed that insulin resistance was associated with ISR and the late "catch-up" phenomenon after DES implantation [7, 8]. Furthermore, Uetani et al. [9] reported that insulin resistance was also associated with post-procedural myocardial injury and an increased risk of adverse clinical outcomes in patients who underwent elective PCI with DES implantation. These results suggest that

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insulin resistance is surely a therapeutic target to improve clinical outcomes, especially in patients with T2DM who require secondary prevention of CV disease.

Pioglitazone, one of the thiazolidinediones, is an antidiabetic agent that acts as an agonist of peroxisome proliferator-activated receptor-gamma (PPARγ) and enhances insulin sensitivity [10, 11]. Previous studies showed that pioglitazone exerted clinically important antiinflammatory and antiatherogenic effects that were partially independent of its glucose-lowering effect [12–16]. Subsequent studies also showed that pioglitazone could reduce coronary plaque burden [17, 18], arterial inflammation [19], neointimal hyperplasia after stent (mainly BMS) implantation, and ISR [20–22]. These results suggest that pioglitazone treatment has a beneficial role in patients with T2DM undergoing elective PCI. However, little is known about the immediate and chronic effects of treatment with pioglitazone prior to elective PCI on cardiometabolic biomarkers and cardiac function. Our goal was to investigate whether pioglitazone treatment before and after elective PCI in Japanese patients with T2DM is safe and can improve cardiometabolic profiles.

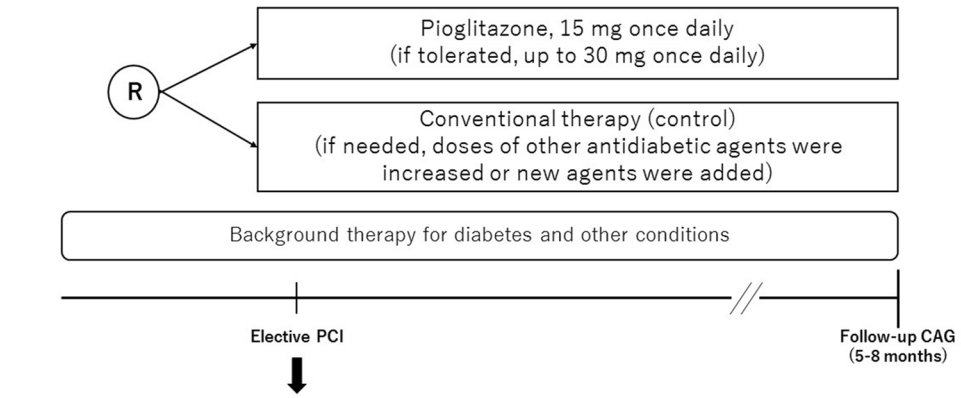
Methods

Study design and population

This study was a prospective, multicenter, open-label, randomized study to investigate the effect of pioglitazone pretreatment on cardiometabolic biomarkers and long-term safety in patients with T2DM undertaking elective PCI.

Between February 2006 and October 2008, patients with T2DM, who undertook elective PCI for coronary artery disease (CAD) and had a medical history of documented T2DM with HbA1c < 10%, were enrolled in the study. Patients who were diagnosed with T2DM according to the local guideline prior to PCI, were also recruited. Exclusion criteria were the presence of symptomatic heart failure (HF) and serious liver or renal dysfunction at the time of elective PCI. In addition, patients were also excluded if they were on insulin therapy, or had a contraindication to pioglitazone according to the label.

The study design is shown in Fig. 1. Prior to elective PCI, eligible patients were randomly assigned to either a pioglitazone (15–30 mg daily) or a conventional therapy (control) group (1:1) using a non-biased table of random numbers. In the pioglitazone group, pioglitazone was initiated on the evening before the PCI procedure and was continued thereafter with morning administration. If the patients could tolerate pioglitazone treatment, the dose was increased to 30 mg daily. In contrast, when any adverse side effect was documented, a decrease in dose or discontinuance of pioglitazone was permitted. In patients who were assigned to the control group, the doses of other antidiabetic agents could be increased, or new agents added if glycemic goal (HbA1c < 7.0%) could not be achieved. In both treatment groups, the background medical treatments for diabetes, hypertension, dyslipidemia or other conditions were continued during the study period, if their medical condition was not compromised by such an approach. However, if participants could not achieve their goals of risk factors, such as blood pressure, glycemic or lipid profiles, it was allowed to newly add agents or increase the doses of background drugs according to the relevant treatment guidelines by study investigators. In both treatment groups, the background medical treatments for diabetes, hypertension, dyslipidemia or other conditions were continued during the study period. The study protocol was approved by the local institutional review boards and independent ethics committees, and the study was conducted in accordance with the Declaration of



	Day 0	Day 1 Elective PCI	Day 2 24h after PCI	Day 3 48h after PCI	Day 4···
Pioglitazone	○ (start at evening)	○ (prior to PCI)	○ (at morning)	○ (at morning)	○ (at morning)
Blood and/or urine sampling	○ (prior to pioglitazone)	-	-	○ (at morning)	-

Fig. 1 Outline of the study. *CAG* coronary angiography, *PCI* percutaneous coronary intervention

Helsinki. All participants provided written informed consent prior to their participation in the study.

Measurements

At study entry, the following demographic variables were recorded: age, sex, body mass index (BMI), blood pressure, smoking status, previous medical history, and the use of medications. Blood and/or urine samples were obtained prior to the administration of pioglitazone on the day before elective PCI (Fig. 1). They were also obtained 48 h after PCI and at follow-up coronary angiography (CAG) (5–8 months). The specific biomarkers that were evaluated included high-sensitive C-reactive protein (hs-CRP), pentraxin3 (PTX3), monocyte chemotactic protein-1 (MCP-1), regulated on activation normal T cell expressed and secreted (RANTES), interleukin-8 (IL-8), and high-molecular weight (HMW)-adiponectin. Where appropriate, these biomarkers were evaluated at the central laboratories (Roche Diagnostics Ltd., Tokyo, Japan; Perseus Proteomics Inc., Tokyo, Japan; Department of Cardiovascular Medicine, Saga University, Saga Japan). The cardiac function biomarkers, brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), were analyzed at baseline, 48 h, and 5–8 months. Left ventricular (LV) systolic and diastolic function parameters were evaluated by echocardiography at baseline and follow-up CAG.

Study endpoints

The primary endpoints of the study were changes in specific cardiometabolic profiles, evaluated at 48 h after PCI and at follow-up CAG. Secondary endpoints were changes from baseline in the following parameters at follow-up CAG: (1) blood pressure; (2) body weight; (3) glycemic control (HbA1c and fasting plasma glucose); (4) biochemical tests (lipid profiles); (5) renal function parameters (estimated glomerular filtration rate (eGFR)), and creatinine-corrected urinary albumin excretion; and (6) echocardiographic cardiac function parameters. Other endpoints included the following: major adverse cardiac events (MACE: CV death and non-fatal myocardial infarction); coronary revascularization; HF requiring hospitalization; and major adverse effects of pioglitazone treatment, such as peripheral edema and hypoglycemia.

Statistical analysis

Categorical variables are shown as numbers (percentage) and were compared using a Chi-square test or Fisher's exact test, where appropriate. Continuous variables are expressed as the median [IQR] and were compared between the pioglitazone and control groups using a Mann–Whitney *U* test for skewed distributions. A Wilcoxon signed rank test was used to compare changes from baseline to 48 h or follow-up CAG in each group. All tests were two-tailed, and *P* values of < 0.05 were considered statistically significant. All the analyses were conducted using the R Statistical Software (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics at baseline

Among 94 patients (pioglitazone group, $N = 48$; control group, $N = 46$) registered into the study, 80 patients (pioglitazone group, $N = 42$; control group, $N = 38$) received an initial check-up and underwent elective PCI at baseline. There were 71 patients (pioglitazone group, $N = 39$; control group, $N = 32$) who had follow-up CAG and completed the study (Fig. 2). In the pioglitazone group, 6 patients were treated with 30 mg of pioglitazone at follow-up CAG, and most of patients received 15 mg of pioglitazone during the study period.

The demographic characteristics of the 80 patients at baseline are shown in Table 1. The prevalence of male sex and current smoking in the pioglitazone group showed a tendency to be higher than those values in the control group, although there was no significant difference between the groups. In both groups, approximately 40% of the patients were receiving treatment for secondary prevention of CV disease prior to the elective PCI. The majority of patients in both groups were on antiplatelet therapy, and two-thirds of the patients were on renin–angiotensin system inhibitors and statin therapy at baseline. Sulfonylureas were more often administered in the pioglitazone group, whereas the use of other antidiabetic agents was comparable between the groups.

The clinical characteristics of elective PCI are shown in Table 2. Twenty-five patients (59.5%) in the pioglitazone group and 21 patients (55.3%) in the control group underwent elective PCI due to stable angina pectoris. The frequency of patients who had multivessel coronary disease was higher in the pioglitazone group than in the control group. Stents were implanted in all the patients during elective PCI (BMSs: 7 [16.7%] in the pioglitazone group, 8 [21.1%] in the control group; first-generation DESs: 35 [83.3%] in the pioglitazone group, 35 [92.1%] in the control group).

Clinical and laboratory results

Table 3 shows baseline data and the changes from baseline in the clinical and laboratory parameters at 48 h and at

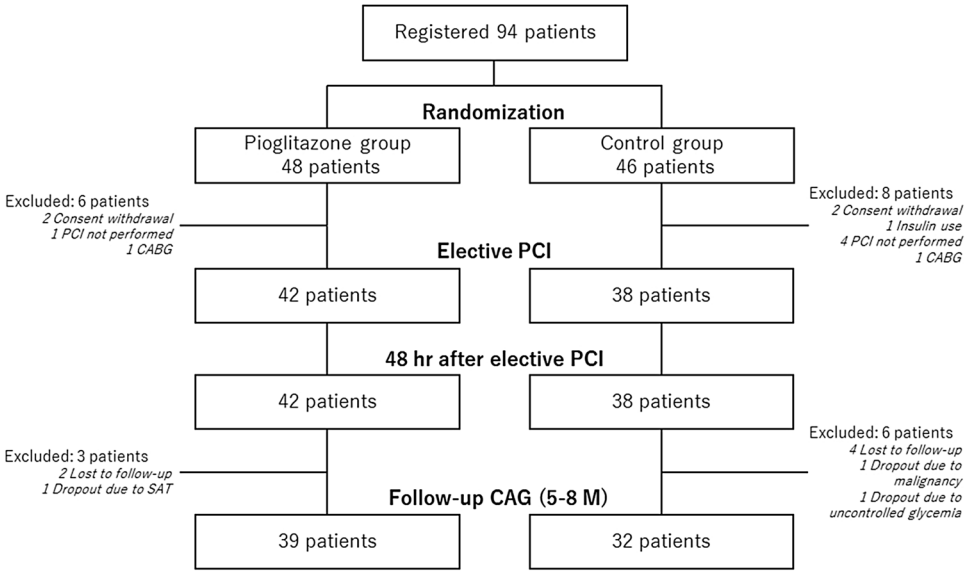


Fig. 2 Participants' flow. *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *SAT* subacute thrombosis, *CAG* coronary angiography

Table 1 Baseline demographic characteristics

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P	Pioglitazone [missing (%)]	Control [missing (%)]
Age (years)	67 [57, 74]	69 [64, 76]	0.197	0 (0)	0 (0)
Male sex	35 (83.3)	24 (63.2)	0.073	0 (0)	0 (0)
Current smoking	25 (59.5)	13 (34.2)	0.065	2 (4.8)	4 (10.5)
Clinical history					
Hypertension	34 (81.0)	30 (78.9)	1.000	0 (0)	0 (0)
Diabetes	42 (100)	38 (100.0)	–	0 (0)	0 (0)
Dyslipidemia	29 (69.0)	25 (65.8)	0.943	0 (0)	0 (0)
Heart failure	3 (7.1)	3 (7.9)	1.000	0 (0)	0 (0)
MI	18 (42.9)	13 (34.2)	0.708	0 (0)	2 (5.3)
PCI	19 (45.2)	15 (39.5)	0.847	0 (0)	1 (2.6)
CABG	1 (2.4)	0 (0.0)	1.000	0 (0)	2 (5.3)
Medications					
Antiplatelet	41 (97.6)	37 (97.4)	1.000	0 (0)	0 (0)
ACEI/ARB	28 (66.7)	25 (65.8)	1.000	0 (0)	0 (0)
β-Blocker	9 (21.4)	6 (15.8)	0.720	0 (0)	0 (0)
CCB	19 (45.2)	14 (36.8)	0.593	0 (0)	0 (0)
Statin	28 (66.7)	27 (71.1)	0.856	0 (0)	0 (0)
Biguanide	2 (4.8)	4 (10.5)	0.672	25 (59.5)	17 (44.7)
SU	15 (35.7)	9 (23.7)	0.006	25 (59.5)	17 (44.7)
α-GI	6 (14.3)	11 (28.9)	0.468	25 (59.5)	17 (44.7)
Glinide	0 (0.0)	3 (7.9)	0.238	25 (59.5)	17 (44.7)

Data are shown as median [IQR] or *N* (%)

MI myocardial infarction; *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *SU* sulfonylurea, *α-GI* alpha-glucosidase inhibitor

follow-up CAG. At follow-up CAG, BMI was unchanged in the pioglitazone group and reduced in the control group. Systolic and diastolic blood pressures were comparable at baseline between the groups, and the changes in these two variables from baseline to follow-up CAG were also similar. The median levels of HbA1c were decreased significantly at follow-up CAG in both groups (pioglitazone group, 6.5 to 6.0%, $P < 0.01$; control group, 6.5 to 5.9%, $P < 0.001$).

Table 2 Clinical characteristics of elective PCI at baseline

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P
Diagnosis			
SAP	25 (59.5)	21 (55.3)	0.874
UAP/NSTEMI	3 (7.1)	4 (10.5)	0.703
STEMI	0 (0.0)	0 (0.0)	–
OMI/RMI	13 (31.0)	13 (34.2)	0.943
Target lesion			
LAD	20 (47.6)	20 (52.6)	0.823
LCX	18 (42.9)	12 (31.6)	0.418
RCA	14 (33.3)	10 (26.3)	0.660
LMT	0 (0.0)	2 (5.3)	0.222
Multivessel	10 (23.8)	3 (7.9)	0.071
Stent			
BMS	7 (16.7)	8 (21.1)	0.830
DES	35 (83.3)	35 (92.1)	0.318

Data are shown as *N* (%)

PCI percutaneous coronary intervention, *SAP* stable angina pectoris, *UAP* unstable angina pectoris, *(N)STEMI* (non-)ST-segment elevation myocardial infarction, *OMI* old myocardial infarction, *RMI* recent myocardial infarction, *LAD* left anterior descending, *LCX* left circumflex artery, *RCA* right coronary artery, *LMT* left main trunk, *BMS* bare-metal stent, *DES* drug-eluting stent

In the pioglitazone group, lipid profiles improved, and liver enzymes decreased significantly. Interestingly, although creatinine-corrected urinary albumin excretion increased significantly in the control group, such increase was less evident in the pioglitazone group.

Table 4 shows the baseline values of the specific biomarkers and changes from baseline to 48 h and follow-up CAG. The trend of serial changes in the levels of hs-CRP, PTX3, MCP-1, and RANTES were comparable between the groups. IL-8 decreased significantly at follow-up CAG in the pioglitazone group, but not in the control group. The levels of HMW-adiponectin at baseline were comparable between the treatment groups. Although HMW-adiponectin decreased significantly 48 h after primary elective PCI in the control group, it was unchanged at 48 h in the pioglitazone group. At follow-up CAG, the level of HMW-adiponectin was significantly higher in the pioglitazone group than in the control group, and the magnitude of the increase in HMW-adiponectin from baseline was also significantly larger in the pioglitazone group than in the control group (Table 4; Fig. 3a). When patients were divided into two subgroups according to the median value of HbA1c at baseline [HbA1c < 6.5%: $N = 20$ (pioglitazone), $N = 18$ (control); HbA1c ≥ 6.5%: $N = 22$ (pioglitazone), $N = 20$ (control)], both subgroups showed a significant increase in HMW-adiponectin at follow-up CAG, and the increase was greater in the pioglitazone group than in the control group (Fig. 3b, c). Furthermore, in the subgroup with baseline HbA1c ≥ 6.5%, HMW-adiponectin at 48 h increased significantly in the pioglitazone group, whereas it decreased significantly in the control group (Fig. 3c).

CV function

Table 5 shows baseline data and changes from baseline in the CV functional parameters. The median values of BNP and NT-proBNP at 48 h were higher than those at baseline; however, the changes from baseline in these parameters were not significant in either group. At follow-up CAG, the plasma levels of BNP and NT-proBNP were comparable between the groups; however, only the levels in the pioglitazone group were significantly reduced from baseline, but not increased. The systolic (LV ejection fraction) and diastolic (peak early diastolic LV velocity/peak atrial velocity ratio and deceleration time) function parameters as assessed by echocardiography also showed no significant changes from baseline at follow-up CAG, and there were no significant differences between the groups.

Clinical safety

In both groups, all the patients received successful PCI procedures and exhibited no procedural complications at elective PCI. However, a patient in the pioglitazone group developed subacute stent thrombosis 3 days after elective PCI and dropped out of the study (Fig. 2). No other CV complications during the acute phase after elective PCI were observed in either group. Long-term clinical events at follow-up CAG were judged by each local investigator, and the result is summarized in Table 6. There were no deaths or MACE in either group during the study interval. Five patients (12.8%) in the pioglitazone group and 5 patients (15.6%) in the control group needed coronary revascularization, including target lesion revascularization (TLR) at follow-up CAG. There was one case of HF that required hospitalization in the control group, but none in the pioglitazone group. In the pioglitazone group, one patient suffered from peripheral leg edema, and another patient demonstrated an episode of hypoglycemia; therefore, pioglitazone was stopped in these two patients at 1 month and 4 months, respectively.

Discussion

The major findings of this study are as follows: (1) pioglitazone treatment reduced HbA1c levels to a similar degree as conventional treatment, without body weight gain; (2) pioglitazone treatment increased HMW-adiponectin levels more than conventional treatment, irrespective of glycemic control; (3) pioglitazone treatment did not increase plasma

Table 3 Baseline and changes from baseline in clinical and laboratory parameters

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P	Pioglitazone [missing (%)]	Control [missing (%)]
BMI (kg/m^2)					
Baseline	24.8 [22.6, 26.7]	24.9 [23.1, 25.9]	0.746	0 (0)	0 (0)
At follow-up CAG	24.4 [22.5, 28.2]	24.4 [22.2, 26.1]	0.609	5 (11.9)	6 (15.8)
Δ	0.0 [−0.6, 0.8]	−0.4 [−0.7, 0.3]*	0.120	5 (11.9)	6 (15.8)
Systolic BP (mmHg)					
Baseline	128 [118, 143]	125 [117, 140]	0.858	2 (4.8)	0 (0)
At follow-up CAG	128 [121, 140]	132 [123, 139]	0.628	5 (11.9)	6 (15.8)
Δ	3 [− 4, 14]	1 [− 9, 8]	0.294	6 (14.3)	6 (15.8)
Diastolic BP (mmHg)					
Baseline	72 [62, 81]	70 [62, 78]	0.380	2 (4.8)	0 (0)
At follow-up CAG	70 [64, 80]	73 [67, 78]	0.457	5 (11.9)	6 (15.8)
Δ	− 1 [− 8, 7]	5 [− 1, 9]	0.197	6 (14.3)	6 (15.8)
HbA1c (%)					
Baseline	6.5 [6.0, 7.8]	6.5 [6.0, 7.2]	0.453	0 (0)	0 (0)
At follow-up CAG	6.0 [5.7, 6.8]	5.9 [5.7, 6.4]	0.490	8 (19.0)	7 (18.4)
Δ	− 0.4 [− 0.9, 0.0]**	− 0.6 [− 0.8, 0.0]***	0.736	8 (19.0)	7 (18.4)
FBS (mmol/L)					
Baseline	6.94 [5.66, 8.38]	7.91 [6.06, 8.87]	0.149	3 (7.1)	4 (10.5)
At 48 h	6.77 [5.33, 8.16]	6.86 [5.54, 9.93]	0.447	9 (21.4)	6 (15.8)
Δ	0.28 [− 0.83, 0.89]	− 0.08 [− 2.22, 3.22]	0.742	9 (21.4)	6 (15.8)
At follow-up CAG	6.47 [5.67, 8.33]	7.74 [6.27, 9.61]	0.337	22 (52.4)	18 (47.4)
Δ	0.31 [−1.50, 0.92]	0.42 [− 1.62, 1.95]	0.846	22 (52.4)	18 (47.4)
TC (mmol/L)					
Baseline	4.86 [4.07, 5.51]	4.73 [4.11, 5.64]	0.674	0 (0)	1 (2.6)
At follow-up CAG	4.22 [3.83, 5.08]	4.42 [3.90, 5.18]	0.634	4 (9.5)	7 (18.4)
Δ	− 0.33 [− 0.71, 0.05]**	− 0.35 [− 0.98, 0.34]	0.828	4 (9.5)	8 (21.1)
LDL-C (mmol/L)					
Baseline	2.65 [2.19, 3.60]	2.79 [2.28, 3.28]	0.876	0 (0)	1 (2.6)
At follow-up CAG	2.15 [1.81, 2.69]	2.28 [1.97, 2.84]	0.495	5 (11.9)	7 (18.4)
Δ	− 0.34 [− 0.75, − 0.10]***	− 0.36 [− 1.07, 0.11]**	0.705	5 (11.9)	8 (21.1)
HDL-C (mmol/L)					
Baseline	1.14 [2.07, 1.32]	1.11 [1.03, 1.34]	0.555	1 (2.4)	1 (2.6)
At follow-up CAG	1.27 [1.06, 1.53]	1.37 [1.06, 1.58]	0.767	5 (11.9)	7 (18.4)
Δ	0.18 [0.03, 0.31]***	0.16 [− 0.05, 0.33]*	0.524	5 (11.9)	8 (21.1)
TG (mmol/L)					
Baseline	1.68 [1.22, 2.60]	1.65 [1.19, 2.17]	0.611	0 (0)	1 (2.6)
At follow-up CAG	1.20 [0.79, 1.83]	1.37 [1.00, 2.02]	0.399	4 (9.5)	7 (18.4)
Δ	− 0.36 [− 0.88, 0.20]**	− 0.33 [− 0.61, 0.14]	0.444	4 (9.5)	8 (21.1)
AST (IU/L)					
Baseline	21.5 [17.2, 28.0]	26.0 [21.0, 31.8]	0.125	0 (0)	0 (0)
At follow-up CAG	20.0 [17.2, 23.5]	26.0 [18.5, 28.5]	0.023	4 (9.5)	7 (18.4)
Δ	− 2.0 [− 6.0, 1.0]*	0.0 [− 5.0, 3.5]	0.225	4 (9.5)	7 (18.4)
ALT, IU/L					
Baseline	24.5 [18.0, 32.8]	26.5 [19.0, 40.5]	0.317	0 (0)	0 (0)
At follow-up CAG	18.5 [14.2, 24.0]	22.0 [17.5, 34.0]	0.026	4 (9.5)	7 (18.4)
Δ	− 4.0 [− 13.8, − 0.2]***	− 1.0 [− 10.5, 3.0]	0.201	4 (9.5)	7 (18.4)
eGFR (mL/min/1.73 m^2)					
Baseline	66.0 [55.2, 77.5]	60.3 [53.9, 73.9]	0.181	2 (4.8)	4 (10.5)

Table 3 (continued)

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P	Pioglitazone [missing (%)]	Control [missing (%)]
At follow-up CAG	63.4 [59.4, 76.0]	61.5 [54.6, 74.2]	0.475	8 (19.0)	15 (39.5)
Δ	0.0 [−7.0, 5.0]	0.0 [− 3.9, 6.9]	0.818	8 (19.0)	15 (39.5)
Creatinine-corrected urinary albumin excretion (mg/g Cre)					
Baseline	13.0 [7.4, 35.3]	12.6 [5.6, 19.6]	0.242	4 (9.5)	2 (5.3)
At follow-up CAG	14.3 [8.5, 45.8]	15.9 [8.0, 51.4]	0.958	12 (28.6)	9 (23.7)
Δ	1.7 [− 2.0, 7.1]	3.0 [0.0, 14.2]*	0.423	13 (31.0)	10 (26.3)

Data are shown as median [IQR]

BMI body mass index, *CAG* coronary angiography, *BP* blood pressure, *FBS* fasting blood sugar, *TC* total cholesterol, LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline

levels of natriuretic peptides rather significantly reduced them, and preserved cardiac performance as assessed by echocardiography without incident hospitalization for worsening HF; (4) pioglitazone treatment starting prior to elective PCI and continuing until primary follow-up CAG may be safe, and the incidence of clinical adverse events was comparable between the groups. To our knowledge, the present study was the first to demonstrate the CV safety, including cardiac function, and efficacy of pioglitazone in Japanese patients with T2DM undergoing elective PCI with first-generation DESs.

It is well known that diabetes is a strong predictor of ISR and worse clinical outcomes in patients with CAD who undergo stent implantation [23, 24]. Previous meta-analysis clearly showed the efficacy of pioglitazone treatment in decreasing ISR and revascularization after BMS implantation in patients with T2DM [25]. Hong et al. [26] also performed intravascular ultrasound and reported that pioglitazone reduced neointimal hyperplasia at the site of stented lesions and plaque burden in the stented segment at 8 months after DES implantation. This suggests that inhibition of unfavorable cellular and molecular actions during the acute phase after stent implantation should be, at least in part, critical for CV safety during the chronic phase. Therefore, in the present study, we administered pioglitazone 1 day prior to stent implantation and then assessed its immediate and chronic effects on cardiometabolic profiles and cardiac function.

Among antidiabetic agents, pioglitazone has the most established evidence of an antiatherosclerotic effect in experimental and human studies. Even short-term (4 weeks) pioglitazone treatment improved vascular endothelial function as assessed by flow-mediated dilation in patients with T2DM, and this was independent of changes in metabolic factors [27]. Pioglitazone significantly attenuated carotid intima–media thickness progression compared with standard therapy, and this effect was also independent of cardiometabolic risk factors [13, 15]. In the coronary arteries, the PERISCOPE trial showed significant attenuation of plaque volume progression by pioglitazone in patients with uncontrolled T2DM [17]. Furthermore, Nitta et al. [19] reported that pioglitazone, compared with glimepiride, decreased coronary artery inflammation depicted by (18)F-fluorodeoxyglucose-positron emission tomography combined with computed tomography angiography, and this was accompanied by a decrease in serum levels of hs-CRP. Also in our study, pioglitazone significantly reduced hs-CRP levels at follow-up CAG by the same amount as conventional treatment. Hong et al. [26] reported that pioglitazone immediately regulated immunological and inflammatory responses via suppression of interleukin 6 and MCP-1-C-C chemokine receptor type 2. The present study also showed that pioglitazone significantly decreased MCP-1 levels at 48 h after stent implantation, but not at follow-up CAG. Furthermore, serum levels of IL-8, which acts as an inflammatory-related mediator to recruit neutrophils into inflammatory sites [28], was significantly decreased by pioglitazone at follow-up CAG. In addition, Igarashi et al. [29] reported that Japanese patients with uncontrolled T2DM treated with pioglitazone for 4 months had reduced serum levels of inflammatory and atherogenic biomarkers, such as including remnant-like particle-cholesterol and tumor necrosis factor-alpha. Given these findings, it appears that pioglitazone can favorably alter vascular remodeling and attenuate local and systemic inflammatory responses in both the early and chronic phase after stent implantation, leading to CV protection in addition to amelioration of metabolic condition.

Adiponectin, which is a major adipocyte-secreted protein, plays a protective role in regulating fat and glucose metabolism [30]. Several studies demonstrated that pioglitazone increases adiponectin levels via PPARγ-mediated AMP-activated protein kinase and STAT3 phosphorylation,

Table 4 Baseline and changes from baseline in biomarkers

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P	Pioglitazone [missing (%)]	Control [missing (%)]
hs-CRP (ng/mL)					
Baseline	1680.0 [581.8, 2972.5]	1100.0 [578.0, 2760.0]	0.615	4 (9.5)	1 (2.6)
At 48 h	5175.0 [3075.0, 7102.5]	3575.0 [2235.0, 7750.0]	0.479	4 (9.5)	2 (5.3)
Δ	2628.5 [305.2, 3930]***	2020.0 [814.2, 4700.2]***	0.773	6 (14.3)	2 (5.3)
Follow-up CAG	640.5 [335.2, 1217.2]	587.0 [396.5, 1035.0]	0.886	24 (57.1)	15 (39.5)
Δ	− 317.5 [− 2863.2, − 46.0]*	− 356.0 [− 2478.0, − 49.0]***	0.899	26 (61.9)	15 (39.5)
PTX3 (ng/mL)					
Baseline	2.9 [1.9, 4.3]	2.7 [2.0, 3.4]	0.478	14 (33.3)	9 (23.7)
At 48 h	4.7 [3.1, 6.7]	3.8 [2.8, 4.8]	0.315	17 (40.5)	9 (23.7)
Δ	1.8 [0.5, 2.8]**	1.1 [0.7, 1.8]***	0.863	17 (40.5)	10 (26.3)
Follow-up CAG	2.7 [2.2, 4.1]	1.7 [1.2, 2.6]	0.063	27 (64.3)	23 (60.5)
Δ	− 0.1 [− 1.3, 0.5]	− 0.6 [− 1.4, − 0.2]	0.554	27 (64.3)	24 (63.2)
MCP-1 (pg/mL)					
Baseline	605.7 [378.3, 951.3]	535.8 [404.5, 949.3]	0.974	1 (2.4)	1 (2.6)
At 48 h	470.3 [369.3, 796.3]	424.7 [285.7, 734.8]	0.452	3 (7.1)	1 (2.6)
Δ	− 116.2 [− 249.3, 29.7]**	− 147.7 [− 265.3, 31.2]**	0.718	3 (7.1)	1 (2.6)
Follow-up CAG	535.8 [393.0, 739.4]	601.0 [419.6, 759.8]	0.632	19 (45.2)	15 (39.5)
Δ	− 77 [− 299.2, 111.7]	− 96.6 [− 198.8, 91.4]	0.777	19 (45.2)	15 (39.5)
RANTES (pg/mL)					
Baseline	6072.0 [4281.4, 8813.3]	8239.6 [5056.4, 15254.4]	0.072	17 (40.5)	8 (21.1)
At 48 h	5744.9 [3479.4, 12781.7]	7401.5 [4120.6, 11437.3]	0.566	17 (40.5)	10 (26.3)
Δ	− 6.8 [− 1038.2, 2489.2]	− 1250.6 [− 5522.8, 378.3]	0.082	22 (52.4)	15 (39.5)
Follow-up CAG	6415.1 [4624.8, 14192.0]	8902.0 [4905.2, 14394.3]	0.869	25 (59.5)	19 (50.0)
Δ	1071.3 [− 632.8, 3027.0]	90.1 [− 1732.1, 5393.7]	0.812	29 (69.0)	22 (57.9)
IL-8 (pg/mL)					
Baseline	29.8 [19.4, 44.5]	34.7 [22.5, 53.4]	0.362	1 (2.4)	2 (5.3)
At 48 h	27.8 [16.8, 50.8]	38.4 [17.8, 47.3]	0.493	4 (9.5)	2 (5.3)
Δ	− 2.7 [− 11.5, 7.2]	− 1.9 [− 13.1, 11.9]	0.743	4 (9.5)	2 (5.3)
Follow-up CAG	19.7 [12.9, 31.2]	23.8 [14.5, 33.4]	0.547	19 (45.2)	16 (42.1)
Δ	− 5.7 [− 18.7, 4.2]*	− 6.1 [− 15.1, 1.5]	0.813	19 (45.2)	16 (42.1)
HMW-adiponectin (μg/mL)					
Baseline	3.0 [1.9, 4.8]	2.7 [1.9, 4.6]	0.857	0 (0)	1 (2.6)
At 48 h	3.0 [1.8, 4.2]	2.2 [1.6, 4.5]	0.307	2 (4.8)	1 (2.6)
Δ	0.2 [− 0.1, 0.4]	− 0.1 [− 0.8, 0.2]*	0.010	2 (4.8)	1 (2.6)
Follow-up CAG	10.3 [6.2, 16.0]	4.3 [2.0, 6.9]	< 0.001	13 (31.0)	9 (23.7)
Δ	5.4 [4.0, 8.3]***	0.7 [0.3, 2.6]***	< 0.001	13 (31.0)	9 (23.7)

Data are shown as median [IQR]

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline

hs-CRP high-sensitive C-reactive protein, *PTX3* pentraxin3, *MCP-1* monocyte chemotactic protein-1, *RANTES* regulated on activation, normal T cell expressed and secreted, *IL-8* interleukin-8, *HMW* high-molecular weight

and subsequently enhances insulin sensitivity [31–34]. An increase in adiponectin levels by pioglitazone treatment was also found in our study, irrespective of glycemic control, and this result was similar to the findings of Otto et al. [35]. Recent animal studies demonstrated that pioglitazone suppressed neointimal formation and vascular smooth muscle cell proliferation via both adiponectin-dependent and adiponectin-independent mechanisms [36]. Furthermore, pioglitazone decreased coronary neointimal hyperplasia, accompanied by increases in circulating microRNA-24 in patients with T2DM [37]. In addition, Pistrosch et al. [38] reported that rosiglitazone, another thiazolidinediones, lessened renal damages and reduced urinary albumin excretion via alterations in intrarenal endothelial function and renal

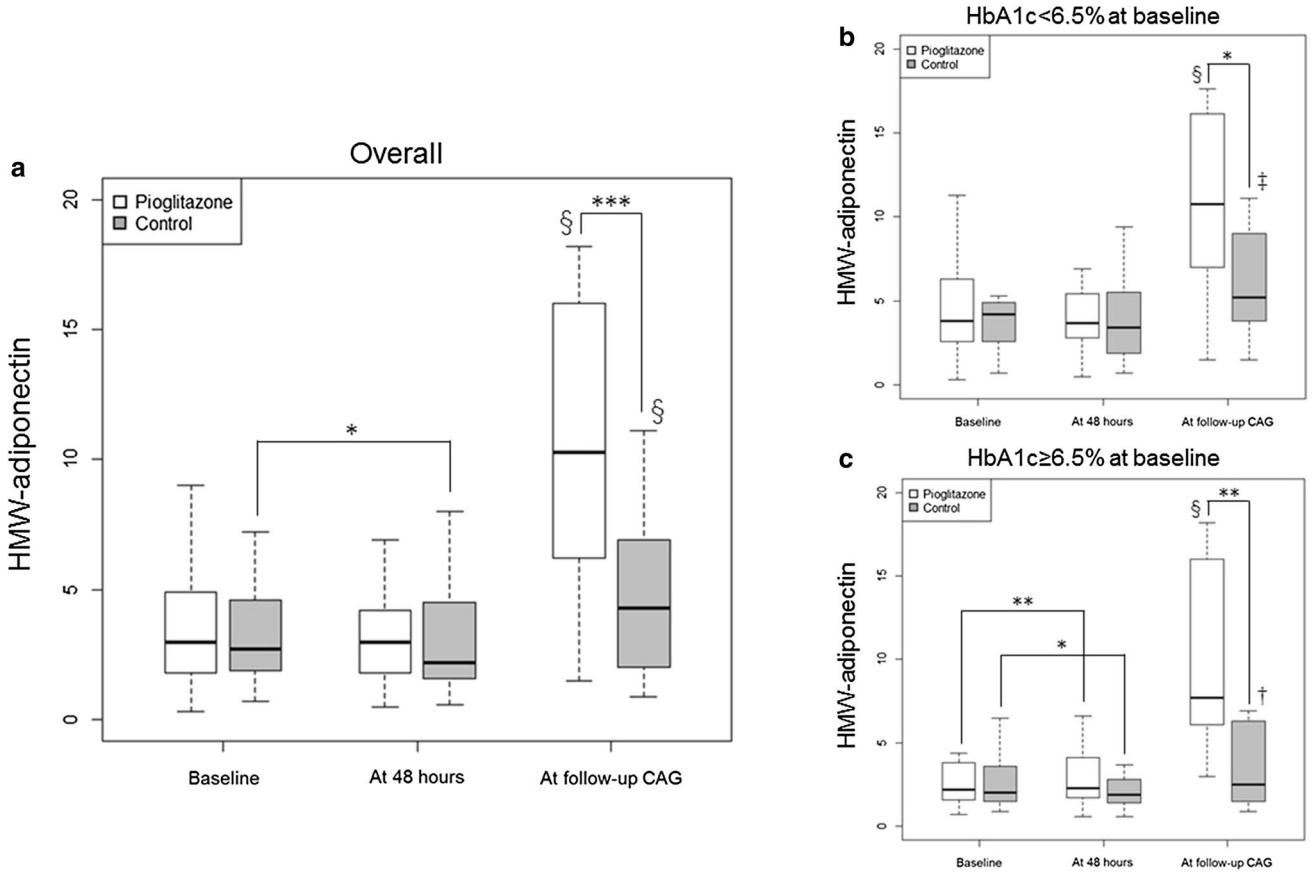


Fig. 3 HMW-adiponectin levels at baseline, 48 h, and follow-up CAG. Overall (**a**), patients with HbA1c at baseline < 6.5% (**b**) and ≥ 6.5% (**c**). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$, $^{\S}P < 0.001$ vs. baseline in each group. *HMW* high-molecular weight, *CAG* coronary angiography

hemodynamics in patients with T2DM and microalbuminuria, although no significant reduction in UACR was observed in our study subjects who were largely normoalbuminuric. Thus, further studies are warranted to elucidate the precise molecular mechanisms underlying the adiponectin-independent pathways of pioglitazone.

In multiple observational studies, the use of pioglitazone in primary care was associated with a reduction in the risk of all-cause mortality and CV events [39–41]. In patients who require secondary prevention of CV disease, previous studies have shown that pioglitazone improved atherosclerotic CV outcomes [42, 43]. A recent meta-analysis to assess the clinical efficacy of pioglitazone on secondary prevention of CV disease also demonstrated similar results, although pioglitazone did not lower the risk of all-cause mortality, and it increased the risk of HF [44]. However, there seems to be controversy on the clinical impact of pioglitazone on incident HF [44–48]. Previous literature clearly demonstrated that pioglitazone was not associated with unfavorable effects on cardiac structure and function, but there were increases in renal sodium reabsorption with subsequent systemic fluid retention and manifestations of edema [49, 50]. In a mouse model of myocardial infarction, pioglitazone treatment significantly reduced cardiac injury, and this effect was partially mediated by a PPARγ-independent pathway [51, 52]. Furthermore, some studies showed that pioglitazone improved cardiac function [53–55]. It is well recognized that patients with both diabetes and CAD have a substantially higher risk of HF compared with those who have either CAD or diabetes alone [56]. Accordingly, pioglitazone treatment in patients who needed secondary prevention of CV disease had a 33% increased risk of HF, whereas there was no increased risk of HF in patients treated for primary prevention of CV disease [44, 57]. In our study, where all participants were treated for secondary prevention of CV disease, pioglitazone treatment did not exacerbate cardiac dysfunction and did not increase the natriuretic peptides and development of HF. In particular, it would be clinically meaningful to prove that pioglitazone treatment is safe before and after elective PCI in patients with T2DM.

This study has several limitations that may impact the interpretation of the results. First, there were considerable problems with the methodology, such as small sample size, simple randomization method, and lack of formal trial

Table 5 Baseline and changes from baseline in parameters of cardiac function

Variables	Pioglitazone ($N = 42$)	Control ($N = 38$)	P	Pioglitazone [missing (%)]	Control [missing (%)]
BNP (pg/mL)					
Baseline	32.1 [15.8, 118.8]	44.3 [17.6, 62.0]	0.961	6 (14.3)	3 (7.9)
At 48 h	57.0 [28.7, 135.8]	49.6 [18.6, 93.8]	0.426	2 (4.8)	0 (0)
Δ	− 0.9 [− 19.1, 11.9]	5.1 [− 9.4, 22.4]	0.285	8 (19.0)	3 (7.9)
At follow-up CAG	31.8 [15.1, 94.2]	24.9 [7.7, 91.7]	0.470	18 (42.9)	15 (39.5)
Δ	− 7.9 [− 39.7, 2.7]*	− 4.1 [− 15.5, 15.1]	0.305	18 (42.9)	15 (39.5)
NT-proBNP (pg/mL)					
Baseline	142.8 [51.3, 434.6]	230.3 [64.8, 365.1]	0.564	1 (2.4)	1 (2.6)
At 48 h	237.2 [95.1, 509.1]	220.8 [131.1, 358.9]	0.980	2 (4.8)	1 (2.6)
Δ	23.2 [− 29.1, 106.9]	18.9 [− 74.6, 62.7]	0.391	3 (7.1)	1 (2.6)
At follow-up CAG	152.4 [76.6, 265.9]	129.2 [46.7, 259.4]	0.470	13 (31.0)	9 (23.7)
Δ	− 65.6 [− 218.6, 4.9]**	− 27.9 [− 135.3, 27.4]	0.353	13 (31.0)	9 (23.7)
LVEF (%)					
Baseline	66 [56, 69]	66 [58, 71]	0.782	1 (2.4)	2 (5.3)
At follow-up CAG	65 [58, 73]	64 [57, 66]	0.435	10 (23.8)	9 (23.7)
Δ	2 [− 3, 6]	− 2 [− 10, 6]	0.396	11 (26.2)	9 (23.7)
E/A					
Baseline	0.8 [0.7, 1.0]	0.7 [0.6, 0.9]	0.018	14 (33.3)	16 (42.1)
At follow-up CAG	0.8 [0.7, 1.0]	0.7 [0.6, 0.9]	0.237	20 (47.6)	18 (47.4)
Δ	0.0 [− 0.1, 0.1]	0.1 [0.0, 0.2]	0.449	21 (50.0)	21 (55.3)
DcT (ms)					
Baseline	223 [200, 243]	199 [166, 241]	0.169	18 (42.9)	16 (42.1)
At follow-up CAG	232 [196, 259]	220 [195, 256]	0.690	20 (47.6)	21 (55.3)
Δ	0 [− 38, 21]	10 [− 13, 72]	0.256	25 (59.5)	22 (57.9)

Data are shown as median [IQR]

BNP brain natriuretic peptide, *CAG* coronary angiography, *NT-proBNP* N-terminal proBNP, *LVEF* left ventricular ejection fraction, *E/A* peak early diastolic LV filling velocity/peak atrial filling velocity ratio, *DcT* deceleration time

*$P < 0.05$, **$P < 0.01$ vs. baseline

Table 6 Clinical adverse events at follow-up CAG

	Pioglitazone ($N = 39$)	Control ($N = 32$)	P
Death	0 (0.0)	0 (0.0)	–
MACE	0 (0.0)	0 (0.0)	–
Coronary revascularization[a]	5 (12.8)	5 (15.6)	1.000
Heart failure requiring hospitalization	0 (0.0)	1 (3.1)	0.451
Peripheral edema	1 (2.6)	0 (0.0)	1.000
Hypoglycemia	1 (2.6)	0 (0.0)	1.000

Data are shown as *N* (%)

MACE major adverse cardiac events

[a]Including target lesion revascularization

registration and independent event assessment committee. Therefore, it may be difficult to draw a strong clinical conclusion. Second, the present study was performed by a PROBE design, but it was not a placebo-controlled study. Therefore, unexpected bias might be introduced in the assessment of results. In addition, there were substantial dropouts from the study and many missing data especially at follow-up CAG, as shown in figure and each table. Third, we could not obtain clinical information, such as stent diameter/length, maximum inflation pressure, lesion length, plaque volume, and the degree of stenosis, at elective PCI or follow-up CAG. Hence, the effect of pioglitazone on in-stent

neointimal formation was not evaluated in our study. Fourth, we could not obtain the data on serum insulin concentration and insulin resistance index, such as the homeostasis model assessment-insulin resistance. Lastly, the participants in our study were recruited from February 2006 to October 2008. Although second-generation DESs are currently used in most PCI procedures in Japan, our study included BMSs and first-generation DESs. Furthermore, newer antidiabetic agents, such as incretin-based agents, were not used. Finally, because our study was designed to evaluate the effects of pioglitazone on CV safety for a limited period from elective PCI to primary follow-up CAG in a small number of participants, further studies are needed to assess the longitudinal CV safety of pioglitazone in patients undergoing PCI.

In summary, the present study demonstrated that pioglitazone treatment prior to elective PCI improved glycemic control without significant body weight gain, and it may be safe for CV function in Japanese patients with T2DM. Furthermore, pioglitazone treatment increased HMW-adiponectin levels more than conventional therapy, irrespective of glycemic control at baseline.

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Compliance with ethical standards

Conflict of interest HY has received honoraria from Takeda. TU has received honoraria from Daiichi Sankyo, Bayer, Mochida, Boehringer Ingelheim; research funding from Daiichi Sankyo. TI has received honoraria from Mochida and Bayer; and scholarships from Abbott, KAATHU JAPAN, GOODMAN, CLINICO, Shionogi, St. Jude Medical, Daiichi Sankyo, Takeda, Mitsubishi Tanabe, Teijin, Boehringer Ingelheim, Boston Scientific Japan, and UNION TOOL. KNo has received honoraria from Daiichi Sankyo, Merck, Pfizer, Eli Lilly, Amgen, Boehringer Ingelheim, Mitsubishi Tanabe, and Astellas; research funding from Bayer, Teijin, Mitsubishi Tanabe, Astellas, Boehringer Ingelheim, and Asahi Kasei; and scholarships from Astellas, Daiichi Sankyo, Sumitomo Dainippon, Takeda, Mitsubishi Tanabe, and Boehringer Ingelheim. The remaining authors have no financial interests to disclose related to this manuscript.

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