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Effects of dipeptidyl peptidase-4 inhibitor sitagliptin on coronary atherosclerosis as assessed by intravascular ultrasound in type 2 diabetes mellitus with coronary artery disease

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ABSTRACT

Background: It is unclear whether the addition of dipeptidyl peptidase-4 inhibitors (DPP4-I) to statins may cause coronary plaque regression in type 2 diabetes mellitus (T2DM) patients with coronary artery disease (CAD).
Methods and results: Seventy-five T2DM patients with CAD who underwent percutaneous coronary intervention under intravascular ultrasound (IVUS) guidance were randomized to receive DPP4-I sitagliptin (sitagliptin group) or not to receive DPP4-I (non-DPP4-I group) as an add-on treatment to statins, and were followed-up for 8–12 months. Patients with analyzable IVUS examinations of the non-culprit segment were included in the primary analysis. Sitagliptin group ($n = 28$) and non-DPP4-I group ($n = 24$) had significant ($p < 0.05$) and similar reduction in low-density lipoprotein cholesterol levels (-12 ± 24 and -12 ± 23 mg/dL), and had no significant changes in hemoglobin A_{1c} levels. Nominal change in percent atheroma volume (PAV), the primary endpoint, was not significant in both the sitagliptin and non-DPP4-I groups [mean (95% CI): +1.1% (−0.5 to 2.7%) and 0.2% (−1.5 to 1.9%)]. The difference in change in PAV between sitagliptin and non-DPP4-I groups was also not significant [0.89% (−1.46%–3.25%)].
Conclusions: The addition of sitagliptin to statins did not cause coronary plaque regression in T2DM with CAD.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a potent risk factor for atherosclerotic cardiovascular disease (ASCVD) [1,2], and among patients with ASCVD, T2DM is significantly associated with a worse prognosis [3,4]. In addition, glycemic control has not been adequately demonstrated to have a favorable effect on ASCVD in patients with T2DM [5–7]. Moreover, there is no sufficient evidence to help guide the choice of class of glucose-lowering medications for reducing cardiovascular events in T2DM [8]. Treatment with statins is a standard therapy for the secondary prevention of ASCVD [9,10], however, they do not completely prevent cardiovascular events and residual risk is still present, especially in T2DM patients with coronary artery disease (CAD).

Dipeptidyl peptidase-4 inhibitors (DPP4-I) are a new class of oral hypoglycemic agents for the treatment of T2DM that do not cause weight gain [11]. DPP4-I promote postprandial insulin secretion and suppress glucagon release by inhibiting the degradation of incretin hormones such as glucagon-like peptide 1, glucose-dependent insulinotropic peptide and other peptides [12]. Recent evidence in animals and humans suggests that DPP4-I may also have anti-atherosclerotic effects. DPP4-I, sitagliptin and alogliptin, have been shown to inhibit the progression of atherosclerosis in apolipoprotein *E*-deficient mice [13–15]. In patients with T2DM, sitagliptin and alogliptin are shown to improve endothelial function, have anti-inflammatory effects, and prevent the progression of carotid atherosclerosis in T2DM patients [16–20]. Therefore, DPP4-I may be useful for the prevention of CAD in T2DM patients.

However, it is still unclear whether DPP4-I may cause coronary plaque regression in T2DM patients with CAD as an add-on to statin therapy. The TOP-SCORE (assessment in patients with Type 2 diabetes mellitus in addition to cOronary artery disease after Percutaneous coronary intervention with regard to Sitagliptin-induced COronary plaque REgression) study was planned to evaluate the effect of the DPP4-I sitagliptin on coronary plaque as assessed by intravascular ultrasound (IVUS) when added to statins in T2DM patients with CAD.

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2. Methods

2.1. Patients and study design

TOP-SCORE was a prospective, open, parallel, randomized, comparative, single-center study to examine the effect of sitagliptin on coronary plaque regression as assessed by IVUS in T2DM patients with CAD. The study was performed according to the Declaration of Helsinki regarding investigations in humans and approved by the ethics committee of Fukuoka University Hospital (EC/IRB: 11-3-03). Written informed consent was obtained from each patient. The present study has been registered with the University Hospital Medical Information Network (UMIN000017861).

Eighty-five T2DM patients 30 years of age or older with CAD who needed percutaneous coronary intervention (PCI) were screened from December 2011 to July 2015 (Fig. 1A). The patients were eligible for enrollment, if the hemoglobin A_{1c} (HbA_{1c}) level was 6.2% to 9.9% in patients who were taking any hypoglycemic agents or 6.5% to 9.9% in patients who were not receiving medical treatment for T2DM.

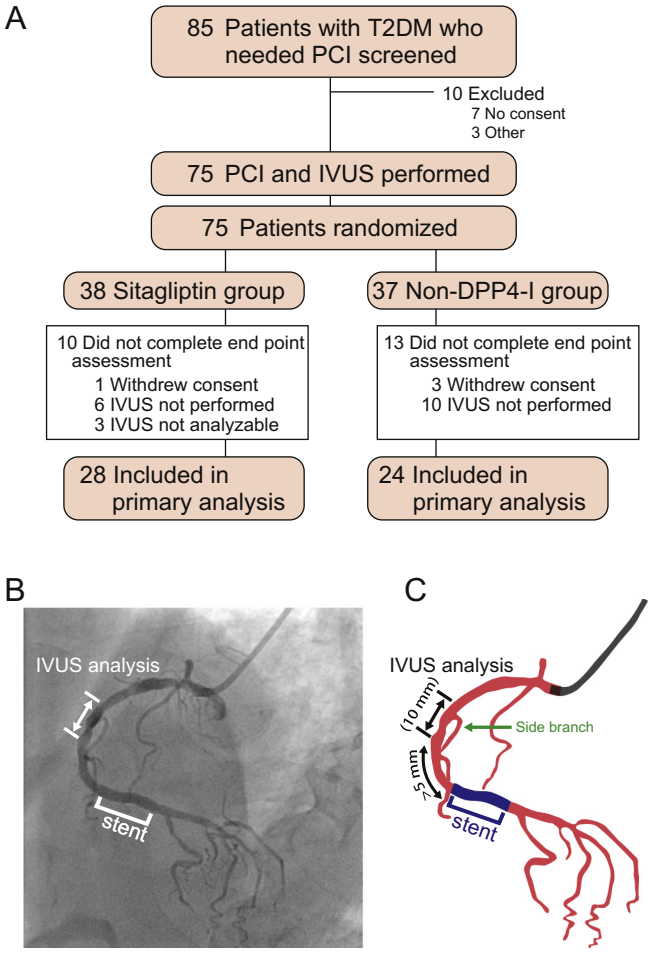

Fig. 1. (A) Flow chart of the study. Seventy-five T2DM patients with CAD who underwent IVUS-guided PCI were randomized to receive sitagliptin (sitagliptin group) or not to receive DPP4-I (non-DPP4-I group). Ultimately, 52 patients who had analyzable IVUS examinations of a non-culprit lesion at baseline and at 8–12 months of follow-up were included in the primary analyses. (B) Representative coronary angiogram of the evaluated vessel for IVUS analysis. The analyzable segment is proximal to the stent deployed in the RCA. (C) The proximal edge of the stent and the side branch were used as a reproducible index for IVUS analysis at baseline and follow-up. The segment for the measurement of IVUS needed to be >5 mm proximal to the PCI site, and the total length of the segment was 10 mm. T2DM, type 2 diabetes mellitus; CAD, coronary heart disease; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; DPP4-I, dipeptidyl peptidase-4 inhibitors; RCA, right coronary artery.

The exclusion criteria were as follows: (1) type 1 diabetes mellitus; (2) patients who had experienced ketosis, diabetic coma and/or precoma within six months prior to providing consent; (3) moderate to severe heart failure [New York Heart Association class ≥III, left ventricular ejection fraction (LVEF) <40%]; (4) severe valvular heart disease; (5) renal dysfunction (creatinine blood level of over 1.5 mg/dL in men and over 1.3 mg/dL in women); (6) familial hypercholesterolemia; (7) contraindication to antiplatelet agent; (8) history of chemical sensitivity to DPP4-I; (9) pregnancy or lactation; and (10) severe infection, trauma or recent surgery.

Seventy-five patients were enrolled and successfully underwent PCI under IVUS guidance (Fig. 1A). Ten patients were not enrolled for no informed consent ($n = 7$) or not suitable for the randomization ($n = 3$).

All of the patients enrolled received a standard antiplatelet and statin treatment, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were appropriately controlled, according to the Japanese Guidelines for Secondary Prevention of Myocardial Infarction [10]. Treatment for dyslipidemia was based on the Japan Atherosclerosis Society Guideline for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases (2007 or 2012 version) [21,22], and the target level of low-density lipoprotein cholesterol (LDL-C) was <100 mg/dL.

The enrolled patients were randomly assigned to receive sitagliptin at a standard dose of 50 mg/day ($n = 38$, sitagliptin group) or not to receive DPP4-I ($n = 37$, non-DPP4-I group) (Fig. 1A). Randomization was stratified by age (≥60 y or <60 y) and LDL-C level (≥100 mg/dL or <100 mg/dL). To achieve a target HbA_{1c} level of <7.0%, the protocol permitted up-titration of sitagliptin to 100 mg/day or addition of other hypoglycemic agent in the sitagliptin group, and addition of hypoglycemic agents except for DPP4-I in the non-DPP4-I group. Hypoglycemic agents were reduced if hypoglycemic symptoms were observed. The safety of the patients was assessed by medical examination and blood tests at 3, 6, and 8 to 12 months of the study period.

Ultimately, a total of 52 patients who had analyzable IVUS examinations at both baseline and follow-up were included in the primary analysis (Fig. 1A). Twenty-three patients were not included in the data analysis for the following reasons: (1) withdrew informed consent (4 patients); (2) follow-up IVUS examination not performed (16 patients); and (3) IVUS image not analyzable (3 patients) (Fig. 1A).

2.2. IVUS procedure and analysis

After IVUS-guided PCI of the culprit segment of coronary artery, IVUS examination was conducted using an imaging catheter and a console (View IT and VISIWAVE, Terumo, Tokyo, Japan). The patients received an intracoronary injection of 1.0 to 2.0 mg of nitroglycerin just before IVUS examination to prevent coronary spasm. The target segment for IVUS analysis was selected at a non-PCI site (>5 mm proximal or distal to the PCI site) on the PCI vessel. For reliable comparisons between baseline and follow-up, a stent edge or an easily definable side branch was used as a reproducible index (Fig. 1B and C). The IVUS catheter was advanced to the distal side of the PCI site and pulled back automatically at a speed of 0.5 mm/s. A total of 10 IVUS frames were extracted at an interval of 1.0 mm for a total length of 10 mm at the selected segment using a motorized pullback system.

After a review of the IVUS images and selection of the target segment (Fig. 1B and C), IVUS analysis was conducted by two experienced physicians (A.I., observer 1; Y.K., observer 2) who were blinded to the patient characteristics and group allocation according to the criteria described in the American College of Cardiology Clinical Expert Consensus document on IVUS [23].

The IVUS analysis was carried out using a new quantitative IVUS analysis system (VISIATLAS, Terumo, Tokyo, Japan), which measures both plaque volume and tissue characteristics of plaque. This new three-dimensional (3-D) IVUS analysis system is comparable with the commonly used IVUS analysis system (echoPlaque™, INDEC Systems, Santa

Clara, CA, USA), and the reliability and validity have been demonstrated previously [24].

For quantitative IVUS analysis, external elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA were manually traced in each cross-section, and atheroma CSA (EEM CSA minus lumen CSA) was automatically calculated (Fig. 2). Vessel volume and lumen volume were automatically calculated as Σ EEM CSA and Σ lumen CSA, respectively.

Total atheroma volume (TAV) and percent atheroma volume (PAV) were calculated as follows:

$$TAV = \Sigma(\text{EEM CSA}-\text{lumen CSA})$$
$$PAV = 100 \times \Sigma(\text{EEM CSA}-\text{lumen CSA})/\Sigma \text{ EEM CSA}$$

The tissue characterization of plaque was analyzed using the software of integrated backscatter IVUS (IB IVUS) attached to the above-mentioned 3-D IVUS analysis system (Fig. 2). The plaque components were classified into 4 categories: lipid, fibrosis, dense fibrosis, and calcification by combining spectral parameters of posterior-scattering signals of IVUS [25]. The area and volume of each plaque component were automatically calculated, and expressed as percentage.

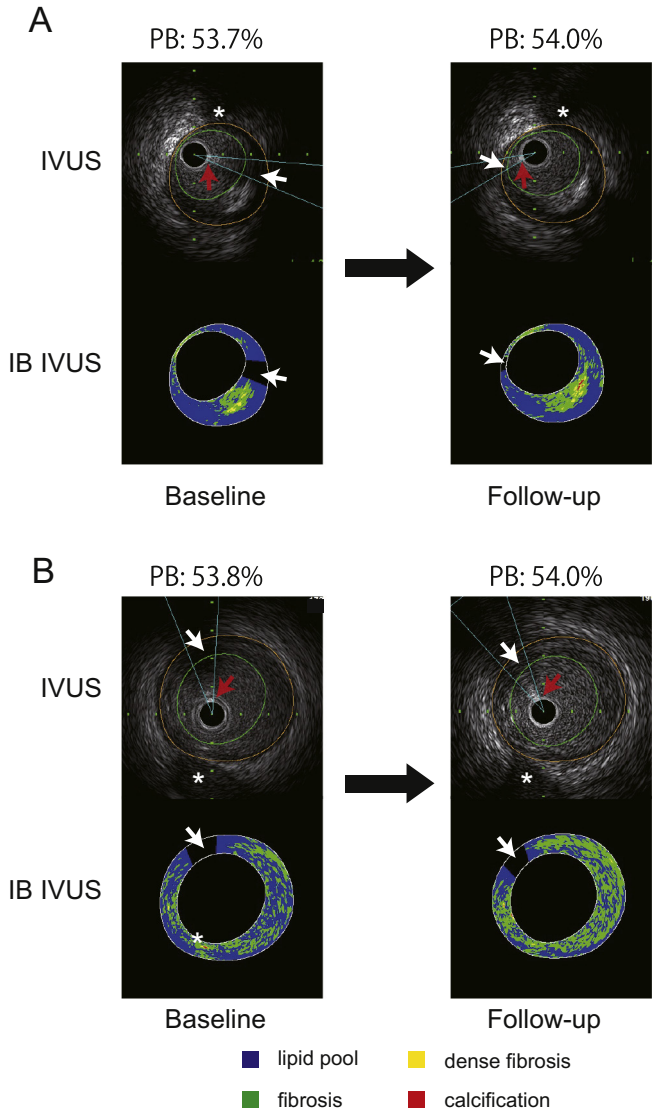

Fig. 2. Representative conventional IVUS and IB IVUS images of the cross sections at baseline and follow-up. (A) sitagliptin group. (B) non-DPP4-I group. The green and yellow lines indicate the edges of the lumen and the external elastic membrane. The red and white arrows indicate the guide wire and the artifact due to the guide wire, respectively. * indicates side branches used as reproducible indices. PB, plaque burden; IVUS, intravascular ultrasound; IB, integrated backscatter; DPP4-I, dipeptidyl peptidase-4 inhibitors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Primary and secondary endpoints

The primary endpoint was the nominal change in PAV at the selected segment from baseline to follow-up.

The secondary endpoint was the percent change in TAV at the selected segment from baseline to follow-up, which was calculated as follows:

$$\text{Percent change in TAV} = (\text{TAV at follow-up-TAV at baseline})/\text{TAV at baseline} \times 100$$

Other secondary endpoints included the nominal changes in the percent volumes of lipid, fibrosis, dense fibrosis, and calcification, and changes in clinical laboratory data during the study period.

2.4. Clinical laboratory examinations

Fasting blood sugar (FBS) level, HbA_{1c} level, serum levels of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and LDL-C, serum creatinine level, high-sensitivity C-reactive protein (hs-CRP) level, and uric acid (UA) level were measured at screening, at randomization, and during the study period at the Fukuoka University Hospital Laboratory Unit. Estimated glomerular filtration rate (eGFR) was calculated as follows: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (male), $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (female).

2.5. Statistical data analysis

Statistical data analyses were performed using the SAS software package (version 9.4, SAS Institute) at Fukuoka University (Fukuoka, Japan). Frequency distributions of categorical variables including gender, risk factors of CAD, and medications at baseline were compared between groups by the chi-square test and/or Fisher's exact test. Continuous variables including clinical laboratory data and IVUS parameters at baseline and follow-up were compared between groups using the Wilcoxon rank-sum test. Non-parametric methods were used due to the relatively small sample size [26]. Changes in continuous variables during the study period for each group were examined by the Wilcoxon signed-rank test, and differences in the changes between groups were examined by the Wilcoxon rank-sum test. The relations between two continuous variables were examined by the Spearman rank correlation. Equal variances of changes in PAV between groups were assessed by the Ansari-Bradley test [27].

For quantitative IVUS analyses at baseline and follow-up, inter-observer agreement of gray-scale IVUS parameters (vessel volume, lumen volume, TAV, and PAV) was assessed with the concordance correlation coefficient (CCC) [28] and Bland Altman analysis [29,30]. CCC was estimated using U-statistic method, which is recommended for small samples [28]. CCC and 95% confidence interval (CI) were computed using the SAS macro of Carrasco et al. [28]. For Bland Altman analysis, the absolute difference and mean value were calculated for each pair of measurement by the two observers and the percent difference between the observers was calculated as absolute difference divided by the mean of two observers. Bland Altman plot was presented as scatter plot of the absolute difference (y axis) verse the mean value (x axis) of the two observers. Normality of the distribution of the absolute differences between two observers was assessed by Shapiro-Wilk test, and the 95% limits of agreement (LOA) were calculated as mean differences $\pm 1.96 \times$ standard deviation (SD) of the differences between the two observers [29,30].

Mean and 95% CI for changes in PAV and percent change in TAV in Sitagliptin and Non-DPP4-I groups were estimated by an analysis of variance (ANOVA), and least-square (LS) mean (95% CI) was estimated by

an analysis of covariance (ANCOVA) adjusting for baseline variables. The standardized mean difference (Cohen's d-statistic) [31] in changes in PAV during the study period between Sitagliptin and Non-DPP4-I groups was used as the measure of effect size for power analysis. The 95% CI for a two sample Cohen's d was computed using the noncentrality parameter CI [32]. Power analysis based on population effect size and sample effect size were performed using noncentral F distribution [33,34]. Power curve, showing changes in power (y axis) with sample size (x axis) for different standardized effect size [35], was prepared using the Graph Template Language (GTL) in SAS [36,37].

Data for continuous variables are presented as mean ± SD, median [interquartile range (IQR, 25th to 75th percentile)], or mean (95% CI). A P value of <0.05 was considered to be statistically significant unless indicated otherwise.

3. Results

3.1. Characteristics of T2DM patients with CAD and clinical laboratory data

Fig. 1 shows the flow chart of the study. Fifty-two T2DM patients with CAD who had complete end point assessment (analyzable IVUS image at both baseline and follow-up) were included in the primary analysis, based on intention-to-treat (ITT) principal. Four patients who were randomized but had HbA_{1c} levels slightly higher or lower than the inclusion criteria were not excluded, because they received no additional treatment with insulin during the study period. Table 1 and Supplementary Table I show the characteristics of T2DM patients with CAD and clinical laboratory data in sitagliptin group ($n = 28$) and non-DPP4-I group ($n = 24$). As shown in Table 1, age, gender, risk factors of CAD, and history of CAD were not significantly different between groups at baseline. All of the T2DM patients with CAD had 1, 2, or 3 diseased vessels and were implanted with drug-eluting stent (DES) except that 3 patients in sitagliptin group were implanted with bare-metal stent (BMS) (Table 1). The average follow-up period for sitagliptin group and non-DPP4-I group was 8.9 ± 1.6 months and 8.5 ± 1.5 months, respectively.

Most of the T2DM patients with CAD in sitagliptin group ($n = 21$, 75%) and non-DPP4-I group ($n = 20$, 83%) were already receiving statins at screening, and all of the patients were treated with statin at randomization. However, two patients in the sitagliptin group stopped statins for side effects after randomization (Table 1). Serum LDL-C levels in sitagliptin group and non-DPP4-I group were already low at baseline (95 ± 33 mg/dL and 87 ± 26 mg/dL, respectively), and were further reduced at follow-up (83 ± 21 mg/dL and 73 ± 25 mg/dL, respectively) (Supplementary Table I).

At baseline and at follow-up, sitagliptin group and non-DPP4-I group were not significantly different in serum levels of LDL-C, HDL-C, TG, hsCRP, eGFR, and UA (Supplementary Table I).

At screening, 57% ($n = 16$) of the T2DM patients with CAD in sitagliptin group were receiving DPP4-I (Table 1). At randomization, all of the patients in sitagliptin group were treated with sitagliptin at a standard dose of 50 mg/day, and concomitant administration of non-DPP4-I hypoglycemic agents were allowed (Table 1), for achieving target level of glycemic control ($HbA_{1c} < 7\%$). The dose of sitagliptin was reduced to 25 mg/day in one patient due to improved glycemic control, increased to 100 mg/day in two patients, and discontinued in one patient at the physician's discretion. Patients in non-DPP4-I group who were receiving DPP4-I at screening ($n = 11$, 46%) were switched to non-DPP4-I hypoglycemic agents for glycemic control at randomization (Table 1). Therefore, non-DPP4-I group had a higher proportion of patients who had insulin use (46% vs 11%, $P = 0.006$) and who received α-GI (42% vs 18%, $P = 0.07$) at baseline as compared to sitagliptin group (Table 1).

HbA_{1c} levels in T2DM patients with CAD in sitagliptin group and non-DPP4-I group were 7.2 ± 1.0% and 7.3 ± 1.2%, respectively, at baseline, and were maintained during the study period (Supplementary Table I). Although HbA_{1c} levels did not change significantly from baseline to follow-up in both sitagliptin group and non-DPP4-I group (0.0 ± 0.7% and 0.2 ± 1.0%, respectively), there was a significant increase in FBS during the study period in both groups (Supplementary Table I).

Patients who were receiving anti-hypertensive drugs at screening continued the medication throughout the study period (Table 1).

Table 1
Baseline characteristics of T2DM patients with CAD in sitagliptin and non-DPP4-I groups.

	Sitagliptin ($n = 28$)	Non-DPP4-I ($n = 24$)	P value
Age, y	70 ± 9	72 ± 10	0.47
Gender, Male (%)	22 (79%)	20 (83%)	0.74
BMI, Kg/m^2	24.8 ± 4.1	25.1 ± 4.1	0.85
Smoking, n (%)	4 (14%)	3 (13%)	1.0
Hypertension, n (%)	22 (79%)	19 (79%)	1.0
Dyslipidemia, n (%)	24 (86%)	21 (88%)	1.0
Hyperuricemia, n (%)	7 (25%)	7 (29%)	0.74
Prior MI, n (%)	3 (11%)	3 (13%)	1.0
Prior PCI, n (%)	8 (29%)	7 (29%)	0.96
Prior CABG, n (%)	2 (7%)	1 (4%)	1.0
Type of CAD, n			
SCAD/NSTE-ACS/STEMI	23/2/3	22/0/2	0.67
Number of diseased vessel, n			
1/2/3	9/14/5	12/9/3	0.49
Target vessel, n			
LAD/LCx/RCA/LMT	13/5/10/0	10/5/8/1	0.90
Stent, n			
DES/BMS	25/3	24/0	0.24
Follow-up period, month	8.9 ± 1.6	8.5 ± 1.5	0.39
Medication at screening, n (%)			
DPP-4 inhibitor	16 (57%)	11 (46%)	0.42
Statin	21 (75%)	20 (83%)	0.52
Medication at baseline, n (%)			
Sitagliptin	28 (100%)	0 (0%)	–
Insulin	3 (11%)	11 (46%)	0.006
Biguaniade	8 (29%)	11 (46%)	0.20
Sulfonylurea	3 (11%)	3 (13%)	1.0
α-GI	5 (18%)	10 (42%)	0.07
Glinide	1 (4%)	1 (4%)	1.0
Thiazolidine	2 (7%)	3 (13%)	0.65
Statin	26 (93%)	24 (100%)	0.49
Ezetimibe	0 (0%)	1 (4%)	0.46
EPA	3 (11%)	4 (17%)	0.69
ARB	18 (64%)	16 (67%)	0.86
ACE-I	3 (11%)	3 (13%)	1.0
CCB	19 (68%)	17 (71%)	0.82
β-blocker	4 (14%)	8 (33%)	0.19
Diuretics	5 (18%)	1 (4%)	0.20
Aldosterone blocker	1 (4%)	1 (4%)	1.0
Long-acting nitrate	4 (14%)	1 (4%)	0.36
Nicorandil	4 (14%)	2 (8%)	0.67
Aspirin	28 (100%)	24 (100%)	–
Thienopyridine	28 (100%)	24 (100%)	–
OAC	2 (7%)	2 (8%)	1.0

Data are presented as mean ± SD for continuous variables or the number (percent) of patients for category variables.
T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; DPP4-I, dipeptidyl peptidase-4 inhibitors; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SCAD, stable coronary artery disease; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; LMT; left main trunk; DES, drug-eluting stent; BMS, bare-metal stent; DPP-4, dipeptidyl peptidase-4; α-GI, α-glucosidase inhibitor; EPA, eicosapentaenoic acid; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; OAC, oral anticoagulants.

3.2. Conventional gray-scale IVUS and IB IVUS parameters for coronary plaque

At baseline and follow-up, the volume and composition of coronary plaque were analyzed in the selected segment of coronary artery using conventional gray-scale IVUS and IB IVUS, respectively (Fig. 1B and C). Representative IVUS images of the same cross sections at baseline and follow-up for patients in sitagliptin group and non-DPP4-I group were shown in Fig. 2. Table 2 shows the volume of coronary plaque as

Table 2
Coronary plaque volume and composition as assessed by gray-scale IVUS and IB IVUS in T2DM patients with CAD in sitagliptin and non-DPP4-I groups at baseline and follow-up.

	Sitagliptin ($n = 28$)	*P* value (within group)	Non-DPP4-I ($n = 24$)	*P* value (within group)	*P* value (between group)
IVUS parameters					
Baseline					
PAV, %	50.2 ± 9.3		49.2 ± 11.8		0.68
TAV, mm^3	72.1 (61.0 to 98.4)		70.0 (57.2 to 90.0)		0.42
Vessel volume, mm^3	150 (124 to 198)		142 (117 to 172)		0.39
Lumen volume, mm^3	78.2 (58.2 to 95.4)		68.1 (46.9 to 94.2)		0.44
Follow up					
PAV, %	51.3 ± 9.8		49.4 ± 11.9		0.48
TAV, mm^3	71.8 (59.6 to 105)		72.6 (56.0 to 87.6)		0.51
Vessel volume, mm^3	153 (119 to 198)		143 (114 to 171)		0.51
Lumen volume, mm^3	71.1 (57.1 to 89.0)		65.0 (46.5 to 96.0)		0.69
Nominal change					
PAV, %	0.7 (−1.4 to 3.5)	0.26	0.2 (−2.7 to 2.7)	0.85	0.49
Regression, n (%)	13 (46.4)		10 (41.7)		0.73
Progression, n (%)	15 (53.6)		14 (58.3)		
TAV, mm^3	−0.6 (−4.7 to 6.6)	0.89	1.3 (−1.9 to 5.0)	0.27	0.59
Vessel volume, mm^3	−1.9 (−5.9 to 1.7)	0.07	0.5 (−2.8 to 2.2)	0.97	0.14
Lumen volume, mm^3	−1.3 (−8.4 to 0.2)	0.016	0.2 (−3.7 to 3.0)	0.74	0.14
Pecent change, %					
TAV, mm^3	−1.3 (−5.4 to 8.7)	0.91	1.6 (−5.9 to 7.0)	0.60	0.73
Vessel volume, mm^3	−1.4 (−3.1 to 0.9)	0.05	0.3 (−2.7 to 1.6)	0.85	0.27
Lumen volume, mm^3	−2.5 (−12.2 to 0.4)	0.02	0.4 (−7.3 to 6.8)	0.98	0.13
IB IVUS parameters, %					
Baseline					
Lipid volume	60.0 (50.9 to 64.9)		53.4 (38.7 to 65.3)		0.28
Fibrous volume	34.1 (28.7 to 40.8)		41.4 (30.2 to 49.7)		0.13
Dense fibrosis volume	3.4 (2.4 to 6.6)		4.1 (2.0 to 6.0)		0.56
Calcified volume	0.8 (0.3 to 1.8)		1.1 (0.4 to 2.0)		0.82
Follow up					
Lipid volume	55.6 (47.6 to 65.0)		50.7 (37.3 to 62.8)		0.28
Fibrous volume	37.1 (30.4 to 46.1)		41.9 (33.6 to 48.9)		0.26
Dense fibrosis volume	4.1 (2.5 to 6.4)		4.8 (2.6 to 9.4)		0.55
Calcified volume	1.2 (0.6 to 2.6)		1.3 (0.4 to 2.8)		0.96
Nominal change					
Lipid volume	−1.5 (−12.0 to 5.6)	0.26	−6.2 (−10.7 to −0.2)	0.014	0.48
Fibrous volume	0.8 (−3.3 to 9.9)	0.24	3.0 (−0.9 to 6.7)	0.029	0.68
Dense fibrosis volume	0.3 (−0.2 to 0.7)	0.27	1.0 (−0.2 to 2.1)	0.016	0.39
Calcified volume	0.1 (−0.2 to 0.7)	0.22	0.2 (0.0 to 1.3)	0.014	0.27

Data are presented as mean ± SD or median (interquartile range).
IB, integrated backscatter; IVUS, intravascular ultrasound; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; DPP4-I, dipeptidyl peptidase-4 inhibitors; PAV, percent atheroma volume; TAV, total atheroma volume.

measured by conventional IVUS analysis (upper panel) and the composition of coronary plaque as measured by IB IVUS (lower panel).

As shown in the upper panel of Table 2, at baseline, PAV in T2DM patients with CAD in sitagliptin group and non-DPP4-I group was 50.2 ± 9.3% and 49.2 ± 11.8%, respectively, and the differences in PAV, TAV, vessel volume, and lumen volume were not significantly different between groups. At follow-up, PAV in T2DM patients with CAD in sitagliptin group and non-DPP4-I group was 51.3% ± 9.8% and 49.4% ± 11.9%, respectively, and PAV, TAV, and vessel volume in each group were not significantly different from the baseline values (Table 2). Lumen volume at follow-up was also not significantly different between sitagliptin and non-DPP4-I groups, but significantly reduced in sitagliptin group as compared to baseline (Table 2).

The nominal changes in PAV from baseline, the primary end point, were not significant in both sitagliptin group and non-DPP4-I group [median (IQR): +0.7% (−1.4% to 3.5%) and 0.2% (−2.7% to 2.7%), respectively] (Table 2). The mean and 95% CI of the nominal changes in PAV were +1.10% (−0.50%–2.70%) for sitagliptin group and +0.20% (−1.52%–1.93%) for non-DPP4-I group (Fig. 3A, left panel). The nominal changes in PAV was not significantly different between sitagliptin and non-DPP4-I groups (Table 2), as indicated by the largely overlaid 95% CIs of nominal changes in PAV (Fig. 3A, left panel).

Percent changes in TAV, the secondary end point, were also not significant in T2DM patients with CAD in sitagliptin group and non-DPP4-I group (Table 2). The difference in percent changes in TAV between sitagliptin and non-DPP4-I groups were also not significant (Table 2), as indicated by the 95% CI range of percent changes in TAV in the two groups, i.e., 95% CI for sitagliptin group was included in that for non-DPP4-I group (Fig. 3A, right panel).

As shown in the lower panel of Table 2, coronary plaque in both T2DM patients with CAD in sitagliptin group and non-DPP4-I group had a high percentage of lipid volume at baseline [median (IQR): 60.0% (50.9%–64.9%) and 53.4% (38.7%–65.3%), respectively]. At follow-up, percent lipid volume did not change significantly from baseline in sitagliptin group, but significantly reduced in non-DPP4-I group (Table 2). However, the nominal changes in lipid volume were not significantly different between sitagliptin group and non-DPP4-I group (Table 2).

3.3. Relation of baseline LDL-C level and PAV with changes in PAV

The variation of changes in PAV was similar in sitagliptin group and non-DPP4-I group, and the changes in PAV were not significantly correlated to baseline LDL-C levels, changes in LDL-C levels, and baseline PAV in all of the patients (Supplementary Fig. I). After adjusting for baseline LDL-C levels or baseline PAV, the change in PAV was not significantly different between sitagliptin group and non-DPP4-I group, as assessed by an ANCOVA, and the LS mean for change in PAV (Supplementary Fig. II) was very similar to the unadjusted mean change in PAV (Fig. 3) in both sitagliptin group and non-DPP4-I group.

3.4. Inter-observer variability of IVUS measurement

The measurement errors for the gray-scale IVUS parameters, i.e., vessel volume, lumen volume, TAV, and PAV, were small and similar

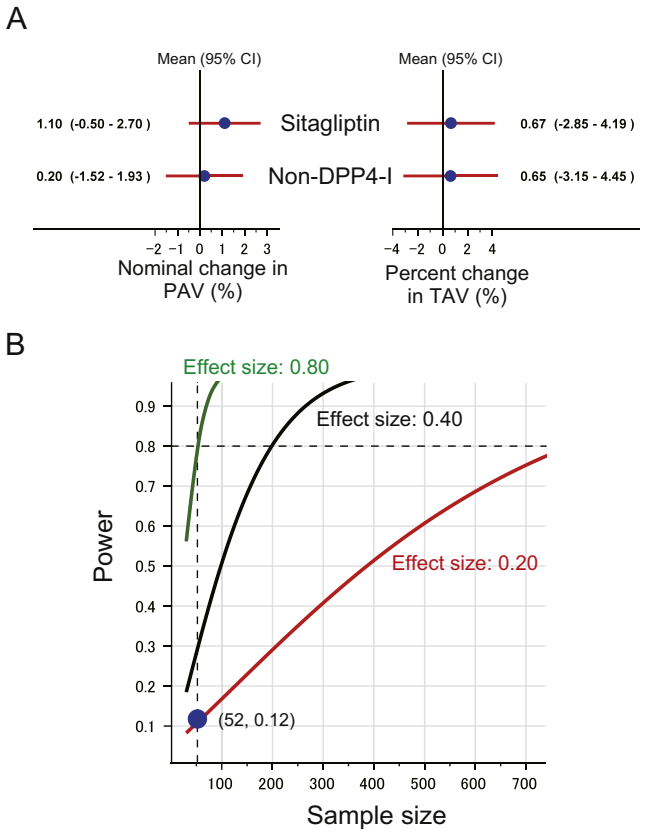

Fig. 3. (A) Mean (filled circle in blue) and 95% CI (bar in red) of nominal change in PAV (left panel) and percent change in TAV (right panel) in T2DM patients with CAD in sitagliptin group and non-DPP4-I group. (B) Power curve plotting power (1-β) as a function of sample size based on assumed population standardized effect size of 0.2, 0.4, and 0.8 at a two-side α of 0.05. Filled circle in blue indicates empirical power estimated based on sample effect size and the total number of patients at at a two-side α of 0.05. CI, confidence interval; PAV, percent atheroma volume; TAV, total atheroma volume; T2DM, type 2 diabetes mellitus; CAD, coronary heart disease; DPP4-I, dipeptidyl peptidase-4 inhibitors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in sitagliptin group and non-DPP4-I group at baseline and follow-up (Supplementary Table II and Fig. 4). In all of the patients, the inter-observer agreement was good for vessel volume, lumen volume, TAV, and PAV measurements at baseline and follow-up, as indicated by CCC (95% CI) [28] and limits of agreement of Bland Altman analyses [29] (Supplementary Table II and Fig. 4). Sitagliptin group and non-DPP4-I group were similar in the inter-observer variability for vessel volume, lumen volume, TAV, and PAV measurement at baseline (Fig. 4a, c, e, g) and follow-up (Fig. 4b, d, f, h), as shown by the Bland Altman plot, which is the scatter plot of the differences between observer 1 and observer 2 versus mean of two observers (Fig. 4). Therefore, the non-significant difference in changes in PAV between sitagliptin group and non-DPP4-I group was not attributed to measurement error of IVUS analysis.

3.5. Sample effect size and statistical power analysis

The mean difference in nominal changes in PAV between sitagliptin group and non-DPP4-I group was 0.89% (95% CI: −1.46%–3.25%), which was apparently not statistically significant because the confidence interval included zero [32]. The statistical power (1-β) of the study, i.e., the probability that under the alternative hypothesis (there is a true differences in changes in PAV between groups) the null hypothesis (there is no differences in changes in PAV between groups) is rejected, was low and estimated to be 12% based on sample effect size at the total sample size of 52 and a two-side α of 0.05 (Fig. 3B, indicated by filled circle in blue). Therefore, a non-significant difference in changes in PAV between sitagliptin group and non-DPP4-I group does not indicate that there is no difference in changes in PAV between group, but suggests that the effect size is small. The sample standardized effect size (Cohen's d) was estimated to be 0.21, and zero was included in the 95% CI of Cohen's d (−0.34%–0.75%).

Statistical power analysis based on population effect size was shown in Fig. 3B. From the power curve, which is the plot of power (1-β) as a function of sample size based on assumed standard effect size of 0.2, 0.4, and 0.8 at a two-side α of 0.05, a large effect size (0.8) would be detected for a total sample size of 50 at 80% power (Fig. 3B).

In summary, in T2DM patients with CAD who were treated with statins, addition of sitagliptin did not show additional effects in regressing coronary plaque under condition of medication for optimal glycemic control.

4. Discussion

The TOP-SCORE study examined the effects of sitagliptin on coronary atherosclerosis in T2DM patients with CAD. We found that sitagliptin, as an add-on therapy to statins, did not have an additional effect on the PAV as assessed by IVUS in T2DM patients with CAD, under condition of medication for optimal glycemic control.

T2DM is an important risk factor of CAD and CAD is the major complication of T2DM that causes death. Therefore, cardiovascular safety of hypoglycemic agents is in concern, and several meta-analyses reported that sitagliptin, linagliptin, and other DPP-4 inhibitors did not increase major adverse cardiovascular events (MACE) [38–40]. Cardiovascular outcome studies in T2DM patients who had, or at high risk for, cardiovascular disease consistently reported that sitagliptin, alogliptin, and saxagliptin did not increase the risk of MACE as compared with placebo [41–43]. In the present study, since the study subjects were high risk T2DM patients who required PCI, the use of placebo was not possible. We added sitagliptin to usual care and compared with non-DPP4-I hypoglycemic agents (Fig. 1A). Our finding that adding sitagliptin to usual care did not have an additional effect on coronary atherosclerosis as compared with non-DPP4-I (Table 2, Fig. 3A) supports those of the cardiovascular outcome studies [41–43].

Recently, DPP4-I is shown to have anti-atherogenic effects in addition to anti-hyperglycemic effects. Animal studies using apoE-deficient mice showed that des-fluoro-sitagliptin and alogliptin inhibit the progression of aortic atherosclerosis [14,15]. More recent studies in patients with T2DM free of apparent cardiovascular disease showed that sitagliptin and alogliprin prevents the progression of carotid atherosclerosis [19,20]. However, the effects of sitagliptin on coronary atherosclerosis in T2DM patients with CAD are not clear.

We did not detect an effect of sitagliptin on the volume of coronary plaque as assessed by gray-scale IVUS (Table 2, Fig. 3A) and lipid component of coronary plaque as assessed by IB IVUS (Table 2). The PAV in our T2DM patients with CAD at baseline (Table 2) was similar to that reported by other studies in Japanese patients with stable angina pectoris and acute coronary syndrome (ACS) at baseline [44,45]. The major reason for this finding is that about 80% of the T2DM patients in the present study had already been receiving statins at screening due to the high risk for CAD (Table 1). Early statin treatment with atorvastatin for 6 month has been shown to reduce coronary plaque in ACS and the percent change in plaque volume was positively correlated to the percent reduction in LDL-C level [46]. Also, early intervention with rosuvastatin for 6 months reduced lipid component of non-culprit plaque of coronary artery in ACS [47]. Therefore, our finding of a non-significant change in PAV in T2DM patients with CAD (Table 2, Fig. 3A) indicates that continued statin treatment prevented the progression of coronary atherosclerosis, under condition of medication with hypoglycemic agents for optimal glycemic control (Supplementary Table I), since diabetes have been shown to have accelerated progression of coronary atherosclerosis [48].

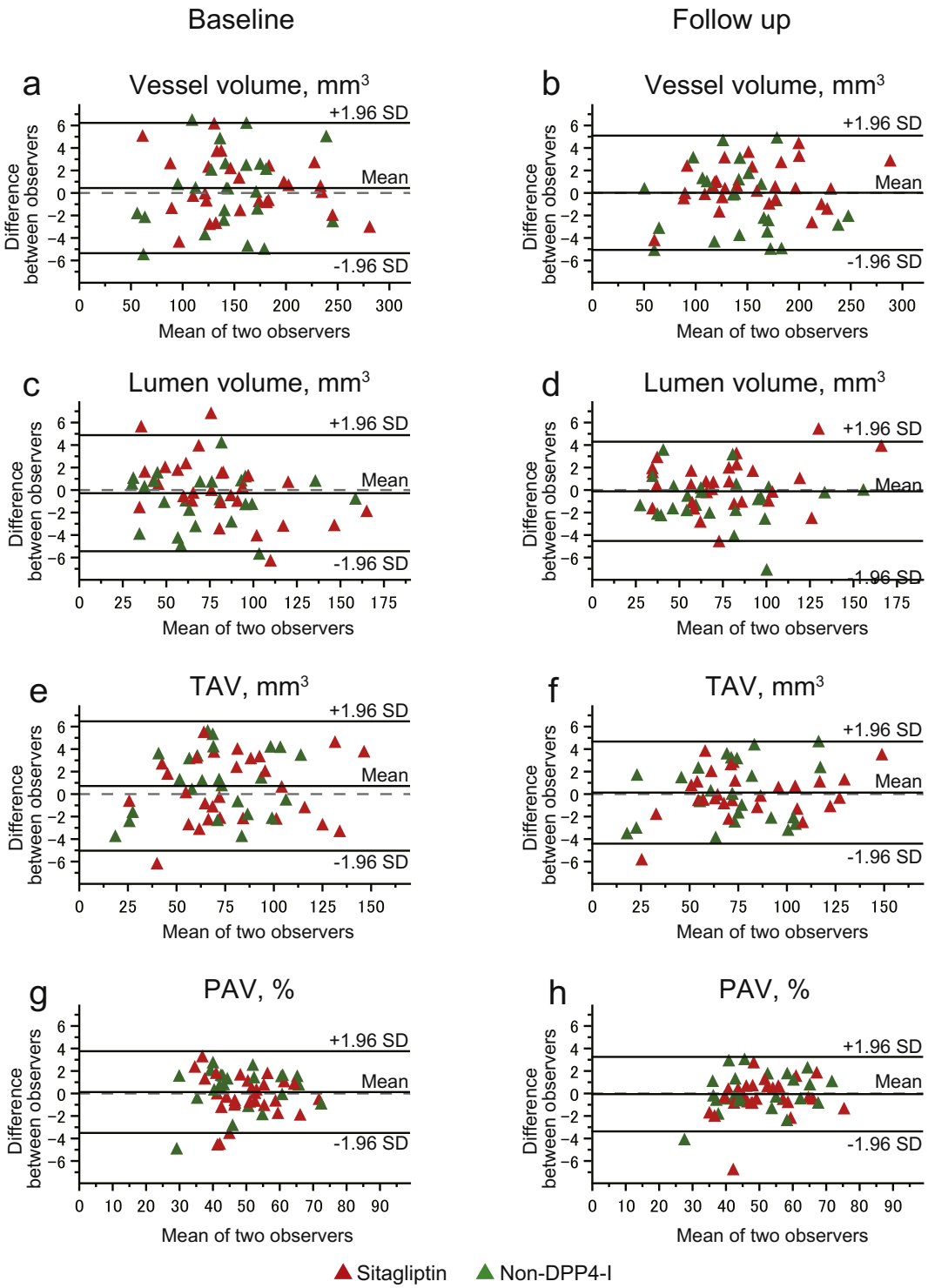

Fig. 4. Scatter plots of the differences in vessel volume (a, b), lumen volume (c, d), TAV (e, f), and PAV (g, h) between observer 1 and observer 2 versus mean of the two observers at baseline (left panel) and follow-up (right panel). The red and green filled triangles indicate data in the sitagliptin group and the non-DPP4-I group, respectively. TAV, total atheroma volume; PAV, percent atheroma volume; DPP4-I, dipeptidyl peptidase-4 inhibitors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

T2DM is associated with increased levels of atherogenic modified LDL including oxidized LDL and electronegative LDL [49]. Statins effectively reduce modified LDL in short term (within 1 month) [50–52]. Therefore, for the same reason, we did not observe a significant correlation between the change in PAV and the reduction in LDL-C level in T2DM patients with CAD (Supplementary Fig. Ib).

In the present study, neither significant progression nor regression of coronary plaque was observed in the 52 T2DM patients with CAD, because 56% ($n = 15 + 14$) of the patients had increased PAV and 44% ($n = 13 + 10$) of the patients had reduced PAV (Table 2). The change in PAV was also not related to baseline LDL-C level and baseline PAV (Supplementary Fig. Ia and Ic).

We observed a favorable change toward stabilization of coronary plaque, as indicated by a reduction in percent lipid volume and an increase in percent fibrosis volume, in non-DPP4-I group, although not in sitagliptin group (Table 2). At follow-up, the non-DPP4-I group tended to have lower TG level (Supplementary Table I), which may be associated with lower level of atherogenic remnant lipoproteins [53]. It is also possible that the class of hypoglycemic agents may be related to the reduced lipid component of coronary plaque in non-DPP4-I group, which, however, needs further investigation.

Our study has the limitation that about 50% of the patients had already been taking DPP4-I before randomization (Table 1), and a wash-out period was not possible. Also, the sample size was small (52 patients were included in the primary analyses) and the follow-up period was not long enough (8–12 months). Therefore, it is possible that the anti-atherogenic effect of sitagliptin was not detected due to the lack of power.

However, we have make the greatest efforts to minimize the measurement error of IVUS parameters, which was shown to be similar in sitagliptin and non-DPP4-I groups at baseline and follow-up (Fig. 4). Although a nonsignificant difference in PAV between sitagliptin and non-DPP4-I groups ($p = 0.49$, Table 2) indicates low statistical power and no conclusion can be made on the null hypothesis that there is no difference in change in PAV between groups [34], the low power in our study can indicate a small effect size (Fig. 3B, Supplementary Fig. II), which is independent of sample size [54]. The mean differences in change in PAV between sitagliptin and non-DPP4-I groups we observed was 0.89%, and the 95% CI range (−1.46%–3.25%) included zero [32]. In fact, a smaller study with T2DM who underwent elective PCI ($n = 28$) [55] reported that changes in PAV in sitagliptin group ($n = 15$) and control group ($n = 11$) were 0.2% ± 2.0% and 0.5% ± 3.5%, respectively. This study of Nozue et al. was a prospective, open-labeled, randomized, multicenter trial performed at 6 Japanese centers, and was published during the revision of this manuscript [55]. Our study is similar to the study of Nozue et al. [55] in that the background of patients was similar and the change in PAV was used as the primary end point. The findings of the two studies are also consistent.

In conclusion, sitagliptin did not cause coronary plaque regression when added to statins in T2DM patients with CAD.

Disclosures

Keijiro Saku (KS) is a director and Shin-ichiro Miura (SM) is a member of ^{NPO} Clinical and Applied Science, Fukuoka, Japan. KS and SM had received a grant from the Public Interest Incorporated Foundation of “Clinical Research Promotion Foundation” in Fukuoka, Japan, and part of the work was transferred to ^{NPO} Clinical and Applied Science, Fukuoka, Japan. KS has an Endowed Department of Molecular Cardiovascular Therapeutics at Fukuoka University supported by MSD Co., Ltd. and SM is a member of the Department. KS also has an Endowed Department of Community and Emergency Medicine at Fukuoka University supported by Izumi City, Kagoshima, Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcme.2017.06.005.

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Supplementary Table I. Clinical laboratory data in T2DM patients with CAD in sitagliptin and non-DPP4-I groups at baseline and follow-up

	Sitagliptin (n=28)	P value (within group)	Non-DPP4-I (n=24)	P value (within group)	P value (between group)
Baseline					
HbA_{1c}, (%)	7.2 ± 1.0		7.3 ± 1.2		0.96
FBS, mg/dL	114 ± 38		108 ± 28		0.47
LDL-C, mg/dL	95 ± 33		87 ± 26		0.49
HDL-C, mg/dL	47 ± 12		49 ± 14		0.54
TG, mg/dL	147 ± 53		131 ± 66		0.13
hsCRP, mg/dL	0.33 ± 0.93		0.61 ± 1.13		0.44
eGFR, mL/min/1.73m^2	64 ± 15		61 ± 17		0.34
UA, mg/dL	5.6 ± 1.7		5.4 ± 1.6		0.83
SBP, mmHg	126 ± 13		131 ± 19		0.56
DBP, mmHg	69 ± 10		70 ± 13		0.69
LVEF, (%)	65 ± 10		66 ± 10		0.67
Follow up					
HbA_{1c}, (%)	7.2 ± 1.0		7.5 ± 1.5		0.64
FBS, mg/dL	124 ± 32		125 ± 37		0.96
LDL-C, mg/dL	83 ± 21		75 ± 25		0.23
HDL-C, mg/dL	49 ± 12		50 ± 15		0.81
TG, mg/dL	138 ± 59		114 ± 65		0.07
hsCRP, mg/dL	0.19 ± 0.29		0.11 ± 0.14		0.78
eGFR, mL/min/1.73m^2	63 ± 18		58 ± 17		0.28
UA, mg/dL	5.5 ± 1.7		5.4 ± 1.5		1.0
SBP, mmHg	126 ± 15		127 ± 14		0.51
DBP, mmHg	69 ± 10		67 ± 11		0.38
LVEF, (%)	65 ± 7		66 ± 8		0.57
Norminal change					
HbA_{1c}, (%)	0.0 ± 0.7	0.97	0.2 ± 1.0	0.56	0.41
FBS, mg/dL	10 ± 27	0.048	16 ± 40	0.042	0.78
LDL-C, mg/dL	-12 ± 24	0.027	-12 ± 23	0.016	0.54
HDL-C, mg/dL	1 ± 11	0.55	1 ± 7	0.50	0.95
TG, mg/dL	-10 ± 64	0.34	-10 ± 49	0.17	0.76
hsCRP, mg/dL	-0.15 ± 0.94	0.53	-0.50 ± 1.15	0.08	0.39
eGFR, mL/min/1.73m^2	-1 ± 11	0.50	-3 ± 6	0.021	0.56
UA, mg/dL	-0.1 ± 0.9	0.42	0.0 ± 1.8	0.65	0.41
SBP, mmHg	0 ± 18	0.96	-4 ± 20	0.40	0.68
DBP, mmHg	0 ± 11	0.89	-4 ± 13	0.18	0.22
LVEF, (%)	1 ± 11	0.64	1 ± 9	0.99	0.71

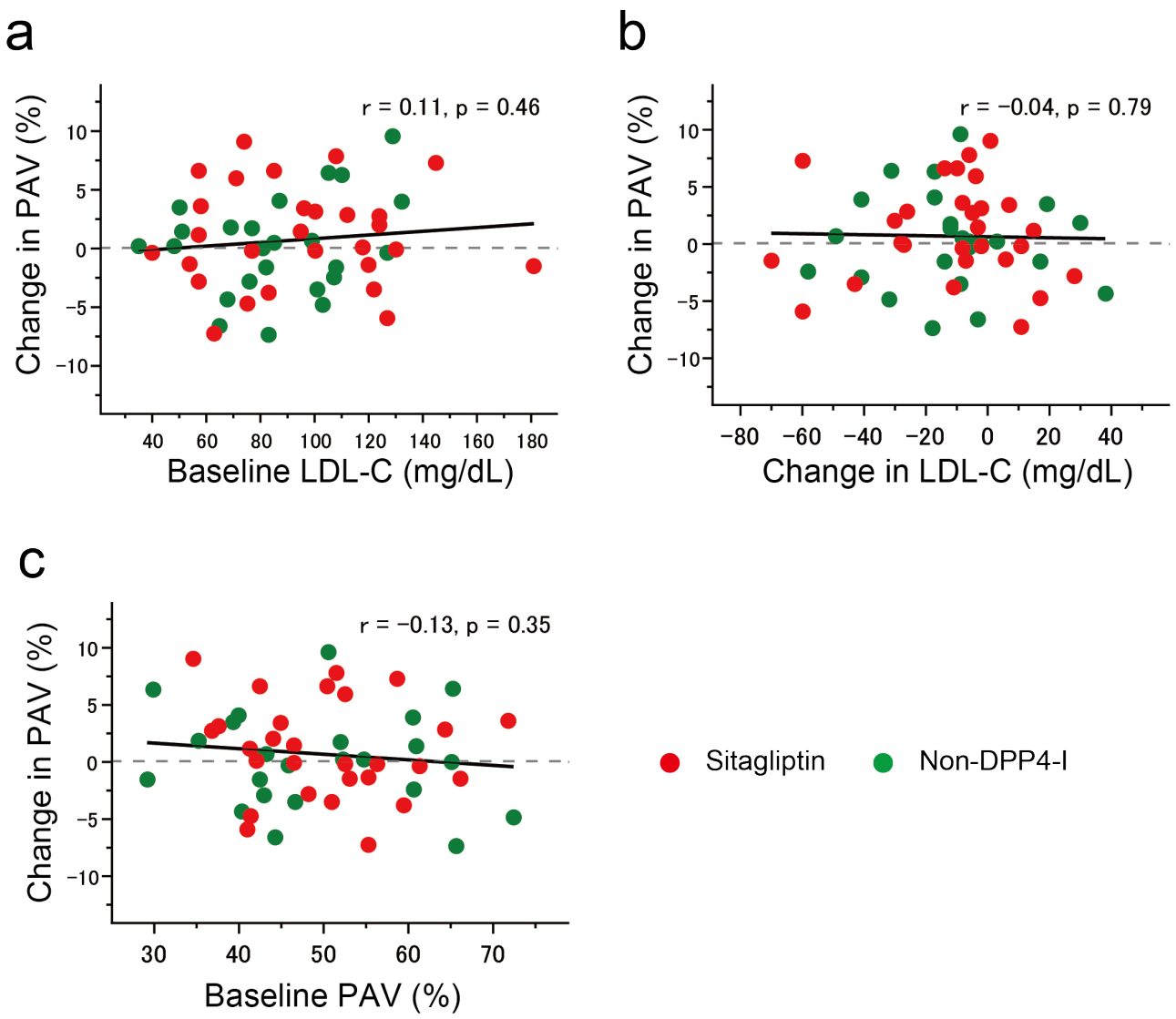
Data are presented as mean ± SD.

T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; DPP4-I, dipeptidyl peptidase-4 inhibitors; HbA_{1c}, hemoglobin A_{1c}; FBS, fasting blood sugar; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; UA, uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction.

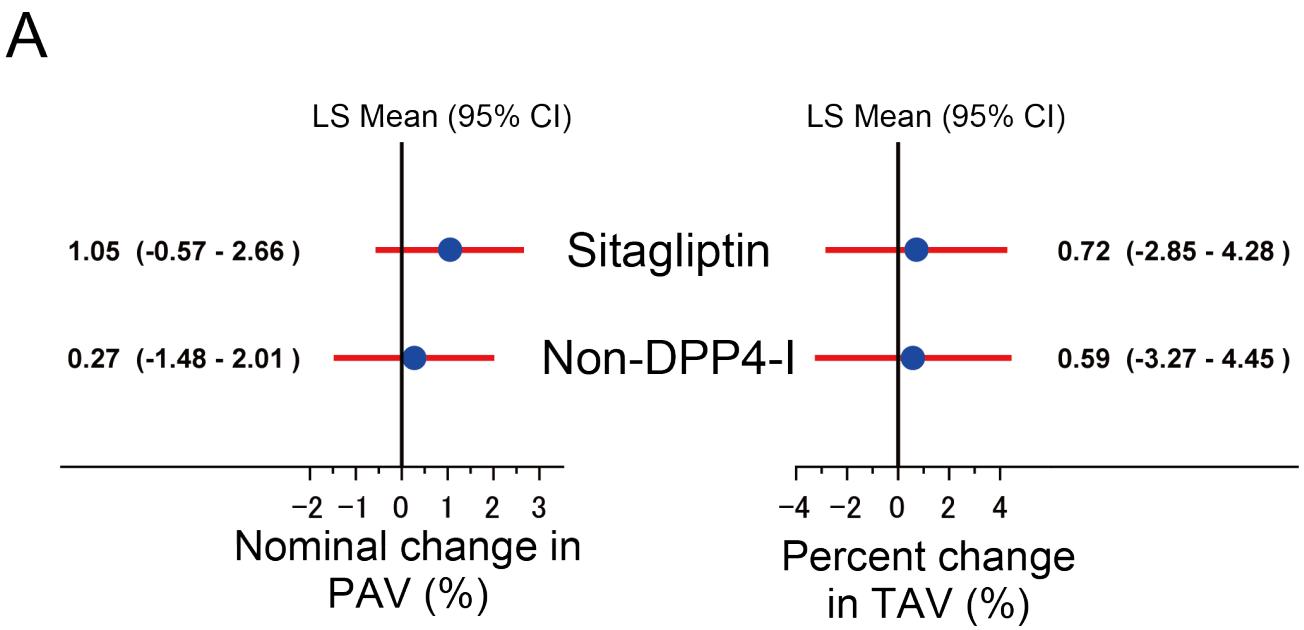
Supplementary Table II. Inter-observer variability for gray-scale IVUS analyses in T2DM patients with CAD at baseline and follow-up

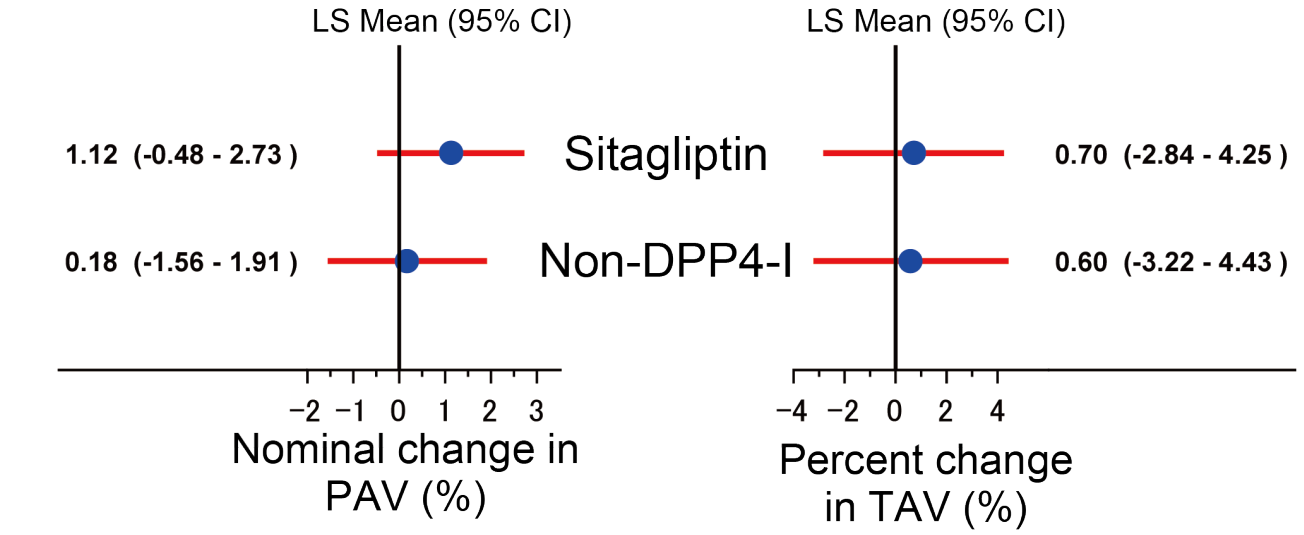
	Mean values		Correlation	Bland Altman analysis			
	Observer 1 (Mean±SD)	Observer 2 (Mean±SD)	CCC (95% CI)	Mean difference (absolute)	Mean difference (%)	Limits of agreement (absolute)	Limits of agreement (%)
Baseline							
Vessel volume, mm^3	151.9 ± 51.2	152.4 ± 51.2	0.998 (0.997, 0.999)	0.44	0.24	± 5.8	± 5.3
Lumen volume, mm^3	76.7 ± 32.5	76.4 ± 31.8	0.997 (0.994, 0.998)	-0.28	-0.03	± 5.2	± 8.5
TAV, mm^3	75.2 ± 28.3	76.0 ± 28.7	0.994 (0.992, 0.996)	0.72	0.47	± 5.7	± 10.8
PAV, %	49.7 ± 10.5	49.8 ± 10.5	0.984 (0.978, 0.989)	0.13	0.23	± 3.6	± 9.0
Follow up							
Vessel volume, mm^3	150.8 ± 50.8	150.8 ± 51.0	0.999 (0.998, 0.999)	0.02	-0.14	± 5.1	± 4.5
Lumen volume, mm^3	74.7 ± 31.6	74.6 ± 31.8	0.997 (0.996, 0.998)	-0.12	-0.16	± 4.4	± 6.8
TAV, mm^3	76.1 ± 28.7	76.2 ± 29.2	0.997 (0.995, 0.998)	0.13	-0.49	± 4.5	± 10.6
PAV, %	50.5 ± 10.6	50.4 ± 11.0	0.988 (0.981, 0.992)	-0.06	-0.36	± 3.3	± 7.9

IVUS, intravascular ultrasound; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; DPP4-I, dipeptidyl peptidase-4 inhibitors; PAV, percent atheroma volume; TAV, total atheroma volume; CCC, concordance correlation coefficient.



Supplementary Figure I. Scatter plots of the changes in PAV versus baseline LDL-C levels (a), changes in LDL-C levels (b), and baseline PAV (c). The red and green filled circles indicate data in the sitagliptin group and the non-DPP4-I group, respectively. PAV, percent atheroma volume; LDL-C, low-density lipoprotein cholesterol; DPP4-I, dipeptidyl peptidase-4 inhibitors.





Supplementary Figure II. Least square (LS) mean (filled circle in blue) and 95% CI (bar in red) of nominal change in PAV (left panel) and percent change in TAV (right panel) in T2DM patients with CAD in sitagliptin group and non-DPP4-I group, adjusting for baseline LDL-C levels (A) or baseline PAV (B) by an analysis of covariance. CI, confidence interval; PAV, percent atheroma volume; TAV, total atheroma volume; T2DM, type 2 diabetes mellitus; CAD, coronary heart disease; DPP4-I, dipeptidyl peptidase-4 inhibitors.