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Glucagon-like Peptide-1 analogues and delipidation of coronary atheroma in statin-treated type 2 diabetic patients with coronary artery disease: The prespecified sub-analysis of the OPTIMAL randomized clinical trial

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ABSTRACT

Background and aims: Randomized clinical trials have demonstrated the ability of glucagon-like peptide-1 analogues (GLP-1RAs) to reduce atherosclerotic cardiovascular disease events in patients with type 2 diabetes (T2D). How GLP-1RAs modulate diabetic atherosclerosis remains to be determined yet.
Methods: The OPTIMAL study was a prospective randomized controlled study to compare the efficacy of 48-week continuous glucose monitoring- and HbA1c-guided glycemic control on near infrared spectroscopy (NIRS)/intravascular ultrasound (IVUS)-derived plaque measures in 94 statin-treated patients with T2D (jRCT1052180152, UMIN000036721). Of these, 78 patients with evaluable serial NIRS/IVUS images were analyzed to compare plaque measures between those treated with (n = 16) and without GLP-1RAs (n = 72).
Results: All patients received a statin, and on-treatment LDL-C levels were similar between the groups (66.9 ± 11.6 vs. 68.1 ± 23.2 mg/dL, p = 0.84). Patients receiving GLP-1RAs demonstrated a greater reduction of HbA1c [-1.0 (-1.4 to −0.5) vs. −0.4 (-0.6 to −0.2)%, p = 0.02] and were less likely to demonstrate a glucose level >180 mg/dL [-7.5 (-14.9 to −0.1) vs. 1.1 (-2.0 - 4.2)%, p = 0.04], accompanied by a significant decrease in remnant cholesterol levels [-3.8 (-6.3 to −1.3) vs. −0.1 (-0.8 - 1.1)mg/dL, p = 0.008]. On NIRS/IVUS imaging analysis, the change in percent atheroma volume did not differ between the groups (−0.9 ± 0.25 vs. −0.2 ± 0.2%, p = 0.23). However, GLP-1RA treated patients demonstrated a greater frequency of $maxLCBI_{4mm}$ regression (85.6 ± 0.1 vs. 42.0 ± 0.6%, p = 0.01). Multivariate analysis demonstrated that the GLP-1RA use was independently associated with $maxLCBI_{4mm}$ regression (odds ratio = 4.41, 95%CI = 1.19–16.30, p = 0.02).
Conclusions: In statin-treated patients with T2D and CAD, GLP-1RAs produced favourable changes in lipidic plaque materials, consistent with its stabilization.

1. Introduction

Current ADA/EASD guidelines recommend glucagon-like peptide-1 receptor analogues (GLP-1RAs) in both high-risk patients with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) [1–3]. This is based on evidence from recent randomized clinical trials which demonstrated the benefits of GLP-1RAs to reduce the risk of major

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Abbreviations and acronyms

ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
CGM	continuous glucose monitoring
GLP-1 RA	glucagon-like peptide-1 receptor analogue
HDL-C	high-density lipoprotein cholesterol
IVUS	intravascular ultrasound
LDL-C	low-density lipoprotein cholesterol
$MaxLCBI_{4mm}$	maximum lipid-core burden index at 4-mm segment
NIRS	near-infrared spectroscopy
PAV	percent atheroma volume
PCI	percutaneous coronary intervention

adverse cardiovascular events in patients with T2D [4–6]. In addition to improving glycemic control, GLP-1RAs modify lipid metabolism, reducing levels of atherogenic lipoproteins [7–11]. These anti-atherosclerotic properties of GLP-1RAs may underscore their benefits on cardiovascular events. How GLP-1RAs modulate diabetic atherosclerosis *in vivo* has not been fully elucidated.

The OPTIMAL-NIRS prospective, randomized controlled study employed serial near-infrared spectroscopy and intravascular ultrasound (NIRS/IVUS) imaging to compare the efficacy of HbA1c-guided and continuous glycemic monitoring (CGM)-guided glycemic management on coronary atherosclerosis in patients with coronary artery disease (CAD) and T2D [12]. While atheroma progression did not differ between two groups, a *post-hoc* exploratory analysis demonstrated greater regression of NIRS-derived maximum lipid-core burden index at 4-mm segment ($maxLCBI_{4mm}$) in those receiving CGM-guided glycemic management. The objective of this prespecified analysis was to evaluate the impact of GLP-1RA treatment on progression and instability of coronary atherosclerosis in patients with CAD and T2D.

2. Methods

2.1. Patient selection

The design of the OPTIMAL trial has been previously described [12,13]. In brief, a total of 94 patients with CAD and T2D requiring percutaneous coronary intervention (PCI) were randomized in a 1:1 fashion to Hb1c-guided and CGM-guided glycemic management for 48 weeks (jRCT1052180152, UMIN000036721). In the HbA1c-guided glycemic control group, endocrinologists were encouraged to control HbA1c <7.0%. CGM (FreeStyle Libre Pro®, Abbott, Chicago, IL, USA) was conducted at baseline and at 48 weeks following PCI, and CGM results were blinded to both patients and physicians. In the CGM-guided glycemic control group, both CGM and HbA1c measurement were performed at baseline and at 12, 24, 36, and 48 weeks after PCI. Achieving the following CGM-derived goals were encouraged; (a) hypoglycemic episodes = 0%, (b) a percent coefficient of variation <36%, and (c) an average glucose level between 70 and 180 mg/dL [14]. Glucose-lowering agents were selected at the discretion of each endocrinologist in both groups. Control of LDL-C was conducted according to the guideline from the Japanese Circulation Society. The intensity of statin and the use of ezetimibe were selected at the discretion of each cardiologist in both groups. NIRS/IVUS imaging was performed following the completion of PCI and at 48 weeks after PCI to monitor non-culprit plaques. Of 94 randomized patients, 82 patients had evaluable serial NIRS/IVUS images. Remnant cholesterol was not measured in 4 patients. As a consequence, the current analysis included 78 patients with paired NIRS/IVUS images, of which 16 patients received GLP-1RAs during the study. Characteristics and changes in NIRS/IVUS-derived measures were compared in patients with T2D, with and without the use of GLP-1RAs (Supplementary Figure).

2.2. Acquisition and analysis of NIRS/IVUS imaging

NIRS/IVUS imaging was performed with a pullback rate of 2 mm/s. All NIRS/IVUS images were analyzed by two independent physicians (YK and SK) who were unaware of patients' clinical characteristics and their assigned glycemic management. 1-Mm cross-sectional IVUS image was manually traced by using commercially available software (QIvus®, Medis, Leiden, the Netherlands). Percent atheroma volume (PAV) was measured as previously described [15]. The aforementioned software was used to analyze NIRS images. Yellow pixels within the analyzed segment were divided by all viable pixels to generate the lipid-core burden index (LCBI). The maximal LCBI value in a 4-mm segment within the imaged artery (=$maxLCBI4_{mm}$) was measured [16–18]. Regression of $maxLCBI4_{mm}$ was defined as any reduction of $maxLCBI4_{mm}$.

2.3. Measurement of lipid parameters

Fasting serum levels of triglycerides and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods (Sekisui Medical, Tokyo, Japan) using an automated analyzer (Hitachi Labospect 008; Hitachi-Hitec, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated by the Friedewald formula, except for triglycerides levels >400 mg/dL. Remnant-like particles cholesterol was measured by enzymatic method (BML, Saitama. Japan). High-intensity statin was defined as either atorvastatin ≥20 mg, rosuvastatin ≥10 mg or pitavastatin ≥4 mg [19].

2.4. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and were compared using the *t*-test if data were normally distributed. Categorical variables were compared using the Fisher exact test or the chi-square test as appropriate. Absolute changes in laboratory parameters and NIRS/IVUS efficacy parameters were determined as the difference from baseline to 48 weeks. Absolute changes in glycemic and lipid measures, and BMI are expressed as means (95% confidence intervals). Absolute changes in NIRS/IVUS efficacy parameters are expressed as means ± standard error. These parameters were compared using analysis of covariance, with adjustment for treatment group, baseline dipeptidyl peptidase-4 and insulin usages, duration of T2D and baseline laboratory parameters or NIRS/IVUS measurements. P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 28 (IBM®, Chicago, IL, USA).

3. Results

3.1. Clinical characteristics and medication use

Table 1 describes the comparison of patients' characteristics between those with and without GLP-1RAs (dulaglutide 43.7%, liraglutide 18.8% and semaglutide 37.5%). Patients receiving GLP-1RAs were younger (65.6 ± 12.3 vs. 70.6 ± 7.5 years, p = 0.02) (Table 1). There were no significant differences in the proportion of coronary risk factors and concomitant atherosclerotic cardiovascular diseases between the two groups (Table 1). At baseline, patients treated with GLP-1RAs were less likely to receive dipeptidyl peptidase 4 inhibitors (12.5 vs. 69.4%, p < 0.001) and more likely to receive insulin (43.8 vs. 14.5%, p = 0.009). During the study, all patients received a statin, with the use of high-intensity statins (68.8 vs. 75.8%, p = 0.57) and ezetimibe (50.0 vs. 50.0%, p = 1.00) comparable between the two groups.

Table 1
Baseline clinical demographics.

	GLP1-RA (−) (n = 62)	GLP1-RA (+) (n = 16)	p-value
Age (years)	70.7 ± 7.7	66.8 ± 12.4	0.11
Female, n (%)	11 (17.7)	6 (37.5)	0.09
Hypertension, n (%)	47 (75.8)	11 (68.8)	0.57
Dyslipidemia, n (%)	54 (87.1)	16 (100.0)	0.12
Current smoking, n (%)	13 (20.9)	3 (18.8)	0.84
Family history of CAD	17 (27.4)	3 (18.8)	0.48
Duration of T2DM (years)	12.1 ± 9.5	17.0 ± 11.9	0.09
Multi-vessel disease, n (%)	39 (62.9)	10 (62.5)	0.97
ACS, n (%)	22 (35.4)	5 (31.2)	0.75
A history of PCI, n (%)	30 (48.3)	5 (31.3)	0.22
A history of stroke, n (%)	6 (9.7)	0 (0.0)	0.20
A history of PAD, n (%)	4 (6.4)	0 (0.0)	0.30
Baseline Medication Use			
Statin, n (%)	44 (70.9)	9 (56.3)	0.26
High-intensity statin, n (%)	23 (37.1)	5 (31.3)	0.66
Ezetimibe, n (%)	16 (25.8)	4 (25.0)	0.94
Metformin, n (%)	24 (38.7)	6 (37.5)	0.93
DPP-4 inhibitor, n (%)	43 (69.4)	2 (12.5)	<0.001
SGLT2 inhibitor, n (%)	18 (29.0)	4 (25.0)	0.75
Insulin, n (%)	9 (14.5)	7 (43.8)	0.009
Concomitant Medication Use			
Statin, n (%)	62 (100.0)	26 (100.0)	1.00
High-intensity statin, n (%)	47 (75.8)	11 (68.8)	0.57
Ezetimibe, n (%)	31 (50.0)	8 (50)	1.00
Metformin, n (%)	28 (45.2)	8 (50)	0.73
DPP-4 inhibitor, n (%)	50 (80.6)	0 (0.0)	<0.001
SGLT2 inhibitor, n (%)	21 (33.9)	5 (31.3)	0.84
Insulin, n (%)	9 (14.5)	6 (37.5)	0.03
Type of GLP1-RA			
Dulaglutide	–	7 (43.7)	–
Liraglutide	–	3 (18.8)	–
Semaglutide	–	6 (37.5)	–

BMI = body mass index, CAD = coronary artery disease, CGM = continuous glucose monitoring, DPP-4 = dipeptidyl peptidase-4, GLP1-RA = glucagon-like peptide-1 receptor analogues, HbA1c = glycated hemoglobin, PAD = peripheral artery disease, PCI = percutaneous coronary intervention, SGLT2 = sodium glucose cotransporter 2, T2DM = type 2 diabetes mellitus.

3.2. Measures of glycemic and lipid control in patients with and without GLP-1 RA

Table 2 summarizes serial changes in glycemic and other metabolic risk factors. Patients receiving GLP-1RAs had higher HbA1c levels (8.4 ± 1.0 vs. 7.3 ± 0.7%, p < 0.001) at baseline (Table 2). At 48 weeks, GLP-1RA treatment associated with greater reductions of HbA1c [−1.0 (−1.4 to −0.5) vs. −0.4 (−0.6 to −0.2)%, p = 0.02], accompanied by a reduced frequency of glucose level >180 mg/dL [−7.5 (−14.9 to −0.1) vs. 1.1 (−2.0 - 4.2)%, p = 0.04]. GLP-1 R A treated patients spent a greater amount of time with glucose in range of 70–180 mg/dL [+8.2 (1.0–15.4) vs. +0.5 (−2.5 to −3.5) %], but this comparison just failed to meet statistical significance (p = 0.06).

Levels of LDL-C at baseline (p = 0.94), on-treatment LDL-C level (p = 0.84) and its absolute change (p = 0.52) did not differ between the two groups. Almost 50% of patients in both groups achieved on-treatment LDL-C <70 mg/dL (p = 0.86). The proportion of those achieving on-treatment LDL-C <55 mg/dL was 25.0% and 30.6% in those with and without GLP-1RA treatment, respectively (p = 0.63). While absolute changes in HDL-C and triglyceride levels were also similar in the two groups, a greater reduction of remnant-like particles cholesterol levels was observed in the GLP-1RA group [−3.8 (−6.3 to −1.3) vs. −0.1 (−0.8 - 1.1) mg/dL, p = 0.008].

3.3. Baseline plaque measures

Baseline angiographic and NIRS/IVUS-derived plaque measures are shown in Table 3. PAV (46.3 ± 13.8 vs. 46.2 ± 14.3%, p = 0.98) and maxLCBI$_{4mm}$ at baseline [321 (202, 481.5) vs. 274 (97.2, 381.7), p = 0.23] were comparable in those treated with and without GLP-1RAs (Table 2). There was a trend toward a greater frequency of maxLCBI$_{4mm}$ ≥ 400 in the GLP-1RA group (37.5 vs. 17.7%), however this just failed to meet statistical significance (p = 0.09) (Table 3).

Table 2
Measures of risk factor control.

	GLP1-RA (−) (n = 62)	GLP1-RA (+) (n = 16)	p-value
Glycemic Measures			
HbA1c			
Baseline	7.3 ± 0.7	8.4 ± 1.0	<0.001
48 weeks	7.0 ± 0.6	6.9 ± 0.8	0.55
Absolute change[a]	−0.4 (−0.6–−0.2)	−1.0 (−1.4–−0.5)	0.02
Frequency of time with glucose in range of 70–180 mg/dL (%)			
Baseline	80.2 ± 14.7	72.1 ± 21.6	0.08
48 weeks	79.2 ± 14.0	82.0 ± 15.5	0.49
Absolute change[a]	0.5 (−2.5 - +3.5)	+8.2 (+1.0 - +15.4)	0.06
Frequency of glucose level >180 mg/dL (%)			
Baseline	16.5 ± 15.4	21.8 ± 22.8	0.27
48 weeks	18.9 ± 14.8	14.4 ± 11.3	0.26
Absolute change[a]	1.1 (−2.0 - +4.2)	−7.5 (−14.9–−0.1)	0.04
Averaged blood glucose (mg/dL)			
Baseline	136.8 ± 25.8	138.9 ± 38.5	0.79
48 weeks	140.6 ± 23.7	134.1 ± 16.5	0.30
Absolute change[a]	2.8 (−2.6 - +8.2)	−8.7 (−21.2 - 3.8)	0.11
Lipid Measures			
LDL-C (mg/dL)			
Baseline	86.6 ± 26.9	87.1 ± 24.4	0.94
48 weeks	68.1 ± 23.2	66.9 ± 11.6	0.84
Absolute change[a]	−19.1 (−25.1–−13.1)	−24.3 (−38.5–−10.1)	0.52
On-treatment LDL-C < 70 mg/dL, n (%)	32 (51.6)	8 (50.0)	0.86
On-treatment LDL-C < 55 mg/dL, n (%)	19 (30.6)	4 (25.0)	0.63
HDL-C (mg/dL)			
Baseline	44.0 ± 11.8	47.0 ± 14.6	0.39
48 weeks	47.9 ± 11.9	49.8 ± 17.6	0.61
Absolute change[a]	4.2 (1.9–6.6)	1.5 (−4.1 - 7.1)	0.39
Triglyceride (mg/dL)			
Baseline	132.5 (92.5, 178.5)	132.5 (103.0, 190.0)	0.98
48 weeks	116.5 (97.2, 155.7)	126.0 (97.5175.5)	0.32
Absolute change[a]	−5.9 (−21.2 - 9.2)	−20.5 (−56.7 - 15.5)	0.48
Remnant-like particles cholesterol (mg/dL)			
Baseline	6.2 ± 5.8	6.7 ± 5.2	0.82
48 weeks	4.3 ± 3.1	3.6 ± 1.7	0.37
Absolute change[a]	−0.1 (−0.8 - 1.1)	−3.8 (−6.3–−1.3)	0.008
Other Measure			
BMI (kg/m^2)			
Baseline	24.4 ± 3.0	25.5 ± 3.4	0.22
48 weeks	24.1 ± 3.1	24.5 ± 2.7	0.61
Absolute change[a]	−0.3 (−0.7 - 0.9)	−1.1 (−2.1–−0.2)	0.13

GLP1-RA = glucagon-like peptide-1 receptor analogues, HbA1c = glycated hemoglobin, HDL-C high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

[a] Adjusted by baseline value, DPP4, insulin, duration of T2DM and assigned group.

3.4. Effects of GLP1RA on plaque progression and lipidic plaque contents

Fig. 1 illustrates serial changes in NIRS/IVUS-derived measures. On IVUS imaging analysis, there was no statistical significance the in change in PAV between patients with and without GLP-1RA use (−0.9 ± 0.25 vs. −0.2 ± 0.2%, p = 0.23, Fig. 1-a). However, GLP-1RA use was associated with a greater frequency of maxLCBI$_{4mm}$ regression (85.6 ± 0.1 vs. 42.0 ± 0.6%, p = 0.01, Fig. 1-b).

Univariate analysis revealed the use of GLP-1RAs as a significant determinant of maxLCBI$_{4mm}$ regression (odds ratio = 3.88, 95%

Table 3
Baseline measures of atheroma burden and lipidic plaque components.

	GLP1-RA (−) (n = 62)	GLP1-RA (+) (n = 16)	p-value
Angiographic Measures			
Location of analyzed non-culprit plaques			
LAD, n (%)	29 (46.7)	11 (68.8)	0.12
Proximal segment of LAD, n (%)	7 (11.3)	1 (6.3)	0.56
RCA, n (%)	28 (45.2)	4 (25.0)	0.14
Proximal segment of RCA, n (%)	9 (14.5)	2 (12.5)	0.83
LCX, n (%)	5 (8.1)	1 (6.2)	0.81
Proximal segment of LCX, n (%)	0 (0.0)	0 (0.0)	1.00
NIRS/IVUS-derived Measures			
Percent atheroma volume (%)	46.2 ± 14.3	46.3 ± 13.8	0.98
$MaxLCBI_{4mm}$	274 (97.2, 381.7)	321 (202, 481.5)	0.23
$MaxLCBI_{4mm} > 400$	11 (17.7)	6 (37.5)	0.09

GLP1-RA = glucagon-like peptide-1 receptor analogues, $MaxLCBI_{4mm}$ = Maximum lipid-core burden index at 4-mm segment.

confidence interval = 1.12–13.41, p = 0.03). Multivariate analysis adjusting age and female continued to demonstrate GLP-1RA use as an independent factor associated with regression of $maxLCBI_{4mm}$ in patients with CAD and T2D (odds ratio = 4.41, 95% confidence interval = 1.19–16.30, p = 0.02, Table 4).

4. Discussion

While randomized clinical trials have demonstrated cardiovascular benefits of GLP-1RAs in high-risk patients with T2D, the mechanisms underscoring this benefit remains unclear. This prespecified analysis of the OPTIMAL study revealed that GLP-1RA use lowered HbA1c and improved glycemic variability and circulating remnant-like particles cholesterol levels. Moreover, on serial NIRS/IVUS imaging, a greater regression of $maxLCBI_{4mm}$ was observed in those treated with GLP-1RAs. These observations provide evidence of the benefits of GLP-1RAs on plaque composition in patients with T2D.

This serial intravascular imaging analysis provides mechanistic insights into the ability of GLP-1RAs to favorably modify the underlying disease substrate in patients with T2D *in vivo*. Improvements of glycemic indices with GLP-1RA use could contribute to the reduction in lipidic plaque contents. Recent intravascular imaging studies reported that achieving a lower level of HbA1c associated with smaller amount of lipidic plaque materials in patients with T2D [20]. Additionally, coronary atherosclerosis is more likely to harbor larger lipid cores in patients with greater glycemic variability [21–23]. In the current study, GLP-1RA use improved the frequency of CGM-derived hyperglycemia (>180 mg/dL), accompanied by a trend toward an increased proportion of optimal glucose range (70–180 mg/dL). Spikes in blood glucose have been shown to promote oxidative stress and the secretion of inflammatory cytokines [24–26]. Since these proatherogenic effects of glycemic variability could induce influx of lipid into the vessel wall [27, 28], control of HbA1c and glycemic variability with GLP-1RAs may potentially stabilize diabetic coronary atherosclerosis.

Observational and intravascular imaging studies have consistently reported the association of triglyceride-rich lipoproteins with atherosclerosis [29–32], suggesting they are a potential therapeutic target. GLP-1RAs modulate metabolism of triglyceride-rich lipoprotein via both decreased production and an increase in clearance [9]. In addition, GLP-1RA induced better insulin sensitivity, which could fabourably affect metabolism of remnant-like lipoprotein chol esterol [33, 34]. In this analysis, GLP-1RA use associated with reduced circulating remnant-like particles cholesterol levels in statin-treated patients with T2D. The aforementioned effects of GLP-1RA could account for a reduction of remnant-like lipoprotein cholesterol in the current study subjects. Since remnant cholesterol easily enters the vessel wall and promotes systemic inflammation [35,36], lowering their levels have the potential to produce favourable reductions in plaque lipid and promote stabilization.

After adjusting for clinical characteristics and control of risk factors, the use of GLP-1RAs remained independently associated with regression of $maxLCBI_{4mm}$. This finding suggests that other GLP-1RA mediated pleiotropic effects may delipidate diabetic coronary atheroma. In several experimental studies, GLP-1RAs have been shown to inhibit monocyte adhesion to endothelial cells, modulate macrophage phenotypes, and attenuate endothelial dysfunction [11,37–39]. Furthermore, GLP-1 exhibits anti-inflammatory properties [10,40]. Several clinical studies reported that liraglutide decreased productions of TNF-alpha and interleukin-1β [41,42]. Given that pharmacological lowering of interleukin-1β reduces the rate of major adverse cardiovascular events in high-risk patients [43], these effects of GLP-1RAs may also contribute to plaque stabilization.

During the 48-week treatment period, change in PAV did not differ between two groups although more regression of lipidic plaque contents was observed in the GLP1-RA group. The treatment period in most

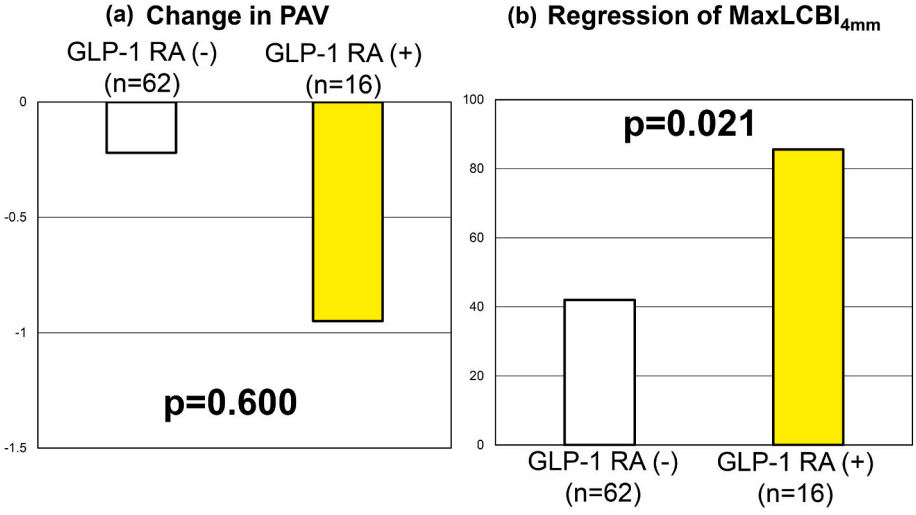

Fig. 1. Comparison of Serial NIRS/IVUS-derived Measures. (a) Change in PAV. (b) Regression of $MaxLCBI_{4mm}$
IVUS = intravascular ultrasound, NIRS = near-infrared spectroscopy, $MaxLCBI_{4mm}$ = maximum lipid-core burden index at 4-mm segment, PAV = percent atheroma volume.

Table 4
Predictors of regression of $MaxLCBI_{4mm}$.

	Univariate Analysis		Multivariate Analysis[$]	
	OR (95%CI)	p value	OR (95%CI)	p value
Age	1.01 (0.95–1.05)	0.78	1.01 (0.94–1.06)	0.86
Female	1.16 (0.39–3.41)	0.78	0.86 (0.26–2.79)	0.80
Hypertension	0.76 (0.27–2.11)	0.60	–	–
Dyslipidemia	1.02 (0.23–4.45)	0.96	–	–
Smoking	0.37 (0.11–1.20)	0.10	0.37 (0.10–1.35)	0.13
Family history	0.58 (0.20–1.63)	0.30	–	–
Duration of T2DM	1.03 (0.98–1.07)	0.18		
High-intensity statin use	0.76 (0.27–2.11)	0.60	–	–
Ezetimibe use	0.90 (0.37–2.19)	0.82	–	–
DPP-4 inhibitor use	0.50 (0.19–1.30)	0.15	–	–
SGLT2 inhibitor use	1.59 (0.61–4.11)	0.33	–	–
Insulin use	1.65 (0.52–5.18)	0.39	–	–
GLP1-RA use	3.88 (1.12–13.41)	0.03	4.41 (1.19–16.30)	0.02
Change in LDL-C	0.99 (0.97–1.01)	0.36	–	–
Change in HDL-C	0.97 (0.92–1.01)	0.23	–	–
Change in Remnant cholesterol	0.93 (0.83–1.04)	0.25	–	–
Change in HbA1c	1.03 (0.66–1.61)	0.89	–	–
Change in average glucose level	0.99 (0.97–1.01)	0.25	–	–
Change in frequency of time with glucose in range of 70–180 mg/dL	1.01 (0.98–1.04)	0.23	–	–
Change in frequency of glucose level >180 mg/dL	0.98 (0.95–1.01)	0.18	–	–

DPP-4 = dipeptidyl peptidase-4, GLP1-RA = glucagon-like peptide-1 receptor analogues, HbA1c = glycated hemoglobin, HDL-C high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, $MaxLCBI_{4mm}$ = Maximum lipid-core burden index at 4-mm segment, SGLT2 = sodium glucose cotransporter 2.
$Multivariate analysis included age, female and variables with p-value <0.15 on univariate analysis.

clinical trials involving serial IVUS is between 18 and 24 months [15, 44]. In the PERISCOPE study, slowing disease progression with pioglitazone was observed during an 18-month follow-up period in patients with CAD and T2D [44]. A longer follow-up period may be required to determine whether GLP1RA use will result in regression of coronary atheroma.

Several caveats should be considered to interpret this analysis. First, the number of patients treated with GLP-1RAs was small, and the use of GLP-1RAs and other anti-diabetic medications was decided according to each physician, but not randomized. These may introduce some degree of selection bias. Second, the current study did not measure levels of inflammatory cytokines. As inflammation has been implicated in diabetic atherosclerosis, further investigation of inflammatory cytokines associated with regression of lipidic contents would be of use. Third, all patients had angiographic CAD requiring PCI, and their history of T2D was greater than 10 years. It remains unknown if the current findings can be translated to the setting of primary prevention and/or early-stage patients with T2D.

In conclusion, in statin-treated patients with CAD and T2D, GLP-1RA use was associated with better improvements of glycemic indices and circulating remnant cholesterol levels compared to those without GLP-1RA treatment. Furthermore, a greater regression of NIRS-derived $maxLCBI_{4mm}$ was observed in those receiving GLP-1RAs. The current findings indicate a favourable property of GLP-1RAs inducing delipidation of diabetic coronary atheroma. This provides a potential mechanism for the improved clinical outcomes observed the use of GLP1RAs in both high-risk patients with T2D and those with ASCVD.

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Disclosures

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athplu.2024.03.001.

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