The impact of Vildagliptin On the daily Glucose profile and coronary plaqUE stability in impaired glucose tolerance patients with coronary artery disease: VOGUE: A multicenter randomized controlled trial.

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Abstract

Background The impact of the reduction in glycemic excursion on the characteristics of coronary plaques remains unknown. The aim of this study was to elucidate whether a lowered dose of a dipeptidyl peptidase 4 inhibitor could reduce the glycemic excursion and stabilize the characteristics of coronary plaques as compared with conventional management in coronary artery disease (CAD) patients with impaired glucose tolerance (IGT).

Methods This was a multi-center, randomized controlled trial including CAD patients with IGT under lipid-lowering therapy who were receiving either vildagliptin (50 mg once a day) or no medication (control group) regarding glycemic treatment. The primary endpoint was changes in the minimum fibrous cap thickness and lipid arc in non-significant native coronary plaques detected by optical coherence tomography at 6 months. Glucose fluctuation was expressed as the mean amplitude of glycemic excursion (MAGE), which was determined by a continuous glucose monitoring (CGM) system. CGM was performed before and 6 months after intervention.

Results A total of 20 participants with 47 lesions were allocated to either the vildagliptin group (10 participants, 22 lesions) or the control group (10 participants, 25 lesions). The adjusted difference of mean changes between the groups was − 18.8 mg/dl (95% confidence interval, -30.8 to -6.8) (p = 0.0064) for the MAGE (mean ± standard deviation: vildagliptin, -20.1 ± 18.0 mg/dl vs control, 2.6 ± 12.7 mg/dl), -22.8° (-40.6 to -5.1) (p = 0.0012) for the mean lipid arc (vildagliptin, -9.0 ± 25.5° vs control, 15.8 ± 16.8°), and 42.7 μm (15.3 to 70.1) (p = 0.0022) for the minimum fibrous cap thickness (vildagliptin, 35.7 ± 50.8 μm vs control, -15.1 ± 25.2 μm).

Conclusions Vildagliptin reduced the MAGE at 6 months and simultaneously decreased the lipid arc and increased the minimum fibrous cap thickness of the coronary plaques in CAD patients with IGT, which may represent its stabilization effect on coronary plaques characteristic in this patient subset.

Name of the registry: VOGUE trial

Trial registration: Registered in the UMIN clinical trial registry (UMIN000008620)

Date of registration: Aug 6, 2012

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Background

Accumulating evidence has revealed that treatment of dyslipidemia can prevent coronary artery disease (CAD), and statin administration is widely used for both primary and secondary prevention of CAD. However, only a 30% reduction in the risk of CAD by statins has been reported [1]. Thus, focus on further managing the residual risk apart from dyslipidemia has emerged. Meanwhile, the number of patients with diabetes mellitus has been greatly increasing worldwide, and the clinical effect of abnormal glucose

metabolism has been recognized in the management of CAD. There is increasing evidence that the postprandial blood glucose state is an important factor contributing to the development of atherosclerosis [2–4]. The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial revealed that a poor postprandial state accelerates atherosclerosis, whereas an improvement in that state prevents atherosclerosis progression in patients with impaired glucose tolerance (IGT). It has long been recognized that glucose levels measured by a 2-hour post-oral glucose tolerance test (OGTT) are strongly associated with mortality and cardiovascular disease [5, 6]. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study reported that high blood glucose concentrations 2 hours after OGTT were associated with an increased risk of death [5]. Furthermore, we have previously reported that glucose fluctuation detected by continuous glucose monitoring (CGM) may impact the formation of lipid-rich plaque and thinning fibrous cap detected by optical coherence tomography (OCT), a high-resolution intravascular imaging modality, in patients with CAD undergoing lipid-lowering therapy [7]. However, whether interventions against glucose fluctuation may affect the coronary plaque properties in CAD patients with IGT under lipid-lowering therapy remains unknown.

Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs [8], which is indicated for type 2 diabetes. A recent report has revealed that the reduction in daily blood glucose profile fluctuations by vildagliptin was superior to that by sitagliptin in Japanese patients with type 2 diabetes [9]. Furthermore, Rosenstock et al. reported that vildagliptin achieved a 32% reduction in postprandial glucose excursions and no evidence of hypoglycemia or weight gain in patients with IGT [10].

The aim of this study was to investigate the effect of vildagliptin on fibrous thickness of coronary plaque detected by OCT in CAD patients with IGT.

Methods

Study design

This was a multicenter open-label randomized controlled trial, conducted at two institutes in Japan: the Kobe University Hospital and Hyogo Brain and Heart Center. This study was enforced between September 1, 2012 and March 2019. The study protocol was approved by the ethical review board of each participating institution. The study was registered in the UMIN clinical trial registry (UMIN000008620). Written informed consent to participate in this study was obtained from all patients.

Participants

Patients with stable CAD and IGT needed to satisfy the following criteria to be included: 1) in those undergoing percutaneous coronary intervention (PCI), "untreated IGT" which was "2-hour plasma/serum glucose level: 140mg/dL to 199 mg/dL in a 75 g OGTT", 2) low-density lipoprotein cholesterol < 120mg/dl and < 100mg/dl in patients with and without statin administration, respectively , 3) being between 20 and 80 years old, and 4) written consent provided for participation in the study. Patients

meeting any of the following conditions were excluded: 1) under treatment for type 2 diabetes or having type 1 diabetes, 2) severe liver dysfunction, 3) severe renal dysfunction, 4) severe heart failure (New York Heart Association stage III or IV), 5) malignancies or other diseases with poor prognosis, 6) pregnant, lactating, and possibly pregnant women and those planning to get pregnant, 7) past medical history of hypersensitivity to investigational drugs, and 8) judged as ineligible by clinical investigators.

Treatment protocol

Patients who consented to participate and fulfilled the inclusion criteria were included in this study; then, PCI was performed for the treatment of culprit lesions causing myocardial ischemia and/or angina symptoms. Participants were randomly divided into those receiving 50 mg vildagliptin once a day for at least 6 months (vildagliptin group) or diet and exercise therapy (control group). Other oral hypoglycemic drugs as for combination treatment were prohibited during the study period. Moreover, the increase and addition of lipid improving agents such as statin preparations, fibrate preparations, and eicosapentaenoic acid were prohibited as well. Coronary angiography, OCT, and CGM were conducted before and 6 months after PCI.

Continuous glucose monitoring system

CGM was performed for more than 3 consecutive days before PCI and 6 months after PCI, and the daily glucose profile was analyzed using data obtained on days 2 and 3 to avoid any bias due to insertion or removal of the sensor. In all patients, CGM analysis software (CareLink iPro, Medtronic, Northridge, CA) calculated the median of the variables measured on days 2 and 3: 24-hour mean glucose levels, time in hyperglycemia/hypoglycemia, and the mean amplitude of glycemic excursion (MAGE) [11]. Time in hyperglycemia and hypoglycemia were defined as the time that blood glucose levels were above 140 mg/dL and under 70 mg/dL, respectively [7]. All patients received optimal meals (25–28 kcal/kg of ideal body weight; 60% carbohydrate, 15–20% protein, and 20–25% fat) during CGM.

OCT imaging

Angiographically non-significant coronary lesions (30% to 70% luminal narrowing via angiography) were enrolled to OCT assessment during index PCI procedure, and deemed to follow-up OCT assessment 6 months after PCI. Images were acquired using a commercially available, frequency-domain OCT imaging system (ILUMIEN; St. Jude Medical Inc., St Paul, MN, USA). In this system, a 2.7-Fr OCT imaging catheter is advanced distal to the lesion, and automated pullback is initiated in concordance with blood clearance by the injection of contrast media. Target plaques are all non-culprit lesions, which form mild to moderate stenosis.

OCT analysis

All OCT images were analyzed by two independent investigators, who were blinded to the angiographic and clinical findings, using Off-line Review Workstation. Using OCT examination, the lipid arc was measured at every 1-mm interval throughout the length of each lesion, and the values were averaged [12].

Lipid length was also measured on the longitudinal view [12]. Fibrous cap was defined as a signal-rich homogenous layer overlying the lipid-rich plaque [13]. The thinnest part of the fibrous cap was measured three times, and its average was defined as the minimum fibrous cap thickness [14]. Calcification was also recorded when an area consisted of a signal-poor or heterogeneous region with a sharply delineated border [15]. Calcification arc was measured at every 1-mm interval throughout the length of each lesion, and the values were averaged. Calcification length was also measured on the longitudinal view [7].

Outcomes

In this trial protocol, the primary endpoint was changes in coronary plaque characteristics, such as the minimum fibrous cap thickness and lipid arc detected by OCT between baseline and 6 months after intervention, and those in the MAGE.The following OCT parameters were determined for analysis: the minimum lumen area, lipid length, lipid mean arc, and minimum fibrous cap thickness for quantitative variables. As outcomes of glycemic metabolic variables, the MAGE; time in hyperglycemia/hypoglycemia; and mean, max, and min blood glucose levels were measured. As clinical outcome, cardiac death, myocardial infarction (MI), cerebral infarction, target lesion revascularization (TLR), and target vessel revascularization (TVR) were set.

Sample size

The needed sample size was not calculated based on statistical power. The sample size in this study was determined by referring to some similar studies, in which minimum sample size was 9 to 19 individuals per group. Referring to these numbers, the sample size needed in this study was determined as 25 per group.

Randomization

Sequence generation

Participants were randomly assigned to either the vildagliptin group or the control group with 1:1 allocation using simple randomization.

Allocation concealment mechanism

Randomization was performed by an allocation stuff member in the Kobe University Hospital who was not a clinician.

Implementation

After a participant who consented to participate and fulfilled the inclusion criteria was enrolled in the study, randomization (1:1 ratio, permuted-block design) was performed by the allocation stuff using an Excel-based allocation system with stratification. Participants and investigators were not masked to the allocation, but OCT images were analyzed in a blinded fashion.

Statistical methods

The data set consisted of all participants enrolled in this study. For the participant baseline data in analysis population, summary statistics were presented by group. The categorical counts and proportion were calculated for nominal variables; number of participants, mean, standard deviation, minimum value, median, and maximum value for continuous variables. For inter-group comparison of nominal and continuous variables, Fisher's exact test and Wilcoxon's rank sum test were used, respectively.

For continuous OCT parameters and glycemic metabolic variables, the adjusted mean difference of means for the change between baseline and 6 months after intervention between the vildagliptin and control groups was estimated, whereas, for binomial OCT parameters, the adjusted odds ratio was estimated, along with 95% confidence interval (CI). Since the observed values of OCT parameters were measured for the lesions, the above estimation was performed with the generalized estimate equation under the assumption of the intra-subject correlation structure of compound symmetry. The least square method was used for the glycemic metabolic variables because of an observed value per person. For both estimations, as independent variables, the baseline value of each parameter along with group variables were included in the statistical model.

For clinical outcomes, risk difference and 95% CI were estimated. A statistical test between the two groups based on z-statistics for OCT parameters, t-statistics for the glycemic metabolic variables, and Fisher's exact test for the clinical outcome were performed and both sides p values were reported. We did not conduct any adjustment for multiplicity for statistical test, as concrete primary and secondary endpoint were not specified in the protocol. All statistical analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, NC).

Results

Participants

Figure 1 shows the participant flow diagram of the study. Of the 20 patients included in this study, 10 were allocated in the vildagliptin group and 10 in the control group.

All 20 participants were followed for 6 months, and outcomes of glycemic metabolic variables and clinical outcomes were measured. In the control group, however, one participant did not perform the 6-month OCT because of renal dysfunction.

Baseline data

Table 1 shows the participant baseline demographic and clinical characteristics. The median (range) of the MAGE was 67.7 mg/dl (50.3 to 88.1) in the vildagliptin group and 61.8 mg/dl (39.5 to 72.1) in the control group (p = 0.307).

Table 1. Baseline patient and lesion characteristics

Variables	Vildagliptin group (n = 10)	Control group (n = 10)	P value
Men, %	100	80	>0.474
Age, years	65.9 ± 10.6	68.3 ± 8.1	0.820
BMI, kg/m^2	24.0 ± 4.0	24.0 ± 4.5	0.909
Smoker, %	70	40	0.133
Familial history, %	10	10	1.000
Stable angina, %	100.0	100.0	
Revascularization vessel, %			0.409
Right coronary artery, %	31.8	34.6	
Left main coronary trunk, %	18.2	7.7	
Left anterior descending coronary artery, %	31.8	34.6	
Left circumflex coronary artery, %	18.2	23.1	
Medication, %			
Beta blocker, %	70.0	50.0	0.649
ACE-I/ARB, %	50.0	50.0	1.000
Statin, %	90.0	100.0	1.000
Other oral DM drugs, % (except DPP-4 inhibitors)	0.0	0.0	
Insulin, %	0.0	0.0	
Prasugrel, %	40.0	60.0	0.656
Clopidogrel, %	60.0	40.0	0.656
Aspirin, %	100.0	100.0	0
Laboratory data			
LDL cholesterol, mg/dl	84.0 ± 14.3	82.9 ± 27	0.791
HDL cholesterol, mg/dl	47.4 ± 14.8	41.5 ± 9.8	0.289
Triglyceride, mg/dl	118.4 ± 52.1	131.6 ± 77.9	0.939
Creatinine, mg/dl	0.8 ± 0.1	0.9 ± 0.3	1.000
1,5 AG, μg/ml	19.9 ± 4.1	22.0 ± 4.1	0.377

HbA1c (NGSP), %	5.9 ± 0.3	5.9 ± 0.4	0.845
HOMA R	1.5 ± 5.7	1.5 ± 0.6	0.909
CRP, mg/dl	0.2 ± 0.4	0.2 ± 0.2	0.879
75 g OGTT			
Fast glucose, mg/dl	97.2 ± 9.0	94.2 ± 11.9	0.471
2-hour glucose, mg/dl	185.7 ± 36.6	169.5 ± 20.5	0.405
Fast IRI, μU/ml	6.6 ± 3.5	6.3 ± 2.7	1.000
2-hour IRI, μU/ml	114.1 ± 80.3	101.3 ± 75.6	0.791

Mean ± standard deviation (n) for continuous variables; frequency count (%) for categorical variables.

1,5 AG, 1,5 anhydroglucitol; 75 g OGTT, 75 g oral glucose tolerance test; ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CRP, C-reactive protein; DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA R, homeostasis model assessment ratio; IRI, immunoreactive insulin; LDL, low-density lipoprotein; NGSP, national glycohemoglobin standardization program.

Numbers of analyzed participants

Numbers of analysis unit were 10 individuals par group for outcomes of glycemic metabolic variable and clinical outcomes, whereas 22 lesions in vildagliptin group and 25 lesions in control group for the evaluation of plaque characteristics.

Outcome measures

For the glycemic metabolic variables, the adjusted mean difference of the changes between two groups are shown in Table 2. The mean change of the MAGE in the vildagliptin group was lower than that in the control group (vildagliptin: -20.1 ± 18.0 mg/dl vs control: 2.6 ± 12.7 mg/dl, p = 0.0064). The representative case of the MAGE in both groups is described in Figure 2.

For the OCT parameters, the mean difference of the changes between two groups for continuous variables and adjusted odds ratio for binomial variables are shown in Table 2. Lipid mean arc was decreased in the vildagliptin group and increased in the control group (vildagliptin: -9.0 ± 25.5° vs control: 15.8 ± 16.8°, p = 0.0117). Moreover, the minimum fibrous cap thickness showed more than 40 μm increased in the vildagliptin group as compared with the control group (vildagliptin: 35.7 ± 50.8 μm vs control: -15.1 ± 25.2 μm, p = 0.0022). Figure 2 shows the representative case of the differences of the minimum fibrous cap thickness in both groups.

Table 3 shows the risk difference of the clinical outcomes. There was no occurrence of cardiac death, MI, or cerebral infarction in both groups. Although there were no cases of TLR and TVR in the vildagliptin

group, one case of TLR and two of TVR were observed in the control group.

Table 2. Variables measured by the continuous glucose monitoring system and plaque characteristics detected by optical coherence tomography

Variables	Change in the Vildagliptin group (6 months - baseline)	Change in the Control group (6 months - baseline)	Difference between mean change		
			Difference	95% confidence interval	P value
Variables measured by the continuous glucose monitoring system					
	(n = 10)	(n = 10)			
MAGE, mg/dl	-20.2 ± 18.0	2.6 ± 12.7	-18.8	-30.8 to -6.8	0.0064
Time in hyperglycemia, hours	-7.9 ± 14.1	-0.8 ± 10.2	-3.7	-11.4 to 3.9	0.350
Time in hypoglycemia, hours	-0.8 ± 3.5	4.7 ± 15.4	-6.1	-15.3 to 3.1	0.209
Mean BS, mg/dl	-3.3 ± 17.3	0.4 ± 13.3	0.3	-9.5 to 10.0	0.960
Maximum BS, mg/dl	-36.3 ± 65.8	1.2 ± 37.6	-11.5	-43.1 to 20.0	0.482
Minimum BS, mg/dl	5.5 ± 24.8	7.6 ± 23.1	4.8	-10.3 to 20.0	0.538
Plaque characteristics detected by optical coherence tomography					
	(n = 22)	(n = 25)			
MLA, mm^2	0.62 ± 1.94	-0.29 ± 0.65	0.99	-0.26 to 2.23	0.120
Lipid length, mm	-0.10 ± 1.40	-0.52 ±2.37	0.03	-1.28 to 1.34	0.963
Lipid arc, °	-9.00 ± 25.57	15.87 ± 16.82	-22.82	-40.56 to -5.09	0.017
Minimum fibrous cap thickness, μm	35.75 ± 50.80	-15.19 ± 25.02	42.73	15.34 to 70.12	0.0022

Mean ± standard deviation (n) for continuous variables.

Time in hyperglycemia was defined as the time when blood glucose levels were above 140 mg/dl. Time in hypoglycemia was defined as the time when blood glucose levels were under 70 mg/dl.

BS, blood sugar; MAGE, mean amplitude of glycemic excursion; MLA, minimum lumen area.

Table 3 Clinical outcomes

Variables	Vildagliptin group (n = 10)	Control group (n = 10)	P value
Cardiac death, %	0	0	
Myocardial infarction, %	0	0	
Cerebral infarction, %	0	0	
Target lesion revascularization, %	0	10	1.000
Target vessel revascularization, %	0	20	0.473

Values are % of patients

Discussion

In this study, we assessed the effect of vildagliptin in CAD patients with IGT under lipid-lowering therapy on non-culprit native coronary plaque detected by OCT. The major findings were as follows: the (1) absolute decrease in the MAGE was greater in the vildagliptin group than in the control group, and (2) absolute increase in the minimum fibrous cap thickness and the absolute decrease in the lipid arc were higher in the vildagliptin group than in the control group.

It has been recently reported that glucose fluctuation, such as hypoglycemia and postprandial hyperglycemia, arising from an early stage of glucose intolerance may be an important contributing factor to the development of CAD, apart from dyslipidemia [2, 5]. Several studies have suggested that glucose fluctuation may be involved in the development of vascular injury, compared with constant high blood glucose levels [16, 17]. Teraguchi et al. reported that glycemic fluctuation assessed by the MAGE is significantly associated with coronary plaque rupture in patients with spontaneous acute MI [18]. These investigations suggest that daily glucose fluctuation could have adverse effects on the function of endothelial cells to promote atherosclerosis progression and the advancement of plaque vulnerability, leading to fatal cardiovascular events.

DPP-4 inhibitors including vildagliptin [19] have *in vitro* anti-atherosclerotic and cardioprotective effects [20, 21]. Kuramitsu et al. revealed that compared with diet and exercise therapy, sitagliptin did not significantly reduce coronary plaque volume in diabetic patients with ACS at 6-month follow-up. However, the percent change in lipid plaque volume significantly decreased in the sitagliptin group (-7.1 ± 21.5% vs.

15.6 ± 41.8%, p = 0.03) in integrated backscatter intravascular ultrasound analysis, suggesting that sitagliptin has a potential to prevent coronary plaque progression [22]. In the present study, the absolute increase in the minimum fibrous cap thickness and absolute decrease in the lipid arc treated by vildagliptin suggested that vildagliptin has a potential benefit to stabilize the plaque vulnerability even in thin-cap fibroatheroma (TCFA), which is considered as the cause of acute coronary syndrome (ACS). As a matter of fact, there were no TLR and TVR cases in the vildagliptin group; however, one TLR (10%) and two TVR (20%) cases were observed in the control group in the present study. Further studies are warranted to elucidate whether early intervention with vildagliptin lead to better clinical outcomes in patients with IGT.

Limitations

This study has several limitations. First, the small sample size led to imprecise estimates of effect measures, differences, odds ratio, and risk differences. However, important outcomes of this study, such as the MAGE, mean lipid arc, and minimum fibrous cap thickness, tended to clearly differ between the two groups.

Another limitation is that the definition of the primary endpoint described in the study protocol was obscure. We could not adjust multiplicity in the data analysis for outcomes because we did not know how many outcomes were used. Therefore, we did not state any statistical significance in this data analysis.

Furthermore, we only assessed patients with stable angina pectoris. Therefore, patients with ACS were not enrolled in this study because this population had multiple confounding factors, such as uncontrolled dyslipidemia, stress hyperglycemia, and drastic changes in diet and medications after admission. Further study is warranted including patients with ACS, as they might be a better target to address the influence of the MAGE on plaque characteristics because vulnerable plaques are more frequently found in such patients.

Moreover, we did not validate the OCT findings with histological examination. Therefore, it is unclear whether vildagliptin could actually stabilize TCFA, which leads to fatal coronary events.

Conclusions

Vildagliptin reduced the MAGE at 6 months and simultaneously decreased the lipid arc and increased the minimum fibrous cap thickness of the coronary plaques in CAD patients with IGT. These findings may represent its stabilization effect on coronary plaques, which are characteristic in this patient subset.

Abbreviations

ACS: acute coronary syndrome; CAD:coronary artery disease; CGM:continuous glucose monitoring; DPP-4:dipeptidyl peptidase-4; IGT:impaired glucose tolerance; MAGE:mean amplitude of glycemic excursion; MI:myocardial infarction; OCT:optical coherence tomography; OGTT:oral glucose tolerance test;

PCI:percutaneous coronary intervention; TCFA:thin-cap fibroatheroma; TLR:target lesion revascularization TVR:target vessel revascularization

Declarations

Ethics approval and consent to participate

This protocol has been approved by the institutional review board of the Kobe University Hospital (number:240030)

Consent for publication

Witten informed consent for publication was obtained by all enrolled participant in this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have contributed significantly, and agree with the content of the manuscript. H.Y, K.M and T.S designed, conducted the study, and H.Y, A.K, T.S wrote the initial draft of the manuscript. T.O mainly analyzed the data. K.H, W.O, H.O, Y.H, and K.S provided technical support and supervised the study. M.K, T.O, T.S, T.T, H.K, N.H, and T.O contributed to the analysis and interpretation of the data and assisted in the preparation of the manuscript. All authors contributed to data collection and interpretation and critically reviewed the manuscript.

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Figures

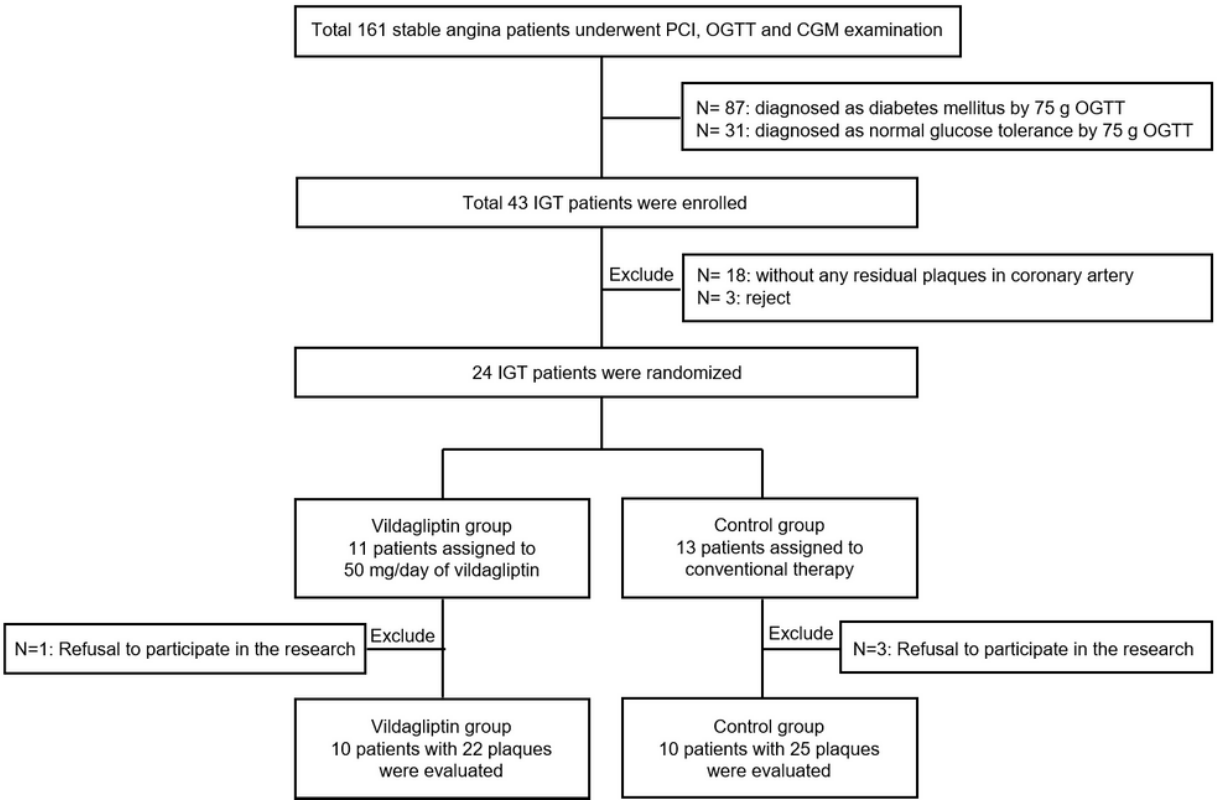

Figure 1

Participant flow diagram of the present study. Abbreviations: OCT, optical coherence tomography; PCI, percutaneous coronary intervention; OGTT, oral glucose tolerance test; CGM, continuous glucose monitoring; IGT, impaired glucose tolerance

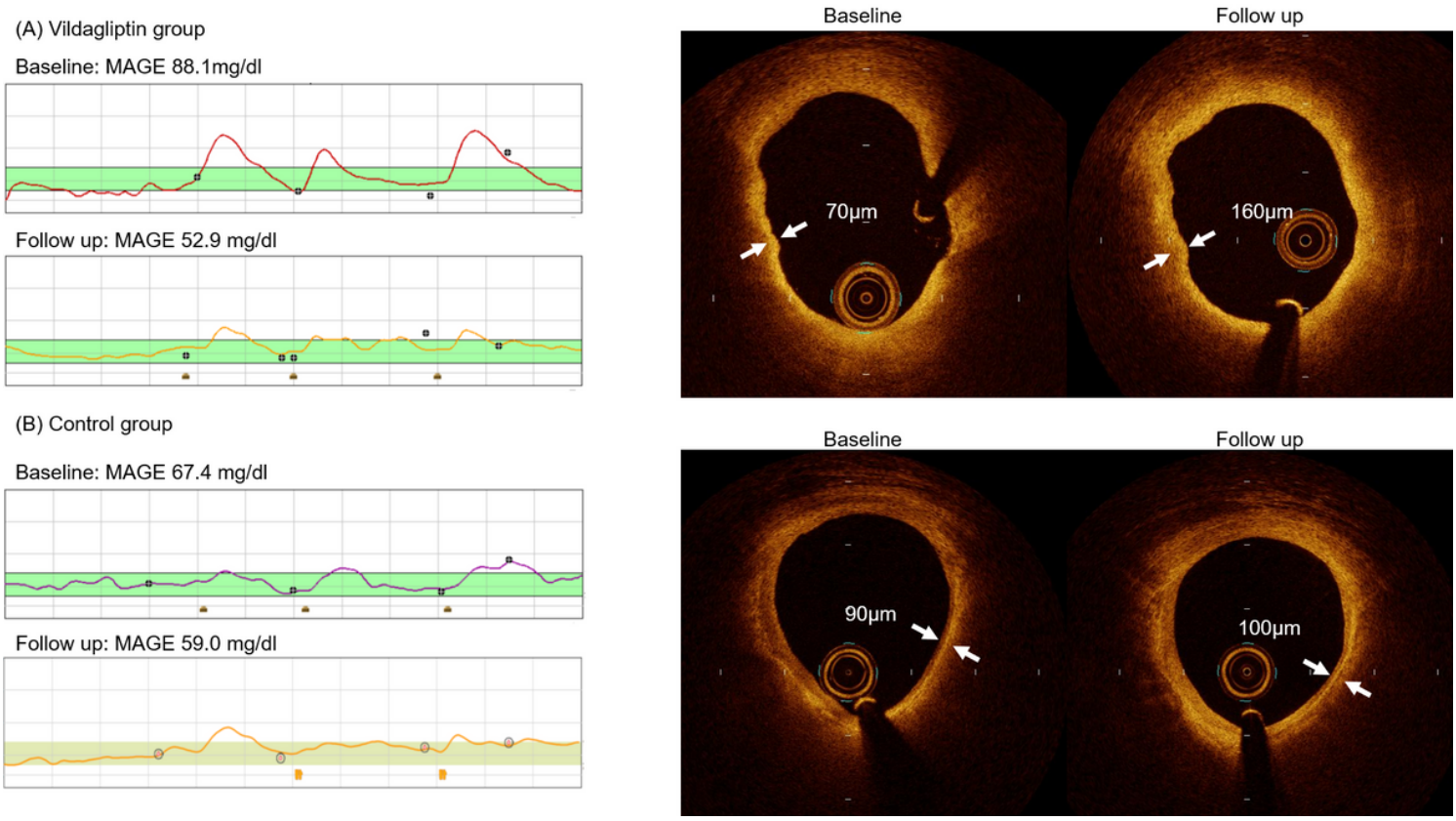

Figure 2

Representative cases of the mean amplitude of glucose excursion (MAGE) and minimum fibrous cap thickness in the vildagliptin and control groups: (a) Representative case of the vildagliptin group. The MAGE was dramatically reduced from 88.1 mg/dl at baseline to 52.9 mg/dl at follow-up. Optical coherence tomography (OCT) imaging showed that the thinnest part of fibrous cap thickness on lipid rich plaque was improved from 70 μm to 160 μg (lengths between white allows showing the minimum fibrous cap thickness). (b) Representative case of the control group. The MAGE was almost unchanged from 67.4 mg/dl at baseline to 59.0 mg/dl at follow-up. OCT imaging showed that the minimum fibrous cap thickness remained thin and virtually unchanged (90 μm at baseline and 100 μg at follow-up).