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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.

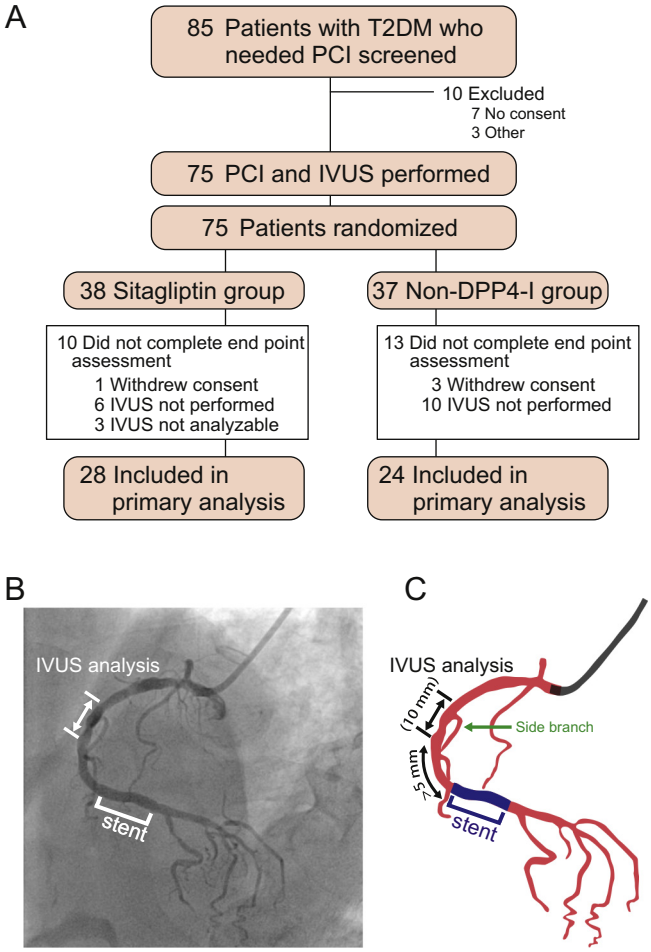

Fig. 1. (A) Flow chart of the study. Seventy-five T2DM patients with CAD who underwent IVUS-guided PCI were randomized to receive sitagliptin (sitagliptin group) or not to receive DPP4-I (non-DPP4-I group). Ultimately, 52 patients who had analyzable IVUS examinations of a non-culprit lesion at baseline 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