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Original article

Effects of alogliptin on fractional flow reserve evaluated by coronary computed tomography angiography in patients with type 2 diabetes: Rationale and design of the TRACT study

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ABSTRACT

Background: Patients with type 2 diabetes are at high risk for developing coronary artery disease (CAD). Noninvasive anatomic assessment by coronary computed tomography angiography (CCTA) is being increasingly used for detecting or excluding CAD. Recently, fractional flow reserve (FFR) using routinely acquired CCTA datasets (FFR_{CT}) has been developed. Although intensive glycemic control can reduce the risk of microvascular complications, intensive glucose control does not seem to be beneficial in preventing major cardiovascular events when compared with standard therapy. However, it has been reported that dipeptidyl peptidase-4 (DPP-4) inhibitors have anti-atherogenic effects in an animal model. In addition, DPP-4 inhibitors attenuate the progression of carotid intima-media thickness in patients with type 2 diabetes. Therefore, this study will be performed to evaluate the effects of alogliptin, a DPP-4 inhibitor, on coronary atherosclerosis using FFR_{CT} in patients with type 2 diabetes.
Methods and design: This study will be a prospective, non-randomized, multicenter trial performed in Japan. Patients with type 2 diabetes who have intermediate coronary artery stenosis (diameter stenosis <70%) as evaluated by CCTA will be treated with 25 mg/day of alogliptin. After 48 weeks' treatment, CCTA will be repeated. The primary endpoint will be changes in FFR_{CT}, and the secondary endpoint will be the change in plaque volume from baseline to the 48-week follow-up.
Conclusion: This study will be the first multicenter trial to evaluate the effects of alogliptin on coronary atherosclerosis using the newly developed FFR_{CT} as the primary endpoint, and the findings will clarify the anti-atherogenic effects of alogliptin.

Introduction

Conventional invasive coronary angiography has been the gold standard for the diagnosis of coronary artery disease (CAD) and decision-making for percutaneous coronary intervention (PCI) for more than a decade. However, the correlation between angiographic findings and physiological stenosis severity is poor [1]. Fractional flow reserve (FFR), which assesses the ratio of flow across a stenosis to putative flow in the absence of a stenosis, has been shown to be a powerful tool for detecting lesion-specific myocardial ischemia and is the accepted reference standard for assessing the functional significance of CAD [2]. In addition, invasive FFR-guided decision-making regarding PCI improves event-free survival compared with coronary angiography-guided decision alone [3]. Thus, FFR measured during invasive coronary angiography is the gold standard for lesion-specific coronary revascularization decisions in patients with stable CAD [4]. On the

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other hand, noninvasive anatomic assessment by coronary computed tomography angiography (CCTA) is being increasingly used as an accurate tool for detecting or excluding CAD [5–7]. Although the absence of coronary artery stenosis according to CCTA is associated with an excellent prognosis [8], stenosis severity evaluated by CCTA overestimates the severity of CAD and does not correlate with functional ischemia assessed using invasive FFR [9]. Recently, a method using computational fluid dynamics to calculate coronary blood flow, pressure, and FFR using routinely acquired CCTA datasets (FFR_{CT}) has been developed [10,11]. FFR_{CT} provides high diagnostic performance for the diagnosis of ischemic lesions of intermediate stenosis severity [11–13].

Patients with type 2 diabetes are at high risk for developing CAD [14]. Although intensive glycemic control can reduce the risk of microvascular complications, intensive glucose control does not seem to be beneficial in preventing major cardiovascular events when compared with standard therapy [15]. Among different hypoglycemic agents, insulin is associated with poor mid-term clinical outcomes in diabetic patients undergoing PCI [16]. However, it has been reported that dipeptidyl peptidase-4 (DPP-4) inhibitors have anti-inflammatory and anti-atherogenic effects in an animal model [17–19]. Furthermore, several recent clinical trials have reported that DPP-4 inhibitors (sitagliptin and alogliptin) attenuate the progression of carotid intima-media thickness [20,21] and significantly improve endothelial function in patients with type 2 diabetes [22,23]. In meta-analyses, DPP-4 inhibitors have also been shown to reduce the risk of cardiovascular events [24,25]. However, DPP-4 inhibitors (saxagliptin and alogliptin) failed to decrease the number of major adverse cardiovascular events in two large clinical trials [26,27]. Thus, the effects of DPP-4 inhibitors on cardiovascular events and atherosclerosis remain controversial, and little is known about the effects of these drugs, particularly on coronary atherosclerosis. Therefore, we will examine the effects of alogliptin, a DPP-4 inhibitor, on coronary atherosclerosis using the newly developed FFR_{CT} as the primary endpoint.

Methods

Study design

Treatment of Alogliptin on Coronary Atherosclerosis Evaluated by Computed Tomography-Based Fractional Flow Reserve (TRACT) study will be a prospective, non-randomized multicenter trial performed in three centers in Japan. Patients who satisfy all the inclusion criteria will be enrolled (Table 1). Patients who meet any of the exclusion criteria will not be enrolled (Table 2). The patients will give written informed consent to analysis of FFR_{CT} using CCTA images at baseline and at the 48-week follow-up. Next, the supervising physician will administer 25 mg/day of alogliptin within 2 weeks after the examination with CCTA. The patients will continue alogliptin until the end of study, until certain endpoints have occurred, or until they decide to discontinue participation in this study. The CCTA examination will be performed at baseline and 48-week follow-up (Fig. 1). Laboratory tests [total cholesterol, low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, plasma glucose, insulin, and hemoglobin A1c (HbA1c)] will be performed at each study visit. During the study period, there will be no lifestyle changes, and antihypertensive and anti-dyslipidemic treatment agents such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and statins used at enrollment will be continued without modifications of the dose.

This study will be conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the three participating institutions. The enrollment of patients is planned to take place between October 2014 and December 2015 or until enrollment has been completed. The study has been registered with the University Hospital Medical Information Network (UMIN; UMIN ID: 000015381).

Table 1
Inclusion criteria.

1. Type 2 diabetes mellitus
2. Intermediate coronary artery stenosis as evaluated by CCTA (diameter stenosis <70%)
3. Judged by physician to administer alogliptin
4. Age more than 20 years
5. Written informed consent obtained

CCTA, coronary computed tomography angiography.

Table 2
Exclusion criteria.

1. Required to undergo PCI
2. Acute coronary syndrome
3. Past history of myocardial infarction
4. Past history of PCI or coronary artery bypass grafting
5. Complex congenital heart disease
6. Body mass index >35 kg/m^2
7. Past history of heart failure
8. Past history of ketoacidosis or diabetic coma
9. Hepatic disorder (aspartate transaminase or alanine transaminase greater than 2 times of the upper limits of normal)
10. Renal dysfunction (estimated glomerular filtration rate 30 ml/min/1.73 m^2 or lower)
11. Severe infection, before or after operation, or serious trauma
12. Allergy to alogliptin
13. Pregnant women, women with suspected pregnancy, or lactating women
14. Other reasons for ineligibility, as determined by physicians

PCI, percutaneous coronary intervention.

CCTA examination and image acquisition

Each center will perform CCTAs in accordance with the Society of Cardiovascular Computed Tomography Guidelines on Performance of CCTA with a variety of different computed tomography scanner platforms [28]. Follow-up images will be acquired by the same machine in every subject. CCTA will be performed on 64 detector row CT scans. Oral and/or intravenous beta-blockers will be used targeting a heart rate <60 beats/min, and sublingual nitrates will be administered to ensure coronary vasodilatation. During acquisition, 50–80 ml of contrast will be injected, followed by a saline flush. Helical or axial scan data will be obtained with retrospective or prospective electrocardiographic gating, respectively. Image acquisition will be prescribed to include the coronary arteries, left ventricle, and proximal ascending aorta.

Computation of FFR_{CT}

CCTA will be transmitted to the FFR_{CT} core laboratory (HeartFlow, Redwood City, CA, USA) for computational analysis. Computation of FFR_{CT} will be performed in a blinded manner. FFR_{CT} will be calculated after semi-automated segmentation of the coronary arteries and left ventricular mass [10]. Briefly, 3-dimensional (3D) blood flow simulations in the coronary vasculature will be performed using proprietary software with quantitative image quality analysis, image segmentation, and physiological modeling using computational fluid dynamics. Coronary blood flow and pressure will be calculated under conditions simulating maximal hyperemia. FFR_{CT} will be obtained by dividing the mean pressure distal to the coronary stenosis by

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