Study Design and Rationale of Cardiac Computed Tomography Angiography and MRI in Patients with Type 2 Diabetes for Detection of Unrecognized Myocardial Scar in Subclinical Coronary Atherosclerosis (ACCREDIT Study)

Objective: Cardiac computed tomography angiography (CCTA) allows the detection of subclinical coronary artery disease (CAD) and delayed-enhancement cardiac magnetic resonance imaging (DE-CMR) enables the diagnosis of occult myocardial scar (OMS). The main objectives of the Assessment with CCTA and MRI in Asymptomatic Patients with Type 2 Diabetes for Detection of Unrecognized Myocardial Scar in Subclinical Coronary Atherosclerosis (ACCREDIT) study are to prospectively investigate the prevalence of OMS on DE-CMR images in asymptomatic patients with type 2 DM and to assess its correlation with subclinical CAD detected by CCTA.

Materials and Methods: This prospective, open-label, non-randomized, fixed-sequence and multicenter study aims to enroll 340 patients with type 2 DM and at least two identified cardiac risk factors, but without chest pain or history of coronary disease. CMR and CCTA examinations will be performed. Patient follow-up will take place over a 5-year period in order to assess the occurrence of major adverse cardiac events (MACE) and cardiac emergent significant diseases (ESD). The prevalence of OMS will be calculated based on the DE-CMR examination. For each main coronary artery, the degree of stenosis, plaque characteristics and the coronary artery calcium score will be determined by CCTA. The prognostic value of OMS on DE-CMR images and subclinical atherosclerosis detected by CCTA for occurrence of MACE and cardiac ESD will be assessed.
INTRODUCTION

Coronary artery disease (CAD) accounts for 65% to 80% of deaths in diabetic patients [1], and in 2007 approximately 17 million Americans had diabetes. By 2050, this number could reach 48 million [2]. Recognizing this, nearly 10 years ago, the American Diabetes Association published a consensus recommendation that clinicians consider a risk factor-guided screening approach to early diagnosis of CAD in both symptomatic and asymptomatic patients. Substantial interest has also been shown in the early detection of asymptomatic CAD by the screening of patients with type 2 diabetes mellitus (DM) [3].

Cardiac computed tomography angiography (CCTA) has emerged as a valid alternative imaging technique for the assessment of patients with known or occult CAD. Thanks to the technological advances that have been made, CCTA has the potential to provide comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque. Recently, it has been suggested that CCTA may potentially also provide better insight into occult CAD in asymptomatic individuals, including asymptomatic patients with type 2 diabetes mellitus (DM) [4-7].

Cardiac magnetic resonance (CMR) imaging can detect and characterize myocardial scar missed by electrocardiography (ECG), conventional wall motion or nuclear scintigraphic techniques but is associated with important occult CAD. Thanks to the technological advances that have been made, CCTA has the potential to provide comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque. Recently, it has been suggested that CCTA may potentially also provide better insight into occult CAD in asymptomatic individuals, including asymptomatic patients with type 2 DM [4-7].

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The purpose of this study is to prospectively investigate the prevalence of OMS on DE-CMR imaging in patients with type 2 DM and subclinical atherosclerosis detected by CCTA, and to assess whether subclinical coronary atherosclerosis detected by CCTA is associated with OMS on DE-CMR images. The prognostic value of OMS on DE-CMR images, coronary atherosclerosis detected by CCTA and traditional risk factors for the occurrence of MACE and cardiac emergent significant diseases (ESD) will also be assessed.

MATERIALS AND METHODS

Ethical considerations

The study is registered on ClinicalTrials.gov with identifier NCT01254552. Informed consent will be obtained for each patient enrolled in the study.

Patients

Patients (male or female, aged between 50 and 75 years) will be recruited in 6 centres in South Korea. Patients with onset of type 2 DM having occurred at the age of 30 years or older with at least two identified cardiac risk factors and scheduled to undergo CMR and CCTA examinations to assess their coronary and cardiac status will be included. The diagnosis of type 2 DM is based on fasting plasma glucose levels ≥126 mg/dL or anti-diabetic drug therapy.

Patients with angina pectoris or chest discomfort, an abnormal stress test or invasive coronary angiography within the 3 years prior to inclusion, a history of MI, overt non-compensated heart failure, or coronary revascularization, a diagnosis of hemodynamic instability, or with a contraindication or intolerance to beta-blocker administration will be excluded. Patients will not be included if they have limited life expectancy due to cancer or end-stage renal or liver disease, if they present with macroalbuminuria, with known severe renal failure (defined as estimated creatinine clearance <30 mL/min), with a history of immediate or delayed major hypersensitivity reaction to an iodinated contrast media or a gadolinium contrast media, or if they received diuretic or biguanide treatment during the 48 hours preceding the CCTA scan, if they received or were going to receive contrast media within 48 hours prior to the enhanced-CCTA, or if they had participated in any investigational drug study during the 30 days prior to inclusion. Pregnant or breastfeeding women will not be included in the study.

Study objectives

The main study objective is to prospectively investigate the
prevalence of OMS following DE-CMR imaging performed with gadoterate meglumine in asymptomatic patients with type 2 DM.

The correlation between OMS on DE-CMR images and coronary atherosclerosis detected by CCTA will be assessed, as well as the accuracy of CCTA performed with iobitridol for coronary artery imaging and delayed-CCTA for identifying OMS in asymptomatic patients with type 2 DM compared to DE-CMR. Another study objective is to assess the prognostic value of OMS on DE-CMR images, coronary atherosclerosis detected by CCTA and traditional risk factors for the occurrence of MACE and cardiac ESD and to confirm the safety of both contrast agents in this population of patients.

Study design
Patients with type 2 DM will be enrolled after having satisfied all eligibility requirements. The patients will then undergo a CMR examination within 60 days after the screening visit (both could take place on the same day). The CCTA examination will be performed within 1 day to 30 days (but no sooner than 24 hours) after the CMR examination. The primary criterion (prevalence of OMS) will be assessed after the data corresponding to the CMR and CCTA examinations have been collected. Patients will be followed up over a 5-year period to assess the occurrence of MACE and cardiac ESD, and the corresponding secondary analysis will be performed at the end of the follow-up period. This follow-up will be based on examination of the patients’ medical records and interviews with the patients’ physicians who will be contacted. In addition, survival data will be obtained from the South Korean National Health Insurance & Assessment Service. The study design is presented in Fig. 1.

Adverse events will be recorded from the patients’ inclusion in the study up to 30 min after the CCTA examination. Patients will be observed for vital signs (supine systolic and diastolic arterial blood pressure and pulse) at the investigational site immediately prior to contrast medium injection, and 15 and 30 min after the injection. Injection site tolerance will be assessed over a 30 min period following contrast medium injection. The renal safety of iobitridol will be assessed through basal serum creatinine matched with blood sampling within 3±1 day post iobitridol administration.

The patients’ participation in the study will start from the time of signing of the consent form and is expected to last 5 years. Patients who successfully complete all protocol-specified visits will be considered as having completed the study.

Imaging protocol
The CMR imaging examination will include two sequences, cine and DE-MRI. Cine CMR will be performed according to the routine clinical practice of each centre. Cardiac DE-MRI sequences will be performed after injection of 0.1 mmol/kg of the gadolinium contrast medium gadoterate meglumine (Dotarem®, Guerbet, France). The following guidelines will be used for DE-MRI: starting time after injection: 10 minutes; short axis view; slice thickness=6 mm and no gap between slices; direction: from apex to base; additional views: 3 slices of 4 chamber views and 2 chamber views. Long axis views are highly recommended in case of subtle subendocardial enhancement suspected on short axis images. The imaging protocol will be performed according to local acquisition guidelines in order to achieve the highest level of image quality with each type of MR equipment.

CCTA-A dose of iobitridol (Xenetix® 350, Guerbet, France) at a concentration of 350 mg iodine/mL will be injected to the patient, followed by a 50 mL normal saline flush. CCTA will be performed using automatic detection software to launch the acquisition 4 s after an enhancement of 150 HU in the ascending aorta. All CCTA parameters including injection rate and volume will be determined by the investigators. A tube power of 100 kVp will be used. Delayed-enhancement CCTA (delayed-CCTA) will be performed 7 min after potential reinjection of iobitridol at a rate of 1 mL/s in three of six institutions in which the delayed-CCTA was already performed in clinical situation.
According to the iobitridol summary of product characteristics, the maximum total volume injected to each patient during the entire examination shall not exceed 180 mL. Iobitridol will be administered at least 24 h after administration of gadoterate meglumine to prevent any carryover effect.

All the CCTA images will be assessed on-site by two experienced radiologists using a consensual reading process. At each site, two designated radiologists/cardiologists with expertise in the CMR imaging interpretation will be appointed at the start of the study to read the DE-CMR images using a consensual reading process and independently of the CCTA reading.

**Assessment**

**Primary criterion**

The prevalence of OMS in asymptomatic patients with type 2 DM will be assessed using DE-CMR.

**Secondary criteria**

**Efficacy**

The parameters characterizing OMS on the DE-CMR images will be assessed as follows: maximal segmental transmural extent will be graded using the following scale: 0 (0%), 1 (1% to 25%), 2 (26% to 50%), 3 (51% to 75%), 4 (76% to 99%), 5 (100%); the nature of the lesions (typical or atypical), the number of infarcted myocardial segments, coronary distribution [left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCX) according to the 17-segment model of the American Heart Association] and the contrast-to-noise ratio [signal intensity difference between infarcted and remote myocardium divided by the standard deviation (SD) of the signal intensity or attenuation within the remote myocardium] will also be determined. For contrast-to-noise ratio, a semi-automatic detection method will be used with a signal intensity threshold of >2 SD above a remote reference region.

Global DE-CMR image quality will be graded according to the following scale: 0=null, 1=poor, 2=adequate and 3=good. Left ventricular ejection function parameters (i.e., number and distribution of hypokinetic segments) will be obtained by cine MRI.

The degree of coronary artery stenosis detected by CCTA will be graded using the following ranking: no stenosis (0%), non-significant stenosis (1% to 50%), significant stenosis (51% to 99%) and occlusion (100%). For each main coronary artery, plaque characteristics will be determined by CCTA and graded as follows: calcified plaque (more than 50% of the plaque area, i.e., density >130 HU in native scans), mixed plaque (less than 50% calcium), non-calcified plaque (plaques without any calcium). Positive remodel and the smallest CT number of the plaque will also be recorded. For each main coronary artery as well as globally for both coronary images and myocardium images obtained by CCTA, image quality will be rated using a 3-point scale: 1 (poor, i.e., presence of image-degrading artifacts and assessment only with low confidence), 2 (adequate, i.e., presence of image-degrading artifacts and assessment with moderate confidence) and 3 (good, i.e., no artifacts, high diagnostic confidence). The coronary artery calcium score (CACS) will be determined at different segment levels (LAD, LCX and RCA) using the following scale: no=0, mild=0.1 to 100, moderate=100.1 to 400, severe calcification >400.

The correlation of the OMS and stenosis degree, coronary arterial plaque characteristics, positive remodel, and CT number will be analysed using vessel level or infarct-related artery, which is the coronary territory where one of the corresponding myocardial segments underwent an OMS shown by the CMR imaging.

The prevalence, maximal segmental transmural extent, nature and coronary distribution of OMS will also be assessed by delayed-CCTA. The correlation of OMS in delayed-CCTA and that of CMR will be also analysed.

**Prognosis**

The prognostic value of OMS on DE-CMR images and subclinical atherosclerosis detected by CCTA for the occurrence of MACE and cardiac ESD in asymptomatic patients with type 2 DM will be calculated. MACE are defined as cardiac death, recurrent nonfatal acute MI, emergency coronary arterial bypass graft (CABG) or repeat percutaneous coronary intervention (PCI) for documented ischemic ECG changes, stroke, or systemic thromboembolic events. Cardiac ESD are defined as hospitalization with cardiovascular events (angina, acute coronary syndrome, and so on) leading to CABG or not recurrent PCI, and not recurrent nonfatal acute MI. Adverse events will be classified as serious or non-serious.

**Safety**

The severity (mild, moderate, or severe), relationship (possible, doubtful, not related) to the contrast agent, and outcomes of the adverse events (AEs; resolved with/without sequelae, ongoing, worsened, death) will be assessed by the investigating radiologist. In case of injection site pain, the patient will have to specify the level of pain using an analogical visual scale ranging from 0 (no pain) to 10 (maximal pain). For renal safety, a decrease in estimated glomerular filtration rate (eGFR) of at least 25% occurring within 3±1 day after the CCTA will be considered as clinically significant and recorded as an AE. eGFR will be calculated using serum creatinine levels and the modification of diet in renal disease (MDRD) formula.
Statistical methods

The sample size required to ensure satisfactory precision of the incidence of OMS on DE-CMR images was calculated to be 307 patients, based on the 28% proportion of patients with OMS on the DE-CMR images in the population analyzed in the article of Kwong et al. [9]. Based on the assumption there will be a 10% drop out rate, a total of 340 patients are required to meet the study’s objective.

Four categories of populations will be analyzed: the all included patient (AIP) population; the intent-to-treat (ITT) population (i.e., efficacy-evaluable population including all patients who have valid DE-CMR and CCTA examinations); the per protocol (PP) population (i.e., all patients who have no significant protocol deviations), and the safety population (i.e., all patients who receive at least one injection of contrast agent regardless of the quantity). The AIP population will be used for the demographic data, clinical history, traditional coronary risk factors, laboratory data and ECG findings. Efficacy analysis will be performed on the ITT population. If the PP population differs from the ITT population by more than 10%, efficacy analyses will be repeated on this population. All safety analyses will be performed using the safety population.

Quantitative variables will be expressed as sample sizes, means, SD, medians and extreme values while qualitative variables will be described in terms of frequencies and percentages of the number of individuals examined. OMS prevalence will be estimated with a 95% confidence interval (CI). The occurrence of OMS on DE-CMR images or significant stenosis detected by CCTA as a function of traditional coronary risk factors (age, sex, duration of DM, body mass index, hypertension, HDL, LDL, total cholesterol, triglycerides, serum creatinine, microalbuminuria, smoking, obesity and heredity) will be analysed by the chi-2 test for categorical variables or Student’s t-test for continuous variables. A logistic regression model will be used to model the probability of detecting OMS on DE-CMR images or significant stenosis on CCTA as a function of the traditional established coronary risk factors. The sensitivity and specificity of delayed-CCTA for detecting subjects with OMS will be computed using the 95% CI of the estimates using DE-CMR as the truth standard. Kappa coefficients will be calculated. Delayed-CCTA will be considered non-inferior to DE-CMR for OMS detection if the lower limit of the 95% CIs of the difference in the proportion of positive results is greater than -10%. The occurrence of MACE will be analyzed in patients without OMS vs. patients with OMS using Kaplan-Meier survival estimates. A log-rank test will assess whether the two survival curves are significantly different using an α (two-sided) type I error (0.05).

Missing data will not be replaced or estimated. All statistical analyses will be performed using SAS® software (SAS Institute, Cary, NC, USA) version 9.4.

DISCUSSION

Assessment with CCTA and MRI in Asymptomatic Patients with Type 2 Diabetes for Detection of Unrecognized Myocardial Scar in Subclinical Coronary Atherosclerosis (ACCREDIT) study is a prospective phase IV, open-label, non-randomized, fixed sequence, multicenter study performed to investigate the prevalence of OMS on CMR imaging and subclinical atherosclerosis detected by CCTA in asymptomatic type 2 DM patients. The correlation between OMS on DE-CMR images and coronary atherosclerosis on CCTA images, as well as the prognostic value of OMS on CMR images, coronary atherosclerosis on CCTA images and traditional risk factors for the occurrence of MACE and ESD in asymptomatic patients with type 2 DM will be assessed.

CAD leads to death in 65~80% of DM patients, and the rate of cardiovascular events is 2- to 4 times higher in patients with DM than in non-DM patients [1]. In DM, CAD generally develops after a short period but remains asymptomatic, presenting as MI or recurrence of angina, and usually as multivessel or diffuse disease [10]. Screening is therefore recommended in patients with at least two risk factors [3].

Non-invasive imaging techniques such as exercise ECG or radioisotope myocardial perfusion imaging (MPI) have been used to detect CAD in DM patients. However, radioisotope MPI screening did not significantly reduce cardiac events in patients with DM [11]. It was also demonstrated that the accuracy of radioisotope MPI for detecting subclinical CAD and differentiating coronary risks was limited [7].

With the technological advances that have been made, CCTA now has the potential to provide comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque. Recently, it has also been suggested that CCTA could be used as a potential tool to provide better insight into the characteristics of plaque as well as into coronary artery stenosis in subclinical CAD in asymptomatic individuals, including patients with type 2 DM. Use of CCTA revealed occult CAD in 64% of DM patients, with 26% of them presenting with significant stenosis [5]. Higher CACS and more frequent multiple plaques were detected by CCTA in DM vs. non-DM patients [12]. The correlation between atherosclerotic plaque detection and the occurrence of cardiovascular events was better with CCTA than with radioisotope MPI [7].

The presence of myocardial scar is widely known to be a poor prognostic factor both in ischemic and non-ischemic cardiomyopathies. According to the study published by Kwong et al. [8] including 107 DM patients suspected to have CAD but without history of MI, a higher rate of MACE was recorded in the 28% of patients with OMS on their DE-CMR images. Even in patients with impaired glucose tolerance, the presence of OMS
is related to higher mortality [13].

A post-marketing survey in more than 61000 patients, including 3632 (5.9%) of them presenting with DM, showed a good safety and efficacy of iohibridol with only 2.3% with adverse effects represented by a feeling of warmth in half of these cases [14]. Moreover, in another post-marketing survey carried out on 52057 patients, including 2938 (5.64%) of them presenting with DM, 30 adverse events and only one severe adverse event was reported out of 2938 examinations carried on the population with DM [15].

Gadoterate meglumine have been used for various imaging purposes and adverse events reported in these trials consist of aphonyria, headaches, sensation of heat, cold and/or injection site pain, nausea, vomiting, and skin reactions. Rare anaphylactic reactions have been reported [16]. In a post-marketing survey carried out to assess the safety profile of gadoterate meglumine, only one adverse reaction was reported in 1416 patients with DM [17]. It has been reported that nephrogenic systemic fibrosis may occur after exposure to gadolinium-based contrast agents (GBCA) in patients with renal impairment. Moreover, most of these reports have been linked to the use of less stable linear GBCAs. Thereby, macrocyclic GBCAs such as gadoterate meglumine are considered to have less risk [18].

To date, no multicenter study using DE-CMR for prognosis or assessing the presence of CAD by CCTA and its relation to prognosis in asymptomatic DM patients has ever been performed. The ACCREDIT study will therefore analyze the prevalence of OMS on DE-CMR images as well as the prevalence of subclinical CAD and plaque characterization by CCTA in the same asymptomatic type 2 DM patients. The relation of OMS and plaque characteristics with patients’ prognosis and the safety of iohibridol and gadoterate meglumine in this specific population will also be assessed.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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