CT Angiography Images of Coronary Artery Stenosis Provide a Better Prediction of Risk Than Traditional Risk Factors in Asymptomatic Individuals With Type 2 Diabetes: A Long-term Study of Clinical Outcomes

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OBJECTIVE

We investigated the efficacy of coronary computed tomography angiography (CCTA) in predicting the long-term risks in asymptomatic patients with type 2 diabetes and compared it with traditional risk factors.

RESEARCH DESIGN AND METHODS

We analyzed 933 patients with asymptomatic type 2 diabetes who underwent CCTA. Stenosis was considered obstructive (≥50%) in each coronary artery segment using CCTA. The extent and severity scores for coronary artery disease (CAD) were evaluated. The primary end point was major adverse cardiovascular events (MACEs), including all-cause mortality, nonfatal myocardial infarction, and late coronary revascularization during a mean follow-up period of 5.5 ± 2.1 years.

RESULTS

Ninety-four patients with MACEs exhibited obstructive CAD with a greater extent and higher severity scores ($P < 0.001$ for all). After adjusting for confounding risk factors, obstructive CAD remained an independent predictor of MACE (hazard ratio 3.11 [95% CI 2.00–4.86]; $P < 0.001$]). The performance of a risk prediction model based on C-statistics was significantly improved (C-index 0.788 [95% CI 0.747–0.829]; $P = 0.0349$) upon the addition of a finding of obstructive CAD using CCTA to traditional risk factors, including age, male, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate, and HbA_{1c}. Both integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analyses further supported this finding (IDI 0.046 [95% CI 0.020–0.072], $P < 0.001$; and NRI 0.55 [95% CI 0.343–0.757], $P < 0.001$). In contrast, the risk prediction power of the coronary artery calcium score remained unimproved (C-index 0.740, $P = 0.547$).

CONCLUSIONS

Based on our data, the addition of CCTA-detected obstructive CAD to models that include traditional risk factors improves the predictions of MACEs in asymptomatic patients with type 2 diabetes.

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Recent guidelines recommend that type 2 diabetes mellitus (T2DM) be treated in a manner similar to coronary heart disease (1) since it is easily accompanied by macrovascular complications according to the large cohort studies (2). Patients with T2DM have a higher prevalence and extent of coronary atherosclerosis and higher rates of silent atherosclerotic lesions without ischemic symptoms than patients without T2DM (3,4). Therefore, the risk predictions are important, and clinicians should consider prophylactic measures even before patients show ischemic symptoms.

Coronary computed tomographic angiography (CCTA) is a noninvasive tool with good diagnostic performance in detecting obstructive coronary artery disease (CAD) (5). In previous reports from the FACTOR-64 study (6) and the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (7), noninvasive screening imaging tests, including CCTA and stress myocardial perfusion imaging, failed to reduce cardiovascular event rates in asymptomatic patients with T2DM. However, care should be taken in generalizing the results of the DIAD and FACTOR-64 studies across all ethnic populations or subgroups of high-risk patients.

A prior study (8) assessed the roles of associated major risk factors and demonstrated that exhibiting more than two risk factors was related to more severe forms of CAD and unfavorable coronary anatomy. Furthermore, as shown in recent case control studies (9–11), obstructive CAD, when detected using CCTA, is an independent predictor of composite major adverse cardiovascular events (MACEs). However, only small numbers of asymptomatic patients with T2DM were enrolled for short-term follow-up periods. Thus, researchers have not clearly determined whether obstructive CAD detected by CCTA in asymptomatic patients with T2DM who are at high-risk of the development of CAD may provide a clinically significant prognostic indicator. We enrolled asymptomatic patients with T2DM who are at high-risk of the development of CAD and compared their long-term cardiovascular outcomes according to the extent and severity of CCTA-detected CAD to address this issue. We also evaluated the incremental value of CCTA-detected obstructive CAD compared with traditional risk factors in predicting long-term adverse clinical outcomes using traditional C-statistical and novel statistical metrics, including net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

RESEARCH DESIGN AND METHODS

Study Population

From January 2006 to December 2010, 933 asymptomatic patients with T2DM who were >30 years and had undergone CCTA were prospectively enrolled in the CRONOS-ADM (Coronary CT Angiography Evaluation for Clinical Outcomes in Asymptomatic Patients with Type 2 Diabetes Mellitus) registry to evaluate CCTA findings and the coronary artery calcium score (CACS) in the divisions of endocrinology and cardiology at two major cardiac centers in Korea (Seoul St. Mary's Hospital, Seoul, Republic of Korea; and St. Vincent's Hospital, Suwon, Republic of Korea). This registry included demographic characteristics; clinical, laboratory, CACS, and CCTA findings; and 7-year long-term clinical outcomes. A flowchart of the study population is depicted in Supplementary Fig. 1. A total of 390 patients refused to participate. A total of 67 patients were excluded for the following reasons: patients with type 1 diabetes, angina, or angina-equivalent symptoms according to the Rose questionnaire (12); patients receiving antiangina medications and patients who had a history of myocardial infarction (MI); patients with previous coronary revascularization (either by percutaneous coronary intervention or bypass). Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were also excluded. The diagnosis of T2DM was made using the 2010 criteria of the American Diabetes Association of fasting glucose ≥126 mg/dL, glycated hemoglobin (HbA_{1c}) ≥6.5% or ≥48 mmol/mol, and/or post-challenge glucose (glucose at 2 h after a 75-g oral glucose load) ≥200 mg/dL (13). A more detailed description of this study population is presented in our recent articles (14,15). No corporation was involved in the design, performance, or analysis of the study. This prospective observational study was approved by the institutional review board of our institution and performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (16). All patients provided written informed consent.

Scanning Protocol and Image Reconstruction

CCTA was performed using either a 64-slice multidetector computed tomography (MDCT) scanner (Light Speed VCT 64; GE Healthcare, Milwaukee, WI) or a dual-source computed tomography (DSCT) scanner (Somatom Definition; Siemens Healthcare, Forchheim, Germany). For the 64-slice MDCT scanning protocol, we used a slice collimation of 64 × 0.625 mm, a gantry rotation time of 350 ms, a pitch of 0.2, a tube voltage of 100–120 kV (depending on the patient's BMI), and a tube current of 600 mA. For the DSCT scan protocol, slice collimation was performed at 2 × 32 × 0.6 mm using a *z*-flying focal spot, a gantry rotation time of 330 ms, a pitch of 0.2–0.5, a tube voltage of 100–120 kVp (depending on the patient's BMI), and a reference tube current of 320 mA with an electrocardiogram-controlled tube current modulation. In each patient, 80 mL of the iodinated contrast agent iopromide (Ultravist 370; Schering AG, Berlin, Germany) or iomeprol (Iomeron 350; Bracco, Milano, Italy) was injected at a flow rate of 5 mL/s along with 50 mL of contrast mixture (15% contrast medium and 85% saline solution) at the same rate, which was controlled by bolus tracking in the ascending aorta (signal attenuation threshold 120 Hounsfield units [HU]). The scan delay was 7 s. In the absence of contraindications, each patient with a heart rate >80 bpm received an intravenous β-blocker, indenol or esmolol (Jeil Brevibloc; Jeil Pharma Co., Ltd., Seoul, Republic of Korea), 1 h before the scan, and a 0.3 mg sublingual dose of nitroglycerin was administered immediately before the scan. The estimated radiation dose ranged from 5 to 14 mSv. Images were reconstructed immediately after completing the scan and transferred to a computer workstation (MDCT: advantage Windows 4.3; GE Healthcare; DSCT: Syngo Multimodality Workplace, version 2008; Siemens Healthcare) for postprocessing, including axial and multiplanar reformatting, maximum intensity projection, and short-axis and cross-sectional views.

CCTA Analysis

All scans were analyzed by two radiologists with experience in interpreting several thousand CCTA scans. In accordance with the guidelines of the Society of Cardiovascular Computed Tomography, coronary

segments were visually scored for the presence of coronary plaques using a 16-segment coronary artery model in an intent-to-diagnose manner (17). Segments were included in the analysis if the diameter was >1.5 mm. The severity of luminal diameter stenosis was scored as none (0% luminal stenosis), nonobstructive (plaques with a lumen narrowing <50%), obstructive (plaques with maximum stenosis ≥50%), or significantly obstructive (plaques with maximum stenosis ≥70%). CAD was diagnosed based on the maximum intraluminal stenosis in any of the segments of the major epicardial coronary arteries at the ≥50% stenosis threshold. Obstructive CAD in the branches of arteries was considered as corresponding to the major epicardial coronary arteries. The number of diseased vessels was assigned as one, two, three, or left main (LM) coronary artery vessels. The extent and severity of the CAD burden were measured using several CCTA scores (18,19). The CACS, atheroma burden obstructive score (ABOS), segment involvement score (SIS), and segment stenosis score (SSS) were included. CACS was assessed using dedicated software (Smartscore version 3.5; GE Healthcare; or Aquarius 3DWorkstation; TeraRecon, San Mateo, CA). Coronary artery calcium levels were identified as the density exceeding the threshold of 130 HU (20). An overall Agatston score was recorded for each patient. The ABOS was defined as the number of plaques with >50% stenosis in the entire coronary artery tree. The SIS was calculated as the total number of coronary artery segments that exhibited plaques, regardless of the degree of luminal stenosis within each segment (minimum one-quarter 0; maximum, one-quarter 16). The SSS was used to measure the overall extent of coronary artery plaques. Each individual coronary segment was graded as having no to severe plaques (i.e., scores from 0 to 3) based on the extent of obstruction of the luminal diameter of the coronary artery. The extent scores of all 16 individual segments were summed to yield a total score that could range from 0 to 48 (19). Plaques without any calcium were defined as noncalcified plaques (NCPs), and others were defined as mixed or calcified plaque (CPs), depending on consistency (using attenuation grade, i.e., mixed plaque ≤130 HU or CP >130 HU with an area ≥1.0 mm^2, respectively) (20,21).

Study End Point and Follow-up

The primary end point was a composite of all-cause mortality, nonfatal MI, and late coronary revascularization (≥90 days). Late coronary revascularization was considered to be ischemia driven if the diameter of the stenotic lesion was ≥50%, according to a quantitative analysis of the electrocardiographic changes observed at rest or a positive functional study in the distribution of the target lesion, or ≥70% with recurrent symptoms at ≥90 days after stent implantation. All clinical outcomes of interest were confirmed by source documents and were centrally adjudicated by a clinical events committee at the Cardiovascular Center of Seoul St. Mary's Hospital, which consisted of an independent group of clinicians whose members were unaware of the patient's status. Information related to censored survival data (death or survival) and cause of death (cardiac or noncardiac death) was obtained from the Korean Office of Statistics with a unique personal identification number to validate the complete follow-up data.

Statistical Analysis

Baseline and biochemical characteristics were summarized as the means ± SD for continuous variables and as absolute numbers and percentages for discrete variables. Differences in continuous variables between groups were evaluated using unpaired *t* tests or Mann-Whitney rank sum tests. Differences in discrete variables between groups were analyzed using χ^2 or Fisher exact tests. Cumulative event rates of CACS, CCTA-diagnosed obstructive CAD, ABOS, SIS, and SSS were calculated using a Kaplan-Meier estimator and compared using the log-rank statistic. A Cox proportional hazards model was used to calculate hazard ratios (HRs) with 95% CIs to describe the relationships between the various measures of CCTA-diagnosed CAD and composites of MACEs, including all-cause mortality, nonfatal MI, and late revascularization. Each measure of CCTA-diagnosed CAD was adjusted for age, male sex, hypertension, hyperlipidemia, smoking, eGFR, and HbA_{1c} and were analyzed using SPSS 20.0 (SPSS-PC Inc., Chicago, IL). Statistical significance was accepted at $P < 0.05$ using a two-tailed test.

The discriminative ability of the models was assessed using Harrell's c-index, which is analogous to the area under the receiver operator characteristic curve and was applied to composite MACE data The IDI was used to express the absolute improvement in the mean discrimination slope and the probability of discrimination between the base model (model A) and the new models (models B to G), whereas the relative IDI illustrated the difference in the separation of MACEs and nonevents over the separation in the base model. We selected the conventional risk model based on the risk factors included in the 10-year atherosclerotic cardiovascular disease risk algorithm, which was published in the 2013 American College of Cardiology/American Heart Association guidelines and referenced in the Framingham study (22–24). The risk factors were matched with the variables adjusted in the Cox regression model. Larger positive IDI and relative IDI values indicate greater improvements in model discrimination. Improvements in subject risk reclassification were further assessed using NRI and were applied to the MACE data. We computed the two versions of the NRI: a category-based and a category-free NRI. The category-based NRI followed typical categories used for determining MACE risk (determined after 1 year as <5%, 5% to <10%, and ≥20%). We used χ^2 values and model Akaike information criterion (AIC) values as the parameters of model fit. The χ^2 test, AIC, c-index, IDI, and NRI were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Baseline characteristics, laboratory findings, and medication information are listed in Table 1. The mean age of the included patients was 63.4 ± 9.6 years, and the mean T2DM duration was 11.7 ± 9.3 years. The mean initial HbA_{1c} level was 8.0 ± 1.9% (63.7 ± 21.1 mmol/mol). Our study population exhibited several comorbidities at baseline such as arterial hypertension, the presence of microalbuminuria, and T2DM retinopathy. Five hundred seven of 933 patients (54.3%) had arterial hypertension, 66 of 284 patients (23.24%) had microalbuminuria, and 217 of 433 patients (50.12%) had T2DMretinopathy. Although 55.6% of the patients were prescribed statins at

Table 1—Baseline characteristics

Variable	Total population (*N* = 933)	No event (*n* = 839)	Event (*n* = 94)	*P* value
Age, years	63.4 ± 9.6	63.0 ± 9.6	66.6 ± 9.8	0.001
Male sex	556 (59.6)	496 (59.1)	60 (63.8)	0.378
BMI, kg/m^2	24.4 ± 3.2	24.4 ± 3.2	23.9 ± 3.1	0.173
Waist-to-hip ratio	0.94 ± 0.07	0.94 ± 0.07	0.96 ± 0.07	0.151
Duration of T2DM, years	11.7 ± 9.3	11.4 ± 9.0	14.8 ± 10.7	0.004
Hypertension	507 (54.3)	450 (53.7)	56 (60.6)	0.416
Duration of HTN, years	9.9 ± 8.4	10.0 ± 8.3	9.6 ± 8.9	0.775
Smoker	271 (29.0)	233 (27.8)	38 (40.4)	0.046
Current smoker	139 (14.9)	117 (13.9)	22 (23.4)	0.042
Dyslipidemia	561 (60.1)	502 (59.8)	59 (62.8)	0.582
Hemoglobin, mg/dL	13.5 ± 1.7	13.6 ± 1.6	13.0 ± 1.9	0.005
Glucose, mg/dL	149.0 ± 56.3	147.8 ± 55.1	160.8 ± 66.0	0.035
2 h postprandial, mg/dL	211.9 ± 79.8	207.2 ± 75.9	250.2 ± 98.7	<0.001
HbA_{1c}, %	8.0 ± 1.9	7.9 ± 1.9	8.6 ± 2.1	0.001
HbA_{1c}, mmol/mol	63.7 ± 21.1	62.9 ± 20.7	70.9 ± 23.0	<0.001
Cr, mg/dL	0.89 ± 0.20	0.88 ± 0.20	0.95 ± 0.22	0.002
MDRD eGFR, mL/min/1.73 m^2	86.2 ± 20.1	86.9 ± 19.8	80.4 ± 21.8	0.003
Total cholesterol, mg/dL	169.1 ± 38.0	169.5 ± 37.5	165.9 ± 41.9	0.392
Triglyceride, mg/dL	137.6 ± 65.3	137.8 ± 95.2	136.2 ± 96.4	0.875
HDL-C, mg/dL	47.5 ± 11.9	47.6 ± 11.9	47.2 ± 12.2	0.875
LDL-C, mg/dL	96.6 ± 33.3	97.1 ± 33.2	92.4 ± 34.5	0.753
hsCRP, mg/L	0.84 ± 3.01	0.89 ± 3.16	0.52 ± 1.60	0.428
MAU, mg/day	123.0 ± 552.2	98.8 ± 333.9	338.5 ± 1417.9	0.234
T2DM management				
Lifestyle modification	98 (10.5)	90 (10.8)	8 (8.6)	0.515
Oral hypoglycemic agent	619 (66.8)	573 (68.7)	46 (49.5)	<0.001
Insulin	63 (6.8)	48 (5.8)	15 (16.1)	<0.001
OHA plus insulin	147 (15.9)	123 (14.7)	24 (25.8)	0.006
Aspirin	402 (43.1)	361 (46.0)	41 (48.8)	0.622
Statin	519 (55.6)	465 (55.4)	54 (57.4)	0.708
β-Blocker	108 (11.6)	96 (11.4)	12 (12.8)	0.704
ACEi/ARB	446 (47.8)	398 (47.4)	48 (51.1)	0.504
CCB	228 (24.4)	196 (23.4)	32 (34.0)	0.022
Diuretics	208 (22.3)	189 (22.5)	19 (20.2)	0.609
Framingham risk scores	8.87 ± 6.52	8.59 ± 6.43	11.16 ± 6.84	0.002

Data are presented as the mean ± SD or *n* (%) as appropriate, unless otherwise indicated. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HDL-C, HDL cholesterol; HTN, hypertension; LDL-C, LDL cholesterol; MAU, microalbuminuria; MDRD, modification of diet in renal disease; OHA, oral hypoglycemic agent. Smokers included current smokers and ex-smokers. HbA_{1c} levels are reported in Diabetes Control and Complications Trial (DCCT)–derived units (as %) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)–recommended units (as mmol/mol).

the time of study enrollment, the mean lipid profile was within the normal range. During a mean follow-up period of 5.5 ± 2.1 years, 94 MACEs occurred. Patients with MACEs were older and had longer T2DM durations; they were more likely to be smokers and to have anemia, hyperglycemia, higher HbA_{1c} levels, decreased eGFR, and a history of insulin treatment.

Primary Outcomes

Among 94 MACEs (10.1%), the number of patients who died of any cause, experienced nonfatal MI, or needed late coronary revascularization were 45 (4.8%), 5 (0.9%), and 49 (5.3%), respectively (Supplementary Table 1). According to CCTA, 40% (*N* = 374) of the study population had coronary artery obstruction of ≥50% and 11% (*N* = 45) had a significant obstruction lesion of ≥70%. Of the patients with normal CCTA findings (20.7%), there was only one cardiac death and no cases of nonfatal MI. In contrast, 63.8% of MACEs occurred in patients with obstructive CAD detected using CCTA.

CCTA Findings and MACE

The CCTA findings are shown in Table 2. Among patients with adverse events, 12.8% had a normal coronary artery, 23.4% had nonobstructive CAD (<50%), 63.8% had obstructive CAD (≥50%), and 24.5% had ≥70% significant obstructive CAD. Normal or nonobstructive CAD seen on CCTA was not associated with an increased risk of MACEs. On the other hand, obstructive CAD with three-vessel disease (3VD) or LM disease significantly contributed to the occurrence of MACEs ($P < 0.001$), whereas patients with obstructive one-vessel disease (1VD) or two-vessel disease (2VD) were similarly distributed between the event group and the nonevent group. Patients with MACEs were more likely to have higher ABOSs, SISs, SSSs ($P < 0.001$ for all), and CACSs ($P = 0.012$).

Table 2—CCTA findings and calcium scores

Variable	Total population (*N* = 933)	No event (*N* = 839)	Event (*N* = 94)	*P* value
Normal CCTA findings	194 (20.7)	182 (21.7)	12 (12.8)	<0.001
Nonobstructive CAD (<50%)	365 (39.1)	343 (40.9)	22 (23.4)	<0.001
Obstructive CAD (≥50%)	374 (40.1)	314 (37.4)	60 (63.8)	<0.001
1VD	184 (19.7)	159 (19.0)	25 (26.6)	0.077
2VD	100 (10.7)	89 (10.6)	11 (11.7)	0.745
3VD or LM disease	90 (9.6)	66 (7.9)	24 (25.5)	<0.001
Significant obstructive CAD (≥70%)	106 (11.4)	83 (10.0)	23 (24.5)	<0.001
1VD	54 (5.8)	43 (5.1)	11 (11.7)	0.010
2VD	26 (2.8)	21 (2.5)	5 (5.3)	0.116
3VD or LM disease	26 (2.8)	19 (2.3)	7 (7.4)	0.004
ABOS (50%)	1.08 ± 1.83	0.98 ± 1.75	1.96 ± 2.26	<0.001
Segment involve score	2.22 ± 2.59	2.08 ± 2.5	3.43 ± 3.03	<0.001
SIS	3.62 ± 4.80	3.35 ± 4.59	6.11 ± 5.85	<0.001
CACS (Agatston)	266.8 ± 530.0	249.0 ± 513.0	433.6 ± 648.5	0.012
Calcium score = 0	231 (24.8)	220 (27.3)	11 (12.8)	0.004
0 < Calcium score ≤100	301 (32.3)	276 (34.2)	25 (29.1)	0.335
100 < Calcium score ≤400	194 (20.8)	170 (21.1)	24 (27.9)	0.145
Calcium score >400	166 (17.8)	140 (17.4)	26 (30.2)	0.004

Values are presented as the mean ± SD or *n* (%), unless otherwise indicated. Obstructive CAD is defined as ≥50% maximal diameter stenosis, significant obstructive CAD is defined as ≥70% maximal diameter stenosis.

CACS and Plaque Distribution

The mean CACS in the study population was 266.8 ± 530. The mean CACS of patients with MACEs was 433.6 ± 648.5 (Table 2). The CACSs and plaque distributions are presented in Supplementary Table 2. A total of 231 (24.8%), 301 (32.3%), 194 (20.8%), and 166 (17.8%) patients had CACSs of 0, 0–100, 100–400, and >400, respectively. Contrary to our expectations, 12.8% of MACEs occurred in patients with a CACS of 0. Even among patients with a CACS ≤100, 110 (11.9%) were found to have obstructive CAD on CCTA. CPs, NCPs, and mixed plaques were detected in 425 (35.7%), 389 (32.6%), and 378 (31.7%) patients, respectively. Among patients with NCPs, 53.2% were also found to have obstruction of >50% on CCTA.

Kaplan-Meier Curves

As noted in the Kaplan-Meier curves, patients with obstructive CAD had a significantly higher cumulative incidence of MACE than the normal and nonobstructed groups during a median follow-up period of 5.5 ± 2.1 years ($P < 0.0001$) (Supplementary Fig. 2A). Significant obstructive CAD was also associated with an 11-fold increase in the risk of composite MACEs in these patients ($P < 0.0001$). Furthermore, a higher CACS was associated with a gradual increase in the incidence of MACE ($P < 0.0001$) (Supplementary Fig. 2B). Among patients with low calcium scores (CACS ≤100), obstructive CAD seen on CCTA was associated with a significantly increased risk of the development of composite MACEs (21 [5%] vs. 15 [13.6%]; $P < 0.001$, log-rank test]). Patients with mixed plaques displayed a significantly worse survival rate than patients without plaques and patients with CPs or NCPs (Supplementary Fig. 2*C*) ($P < 0.001$, $P < 0.001$, and $P = 0.022$, respectively). Significant differences in event-free survival were not observed between patients with CPs and NCPs ($P = 0.63$). Supplementary Fig. 2*D* shows a positive relationship between the number of vessels with obstructive CAD and the risk of adverse events (all $P < 0.001$ compared with the reference). Significantly higher event rates were observed in patients with 3VD or LM disease compared with patients with 1VD or 2VD ($P < 0.001$ vs. 1VD, $P = 0.011$ vs. 2VD).

Risk Prediction

In the univariate Cox analysis, factors related to a greater risk of the primary

Table 3—Independent predictors of the primary outcome

	Outcome: All death + MI + late coronary revascularization			
CCTA findings and CACS	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Obstructive CAD (≥50%)	4.45 (2.92–6.78)	<0.0001	3.83 (2.45–5.98)	<0.0001
Significant obstructive CAD (≥70%)	11.33 (7.45–17.24)	<0.0001	8.49 (5.37–13.40)	<0.0001
ABOS (≥3)	6.07 (3.69–9.99)	<0.0001	5.07 (2.97–8.65)	<0.0001
SIS (≥4)	3.94 (2.47–6.30)	<0.0001	2.99 (1.82–4.92)	<0.0001
SSS (≥6)	5.43 (3.44–8.58)	<0.0001	4.52 (2.77–7.37)	<0.0001
CACS	1.28 (1.16–1.40)	<0.0001	1.21 (1.09–1.34)	0.0002

Multivariable Cox proportional hazard analysis: each variable of CCTA-diagnosed CAD was adjusted for age, sex, hypertension, hyperlipidemia, smoking, eGFR, and HbA_{1c}. Obstructive CAD is defined as ≥50% maximal diameter stenosis; significant obstructive CAD is defined as ≥70% maximal diameter stenosis; hyperlipidemia is defined as LDL ≥160 mg/dL.

outcome were old age, and had high HbA_{1c} levels, a long T2DM duration, a history of insulin treatment, anemia, and low eGFR (Supplementary Table 3). Male sex and the presence of hypertension and hyperlipidemia showed a trend of increased HRs. More obstructive CAD; significant obstructive CAD; higher ABOSs, SISs, and SSSs on CCTA; and higher CACSs were identified as significant predictors of MACEs (Table 3). The unadjusted HRs (95% CIs) in these patients were 4.45, 11.33, 6.07, 3.94, 5.43, and 1.28 (all $P <$ 0.001), respectively. After adjusting for variables such as age, male sex, hypertension, hyperlipidemia, smoking, eGFR, HbA_{1c}, CACS, and CCTA findings, the multivariate Cox proportional hazard analysis revealed that obstructive CAD, CACS, ABOS, SIS, SSS, and CACS were associated with increased occurrences of MACEs during the 5-year follow-up period. The individually adjusted HRs for each of these factors were 3.83, 8.49, 5.07, 2.99, 4.52, and 1.21, respectively ($P < 0.001$ for all). Coronary obstruction >70% was associated with the largest increase in the risk of developing composite MACE.

Discrimination and Reclassification

Table 4 shows the incremental value of CCTA findings over conventional risk factors using conventional parameters of model fit (χ^2 value and model AIC value) and model global performance (changes in C-statistic, IDI, and continuous NRI). Model A was the baseline, which consisted of conventional CAD risk factors such as age, male sex, hypertension, hyperlipidemia, smoking, eGFR, and HbA_{1c} (C-index = 0.716). The addition of obstructive CAD ≥50% (model B) significantly improved the predictive accuracy for discrimination (C-index 0.788 [95% CI 0.747–0.829]), IDI 0.046 (95% CI 0.020–0.072); $P = 0.0349$ and $P = 0.0006$, respectively. Moreover, model B was significantly better at predicting the probability of reclassification (NRI 0.550 [95% CI 0.343–0.757]; $P < 0.0001$). The inclusion of obstructive CAD ≥70% and ABOS also significantly improved the discrimination and reclassification power of the model (C-index 0.805 and 0.792, $P = 0.0146$ and 0.0258, respectively). However, adding the SIS, SSS, and CACS to risk model A did not improve its predictive value. Models E, F, and G had C-indexes of 0.756, 0.782, and 0.740, respectively (all $P > 0.05$). The inclusion of insulin treatment, the duration of diabetes, or hemoglobin level did not change the results in the multivariable Cox regression and discrimination models.

CONCLUSIONS

In this study, the addition of CCTA-diagnosed obstructive CAD resulted in a significantly higher predictive power for MACEs in asymptomatic patients with T2DM than the use of traditional risk factors alone during a long-term follow-up period of 5.5 years. The CACS failed to improve either the discrimination or reclassification power. Asymptomatic patients with T2DM and a greater coronary atherosclerotic burden on CCTA had a higher risk of MACEs, and patients with MACEs were more likely to have obstructive CAD and higher ABOSs, SISs, SSSs, and CACSs.

Current guidelines from the American Diabetes Association (25) state that routine screening of asymptomatic patients with T2DM is not recommended even for those with a high atherosclerotic cardiovascular risk, since CCTA screening did not significantly reduce composite MACEs in asymptomatic patients with T2DM in the recent FACTOR-64 study (6). However, the FACTOR-64 study was not adequately powered, with a lower event rate (7.6%) than expected (16%), and the study population was exclusively Caucasian (6). Hence, the efficacy of routine CCTA screening in the actual high-risk asymptomatic T2DM population remains unclear. According to some studies, CCTA could be used more effectively in asymptomatic individuals with a higher risk of cardiac events, such as asymptomatic patients with a long T2DM duration or T2DM with microalbuminuria (6,14,15,26). Our study population showed high-risk characteristics, including a mean T2DM duration of 11.7 ± 9.3 years, a mean HbA_{1c} level of 8.0 ± 1.9% (63.7 ± 21.1 mmol/mol), and the presence of several comorbidities such as arterial hypertension (54.3%), microalbuminuria (23.24%), and T2DM retinopathy (50.12%). Over half (59.1%) of patients with microalbuminuria and 34.1% of patients with T2DM retinopathy had obstructive CAD seen on CCTA. Although these patients were initially asymptomatic, they had a 10.1% incidence of MACE during the 5.5-year follow-up period. A majority of the included patients (79%) had silent atherosclerotic lesions (both nonobstructive

Table 4—Effects of variables on the prediction accuracy and risk reclassification of each model (comparison of model A with other model)

Model	Included variables	C-index (95% CI)	*P* value	IDI (95% CI)	*P* value	NRI continuous (95% CI)	*P* value	AIC	χ^2 value
A	Age, male sex, HTN, smokers, hyperlipidemia, eGFR, and HbA_{1c}*	0.716 (0.769–0.664)						1,124.747	44.9206
B	Model A + obstructive CAD (≥50%)	0.788 (0.829–0.747)	0.0349	0.046 (0.020–0.072)	0.0006	0.550 (0.343–0.757)	<0.0001	1,089.99	78.1499
C	Model A + obstructive CAD (≥70%)	0.805 (0.853–0.757)	0.0146	0.139 (0.084–0.195)	<0.0001	0.438 (0.229–0.646)	<0.0001	1,058.749	144.1073
D	Model A + ABOS	0.792 (0.833–0.751)	0.0258	0.053 (0.023–0.082)	0.0005	0.548 (0.341–0.755)	<0.0001	1,089.014	84.5118
E	Model A + SIS	0.756 (0.801–0.711)	0.2639	0.021 (−0.001 to 0.043)	0.0587	0.348 (0.137–0.559)	0.0016	1,109.905	1,151.409
F	Model A + SSS	0.782 (0.826–0.738)	0.0599	0.051 (0.019–0.084)	0.0019	0.318 (0.103–0.534)	0.004	1,093.015	83.3443
G	Model A + CACS, log transformed	0.740 (0.795–0.684)	0.5468	0.020 (0.003–0.038)	0.022	0.304 (0.080–0.527)	0.0085	1,012.355	53.9371

*Hyperlipidemia is defined as LDL concentration ≥160 mg/dL; smokers, current and ex-smokers vs. nonsmokers vs. unknown (missing).

and obstructive) at baseline. Obstructive CAD was found in 40.1% of the patients, and significant obstructive CAD was found in 11.4% of the patients on CCTA, with 9.6% of patients having 3VD and 2.8% having LM disease, which were associated with poor prognostic outcomes. The long-term prognosis for patients with normal CCTA findings was favorable: only one cardiac death and no cases of nonfatal MI occurred. The high-risk features of asymptomatic individuals with T2DM and the longer follow-up period used in our study may have contributed to the usefulness of CCTA as a tool for predicting risk beyond the use of traditional risk factors alone, even after adjusting for a number of conventional CAD risk factors, including age, male sex, hypertension, hyperlipidemia, smoking, eGFR, and HbA_{1c}. Prior studies (27,28) have focused on the use of CACS for predicting risk in asymptomatic patients with T2DM. According to a recent study (29) of 10,377 patients who were evaluated with CACS, patients with T2DM displayed a significantly higher risk of mortality than patients without T2DM across all CACS groups, including the 0 category of CACS. Some studies (29,30) have demonstrated that almost 40% of diabetes patients had a CACS of 0 in their coronary arteries. In this cohort of asymptomatic T2DM patients, 12.8% of MACEs occurred in patients in the 0 CACS category (Table 2). Based on these data, CACS alone is not sufficient for properly assessing risk and specifying lesions and vessels. Asymptomatic patients with T2DM, even patients without coronary calcification, should still be assessed with other risk prediction tools since calcification is only one component of coronary plaques. CCTA can be used to detect large calcifications and CPs as well as NCPs and spotty calcification. Recently, plaques with an NCP of $<$30 HU and spotty calcification were found to have a high positive predictive value for the development of an acute coronary syndrome occurrence (31). In our study, 32.6% of the plaques were detected as NCPs, which is consistent with recent findings from studies evaluating asymptomatic patients with T2DM using CCTA (32).

Limitations

This study has several limitations. First, patients were recruited from only two centers and the sample size was moderate. We have not validated our findings in different study populations. Second, the therapeutic plans regarding the coronary angiograms and/or percutaneous coronary interventions and medications after CCTA were not standardized to a specific protocol. Patients were treated at the discretion of each diabetologist and cardiologist in charge. Third, our asymptomatic T2DM population included patients with high-risk features such as the presence of microalbuminuria, T2DM retinopathy, a long T2DM duration of $>$10 years, and other comorbidities, which may have contributed to the comparatively higher number of MACEs. Therefore, our findings on the ability of CCTA to predict risk cannot be generalized to all asymptomatic patients with T2DM. Further studies are needed to investigate the role of screening for CAD in specific subgroups of asymptomatic patients with T2DM.

Conclusions

In our study, asymptomatic patients with T2DM had a median T2DM duration of 11 years, a mean HbA_{1c} level of 8.0 $\pm$ 1.9% (63.7 $\pm$ 21.1 mmol/mol), and a 10.1% incidence of MACEs. CCTA measurements of CAD prevalence, extent, and severity independently and incrementally predicted the occurrence of MACEs in patients with T2DM without angina. In a subsequent discrimination and reclassification analysis, the addition of obstructive CAD detected using CCTA provided a significant increase in prognostic value compared with conventional risk factors alone, whereas the addition of CACS did not.

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