

Risk Score Model for the Assessment of Coronary Artery Disease in Asymptomatic Patients With Type 2 Diabetes

Gyung-Min Park, MD, Hyonggin An, PhD, Seung-Whan Lee, MD, Young-Rak Cho, MD, Eun Ha Gil, MS, Sung Ho Her, MD, Young-Hak Kim, MD, Cheol Whan Lee, MD, Eun Hee Koh, MD, Woo Je Lee, MD, Min-Seon Kim, MD, Ki-Up Lee, MD, Joon-Won Kang, MD, Tae-Hwan Lim, MD, Seong-Wook Park, MD, Seung-Jung Park, MD, and Joong-Yeol Park, MD

Abstract: No model has been developed to predict significant coronary artery disease (CAD) on coronary computed tomographic angiography (CCTA) in asymptomatic type 2 diabetes. Therefore, we sought to develop a model for the prediction of significant CAD on CCTA in these patients.

We analyzed 607 asymptomatic patients with type 2 diabetes who underwent CCTA. The cardiac event was defined as a composite of cardiac death, nonfatal myocardial infarction, acute coronary syndrome, and coronary revascularization.

Significant CAD (diameter stenosis $\geq 50\%$) in at least one coronary artery on CCTA was observed in 188 (31.0%). During the follow-up period (median 4.3 [interquartile range, 3.7–4.8] years), 71 patients had 83 cardiac events. Clinical risk factors for significant CAD were age, male gender, duration of diabetes, hypertension, current smoking, family history of premature CAD, previous history of stroke, ratio of total cholesterol to high-density lipoprotein cholesterol, and neuropathy. Using these variables, we formulated a risk score model, and the scores ranged from 0 to 17 (area under the curve = 0.727, 95% confidence interval = 0.714–0.739, $P < 0.001$). Patients were categorized into low (≤ 3), intermediate (4–6), or high (≥ 7) risk group. There were significant differences between the risk groups in the probability of significant CAD (12.6% vs 29.4% vs 57.7%, P for all < 0.001) and 5-year cardiac event-free survival rate (96.6% \pm 1.5% vs 88.9% \pm 1.8% vs 73.8% \pm 4.1%, log-rank P for trend < 0.001).

This model predicts significant CAD on CCTA and has the potential to identify asymptomatic type 2 diabetes with high risk.

(*Medicine* 94(4):e508)

Editor: Xiwen Cheng.

Received: September 23, 2014; revised: November 19, 2014; accepted: January 6, 2015.

From the Department of Cardiology (G-MP, EH, SHH), Daejeon St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Daejeon; Department of Biostatistics (HA), College of Medicine, Korea University; Departments of Cardiology (S-WL, Y-HK, CWL, S-WP, S-JP); Endocrinology (EHK, WJL, M-SK, K-UL, J-YP); Radiology (J-WK, T-HL), Asan Medical Center, College of Medicine, University of Ulsan, Seoul; and Department of Cardiology (Y-RC), Dong-A University hospital, Busan, Korea.

Correspondence: Seung-Whan Lee, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Cardiac Center, 388-1 Poongnap-dong, Songpa-gu, Seoul, 138-736, Korea (e-mail: seungwlee@amc.seoul.kr).

G-MP and HA equally contributed to this article.

The authors have no funding and conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000508

Abbreviations: CAD = coronary artery disease, CCTA = coronary computed tomographic angiography, CI = confidence interval, DIAD = the Detection of Ischemia in Asymptomatic Diabetics study, UKPDS = the UK Prospective Diabetes Study.

INTRODUCTION

Over the past decades, the prevalence of diabetes has increased rapidly and diabetes has become a major public health concern.¹ Furthermore, diabetes is associated with a higher prevalence of coronary artery disease (CAD),² with CAD being the leading cause of morbidity and mortality in patients with type 2 diabetes.³ Coronary computed tomography angiography (CCTA) is a noninvasive imaging test that provides not only comprehensive information regarding CAD but also high diagnostic performance for the detection and exclusion of CAD.⁴ Previous studies, including a large international cohort study, showed that diabetic patients had a higher CAD burden as determined by CCTA, and CCTA had prognostic value in these patients.^{5–7} Prior observational studies using CCTA in asymptomatic patients with type 2 diabetes also found that the prevalence of CAD was not negligible.^{8–11} The current standards of medical care in asymptomatic patients with type 2 diabetes emphasize the need for the reduction of cardiovascular risk factors.¹² However, tailored approaches, following risk stratification based on the presence of CAD, may have an additional role in these patients. Therefore, we sought to develop a CAD risk score model using clinical parameters in a large cohort of asymptomatic patients with type 2 diabetes who underwent CCTA evaluation.

METHODS

Study Population

Between February 2008 and June 2012, 607 asymptomatic patients with type 2 diabetes, who had undergone CCTA evaluation in diabetes center at the Asan Medical Center, were prospectively enrolled.¹¹ Diabetic mellitus was defined as a fasting plasma glucose concentration ≥ 126 mg/dL or self-reported history of diabetes and/or treatment with dietary modification, oral hypoglycemic agents, or insulin. Exclusion criteria were abnormal resting electrocardiographic results, that is, pathological Q waves, ischemic ST segment or T wave changes, or left bundle-branch block; exertional dyspnea, angina pectoris, or chest discomfort evaluated with a positive Rose questionnaire¹³; renal insufficiency (creatinine ≥ 1.5 mg/dL); history of open heart surgery; history of myocardial infarction, coronary revascularization, or heart failure; uncontrolled arrhythmia; history of allergy to contrast dye; pregnancy or women of childbearing age who were not using

contraceptives. This study was approved by the local Institutional Review Board at the Asan Medical Center, Seoul, Korea. All patients provided written informed consent.

Basic demographic data were obtained by a review of patients' medical records. Any medical history of hypertension, stroke, or peripheral artery disease; family history of premature CAD; duration of type 2 diabetes; current medication profiles; and smoking status were documented. Body weight, height, body mass index, and blood pressure were also measured. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting plasma glucose, glycated hemoglobin, serum creatinine, and C-peptide values were measured after at least a 12-hour fasting period during their visit. Hypertension was defined as a self-reported history of hypertension and/or use of antihypertensive medication or a blood pressure $\geq 140/90$ mm Hg. Hyperlipidemia was defined as total cholesterol >200 mg/dL or receiving antihyperlipidemic treatment. Neuropathy was defined as a just noticeable difference >15 in the hands or >20 in the feet according to a vibration sensory threshold test.¹⁴ Retinopathy was evaluated by fundoscopic examination. Nephropathy was defined as >20 $\mu\text{g}/\text{min}$ of albuminuria. Nonfatal CAD 10-year risk score was calculated by the UK Prospective Diabetes Study (UKPDS) risk engine.¹⁵

CCTA Image Acquisition and Analysis

Multidetector computed tomographic angiography was performed using a dual source scanner (Somatom Definition, Siemens, Germany), with the following acquisition parameters: tube voltage, 80 to 120 kVp based on the body habitus of the patient; tube current, 240 to 400 mAs per rotation depending on the body habitus of the patient; detector collimation, 0.6 mm; adaptive pitch value of 0.2 to 0.5 based on the patient's heart rate; retrospective electrocardiogram gating and pulsing. We used contrast media of 400 mg/mL iodine concentration (Iomeron 400, Bracco, Italy) in the amount of 55 to 80 mL at a rate of 4 mL/s followed by a saline chaser. The CT scan range was from the carina to the diaphragm. We used 0.3 mg of nitroglycerin sublingually or an oral spray 2 minutes before CT. β -Blocker (bisoprolol 2.5 mg) was administered orally for lowering heart rate when the patient's heart rate exceeded 90 beats per minute. Optimal phase reconstruction was selected manually or using automated software (Bestphase, Siemens, Germany).

All CCTA scans were analyzed using a dedicated workstation (Volume Wizard, Siemens) by two cardiovascular radiologists (T.-H.L. and J.-W.K.). According to the guidelines of the Society of Cardiovascular Computed Tomography, a 16-segment coronary artery tree model was used.¹⁶ A coronary artery calcium score was measured as described, with patients categorized by scores of 0, 1 to 10, 11 to 100, 101 to 400, and >400 .¹⁷ Plaques were defined as structures >1 mm² within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques occupied by calcified tissue $>50\%$ of the plaque area (density >130 Hounsfield unit in native scans) were classified as calcified, plaques with $<50\%$ calcium were classified as mixed, and plaques without any calcium were classified as noncalcified lesions.¹⁸ The contrast-enhanced portion of the coronary lumen was traced at the maximally stenotic site and compared with the mean value of the proximal and distal reference sites. Diameter stenosis $\geq 50\%$ was defined as significant. In addition, overall plaque burden was determined based on coronary artery plaque scores using modified Duke

prognostic scores, segment stenosis scores, and segment involvement scores, as previously described.¹⁹

Clinical Outcomes

Follow-up clinical data were obtained by a review of medical records or telephone interviews using trained personnel through to the end of July 2013. The cardiac event was defined as a composite of cardiac death, nonfatal myocardial infarction, acute coronary syndrome requiring hospitalization, and coronary revascularization, while cardiac death, nonfatal myocardial infarction, and acute coronary syndrome requiring hospitalization were classified as major cardiac events.⁶ Death was considered to be cardiac in etiology unless an unequivocal noncardiac cause was established. The diagnosis of myocardial infarction was based on the presence of new Q waves in at least two contiguous leads or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of the normal range at follow-up. Revascularization was performed if there was a stenosis of at least 50% of the diameter with a positive stress test or if there was a stenosis of at least 70%.²⁰

Statistical Analysis

Continuous variables were compared with the one-way analysis of variance or nonparametric Kruskal–Wallis test, and categorical variables were compared with the χ^2 statistics or Fisher exact test, as appropriate. A logistic regression model was developed to predict significant CAD on CCTA using a bootstrap method. The first step of the model development was to evaluate bivariate relationship between patient characteristics and significant CAD on CCTA (Table 1). Risk factors that significantly ($P < 0.3$) correlated with significant CAD were chosen as candidate variables and used to develop the logistic regression. Next, the predictive value of univariate findings was subsequently tested with a bootstrap resampling procedure in which the logistic regression model with a backward elimination procedure was repeated for each of the 1000 bootstrap resamplings. The relative frequency of selection of the bootstrap resampling of 50% was used as a criterion for inclusion of predictors in the final logistic model.²¹ To evaluate the fit of the final logistic model, the C-statistic ($= 0.747$) was used to measure discrimination and the Hosmer–Lemeshow test (P value $= 0.988$) was used to measure calibration.^{22,23} In addition, to investigate overfitting of the final model, the slope of linear predictor (shrinkage) was computed (shrinkage slope $= 0.904$).²⁴ A bias-corrected coefficient for the model was determined through a bootstrap resampling method (Supplemental Table 1, <http://links.lww.com/MD/A199>). The CAD risk score model was developed based on the final logistic model using the method described by Sullivan et al.²⁵ The constant of the scoring system was defined as the increase in risk associated with a 10-year increase in age (ie, $0.489 = 10 \times 0.0489$). This constant corresponded to one point on the CAD risk score system. For each predictive factor, its distance from the base category in regression coefficient units was divided by this constant and rounded to the nearest integer to get its point value. A patient's total CAD risk score was calculated by adding up the points for all existing predictive factors. Based on CAD risk scores, patients were categorized into low (≤ 3), intermediate (4–6), or high (≥ 7) risk groups (for significant CAD on CCTA) according to the model-based CAD risk $<20\%$, 20% to 50%, or $>50\%$. The derived risk groups were internally and externally validated by comparing the CCTA variables and clinical outcomes. For clinical outcomes, event-free survival curves were

TABLE 1. Baseline Characteristics and Univariate Analysis

Characteristics	Cohort (n = 607)	Significant CAD on CCTA		
		C-OR	95% CI	P Value
Age, y	62.2 ± 8.3	1.062	1.037–1.086	<0.001
Male, no. (%)	358 (59.0)	1.638	1.143–2.348	0.007
Duration of diabetes, years	12.4 ± 7.7	1.062	1.038–1.086	<0.001
Body mass index, kg/m ²	24.9 ± 3.1	0.977	0.923–1.034	0.421
Systolic blood pressure, mm Hg	132.7 ± 14.8	1.011	0.999–1.023	0.071
Diastolic blood pressure, mm Hg	73.8 ± 8.6	0.988	0.968–1.008	0.232
Hypertension, no. (%)	357 (58.8)	1.770	1.232–2.542	0.002
Current smoker, no. (%)	116 (19.1)	1.615	1.061–2.458	0.025
Family history of premature CAD, no. (%)	15 (2.5)	4.652	1.567–13.805	0.006
Hyperlipidemia, no. (%)	317 (52.2)	0.826	0.586–1.166	0.278
Previous history of stroke, no. (%)	31 (6.1)	4.032	2.025–8.028	<0.001
Previous history of PAD, no. (%)	8 (1.3)	3.789	0.896–16.021	0.070
Fasting blood glucose, mg/dL	142.1 ± 39.7	1.002	0.998–1.006	0.298
Glycated hemoglobin, % (mmol/mol)	7.5 ± 1.2 (58.8 ± 13.5)	1.147	0.999–1.317	0.051
C-peptide, ng/mL	2.0 ± 1.4	1.039	0.923–1.169	0.526
Creatinine, mg/dL	0.9 ± 0.2	3.735	1.507–9.255	0.004
Ratio of total cholesterol to HDL cholesterol	3.7 ± 1.0	1.324	1.111–1.578	0.002
LDL cholesterol, mg/dL	109.0 ± 30.8	1.000	0.995–1.006	0.922
Triglyceride, mg/dL	136.1 ± 76.6	1.001	0.999–1.003	0.446
Insulin treatment, no. (%)	77 (12.7)	1.815	1.113–2.958	0.017
Neuropathy, no. (%)	172 (28.3)	2.283	1.577–3.305	<0.001
Retinopathy, no. (%)	172 (28.3)	2.126	1.469–3.078	<0.0001
Nephropathy, no. (%)	122 (20.1)	1.764	1.158–2.635	0.008

Data are expressed as n (%) or as mean ± SD. CAD = coronary artery disease, CCTA = coronary computed tomographic angiography, CI = confidence interval, C-OR = crude odds ratio, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PAD = peripheral artery disease.

constructed using the Kaplan–Meier method and compared using a log-rank test. To compare the model performance between UKPDS risk engine and new risk model, the discrimination ability and contribution for predicting significant CAD on CCTA was evaluated by C-statistic. Statistical comparison of C-statistic between models was performed, as described by Delong et al,²⁶ and confidence intervals (CIs) for the difference in C-statistics between models were calculated by bootstrap sampling. We also calculated the category-free net reclassification improvement and the integrated discrimination improvement to quantify the performance and the net benefit.²⁷ All reported P values are two sided, and P values of <0.05 were considered statistically significant. Data manipulation and statistical analyses were conducted using SAS Version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Population Characteristics

The baseline characteristics of the study population are listed in Table 1. The mean age of the study population was 62.2 ± 8.3 years, and 59.0% were men. The mean duration of diabetes was 12.4 ± 7.7 years and the mean hemoglobin A1C was 7.5% ± 1.2%. Diabetes treatment consisted of lifestyle modifications in 8 patients (1.3%), oral hypoglycemic agents in 552 (86.0%), and insulin in 77 (12.7%). The average nonfatal CAD 10-year risk score by UKPDS engine was 20.1% ± 12.6%. On CCTA, atherosclerotic plaques were detected in 430

(70.8%) patients, with 188 (31.0%) having significant CAD (diameter stenosis ≥50%).

Clinical Risk Factors and Development of Risk Score Model

Potential variables were evaluated for model inclusion (Table 1). After excluding the statistically less significant variables, multivariable analyses showed that age, male gender, duration of diabetes, hypertension, current smoking, family history of premature CAD, previous history of stroke, ratio of total cholesterol to high-density lipoprotein cholesterol, and neuropathy were independent clinical risk factors for significant CAD on CCTA. A prediction model for significant CAD on CCTA was developed based on these variables (Supplemental Table 1, <http://links.lww.com/MD/A199>).

We assigned weighted points to each risk factor, and scores ranged from 0 to 17 (Table 2 and Supplemental Table 2, <http://links.lww.com/MD/A199>). After CAD scores were assigned to all patients by summation of risk factor points, a receiver operating characteristic analysis showed that the CAD risk score model was reliable (area under the curve = 0.727, 95% CI = 0.714–0.739, P < 0.001). Based on CAD risk scores, patients were categorized into low (≤3), intermediate (4–6), or high (≥7) risk groups for significant CAD on CCTA. There was a significant difference in the probability of significant CAD (12.6% vs 29.4% vs 57.7%, P for all < 0.001) between the risk groups. The derived risk groups were also internally validated through detailed CCTA variables (Table 3).

TABLE 2. Risk Score Model Assessing for Significant Coronary Artery Disease on Coronary Computed Tomographic Angiography

	Categories	Point
Age	<60	0
	60–70	1
	≥70	2
Gender	Female	0
	Male	1
Duration of diabetes	<5	0
	5–15	1
	≥15	2
Hypertension	No	0
	Yes	1
Current smoking	No	0
	Yes	1
Family history of premature coronary artery disease	No	0
	Yes	4
Previous history of stroke	No	0
	Yes	3
Ratio of total cholesterol to high-density lipoprotein cholesterol	<3	0
	3–4.3	1
	≥4.3	2
Neuropathy	No	0
	Yes	1
Total score range	0–17	
	Low-risk group	0–3
	Intermediate-risk group	4–6
High-risk group	7–17	

When assessed by the category-free net reclassification improvement and the integrated discrimination improvement, new risk model significantly improves the predictive ability over the UKPDS risk engine for predicting significant CAD on CCTA (Supplemental Table 3, <http://links.lww.com/MD/A199>).

Clinical Outcomes According to Risk Groups

Over a median follow-up period of 4.3 (interquartile range, 3.7–4.8) years, a total of 83 events occurred in 71 patients: 7 cardiac deaths, 2 nonfatal myocardial infarctions, 8 acute coronary syndromes requiring hospitalization, and 66 coronary revascularizations (Supplemental Table 4, <http://links.lww.com/MD/A199>). Cardiac events significantly differed between the risk groups. After excluding revascularizations, the incidence of major cardiac events also increased. Figure 1 showed that risk stratification based on the CAD risk score model was feasible to predict the 5-year cardiac event-free survival rates (96.6% ± 1.5% vs 88.9% ± 1.8% vs 73.8% ± 4.1%, log-rank *P* for trend <0.001) and 5-year major cardiac event-free survival rates (99.3% ± 0.7% vs 96.4% ± 1.1% vs 94.5% ± 2.2%, log-rank *P* for trend = 0.040).

DISCUSSION

In this study, we observed that 31.0% of asymptomatic patients with type 2 diabetes had significant CAD in at least one coronary artery on CCTA. Using clinical parameters and simple laboratory tests, we developed a CAD risk score model to assess the presence of significant CAD on CCTA. Risk stratification using this model enabled us to categorize asymptomatic type 2 patients with type 2 diabetes into low-, intermediate-, or high-risk group for significant CAD as well as to predict the cardiac events. Therefore, the model described here might be a useful

TABLE 3. Coronary Computed Tomographic Angiographic Analysis According to Risk Groups

CCTA characteristics	Overall Cohort (n = 607)	Low-Risk Group (n = 151)	Intermediate-Risk Group (n = 333)	High-Risk Group (n = 123)	<i>P</i> Value
Mean CACS	196.7 ± 480.0	33.8 ± 97.8	156.3 ± 368.7	506.4 ± 792.9	<0.001
CACS classification, no. (%)					<0.001
0	229 (37.7)	93 (61.6)	122 (36.6)	14 (11.4)	
1–10	70 (11.5)	23 (15.2)	37 (11.1)	10 (8.1)	
11–100	121 (19.9)	23 (15.2)	75 (22.5)	23 (18.7)	
101–400	104 (17.1)	9 (6.0)	58 (17.4)	37 (30.1)	
>400	83 (13.7)	3 (2.0)	41 (12.3)	39 (31.7)	
Any plaques, no. (%)	430 (70.8)	70 (46.4)	250 (75.1)	110 (89.4)	<0.001
Plaque characteristics, no. (%)					
Calcified plaque	322 (53.0)	46 (30.5)	180 (54.1)	96 (78.0)	<0.001
Noncalcified plaque	199 (32.8)	32 (21.2)	116 (34.8)	51 (41.5)	0.001
Mixed plaque	134 (22.1)	10 (6.6)	81 (24.3)	43 (35.0)	<0.001
Modified Duke prognostic index	1.8 ± 1.3	1.3 ± 0.6	1.7 ± 1.2	2.6 ± 1.6	<0.001
Segment stenosis score	2.7 ± 4.5	0.7 ± 1.7	2.4 ± 3.9	5.8 ± 6.1	<0.001
Segment involvement score	2.6 ± 2.7	1.0 ± 1.6	2.6 ± 2.5	4.6 ± 3.1	<0.001
Number of stenosed vessels, no. (%)					
Significant CAD	188 (31.0)	19 (12.6)	98 (29.4)	71 (57.7)	<0.001
Multivessel disease	97 (16.0)	3 (2.0)	46 (13.8)	48 (39.0)	<0.001
Left main or proximal LAD CAD	103 (17.0)	9 (6.0)	50 (15.0)	44 (35.8)	<0.001

Data are expressed as n (%) or as mean ± SD. CACS = coronary artery calcium score, CAD = coronary artery disease, CCTA = coronary computed tomographic angiography, LAD = left anterior descending artery.

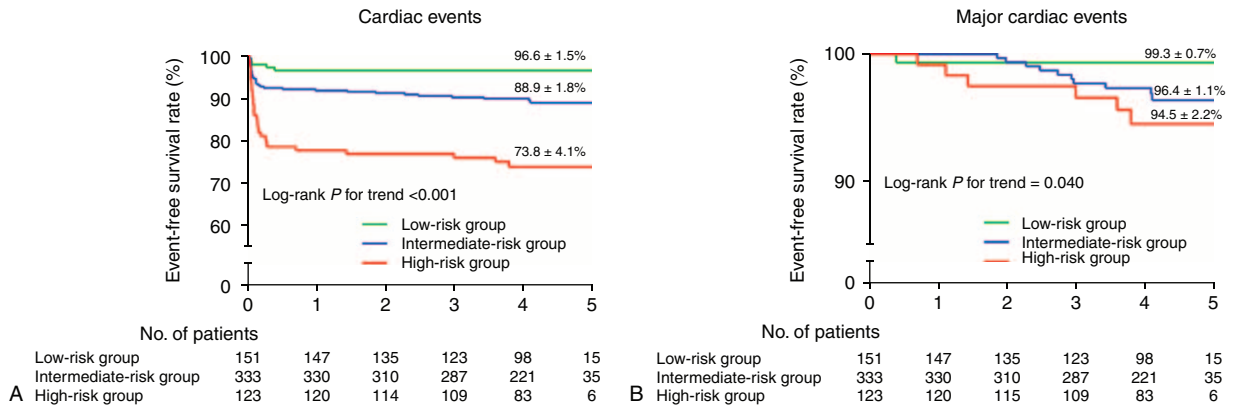


FIGURE 1. Kaplan–Meier event-free survival curves of 5-year cardiac events (A) and 5-year major cardiac events (B). The numbers in each figure represent the 5-year event-free survival rates.

tool for deciding whether further evaluation of CAD is required in asymptomatic patients with type 2 diabetes.

The independent covariates in our CAD risk score model were age, male gender, duration of diabetes, hypertension, current smoking, family history of premature CAD, previous history of stroke, ratio of total cholesterol to high-density lipoprotein cholesterol, and neuropathy. In the UKPDS risk engine, age, duration of diabetes, male gender, ethnicity, current smoking, glycated hemoglobin, systolic blood pressure, and ratio of total cholesterol to high-density lipoprotein cholesterol ratio were associated with the development of sudden death or myocardial infarction.¹⁵ Furthermore, in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, male gender, duration of diabetes, microalbuminuria/proteinuria, serum creatinine, symptoms of peripheral neuropathy, diminished peripheral sensation, cardiac autonomic dysfunction, peripheral vascular disease, elevated low-density lipoprotein levels, and family history of premature CAD were independent predictors of cardiac death and myocardial infarction.²⁸ In our model, the predictive clinical risk factors did not differ from those in prior studies.

The prevalence of CAD is higher in patients with type 2 diabetes compared to nondiabetic subjects.² In addition, the prevalence, extent, and severity of CAD are higher in diabetic than matched nondiabetic individuals, as examined by CCTA.⁵ However, less is known about CAD evaluated by CCTA in asymptomatic patients with type 2 diabetes. In previous observational studies, approximately 64% to 91.4% of asymptomatic patients with type 2 diabetes had atherosclerotic plaques and 26% to 33.3% had significant CAD.^{8–11} Consistent with the results of previous studies, in our large cohort, atherosclerotic plaques were identified in 430 (70.8%) and 188 (31.0%) had significant CAD. These findings suggest that CAD in asymptomatic patients with type 2 diabetes is a problem, which should not be overlooked.

In this cohort, among patients with significant CAD, 97 (16.0%) and 103 (17.0%) had multivessel diseases and significant lesions in the left main or proximal left anterior descending artery, which has been known to be associated with a poor prognosis.¹⁹ Increased severity of CAD was associated with an increased risk of mortality in diabetic patients.⁵ Previous studies, including a large international cohort study, demonstrated that CCTA had prognostic value in diabetic patients.^{5–7} Furthermore, in patients with high-risk CAD evaluated by CCTA, coronary revascularization conferred a survival benefit.²⁹ Even in the DIAD study, patients with moderate to

large ischemia had a 6-fold greater cardiac risk than those with normal test results or small perfusion defects.²⁸ These findings imply that we should make an effort to find high-risk patients even in asymptomatic type 2 diabetes.

In this study, our risk score model showed reliable model performances to classify patients into low-, intermediate-, or high-risk group for significant CAD on CCTA as well as to predict the cardiac events. Our model was not developed to predict the absolute risk of CAD-associated clinical outcomes, but the presence of significant CAD on CCTA. However, because CAD is the most common cause of death in patients with diabetes and our model reflected the atherosclerotic burden,³ the prognostic value of the model is not surprising. In the DIAD study, although the annual cardiac event rate was low (an average of 0.6% per year) and not altered by routine screening for inducible ischemia,²⁸ a post hoc analysis showed that the incidence of cardiac events was higher in the high-risk group classified by the UKPDS risk engine (1.2% vs 2.5% vs 9.9%, $P = 0.002$).³⁰ Similarly, our study showed that the high-risk group had higher cardiac and major cardiac events. Therefore, even in the absence of symptoms, tailored approaches by risk stratification could be beneficial in identifying high-risk patient subgroups.

Based on our CAD risk score model, we propose an algorithm for CAD screening in asymptomatic patients with type 2 diabetes. In low-risk patients, further evaluation for CAD is not recommended because these patients have a low risk of developing significant CAD and cardiac events. The presence of any degree of coronary calcium has proven predictive for future cardiovascular events in asymptomatic diabetic patients. Assessment of coronary calcium score may also aid in identifying diabetic patients with a higher likelihood of inducible ischemia. Therefore, in intermediate-risk patients, coronary calcium evaluation may be appropriate as a screening test for CAD, as previously recommended.³¹ In high-risk patients, with high probability of significant CAD and worse clinical prognosis than other risk groups, CCTA or myocardial perfusion imaging might be considered as a first-line test (Figure 2).

We have described the development of the CAD risk score model, which predicts significant CAD in at least one coronary artery in asymptomatic patients with type 2 diabetes. The strengths of this study were that analysis was confined to asymptomatic patients with type 2 diabetes, and this CAD risk score model was developed based on clinical parameters and simple laboratory tests to immediately apply in the field.

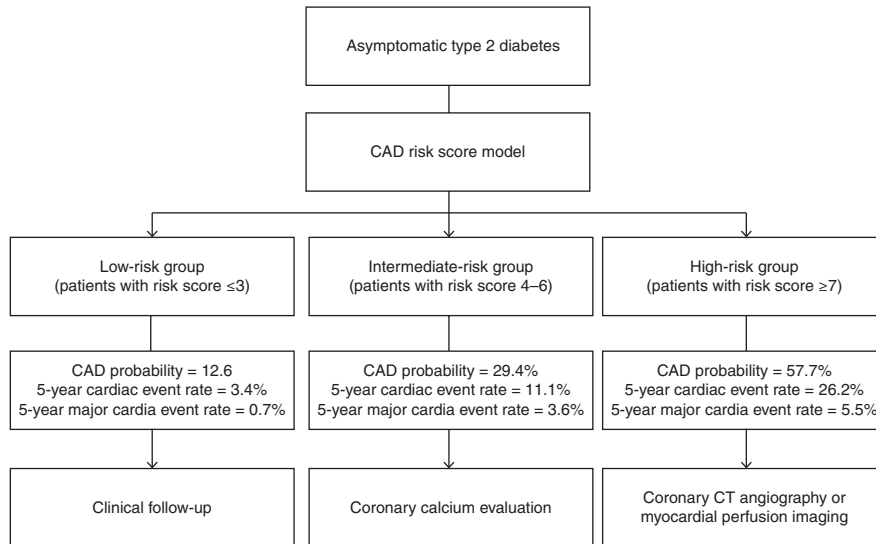


FIGURE 2. Proposed algorithm for individualized coronary artery disease screening in asymptomatic type 2 diabetes based on our risk score model. CAD = coronary artery disease.

Our study has also several limitations. First, since this study was conducted in a single center and CCTA examination was performed at the discretion of the attending endocrinologist, there is a potential for selection bias. In addition, since clinical differences in type 2 diabetes have been noted between Asian and Western populations, the applicability of this model to other ethnic groups may be limited. Second, a higher CACS may result in overestimation of significant CAD on CCTA. Third, a major concern with CCTA use is exposure to radiation. Although recent technological advances have reduced radiation exposure,³² the potential advantages gained from performing CCTA must be weighed against these drawbacks.

In conclusion, the risk score model described here provides a formula for estimating the risk of significant CAD on CCTA in asymptomatic patients with type 2 diabetes. Tailored approaches using this model may have a potential role in identifying patients with high cardiac risks, whose outcome might be improved through aggressive interventions. However, this proposed model should be evaluated about the prognostic impact and cost-effectiveness.

REFERENCES

- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414-1431.
- Goraya TY, Leibson CL, Palumbo PJ, et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol*. 2002;40:946-953.
- Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100:1134-1146.
- Min JK, Shaw LJ, Berman DS. The present state of coronary computed tomography angiography a process in evolution. *J Am Coll Cardiol*. 2010;55:957-965.
- Rana JS, Dunning A, Achenbach S, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (CORonary CT Angiography Evaluation For Clinical Outcomes): an International Multicenter Registry. *Diabetes Care*. 2012;35:1787-1794.
- Van Werkhoven JM, Cademartiri F, Seitun S, et al. Diabetes: prognostic value of CT coronary angiography—comparison with a nondiabetic population. *Radiology*. 2010;256:83-92.
- Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care*. 2010;33:1358-1363.
- Rivera JJ, Nasir K, Choi EK, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. *Atherosclerosis*. 2009;203:442-448.
- Iwasaki K, Matsumoto T, Aono H, et al. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. *Coron Artery Dis*. 2008;19:195-201.
- Scholte AJ, Schuijf JD, Kharagitsingh AV, et al. Prevalence of coronary artery disease and plaque morphology assessed by multi-slice computed tomography coronary angiography and calcium scoring in asymptomatic patients with type 2 diabetes. *Heart*. 2008;94:290-295.
- Park GM, Lee SW, Cho YR, et al. Coronary computed tomographic angiographic findings in asymptomatic patients with type 2 diabetes mellitus. *Am J Cardiol*. 2014;113:765-771.
- American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care*. 2012;35(Suppl 1):S11-S63.
- Lawlor DA, Adamson J, Ebrahim S. Performance of the WHO Rose angina questionnaire in post-menopausal women: are all of the questions necessary? *J Epidemiol Community Health*. 2003;57:538-541.
- Dyck PJ, O'Brien PC, Kosanke JL, et al. A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. *Neurology*. 1993;43:1508-1512.
- Stevens RJ, Kothari V, Adler AI, et al., United Kingdom Prospective Diabetes Study G. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)*. 2001;101:671-679.

16. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr*. 2009;3:122–136.
17. Rumberger JA, Brundage BH, Rader DJ, et al. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc*. 1999;74:243–252.
18. Leber AW, Becker A, Knez A, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. *J Am Coll Cardiol*. 2006;47:672–677.
19. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170.
20. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.
21. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med*. 1992;11:2093–2109.
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
23. Hosmer DW, Lemeshow S. Applied logistic regression. New York, NY: John Wiley and Sons; 1989.
24. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
25. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med*. 2004;23:1631–1660.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
27. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172discussion 207–112.
28. Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;301:1547–1555.
29. Min JK, Berman DS, Dunning A, et al. All-cause mortality benefit of coronary revascularization vs. medical therapy in patients without known coronary artery disease undergoing coronary computed tomographic angiography: results from CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: an InteRnational Multicenter Registry). *Eur Heart J*. 2012;33:3088–3097.
30. Bansal S, Wackers FJ, Inzucchi SE, et al. Five-year outcomes in high-risk participants in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study: a post hoc analysis. *Diabetes Care*. 2011;34:204–209.
31. Perrone-Filardi P, Achenbach S, Mohlenkamp S, et al. Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology. *Eur Heart J*. 2011;32:1986–19931993a, 1993b.
32. Ghoshhajra BB, Engel LC, Major GP, et al. Evolution of coronary computed tomography radiation dose reduction at a tertiary referral center. *Am J Med*. 2012;125:764–772.