ORIGINAL RESEARCH

Long-Term Prognostic Value of Coronary Computed Tomography Angiography in an Asymptomatic Elderly Population

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***Background*—**The prognostic value of coronary computed tomographic angiography (CCTA) for evaluating coronary artery disease in asymptomatic older adults is controversial. We investigated the prognostic value of CCTA in community-dwelling elderly Koreans.

***Methods and Results*—**Participants (n=470; mean age: 75.1±7.3 years) who underwent CCTA were enrolled from KLoSHA (Korean Longitudinal Study on Health and Aging), a community-based prospective cohort. Using CCTA, coronary artery disease was classified as *normal, nonobstructive*, or *obstructive* according to the presence of 0%, <50%, or ≥50% stenosis, respectively. Coronary artery calcium scores were investigated together with Framingham risk score, atherosclerotic cardiovascular disease score, and individual risk factors. Major adverse cardiac events (MACE) were defined as a composite of cardiac event–related death or nonfatal myocardial infarction. During a median follow-up of 8.2 years (interquartile range: 7.7–10.1 years), MACE occurred in 24 participants (5.1%). Compared with the normal group, participants in the obstructive group showed higher incidence of MACE (hazard ratio: 5.65; 95% CI, 1.22–26.16; *P*=0.027), whereas there were no significant differences in MACE between the normal and nonobstructive groups. The 8-year event-free survival rates were 98.1±1.1%, 94.9±1.6%, and 81.7±4.8% in the normal, nonobstructive, and obstructive groups, respectively. Compared with the Framingham risk score and coronary artery calcium score model, CCTA improved risk prediction by C-index (from 0.698 to 0.749) and category-free net reclassification index (0.478; *P*=0.022).

***Conclusions*—**CCTA showed better long-term prognostic value for MACE than coronary artery calcium score in this asymptomatic older population. **(*J Am Heart Assoc*. 2019;8:DOI: e013523. DOI: 10.1161/JAHA.119.013523.)**

Key Words: Asian • elderly • major adverse cardiac outcome • prognosis • subclinical atherosclerosis

Coronary artery disease (CAD) is a major cause of death worldwide.[1] It often occurs without typical symptoms in older populations, and this hampers its timely detection. Higher CAD-related mortality rates are frequently observed in these groups.[2] Screening for CAD in older populations by using an appropriate method is likely to bring substantial benefits for health care.

As a screening tool for CAD, the coronary artery calcium score (CACS) has shown powerful predictive value beyond conventional cardiac risk factors in asymptomatic people, including older adults.[3,4] Given this background, coronary computed tomographic angiography (CCTA) has received much attention as an advanced screening tool for CAD because it can provide comprehensive information on coronary arteries based on reliable visualization.[5] In addition, CCTA showed improved predictive value over conventional cardiac risk factors, even among patients who were not recommended to be tested by CCTA according to the current guidelines.[6]

Over the past decade, many researchers have investigated the prognostic value of CCTA over CACS or cardiovascular risk scores.[7–11] In a large multicenter registry study, CCTA failed to show additional gain versus CACS in the predictability of hard outcomes among generally asymptomatic people during 2-year follow-up.[9] In contrast, more recent studies

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Clinical Perspective

What Is New?

- In this long-term prospective cohort study with 470 asymptomatic older adults (median follow-up: 8.2 years; mean age: 75.1±7.3 years), coronary computed tomographic angiography showed better prognostic value for cardiac events than coronary artery calcium scores and conventional risk factors.

What Are the Clinical Implications?

- Information obtained from coronary computed tomographic angiography likely gives more reliable clinical guidance to prevent or delay future cardiac events in asymptomatic older adults than traditional methods.
- Additional studies are needed to evaluate whether treatment changes according to coronary computed tomographic angiography findings affect cardiac outcomes.

demonstrated that CCTA had additional predictive value over CACS in asymptomatic patients with high-risk features, such as high CACS and the presence of diabetes mellitus (DM) and multiple risk factors.[7,8,11,12]

Aging is a strong risk factor for CAD[13]; however, few studies have examined the prognostic value of CCTA among asymptomatic elderly populations in particular. A recent study showed that CCTA had better prognostic value than did cardiac risk factors or CACS for predicting major adverse cardiac events (MACE) in asymptomatic older adults.[14] However, the 26-month follow-up was too short to confirm CCTA's prognostic value robustly. A debate remains regarding the use of CCTA as a screening tool, particularly in asymptomatic people. In this study, we aimed to investigate the prognostic value of CCTA compared with CACS and conventional risk factors in asymptomatic elderly Korean people over a long period.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

KLoSHA (Korean Longitudinal Study on Health and Aging) is a community-based prospective cohort study on health, aging, and common geriatric diseases among Korean older adults.[15] At baseline, 1000 participants aged ≥65 years were recruited via an age- and sex-stratified random sampling of residents of Seongnam-City, South Korea. All baseline evaluations were performed by trained researchers at the Seoul National University Bundang Hospital (SNUBH) in 2005–2006.

Study Population

Among the participants of this cohort, CCTA was performed on 541 patients who agreed to the procedure and had no contraindications medically for injection with a contrast dye. To select asymptomatic participants without a known history of CAD, we excluded 71 participants with the exclusion criteria (Data S1). Finally, 470 asymptomatic participants aged ≥65 years were enrolled in the study, which was approved by the institutional review board of SNUBH (B-1507/306-306), and all participants signed an informed consent form.

Anthropometric and Biochemical Parameters

Medical histories were obtained from the personal interview or medical records. The 10-year Framingham risk score (FRS) and the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score were calculated.[16,17] Changes in the levels of antiplatelet agents and statins were evaluated during the follow-up periods and adjusted in multivariate analyses (Data S1).

Image Acquisition and Analysis

CCTA was performed using a 64-slice multidetector-row computed tomography scanner (Brilliance 64; Philips Medical Systems). A standard scanning protocol was used, as described previously.[18] Detailed methods for image acquisition are described in Data S1.

Two experienced radiologists who were blinded to the clinical information analyzed all scanned images independently and provided a consensus interpretation of each final CCTA diagnosis. CACS was acquired simultaneously during CCTA examination. We adopted 4 CACS categories (0–100, 101–400, 401–1000, and >1000) with prognostic values that were validated in an elderly population in a previous study.[4] The diameter of stenosis of each coronary artery segment was defined as the proportion that was enhanced by the contrast dye, which was semiautomatically traced at the site of maximal stenosis and compared with the mean value of proximal and distal reference sites, as shown in our previous study.[19] Plaques were categorized as *calcified, mixed*, or *noncalcified* according to the extent of calcification (Data S1).

We applied several methods to categorize coronary artery findings in CCTA. First, the severity of CAD was categorized according to the highest value of stenosis of the diameter among segments (*normal*, 0% stenosis; *nonobstructive* CAD,

1–49% stenosis; *obstructive* CAD, ≥50% stenosis).[9] Within the category of obstructive CAD, we further divided CCTA findings as 1-, 2-, or 3-vessel disease/left main (Data S1).

We used 3 coronary artery plaque scoring systems—a segment involvement score (SIS), a segment stenosis score (SSS), and a modified Duke CAD index—to categorize the CCTA findings in detail, as described in previous studies.[9] In addition to per-score–based analyses, we applied categories for each scoring system as follows, according to its distribution: 0, 1 to 4, or ≥5 for SIS and SSS and 1, 2, or ≥3 for modified Duke score.

Clinical Outcomes

We gathered clinical outcome data by reviewing medical records at the end of the follow-up period, in June 2018. As the primary end point, a MACE was defined as a composite outcome of cardiac death and nonfatal myocardial infarction (Data S1). Coronary revascularizations were performed at the cardiologists' discretion. Revascularizations for reasons other than myocardial infarction were regarded as censored because this could affect future outcomes significantly.

Statistical Analyses

One-way ANOVA was used to compare continuous variables, and the χ^2 test was used to compare categorical variables. To construct event-free survival curves, we used Kaplan–Meier analysis and log-rank tests. Univariable or multivariable Cox proportional hazards regression analyses were used to calculate the hazards for the association of the various measures of CCTA findings with MACE outcomes. Cardiovascular risk factors (FRS and ASCVD risk scores), CACS, and medication changes (statins and antiplatelet agents) were adjusted for in the multivariable Cox proportional hazards regression analysis. However, because the FRS and ASCVD risk score have not been validated in adults aged >74 and >79 years, respectively, we also applied individual risk factors (age, sex, systolic blood pressure, antihypertensive drug usage, current smoking status, DM, HDL [high-density lipoprotein] cholesterol level, and total cholesterol level) that were used in a previous study of an elderly population.[20]

To test the discriminative ability for the prognosis of various measures of CCTA findings in addition to cardiovascular risk factors and CACS, we calculated C statistics, the categorical net reclassification index (cNRI), and the category-free net reclassification index (cfNRI) (Data S1). In each analysis, $P<0.05$ was considered statistically significant. Statistical analyses were performed using Stata software (v13; StataCorp) and R v3.4.2 (R Foundation for Statistical Computing).

Results

Baseline Characteristics

The baseline characteristics of the study participants are shown in Table 1. Among the 470 participants, the mean age was 75.1±7.3 years, and 242 (51.5%) were male. The mean 10-year FRS and 10-year ASCVD risk score were 33.4±20.4% and 32.3±20.5%, respectively. During the total follow-up period, antiplatelet agents and statins were used by 28.1% and 12.8% of participants, respectively (Table S1). Individuals in the obstructive CAD group had a higher FRS and ASCVD risk score compared with those in the normal and nonobstructive groups.

CCTA Findings in All Participants

Detailed information regarding CCTA findings among the study population is provided in Table 2. Nonobstructive CAD was observed in 47.7% of participants, and 16.2% had obstructive CAD as assessed by CCTA. Among the latter group, 4.5% of participants had obstructive lesions in 3-vessel disease/left main, and 63.8% had any kind of plaque: calcified plaques in 38.5%, mixed plaques in 32.4%, and noncalcified plaques in 9.1% of participants (one person can have multiple plaque sites). In the CACS evaluation, 28.9% of participants had a CACS >100 and 12.1% had a CACS >400. The proportion of participants with a CACS >400 was significantly higher in the obstructive CAD group compared with the normal group (Table S2).

Clinical Outcomes and Survival

During the 8.2-year median follow-up period (interquartile range: 7.7–10.1 years), MACE occurred in 24 participants (5.1%). Cardiac death and nonfatal myocardial infarction rates increased significantly according to the severity of CAD findings (Table 3). Noncardiac death occurred in 88 participants (18.7%). The detailed causes of death are shown in Table S3. The Kaplan–Meier curve based on the severity of CAD showed that the 8-year event-free survival rates were 98.1±1.1%, 94.9±1.6%, and 81.7±4.8% in the normal, nonobstructive, and obstructive groups, respectively, with a significant difference observed between the normal/nonobstructive and the obstructive groups ($P<0.001$; Figure A). Among the individuals with obstructive CAD, the event-free survival rates decreased in proportion to the number of diseased vessels (Figure B).

When using coronary artery plaque score systems such as SIS, SSS, and modified Duke score, participants in higher score categories showed progressively poorer prognosis than did those in a lower score category (log-rank $P<0.001$ for all; Figure E).

Table 1. Baseline Characteristics of Asymptomatic Older Adults According to CAD Severity as Measured by CCTA

	Total (n=470)	Normal (n=170)	Nonobstructive CAD (n=224)	Obstructive CAD (n=76)	*P* Value
Age, y	75.1±7.3	72.7±5.4	75.7±7.4	78.8±8.8	<0.001
Men	242 (51.5)	65 (38.2)	129 (57.6)	48 (63.2)	<0.001
Body mass index, kg/m^2	24.2±3.2	24.2±3.1	24.2±3.2	24.4±3.5	0.912
Systolic blood pressure, mm Hg	133.3±17.7	130.7±18.5	134.3±17.1	135.8±17.6	0.055
Diastolic blood pressure, mm Hg	83.7±10.7	82.4±11.6	84.3±9.6	84.5±11.3	0.168
Fasting blood glucose, mg/dL	112.3±27.0	108.6±24.4	112.8±26.0	118.7±33.6	0.023
HbA1c, %	6.1±0.9	6.0±0.8	6.1±0.9	6.2±1.0	0.057
Total cholesterol, mg/dL	203.6±37.3	204.7±38.5	204.9±37.5	197.1±34.2	0.262
Triglyceride, mg/dL	141.3±92.6	141.5±100.8	146.2±94.5	126.3±62.2	0.270
HDL-C, mg/dL	45.7±12.6	47.5±13.0	44.9±11.5	43.8±12.7	0.045
LDL-C, mg/dL	129.6±34.5	128.9±35.8	130.7±34.9	128.1±30.8	0.796
Serum creatinine, mg/dL	1.09±0.20	1.05±0.22	1.11±0.19	1.11±0.19	0.016
MDRD eGFR, mL/min/1.73 m^2	59.6±10.7	60.2±11.5	59.1±9.8	59.6±11.7	0.622
DM	133 (28.3)	36 (21.2)	64 (28.6)	33 (43.4)	0.002
Antidiabetic medication	82 (17.4)	20 (11.8)	42 (18.8)	20 (26.3)	0.016
Hypertension	317 (67.4)	105 (61.8)	152 (68.2)	60 (78.9)	0.028
Antihypertensive medication	187 (39.8)	51 (30)	98 (43.8)	38 (50)	0.003
Dyslipidemia (ATP III)*	354 (75.3)	111 (65.3)	179 (79.9)	64 (84.2)	0.001
Antiplatelet agent usage	87 (18.5)	23 (13.5)	43 (19.2)	21 (27.6)	0.029
Lipid-lowering medication	37 (7.9)	13 (7.6)	14 (6.3)	10 (13.2)	0.153
Current or past smoker	199 (42.3)	57 (33.5)	103 (46.0)	39 (51.3)	0.010
Family history of CAD	38 (8.1)	13 (7.6)	18 (8.0)	7 (9.2)	0.917
10-year FRS, %	33.4±20.4	25.3±16.6	36.1±20.6	43.6±21.0	<0.001
10-year ASCVD risk, %	32.3±20.5	23.7±15.0	34.4±20.4	45.6±23.0	<0.001
CACS, median (IQR)	17.6 (0.0–126.5)	0.0 (0.0–0.0)	60.2 (18.7–136.3)	477.4 (92.5–903.1)	<0.001

Continuous values are mean±SD, and categorical values are numbers and percentages (%), except as noted. ASCVD indicates atherosclerotic cardiovascular disease; ATP III, Adult Treatment Panel III; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease.

*Dyslipidemia (ATP III) refers to dyslipidemia defined using individualized LDL-C levels according to the ATP III guideline.

Cox Regression Models of Cardiovascular Risk Factors, CACS, and CCTA Findings

In unadjusted Cox regression analyses, CACS, FRS, ASCVD risk score, and individual risk factors were significantly associated with MACE (Table S4). In turn, after adjustment for the FRS, ASCVD risk score, or individual risk factors, a high CACS still showed a significant association with MACE. Next, to evaluate the prognostic value of various measures from CCTA findings, we performed multivariate analyses adjusted according to CACS and the FRS, ASCVD risk score, or individual risk factors (Table 4). In the multivariate analyses, obstructive CAD findings were significantly associated with MACE in the model adjusted for FRS and CACS, in the model adjusted for ASCVD risk score and CACS, and in the model adjusted for individual risk factors and CACS (hazard ratio: 5.65 [95% CI, 1.22–26.16; *P*=0.027], 5.68 [95% CI, 1.24–25.98; *P*=0.025], and 5.15 [95% CI, 1.08–24.64; *P*=0.040], respectively). Conversely, nonobstructive CAD lesions were not associated with MACE in all 3 models. Among the participants in the obstructive CAD group, the number of involved vessels was independently associated with MACE in all 3 adjusted models, whereas hazard ratios increased with the increasing number of diseased vessels. Individual higher categories of SIS, SSS, and modified Duke scores were also associated with MACE proportionately (Table 4).

In addition, we performed Cox regression analyses of plaque characteristics among CCTA findings (Table S5). When adjusting for conventional risk factors and medication changes (statins and antiplatelet agents), noncalcified plaques

Table 2. Results of CCTA Findings in Asymptomatic Older Adults

CCTA Finding	Participants, n (%)
Severity of CAD	
Normal	170 (36.2)
Nonobstructive CAD	224 (47.7)
Obstructive CAD	76 (16.2)
Number of diseased vessels	
1-VD	45 (9.6)
2-VD	10 (2.1)
3-VD/LM	21 (4.5)
Segment involvement score	
0	289 (61.5)
1–4	151 (32.1)
≥5	30 (6.4)
Segment stenosis score	
0	289 (61.5)
1 to 4	131 (27.9)
≥5	50 (10.6)
Modified Duke score	
1	338 (71.9)
2	75 (16.0)
≥3	57 (12.1)
Plaques*	
None	170 (36.2)
Noncalcified	43 (9.1)
Mixed	152 (32.4)
Calcified	181 (38.5)
CACS categories	
0–100	334 (71.1)
101–400	79 (16.8)
401–1000	38 (8.1)
>1000	19 (4.0)

CACS indicates coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; LM, left main; VD, vessel disease.
*Multiple plaque sites are possible in participants.

showed a significant association with MACE (hazard ratio: 2.46; 95% CI, 1.02–5.96; *P*=0.046); however, these associations disappeared when additionally adjusting for CACS or the severity of CAD.

Prognostic Value of CCTA Findings

To evaluate the additional prognostic value of CCTA findings over CACS and other conventional cardiovascular risk factors, we used C statistics, cNRI, and cfNRI (Table 5). The C index was 0.698 in the model including the FRS and CACS, 0.733 in the model including ASCVD risk score and CACS, and 0.738 in the model including individual risk factors and CACS. When the severity of CAD among the CCTA findings was added to all 3 models, C indexes increased to 0.749 in the model including the FRS and CACS, 0.774 in the model including ASCVD risk score and CACS, and 0.785 in the model including individual risk factors and CACS. The respective cfNRI values were also significant for these models: 0.478 (95% CI, 0.070–0.886; *P*=0.022), 0.752 (95% CI, 0.347–1.156; *P*<0.001), and 0.495 (95% CI, 0.089–0.901; *P*=0.017). Moreover, the respective cNRI values were significant for these 3 models: 0.259 (95% CI, 0.032–0.486; *P*=0.026), 0.319 (95% CI, 0.124–0.514; *P*=0.001), and 0.303 (95% CI, 0.067–0.538; *P*=0.012). Event cNRI and nonevent cNRI were both positive in all 3 models (Table 5 and Table S6). Additional predictability was also obtained in the models that were further adjusted for the number of diseased vessels, SIS, SSS, or modified Duke score (Table 5). Analyses using other CACS categories are shown in Table S7 (CACS categories: 0–10, 11–100, 101–400, and >400) and Table S8 (CACS categories: 0, 1–100, 101–400, and >400). Similar results were found with these different CACS categories.

Prognostic Value of CCTA According to Sex and Age Subgroups

Among 242 male and 228 female participants, MACE occurred in 15 men and 9 women. Because no MACE occurred in the CACS 101–400 group of women and in the normal CAD group of men, we adopted slightly modified categories of CACS and CCTA findings (Table S9). As in the total population, CCTA findings in male participants were significantly associated with MACE, and their cfNRI values confirmed the incremental predictive values of CCTA over CACS. In female participants, Cox regression analyses showed insufficient association between CCTA findings and MACE after adjusting for CACS. In addition, for the subgroup analyses with age groups, there were 366 participants aged <80 years and 104 participants aged ≥80 years, and MACE occurred in 14 and 10 participants, respectively. In the subgroup aged <80 years, Cox regression analyses and cfNRI showed an additive predictive value over CACS (Table S10). In contrast, in the subgroup aged ≥80 years, both analyses failed to show additional predictive value.

Discussion

In this population-based prospective cohort study with a median follow-up of 8.2 years, information about significant

Table 3. Cardiac Outcomes According to the Severity of CAD on CCTA During Median Follow-up of 8.2 Years (IQR: 7.7–10.1 Years)

	Total (n=470)	Normal (n=170)	Nonobstructive CAD (n=224)	Obstructive CAD (n=76)	*P* Value
Death	104 (22.1)	26 (15.3)	52 (23.2)	26 (34.2)	0.004
Cardiac	16 (3.4)	3 (1.8)	5 (2.2)	8 (10.5)	0.001
Noncardiac	88 (18.7)	23 (13.5)	47 (21.0)	18 (23.7)	0.082
Nonfatal MI	8 (1.7)	0 (0.0)	4 (1.8)	4 (5.3)	0.011
MACE (cardiac death or nonfatal MI)	24 (5.1)	3 (1.8)	9 (4.0)	12 (15.8)	<0.001

Values are number (percentage). CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; IQR, interquartile range; MACE, major adverse cardiac event; MI, myocardial infarction.

stenosis and presence of atheromatous plaques in coronary arteries obtained from CCTA had long-term prognostic value for the prediction of MACE in an asymptomatic elderly population and was better than that obtained considering CACS and other conventional cardiovascular risk factors. Although the older adults in this population were asymptomatic, the incidence of obstructive CAD defined as >50% stenosis by CCTA was not negligible (16.2%). Moreover, these participants exhibited a poor 8-year event-free survival rate compared with the individuals in the normal and nonobstructive CAD groups, who showed very good 8-year event-free survival rates. These findings confirmed the good negative predictiveness for CCTA reported in previous studies.[7,9,14,21]

To predict cardiac events among asymptomatic people, previous studies used a variety of screening tools such as the FRS, biomarkers, and CACS.[3,22,23] Among them, CACS proved to have better predictive value than did the FRS in asymptomatic people.[3] Moreover, in older adult populations, it is known that conventional risk factors cannot predict cardiovascular events satisfactorily,[24,25] and CACS was shown to have good predictability among asymptomatic older populations.[4,20,26] However, a CACS simply indicates the burden of calcium deposits in the coronary vessels and is not able to indicate stenosis or reflect plaque burden. In contrast, CCTA has the advantage of providing comprehensive information on the health status of coronary arteries via direct visualization. Of note, among participants with very low CACS in a previous study, the number of participants with noncalcified plaque or stenotic lesions detected by CCTA was not negligible, consistent with our findings.[27] Nonetheless, contrary to our expectations, CCTA failed to show an additional predictiveness over CACS among general asymptomatic individuals in a large multicenter registry study.[9] In addition, in a randomized controlled study of asymptomatic patients with DM over 4 years, no differences in outcomes were found between those who underwent CCTA as a screening tool and those who did not.[10] However, recent studies have demonstrated an additive predictive value of CCTA over the CACS in asymptomatic patients with high-risk features, such as a high CACS, presence of DM, and multiple risk factors.[7,8,11,28] In addition, a recent randomized controlled study showed that the use of CCTA information improved cardiovascular outcomes compared with standard care alone in patients with stable chest pain, and this finding was also shown in the elderly subgroup.[29]

A recent study that analyzed asymptomatic older adults in CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), revealed the prognostic value of detailed information from CCTA over that of the CACS and FRS.[14] However, the median follow-up of that study was only 26 months. Another recent study conducted using CONFIRM revealed longer diagnostic utility of CCTA in an elderly population (mean follow-up of 5.6 years), but considerable numbers of symptomatic patients (chest pain, 56.7%; dyspnea, 42.4%) were included.[30] Both studies had limitations that their primary outcomes were all-cause mortality, not cardiac death, which can be important in older adults because substantial numbers died from noncardiac causes in this population. In addition, therapeutic information after CCTA was not considered in these studies. Our present study addresses to these limitations.

To the best of our knowledge, this study is the first to assess the long-term (>8 years) prognostic value of CCTA among an asymptomatic group recruited from a community-based elderly cohort. Our results provided new information. The incidence of obstructive CAD was not trivial (16.2%), although the participants were asymptomatic. Among those in the low CACS groups, the proportions of participants with obstructive CAD identified from CCTA were not negligible in this study (4.6% in the group with a CACS of 0–10; 7.8% in the group with a CACS of 11–100; Table S2), which suggests that CCTA might be a better screening tool for cardiovascular disease than CACS alone in older populations.

In the sex comparison, there were no significant associations between CCTA findings and MACE in the female group. However, there were increasing tendencies of hazard ratios between abnormal CCTA findings and MACE with positive cfNRI values. This result might have been caused by the

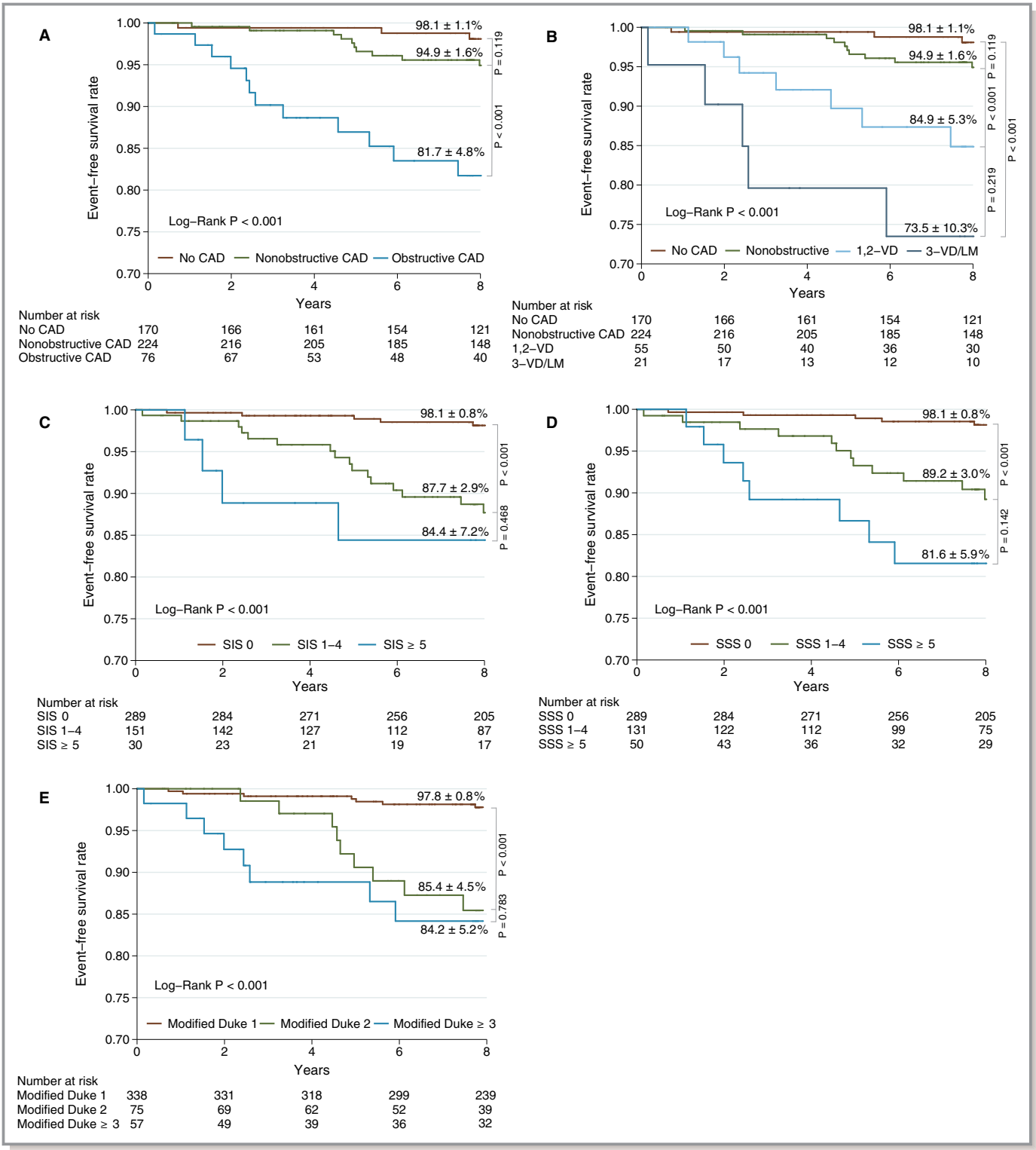

Figure. Kaplan–Meier curves for cardiac event-free survival based on coronary computed tomographic angiography (CCTA) findings among asymptomatic older adults. Event-free survival curves according to (**A**) the severity of coronary artery disease (CAD), (**B**) the number of diseased vessels, (**C**) segment involvement score (SIS), (**D**) segment stenosis score (SSS), and (**E**) modified Duke score. LM, left main; VD, vessel disease.

relatively few MACE in female participants. In addition, CCTA showed insufficient additive prognostic value over CACS in the subgroup aged ≥80 years in our study. This result might also have arisen from the small number of participants in this subgroup. Future studies with more female participants or people aged ≥80 years are needed to confirm this finding.

Table 4. Cox Regression Analyses of CCTA Findings for MACE, Adjusted by CACS and Conventional Cardiovascular Risk Factors

	Univariable		Multivariable					
			FRS* +CACS†		ASCVD*+CACS†		IRF*+CACS†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Severity of CAD‡								
Nonobstructive	2.39 (0.65–8.83)	0.191	1.53 (0.37–6.30)	0.555	1.47 (0.36–6.07)	0.596	1.36 (0.32–5.74)	0.675
Obstructive	11.21 (3.16–39.76)	<0.001	5.65 (1.22–26.16)	0.027	5.68 (1.24–25.98)	0.025	5.15 (1.08–24.64)	0.040
Number of diseased vessels‡								
Nonobstructive	2.39 (0.65–8.83)	0.191	1.55 (0.38–6.35)	0.543	1.51 (0.37–6.22)	0.569	1.37 (0.33–5.77)	0.665
1- or 2-VD	8.83 (2.28–34.17)	0.001	5.05 (1.06–23.98)	0.042	5.34 (1.15–24.82)	0.033	4.68 (0.96–22.93)	0.057
3-VD/LM	18.03 (4.30–75.53)	0.001	12.18 (1.77–83.57)	0.011	10.59 (1.47–76.19)	0.019	9.17 (1.20–70.32)	0.033
SIS (category)‡								
1–4	6.37 (2.31–17.52)	<0.001	4.32 (1.37–13.64)	0.013	4.50 (1.46–13.87)	0.009	4.38 (1.37–14.07)	0.013
≥5	9.96 (2.67–37.10)	0.001	5.72 (1.00–32.65)	0.050	6.49 (1.15–36.65)	0.034	5.68 (0.93–34.61)	0.059
SSS (category)‡								
1–4	5.36 (1.86–15.43)	0.002	4.12 (1.29–13.21)	0.017	4.27 (1.36–13.39)	0.013	4.23 (1.30–13.74)	0.016
≥5	11.34 (3.71–34.69)	<0.001	7.86 (1.52–40.54)	0.014	8.57 (1.68–43.74)	0.010	7.97 (1.43–44.46)	0.018
Modified Duke score (category)‡								
2	6.65 (2.48–17.86)	<0.001	5.10 (1.62–16.06)	0.005	5.22 (1.72–15.82)	0.003	5.38 (1.67–17.30)	0.005
≥3	8.45 (3.06–23.33)	<0.001	6.01 (1.61–22.45)	0.008	6.07 (1.62–22.69)	0.007	6.06 (1.50–24.50)	0.011

ASCVD indicates atherosclerotic cardiovascular disease risk score; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FRS, Framingham risk score; HR, hazard ratio; IRF, individual risk factors; LM, left main; MACE, major adverse cardiac events; SIS, segment involvement score; SSS, segment stenosis score; VD, vessel disease.

*All multivariable analyses were adjusted for conventional risk factors, CACS, and medication change (antiplatelet agents, statins) during the follow-up period. As conventional risk factors, FRS, ASCVD risk score, and IRFs were used individually. The FRS and ASCVD risk score were adjusted as continuous variables. For IRFs, variables included in the FRS and ASCVD risk score (age, sex, systolic blood pressure, antihypertensive medication use, current smoking, diabetes mellitus, HDL [high-density lipoprotein] cholesterol level, and total cholesterol level) were used.

†CACS was adjusted as a categorical variable: 0 to 100, 101 to 400, 401–1000, >1000.

‡Reference categories are 0% stenosis for the severity of CAD, 0-VD for the number of diseased vessels, 0 for SIS (category) and SSS (category), and 1 for the modified Duke score (category), respectively.

In a previous study of asymptomatic older adults conducted using the CONFIRM registry, the prevalence of any CAD in the highest tertile of the aged population was similar to that in our study (67.9% versus 63.6%), despite the participants in our study being older and having worse metabolic profiles (Table S11).[14] However, several studies have reported that East Asian people have lower CACSs than those of European ancestry, and this difference is more prominent in the older adult population.[31,32] Our study comprised participants with Korean ethnicity, whereas CONFIRM was conducted mainly with North American and European participants; consequently, there might be ethnic differences in the development of CAD, including CACS.[33]

It is well known that aging itself contributes to the development of cardiovascular disease.[13] In turn, CAD is a major cause of death in older adults, who are frequently asymptomatic. From this point of view, our finding is clinically important because CCTA can be a good screening tool for CAD in elderly populations. There has been concern about radiation exposure from CCTA. However, modern multidetector-row computed tomography technologies have reduced radiation dosages.[34] In addition, the incidence of secondary cancers after radiation exposure at old age is not high, and radiation-related secondary cancers usually occur >2 decades after exposure.[35,36]

This study had several limitations. First, it included only a single Asian ethnic group. Second, the FRS and ASCVD risk score used in this study have not been validated in adults aged >74 and >79 years, respectively. Therefore, we used individual risk factors to avoid this problem. Third, in KLoSHA, participants who underwent CCTA were younger compared with those who did not, and there were greater proportions of men and DM, with higher fasting glucose and HbA1c levels (CCTA group) (Table S12). This might attenuate the generalization of our findings. Last, participants with obstructive CAD were advised to consult doctors for optimal medical therapies, and this might have modified or attenuated our results.

Table 5. Additive Prognostic Value of CCTA Over Conventional Risk Factors and CACS Using C-Index, cfNRI, and cNRI

	C Index (95% CI)	cfNRI (95% CI)	*P* Value*	cNRI (95% CI)	*P* Value†	Event cNRI	Nonevent cNRI
FRS							
FRS	0.665 (0.554–0.775)	. . .	. . .	. . .	. . .	. . .	. . .
FRS+CACS‡	0.698 (0.576–0.819)	0.620 (0.217–1.023)	0.003	0.385 (0.089–0.682)	0.011	0.125	0.260
FRS+CACS+severity of CAD§	0.749 (0.633–0.865)	0.478 (0.070–0.886)	0.022	0.259 (0.032–0.486)	0.026	0.167	0.092
FRS+CACS+number of diseased vessels§	0.753 (0.636–0.870)	0.552 (0.149–0.956)	0.007	0.320 (0.085–0.556)	0.008	0.208	0.112
FRS+CACS+SIS (category)§	0.748 (0.634–0.861)	0.631 (0.234–1.028)	0.002	0.253 (0.033–0.473)	0.024	0.125	0.128
FRS+CACS+SSS (category)§	0.748 (0.634–0.862)	0.636 (0.239–1.032)	0.002	0.262 (0.042–0.482)	0.020	0.125	0.137
FRS+CACS+modified Duke score (category)§	0.758 (0.648–0.867)	0.723 (0.321–1.125)	<0.001	0.272 (0.035–0.508)	0.025	0.083	0.188
ASCVD							
ASCVD	0.699 (0.593–0.805)	. . .	. . .	. . .	. . .	. . .	. . .
ASCVD+CACS‖	0.733 (0.621–0.844)	0.629 (0.226–1.032)	0.002	0.295 (0.037–0.552)	0.025	0.167	0.128
ASCVD+CACS+severity of CAD§	0.774 (0.672–0.875)	0.752 (0.347–1.156)	<0.001	0.319 (0.124–0.514)	0.001	0.167	0.152
ASCVD+CACS+number of diseased vessels§	0.778 (0.676–0.881)	0.554 (0.147–0.961)	0.008	0.278 (0.062–0.494)	0.012	0.125	0.152
ASCVD+CACS+SIS (category)§	0.782 (0.692–0.873)	0.636 (0.239–1.032)	0.002	0.269 (0.004–0.533)	0.046	0.208	0.061
ASCVD+CACS+SSS (category)§	0.787 (0.697–0.878)	0.766 (0.393–1.140)	<0.001	0.236 (−0.045 to 0.518)	0.100	0.167	0.070
ASCVD+CACS+modified Duke score (category)§	0.795 (0.708–0.882)	0.727 (0.325–1.129)	<0.001	0.199 (−0.078 to 0.475)	0.159	0.042	0.157
IRFs from FRS and ASCVD							
IRFs	0.696 (0.585–0.806)	. . .	. . .	. . .	. . .	. . .	. . .
IRFs+CACS¶	0.738 (0.631–0.846)	0.611 (0.208–1.014)	0.003	0.303 (0.039–0.566)	0.025	0.208	0.094
IRFs+CACS+severity of CAD§	0.785 (0.685–0.886)	0.495 (0.089–0.901)	0.017	0.303 (0.067–0.538)	0.012	0.208	0.094
IRFs+CACS+number of diseased vessels§	0.786 (0.681–0.890)	0.590 (0.183–0.997)	0.005	0.274 (0.020–0.528)	0.034	0.167	0.108
IRFs+CACS+SIS (category)§	0.779 (0.685–0.873)	0.631 (0.234–1.028)	0.002	0.228 (0.010–0.446)	0.040	0.125	0.103
IRFs+CACS+SSS (category)§	0.785 (0.692–0.878)	0.465 (0.057–0.872)	0.026	0.235 (0.016–0.453)	0.035	0.125	0.110
IRFs+CACS+modified Duke score (category)§	0.796 (0.707–0.885)	0.678 (0.275–1.080)	0.001	0.352 (0.114–0.589)	0.004	0.208	0.143

ASCVD indicates atherosclerotic cardiovascular disease risk score; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; cNRI, categorical net reclassification index; cfNRI, category-free net reclassification index; FRS, Framingham risk score; IRFs, individual risk factors; SIS, segment involvement score; SSS, segment stenosis score.

**P* values for cfNRI.

†*P* values for cNRI.

‡FRS was used as a reference.

‖ASCVD was used as a reference.

§The CACS-added model was used as a reference.

¶IRFs were used as a reference.

Conclusions

In this community-based cohort from an asymptomatic elderly Korean population, CCTA proved to have better long-term prognostic value than did CACS with conventional cardiovascular risk factors. In addition, the highly negative predictability of CCTA was shown in normal groups over >8-year follow-up. Additional studies are needed to evaluate whether changes in treatment according to CCTA findings affect cardiovascular outcomes and the type of treatment that

would be suitable for an asymptomatic elderly population with abnormal CCTA findings.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods and Results

Exclusion Criteria

The exclusion criteria were a previous diagnosis of stable angina, variant angina, acute coronary syndrome, or heart failure; a history of percutaneous coronary intervention, coronary artery bypass grafting surgery, or other open-heart surgery; and current or past symptoms of angina pectoris or exertional dyspnea.

Assessment of Anthropometric and Biochemical Parameters

Diabetes mellitus (DM) was defined as being present in individuals who were taking antidiabetic drugs, who had a history of DM, whose fasting blood sugar level was ≥126 mg/dL, or whose glycosylated hemoglobin level was ≥6.5%. Hypertension was defined as a condition affecting individuals who were taking antihypertensive drugs, who had a history of hypertension, or whose blood pressure was ≥140/90 mmHg. Dyslipidemia in this study was defined based on the National Cholesterol Education Program–Adult Treatment Panel III guideline: i.e., the level of low-density lipoprotein-cholesterol was greater than the individualized recommended level.[1] Current smokers were defined as individuals who smoked at the time of enrollment, or who had quit smoking less than 1 year before enrollment. For assessing changes in antiplatelet agents and statins, newly started agents or dose increases were

considered as escalation, whereas stopping or dose decreases were considered as de-escalations. For each drug, escalation was classified as +1, de-escalation as –1, and maintenance as 0, and the sums of the total scores of both antiplatelet agents and statins were used for adjustment in further analyses.

Image Acquisition in Detail

Before CCTA imaging, individuals with a heart rate >70 beats/min received 10–30 mg of intravenous esmolol (Jeil Pharmaceutical Co., Ltd., Seoul, South Korea). A standard scanning protocol was used, as described previously.[2] For the contrast medium, we injected a bolus of 80 mL iomeprol (Iomeron 400; Bracco, Milan, Italy) intravenously at a velocity of 4 mL/s, followed by a 50 mL saline chaser. Once a threshold of 150 Hounsfield units was reached with bolus tracking, image acquisition was started automatically. Images were reconstructed at the mid-diastolic phase of the cardiac cycle (75% of the R–R interval) using matched recorded electrocardiograms.

Defining Plaques

A plaque was defined as a structure >1 mm^2 located within and/or adjacent to the vessel lumen and that could be clearly distinguished from the lumen and surrounding pericardial tissue.[3] Plaque burdens were analyzed on a per-segment basis according to a 16-segment coronary artery tree model used in a prior study.[4] The diameter of stenosis of each segment was defined as the proportion of the coronary artery that was enhanced by the contrast dye, which was semiautomatically traced at the site of maximal stenosis and compared with the mean value of proximal and distal reference sites, as shown in our previous study.[5] For Cox regression

analysis, we defined plaque characteristics when two or more segments had the same plaque features.

Defining Vessel Diseases

Within the category of obstructive CAD, we further divided CCTA findings as 1-, 2-, or 3-vessel disease (VD)/left main (LM), which involved one to three arteries among the left anterior descending artery (LAD), the left circumflex artery (LCX), and the right coronary artery (RCA) systems. Stenoses in diagonal branches, obtuse marginal branches, and the posterolateral branch were considered as part of the LAD, LCX, or RCA systems, respectively. We regarded the posterior descending coronary artery as part of the LCX or RCA system, depending on the local dominance of the coronary artery.

Defining Cardiac Death and Myocardial Infarction

Cardiac death was defined as being linked to a reasonable cardiac cause based on medical records. We defined myocardial infarction as the presence of cardiac enzyme elevation (positive serum creatine kinase-MB or troponin-I levels, or an elevation in the creatine kinase level to at least two times the upper limit of the normal range) accompanied by at least one of the following parameters: prolonged chest pain requiring hospital admission; development of Q waves; or other ECG changes suggesting myocardial infarction.

Predicted Risk Categories Used for Categorical Net Reclassification Index (cNRI)

For FRS and individual risk factors, we defined the predicted risk categories as follows: (1) <2.5%; (2) 2.5% to <7.5%; (3) 7.5% to <15%; and (4) ≥15%. These categories were derived from a previous study with a similar follow-up period.[6] For the atherosclerotic cardiovascular disease (ASCVD) risk score, we defined risk categories as follows, regarding the follow-up time of our study: (1) <3.3%; (2) 3.3% to <5.0%; (3) 5.0% to <10%; and (4) ≥10%. These categories were derived from the 10-year ASCVD risk score categories used in a previous study of the elderly (<5%; 5% to <7.5%; and 7.5% to <15%).[7]

Table S1. Changes in Medications (Antiplatelet Agents and Statins) During the Follow-up Period.

	Total	Normal	Nonobstructive CAD	Obstructive CAD	P value
	n = 470	*n* = 170	*n* = 224	*n* = 76	
Antiplatelet agents*					
Use at baseline	87 (18.5)	23 (13.5)	43 (19.2)	21 (27.6)	0.029
Use during total follow-up period	132 (28.1)	39 (22.9)	63 (28.1)	30 (39.5)	0.029
Change in medication†					0.572
De-escalated	3 (0.6)	0 (0.0)	2 (0.9)	1 (1.3)	
Maintained	422 (89.8)	155 (91.2)	201 (89.7)	66 (86.8)	
Escalated	45 (9.6)	15 (8.8)	21 (9.4)	9 (11.8)	
Statin**					
Use at baseline	29 (6.2)	11 (6.5)	11 (4.9)	7 (9.2)	0.421
Use during total follow-up period	60 (12.8)	21 (12.4)	27 (12.1)	12 (15.8)	0.687
Change in medication†					0.760
De-escalation	3 (0.6)	1 (0.6)	2 (0.9)	0 (0.0)	
Maintain	433 (92.1)	158 (92.9)	207 (92.4)	68 (89.5)	
Escalation	34 (7.2)	11 (6.5)	15 (6.7)	8 (10.5)	
Combined medication change score, mean (SD) ‡	0.15 (0.51)	0.15 (0.48)	0.14 (0.52)	0.18 (0.56)	0.824

Values are numbers and percentages (%).

*Antiplatelet agents used during the follow-up period were aspirin, clopidogrel, cilostazol and triflusal.

**Statins used in this study included atorvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin, and fluvastatin.

† Newly started or dose increases were considered as escalation; stopping or dose decreases were considered as de-escalation.

‡ For each drug, escalation was calculated as +1, de-escalation as -1 and maintenance as 0, and the sum of total scores of both antiplatelets and statins was used in further analyses.

Table S2. Population Distribution of Each CACS Category According to the Severity of CAD by CCTA.

	Total (n = 470)	Normal (n = 170)	Nonobstructive CAD (n = 224)	Obstructive CAD (n = 76)	*P* value
CACS category					<0.001
0–100	334 (100.0)	169 (50.6)	146 (43.7)	19 (5.7)	
0–10	219 (100.0)	168 (76.7)	41 (18.7)	10 (4.6)	
11–100	115 (100.0)	1 (0.9)	105 (91.3)	9 (7.8)	
101–400	79 (100.0)	1 (1.3)	61 (77.2)	17 (21.5)	
400–1000	38 (100.0)	0 (0.0)	15 (39.5)	23 (60.5)	
>1000	19 (100.0)	0 (0.0)	2 (10.5)	17 (89.5)	

Values in normal, nonobstructive CAD, and obstructive CAD are numbers and percentages for the totals in the same row.

CACS, coronary artery calcium score.

Table S3. Causes of Death.

Cause	No.	% of total deaths	% of the total population
Cardiac death	16	15.4	3.4
Stroke	8	7.7	1.7
Cancer	40	38.5	8.5
Senility	7	6.7	1.5
Liver cirrhosis	3	2.9	0.6
Pneumonia/obstructive lung disease	8	7.7	1.7
Neurocognitive disorders	9	8.7	1.9
Infection/sepsis	4	3.8	0.9
Others	9	8.7	1.9
Total	104	100.0	22.1

Table S4. Cox Regression Analyses with CACS, FRS, ASCVD and Individual Risk Factors for Major Adverse Cardiac Events.

	CACS*	FRS*	ASCVD*	Individual RF†	Medication change‡	CACS + FRS + Medication change‡	CACS + ASCVD+ Medication change‡	CACS + Individual RF + Medication change‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
CACS category								
0–100	1.00 (Reference)	-	-	-	-	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
101–400	3.24 (1.23-8.52)	-	-	-	-	2.79 (1.03-7.50)	2.66 (0.98-7.21)	2.63 (0.96-7.24)
401–1000	3.18 (0.87-11.57)	-	-	-	-	2.62 (0.72-9.59)	2.10 (0.56-7.95)	2.49 (0.65-9.50)
>1000	7.96 (2.49-25.39)	-	-	-	-	6.27 (1.93-20.34)	4.06 (1.12-14.74)	5.45 (1.44-20.60)
FRS (per score)	-	1.03 (1.01-1.05)	-	-	-	1.02 (1.00-1.04)	-	-
ASCVD (per score)	-	-	1.03 (1.02-1.05)	-	-	-	1.02 (1.01-1.04)	-
Age§	-	-	-	2.04 (1.25-3.35)	-	-	-	1.60 (0.94-2.73)
Male sex	-	-	-	1.67 (0.70-4.03)	-	-	-	1.78 (0.74-4.27)
Systolic BP	-	-	-	1.00 (0.98-1.02)	-	-	-	0.99 (0.97-1.02)
Anti–HT medication	-	-	-	1.59 (0.70-3.61)	-	-	-	1.49 (0.65-3.41)
Current smoking	-	-	-	2.17 (0.84-5.63)	-	-	-	1.95 (0.75-5.09)
Diabetes mellitus	-	-	-	1.63 (0.71-3.72)	-	-	-	1.49 (0.65-3.42)
HDL–cholesterol	-	-	-	0.83 (0.22-3.17)	-	-	-	0.67 (0.18-2.56)
Total cholesterol	-	-	-	1.31 (0.85-2.00)	-	-	-	1.31 (0.85-2.02)

Medication change‡ (Antiplatelet, Statin)	-	-	-	-	0.87 (0.37-2.01)	0.79 (0.37-1.71)	0.79 (0.35-1.80)	0.74 (0.32-1.67)

Anti–HT, antihypertensive; ASCVD, Atherosclerotic Cardiovascular Disease risk score; BP, blood pressure; FRS, Framingham risk score; RF, risk factor.

* Univariable analyses.

† Multivariable analyses with individual risk factors consisting of FRS and ASCVD.

‡ Antiplatelet agents and statin drugs were included in this analysis. For each drug, the escalation was calculated as +1, de-escalation as -1 and maintenance as 0, and the sums of total scores were used.

§ Per 10-years increase was used. SI units (mmol/L) were used for HDL-cholesterol and total cholesterol.

Table S5. Cox Regression Analyses of Plaque Features for MACEs.

	Calcified Plaque*		Mixed Plaque*		Noncalcified Plaque*	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Plaque character (Univariate)	2.15 (0.92-5.03)	0.077	2.63 (1.09-6.35)	0.031	2.88 (1.19-6.94)	0.019
Plaque character + FRS + medication change†	1.57 (0.70-4.02)	0.249	2.24 (0.93-5.43)	0.074	2.46 (1.02-5.96)	0.046
Plaque character + FRS + medication change† + CACS	0.78 (0.28-2.18)	0.640	1.31 (0.49-3.52)	0.597	1.41 (0.52-3.83)	0.502
Plaque character + FRS + medication change† + Severity of CAD	1.07 (0.44-2.62)	0.881	1.12 (0.43-2.89)	0.817	1.32 (0.52-3.39)	0.560

FRS, Framingham risk score; HR, hazard ratio; MACE, major adverse cardiac event.

* Analyses were done for each kind of plaques separately. No plaque or different types of plaques were used as reference values. Plaque characteristics were defined when two or more segments had the same plaque feature.

† Changes in the use of antiplatelet agents and statins were included in this analysis.

Table S6. Predicted Risk of MACE Using Multivariate Risk Prediction Model With and Without CCTA (Severity of CAD).

FRS						ASCVD						Individual Risk factors*					
	Model with CCTA						Model with CCTA						Model with CCTA				
Model without CCTA†	0.0-2.4%	2.5-7.4%	7.5-14.9%	≥15%	Total	Model without CCTA†	0.0-3.32%	3.33-4.9%	5.0-9.9%	≥10%	Total	Model without CCTA†	0.0-2.4%	2.5-7.4%	7.5-14.9%	≥15%	Total
Events						**Events**						**Events**					
0.0-2.4%	3 (13%)	1 (4%)	0 (0%)	0 (0%)	4 (17%)	0.0-3.32%	4 (17%)	0 (0%)	1 (4%)	0 (0%)	5 (21%)	0.0-2.4%	2 (8%)	1 (4%)	0 (0%)	0 (0%)	3 (13%)
2.5-7.4%	0 (0%)	4 (17%)	3 (13%)	0 (0%)	7 (29%)	3.33-4.9%	1 (4%)	1 (4%)	0 (0%)	0 (0%)	2 (8%)	2.5-7.4%	0 (0%)	4 (17%)	1 (4%)	1 (4%)	6 (25%)
7.5-14.9%	0 (0%)	1 (4%)	2 (8%)	2 (8%)	5 (21%)	5.0-9.9%	0 (0%)	0 (0%)	3 (13%)	4 (17%)	7 (29%)	7.5-14.9%	0 (0%)	0 (0%)	5 (21%)	4 (17%)	9 (38%)
≥15%	0 (0%)	0 (0%)	1 (4%)	7 (29%)	8 (33%)	≥10%	0 (0%)	0 (0%)	0 (0%)	10 (42%)	10 (42%)	≥15%	0 (0%)	0 (0%)	2 (8%)	4 (17%)	6 (25%)
Total	3 (13%)	6 (25%)	6 (25%)	9 (38%)	24 (100%)	Total	5 (21%)	1 (4%)	4 (17%)	14 (58%)	24 (100%)	Total	2 (8%)	5 (21%)	8 (33%)	9 (38%)	24 (100%)
Nonevents						**Nonevents**						**Nonevents**					
0.0-2.4%	116 (26%)	7 (2%)	5 (1%)	0 (0%)	128 (29%)	0.0-3.32%	210 (47%)	0 (0%)	5 (1%)	4 (1%)	219 (49%)	0.0-2.4%	146 (33%)	3 (1%)	2 (0%)	0 (0%)	151 (34%)
2.5-7.4%	54 (12%)	154 (35%)	13 (3%)	8 (2%)	229 (51%)	3.33-4.9%	37 (8%)	32 (7%)	2 (0%)	2 (0%)	73 (16%)	2.5-7.4%	46 (10%)	133 (30%)	14 (3%)	2 (0%)	195 (44%)
7.5-14.9%	0 (0%)	27 (6%)	20 (4%)	15 (3%)	62 (14%)	5.0-9.9%	9 (2%)	38 (9%)	30 (7%)	23 (5%)	100 (22%)	7.5-14.9%	0 (0%)	29 (7%)	20 (4%)	21 (5%)	70 (16%)
≥15%	0 (0%)	3 (1%)	5 (1%)	19 (4%)	27 (6%)	≥10%	0 (0%)	1 (0%)	19 (4%)	34 (8%)	54 (12%)	≥15%	0 (0%)	2 (0%)	7 (2%)	21 (5%)	30 (7%)

Total	170 (38%)	191 (43%)	43 (10%)	42 (9%)	446 (100%)	Total	256 (57%)	71 (16%)	56 (13%)	63 (14%)	446 (100%)	Total	192 (43%)	167 (37%)	43 (10%)	44 (10%)	446 (100%)

Values are numbers and percentages (%).

ASCVD, Atherosclerotic Cardiovascular Disease risk score; FRS, Framingham risk score; IRFs, individual risk factors from FRS and ASCVD.

* Variables included in FRS and ASCVD risk score (age, sex, systolic blood pressure, antihypertensive medication use, current smoking, diabetes, high-density lipoprotein cholesterol, total cholesterol) were used for individual risk factors.

† Conventional risk factors (FRS, ASCVD risk score or Individual risk factors) and coronary calcium scores were adjusted in this model.

Table S7. Cox Regression Analyses and cfNRI of CCTA Findings, Adjusted by other CACS category (0-10, 11-100, 101-400, >400).

	Multivariable with FRS* +CACS†			Multivariable with ASCVD*+CACS†			Multivariable with Individual RF*+CACS†		
	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§
Severity of CAD	-	0.602 (0.198-1.005)	0.004	-	0.596 (0.190-1.003)	0.004	-	0.525 (0.122-0.929)	0.011
Nonobstructive	0.65 (0.08-5.42)	-	-	0.65 (0.08-5.24)	-	-	0.64 (0.08-5.05)	-	-
Obstructive	2.72 (0.33-22.74)	-	-	2.78 (0.34-22.48)	-	-	2.71 (0.34-21.78)	-	-
Number of VD	-	0.473 (0.067-0.879)	0.023	-	0.374 (-0.033-0.781)	0.072	-	0.359 (-0.051-0.768)	0.086
Nonobstructive	0.65 (0.08-5.35)	-	-	0.66 (0.08-5.24)	-	-	0.62 (0.08-4.91)	-	-
1,2-VD	2.34 (0.28-19.76)	-	-	2.54 (0.31-20.64)	-	-	2.32 (0.28-19.08)	-	-
3-VD/LM	6.25 (0.59-66.50)	-	-	5.62 (0.51-61.80)	-	-	5.17 (0.47-56.33)	-	-
SIS (category)‡	-	0.640 (0.243-1.037)	0.002	-	0.640 (0.243-1.037)	0.002	-	0.710 (0.323-1.097)	<0.001
1-4	3.72 (1.14-12.13)	-	-	3.93 (1.23-12.55)	-	-	4.02 (1.23-13.12)	-	-
≥5	5.42 (0.94-31.17)	-	-	5.78 (1.00-33.39)	-	-	5.24 (0.85-32.36)	-	-
SSS (category)‡	-	0.793 (0.420-1.167)	<0.001	-	0.845 (0.488-1.203)	<0.001	-	0.710 (0.323-1.097)	<0.001
1-4	3.52 (1.06-11.71)	-	-	3.71 (1.14-12.10)	-	-	3.82 (1.15-12.69)	-	-
≥5	7.56 (1.55-36.81)	-	-	8.11 (1.65-39.78)	-	-	7.95 (1.52-41.55)	-	-
Duke (category) ‡	-	0.811 (0.416-1.206)	<0.001	-	0.811 (0.416-1.206)	<0.001	-	0.716 (0.320-1.112)	<0.001
2	4.13 (1.29-13.26)	-	-	4.33 (1.39-13.47)	-	-	4.69 (1.44-15.30)	-	-
≥3	5.94 (1.63-21.71)	-	-	6.03 (1.65-22.07)	-	-	6.36 (1.62-24.90)	-	-

ASCVD, atherosclerotic cardiovascular disease risk score; CI, confidence interval; Duke, modified Duke score; FRS, Framingham risk score; HR, hazard ratio; SIS, segment involvement score; SSS, segment stenosis score; VD, vessel disease; LM, left main.

*All multivariable analyses were adjusted for conventional risk factors, CACS, and medication change (antiplatelet agents, statins) during the follow-up period. As conventional risk factors, FRS, ASCVD risk score, and individual risk factors were used individually. FRS and ASCVD risk score were adjusted as continuous variables. For individual risk factors, variables included in FRS and ASCVD risk score (age, sex, systolic blood pressure, antihypertensive medication use, current smoking, diabetes, high-density lipoprotein cholesterol level, and total cholesterol level) were used.

†CACS was adjusted as a categorical variable; 0–10, 11–100, 101–400, >400.

‡The reference categories of these variables are 0 for SIS (category) and SSS (category), and 1 for Duke score (category).

§*P-values* for cfNRI were used.

Table S8. Cox Regression Analyses and cfNRI of CCTA Findings, Adjusted by other CACS category (0, 1-100, 101-400, >400).

	Multivariable with FRS* +CACS†			Multivariable with ASCVD*+CACS†			Multivariable with Individual RF*+CACS†		
	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§
Severity of CAD	-	0.691 (0.285-1.096)	0.001	-	0.664 (0.258-1.070)	0.001	-	0.777 (0.375-1.178)	<0.001
Nonobstructive	1.13 (0.17-7.53)	-	-	1.12 (0.17-7.34)	-	-	1.07 (0.17-6.86)	-	-
Obstructive	4.47 (0.66-30.07)	-	-	4.54 (0.69-30.12)	-	-	4.30 (0.65-28.29)	-	-
Number of VD	-	0.605 (0.206-1.004)	0.003	-	0.634 (0.230-1.038)	0.002	-	0.727 (0.321-1.132)	<0.001
Nonobstructive	1.15 (0.17-7.59)	-	-	1.15 (0.18-7.46)	-	-	1.07 (0.17-6.83)	-	-
1,2-VD	3.89 (0.57-26.53)	-	-	4.19 (0.63-27.95)	-	-	3.76 (0.56-25.37)	-	-
3-VD/LM	9.92 (1.13-87.10)	-	-	8.80 (0.96-80.88)	-	-	7.89 (0.86-72.74)	-	-
SIS (category)‡	-	0.640 (0.243-1.037)	0.002	-	0.636 (0.239-1.032)	0.002	-	0.631 (0.234-1.028)	0.002
1-4	4.07 (1.24-13.32)	-	-	4.29 (1.34-13.74)	-	-	4.30 (1.31-14.09)	-	-
≥5	5.93 (1.03-34.13)	-	-	6.30 (1.09-36.46)	-	-	5.59 (0.91-34.52)	-	-
SSS (category)‡	-	0.793 (0.420-1.167)	<0.001	-	0.845 (0.488-1.203)	<0.001	-	0.622 (0.225-1.019)	0.002
1-4	3.86 (1.16-12.90)	-	-	4.06 (1.24-13.29)	-	-	4.10 (1.23-13.67)	-	-
≥5	8.42 (1.71-41.51)	-	-	8.97 (1.80-44.64)	-	-	8.60 (1.63-45.52)	-	-
Duke (category)‡	-	0.736 (0.334-1.138)	<0.001	-	0.811 (0.416-1.206)	<0.001	-	0.629 (0.226-1.032)	0.002
2	4.55 (1.39-14.86)	-	-	4.76 (1.51-15.03)	-	-	5.07 (1.54-16.69)	-	-
≥3	6.27 (1.71-22.98)	-	-	6.35 (1.73-23.28)	-	-	6.57 (1.68-25.65)	-	-

ASCVD, atherosclerotic cardiovascular disease risk score; CI, confidence interval; Duke, modified Duke score; FRS, Framingham risk score; HR, hazard ratio; SIS, segment involvement score; SSS, segment stenosis score; VD, vessel disease; LM, left main.

*All multivariable analyses were adjusted for conventional risk factors, CACS, and medication change (antiplatelet agents, statins) during the follow-up period. As conventional risk factors, FRS, ASCVD risk score, and individual risk factors were used individually. FRS and ASCVD risk score were adjusted as continuous variables. For individual risk factors, variables included in FRS and ASCVD risk score (age, sex, systolic blood pressure, antihypertensive medication use, current smoking, diabetes, high-density lipoprotein cholesterol level, and total cholesterol level) were used.

†CACS was adjusted as a categorical variable; 0, 1–100, 101–400, >400.

‡The reference categories of these variables are 0 for SIS (category) and SSS (category), and 1 for Duke score (category).

§*P-values* for cfNRI were used.

Table S9. Subgroup Analysis of Cox Regression and cfNRI, According to Sex.

	Multivariable with FRS* +CACS†			Multivariable with ASCVD*+CACS†			Multivariable with Individual RF*+CACS†		
	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§	HR (95% CI)	cfNRI (95% CI)	*P*-value§
Male									
Severity of CAD‡	-	0.714 (0.200-1.229)	0.007		0.723 (0.209-1.237)	0.006		0.555 (0.039-1.070)	0.035
Normal/NonObs	Reference	-	-	Reference	-	-	Reference	-	-
Obstructive	4.88 (1.49-15.98)	-	-	5.65 (1.73-18.47)	-	-	5.08 (1.53-16.89)	-	-
Number of VD‡	-	0.750 (0.236-1.263)	0.004	-	0.750 (0.236-1.263)	0.004	-	0.758 (0.245-1.272)	0.004
Normal/NonObs	Reference	-	-	Reference	-	-	Reference	-	-
1,2-VD	4.09 (1.17-14.34)	-	-	4.65 (1.33-16.23)	-	-	4.13 (1.17-14.59)	-	-
3-VD/LM	16.12 (2.62-99.10)	-	-	18.91 (3.09-115.8)	-	-	22.97 (3.43-153.99)	-	-
Female									
Severity of CAD‡	-	0.697 (0.043-1.351)	0.037	-	0.292 (-0.332-0.917)	0.359	-	0.664 (0.005-1.322)	0.048
Normal/NonObs	Reference	-	-	Reference	-	-	Reference	-	-
Obstructive	4.73 (0.70-32.23)	-	-	3.12 (0.44-22.10)	-	-	4.42 (0.37-53.15)	-	-
Number of VD‡	-	0.697 (0.043-1.351)	0.037	-	0.207 (-0.343-0.757)	0.461	-	0.496 (-0.162-1.154)	0.139
Normal/NonObs	Reference	-	-	Reference	-	-	Reference	-	-
1,2-VD	4.66 (0.66-33.03)	-	-	3.30 (0.48-22.71)	-	-	5.16 (0.43-61.82)	-	-
3-VD/LM	5.17 (0.33-80.03)	-	-	2.07 (0.12-36.49)	-	-	1.32 (0.04-47.36)	-	-

ASCVD, atherosclerotic cardiovascular disease risk score; CI, confidence interval; FRS, Framingham risk score; HR, hazard ratio; Normal/NonObs, normal or nonobstructive; VD, vessel disease; LM, left main.

*All multivariable analyses were adjusted for conventional risk factors, CACS, and medication change (antiplatelet agents, statins) during the follow-up period. As conventional risk factors, FRS, ASCVD risk score, and individual risk factors were used individually. FRS and ASCVD risk score were adjusted as continuous variables. For individual risk factors, variables included in FRS and ASCVD risk score except for sex were used.

†Because no MACE occurred in CACS 101-400 group of female, CACS was categorized as follows; 0–400, 401–1000, >1000.

‡Because no MACE occurred in normal CAD group of male, normal or nonobstructive CAD group was used as the reference group.

§*P-values* for cfNRI were used.

Table S10. Subgroup Analysis of Cox Regression and cfNRI According to Age.

	Multivariable with FRS* +CACS†			Multivariable with ASCVD*+CACS†			Multivariable with Individual RF*+CACS†		
	HR (95% CI)	cfNRI (95% CI)	*P*-value‡	HR (95% CI)	cfNRI (95% CI)	*P*-value‡	HR (95% CI)	cfNRI (95% CI)	*P*-value‡
Age < 80 years									
Severity of CAD	-	0.910 (0.387-1.433)	0.001		0.950 (0.428-1.472)	<0.001		0.751 (0.226-1.276)	0.005
Nonobstructive	1.15 (0.19-7.06)	-	-	1.17 (0.19-7.17)	-	-	1.10 (0.17-6.94)	-	-
Obstructive	7.48 (1.15-48.66)	-	-	8.24 (1.30-52.27)	-	-	7.73 (1.14-52.57)	-	-
Number of VD	-	0.841 (0.314-1.368)	0.002	-	0.841 (0.314-1.368)	0.002	-	0.910 (0.387-1.433)	0.001
Nonobstructive	1.01 (0.16-6.35)	-	-	1.03 (0.16-6.53)	-	-	1.04 (0.16-6.73)	-	-
1,2-VD	4.65 (0.66-32.86)	-	-	5.35 (0.78-36.89)	-	-	5.12 (0.69-38.04)	-	-
3-VD/LM	39.49 (4.39-355.1)	-	-	36.51 (4.22-316.0)	-	-	43.00 (4.33-426.84)	-	-
Age ≥ 80 years									
Severity of CAD	-	-0.119 (-0.756-0.518)	0.714	-	0.102 (-0.498-0.702)	0.739	-	0.115 (-0.525-0.755)	0.725
Nonobstructive	1.67 (0.17-16.80)	-	-	1.33 (0.13-14.05)	-	-	1.66 (0.13-21.77)	-	-
Obstructive	1.99 (0.13-30.33)	-	-	1.60 (0.11-24.23)	-	-	1.54 (0.08-30.40)	-	-
Number of VD	-	-0.192 (-0.842-0.459)	0.564	-	-0.179 (-0.819-0.461)	0.584	-	-0.013 (-0.651-0.626)	0.969
Nonobstructive	1.66 (0.16-16.80)	-	-	1.30 (0.12-13.92)	-	-	1.79 (0.13-24.40)	-	-
1,2-VD	2.02 (0.13-31.79)	-	-	1.69 (0.11-25.68)	-	-	2.44 (0.10-61.67)	-	-
3-VD/LM	1.88 (0.08-46.70)	-	-	1.32 (0.05-32.67)	-	-	0.93 (0.03-25.54)	-	-

ASCVD, atherosclerotic cardiovascular disease risk score; CI, confidence interval; FRS, Framingham risk score; HR, hazard ratio; Normal/NonObs, normal or nonobstructive; VD, vessel disease; LM, left main.

*All multivariable analyses were adjusted for conventional risk factors and CACS during the follow-up period. Medication change variable was not adjusted, because no MACE occurred in a few categories of medication change in the age ≥75 group. As conventional risk factors, FRS, ASCVD risk score, and individual risk factors were used individually. FRS and ASCVD risk score were adjusted as continuous variables. For individual risk factors, variables included in FRS and ASCVD risk score (age, sex, systolic blood pressure, antihypertensive medication use, current smoking, diabetes, high-density lipoprotein cholesterol level, and total cholesterol level) were used.

†CACS was adjusted as a categorical variable; 0–100, 101–400, 401–1000, >1000.

‡*P-values* for cfNRI were used.

Table S11. Comparison Between CONFIRM Registry[8] and KLoSHA Study.

	CONFIRM* (Third age tertile)	KLoSHA†
Baseline characteristics		
n	1065	470
Follow up duration (median year) (IQR)	2.2 (1.5-3.4)	8.2 (7.7–10.1)
Ethnicity	Multi-ethnic	Korean
Age (years)	68.6 ± 5.4	75.1 ± 7.3
Male sex	594 (55.8)	242 (51.5)
Body mass index (kg/m^2)	26.3 (4.0)	24.2 (3.2)
Hypertension	599 (57.1)	317 (67.4)
Diabetes mellitus	184 (17.3)	133 (28.3)
Dyslipidemia	646 (61.4)	354 (75.3) (ATP III) 286 (60.9) (TC >200)
Current smoking	96 (9.0)	67 (14.3)
CCTA results		
CACS		
0–100	699 (65.7)	334 (71.1)
101–400	200 (18.8)	79 (16.8)
>400	166 (15.6)	57 (12.1)
Severity of CAD		
Any CAD (%)	67.9	63.6
Obstructive CAD (%)	21.7	16.2
Clinical outcomes		
All cause death + Nonfatal MI	36 (3.38)	112 (23.83)
Cardiac death + Nonfatal MI	Not available	24 (5.11)
Prognostic value of CCTA		
C-statistic (95% CI)		
FRS+CACS	0.70 (0.47-0.68)	0.70 (0.58-0.82)
FRS+CACS+CCTA	0.75 (0.68-0.83)	0.75 (0.63-0.87)
Category-free NRI (95% CI)		
FRS+CACS+CCTA	0.75 (0.46-1.04)	0.48 (0.07-0.89)

Event NRI/Nonevent NRI	0.50/0.25	0.08/0.39

Continuous values are given as the mean ± SD and categorical values are numbers and percentages (%).

NRI, net reclassification index; FRS, Framingham risk score; IQR, interquartile range; MI, Myocardial infarction; TC, Total Cholesterol.

* The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter.

† The Korean Longitudinal Study on Health and Aging.

Table S12. Baseline Characteristics of Subjects with and without CCTA.

	No CCTA (n = 459)	CCTA (n = 541)	*P* value
Age (years)	79.7 ± 9.0	75.1 ± 7.2	<0.001
Men	168 (36.6)	271 (50.1)	<0.001
Family history of CAD	32 (7.0)	46 (8.5)	NS
Current or ex-smokers	166 (36.2)	223 (41.2)	NS
Systolic blood pressure (mm Hg)	132.2 ± 18.5	132.7 ± 17.6	NS
Diastolic blood pressure (mm Hg)	82.0 ± 10.3	83.4 ± 10.8	NS
Fasting blood glucose (mg/dL)	103.9 ± 23.9	111.8 ± 25.7	<0.001
HbA1c (%)	5.9 ± 0.8	6.1 ± 0.9	<0.001
Total cholesterol (mg/dL)	203.6 ± 38.3	202.1 ± 37.6	NS
Triglyceride (mg/dL)	127.3 ± 66.9	140.8 ± 91.1	NS
HDL-cholesterol (mg/dL)	44.6 ± 13.0	45.5 ± 12.4	NS
LDL-cholesterol (mg/dL)	133.6 ± 33.7	128.4 ± 34.8	NS
Serum creatinine (mg/dL)	1.14 ± 0.44	1.09 ± 0.20	NS
10-year FRS (%)	32.1 ± 19.5	32.9 ± 20.2	NS
Medical history, n (%)			
Diabetes mellitus	82 (17.9)	154 (28.5)	<0.001
Hypertension	334 (72.9)	373 (69.1)	NS
Dyslipidemia (ATP III)*	332 (73.3)	412 (76.2)	NS

Continuous values are means ± SD or categorical values are numbers and percentages (%). ATP III, Adult Treatment Panel III; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FRS, Framingham risk score; HDL, high-density lipoprotein; LDL, low-density lipoprotein. A Bonferroni correction was applied to the statistical analysis.

* Dyslipidemia (ATP III) refers to dyslipidemia defined using individualized LDL-cholesterol levels according to the ATP III guideline.

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