SUPPLEMENTAL MATERIAL
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. 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. 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 mm² located within and/or adjacent to the vessel lumen and that could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaque burdens were analyzed on a per-segment basis according to a 16-segment coronary artery tree model used in a prior study. 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. 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.\textsuperscript{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%).\textsuperscript{7}
Table S1. Changes in Medications (Antiplatelet Agents and Statins) During the Follow-up Period.

|                           | Total  | Normal | Nonobstructive CAD | Obstructive CAD | P value |
|---------------------------|--------|--------|--------------------|-----------------|---------|
| Total                     | 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.

| CACS category | Total (n = 470) | Normal (n = 170) | Nonobstructive CAD (n = 224) | Obstructive CAD (n = 76) | P value |
|---------------|----------------|------------------|-----------------------------|--------------------------|---------|
| 0–100         | 334 (100.0)    | 169 (50.6)       | 146 (43.7)                  | 19 (5.7)                 | <0.001  |
| 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                      |
| CACS category | CACS\* | FRS\* | ASCVD\* | Individual RF\† | Medication change‡ | CACS + FRS + Medication change‡ | CACS + ASCVD + Medication change‡ | CACS + Individual RF + Medication change‡ |
|---------------|--------|-------|---------|-----------------|-----------------|-------------------------------|-------------------------------|--------------------------------|
| 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‡       | 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.
|                   | Calcified Plaque* | Mixed Plaque* | Noncalcified Plaque* |
|-------------------|-------------------|---------------|----------------------|
|                   | HR (95% CI)       | P             | HR (95% CI)          | P             | HR (95% CI)       | P             |
| Plaque character  | 2.15 (0.92-5.03)  | 0.077         | 2.63 (1.09-6.35)     | 0.031         | 2.88 (1.19-6.94)  | 0.019         |
| (Univariate)      |                   |               |                      |               |                   |               |
| + 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         |
| + 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         |
| + 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       | Model with CCTA | ASCVD   | Model with CCTA | Individual Risk factors† |
|-----------|-----------------|---------|-----------------|---------------------------|
| Model     | 0.0- 2.5- 7.5- | 0.0- 3.32- 4.9- | 0.0- 2.5- 2.4% | 0.0- 2.5- 2.4% |
| without   | 2.4% 7.4% 14.9% | 3.32% 4.9% 9.9% | 4.9% 14.9% | 7.4% 14.9% |
| CCTA†     | 0               | 10.0%   | 10.0%           | 10.0%                     |
| Events    |                 |         |                 |                           |
| 0.0-2.4%  | 3 (13%)         | 4 (17%) | 2 (8%)          | 2 (8%)                    |
| 2.5-7.4%  | 0 (0%)          | 1 (4%)  | 0 (0%)          | 0 (0%)                    |
| 7.5-14.9% | 0 (0%)          | 1 (4%)  | 0 (0%)          | 0 (0%)                    |
| ≥15%      | 0 (0%)          | 1 (4%)  | 0 (0%)          | 0 (0%)                    |
| Total     | 3 (13%)         | 6 (26%) | 5 (21%)         | 5 (21%)                   |
| Nonevents | 116 (26%)       | 7 (2%)  | 5 (2%)          | 4 (1%)                    |
| 0.0-2.4%  | 10 (26%)        | 9 (26%) | 5 (26%)         | 4 (26%)                   |
| 2.5-7.4%  | 1 (12%)         | 3 (35%) | 1 (35%)         | 1 (35%)                   |
| 7.5-14.9% | 0 (0%)          | 2 (6%)  | 0 (0%)          | 0 (0%)                    |
| ≥15%      | 0 (0%)          | 3 (12%) | 0 (0%)          | 0 (0%)                    |
| Total     | 128 (29%)       | 12 (2%) | 12 (2%)         | 12 (2%)                   |
| Events    |                 |         |                 |                           |
| 0.0-2.4%  | 4 (17%)         | 0 (0%)  | 0 (0%)          | 0 (0%)                    |
| 2.5-7.4%  | 1 (4%)          | 1 (4%)  | 0 (0%)          | 0 (0%)                    |
| 7.5-14.9% | 0 (0%)          | 0 (0%)  | 0 (0%)          | 0 (0%)                    |
| ≥10%      | 0 (0%)          | 1 (4%)  | 0 (0%)          | 0 (0%)                    |
| Total     | 5 (21%)         | 1 (4%)  | 4 (17%)         | 4 (17%)                   |
| Nonevents | 24 (100%)       | 9 (21%) | 5 (21%)         | 3 (21%)                   |
| 0.0-2.4%  | 210 (47%)       | 0 (0%)  | 5 (10%)         | 4 (10%)                   |
| 2.5-7.4%  | 37 (8%)         | 32 (8%) | 2 (4%)          | 2 (4%)                    |
| 7.5-14.9% | 9 (2%)          | 38 (9%) | 30 (9%)         | 23 (9%)                   |
| ≥10%      | 0 (0%)          | 1 (4%)  | 19 (8%)         | 34 (8%)                   |
| Total     | 219 (49%)       | 0 (0%)  | 5 (10%)         | 4 (10%)                   |
| Nonevents | 151 (38%)       | 9 (21%) | 5 (21%)         | 3 (21%)                   |
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.
| Severity of CAD | Multivariable with FRS* +CACS† | Multivariable with ASCVD*+CACS† | Multivariable with Individual RF*+CACS† |
|----------------|--------------------------------|---------------------------------|--------------------------------------|
|                | HR (95% CI)                  | cfNRI (95% CI)                  | P- value§                             |
|                | cfNRI (95% CI)               | P- value§                       |
|                | P- value§                    |                                |
|                | HR (95% CI)                  | cfNRI (95% CI)                  | P- value§                             |
|                | cfNRI (95% CI)               | P- value§                       |
|                | P- value§                    |                                |
| Nonobstructive | 0.65 (0.08-5.42)             | -                               | 0.65 (0.08-5.24)                      | - |
|                | 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)            | -                               | 2.71 (0.34-21.78)                     | - |
| Nonobstructive | 0.65 (0.08-5.35)             | -                               | 0.66 (0.08-5.24)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |
| 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)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |
| 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)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |
| 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)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |
| 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)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |
| 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)                      | - |
| Obstructive    | 2.34 (0.28-19.76)            | -                               | 2.54 (0.31-20.64)                     | - |
|                | 2.32 (0.28-19.08)            | -                               | 2.32 (0.28-19.08)                     | - |

Table S7. Cox Regression Analyses and cfNRI of CCTA Findings, Adjusted by other CACS category (0-10, 11-100, 101-400, >400).
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§                               |
|                     |                               |                                 |                                        |
| **Male**            |                               |                                 |                                        |
| Severity of CAD‡    | -                             | 0.714 (0.200-1.229)             | 0.007                                  |
| Normal/NonObs       | 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                                  |
| Normal/NonObs       | 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                                  |
| Normal/NonObs       | 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                                  |
| Normal/NonObs       | 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     |             |                |          |             |                |          |             |                |          |
| 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\textsuperscript{8} and KLoSHA Study.

| Baseline characteristics | CONFIRM\textsuperscript{*} | KLoSHA\textsuperscript{†} |
|--------------------------|---------------------------|---------------------------|
| (Third age tertile) | | |
| 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\textsuperscript{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) |
| 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.
Supplemental References:

1. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii). *JAMA*. 2001;285:2486-2497.

2. Lim S, Choi HJ, Shin H, Khang AR, Kang SM, Yoon JW, Choi SH, Jeong IK, Cho SI, Park KS, Jang HC. Subclinical atherosclerosis in a community-based elderly cohort: The korean longitudinal study on health and aging. *Int J Cardiol*. 2012;155:126-133.

3. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, Ohnesorge B, Fayad ZA, Becker CR, Reiser M, Steinbeck G, Boekstegers P. 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.

4. Cho I, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Callister TQ, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Maffei E, Cademartiri F, Kaufmann P, Shaw LJ, Raff GL, Chinnaiyan KM, Villines TC, Cheng V, Nasir K, Gomez M, Min JK. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the confirm registry (coronary ct angiography evaluation for clinical outcomes: An international multicenter registry). *Circulation*. 2012;126:304-313.

5. Lim S, Shin H, Lee Y, Yoon JW, Kang SM, Choi SH, Park KS, Jang HC, Choi SI, Chun EJ. Effect of metabolic syndrome on coronary artery stenosis and plaque characteristics as assessed with 64-detector row cardiac ct. *Radiology*. 2011;261:437-445.

6. Auer R, Bauer DC, Marques-Vidal P, Butler J, Min LJ, Cornuz J, Satterfield S, Newman AB, Vittinghoff E, Rodondi N. Association of major and minor ecg abnormalities with coronary heart disease events. *Jama*. 2012;307:1497-1505.

7. Mortensen MB, Fuster V, Munthad P, Mehran R, Baber U, Sartori S, Falk E. A simple disease-guided approach to personalize acc/aha-recommended statin allocation in elderly people: The bioimage study. *J Am Coll Cardiol*. 2016;68:881-891.
8. Han D, Hartaigh BO, Gransar H, Lee JH, Rizvi A, Baskaran L, Schulman-Marcus J, Dunning A, Achenbach S, Al-Mallah MH, Berman DS, Budoff MJ, Cademartiri F, Maffei E, Callister TQ, Chinaiyan K, Chow BJW, DeLago A, Hadamitzky M, Hausleiter J, Kaufmann PA, Raff G, Shaw LJ, Villines TC, Kim YJ, Leipsic J, Feuchtner G, Cury RC, Pontone G, Andreini D, Marques H, Rubinshtein R, Hindoyan N, Jones EC, Gomez M, Lin FY, Chang HJ, Min JK. Incremental prognostic value of coronary computed tomography angiography over coronary calcium scoring for major adverse cardiac events in elderly asymptomatic individuals. *Eur Heart J Cardiovasc Imaging*. 2018;19:675-683.