Clinical Significance of Body Fat Distribution in Coronary Artery Calcification Progression in Korean Population

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Background: Although obesity differs according to ethnicity, it is globally established as a solid risk factor for cardiovascular disease. However, it is not fully understood how obesity parameters affect the progression of coronary artery calcification (CAC) in Korean population. We sought to evaluate the association of obesity-related parameters including visceral adipose tissue (VAT) measurement and CAC progression.

Methods: This retrospective observational cohort study investigated 1,015 asymptomatic Korean subjects who underwent serial CAC scoring by computed tomography (CT) with at least 1-year interval and adipose tissue measurement using non-contrast CT at baseline for a routine checkup between 2003 and 2015. CAC progression, the main outcome, was defined as a difference of ≥2.5 between the square roots of the baseline and follow-up CAC scores using Agatston units.

Results: During follow-up (median 39 months), 37.5% of subjects showed CAC progression of a total population (56.4 years, 80.6% male). Body mass index (BMI) ≥25 kg/m², increasing waist circumferences (WC), and higher VAT/subcutaneous adipose tissue (SAT) area ratio were independently associated with CAC progression. Particularly, predominance of VAT over SAT at ≥30% showed the strongest prediction for CAC progression (adjusted hazard ratio, 2.20; P<0.001) and remained of prognostic value regardless of BMI or WC status. Further, it provided improved risk stratification of CAC progression beyond known prognosticators.

Conclusion: Predominant VAT area on CT is the strongest predictor of CAC progression regardless of BMI or WC in apparently healthy Korean population. Assessment of body fat distribution may be helpful to identify subjects at higher risk.

Keywords: Body fat distribution; Coronary artery disease; Multidetector computed tomography; Obesity, abdominal

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide, leading to a high medical and socioeconomic burden [1]. Recently, efforts have been focused more on disease prevention to identify subjects at a higher risk and to manage the related risk factors to prevent development and progression of atherosclerosis. Assessment of coronary artery calcification (CAC) using coronary artery calcium scores (CACS) has been established as a screening tool for CAD, with a relatively low amount of radiation, cost, and time [2]. In particular, CAC progression assessed by repeated measurements of CACS is a strong predictor of cardiovascular events and superior to baseline CACS even in asymptomatic cohort studies [3,4].

Obesity is one of the most contributing factors to CAD development and progression, and causes other traditional risk
factors [5]. Especially, visceral adiposity as a sick fat plays an important role in the deterioration of cardiometabolic profile. It is well known that cytokines from visceral fat induce inflammation and endothelial dysfunction, followed by atherosclerosis, and lead to CAD [6,7]. Previous large-scale studies have demonstrated that visceral adiposity is significantly associated with various cardiovascular diseases from incident CAD to myocardial infarction and cardiac death [8-10]. Although simple anthropometric measurements such as body mass index (BMI) and waist circumferences (WC) have been suggested as surrogate markers of visceral adiposity, they have some limits to explain the cardiometabolic heterogeneity, to selectively distinguish visceral fat, and to understand the mechanism by which body fat distribution could affect cardiovascular risk [11]. Furthermore, considering that obesity weighs on CAD differently according to ethnicity and most studies have been conducted in Caucasians, an in-depth study on the Asian population is required [12,13]. Thus, we sought to investigate the clinical significance of different body fat compositions on CAC progression in apparently healthy Korean population.

METHODS

Study population
We retrospectively reviewed the medical records and imaging studies of 46,637 consecutive adult subjects who underwent adipose tissue measurement using non-contrast abdominal computed tomography (CT) for general health checkup at Seoul National University Hospital Healthcare System Gangnam Center, between January 2003 and February 2015. Among the initial fat cohort, 6,049 Korean subjects who underwent CAC scoring on the same day of abdomen CT were enrolled. These subjects chose to take the exams on their own will because they had one or more cardiovascular risk factors or atypical chest pain. Among 6,049 subjects, 4,973 subjects without a follow-up CAC scoring, 18 subjects with a history of coronary revascularization, 39 subjects without clinical information available, and four subjects with uninterpretable imaging data were excluded from the analysis. Finally, 1,015 subjects were analyzed for this study.

The study protocol conforms to the ethical guidelines in the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (H-0907-045-286). The requirement for written informed consent was waived by the board due to the retrospective nature of the study.

Clinical and laboratory evaluation
The methods used for this study have been previously described [14]. Anthropometric information including height, weight, WC, and blood pressure (BP) were collected by a trained nurse on the day of baseline CT. BMI was calculated as weight divided by height in meters (kg/m²), and WC was measured at the midpoint between the lower costal margin and the iliac crest. BP was taken as an average after measuring twice using an automated BP monitor with at least 5-minute interval in a seated resting position. A self-reported questionnaire was utilized to assess smoking, defined as a consumption of at least 1 cigarette a day for the previous 12 months, and prior medication history including antiplatelet agent and statin. Laboratory evaluations included serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting glucose, fasting insulin, glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP), and homocysteine levels. An automatic analyzer at the Department of Laboratory Medicine at Seoul National University Hospital (Toshiba 200 FR autoanalyzer; Toshiba, Tokyo, Japan) was used for the analysis of all biochemical tests. A previous medical history was defined as follows: hypertension as a systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or the use of anti-hypertensive medication; diabetes mellitus (DM) as a fasting glucose ≥126 mg/dL or HbA1c ≥6.5%, and/or treatment by an oral hypoglycemic agent or insulin; dyslipidemia as total cholesterol ≥240 mg/dL, LDL-C ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-C < 40 mg/dL, or the use of statin; and chronic kidney disease as Modification of Diet in Renal Disease glomerular filtration rate <60 mL/min/1.73 m² or sustained albuminuria for 3 months.

Measurement of CAC and its progression
All subjects underwent unenhanced calcium scan for CAC scoring using 16- (SOMATOM Sensation 16; Siemens Medical Solutions, Forchheim, Germany) or 256-detector row CT scanner (Brilliance iCT 256; Philips Medical Systems Inc., Cleveland, OH, USA). A standard protocol was applied, with a prospective electrocardiography triggering and image acquisition initiated at 70% of the cardiac cycle for motion-free images of the coronary arteries (3 mm thick slice, 200 mm field of view, 120 kV tube voltage, 110 mA tube current). Scanned images were reconstructed retrospectively with a non-overlapping slice thickness of 2.5 mm. CACS was automatically calculated using the Agatston scoring system (in units) with dedicated
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software (Rapidia 2.8; INFINITT, Seoul, Korea) and graded as follows: 0, 1 to 99, 100 to 399, and ≥400 [15]. CAC progression was the main outcome measure of this study, which was defined as a difference of ≥2.5 between the square roots (√) of the baseline and follow-up CACS (∆√transformed CAC) to minimize the effect of interscan variability [16].

Measurement of adipose tissue area using CT
On the same day, all participants underwent abdominal fat CT to evaluate the fat distribution including visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and total adipose tissue (TAT) areas, as described previously [17-19]. In brief, the adipose tissue areas were measured at the transverse section of the umbilicus level using a 16-detector row CT scanner (SOMATOM Sensation 16) with a thickness of 5 mm (120 kV tube voltage, 260 mA tube current). Settings for the attenuation values specific for adipose tissue, which ranged from −250 to −50 Hounsfield units [17-19], were applied to electronically calculate the fat areas and distribution, using Rapidia 2.8 CT software.

Statistical analysis
All analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA) and MedCalc for Windows version 13.1.2.0 (MedCalc Software, Ostend, Belgium). Continuous variables were presented as mean±standard deviation or median and interquartile range (IQR), and categorical variables were expressed as numbers and percentages. Intergroup differences of continuous variables were compared using Student’s t-test for independent samples or the Mann-Whitney test, while those of categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate. The Cox proportional hazard model with a forward selection method was used to estimate the risk of CAC progression, according to clinical, laboratory, and obesity-related parameters. The risk of CAC progression was expressed as a hazard ratio (HR) and corresponding 95% confidence interval from univariable and multivariable analyses in order. Receiver-operating characteristic (ROC) curves were plotted to determine VAT/SAT ratio for the prediction of CAC progression, and the optimal cutoff was determined by the maximum sum of sensitivity and specificity. To show the independent and stronger impact of body fat distribution on CAC progression, the relationship of VAT/SAT ratio with CAC progression was analyzed according to BMI and WC subgroups. In addition, a sequential Cox analysis using three incremental models was performed to evaluate the additive value of body fat distribution over clinical risk factors and conventional obesity surrogate markers in predicting CAC progression. Model 1 consisted of clinical risk factors represented by the Framingham risk score (FRS)+obesity defined by BMI; Model 2 of FRS+obesity defined by BMI+increased WC; and Model 3 of FRS+obesity defined by BMI+increased WC+increased VAT/SAT ratio. The change in overall log-likelihood ratio chi-square was used to assess increases in predictive power with subsequent parameters. A value of P<0.05 was considered statistically significant.

RESULTS
Baseline characteristics of the study population
The baseline characteristics of the 1,015 study participants (mean age, 56.4 years; men 80.6%) are summarized in Table 1. On the basis of the FRS, 64.6% of the studied patients were classified as low risk (10-year risk <10%), 28.5% as intermediate risk (10% to 20%), and 6.9% as high risk (>20%), and their mean homeostatic model assessment for insulin resistance (HOMA-IR) was 2.5, indicating low insulin resistance. Both pre-existing hypertension, DM, and dyslipidemia were found in 28.9%, 19.3%, and 35.3% of the total subjects, respectively. One-third of the study participants were on antiplatelet agent or statin treatment. The mean BMI and WC were 24.6 kg/m² and 88.1 cm, respectively, and approximately 40% of the study population was considered obese according to the criteria from the World Health Organization (WHO)’s Asia-Pacific guideline [20]. VAT, SAT, and VAT areas from CT were 279.1, 136.2, and 137.0 cm², respectively. The mean CACS at baseline calcium scan was 81.0 and that at follow-up scan was 149.9. Among the study participants, 546 subjects (53.8%) did not have detectable CAC (CACS 0) and 181 (17.8%) had CACS ≥100 at baseline. From 546 with an initial score of zero, 103 subjects exhibited coronary calcification at follow-up. The median interval between baseline and follow-up calcium scans was 39 months (IQR, 25 to 54 months), and the distributions of CACS of baseline and follow-up calcium scans were displayed in Fig. 1.

Progression of CAC
CAC progression was found in 381 subjects (37.5%). The median interval between baseline and follow-up calcium scans was significantly shorter in CAC progressors than that in CAC
Table 1. Baseline and imaging characteristics according to status of CAC progression

| Variable                        | Total (n=1,015) | CAC progressor (n=381) | CAC non-progressor (n=634) | P value |
|---------------------------------|----------------|------------------------|-----------------------------|---------|
| **Clinical parameters**         |                |                        |                             |         |
| Age, yr                         | 56.4±7.2       | 58.4±7.7               | 55.7±7.1                    | <0.001  |
| Male sex                        | 817 (80.6)     | 335 (88.2)             | 482 (76.0)                  | <0.001  |
| Current smoking                 | 205 (20.2)     | 100 (26.2)             | 105 (16.6)                  | <0.001  |
| BMI, kg/m²                      | 24.6±2.6       | 24.9±2.7               | 24.4±2.6                    | 0.001   |
| BMI ≥25 kg/m²                   | 432 (42.6)     | 188 (49.6)             | 244 (38.7)                  | 0.001   |
| WC, cm                          | 88.1±7.1       | 89.3±7.6               | 87.5±6.8                    | <0.001  |
| WC ≥90 cm (male) or 85 cm (female) | 448 (44.1)   | 178 (46.7)             | 270 (42.6)                  | 0.199   |
| Hypertension                    | 293 (28.9)     | 132 (34.6)             | 161 (25.4)                  | 0.002   |
| Diabetes mellitus               | 196 (19.3)     | 107 (28.1)             | 89 (14.0)                   | <0.001  |
| Dyslipidemia                    | 358 (35.3)     | 137 (36.0)             | 221 (34.9)                  | 0.722   |
| Chronic kidney disease          | 85 (8.4)       | 37 (9.7)               | 48 (7.6)                    | 0.233   |
| Framingham risk score           | 7.6±5.7        | 9.1±5.8                | 6.7±5.6                     | <0.001  |
| Low                             | 656 (64.6)     | 203 (53.3)             | 453 (71.5)                  |         |
| Intermediate                    | 289 (28.5)     | 142 (37.3)             | 147 (23.2)                  |         |
| High                            | 70 (6.9)       | 36 (9.4)               | 34 (5.4)                    |         |
| **Laboratory parameters**       |                |                        |                             |         |
| SBP, mm Hg                      | 120.2±14.6     | 121.5±14.7             | 119.4±14.5                  | 0.029   |
| Total cholesterol, mg/dL        | 199.1±34.1     | 198.2±34.7             | 199.7±33.8                  | 0.496   |
| HDL-C, mg/dL                    | 51.8±12.4      | 51.0±11.9              | 52.3±12.7                   | 0.113   |
| Triglyceride, mg/dL             | 107.0 (76.0–152.0) | 111.5 (78.3–153.0) | 105.5 (74.0–152.0) | 0.294   |
| LDL-C, mg/dL                    | 124.8±32.6     | 122.2±32.0             | 126.3±32.9                  | 0.180   |
| Fasting glucose, mg/dL          | 104.5±22.2     | 108.9±27.2             | 101.8±18.1                  | <0.001  |
| HbA1c, %                        | 5.9±0.7        | 6.1±0.8                | 5.8±0.6                     | <0.001  |
| hs-CRP, mg/L                    | 0.5 (0.1–1.6)  | 0.6 (0.1–1.6)          | 0.5 (0.1–1.6)               | 0.737   |
| Homocysteine, umol/L            | 8.7±2.6        | 9.6±2.8                | 8.0±2.2                     | 0.056   |
| HOMA-IR                          | 2.5±1.4        | 2.6±1.6                | 2.3±1.2                     | 0.088   |
| **Imaging parameters**          |                |                        |                             |         |
| CACS at baseline                | 81.0±233.9     | 153.7±251.0            | 37.3±211.5                  | 0.003   |
| TAT, cm²                        | 279.1 (231.1–335.2) | 281.9 (232.8–341.7) | 277.9 (230.6–333.2) | 0.500   |
| VAT, cm²                        | 136.2 (102.3–173.9) | 144.3 (106.0–178.0) | 133.1 (100.0–168.6) | 0.018   |
| Height-indexed VAT, cm²/m       | 81.4 (61.6–103.0) | 84.5 (64.4–106.2) | 79.1 (59.8–100.8) | 0.001   |
| SAT, cm²                        | 137.0 (108.6–174.0) | 133.3 (103.9–173.6) | 137.8 (112.7–174.5) | 0.463   |
| VAT/SAT ratio                   | 1.03±0.45      | 1.10±0.46              | 0.99±0.44                   | <0.001  |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

CAC, coronary artery calcification; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; CACS, coronary artery calcium scores; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
non-progressors (median, 37 months [IQR, 25 to 50] vs. 40 months [IQR, 27 to 60], *P* < 0.001). Compared with non-progressors, CAC progressors were older, with male predominance, and smokers. Comorbidities such as hypertension and DM were more frequent, and FRS was higher in CAC progressors. The adipose tissue area quantified by CT was significantly higher in CAC progressors than in non-progressors. On average, CAC progressors had VAT of 10% more than SAT, while CAC non-progressors had VAT and SAT at a similar proportion (VAT/SAT ratio of 1.10 in CAC progressors vs. 0.99 in non-progressors, *P* < 0.001).

**Predictors of CAC progression**

To evaluate the significant predictors of CAC progression, the Cox regression analyses of the clinical and imaging characteristics were performed (Table 2). Among the clinical parameters, age, male sex, current smoking, hypertension, diabetes mellitus, dyslipidemia, high FRS, obesity-related parameters, and adipose tissue area quantified by CT were significant predictors of CAC progression.

### Table 2. Univariable and multivariable analysis of factors associated with CAC progression

| Variable | Univariable analysis | Multivariable analysis | Adjusted HR (95% CI) | *P* value |
|----------|----------------------|------------------------|----------------------|-----------|
| Clinical and laboratory parameters | | | | |
| Age (per 10 years increment) | 1.54 (1.31–1.81) | <0.001 | | |
| Male sex | 2.35 (1.64–3.37) | <0.001 | | |
| Current smoking | 1.79 (1.32–2.44) | <0.001 | | |
| Hypertension | 1.59 (1.15–2.79) | <0.001 | | |
| Diabetes mellitus | 2.64 (1.23–4.23) | <0.001 | | |
| Dyslipidemia | 1.64 (1.09–3.52) | <0.001 | | |
| Chronic kidney disease | 1.31 (0.94–2.06) | 0.234 | | |
| High FRS | 1.77 (1.44–2.18) | <0.001 | | |
| Prior use of antiplatelet agent | 0.91 (0.67–1.01) | 0.069 | | |
| Prior use of statin | 0.88 (0.55–1.25) | 0.102 | | |
| SBP ≥140 mm Hg | 1.72 (1.12–2.63) | 0.012 | | |
| Triglyceride ≥200 mg/dL | 1.17 (0.79–1.74) | 0.433 | | |
| HDL-C <40 mg/dL | 1.00 (0.69–1.45) | 0.989 | | |
| LDL-C ≥160 mg/dL | 0.92 (0.55–1.55) | 0.764 | | |
| Fasting glucose ≥100 mg/dL | 1.45 (1.12–1.87) | 0.004 | | |
| hs-CRP ≥2.0 mg/L | 1.28 (1.04–1.67) | 0.034 | | |
| HOMA-IR ≥3.0 | 0.92 (0.69–1.24) | 0.598 | | |
| Obesity-related parameters | | | | |
| BMI ≥25 kg/m² | 1.56 (1.21–2.02) | 0.001 | 1.42 (1.09–1.86) | 0.009 |
| WC ≥90 cm (male) or 85 cm (female) | 1.18 (1.02–1.53) | 0.029 | 1.10 (1.01–1.43) | 0.042 |
| TAT<sup>b</sup> | 1.00 (0.99–1.01) | 0.869 | - | - |
| VAT<sup>b</sup> | 1.03 (1.01–1.06) | 0.007 | 1.01 (0.99–1.04) | 0.399 |
| Highest quartile of VAT (Q4) | 1.78 (1.34–2.36) | <0.001 | 1.43 (1.05–2.15) | 0.016 |
| Height-indexed VAT<sup>c</sup> | 1.05 (1.02–1.09) | 0.007 | 1.00 (1.00–1.01) | 0.098 |
| SAT<sup>b</sup> | 0.99 (0.99–1.00) | 0.079 | - | - |
| VAT/SAT ratio | 2.87 (1.79–4.38) | <0.001 | 1.69 (1.27–2.24) | <0.001 |
| VAT/SAT ratio ≥1.30 | 3.01 (2.25–4.03) | <0.001 | 2.20 (1.74–2.78) | <0.001 |

CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; FRS, Framingham risk score; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; WC, waist circumference; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

* Multivariable analysis was performed by adjusting for FRS, a history of diabetes mellitus, and hs-CRP >2.0 mg/L.  
  * Total, visceral, and subcutaneous fat area were assessed per 1 cm² increment.  
  * Height-indexed visceral fat area was assessed per 1 cm²/m increment.
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Factors, age, male sex, current smoking, a history of hypertension, DM, or dyslipidemia, higher FRS, elevated BP, serum fasting glucose, and hs-CRP were significantly associated with CAC progression. Among obesity-related parameters, BMI ≥ 25 kg/m² (unadjusted HR, 1.56; P = 0.001) and increased WC (unadjusted HR, 1.18; P = 0.029) significantly advanced coronary calcification. Moreover, the absolute visceral fat area was a solid predictor of CAC progression (unadjusted HR, 1.03, P = 0.007 for every 1 cm² increase of VAT; unadjusted HR, 1.05, P = 0.007 for height-indexed VAT). When stratified by VAT quartiles, the risk of CAC progression tended to increase gradually with increasing VAT areas (Fig. 2). Particularly, VAT/SAT ratio showed the strongest association with CAC progression (unadjusted HR, 2.87; P < 0.001). In the ROC analysis, the optimal cutoff for VAT/SAT ratio to predict CAC progression was determined as 1.30 (area under the curve 0.691, sensitivity 75.6%, specificity 55.7%, P < 0.001). Overall, subjects with VAT/SAT ratio ≥ 1.30 tended to have more traditional cardiovascular risk factors than those with VAT/SAT ratio < 1.30 (Supplementary Table 1). It is noteworthy that higher triglyceride, hs-CRP, and HOMA-IR were evident in subjects with VAT/SAT ratio ≥ 1.30, recalling attention to the close relationship of visceral obesity with these parameters. VAT/SAT ratio ≥ 1.30 demonstrated a greater than 3-fold hazard increment of CAC progression (unadjusted HR, 3.01; P < 0.001). In particular, the risk of CAC progression by VAT/SAT ratio ≥ 1.30 was considerably higher in subjects with CACS 0 at baseline (unadjusted HR, 3.28; P < 0.001) than those with CACS > 0 at baseline.

Fig. 1. The distribution of coronary artery calcium scores (CACS) at (A) baseline and (B) follow-up calcium scans. CAC, coronary artery calcification.

| VAT quartiles | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|---------------|------------------------|---|---------------------|---|
| Q1            | Reference              | - | Reference           | - |
| Q2            | 1.13 (0.83–1.53)       | 0.433 | 1.05 (0.77–1.44) | 0.734 |
| Q3            | 1.36 (1.02–1.82)       | 0.032 | 1.27 (1.00–1.72)   | 0.047 |
| Q4            | 1.78 (1.34–2.36)       | <0.001 | 1.53 (1.13–2.07) | 0.006 |

Fig. 2. Kaplan-Meier curve for the risk of coronary artery calcification (CAC) progression according to visceral adipose tissue (VAT) on computed tomography. When stratified by VAT quartiles, the risk of CAC progression tended to increase gradually with increasing VAT areas. CI, confidence interval; HR, hazard ratio; Q, quartile. *The multivariable model was adjusted for Framingham risk score, a history of diabetes mellitus, and higher high-sensitivity C-reactive protein.
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Importance of body fat distribution beyond traditional obesity surrogate markers
Consistent with prior results [21-23], our study demonstrated that various obesity-related parameters were predictive of CAC progression. However, each component did not show a strong correlation (BMI and VAT/SAT ratio, \( r=0.139, P<0.001 \); WC and VAT/SAT ratio, \( r=0.173, P<0.001 \)). To verify the clinical implication of CT-derived VAT/SAT ratio as a new indicator of obesity and a powerful predictor of CAC progression, we compared the risk to worsen coronary calcification by VAT/SAT ratio according to the BMI and WC status. VAT/SAT ratio and VAT/SAT ratio \( \geq 1.30 \) were consistently able to stratify the risk of CAC progression in all subgroups, independent of BMI and WC status (Table 3). This shows us the importance of body fat distribution beyond the traditional parameters to define obesity, by an increase in the HR for CAC progression when VAT is \( \geq 30\% \) greater than SAT (adjusted HR, 4.42, \( P<0.001 \) for normal BMI; adjusted HR 6.34, \( P<0.001 \) for overweight BMI; adjusted HR 3.98, \( P<0.001 \) for normal WC). When we also evaluated additional predictive value of VAT/SAT ratio \( \geq 1.30 \) on top of a model with conventional risk factors, VAT/SAT ratio \( \geq 1.30 \) provided further information on progressing CAC (Supplementary Table 4, Supplementary Fig. 1).

DISCUSSION
The main findings of the present study are as follows: (1) various parameters representing obesity significantly affected CAC progression in apparently healthy Korean population; (2) the distribution of body fat demonstrated better the impact on CAC progression than the excess adiposity per se; and (3) specifically, predominance of VAT over SAT at \( \geq 30\% \) was the independent strongest predictor of CAC progression and provided further risk stratification beyond clinical risk factors and traditional obesity surrogate markers. Altogether, this study evaluated the clinical implication of regional body fat distribution assessed using CT by redeeming the limitations of traditional obesity surrogate markers in apparently healthy Korean
subjects and suggested that body fat distribution may be potentially helpful for clinical decision making regarding the prevention and management of future cardiovascular disease. Obesity is one of the biggest health concerns across the country, and its prevalence is steadily increasing in Korea [24]. As traditional obesity surrogate markers, simple anthropometric indices, such as BMI and WC, have been widely used to estimate cardiovascular risk in previous studies and clinical practice [11]. However, these parameters are insufficient to distinguish where body fat is mainly located and whether an individual is metabolically healthy or not, since different body compositions matters in metabolic outcomes [11,25]. Hence, recent large studies have focused on the regional distribution of body fat by means of the advance of imaging modalities, and at present, body fat assessment by CT is considered the gold standard for body fat distribution and quantification [11,26]. In many prior researches using CT, excessive intra-abdominal fat deposition is significantly associated with CAC, in the development of atherosclerosis and subclinical CAD in the general population [18,21,27]. Our group has also previously reported convincing evidence that increased visceral fat on CT was tightly associated with moderate to severe coronary calcification in 1,336 healthy Korean men [18]. However, studies evaluating the temporal relationship between visceral adiposity and CAC progression are scarce. The present study is one of the largest cohort studies that investigated the impact of body fat distribution on subclinical CAD based on CAC progression. Obviously, CAC progressors were more of obesity than non-progressors, despite under different definitions. After adjusting for confounding factors, VAT/SAT ratio showed an independent prognostic value for CAC progression, whereas VAT area per se lost the statistical significance. In addition, when dividing the study population in accordance with BMI or WC, predominance of visceral fat and VAT/SAT ratio ≥1.30 were consistently predictive of CAC progression even in subjects with normal BMI or normal WC. These call attention to body fat composition rather than the absolute amount itself, and warn individuals who are assumed “normal” by BMI or

| Variable | Adjusted HR (95% CI)* | P value |
|----------|-----------------------|---------|
| According to BMI | | |
| Normal BMI (BMI <23 kg/m²) | | |
| VAT/SAT ratio | 2.33 (1.89–4.84) | <0.001 |
| VAT/SAT ratio ≥1.30 | 4.42 (2.32–8.45) | <0.001 |
| Overweight (BMI 23–25 kg/m²) | | |
| VAT/SAT ratio | 4.34 (1.38–9.89) | 0.001 |
| VAT/SAT ratio ≥1.30 | 6.34 (3.26–12.34) | <0.001 |
| Obese (BMI ≥25 kg/m²) | | |
| VAT/SAT ratio | 1.71 (1.16–2.92) | 0.030 |
| VAT/SAT ratio ≥1.30 | 2.74 (1.78–4.22) | <0.001 |
| According to WC | | |
| Normal WC (WC <90 cm male or 85 cm female) | | |
| VAT/SAT ratio | 3.16 (2.33–4.29) | <0.001 |
| VAT/SAT ratio ≥1.30 | 3.98 (2.83–5.57) | <0.001 |
| Increased WC (WC ≥90 cm male or 85 cm female) | | |
| VAT/SAT ratio | 3.50 (2.12–5.32) | <0.001 |
| VAT/SAT ratio ≥1.30 | 5.73 (3.63–9.16) | <0.001 |

CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; WC, waist circumference.

*Multivariable analysis was performed by adjusting for Framingham risk score, a history of diabetes mellitus, and high-sensitivity C-reactive protein >2.0 mg/L.
WC but possess VAT-dominant body fat pattern. In addition, VAT/SAT ratio ≥ 1.30 added the incremental prognostic value over clinical risk factors and traditional obesity surrogate markers. Consequently, our findings emphasize the clinical implication of visceral adiposity on promoting the calcification in the coronary artery and suggest that CT-assessed body fat distribution may perform better in identifying high-risk subjects who might benefit from meticulous surveillance and aggressive preventive strategy for CAD.

Obesity, in particular, visceral obesity, is a well-known risk factor of cardiovascular disease. However, considering that obesity differs by ethnicity and most studies were done on Caucasian in multi-ethnic cohorts of Western countries [28-30], the main issues regarding obesity should be addressed in Asian population. As presented in our baseline characteristics, Koreans have relatively lower BMI and WC than those from other Western studies, showing only 22 subjects (2.2%) with BMI ≥ 30 kg/m², who would be regarded as "obese" by general definition in the Western countries. On the contrary, the amount of body fat composition calculated on CT was comparable with that in other Western studies [31,32]. Additionally, hypertriglyceridemia, increased HOMA-IR, and WC, which typify hypertriglyceridemic obesity, were reported to be less frequent in our study population, compared with studies on Caucasian [33,34]. These findings in the present study coincide with prior reports that Asians have lower BMI but higher body fat percentage than Caucasians [35,36] and support the legitimacy of the WHO’s Asia-Pacific region-specific classification of obesity [20]. Recent shift from anthropometry to imaging to define obesity is derived from the considerable variation in visceral adiposity at a given body weight, BMI, or WC [11,37,38]. Nevertheless, the ease in measurement and good correlation with visceral adiposity allow anthropometric indices to be used still in routine clinical practice [11,39]. However, this study revealed weaker correlations between VAT area and BMI or WC than other Western studies, implying the tricky interpretation of simple anthropometry and greater necessity of CT-assessed body fat distribution in Asians. Accordingly, the direct assessment of body fat composition using CT is expected to explain well the influence on CAC progression and to lead to an appropriate risk management better than BMI or WC in Asians.

The current study has several limitations. First, this is a retrospective observational study; thus, the subsequent management of risk factors and disease, such as medications, were not guided or followed by a specific protocol and might have been influenced by the initial health examination results, including VAT quantification. However, such effects are inevitable in studies observing the diagnostic and therapeutic pathways in clinical practice, and the prognostic value of visceral adiposity on CT remains significance after adjusting for the conventional cardiovascular risk factors. In addition, male subjects were predominant in the study population (80.6%), which was different from the general composition of the society. It might restrict the generalizability of the results. However, since the sex-specific analysis consistently provided a strong association between body fat distribution and CAC progression across sex (Supplementary Table 3), our findings can be applied on both sexes. Second, CAC progression, representing of subclinical CAD, was evaluated by CACS. Because CACS can reflect overall coronary atherosclerotic plaque burden only, the correlation with the severity of stenosis or the probability of rupture-prone plaque, considered the major cause of cardiovascular adverse events, are unknown [40]. However, many previous studies have proved that CACS can predict clinical events from cardiac death to subclinical CAD in asymptomatic population cohorts, as we described above [3,4]. Moreover, given that our study population is comprised of self-referred subjects with a relatively low risk, comprehensive evaluation using coronary CT angiography for primary screening is not recommended. Third, radiation hazard regarding CT should be considered, even though the study participants agreed to perform non-contrast abdomen CT after being informed. Finally, the specific VAT/SAT ratio is expected to help guide physicians in cardiovascular risk management, but should be interpreted with caution. Further multi-ethnic prospective studies are required to validate our results.

In conclusions, body fat distribution is important in CAC progression. Predominance of VAT over SAT at ≥30% is the strongest predictor of CAC progression, even with normal BMI or WC in apparently healthy Korean population. Assessment of body fat distribution may provide further risk stratification over known clinical risk factors and traditional obesity surrogate markers.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0161.
CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: H.L., H.E.P., S.Y.C.
Acquisition, analysis, or interpretation of data: H.L., H.E.P., J.W.Y., S.Y.C.
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**Supplementary Table 1.** Baseline characteristics according to body fat distribution

| Variable                                      | Total (n=1,015) | VAT/SAT ≥ 1.30 (n=588) | VAT/SAT < 1.30 (n=427) | P value |
|-----------------------------------------------|-----------------|------------------------|------------------------|---------|
| **Clinical parameters**                       |                 |                        |                        |         |
| Age, yr                                       | 56.4±7.2        | 57.1±7.6               | 56.2±7.3               | 0.734   |
| Male sex                                      | 817 (80.6)      | 562 (95.7)             | 255 (59.7)             | <0.001  |
| Current smoking                               | 205 (20.2)      | 155 (26.4)             | 50 (11.7)              | <0.001  |
| BMI, kg/m²                                    | 24.6±2.6        | 24.8±2.3               | 24.3±3.0               | <0.001  |
| BMI ≥25 kg/m²                                 | 432 (42.6)      | 265 (45.1)             | 167 (39.1)             | 0.062   |
| WC, cm                                        | 88.1±7.1        | 88.9±6.3               | 87.1±8.0               | <0.001  |
| WC ≥90 cm (male) or 85 cm (female)            | 448 (44.1)      | 270 (45.9)             | 178 (41.7)             | 0.180   |
| Hypertension                                  | 293 (28.9)      | 198 (33.7)             | 95 (22.2)              | <0.001  |
| Diabetes mellitus                             | 196 (19.3)      | 135 (23.0)             | 61 (14.3)              | 0.001   |
| Dyslipidemia                                  | 358 (35.3)      | 242 (41.2)             | 116 (27.2)             | <0.001  |
| Chronic kidney disease                        | 85 (8.4)        | 49 (8.3)               | 36 (8.4)               | 0.956   |
| Framingham risk score                         | 7.6±5.7         | 8.2±5.8                | 7.0±3.2                | <0.001  |
| **Low**                                       | 656 (64.6)      | 362 (61.6)             | 294 (68.9)             | <0.001  |
| **Intermediate**                              | 289 (28.5)      | 180 (30.6)             | 109 (25.5)             |         |
| **High**                                      | 70 (6.9)        | 46 (7.8)               | 24 (5.6)               |         |
| **Medications**                               |                 |                        |                        |         |
| Prior use of antiplatelet agent               | 313 (30.8)      | 187 (31.8)             | 126 (29.5)             | 0.435   |
| Prior use of statin                           | 293 (28.9)      | 172 (29.3)             | 121 (28.3)             | 0.751   |
| **Laboratory parameters**                     |                 |                        |                        |         |
| Systolic blood pressure, mmHg                 | 120.2±14.6      | 121.8±14.3             | 118.1±14.7             | 0.542   |
| Total cholesterol, mg/dL                      | 199.1±34.1      | 199.3±34.3             | 198.9±33.9             | 0.611   |
| HDL-C, mg/dL                                  | 51.8±12.4       | 50.4±11.5              | 53.8±13.3              | 0.003   |
| Triglyceride, mg/dL                           | 107.0 (76.0–152.0) | 119.0 (87.0–165.0)  | 94.0 (66.0–133.0)      | 0.001   |
| LDL-C, mg/dL                                  | 124.8±32.6      | 125.1±33.8             | 124.5±30.8             | 0.073   |
| Fasting glucose, mg/dL                        | 104.5±22.2      | 107.5±23.8             | 100.3±19.1             | <0.001  |
| HbA1c, %                                      | 5.9±0.7         | 6.1±0.8                | 5.9±0.6                | <0.001  |
| hs-CRP, mg/L                                  | 0.5 (0.1–1.6)   | 0.6 (0.1–1.6)          | 0.4 (0.1–1.4)          | 0.019   |
| Homocysteine, umol/L                          | 8.7±2.6         | 9.0±2.9                | 8.1±1.6                | 0.205   |
| HOMA-IR                                       | 2.5±1.4         | 2.6±1.5                | 2.2±1.2                | 0.002   |
| CACS at baseline                              | 81.0±233.9      | 96.5±226.7             | 59.6±242.1             | 0.003   |

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; CACS, coronary artery calcium scores.

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### Supplementary Table 2. Univariable and multivariable analysis of factors associated with CAC progression

| Variable | Univariable analysis | Multivariable analysis<sup>a</sup> |
|----------|----------------------|-----------------------------------|
|          | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
| Clinical and laboratory parameters | | | |
| Age (per 10 years increment) | 1.54 (1.31–1.81) | <0.001 |  |
| Male sex | 2.35 (1.64–3.37) | <0.001 | |
| Current smoking | 1.79 (1.32–2.44) | <0.001 | |
| Hypertension | 1.59 (1.15–2.79) | <0.001 | |
| Diabetes mellitus | 2.64 (1.23–4.23) | <0.001 | |
| Dyslipidemia | 1.64 (1.09–3.52) | <0.001 | |
| Chronic kidney disease | 1.31 (0.94–2.06) | 0.234 | |
| High FRS | 1.77 (1.44–2.18) | <0.001 | |
| Prior use of antiplatelet agent | 0.91 (0.67–1.01) | 0.069 | |
| Prior use of statin | 0.88 (0.55–1.25) | 0.102 | |
| SBP ≥140 mm Hg | 1.72 (1.12–2.63) | 0.012 | |
| Triglyceride ≥200 mg/dL | 1.17 (0.79–1.74) | 0.433 | |
| HDL-C <40 mg/dL | 1.00 (0.69–1.45) | 0.989 | |
| LDL-C ≥160 mg/dL | 0.92 (0.55–1.55) | 0.764 | |
| Fasting glucose ≥100 mg/dL | 1.45 (1.12–1.87) | 0.004 | |
| hs-CRP ≥2.0 mg/L | 1.28 (1.04–1.67) | 0.034 | |
| HOMA-IR ≥3.0 | 0.92 (0.69–1.24) | 0.598 | |
| Obesity-related parameters | | | |
| BMI ≥25 kg/m² | 1.56 (1.21–2.02) | 0.001 | 1.14 (0.90–1.44) | 0.293 |
| WC ≥90 cm (male) or 85 cm (female) | 1.18 (1.02–1.53) | 0.029 | 1.03 (0.85–1.31) | 0.429 |
| TAT<sup>b</sup> | 1.00 (0.99–1.01) | 0.869 | - | - |
| VAT<sup>b</sup> | 1.03 (1.01–1.06) | 0.007 | 1.02 (1.00–1.05) | 0.061 |
| Highest quartile of VAT (Q4) | 1.78 (1.34–2.36) | <0.001 | 1.21 (0.99–1.62) | 0.064 |
| Height-indexed VAT<sup>c</sup> | 1.05 (1.02–1.09) | 0.007 | 1.00 (1.00–1.00) | 0.496 |
| SAT<sup>b</sup> | 0.99 (0.99–1.00) | 0.079 | - | - |
| VAT/SAT ratio | 2.87 (1.79–4.38) | <0.001 | 1.57 (1.28–1.95) | 0.009 |
| VAT/SAT ratio ≥1.30 | 3.01 (2.25–4.03) | <0.001 | 1.95 (1.39–2.83) | 0.021 |

CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; FRS, Framingham risk score; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; WC, waist circumference; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

<sup>a</sup>Multivariable analysis was performed by adjusting for age, male sex, current smoking, a history of hypertension, diabetes mellitus, and dyslipidemia, SBP ≥140 mm Hg, glucose ≥100 mg/dL, and hs-CRP >2.0 mg/L. <sup>b</sup>Total, visceral, and subcutaneous fat area were assessed per 1 cm² increment. <sup>c</sup>Height-indexed visceral fat area was assessed per 1 cm²/m increment.
**Supplementary Table 3. Risk of CAC progression according to sex (817 male and 198 female)**

| Variable                                      | Male                                              | Female                                               |
|-----------------------------------------------|---------------------------------------------------|------------------------------------------------------|
|                                               | Unadjusted HR (95% CI)  | P value                                              | Unadjusted HR (95% CI)  | P value      |
| **Clinical and laboratory parameters**        |                                    |                                                      |                          |              |
| Age (per 10 years increment)                  | 1.22 (1.07–1.42)          | 0.004                                                | 1.99 (1.31–3.04)          | 0.001         |
| Current smoking                               | 1.57 (1.47–1.73)          | <0.001                                               | Current smoking           | 2.14 (0.29–15.72) | 0.454           |
| Hypertension                                  | 1.56 (1.08–2.77)          | 0.004                                                | Hypertension              | 1.17 (0.62–1.63) | 0.591           |
| Diabetes mellitus                             | 2.50 (2.18–2.91)          | 0.001                                                | Diabetes mellitus         | 2.17 (1.14–4.11) | 0.018           |
| Dyslipidemia                                  | 1.38 (1.10–1.73)          | 0.005                                                | Dyslipidemia              | 1.65 (0.84–3.22) | 0.143           |
| Chronic kidney disease                        | 1.10 (0.85–1.61)          | 0.622                                                | Chronic kidney disease    | 1.48 (0.70–3.63) | 0.392           |
| High FRS                                      | 1.75 (1.40–2.23)          | 0.007                                                | High FRS                  | 1.05 (0.95–1.16) | 0.376           |
| Prior use of antiplatelet agent               | 0.92 (0.68–1.05)          | 0.073                                                | Prior use of antiplatelet agent | 0.95 (0.91–1.37) | 0.091           |
| Prior use of statin                           | 0.87 (0.56–1.35)          | 0.537                                                | Prior use of statin       | 2.10 (1.15–3.83) | 0.016           |
| SBP ≥140 mm Hg                                | 1.71 (1.04–2.27)          | 0.016                                                | SBP ≥140 mm Hg            | 1.42 (0.97–1.78) | 0.237           |
| Triglyceride ≥200 mg/dL                       | 1.35 (0.83–2.33)          | 0.683                                                | Triglyceride ≥200 mg/dL   | 0.68 (0.18–1.22) | 0.119           |
| HDL-C < 40 mg/dL                              | 0.87 (0.65–1.17)          | 0.350                                                | HDL-C < 40 mg/dL           | 0.98 (0.50–1.92) | 0.941           |
| LDL-C ≥160 mg/dL                              | 0.85 (0.40–2.45)          | 0.859                                                | LDL-C ≥160 mg/dL          | 1.56 (1.05–8.16) | 0.003           |
| Fasting glucose ≥100 mg/dL                    | 1.23 (1.04–1.50)          | 0.006                                                | Fasting glucose ≥100 mg/dL | 1.59 (0.87–2.91) | 0.133           |
| hs-CRP ≥2.0 mg/L                              | 1.18 (1.01–1.63)          | 0.039                                                | hs-CRP ≥2.0 mg/L          | 0.73 (0.28–1.90) | 0.524           |
| HOMA-IR ≥3.0                                  | 0.92 (0.67–1.25)          | 0.584                                                | HOMA-IR ≥3.0              | 0.76 (0.14–1.62) | 0.234           |
| **Obesity-related parameters**                |                                    |                                                      |                          |              |
| BMI ≥25 kg/m²                                  | 1.41 (1.14–1.75)          | 0.002                                                | BMI ≥25 kg/m²             | 1.13 (0.61–1.82) | 0.708           |
| WC ≥90 cm (male) or 85 cm (female)            | 1.17 (1.05–1.54)          | 0.008                                                | WC ≥90 cm (male) or 85 cm (female) | 0.86 (0.53–1.70) | 0.658           |
| TATa                                          | 1.00 (1.00–1.01)          | 0.309                                                | TATa                      | 1.00 (0.99–1.00) | 0.997           |
| VATa                                          | 1.02 (1.01–1.05)          | 0.028                                                | VATa                      | 1.01 (0.94–1.08) | 0.789           |
| Highest quartile of VAT (Q4)                  | 1.80 (1.33–2.04)          | <0.001                                               | Highest quartile of VAT (Q4) | 1.44 (1.13–2.32) | 0.022           |
| Height-indexed VATb                           | 1.02 (1.00–1.09)          | 0.064                                                | Height-indexed VATb       | 1.00 (0.99–1.01) | 0.715           |
| SATb                                          | 0.99 (0.99–1.00)          | 0.202                                                | SATb                      | 0.99 (0.99–1.00) | 0.022           |
| VAT/SAT ratio                                 | 2.63 (2.24–3.28)          | <0.001                                               | VAT/SAT ratio             | 3.22 (2.48–6.42) | <0.001           |
| VAT/SAT ratio ≥1.30                           | 2.81 (2.38–3.39)          | <0.001                                               | VAT/SAT ratio ≥1.30       | 3.52 (1.86–6.67) | <0.001           |

CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; FRS, Framingham risk score; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; WC, waist circumference; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

aTotal, visceral, and subcutaneous fat area were assessed per 1 cm² increment, bHeight-indexed visceral fat area was assessed per 1 cm²/m increment.
### Supplementary Table 4. The multivariable Cox models for CAC progression

| Variable                                | Adjusted HR (95% CI)* | P value |
|-----------------------------------------|-----------------------|---------|
| **Model 1**                             |                       |         |
| FRS                                     | 1.13 (1.08–1.17)      | <0.001  |
| BMI ≥25 kg/m²                            | 1.42 (1.08–1.85)      | 0.011   |
| **Model 2**                             |                       |         |
| FRS                                     | 1.13 (1.08–1.18)      | <0.001  |
| BMI ≥25 kg/m²                            | 1.49 (1.08–2.04)      | 0.015   |
| WC ≥90 cm (male) or 85 cm (female)      | 1.02 (0.97–1.26)      | 0.062   |
| **Model 3**                             |                       |         |
| FRS                                     | 1.11 (1.06–1.16)      | <0.001  |
| BMI ≥25 kg/m²                            | 1.49 (1.09–2.06)      | 0.013   |
| WC ≥90 cm (male) or 85 cm (female)      | 1.01 (0.96–1.25)      | 0.055   |
| VAT/SAT ratio ≥1.30                     | 3.25 (2.20–4.81)      | <0.001  |

CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; FRS, Framingham risk score; BMI, body mass index; WC, waist circumference; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

*Multivariable analysis was performed by adjusting for FRS, a history of diabetes mellitus, and high-sensitivity C-reactive protein >2.0 mg/L.
Supplementary Fig. 1. Receiver-operating characteristic analysis with 3 sequential Cox models including Framingham risk score (FRS), body mass index (BMI), waist circumference (WC), and visceral adipose tissue (VAT)/subcutaneous adipose tissue (SAT) ratio ≥1.30. VAT/SAT ratio ≥1.30 showed incremental prognostic value over known prognosticators of CAC progression including higher FRS, BMI ≥25 kg/m², and increased WC.