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Relation of Risk Factors and Abdominal Aortic Calcium to Progression of Coronary Artery Calcium (From the Framingham Heart Study)

Oyere K. Onuma, MD MS[a,c], **Karol Pencina, PhD**[b], **Saadia Qazi, DO, MPH**[a,d], **Joseph M. Massaro, PhD**[b], **Ralph B. D'Agostino Sr., PhD**[b], **Michael L. Chuang, MD**[a], **Caroline S. Fox, MD MPH**[a], **Udo Hoffmann, MD MPH**[a,c], and **Christopher J. O'Donnell, MD MPH**[a,c,d]

[a]The National Heart, Lung, and Blood Institute's the Framingham Heart Study, Framingham, Massachusetts

[b]Department of Mathematics, Boston University, Boston, Massachusetts

[c]Cardiac MR PET CT Program, Department of Radiology and the Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[d]Cardiology Section, Department of Medicine, Boston Veteran's Administration Healthcare, Boston, MA

Abstract

Coronary artery (CAC) and abdominal aortic calcium (AAC) on multi-detector computed tomography (MDCT) permit assessment of the presence and burden of coronary and systemic atherosclerosis. Risk factors for progression of CAC and AAC, and the association of AAC with CAC progression have not been well characterized in a community-dwelling cohort. We studied 1,959 asymptomatic participants from the Framingham Heart Study who underwent serial MDCT scan with a median interval of 6.1 years. Primary outcomes were: (a) the incidence of coronary and abdominal aortic calcium (CAC > 0 and AAC > 0 with baseline CAC = 0 and AAC = 0; and (b) absolute progression of CAC (CAC > baseline CAC and AAC > baseline AAC). Covariates were collected at adjacent cycle exams, and included; age, sex, use of antihypertensive therapy, use of lipid-lowering therapy, cigarette smoking, and total and HDL cholesterol. Predictors for CAC and AAC progression included: baseline CAC, baseline AAC, lipid-lowering therapy, diabetes, HDL cholesterol, BMI, and serum creatinine. Multivariable stepwise logistic and linear regression models were used to test the association of these risk factors with CAC and AAC. Those who developed incident CAC on follow-up scanning comprised 18.8% of 1,124 participants, and 84.9% of 780 participants, with detectable baseline CAC, had further

Corresponding Author: Christopher J. O'Donnell, MD, MPH, Senior Investigator, The Framingham Heart Study, Chief of Cardiology, Cardiology Section Administration, Boston VA Healthcare System, Building 1, 5th Floor Room 5B-113, 1400 VFW Parkway, West Roxbury, MA 02132, Office: (857)203-5673, odonnellc@nhlbi.nih.gov.

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progression. Baseline AAC was a predictor of both CAC incidence and progression, independent of other risk factors. In stepwise models, addition of baseline AAC slightly improved the area under the curve (AUC) from 0.72 (0.68, 0.76) to 0.74 (0.70, 0.78). In conclusion, standard cardiovascular disease (CVD) risk factors are associated with incidence and progression of CAC and AAC, and AAC augments CAC incidence and progression above CVD risk factors.

Keywords

Coronary Artery Calcium; Abdominal Aortic Calcium; Cardiovascular Disease Risk Factors

Introduction

Coronary artery (CAC) and abdominal aortic (AAC) calcium are independent predictors of incident cardiovascular disease (CVD).[1,2] Progression of CAC, defined by sequential increase in the CAC score, is also associated with future incidence of adverse CVD events and increasing cardiovascular mortality.[3] Prior studies have demonstrated age, male sex, white race, hypertension, body mass index, diabetes mellitus, glucose, and family history of myocardial infarction are associated with CAC progression. However, CAC and AAC progression has been described in restricted populations such as diabetics[4,5] or in patients with chronic kidney disease.[6] Additionally, risk factor determinants of AAC progression have not been as extensively characterized as those for CAC. We sought to describe the incidence and rate of progression of CAC and AAC identified on multidetector computed tomography (MDCT) in asymptomatic men and women in the Framingham Heart Study, determine the risk factors for progression, and characterize the impact of AAC on CAC progression. We hypothesize that progression of CAC and AAC is related to both traditional risk factors and the extent and progression of subclinical atherosclerotic disease.

Methods

Participants of the Framingham Offspring and Third Generation Cohorts underwent MDCT scanning from 2002–2005 with repeat scans occurring from 2008–2010. The MDCT sub-study included men aged ≥35 years and non-pregnant, women aged ≥40 years. Due to MDCT scanner constraints, those who weighed >160kg were excluded. All participants provided written informed consent, and the study was approved by the institutional review boards of the Boston University Medical Center and the Massachusetts General Hospital.

A total of 2,118 participants underwent complete imaging in both the first and second MDCT scan studies. We excluded 159 participants with missing records or clinically apparent CVD occurring before the first MDCT examination, which consisted of prevalent CVD, previous coronary artery bypass grafting, percutaneous coronary stenting, pacemaker/implantable cardioverter-defibrillator placement, or valve replacement.

Clinical covariates were collected at the Offspring cycle 7 (1998 – 2001) or Third Generation cycle 1 (2002 – 2005) examinations, which have been described elsewhere.[7] Each cycle examination included a physician-performed interview, a physical exam, and blood samples obtained after a 12-hour fast. Diabetes mellitus was defined as a fasting

plasma glucose of > 126 mg/dl or treatment with insulin or a hypoglycemic agent. Current smoking status was defined by participant report of smoking >1 cigarette daily in the previous year. Hypertension was defined as systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of ≥90 mm Hg on the average of 2 physician-performed measurements or by the use of antihypertensive medication. Hyperlipidemia was defined as serum total cholesterol of ≥240 mg/dl or the use of lipid lowering medication treatment. A panel of 3 physicians, who were blinded to the MDCT data, adjudicated CVD events using previously described standardized criteria.[8] A separate review committee that included a neurologist adjudicated cerebrovascular events.

Participants underwent imaging with an 8-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, Wisconsin) as previously described[8,9] with follow-up scans conducted a median of 6.1 years from the baseline scans. Coronary scanning consisted of 48 contiguous 2.5-mm thick slices (120 kVp, 320 or 400 mA, for body weight < or ≥ 100 kg respectively, 500-ms gantry rotation time, radiation exposures of 1.0 or 1.25 mSv corresponding to 320 or 400 mA respectively), as described previously.[8,10] For abdominal imaging, the top of the S1 vertebral body was prospectively selected as the most caudal extent of the abdominal volume to be imaged. Thirty contiguous 5-mm-thick slices were obtained cranial to S1 for a total coverage of 15 cm in the Z-direction (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1, effective radiation exposure was 2.7 mSv), as previously described in detail.[10] All participants were scanned twice consecutively. The CT scans were analyzed by an experienced reader for the presence and amount of CAC and AAC, and a score was assigned using the Agatston method.[11]

Participants free of baseline CAC or AAC who then had a CAC or AAC score >0 at follow-up, were categorized as incident CAC or AAC. Among those with CAC or AAC >0 scores at baseline, “calcified plaque progression” was defined as the absolute difference between the baseline and follow-up CAC scores. In a secondary analysis that included the entire cohort (baseline CAC=0 and baseline CAC>0), each participant was classified as a “progressor” or “non-progressor.” A participant was classified as a “progressor” if the CAC increased above a category-specific threshold calculated for each CAC stratum (CAC=0, 0<CAC≤100, 100<CAC≤300, 300<CAC≤1000 or CAC>1000). The thresholds were determined based on the difference between consecutive scans to account for any variability due to noise.

Descriptive statistics were presented as a mean and standard deviation for baseline demographics, median and quartiles for calcium, and counts and percent by category for categorical variables. The yearly incidence rate of CAC and AAC were presented as percentages per annum and the absolute and annual CAC and AAC score change were presented for different age and sex categories. To determine the significant risk factors that predict incident AAC and CAC, age and sex-adjusted logistic regression analysis was used, followed by a multivariable model using a stepwise selection algorithm (with p≤0.1 for entry and stay criteria).

Among those with CAC or AAC >0 at baseline, the association between risk factors and calcified plaque progression was determined using univariate linear regression, and then an overall multivariable model was developed using a stepwise selection algorithm. Candidates

for the stepwise selection algorithm (age, sex and baseline calcium (CAC or AAC) were forced into the model) included antihypertensive treatment, lipid lowering treatment, current cigarette smoking, diabetes, fasting plasma glucose levels (mg/dl), body mass index (kg/m^2), SBP (mmHg), DBP (mmHg), total cholesterol (mg/dl), HDL cholesterol (mg/dl), C-reactive protein (mg/l) and serum creatinine (mg/dl) at a $p \leq 0.1$ level of significance of entry. To test the effect of AAC on incidence of CAC, we examined the multivariable logistic regression models with and without AAC and assessed the discrimination of the two models using the area under the curve (AUC) of the receiver-operator characteristic.

As our secondary analysis, we determined the risk factor predictors of the dichotomous outcome of CAC progressed vs. not progressed using univariate and multivariable logistic regression analysis. In this analysis, we also examined models with and without AAC. Statistical significance was set at a two-sided 0.05 alpha level. All analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC).

Results

A total of 1,959 participants (N = 1,904 in the CAC group and N = 1940 in the AAC group) were included in the overall analysis. There were 1,124 participants free of CAC at the baseline scan, of which 18.8% developed CAC in the follow-up scan. Of the 780 participants with detectable CAC at baseline, 84.9% had progression of CAC on follow-up scan. The median duration of follow-up was 6.1 years (IQR 5.7, 6.6). The average age in those free of CAC at baseline was 46.7 years (42% male), and the average age in those with baseline CAC > 0 was 54.6 (61.4% male). As expected, there were consistently higher levels of risk factors as well as higher baseline AAC scores noted in the group with baseline CAC > 0 compared with those with baseline CAC = 0.

Among participants free of coronary calcium at the baseline scan (N=740), the proportion of incident CAC was lower compared to incident AAC in all age groups, for both men and women (Supplemental Table 1). However, the rate of incident CAC and AAC increased with age for both sexes.

In the remaining participants with CAC or AAC >0 at baseline, the annual increase in mean CAC was 14.2% while the corresponding change in mean AAC was 17.2%, as detailed in Supplemental Table 2. AAC scores increased with increasing CAC scores, although the absolute AAC scores were consistently greater.

In univariate logistic regression analysis in participants free of CAC at baseline, significant predictors of incident CAC included hypertension, anti-hypertensive therapy, current cigarette smoking, diabetes mellitus, body mass index, lipid-lowering therapy, and total cholesterol. For incident AAC, similar significant risk factors were predictors, with the exception of diabetes, anti-hypertensive therapy, and a borderline association of lipid-lowering therapy (Supplemental Table 3). In step-wise multivariable logistic regression models, significant predictors of both incident CAC and incident AAC included age, lipid lowering therapy, current cigarette smoking and total cholesterol. Meanwhile, HDL

cholesterol was protective (Table 2). In addition, antihypertensive therapy was a predictor of incident CAC while BMI was a predictor of incident AAC.

For predictors of CAC and AAC progression, results of the univariate linear regression analyses are described in Supplemental Table 4. In step-wise multivariable analyses, the predictors of CAC progression included presence of baseline CAC, diabetes mellitus, BMI, HDL cholesterol, and serum creatinine. Predictors of AAC progression included age, baseline AAC, diabetes mellitus, and systolic blood pressure (Table 3). In additional models that included baseline AAC, it was a significant predictor of CAC progression (for both incident CAC and progression from baseline CAC >0) independent of other risk factors. With the addition of AAC to the logistic regression model for incident CAC, there was an improvement in the discrimination of the model. The c-statistic incrementally improved to 0.74 (95% CI 0.70, 0.78) compared to 0.72 (95% CI 0.68, 0.76) for the model without AAC (Figure 1).

In the secondary analysis, the univariate predictors of dichotomous progression were similar to those in the prior models predicting incident CAC and progression. In the multivariable model, the risk factors that remained independently significant included age, sex, antihypertensive therapy, lipid-lowering therapy, current cigarette smoking, diabetes, total cholesterol and HDL cholesterol (Table 4). Similarly, after the addition of AAC to the baseline model predicting overall progression, discrimination of the model improved slightly from an AUC of 0.79 (95% CI: 0.77, 0.81) for the baseline model to 0.80 (95% CI: 0.78, 0.82) for the model including AAC.

Discussion

In this study, we report on the risk factors associated with progression of CAC and AAC. Our analyses suggest that the progression of CAC and AAC are strongly associated with traditional risk factors including hypertension, hyperlipidemia and cigarette smoking, and that the presence of baseline AAC is an independent predictor of the progression of CAC in multivariable-adjusted models.

Prior studies have found incidence and progression of CAC, is related to several traditional risk factors including age, male sex, hypertension and higher BMI.[3] In our study, we confirm the importance of risk factors including hypertension, hyperlipidemia and current cigarette smoking in the incidence of calcium in addition to other markers, such as lipid lowering therapy, diabetes mellitus, in the progression of CAC and AAC.

Our findings suggest that the risk factors for incidence and progression of CAC and AAC are generally similar. However, Criqui et al described marked differences in the risk factors for baseline AAC and CAC in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. In their study, AAC showed a much stronger association with cigarette smoking and dyslipidemia than CAC, which was an unexpected finding per the authors.[12] However, this report focused on prevalent CAC and AAC, and data comparing risk factors for progression in a single cohort are limited. An analysis of CAC and AAC progression in the Veterans Administration Diabetes Trial (VADT) suggests that the determinants of progression may

differ for CAC and AAC, albeit in a small cohort with diabetes.[13] Our study was in a single ethnic group, initially free of clinical CVD and with a low prevalence of diabetes. Although the coronary arteries and abdominal aorta are structurally and physiologically different, there are similarities in the underlying pathobiologic mechanisms of atherosclerosis in different vascular beds and their associated CVD risk factors.[14]

Several randomized trials have failed to show reduced progression of CAC and reduced CVD events among asymptomatic individuals with prevalent CAC, who underwent statin therapy, despite lowering of LDL levels.[15,16] Recent studies have suggested statin use may induce or promote the progression of calcium.[17,18] In our study, use of lipid lowering therapy was associated with an increased incidence of both CAC and AAC but was not significantly associated with progression in those with baseline detectable levels of CAC or AAC. Ninety percent of those on lipid-lowering therapy were on statin therapy.[19] Notably, high baseline cholesterol was also associated with increased risk of incident CAC and AAC. Similar to the observed association of anti-hypertensive therapy with increased incidence of CAC, it is likely that use of lipid-lowering therapy is a marker of hyperlipidemia rather than a cause of calcium. However, it is not possible to distinguish between these explanations, and randomized trials would be needed to further investigate confounding by indication versus causality.

The greatest absolute progression of CAC was evident in the group with CAC scores >300. The pathophysiology of plaque progression suggests that the presence of calcium induces a deleterious feedback loop promoting the activity of pro-inflammatory cytokines and macrophages, leading to increased formation and deposition of calcium in the arterial tree.[20] In our analysis, incident AAC appears to occur more frequently than incident CAC in the same cohort. The absolute progression of AAC is also higher than CAC. The reasons for this differential calcification and progression are unclear but could be related to the larger surface area of the abdominal aorta and hence increased overall calcium burden, which could allow for earlier calcium detection.[10] Other studies of pathology in young adults suggest that abdominal aortic atherosclerosis also occurs earlier than coronary atherosclerosis,[21] and our findings of higher incident calcium in the aorta versus coronary arteries likely reflect a similar pattern.

Our analysis suggests that AAC is an independent predictor of CAC progression and its addition to the multivariable model improves discrimination in the prediction of CAC progression. This result was confirmed in our secondary analysis for overall CAC progression in the cohort. Prior studies in the Framingham Cohort have shown the presence of AAC, as seen on plain radiographs and MDCT scans, in middle-aged men and women, was associated with increased incidence of CVD, coronary heart disease (CHD), heart failure (HF), and cardiovascular and all-cause mortality.[22,23,24] Thus, the presence of extra-coronary calcium such as AAC could be an early marker of the likelihood of CAC progression and can further identify a subgroup of asymptomatic individuals who may be at increased risk of adverse CVD outcomes. Given the increased use of abdominal CT imaging in routine medical care, abdominal calcium is increasingly reported as an incidental finding and may have added clinical utility.[25]

Strengths of this analysis include the use of a robust and well-characterized community-dwelling cohort with long-term follow-up and serial collections of risk factors. Furthermore, the analysis of progression in this cohort is strengthened by the minimization of inter-scan variability and improved measurement reproducibility as previously demonstrated by Hoffmann et al in the Framingham Cohort.[8] However, given known differences in CAC and AAC distribution in different ethnic groups,[3,26] the results from our predominantly white, Framingham cohort may not generalize to other ethnic groups. Furthermore, the role of AAC and CAC progression, as measured by MDCT scanning, in refining the prediction of risk, needs further clarification by correlating these measures with adverse cardiovascular events.

In conclusion, multiple CVD risk factors are associated with the incidence and progression of CAC and AAC in a community-dwelling cohort. AAC is an independent predictor of both CAC incidence and progression. Addition of AAC improves discrimination for CAC incidence and progression. Knowledge of the presence of extra-coronary calcium such as AAC could help further characterize asymptomatic individuals with subclinical disease who are at higher risk for CAC progression and incidence of adverse CVD outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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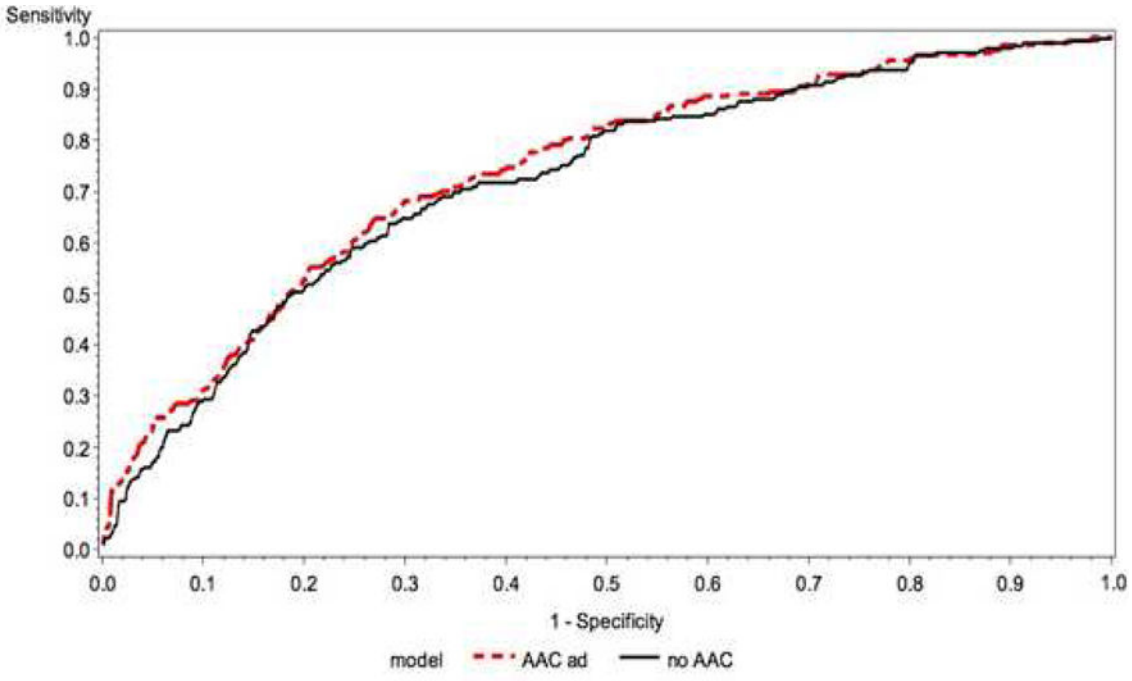

C-statistic for model without AAC = 0.72

C-statistic for model with AAC = 0.74

Figure 1.

Receiver operating characteristic curves for multivariable logistic regression models that include predictors of incident coronary artery calcium with and without continuous abdominal aortic calcium as a predictor.

Table 1

Characteristics of Participants with Baseline Coronary Artery Calcium (CAC) = 0 and Baseline CAC > 0.

Risk Factors	Baseline Coronary Artery Calcium = 0 (N= 1124)	Baseline Coronary Artery Calcium > 0 (N = 780)
Age, (years)	46.7 (7.6)	54.6 (9.8)
Men	42.0%	61.4%
Hypertension	16.9%	37.4%
Hyperlipidemia	15.5%	29.4%
Diabetes mellitus	2.2%	6.3%
Hypertension Treatment	8.9%	22.7%
Hyperlipidemia Treatment	6.6%	16.9%
Current cigarette smoking	10.2%	8.6%
Body mass index, (kg/m^2)	26.9 (5.1)	28.5 (4.9)
Systolic blood pressure, (mmHg)	118.1 (18.8)	126.1 (17.3)
Diastolic blood pressure, (mmHg)	76.5 (25.2)	77.1 (9.6)
Total cholesterol, (mg/dl)	194.6 (34.9)	203.2 (34.0)
HDL cholesterol, (mg/dl)	56.2 (16.5)	51.5 (15.9)
Cigarettes/day	1.3 (4.9)	1.2 (4.9)
Novel Risk Factors		
C-reactive protein, (mg/l)	2.6 (4.4)	3.1 (4.6)
Creatinine, (mg/dl)	0.9 (0.2)	1.0 (0.2)
Vascular Calcium Outcomes		
Baseline CAC score	0	207.7 (495.5)
Baseline AAC score	125.1 (468.7)	1127.3 (2010.4)
Follow-up CAC score	4.8 (16.2)	385.2 (714.2)
Follow-up AAC score	323.9 (994.6)	2167.4 (3291.3)

Table 2

Stepwise Multivariable Logistic Regression Models (Age and Sex-Adjusted) Predicting Incident Coronary (CAC) and Abdominal Aortic Calcium (AAC).

Risk Factors	Coronary Artery Calcium (N=1124)		Abdominal Aortic Calcium (N=942)	
	OR	P-value	OR	P-value
Age (per 5 years)	1.44	<0.001	1.86	<0.001
Male sex	1.88	0.001	1.36	0.104
Antihypertensive therapy	1.68	0.040	–	–
Lipid lowering therapy	1.75	0.044	1.86	0.049
Current cigarette smoking	2.84	<0.001	3.69	<0.001
Diabetes mellitus	–	–	–	–
Body mass index (per 1 SD)	–	–	1.047	0.011
Total cholesterol (per 1 SD)	1.26	0.004	1.25	0.006
HDL cholesterol (per 1 SD)	0.75	0.004	0.78	0.011

Per One Standard Deviation (per 1 SD)

Table 3

Stepwise Multivariable Linear Regression Analysis for Coronary Artery (CAC) and Abdominal Aortic Calcium (AAC) Progression.

Risk Factors	Coronary Artery Calcium (N = 780)		Abdominal Aortic Calcium (N = 998)	
	β	P-value	β	P-value
Age (per 5 years)	−6.24	0.316	44.59	0.045
Male Sex	−8.11	0.754	−225.90	0.0015
Baseline CAC (per 100 AU)	0.28	<0.001	–	–
Baseline AAC (per 100 AU)	–	–	0.55	<0.001
Antihypertensive therapy	47.93	0.052	–	–
Lipid lowering therapy	0.56	0.99	99.92	0.07
Smoking: cigarettes/day (per 1 SD)	–	–	–	–
Diabetes mellitus	187.50	<0.0001	451.11	0.002
Glucose (per 1 SD)	–	–	–	–
Body mass index (per 1 SD)	6.04	0.006	−11.65	0.087
Systolic blood pressure (per 1 SD)	19.09	0.099	141.61	0.0005
Diastolic blood pressure (per 1 SD)	–	–	–	–
Total cholesterol (per 1 SD)	–	–	–	–
HDL cholesterol (per 1 SD)	26.72	0.027	–	–
Creatinine (per 1 SD)	70.45	<0.0001	–	–

Per One Standard Deviation (per 1 SD)

Table 4

Univariate and Stepwise Multivariable Logistic Regression Model Predicting Overall Coronary Artery Calcium (CAC) Progression (Defined as Difference Between the Baseline and Follow-up Scores Was Greater than the Standard Deviation (SD) Within the Appropriate CAC Strata).

Risk Factors	Univariate		Multivariable	
	OR	P-value	OR	P-value
Age (per 5 years)	–	–	1.59	<0.001
Male Sex	–	–	2.50	<0.001
Hypertension	1.51	<0.001	–	–
Antihypertensive therapy	1.83	<0.001	1.65	0.002
Hyperlipidemia	1.62	0.001	–	–
Lipid lowering therapy	1.87	0.002	1.85	<0.001
Current cigarette smoking	1.95	0.001	1.96	<0.001
Smoking: cigarettes/day (per 1 SD)	1.18	0.001	–	–
Diabetes mellitus	3.08	0.003	2.45	0.004
Glucose (per 1 SD)	1.22	0.004	–	–
Body mass index (per 1 SD)	1.03	0.003	–	–
Systolic blood pressure (per 1 SD)	1.10	0.075	–	–
Diastolic blood pressure (per 1 SD)	1.00	0.959	–	–
Total cholesterol (per 1 SD)	1.17	0.003	1.21	0.004
HDL cholesterol (per 1 SD)	0.83	0.002	0.86	0.022
Novel Risk Factors				
C-reactive protein (per 1 SD)	1.03	0.587	–	–
Creatinine (per 1 SD)	1.09	0.179	–	–

Per One Standard Deviation (per 1 SD)