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Relation of Iliac Artery Calcium with Adiposity Measures and Peripheral Artery Disease

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Abstract

Arterial calcification is associated with cardiovascular morbidity and mortality. To improve the understanding of the pathogenesis involved with iliac artery calcium (IAC), we sought to examine the associations between the burden of IAC with adiposity measures and peripheral artery disease (PAD). Participants (n=1,236; 52% women; mean age 60 years) were drawn from the Framingham Heart Study Offspring cohort who underwent multi-detector computed tomography. The extent of IAC was quantified based on calcified atherosclerotic plaques detected in the iliac arteries. High IAC was defined based on sex-specific 90th percentile cutoff points from a healthy referent sub-sample. PAD was defined as an ankle-brachial Index < 0.9, intermittent claudication, and/or history of lower-extremity revascularization. The association between PAD and IAC was assessed using multivariable-adjusted logistic regression models. The burden of high IAC was 20.5% in

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women and 25.5% in men. High IAC was not associated with generalized (body mass index) or area-specific (waist circumference, and volumes of thoracic periaortic, abdominal subcutaneous and visceral adipose tissue) adiposity measures (all $p > 0.22$). High IAC was associated with increased odds of PAD (odds ratio 10.36, 95% confidence interval 4.28, 25.09). This association persisted even after additionally adjusting for coronary artery calcium (odds ratio 11.25, 95% confidence interval 4.29, 29.53). Burden of IAC was associated with an increased risk of PAD.

Keywords

Peripheral vascular disease; epidemiology; iliac artery

Introduction

This study had 2 purposes. First, to determine the relation of iliac artery calcium (**IAC**) with thoracic periaortic adipose tissue. Owing to the location of the fat that surrounds the blood vessels rather than fat distribution in the subcutaneous or visceral locations in the abdomen, we hypothesized that IAC would be more closely associated with thoracic periaortic adipose tissue, as compared to other adiposity measures, including generalized adiposity [body mass index (**BMI**)] and area-specific adiposity measures (waist circumference, abdominal subcutaneous and visceral adipose tissue). Second, to determine if the burden of high IAC is cross-sectionally associated with peripheral artery disease (**PAD**), as defined by an ankle-brachial index (**ABI**) of < 0.9 , presence of intermittent claudication, and/or history of lower-extremity revascularization. We hypothesized that IAC would be associated with PAD even after adjusting for covariates, as well as coronary artery calcium and abdominal aortic calcium, which are the measures of atherosclerosis in different vascular beds.

Methods

The Framingham Heart Study is a community-based cohort study that has monitored individuals across 3 generations since 1948 to explore risk factors for developing cardiovascular disease. The participants of this study were drawn from the Offspring cohort who participated in the seventh examination cycle from 1998 to 2001. Among those, participants who underwent multi-detector computed tomography (**MDCT**) from 2002 to 2005 were selected. Inclusion criteria and study design of the Offspring cohort has been described in detail elsewhere.¹ Among the sample of 1,400 participants who underwent chest and abdominal MDCT scans, we excluded individuals missing any of the following: 1) iliac calcium measurements ($n=8$); 2) thoracic periaortic adipose tissue volume ($n=40$); 3) ABI measurement or $ABI > 1.4$. ($n=62$); and 4) covariates ($n=101$); resulting in a total of 1,236 participants (52% women). In addition, 72 individuals from the 1,236 overall participants were additionally excluded due to missing coronary artery calcium measurements; resulting in a total of 1,164 participants for the analysis including coronary artery calcium. Similarly, 1,232 participants were available for the analysis including abdominal aortic calcium.

A healthy referent sub-sample was created by identifying participants free of clinically apparent cardiovascular disease or traditional cardiovascular disease risk factors. High IAC

was defined on the basis of the sex-specific 90th percentile IAC Agatston score cutoff point from this healthy referent sub-sample. Among the 1,236 overall participants, we excluded individuals with 1) cardiovascular disease (n=147); 2) hypertension (n=506); 3) hyperlipidemia (n=384); 4) diabetes mellitus (n=121); 5) current smoking (n=122); and 6) obesity (n=364); which resulted in a total sample size of 370 (204 women and 166 men) for the healthy referent sub-sample. The 90th percentile Agatston score cutoff point for high IAC in this healthy referent sample was 823 for women and 1808 for men. The institutional review boards of Boston University Medical Center and Massachusetts General Hospital approved the study protocol. Written informed consent was provided by all participants.

The study participants underwent imaging of the chest (from the carina to the diaphragm) and abdominal (from the upper edge of the S1 vertebrae to 125 mm superiorly) areas on an eight slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI) while lying in a supine position.^{2,3} Relevant computed tomography (CT) slices were selected to evaluate the calcified regions of iliac and coronary arteries, as well as abdominal aorta; and volumes of thoracic periaortic, subcutaneous, and visceral adipose tissue.

The definition of a calcified plaque in the iliac and coronary arteries, and abdominal aorta was consistent with the scoring method previously described in the Multi-Ethnic Study of Atherosclerosis.⁴ All CT images were evaluated by the trained reader to identify the first slice that contains the iliac arteries. The first slice was detected immediately below the aortic bifurcation, where the dividing aortic branches maintain <50% of the shared lumen wall. The presence and amount of iliac artery calcium was assessed from the initial MDCT image downwards to the final slice of the scan by using a state-of-art offline workstation (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA). The atherosclerotic lesions were counted if the lesions met the pre-specified area of 1mm² and range of 130 Hounsfield unit (HU) with at least 3 contiguous voxels by applying 3-dimensional connectivity criteria. The system automatically computed the calcified lesion in Agatston score, which was essentially multiplying the pixel area of each lesion (in mm²) with weighted attenuation values (1=130 to 199HU; 2=200 to 299HU; 3=300 to 399HU; 4=400HU) depending on the lesion's maximal HU levels.⁵ If 1 or more lesion was detected, the score from each lesion were combined to calculate the overall IAC score. The Agatston scores of the right and left vessels of the iliac beds were combined to compute the final calcium score to account for both of the iliac arteries. Because not all the participants had the identical number of CT slices available for the IAC measurement, the start and the end of the CT slices and also the number of available slices were documented. The median (25th–75th percentile) of the CT slices was 22 (17–26). On a random sample of 100 participants, intra-reader reproducibility of the IAC measurement was 0.99.

An identical method was applied to compute the Agatston score for coronary artery calcium and abdominal aortic calcium from the CT scans.^{6,7} High inter- and intra-reader reproducibility of this method was previously documented.^{7,8}

BMI was defined as the weight in kilograms divided by height in square meters. Waist circumference was ascertained at the umbilicus to the nearest 0.25 inch. Thoracic periaortic, subcutaneous, and visceral adipose tissue volumes were assessed in a semi-automated

method by evaluating the MDCT scans via a 3-dimensional workstation tool (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA) as previously described elsewhere.^{2,3} Briefly, an experienced reader manually selected the specific tissue borders instructed by the standard protocol. By using the threshold-based algorithm, the software automatically computed the volumes of the specified areas based on the CT attenuation thresholds of window width between -195 and -45HU with window center of -120HU. For the assessment of intrathoracic periaortic adipose tissue, a total of 27 MDCT slices (67.5mm thickness) starting from immediately below the level of pulmonary artery bifurcation were used to assess the fat surrounding the thoracic aorta.^{2,9} High reproducibility of these MDCT-acquired adipose tissue measurements were previously indicated, with inter- and intra-reader reliability >0.98.^{9,10}

All risk factors were evaluated during the Offspring seventh examination cycle. Blood samples were collected in the morning after a minimum of 8-hour fasting for the assessment of fasting plasma glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, and C-reactive protein. Systolic and diastolic blood pressures were measured twice in the left arm after the participants were seated for a minimum of five minutes by the research physician using a standard protocol. The average of the 2 systolic and diastolic blood pressure measurements was used in this study. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL or current use of hypoglycemic treatment. Cardiovascular disease was defined as the occurrence of stroke, transient ischemic attack, congestive heart failure, intermittent claudication, angina pectoris, coronary insufficiency or myocardial infarction. All cardiovascular disease outcomes were adjudicated by 3 physicians. A series of questionnaires and interviews were administered to collect medication history and health behaviors, including antihypertensive treatment, lipid-lowering treatment, smoking status, hormone replacement therapy, and postmenopausal status. Never smoker was defined as neither a former nor a current smoker. Former smoker was considered as not a current smoker but previously smoked >1 cigarette per day for at least a year. Current smoker was classified as smoking >1 cigarette per day within the previous year.

Prevalence of PAD was determined by having an ABI of <0.9, intermittent claudication, and/or history of lower-extremity revascularization. The left and right ankle and brachial systolic blood pressures were assessed twice via a 9.6-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Parks Medical Electronics, Inc, Aloha, OR) at the Offspring cohort seventh examination cycle between 1998 and 2001.^{2,11} The ABI was defined as a ratio of the left or right systolic blood pressure in the ankle divided by the higher mean among the systolic blood pressure in the left and right arm (i.e., left ankle/high arm and right ankle/high arm). Among the left and right ankle's ABI measurements, the lower ABI value was used to determine PAD.

Medical history regarding symptoms of intermittent claudication and lower-extremity revascularization were obtained during a standardized physician-administered interview. Intermittent claudication was defined as symptoms of exertional calf and lower-extremity discomfort while walking uphill or at a more rapid walking pace and was relieved while

resting.¹² Determination of intermittent claudication was adjudicated by an end-point review panel of 3 senior physicians at the Framingham Heart Study.

High IAC was defined as having an IAC Agatston score >90th percentile sex-specific cutoff points derived from a healthy referent sub-sample. IAC, coronary artery calcium, and abdominal aorta calcium scores were natural log-transformed to normalize their skewed distributions. Stepwise logistic regression model was performed to identify variables that are associated with high IAC. Age, sex, and CT slice number were forced into the stepwise regression model. The candidate risk factors included fasting plasma glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, C-reactive protein, systolic blood pressure, diastolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive treatment, lipid-lowering treatment, smoking status (former vs. never, current vs. never), hormone replacement therapy, and postmenopausal status. A significant p -value <0.05 was required for the candidate risk factors to enter and remain in the stepwise regression model. The variables selected in this analysis were subsequently included as covariates in our primary analysis to assess the relation of IAC with adiposity measures and IAC with PAD while adjusting for important predictors of IAC. Next, multivariable-adjusted logistic regression models predicting high IAC from each adiposity measure (BMI, waist circumference, thoracic periaortic adipose tissue, abdominal subcutaneous and abdominal visceral adipose tissue) were performed to explore the relationship between high IAC and adiposity.

Finally, multivariable-adjusted logistic regression models were used to examine the cross-sectional association between IAC and PAD. Models were additionally adjusted for natural log transformed coronary artery calcium or natural log transformed abdominal aortic calcium to assess whether the association between IAC and PAD is attenuated in the presence of atherosclerosis in other vascular beds.

Sensitivity analyses were performed using linear regression models on log IAC score to determine the association with adiposity measures and PAD. Analyses were performed with SAS version 9.1.3. A p -value <0.05 was considered statistically significant.

Results

Characteristics of the study sample ($n=1,236$; 52% women) are shown in Table 1. A total of 60 participants (5%) had PAD defined as at least 1 of the following: ABI <0.9, symptoms of intermittent claudication, or history of lower-extremity revascularization. Among these, 2.8% ($n=35$) of the participants had ABI <0.9; 2.9% ($n=36$) had intermittent claudication; and 0.6% ($n=8$) had history of lower-extremity revascularization. The prevalence of high IAC was 20.5% (132/644) in women, and 25.5% (151/592) in men. In men, the proportion of high IAC increased from 5% to 50% among the age group under 50 years to over 70 years indicating that IAC increases with increasing age. A similar association was noted in women (data not shown).

After forcing age, sex, and CT slice number into the model, the selection procedure identified a total of seven risk factors for IAC (all $p < 0.05$) (Table 2). Among the risk factors forced in the model, only age was associated with an increased odds of high IAC.

Measures of adiposity including BMI, waist circumference, thoracic periaortic adipose tissue, and subcutaneous adipose tissue were generally not associated with high IAC (all $p \geq 0.22$) (Supplemental Table 1). We did not observe any significant sex-interaction between the relation of adiposity measures and IAC (all $p \geq 0.14$).

Multivariable-adjusted logistic regression models were constructed to explore the association between IAC burden and PAD (Table 3). High IAC was significantly associated with increased odds of PAD in the age and sex-adjusted model (OR 18.45; 95% CI 8.11, 41.99) and multivariable-adjusted model (OR 10.36; 95% CI 4.28, 25.09). This significant association persisted even after further adjusting for coronary artery calcium (OR 11.25; 95% CI 4.29, 29.53) or abdominal aortic calcium (OR 9.18; 95% CI 3.34, 25.27) and even after excluding participants with prevalent cardiovascular disease (data not shown). A similar trend was observed with the continuous IAC score and PAD (all $p < 0.05$) (Table 3). Figure 1 depicts the sex-specific frequency distributions of IAC by PAD status. Participants with PAD tended to have a higher IAC Agatston score, as compared with individuals without PAD.

Discussion

Our principal findings are 3 fold. First, three-quarters of our study sample had a detectable IAC score and nearly a quarter of the sample had high IAC. Second, a burden of high IAC was cross-sectionally associated with an increased odds of PAD. This association remained significant when the IAC was analyzed as a dichotomous or continuous variable, and even after additionally adjusting for variables associated with high IAC, as well as coronary artery calcium or abdominal aortic calcium. Third, we did not observe an association between IAC with generalized or area-specific adiposity measures.

Prior investigations explored the associations between IAC and adiposity measures, including BMI,¹³ % body fat,¹³ overall abdominal fat,¹⁴ subcutaneous fat,¹⁴ visceral fat,^{13,14} pericardial fat,¹⁵ and intramuscular fat.¹⁴ Consistent with our findings, none of these studies observed significant associations between IAC and adiposity measures. An exception was reported in an epidemiologic study of 394 participants, in which IAC and pericardial adipose tissue was associated even after adjusting for potential confounders, BMI, and abdominal visceral adipose tissue (all $p = 0.01$).¹⁵ In this study, we extend the literature by incorporating thoracic periaortic adipose tissue that is intrinsically different (i.e., fat around the blood vessel itself), as compared to the fat measures used in the aforementioned studies.

Our study documents the association between the burden of IAC assessed by MDCT with PAD, while adjusting for coronary artery calcium and abdominal aortic calcium, which are the markers of atherosclerosis in different locations of the vascular beds. Moreover, we expand the existing literature by incorporating thoracic periaortic adipose tissue, a more

precise region-specific adiposity measure ascertained by MDCT, to assess the association with IAC.

IAC was not associated with thoracic periaortic adipose tissue or the other adiposity measures evaluated, including generalized obesity, abdominal adiposity, and MDCT-acquired abdominal adipose tissue depots. Our *a priori* hypothesis was constructed based on the previous findings that excess accumulation of ectopic fat depots are associated with abnormal lipid profiles, facilitate inflammation, and oxidative stress, as well as increases in unstable plaques in the vessels via systemic and local effects, that consequently leads to manifestation of cardiometabolic disease.¹⁶ Perivascular fat has been recognized as a metabolically active depot that has direct effects on adjacent blood vessels via promoting vasoconstriction¹⁷ and atherosclerosis.¹⁸ Prior studies confirmed the local toxic effect of fat on vascularity by demonstrating the association between thoracic periaortic adipose tissue and arterial calcification.^{19,20} Of interest, we have previously reported the significant association between thoracic periaortic adipose tissue with calcium accumulation in the aorta.²⁰ Accordingly, we initially hypothesized that calcification in the iliac beds would be more closely associated with abdominal periaortic adipose tissue (i.e., fat around the abdominal aorta), as compared to other fat depots due to the local toxic effect of fat attributed to the closer anatomical proximity to the iliac arteries. However, we were unable to include abdominal periaortic adipose tissue owing to the technical limitations that constrained the ability to adequately visualize this fat depot.² Presumptively, a better measure of adipose tissue depot with a more direct local effect, such as peri-iliac artery adipose tissue or abdominal periaortic adipose tissue, would be needed to precisely examine the local toxic effect of fat on IAC.

The association of IAC and PAD may be explained by the extent of IAC detected via CT as a marker of vascular disease that contributes to the manifestation of PAD.²¹ Anatomically, the areas of bifurcation in the arterial tree are vulnerable for developing atherosclerotic lesions due to the altered hemodynamics at the branch point.²² In particular, the lower shear stress area (i.e., lateral wall) of the bifurcation has been associated with elevated gene expression of proatherogenic inflammatory mediators and matrix metalloproteinase activity (i.e., a marker of reduced collagen),^{23,24} as well as multiple markers of endothelial dysfunction that are essential for plaque formation and progression.²⁵ The increased likelihood of atherosclerosis due to the anatomical location of the iliac arteries may locally limit the circulation of blood flow in the lower extremities, subsequently constraining oxygen and nutrient supplies to the peripheral arteries and contribute to the development of PAD.

Strengths of this study include the use of a large community-based population with robust clinical data. There are several limitations of the present analysis. First, generalization of our findings cannot be made to other ethnic groups besides non-Hispanic Whites. Second, we were unable to measure the abdominal periaortic adipose tissue due to the limitations involved with CT imaging techniques, which precluded our attempts to examine the local toxic effect of fat on arterial calcification. Alternatively, we used thoracic periaortic adipose tissue, a perivascular fat that surrounds the thoracic aorta, which has the closest proximity to the vascular system, as compared to the other fat measures evaluated in this study. Third, the average time interval between assessment of the IAC and PAD was 4.2 years. It is possible

that the observed association between IAC and PAD may have been influenced by the nonsynchronous time period of the assessments of exposure and outcome variables. Future longitudinal and mechanistic studies are warranted to confirm the temporal and causal associations of IAC and PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Frequency distribution of iliac artery calcium. The sex-specific frequency distributions of iliac artery calcium are shown according to individuals with and without peripheral arterial disease (PAD).

Table 1

Study sample characteristics

Characteristic	Overall Participants (n=1236)
Demographics	
Age (years)	60 ± 9
Women	644 (52%)
Calcium Measures	
Iliac Artery Calcium [*] (Agatston score)	207 (0–1240)
Iliac Artery Calcium > 0	920 (74%)
Adiposity Measures	
Body Mass Index (kg/m ²)	28 ± 5
Waist Circumference (cm)	99 ± 13
Thoracic Periaortic Adipose Tissue (cm ³)	17 ± 9
Subcutaneous Adipose Tissue (cm ³)	3004 ± 1323
Visceral Adipose Tissue (cm ³)	2109 ± 1098
Clinical Peripheral Arterial Disease Measure	
Peripheral Arterial Disease [†]	60 (5%)
Covariates	
Fasting Plasma Glucose (mg/dL)	102 ± 24
Triglycerides [*] (mg/dL)	115 (78–165)
Low-Density Lipoprotein Cholesterol (mg/dL)	120 ± 32
High-Density Lipoprotein Cholesterol (mg/dL)	53 ± 16
Fibrinogen [*] (mg/dL)	368 (326–415)
C-Reactive Protein [*] (mg/L)	2 (1–5)
Systolic Blood Pressure (mmHg)	125 ± 18
Diastolic Blood Pressure (mmHg)	75 ± 9
Diabetes Mellitus [‡]	121 (10%)
Cardiovascular Disease	147 (12%)
Antihypertensive Treatment	372 (30%)
Lipid-Lowering Treatment	244 (20%)
Smoking Status	
Never	468 (38%)
Former [§]	646 (52%)
Current	122 (10%)
Postmenopausal Status (women only)	533/644 (83%)
Hormone Replacement Therapy (women only)	221/644 (34%)
Coronary Artery Calcium ^{*,#} (Agatston score)	37 (0–249)
Coronary Artery Calcium [#] >100	436/1164 (38%)

Unless otherwise indicated, data are shown as means ± standard deviations for continuous variables or counts (proportions) for dichotomous variables.

* Described as medians (25th–75th percentiles) due to their skewed distribution.

[†] Defined as ankle-brachial index <0.9, intermittent claudication, and/or history of revascularization.

[‡] Defined as fasting glucose ≥126 mg/dL or use of hypoglycemic medication.

[§] Defined as not a current smoker but previously smoked >1 cigarette/day for at least a year.

^{||} Defined as smoking >1 cigarette/day within 1 year prior to the exam.

[#] Data are limited to participants who had available coronary artery calcium score (n=1164).

Table 2

Results of stepwise logistic regression model for the identification of variables associated with high iliac artery calcium^{*}

Risk Factors[†]	Odds Ratio (95% Confidence Interval)	p-Value
Age (10 years)	3.14 (2.47, 3.98)	<0.0001
Sex (Women vs. Men)	1.36 (0.94, 1.96)	0.11
Computed Tomography Slice Number	1.02 (0.99, 1.05)	0.16
High-Density Lipoprotein Cholesterol (1-standard deviation)	0.69 (0.56, 0.84)	0.0002
Systolic Blood Pressure (1-standard deviation)	1.32 (1.12, 1.55)	0.0009
Diabetes Mellitus	1.88 (1.18, 2.99)	0.008
Cardiovascular Disease	2.41 (1.54, 3.77)	0.0001
Antihypertensive Treatment	1.62 (1.14, 2.30)	0.007
Lipid-Lowering Treatment	1.65 (1.11, 2.43)	0.01
Smoking Status	–	<0.0001
Former vs. Never	3.86 (2.61, 5.71)	–
Current vs. Never	12.33 (6.83, 22.25)	–

Data are shown as odds ratios (95% confidence interval).

^{*} Defined based on 90th percentile Agatston score cutoff point from a healthy referent sub-sample.

[†] Candidate variables for possible inclusion in the stepwise logistic regression were as follows (age, sex, computed tomography slice number were forced into model); fasting plasma glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, C-reactive protein, systolic blood pressure, diastolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive treatment, lipid-lowering treatment, smoking status (former vs. never, current vs. never), hormone replacement therapy (woman only), postmenopausal status (woman only). Variables with *p*-value less than 0.05 were selected to enter and remain in the regression model.

Table 3

Multivariable-adjusted logistic regression models: odds of peripheral artery disease from iliac artery calcium

Exposure	Model [‡]	Odds Ratio (95% Confidence Interval)	p-Value
High Iliac Artery Calcium* (Dichotomous)	Age and Sex	18.45 (8.11, 41.99)	<0.001
	MV	10.36 (4.28, 25.09)	<0.001
	MV + CAC	11.25 (4.29, 29.53)	<0.001
Iliac Artery Calcium Score [‡] (Continuous)	Age and Sex	2.11 (1.62, 2.74)	<0.001
	MV	1.66 (1.27, 2.17)	0.0002
	MV + CAC	1.66 (1.24, 2.22)	0.0006

The extent of iliac artery calcium was defined in two different ways for the analysis: 1) high iliac artery calcium determined by the 90th percentile Agatston score cutoff from a healthy referent sub-sample as a dichotomous variable; and 2) iliac artery calcium score denoted in Agatston score as a continuous variable.

In this analysis, 72 individuals from the 1236 overall participants were additionally excluded due to missing coronary artery calcium measurements. Thus, final analysis population was 1164.

* Defined based on 90th percentile cutoff points from a healthy referent group.

[‡] Modeled as natural log (iliac artery calcium + 1) due to its skewed distribution. Odds ratios present odds of peripheral artery disease per 1 standard deviation increment in natural log transformed IAC.

[‡] Age and sex model was adjusted for age and sex. Multivariable adjustment included age, sex, diabetes mellitus, high-density lipoprotein cholesterol, systolic blood pressure, cardiovascular disease, antihypertensive treatment, lipid-lowering treatment, and smoking status (former vs. never, current vs. never). MV + CAC model was additionally adjusted for CAC score. Due to the skewed distribution, CAC was modeled as natural log (CAC + 1).

Abbreviations: CAC, coronary artery calcium; MV, multivariable.