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Influence of Subclinical Atherosclerosis Burden and Progression on Mortality

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ABSTRACT

BACKGROUND Atherosclerosis is a dynamic process. There is little evidence regarding whether quantification of atherosclerosis extent and progression, particularly in the carotid artery, in asymptomatic individuals predicts all-cause mortality.

OBJECTIVES This study sought to evaluate the independent predictive value (beyond cardiovascular risk factors) of subclinical atherosclerosis burden and progression and all-cause mortality.

METHODS A population of 5,716 asymptomatic U.S. adults (mean age 68.9 years, 56.7% female) enrolled between 2008 and 2009 in the BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At Risk Population) study underwent examination by vascular ultrasound to quantify carotid plaque burden (cPB) (the sum of right and left carotid plaque areas) and by computed tomography for coronary artery calcium (CAC). Follow-up carotid vascular ultrasound was performed on 732 participants a median of 8.9 years after the baseline exam. All participants were followed up for all-cause mortality, the primary outcome. Trend HRs are the per-tertile increase in each variable.

RESULTS Over a median 12.4 years' follow-up, 901 (16%) participants died. After adjustment for cardiovascular risk factors and background medication, baseline cPB and CAC score were both significantly associated with all-cause mortality (fully adjusted trend HR: 1.23; 95% CI: 1.16-1.32; and HR: 1.15; 95% CI: 1.08-1.23), respectively (both $P < 0.001$), thus providing additional prognostic value. cPB performed better than CAC score. In participants with a second vascular ultrasound evaluation, median cPB progressed from 29.2 to 91.3 mm^3. cPB progression was significantly associated with all-cause mortality after adjusting for cardiovascular risk factors and baseline cPB (HR: 1.03; 95% CI: 1.01-1.04 per absolute 10-mm^3 change; $P = 0.01$).

CONCLUSIONS Subclinical atherosclerosis burden (cPB and CAC) in asymptomatic individuals was independently associated with all-cause mortality. Moreover, atherosclerosis progression was independently associated with all-cause mortality. (JACC. 2024;84:1391-1403) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

cIMT = carotid intima-medial thickening

cPB = carotid plaque burden

CT = computed tomography

CVD = cardiovascular disease

CVRF = cardiovascular risk factor

FRS = Framingham risk score

LDL-C = low-density lipoprotein cholesterol

SBP = systolic blood pressure

VUS = vascular ultrasound

Cardiovascular disease (CVD) is the leading cause of death worldwide,[1] and the clinical manifestations of the disease are usually preceded by many years by the underlying process of atherosclerosis. Current tools for cardiovascular risk prediction like the Framingham risk score (FRS) are based on conventional cardiovascular risk factors (CVRFs)[2]; however, while these equations work at the population level, their accuracy at the individual level is limited, especially for long-term risk prediction.[3]

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The visualization and quantification of subclinical atherosclerosis by noninvasive vascular imaging is gaining an expanding role in cardiovascular risk assessment.[4] Previous studies have revealed that atherosclerosis is very frequent even in apparently healthy middle-aged populations[5,6]; moreover, CVD risk prediction based on CVRFs is improved by additionally considering the presence of subclinical atherosclerosis in the carotid or femoral arteries assessed by vascular ultrasound (VUS) or the presence of coronary artery calcium (CAC) detected by noncontrast computed tomography (CT).[7-10] Risk classification can be further improved by considering not merely the presence of subclinical atherosclerosis but its extent (atherosclerotic burden), quantified either as the CAC score or as VUS-detected carotid plaque burden (cPB), both of which correlate with long-term CV events.[4,11] Atherosclerosis is a dynamic process, and plaque burden can remain stable, progress, or even regress over time, and plaque progression has been shown to increase substantially with the increasing presence of CVRFs.[12] These changes in atherosclerosis burden can modify the predictive capacity of cross-sectional imaging. It is therefore plausible that the risk-predictive capacity of atherosclerosis imaging could be further improved by quantifying atherosclerosis progression. However, this possibility in relation to the cPB has not been tested before.

The CAC score has been extensively used to improve risk prediction over CVRFs alone[4,13]; however, it is less than optimal for detecting early atherosclerosis or for longitudinal evaluations. Plaque calcification occurs at late stages of plaque formation,[14] and CAC analysis thus will not detect early, noncalcified plaques. Moreover, although CAC progression has been recently shown to correlate with all-cause mortality,[15] it may reflect plaque stabilization rather than disease progression, thus potentially reducing prognostic value, especially in patients who have initiated lipid-lowering therapy.[14,16] VUS examination of easily accessible peripheral arteries (commonly the carotids and femorals) has theoretical advantages over CAC analysis because it can identify early noncalcified plaques and monitor their progression.[5,12,17,18] While some studies have demonstrated that VUS-detected atherosclerotic burden in peripheral arteries provides incremental predictive value for ischemic events over CVRFs alone,[4,19] and others have shown that the percentage of carotid stenosis by VUS predicts mortality,[20,21] there is a paucity of data regarding the independent predictive value of VUS-detected subclinical cPB and its progression and all-cause mortality.

The aim of this study was to evaluate the association with all-cause mortality of atherosclerotic burden (cPB by VUS and CAC by noncontrast CT) and cPB progression in a population of asymptomatic individuals.

STUDY DESIGN AND PARTICIPANTS. The BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At Risk Population; NCT00738725) study is a prospective study that, between January 2008 and June 2009, enrolled 7,687 asymptomatic members of the Humana Health System (men 55-80 years of age and women 60-80 years of age) residing in the Chicago, Illinois, or Fort Lauderdale, Florida, metropolitan areas. Methodological aspects have been described in detail.[22] Eligibility criteria included freedom from previous CVD (myocardial infarction, stroke, angina, heart failure, or arterial revascularization) and from active cancer treatment or any medical condition precluding long-term participation. A total of 6,102 participants entered the imaging arm of the study and were assessed by carotid VUS and CAC scoring. Of these participants, 732 had a second carotid VUS performed a median of 8.9 years (range: 8.4-9.7 years) later to assess cPB progression. Participants were followed until October 2021. Deaths were identified from Social Security and National Death Index searches.

The BioImage study was approved by the Institutional Review Board, and all participants provided written informed consent and Health Insurance Portability and Accountability Act authorization.

BASELINE EXAMINATIONS. All participants had an in-person baseline examination and interview. Diabetes mellitus was defined as current medication with oral hypoglycemic agents or insulin or self-reported

diagnosis. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Current smoking status was self-reported. A nonfasting venous blood sample was processed for routine biochemistry tests, including determination of plasma lipid levels.

CAROTID VUS. Plaque burden in both carotid arteries was assessed at baseline using a high-resolution, 2-dimensional L9-3 linear array transducer using a Philips iU22 ultrasound system (Philips Healthcare), with scanning in longitudinal and cross-sectional orientations from the proximal common carotid artery to the distal internal carotid artery on each side. Ultrasound scans were read by a core laboratory at the Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Denmark. cPB was obtained as the sum of plaque areas from all images in the cross-sectional sweeps from the right and left carotid arteries, providing a quantitative metric of total plaque area (mm^2) along the length of the visualized bilateral carotids using Philips QLAB quantification software (QLAB-VPQ, version 13, Philips). Interobserver agreement has been previously described with an intraclass correlation coefficient of 0.823.[23] In addition, from December 2008, all consecutively enrolled participants were also examined by carotid VUS using a real-time VL13-5 3D linear array transducer (Philips Healthcare), ensuring that the third dimension is acquired in a standardized way over a period of about 3 seconds, and total plaque volume (mm^3) was calculated as the sum of plaque volumes in the same longitudinal segments from both carotids, as previously described.[22,24] Participants undergoing follow-up carotid VUS were examined with the 3-dimensional transducer, and plaque progression was defined as any increase in cPB from baseline to the follow-up VUS scan. Absence of plaque progression was defined as a decrease in cPB from baseline to follow-up (plaque regression) or cPB = 0 at both baseline and follow-up (no carotid atherosclerosis). Baseline and follow-up 3-dimensional images of participants from the progression cohort were analyzed in a blinded fashion at Centro Nacional de Investigaciones Cardiovasculares (Madrid, Spain) using the Carotid Model CM2020 software version 2.1 (Philips Research). Interobserver variability was assessed in the first 56 cases by 2 independent readers (1 from each site) with an intraclass correlation agreement of 0.92 (95% CI: 0.86-0.96). Intraobserver concordance has been previously reported, with an intraclass correlation coefficient of 0.998 (95% CI: 0.996-0.999).[24]

CAC QUANTIFICATION. CAC was measured by the Agatston method from noncontrast multidetector CT scans of the coronary arteries obtained using a Philips Brilliance 64-slice CT scanner (Philips Healthcare) with prospectively electrocardiographically gated acquisition. All operators and core laboratory readers were blinded to clinical data and results from other imaging modalities.

STATISTICAL ANALYSIS. Baseline characteristics were expressed as mean ± SD for continuous variables or median (Q1-Q3) if marked skewness existed, and as number and percentage for categorical variables. For each imaging modality, participants were classified as either having no atherosclerosis or by tertile of increasing CAC score or cPB.

Associations between baseline characteristics and cPB or CAC score tertiles were analyzed using trend tests across groups. Predictors of extent of plaque progression were assessed with a multivariate linear regression analysis.

All-cause mortality was plotted against cPB and CAC score tertiles using the Kaplan-Meier method, and mortality rates were compared among groups by the log-rank test. Associations between cPB or CAC score (categorized as tertiles or as continuous log-transformed variables) and all-cause mortality were assessed by Cox proportional hazards regression. Trend HRs were calculated as per tertile increase in cPB or CAC score. Potential confounders were adjusted for in 2 models: model 1, including age, sex, and race; and model 2, including age, sex, race, diabetes mellitus, current smoking, body mass index, SBP, antihypertensive medication, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and use of lipid-lowering or hypertensive drugs. To evaluate the incremental risk predictive value of CAC score or cPB relative to model 1 and model 2, we assessed each model for overall fit (likelihood ratio test), discrimination (Harrell's C-index), and calibration (Hosmer-Lemeshow test). To examine the impact of cPB progression on all-cause mortality, participants in the subcohort with follow-up VUS data were classified as showing no progression between baseline and follow-up (no atherosclerosis if cPB = 0 at both time points, or regression when cPB decreased from the first to the second examination) or progression if cPB increased. All-cause mortality rates were plotted using the Kaplan-Meier method and compared between groups by the log-rank test. Cox proportional hazards analysis was used to assess the association between progression as a continuous variable and all-cause mortality, with adjustment for CVRFs at the time of the second VUS

FIGURE 1 Enrollment Flowchart

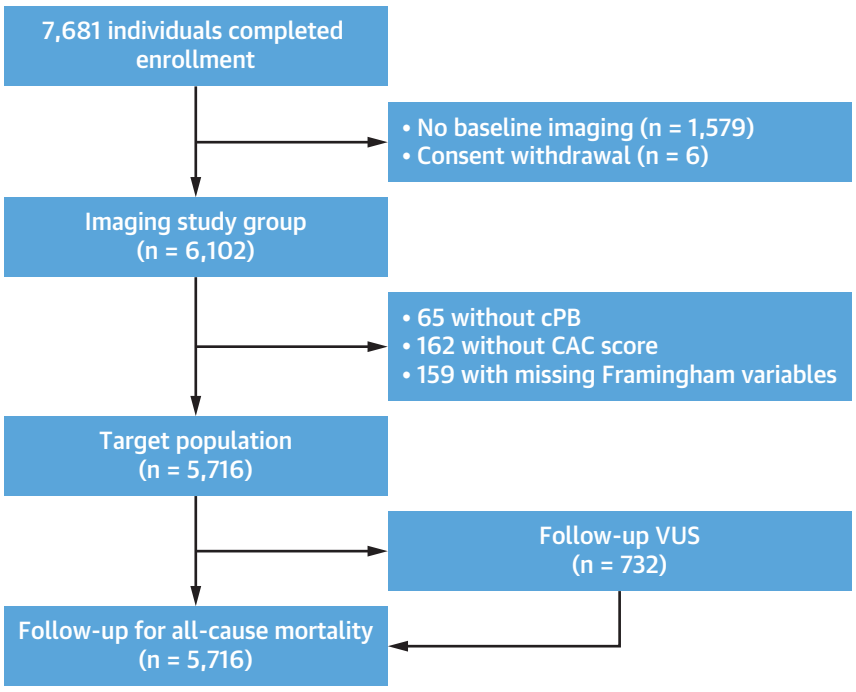


Diagram depicting total number of subjects enrolled and reasons for exclusion. CAC = coronary artery calcium; cPB = carotid plaque burden; VUS = vascular ultrasound.

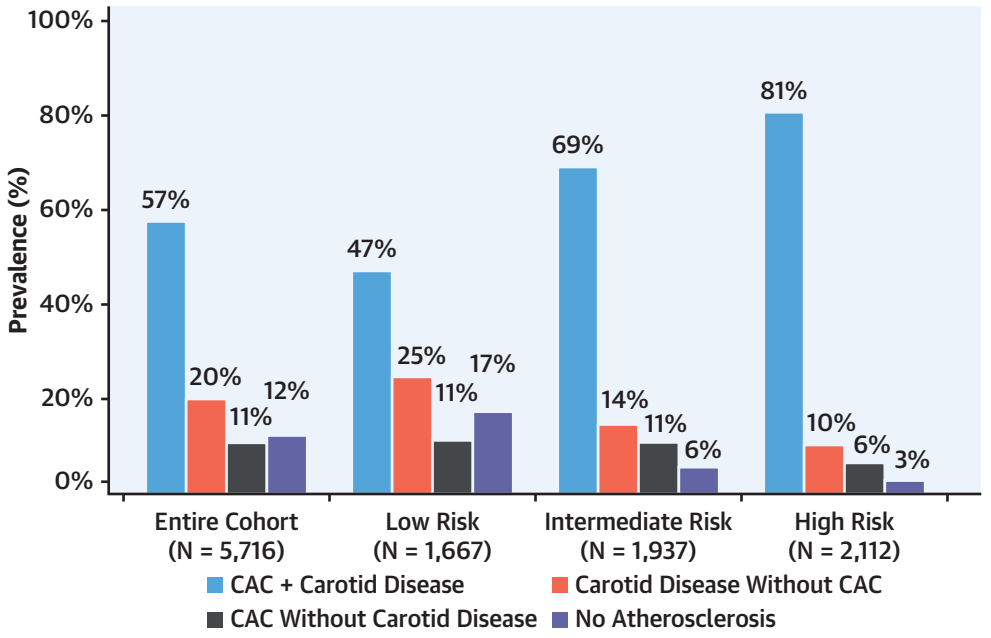
and baseline (continuous log-transformed) cPB. All study participants were followed until time of death or close of study (October 2021), whichever came first. All analyses were performed with Stata version 17 (StataCorp).

RESULTS

A total of 7,687 participants were enrolled, of whom 6,102 underwent imaging. Of these, 386 were excluded due to missing data on carotid VUS, CAC imaging, or any of the variables required to calculate the FRS, yielding a final population of 5,716 study participants, 732 of whom underwent a second carotid VUS examination a median 8.9 years later to assess cPB progression. Study participant flow is depicted in **Figure 1**. Participants in the excluded population had a higher cardiovascular risk due to a higher percentage of males and diabetes and slightly higher body mass index, total cholesterol, and LDL-C (Supplemental Table 1).

PREVALENCE OF SUBCLINICAL ATHEROSCLEROSIS AT BASELINE. The mean participant age was 68.9 years, and 56.7% were female; baseline characteristics are summarized in Supplemental Table 1. At baseline, 87.7% of participants had subclinical atherosclerosis; 57.6% had multiterritorial disease (some cPB in 1 or both carotids and CAC score>0), 19.7% had disease only in the carotids, and 10.5% had only CAC (**Figure 2**). When stratified by FRS groups, the prevalence of multiterritorial atherosclerosis was 47% in the low-risk group, increasing to 69% in the intermediate-risk group and 81% in the high-risk group. While the prevalence of isolated CAC remained similar in all risk groups (approximately 10%), isolated carotid disease was significantly more prevalent in the low-risk group (25%) and decreased with increasing FRS. To better evaluate the factors associated with subclinical atherosclerosis at baseline, the population was divided into tertiles of cPB and CAC score (**Tables 1 and 2**). Increasing tertiles of cPB and CAC score were associated with older age; male sex; White race; and CVRFs including smoking, diabetes, higher SBP, higher FRS, and lipid-lowering and antihypertensive therapy. The distributions of baseline cPB and CAC score are shown in Supplemental Figure 1.

FIGURE 2 Prevalence of CAC and Carotid Atherosclerosis in the Overall Cohort and by Framingham Risk Groups



The presence of multiterritorial atherosclerosis (carotid atherosclerosis and coronary artery calcium [CAC]) increases with increasing Framingham risk score. Blue indicates carotid atherosclerosis and CAC; red indicates only carotid atherosclerosis; black indicates only CAC; gray indicates no atherosclerosis.

TABLE 1 Baseline Characteristics and Mortality Stratified by Vascular Ultrasound-Measured Carotid Plaque Burden Tertile

	Vascular Ultrasound-Carotid Plaque Burden (mm^2)				
	No Disease (n = 1,305)	**Tertile 1 (n = 1,471)**	**Tertile 2 (n = 1,471)**	**Tertile 3 (n = 1,469)**	***P* Value (Trend)**
Age, y	67.4 ± 5.7	68.2 ± 5.9	69.4 ± 6.0	70.3 ± 5.9	<0.001
Sex					<0.001
Female	870 (66.7)	955 (64.9)	814 (55.3)	602 (41.0)	
Male	435 (33.3)	516 (35.1)	657 (44.7)	867 (59.0)	
White	834 (63.9)	1,090 (74.1)	1153 (78.4)	1156 (78.7)	<0.001
Diabetes mellitus	184 (14.1)	203 (13.8)	220 (15.0)	263 (17.9)	0.003
Current smoker	54 (4.1)	107 (7.3)	112 (7.6)	210 (14.3)	<0.001
BMI, kg/m^2	29.5 ± 5.8	29.1 ± 5.6	29.1 ± 5.6	28.5 ± 5.1	<0.001
LDL cholesterol, mg/dL	114.1 ± 32.5	114.4 ± 32.7	114.8 ± 33.1	113.6 ± 34.5	0.75
HDL cholesterol, mg/dL	58.1 ± 15.2	57.3 ± 15.1	55.4 ± 14.9	53.7 ± 15.0	<0.001
Total cholesterol, mg/dL	202.4 ± 37.6	203.4 ± 38.1	202.5 ± 37.0	199.4 ± 38.5	0.02
Triglycerides, mg/dL	151.3 ± 71.4	158.5 ± 72.9	161.7 ± 71.4	160.7 ± 74.2	<0.001
SBP, mm Hg	136.7 ± 18.2	137.7 ± 17.8	140.2 ± 19.0	142.8 ± 18.6	<0.001
DBP, mm Hg	79.2 ± 9.4	78.1 ± 8.7	77.9 ± 9.0	77.6 ± 9.1	<0.001
Lipid-lowering therapy	300 (23.0)	427 (29.0)	458 (31.1)	480/1,469 (32.7)	<0.001
Antihypertensive therapy	291 (22.3)	340 (23.1)	428 (29.1)	494/1,469 (33.6)	<0.001
Framingham 10-y risk, %	5.8 (3.0-10.6)	6.4 (3.5-11.9)	9.1 (4.4-15.9)	12.4 (7.1-18.5)	<0.001
Framingham 10-y risk group					<0.001
Low risk (≤10%)	952 (73.0)	1,003 (68.2)	799 (54.3)	558 (38.0)	
Intermediate risk (10%-20%)	294 (22.5)	365 (24.8)	483 (32.8)	613 (41.7)	
High risk (>20%)	59 (4.5)	103 (7.0)	189 (12.8)	298 (20.3)	
Deaths	122 (9.3)	174 (11.8)	250 (17.0)	355 (24.2)	<0.001
Mean follow-up time, y	12.3	12.1	11.7	11.3	

Values are mean ± SD, n (%), median (Q1-Q3), or n/N (%), unless otherwise indicated. Carotid plaque burden tertiles: no disease, 0 mm^2; tertile 1, 0-169.5 mm^2; tertile 2, 169.5-534.3 mm^2; tertile 3, >534.3 mm^2.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

TABLE 2 Baseline Characteristics and Mortality Stratified by Noncontrast Computed Tomography-Measured CAC Score Tertile

	CAC Score				
	No Disease (n = 1,829)	Tertile 1 (n = 1,289)	Tertile 2 (n = 1,300)	Tertile 3 (n = 1,298)	*P* Value (Trend)
Age, y	67.1 ± 5.6	68.5 ± 5.9	69.7 ± 5.9	70.8 ± 5.8	<0.001
Sex					<0.001
Female	1,306 (71.4)	774 (60.0)	707 (54.4)	454 (35.0)	
Male	523 (28.6)	515 (40.0)	593 (45.6)	844 (65.0)	
White	1,185 (64.8)	924 (71.7)	1,024 (78.8)	1,100 (84.7)	<0.001
Diabetes mellitus	216 (11.8)	172 (13.3)	213 (16.4)	269 (20.7)	<0.001
Current smoker	117 (6.4)	107 (8.3)	110 (8.5)	149 (11.5)	<0.001
BMI, kg/m^2	28.8 ± 5.6	29.1 ± 5.4	29.2 ± 5.4	29.1 ± 5.6	0.11
LDL cholesterol, mg/dL	117.6 ± 32.5	114.5 ± 33.7	113.6 ± 32.8	109.7 ± 33.6	<0.001
HDL cholesterol, mg/dL	58.7 ± 15.1	55.8 ± 15.0	55.8 ± 15.4	52.8 ± 14.5	<0.001
Total cholesterol, mg/dL	206.6 ± 37.0	202.5 ± 38.3	201.6 ± 37.7	195.0 ± 37.7	<0.001
Triglycerides, mg/dL	151.5 ± 70.1	160.6 ± 73.0	161.0 ± 72.7	162.6 ± 75.0	<0.001
SBP, mm Hg	137.3 ± 18.6	139.0 ± 18.5	140.3 ± 18.4	142.2 ± 18.4	<0.001
DBP, mm Hg	78.3 ± 9.0	78.4 ± 8.9	77.8 ± 9.1	78.1 ± 9.2	0.18
Lipid-lowering drug	398 (21.8)	371 (28.8)	435 (33.5)	461 (35.5)	<0.001
Antihypertensive agent	399 (21.8)	332 (25.8)	377 (29.0)	445 (34.3)	<0.001
Framingham 10-y risk, %	5.4 (3.0-9.7)	7.6 (4.1-13.8)	9.5 (5.0-15.3)	13.6 (7.7-19.6)	<0.001
Framingham 10-y risk group					<0.001
Low risk (≤10%)	1,391 (76.1)	798 (61.9)	684 (52.6)	439 (33.8)	
Intermediate risk (10%-20%)	355 (19.4)	380 (29.5)	465 (35.8)	555 (42.8)	
High risk (>20%)	83 (4.5)	111 (8.6)	151 (11.6)	304 (23.4)	
Deaths	184 (10.1)	175 (13.6)	221 (17.0)	321 (24.7)	<0.001
Mean follow-up time, y	12.2	12.0	11.8	11.3	

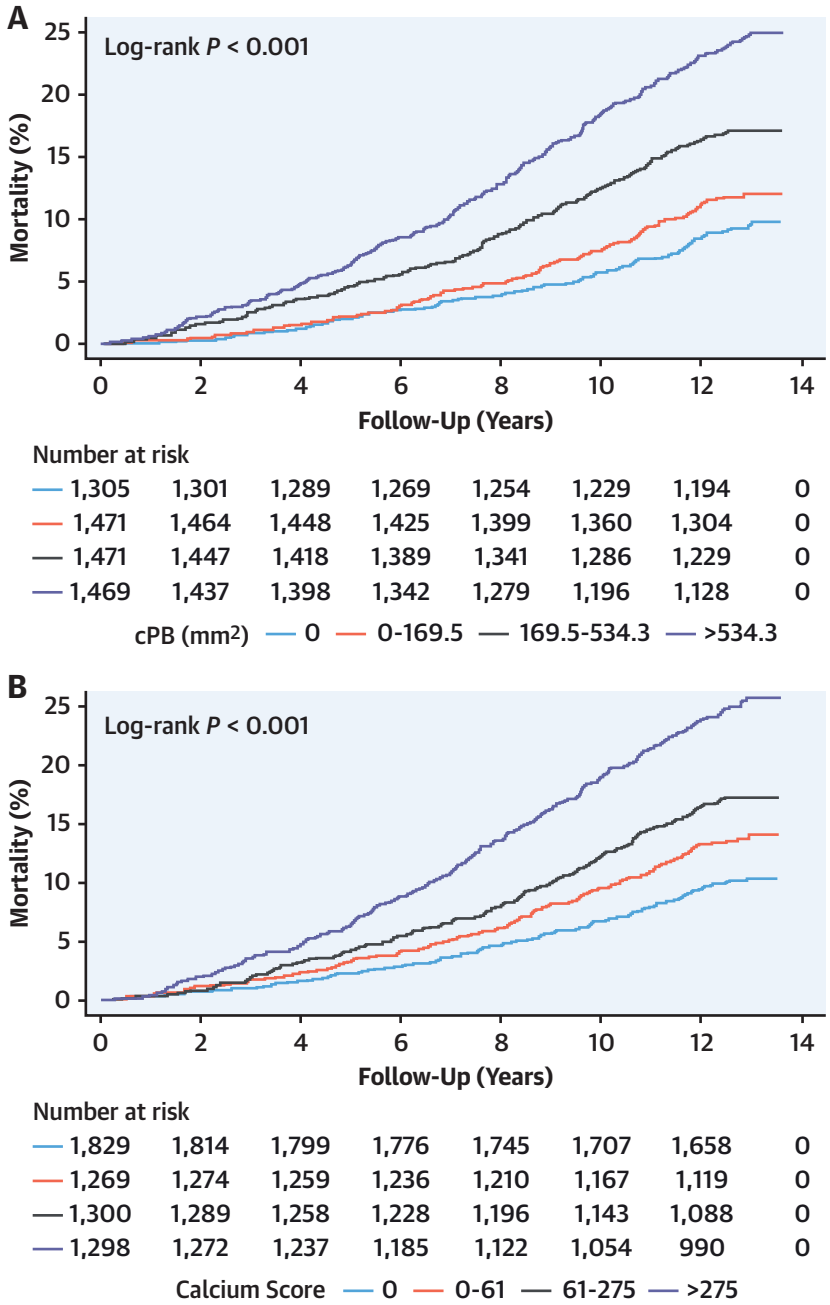
Values are mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. CAC score tertiles (Agatston score): no disease, 0; tertile 1, 1-61; tertile 2, 61-275; tertile 3, >275.
CAC = coronary artery calcium; other abbreviations as in Table 1.

ASSOCIATION BETWEEN SUBCLINICAL ATHEROSCLEROSIS AND ALL-CAUSE MORTALITY. Over a median follow-up of 12.4 years (Q1-Q3: 12.2-12.9 years), 901 (11.7%) participants died. Higher mortality rates were observed with increasing tertiles of cPB (log-rank $P < 0.001$) (Figure 3A, Table 1) and CAC score (log-rank $P < 0.001$) (Figure 3B, Table 2). Baseline cPB and CAC score both remained significantly associated with higher all-cause mortality after adjustment for the variables in model 1 (age, sex, and race) and model 2 (model 1 plus risk factors and medications; see Methods), with trend fully adjusted HRs of 1.23 (95% CI: 1.16-1.32) and 1.15 (95% CI: 1.08-1.23), respectively (both $P < 0.001$) (Figure 4, Table 3). Similar evidence was obtained when cPB and CAC score were considered as continuous log-transformed variables. Moreover, the addition of cPB and CAC score, both separately and in combination, significantly improved the performance of models 1 and 2 (Supplemental Table 2). The improvement was greater with cPB than with CAC score.

ASSOCIATION BETWEEN PLAQUE PROGRESSION AND ALL-CAUSE MORTALITY. A subgroup of 732 (12.8%) participants underwent follow-up carotid VUS 8.9 years (range 8.4-9.7 years) after the baseline exam. The baseline characteristics of this subgroup are compared with the rest of the study population in Supplemental Table 3. Within the follow-up VUS subgroup, 571 (78.0%) participants showed progression of cPB, 63 (8.6%) showed cPB regression, and 98 (13.4%) remained free of carotid atherosclerosis. The number of deaths and 3-year risk were 33 (5.4%), 2 (2.0%), and 1 (1.6%), respectively. Baseline characteristics of the follow-up VUS subgroup stratified by progression profile are summarized in Table 4. Significant predictors of progression were baseline cPB, male sex, central obesity, serum triglyceride level, and age (Supplemental Table 4). Supplemental Figure 2 is a plot of follow-up vs baseline cPB in all participants.

Individuals with cPB progression had significantly higher all-cause mortality compared with individuals with cPB regression or absence of disease (log-rank $P = 0.04$) (Figure 5, Table 4). The association between cPB progression (as a continuous measurement, not as a dichotomous one) and all-cause mortality remained significant after adjustment for baseline

FIGURE 3 Associations of cPB and CAC Score With All-Cause Mortality



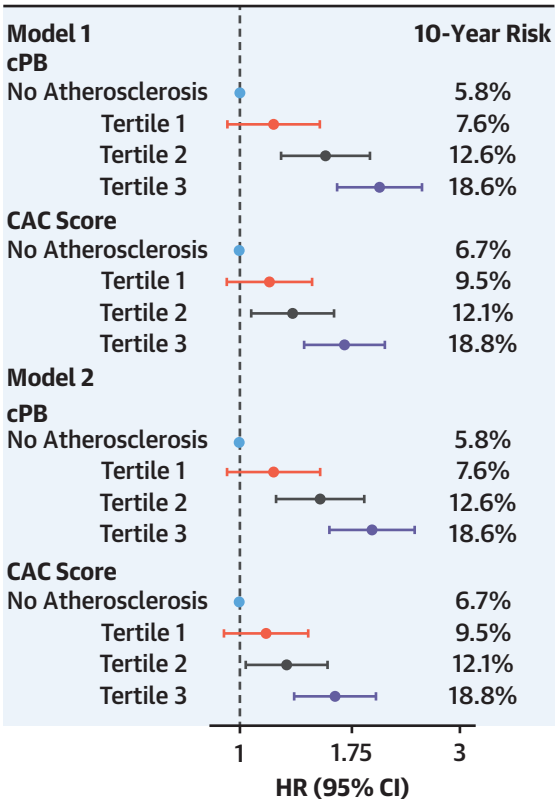
(A) Kaplan-Meier plot of all-cause mortality according to vascular ultrasound-measured cPB tertiles; (B) Kaplan-Meier plot of all-cause mortality according to CAC score tertiles. Abbreviations as in Figure 1.

cPB and the variables in model 1 (age, sex, and race) and model 2 (model 1 plus risk factors and medications) (HR: 1.03; 95% CI: 1.01-1.04 per absolute 10-mm^3 change; P = 0.01) (Table 5, Central Illustration).

DISCUSSION

In a contemporary prospective cohort of 5,716 asymptomatic adults in the United States assessed by carotid VUS and CAC scoring, the presence of

FIGURE 4 HRs and 95% CIs for the Association of All-Cause Mortality With Vascular Ultrasound-Measured cPB and CAC Score



Kaplan-Meier estimates of 10-year risk (cumulative incidence) is shown in the last column. Abbreviations as in Figure 1.

subclinical atherosclerosis at baseline detected with either imaging modality was significantly associated with all-cause mortality, and these associations remained after multivariate adjustment. While both imaging modalities provided additional predictive value beyond CVRFs alone, carotid VUS performed significantly better than CAC. Moreover, VUS-detected cPB progression independently predicted all-cause mortality even after adjustment for CVRFs, background medication, and baseline cPB.

PREVALENCE OF SUBCLINICAL ATHEROSCLEROSIS DETECTED BY CAC AND VUS AND ITS ASSOCIATION WITH FRS. The prevalence of subclinical atherosclerosis detected with either modality at enrollment in this population was very high (near 80%), as previously reported by Baber et al.[4] This prevalence is substantially higher than described in other cohorts,[5,25] likely reflecting the older age and higher risk profile of the BioImage study population, as well as the greater sensitivity of the modalities used to detect atherosclerosis. Most of the BioImage participants, particularly those with an intermediate or high FRS, already had multiterritorial subclinical atherosclerosis at baseline affecting the carotid and coronary arteries. VUS detected disease in 72%, 83%, and 91% of participants with a low, intermediate, and high FRS, respectively, whereas CAC scoring detected disease in 58%, 80%, and 87% of participants in these categories. Interestingly, although the percentage of patients with isolated CAC was similar in each FRS category (~10%), the percentage of patients with isolated carotid disease was substantially higher in the low-FRS group (25%) and decreased with increasing FRS category. This suggests that VUS is a more sensitive detector of subclinical atherosclerosis in individuals assigned a low cardiovascular risk based on CVRFs (in whom conventional scores may underestimate risk) and before the onset of calcification of coronary lesions.

ASSOCIATION BETWEEN IMAGING-DETECTED SUBCLINICAL ATHEROSCLEROSIS AND ALL-CAUSE MORTALITY. Subclinical atherosclerosis detected by carotid VUS or CAC scoring was positively associated with all-cause

TABLE 3 HRs for All-Cause Mortality Associated With Carotid Plaque Burden and CAC Score

	Continuous Variable[a]	No Atherosclerosis	Tertile 1	Tertile 2	Tertile 3	Trend HR[b]	*P* Value (Trend)
Carotid plaque burden							
Model 1[c]	1.06 (1.04-1.08)	1.0 (ref)	1.19 (0.94-1.50)	1.53 (1.23-1.91)	2.01 (1.62-2.49)	1.27 (1.19-1.36)	<0.001
Model 2[d]	1.05 (1.03-1.07)	1.0 (ref)	1.17 (0.92-1.47)	1.49 (1.19-1.86)	1.84 (1.48-2.28)	1.23 (1.16-1.32)	<0.001
Calcium score							
Model 1[c]	1.04 (1.03-1.06)	1.0 (ref)	1.16 (0.94-1.43)	1.30 (1.06-1.59)	1.69 (1.38-2.06)	1.19 (1.11-1.27)	<0.001
Model 2[d]	1.04 (1.02-1.05)	1.0 (ref)	1.11 (0.90-1.36)	1.22 (0.99-1.49)	1.52 (1.24-1.86)	1.15 (1.08-1.23)	<0.001

Values are HR (95% CI). [a]HR per unit increase in log(Cpb) or log(calcium score). [b]HR per tertile increase, modelled by scoring 0, 1, 2, or 3 for no atherosclerosis, tertile 1, tertile 2, or tertile 3 fitted as a linear term, respectively. [c]Adjusted for age, sex, and race. [d]Adjusted for age, sex, race, diabetes mellitus, current smoking, BMI, SBP, antihypertensive agent use, LDL cholesterol, HDL cholesterol, and use of lipid-lowering drugs.

Abbreviations as in Tables 1 and 2.

mortality at a median follow-up of 12.4 years. The positive association between increasing cPB or CAC score tertile and all-cause mortality was also observed when atherosclerosis burden was considered as a continuous variable. In the multivariate analysis, the association between atherosclerosis burden detected with either modality and all-cause mortality remained statistically significant after adjustment for CVRFs and background medication, highlighting the incremental prognostic value of direct atherosclerosis imaging in asymptomatic individuals. In our cohort, from the fully adjusted model we know that only age and cigarette smoking had a stronger prediction of mortality risk than carotid plaque burden. Moreover, while both imaging modalities improved the performance of the multivariate model incorporating CVRFs and background medication (model 2), carotid VUS performed significantly better than CAC scoring. It would thus appear that, while both imaging techniques improve risk prediction and reclassification based on traditional risk factors, carotid VUS more accurately refines the risk of all-cause mortality. There have been few direct comparisons of risk prediction with CAC scoring vs carotid vascular disease metrics such as carotid intima-media thickening (cIMT), maximal plaque thickness, or plaque burden. A previous study of the BioImage cohort showed that the addition of CAC score or cPB to traditional CVRFs produced a similar improvement in the prediction of a composite outcome of cardiovascular death, myocardial infarction, or ischemic stroke at a median follow-up of 2.7 years.[4] However, given the short follow-up, this earlier study lacked sufficient statistical power to assess differences in all-cause mortality prediction. In a meta-analysis of 25 studies assessing the added value of flow-mediated dilatation, CAC score, cIMT, or carotid plaque (using a variety of indicators such as presence of plaque, sum of all plaque areas, or sum of segments with plaque) for the stratification of CVD risk, CAC scoring performed slightly better than the other parameters, although it should be noted that the population characteristics differed between studies.[13] Two key considerations may underlie our findings. First, volumetric measurement of cPB is a more accurate than other atherosclerosis measures such as cIMT, which is no longer recommended for cardiovascular risk assessment because it instead reflects hypertensive or age-related changes.[26] Indeed, Nicolaides et al[19] demonstrated that VUS-detected carotid plaque area provided better prediction of future atherosclerotic CVD events than cIMT or carotid plaque thickness. Moreover, the novel volumetric measurement used in this study has a very intra- and interobserver concordance, with intraclass correlation coefficients higher than 0.9. The second consideration is the particular characteristics of the BioImage study population, in which 20% of participants with zero CAC had evidence of

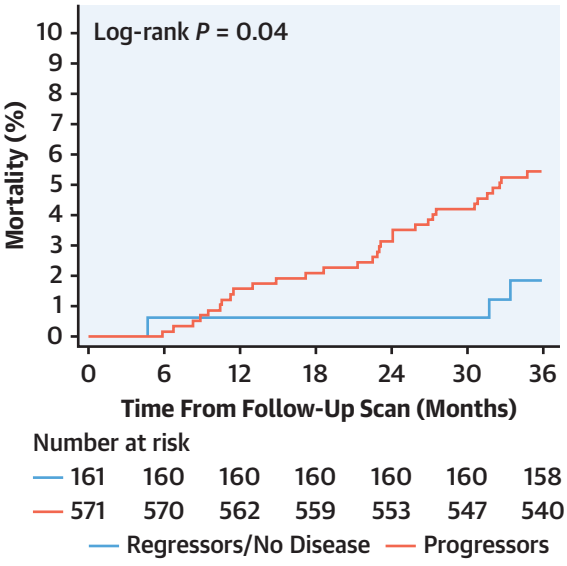
TABLE 4 Baseline Characteristics and Mortality of Participants With Follow-Up VUS Stratified According to Progression

	cPB Regression/ No Atherosclerosis (n = 161)	cPB Progression (n = 571)	*P* Value
Demographics			
Age, y	67.3 ± 5.5	69.2 ± 5.4	<0.001
Sex			0.66
Female	99 (61.5)	362 (63.4)	
Male	62 (38.5)	209 (36.6)	
White	124 (77.0)	501 (87.7)	<0.001
Medical history			
Current smoker	8 (5.0)	28 (4.9)	0.97
Obesity	59 (36.6)	180 (31.5)	0.22
Central obesity	113 (70.2)	424 (74.3)	0.30
Dyslipidemia	77 (47.8)	295 (51.7)	0.39
Hypertension	80 (49.7)	308 (53.9)	0.34
Diabetes mellitus	22 (13.7)	60 (10.5)	0.26
BMI, kg/m^2	28.1 ± 5.4	28.3 ± 4.9	0.71
SBP, mm Hg	134.4 ± 18.4	135.9 ± 17.7	0.37
DBP, mm Hg	76.8 ± 8.6	76.1 ± 8.6	0.32
VUS imaging and CAC score			
cPB at baseline, mm^3	0.0 (0.0-29.1)	42.2 (10.2-112.5)	<0.001
cPB at follow-up, mm^3	0.0 (0.0-20.4)	132.3 (56.7-264.7)	<0.001
Calcium score	2.5 (0.0-92.5)	52.0 (0.0-229.0)	<0.001
Biochemistry			
eGFR, mL/min/1.73 m^2	71.6 ± 12.4	71.9 ± 12.9	0.82
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.8-1.0)	0.16
Total cholesterol, mg/dL	196.4 ± 40.6	203.6 ± 36.3	0.03
LDL cholesterol, mg/dL	107.1 ± 30.6	113.1 ± 31.4	0.03
HDL cholesterol, mg/dL	57.1 ± 17.6	57.1 ± 14.7	1.00
Triglycerides, mg/dL	153.0 (106.5-190.5)	150.0 (107.0-216.0)	0.24
Glucose, mg/dL	98.0 (90.0-110.0)	97.0 (90.0-107.0)	0.23
Uric acid, mg/dL	5.1 ± 1.5	5.2 ± 1.5	0.29
GGT, μ/L	22.0 (16.0-31.0)	22.0 (16.0-31.0)	0.59
Pharmacological treatment			
Lipid-lowering drug	49 (30.4)	192 (33.6)	0.45
Antihypertensive agent	34 (21.1)	142 (24.9)	0.33
Antidiabetic	18 (11.2)	42 (7.4)	0.12
10-y CVD risk scores			
Framingham 10-y risk, %	5.8 (3.0-11.8)	6.5 (3.5-13.1)	0.14
Framingham 10-y risk group			0.62
Low risk (≤10%)	108 (67.5)	366 (64.7)	
Intermediate risk (10%-20%)	42 (26.3)	152 (26.9)	
High risk (>20%)	10 (6.3)	48 (8.5)	
Follow-up			
Deaths	3 (1.9)	33 (5.8)	0.04
Mean follow-up time, y	12.3	12.3	

Values are mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. Progression is defined as a positive change of any magnitude in cPB. cPB regression is defined as a negative change of any magnitude in 3-dimensional plaque volume. No atherosclerosis is defined as having zero plaque burden at both baseline and follow-up.

cPB = carotid plaque burden; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; VUS = vascular ultrasound; other abbreviations as in Tables 1 and 2.

FIGURE 5 Kaplan-Meier Plot for All-Cause Mortality According to Carotid Plaque Burden Progression



The red curve represents participants showing regression of atherosclerosis or absence of atherosclerosis in both evaluations, whereas the blue line represents participants with progression of atherosclerosis between follow-up and baseline evaluation.

subclinical carotid atherosclerosis that may help to redefine mortality risk, whereas only 11% had isolated CAC.

ASSOCIATION BETWEEN VUS-DETECTED CAROTID ATHEROSCLEROSIS PROGRESSION AND ALL-CAUSE MORTALITY. The wide availability of VUS, which is safe and inexpensive, makes it an ideal technique for monitoring atherosclerosis progression. In our study, 732 participants underwent a second carotid VUS examination after a median interval of ~9 years. Approximately two-thirds of these participants showed some degree of cPB progression, which was significantly related to older age, male sex, central obesity, serum triglyceride levels, and a higher cPB at baseline. The remaining third of participants showed cPB regression or remained free of carotid atherosclerosis. In a very recent study of the PESA (Progression of Early Subclinical Atherosclerosis) cohort (baseline age 40-55 years, 36% female), progression—defined as a ≥100% increase in carotid and femoral plaque burden from baseline to 6 years—occurred in 32.7% of individuals and was associated with older age, male sex, smoking, LDL-C, and SBP.[27] While the association with age and male sex was similarly predominant in our study, baseline cPB, central obesity, and serum triglycerides had a greater predictive capacity than both LDL-C and SBP. This likely reflects the significantly older age profile of our population (mean age at enrollment 67 vs 47 years), the higher proportion of participants receiving antihypertensive and lipid-lowering therapy (22% vs 7%) and the differential effect of SBP and LDL-C according to age.[27] Moreover, not just the baseline risk factors, but also the longitudinal changes in risk factor control throughout life may have also contributed. Interestingly, cPB progression between VUS evaluations in our study population was significantly associated with all-cause mortality even after adjusting for baseline cPB and for CVRFs and background medication at the time of the second carotid VUS examination. Differences in mortality between progressors and individuals with regression or free of disease did not reach statistical significance probably due to limited statistical power (just 3 deaths in the regression/absence of disease category).

To our knowledge, this is the first report showing an association between cPB progression and all-cause mortality. Previous studies have reported associations between imaging-assessed plaque progression in the coronary tree and the incidence of acute coronary events. In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study,[28] nonculprit lesions detected by intravascular ultrasound doubled in size between the baseline assessment and the diagnosis of acute coronary syndrome. In a cohort of 449 patients monitored by serial coronary artery CT, plaque progression was an independent predictor of acute coronary syndrome.[29] Eghtedari et al[15] recently showed that, in 3,260 individuals referred by their primary physician for CAC measurement, annualized CAC

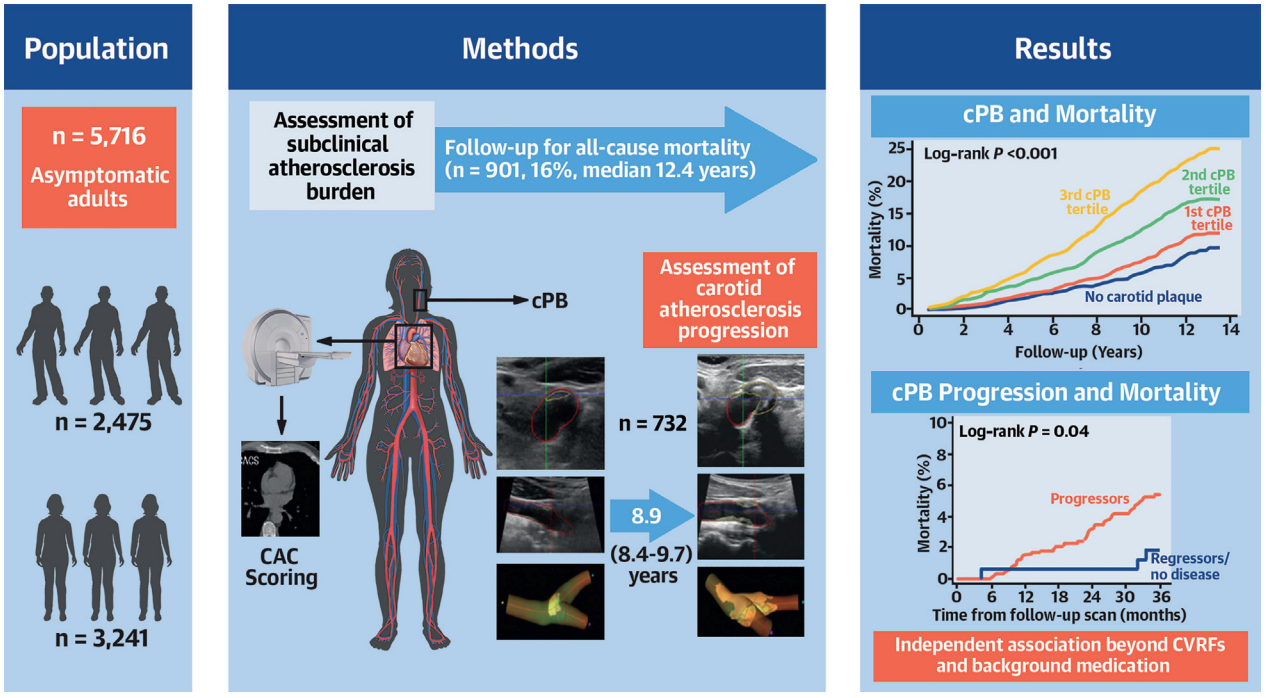
TABLE 5 HRs for All-Cause Mortality Associated With cPB Progression

	HR (95% CI)	*P* Value
Model 1		
cPB progression trajectory		
Regressors[a]/absence of disease[b]	Reference group	
Progressors	2.73 (0.79-9.46)	0.11
Absolute change in cPB (per 10 mm^3)	1.03 (1.01-1.04)	0.01
Model 2		
cPB progression trajectory		
Regressors[a]/absence of disease[b]	Reference group	
Progressors	2.93 (0.84-1.0.22)	0.09
Absolute change in cPB (per 10 mm^3)	1.03 (1.01-1.04)	0.01

Model 1 is adjusted for baseline 3D plaque volume, age at follow-up scan, sex and race. Model 2 is adjusted for baseline 3D plaque volume, age, sex, race, diabetes mellitus, current smoking, body mass index, systolic blood pressure, antihypertensive agent use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and use of lipid-lowering drugs at follow-up scan. Follow-up time is time from follow-up scan to the first of end of study, loss to follow-up or death. [a]Defined as a negative change of any magnitude in 3D plaque volume. [b]Defined as having zero 3D plaque volume at both baseline and second scan.

3D = 3-dimensional; cPB = carotid plaque burden.

CENTRAL ILLUSTRATION Scheme of the Study Design and Main Results



Fuster V, et al. JACC. 2024;84(15):1391–1403.

The BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At Risk Population) study enrolled 5,716 asymptomatic individuals who underwent assessment of subclinical atherosclerosis by coronary artery calcium (CAC) score and carotid plaque burden (cPB) quantification and evaluation of cardiovascular risk factors (CVRFs). Of them, 732 were reassessed a median of 8.9 years later. All were followed for all-cause mortality. Atherosclerosis burden at enrollment and, moreover, carotid atherosclerosis progression, were significantly associated with all-cause mortality beyond CVRFs and background medication.

progression of >20 U/y independently predicted all-cause mortality. In addition, Sabeti et al[30] demonstrated that progression of carotid stenosis within a 6- to 9-month interval by VUS predicted the occurrence of major adverse cardiovascular events. Our study supports these previous works that have demonstrated the prognostic relevance of the progression of atherosclerosis and adds that cPB progression (even without causing stenosis) is associated with greater all-cause mortality. These results suggest that noninvasive atherosclerosis monitoring has potential to improve primary prevention by reinforcing lifestyle recommendations, establishing finer control of CVRFs, and facilitating closer follow-up of patients showing disease progression with the ultimate goal of improving their survival. However, selecting the best imaging modality is not straightforward because plaque characteristics can change in response to lipid-lowering therapy. Several imaging studies have demonstrated that intensive statin therapy reduces total plaque burden and progression by decreasing necrotic core volume but typically increases fibrous cap thickness and the degree of calcification.[31-33] The consistent increase in plaque calcification observed with statin therapy[33,34] makes plaque volume a more useful prognostic indicator than parameters that record calcium volume, such as CAC scoring. In addition, VUS is an ideal method for this purpose due to its wide availability, patient safety, and low cost. Currently, it requires some training, but it might change in the future with the use of automatic AI measurements.[35] Further research comparing the predictive accuracy of cPB and CAC progression would be needed to confirm which technique may provide more clinically useful information.

STUDY LIMITATIONS. First, all-cause mortality was identified from Social Security and National Death Index searches, and we do not have reliable access to the cause of death or the incidence of other cardiovascular events. While we duly acknowledge this limitation, all-cause mortality remains the main hard

event in all studies of mortality risk and has unquestionable relevance to the study of predictive factors and the evaluation of potential preventive measures. Second, the BioImage study participants were mostly White and about half were women, and the study population was older than others examined in previous primary prevention cohorts, so the results may not be fully generalizable. Third, baseline characteristics of the 385 (6.3%) participants excluded due to missing values significantly differed from the analysis population because of a higher cardiovascular risk. This fact has probably reduced the statistical power to demonstrate an association between atherosclerosis and mortality but reinforces the potential prognostic value of imaging in a population that was mostly low-intermediate risk. Finally, the participant subcohort available for assessment of atherosclerosis progression was relatively small, due to difficulties in locating participants or death before contact. The number of deaths between the second VUS and the end of follow-up was limited, and the death of some patients before the second VUS could be performed introduces a competing risk, as death precludes progression. However, even though this effect would tend to reduce the statistical power and dilute the association, we found a statistically significant association between progression and mortality adjusted for baseline plaque burden at enrollment.

CONCLUSIONS

In a population of asymptomatic individuals without previous clinical CVD, the identification and quantification of subclinical atherosclerosis by CAC scoring and carotid VUS was independently associated with all-cause mortality, improving prediction based on CVRFs and background medication. VUS performed better than CAC, adding value even beyond CAC scoring. Furthermore, carotid atherosclerosis progression assessed by carotid VUS independently predicted all-cause mortality adjusted for baseline plaque burden.

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KEY WORDS all-cause mortality, coronary calcium score, subclinical atherosclerosis, vascular ultrasound

APPENDIX For supplemental figures and tables, please see the online version of this paper.