JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 22, 2023

ORIGINAL INVESTIGATIONS

Determinants of Progression and Regression of Subclinical Atherosclerosis Over 6 Years

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ABSTRACT

BACKGROUND Atherosclerosis is a systemic disease that frequently begins early in life. However, knowledge about the temporal disease dynamics (ie, progression or regression) of human subclinical atherosclerosis and their determinants is scarce.

OBJECTIVES This study sought to investigate early subclinical atherosclerosis disease dynamics within a cohort of middle-aged, asymptomatic individuals by using multiterritorial 3-dimensional vascular ultrasound (3DVUS) imaging.

METHODS A total of 3,471 participants from the PESA (Progression of Early Subclinical Atherosclerosis) cohort study (baseline age 40-55 years; 36% female) underwent 3 serial 3DVUS imaging assessments of peripheral arteries at 3-year intervals. Subclinical atherosclerosis was quantified as global plaque volume (mm^3) (bilateral carotid and femoral plaque burden). Multivariable logistic regression models for progression and regression were developed using stepwise forward variable selection.

RESULTS Baseline to 6-year subclinical atherosclerosis progression occurred in 32.7% of the cohort (17.5% presenting with incident disease and 15.2% progressing from prevalent disease at enrollment). Regression was observed in 8.0% of those patients with baseline disease. The effects of higher low-density lipoprotein cholesterol (LDL-C) and elevated systolic blood pressure (SBP) on 6-year subclinical atherosclerosis progression risk were more pronounced among participants in the youngest age stratum ($P_{interaction} = 0.04$ and 0.02, respectively).

CONCLUSIONS Over 6 years, subclinical atherosclerosis progressed in one-third of middle-age asymptomatic subjects. Atherosclerosis regression is possible in early stages of the disease. The impact of LDL-C and SBP on subclinical atherosclerosis progression was more pronounced in younger participants, a finding suggesting that the prevention of atherosclerosis and its progression could be enhanced by tighter risk factor control at younger ages, with a likely long-term impact on reducing the risk of clinical events. (Progression of Early Subclinical Atherosclerosis [PESA; also PESA-CNIC-Santander]; NCT01410318) (J Am Coll Cardiol 2023;82:2069-2083) © 2023 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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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2023.09.814

ABBREVIATIONS AND ACRONYMS

3DVUS = 3-dimensional vascular ultrasound

ASCVD = atherosclerotic cardiovascular disease

BPLT = blood pressure–lowering treatment

CAC = coronary artery calcium

CV = cardiovascular

CVD = cardiovascular disease

CVRF = cardiovascular risk factor

GPV = global plaque volume

hs-CRP = high-sensitivity C-reactive protein

ICC = intraclass correlation coefficient

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering treatment

SA = subclinical atherosclerosis

SBP = systolic blood pressure

Despite remarkable advances in cardiovascular (CV) medicine over the past decades, atherosclerotic CV disease (ASCVD) continues to be the leading cause of morbidity, mortality, and health care expenditure worldwide.[1] Atherosclerosis is a progressive disease characterized by a long asymptomatic course, often first manifesting as an acute atherothrombotic event (myocardial infarction or stroke). Recent data suggest that ASCVD event rates are likely to improve if preventive interventions are begun at younger ages.[2,3] Because atherosclerosis frequently begins early in life and progresses silently,[4] detection of the disease during its subclinical phase seems key to initiating timely preventive measures to mitigate its progression effectively and potentially avoid ASCVD events.

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Atherosclerosis in asymptomatic individuals (subclinical atherosclerosis [SA]) is an established risk modifier in current clinical practice guidelines.[5,6] Imaging-based biomarkers of SA, such as the coronary artery calcium (CAC) score, have been proposed to improve individual CV risk predictions.[7,8] However, CAC testing explores only the coronary territory and may miss earlier atherosclerosis (before calcification has occurred), especially in young persons at low to intermediate 10-year ASCVD risk.[5] Because atherosclerosis is a systemic phenomenon, radiation-free 3-dimensional vascular ultrasound (3DVUS) is a promising alternative for the noninvasive assessment of atherosclerosis burden through the evaluation of peripheral, readily accessible territories such as the carotid and femoral arteries.

Knowledge about the dynamics of atherosclerosis (progression, stabilization, or regression), its determinants, or disease development patterns in different vascular territories, is scarce. The PESA (Progression of Early Subclinical Atherosclerosis ; also abbreviated PESA-CNIC [National Center of Cardiovascular Investigations]-Santander) study cohort has uniquely undergone serial multiterritorial imaging. In this study, we have investigated the temporal disease dynamics of SA in this cohort of apparently healthy, middle-aged, asymptomatic individuals by using data from serial 3DVUS imaging examinations performed at baseline and at 6-year follow-up.

METHODS

STUDY DESIGN AND PARTICIPANTS. PESA-CNIC-Santander (NCT01410318) is a longitudinal cohort study that enrolled 4,184 healthy volunteers (aged 40-55 years; 37% women) with no history of CV disease (CVD) between 2010 and 2014.[9] The present study includes participants with complete data on carotid and femoral plaque volumes obtained by 3DVUS imaging at baseline and at 6-year follow-up (study visit 3). The study protocol was approved by the Ethics Committee of the Carlos III Institute of Health, and all participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[10]

PROCEDURES. Participants underwent 3 in-person clinical interviews and physical and CV imaging examinations at baseline (visit 1) and at 3- and 6-year follow-up (visits 2 and 3, respectively). The imaging examinations included 3DVUS to assess peripheral atherosclerosis in the carotid and femoral arteries and noncontrast cardiac computed tomography (CT) to measure CAC. Participants' global plaque volume (GPV) (in mm^3) was calculated as the sum of plaque volumes in each of the 4 explored sites (right and left carotid and femoral arteries). CAC imaging was performed according to published methodologies.[11] At every study visit, participant information on demographics, lifestyle factors (smoking status, daily total energy intake, alcohol consumption, physical activity, hours of sleep), and medical and CVD family

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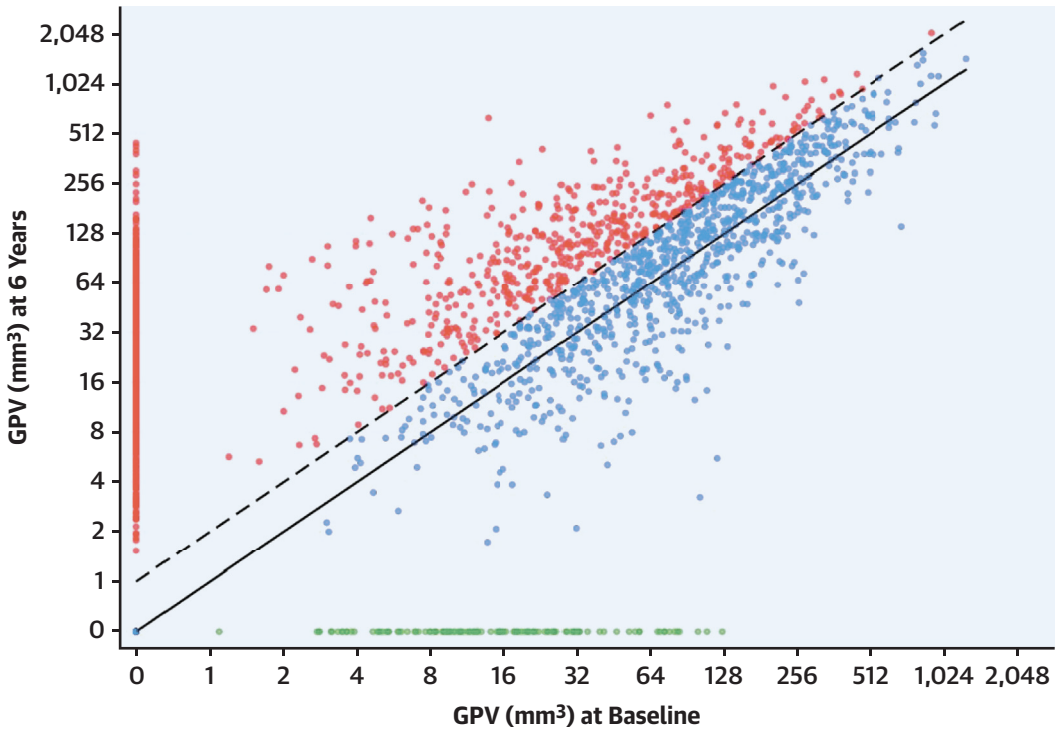
Carl Lavie, MD, served as Guest Associate Editor for this paper. Christopher O'Connor, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 25, 2023; revised manuscript received September 13, 2023, accepted September 22, 2023.

FIGURE 1 Individual Participant GPV (mm^3) Measurements at 6 Years vs Baseline



Progressors have been shaded in red, regressors in green, and stable disease participants in blue. The dashed line marks ≥100% increase in global plaque volume (GPV) between visits 1 and 3 and therefore identifies those participants with disease progression. The solid line corresponds to the line of equality ($y = x$ line).

history was recorded, and physical examinations (including the measurement of weight, height, waist circumference, and blood pressure) and laboratory tests (complete blood cell count, renal and liver function parameters, lipid and glycemic panels, and inflammatory markers) were performed. Active smoking included current and social smoking. The average of the second and third of 3 blood pressure readings, measured with a validated arm-cuff blood pressure monitor, were taken as the systolic blood pressure (SBP) and diastolic blood pressure after participants had been sitting quietly for 5 minutes. Additional information on data collection and assessment of study variables has been reported previously.[9] The image acquisition methodologies and protocols used in the PESA study have been published in detail elsewhere.[12-14]

OUTCOMES. The primary outcomes of this study were progression and regression of SA from baseline to 6 years, as measured by 3DVUS. Progression of SA was defined as a ≥100% increase in GPV from baseline to 6 years, as previously defined.[11] SA regression was adjudicated on detection of a 100% reduction in GPV from baseline to 6 years. According to GPV measurements obtained at baseline and 6-year follow-up, participants were classified into 3 different SA disease dynamic profiles: 1) progressors; 2) regressors; and 3) stable participants (not meeting criteria for progression or regression). Among participants with 6-year progression of SA, 2 subgroups were further studied: those with prevalent disease at enrollment (GPV >0 mm^3) and those with no baseline disease (GPV = 0 mm^3).

STATISTICAL METHODS. The intention to investigate SA disease dynamics at 6 years of follow-up was prespecified, but the details of statistical analysis were undertaken in an exploratory manner. Multivariable logistic regression models were used to investigate the relationship between participant characteristics at baseline and the occurrence of: 1) SA progression at 6 years; and 2) SA regression at 6 years. First, on the basis of subject matter knowledge,[15,16] a preselection of baseline candidate predictor variables was conducted, and associations

TABLE 1 Baseline Participant Characteristics Both Overall and Stratified by 3DVUS Peripheral Subclinical Atherosclerosis 6-Year Progression Trajectory (N = 3,471)

	Total (N = 3,471)	Progressors (n = 1,134)	Stable (n = 2,214)	Regressors (n = 123)	*P* Value[a]
Demographics					
Age, y	45.8 (42.5-49.5)	46.8 (43.2-50.2)	45.4 (42.2-49.1)	44.9 (42.5-49.2)	<0.0001
Sex					
Male	2,205 (64)	786 (69)	1,345 (61)	74 (60)	<0.0001
Female	1,266 (36)	348 (31)	869 (39)	49 (40)	
Race[b]					
White	4,166 (100)	1,132 (100)	2,211 (100)	123 (100)	0.83
Asian	2 (0)	0 (0)	1 (0)	0 (0)	
Other	4 (0)	2 (0)	2 (0)	0 (0)	
Education					
Not specified	52 (1)	6 (1)	19 (1)	1 (1)	0.0053
High school or lower	1,030 (25)	319 (28)	497 (22)	24 (20)	
College degree or higher	3,090 (74)	809 (71)	1,698 (77)	98 (80)	
Medical history					
Active smoking[c]	939 (27)	333 (30)	584 (27)	22 (18)	0.017
CVD family history[d]	414 (12)	134 (12)	266 (12)	14 (11)	0.97
Obesity[e]	494 (14)	186 (16)	290 (13)	18 (15)	0.035
Central obesity[f]	1,697 (49)	580 (51)	1,062 (48)	55 (45)	0.14
Dyslipidemia[g]	1,425 (41)	551 (49)	828 (37)	46 (37)	<0.0001
Hypertension[h]	388 (11)	148 (13)	231 (10)	9 (7)	0.029
Diabetes[i]	57 (2)	24 (2)	32 (1)	1 (1)	0.27
BMI, kg/m^2	26.1 ± 3.8	26.4 ± 3.7	25.9 ± 3.8	25.9 ± 3.8	0.0018
SBP, mm Hg[j]	115.7 ± 12.2	117.2 ± 12.0	115.0 ± 12.3	113.7 ± 12.7	<0.0001
DBP, mm Hg[j]	72.1 ± 9.4	73.0 ± 9.3	71.6 ± 9.3	70.6 ± 11.2	<0.0001
Number of CVRFs[k]					
0	810 (24)	212 (19)	557 (25)	41 (34)	<0.0001
1	1,553 (45)	488 (43)	1,011 (46)	54 (45)	
2	873 (25)	341 (30)	511 (23)	21 (18)	
≥3	201 (6)	85 (8)	112 (5)	4 (3)	
3DVUS imaging					
GPV at baseline, mm^3	0.0 (0.0-40.0)	0.0 (0.0-25.6)	0.0 (0.0-57.6)	14.2 (8.0-25.7)	<0.0001
GPV at 6 y, mm^3	12.1 (0.0-76.8)	50.0 (16.4-123.4)	0.0 (0.0-53.1)	0.0 (0.0-0.0)	<0.0001
Coronary artery calcium scores					
CAC score at baseline					
0	2,853 (82)	898 (79)	1,843 (83)	112 (91)	0.0010
>0	615 (18)	234 (21)	370 (17)	11 (9)	
At baseline, AU	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.30
CAC score at 6 y					
0	2378 (71)	704 (64)	1,575 (74)	99 (82)	<0.0001
>0	973 (29)	389 (36)	563 (26)	21 (18)	
CAC score at 6 y, AU	0.0 (0.0-3.0)	0.0 (0.0-11.6)	0.0 (0.0-1.1)	0.0 (0.0-0.0)	0.30
Biochemistry					
eGFR, mL/min/1.73 m^2[l]	104.0 ± 9.0	103.6 ± 9.2	104.1 ± 8.9	104.6 ± 8.4	0.24
Fasting plasma glucose, mg/dL	90.3 ± 12.8	91.5 ± 16.1	89.8 ± 10.9	88.1 ± 9.1	0.00020
Hemoglobin A1c, %	5.4 ± 0.4	5.4 ± 0.5	5.4 ± 0.4	5.4 ± 0.4	0.045
HOMA-IR, mg/dL	1.1 (0.8-1.7)	1.2 (0.8-1.7)	1.1 (0.7-1.6)	1.1 (0.7-1.6)	0.039
Total cholesterol, mg/dL[m]	200.3 ± 33.0	203.7 ± 33.4	198.8 ± 32.6	196.3 ± 33.9	0.00010
Triglycerides, mg/dL	79.0 (60.0-111.0)	84.0 (62.0-116.0)	77.0 (58.0-108.0)	71.0 (55.0-104.0)	0.029
HDL-C, mg/dL[m]	49.2 ± 12.2	48.1 ± 12.3	49.8 ± 12.2	48.1 ± 10.7	0.00050
LDL-C, mg/dL[m]	132.3 ± 29.4	136.0 ± 29.5	130.5 ± 29.3	129.4 ± 29.0	<0.0001
Non-HDL-C, mg/dL[m]	151.1 ± 33.5	155.6 ± 33.2	149.0 ± 33.4	148.3 ± 34.0	<0.0001
High-sensitivity C-reactive protein, mg/dL	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.45
Fibrinogen, mg/dL	265.2 ± 47.6	266.6 ± 47.9	265.1 ± 47.6	255.6 ± 44.1	0.049
P-selectin, ng/mL	131.6 ± 40.4	135.1 ± 41.7	129.7 ± 39.7	131.7 ± 40.1	0.0011

Continued on the next page

TABLE 1 Continued

	Total (N = 3,471)	Progressors (n = 1,134)	Stable (n = 2,214)	Regressors (n = 123)	*P* Value[a]
Active pharmacologic treatment					
Lipid-lowering	246 (7)	94 (8)	145 (7)	7 (6)	0.15
BP-lowering	254 (7)	96 (8)	154 (7)	4 (3)	0.060
Antidiabetic	45 (1)	19 (2)	25 (1)	1 (1)	0.37
Number of CVRF medications[n]					
0	3,015 (87)	963 (85)	1,939 (88)	113 (92)	0.13
1	375 (11)	138 (12)	229 (10)	8 (7)	
2	73 (2)	28 (2)	43 (2)	2 (2)	
3	8 (0)	5 (0)	3 (0)	0 (0)	
10-y ASCVD risk estimates					
SCORE2, %	2.0 (1.3-3.1)	2.3 (1.5-3.4)	1.9 (1.2-3.0)	1.7 (1.2-2.7)	<0.0001
SCORE2 risk category					
Low	2,729 (79)	851 (76)	1,774 (81)	104 (87)	0.0020
Intermediate	703 (20)	273 (24)	414 (19)	16 (13)	
High	5 (0)	2 (0)	3 (0)	0 (0)	

Values are median (IQR), n (%), or mean ± SD. Number of missing values: 12 (0.3%) for race and education; 32 (0.9%) for active smoking; 5 (0.1%) for CVD family history; 2 (0.1%) for hypertension, SBP, and DBP; 34 (1.0%) for number of CVRFs; 3 (0.1%) for CAC score at baseline, n, and CAC score at baseline, AU; 120 (3.5%) for CAC score at 6 y, n, and CAC score at 6 y, AU; 1 (0.0%) for P-selectin; 34 (1.0%) for SCORE2 and SCORE2 risk category. [a]*P* value obtained from the chi-square test for categorical variables and from analysis of variance for continuous variables. [b]Other refers to American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander, no Black or African American participants were included. [c]Defined as current and social smoking. [d]Defined as having a first-degree relative with a diagnosis of atherosclerosis before 55 years of age in men and 65 years of age in women. [e]Defined as BMI ≥30 kg/m^2. [f]Defined as waist circumference (WC) ≥94 cm for men and ≥80 cm for women. [g]Defined as total cholesterol ≥240 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, or use of lipid-lowering drugs. [h]Defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or use of antihypertensive medication. [i]Defined as fasting plasma glucose ≥126 mg/dL or treatment with insulin or oral hypoglycemic medication. [j]Calculated as the average of the second and third of 3 blood pressure readings. [k]Includes current, social, and former smoking, hypertension, diabetes, and dyslipidemia. [l]Calculated using the CKD-Epidemiology Collaboration equation. [m]To get from mg/dL to SI in mmol/L, multiply by 0.02586. [n]Includes lipid-lowering treatment, BP-lowering treatment, and antidiabetic treatment.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CVD = cardiovascular disease; CVRF = cardiovascular risk factor; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GPV = global plaque volume; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = HOmeostatic Model Assessment for Insulin Resistance; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SBP = systolic blood pressure; SCORE2 = Systemic Coronary Risk Estimation 2; 3DVUS = 3-dimensional vascular ultrasound.

between each primary outcome and the preselected candidate predictors were investigated using univariable logistic regression. A threshold *z*-score ≥2.00 (corresponding to P <0.05) was used to consider variables for inclusion in the final model. Because missing data were minimal (never exceeding 3.5%), single-imputation methods were performed for missing values.

Second, multivariable model building used forward stepwise variable selection, with $P < 0.05$ required for inclusion in the progression and regression risk models. The variables age, sex, and baseline GPV were forced into all variable selection procedures a priori. For each outcome, a model was fit, including baseline GPV as a continuous log-transformed variable (where 0 was arbitrarily fitted as log 0.5).

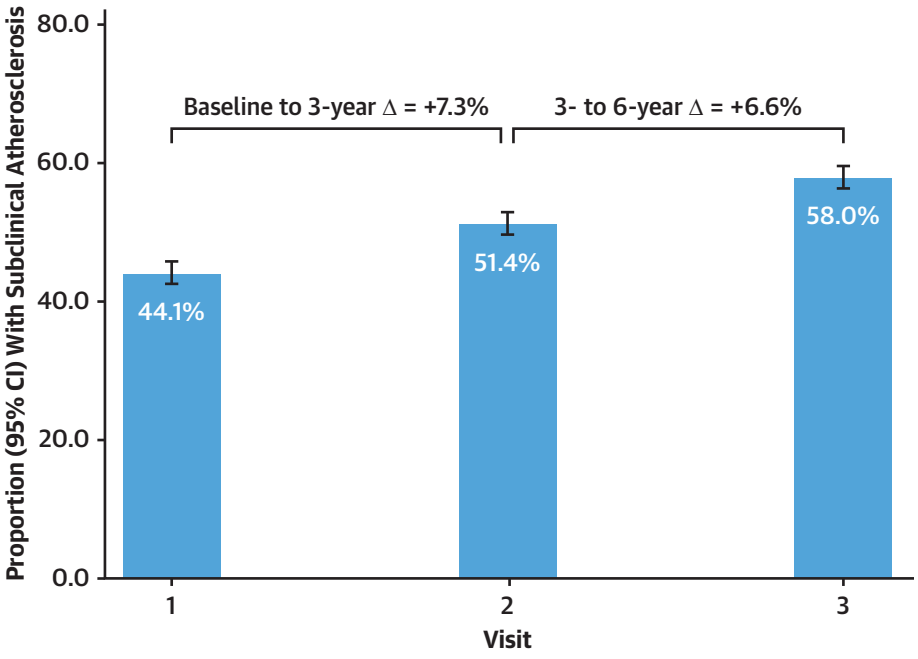
Third, participants were categorized into equal-sized one-thirds of increasing risk for each outcome, on the basis of the distributions of the progression and regression risk scores calculated from their multivariable models. Model discrimination (using C-statistics) and calibration (by plotting the observed vs predicted 6-year risk by one-thirds of the risk score) were evaluated for both outcomes. Subgroup analyses were performed by re-running the 6-year progression multivariable model in separate subsets of participants, according to SA disease prevalence at enrollment.

Interaction tests on the relative scale examined whether the associations with progression of low-density lipoprotein cholesterol (LDL-C) and SBP, respectively, varied with age. Interaction P values were obtained from the 6-year progression multivariable model, including age and GPV (log-transformed) as continuous variables. These interactions were also graphically displayed using forest plots for associations between LDL-C/progression and SBP/progression in 3 equal-sized age groups. Sensitivity analyses investigated the impact of the different predictors in the progression and regression multivariable models after adjusting for the following covariates, 1 at a time: 1) lipid-lowering treatment (LLT) at baseline; and 2) blood pressure–lowering treatment (BPLT) at baseline. All analyses were performed using Stata software version 17.0 (StataCorp, LLC).

RESULTS

Between baseline and 6-year follow-up, 3,471 of the 4,184 (83%) participants originally enrolled

FIGURE 2 Prevalence of Subclinical Atherosclerosis at Baseline and at 3-Year and 6-Year Follow-Up



A total of 3,471 PESA (Progression of Early Subclinical Atherosclerosis) participants underwent serial 3-dimensional vascular ultrasound examination of carotid and femoral territories at baseline and at 3- and 6-year follow-up. The prevalence of atherosclerosis was calculated as the percentage of participants with global plaque volume (GPV) >0 mm^3 at each time point. Global plaque volume was calculated from the sum of plaque volumes in each of the 4 explored sites (right and left carotid and femoral arteries). Δ = change.

underwent 3DVUS imaging of the left and right carotid and femoral arteries at visit 1 and visit 3 (**Figure 1**, Supplemental Tables 1 and 2). Sixty-five participants (1.9%) missed the 3-year (visit 2) 3DVUS assessment. Twenty participants died during follow-up, and 203 participants (5.3%) withdrew consent (Supplemental Figure 1).

TRAJECTORIES OF SUBCLINICAL ATHEROSCLEROSIS IN MIDDLE-AGED SUBJECTS OVER 6 YEARS. At baseline, participants had a median age of 45 years (IQR: 42-49 years), and 36% were women (**Table 1**). The median follow-up time was 6.1 years (IQR: 5.7- 6.6 years). Peripheral SA prevalence at baseline was 44.1%, increasing to 58.0% at 6-year follow-up (**Figure 2**). Importantly, approximately 1 in every 3 participants (36.5% incidence) without prevalent disease at enrollment had SA at 6 years (**Table 2**). The femoral territory was the most frequently diseased territory both at baseline (31.0%) and at follow-up (41.8%). Prevalence of carotid disease at baseline was 24.9%, increasing to 37.8% at 6-year follow-up (Supplemental Figures 2A and 2B). Over time, changes in GPV for the defined 6-year peripheral SA disease profiles are shown in **Figure 3**. Corresponding data for carotid and femoral plaque volume are shown in Supplemental Figures 3A and 3B.

Progression of SA was detected in 1,134 (32.7%) of the 3,471 participants included in the study, whereas regression was detected in 123 participants (8.0% of the 1,529 participants prevalent disease at enrollment) (**Figure 1**). Examples of progression and regression of SA according to 3DVUS findings during the 6-year follow-up period are shown in **Figure 4**. As shown in Supplemental Figures 4A and 4B, the distributions of GPV at baseline and at 6 years of follow-up were highly skewed. Among the 1,134 progressors, 527 (46.5%) had prevalent disease at enrollment and 607 (53.5%) did not. The remaining 2,214 participants (63.8%), who had neither progression nor regression of disease, were termed "stable." Among stable participants, 879 (39.7%) had prevalent disease at enrollment, whereas 1,335 (60.3%) remained free of disease in the carotid and femoral territories throughout the study period (Supplemental Table 1).

DETERMINANTS OF SUBCLINICAL ATHEROSCLEROSIS PROGRESSION AND REGRESSION. Progressors were more likely to be male, older, and to smoke than were stable or regressor participants. Progressors had the

TABLE 2 Disease Prevalence and Extent by 3-Dimensional Vascular Ultrasound at Baseline and at 3- and 6-Year Follow-Up, and Baseline to 3-Year and 6-Year Changes (N = 3,471)

	At Baseline	At 3 Years[a]	At 6 Years
Participants with prevalent disease (carotid and/or femoral)	1,529 (44.1)	1,783 (51.4)	2,013 (58.0)
Participants with prevalent disease in carotid territory	865 (24.9)	1,116 (32.2)	1,312 (37.8)
Participants with prevalent disease in femoral territory	1,074 (31.0)	1,234 (35.6)	1,450 (41.8)
Participants with prevalent disease in both carotid and femoral territories	410 (11.8)	567 (16.6)	749 (21.6)
GPV in participants with prevalent disease, mm^3	52.0 (19.9-121.2)	48.0 (18.2-113.0)	61.2 (21.8-150.4)
Carotid territory plaque volume in participants with carotid disease, mm^3	24.3 (10.4-49.3)	20.0 (9.0-46.6)	24.4 (10.8-55.0)
Femoral territory plaque volume in participants with femoral disease, mm^3	63.4 (27.6-135.8)	58.4 (26.2-129.7)	72.2 (32.0-159.1)
	Baseline to 3-Year Change[a]	**3- to 6-Year Change[a,b]**	**Baseline to 6-Year Change**
Participants with new disease (carotid and/or femoral)	393/1,919 (20.5)	308/1,526 (20.2)	701/1,919 (36.5)
Risk of new carotid disease	403/2,565 (15.7)	339/2,162 (15.7)	742/2,565 (28.9)
Risk of new femoral disease	264/2,366 (11.2)	227/2,102 (10.8)	491/2,366 (20.8)

Values are n (%), n/N (%), or median (IQR). [a]A total of 65 participants have missing data for 3-year 3-dimensional vascular ultrasound measurements (1.8%). [b]Denominators for the calculation of disease incidence exclude participants with disease at baseline or 3 years.

Abbreviations as in Table 1.

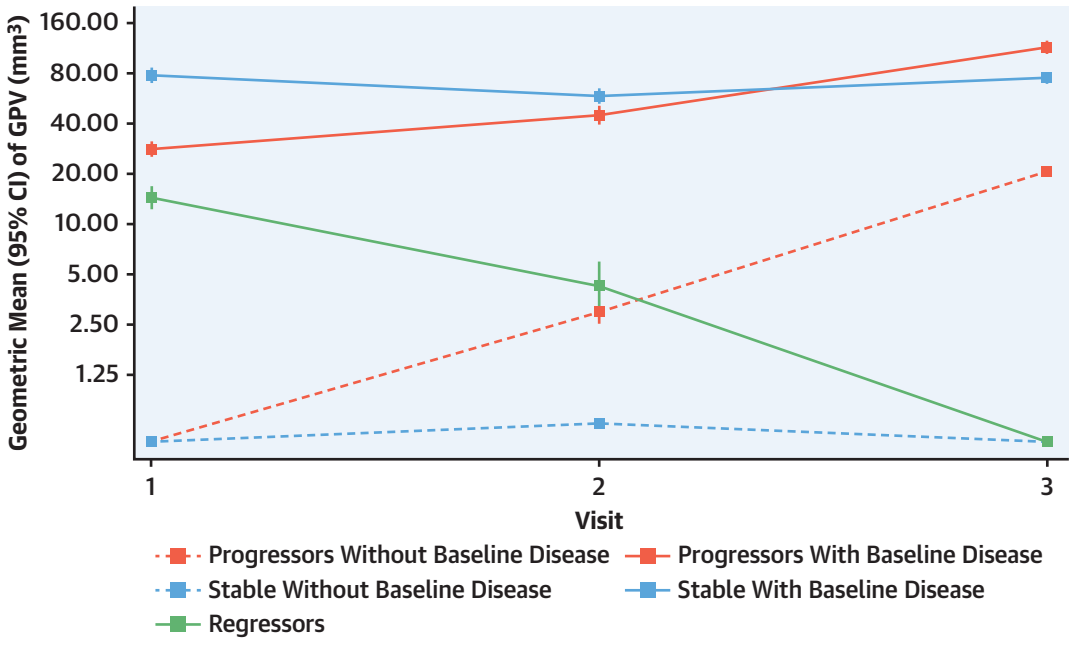
highest mean LDL-C and SBP levels relative to stable and regressor participants. Regressors were more likely to lack CAC at baseline (91%) than were progressors and stable disease participants (79% and 83%, respectively). The proportion of progressors with a low (<2.5%) Systemic Coronary Risk Estimation 2 (SCORE2) estimate of 10-year ASCVD risk was 76%, compared with 81% and 87% for stable disease and regressor participants, respectively (Table 1). Stratification of the baseline characteristics of progressors vs nonprogressors (ie, stable disease and regressor participants) according to baseline disease prevalence showed that nonprogressors without disease at enrollment had the healthiest CV profile, whereas the least favorable profile was found in progressors with prevalent disease at enrollment (Supplemental Table 3).

Among participants who developed incident peripheral SA at 6 years, 88% lacked CAC at baseline, and conversely, among participants showing progression of prevalent disease at enrollment, just 69% lacked CAC at baseline. By 6-year follow-up, the prevalence of a CAC score of 0 had declined to 76% among participants with incident peripheral SA and 51% among participants with prevalent disease at enrollment (Supplemental Table 3). The overall prevalence of CAC at 6 years was markedly lower (29%) than the prevalence of peripheral SA at 6 years (58%).

Supplemental Table 4 lists the baseline candidate predictor variables taken forward for consideration in the multivariable prediction models for 6-year progression (17 variables) and regression (16 variables). Using stepwise forward variable selection (with $P < 0.05$ required for inclusion), the resulting prediction model for 6-year peripheral SA progression included older age as the strongest predictor, followed by higher LDL-C. These 2 predictors were then followed by male sex, active smoking, and increased SBP (all $P < 0.01$) (Table 3). A predictive model for 6-year peripheral SA regression was also developed following the same variable selection strategy (with $P < 0.05$ required for inclusion). Here, the strongest predictors were being a nonsmoker, female sex, and lower fibrinogen levels. These were then followed by younger age and lower LDL-C (all $P < 0.05$) (Table 4). To facilitate the interpretation of effect estimates for baseline GPV, the progression and regression multivariable models fitting baseline GPV as a categorical variable have been provided in Supplemental Tables 5 and 6, respectively. Participants with smaller baseline GPVs were more likely to have both progression and regression of disease. Supplemental Figures 5 and 6 show the distribution of progression and regression risk scores (from low to high) for individual participants calculated using the coefficients in the progression and the regression models, respectively. Supplemental Figures 7 and 8 show good agreement between the observed and predicted participant risks of progression and regression at 6 years.

Supplemental Table 7 shows subgroup analyses for incident peripheral SA at 6 years (ie, no baseline disease [model A]) and progression of prevalent peripheral SA at enrollment (model B). The predictors, older age, increased SBP, and male sex showed a similar effect on the risk of 6-year progression of SA regardless of the presence of disease at baseline. LDL-C predicted only incident disease and not progression of prevalent disease at enrollment, whereas

FIGURE 3 Global Plaque Volume Across Time According to Clusters of Individuals



Clusters of individuals were identified according to their change in global plaque volume (GPV) between baseline and the 6-year 3-dimensional vascular ultrasound examination: progressors (≥100% increase in GPV from baseline to 6 years) are shown in red, regressors (100% reduction in GPV from baseline to 6 years) in green, and the stable group (not fulfilling any of the 2 previous criteria) in blue. Solid lines represent subjects in each cluster with prevalent disease at baseline, whereas dashed lines do so for subjects with no disease on baseline examination. The box plots represent the geometric mean, and whiskers represent the 95% CI of GPV (mm^3).

active smoking predicted only progression of prevalent disease at enrollment but not incident disease.

The prevalence of LLT and BPLT use generally increased throughout the study period. It was highest among progressors at the 3 time points examined, and initiation and discontinuation rates were similar regardless of 6-year disease progression profile (Supplemental Table 8) and/or disease prevalence at enrollment (Supplemental Table 9). Predictor effect estimates and strength of association with the progression and regression outcomes in the multivariable models remained largely similar after adjusting for LLT and BPLT at baseline, each variable at a time (Supplemental Table 10).

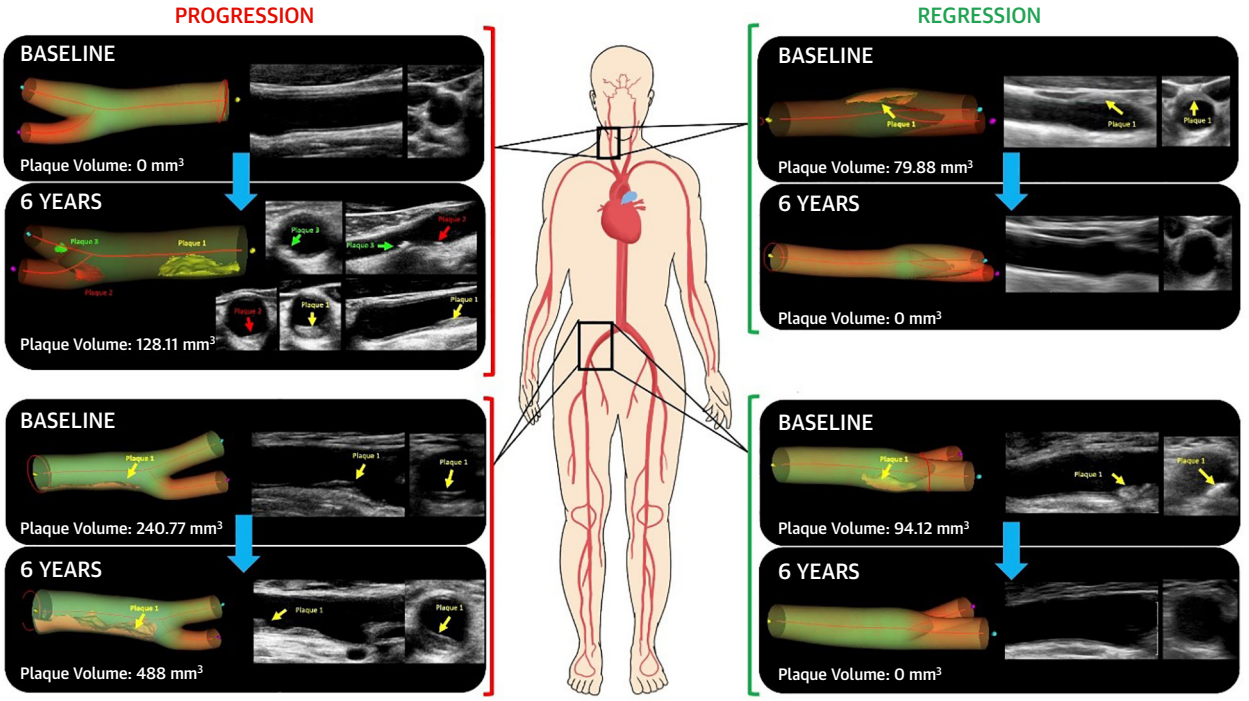
INTERACTION BETWEEN AGE AND RISK FACTORS FOR ATHEROSCLEROSIS PROGRESSION. Given the strong separate associations of age, LDL-C, and SBP with the outcome of disease progression at 6 years (**Table 3**), interactions between age and LDL-C and between age and SBP were investigated. Across strata of increasing age at baseline, there was an attenuation in the odds of 6-year SA progression for every 10 mg/dL increase in baseline LDL-C (9.1% increase in participants aged between 40 and 43 years, 6.5% increase in participants aged between 44 and 47 years, and 2.5% increase in participants over the age of 48 years; $P_{interaction} = 0.04$) (**Figure 5A**). Similarly, the odds of 6-year SA progression for every 10 mm Hg increase in baseline SBP were attenuated across increasing age strata at baseline: 27.5% increase in participants aged between 40 and 43 years, 10.4% increase in participants aged between 44 and 47 years, and 4.8% increase in participants over the age of 48 years ($P_{interaction} = 0.02$) (**Figure 5B**). No interactions were identified between sex and age.

DISCUSSION

In this study, we have evaluated the 6-year trajectories of peripheral SA in a cohort of 3,471 middle-aged asymptomatic individuals. To our knowledge, this is the first longitudinal study evaluating trajectories of early multiterritorial SA and its determinants. The main results are as follows:

1. Progression of peripheral SA from baseline to 6-year follow-up occurred in 32.7% of individuals

FIGURE 4 The 6-Year Subclinical Atherosclerosis Dynamics by 3-Dimensional Vascular Ultrasound: Individual PESA (Progression of Early Subclinical Atherosclerosis) Participant Examples



(17.5% presenting with incident SA and 15.2% progressing from prevalent disease at enrollment). The strongest baseline predictors of SA progression were older age, higher LDL-C, male sex, active smoking, and higher SBP.

2. Higher LDL-C is the risk factor showing the strongest association with progression among participants developing incident (ie, new onset) SA at 6 years, but its relevance to disease progression among those patients with prevalent disease at enrollment appears to be less certain. Conversely, active smoking is the CV risk factor (CVRF) most strongly associated with progression of prevalent disease at enrollment.
3. The impact of higher LDL-C and higher SBP on SA progression was more marked in younger participants (ie, across strata of increasing age, there was an attenuation in the odds of SA progression at 6 years for every 10-unit increase in LDL-C and SBP, respectively).
4. Regression of SA (100% decrease in GPV) occurred in 8.0% of individuals with prevalent disease at enrollment. The chances of 6-year regression of SA were inversely related to baseline active smoking, male sex, higher fibrinogen, higher LDL-C, and older age (**Central Illustration**).

TEMPORAL DISEASE DYNAMICS OF SUBCLINICAL ATHEROSCLEROSIS. The most frequently affected territory at baseline and 3-year examinations was the femoral region.[11,12,14] At 6 years of follow-up, disease prevalence rates were similar in the femoral (41.8%) and carotid (37.8%) territories (**Table 2**, Supplemental Figures 2A and 2B). Moreover, incident disease both at 3- and 6-year follow-up was somewhat higher in the carotid territory vs the femoral territory. At 6 years, coexistence of femoral and carotid SA was detected in 749 individuals (21.6%).

Other researchers have studied CAC as a surrogate for SA.[17] However, vascular calcification is a later phenomenon in the atherosclerotic process.[18] We therefore focused on the evaluation of peripheral arteries by 3DVUS to explore the trajectories of early SA and found that the prevalence of CAC at 6 years was markedly lower (29%) compared with the prevalence of peripheral SA (≈60%) at 6 years. In line with these findings, the Miami Heart Study,[19] which enrolled an asymptomatic U.S. group (mean age 53 years; 50% female), recently showed that 16% of participants without CAC had noncalcified plaque on coronary CT angiography. The 3DVUS assessment of peripheral arteries thus emerges as a promising tool in ASCVD risk assessment of younger, asymptomatic

TABLE 3 Multivariable Predictors of 6-Year Peripheral Subclinical Atherosclerosis Disease Progression (N = 3,471)[a]

	Total	OR (95%CI)	Chi-Square Statistic	*P* Value[b]
Age (per 1 y)[c]	45.8 [42.5-49.5]	1.06 (1.04-1.08)	38.2	<0.0001
LDL-C (per 10 mg/dL)[c,d]	132.3 ± 29.4	1.06 (1.03-1.08)	18.7	<0.0001
Sex				
Female	1,266 (36)	1.00	11.6	0.00070
Male	2,205 (64)	1.35 (1.14-1.61)		
Active smoking[e]				
No	2,500 (73)	1.00	10.7	0.0011
Yes	939 (27)	1.31 (1.12-1.55)		
SBP (per 10 mm Hg)[c]	115.7 ± 12.2	1.11 (1.04-1.19)	9.3	0.0023
Log of GPV, mm^3[c,f]	0.0 [0.0-40.0]	0.89 (0.86-0.92)	48.5	<0.0001

Values are median [IQR], mean ± SD, n (%) unless otherwise specified. [a]Multivariable predictors of peripheral subclinical atherosclerosis progression at 6 years by 3-dimensional vascular ultrasound fitting GPV as a continuous covariate (C-statistic = 0.62). Number of missing values: 2 (0.9%) for active smoking; 2 (0.1%) for SBP. In this analysis, progressors are compared with nonprogressors, the latter including the stable and regressor groups. [b]*P* value from a likelihood-ratio test. [c]Modeled as continuous variables. [d]To convert from mg/dL to SI in mmol/L multiply by 0.02586. [e]Defined as current and social smoking. [f]Values of GPV of 0 mm^3 have been fitted as the log of 0.5.

Abbreviations as in Table 1.

individuals, in whom plaque calcification may not have yet occurred. Previous studies performed by our group[11,13] demonstrated the high sensitivity of 3DVUS for plaque detection (100%), with high interobserver and intraobserver agreement (κ coefficient 0.84-0.97 and 0.94-1, respectively) and high accuracy and concordance in plaque volume quantification (intraclass correlation coefficient [ICC]: 0.99; 4.02-92.5 mm^3 size); interobserver and intraobserver variability (ICC: 0.89; 95% CI: 0.86-0.91) and (ICC: 0.87; 95% CI: 0.83-0.90, respectively), thus further underlining the potential of 3DVUS to become a key large-scale screening tool for identifying at-risk individuals.

PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS. The current scientific consensus is that LDL-C is a causal factor in the development of atherosclerosis.[20] Consistently, the strongest predictors of 6-year SA progression identified here are older age and increasing LDL-C. Moreover, at any level of plaque burden, arterial wall injury is exacerbated by exposures such as smoking and elevated SBP.[21] LDL-C is the CVRF showing the greatest strength of association with 6-year incident disease, whereas among participants progressing from prevalent disease at enrollment, LDL-C appears less relevant, and other CVRFs (active smoking, biologic sex, and SBP) are more strongly associated with disease progression (Supplemental Table 7).

Atherosclerosis frequently begins early in life, and its progression is accelerated by exposure to risk factors during childhood and adolescence; growing evidence supports an association between early risk factor exposure and an increased risk of subsequent ASCVD events later in life.[22,23] Although no intervention studies have directly tested this hypothesis, perhaps the best evidence that early intervention may be beneficial is from the study by Luirink et al,[24] where initiation of statin therapy during childhood slowed the progression of carotid intima-media thickness and reduced the risk of CVD in adulthood. Considering that in midlife, SA can occur in the absence of CVRFs and is even associated with LDL-C levels currently considered normal,[25] we cannot refute the idea that these established ranges may not actually be physiological. Similarly, in the MESA (Multi-Ethnic Study of Atherosclerosis) study,[26] a stepwise increase in the presence of CAC and the risk of incident ASCVD was found for SBP levels as low as 90 mm Hg (mean age 58 years). In the Cooper Center Longitudinal Study,[27] LDL-C and non-high-density lipoprotein cholesterol ≥160 mg/dL were associated with a 50% to 80% increased relative risk of ASCVD mortality even in individuals with a low 10-year estimated ASCVD risk. Furthermore, both the Bogalusa Heart Study[28] and the Cardiovascular Risk in Young Finns Study[29] found that risk factor measurement at younger ages was a better predictor of intima-media thickness than when measured during the fourth decade of life. Indeed, in the CARDIA (Coronary Artery Risk Development in Young Adults) study, exposure to high LDL-C concentrations at a young age predicted higher incident CVD risk than equivalent dose exposures at older ages.[2] Our results provide further insight into these associations: higher baseline LDL-C and SBP had a more marked effect on the risk of SA progression over 6 years at younger ages (Figures 5A and 5B).

Supporting these observations, recent studies have consistently suggested that initiating lipid control measures early in life is likely to improve current ASCVD rates.[2,20] Indeed, the results of a Mendelian randomization study show that prolonged exposure to lower LDL-C beginning early in life has as much as a 3-fold greater clinical benefit for each LDL-C unit reduction than starting statin treatment later in life.[30] Our findings highlight the idea that exposure to high LDL-C or elevated SBP early in life has a more marked effect on atherosclerosis progression than later exposure. Worth emphasizing is that, although it was the Prospective Studies Collaboration that first identified an attenuation of the effects of blood pressure and lipids on ASCVD events risk with increasing age,[31,32] our study provides new data that could explain the mechanisms underlining such patterns (ie, through the development and progression of

atherosclerosis). The surveillance of SA and early CVRF control are thus vital in the primary prevention of CVD, given that ASCVD events occur through progression of the disease (our primary study outcome). These results underscore the importance of optimal CVRF control during young adulthood in the prevention of SA progression, and indeed they go further, suggesting that starting interventions earlier in life can delay the onset and perhaps reduce the incidence of ASCVD.

In PESA, all participants undergo CAC testing at each visit. Although the increased risk prediction of atherosclerosis imaging has been consistently reported using CAC scoring,[33] in this analysis we have not used CAC changes to evaluate SA disease dynamics. The reason is 2-fold: 1) LLT is known to increase CAC scores[34]; and 2) even though CAC progression has been associated with increased risk,[35] CAC appeared suboptimal for the serial evaluation of progression and regression of disease given that its interplay with risk factors (mainly LDL-C) makes it complex to incorporate in a strategy for serial follow-up.

REGRESSION OF SUBCLINICAL ATHEROSCLEROSIS. In our study, the chances of disease regression at 6-year follow-up were inversely related to active smoking, male sex, higher fibrinogen, higher LDL-C, and older age at baseline (**Table 4**). Further, regression at 6-year follow-up was detected only among participants with a low SA burden at baseline (GPVs <126.5 mm^3) (**Figure 1**, Supplemental Table 6). Indeed, in having undergone fibrosis and calcification, it is biologically plausible that larger plaques found in the more advanced stages of SA are less susceptible to regression.[36] Moreover, younger age is a predictor of 6-year disease regression (**Table 4**). In addition, in the absence of a cholesterol-related genetic disorder, chronological age is likely to correspond to atherosclerotic disease stage because it is a direct measure of lifetime exposure to LDL-C and other CVRFs. Considering that LDL-C plays a role in both the initiation and the regression of the atherosclerotic process, and that atherosclerosis begins early in life, our results call for an urgent shift in the current approach to the disease: given the greater likelihood of achieving atherosclerotic plaque regression at younger ages and smaller plaque burdens, efforts in the prevention of CVD must begin earlier in life. We have investigated the spectrum of risk for both plaque progression and regression phenomena and have found that participants with smaller plaque volumes were more likely to experience both progression and regression of disease (Supplemental Tables 5 and 6). Screening for SA at younger ages seems therefore critical because initiating CVRF management strategies in its most premature phases is more likely to result in regression of the disease or to mitigate its progression.

TABLE 4 Multivariable Predictors of 6-Year Peripheral Subclinical Atherosclerosis Disease Regression (N = 1,529)[a]

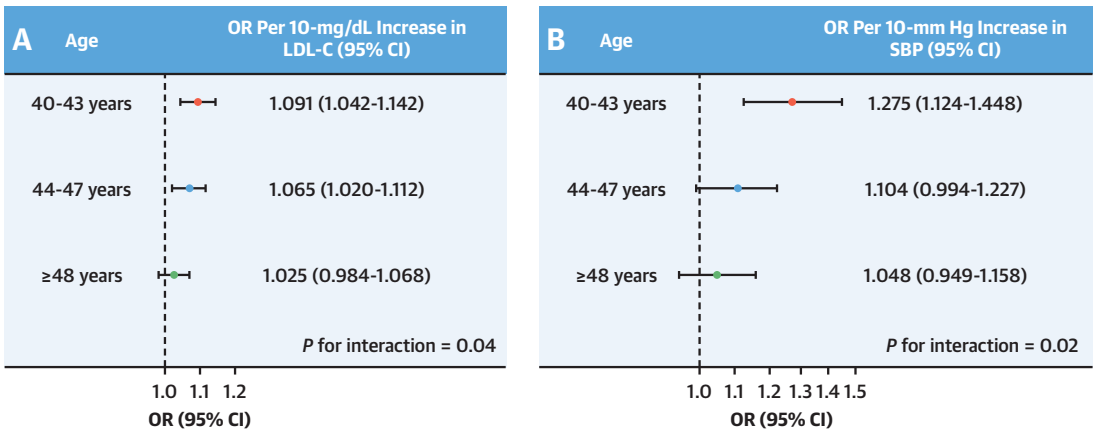
	Total	OR (95%CI)	Chi-Square Statistic	*P* Value[b]
Active smoking[c]				
No	1,018 (67)	1.00	12.0	0.00050
Yes	493 (32)	0.43 (0.26-0.72)		
Sex				
Female	340 (22)	1.00	6.3	0.012
Male	1,189 (78)	0.57 (0.37-0.88)		
Fibrinogen (per 10 mg/dL)[d]	269.2 ± 50.0	0.94 (0.90-0.99)	6.2	0.013
LDL-C (per 10 mg/dL)[d,e]	138.5 ± 30.1	0.93 (0.86-1.00)	4.5	0.034
Age (per 1 y)[d]	47.5 [44.0-51.2]	0.95 (0.91-1.00)	3.9	0.050
Log of GPV, mm^3[d]	52.0 [19.9-121.2]	0.45 (0.37-0.53)	85.9	<0.0001

Values are median [IQR], mean ± SD, or n (%), unless otherwise specified. [a]Multivariable predictors of peripheral subclinical atherosclerosis regression at 6 years by 3-dimensional vascular ultrasound fitting GPV as a continuous covariate (C-statistic = 0.82). Number of missing values: 18 (1.2%) for active smoking. Only participants with GPV >0 mm^3 at baseline are included in this analysis (N = 1,529). In this analysis, regressors are compared with nonregressors, the latter including the stable and progressor groups. Note that, as opposed to progression of disease, 6-year regression is a positive outcome and therefore ORs are all <1.0. [b]*P* value from a likelihood-ratio test. [c]Defined as current and social smoking. [d]Modeled as continuous variables. [e]To convert from mg/dL to SI in mmol/L, multiply by 0.02586.

Abbreviations as in **Table 1**.

The relationship between fibrinogen and ASCVD risk is well known. The Framingham study reported this positive relationship over its 12-year follow-up analysis, by showing that the effect of high plasma fibrinogen concentrations on CVD risk was similar to that of other CVRFs.[37] More recently, an analysis of 52 prospective studies (including 246,669 individuals without CVD) demonstrated the added value of fibrinogen to risk prediction, by suggesting that its assessment could be particularly advantageous in intermediate-risk persons.[38] Fibrinogen is regulated by acute-phase proteins (mainly interleukin-6)[39] and therefore increases during inflammation. Consistent with the biology, the chances of disease regression were inversely related to higher fibrinogen levels, thus indicating that the disappearance of plaque is more likely to occur under conditions of low systemic inflammation. Worth noting is that we did not find an association between high-sensitivity C-reactive protein (hs-CRP) and regression of SA. Perhaps this is because hs-CRP levels increase with age and are heavily influenced by lifestyle habits and CVRFs, and PESA participants comprise a middle-aged, mostly low-CV risk cohort with easy access to a Mediterranean diet. Nonetheless, these results call for further research because they inevitably lead to the question whether, in the subclinical phases of atherosclerosis, fibrinogen levels rise earlier, before any increases in

FIGURE 5 Effects of Higher LDL-C and Elevated SBP on 6-Year Subclinical Atherosclerosis Progression



(A) Effect of low-density lipoprotein cholesterol (LDL-C) on 6-year subclinical atherosclerosis progression across different age group strata. (B) Effect of systolic blood pressure (SBP) on 6-year subclinical atherosclerosis progression across different age group strata.

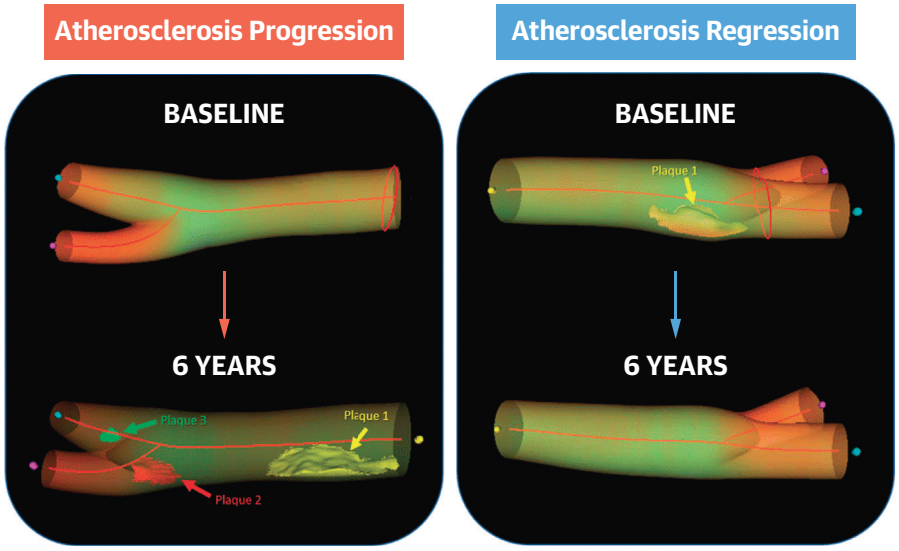
hs-CRP can be detected, while also highlighting that the role of chronic low-grade inflammation during young adulthood and middle age has been relatively unexplored to date.

Although the effect of plaque volume changes on the risk of future ASCVD events remains to be determined, our results demonstrate that complete regression of atherosclerosis occurred in a small proportion of individuals (8.0%) over a 6-year period. Plaque evolution in the early stages of atherosclerosis thus seems to be highly dynamic and possibly more susceptible to interventions, thereby further underscoring the importance of ensuring tighter control of CVRFs early in the life span to mitigate lifetime ASCVD risk.

CLINICAL IMPLICATIONS. The clinical implications of our study are several. First, the study significantly contributes to the emerging notion that CVRF control should be implemented earlier in life to effectively prevent the development and progression of atherosclerosis, which is the main driver of long-term future ASCVD events. Second, it provides an easy-to-implement means of assessing individual vulnerability to CVRFs. The 3DVUS assessment of peripheral arteries is an easy-to-use, noninvasive method to identify which persons are already developing the disease. This should further reinforce the role of plaque visualization as a risk modifier. Current clinical practice guidelines have just begun to consider its value, but the recommendation is still weak (ie, IIb).[40,41] Although the cost-effectiveness of a universal aggressive approach to CVRF control early in life should be determined, implementing a personalized approach whereby most efforts are placed in persons with evidence of atherosclerosis detected using 3DVUS appears to be an affordable alternative. Third, the fact that "cure" of atherosclerosis disease (ie, total remission of plaques) is possible in its early stages opens the possibility for a change in perception of this entity. We speculate that the relatively small proportion of atherosclerosis remissions seen in our study (8.0%) could be significantly increased through the implementation of CVRF control measures. Our study should serve as the basis for future intervention studies testing this concept. Finally, our results are capable of changing the mindset and attitudes of both medical and patient communities on atherosclerosis. Until now, the prevailing notion has been that atherosclerosis is a progressive disease and that efforts should be placed on avoiding its transition to the clinical stages and consequent ASCVD events. Delivering the concept of atherosclerosis remission as a realistic and attainable goal if tackled early is a key message likely to affect not only health care providers, but also policymakers and the general population.

STUDY LIMITATIONS. First, we studied mainly European/White, middle-aged workers, and thus the generalizability of our findings should be considered with caution. Despite the substantial testing that PESA participants underwent at each study visit, some variables with the potential to affect the outcome of 6-year SA progression and regression, such as air pollution, were not measured. Second, we have found that the effect of higher baseline LDL-C and SBP on the progression of SA over a 6-year

CENTRAL ILLUSTRATION Atherosclerosis Progression and Regression Determinants



Evolution of atherosclerosis

- Atherosclerosis ↑ in **34%** of subjects with baseline disease (527/1,529)
- New onset atherosclerosis in **31%** without baseline disease (607/1,942)
- Remission of atherosclerosis in **8%** of subjects with baseline disease

Independent predictors

↑ LDL-C, ↑ SBP, smoker, older age, male

↓ LDL-C, nonsmoker, ↓ fibrinogen, younger age, female

INTERACTION!
LDL-C and SBP greater impact on progression in younger subjects

Mendieta G, et al. J Am Coll Cardiol. 2023;82(22):2069–2083.

The 6-year trajectories of subclinical atherosclerosis show that one-third of study participants display atherosclerosis progression during 6 years of follow-up. Several factors are independently associated with progression and with regression respectively. Of note, interactions between age and the effect of low-density lipoprotein cholesterol (LDL-C) levels and systolic blood pressure (SBP) on atherosclerosis were found.

period was more marked at younger ages, but because we lack participants' LDL-C and SBP values before study enrollment, we cannot ascertain whether our baseline measurements reflect persistent levels from earlier ages. Third, 6-year SA regression was defined using very stringent criteria, which may have resulted in a loss of statistical power. However, it was set as complete disappearance of prevalent SA at enrollment to detect unquestionable remission of the disease. Finally, the outcome of progression of SA was set as a ≥100% increase in GPV at 6 years following a previously proposed definition.[11] Nonetheless, sensitivity analyses using other progression thresholds (ie, ≥50% increase in GPV at 6 years) yielded similar results, thus suggesting that the results are unlikely to be driven by the definition used.

CONCLUSIONS

At 6 years, peripheral SA progressed in one-third of the study group and regressed in a small proportion of individuals. The impact of baseline LDL-C and SBP on SA progression was more pronounced in younger participants. These results suggest that tighter risk factor control at younger ages can prevent atherosclerotic progression, with a likely long-term impact on reducing the risk of clinical events.

ACKNOWLEDGMENTS The authors acknowledge Simon Bartlett, who provided English editing. The authors are indebted to the support provided by Jose M. Mendiguren.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The PESA study is funded by the National Center for Cardiovascular Investigations (CNIC) and Santander Bank. The CNIC is supported by the Carlos III Institute of Health (ISCIII), the Ministry of Science and Innovation, and the Pro CNIC Foundation. CNIC is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIN/AEI/10.13039/501100011033). Dr Sánchez-González is an employee of Philips. Dr Ibáñez has received support from the European Commission (ERC-CoG 819775, and H2020-HEALTH 945118), the Spanish Ministry of Science and Innovation (PID2019-110369RB-I00), and the Community of Madrid (P2022/BMD-7403, RENIM-CM). Dr Mendieta was recipient of the 2020 "CardioJoven" Fellowship funded by the Spanish Society of Cardiology and the Centro Nacional de Investigaciones Cardiovasculares. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SA often progresses in middle-aged individuals, particularly when LDL-C and blood pressure are elevated, and regression of early atherosclerosis occurs in a small proportion of people.

TRANSLATIONAL OUTLOOK: Screening for SA early in life and aggressive risk factor control could help alleviate the global burden of CVDs.

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KEY WORDS 3D vascular ultrasound, blood pressure, LDL, progression, regression, risk factors, subclinical atherosclerosis

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