Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort

The PESA (Progression of Early Subclinical Atherosclerosis) Study

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Background—Data are limited on the presence, distribution, and extent of subclinical atherosclerosis in middle-aged populations.

Methods and Results—The PESA (Progression of Early Subclinical Atherosclerosis) study prospectively enrolled 4184 asymptomatic participants 40 to 54 years of age (mean age, 45.8 years; 63% male) to evaluate the systemic extent of atherosclerosis in the carotid, abdominal aortic, and iliofemoral territories by 2-/3-dimensional ultrasound and coronary artery calcification by computed tomography. The extent of subclinical atherosclerosis, defined as presence of plaque or coronary artery calcification ≥1, was classified as focal (1 site affected), intermediate (2–3 sites), or generalized (4–6 sites) after exploration of each vascular site (right/left carotids, aorta, right/left iliofemorals, and coronary arteries). Subclinical atherosclerosis was present in 63% of participants (71% of men, 48% of women). Intermediate and generalized atherosclerosis was identified in 41%. Plaques were most common in the iliofemorals (44%), followed by the carotids (31%) and aorta (25%), whereas coronary artery calcification was present in 18%. Among participants with low Framingham Heart Study (FHS) 10-year risk, subclinical disease was detected in 58%, with intermediate or generalized disease in 36%. When longer-term risk was assessed (30-year FHS), 83% of participants at high risk had atherosclerosis, with 66% classified as intermediate or generalized.

Conclusions—Subclinical atherosclerosis was highly prevalent in this middle-aged cohort, with nearly half of the participants classified as having intermediate or generalized disease. Most participants at high FHS risk had subclinical disease; however, extensive atherosclerosis was also present in a substantial number of low-risk individuals, suggesting added value of imaging for diagnosis and prevention.

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The natural history of atherosclerosis involves a protracted subclinical phase, with disease often detected only at an advanced stage or after a cardiovascular event. This is of particular importance because cardiovascular events are often fatal and many deaths attributable to coronary artery disease are sudden.[1] There is thus a clear need to identify disease at an early stage, and as a result, primary prevention forms the cornerstone of management. Currently, risk stratification scores rely on the presence of identifiable risk factors and levels of biochemical markers. However, conventional risk assessment has well-recognized limitations, notably in lower-risk groups such as women and younger people.[2,3] Detection of atherosclerosis in its subclinical stage may help identify strategies to arrest disease development. Indeed, the significance of subclinical carotid atherosclerosis and coronary artery calcification (CAC) in relation to clinical outcomes has been established in the Multi-Ethnic Study of Atherosclerosis (MESA) study[4–6] and in the recently published US High Risk Plaque Study.[7]

Clinical Perspective on p 2113

The introduction of noninvasive imaging techniques has unlocked the potential to evaluate atherosclerosis in asymptomatic populations. Specific imaging modalities include vascular ultrasound, computed tomography, and magnetic resonance imaging.[8,9] Many imaging studies evaluated individual vascular territories, but given the systemic nature of atherosclerosis, a multiterritorial analysis has the potential to provide a more comprehensive overview of the distribution and burden of atherosclerosis.

The PESA (Progression of Early Subclinical Atherosclerosis) study evaluates atherosclerosis in the carotid, aortic, coronary, and iliofemoral territories using accessible noninvasive imaging techniques in asymptomatic middle-aged individuals.[10] By evaluating multiple vascular beds in relatively young adults, we aim to improve our understanding of the origin and progression of atherosclerosis. Here, we present the prevalence, vascular distribution, and extent of subclinical atherosclerosis in the PESA cohort and their relation to cardiovascular risk algorithms.

Methods

Study Sample

The rationale and design of the PESA study have been described.[10] Briefly, PESA-CNIC-Santander is a prospective cohort study of asymptomatic employees of the Santander Bank in Madrid who are 40 to 54 years of age and were consecutively recruited between June 2010 and February 2014. Participants with prior cardiovascular disease and any condition reducing life expectancy or affecting study adherence were not included. Participants were examined at baseline by ankle-brachial index (ABI), vascular ultrasound, and noncontrast computed tomography and will be followed up at 3 and 6 years. In addition, each visit includes clinical interviews, physical examination, fasting blood draw, urine sample, and a 12-lead ECG. The study protocol has been approved by the Instituto de Salud Carlos III Ethics Committee, and all eligible participants have provided written informed consent.

Traditional cardiovascular risk factors were determined from blood samples and interviews as follows: (1) diabetes mellitus: fasting plasma glucose ≥126 mg/dL or treatment with insulin or oral hypoglycemic medication[11]; (2) arterial hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication[11]; (3) dyslipidemia: total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or use of lipid-lowering drugs[12]; (4) smoking: current smoking status or a lifetime consumption of >100 cigarettes[8,13]; and (5) family history of cardiovascular disease: first-degree relative diagnosed with atherosclerosis before 55 years of age in men and 65 years of age in women.[14] Obesity, defined as body mass index ≥30 kg/m^2, was also assessed.[14] Cardiovascular risk was evaluated by the 10-year risk of coronary heart disease and the 30-year risk of cardiovascular disease from the Framingham Heart Study (FHS),[13,15] as well as by the European Society of Cardiology's SCORE (Systematic Coronary Risk Evaluation), which calculates 10-year risk of fatal cardiovascular disease,[14] using the low cardiovascular risk charts applicable to Spain. FHS scores were classified as low (<10%), moderate (10–20%), or high (<20%) risk and the SCORE risks as low (<1%) and moderate to high (≥1%). In light of recent US guidelines for statin therapy,[16] we also calculated 10-year risk using the atherosclerotic cardiovascular disease (ASCVD) algorithm, an atherosclerotic risk calculator based on Pooled Cohort Equations,[9] and cutoff values were defined as <5%, 5% to <7.5%, and ≥7.5% risk.

Vascular Ultrasound Imaging

The 2-/3-dimensional vascular ultrasound protocol has been described.[7] The presence of atherosclerotic plaques was assessed by cross-sectional sweep of carotids, infrarenal abdominal aorta, and iliofemoral arteries. Plaque was defined as a focal protrusion into the arterial lumen of thickness >0.5 mm or >50% of the surrounding intima-media thickness or a diffuse thickness >1.5 mm measured between the media-adventitia and intima-lumen interfaces.[7,17] Semiautomated detection of carotid and femoral intima-media thickness was also assessed (details are given in the online-only Data Supplement). Ultrasound studies were analyzed with QLab9 (Philips Healthcare, Bothel, WA) at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) Core Imaging Laboratory.[7] Imaging quality was evaluated as optimal, suboptimal, or noninterpretable, and inclusion of studies was determined by consensus. Good reproducibility was found for the presence of plaque in all territories (κ= 0.75 for carotids, 0.89 for aorta, 0.88 for iliofemorals). The ABI was calculated as the ratio of systolic blood pressure in the posterior tibial artery to systolic blood pressure in the brachial artery using Doppler ultrasound and a standard sphygmomanometer. ABI values <0.9 were considered abnormal.[18]

CAC by Computed Tomography

CAC was detected with a 16-slice computed tomography scanner (Philips Brilliance, Philips Healthcare, Andover, MA) using noncontrast prospective electrocardiography-gated acquisition. Estimated absorbed radiation was 0.6 to 1.2 mSv. CAC score (CACS) was calculated by the Agatston method and graded as 1 to 99, 100 to 399, and ≥400.[4] Three trained technicians blinded to other imaging results and supervised by experienced physicians quantified CACS.

Definition of Subclinical Atherosclerosis

Subclinical atherosclerosis was defined as the presence of atherosclerotic plaques in the carotid, aortic, or iliofemoral territories or CACS ≥1. The multiterritorial extent of subclinical atherosclerosis was defined according to the number of vascular sites affected (right carotid, left carotid, abdominal aorta, right iliofemoral, left iliofemoral, and coronary arteries). Participants were classified as disease free (0 vascular sites affected) or as having focal (1 site), intermediate (2–3 sites), or generalized (4–6 sites) atherosclerosis.

Statistical Analysis

Baseline characteristics were calculated using mean and standard deviation for continuous variables and count and proportions for categorical variables. Differences between continuous variables and categorical variables were tested with unpaired *t* tests and χ^2 tests,

Table 1. Demographic Characteristics and Cardiovascular Risk Factors

	Total (n=4066)	Men (n=2573)	Women (n=1493)	*P* Value
Baseline characteristics				
Age, y	45.8±4.3	46.3±4.4	45±3.9	<0.001
BMI, kg/m^2	26.2±3.8	27.4±3.4	24.1±3.6	<0.001
Obesity (BMI ≥30 kg/m^2), n (%)	598 (15)	493 (19)	105 (7)	<0.001
SBP, mm Hg	116±12.5	121±11.1	109±11	<0.001
DBP, mm Hg	72.5±9.4	74.7±9.1	68.7±8.7	<0.001
Total cholesterol, mg/dL	201±33.3	203±34.2	196±31.2	<0.001
LDL-C, mg/dL	132±29.8	136±30.3	125±27.5	<0.001
HDL-C, mg/dL	49±12.2	44.8±10.2	56.3±11.9	<0.001
Triglycerides, mg/dL	95±57.2	109±64	70.6±29.9	<0.001
Fasting glucose, mg/dL	90.6±13.8	93.4±15	85.7±9.7	<0.001
Hemoglobin A_{1c}, %	5.44±0.5	5.49±0.5	5.36±0.4	<0.001
Lipid-lowering therapy, n (%)	287 (7)	242 (9)	45 (3)	<0.001
Antihypertensive therapy, n (%)	309 (8)	266 (10)	43 (3)	<0.001
Antidiabetic therapy, n (%)	64 (2)	56 (2)	8 (0.5)	<0.001
Traditional CV risk factors, n (%)				
Dyslipidemia	1691 (42)	1374 (53)	317 (21)	<0.001
Total cholesterol ≥240 mg/dL	475 (12)	345 (13)	130 (9)	<0.001
LDL-C ≥160 mg/dL	688 (17)	522 (20)	166 (11)	<0.001
HDL-C <40 mg/dL	983 (24)	880 (34)	103 (7)	<0.001
Current smoking	835 (21)	486 (19)	349 (23)	<0.001
Family history of CV disease	646 (16)	398 (16)	248 (17)	0.337
Hypertension	481 (12)	409 (16)	72 (5)	<0.001
Diabetes mellitus	81 (2)	72 (3)	9 (0.6)	<0.001
No. of CV risk factors, n (%)				
0	1535 (38)	777 (30)	758 (51)	<0.001
1	1572 (39)	1053 (41)	519 (35)	<0.001
2	746 (18)	569 (22)	177 (12)	<0.001
>2	213 (5)	174 (7)	39 (3)	<0.001

Data are expressed as mean±SD when appropriate. *P* values are derived from independent *t* tests for continuous variables and χ^2 for categorical variables. BMI indicates body mass index; CV, cardiovascular; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

respectively. Nonnormally distributed variables (triglycerides, fasting glucose, hemoglobin A_{1c}, CACS, and cardiovascular risk scales) were log transformed before analysis to normalize the distribution. Age- and sex-adjusted associations between vascular disease in each territory were examined by use of logistic regression models. The reproducibility of ultrasound measurements was studied by replicating the analysis of a random sample of 60 studies 3 months after the initial assessment, and the Cohen κ was used for the agreement analysis. Statistical analyses were conducted with Stata 12 (StataCorp, College Station, TX).

Results

The PESA cohort comprised 4184 participants (78% of the eligible population). At the time of publication, 34 individuals (0.8%) had discontinued the study, and 84 (2%) either were excluded for missing data or were pending evaluation, resulting in 4066 participants available for analysis. After exclusion of noninterpretable images (64 participants, 1.5%), the sample available for imaging analysis was 4002 (98% of the cohort). Only 1 case of abnormal ABI was detected in the first 2536 participants; therefore, the protocol was amended to discontinue measurement of ABI in subsequent examinations. Baseline demographic characteristics and cardiovascular risk factors are summarized in Table 1. The average age of the participants was 45.8 years; 63% were male; and 99.9% were white. The most prevalent traditional risk factor was dyslipidemia (42%), followed by smoking (21%), family history (16%), hypertension (12%), and diabetes mellitus (2%). Additionally, obesity was found in 15% of PESA participants. The presence of traditional risk factors and obesity was higher in men, with the exception of smoking (23% women and 19% men) and family history (17% women and 16% men). Most participants (62%) had at least 1 traditional risk factor, 18% had 2 risk factors, and 5% had ≥3 risk factors. Aside from family history, the prevalence of traditional risk factors except for smoking and diabetes mellitus in women increased with age (Table I in the online-only Data Supplement). Risk-factor distribution was not significantly different in the participants not included in the imaging analysis (1.5%), thus excluding systematic bias.

Prevalence, Vascular Distribution, and Extent of Subclinical Atherosclerosis

The prevalence of subclinical atherosclerosis (presence of plaque or CACS ≥1) was 63%. Plaques were detected by ultrasound in 60% of participants (31% in the carotids, 25% in the aorta, and 44% in the iliofemoral arteries), and 18% had CAC (CACS: 1–99 in 14%, 100–399 in 3%, and ≥400 in 0.7%). In men, subclinical atherosclerosis was more prevalent (71% versus 48% in women) across all vascular territories, with differences most pronounced in the iliofemoral and coronary arteries (Figure 1). Of the 23 participants with CACS ≥400, only 1 participant was female (Table I in the online-only Data Supplement). Atherosclerosis prevalence increased with age for both sexes and across all vascular territories, and only the presence of aortic disease was found to be independent of sex (Figure 2). Associations between subclinical atherosclerosis in different territories and each individual risk factor are shown in Table II in the online-only Data Supplement (details are provided in the online-only Data Supplement).

The presence of iliofemoral disease was more strongly correlated with aortic disease and CAC than with carotid disease (Table 2). Furthermore, having disease in the iliofemorals corresponds to a 70% probability of finding disease in any other territory explored. Conversely, the absence of plaque in the

iliofemorals confers a 67% probability of being disease free in the other vascular territories. In participants with carotid disease, the odds ratio for coexisting plaque was slightly higher in the aortic and iliofemoral territories compared with CAC, and the probability of subclinical atherosclerosis in any other territory was 72%, with a negative predictive value of 55%. Among participants with CACS ≥1, 87% had plaques present at other vascular sites, whereas 54% of participants with CACS of 0 had plaques in other territories (37% in iliofemorals, 27% in carotids, and 20% in aorta).

Classification of participants according to the extent of atherosclerosis showed focal disease in 21%, intermediate disease in 28%, and generalized disease in 13%. The prevalence of generalized atherosclerosis was greater in men, increased with age, and was related to the presence of obesity and traditional risk factors (Figure I and Table III in the online-only Data Supplement). Notably, the extent of subclinical atherosclerosis in men 40 to 44 years was similar to that in women 5 to 10 years older (Figure I in the online-only Data Supplement). Among those participants having focal disease, the iliofemoral was the most likely territory to be affected, independently of age, sex, or risk profile (Table IV in the online-only Data Supplement). In an attempt to highlight differences between participants with atherosclerosis in a single territory (focal disease) and those with multiple territories affected (intermediate or generalized disease), we performed a subgroup analysis, finding a significantly higher prevalence for all traditional risk factors among those participants with multiterritorial atherosclerosis (Table 3).

Cardiovascular Risk Scales and Subclinical Atherosclerosis

Mean FHS 10-year score in the PESA cohort was 6%, and most participants (85%) were at low risk compared with 14% at moderate risk and 1% at high risk. Similarly, most individuals (85%) were at low risk by the European SCORE compared with 15% at moderate to high risk. To assess longer-term risk, FHS 30-year score was calculated, yielding a mean value of 18% and higher proportions of participants at moderate and high risk (30% and 35%, respectively).

The relationship between cardiovascular risk scales and subclinical atherosclerosis is shown in Figures 3 and 4. Among participants at low 10-year FHS risk, 58% had subclinical atherosclerosis, including 36% with intermediate or generalized disease. Most FHS high-risk participants (95%) had atherosclerosis, with intermediate or generalized disease in 86%. Similarly, among participants with a low European SCORE, 58% had subclinical atherosclerosis, including 35% with intermediate or generalized disease, and almost 80% of moderate- to high-risk participants had intermediate or generalized disease. Given the low numbers of individuals at high-risk using the 10-year FHS scale (55 participants), we also examined the relationship between atherosclerosis and 30-year FHS score. Among individuals at high 30-year FHS risk, 83% had subclinical atherosclerosis, with intermediate or generalized disease in 66%, whereas among low-risk individuals, 43% had atherosclerosis and 22% had intermediate or generalized disease. Such associations were also observed for each vascular territory analyzed separately (Figures II–IV in the online-only Data Supplement).

A further analysis was performed to explore subclinical atherosclerosis according to the 10-year ASCVD risk algorithm.[16] The prevalence of the ASCVD risk subgroups across the PESA sample was 11%, 79%, and 10% for the <5%, 5% to <7.5%, and ≥7.5% risk groups. The <5% risk group had a significantly lower prevalence of subclinical atherosclerosis compared with the 5% to <7.5% and ≥7.5% risk groups (57% versus 80% versus 92%; $P<0.001$). Comparison of the <5%, 5% to <7.5%, and ≥7.5% risk groups by vascular territory revealed carotid disease in 29% versus 42% versus 57%, aortic

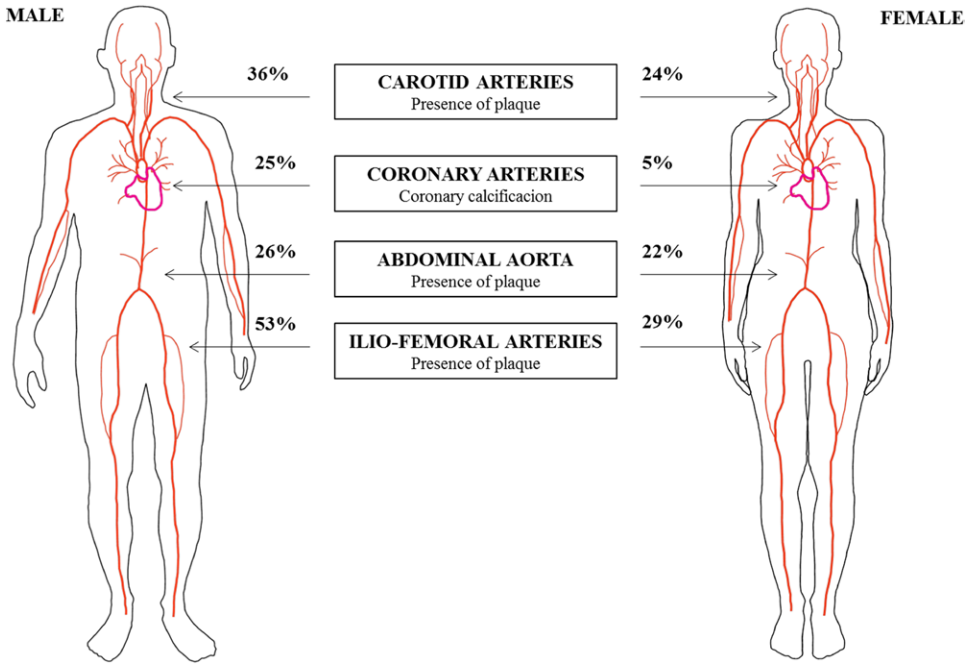

Figure 1. Prevalence of subclinical atherosclerosis by vascular territory in PESA (Progression of Early Subclinical Atherosclerosis).

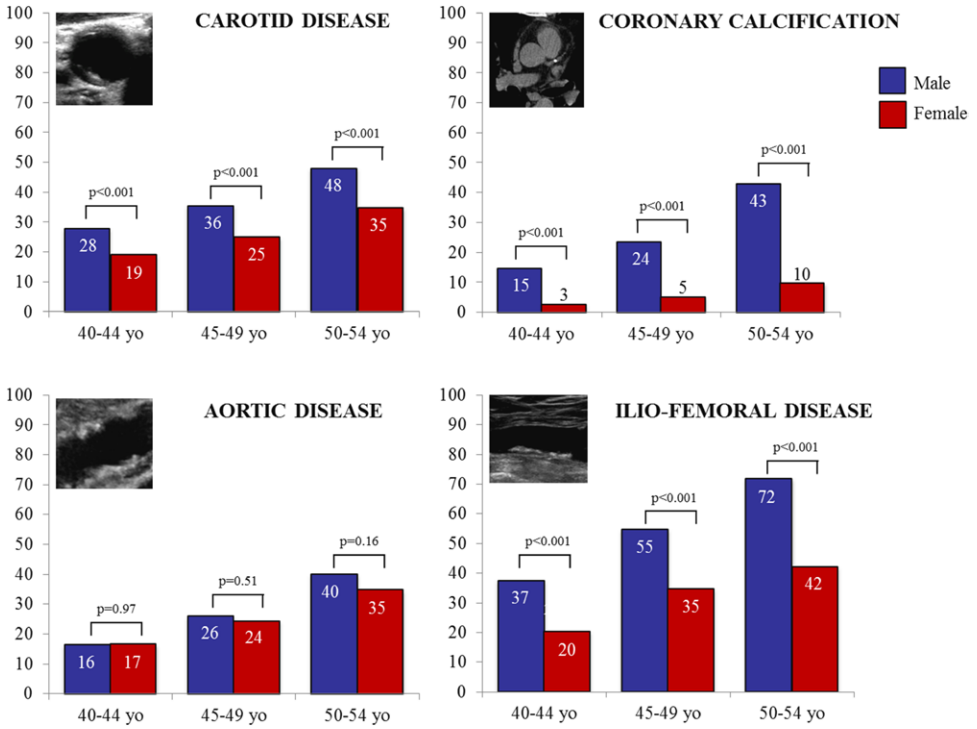

Figure 2. Prevalence of subclinical atherosclerosis by age and sex in each vascular territory.

disease in 21% versus 35% versus 42%, CACS ≥1 in 12% versus 33% versus 45%, and iliofemoral disease in 37% versus 64% versus 79% (P<0.001 for all comparisons). Figure 5 shows the relation between the extent of atherosclerosis and the groups who meet the American Heart Association/American College of Cardiology criteria for statin treatment (≥7.5% ASCVD risk, diabetes mellitus, or low-density lipoprotein ≥190 mg/dL), those considered for statin (5%–<7.5% ASCVD risk), and those not considered for statin (<5% ASCVD risk). Interestingly, the prevalence of generalized disease increased with higher ASCVD risk score (8% versus 24% versus 37% in the <5%, 5%–<7.5%, and ≥7.5% risk groups, respectively).

Discussion

The main findings from the PESA cohort are as follows: Subclinical atherosclerosis is highly prevalent in this middle-aged asymptomatic sample; the iliofemoral territory is the most frequently affected vascular site in the early stages of atherosclerosis; and most individuals classified at high risk by traditional scales (FHS and European SCORE) had subclinical

Table 2. Associations Between the Presence of Atherosclerosis in Individual Vascular Territories

	Carotid Disease	Coronary Calcification	Aortic Disease	Iliofemoral Disease
Carotid disease				
OR (95% CI)	…	2.06 (1.73–2.47)	2.80 (2.40–3.27)	2.13 (1.84–2.46)
P value		<0.001	<0.001	<0.001
Coronary calcification				
OR (95% CI)	2.06 (1.73–2.47)	…	2.48 (2.06–2.99)	3.16 (2.60–3.84)
P value	<0.001		<0.001	<0.001
Aortic disease				
OR (95% CI)	2.80 (2.40–3.27)	2.48 (2.06–2.99)	…	4.85 (4.09–5.75)
P value	<0.001	<0.001		<0.001
Iliofemoral disease				
OR (95% CI)	2.13 (1.84–2.46)	3.16 (2.60–3.84)	4.85 (4.09–5.75)	
P value	<0.001	<0.001	<0.001	…

Data are expressed as odds ratio (OR) and 95% confidence interval (CI) adjusted by age and sex and calculated with logistic regression models. Coronary artery calcification (CAC) was defined as a CAC score ≥1.

Table 3. Comparison of Demographics, Physical Examination, Traditional Cardiovascular Risk Factors, and Risk Scores Between Participants With Atherosclerosis in a Single Territory (Focal Disease) and Those With Multiple Territories Affected (Intermediate or Generalized Disease)

	Single Territory (n=849)	Multiple Territories (n=1651)	*P* Value
Demographics and physical examination			
Age, y	45.4±4.1	47.4±4.2	<0.001
Male sex, n (%)	530 (62)	1255 (76)	<0.001
BMI, kg/m^2	26±3.8	26.7±3.6	<0.001
SBP, mm Hg	116±12	119±12.5	<0.001
DBP, mm Hg	72.1±9.6	74.5±9.4	<0.001
Total cholesterol, mg/dL	200±32.7	208±33.9	<0.001
LDL-C, mg/dL	132±28.9	139±30.2	<0.001
HDL-C, mg/dL	49.9±12.1	46.5±11.5	<0.001
Triglycerides, mg/dL	90.9±57.2	107±62.8	<0.001
Fasting glucose, mg/dL	90.3±10.5	92.9±17.4	<0.001
Hemoglobin A_{1c}, %	5.44±0.5	5.54±0.5	<0.001
Lipid-lowering treatment, n (%)	45 (5)	181 (11)	<0.001
Antihypertensive treatment, n (%)	50 (6)	191 (12)	<0.001
Antidiabetic treatment, n (%)	11 (1)	39 (2)	0.071
Traditional CV risk factors, n (%)			
Dyslipidemia	318 (38)	893 (54)	<0.001
Total cholesterol ≥240 mg/dL	100 (12)	263 (16)	0.005
LDL-C ≥160 mg/dL	123 (15)	387 (23)	<0.001
HDL-C <40 mg/dL	171 (20)	515 (31)	<0.001
Current smoking	154 (18)	466 (28)	<0.001
Family history of CV disease	121 (14)	292 (18)	0.029
Hypertension	82 (10)	278 (17)	<0.001
Diabetes mellitus	14 (2)	52 (3)	0.027
No. of risk factors			
0	345 (41)	418 (25)	<0.001
1	343 (40)	661 (40)	0.860
2	139 (16)	423 (26)	<0.001
>2	22 (3)	149 (9)	<0.001
CV risk scores, %			
10-y FHS	5.3±3.6	7.8±5	<0.001
30-y FHS	16.1±9.8	23.4±12.9	<0.001
European SCORE	0.47±0.5	0.83±0.7	<0.001
ASCVD score	2.71±2.5	4.7±3.9	<0.001

Data are expressed as mean±SD when appropriate. *P* values are derived from independent *t* tests for continuous variables and χ^2 for categorical variables. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; FHS, Framingham Heart Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and SCORE, Systematic Coronary Risk Evaluation.

atherosclerosis, but atherosclerosis is also present in nearly 60% of participants classified at low risk, with intermediate or generalized disease in one third. Ongoing PESA follow-up over at least 6 years will enable study of associations between subclinical disease evaluated at baseline and subsequent cardiovascular events.

Subclinical Atherosclerosis Is Prevalent in Middle-Aged Individuals

Few population studies have investigated the prevalence and extent of subclinical atherosclerosis across multiple vascular sites in a middle-aged sample, despite atherosclerosis being a systemic disease with a long latent subclinical phase. In the MESA and Coronary Artery Risk Development in Young Adults (CARDIA) studies, evaluation of atherosclerosis was limited to carotid intima-media thickness and CAC.[3,8] The Atherosclerosis Risk in Communities (ARIC) study focused only on carotid and popliteal territories assessed by ultrasound.[19] The Heinz Nixdorf Recall, High Risk Plaque, and Rotterdam studies recruited older individuals with prior cardiovascular disease or a high-risk profile.[1,7,20] Using a multiterritorial evaluation, the PESA study detects a high prevalence of subclinical disease, with nearly half the participants classified as having intermediate or generalized disease despite being predominantly at low risk according to traditional scales. This finding is probably attributable to the examination of several territories, including vascular areas more susceptible to disease such as the iliofemoral arteries, which were not explored in earlier studies. Other studies that investigated multiple vascular sites included only men with at least 1 risk factor,[21] examined participants at higher risk,[22] or explored fewer territories.[23]

An innovation of PESA is the early detection of atherosclerosis in other vascular territories even in the absence of CAC. A CACS of 0 could be considered indicative of absence of disease, but among PESA participants with CACS=0, nearly 60% had plaques at other vascular sites. Therefore, in this low-risk sample, the absence of CAC does not necessarily indicate that a participant is disease free. We hypothesize that by studying other vascular territories in subjects with CACS=0, we could identify those who will develop CAC in the future and who would likely benefit from more intensive preventive management. Although follow-up will be needed to confirm this hypothesis, multiterritorial assessment with vascular ultrasound—a safe, cost-efficient, reproducible, and simple technique—might be especially important at early stages of atherosclerosis in younger people with a high probability of zero CAC.

The added clinical value of a multiterritorial vascular evaluation is supported by the Carotid-Femoral Ultrasound Morphology and Cardiovascular Events (CAFES-CAVE) study, which showed that scanning only carotids or only femorals predicts 15% and 13% fewer events than examining both territories in a 10-year follow-up.[24] This finding supports the view that the wider sampling that comes from exploring several territories overcomes the problem of not detecting a lesion when only 1 territory is examined. The predictive value of multiterritorial imaging will be assessed in detail with the appearance of events during PESA follow-up. The prognostic relevance of subclinical atherosclerosis is also supported by the MESA study[4–6] and the recently published US High Risk Plaque Study,[7] in which strong associations have been shown between cardiovascular events and subclinical carotid and coronary disease. Similarly, the Northern Manhattan Study demonstrated that subclinical carotid plaque is a precursor of cardiovascular events.[25] These studies highlight the potential value of evaluating subclinical

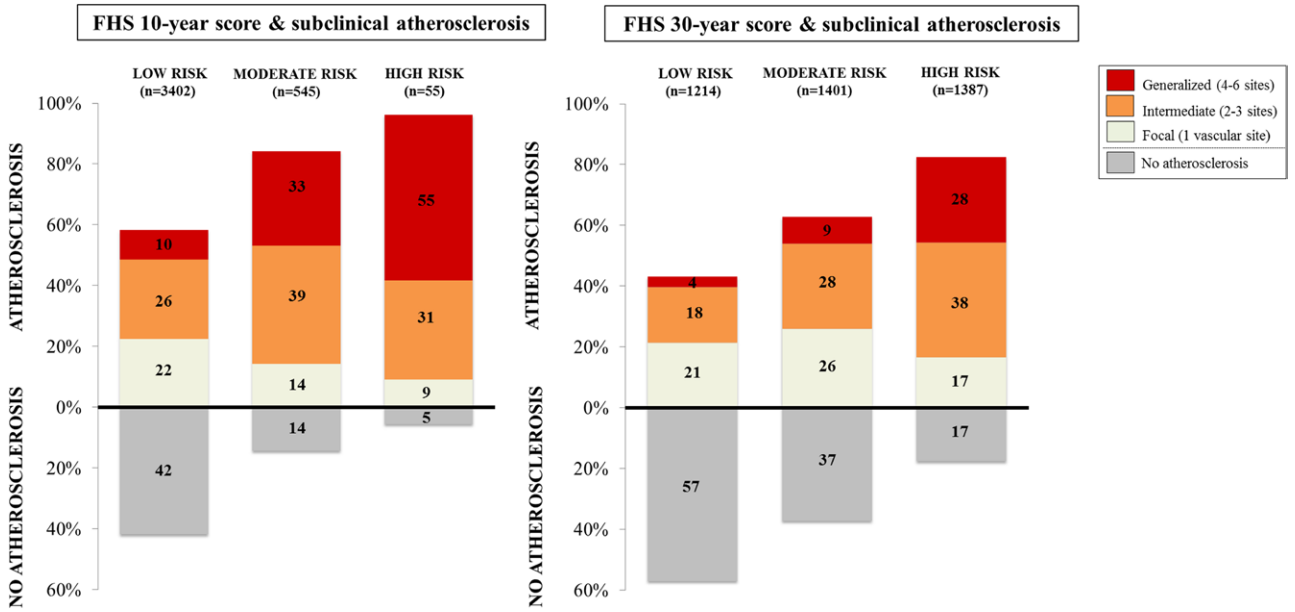

Figure 3. Distribution of subclinical atherosclerosis detected by noninvasive imaging according to Framingham Heart Study risk (FHS) categories. Vascular sites examined were the right and left carotids, the abdominal aorta, and the right and left iliofemoral arteries (presence of plaque), as well as the coronary vessels (coronary artery calcification). FHS scores were classified as low (<10%), moderate (≥10%–20%), or high (>20%) risk.[13,15]

atherosclerosis in multiple territories for cardiovascular event prediction.

The association of increased subclinical atherosclerosis prevalence with male sex and age is consistent with previous reports[26] and may be related to the natural history of the disease. In fact, the risk of atherosclerosis in men is similar to that in women 5 to 10 years older in this cohort. This discovery may assist in determining the most appropriate time window for atherosclerosis screening and intensification of primary cardiovascular prevention. We interestingly found that individuals at ≥7.5% ASCVD risk had substantial atherosclerosis compared with lower-risk individuals, especially in terms of CAC, and had a 4-fold higher prevalence of generalized disease. This interesting finding is in line with the proposed intensification of statin treatment in the most recent guidelines on the treatment of blood cholesterol.[16]

The Iliofemoral Territory Is the Most Frequently Affected Vascular Site

The clear predominance of disease in the iliofemoral arteries is possibly related to specific patterns of shear stress and disturbed flow caused by the vessel curvature.[27] In PESA participants, the presence of iliofemoral disease increases the risk of concurrent CAC and is predictive of disease elsewhere. Moreover, the absence of iliofemoral disease is strongly associated with the absence of atherosclerosis at other vascular sites. Thus, imaging of peripheral arteries may be a useful population-wide screening tool for detecting atherosclerosis in its early stages. Follow-up will be extremely valuable to clarify the impact of early detection of iliofemoral disease on the primary prevention of peripheral arterial disease because advanced stages are associated with higher risk of myocardial infarction and stroke.[28]

The iliofemoral territory has traditionally not been examined as extensively as the carotids and CAC. Because of the inclusion of this territory in PESA, comparisons with other more commonly examined vascular sites are available. Indeed, evaluation of the iliofemoral arteries appears to be more valuable than CAC for detecting subclinical atherosclerosis, given the high prevalence (82%) of an CACS of 0 in this low-risk middle-aged sample, suggesting that CAC represents a more advanced stage of disease. Notably, the prevalence of abnormal ABI is low in PESA, consistent with previous studies that found a low prevalence in middle-aged individuals.[29–31] This finding supports the idea that ABI adds little valuable

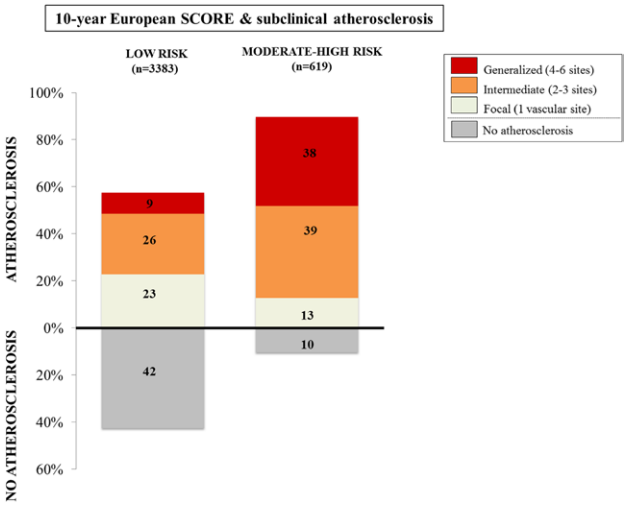

Figure 4. Distribution of subclinical atherosclerosis detected by noninvasive imaging according to European SCORE (Systematic Coronary Risk Evaluation) categories. European SCORE was classified as low (<1%) and moderate to high (≥1%) risk.[14]

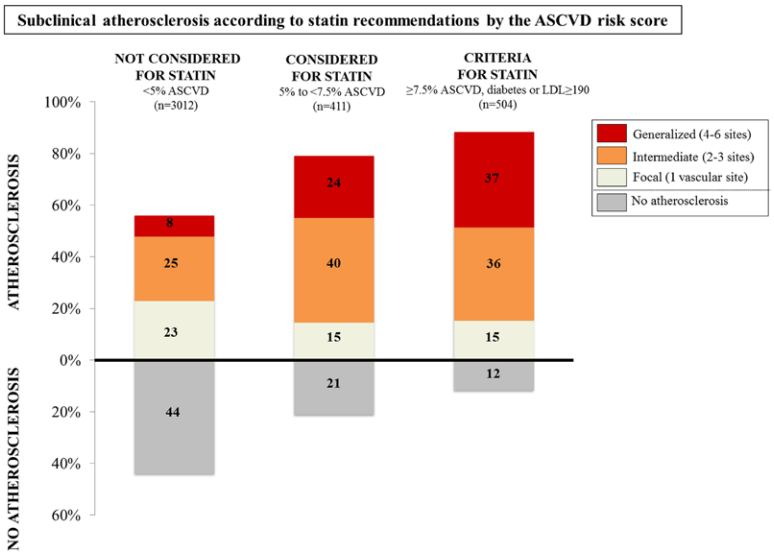

Figure 5. Distribution of subclinical atherosclerosis across participants meeting American Heart Association/American College of Cardiology criteria for statin treatment (≥7.5% atherosclerotic cardiovascular disease [ASCVD] risk, diabetes mellitus, or low-density lipoprotein ≥190 mg/dL), those considered for statin (5%–<7.5% ASCVD risk), and those not considered for statin (<5% ASCVD risk).

information to the screening of subclinical atherosclerosis in the early stages of the disease.

Subclinical Atherosclerosis and Traditional Cardiovascular Risk Scales

Current risk stratification strategies have successfully identified individuals at risk of cardiovascular events. Traditional risk scales include the widely used FHS and SCORE, an adaptation of FHS that avoids risk overestimation in European populations with less coronary heart disease.[14,32] However, the impact of these scales in younger, low-risk populations is limited, with many individuals still experiencing cardiovascular events and little success in promoting lifestyle changes.[3] In a cohort of 122 458 patients with coronary disease, 9% to 13% of those <55 years of age had no conventional risk factors,[33] indicating a disparity between traditional risk factors and the presence of disease in younger populations. The limited value of cardiovascular risk assessment by FHS alone in young healthy adults was raised in a recent study by Armstrong et al[34] that demonstrated improved discrimination when risk classification includes left ventricular mass as an additional independent predictor of cardiovascular disease.

Although the FHS and the European SCORE scales were designed to assess risk of cardiovascular events derived from atherosclerosis, not the presence of subclinical atherosclerosis, we aimed to complement these predictive models by comparing the presence and extent of subclinical disease across different risk categories. Most individuals classified at high risk have subclinical atherosclerosis, with a high proportion having intermediate or generalized disease. However, subclinical atherosclerosis is also present in nearly 60% of PESA participants at low risk, with one third having at least 2 sites affected. In this regard, a substudy of the MESA and CARDIA participants detected higher carotid intima-media thickness and higher CAC in individuals with low 10-year but high lifetime risk compared with individuals with low 10-year and low lifetime risk.[3] Together, these results strongly suggest an association of atherosclerosis with characteristics not considered in standard risk scales, and that will be the basis of further investigation in PESA. We also propose that individuals presenting multiterritorial atherosclerosis, despite being classified at low risk, will be more likely to develop clinical events. Future confirmation of this hypothesis in longitudinal follow-up could support the broader application of multiterritorial imaging, a reasonable expectation given the systemic nature of atherosclerosis. Multiterritorial vascular imaging therefore appears to have the potential to help identify new factors and thus complement traditional risk scales, helping to achieve the goal of individualized risk assessment.

Limitations

This study presents a cross-sectional analysis of the PESA cohort at baseline and therefore cannot yet evaluate clinical events, precluding the possibility of establishing causality; these current findings will be complemented by long-term monitoring of atherosclerosis progression. Follow-up data from PESA will help to clarify the clinical significance of early detection of nonobstructive disease, including iliofemoral atherosclerosis, and the predictive value of multiterritorial atherosclerosis in low-risk individuals. The present analysis of the PESA baseline cohort sets the basis for understanding the relationship between the extent and progression of subclinical disease and future cardiovascular events. The PESA sample consists of middle-aged, predominantly male white-collar workers, which may limit the generalizability of the results. Although the prevalence of disease might not be universally representative given the specific characteristics of our participants, the observed associations between cardiovascular risk profile and the presence and extent of atherosclerosis could be extrapolated to other cohorts. It is challenging to assess whether the distribution of risk factors in PESA is similar to that in an age- and sex-matched representative population because we included younger individuals than in most previous population-based studies. The present results, however, will complement ongoing studies on atherosclerosis by giving considerable insight into the early stages of atherosclerosis. Detection of plaques in the iliac arteries may be limited by the penetration of the vascular probe used and the presence of air (23% of iliac studies were suboptimal

compared with 2% for carotids, 10% for aorta, and 6% for femorals). However, a further evaluation of variability in the iliac arteries showed good results (κ=0.84), and only 1% of iliac studies were noninterpretable. In the classification of the extent of subclinical atherosclerosis, aortic and coronary sites were considered single territories, with greater weight therefore given to carotid and iliofemoral territories; however, the multiterritorial extent of disease includes the concept of laterality and introduces a novel evaluation of atherosclerosis. Although CAC is a well-established evaluation of subclinical coronary disease, it is not suitable for noncalcified plaques. In the interest of clarity and ease of clinical application, atherosclerotic plaques and CAC were considered dichotomized variables (presence or absence) to evaluate the extent of subclinical atherosclerosis.

Conclusions

Subclinical atherosclerosis is highly prevalent in this middle-aged, asymptomatic cohort, with nearly half the participants presenting with intermediate or generalized disease. Prevalence is higher in men and in the iliofemoral arteries, highlighting the value of screening this territory. Because a substantial proportion of low-risk participants had subclinical atherosclerosis, imaging of early atherosclerosis may be particularly valuable in this setting. Long-term follow-up will determine whether detection of early atherosclerosis has any impact on predicting and preventing cardiovascular events.

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This paper is dedicated to the memory of Don Emilio Botín, former chairman of the Banco Santander (1934-2014), whose vision and enthusiasm made this project a reality.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Atherosclerosis is a slow-progressing disease characterized by a long latent stage; it is often detected only at an advanced stage or after a cardiovascular event. Detection of atherosclerosis in its subclinical stage may help to arrest disease development. Noninvasive bioimaging is one of the most promising approaches to improving early atherosclerosis detection and cardiovascular prevention. In the PESA (Progression of Early Subclinical Atherosclerosis) study, we performed an exhaustive vascular evaluation using ultrasound and computed tomography to detect subclinical atherosclerosis in >4000 individuals 40 to 54 years of age. Given the systemic nature of atherosclerosis, PESA includes a multiterritorial imaging assessment of the carotid arteries, abdominal aorta, and coronary and iliofemoral arteries to better characterize the vascular distribution and extent of the disease in the early asymptomatic phases. Interestingly, the most frequently affected vascular site at these early stages is the iliofemoral territory. This novel finding suggests the value of exploring this territory, which has received less attention than more commonly evaluated sites such as the carotids or the coronary arteries. We also explored the relationship between the systemic extent of atherosclerosis and cardiovascular risk scores. As expected, most individuals classified at high risk have subclinical disease; however, atherosclerosis is also present in nearly 60% of low-risk participants, with one third having multiple vascular sites affected, suggesting added value of imaging for prevention. The PESA study provides a new and comprehensive overview of the distribution and extent of early multiterritorial atherosclerosis in a relatively young cohort and has the potential to complement traditional risk scales.