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ORIGINAL INVESTIGATIONS

Femoral and Carotid Subclinical Atherosclerosis Association With Risk Factors and Coronary Calcium

The AWHS Study

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ABSTRACT

BACKGROUND Early subclinical atherosclerosis has been mainly researched in carotid arteries. The potential value of femoral arteries for improving the predictive capacity of traditional risk factors is an understudied area.

OBJECTIVES This study sought to evaluate the association of subclinical carotid and femoral plaques with risk factors and coronary artery calcium score (CACS) in middle-aged men.

METHODS Participants (n = 1,423) of the AWHS (Aragon Workers' Health Study), a study designed to assess cardiovascular risk and subclinical atherosclerosis in a cohort of middle-aged men (40 to 59 years of age), underwent carotid and femoral ultrasound plus noncontrast coronary computed tomography. Subclinical atherosclerosis was defined as the presence of any plaque in carotid or femoral arteries and/or CACS ≥1. Logistic regression models were used to estimate the prevalence of atherosclerosis adjusted for risk factors and age, to evaluate the association of atherosclerosis with risk factors, and to calculate areas under the receiver-operating characteristic curves for the presence of positive CACS.

RESULTS Subclinical atherosclerosis was found in 72% of participants. Plaques were most common in femoral arteries (54%), followed by coronary calcification (38%) and carotid plaques (34%). Association of atherosclerosis with risk factors was stronger in femoral arteries than carotid or coronary arteries. The area under the receiver-operating characteristic curve for prediction of positive CACS increased from 0.665 when considering only risk factors (dyslipidemia, current smoking, hypertension, diabetes, and age) to 0.719 when adding femoral and carotid plaques ($p < 0.001$). In this model, the femoral odds ratio (2.58) exceeded the carotid odds ratio (1.80) for prediction of positive CACS.

CONCLUSIONS Subclinical atherosclerosis was highly prevalent in this middle-aged male cohort. Association with risk factors and positive CACS was stronger in femoral than carotid arteries. Screening for femoral plaques may be an appealing strategy for improving cardiovascular risk scales and predicting coronary disease. (J Am Coll Cardiol 2016;67:1263–74) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CACS = coronary artery calcification score

CT = computed tomography

CVD = cardiovascular disease

HDL = high-density lipoprotein

ROC = receiver-operating characteristic

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality and disability in most countries (1). Approximately 30% of first acute events are fatal, and survivors often experience sequelae and a shortened life expectancy (2,3). Primary prevention is thus the best approach to fighting this pandemic disease. Current algorithms for risk detection, which combine behavioral, clinical, and biochemical markers, are of limited accuracy, and better risk stratification methods are definitely needed (4,5).

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Used in combination with traditional risk factors, data on subclinical atherosclerosis can provide additional information about the risk of myocardial infarction, stroke, and cardiovascular disease (CVD) mortality (6–8). Carotid wall intima-media thickness estimated from ultrasonographic images has been proposed as a surrogate measure of subclinical atherosclerosis (9). Whereas some prospective studies have shown that intima-media thickness adds predictive capacity to traditional risk prediction models (10), others have not been able to confirm this (7,8,11), and consequently, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for CVD risk prediction no longer recommends its measurement (5). A higher predictive value has been attributed to the presence of carotid plaques, which added a significant net reclassification index of 7.3% in the Framingham Offspring Study cohort (6) and up to 17.7% in subjects with intermediate CVD risk (clinical net reclassification index) in the ARIC (Atherosclerosis Risk In Communities) study (10). In this study, considering plaques together with intima-media thickness further boosted the reclassification index to 21.7%. Moreover, the association of plaque with events has been confirmed in a meta-analysis of 11 cohort studies including 54,336 subjects (12).

The potential value of studying the presence of atherosclerotic plaques in other vascular territories, such as the femoral arteries, for further improving the predictive capacity of traditional risk factors is an understudied area. In a post-mortem study in the Netherlands, the femoral artery was the artery most frequently affected by atherosclerosis among 5 peripheral vascular sites, including the common carotid artery (13). Moreover, recent data from the PESA (Progression of Early Subclinical Atherosclerosis) study have shown a higher prevalence of femoral compared with carotid plaques in an asymptomatic cohort composed of middle-aged men and women (14). With this background, we hypothesize that early femoral plaques would be more closely associated with traditional risk factors than carotid plaques and, furthermore, that calcification of coronary arteries assessed by computed tomography (CT) would be more associated with femoral than with carotid plaques. The analyses to investigate these hypotheses were conducted on data from the AWHS (Aragon Workers' Health Study), a prospective study designed to identify risk factors for the development of preclinical and clinical atherosclerosis (15).

METHODS

STUDY SAMPLE. Beginning in February 2009, factory workers at the General Motors automobile assembly plant in Figueruelas (Zaragoza, Spain) were invited to participate in the AWHS, a longitudinal cohort study that collected data during workers' programmed annual health examinations (15). After obtaining written informed consent, the research team gathered the clinical examination, collected blood and urine samples, and conducted questionnaires on cardiovascular and lifestyle risk factors. In addition, starting in 2011, all participants between 40 and 59 years of age were invited to undergo a noninvasive imaging exploration of subclinical atherosclerosis. Imaging included ultrasound measurements of the carotid and femoral arteries and CT to calculate the

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coronary artery calcium score (CACS). A total of 2,121 participants were recruited into the AWHS imaging study between January 2011 and December 2013 (2,013 men and 108 women, all Caucasians) and 1,564 completed the imaging exams in all targeted territories. Due to under-representation of the female sex in this cohort (only 80 women), women were excluded from the analysis, together with 61 male participants with incomplete cardiovascular profile data, rendering a final sample size of 1,423 male participants. The Aragon regional government's Ethics Committee for Clinical Research approved the study.

SUBCLINICAL ATHEROSCLEROSIS IMAGING. The presence of plaques in both carotid and femoral arteries was determined using the Philips IU22 ultrasound system (Philips Healthcare, Bothell, Washington). Ultrasound images were acquired with linear high-frequency 2-dimensional probes (Philips Transducer L9-3, Philips Healthcare), using the Bioimage Study protocol for the carotid arteries (16) and a specifically designed protocol for the femoral arteries (17) (Online Appendix). Plaque was defined as a focal structure protruding ≥0.5 mm into the lumen or reaching a thickness ≥50% of the surrounding intima, and all measurements were analyzed using electrocardiogram (ECG)-gated frames corresponding to end-diastole (R-wave) (16). Examination of the carotid territory included the terminal portion (10 mm) of the common carotid, the bulb, and the initial portion (10 mm) of the internal and external carotid arteries. The 20-mm segment of the common femoral artery, proximal to the bifurcation of the deep femoral artery, was considered in the search for femoral plaques. In all cases, plaques were recorded in both longitudinal and transverse planes to account for circumferential asymmetry.

CACS was obtained with a multidetector-row CT scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, the Netherlands) using a low-dose, prospectively ECG-triggered, high-pitch spiral acquisition protocol. During a single breath hold, images were acquired from the tracheal bifurcation to below the base of the heart. Scan parameters were 8 × 3 mm collimation, 220-mm field of view, 120 kVp, 55 mA, and 3-mm section thickness. Coronary calcium was quantified with calcium scoring software (Workspace CT viewer, Philips Medical Systems) that follows the Agatston method (18). The presence of coronary calcium was defined as any calcium score ≥1 and was considered to identify atherosclerotic disease of the coronary wall.

A positive finding for subclinical atherosclerosis was defined as the detection of at least 1 plaque in any of the segments studied with vascular ultrasound or a CACS ≥1 for coronary arteries. A variable termed "any atherosclerosis" was defined as positive if any of the 5 territories (coronary, both carotid, and both femoral arteries) was positive. A territory count was considered to also convey information about the extent of atherosclerosis, and participants were classified as disease-free (0 vascular sites affected) or as having focal (1 site), intermediate (2 to 3 sites), or generalized atherosclerosis (4 to 5 sites).

CLINICAL CHARACTERISTICS AND LABORATORY DATA. Clinical and laboratory data were obtained during the annual medical examination. All study procedures were described in standard operating procedures. The study protocols conform to the ISO9001-2008 quality standard. Clinical data included medical history, current medication, anthropometry, blood pressure, and heart rate. Blood pressure was obtained as the mean of 3 consecutive measurements with an OMRON M10-IT automatic oscillometric sphygmomanometer (OMRON Healthcare Co. Ltd., Kyoto, Japan), with the participant resting in a seated position for 5 min between readings. Arterial hypertension was defined as having systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication (19). Blood and urine specimens were collected after overnight (>8 h) fasting and were processed for laboratory analyses the same day. Fasting serum glucose, triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by spectrophotometry (Chemical Analyzer ILAB 650, Instrumentation Laboratory SpA, Bedford, Massachusetts). Low-density lipoprotein was calculated. Whole blood glycosylated hemoglobin was measured by reverse-phase cation exchange chromatography and quantified by double wavelength colorimetry (ADAMS A1c HA-810 Analyzer, Arkray Factory, Minneapolis, Minnesota). Dyslipidemia was defined as having total cholesterol ≥240 mg/dl, low-density lipoprotein cholesterol ≥160 mg/dl, HDL cholesterol <40 mg/dl, or self-reported use of lipid-lowering drugs (20). Diabetes was defined as fasting plasma glucose ≥126 mg/dl or self-reported treatment with hypoglycemic medication (19). Current smoking was defined as smoking in the present or having smoked in the last year. Being a former smoker was defined as a subject having smoked at least 50 cigarettes in his lifetime, but not having smoked in the last year. A variable was created counting how many of the following 4 risk factors were present: hypertension, dyslipidemia, diabetes, and current smoking. In addition, the estimation of 10-year ASCVD risk was calculated using the Pooled Cohort Equations for white males, which are on

TABLE 1 Baseline Characteristics of the Total Study Population and According to the Presence of Any Subclinical Atherosclerosis

	Total (N = 1,423)	No Atherosclerosis (n = 403)	Atherosclerosis in Any Territory (n = 1,020)	p Value (None vs. Any)
Baseline characteristics				
Age, yrs	51.0 ± 3.7	49.6 ± 4.1	51.6 ± 3.4	<0.001
BMI, kg/m^2	27.6 ± 3.3	27.1 ± 3.2	27.9 ± 3.3	<0.001
Systolic blood pressure, mm Hg	126.2 ± 13.9	123.3 ± 12.4	127.4 ± 14.3	<0.001
Diastolic blood pressure, mm Hg	83.2 ± 9.2	81.8 ± 8.7	83.7 ± 9.3	<0.001
Total cholesterol, mg/dl	223.1 ± 36.2	218.5 ± 36.1	224.9 ± 36.1	0.002
LDL-C, mg/dl	140.5 ± 31.6	136.7 ± 30.9	142.1 ± 31.7	0.004
HDL-C, mg/dl	52.8 ± 11.3	55.3 ± 11.8	51.8 ± 10.9	<0.001
Triglycerides, mg/dl	153.0 ± 96.0	136.2 ± 89.5	159.6 ± 97.7	<0.001
Fasting glucose, mg/dl	98.1 ± 16.6	97.2 ± 17.3	98.5 ± 16.3	0.196
HbA_{1c}, %	5.5 ± 0.5	5.4 ± 0.5	5.6 ± 0.5	<0.001
Lipid-lowering therapy	14.8 (210)	9.7 (39)	16.8 (171)	0.001
Antihypertensive therapy	20.3 (289)	11.9 (48)	23.6 (241)	<0.001
Antidiabetic therapy	3.3 (47)	1.7 (7)	3.9 (40)	0.056
Never smoker	31.8 (452)	45.9 (185)	26.2 (267)	<0.001
Former smoker	35.2 (501)	35.2 (142)	35.2 (359)	1.000
CV risk factors				
Dyslipidemia	50.9 (724)	40.2 (162)	55.1 (562)	<0.001
Total cholesterol ≥240 mg/dl	30.4 (432)	25.3 (102)	32.4 (330)	0.011
LDL-C ≥160 mg/dl	25.4 (355)	21.0 (83)	27.2 (272)	0.019
HDL-C <40 mg/dl	9.1 (129)	5.5 (22)	10.5 (107)	0.004
Hypertension	38.7 (550)	26.1 (105)	43.6 (445)	<0.001
Current smoking	33.0 (470)	18.9 (76)	38.6 (394)	<0.001
Diabetes	5.3 (76)	3.0 (12)	6.3 (64)	0.018
Number of CV risk factors				
0	20.7 (294)	34.2 (138)	15.3 (156)	<0.001
1	41.4 (589)	45.9 (185)	39.6 (404)	0.035
2	28.0 (399)	17.4 (70)	32.3 (329)	<0.001
>2	9.9 (141)	2.5 (10)	12.8 (131)	<0.001

Values are mean ± SD or % (n).

BMI = body mass index; CV = cardiovascular; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

the basis of age, total cholesterol, HDL cholesterol, treated or untreated systolic blood pressure, diabetes, and smoking status (5). ASCVD risk was classified as low (<5%), moderate (5% to 7.5%), or high (≥7.5%).

STATISTICAL ANALYSES. Data are expressed as mean ± SD or as percentages. Confidence interval (CI) width is 95% unless otherwise stated. Basic group comparisons were performed using the Student *t* and chi-square tests. Atherosclerosis prevalence and associated 95% CIs for each territory were calculated after adjusting for age and presented as estimations for an age of 50 years. These were calculated by risk factor count. We also calculated a more detailed table of prevalence, stratified not only by risk factor count, but also by specific combinations of risk factors. Estimates were computed from logistic regression models.

In addition, a logistic model including all of the considered risk factors was used to estimate the independent odds ratios of each risk factor adjusted for age (as a linear variable) for the presence of atherosclerosis in each explored territory. Finally, the association of the presence of plaques in the carotid and femoral arteries with positive coronary calcium was also studied with logistic regression models, adjusted for age (as a linear variable) and traditional risk factors, to estimate potential increases of the area under the receiver-operating characteristic (ROC) curve that may result from adding 1 or both peripheral atherosclerotic measurements to the logistic prediction model and to calculate diagnostic odds ratios. As a sensitivity analysis, we repeated this procedure to estimate the area increases above a logistic prediction on the basis of the calculated ASCVD risk. All statistical processing was performed with R statistical software (21), and ROC curves were calculated with the package pROC (22), using DeLong's methods.

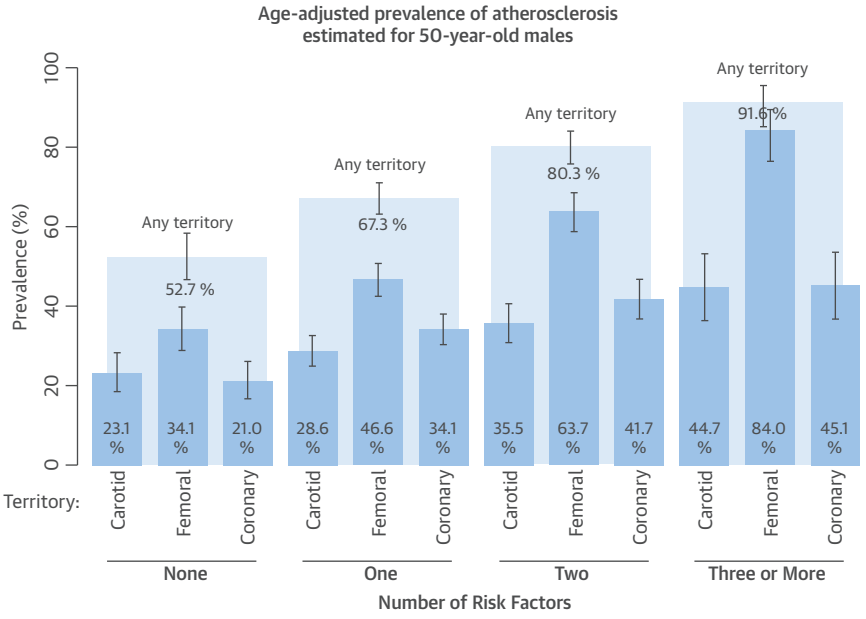
RESULTS

The studied sample included 1,423 men with a mean age of 51.0 ± 3.7 years. At least 1 atherosclerotic lesion was present in 1,020 participants (72%). Plaques were detected by ultrasound in 65% of participants (34% in the carotid and 54% in the femoral arteries), and 38% had positive coronary calcification (CACS 1 to 299 in 34.5% and ≥300 in 3.7%).

ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS WITH TRADITIONAL RISK FACTORS. Subclinical atherosclerosis was associated with higher prevalence, higher values, and higher number of known cardiovascular risk factors (Table 1). Figure 1 shows estimates of the expected prevalence and location of subclinical atherosclerosis at 50 years of age, depending on the participants' number of risk factors. Even for participants with no risk factors according to the National Cholesterol Education Program Adult Treatment Panel III thresholds, the estimated prevalence of atherosclerosis in at least 1 territory surpassed 50% and ranged between 21% and 34% for each individual vessel, whereas the calculated prevalence of atherosclerosis in at least 1 territory reached up to 92% for participants with 3 or more risk factors. Detailed age-strata exploration showed that the prevalence of any atherosclerosis rose among participants with no cardiovascular risk factors across the 5-year age strata from 35% (95% CI: 21% to 52%) in the 40- to 44-year age group to 65% (95% CI: 50% to 77%) in the 55- to 59-year age interval (Online Tables 1 and 2).

All traditional risk factors had independent effects on the presence of femoral subclinical atherosclerosis

FIGURE 1 Prevalence of Subclinical Atherosclerosis in Different Vascular Territories



Presence of atherosclerosis in each territory is adjusted for age and stratified by number of cardiovascular risk factors.

(Table 2). Current smoking was the independent factor most strongly associated with femoral and carotid plaques, whereas hypertension was the risk factor most strongly associated with the presence of coronary calcium. Only 76 participants had diabetes, and the adjusted association did not show statistical significance for diabetes in the carotid or coronary territories, whereas it was significant for femoral plaques. The accumulation of risk factors had a strong effect on femoral atherosclerosis, which was the territory that drove most of the rise in the association of risk factors with atherosclerotic presence in any territory (Table 2). Figure 2 shows odds ratios of traditional risk factors for subclinical atherosclerosis in each territory. In addition to dependence on modifiable risk factors, the odds of the presence of any atherosclerosis increased by 14% (95% CI: 10% to 18%) per year of age in the studied age range, independently of the existence of other cardiovascular risk factors. This increase was similar for all arteries (carotid: 11%; femoral: 10%; coronary: 13%).

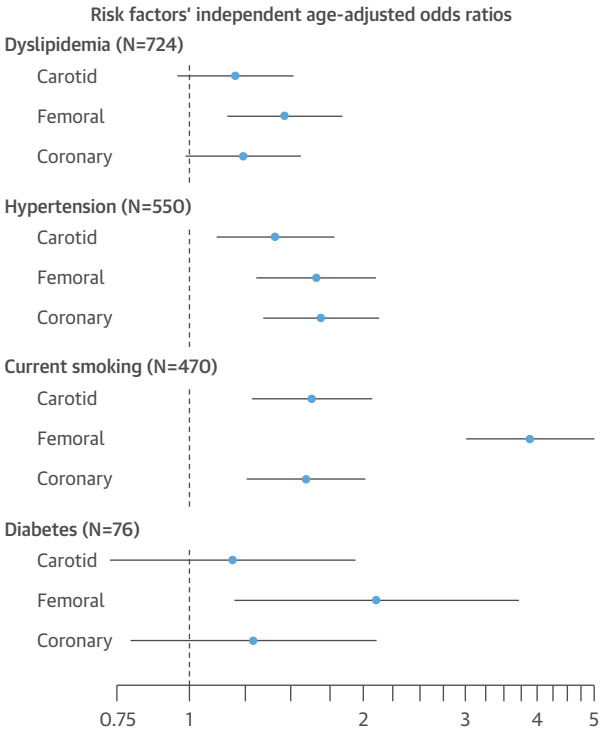
Online Table 3 shows additional data on the age-adjusted prevalence of subclinical atherosclerosis in the different examined locations, according to participants' numbers and types of risk factors.

TABLE 2 Odds Ratios of Subclinical Atherosclerosis Presence (vs. Absence) for CV Risk Factors (Age-Adjusted)

	n	Any Atherosclerosis (n = 1,020)	Carotid (n = 483)	Femoral (n = 772)	Coronary (n = 544)
CV risk factors					
Dyslipidemia	724	1.53 (1.19–1.96)	1.20 (0.96–1.51)	1.46 (1.17–1.83)	1.24 (0.99–1.55)
Hypertension	550	1.95 (1.49–2.56)	1.41 (1.12–1.78)	1.66 (1.31–2.10)	1.69 (1.34–2.13)
Current smoking	470	3.22 (2.40–4.33)	1.63 (1.28–2.07)	3.88 (3.01–5.00)	1.59 (1.26–2.01)
Diabetes	76	1.55 (0.79–3.02)	1.19 (0.73–1.94)	2.11 (1.20–3.70)	1.29 (0.79–2.10)
Number of CV risk factors					
0	294	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1	589	1.85 (1.38–2.48)	1.33 (0.97–1.84)	1.69 (1.26–2.26)	1.95 (1.40–2.70)
2	399	3.66 (2.57–5.20)	1.84 (1.31–2.58)	3.40 (2.47–4.69)	2.69 (1.91–3.79)
3 or 4	141	9.81 (4.92–19.56)	2.69 (1.75–4.15)	10.13 (5.94–17.30)	3.09 (1.99–4.78)

Values are point estimates (95% confidence intervals). Cardiovascular (CV) risk factors are ordered from highest to lowest prevalence in our sample.

FIGURE 2 Odds of Atherosclerosis Presence According to Traditional Risk Factors



Independent odds ratios of traditional risk factors for subclinical atherosclerosis in each territory adjusted for age.

The relationship between ASCVD 10-year risk and the extent of subclinical atherosclerosis is shown in Figure 3. Among participants at low 10-year risk (<5%), 57% had subclinical atherosclerosis, including 31% with intermediate or generalized disease. Of note, 88% of the participants evaluated as having high 10-year risk (≥7.5%) had subclinical atherosclerosis, with intermediate or generalized disease in 71%.

ASSOCIATION OF CAROTID AND FEMORAL PLAQUES WITH CORONARY CALCIFICATION. Femoral plaques were more strongly associated with CACS ≥1 than carotid plaques. Only 53 participants had a CACS ≥300, which is the threshold suggested in the 2013 ACC/AHA guidelines for recommendation of statin therapy in the absence of any other indication (4). Of these 53 participants, 50 had femoral plaques, whereas 34 had carotid plaques. Odds ratios of carotid and femoral plaques for detection of CACS ≥1 and of CACS ≥300 adjusted for cardiovascular risk factors and age are shown in Table 3. The area under the ROC curve for prediction of CACS ≥1, considering a model that included dyslipidemia, current smoking, hypertension, diabetes, and age (model 1), increased from 0.665 to 0.689 when the presence of carotid plaques was added into the model (model 2) ($p = 0.003$) and to 0.706 when the presence of femoral plaques was added (model 3) ($p < 0.001$). Including both carotid and femoral plaques into the model (model 4) was even better, providing an increase from 0.665 to 0.719 ($p < 0.001$) (Figure 4). In this extended model, the diagnostic odds ratio for detecting CACS ≥1 was 1.80 for carotid plaques and 2.58 for femoral plaques. Even more remarkable were the statistically significant differences between the areas under the ROC curves of the basic model (model 1) and the extended model including both carotid and femoral plaques (model 4) for prediction of CACS ≥300: in this case, the area under the ROC curve increased from 0.743 to 0.827 ($p < 0.001$) (Figure 4). In this model, the diagnostic odds ratio was 8.60 for the femoral arteries and 2.11 for the carotid arteries. Incremental areas under the ROC curves when considering subclinical atherosclerosis are shown in the Central Illustration. Remarkably, using ASCVD risk as the base model, an even greater increase in area was observed after taking plaque detection into account (Online Table 4, Online Figures 1 and 2).

DISCUSSION

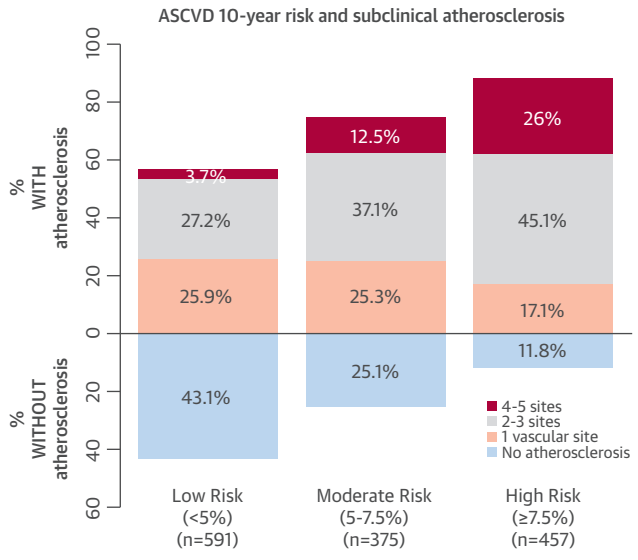
The most important findings of the present study are that subclinical atherosclerosis in an otherwise healthy middle-aged male cohort is most likely identifiable in femoral arteries, that femoral atherosclerosis shows the strongest association with cardiovascular risk factors, and that femoral plaques show a higher sensitivity than carotid plaques for the presence of calcified coronary disease (CACS ≥1 or ≥300) (Central Illustration). These results validate and further expand on those from the recently reported PESA study (Figure 5), which also showed a notably high prevalence of femoral subclinical atherosclerosis in middle-aged subjects, even among those without traditional risk factors (14). In addition, our work also confirms the inaccuracy of the overlap between risk estimated with clinical data and the actual presence and burden of subclinical atherosclerosis (14,23,24).

EARLY DETECTION OF ATHEROSCLEROSIS TO IMPROVE CARDIOVASCULAR RISK ASSESSMENT. Early detection and treatment initiation of patients in the process of developing atherosclerosis might be essential for improvement in the prevention of cardiovascular events. Attempts to incorporate carotid intima-media thickness as a marker of risk has yielded mixed data, succeeding in the ARIC study (10), but failing in others (7,8,11). In the meantime, the

evaluation of carotid plaques and coronary calcium scores appeared as valuable markers to increase the predictive capacity of traditional risk prediction models (12,25). Nonetheless, in the 2013 ACC/AHA guideline for CVD risk prediction, there is no mention of carotid ultrasound as a potential additional instrument for risk assessment (5). In the HRP (High Risk Plaque) trial (26), the presence of carotid plaques or positive coronary calcium score in an asymptomatic cohort 55 to 80 years of age predicted the risk of hard cardiovascular events after adjustment for the risk factor set described in the Framingham cohort. Although our study represents a cross-sectional analysis and therefore cannot yet evaluate clinical events, we aimed to complement the predictive models on the basis of traditional risk factors by comparing the presence, location, and extent of subclinical disease across different risk categories. Our results match those of the PESA study (14), showing that most subjects (88% in our study) classified as high risk using a well-established risk scale have subclinical atherosclerosis, with a high proportion having intermediate or generalized disease. More striking is the finding that subclinical atherosclerosis was also present in up to 57% of the AWHS participants considered to be at low risk (58% in the PESA cohort). These results further suggest an association of early atherosclerosis with characteristics not considered in standard risk scales, an aspect that needs further investigation. We propose that patients presenting with subclinical atherosclerosis, despite being classified at low risk, will be more likely to develop clinical events. Follow-up data from AWHS, and from other similar cohorts, will definitely clarify the clinical relevance and the predictive value of early detection of asymptomatic atherosclerosis in otherwise low-risk subjects.

FEMORAL PLAQUES AS A BETTER INDICATOR OF CARDIOVASCULAR RISK. Our data show differences in the association of cardiovascular risk factors with subclinical atherosclerosis in each specific territory. Although the CIs for the odds ratios were wide and partially overlapping, carotid artery atherosclerosis consistently showed a weaker association with traditional cardiovascular risk factors than that observed for femoral atherosclerosis. This might indicate that carotid subclinical atherosclerosis is less useful as a predictive marker than femoral findings. The femoral territory showed a tight association with the independent effect of risk factors, particularly with their confluence in the same person, suggesting that it better reflects the effect of these risk factors and discriminates individual

FIGURE 3 Presence of Subclinical Atherosclerosis According to Traditional Risk Equations



Presence and extent of subclinical atherosclerosis according to the 10-year risk for atherosclerotic cardiovascular disease (ASCVD) calculated using the Pooled Cohort Equations, classified as low (<5%), moderate (5% to 7.5%), or high (≥7.5%) risk.

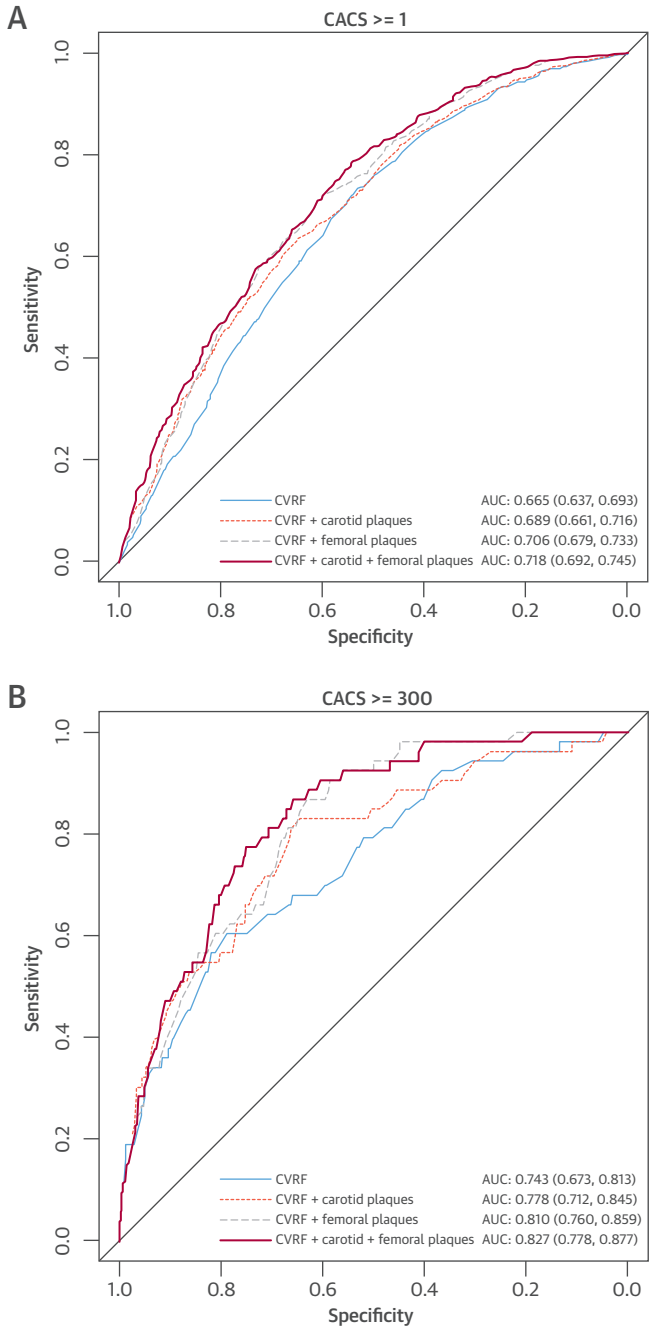
TABLE 3 Diagnostic ORs of Carotid and Femoral Plaques for Detection of Positive (≥1) or High (≥300) CACS, Adjusted for CV Risk Factors and Age, and Changes in Areas Under the Curve for Prediction

For Detection of:	Diagnostic OR	Area Under the Curve	p Value Carotid vs. Femoral	p Value vs. Base	p Value vs. Full
CACS ≥1 (n = 544)					
Model 1 (basic model)	-	0.665 (0.637–0.693)		(Ref.)	<0.001
Model 2 (+ carotid plaques)	2.04	0.689 (0.661–0.716)	(Ref.)	0.003	<0.001
Model 3 (+ femoral plaques)	2.80	0.706 (0.679–0.733)	0.137	<0.001	0.012
Model 4 (+ carotid plaques + femoral plaques)	1.80 2.58	0.719 (0.692–0.745)		<0.001	(Ref.)
CACS ≥300 (n = 53)					
Model 1 (basic model)	-	0.743 (0.673–0.813)		(Ref.)	<0.001
Model 2 (+ carotid plaques)	2.63	0.778 (0.712–0.845)	(Ref.)	0.046	0.003
Model 3 (+ femoral plaques)	9.91	0.810 (0.760–0.859)	0.142	0.001	0.088
Model 4 (+ carotid plaques + femoral plaques)	2.11 8.60	0.827 (0.778–0.877)		<0.001	(Ref.)

Area under the curve values are point estimates (95% confidence intervals). The basic model includes dyslipidemia, current smoking, hypertension, diabetes, and age. The 3 right columns show the statistical significance of the differences between the models: the first of these columns evaluates the area of the model that adds femoral plaques using the model that adds carotid plaques as a reference; the second column uses the base model as a reference; and the third column uses the full model as a reference.

CACS = coronary artery calcium score; CV = cardiovascular; OR = odds ratio; Ref. = reference.

FIGURE 4 Improvement in the Prediction of Coronary Calcification Conferred by Adding the Presence of Atherosclerosis in Different Territories to Classical Risk Factors

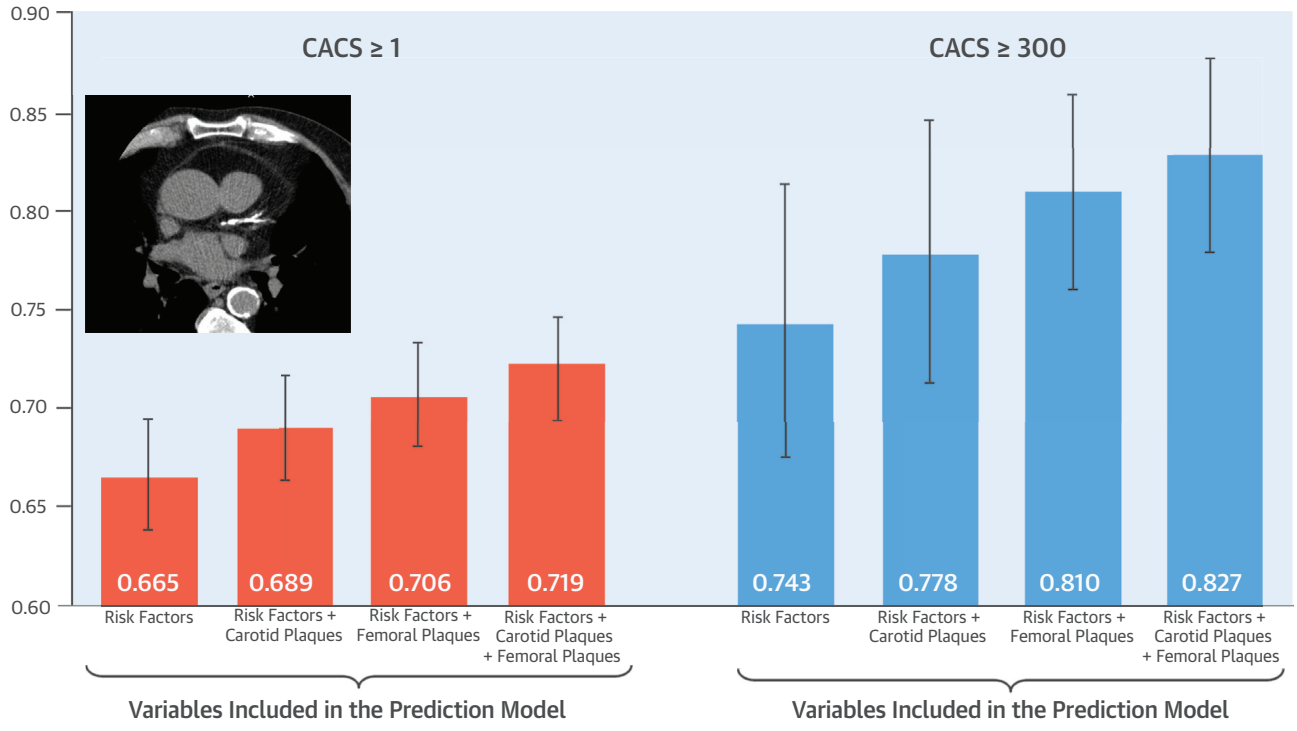


Receiver-operating characteristic curves for positive (≥1) **(A)** or high (≥300) **(B)** coronary artery calcium score (CACS), comparing models on the basis of only traditional cardiovascular risk factors (CVRF) (dyslipidemia, current smoking, hypertension, diabetes, and age) with models that additionally consider the presence of plaques in the carotid and/or femoral arteries. AUC = area under the receiver-operating characteristic curve.

susceptibilities to cardiovascular disease. However, the disproportionately high association of current smoking with femoral subclinical atherosclerosis might indicate that detection of femoral plaques is a less specific marker in smokers than in nonsmokers. Tobacco consumption is highly associated with lower extremity peripheral arterial disease (27), increasing the risk of this disease by 2- to 6-fold and the risk of intermittent claudication by 3- to 10-fold (28–30). Subclinical disease reproduces this known higher clinical effect of tobacco on the femoral arteries than on other territories: our data show that the prevalence of femoral plaques is much higher among current smokers. Nevertheless, in sensitivity analyses, the overall predictive capacity of femoral subclinical atherosclerosis was not affected by adjusting the models for former smoker status, and current smoking was not an effect modifier of the association of femoral plaques with positive coronary calcium (data not shown). Our conclusions can thus be applied to smokers and nonsmokers, but future studies should explore how these associations might change among smokers and how to control this potential problem.

FEMORAL PLAQUES FOR PREDICTION OF CORONARY CALCIFICATION. In autopsy studies, the presence of femoral plaques was much more strongly associated with coronary plaques and coronary deaths (31) than plaques in the common carotid arteries (32). As a clinical reflection of these anatomic studies, patients with symptomatic lower extremity peripheral artery disease are characterized by extensive and concomitant atherosclerosis in other territories and have a high risk of cardiac events (27,33), a risk even higher than that of ischemic limb events (33). In a study of CVD in older patients, 68% with peripheral artery disease had coexistent coronary disease (34). In the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial, >50% of patients who enrolled in the study because of peripheral artery disease had concomitant coronary or cerebrovascular disease (35), and the presence of symptomatic peripheral artery disease was associated with an approximately 4-fold excess of coronary events (36). One could argue that early, asymptomatic phases of peripheral artery disease might not show similar associations. However, men included in the ARIC study with an ankle-brachial index <0.90, an indicator of lower extremity peripheral artery disease, were twice as likely to have prevalent coronary heart disease (37). Together, these findings demonstrate that both early and late stages of lower-extremity arteriosclerotic disease are highly indicative of

CENTRAL ILLUSTRATION **Subclinical Atherosclerosis in Femoral Arteries: Area Under the ROC Curve for Positive CACS**



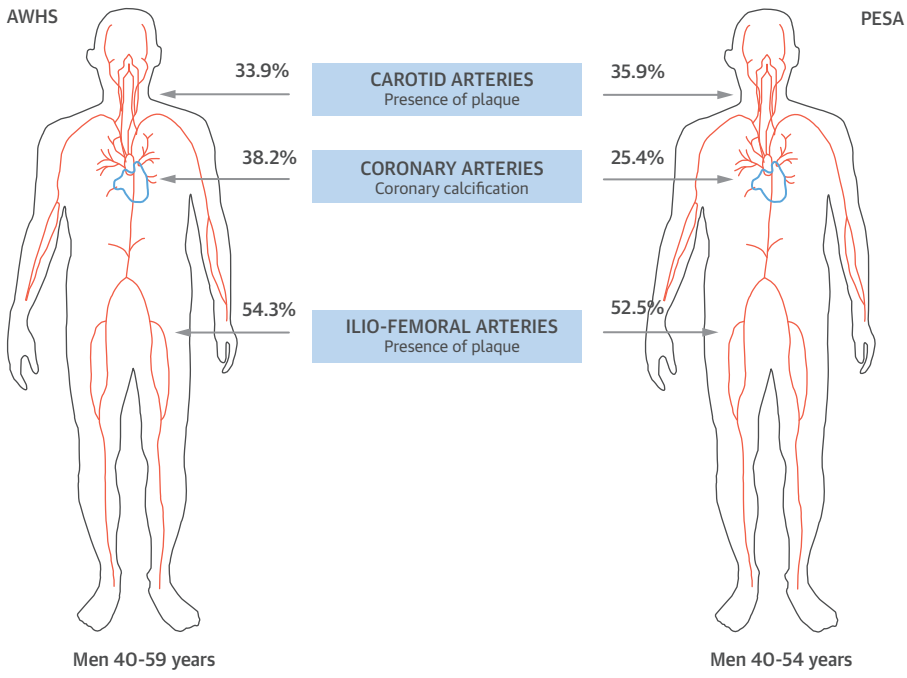
Laclaustra, M. et al. J Am Coll Cardiol. 2016; 67(11):1263–74.

Shown is the improvement in the prediction of coronary calcification conferred by adding the presence of atherosclerosis in different territories to classical risk factors. Areas under the receiver-operating characteristic (ROC) curve for prediction of positive (≥1) or high (≥300) coronary artery calcium score (CACS) are shown on the basis of age and cardiovascular risk factors alone and then taking into account the presence of carotid and/or femoral plaques.

generalized atherosclerosis and support our data indicating that early detection of femoral plaques has strong potential as a marker for coronary disease risk prediction. In fact, our analysis demonstrates that diagnostic accuracy for prediction of coronary calcification in asymptomatic subjects (used as the best available noninvasive surrogate for coronary atherosclerosis), using either individual risk factors or the Pooled Cohort Equations for risk estimation, can be significantly improved by considering the presence of carotid and/or femoral plaques, especially the presence of femoral plaques (Central Illustration).

STUDY LIMITATIONS AND STRENGTHS. Our study has several limitations. First, this is a cross-sectional analysis, which limits the temporal interpretation of predictive measurements. Second, because a positive coronary calcium score is only an indirect surrogate marker of clinical atherosclerotic disease, our data do not directly demonstrate a predictive clinical value for femoral plaques, and we cannot deduce that femoral atherosclerosis will be a better predictor of coronary events than carotid plaques. However, coronary calcium does reflect pathological alteration of the coronary arteries, and our findings therefore demonstrate an association of femoral plaques with situations in which the coronary territory is affected by atherosclerosis to a certain extent. Third, our sample is composed of middle-aged men, which limits generalizability of the findings, especially to women. In addition, extrapolation of our results to non-Mediterranean populations might also be imprecise, and for this reason, our results should be validated in other cohorts. Also, the relative influence of each risk factor within an individual territory must be interpreted with caution for 2 reasons: these comparisons did not form part of the design of this study, and the CIs were wide. Consequently,

FIGURE 5 Prevalence of Subclinical Atherosclerosis in 2 Contemporaneous Cohort Studies: AWHS and PESA



Prevalence of subclinical atherosclerosis by vascular territory in males in the AWHS (Aragon Workers' Health Study) and PESA (Progression of Early Subclinical Atherosclerosis) (8) studies.

conclusions about which risk factor might be the most influential are uncertain, with the exception of smoking, which had a strong signal.

Strengths of our study include the collection of clinical and imaging data according to strict protocols and the defined age range in this male population. Indeed, the homogeneous age profile and the restriction to men helped to control for the most important confounding factors. Potential confounders have been addressed in the regression models, and the prospective design of AWHS and other ongoing studies will eventually provide comprehensive information about the prospective predictive value of the measurements studied here.

CONCLUSIONS

The data presented here show that femoral atherosclerotic plaques are the most frequent subclinical atherosclerotic alterations in middle-aged men that are accessible by noninvasive diagnostic imaging. Compared with plaques in the carotid arteries, femoral plaques show stronger associations with traditional cardiovascular risk factors and with a positive coronary calcium score. Screening for femoral plaques, alone or together with carotid plaques, adds predictive value to traditional cardiovascular risk factors for the detection of coronary artery calcification. Assessment of femoral plaques with vascular ultrasound is an appealing strategy for predicting future coronary events and a potential tool for improving patient stratification to achieve more efficient primary prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The most frequently affected site at early asymptomatic stages of atherosclerosis is the femoral territory. Compared with plaques in the carotid arteries, femoral plaques show stronger associations with traditional cardiovascular risk factors and with the presence of coronary calcification.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Subclinical atherosclerosis is present in up to 57% of the AWHS participants who are considered to be at low risk when applying risk scales on the basis of traditional risk factors. This result further suggests an association of early atherosclerosis with characteristics not considered in standard risk scales, an aspect that needs further investigation.

TRANSLATIONAL OUTLOOK: Follow-up data from AWHS and from other similar cohorts will definitely clarify the clinical relevance and the predictive value of early detection of asymptomatic atherosclerosis in otherwise low-risk patients. Screening for femoral plaques, rather than carotid plaques, may be an appealing strategy for improving cardiovascular risk scales and predicting coronary disease.

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KEY WORDS cohort, computed tomography, risk assessment, ultrasonography

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