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ORIGINAL PAPER

Association between subclinical atherosclerosis burden and unrecognized myocardial infarction detected by cardiac magnetic resonance in middle-aged low-risk adults

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Aims Evidence on the association between subclinical atherosclerosis (SA) and cardiovascular (CV) events in low-risk populations is scant. To study the association between SA burden and an ischaemic scar (IS), identified by cardiac magnetic resonance (CMR), as a surrogate of CV endpoint, in a low-risk population.

Methods and results A cohort of 712 asymptomatic middle-aged individuals from the Progression of Early SA (PESA-CNIC-Santander) study (median age 51 years, 84% male, median SCORE2 3.37) were evaluated on enrolment and at 3-year follow-up with 2D/3D vascular ultrasound (VUS) and coronary artery calcification scoring (CACS). A cardiac magnetic study (CMR) was subsequently performed and IS defined as the presence of subendocardial or transmural late gadolinium enhancement (LGE). On CMR, 132 (19.1%) participants had positive LGE, and IS was identified in 20 (2.9%) participants. Individuals with IS had significantly higher SCORE2 at baseline and higher CACS and peripheral SA burden (number of plaques by 2DVUS and plaque volume by 3DVUS) at both SA evaluations. High CACS and peripheral SA (number of plaques) burden were independently associated with the presence of IS, after adjusting for SCORE2 [OR for 3rd tertile, 8.31; 95% confidence interval (CI) 2.85–24.2; $P < 0.001$; and 2.77; 95% CI, 1.02–7.51; $P = 0.045$, respectively] and provided significant incremental diagnostic value over SCORE2.

Conclusion In a low-risk middle-aged population, SA burden (CAC and peripheral plaques) was independently associated with a higher prevalence of IS identified by CMR. These findings reinforce the value of SA evaluation to early implement preventive measures.

Clinical Trial Registration Progression of Early Subclinical Atherosclerosis (PESA) Study Identifier: NCT01410318.

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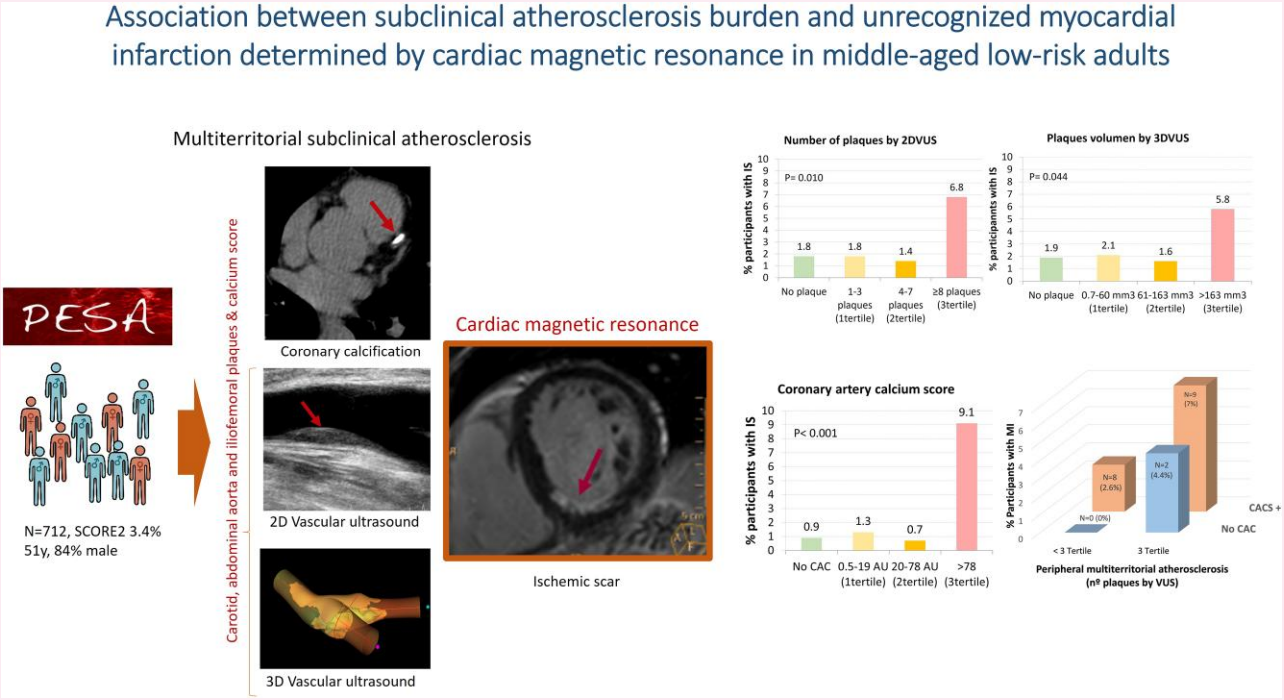
Graphical Abstract



Keywords cardiac magnetic resonance • subclinical atherosclerosis • ischaemic scar

Introduction

Atherosclerosis is a systemic disease that initiates early in life and develops decades before it becomes clinically manifest. This long pre-symptomatic period, commonly referred to as subclinical atherosclerosis (SA), offers the opportunity for screening using non-invasive imaging modalities. However, the class of recommendation in ESC guidelines for routine SA evaluation is still low (IIb) due to limited evidence.[1] Detection of coronary artery calcification (CAC), particularly if higher than 1000 AU, has been demonstrated to predict cardiovascular (CV) disease events[2] and to improve risk discrimination in several populations[3,4] whereas carotid plaque identification using vascular ultrasound (VUS) is considered by current guidelines a reasonable option when CAC score is not available for selected individuals.[1] In this line, the assessment of plaques at multiple territories (i.e. both carotids and/or carotid and femoral arteries) may increase predictive accuracy.[5,6] However, there is still scant evidence regarding the association of SA and CV events in low-risk populations.

Early identification of individuals at risk of CV events is crucial due to prognostic implications, the possibility of modifying the natural course of the disease through preventive measures, and the associated health system expenditures attributable to CV disease. Myocardial infarction (MI) represents a main clinical manifestation of atherosclerosis, that can lead to heart failure or cardiac arrest.[7] Previous studies have shown that silent or unrecognized MI, which can be detected by cardiac imaging, accounts for one-third to one-half of all MI[8,9] but provides prognostic significance comparable to that of clinically manifest MI.[10]

This study aimed to investigate the association between the presence, extent, and progression of SA (peripheral plaque by multiterritory 2D/3D VUS and CACS) and the identification of an ischaemic scar (IS) consistent with unrecognized MI by cardiac magnetic resonance (CMR)[11] in a middle-aged low-risk asymptomatic population.

Methods

Population and study design

The PESA (Progression of Early Atherosclerosis) is an observational prospective cohort study of 4184 asymptomatic, middle-aged (40–54 years on enrolment) individuals without known prior history of CV disease.[12] Participants were consecutively recruited from June 2010 to February 2014 and exhaustively screened for SA at enrolment and 3 years later. The PESA main objective is to study the prevalence and progression of SA by serial 2D and 3D multi-territorial VUS, and non-contrast cardiac computed tomography (CT). A sub-cohort of participants with documented SA on VUS or CT, the PESA advanced imaging cohort, underwent a CMR after the second SA assessment.[13] CV risk was assessed with the SCORE2 prediction algorithm calibrated to the 40–69-year-old European population that measures the risk of CV hard events at 10 years using the following variables: age, sex, smoking, blood pressure, diabetes, total and high-density lipoprotein cholesterol.[14] In addition, participants with SCORE2 < 2.5% were classified as low to moderate risk, whereas those with SCORE2 > 5% were classified as high or very high risk, according to the current guidelines.[1] Clinical follow-up was prospectively performed, and all cases of symptomatic MI from enrolment to CMR evaluation were registered. The institutional Ethics Committee approved the study protocol and all participants provided written informed consent.

Cardiac magnetic resonance

All studies were performed on a 3.0-T magnet (Achieva Tx, Philips Medical Systems), using a dedicated cardiac 32-channel phased-array surface coil and electrocardiographic synchronization. Steady-state free precession cine sequences were acquired with retrospective gating in 10–15 contiguous short-axis slices covering both ventricles from base to apex and reconstructed into 30 cardiac phases each for the evaluation of biventricular volumes and systolic

function. Late gadolinium enhancement (LGE) imaging was acquired in the same image positions as the cine images 10 min after the administration of gadolinium (Gadovist 0.2 mmol/Kg), using a prospectively triggered T1-weighted 2D segmented inversion recovery gradient echo sequence.

CMR images were analyzed using specialized software (ViewForum and Intellispace Portal, Philips, The Netherlands) by experienced researchers blinded to any clinical variable and SA data. On cine images, biventricular endocardial contours were manually traced in end-diastole and end-systole in all short-axis slices for the calculation of biventricular volumes and ejection fractions. Papillary muscles and trabeculations were included within the left ventricular (LV) cavity. LV and right ventricular (RV) volumes were indexed by body surface area calculated with Dubois's formula. LV epicardial contours were additionally measured in end-diastole to quantify LV mass. The presence of segmental wall motion abnormalities (hypokinesis, akinesis, dyskinesis) was assessed according to the American Heart Association 17 myocardial segment model.[15] Positive LGE scars were categorized as ischaemic when predominantly involving the subendocardium and following a coronary distribution, or non-ischaemic in case of a midventricular and/or subepicardial pattern.[16] The location and extent of LGE were also defined using the standard 17-segment model, and myocardial segments were assigned to coronary territories according to established criteria.[15]

Subclinical atherosclerosis assessment

The 2D/3D VUS and CT protocol has been previously described in detail.[12,17] Briefly, SA was defined as the presence of one or more atherosclerotic plaques[18] in the carotid, infra-renal abdominal aortic, or ilio-femoral territories by 2DVUS, or CACS ≥ 1. Global plaque volume by 3D VUS was calculated as the sum of plaque volumes in the bilateral carotid and femoral arteries. Ultrasound studies were analyzed with QLab10.2 and the Vascular Plaque Quantification (VPQ) tool (Philips Healthcare, Bothell, WA, USA), as reported.[12] Non-contrast CACS was calculated by the Agatston method[19] (IntelliSpace Portal, Philips). Atherosclerosis progression for each modality was defined using previously reported criteria: ≥ 2 point increase in the 2D VUS plaque number score, a ≥ 100% increase in 3D-global plaque volume, *de novo* atherosclerosis development defined as transitioning from absence of detectable atherosclerosis by 3DVUS at baseline to detectable atherosclerosis with plaque volume >0 at follow-up, and >2.5 change in the square-root method for CACS.[20]

Statistical analysis

Baseline characteristics were summarized as mean ± standard deviation or median (interquartile range) for continuous variables and count and percentages for categorical variables. Comparisons between participants with and without an IS, CACS, or high peripheral SA (above and below third tertile) were performed using chi-square or Fisher exact tests for categorical variables and the Student t or Wilcoxon signed rank tests for continuous variables. Linear trends across disease groups (defined by tertiles of plaque number and volume, and CACS) for the presence of IS were assessed by an extension of the nonparametric Wilcoxon rank sum test. Associations between SA and IS, adjusted by SCORE2, were estimated using the odds ratio (OR) with its 95% confidence interval (CI) and the beta coefficient (β) with its 95% CI. The additional value of CAC and high peripheral SA over SCORE2 to detect IS was assessed through the likelihood ratio test and net reclassification improvement (NRI). Statistical analyses were conducted using Stata 17 (StataCorp, College Station, TX, USA). A *P*-value < 0.05 was considered statistically significant.

Results

The study population was constituted of 712 PESA participants who underwent CACS and VUS on enrolment and 3-years later (median of 2.8, range 2.6–3.0 years), and a CMR study following the last SA evaluation (median of 1.2, range 0.9–1.6 years later). *Table 1* summarizes the study population characteristics at both SA evaluation timepoints. Median age was 48.6 years at enrolment (51.4 years at the second evaluation), and participants were predominantly men (83.6%). The most frequent risk factor was dyslipidemia, and most individuals were classified in low to moderate risk category according to the SCORE2 (61.2 and 60.1%, at the first and second evaluation, respectively). All participants had SA in line with the definition of the advanced imaging cohort: 92.5% individuals had some degree of peripheral plaque identified by VUS and 62.8% of individuals had positive CACS at enrolment on CMR evaluation, median LV ejection fraction was 60.7 (57.1–64%) and 5.6% of the participants showed regional wall motion abnormalities, mostly in the right coronary artery territory. A total of 132 (19.1%) participants had positive LGE. Of them, 20 (2.9%) participants presented an ischaemic LGE pattern fulfilling the diagnosis of unrecognized MI.[11] The right coronary artery territory was the most affected area in individuals with MI, particularly the basal inferior wall, followed by the left anterior descending artery and the left circumflex territories (50, 40, and 30%, respectively, Supplementary data online, *Figure S1*). During the lapse of time between enrolment and the CMR study, three patients had a symptomatic MI.

Subclinical atherosclerosis according to the presence of IS

Individuals with an IS on CMR (85% silent MI) had significantly higher SCORE2 at baseline and higher CACS and peripheral SA burden (number of plaques by 2DVUS and plaque volume by 3DVUS) at both SA evaluations (*Table 2*). In addition, individuals with IS on CMR showed a significant progression of CACS during follow-up.

As shown in *Figure 1*, participants with MI were mainly found in the highest tertiles of CACS and peripheral SA, as assessed by 2D or 3DVUS. When participants were classified according to the presence of CAC or high multi-territorial SA (*Table 3*), those with positive CAC showed a higher prevalence of IS, larger LV mass and biventricular end-diastolic and end-systolic LV volumes and lower biventricular ejection fractions, reaching all statistical significance. High CAC burden remained significantly associated with LV mass and the presence of IS (OR for the third tertile =8.31; 95% CI 2.85–24.2; $P < 0.001$) after adjustment for baseline risk (SCORE2). Moreover, high CAC burden provided significant additional value for IS identification (LR test $P < 0.001$) and improved participant classification over SCORE2 (NRI = 0.99, $P < 0.001$). Conversely, there was no association between the presence and burden of CAC and non-IS. In individuals with IS, a significant concordance between the territory of CAC and LGE was found for the right coronary artery and the left circumflex (see Supplementary data online, *Table S1*).

Similarly, participants with higher multi-territorial peripheral SA, determined as ≥8 plaques (highest tertile) by 2D VUS, had a significantly higher prevalence of IS and greater LV mass (*Table 3*). Likewise, high number of peripheral plaques was independently associated with IS after SCORE2 adjustment (OR = 2.77, 95% CI: 1.02–7.51; $P = 0.045$) and showed significant diagnostic value (LR test $P = 0.048$) and participant classification (NRI = 0.56, $P = 0.012$). Although the association between 3DVUS plaque burden and IS was no longer statistically significant after adjusting by SCORE2, 3DVUS plaque burden was still useful for patient reclassification (NRI = 0.51, $P = 0.020$). The combination of having both CAC and high peripheral plaque burden increased the probability of presenting an IS than high peripheral SA burden or CAC alone (*Table 4* and *Figure 2*). As occurred for CAC, there was no association between the burden of peripheral SA and the presence of non-IS.

Discussion

The main findings of our study are: (i) In a low-risk, middle-aged population, a higher SA burden (CACS and peripheral plaque) was

Table 1 CV risk factors, subclinical atherosclerosis, and CMR findings at baseline and 3-year follow-up

	N	Baseline evaluation	3-year evaluation
CV risk factors			
Age (years)	712	48.6 [44.7–51.9]	51.4 [47.8–54.8]
Dyslipidemia, *n* (%)	712	405 (56.9)	414 (58.1)
Obesity, *n* (%)	712	137 (19.2)	126 (17.7)
Hypertension, *n* (%)	711	130 (18.3)	164 (23.1)
Current smoking, *n* (%)	712	174 (25.0)	157 (22.1)
Diabetes, *n* (%)	712	29 (4.1)	38 (5.3)
SCORE2 (%)	684	3.30 [2.14–4.11]	3.37 [2.45–4.40]
hs-CRP mg/dL	712	0.11 [0.06–0.21]	0.10 [0.05–0.19]
Subclinical atherosclerosis			
2DVUS: number of plaques (*n*)	688	4 [2–7]	4 [2–8]
3DVUS: global plaque volume (mm^3)	692	75.2 [14.2–177.9]	77.8 [17.8–179.5]
–Carotid plaque volume (mm^3)	692	3.9 [0–37.4]	8.2 [0–39.5]
–Femoral plaque volume (mm^3)	692	45.3 [0–138.7]	50.3 [0–140.9]
CT: Coronary calcium score (Agatston units)	707	5.2 [0–33.4]	10.8 [0.0–64.4]
CACS 0	707	264 (37.2)	239 (33.8)
CACS 1–99	707	368 (51.8)	343 (48.5)
CACS 100–399	707	62 (8.7)	100 (14.1)
CAC >400	707	16 (2.3)	25 (3.6)
Cardiac magnetic resonance			
LVEDVI (mL/m^2)	712	—	81.4 [73.1–90.8]
LVESVI (mL/m^2)	712	—	32.1 [27.2–37.2]
LV ejection fraction (%)	712	—	60.7 [57.1–64.0]
LV Mass index (g/m^2)	712	—	48.7 [42.7–55.1]
Wall motion abnormalities, *n* (%)	712	—	40 (5.6)
RVEDVI (mL/m^2)	712	—	83.0 [74.0–93.9]
RVESVI (mL/m^2)	712	—	33.7 [28.0–39.5]
RV ejection fraction (%)	712	—	59.4 [56.1–63.0]
Late gadolinium enhancement		—	
Presence of LGE, *n* (%)	692	—	132 (19.1)
* Ischaemic	20	—	20 (2.9)
Subendocardial		—	16 (80%)
Transmural		—	4 (20%)
* Non-ischaemic	112	—	112 (16.2)

2DVUS, 2D vascular ultrasound; 3DVUS, 3D vascular ultrasound; CACS, coronary calcium score; CMR, cardiac magnetic resonance; CT, computed tomography; CV, cardiovascular; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVI, indexed left ventricle end-diastolic volume; LVESVI, indexed left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; RVEDVI, indexed right ventricle end-diastolic volume; RVESVI, indexed right ventricle end-systolic volume; RVEF, left ventricle ejection fraction.

independently associated with the presence of an IS; (ii) Both high CACS and multi-territorial peripheral SA burden detected by VUS provided significant diagnostic value over SCORE2; (iii) the probability of an IS was higher when both CACS and higher peripheral SA burden were present; (iv) there was no association between peripheral SA burden and the presence of non-ischaemic LGE.

Prevalence and implications of unrecognized MI

The presence of an IS, even if clinically silent, has been associated with poor cardiac performance and CV events, with a similar prognosis compared with clinically manifest MI.[21–23] The prevalence of subclinical MI as detected by CMR varies across studies, ranging from 0.2 to 35%,[23–25] largely depending on the age and overall CV risk of the populations studied. A metanalysis (including eight studies and 2009 individuals) aimed to confirm the prognostic impact of unrecognized MI, reported a median prevalence of 10.8%.[24] In the ICELAND MI cohort of the AGES-Reykjavik study that included 936 participants, with a more advanced age (67–93 years-old) and a larger proportion of diabetes, the occurrence of unrecognized MI was 17%.[16] In contrast, in the MultiEthnic Study of Atherosclerosis (MESA), which involved 1840 individuals with a mean age of 68 years and 48% females, ischaemic LGE was identified in 3.9%.[8] Our cohort showed a slightly lower prevalence of IS (2.9% including unrecognized and incident clinically manifest MI), which may be related to the different demographic characteristics of the PESA population (mean age 51 years) and the lower CV risk

Table 2 CV risk factors, subclinical atherosclerotic burden, and progression between patients with and without IS

	n	Absence of IS (*n* = 672)	Presence of IS (*n* = 20)	*P*-value
Baseline evaluation				
SCORE2	635	3.00 [2.12–4.10]	4.48 [3.05–5.46]	**0.009**
CAC presence, *n* (%)	690	417 (62.2)	16 (80.0)	0.079
CACS, HU	690	4.8 [0–31.2]	94.0 [16.9–315.1]	**<0.001**
2D plaque presence, *n* (%)	678	608 (92.3)	19 (100)	0.222
Number of 2D plaques	678	4 [2–7]	8 [2–11]	**0.019**
3D plaque presence, *n* (%)	633	492 (79.7)	15 (93.7)	0.139
3D plaque volume, mm^3	633	72.8 [11.6–172]	118.6 [44.6–296.9]	0.086
3-year evaluation				
SCORE2	632	3.36 [2.41–4.40]	3.71 [2.61–5.74]	0.102
CAC presence, *n* (%)	687	439 (65.7)	17 (89.5)	**0.021**
CACS, HU	687	10.1 [0–61.5]	159.8 [32.7–457.5]	**<0.001**
2D plaque presence, *n* (%)	668	594 (91.7)	19 (95.0)	0.498
Number of 2D plaques	668	4 [2–8]	9.5 [3–14.5]	**0.007**
3D plaque presence, *n* (%)	672	548 (84.0)	18 (90.0)	0.365
3D plaque volume, mm^3	672	76.9 [17.3–174.5]	238.1 [39.3–365.0]	**0.018**
3-year progression				
SCORE2	611	0.34 [−0.02–0.74]	0.51 [0.13; 1.26]	0.225
CAC progression, *n* (%)	569	138 (24.9)	11 (73.3)	**<0.001**
CACS, HU	686	3.6 [0–24.3]	74.0 [7.9; 159]	**<0.001**
2D plaque progression, *n* (%)	569	176 (31.8)	7 (46.7)	0.223
Δ Number of 2D plaques	657	0 [−1; 2]	1 [−1; 4]	0.278
3D plaque progression, *n* (%)	569	117 (21.1)	5 (33.3)	0.255
Δ 3D plaque volume, mm^3	615	0 [−20.9; 40.9]	9.2 [−38.2; 118.1]	0.527

CAC, coronary artery calcium; CACS, coronary artery calcium score. Significant *P* value (less than 0.05) in bold numbers.

profile (median SCORE2 of 3.37). Yet, the prevalence in this advanced imaging cohort of PESA (integrated by individuals with known SA) was higher than in other studies of general populations.[23,26]

Association between subclinical atherosclerosis and IS

To our knowledge, this is the first large-sized longitudinal study reporting the association between SA at different territories (CAC and peripheral plaque, including the carotid and femoral territory) and unrecognized or clinically incident MI in predominantly low-risk individuals. As a particularity of our study, previous cohorts (MESA, BioImage, Rotterdam, and Heinz Nixdorf Recall Studies) focused on higher-risk populations, and femoral vascular assessment was not included.[3,13,27–29] We found that the presence and burden of CAC and higher peripheral SA were significantly associated with a higher prevalence of ischaemic (but not of non-ischaemic) scar and larger LV mass, and biventricular volumes and lower ejection fractions. The association between SA burden (CAC or number of peripheral plaques) and IS was independent from the SCORE2 results suggesting that, in the presence of commonly considered CV risk factors (namely those included in the SCORE2), having a higher SA burden increases the risk of an unrecognized MI. One possible explanation is that the presence of SA reflects the effect of these 'classical' CV risk factors but also others, such as insulin resistance, inflammation, or genetic predisposition. Moreover, individuals with an IS showed a significantly larger progression of CAC during the preceding 3 years, thus suggesting 'active' atherosclerosis. The significant association between CACS and biventricular volumes might be the expression of atherosclerosis at the level of the microvasculature. Previous studies have demonstrated an association between CACS and myocardial involvement. In MESA, high local CACS was related to regional motion abnormalities in the corresponding coronary territory[30] and the progression of CAC over a median of 9.6 years was associated with increased LV volumes and incident heart failure.[31] Another publication from CARDIA found that higher CAC was associated with increased LV mass and volumes, and reduced LV longitudinal strain as assessed by echocardiogram.[32] The association of CAC and unrecognized or clinically incident MI has been also previously published in older populations with a higher risk. Thereby, in MESA and ICELAND MI, baseline CACS was significantly higher in participants with myocardial LGE,[8,33] and added significant diagnostic value over traditional risk factors.[8] Our results concur with these previous findings and, remarkably, extend them to a younger and consequently, lower risk cohort.

Regarding peripheral atherosclerosis, we observed that the presence of an IS was not associated with the mere presence of plaque (since it was present in near 92% of our cohort), but rather with a substantially high plaque burden. Thus, the fact of having high peripheral SA (defined as the higher tertile in the number of plaques or 3DVUS plaque volume) provided significant diagnostic value over SCORE2 and demonstrated a cumulative effect over CAC on the risk of an IS. This finding is interesting and reinforces the clinical utility of assessing peripheral SA by VUS,

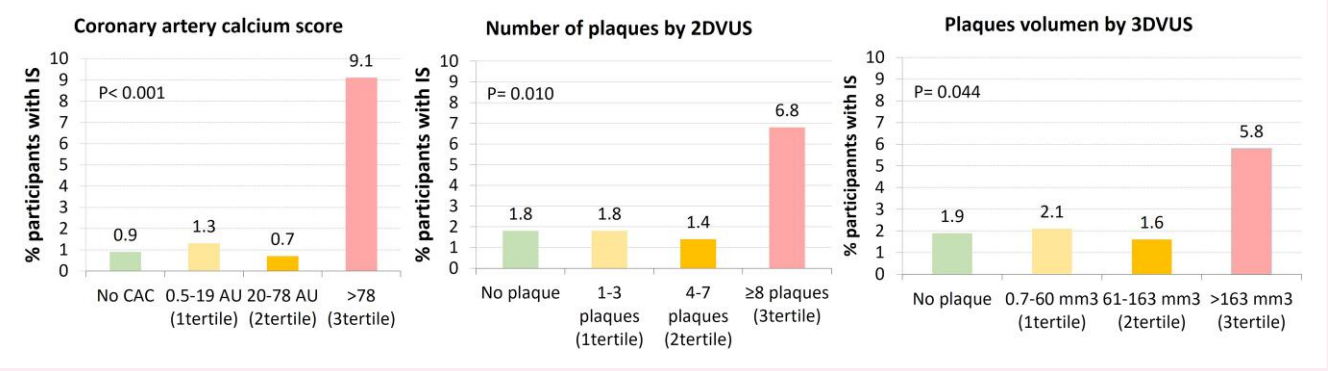


Figure 1 Prevalence of IS according to CAC, number of plaques by 2DVUS, and plaque volume by 3DVUS. CAC, Coronary artery calcification; MI, Myocardial infarction.

Table 3 CMR findings according to the presence of CAC or higher peripheral atherosclerosis burden by 2DVUS

	CAC			Peripheral atherosclerosis		
	Absence ($n = 239$)	**Presence ($n = 468$)**	***P***	**<Highest tertile (<8 plaques) ($n = 505$)**	**≥Highest tertile (≥8 plaques) ($n = 183$)**	***P***
LVEDVI (mL/m^2)	80.0 [71.8–88.9]	83.1 [73.9–91.2]	**0.011**	81.8 [73.2–90.8]	81.9 [73.3–91.1]	0.568
LVESVI (mL/m^2)	31.1 [26.3–36.1]	32.8 [27.8–37.9]	**0.002**	32.1 [27.1–37.4]	32.4 [27.4–37.5]	0.653
LVEF (%)	61.1 [58.0–64.6]	60.0 [56.8–63.6]	**0.015**	60.8 [57.1–63.8]	60.2 [56.9–64.2]	0.672
LVMI (g/m^2)	45.8 [39.4–53.2]	49.7 [44.1–55.9]	**<0.001**	48.4 [42.2–54.8]	49.0 [43.5–56.1]	0.130
Wall motion abnormalities	8 (3.3)	31 (6.6)	0.071	25 (4.9)	15 (8.2)	0.108
RVEDVI (mL/m^2)	81.2 [72.3–92.4]	83.8 [75.0–94.5]	**0.024**	83.7 [74.7–94.3]	81.4 [73.1–93.3]	0.184
RVESVI (mL/m^2)	31.8 [26.5–38.6]	34.4 [28.8–39.9]	**0.003**	34.4 [28.5–39.9]	32.7 [27.3–39.2]	0.114
RVEF (%)	60.2 [56.3–63.7]	59.0 [56.0–62.6]	**0.011**	59.3 [56–63]	59.7 [57–63.2]	0.168
LGE	32 (13.8)	98 (21.5)	**0.016**	82 (16.7)	44 (24.9)	**0.017**
Ischaemic	2 (0.9)	17 (3.7)	**0.031**	8 (1.6)	12 (6.8)	**0.001**
Non-ischaemic	30 (13.0)	81 (17.8)	0.108	74 (15.1)	32 (18.1)	0.348

CAC, coronary calcium score; LVEDVI, indexed left ventricle end-diastolic volume; LVESVI, indexed left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; LVMI, indexed left ventricle mass; RVEDVI, indexed right ventricle end-diastolic volume; RVESVI, indexed right ventricle end-systolic volume; RVEF, left ventricle ejection fraction; LGE, late gadolinium enhancement. Significant *P* value (less than 0.05) in bold numbers.

a radiation-free technique, and suitable to be repeated in follow-up evaluations. Intringly, although both peripheral SA measures provided significant value, the number of plaques but not the 3DVUS plaque volume remained significantly associated with IS after adjusting by CV risk factors. The most plausible explanation for this finding is that plaque volume has been demonstrated to be very closely related to CV risk factors[17] and because a higher number of plaques along the carotid and femoral arteries reflects a diffuse stage of atherosclerosis. The comparable results we obtained for CAC and VUS contrast with previous studies demonstrating the superiority of CAC over other measurements of peripheral SA, like carotid intima-media thickness, probably because VUS has demonstrated to better predict CV events than intima-media thickness,[6,34] which is no longer recommended for CV risk assessment because it rather reflects hypertensive or age-related changes.[1,35] In addition, in our cohort VUS examination was multi-territorial since it included both carotid, femoral arteries, and abdominal aorta. This approach has demonstrated diagnostic value, particularly VUS of femoral arteries, in low-risk populations and the ability to increase the prediction of cardiovascular events compared with the measurement from a single site.[6] In the BioImage study,[3] which included ~6000 asymptomatic adults (mean age of 68.9 years), the impact of peripheral SA (as assessed by VUS of both carotid arteries) and CAC was cumulative suggesting that both techniques may be complementary in estimating CV risk. We obtained similar results using IS on CMR as an outcome instead of clinical events, due to the young and low-risk PESA population. In this line, scarce information exists regarding associations between peripheral atherosclerotic plaques and IS determined by CMR. In the study by Barbier et al, the presence of ≥50% arterial stenosis at whole-body magnetic resonance angiography was not associated with the presence of unrecognized MI.[36] This finding might be related to the different methods to assess atherosclerosis (severity of stenosis vs. plaque burden) and the larger diagnostic value of a measurement of the extension of disease than the presence of 'focal' narrowing.

Table 4 CMR findings according to the presence of CAC and peripheral atherosclerosis by 2DVUS

	Non-peripheral plaque non-CACS ($n = 21$)	Peripheral plaque without CACS ($n = 211$)	CACS without peripheral plaque ($n = 35$)	Peripheral plaque with CACS ($n = 416$)	*P*-value for trend
LVEDVI (mL/m$_2$)	77.3 [69.4–88.0]	80.9 [72.8–89.4]	79.5 [71.6–90.8]	83.5 [74.2–92.1]	**0.005**
LVESVI (mL/m$_2$)	29.0 [24.0–38.6]	31.6 [26.4–36.1]	31.4 [25.3–36.3]	33.1 [28.1–38.1]	**0.001**
LVEF (%)	62 [59–65]	61 [58–64.5]	60.1 [57.8–64]	60 [56.7–63.4]	**0.011**
LVMI (g/m$_2$)	40.7 [36.9–47.1]	46.3 [40.2–53.8]	47.2 [41.7–53.9]	49.8 [44.4–56.0]	**<0.001**
Wall motion abnormalities	1 (4.8)	7 (3.3)	2 (5.7)	29 (7.0)	0.080
RVEDVI (mL/m^2)	80.7 [67.8–89.8]	81.4 [72.9–93.2]	82.3 [70.6–94.4]	84.3 [75.4–95.1]	**0.015**
RVESVI (mL/m^2)	29.1 [25.1–36.5]	32.6 [26.7–39.0]	33.9 [29.3–39.2]	34.5 [28.8–40.4]	**0.003**
RVEF (%)	61.5 [58.9–64]	60 [56.1–63.5]	58.4 [55.6–61.4]	59 [56–62.6]	**0.020**
LGE	3 (15.0)	28 (13.7)	5 (14.7)	88 (21.7)	**0.017**
Ischaemic	0 (0)	2 (1.0)	1 (2.9)	16 (3.9)	**0.041**
Non-ischaemic	3 (15.0)	26 (12.7)	4 (11.8)	72 (17.8)	0.120

CAC, coronary calcium score; LVEDVI, indexed left ventricle end-diastolic volume; LVESVI, indexed left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; LVMI, indexed left ventricle mass; RVEDVI, indexed right ventricle end-diastolic volume; RVESVI, indexed right ventricle end-systolic volume; RVEF, left ventricle ejection fraction; LGE, late gadolinium enhancement. Significant *P* value (less than 0.05) in bold numbers.

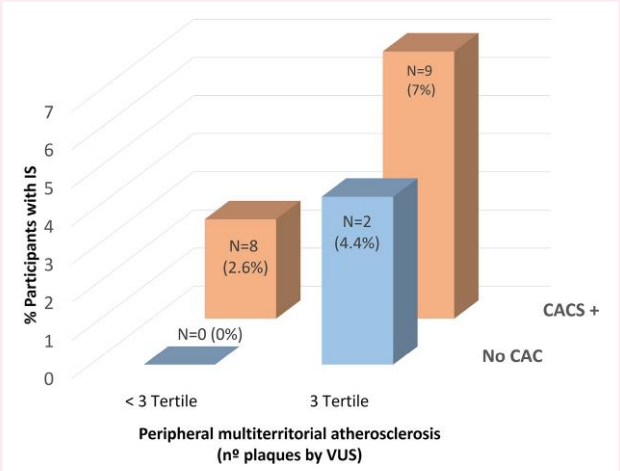


Figure 2 Cumulative prevalence of IS according to the presence of CAC and relevant peripheral SA (>highest tertile). CAC, Coronary artery calcification.

Our approach using IS assessed by CMR as an endpoint also helped us to evaluate cardiac performance, confirming that individuals with SA also displayed slightly lower biventricular ejection fraction and higher volumes, albeit parameters remained within normal values. Altogether, our results, performed in a low-risk population, support the usefulness of SA detection in order to identify individuals at a higher risk and implement primary or secondary prevention measures from early stages to avoid adverse evolution towards LV dysfunction, heart failure, or cardiac sudden death.

Several limitations should be acknowledged. CMR was performed in the advanced imaging cohort of PESA population (with known pre-existing SA) and consequently, the range of values for SA (i.e. absence of SA at any location, particularly in the case of peripheral plaque) was reduced, affecting the statistical power to detect differences and the extrapolation of results to the general population. The prevalence of IS was low also affecting the statistical power to observe differences. In addition, as CMR was performed once we cannot know if the IS was present at enrolment or manifested during follow-up. Clinical outcomes are still scarce, but a planned long-term PESA follow-up is ongoing.

Conclusions

In a low-risk middle-aged population, SA burden assessed by CAC and multi-territorial peripheral VUS were independently associated with the presence of IS assessed by CMR and provided additional diagnostic value over CV risk factors. These findings reinforce the value of identifying and quantifying SA even in low-risk individuals to implement prevention measures from early stages and thus avoid adverse CV events.

Authors' contributions

L.F.F., B.I., and V.F. designed the study protocol. L.F.F. and A.G.A. reviewed imaging and clinical data, reviewed previous literature, and drafted the manuscript. I.G. performed the imaging analysis of CMR studies. I.G.L., A.M., and S.G.T. participated in the interpretation of the data. C.P.H. helped in the study organization. J.S.G. and V.M.V. reviewed the imaging protocol. A.G.A., X.R., and B.O. made the statistical analysis. H.B., A.F.O., B.I., and V.F. reviewed the manuscript writing.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest. J.S.-G. is an employee of Philips Healthcare.

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Data availability

It is feasible as far as it is required.

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