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A new score for improving cardiovascular risk prediction and prevention

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Abstract *Background and aims:* The ultrasonographic detection of subclinical atherosclerosis (scATS) at carotid and femoral vascular sites using the atherosclerosis burden score (ABS) improves the risk stratification for atherosclerotic cardiovascular disease beyond traditional cardiovascular (CV) risk factors. However, its predictive value should be further enhanced. We hypothesize that combining the ABS and the Framingham risk score (FHRS) to create a new score called the FHRABS will improve CV risk prediction and prevention. We aim to investigate if incorporating the ABS into the FHRS improved CV risk prediction in a primary prevention setting.
Methods and results: 1024 patients were included in this prospective observational cohort study. Carotid and femoral plaques were ultra-sonographic detected. Major incident cardiovascular events (MACEs) were collected. The receiver operating characteristic curve (ROC-AUC) and Youden's index (Ysi) were used to compare the incremental contributions of each marker to predict MACEs.

After a median follow-up of 6.0 ± 3.3 years, 60 primary MACEs (5.8%) occurred. The ROC-AUC for MACEs prediction was significantly higher for the FHRABS (0.74, $p < 0.024$) and for the ABS (0.71, $p < 0.013$) compared to the FHRS alone (0.71, $p < 0.46$). Ysi or the FHRABS (42%, $p < 0.001$) and ABS (37%, $p < 0.001$) than for the FHRS (31%). Cox proportional-hazard models showed that the CV predictive performance of FHRS was significantly enhanced by the ABS (10.8 vs. 5.5, $p < 0.001$) and FHRABS (HR 23.30 vs. 5.50, $p < 0.001$).
Conclusions: FHRABS is a useful score for improving CV risk stratification and detecting patients at high risk of future MACEs. FHRABS offers a simple-to-use, and radiation-free score with which to detect scATS in order to promote personalized CV prevention.
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1. Introduction

Traditional risk scales, such as the Framingham risk score (FHRS) equation, based on well-established risk factors for atherosclerotic cardiovascular disease (ASCVD) are a cornerstone of cardiovascular (CV) risk stratification from a clinical point of view, despite their limited accuracy in predicting future atherosclerotic CV events (CVEs) [1–3]. However, a substantive percentage of the at-risk population remains unidentified until their first clinical event, showing the modest impact of these scales in classifying individual CV risk [4]. Because atherosclerosis (ATS) is a slowly progressive focal and disseminated disease that occurs for many years before any CVE, it provides a rare opportunity for early detection to promote personalized prevention. While invasive coronary angiography is the gold standard in the detection of clinical coronary ATS, the assessment of extra-coronary subclinical atherosclerosis (scATS), especially at carotid sites, has shown potential in improving CV risk stratification than FHRS in predicting future CVEs [5–10]. Furthermore, the results from the CAFES-CAVE study, in which even the presence of carotid or femoral plaques exhibited a similar predictive value for CVEs, show that the co-occurrence of carotid and femoral plaques further increased the risk [11]. Similar results from other studies show that scATS detection in femoral arteries can enhance CV risk assessment as compared to ATS evaluation in carotid arteries alone [12–16]. The PESA (Progression of Early Subclinical Atherosclerosis) study, which evaluated the prevalence of scATS in asymptomatic middle-aged individuals in multiple vascular beds, showed that 60% of the participants classified “at low CV risk” presented multi-vessel scATS with high prevalence in both carotids and ilio-femoral arteries [17]. In addition, we previously highlighted the added value of multi-site scATS assessments on FHRS to predict the presence and extension of coronary artery disease using the ultrasonographic atherosclerosis burden score (ABS), which quantifies the number of carotid and femoral arteries containing plaques [18,19].

However, even if the multi-vessel detection of extra-coronary scATS results in a better stratification of CV risk, its assessment was previously advocated as a complementary method for predicting CV risk, whilst its synergistic power with FHRS as a combined score had not been tested until now [20–23]. In the present study, we hypothesized that the prediction of ASCVD risk could be enhanced by combining the traditional FHRS with the presence and extent of scATS via ABS, the resulting score being called the FHRABS.

2. Methods

2.1. Study population

The Lausanne Atherosclerosis Cohort Study is an observational, prospective, population-based cohort study carried out at the Lipid Clinic and Angiology Center of the University Hospital of Lausanne (Centre Hospitalier Universitaire Vaudois, CHUV). Between 1994 and 2008, 1024 consecutive patients without clinical evidence of cardiovascular disease (CVD) referred for evaluation of their CV risk and for therapeutic advice were included in the study.

All patients included in the study were referred by their primary care physician for CV risk assessment at our center. Accordingly, all study procedures were part of a routine standard consultation for CV risk assessment. Consequently, there was neither for the center neither for the patient any additional cost as compared to a standard angiology CV risk evaluation performed at our center.

All the participants underwent a baseline visit integrating clinical interviews, standardized lifestyle questionnaires, a physical examination and fasting blood draw, and ultrasonographic (US) measurement for ATS detection in the carotid and femoral territories. All the study participants were prospectively followed up for a period up to 14 years to record their personal clinical history. Patients which were lost at follow-up were not included in the study. The study was carried out in accordance with the Helsinki Declaration and was approved by the local Swiss ethics committee. All the participants provided informed written consent. The data and analyses are presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [24].

2.2. Assessment of CV risk factors and CV risk score: definitions

Clinical, anthropometric, and laboratory data were collected according to a standardized study protocol. All the study participants underwent a detailed medical examination and a standardized interview asking for sociodemographic, personal and family medical history, and medication anamnesis information.

Traditional CV risk factors were assessed, i.e., dyslipidemias, smoking, hypertension, diabetes, obesity, and a family history of premature CV disease [25]. The traditional CV risk factors were defined as follows:

i) Age: men $\geq$45 years; women $\geq$55 years;
ii) Diabetes mellitus: fasting plasma glucose $\geq$126 mg/dL (>6.99 mmol/L) or the use of insulin and/or oral hypoglycemic medication;
iii) Hypertension: systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or the current use of antihypertensive medication;
iv) Hypercholesterolemia: total cholesterol $\geq$240 mg/dL (>6.21 mmol/L), low-density lipoprotein cholesterol (LDL) $\geq$160 mg/dL, ($\geq$4.14 mmol/L), or the use of lipid-lowering drugs;
v) Low-high-density lipoprotein cholesterol (HDL) < 40 mg/dL, (<1.04 mmol/L);
vi) Hypertriglyceridemia: triglycerides (TG) > 200 mg/dL, (>2.29 mmol/L);
vii) Smoking: self-reported current smoking status;

viii) Family history of coronary heart disease (CHD): first-degree relatives with CHD diagnosed, <55 years of age in men, and <65 years of age in women.
ix) Obesity, considered as a body mass index (BMI) ≥ 30 kg/m^2).

Blood samples were drawn from every participant from the cubital vein or one of its branches in the supine position and sent to our central laboratory for immediate analysis. The lipid profile was determined from blood samples obtained after 12 h of fasting using standard assays.

HDL cholesterol, triglycerides, and total cholesterol levels were measured with standard methods.

LDL cholesterol was calculated according to the Friedewald formula [26].

FHRS, is recommended by the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATP-III) guidelines for the identification of high-risk individuals for lipid-lowering treatment. The FHRS model considers six traditional risk factors, age, sex, smoking, hypertension, HDL-C, and total cholesterol, to estimate a person's absolute 10-year risk of incident CHD.

Therefore, in the present study, for each subject, FHRS was calculated based on age, smoking, diabetes, blood pressure (treated and untreated), cholesterol and HDL-cholesterol.

The individual Framingham risk equations were then used to calculate the predicted risk of developing CHD events over the next 10 years. Subjects were divided into 3 risk categories based on their 10-year FHRS: low CHD risk: 0–1 risk factors (<10%); intermediate CHD risk: $\geq$2 risk factors and 10-year risk (<20%); high risk: 10-year CHD risk >20% and/or diabetes mellitus as a CHD equivalent according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines [25].

2.3. US assessment of ABS

All the arterial scans were performed by stren operator using color B-mode ultrasound systems connected to a 7–10 MHz linear array transducer. For arterial wall analysis, the system was equipped with the M'ATH software (Metris, Paris, France), which performs semvai-automatic measurements on frames.

Both left and right carotid and femoral arteries were examined (four arterial sites). The carotid investigation included the common carotid artery, the carotid bulb, and the origin of the internal and external branches. Femoral arteries were examined from 4 cm above the bifurcation spur to 4 cm in the femoral superficial branch in addition to the origin of the profound branch. To acquire the best image resolution, all the images were acquired at a maximal depth of 4 cm, ensuring the best screen resolution. All the plaques were analyzed by transversal and longitudinal scanning in all the above-described arterial segments. An ATS plaque was defined as a focal intima–media thickening (IMT) $\geq$ 1200 μm protruding into the arterial lumen or $\geq$ 50% focal thickening [28,29].

2.4. Definition of scATS and ABS calculation

ScATS was defined as the presence of ATS plaques in each of the carotid or femoral territories. The number of affected vascular sites (right/left carotid and right/left femoral arteries) was used to determine the extent of scATS.

The ABS, ranging from 0 to 4, was calculated by quantifying the number of arterial sites with at least one plaque. Thus, the participants were classified into three categories of CV risk based on the ABS: low-risk, ABS 0 (i.e., the absence of an ATS plaque); intermediate-risk, ABS 1 (i.e., the presence of at least one ATS plaque in one of the four explored arterial sites); high-risk, ABS 2–4 (i.e., the presence of ATS plaques on two or more explored arterial sites).

2.5. Definition of FHRABS

FHRABS (1–7) was created by combining the FHRS (1–3) and ABS (0–4) scores. The patients were classified into three categories of CV risk as follows: low-risk, score = 0–1; intermediate risk, score = 2–3; high risk, score = 4–7.

2.6. Endpoints

Information on CVEs affecting the participants during the study period was collected during the follow-up visits or by phone calls.

The primary endpoint included all major incident cardiovascular events (MACEs) such as CV death, acute myocardial infarction, coronary revascularization, stroke, or the revascularization of peripheral artery disease.

2.7. Statistical analysis

The baseline characteristics are presented as the mean $\pm$ SD or median for continuous variables, and percentages for categorical variables. The differences between continuous variables and categorical variables were tested with unpaired t-tests and $\chi 2$ tests, respectively. Variables with non-normal distributions were log-transformed before comparison.

The distribution of the ABS and FHRABS according to the 10-year FHRS was also explored.

The incidence of MACEs was analyzed according to the FHRS, ABS, and FHRABS categories, in all the sample populations and by sex.

Receiver operating characteristic curve analysis (ROC) was performed to evaluate the performance of the FHRS, ABS, and FHRABS in predicting the presence of scATS and CVEs. The sensitivity and specificity and the optimal cut-off values were calculated. The Youden Index (*Ysi*) was also calculated. It is a measure of diagnostic accuracy of a diagnostic marker enabling the identification of optimal cutoff value (cutoff point) for the diagnostic marker. Overall, Ysi represents a global measure of a test performance, used in assessing the discriminatory power of a diagnostic procedure. It is computed by subtracting 1 from the sum of the

Table 1 Baseline Characteristics of the study population (n = 1024 subjects).

	Overall (n = 1024)	Men (n = 620)	Women (n = 404)	Statistical difference p-value (men vs women)
Characteristics				
Age, years	49.2 ± 12.4	49.2 ± 11.4	49.3 ± 13.9	0.933
Cholesterol, mg/dL (mmol/L)	268.1 ± 73.1 (**6.93 ± 1.89**)	264.6 ± 77.0 (**6.84 ± 1.99**)	273.4 ± 66.5 (**7.07 ± 1.72**)	0.060
LDL-C, mg/dL (mmol/L)	175.4 ± 57.0 (**4.54 ± 1.47**)	172.2 ± 53.7 (**4.45 ± 1.39**)	180.0 ± 61.1 (**4.65 ± 1.58**)	0.044
HDL- C, mg/dL (mmol/L)	53.4 ± 18.5 (**1.38 ± 0.48**)	47.8 ± 15.7 (**1.24 ± 0.41**)	62.0 ± 19.3 (**1.6 ± 0.50**)	<0.001
Triglycerides ($\log_{10}$), mg/dL (mmol/L)	2.1 ± 0.29 (**0.25 ± 0.33**)	2.26 ± 0.35 (**0.31 ± 0.35**)	2.20 ± 0.33 (**0.16 ± 0.29**)	<0.001
BMI, kg/m^2	25.4 ± 4.2	26.0 ± 3.8	24.5 ± 4.7	<0.001
Systolic Blood Pressure, mmHg	129.0 ± 15.6	131.5 ± 14.1	125.1 ± 16.9	<0.001
Diastolic Blood Pressure, mmHg	80.6 ± 10.0	82.0 ± 9.8	78.4 ± 9.9	<0.001
CV Risk Factors				**p-value**
Age as risk factor[a]	551 (54)	394 (64)	157 (39)	<0.001
Family History of CVD[b]	145 (14)	78 (13)	67 (17)	0.072
Hypertension[c]	237 (23)	155 (25)	82 (20)	0.081
Total Cholesterol>240 mg/dL, (>6.21 mmol/L)[d]	578 (56)	323 (52)	255 (63)	<0.001
HDL-C <40 mg/dL, (<1.04 mmol/L)	251 (25)	206 (33)	45 (11)	<0.001
Triglycerides >200 mg/dL, (>2.29 mmol/L)	318 (31)	231 (37)	87 (22)	<0.001
Current smoking	304 (30)	203 (33)	101 (25)	0.008
Diabetes mellitus	52 (5)	36 (6)	16 (4)	0.188
Obesity	136 (13)	80 (13)	56 (14)	0.659
CV Risk Factors				**p-value**
0 CV risk factor	77 (8)	26 (4)	51 (13)	<0.001
1 CV risk factor	214 (21)	119 (19)	95 (23)	0.193
2 CV risk factors	331 (33)	194 (31)	137 (34)	0.561
3 CV risk factors	235 (23)	160 (26)	75 (18)	0.037
4-8 CV risk factors	167 (16)	121 (20)	46 (12)	0.003

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; CV, cardiovascular.
[a] Age as risk factor, i.e. women ≥55 years Men ≥45 years.
[b] First-degree with CHD diagnosed, <55 years of age in men, and <65 years of age in women.
[c] Systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or the current use of antihypertensive medication.
[d] Total cholesterol ≥240 mg/dL (>6.21 mmol/L), low-density lipoprotein cholesterol ≥160 mg/dL, (≥4.14 mmol/L), or the use of lipid-lowering drugs. Continuous data are expressed as mean ± standard deviation; categorical variables are expressed as number and (%).

test's sensitivity and specificity, which is expressed not in percentage but as a part of an all-number, i.e., Ysi (sensitivity + specificity) − 1. For a test with a poor diagnostic accuracy, the Youden's index is 0, whereas the Ysi for a perfect test is 1 [27].

The Kaplan−Meier analysis with the log-rank test was used to estimate the difference in the cumulative incidence of MACEs stratified by the different categories of CV risk estimated by the FHRS, ABS, and FHRABS. Cox's proportional-hazard models were constructed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the CV outcomes from the FHRS, ABS, and FHRABS. A $p < 0.05$ was considered significant. Statistical analyses were conducted with Stata version 16 (Stata Corp., College Station, Texas).

3. Results

3.1. Baseline characteristics of the sample

Table 1 summarizes the baseline characteristics and the CV risk factors of the 1024 patients, stratified by sex. The majority (60%) were men, and the mean age of the participants was 49.2 years.

The most prevalent traditional risk factor was hypercholesterolemia (56%), followed by smoking (30%), hypertension (23%), family history (14%), and diabetes mellitus (5%). Additionally, obesity was found in 13% of our cohort.

The prevalence of traditional risk factors was significantly higher in men, except for hypercholesterolemia (63% women and 52% men) and family history (17% women and 13% men).

Most of the participants (92%) had at least one traditional risk factor, 31% had two risk factors, and 39% had ≥3 risk factors. Regarding sex, more of the men had more than one risk factor compared to the women (96% vs. 87%, $p < 0.001$).

3.2. Vascular risk stratification based on FHRS, ABS, and FHRABS

According to the FHRS, most of the participants (60%) were classified as being at low 10-year CHD risk, compared to 27% at moderate risk and 13% at high risk. Higher proportions of men compared to women were at moderate and high risk (33% and 18%, respectively, vs. 20% and 5%; p-value < 0.001). For ABS, 45% of the patients were stratified at low-risk, 15% at intermediate risk, and 40% at high risk, with statistical differences in the ABS categories distribution between men and women for the low-risk (38% vs. 55%; p < 0.001) and for the high-risk groups (46% vs. 31%). For the FHRABS, 34%, 33%, and 33% of population was categorized into the low-, intermediate-, and high-risk categories, respectively.

A statistically significant differences in FHRABS risk categories distribution between men and women were found in the low-risk (25% vs. 47%; p-value < 0.001) and high-risk categories (41% vs. 21%; p-value < 0.001) (Supplementary Material, Table 1).

3.3. Distribution of ABS and FHRABS according to 10-year FHRS

The relationships between the ABS and FHRABS according to the FHRS are shown in Fig. 1 (A, B). Among the patients classified in the low 10-year FHRS group, 43% showed scATS, with a higher proportion (27%) of patients with generalized disease according to the ABS (high ABS, i.e., 2–4 plaques detected). By contrast, 30% of the patients with an intermediate FHRS were free of scATS, this percentage reaching 19% for patients in the high-FHRS group.

When considering the relationships between the FHRABS and FHRS (Fig. 1 B), 43% of the patients classified with a low 10-year FHRS demonstrated an intermediate or high FHRABS. However, no patients with an intermediate or high FHRS were considered to have a low FHRABS. Similar trends in the relationships between the ABS, FHRABS, and FHRS were found when analyzing the distribution by sex (Supplementary Material, Fig. 1).

3.4. Distribution of predicted CV risk and observed MACEs (%) according to the CV risk categories based on FHRS, ABS, and FHRABS

Over a median follow-up of 6 years (±3.3 years), there were 60 first MACEs (5.8%). Fig. 2 shows the distribution of the predicted CHD risk stratification and observed MACEs according to the different CV risk categories based on the FHRS (Fig. 2 A), ABS (Fig. 2 B), and FHRABS (Fig. 2 C).

Based on the FHRS, 13%, 27%, and 60% were distributed in the low-, intermediate-, and high 10-year predicted CHD risk groups, but the observed MACEs were almost equally distributed in each of these three risk categories. Conversely, based on the ABS and FHRABS, the observed MACEs were mainly distributed in patients classified as being at intermediate and high predicted CHD risk. The FHRABS showed the highest distribution of MACEs in patients at intermediate and high risk—93% vs. 85%—compared to the ABS categories (p-value <0.001). Furthermore, only 7% and 15% of the MACEs were observed in low-risk patients stratified by the FHRABS and ABS.

3.5. Rates of MACEs by sex, age, FHRS, ABS, and FHRABS categories

As shown in the Supplementary Material Fig. 1 (A, B, C, D), the MACEs incidence rate increased significantly for men with each category of age, FHRS, ABS, and FHRABS. For

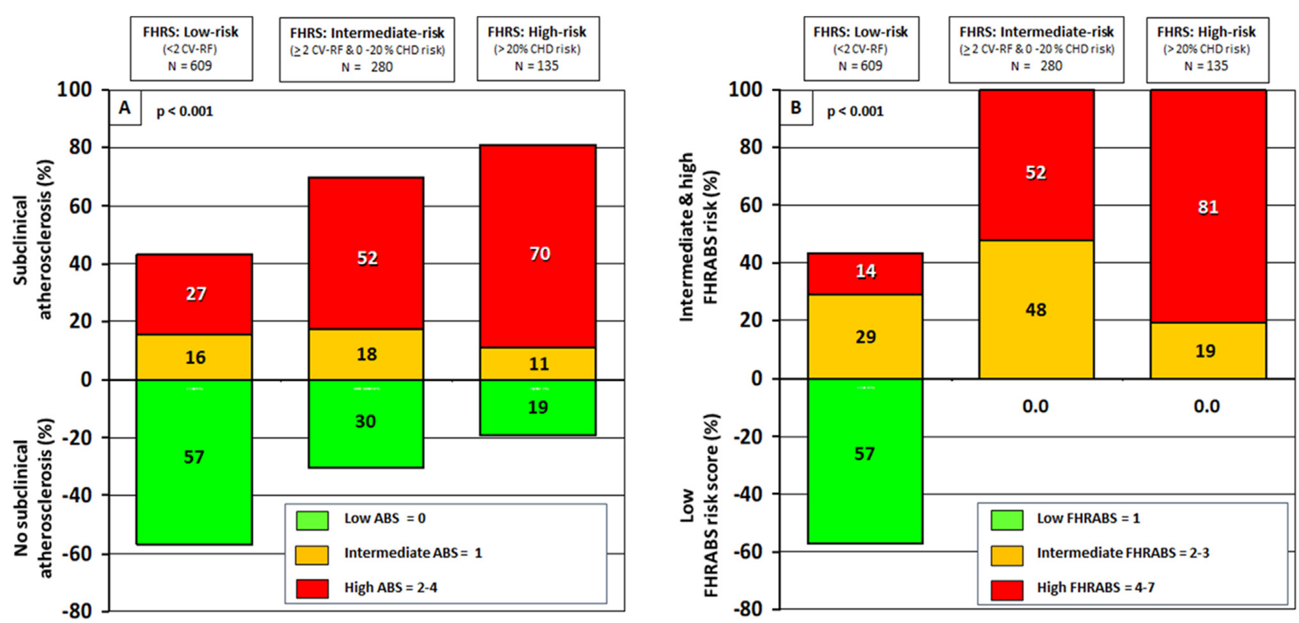

Figure 1 Distribution of ABS and FHRABS risks scores according to 10-year FHRS. FHRS, Framingham Heart Risk Score; ABS, Atherosclerosis Burden Score; FHRABS, combined FHRS + ABS. p-value indicates differences according categories.

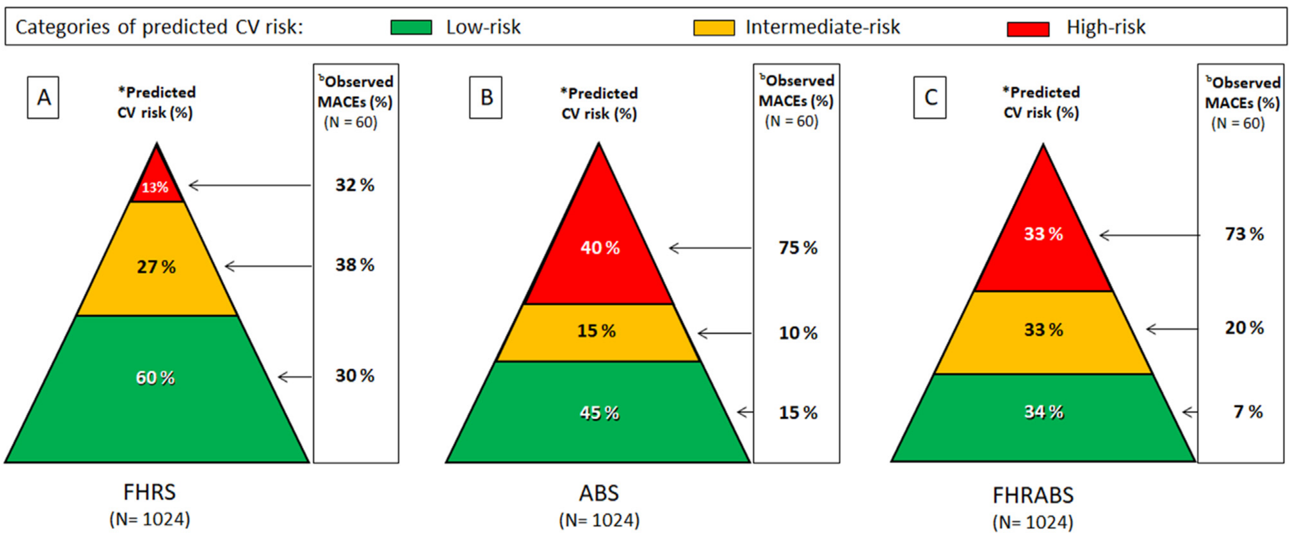

Figure 2 Distribution (%) of predicted CV risk and observed MACEs according to FHRS, ABS and FHRABS. FHRS, Framingham Heart Risk Score; ABS, Atherosclerosis Burden Score; FHRABS, combined FHRS + ABS; MACEs, major cardiovascular events. FHRS: low-risk if <2 CV-RF; intermediate-risk if ≥ 2 CV-RF & 0–20% CHD risk; high-risk if > 20% CHD risk. ABS: low-risk if ABS = 0; intermediate-risk if ABS = 1; high-risk if ABS = 2–4. FHRABS: low-risk if FHRABS = 1; intermediate-risk if FHRABS = 2–3; high-risk if FHRABS = 4–7. *Statistical difference in stratification of CV risk between scores of FHRS (reference) and ABS or FHRABS: p value = <0.001; and between scores of ABS and FHRABS: p value = <0.001 [b]Statistical difference in distribution of MACEs between scores of FHRS (reference) and ABS or FHRABS: p value = <0.001; and between scores of FHRS and FHRABS: p value = <0.14.

women, a similar statistically significant trend was observed, but only in the categories of intermediate and high risk, and in the three categories of ABS and FHRABS.

3.6. Prediction of MACEs with the different CV risk prediction models

As seen in Table 2, the predictive values for MACEs between the different markers of CV risk were significantly higher for the FHRABS compared to the ABS and FHRS when expressed by Youden's index or by the ROC curves. As illustrated in Fig. 3, the ROC-AUC of the FHRABS was significantly higher (0.743, $p < 0.024$) than that of the FHRS, the reference value (0.676), or ABS (0.707, $p = 0.013$).

The Kaplan–Meier analysis again showed that the predictive performance of the FHRS in terms of predicting MACEs was strengthened by adding the ABS. Patients with high FHRS had a significantly higher cumulative incidence of MACEs than patients with low FHRS (FHRS: log-rank = 34.8, $p < 0.001$, Fig. 4 A). A similar but larger difference in cumulative CV events was observed after stratification using the ABS (ABS: log-rank = 60.8, $p < 0.001$, Fig. 4 B) and FHRABS (FHRABS: log-rank = 72.4, $p < 0.001$, Fig. 4 C).

In the univariate probability-weighted Cox proportional-hazard analyses, each of these three risk markers was associated with incidence of MACEs. The HR of the cumulative incidence of MACEs increased significantly among patients classified as low-, intermediate-, and high-risk patients using the FHRS, ABS, or FHRABS. In addition, these results also showed that the HR among the high-risk patients was the highest for the FHRABS (23.3), compared with the ABS (10.5) or FHRS (5.5). Similar trends were also ascertained when these analyses were performed with models adjusted for CV risk factors.

4. Discussion

The present study confirmed that, compared to the FHRS and ABS, the FHRABS provides a significant improvement in CV risk stratification and prediction of future MACEs,

Table 2 Comparison of predictive values of MACEs between the different markers of CV risk.

	FHRS (1–3)	ABS (0–4)*	FHRABS (1–7)**
	(Cut off value ≥ 2 vs 1)	(Cut off value ≥ 2 vs ≤ 1)	(Cut off value ≥ 4 vs ≤ 3)
Sensitivity (%)	70	75	73
Specificity (%)	61	62	69
Youden's Index (%)			
(sensitivity + specificity) − 1	0.31	0.37	0.42
Statistical difference	Reference	*p = 0.001	*p = 0.001/**p = 0.001

Abbreviations: FHRS, Framingham Heart study Risk score; ABS, atherosclerosis burden score; FHRABS, combined FHRS + ABS; Youden's index = (sensitivity + specificity) − 1; MACEs, major cardiovascular events. *p-value for comparison Youden's Index: *FHRS vs ABS or FHRABS; **ABS vs FHRABS.

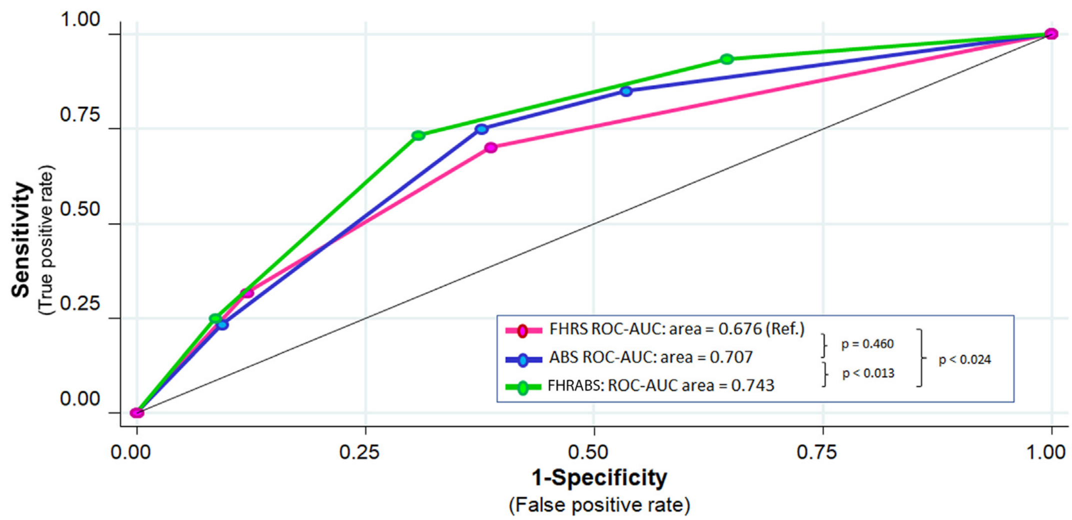

Figure 3 Comparative ROC curves area for MACEs between the 3 different CV risk predictors. ROC-AUC, Receiver-operating characteristic curves, area under the curve; FHRS, Framingham Heart Risk Score; ABS, Atherosclerosis Burden Score; FHRABS, combined FHRS + ABS; MACEs, major cardiovascular *events.* ∗Statistical difference between the ROC-AUC expressed by p values.

among the low-to-intermediate-risk individuals included in our large prospective cohort of patients free from prior ASCVD.

To the best of our knowledge, this is the first study to demonstrate the clinical utility of the FHRABS: a new comprehensive score that combines the ABS—a multi-territorial scATS score—with the FHRS based on traditional CV risk factors.

Despite the potential limitations associated with its use, the FHRS remains one of the most validated and widely used equations for CV risk estimation in clinical practice.

However, it is important to note that the FHRS equation does not consider the heterogeneity of atherosclerosis development and progression in asymptomatic individuals. This means that many risk factors strongly related to the development of atherosclerosis, such as physical inactivity, an unhealthy diet, hypertriglyceridemia, dyslipidemia, and inflammation, are not included in the calculation estimate [30]. In addition, it does not take into account protective factors against ATS. Therefore, its CHD risk classification performance is limited. Thus, different invasive and non-invasive markers of scATS, such as the CT coronary artery calcium score (CACS), *C*-IMT, ankle-brachial index (ABI), and presence of carotid and femoral plaques, have been explored as alternative risk markers in addition to the FHRS to enhance CV risk prediction among individuals categorized as low and intermediate risk when using the FHRS [21,22].

A recent systematic review and meta-analysis of six cohort studies, including 17,961 participants during a mean follow-up from 4.4 to 10.3 years and in which 1043 CVEs occurred, showed that the CACS added further discrimination to traditional CVD risk assessment equations. However, the gain was modest in terms of CVD outcomes when considering changes in ROC-AUC values ranging from 0.020 (95%, −0.020−0.042) to 0.088 (95%, 0.025 to 0.151), mean = 0.036 (95% CI, 0.020−0.052) [31].

Ethnic Study of Atherosclerosis, a large ethnically heterogeneous cohort of individuals without clinically evident CVD at baseline and with over 11 years of follow-up, assessed the incremental gain from the addition of the CACS to a standard CVD risk calculator, such as the FHRS or other CVD risk factor models. The main finding of this study was that both the CACS and the carotid plaque score improve the prediction of CVD and CHD events when added to traditional CV risk factors alone. This was shown with a significant increase in ROC-AUC from 0.74 for CV risk factors alone to 0.78 and 0.79 per 1 SD of CACS ($p < 0.001$), respectively, and from 0.74 to 0.75 and 0.75 per 1 SD of plaque score, respectively ($p < 0.034$, $p < 0.049$). However, for the prediction of stroke and TIA events, the CACS and the carotid plaque score performed similarly [32].

Another systematic review and meta-analysis of 15 articles reported that the *C*-IMT, as measured by B-mode ultrasound, was associated with future CVEs. However, the addition of the *C*-IMT to traditional CV risk prediction models did not lead to a statistically significant increase in the performance of those models, as shown by the comparison of the ROC-AUC between the two models, the lowest difference being from 0.726 to 0.729 and the highest difference being from 0.614 to 0.662 [33].

As recently summarized by Aczui-Aparicio et al. in a systematic review of 30 publications, an improvement in the CV risk prediction for asymptomatic low-to-intermediate risk individuals was demonstrated when adding carotid plaques to traditional CV risk factors. A net reclassification improvement of risk (NRI) varying from 2% to 23% was reported in six studies. However, as compared to the CACS, carotid plaque measurements were weaker candidates (NRI = 2%) in terms of enhancing the risk prediction of CVD in these groups of individuals [21].

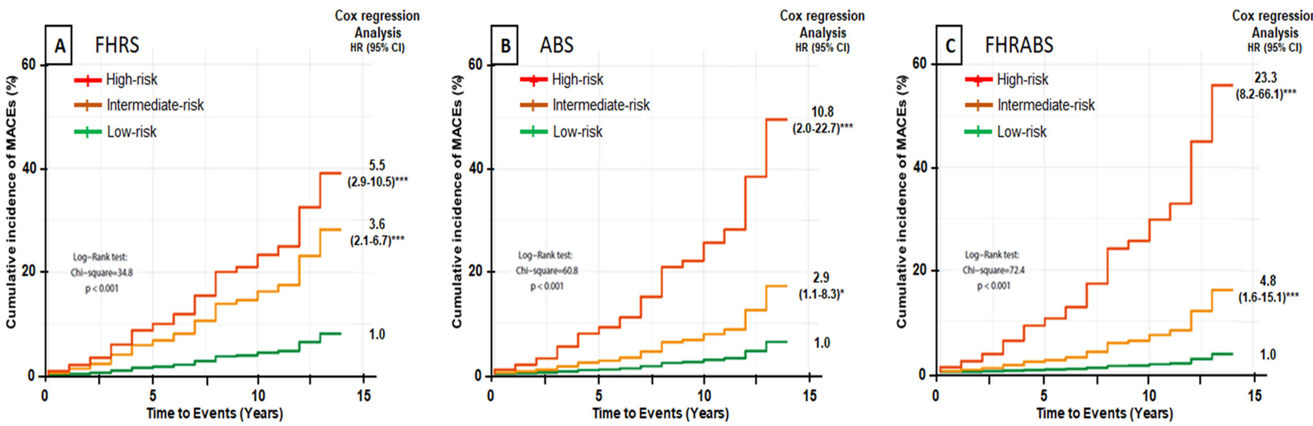

Figure 4 Kaplan-Meier Estimates and Cox regression analysis for cumulative incidence of major cardiovascular events (MACEs) by CV risk categories of FHRS, ABS and FHRABS. Cumulative event rates of cardiovascular disease events (MACEs) for low-, intermediate- and high-risk of FHRS (A); ABS (B) and FHRABS (C). Abbreviations: FHRS, Framingham Heart study Risk Score; ABS, atherosclerosis burden score; FHRABS, combined FHR + ABS; HR, hazard ratio obtained by Cox regression analysis, Statistical significance for differences between hazard ratio: $*p = 0.05$; $***P = 0.001$.

As femoral plaques are more common than carotid plaques among patients with ATS, the potential predictive value of multi-territorial scATS has gained interest over the last decade, to further enhance the performance of cardiovascular risk prediction in the asymptomatic population [15,21,22,34,35].

Interestingly, our results are in accordance with the findings of the AWHS study (Aragon Workers' Health Study) and the PESA study, which reported a similarly high prevalence of scATS detected by ABS in the groups of patients classified by the FHRS as being at low CHD risk (43% vs. 57% and 58%) and at intermediate CHD risk (70% vs. 75% and 86%) [14,17].

Our data are also supported by the results of prospective cohorts, which have shown that plaque occurrence in the carotid and femoral arteries was a better predictor of CVEs than carotid plaques, independently of traditional CV risk factors [11–13,36,37].

Nevertheless, the main findings of our study are based on the added value of the FHRABS over FHRS or ABS alone in terms of improving CV risk stratification and more accurately identifying patients at a high risk of future MACEs. This is expressed by Youden's Index, the ROC-AUC, and by the hazard ratio of the cumulative incidence of MACEs based on Cox's proportional-hazard models. It is important to note that the area under the ROC curve of 0.743 for the FHRABS obtained in our study is similar to the areas described for the CACS (0.665) in the Aragon Workers' Health Study [14] or in the recent systematic review and meta-analysis reported by Bell et al., which oscillated between 0.699 and 0.800 [31].

Furthermore, despite the small number of MACEs observed in our cohort, our results suggest that the FHRABS could also be relevant for women. Thus, this study provides part proof of the concept suggested by various authors [8,38–40] for improving CV risk prediction by creating a new comprehensive score that combines a well-recognized CV risk factor equation with a simple score that rates the extent of multi-site scATS.

In the ESC guidelines on CV risk prediction, the concept of "negative risk markers" was introduced, implying a reduced CV risk when carotid or femoral plaques are absent and recommending re-classifying subjects at very high CV risk when carotid or femoral plaques are detected [41].

Therefore, we believe that, in an era of more personalized care, imaging-based biomarkers should be combined with the FHRS as a first-line approach in CV risk estimation. The ABS appears to be an easy-to-use, radiation-free clinical tool that may be useful in daily clinical practice [42,43]. By promoting personalized CV risk prevention beyond the use of conventional risk factors, the FHRABS can contribute to better CV risk management by considering ATS plaque development and progression under the weight of CV risk factors, reducing the risk of ASCVD in the future.

5. Strengths and limitations

The present study has several strengths. Firstly, this is the first report to evaluate the synergic role of the multi-vascular assessment of the scATS and FHRS for CV risk discrimination and the prediction of future CVEs in a large prospective cohort of European men and women, who were initially free of CV disease.

Secondly, a rigorous methodology control for carotid and femoral image acquisition and ultrasonographic measurement for plaque detection, was performed. In our study the sonographer involved was a trained and certified vascular physician. Nevertheless, is important to note that ultra-sonographic detection of the presence of plaques at the carotid and femoral bifurcation (i.e.: detection of presence/absence of plaques), without any additional requirement of morphological plaque characterization and without any descriptions of the hemodynamic impacts of plaque, represents a feasible and rapidly procedures in a clinical setting.

Thirdly, among different scoring systems for atherosclerotic plaques to predict CV risk, the literature review revealed a large heterogeneity in both the use of methodologies and techniques, in the cut-off values, and in the complexity in clinical practice [41,42]. For these reasons, we have chosen the ABS—a score similar to that described in the Rotterdam study; [28]—for its simplicity in defining multi-vessel plaque development beyond simple plaque identification and its composition and characteristics in terms of quantifying the number of carotid and femoral arteries containing plaques.

Fourth, other advantages include the lower cost (as compared with other techniques) of adding US carotid and femoral ATS detection to the FHRS equation. There are intrinsic advantages related to using US for ATS burden detection, including the absence of a radiation burden, the technical reproducibility and rapidity, and the comfort for patients [15,22].

For all these reasons, we believe that the use of a US atherosclerosis burden assessment, such as the ABS, is the most convenient technique to combine with the Framingham risk prediction equation for clinical practice.

Nevertheless, we have to acknowledge potential limitations of the study. Firstly, scATS plaques were defined according to selected criteria, and therefore, a change in this definition could modify our results. Secondly, as the population under study was a selected population of patients attending our cardiovascular prevention clinic, selection bias cannot be excluded. For this reason, our results need to be validated in a more representative sample of the general population. Third, the present prospective cohort study was not designed to investigate the effect of medication (i.e., lipid-lowering drugs and other medications) during the follow-up period, and therefore we are unable to test the impact of this factor, analogously with other prospective CV risk prediction studies [11,36,37,44,45]. Therefore, we are unable to determine the potential impact of medications (prescribed because of atheroma discovery) in Cox model, on FHRABS for MACE prediction.

Lastly, but not at the end, future randomized trials should be performed to determine the generalizable statements of the potential benefit of FHRABS predictive role on MACEs and to determine the role of these findings in therapeutic decision making to optimize MACEs outcomes. A future larger interventional study should be planned to more clearly explore whether treatment based on FHRABS vs. FHRS alone, would be associated with improved MACEs.

6. Conclusions

Overall, our findings demonstrate that the FHRAB improved the CV predictive ability of the FHRS. The FHRABS is an easy-to-use, inexpensive, and radiation-free tool that contributes to better CV risk stratification and personalized CV prevention among patients classified as being at low and intermediate CHD risk based on the FHRS. Further cost-effectiveness analyses and randomized controlled trials should be carried out in order to explore the widespread introduction of the FHRABS in everyday clinical practice.

Author's contributions

R.D.G. and M.R. equally contributed; M.D. and R.D. equally contributed. All authors revised and approved the final version of the manuscript.

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Declaration of competing interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.04.019.

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