Year : 2017

The Atherosclerosis Burden score (ABS) : a convenient ultrasound- based score of peripheral atherosclerosis for coronary artery disease prédiction

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THESE

préparée sous la direction du Docteur Michèle Depairon

(avec la collaboration du Professeur honoraire Roger Darioli)

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

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Médecin diplômé de la Confédération Suisse
Originaire de La Roche (Fribourg)

Lausanne

2016

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse	Madame la Docteure **Michèle Depairon**
Co-Directeur de thèse	
Expert	
Vice-Directeur de l'Ecole doctorale	Monsieur Le Professeur **John Prior**

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Monsieur Patrick YERLY

intitulée

The Atherosclerosis Burden score (ABS) : a convenient ultrasound-based score of peripheral atherosclerosis for coronary artery disease prediction

Lausanne, le 6 décembre 2016

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

The Atherosclerosis Burden Score (ABS): a Convenient Ultrasound-Based Score of Peripheral Atherosclerosis for Coronary Artery Disease Prediction

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Abstract Ultrasonographic detection of subclinical atherosclerosis improves cardiovascular risk stratification, but uncertainty persists about the most discriminative method to apply. In this study, we found that the "atherosclerosis burden score (ABS)", a novel straightforward ultrasonographic score that sums the number of carotid and femoral arterial bifurcations with plaques, significantly outperformed common carotid intima-media thickness, carotid mean/maximal thickness, and carotid/femoral plaque scores for the detection of coronary artery disease (CAD) (receiver operating characteristic (ROC) curve area under the curve (AUC)=0.79; P=0.027 to <0.001 with the other five US endpoints) in 203 patients undergoing coronary angiography. ABS was also more correlated with CAD extension (R=0.55; P<0.001). Furthermore, in a second group of 1128 patients without cardiovascular disease, ABS was weakly correlated with the European Society of Cardiology chart risk categories (R^2=0.21), indicating that ABS provided information beyond usual cardiovascular risk factor-based risk stratification. Pending prospective studies on hard cardiovascular endpoints, ABS appears as a promising tool in primary prevention.

Keywords Cardiovascular disease prevention · Cardiovascular risk stratification · Atherosclerosis imaging · Carotid intima-media thickness · Carotid plaques · Femoral plaques · Coronary artery disease

Abbreviations

ABS	Atherosclerosis burden score
ATS	Atherosclerosis
CAD	Coronary artery disease
CV	Cardiovascular
C-IMT	Carotid intima-media thickness
ESC	European Society of Cardiology
IMT	Intima-media thickness
RF	Risk factors
US	Ultrasound

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Introduction

During the last two decades, ultrasound (US) screening for presymptomatic peripheral atherosclerosis (ATS) has been proposed as a useful mean to improve the ability of the current algorithms to detect subjects at high risk of cardiovascular (CV) events [1–4]. So far, the assessment of peripheral ATS mainly concentrated on the measurement of intima-media thickness (IMT) on predefined wall segments of carotid arteries (carotid intima-media thickness (C-IMT)), and C-IMT "alone" is considered as a surrogate of generalized ATS [5]

and as an independent predictor of CV events and mortality [1–3, 6–11], including in populations aged over 65 years [9]. However, the assessment of C-IMT is not considered more than "reasonable" in current practice guidelines [12, 13], mainly because of the lack of reference threshold values [14, 15] and because of the influence of non-ATS factors affecting media thickness [16, 17]. Moreover, concerns have been raised regarding the poor added contribution of C-IMT to the estimation of an individual's risk as compared to CV risk factor (RF) alone [18], with low or even unsignificant "net reclassification improvement" in the general population [19] and in older people [20].

To circumvent these limitations and because ATS is a focal disease that involves localized portions of the arterial wall and spares adjacent segments, several authors proposed alternative strategies based on the detection of ATS plaques on wider arterial segments rather than the measurement of the IMT on predefined arterial portions such as the far wall of the common carotid arteries. The presence and burden of plaques have been associated with CV events and mortality [1, 10, 21–31], but the arterial sites targeted for the detection of plaques and the methods applied to quantify them highly varied between studies. Most authors focused on carotid arteries [1, 10, 23, 24, 26, 27, 29, 30, 32–34]. They reported plaques as either present or absent [25, 31, 34, 35] or quantified them by measuring their maximal thickness [9, 18, 30] or their total trans-sectional area [24, 26, 32, 33], with [9, 18] or without [30] combination with C-IMT. As opposed to C-IMT, carotid plaques were recently found to provide a significant net reclassification improvement for high-risk subject identification on top of conventional CVRF [19].

On the other hand, only few studies investigated femoral arteries, although their superficial location allows US imaging with the same resolution as in carotid arteries [21, 22, 25, 28, 36, 37]. Considering that ATS is a focal disease with lesions simultaneously or successively disseminated through the whole arterial tree, combining imaging at both carotid and femoral sites may offer additional information and enhance the discriminative strength of arterial US to detect high-risk subjects [21, 37]. In this study, we sought to investigate a very straightforward and convenient US score of peripheral ATS that we called "ABS", or "atherosclerosis burden score", and that simply sums the number of carotid and femoral arteries which display plaques.

In a cohort of patients referred for a first coronary angiography, we first investigated the contribution of ABS to predict the presence and severity of coronary artery disease (CAD) in comparison to C-IMT, carotid plaque score, and femoral plaque score. Secondly, in a separate cohort of outpatients with no clinical evidence of cardiovascular disease (CVD), we evaluated the agreement between ABS and CV risk as assessed by the usual CVRF-based chart of the European Society of Cardiology (ESC).

Materials and Methods

Study Population

This study comprises two groups of patients. Group I included 203 consecutive patients aged 20–70 years referred to the cardiology department for their first coronary angiography. Coronary angiography was performed for acute coronary syndrome or angina pectoris in 71 % of subjects, preoperative evaluation in the context of pericardial or valvular heart disease in 17 %, and cardiomyopathy investigation in 12 %. Group II included 1128 consecutive patients (20–70 years) without clinical evidence of CVD that attended our institution's ambulatory "lipid clinic" for the evaluation of their CV risk. None of these subjects underwent coronary angiography. Patients with diabetes mellitus or end-stage renal disease were excluded from both groups. All participants gave written informed consent, and the protocol was approved by the local ethics committee.

Cardiovascular Risk Factors and Risk Score

All patients were administered a physical examination and a detailed questionnaire regarding demographic characteristics, personal and family history of CVD, medical history, medication, and CVRF. Venous blood was drawn in the morning after an overnight fast for the measurements of total plasma cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) concentrations.

The risk factors taken into account were male sex, age (≥45/55 years in men/women), family history of premature CVD (CVD in male/female first-degree relatives ≥55/65 years), current cigarette smoking, hypertension (blood pressure ≥140/90 mmHg or current use of anti-hypertensive drug therapy), obesity (body mass index (BMI)≥30 kg/m^2), high LDL-cholesterol (LDL-C) (≥160 mg/dL or use of lipid-lowering therapy), hypertriglyceridemia (TG≥200 mg/dL), and low HDL-C (≤40 mg/dL).

Finally, a risk score category (low, moderate, or high risk) was computed according to the current ESC guidelines [12].

Ultrasonography

All scans were performed by two experienced operators (PY and MD) with a System 5 (Vingmed/General Electric, Milwaukee, Wisconsin, USA) connected with a 10 MHz linear array transducer. For arterial wall analysis, the system was equipped with the M'ATH software (Metris, Paris, France), which performs semi-automatic measurements on frames. In group II, ultrasonographic investigations were performed before patients underwent coronary angiography.

Both left and right carotid and femoral arteries were examined (four arterial sites). Carotid investigation included

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common carotid artery (CCA), bulb, and the origin of the internal and external branches. Femoral arteries were examined from 4 cm above bifurcation spur to 4 cm in the superficial branch in addition to the origin of the profound branch. All scans were acquired at a maximal depth of 4 cm, allowing best resolution on screen [15].

According to current guidelines, standardized C-IMT was measured on the far wall of both CCAs on a 10 mm segment located 2 cm upstream from flow divider [15]. Optimal longitudinal frames were frozen in late diastole before analysis with the M'ATH software. The recorded C-IMT was the average of right and left mean thickness values measured along the whole segments. Carotid "maximal thickness" (C-IMTmax) was defined as the maximal IMT observed on all the above-mentioned segments of the right and left carotid bifurcations and carotid "mean maximal thickness" (C-IMTmax-mean) as the average of the maximal thickness values measured on both left and right carotid bifurcations.

ATS plaques were considered as focal wall thickening ≥1200 μm protruding into the arterial lumen [35, 36, 38, 39]. Plaques were looked for on the near and far walls in all the above-described arterial segments by transversal and longitudinal scanning. Carotid/femoral plaque scores and ABS were calculated by summing the number of arterial sites involved with at least one plaque. Each site contributed to one unit of the respective scores, which accordingly ranged from 0 to 2 for carotid/femoral plaque scores and from 0 to 4 for the ABS.

Coronary Angiography

Coronary angiography was performed with standard Judkins technique by cardiologists who were blinded to the ultrasonography results. The degree of diameter narrowing of coronary vessels was visually estimated, and quantitative computerized assessment was used in cases of mild stenosis. CAD was considered as present if ≥1 segment of ≥1 epicardial artery carried a ≥30 % stenosis and was diagnosed in 130 patients. Forty-six had one-vessel disease, 45 had two-vessel disease, and 39 had three-vessel disease. The remaining 73 subjects had no detectable coronary lesions or coronary stenosis <30 % and were considered as controls.

The severity of CAD was quantified using the Jenkins score, which ranges from 0 to 32 depending on the degree of stenosis of each coronary lesion and their extent on the coronary tree [40]. The functional significance of CAD was evaluated using the Gensini score [41].

Statistical Analysis

All analyses were performed using STATA 8.0 (Stata Corp., College Station, Texas, USA) software, and graphs were generated with Sigmaplot 11.5 (Systat Software, Chicago,

Illinois, USA). In order to allow comparison between the six selected ATS markers, continuous variables were transformed into categorical variables. Therefore, standardized C-IMT, C-IMTmax-mean, and C-IMTmax were categorized into quartiles. For the first aim of the study, receiver operating characteristic (ROC) curves were used to compare the ability of ABS, C-IMT, and carotid/femoral plaque scores to detect CAD in group I. The imaging endpoints' best threshold values to identify CAD were considered as the quartile or the score with the highest sensitivity and specificity summation (validity index (VI)). Spearman correlation tests were performed to test the association between all ATS markers and CAD severity. For the second aim of the study, linear regression analysis was performed to compare the association between ABS and ESC risk categories, and Spearman correlation tests were done to test the association between ABS and the other five US endpoints.

Results

The demographic, clinical, and ultrasonographic characteristics of both study groups are presented in Table 1. The patients undergoing coronary artery angiography (group I) were significantly older, had more hypertension, family history of premature CVD, obesity, and smoking habits, but they had less hypercholesterolemia. Regarding peripheral ATS, group I patients showed thicker standardized C-IMT, C-IMTmax-mean, and C-IMTmax, and they had more arterial sites involved with plaques at both carotid and femoral levels.

US Endpoints and CAD

CAD was found in 130 subjects (64 %) in group I when defined by the presence of ≥1 stenosis ≥30 % on ≥1 pericardial vessel and in 117 (58 %) when defined by the presence of stenoses ≥50 %. The six US endpoints were significantly associated with the presence of CAD, and the strongest correlation was found for ABS ($R=0.504, P<0.001$). CAD incidence increased from 11 % in subjects with ABS=0 to 87 % in subjects with ABS=4. By contrast, standardized C-IMT was only weakly correlated with CAD ($R=0.164; P=0.02$), with a 55 % occurrence in quartile 1 and 74.5 % in quartile 4. The other US endpoints had intermediate correlation coefficients: $R=0.449 (P<0.001)$ for femoral plaques, $R=0.399 (P<0.001)$ for carotid plaques, $R=0.387 (P<0.001)$ for C-IMTmax-mean, and $R=0.346 (P<0.001)$ for C-IMTmax.

ROC curve analysis showed that the US endpoint with the largest AUC was ABS (AUC=0.79; 95 % CI 0.73–0.86), which significantly outperformed the five other endpoints ($P=0.027$ to <0.001 for AUC difference) (Fig. 1). On the other hand, standardized C-IMT displayed the smallest AUC (AUC=0.59; 95 % CI 0.52–0.67). The best threshold values

Table 1 Clinical, laboratory, and ultrasonographic characteristics of the study population

	Group I	Group II
Number of subjects	203	1128
Female sex (%)	63 (31)	444 (39)
Age $\geq$45 years (males)/$\geq$55 years (females) (%)	145 (71)	542 (48)**
History of premature CVD (%)	61 (30)	180 (16)**
Hypertension (%)	122 (61)	427 (38)**
Current smoking (%)	60 (30)	332 (30)
BMI (kg/m^2)	26.6±4.0	25.2±4.2
Obesity (BMI $\geq$30 kg/m^2) (%)	37 (18)	124 (11)*
Total cholesterol (mg/dL)	213±46	267±77 **
LDL-cholesterol (mg/dL)	143±45	174±59**
Hypercholesterolemia (LDL-C $\geq$160 mg/dL or treatment)	91 (45)	781 (69)**
HDL-cholesterol (mg/dL)	52±19	53±18
Subjects with HDL-C <40 mg/dL (%)	57 (28)	258 (23)
Triglycerides (mg/dL) (median)	160	171
Subjects with TG $\geq$200 mg/dL (%)	50 (24)	310 (28)
Standardized C-IMT	745±118	671±116*
C-IMTmax	1917±856	1043±694**
C-IMTmax-mean	1609±708	904±52**
Subjects with $\geq$1 carotid artery with plaque(s)	158 (78)	336 (30)**
Subjects with $\geq$1 femoral artery with plaque(s)	166 (82)	479 (43)**
ABS	2.7±1.32	1.1±1.4**
Subjects with ABS $\geq$1	184 (91)	571 (51)**

Data presented as mean±1 SD

CVD cardiovascular disease, *BMI* body mass index, *TG* triglycerides, *ABS* atherosclerosis burden score
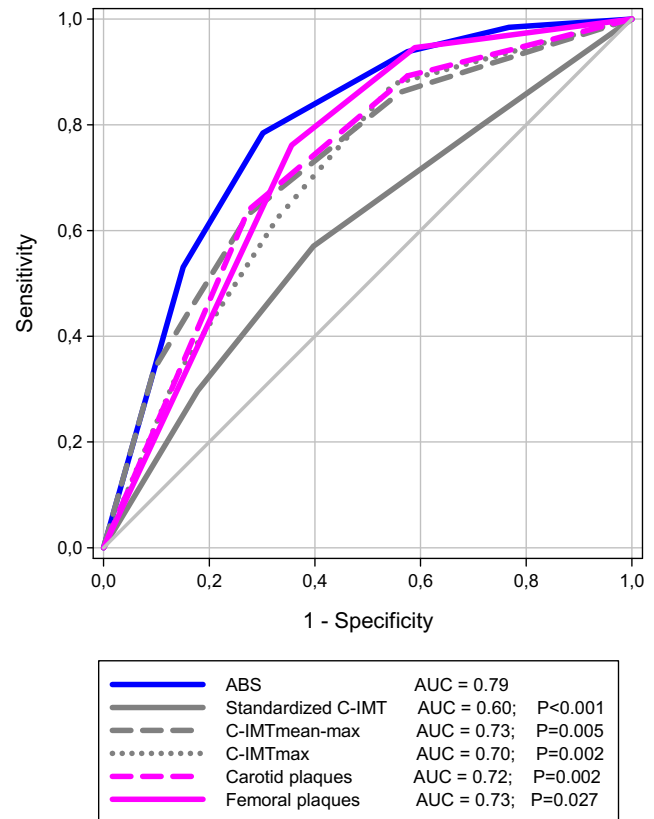
*$P \leq 0.05$

**$P \leq 0.01$ for comparison between groups I and II

Fig. 1 ROC curves and areas under the curves (AUCs) of the six US endpoints for the detection of CAD in group I. *P* values are given for comparison with ABS AUC

of the six ATS markers and ESC risk score are displayed in Table 2, with their respective sensitivity, specificity, and predictive values. These data show that ABS allows a 32 % sensitivity-specificity gain as compared to standardized C-IMT for CAD identification.

Finally, all US endpoints were correlated with the number of affected coronary arteries as described by one-, two-, or three-vessel disease [$R=0.18$ ($P=0.01$) for standardized IMT; $R=0.49$ ($P<0.001$) for IMTmean-max; $R=0.43$ ($P<0.001$) for IMTmax; $R=0.48$ ($P<0.001$) for carotid plaque score; $R=0.42$ ($P<0.001$) for femoral plaque score, and $R=0.54$ ($P<0.001$) for ABS]. All markers were also significantly correlated with CAD extension score (Jenkins score) and CAD functional severity score (Gensini score) at the exception of standardized C-IMT with the Gensini score (Figs. 2 and 3). Consistent with the ROC curve analysis, the ABS showed the highest correlation with both scores whereas standardized C-IMT displayed the lowest correlation.

US Endpoints and CV Risk

All group II patients were categorized according to the ESC risk score. The majority was graded as low [$n=$ 812 (71.9 %)] or moderate risk [$n=246$ (21.8 %)], and only 70 subjects (6.2 %) were high risk. Linear regression analysis showed that ABS was significantly associated with the risk categories (standardized β-coefficient=0.456; $P<0.001$). However, the proportion of ABS variability accounting for ESC risk categories was modest ($R^2=0.21$), demonstrating that CV risk as assessed by the CVRF-based chart of the ESC exerts only mild explanatory effects on ABS. Along that line, rather high burdens of ATS were observed in patients classified in the low- (5.8/4.2 % of the subjects with ABS 3/4) and moderate-risk categories (17.9/20.2 % of the subjects with ABS 3/4), underlying the low

Table 2 Sensitivity, specificity, predictive values, and validity index of the six US endpoints at their best threshold value for the detection of CAD (group I)

	Best threshold value	Sensitivity	Specificity	Positive pred value	Negative pred value	Validity index
Standardized C-IMT	Quartile 3	0.58	0.6	0.72	0.44	1.18
C-IMTmax-mean	Quartile 3	0.63	0.73	0.81	0.52	1.36
C-IMTmax	Quartile 3	0.62	0.67	0.77	0.5	1.29
Carotid plaque score	2 Plaques	0.64	0.73	0.74	0.69	1.36
Femoral plaque score	2 Plaques	0.76	0.64	0.79	0.6	1.4
ABS	3 Plaques	0.78	0.71	0.83	0.65	1.5

concordance between the burden of asymptomatic peripheral ATS and CVRF-based risk categories (Fig. 4). Finally, in group II, ABS was poorly correlated with standardized C-IMT ($R=0.47$; $P<0.001$) and moderately with C-IMTmean-max ($R=0.63$; $P<0.001$), C-IMTmax ($R=0.61$; $P<0.001$), carotid plaque score ($R=0.71$; $P<0.001$), and femoral plaque score ($R=0.79$; $P<0.001$).

Fig. 2 Correlation between the six US endpoints and the Jenkins CAD severity score in group I
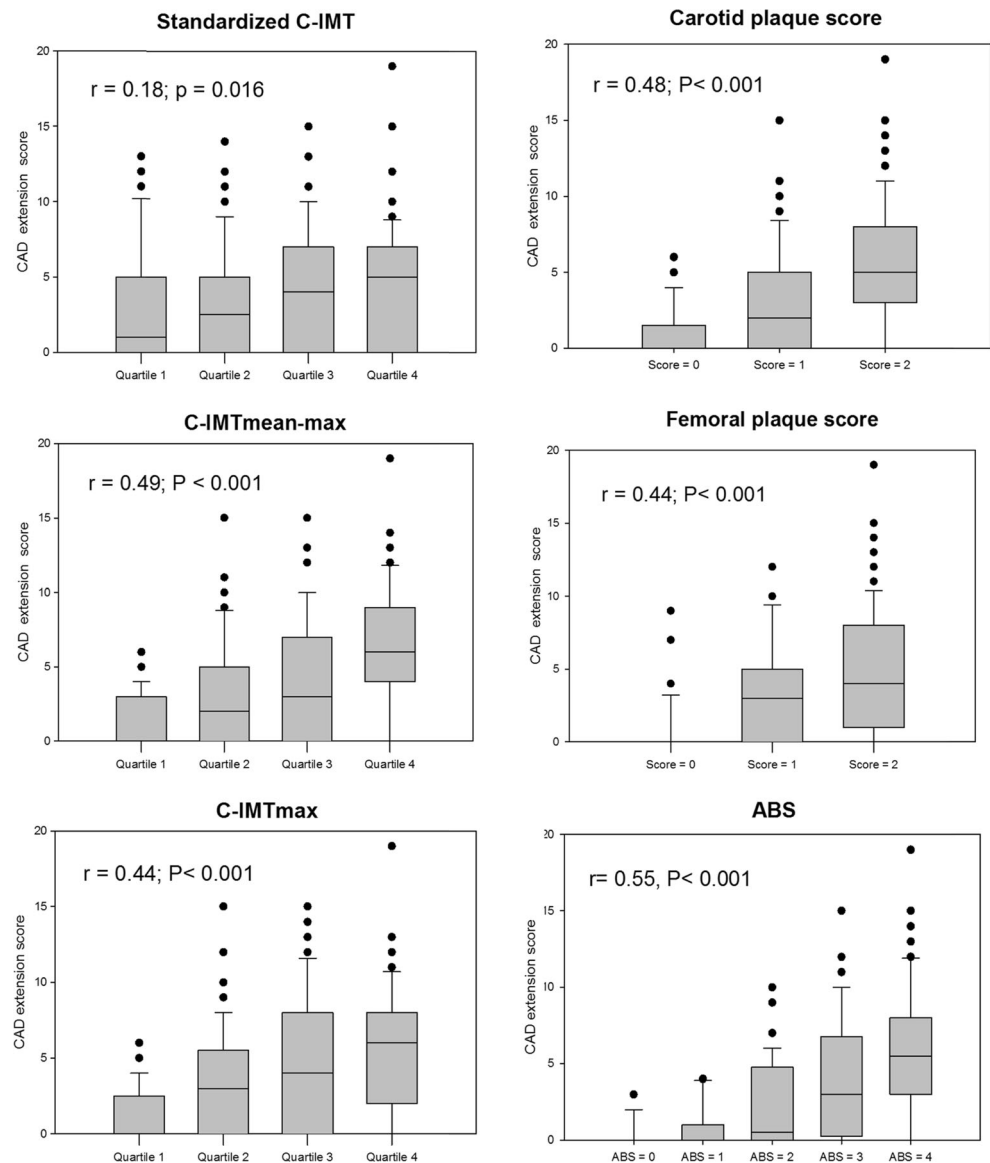
Fig. 3 Correlation between the six US endpoints and the Gensini CAD severity score in group I
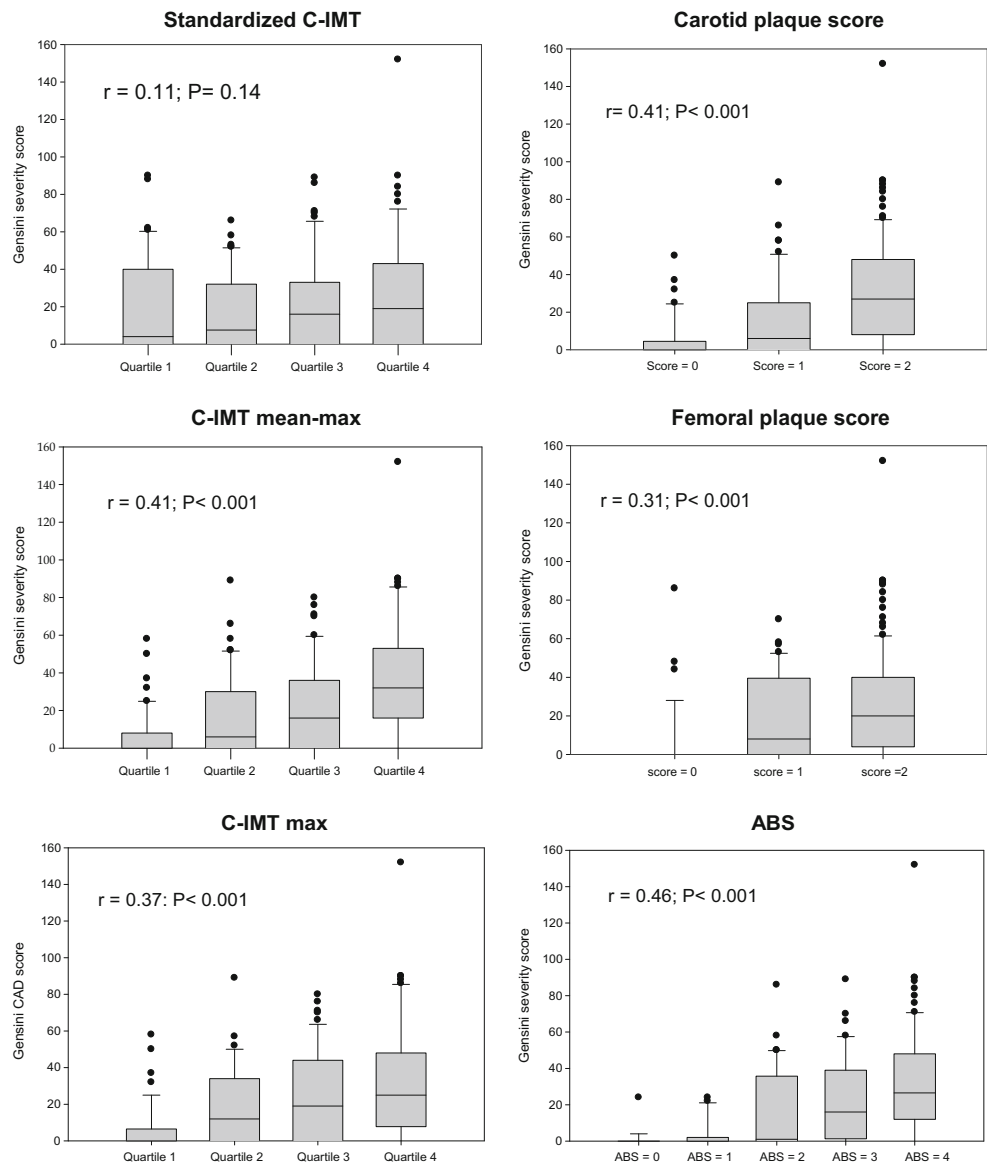
Discussion

The purpose of this study was to investigate the ABS as a new straightforward and convenient score of ultrasonographically assessed peripheral ATS which may ultimately be clinically used as a tool for cardiovascular risk assessment.

An important prerequisite for a new marker to be helpful in the prediction of CV events is that it also predicts the presence and extension of coronary ATS, which stands as the necessary background for eventual acute ischemic events at the heart level. In this study, we found out rather large variations in the association between the different investigated peripheral ATS endpoints and angiographically defined CAD, but ABS consistently came out as the marker with the strongest predictive power for both the presence and extension of CAD. We hypothesize that the focal nature of ATS, which allows healthy

wall segments to appear between diseased arterial portions explains why ABS outperforms standardized C-IMT, which is measured on a predefined wall segment of the common carotid artery that may actually be free of plaques. We also hypothesize that the disseminated nature of ATS, with lesions simultaneously or successively scattered throughout multiple locations across the arterial tree, explains why the accounting of US endpoints collected in four different sites helps to increase accuracy in the prediction of CAD as compared to endpoints taken at two sites (two carotid sites or two femoral sites).

In this study, we have chosen a 30 % stenosis cutoff for CAD diagnosis because most coronary plaques with large necrotic cores and thin fibrous caps that are at the origin of acute coronary events do not present with high degrees of stenosis [42]. However, thanks to compensatory vasodilation

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mechanisms, large amounts of ATS may accumulate in the coronary wall before any lumen encroachment becomes evident on angiography [43]. This technical limitation unavoidably lessens specificity for all US endpoints including ABS. Another limitation of our approach is that the correlation between ABS and CAD was mostly derived from symptomatic patients that are not representative of the population targeted for the use of ABS in a primary prevention setting. The superiority of ABS for CAD prediction seen in this group constitutes an important rationale to investigate ABS in further prospective studies with hard CV endpoints.

A second important prerequisite for a new marker to be helpful in enhancing the accuracy of cardiovascular risk prediction is that the information it provides does not overlap with the already existing information. Actually, we believe that the non-invasive detection of subclinical ATS like ABS can only be used in addition to the current risk factor-based charts and not in replacement of them. Along that line, ABS should add to the information provided by the traditional risk factors and ultimately allow to reclassify patients in more accurate risk categories. In a collective of 1128 consecutive asymptomatic individuals attending our lipid clinic for evaluation of their CV risk, ABS was only mildly associated with the CV risk categories as determined by the currently recommended CVRF-based charts of the ESC, indicating that the information provided by both evaluations are quite different and may be complimentary to each other. In the supposed "low- and moderate-risk" groups that still constitute the majority of patients with myocardial infarctions [44, 45], we found respectively 10 and 38.1 % of subjects with ABS scores ≥3. It appears likely that such a high burden of asymptomatic ATS may enhance the apparent risk of CV event and characterize subjects that may benefit from intensive therapy. The rationale underlying discrepancies between ATS burden and CVRF-based risk prediction is unclear. However, ATS

development relies on many more factors than those included in the risk assessment charts. For instance, inflammation and metabolic syndrome, which are of paramount importance as trigger of CV event and disease amplifier [46, 47], are missed in charts. On the other hand, genetically mediated or nutritional factors with anti-atherogenic effects may also lessen the burden of ATS despite apparently high risk [48, 49].

Conceptually, ABS is a very convenient score that simply depicts the sum of four sites involved with ATS out of both right and left carotid and femoral arterial beds. Its practical advantage relies on the requirement of a qualitative instead of quantitative assessment of the investigated vascular sites (i.e., ATS yes or no). As compared to standardized C-IMT, ABS does not require any expensive additional software for automated edge detection and serial measurements on a very small arterial wall segment. Also, as compared to thickness-based markers of plaques, ABS does not require any repeated assessments of numerous plaques that may appear equally thick in a patient with several lesions on a single arterial site and is not subject to measurement errors due to beam angulation, especially when done by less experienced investigators. Finally, the assessment of the simple presence or absence of ATS lesions is generally quite obvious and straightforward, and ABS can generally be assessed in no more than 10 min.

Consistent with our findings, several studies have shown that the US detection of ATS in femoral arteries provides additional information regarding CV risk as compared to investigation limited to carotid arteries [21, 22, 36, 37]. Actually, as already noted in the CAFES-CAVE study, Davidsson et al. showed that the occurrence of plaques at carotid or femoral levels had similar predictive value for CV events [21, 37] but that the occurrence of plaque in both carotid and femoral arteries increased the risk further (OR 2.09/1.99 for carotid/femoral plaques and 2.62 for bi-level plaques). Of note, in the CAFES-CAVE study, 30 % of the subjects with normal carotid arteries had femoral plaques, which is concordant with our data where 29.6 % (235/792) of the patients with no carotid plaques had yet femoral ATS. More recently, Postley et al. also noticed that failure to interrogate femoral in addition to carotid arteries would have missed 56/31 % of low to intermediate-risk women/men with subclinical ATS [50].

Nevertheless, only few studies combined carotid and femoral investigations by simply scoring the number of arterial sites involved with plaques. In agreement with our findings, two case-control studies reported that odds ratios for established CVD increased with the number of carotid/femoral sites involved with plaques (OR=1.79 with ATS on one site and 14.4 with ATS on four sites in the study by Tartière et al., and OR=3.1 with ATS on one site and 31.08 with ATS on four sites in the study by Griffin et al.) but not with C-IMT in the study by Tartière et al (OR=0.95 for one SD increment of IMT) [25, 31]. Griffin et al. further found that the association between the number of sites with plaques and
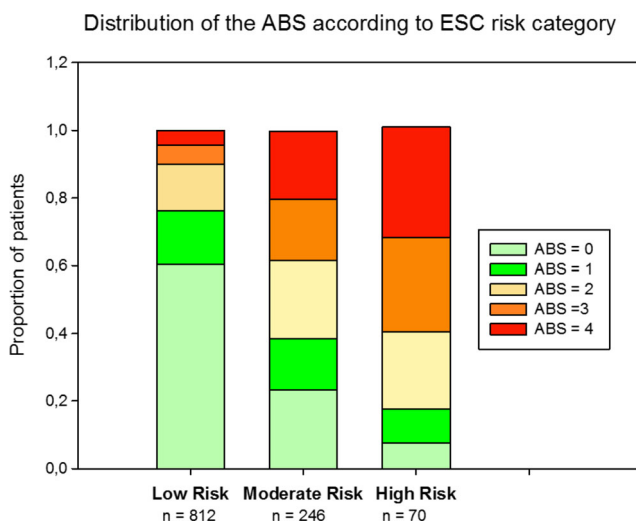
Fig. 4 Distribution of the ABS according to ESC risk category

prevalent CVD persisted after adjustment for CVRF as opposed to C-IMT [31]. In this report, the occurrence of plaques in three and four sites also outperformed carotid maximal plaque thickness and total plaque thickness in combined carotid and femoral arteries. In regard to these works, our study further defines that high ABS scores (≥3), which corresponds with plaques on three and four sites in the studies by Tartière and Griffin, can occur with a fairly high prevalence in supposed low- or intermediate-risk asymptomatic subjects and that this score is useful to predict CAD.

In conclusion, our study shows that a convenient score of subclinical ATS that accounts for both the focal and disseminated nature of ATS like ABS highly predicts CAD occurrence and extension and outperforms usual US-based endpoints like C-IMT and carotid/femoral plaque scores. Furthermore, ABS provides further information as compared to our usual way of CV risk prediction and appears as a promising alternative to C-IMT to enhance the accuracy of our current risk assessment charts. Of course, prospective studies on hard cardiovascular endpoints are still needed to confirm the interest of this new marker in preventive cardiology.

Conflict of Interest No conflict of interest exists for any of the authors.

Human Subjects/Informed Consent Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

References

1. Van der Meer, I., Bots, M., Hofman, A., Iglesias del Sol, A., van der Kuip, D., & Witteman, J. (2004). Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction. The Rotterdam study. *Circulation, 109*, 1089–1094.

2. Lorenz, M., Markus, H. S., Bots, M. L., Rosvall, M., & Sitzer, M. (2007). Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation, 115*, 459–467.

3. Kullo, I. J., & Malik, A. R. (2007). Arterial ultrasonography and tonometry as adjuncts to cardiovascular risk stratification. *Journal of the American College of Cardiology, 49*, 1413–1426.

4. Fernandez-Frieira, L., Ibanez, B., & Fuster, V. (2014). Imaging subclinical atherosclerosis: is it ready for prime time? A review. *Journal of Cardiovascular Translational Research, 7*, 623–634.

5. De Groot, E., Hovingh, G., Wiegman, A., Duriez, P., Smit, A., Fruchart, J. C., & Kastelein, J. (2004). Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation, 109*(Suppl III), III-33–III-38.

6. Bots, M., Hoes, A., Koudstaal, P., Hofman, A., & Grobee, D. (1997). Common carotid intima-media thickness and risk of stroke and myocardial infarction. The Rotterdam Study. *Circulation, 96*, 1432–1437.

7. Chambless, L., Heiss, G., Folsom, A., Rosamond, W., Szklo, M., Sharrett, A., & Clegg, L. (1997). Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987-93. *American Journal of Epidemiology, 146*, 483–494.

8. Peters, S. A., Grobbee, D. E., & Bots, M. L. (2011). Carotid intima-media thickness: a suitable alternative for cardiovascular risk as outcome? *European Journal of Cardiovascular Prevention and Rehabilitation, 18*, 167–174.

9. O'leary, D., Polak, J., Kronmal, R., Manolio, T., Burke, G., & Wolfson, S. (1999). for the cardiovascular health study collaborative research group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *The New England Journal of Medicine, 340*, 14–22.

10. Hollander, M., Hak, A. E., Koudstaal, P. J., et al. (2003). Comparison between measures of atherosclerosis and risk of stroke: The Rotterdam Study. *Stroke, 34*, 2367–2373.

11. Rosvall, M., Janzon, L., Berglund, G., et al. (2005). Incident coronary events and case fatality in relation to common carotid intima-media thickness. *Journal of Internal Medicine, 257*, 430–437.

12. Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, W. M., Albus, C., Benlian, P., Boysen, G., Cifkova, R., Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice; European Association for Cardiovascular Prevention and Rehabilitation, et al. (2012). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Atherosclerosis, 223*, 1–68.

13. Greenland, P., Alpert, J., Beller, G., Benjamin, E., Budoff, M., Fayad, Z., Foster, E., Hlatky, M., Hodgson, J., Kushner, F., Lauer, M., Shaw, L., Smith, S., Taylor, A., Weintraub, W., & Wenger, N. (2010). 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology, 56*, e50–e103.

14. Taylor, A., Merz, C., & Udelson, J. (2003). 34th Bethesda Conference: can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? *Journal of the American College of Cardiology, 41*, 1855–1917.

15. Touboul, P., Hennerici, M., Meairs, S., Adams, H., Amarenco, P., Bornstein, N., Csiba, L., Desvarieux, M., Ebrahim, S., et al. (2012). Mannheim Carotid Intima Media Thickness and Plaque Consensus (2004–2006–2011): an update on Behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovascular Diseases, 34*, 290–296.

16. Bots, M., Hofman, A., & Grobbee, D. E. (1997). Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam study. *Stroke, 28*, 2442–2447.

17. Roman, M., Pickering, T., Pini, R., Schwartz, J., & Devereux, R. (1995). Prevalence and determinants of cardiac and vascular hypertrophy in hypertension. *Hypertension, 26*, 369–373.

18. Iglesias del Sol, A., Moons, K., Hollander, M., Hofman, A., Koudstaal, P., Grobbee, D., Breteler, M., Witteman, J., & Bots, M. (2001). Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. *Stroke, 32*, 1532–1538.

19. Peters, S., den Ruijter, H., Bots, M., & Moons, K. (2012). Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart, 98*, 177–184.

20. Elias-Smale, S. E., Kavousi, M., Verwoert, G. C., Koller, M. T., Steyerberg, E. W., Mattace-Raso, F. U., Hofman, A., Hoeks, A. P., Reneman, R. S., & Witteman, J. C. (2012). Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study. *European Journal of Preventive Cardiology, 19*, 698–705.

21. Belcaro, G., Nicolaides, A., Ramaswami, G., Cesarone, M., De Sanctis, M., Incandela, L., Ferrari, P., Geroulakos, G., Barsotti, A., Griffin, M., Dhanjil, S., Sabetai, M., Bucci, M., & Martines, G. (2001). Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study. (The CAFES-CAVE study). *Atherosclerosis, 156*, 379–387.

22. Held, C., Hjemdahl, P., Eriksson, S., Björkander, I., Forslund, L., & Rehnqvist, N. (2001). Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris. *European Heart Journal, 22*, 62–72.

23. Hollander, M., Bots, M., Iglesias del Sol, A., Koudstaal, P., Witteman, J., Grobbee, D., Hofman, A., & Breteler, M. (2002). Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly. The Rotterdam Study. *Circulation, 105*, 2872–2877.

24. Spence, J. D. (2002). Ultrasound measurement of carotid plaque as a surrogate outcome for coronary artery disease. *The American Journal of Cardiology, 89*(Suppl), 10B–16B.

25. Tartière, J. M., Henry, O., Safar, H., Bureau, J. M., Girerd, X., Safar, M., & Blacher, J. (2003). Carotid intima-media thickness and carotid and/or iliofemoral plaques: comparison of two markers of cardiovascular risk in hypertensive patients. *Journal of Hypertension, 21*, 739–746.

26. Chan, S., Mancini, G., Kuramoto, L., Schulzer, M., Frohlich, J., & Ignaszewski, A. (2003). The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. *Journal of the American College of Cardiology, 42*, 1037–1043.

27. Störk, S., van den Beld, A., von Schacky, C., Angermann, C., Lamberts, S., Grobbee, D., & Bots, M. (2004). Carotid plaque burden, stiffness and mortality Risk in elderly men. A prospective, population-based Cohort study. *Circulation, 110*, 344–348.

28. Schmidt, C., Fagerberg, B., & Hulthe, J. (2005). Non-stenotic echolucent ultrasound-assessed femoral artery plaques are predictive for future cardiovascular events in middle-aged men. *Atherosclerosis, 181*, 125–130.

29. Rosvall, M., Janzon, L., Berglund, G., Engström, G., & Hedblad, B. (2005). Incidence of stroke is related to carotid IMT even in the absence of plaque. *Atherosclerosis, 179*, 325–331.

30. Baldassarre, D., Amato, M., Pustina, L., Castelnuovo, S., Sanvito, S., Gerosa, L., Veglia, F., Keidar, S., Tremoli, E., & Sirtori, C. (2007). Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events. *Atherosclerosis, 191*, 403–408.

31. Griffin, M., Nicolaides, A., Tyllis, T., Georgiou, N., Martin, R., Bond, D., Panayiotou, A., Tziakouri, C., Doré, C., Fessas, C., & the Cyprus heart Foundation. (2009). Carotid and femoral arterial wall changes and the prevalence of clinical cardiovascular disease. *Vascular Medicine, 14*, 227–232.

32. Spence, J., Eliasziw, M., DiCicco, M., Hackam, D., Galil, R., & Lohmann, T. (2002). Carotid plaque area. A tool for targeting and evaluating vascular preventive therapy. *Stroke, 33*, 2916–2922.

33. Brook, R., Bard, R., Patel, S., Rubenfire, M., Clarke, N., Kazerooni, E., Wakefield, T., Henke, P., & Eagle, K. (2006). A negative carotid plaque area test is superior to other non-invasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 26*, 656–662.

34. Nambi, V., Chambless, L., Folsom, A. R., He, M., Hu, Y., Mosley, T., Volcik, K., Boerwinkle, E., & Ballantyne, C. M. (2010). Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk. The ARIC (Atherosclerosis Risk In Communities) Study. *Journal of the American College of Cardiology, 55*, 1600–1607.

35. Ebrahim, S., Papacosta, O., Whincup, P., Wannamethee, G., Walker, M., Nicolaides, A., Dhanjil, S., Griffin, M., Belcaro, G., Rumley, A., & Lowe, G. (1999). Carotid plaque, intima-media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women; the British regional heart study. *Stroke, 30*, 841–850.

36. Yerly, P., Rodondi, N., Viswanathan, B., Riesen, W., Vogt, P., & Bovet, P. (2013). Association between conventional risk factors and different ultrasound-based markers of atherosclerosis at carotid and femoral levels in a middle-aged population. *The International Journal of Cardiovascular Imaging, 29*, 589–599.

37. Davidsson, L., Fagerberg, B., Bergstrom, G., & Schmidt, C. (2010). Ultrasound-assessed plaque occurrence in the carotid and femoral arteries are independent predictors of cardiovascular events in middle-aged men during 10 years follow-up. *Atherosclerosis, 209*, 469–473.

38. Depairon, M., Chessex, S., Sudre, P., Rodondi, N., Doser, N., Chave, J. P., Riesen, W., Nicod, P., Darioli, R., Telenti, A., & Mooser, V. (2001). With the Swiss HIV cohort study. Premature atherosclerosis in HIV infected individuals—focus on protease inhibitor therapy. *AIDS, 15*, 329–334.

39. Depairon, M., Tutta, P., van Melle, G., Hayoz, D., Kappenberger, L., & Darioli, R. (2000). Reference values of intima-medial thickness of carotid and femoral arteries in subjects aged 20 to 60 years and without cardiovascular risk factors. *Archives des Maladies du Cœur et des Vaisseaux, 93*, 721–726.

40. Jenkins, P. J., Harper, R. W., & Nestel, P. J. (1978). Severity of coronary atherosclerosis related to lipoprotein concentration. *BMJ, 2*, 388–391.

41. Gensini, G. G. (1983). A more meaningful scoring system for determining the severity of coronary heart disease. *The American Journal of Cardiology, 51*, 606–608.

42. Virmani, R., Kolodgie, F. D., Burke, A. P., Farb, A., & Schwartz, S. M. (2000). Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arteriosclerosis, Thrombosis, and Vascular Biology, 20*, 1262–1275.

43. Sakakura, K., Nakano, M., Otsuka, F., Ladich, E., Kolodgie, F. D., & Virmani, R. (2013). Pathophysiology of atherosclerosis plaque progression. *Heart, Lung & Circulation, 22*, 399–411.

44. Assmann, G., Cullen, P., & Schulte, H. (2002). Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) Study. *Circulation, 105*, 310–315.

45. Akosah, K. O., Schaper, A., Cogbill, C., & Schoenfeld, P. (2003). Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *Journal of the American College of Cardiology, 41*, 1475–1479.

46. Libby, P., Ridker, P. M., & Hansson, G. K. (2009). Leducq transatlantic network on atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. *Journal of the American College of Cardiology, 54*, 2129–2138.

47. Kaur, J. (2014). A comprehensive review on metabolic syndrome. *Cardiology Research and Practice*. doi:10.1155/2014/943162.

48. Caselli, C., D'Amico, A., Cabiati, M., Prescimone, T., Del Ry, S., & Giannessi, D. (2014). Back to the heart: the protective role of adiponectin. *Pharmacological Research, 82C*, 9–20.

49. Wallert, M., Schmölz, L., Galli, F., Birringer, M., & Lorkowski, S. (2014). Regulatory metabolites of vitamin E and their putative relevance for atherogenesis. *Redox Biology, 2*, 495–503.

50. Postley, J. E., Perez, A., Wong, N. D., & Gardin, J. M. (2009). Prevalence and distribution of sub-clinical atherosclerosis by screening vascular ultrasound in low and intermediate risk adults: the New York physicians study. *Journal of the American Society of Echocardiography, 22*, 1145–1151.