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Carotid Plaque Burden as a Measure of Subclinical Atherosclerosis

Comparison With Other Tests for Subclinical Arterial Disease in the High Risk Plaque BioImage Study

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OBJECTIVES The purpose of this study was to compare carotid plaque burden, carotid intima-media thickness (cIMT), ankle-brachial index (ABI), and abdominal aortic diameter (AAD) to coronary artery calcium score (CACS) in people without known cardiovascular disease.

BACKGROUND The clinical utility of risk factors to predict cardiovascular events is limited. Detection of subclinical atherosclerosis by noninvasive tests such as CACS, cIMT, carotid plaque burden, AAD, and ABI may improve risk prediction above that of established risk scoring models, namely, Framingham Risk Score.

METHODS The High Risk Plaque BioImage study investigated 6.101 asymptomatic persons and reports baseline CACS, cIMT, ABI, and AAD. In addition, we present findings from a new 3-dimensional–based ultrasound approach, where the carotid artery was investigated in cross section from proximal in the neck to as distal as possible. From the resulting 10-s video, plaque was outlined on cross-sectional images and all plaque areas were summarized into "plaque burden."

RESULTS The mean age was 68.8 years, and 65.3% of subjects had intermediate Framingham Risk Score (6% to 20% 10-year risk). Carotid plaques were identified in 78% of cases, abnormal ABI in 10%, AAD >20 mm in 28%, and coronary calcium in 68% of participants. Carotid plaque burden was found to correlate stronger with CACS (chi-square 450, $p < 0.0001$) than did cIMT (chi-square 24, $p < 0.0001$), AAD (chi-square 2.9, $p = 0.091$), and ABI (chi-square 35.2, $p < 0.0001$).

CONCLUSIONS In the BioImage study, a new 3-dimensional–based ultrasound method identified more carotid plaques than in previous studies. Compared to other methods, carotid plaque burden was the strongest cross-sectional predictor of CACS, and its clinical utility as predictor of future cardiovascular events is being evaluated in the BioImage study. (BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population; NCT00738725) (J Am Coll Cardiol Img 2012;5:681–9)

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Causal risk factors for atherosclerotic cardiovascular disease are known and constitute important therapeutic targets, but their usefulness as accurate predictors for developing the disease is limited (1). Most heart attacks and strokes occur in people at average risk factor level who are classified by traditional risk factor scoring as low or intermediate risk (2). Conversely, others are misclassified as high risk and mistakenly advised to take drugs to reduce their risk factors for the rest of their life. These facts remind us that, although exposure to causal factors is important, susceptibility to these factors and the disease in question might be more important. Despite great promise, genetic testing for susceptibility has not yet proven useful for risk stratification (3). In contrast, tests for subclinical atherosclerosis may provide prognostic information beyond that provided by traditional risk factor scoring alone (4). Subclinical atherosclerosis can be detected and quantified noninvasively, to show the cumulative effect of all risk and susceptibility factors combined—known and unknown (5).

ABBREVIATIONS AND ACRONYMS

AAD = abdominal aortic diameter

CACS = coronary artery calcium score

CCA = common carotid artery

cIMT = carotid intima-media thickness

CT = computed tomography

MRI = magnetic resonance imaging

3D = 3-dimensional

Noninvasive tests that have been shown to correlate with cardiovascular outcomes include coronary artery calcium score (CACS) determined by computed tomography (CT), carotid intima-media thickness (cIMT), carotid plaque and abdominal aortic diameter (AAD) assessed by ultrasound imaging, and the ankle-brachial index (ABI) test (5–14).

The 2010 American College of Cardiology Foundation/American Heart Association guideline for cardiovascular risk assessment recommends (class IIa) use of CACS by CT, cIMT and carotid plaque by ultrasound, and ABI in asymptomatic adults at intermediate risk according to traditional risk factor scoring (4).

The High Risk Plaque (HRP) BioImage study was initiated to explore the predictive value of noninvasive tests for detection and assessment of subclinical atherosclerosis and risk prediction. We introduced a novel 3-dimensional (3D) carotid ultrasound method to optimize detection of plaque and to quantify the amount of plaque (carotid plaque burden). This paper reports on the prevalence and severity of subclinical arterial disease in 4 vascular territories at baseline in the BioImage study, focusing in particular on the ability to predict coronary atherosclerosis (CACS) from measurements performed in other arteries (cIMT, carotid plaque, ABI, and AAD).

METHODS

The HRP BioImage study. The design and objectives of the BioImage study (NCT00738725) have been published in detail (15). In brief, the BioImage study is investigating whether imaging of target arteries for subclinical atherosclerosis and measurement of ABI and circulating biomarkers add to the predictive value of traditional risk factor scoring systems, namely, the Framingham Risk Score. This population-based study is a prospective, combined cross-sectional and longitudinal observational study. The cross-sectional analyses, which pertain to baseline findings, include the present study.

Enrollment in the BioImage study (January 2008 to June 2009) resulted in inclusion of 7,687 asymptomatic Americans ages 55 to 80 years from the Humana Health System resident in Chicago, Illinois, or Fort Lauderdale, Florida. Of these, 6,104 entered the imaging arm of the study. The BioImage study and method of selection and recruitment was approved by the Western Institutional Review Board, Olympia, Washington. All study participants provided written informed consent and Health Insurance Portability and Accountability Act authorization before enrollment.

Baseline assessments. The baseline examination included blood tests for risk factors, ultrasound imaging of the carotid arteries and infrarenal aorta, ABI measurements, and CT for CAC scoring. Selected participants underwent advanced imaging as previously described (15).

Ultrasound imaging. Philips iU22 ultrasound systems (Philips Healthcare, Bothell, Washington) with various transducers were used for all studies. Four experienced registered vascular technologists performed all imaging studies unaware of findings from other imaging modalities. The scanning protocol included standard imaging of the carotid artery and its branches using generally accepted Doppler criteria for assessment of any degree of narrowing (16).

Measurement of cIMT was performed off line from a 10-s video clip of the distal CCA recorded in longitudinal mode, ensuring the CCA was parallel to the transducer surface (horizontal in the image). Focal zone was set to the far CCA wall, and gain was adjusted high enough so echoes were just observed in the lumen.

In addition, we introduced 3D imaging of the carotid arteries to identify lesions located in the cervical part of the CCA and internal carotid artery (internal carotid artery). With the lack of fully developed

3D technology for carotid imaging at the start of the study, assessment of plaque was undertaken using a high-resolution, linear array 2-dimensional transducer and scanning the artery in cross-section, slowly moving the transducer manually in the cranial direction from the proximal CCA into the distal internal carotid artery (i.e., from the clavicle to jawbone). The speed of the transducer was not controlled, but was assumed to be relatively consistent from participant to participant, on the basis of registered vascular technologist training and the imaging protocol. The resulting 10-s digital video clip of this "manual 3D" cross-sectional sweep was examined in the core ultrasound laboratory for the presence and quantification of plaque.

The infrarenal aorta was examined in cross-section from the renal arteries to the aortic bifurcation, and 1 cross-sectional still image was recorded from the location with greatest diameter.

All ultrasound recordings were read in the core laboratory at the Department of Vascular Surgery, Rigshospitalet, University of Copenhagen (Copenhagen, Denmark) using Philips QLAB quantification software, which was enhanced with specially developed, semiautomated plaque analysis software, QLAB-VPQ (vascular plaque quantification) (Fig. 1). All core laboratory reads were performed by blinded readers, using their individual reading station and unaware of results from other imaging modalities.

Carotid plaque presence and burden. Carotid plaque was defined as local thickening of the cIMT of >50% compared to the surrounding vessel wall, an IMT >1.5 mm, or local thickening >0.5 mm (10,17). If plaque was identified when reviewing the manual 3D sweep movies, the QLAB-VPQ plug-in was used to outline vessel walls and residual lumen in contiguous frames where plaque was present (Fig. 1).

The total of all plaque areas from all images showing plaque was defined as "carotid plaque burden." In case of bilateral or multiple unilateral plaques, the sum of all areas of all plaques was considered as the carotid plaque burden for the patient, which was used for all analyses and comparisons in this study.

Interobserver variability was evaluated by 83 scans being read by both readers, each blinded from the other's findings.

Carotid IMT. Measurement of cIMT was performed with Philips QLAB IMT plug-in, using the 10-s video clips of the distal 10 mm of the CCA in longitudinal view obtained from the lateral aspect of the neck. The reader selected frames with good perpendicular alignment and image quality and adjusted IMT box position if necessary to ensure measurement of mean cIMT over the distal 10 mm of the far wall of the CCA. For every participant, 5 to 10 mean IMT measurements were taken at the same phase of the cardiac cycle (electrocardiography gated) on each artery (right/left) for every participant. All cIMT measurements from both arteries were averaged to create an IMT score.

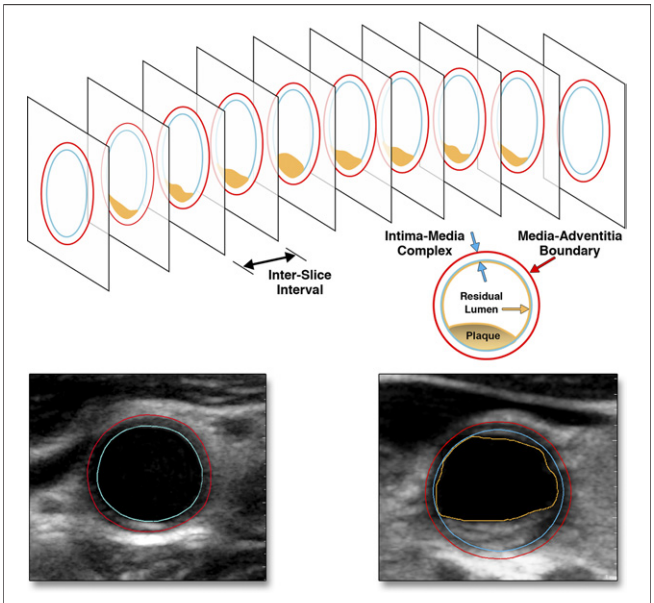

Figure 1. Images of Carotid Plaque Burden

Segment of carotid artery with a plaque (**orange**), which is scanned with a linear array transducer as a series of image slices in transverse section (**top**). Each image is analyzed with semiautomated software to quantify plaque area, plaque grayscale statistics, percent stenosis, and other metrics of interest. Plaque areas from all images in the entire image sequence were summed as "plaque burden." (**Lower left**) Common carotid artery (CCA) with no plaque. The **blue border** represents the lumen/intima border; the **red border** represents the media–adventitia boundary. (**Lower right**) Common carotid artery with plaque. The **red border** and **blue border** are the same as in previous image, but the **orange border** represents the boundary of the plaque.

Abdominal aortic diameter. The iU22 distance calipers were placed at the anterior and posterior wall, tracking the outer vessel wall of the abdominal aorta. Because participants were not fasting, a substantial number of cases (1.028 [16.8%]) had inconclusive scans mainly due to bowel gas, although obesity also precluded usable scans in some.

Ankle-brachial index. After rest for 15 min and with manual blood pressure cuff around the ankle, the dorsal pedal and posterior tibial arteries were identified using a hand-held Doppler device. Once insonated, the cuff was inflated until Doppler signals disappeared and then slowly deflated until

Doppler signals were audible again. The test was repeated 3 times for each of the 2 arteries on both feet and an average blood pressure value for each foot recorded.

For reference, blood pressures were measured on both arms and the highest brachial artery blood pressure was used for reference. The higher blood pressure of the 2 arteries in 1 foot was used for the limb ABI. The lower of 2 limbs ABI was used to classify the participant.

Coronary artery calcification by CT. Noncontrast multidetector CT scans of the coronary arteries were performed using Philips Brilliance 64-slice CT with prospective electrocardiography-gated acquisition. The average estimated radiation was 0.8 to 1.2 mSv. The CT scans were interpreted at the CT core laboratory at Mount Sinai School of Medicine (New York, New York) by board-certified cardiologists or radiologists using Philips EBW or Terarecon Advanced Workstations. Coronary calcium was quantified according to the Agatston method.

Statistical analysis. Power calculations for the BioImage study were conducted to determine the number of subjects required to detect imaging and/or circulating biomarkers with incremental predictive value over traditional cardiovascular risk factors (15).

For the purpose of this cross-sectional study, we chose to compare the imaging methods and ABI assessment to that of CACS, which has been shown to provide incremental predictive information for hard coronary heart disease endpoints. Ordinal logistic regression was used to evaluate individually the association of CACS individually with the following 4 parameters: ABI, AAD, cIMT, and carotid plaque burden. Separate regression models were fit for each of these predictor variables. Coronary artery calcium score, treated as the dependent variable, was categorized into the 4 ordered categories of 0, 1 to 100, 101 to 400, and >400 (8,15). Each predictor variable was treated as follows. The ABI was dichotomized into 2 categories, 0.9 to 1.3 (normal), and <0.9 or >1.3 (abnormal). Abdominal aortic diameter and carotid IMT were treated as untransformed, continuous variables. In a separate analysis, carotid IMT was also considered as a categorical variable, categorized into 4 categories by quartiles of the distribution (<0.65 mm, 0.65 to 0.73 mm, 0.74 to 0.83 mm, and >0.84 mm). Carotid plaque burden was categorized into 4 categories, namely 0, and tertiles of the nonzero values (as in Table 2). The chi-square values from the Wald test are reported for the predictor variables. In each of the ordinal logistic regression models, only subjects complete on CACS and on the predictor variable of interest, and on all other covariates considered in each model, were considered. Data were available for 5,937 subjects for CACS, 6,090 for carotid plaque burden, 6,086 for cIMT, 6,042 for ABI, and 5,073 for AAD. The AAD variable, considered in this study as a continuous variable, exhibited no nonlinearity in association with CACS, and as such no transformation was applied.

The intraclass correlation coefficient was calculated to assess the measurement reproducibility of multiple observers. Values of the intraclass correlation coefficient range from 0 to 1, with values closer to 1 indicating greater homogeneity. The intraclass correlation coefficient was calculated as described by Lohr (18).

No imputation of missing values was performed. No adjustment for any putative outlier parameter values was applied. All p values were 2-tailed. Statis-

Table 1. Baseline Observations

	All Subjects (n = 6,101)
Age, yrs	68.8 ± 6.0
Male	2,663 (43.6%)
Body mass index, kg/m^2	29.1 ± 5.6
Diabetes mellitus	950 (15.6%)
Current smoker	519 (8.5%)
Ethnicity	
White	4,513 (74.0%)
Black	932 (15.3%)
Asian	122 (2.0%)
Hispanic	375 (6.1%)
Other	159 (2.6%)
Cholesterol, mg/dl	
LDL-C	114.1 ± 33.3
HDL-C	55.6 ± 15.3
TC	202.5 ± 38.7
TC:HDL-C ratio	3.85 ± 1.12
Blood pressure, mm Hg	
SBP	139.5 ± 18.5
DPB	78.2 ± 9.1
Renal insufficiency*	238 (3.9%)
Framingham 10-year CHD risk†	
<6%	1,251 (21.1%)
6%–20%	3,877 (65.3%)
>20%	805 (13.6%)

Values are mean ± 1 SD or n (%). Continuous variables are compared using Student *t* test or analysis of variance test for overall difference; categorical variables are compared using the chi-square test. *Renal insufficiency if creatinine ≥1.5 mg/dl for men, ≥1.3 mg/dl for women. †Using LDL-C FRS score sheets (19). Evaluated on subjects complete on all Framingham Risk Score parameters.

CHD = coronary heart disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol.

Table 2. Findings in Each of the Imaging Modalities

CACS (N = 5,937)			
CACS 0	CACS 1–100	CACS 101–400	CACS >400
(n = 1,904)	(n = 1,721)	(n = 1,316)	(n = 996)
Plaque burden (N = 6,090)			
No plaque on either carotid artery	Tertile 1 (<2.58 cm^2)	Tertile 2 (2.58–4.21 cm^2)	Tertile 3 (>4.21 cm^2)
(n = 1,360)	(n = 1,570)	(n = 1,585)	(n = 1,575)
Carotid intima-media thickness (N = 6,086)			
Quartile 1	Quartile 2	Quartile 3	Quartile 4
<0.65 mm	0.65–0.73 mm	0.74–0.83 mm	≥0.84 mm
(n = 1,449)	(n = 1,568)	(n = 1,496)	(n = 1,573)
Aortic diameter (N = 5,073)	<20 mm (n = 3,630)	20–25 mm (n = 1,330)	>25 mm (n = 113)
ABI (N = 6,042)			
0–0.59	0.60–0.89	0.90–1.29	≥1.30
(n = 36)	(n = 327)	(n = 5,451)	(n = 228)

ABI = ankle-brachial index; CACS = coronary artery calcium score.

tical analyses were conducted with the use of SAS software, version 9.0 (SAS Institute, Cary, North Carolina), and R software, version 2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 6,104 participants enrolled in the imaging arm of the BioImage study, 3 were excluded because of incomplete informed consent. Baseline characteristics are shown in Table 1 (19). Most of the participants were white (74%) and belonged to the intermediate risk category by Framingham Risk Score (65.3%). There was a slight majority of women (56.4%).

Imaging data for comparisons were available in 5,937 of cases for CACS, 6,090 for carotid plaque burden, 6,086 for cIMT, 6,042 for ABI, and 5,073 for AAD.

Distributions of parameter variables derived using the various tests for subclinical arterial disease are shown in Figure 2. The CACS and carotid plaque burden revealed left skewed distributions as

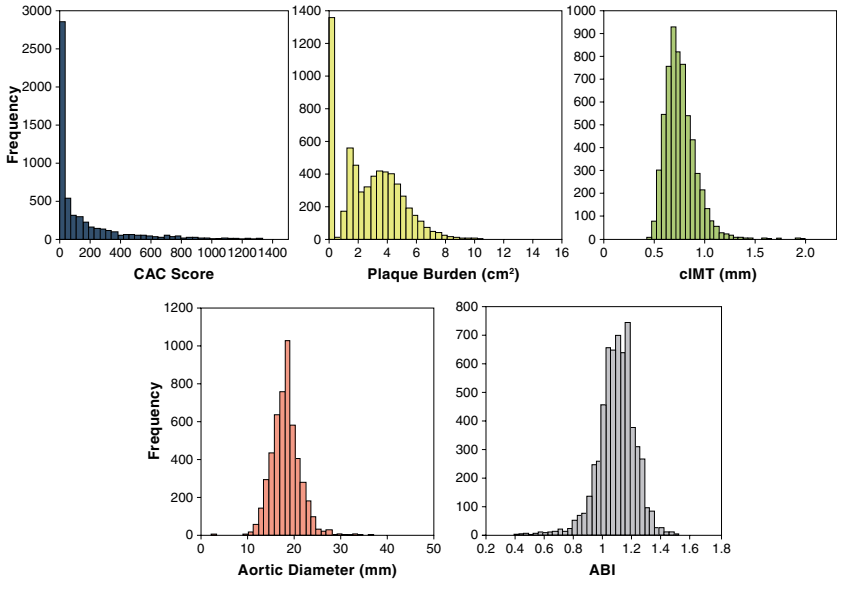

Figure 2. Distributions of Findings Using Different Imaging Modalities and ABI Measurement

Whereas carotid intima-media thickness (cIMT), aortic diameter, and ankle-brachial index (ABI) were normally distributed, coronary artery calcium (CAC) score, and carotid plaque burden were left skewed.

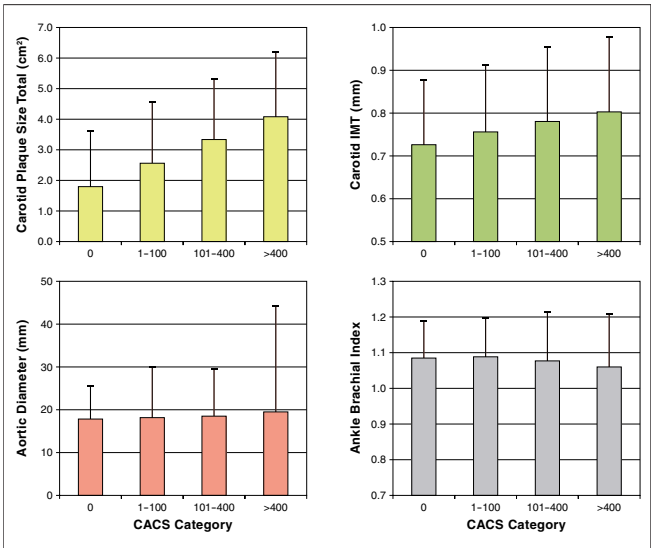

Figure 3. Findings in Different Imaging Methods and ABI Measurements Compared to CACS Groups

(Upper left) Carotid plaque burden. **(Upper right)** Carotid intima-media thickness (cIMT). **(Lower left)** Abdominal aortic diameter. **(Lower right)** Ankle-brachial index (ABI). CACS = coronary artery calcium score.

no calcium or no plaque would be "normal" whereas cIMT, AAD, and ABI measurement were normally distributed. A considerable number of participants had positive findings (Table 2): 4,033 (68%) had CACS >0, and unilateral or bilateral carotid plaque was found in 78% of participants. A normal AAD was found in 3,630 (72%) whereas an aneurysm (AAD >30 mm) was observed in 44 participants (0.9%). The ABI assessment revealed 5,451 (90%) of participants with observations within the normal range (0.9 to 1.3) (Table 2).

Among the imaging modalities and ABI, CACS was most strongly associated with carotid plaque burden (Fig. 3), also after adjustment for a full complement of clinical characteristics comprising sex, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, and smoking status (fully adjusted parameter chi-square value of 450.0, indicating a highly significant model fit) (Table 3). The strength of the association was also evidenced by the high odds ratios for the categories of plaque burden reported in Table 3. For example, compared to patients with no plaque burden, patients in the highest category of plaque burden had a 7.34 (95% CI: 6.36 to 8.47) times greater odds of being in the highest category of CACS (unadjusted), as opposed to in lower CACS categories, than patients in the lowest category of plaque burden (Table 3). By comparison, the analogous odds ratio for patients in the highest quartile of carotid IMT was substantially lower, 2.49 (95% CI: 2.18 to 2.84), indicating a weaker association between high carotid IMT and high CACS values. Carotid IMT (treated either as a continuous or categorized variable) and ABI (categorized as normal or abnormal) were comparable in their individual associations with CACS (fully adjusted chi-square values of 24.0 [continuous] and 28.5 [categorized] for carotid IMT, and 35.2 for ABI). The association of AAD with CACS was attenuated upon adjustment for the full set of clinical factors and was no longer significantly associated with CACS in the fully adjusted model.

Table 3. Results of Ordinal Logistic Regression Models Evaluating Association of Each Imaging Variable Individually With CACS

	Model 0				Model 1				Model 2			
	n	Odds Ratio (95% CI)	Wald Chi-Square	p Value	n	Odds Ratio (95% CI)	Wald Chi-Square	p Value	n	Odds Ratio (95% CI)	Wald Chi-Square	p Value
Plaque burden	5,927	T3: 7.34 (6.36–8.47)	826.5	<0.0001	5,927	T3: 5.37 (4.64–6.22)	554.8	<0.0001	5,898	T3: 4.79 (4.11–5.57)	450.0	<0.0001
		T2: 3.63 (3.17–4.17)				T2: 2.93 (2.55–3.38)				T2: 2.73 (2.36–3.15)		
		T1: 1.97 (1.71–2.26)				T1: 1.79 (1.55–2.06)				T1: 1.70 (1.47–1.96)		
cIMT (continuous)	5,923	1.37 (1.31–1.44)	158.7	<0.0001	5,923	1.15 (1.10–1.21)	31.7	<0.0001	5,894	1.14 (1.08–1.19)	24.0	<0.0001
cIMT (quartiles)	5,923	Q4: 2.49 (2.18–2.84)	202.1	<0.0001	5,923	Q4: 1.55 (1.35–1.78)	40.7	<0.0001	5,894	Q4: 1.46 (1.27–1.69)	28.5	<0.0001
		Q3: 1.64 (1.44–1.88)				Q3: 1.23 (1.08–1.41)				Q3: 1.21 (1.05–1.39)		
		Q2: 1.97 (1.13–1.47)				Q2: 1.15 (1.00–1.31)				Q2: 1.13 (0.99–1.30)		
Aortic diameter	4,940	1.30 (1.23–1.37)	94.5	<0.0001	4,940	1.06 (1.01–1.13)	4.8	0.029	4,916	1.05 (0.99–1.11)	2.9	0.091
ABI	5,879	2.11 (1.80–2.48)	83.0	<0.0001	5,879	1.78 (1.51–2.10)	47.8	<0.0001	5,850	1.65 (1.40–1.95)	35.2	<0.0001

Model 0 = univariate. Model 1 = model 0 adjusted for age and sex. Model 2 = model 0 adjusted for age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, and smoking status. Variables are defined as discussed in the Methods section. Categorical variable odds ratios are relative to lowest category. Odds ratio for ankle-brachial index (ABI) is relative to the category comprising values from 0.9 to 1.3, inclusive. The number of subjects available (n) is the intersection of all subjects having a coronary artery calcium score (CACS) (n = 5,937) and also complete on the indicated imaging parameter.
CI = confidence interval; cIMT = carotid intima-media thickness; Q = quartile.

Testing for interobserver variation of reading, the intraclass correlation coefficient was 0.823 when plotting the 2 readers' findings of "plaque burden." Classifying cases into 4 groups—no plaque and tertiles of quantified plaques—the kappa value was 0.55 comparing the 2 readers' findings.

DISCUSSION

The HRP BioImage study is the first large population-based study to evaluate the presence and severity of subclinical arterial disease in 4 different vascular beds at the same baseline examination. A novel 3D-based approach using ultrasound imaging to quantify carotid plaque burden in the carotid arteries was found to correlate more closely with coronary atherosclerosis (CACS) than cIMT, ABI, and AAD. That atherosclerosis is a generalized disease was confirmed by investigating 4 different vascular beds.

New approach to quantify atherosclerosis in carotid arteries. Using a novel "manual 3D" ultrasound approach to screen the carotid arteries to identify atherosclerotic lesions, the prevalence of carotid plaques was found to be 78%. This prevalence is nearly 2-fold higher than what has been reported in the literature (20–23). The higher prevalence in our study likely reflects the systematic use of 3D ultrasound screening approach along the full length of the accessible carotid arteries from the clavicle to the jaw, but also to some extent that the participants were older than average in the studies compared to. The only study, which until now has reported prevalence of carotid plaque near to what we found, was a substudy of the Rotterdam Study. In this older population, of whom not all were free from clinical atherosclerosis, carotid plaque was identified in 67% (20). Our manual 3D approach to carotid ultrasound scanning identified more atherosclerotic lesions than reported by others using regular 2-dimensional ultrasound. This original observation is supported by our findings in CACS, the other imaging methods, and ABI measurement, which are similar to those reported by other studies with respect to subclinical atherosclerosis observed, in a population with comparable Framingham Risk Score (see following text).

Identifying carotid atherosclerotic lesions in the majority of our subjects (78%), who were all free from clinical atherosclerotic disease at the time of investigations, raises the question of clinical relevance. However, similar to coronary calcium, which also could be detected in the majority of subjects, we think quantification is important. Therefore, we summarized all measured plaque areas into plaque burden, which revealed a large spread of observations. The hypothesis of quantification is, the greater amount of atherosclerosis, the higher the risk.

BioImage compared to other population-based studies. With an average age of participants of 68.8 years, we found coronary calcium of varying degrees in 68% of participants. This finding, and the distribution between CACS groups, 0, 1 to 99, 100 to 399, and >400, corresponds well with what has been reported in other studies investigating people without known coronary heart disease, taking sex, age, and ethnicity of the investigated population into account (6,20,23–25). We identified 9.1% having abnormal ABI among the BioImage participants, 6% with ABI <0.9 and 3.1% with ABI >1.3. This also compares well with findings in other studies (12,13), again considering the population investigated. The ABI captures later stages of atherosclerosis, since not only should plaque be present in the lower limb arteries, it should also reduce the residual lumen in the affected artery significantly, combined with insufficient collateral blood supply to keep resting circulation within normal range. A normal aorta was found in 72% of cases whereas 26% had a diameter of 20 to 25 mm and 2% an AAD >25 mm. The Cardiovascular Health Study found 58% of participants to have aortic diameter <20 mm, 34% to be in the group 20 to 25 mm, and 8% to have an AAD >25% (14). However, the participants in the Cardiovascular Health Study were older as the average age was 75 years compared to 68.8 years in our study. Aortic aneurismal disease is known to be a condition of the elderly.

Subclinical arterial disease in noncoronary versus coronary arteries. We found that carotid plaque burden, quantified by ultrasonography as described in this paper, was more strongly correlated to CACS than any of the other tests used to assess noncoronary arterial disease (cIMT, ABI, and AAD). It is assumed that in view of the performance of CACS, this closer correlation will correspond to improved risk prediction. As carotid plaque burden assesses findings ranging from no plaque to extremes, just like CAC assessment identifies persons with no calcium at one end of the spectrum to persons with much calcium (>400), that may not be surprising. However, considering that atherosclerosis is a systemic disease, namely, developing in many vascular beds more or less

simultaneously, and that atherosclerotic plaques develop from fatty streaks into complex plaques where calcium eventually is deposited, it was interesting to notice that in a considerable number of participants with no coronary calcium, carotid plaque was present. This finding represents early stages of atherosclerosis development in the carotid artery where the counterpart in the coronary arteries have not reached the late stage where calcification takes place, revealing a further potential of quantification of plaque by 3D ultrasound. That carotid plaque quantification in this paper expressed as carotid plaque burden correlates strongly with CACS, and the fact that ultrasonography is noninvasive and does not involve radiation suggests advantages of this novel method. Although with methodological limitations, assessing plaque area in 2-dimensional carotid images has indicated the potential of carotid plaque quantification. The Tromsø Study showed that carotid plaque area was a stronger predictor of first ever myocardial infarction than was cIMT (26). However, evaluation of the true predictive potential of carotid plaque quantification by 3D ultrasound awaits cardiovascular endpoints in the BioImage and other studies. The BioImage study is expected to report the first outcomes analysis in 2012.

The poorer correlation of ABI and AAD with CACS may not be surprising. As already noted, reduced ABI is found in late stages of atherosclerosis causing blood flow obstruction, thus, small calcified plaques in the coronary arteries may well be identified in patients with similarly nonobstructive lesions in the lower limbs. Similarly, aortic dilation most often occurs in the elderly, so younger persons with subclinical coronary calcification may have normal aortic dimensions. Conversely, patients with low ABI and AADs >25 mm had high calcium score: participants with ABI <0.9 on average had average CACS of 444 compared to 216 in participants with normal ABI (0.9 to 1.3; $p <$ 00001). Similarly, patients with AAD >25 mm had an average CACS of 654 as compared to 191 observed in patients with normal AAD (<20 mm; $p < 0.0001$).

Study limitations. Even though CACS has been shown to be a strong predictor of future cardiovascular events, the choice of CACS as the surrogate endpoint/gold standard for comparisons of imaging methods and ABI measurement does not necessarily translate into clinical relevance. Because of the manual nature of the cross-sectional sweep of the carotid artery, plaque burden is an approximation of the amount of atherosclerotic disease, and is not a true measurement of the plaque volume present. Nonetheless, this approach is simple and may be sufficient to categorize the amount of disease present as none, minor, moderate, or severe. Factors that might influence acquisition of plaque burden are speed of movement of the transducer when performing the carotid sweep and frame rate. Concerning changes in the latter, default depth was 4 cm with which the majority of cases were examined. Changing to 3 cm would result in a 9% increase in frame rate whereas a change to a depth of 5 cm would result in a decrease of 6%. As mentioned earlier in the discussion, full reproducibility will be reported separately. Reproducibility of reading revealed a fair kappa value for classifying into groups of increasing plaque burden. The cIMT method used in the BioImage study included only acquisition from 1 angle of the distal CCA and seems reasonable and justified by recent observations (27,28) even though it does not follow "standard protocol" (10). However, rather than assessing IMT in only 1 image, we assessed IMT in 5 different images from each CCA, to obtain a representative value from the distal 10 mm CCA segment.

CONCLUSIONS

We found carotid plaque burden correlated stronger with coronary atherosclerosis (CACS) than did cIMT, ABI, and AAD at baseline in the BioImage study. Thus, 3D quantification of carotid plaque by ultrasound may be a stronger predictor of atherosclerotic cardiovascular disease than the current 2-dimensional approach. However, the predictive value of this novel approach remains unknown until we have prospective outcome data.

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Key Words: ABI ■ aortic diameter ■ cardiovascular disease ■ cardiovascular risk prediction ■ carotid plaque ■ coronary calcium ■ IMT.