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ORIGINAL INVESTIGATIONS

Prevalence, Impact, and Predictive Value of Detecting Subclinical Coronary and Carotid Atherosclerosis in Asymptomatic Adults

The BioImage Study

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ABSTRACT

BACKGROUND Although recent studies suggest that measuring coronary artery calcification (CAC) may be superior to indirect atherosclerotic markers in predicting cardiac risk, there are limited data evaluating imaging-based biomarkers that directly quantify atherosclerosis in different vascular beds performed in a single cohort.

OBJECTIVES The BioImage Study (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) sought to identify imaging biomarkers that predict near-term (3-year) atherothrombotic events.

METHODS The BioImage Study enrolled 5,808 asymptomatic U.S. adults (mean age: 69 years, 56.5% female) in a prospective cohort evaluating the role of vascular imaging on cardiovascular risk prediction. All patients were evaluated by CAC and novel 3-dimensional carotid ultrasound. Plaque areas from both carotid arteries were summed as the carotid plaque burden (cPB). The primary endpoint was the composite of major adverse cardiac events (MACE) (cardiovascular death, myocardial infarction, and ischemic stroke). A broader secondary MACE endpoint also included all-cause death, unstable angina, and coronary revascularization.

RESULTS Over a median follow-up of 2.7 years, MACE occurred in 216 patients (4.2%), of which 82 (1.5%) were primary events. After adjustment for risk factors, and compared with individuals without any cPB, hazard ratios for MACE were 0.78 (95% confidence interval [CI]: 0.31 to 1.91), 1.45 (95% CI: 0.67 to 3.14), and 2.36 (95% CI: 1.13 to 4.92) with increasing cPB tertile, with similar results for CAC. Net reclassification significantly improved with either cPB (0.23) or CAC (0.25). MACE rates increased simultaneously with higher levels of both cPB and CAC.

CONCLUSIONS Detection of subclinical carotid or coronary atherosclerosis improves risk predictions and reclassification compared with conventional risk factors, with comparable results for either modality. Cost-effective analyses are warranted to define the optimal roles of these complementary techniques. (BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population; NCT00738725) (J Am Coll Cardiol 2015;65:1065–74) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

cIMT = carotid intima-media thickness

cPB = carotid plaque burden

CRF = conventional risk factor(s)

CT = computed tomography

CVD = cardiovascular disease

HRP = high-risk plaque

MACE = major adverse cardiac event(s)

MI = myocardial infarction

NRI = net reclassification index

US = ultrasound

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both industrialized and low-income to middle-income countries (1,2). Global expenditures attributable to CVD are projected to rise as cardiac risk factors continue to increase in prevalence. Prevention of CVD is less costly than treating its complications (3), thus, identification of subclinical disease in the asymptomatic phase has emerged as a public health and economic imperative.

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Within this context, cardiac risk stratification begins with calculating the probability of an incident event using conventional algorithms, such as the Framingham equation. However, most initial cardiac events do not occur among those considered "high risk," highlighting the need to improve risk stratification over existing approaches (4). Because atherosclerosis is a systemic process, it is intuitive that assessing disease at multiple, rather than single, vascular sites may provide greater insight on the overall burden and risk associated with subclinical atherosclerosis. Although multiple studies have examined such associations, many combined direct (i.e., coronary artery calcium [CAC]) and indirect (i.e., carotid intima-media thickness [cIMT]) markers of atherosclerosis, or classified disease using semiquantitative approaches (i.e., present/absent), potentially rendering risk estimates imprecise (5–12). Moreover, the clinical relevance of detecting subclinical disease rests on improving prediction of CVD risk over traditional factors (13). Accordingly, we sought to evaluate the prevalence and risk associated with subclinical atherosclerosis using CAC and a novel carotid ultrasound (US) approach among asymptomatic adults. We also examined the impact of each technique on improving risk prediction and reclassification compared with traditional risk factors.

METHODS

The BioImage Study (BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population; NCT00738725) was a prospective study evaluating cross-sectional associations among imaging and circulating biomarkers and their ability to predict atherothrombotic events in asymptomatic subjects. Methodological aspects were previously described in detail (14). Herein, we report on the primary objective of the BioImage Study, which was to identify imaging biomarkers that predict near-term (3-year) atherothrombotic events.

STUDY POPULATION. Between January 2008 and June 2009, the BioImage Study enrolled 7,687 asymptomatic men 55 to 80 years of age and women 60 to 80 years of age who were members of the Humana Health System and residents of the Chicago, Illinois, or Fort Lauderdale, Florida, metropolitan areas. Of these, 6,102 subjects entered the imaging arm of the study. Subject eligibility, including freedom from previous history of cardiovascular disease (myocardial infarction [MI], stroke, angina, heart failure, arterial revascularization), was ascertained by baseline review of administrative claims data, followed by telephone interview, and finally by in-person baseline examination and interview. Participants were additionally required to be free of active cancer treatment, any medical condition precluding long-term participation or inability to complete 3-year follow-up, chest computed tomography (CT) scan within the previous 12 months, and have no language barrier or inability to comply with study procedures. The BioImage Study was approved by Institutional Review Board review. Before enrollment, all study participants provided written informed consent and Health Insurance Portability and Accountability Act authorization.

BASELINE EXAMINATIONS. A nonfasting venous blood sample was processed for routine chemistry tests, including serum creatinine and lipid levels. Diabetes mellitus was defined as current use of oral hypoglycemic agents, insulin, or self-report of the

AstraZeneca, The Medicines Company, Bristol-Myers Squibb/Sanofi, and Lilly/Daiichi Sankyo; consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen Pharmaceuticals, Maya Medical, Merck & Co., Regado Biosciences, and Sanofi; and serves on the advisory boards of Covidien, Janssen Pharmaceuticals, Merck & Co., Endothelix, Inc., and Sanofi. Dr. Sillesen has received honoraria from Cardoz, Philips, Novartis, and Takeda. Dr. Muntendam is a former employee of BG Medicine, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Tasneem Naqvi, MD, served as Guest Editor for this paper.

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diagnosis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Current smoking status was self-reported.

US ASSESSMENT OF TOTAL PLAQUE BURDEN. Details regarding US plaque quantification were previously published (15). Carotid plaque was defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm; or 50% of the surrounding IMT value; or demonstrating a thickness >1.5 mm, as measured from the media-adventitia interface to the intima-lumen interface (16,17). Assessment of plaque in both carotid arteries was undertaken using a high-resolution, linear array, 2-dimensional transducer by scanning in longitudinal and cross section from the proximal common carotid artery into the distal internal carotid artery. Plaque areas from all images in the cross-sectional sweeps from both the right and left carotid arteries were summed as *plaque burden*, a quantitative metric of the total plaque area (mm^2) across the length of the visualized carotid (15). US scans were read in the University of Copenhagen core laboratory. Technologists performing all imaging studies, and core laboratory readers were blinded to results from other imaging modalities.

CAC SCORE. A Philips Brilliance 64-slice CT (Philips Healthcare, Andover, Massachusetts) with prospective electrocardiographically gated acquisition was used for noncontrast multidetector CT scans of the coronary arteries to evaluate CAC. CT scans were interpreted at the Icahn School of Medicine at Mount Sinai core laboratory. Coronary calcium was quantified using the Agatston method. Patients and physicians were notified of results if any of the following were detected: emergent findings needing immediate clinical evaluation, very high CAC score (>75th percentile), or abdominal aortic aneurysm.

ENDPOINTS. An independent clinical events committee used source medical records to adjudicate nonfatal and fatal events. Deaths were identified by Social Security and National Death Index searches. Upon confirmation of Health Insurance Portability and Accountability Act authorization, source medical records for both deaths and nonfatal events were attained from healthcare institutions identified through Humana Health System administrative claims data. MI was defined according to the 2007 Universal Definition (18). Unstable angina was defined according to the Braunwald classification (19,20). Stroke was defined as a sudden focal neurological deficit of cerebrovascular etiology persisting beyond 24 h and not due to another identifiable cause, such as a tumor or seizure, or as a clinically relevant new lesion detected on CT or magnetic resonance imaging (21). Deaths were classified as cardiovascular or noncardiovascular. The primary endpoint included cardiovascular death, spontaneous MI, or ischemic stroke (major adverse cardiovascular events [MACE]). The secondary MACE endpoint comprised all-cause death, spontaneous MI, ischemic stroke, unstable angina, or coronary revascularization.

STATISTICAL APPROACH. Baseline characteristics were summarized using means and percentages for continuous and categorical variables, respectively. For each modality we grouped participants as either having no measurable atherosclerosis or by tertile of increasing CAC or carotid plaque burden (cPB). CAC scores corresponding to the 1st, 2nd, and 3rd tertiles were 1 to 62, 63 to 275, and 276 to 7,588, respectively. The corresponding values for cPB in the 1st, 2nd, and 3rd tertiles were 4.3 to 169.4 mm^2, 169.5 to 536.1 mm^2, and 536.2 to 6962.7 mm^2, respectively. We performed several cross-sectional analyses. First, we calculated the prevalence of polyvascular atherosclerosis, defined as any measurable atherosclerosis in both territories, for the entire cohort and within Framingham risk groups. As many BioImage Study participants were on lipid-lowering medications at baseline, we assigned Framingham risk groups using the office-based version of the CVD risk prediction equation, which substitutes body mass index for cholesterol values (22). Secondly, we calculated the prevalence of CAC within each cPB stratum and compared frequencies across groups using the chi-square test.

Rates of adverse events were estimated at 3 years using the Kaplan-Meier method and compared across groups using the log-rank test. Associations between CAC, cPB, and adverse events were assessed using Cox proportional hazards regression. For each imaging modality, we first generated a multivariable model that included the following covariates: age; race; and sex (Model 1). Subsequently, Model 2 was additionally adjusted for diabetes mellitus; current smoking; body mass index; systolic blood pressure; antihypertensive agent use; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; and use of lipid-lowering drugs. The significance of increasing CAC or cPB was assessed using a trend test across groups. As exploratory analyses, we examined these associations using quartiles of CAC or cPB and performed formal interaction tests between the main effects of CAC, cPB, and baseline use of lipid-lowering therapy.

To evaluate the incremental value of adding CAC or cPB to conventional risk factors (CRF) for risk prediction, we compared the following metrics of model

performance after adding CAC or cPB to our baseline CRF model: overall fit; discrimination; calibration; and reclassification. For these analyses, CAC and cPB were entered as continuous variables after log transformation. Changes in model fit were assessed using the likelihood ratio test (23). Discrimination was evaluated with the Harrell's c-index (24). Changes in the c-index were calculated using a cross-fold validation approach, as described by Newson (25). Calibration was assessed using a modified version of the Hosmer-Lemeshow test (26). Reclassification was calculated using the category-free and categorical versions of the net reclassification index (NRI), as described by Pencina et al. (27,28). Reclassification tables were generated on the basis of Framingham risk categories using the CVD risk prediction equation (22) with CAC or cPB values >2nd tertile leading to up-classification (high), values <2nd tertile leading to down-classification (low), and values within the 2nd tertile as intermediate (29). Separate calculations were made for reclassification among intermediate-risk participants alone to provide the clinical NRI. Analogous NRI calculations were performed on the basis of pooled cohort risk equations.

Per the study protocol, participants were followed for a minimum of 3 years or until 600 events were identified via semiannual questionnaires or claims analysis. All study participants were followed until time of death, end of enrollment in the Humana Health System, or close of study, whichever came first. All analyses were performed using Stata version 12.1 (College Station, Texas) and R software for Macintosh (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 1 Flow of Study Participants in the HRP BioImage Study

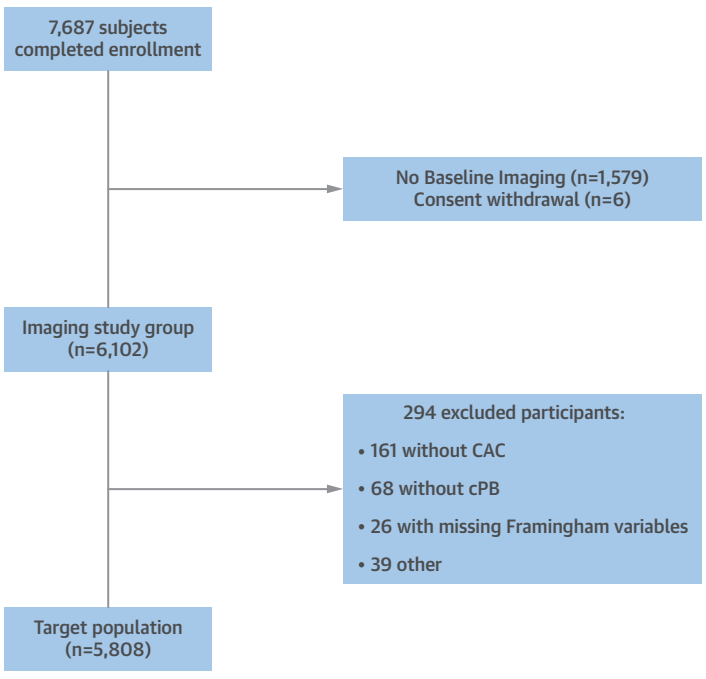


Diagram depicting total number of subjects enrolled and reasons for exclusion for the present analysis. HRP = high-risk plaque.

RESULTS

Participant flow in the high-risk plaque (HRP) BioImage Study is shown in **Figure 1**. Of 7,687 Humana members who completed enrollment, a total of 6,102 were included in the bioimaging study group. Among these, 294 were excluded due to missing covariates and/or imaging data, yielding a final study population of 5,808 adults. By the study end, a total of 1,139 (19.6%) study participants no longer were Humana members and had not experienced any adverse events during their membership. Median follow-up among these individuals was 1.1 years. All analyses were repeated after excluding these participants, yielding similar results to the overall cohort.

Table 1 shows baseline demographic and clinical characteristics for the entire cohort. The average age was approximately 69 years, and 56% of participants were female. The prevalence of polyvascular atherosclerosis is shown in **Figure 2**. Any subclinical atherosclerosis in both carotid and coronary arteries was detected in 58% of the entire cohort. This prevalence increased with higher Framingham risk group. Cross-sectional associations between CAC and cPB are shown in Online Figure 1. The prevalence of CAC increased in a graded fashion with greater cPB.

Over a median follow-up of 2.7 years (interquartile range: 2.5 to 3.1 years), there were a total of 216 first MACE events (4.2%) including 108 deaths (2.2%), of which 27 were cardiovascular (0.5%), 34 spontaneous MIs (0.7%), 30 ischemic strokes (0.6%), 18 hospitalizations for unstable angina (0.3%), and 79 coronary revascularization procedures (1.6%). There were a total of 82 primary MACE events with a cumulative incidence of 1.5% at 3 years. **Figures 3A to 3D** show the crude 3-year event rates for primary and secondary MACE by cPB and CAC groups. Marked trends of higher risk were observed with increasing CAC and cPB (log rank $p < 0.001$ for all). Similar patterns were observed for the secondary MACE endpoint.

The **Central Illustration** shows 3-year event rates among all study participants after cross-classification by both CAC and cPB. The lowest-risk participants were those without any measurable CAC or cPB, whereas event rates were highest among those in the

third tertile for both techniques. Within each stratum of CAC, event rates increased with higher levels of cPB and vice versa.

Table 2 shows hazard ratios for MACE associated with CAC and cPB categories. Significant trends for increasing risk associated with either CAC or cPB persisted after adjusting for all risk factors for both endpoints (Models 1 and 2). As shown in Online Tables 1A and 1B, similar patterns of increasing risk were observed with mutual adjustment for both imaging modalities. Associations between atherosclerosis and MACE remained similar in magnitude and direction after repeating all analyses using age/sex-specific tertiles for CAC and cPB. Results were unchanged when using quartiles of CAC or cPB (Online Tables 2A and 2B). Formal interaction tests between CAC, cPB, and baseline use of lipid-lowering therapy use were nonsignificant for both MACE endpoints (all p interaction > 0.1).

Table 3 shows the impact on model performance of adding CAC or cPB to the baseline CRF model. Both imaging parameters significantly improved model fit. C-statistics for the primary and secondary MACE outcomes associated with the baseline CRF model were 0.66 and 0.68, respectively, comparable to results obtained with traditional risk factors in cohorts with a similar age to BioImage Study participants (31,32). The addition of CAC to the baseline model significantly improved the c-statistic for both outcomes, whereas cPB did not significantly change the c-statistic for the primary MACE outcome. All models were well calibrated, indicating good agreement between observed events and predicted estimates.

As shown in **Table 3**, both cPB (0.23) and CAC (0.25) significantly improved category-free NRI when added to the baseline CRF model. Online Tables 3 and 4 are reclassification tables for the categorical NRI on the basis of the Framingham risk score, showing comparable changes for both CAC and cPB. As shown in Online Figure 2, the clinical NRIs for the primary MACE outcome with CAC and cPB were 0.53 and 0.49, respectively. Similar results were noted for the secondary MACE outcome. Results for the categorical and clinical NRIs on the basis of the Pooled Cohort Risk Equations are shown in Online Tables 5 and 6, and Online Figure 3, which also showed comparable findings for CAC and cPB.

DISCUSSION

In the present study of approximately 6,000 asymptomatic adults who underwent multimodality vascular imaging of both coronary and carotid arteries, we found that subclinical atherosclerosis was highly prevalent, detectable in both vascular territories in close to 60% of participants. Rates of adverse events increased in a graded fashion with increasing CAC or cPB, and associations remained significant after

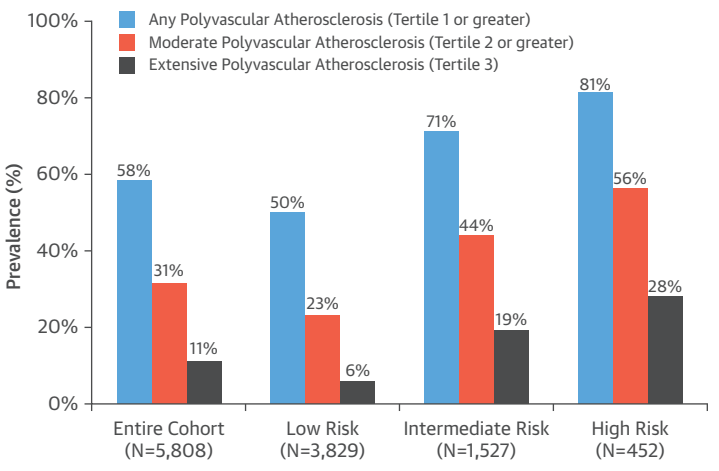
TABLE 1 Baseline Characteristics of the HRP BioImage Cohort (N = 5,808)

Age, yrs	68.9 ± 6.0
Female	3,281 (56.5)
White race	4,301 (74.0)
Diabetes mellitus	857 (14.8)
Current smoker	496 (8.5)
Hypertension	3,614 (62.2)
BMI, kg/m^2	29.0 ± 5.5
LDL-C, mg/dl	114.2 ± 33.2
HDL-C, mg/dl	55.7 ± 15.3
Total cholesterol, mg/dl	202.5 ± 38.6
Systolic BP, mm Hg	139.4 ± 18.5
Diastolic BP, mm Hg	78.2 ± 9.1
Lipid-lowering therapy	1,993 (34.3)
Serum creatinine, mg/dl	0.97 ± 0.21
Framingham 10-yr risk, mean	9.2%
<10%	3,829 (65.9)
10% to 20%	1,527 (26.3)
≥20%	452 (7.8)
Pooled Equation 10-yr risk,* mean	7.2%
<7.5%	3,703 (64.0)
7.5% to 20%	1,879 (32.3)
≥20%	223 (3.8)

Values are mean ± SD or n (%). *10-Year risk estimates obtained from Pooled Cohort Risk Equations (30).

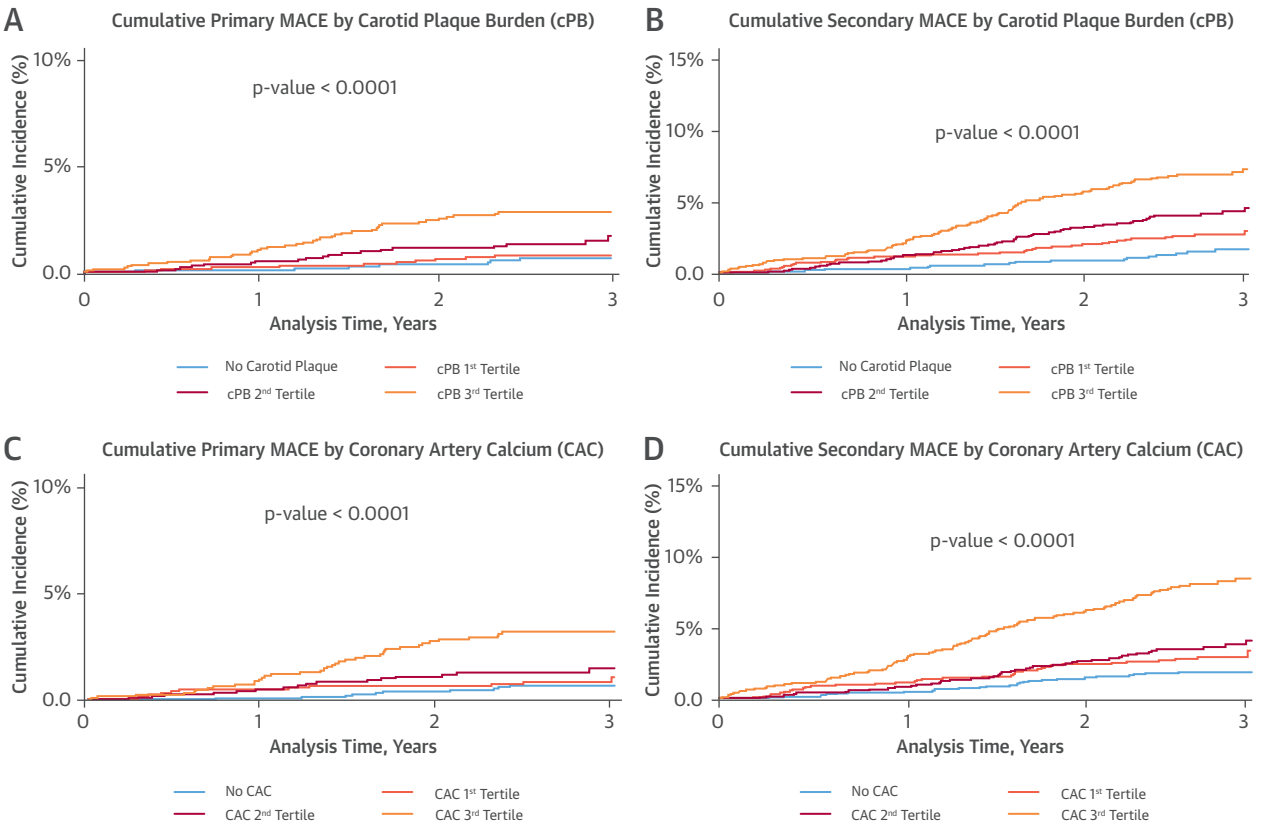
BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; HRP = high-risk plaque; LDL-C = low-density lipoprotein cholesterol.

FIGURE 2 Prevalence of Polyvascular Atherosclerosis in the Overall Cohort and by Framingham Risk Groups



Polyvascular atherosclerosis was defined as coronary artery calcium >0 and carotid plaque burden >0. **Bar graphs** show prevalence of any (tertile 1 or greater), moderate (tertile 2 or greater), and extensive (tertile 3) polyvascular atherosclerosis.

FIGURE 3 Cumulative Incidence for Primary and Secondary MACE Endpoints Over 3 Years



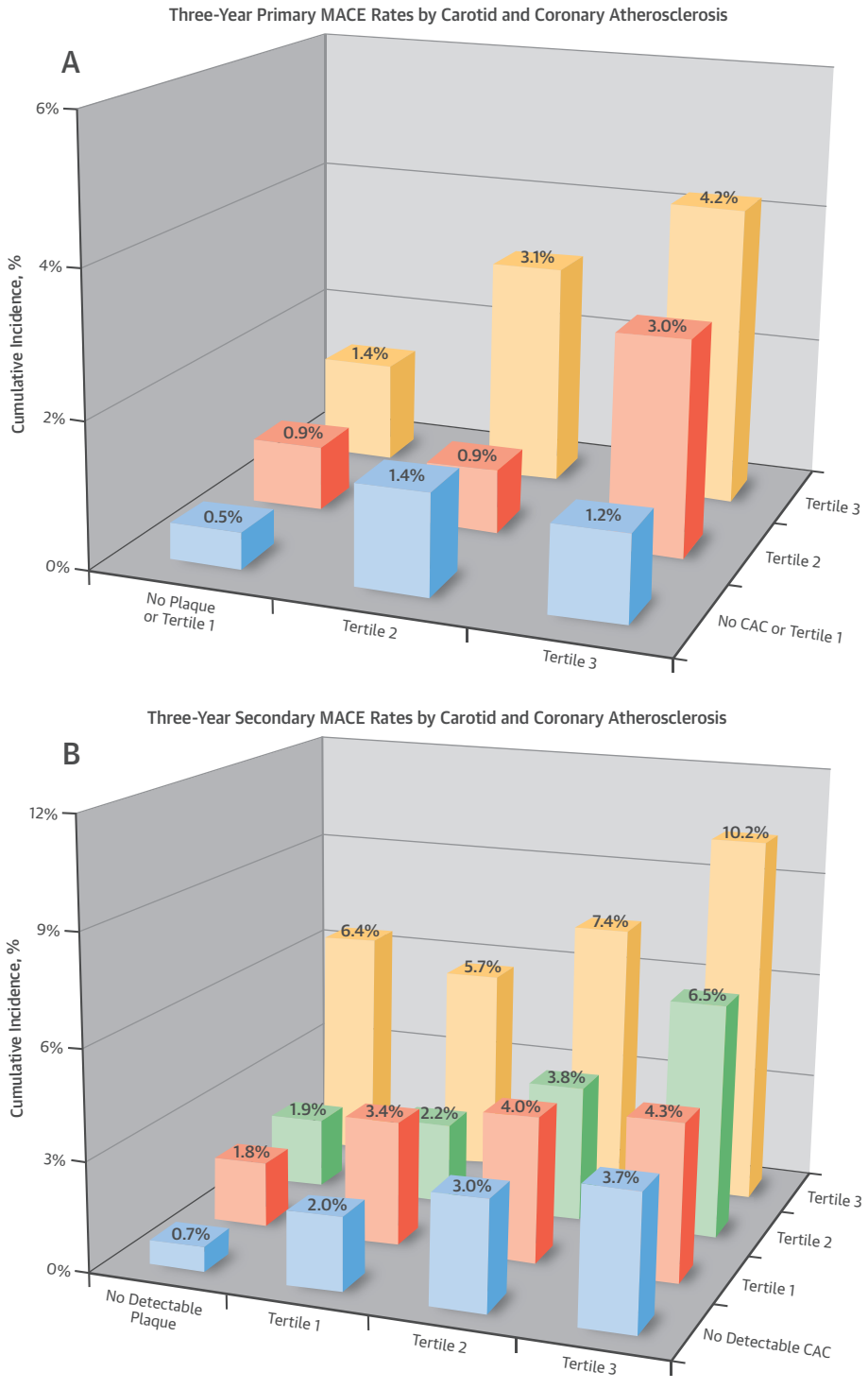
Crude rates calculated as Kaplan-Meier estimates at 3 years for primary and secondary major adverse cardiac event(s) (MACE) by **(A,B)** carotid plaque burden (cPB) and **(C,D)** coronary artery calcium (CAC).

multivariable adjustment. Gradients in risk were most apparent when considering results from both modalities, suggesting a synergistic influence of polyvascular atherosclerosis on short-term CVD risk. Moreover, we found that quantifying atherosclerosis with either CAC or a novel 3-dimensional carotid US-based method yields comparable gains over classical risk factors in CVD risk prediction.

PREVALENCE. We observed a substantially higher prevalence of polyvascular atherosclerosis than estimated from other primary prevention cohorts (6,7). For example, Lamina et al. (7) detected atherosclerosis in both arteries in 38% of participants in a German sample with a mean age of 50 years evaluated by US in the carotid and femoral arteries. The greater burden of atherosclerosis we observed likely reflects the older age of HRP BioImage participants, coupled with the use of more sensitive modalities to detect atherosclerosis. Specifically, our method for detection of carotid atherosclerosis involved interrogation of both carotid arteries from the clavicle to the jaw, rather than focusing on the carotid bifurcation alone, which increased our sensitivity to detect carotid plaques (15). Despite these differences, our results and prior data consistently found that a substantial proportion of individuals with atherosclerosis are classified as low risk using standard risk prediction algorithms (6). Our findings, combined with earlier data, reinforce the imprecision inherent in relying on traditional risk factors alone to classify CVD risk.

ASSOCIATIONS BETWEEN CAC, cPB, AND ADVERSE EVENTS. Consistent with earlier reports examining coronary or carotid atherosclerosis in isolation, we found that rates of adverse events increased in a stepwise fashion with greater CAC or cPB (5,7,8,33,34). By evaluating both modalities in concert, however, we showed that the risk within each vascular stratum was not uniform, but varied by the degree of atherosclerosis in the corresponding

CENTRAL ILLUSTRATION **Cumulative 3-Year Rates for Primary and Secondary MACE Endpoints by CAC and cPB Categories**



Baber, U. et al. J Am Coll Cardiol. 2015; 65(11):1065–74.

Crude rates were calculated as Kaplan-Meier estimates at 3 years. **(A)** Primary MACE endpoints, with the no atherosclerosis and 1st tertile groups combined. **(B)** Secondary MACE endpoints. CAC = coronary artery calcium; cPB = carotid plaque burden; MACE = major adverse cardiac event(s).

TABLE 2 Hazard Ratios (95% CI) for Primary and Secondary MACE Endpoints Associated With CAC and cPB

	No Atherosclerosis	Tertile 1	Tertile 2	Tertile 3	p Value (Trend)
Hazard ratios (95% CI) for primary MACE endpoint					
cPB					
Model 1	1.0 (ref)	0.87 (0.36–2.10)	1.56 (0.72–3.36)	2.85 (1.39–5.82)	<0.001
Model 2	1.0 (ref)	0.78 (0.31–1.91)	1.45 (0.67–3.14)	2.36 (1.13–4.92)	0.03
CAC					
Model 1	1.0 (ref)	1.13 (0.52–2.50)	1.54 (0.74–3.22)	3.15 (1.60–6.21)	<0.001
Model 2	1.0 (ref)	1.11 (0.49–2.53)	1.58 (0.74–3.38)	2.99 (1.48–6.05)	0.01
Hazard ratios (95% CI) for secondary MACE endpoint					
cPB					
Model 1	1.0 (ref)	1.59 (0.92–2.74)	2.27 (1.36–3.79)	3.41 (2.08–5.58)	<0.001
Model 2	1.0 (ref)	1.53 (0.89–2.65)	2.14 (1.28–3.59)	2.87 (1.73–4.74)	0.001
CAC					
Model 1	1.0 (ref)	1.47 (0.91–2.36)	1.66 (1.04–2.64)	3.32 (2.16–5.10)	<0.001
Model 2	1.0 (ref)	1.39 (0.85–2.25)	1.54 (0.96–2.47)	2.97 (1.92–4.60)	<0.001

Model 1 was adjusted for age, race, and sex. Model 2 was additionally adjusted for: diabetes mellitus; current smoking; body mass index; systolic blood pressure; antihypertensive agent use; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; and use of lipid-lowering drugs.

CAC = coronary artery calcium; CI = confidence interval; cPB = carotid plaque burden; CVD = cardiovascular; MACE = major adverse cardiovascular event(s).

vascular bed. Gradients in risk between increasing CAC or cPB and adverse events remained independent of one another and of other risk factors, highlighting the incremental impact of systemic atherosclerosis on short-term CVD risk. Although several previous studies examined similar associations, many combined direct and indirect markers of atherosclerosis or relied on semiquantitative approaches to measure disease. In a predominantly Caucasian cohort from Rotterdam, for example, van der Meer et al. (8) found that the risk for MI was strongly associated with a composite atherosclerosis score. By contrast, we studied a more contemporary and racially diverse population in whom atherosclerosis was directly quantified on a continuous scale, allowing us to more precisely estimate the accentuated risk with increasing atherosclerotic burden. In addition, when simultaneously adjusting for both imaging modalities together, risk estimates for the broader endpoint comprising all-cause mortality associated with cPB were numerically higher compared with the narrower primary MACE endpoint. By contrast, risk ratios associated with CAC were similar for both endpoints. These findings suggest that mortality risk may vary by vascular bed, and are consistent with the results of Allison et al. (35).

TABLE 3 Impact of Adding cPB or CAC to Conventional Risk Factors on Model Performance for Prediction of Primary and Secondary MACE Endpoints

	Model Fit*		Discrimination	Calibration		Reclassification
Model	χ^2	p Value	Change in C-Index (95% CI)†	χ^2	p Value	NRI‡ (95% CI)
Impact on model performance for prediction of primary MACE endpoint						
Model 1 (CRF)	41.5	Ref. Model	Ref. Model	4.3	0.37	Ref. Model
Model 1 + cPB	50.1	0.003	0.01 (−0.02 to 0.04)	3.4	0.49	0.23 (0.05 to 0.31)
Model 1 + CAC	61.5	<0.001	0.04 (0.01 to 0.08)	2.0	0.74	0.25 (0.12 to 0.36)
Impact on model performance for prediction of secondary MACE endpoint						
Model 1 (CRF)	92.3	Ref. Model	Ref. model	7.8	0.09	Ref. model
Model 1 + cPB	115.6	<0.001	0.02 (0.00 to 0.04)	4.6	0.33	0.17 (0.11 to 0.26)
Model 1 + CAC	131.1	<0.001	0.03 (0.002 to 0.05)	3.1	0.55	0.22 (0.14 to 0.29)

*Changes in model fit assessed using the likelihood ratio test (23). †Differences in c-index between models and 95% CI were calculated using the method of Newson (25). Calibration was assessed as described by May and Hosmer (26). ‡NRI calculated using the category-free version.

CRF = conventional risk factor(s); NRI = net reclassification improvement; other abbreviations as in Table 2.

PREDICTIVE PERFORMANCE. The associations we observed between CAC, cPB, and adverse events notwithstanding, the clinical utility of detecting subclinical disease is predicated on improving predictive measures over traditional risk factors (13). Within this context, our results suggest that imaging-based biomarkers that directly quantify atherosclerosis, irrespective of anatomic territory, may be ideally suited as adjuncts to conventional risk factors in CVD risk stratification. Specifically, we found that adding CAC or cPB to traditional risk factors improved risk prediction and reclassification to a similar degree. As a result, these techniques may serve a complementary role to conventional risk factors in refining short-term cardiovascular risk estimation. Indeed, the comparable results we obtained with both cPB and CAC contrast with reports showing the superiority of CAC over other metrics of carotid vascular disease, such as cIMT, in CVD risk prediction. The most plausible explanation for these differences is that cIMT is a more sensitive marker of vascular changes that are due to hypertension, rather than intimal atherosclerotic plaque (36,37). Previous studies, for example, have shown the superiority of carotid atherosclerosis as a predictor of thrombotic events compared with cIMT (38–40). In one report, Mathiesen et al. (38) found that the highest quartile of carotid plaque area was significantly associated with increased risk for incident stroke in asymptomatic men and women, whereas similar associations were nonsignificant for cIMT. Others have shown that alternative methods of measuring carotid atherosclerosis, such as quantifying plaque thickness, are also linked with higher risk for vascular events (41). Thus, it is not entirely unexpected that direct, albeit separate, measures of atherosclerosis yield similar results in atherothrombotic risk prediction. Moreover, from a biological perspective, our findings are concordant with the existing paradigm of atherosclerosis as a diffuse

and systemic disease. As such, the presence of subclinical atherosclerosis in a certain vascular bed does not preclude focal manifestations in a separate anatomic territory.

STUDY LIMITATIONS. The design of our study introduced several limitations. First, reliance on health insurance claims to identify adverse events may have resulted in a lower than expected rate of adverse events. Although we obtained original source documents and adjudicated all events to minimize misclassification, it is possible that certain events were missed. However, we would expect such underreporting to attenuate our point estimates to the null, suggesting that the true associations between CAC, cPB, and CVD risk are larger than we observed. Second, the follow-up period of approximately 3 years is relatively short when considered in the context of other primary prevention CVD studies and cohorts. Third, BioImage Study participants were somewhat older compared with typical primary prevention cohorts. Although this may not be the typical patient population targeted for screening, the limitations of classical risk factors in predicting CVD risk in older (compared with younger) individuals highlight the need to identify methods that might enhance risk estimation in this growing segment of the adult population (29,30,42). Fourth, because all participants were members of Humana insurance, our findings may not be generalizable to individuals with different types of or no health insurance. Fifth, differences in neck anatomy and carotid artery length between study subjects may have introduced variability in our methodology to quantify carotid atherosclerosis. Therefore, there may theoretically be some proximal and distal parts of the common carotid artery and some distal parts of the internal carotid artery that were scanned at lesser length in people with very short necks. However, we would expect this to be of modest overall impact, because most carotid atherosclerotic plaque is located at the bifurcation, which is readily visualized by US in the vast majority of individuals.

CONCLUSIONS

We found that detecting subclinical carotid or coronary atherosclerosis identifies healthy individuals at increased risk for adverse events and enhances risk prediction compared with conventional risk factors, with comparable results for either modality. Cost-effective analyses are warranted to define the optimal role of these complementary techniques as tools for CVD prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Detection of subclinical carotid atherosclerosis adds incremental value beyond traditional risk factors and is comparable to CAC in predicting short-term cardiovascular risk.

COMPETENCY IN PATIENT CARE: Incorporating detection of subclinical atherosclerosis, irrespective of anatomic territory should be considered when patient management decisions are not sufficiently informed by assessment of conventional cardiovascular risk factors.

TRANSLATIONAL OUTLOOK: Future studies should compare the cost effectiveness of various noninvasive vascular imaging modalities for assessment of cardiovascular risk.

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KEY WORDS atherosclerosis, carotid ultrasound, coronary artery calcification, risk prediction

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