JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 4, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.10.022

Digital Mammography and Screening for Coronary Artery Disease

Laurie Margolies, MD, Mary Salvatore, MD, Harvey S. Hecht, MD, Sean Kotkin, MD, Rowena Yip, MPH, Usman Baber, MD, Vivian Bishay, MD, Jagat Narula, PhD, MD, David Yankelevitz, MD, Claudia Henschke, PhD, MD

ABSTRACT

OBJECTIVES This study sought to determine if breast arterial calcification (BAC) on digital mammography predicts coronary artery calcification (CAC).

BACKGROUND BAC is frequently noted but the quantitative relationships to CAC and risk factors are unknown.

METHODS A total of 292 women with digital mammography and nongated computed tomography was evaluated. BAC was quantitatively evaluated (0 to 12) and CAC was measured on computed tomography using a 0 to 12 score; they were correlated with each other and the Framingham Risk Score (FRS) and the 2013 Cholesterol Guidelines Pooled Cohort Equations (PCE).

RESULTS BAC was noted in 42.5% and was associated with increasing age ($p < 0.0001$), hypertension ($p = 0.0007$), and chronic kidney disease ($p < 0.0001$). The sensitivity, specificity, positive and negative predictive values, and accuracy of BAC >0 for CAC >0 were 63%, 76%, 70%, 69%, and 70%, respectively. All BAC variables were predictive of the CAC score ($p < 0.0001$). The multivariable odds ratio for CAC >0 was 3.2 for BAC 4 to 12, 2.0 for age, and 2.2 for hypertension. The agreements of FRS risk categories with CAC and BAC risk categories were 57% for CAC and 55% for BAC; the agreement was 47% for PCE risk categories for CAC and 54% by BAC. BAC >0 had area under the curve of 0.73 for identification of women with CAC >0, equivalent to both FRS (0.72) and PCE (0.71). BAC >0 increased the area under the curve curves for FRS (0.72 to 0.77; $p = 0.15$) and PCE (0.71 to 0.76; $p = 0.11$) for the identification of high-risk (4 to 12) CAC. With the inclusion of 33 women with established CAD, BAC >0 was significantly additive to both FRS ($p = 0.02$) and PCE ($p = 0.04$) for high-risk CAC.

CONCLUSIONS There is a strong quantitative association of BAC with CAC. BAC is superior to standard cardiovascular risk factors. BAC is equivalent to both the FRS and PCE for the identification of high-risk women and is additive when women with established CAD are included. (J Am Coll Cardiol Img 2016;9:350–60) © 2016 by the American College of Cardiology Foundation.

Breast cancer and cardiovascular disease affect millions of women; cardiovascular disease is the leading cause of mortality (1) and breast cancer is the most feared disease (2). Women are commonly screened for breast cancer with mammography; 47.5% of women between 40 and 49 and 57.2% of women between 50 and 74 had mammograms in 2011 (3). However, there is no routine screening for coronary artery disease (CAD). Nonetheless, the presence or absence of breast arterial calcification (BAC) has been correlated with CAD (3-14) and with the presence or absence of coronary artery calcium (CAC) in a limited number of studies (7-9,14). This study was designed to quantitatively evaluate the relationship between BAC on digital mammography and CAC on noncontrast computed tomography (CT) scans, and their correlation with the Framingham Risk Score (FRS) (15) and the 2013 Cholesterol Guidelines Pooled Cohort Equations (PCE) (16). A significant relationship would provide the opportunity

From the Icahn School of Medicine at Mount Sinai, New York, New York. This study was supported in part by the Flight Attendants Medical Research Institute. Dr. Hecht is a consultant for Philips Medical Systems. Dr. Yankelevitz serves on the scientific advisory board (unpaid) for Give-A-Scan, Lung Cancer Alliance. Dr. Henschke is President of the Early Diagnosis and Treatment Research Foundation (unpaid). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Daniel Berman, MD, served as Guest Editor for this paper.

Manuscript received July 29, 2015; revised manuscript received September 21, 2015, accepted October 5, 2015.

for large-scale cardiac risk assessment of peri- and post-menopausal women undergoing mammography without additional cost and radiation exposure.

METHODS

Institutional review board approval was obtained for this HIPAA-compliant study and informed consent was waived. A search of the radiology department database was made for all women who had mammograms and noncontrast CT scans of the chest for routine clinical indications, and complete risk factor information, within 1 year of each other during the years of 2011 to 2013. A total of 325 asymptomatic women were identified; 33 had established CAD by chart review and were excluded from further analysis, leaving 292 subjects for primary analysis. Selected analyses of the entire cohort of 325 patients are provided in Online Figure 1 and Online Table 1.

SEE PAGE 361

CT SCAN. Chest CT scans were acquired on the following scanners: GE VCT 64 slice (General Electric Medical Systems, Milwaukee, Wisconsin); and Siemens Somatom Definition AS-40 slice, Siemens DEFINITION AS128, and Siemens SENSATION 64 Cardiac (Siemens Medical Solutions, Forchheim, Germany) with 5-mm slice thickness, 120 kVp, and mA varying according to the patient size.

A chest radiologist with more than 20 years of experience measured the ordinal CAC score as previously described (17). Each of the 4 main coronary arteries was identified (left main, left anterior descending, circumflex, and right) and the extent of CAC in each artery was categorized as being absent, mild, moderate, or severe and scored as 0, 1, 2, or 3, respectively. The extent of CAC was classified as mild when less than one-third of the length of the entire artery showed calcification, moderate when one-third to two-thirds of the artery showed calcification, and severe when more than two-thirds of the artery showed calcification. With 4 arteries thus scored, each participant received a score from 0 to 12. The CAC scores were divided into 3 categories of increasing severity: 0, 1 to 3, and 4 to 12, which have been shown to be strongly predictive of cardiac outcomes in a long-term follow-up of 8,782 patients (17).

DIGITAL MAMMOGRAPHY. Standard full-field digital mammograms were acquired in the craniocaudal and mediolateral oblique positions on either a GE Essentials Unit General Electric (Buc, France) or Hologic Dimensions Unit (Bedford, Massachusetts). A second radiologist with more than 20 years of experience in mammography, blinded to the CAC results, reviewed the mammograms of the 325 women. All mammograms were reviewed on standard 5 megapixel mammography monitors. All standard tools including magnification and inversion were available for use at the radiologist's discretion. For those women with BAC, the number of vessels involved in each breast was recorded and numerically coded as 1 to 6; if there were more than 6 BAC, then 6 was coded. The longest length of vessel involvement was recorded as none (scored as 0), less than one-third (scored as 1), between one-third and two-thirds (scored as 2), and greater than two-thirds (scored as 3). The density of calcium in the most severely affected segment was recorded as none (scored as 0), mild with clear visualization of the lumen and/or only 1 vessel wall involved (scored as 1), moderate with clouding of the lumen and calcification of both tangential walls (scored as 2), and severe with no visible lumen (scored as 3) (**Figure 1**). Thus each woman received an ordinal BAC score between 0 and 12 after summing up these 3 numbers for each breast. As with the CAC score, the BAC results were divided into 3 categories of increasing severity: 0, 1 to 3, and 4 to 12.

RISK FACTORS. Risk factor history was obtained for all patients based on chart review and the 10-year FRS and PCE scores were calculated. The FRS were divided into the conventional low (<10%), intermediate (10% to 20%), and high (>20%) risk categories. The PCE were classified as <5% (statins not needed), 5% to 7.4% (reasonable to offer moderate intensity statins), and ≥7.5% (should be treated with moderate/high intensity statins).

STATISTICS. All statistical analyses were performed using SAS version 9.2 (Statistical Analysis System, Cary, North Carolina). Frequencies and descriptive statistics were obtained for all the variables. Quantitative data were compared using chi-square tests, Fisher exact tests, and Student *t* tests. Logistic regression analysis was used to address the relationship of the prevalence and extent of CAC to BAC findings while adjusting for the other available risk factor of age. The age categories in years were <60, 60 to 69, and ≥70. The extent of CAC was analyzed for the 3 CAC categories and their relationship to the 3 BAC categories using polytomous logistic regression analysis. The dose-response relationship of CAC on the BAC score (using both linear and quadratic terms) was analyzed using regression analysis and the F statistic was used to test the significance of the linear and quadratic terms. Logistic regression analysis was

ABBREVIATIONS AND ACRONYMS

BAC = breast arterial calcification

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

FRS = Framingham Risk Score

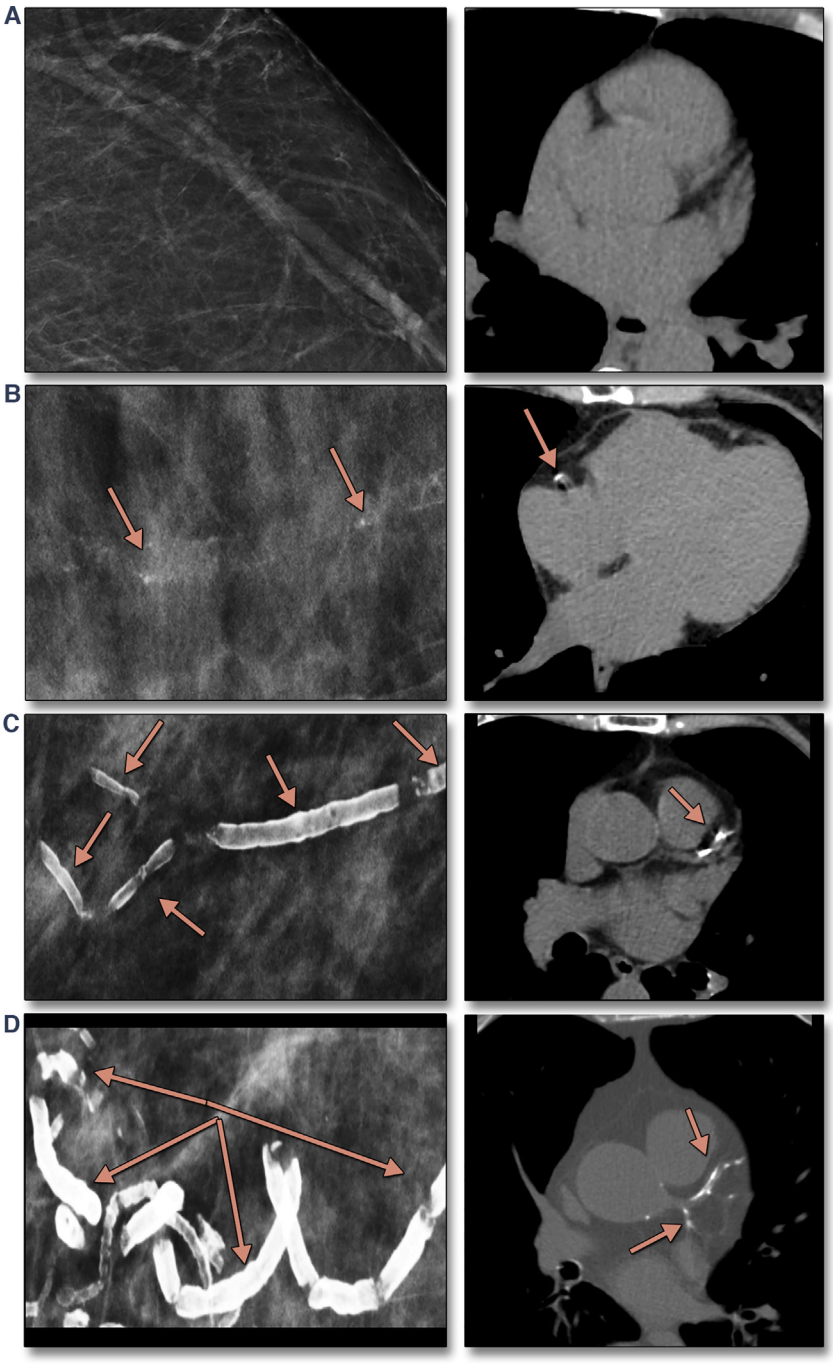
IQR = interquartile range

OR = odds ratio

PCE = 2013 Cholesterol Guidelines Pooled Cohort Equations

ROC = receiver-operating characteristic

FIGURE 1 Examples of Breast and Coronary Arterial Calcification



(A) A 48-year-old woman with normal mammogram with BAC = 0 **(left)** and normal CT scan with CAC = 0 **(right)**. **(B)** A 58-year-old woman with mammogram with BAC = 1 **(left)** and CT scan with CAC = 2 in the right coronary artery **(right)**. **(C)** A 54-year-old woman with mammogram with BAC = 9 **(left)** and CT scan with CAC = 7 in the left anterior descending coronary artery **(right)**. **(D)** A 61-year-old woman with mammogram with BAC = 12 **(left)** and CT scan with CAC = 12 in the left anterior descending and left circumflex coronary arteries **(right)**. **Arrows** point to arterial calcification. BAC = breast arterial calcium; CAC = coronary artery calcium; CT = computed tomography.

used to address the relationship of BAC to CAC while adjusting for the standard risk factors of age, sex, diabetes, hypercholesterolemia, smoking, and hypertension as reported on a background questionnaire. The extent of CAC was analyzed for the 3 categories of CAC (0, 1 to 3, 4 to 12) using ordered logistic regression analysis adjusting for the other risk factors of CAC. Discrimination for the outcomes of any CAC (CAC score exceeding 0) or moderate CAC (CAC score ≥4) was examined using receiver-operating characteristic (ROC) curves. The respective C-statistics generated with Framingham risk factors, Pooled Cohort Risk Equation, and BAC were separately calculated and compared among each other. In addition, the incremental change in the C-statistic from the addition of BAC to either Framingham or Pooled Cohort Risk Predictions was calculated.

RESULTS

DEMOGRAPHICS. BAC was found in 42.5% of the population (Table 1). BAC-positive patients were significantly older than BAC-negative patients ($p < 0.0001$), had more hypertension ($p = 0.0007$) and chronic kidney disease ($p < 0.0001$), and were less often smokers ($p < 0.009$). There were no significant differences in the incidence of hyperlipidemia and diabetes mellitus. CAC was noted in 47.6% of the total group. CAC-positive patients were significantly older than CAC-negative subjects ($p < 0.0001$), and had more hypertension ($p < 0.0001$), chronic kidney disease ($p < 0.001$), and diabetes ($p = 0.01$); there were no differences in hyperlipidemia and smoking. Indications for CT scanning were pulmonary nodule (39%), lung cancer screening (10%), interstitial lung disease (9%), dyspnea (9%), abnormal study follow-up (8%), other cancer (8%), infection (6%), obstructive lung disease (6%), lung cancer (4%), and miscellaneous (1%).

BAC AND CAC SCORE DISTRIBUTIONS. The mean BAC score was 2.2 ± 2.9 (median 0.0; interquartile range [IQR]: 0.0 to 4.0) (Table 2). The frequency of BAC >0 was 27% for women younger than 60 (39 to 59 years of age), increasing to 47% for women 60 to 69 years of age, and to 69% for women 70 to 92 years of age ($p < 0.0001$). The mean CAC score was 1.6 ± 2.5 (median 0.0; IQR: 0.0 to 2.0). For the 3 age categories, the presence of CAC increased from 28% to 55% to 79% ($p < 0.0001$). The frequency distributions of the number of calcified breast arteries, maximum length of the vascular calcifications, and maximum density of the calcifications for the 3 age categories rose with increasing age ($p < 0.0001$) as well.

RELATIONSHIP OF BAC AND CAC SCORES. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of BAC >0 for the presence of CAC >0 were 63%, 76%, 70%, 69%, and 70%, respectively (Table 3). Sensitivity increased from 50% to 75% and specificity decreased from 83%

TABLE 1 Demographics and Comparison of BAC- and CAC-Positive and -Negative Patients

	All	BAC-Positive	BAC-Negative	p Value
N	292	124 (42.5)	168 (57.5)	
Mean age	61.5 ± 10.8	66.5 ± 10.3	57.7 ± 9.5	<0.0001
Hyperlipidemia	104	38 (31)	66 (39)	0.13
Hypertension	179	90 (73)	89 (53)	0.0007
DM	79	39 (31)	40 (24)	0.15
Smoking	53	14 (11)	39 (23)	0.009
CKD	57	44 (35)	13 (8)	<0.0001
	All	**CAC-Positive**	**CAC-Negative**	**p Value**
N	292	139 (47.6)	153 (52.4)	
Mean age	61.5 ± 10.8	66.6 ± 10.1	56.8 ± 9.1	<0.0001
Hyperlipidemia	104	46 (37)	58 (35)	0.39
Hypertension	179	106 (85)	73 (43)	<0.0001
DM	79	47 (38)	32 (19)	0.01
Smoking	53	23 (19)	30 (18)	0.50
CKD	57	38 (31)	19 (11)	0.001

Values are n, n (%), or mean ± SD.

BAC = breast arterial calcium; CAC = coronary artery calcium; CKD = chronic kidney disease; DM = diabetes mellitus.

TABLE 2 Frequency of CAC, BAC, and BAC Characteristics by Age Distribution

	Age at Time of Mammogram				
	39–59 (n = 143)	60–69 (n = 77)	70–92 (n = 72)	Total (n = 292)	p Value
CAC 0	103 (72)	35 (45)	15 (21)	153 (52)	<0.0001*
CAC >0	40 (28)	42 (55)	57 (79)	139 (48)	
CAC 1–3	32 (22)	26 (34)	33 (46)	91 (31)	<0.0001†
CAC 4–12	8 (6)	16 (21)	24 (33)	48 (16)	
BAC 0	105 (73)	41 (53)	22 (31)	168 (58)	<0.0001*
BAC >0	38 (27)	36 (47)	50 (69)	124 (42)	
BAC 1–3	17 (12)	12 (16)	13 (18)	42 (14)	<0.0001†
BAC 4–12	21 (15)	24 (31)	37 (51)	82 (28)	
Number of breast vessel involvement					
None	105 (73)	41 (53)	22 (31)	168 (58)	<0.0001
1–3	32 (22)	34 (44)	47 (65)	113 (39)	
≥4	6 (4)	2 (3)	3 (4)	11 (4)	
Length of breast vessel involvement					
None	105 (73)	41 (53)	22 (31)	168 (58)	<0.0001
<1/3	21 (15)	16 (21)	23 (32)	60 (21)	
1/3–2/3	8 (6)	6 (8)	16 (22)	30 (10)	
≥2/3	9 (6)	14 (18)	11 (15)	34 (12)	
Density of breast vessel involvement					
None	105 (73)	41 (53)	22 (31)	168 (58)	<0.0001
Mild	27 (19)	21 (27)	28 (39)	76 (26)	
Moderate	7 (5)	8 (10)	15 (21)	30 (10)	
Severe	4 (3)	7 (9)	7 (10)	18 (6)	

Values are n (%). *p Value from chi-square test comparing the presence of CAC and BAC scores with age group at time of mammogram. †p Value from chi-square test comparing the 3 ordinal categories of CAC and BAC scores with age group at time of mammogram.

Abbreviations as in Table 1.

TABLE 3 Accuracy of BAC for the Presence of CAC

		95% CI
All patients		
Sensitivity	63 (87/139)	54–71
Specificity	76 (116/153)	68–82
Positive predictive value	70 (87/124)	61–78
Negative predictive value	69 (116/168)	61–76
Accuracy	70 (203/292)	64–75
Age 39–59 yrs		
Sensitivity	50 (20/40)	34–66
Specificity	83 (85/103)	74–89
Positive predictive value	53 (20/38)	36–69
Negative predictive value	81 (85/105)	72–88
Accuracy	73 (105/143)	65–80
Age 60–69 yrs		
Sensitivity	57 (24/42)	41–72
Specificity	66 (23/35)	48–81
Positive predictive value	67 (24/36)	49–81
Negative predictive value	56 (23/41)	40–72
Accuracy	61 (47/77)	49–72
Age 70–92 yrs		
Sensitivity	75 (43/57)	62–86
Specificity	53 (8/15)	27–79
Positive predictive value	86 (43/50)	73–94
Negative predictive value	36 (8/22)	17–59
Accuracy	71 (51/72)	59–81

Values are % (n/N).
CI = confidence interval; other abbreviations as in Table 1.

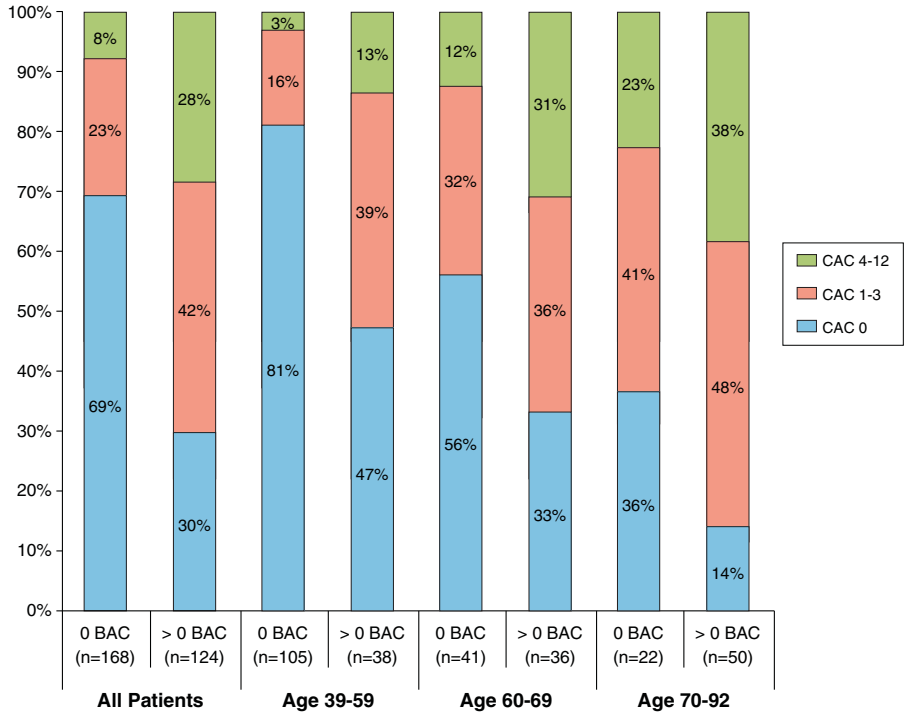
to 53% with increasing age. In a similar manner, the positive predictive value increased from 53% to 86 % and the negative predictive value decreased from 81% to 36% with increasing age (Table 3). The CAC burden in patients with and without BAC by age distribution is shown in Figure 2, revealing the increasing frequency of both BAC and CAC with increasing age and the increasing percentages of higher CAC in those with BAC in each age group. The relationships of the BAC score and the individual BAC findings to the CAC score are displayed by categories in Table 4 and were all highly significant ($p < 0.0001$). The agreement between BAC and CAC scores was also highly significant ($p < 0.0001$; kappa = 0.26; weighted kappa = 0.33). In 76% of the 0 CAC patients, the BAC was also 0; 10% had BAC of 1 to 3 and 14% were 4 to 12. In the intermediate 1 to 3 CAC category, the BAC was fairly evenly distributed. In the high-risk 4 to 12 CAC group, 56% were high risk on BAC; 17% had 1 to 3 BAC and 27% had 0 BAC. The individual BAC variables were all significantly predictive of the CAC score ($p < 0.0001$). Unadjusted and adjusted odds ratios (ORs) of BAC, age, hypertension, hyperlipidemia, smoking, and diabetes mellitus for having CAC >0 are shown in Table 5. In the unadjusted model, BAC 4 to 12, age, hypertension, diabetes mellitus, and chronic kidney disease were significant. In the multivariable model, only BAC 4 to 12 (OR: 3.2), age (OR: 2.0), and hypertension (OR: 2.2) were significant.

COMPARISON WITH FRS. The mean 10-year FRS was 4.6 ± 4.7% (median 3.0%; IQR: 0.0% to 6.0%) (Table 6). Most (84.6%) were low risk (<10% FRS); 59% had 0 BAC and 63% had 0 CAC. However, 15% had intermediate BAC of 1 to 3 and 22% had high-risk BAC of 4 to 12; 29% had intermediate CAC of 1 to 3 and 13% had high-risk CAC of 4 to 12. In the small (14.4%) intermediate FRS risk group (10% to 20%), 45% and 12% were intermediate risk by CAC and BAC, respectively, and 36% and 64% were high risk by CAC and BAC, respectively. Zero CAC and BAC were present in 19% and 24%, respectively. Only 0.6% (3 patients) were high FRS risk (>20%); 2 were high risk by CAC and 1 by BAC. For the entire patient cohort, the agreements of FRS risk categories with CAC and BAC risk categories were only 57% for CAC and 55% for BAC.

BAC and FRS were equivalent for the identification of women with CAC >0 and CAC 4 to 12; the area under the curve (AUC) was 0.73 and 0.72 ($p = 0.83$), respectively, for both CAC >0 and CAC 4 to 12. The addition of BAC >0 to the FRS increased the area under the ROC curve for CAC 4 to 12 of 0.72 for FRS to 0.77 but this was not statistically significant ($p = 0.15$) (Table 7, Figure 3). Similarly, for the identification of women with CAC >0, BAC >0 increased the area under the ROC curve for FRS from 0.72 to 0.76 ($p = 0.16$). Analysis of the 325-patient cohort, including the 33 with established CAD, revealed significant additive value of BAC >0 to FRS for the identification of women with CAC 4 to 12 (AUC: 0.68 vs. 0.76; $p = 0.02$) and with CAC >0 (AUC: 0.72 to 0.77; $p = 0.02$). All other analyses were unchanged from the 292-patient cohort.

COMPARISON WITH PCE. The mean PCE risk was 11.8 ± 12.5% (median 7.2%; IQR: 2.6% to 16.9%) (Table 8). In sharp contrast to the FRS, only 42% were in the lowest risk category, 9.2% were intermediate, and 49% were in the ≥7.5% high-intensity statin-requiring group. In the low-risk (<5%) category, 74% and 76% had 0 CAC and 0 BAC, respectively. However, in the high-risk (>7.5%) category, only 27% were high risk by CAC and 43% by BAC; 33% and 40% had 0 CAC and 0 BAC, respectively. In the intermediate-risk (5% to 7.4%) group, only 33% of CAC and 15% of BAC had intermediate risk scores of 1 to 3. For the entire patient cohort, the agreements of PCE risk categories with CAC and BAC risk categories were only 47% for CAC and 54% for BAC.

FIGURE 2 CAC Burden in Patients With and Without BAC by Age Distribution



Abbreviations as in Figure 1.

BAC and PCE were equivalent for the identification of women with CAC >0 and CAC 4 to 12; the AUC was 0.73 and 0.71 ($p = 0.66$), respectively, for both CAC >0 and CAC 4 to 12. The addition of BAC >0 to the PCE increased the area under the ROC curve for CAC 4 to 12 of 0.71 for PCE to 0.76 ($p = 0.11$) (Table 7, Figure 3). The addition of BAC to PCE for the identification of women with CAC >0 was of borderline significance; AUC increased from 0.71 to 0.76 ($p = 0.08$). Analysis of the 325-patient cohort, including the 33 with established CAD, revealed significant additive value of BAC >0 to PCE for the identification of women with CAC 4 to 12 (AUC: 0.70 vs. 0.76; $p = 0.04$). All other analyses were unchanged from the 292-patient cohort.

DISCUSSION

This study is the first to demonstrate the strong quantitative association of BAC by digital mammography with CAC in a large female cohort, its superiority to individual standard cardiovascular risk factors, and its equivalence to the risk factor-based paradigms for the identification of women with CAC, with borderline additive value to the PCE.

PRIOR REPORTS. There are few studies comparing BAC with CAC. In 2003, Pecchi et al. (7) semi-quantitatively compared BAC with CAC in 74 post-menopausal women and found a strong correlation (0.55 to 0.89 after risk factor adjustment); digital mammography was not used. In 2007, Maas et al. (8) reported a significant association of any BAC with subsequent CAC after 9 years of follow-up in 499 women (OR: 3.1); neither the CAC nor BAC were quantified. Matsumura et al. (9), in 2013, evaluated 98 women with BAC and 104 women without BAC with CT and found that BAC was an independent predictor of CAC with an OR of >22; those with Agatston CAC scores of >400 were more likely to have BAC ($p = 0.006$). BAC continued to be associated with Agatston scores of >400 when adjusted for age, diabetes, smoking, hyperlipidemia, and family history (9). Only Agatston scores >400 were considered to be CAC-positive and their results, therefore, are of limited value.

Many more reports have evaluated the relationship between BAC and variably defined CAD in general. In a 2013 review of data from 25 studies and 35,542 patients (10), 19 studies examined the relationship between BAC and cardiovascular disease, 13 of which

TABLE 4 Ordinal BAC Score, Number of Involved Breast Arteries, Maximum Length of Vascular Calcification, and Maximum Density in the Ordinal CAC Score Categories

	CAC Score				
	0 (n = 153)	1-3 (n = 91)	4-12 (n = 48)	Total (n = 292)	p Value
BAC score					
None	116 (76)	39 (43)	13 (27)	168 (58)	<0.0001
1-3	16 (10)	18 (20)	8 (17)	42 (14)	
4-12	21 (14)	34 (37)	27 (56)	82 (28)	
No. of BAC vessels					
None	116 (76)	39 (43)	13 (27)	168 (58)	<0.0001
1-3	34 (22)	49 (54)	30 (63)	113 (39)	
≥4	3 (2)	3 (3)	5 (10)	11 (4)	
Maximum BAC length					
None	116 (76)	39 (43)	13 (27)	168 (58)	<0.0001
<One-third	20 (13)	27 (30)	13 (27)	60 (21)	
One-third to two-thirds	8 (5)	13 (14)	9 (19)	30 (10)	
≥Two-thirds	9 (6)	12 (13)	13 (27)	34 (12)	
Maximum BAC density					
None	116 (76)	39 (43)	13 (27)	168 (58)	<0.0001
Mild	28 (18)	36 (40)	12 (25)	76 (26)	
Moderate	7 (5)	12 (13)	11 (23)	30 (10)	
Severe	2 (1)	4 (4)	12 (25)	18 (6)	

Values are n (%).
Abbreviations as in Table 1.

TABLE 6 Relationship of CAC and BAC Risk Groups to the 10-Year Framingham Risk Score

	Low <10%	Intermediate 10%-20%	High >20%	Total
CAC				
None	145 (59)	8 (19)	0 (0)	153 (52)
1-3	71 (29)	19 (45)	1 (33)	91 (31)
4-12	31 (13)	15 (36)	2 (67)	48 (16)
Total	247 (100)	42 (100)	3 (100)	292 (100)
BAC				
None	156 (63)	10 (24)	2 (67)	168 (58)
1-3	37 (15)	5 (12)	0 (0)	42 (14)
4-12	54 (22)	27 (64)	1 (33)	82 (28)
Total	247 (100)	42 (100)	3 (100)	292 (100)

Values are n (%).
Abbreviations as in Table 1.

reported a statistically significant association of BAC and CAD; an additional 2 reported that the correlation was only significant when CAD ≥50% stenosis was present. The adjusted ORs were 1.87 to 8.13 for the relationship between BAC and variably defined CAD, ranging from angiographically proven CAD to patient self-reporting. In the most recent review (11), with a meta-analysis of 63 studies chosen after critical appraisal, the adjusted hazard ratios for coronary disease ranged from 1.32 (95% confidence interval [CI]: 1.08 to 1.60) to 1.44 (95% CI: 1.02 to 2.05). The overall prevalence of BAC was 12.7%. Diabetes mellitus (pooled OR: 1.88; 95% CI: 1.36 to 2.59), parity as opposed to nulliparity (pooled OR: 3.43; 95% CI: 2.23 to 5.27), and age (pooled OR: 2.98; 95% CI: 2.31 to 3.85 for every 10 years) were associated with an increased prevalence of BAC. There was no significant relationship to dyslipidemia, obesity, and hypertension; smoking had a lower BAC prevalence (pooled OR: 0.48; 95% CI: 0.39 to 0.60).

Several studies in symptomatic women undergoing either invasive coronary angiography or coronary CT angiography have found no association between BAC and CAD. In 172 women referred for coronary angiography, no significant correlation was found between BAC and the degree of coronary stenosis (12). Obstructive disease on coronary angiography in 94 symptomatic women did not correlate with the presence or absence of BAC (13). In 150 patients with suspected CAD, there was no correlation between BAC and either CAC or degree of stenosis in coronary

TABLE 5 Ordinal Logistic Regression Analysis for the Relationship of the BAC Categories and Risk Factors to the Presence of CAC

	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
BAC categories				
None (0)	Ref.		Ref.	
Mild (1-3)	3.4 (1.8-6.5)	0.35	2.3 (1.1-4.7)	0.45
Marked (4-12)	6.4 (3.7-10.9)	<0.0001	3.2 (1.8-5.9)	0.01
Age (in decades)	2.6 (2.0-3.3)	<0.0001	2.0 (1.5-2.6)	<0.0001
Hypertension	3.6 (2.2-5.8)	<0.0001	2.2 (1.3-3.8)	0.01
Hyperlipidemia	0.9 (0.6-1.4)	0.63	1.3 (0.8-2.1)	0.35
Diabetes mellitus	1.8 (1.1-3.0)	0.02	1.3 (0.8-2.3)	0.33
Smoking	0.8 (0.4-1.4)	0.37	1.2 (0.7-2.3)	0.50
CKD	3.0 (1.7-5.2)	<0.0001	1.1 (0.6-2.0)	0.82

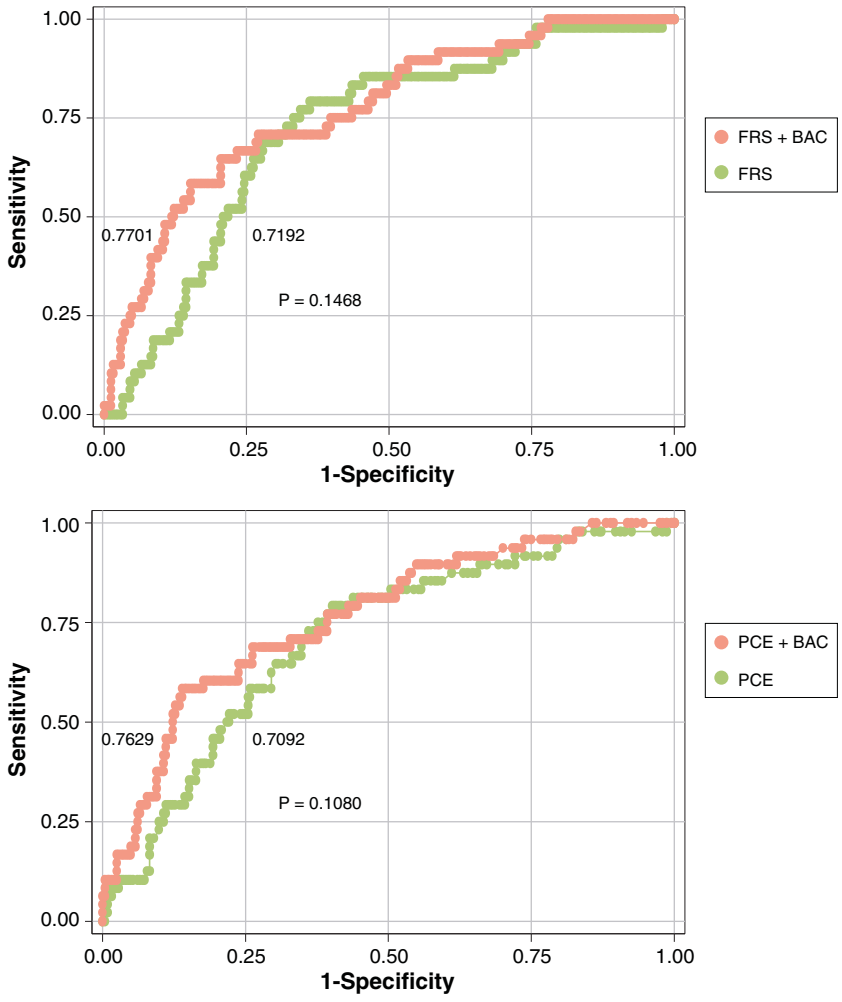
OR = odds ratio; other abbreviations as in Tables 1 and 3.

TABLE 7 Comparison of AUC of BAC >0 and Risk Scores for the Presence of CAC

	AUC	p Value
CAC 4-12		
FRS vs. BAC	0.72 vs. 0.73	0.83
FRS vs. FRS + BAC	0.72 vs. 0.77	0.15
PCE vs. BAC	0.71 vs. 0.73	0.66
PCE vs. PCE + BAC	0.71 vs. 0.76	0.11
CAC >0		
FRS vs. BAC	0.72 vs. 0.73	0.83
FRS vs. FRS + BAC	0.72 vs. 0.76	0.16
PCE vs. BAC	0.71 vs. 0.73	0.66
PCE vs. PCE + BAC	0.71 vs. 0.76	0.08

AUC = area under curve; FRS = Framingham Risk Score; PCE = Pooled Cohort Equations; other abbreviations as in Table 1.

FIGURE 3 Receiver-Operating Characteristic Curves



(Top) Receiver-operating characteristic curves and C-statistic of FRS and FRS+BAC for the prediction of high risk CAC 4 to 12. **(Bottom)** Receiver-operating characteristic curves and C-statistic of PCE and PCE+BAC for the prediction of high-risk CAC 4 to 12. FRS = Framingham Risk Score; PCE = Pooled Cohort Equations; other abbreviations as in Figure 1.

CT angiography (p = 0.09) (14). However, this was a symptomatic population; greater numbers may have yielded significant results.

The use of digital mammography in the current study may explain the significantly higher prevalence of BAC compared with prior reports: 45.5% versus 12.7% in the largest meta-analysis (11). As of March 2015, 96% of the mammography units in the United States were digital (18) and are therefore very sensitive to the presence of calcification. There are not sufficient details provided in prior studies to assess the mammography technique or differences in patient populations that would clearly explain their lower prevalence.

QUANTITATIVE RELATIONSHIPS. The data clearly demonstrate that BAC was significantly and quantitatively associated with CAC. Moreover, it was superior to conventional risk factors; in a multivariate analysis adjusted for all risk factors including age, the OR for BAC 4 to 12 was 3.2 compared with BAC 0 (Table 5). In addition to the significant association of the total BAC score, each of the 3 components of the BAC score was quantitatively related to CAC (Table 2). A significant relationship was present for age and hypertension in multivariate analysis, and for diabetes and chronic kidney disease in univariate analysis alone; there were no significant associations for smoking and hyperlipidemia.

TABLE 8 Relationship of CAC and BAC Risk Groups to the 10-Year Pooled Cohort Equation Risk Estimate

	<5.0%	5.0%–7.4%	≥7.5%	Total
CAC				
None	90 (74)	16 (59)	47 (33)	153 (52)
1–3	24 (20)	9 (33)	58 (41)	91 (31)
4–12	8 (7)	2 (7)	38 (27)	48 (16)
Total	122 (100)	27 (100)	143 (100)	292 (100)
BAC				
None	93 (76)	18 (67)	57 (40)	168 (58)
1–3	14 (11)	4 (15)	24 (17)	42 (14)
4–12	15 (12)	5 (19)	62 (43)	82 (28)
Total	122 (100)	27 (100)	143 (100)	292 (100)

Values are n (%).
Abbreviations as in Table 1.

CONVENTIONAL RISK SCORES AND AREA UNDER THE ROC CURVE. The relatively poor agreement of BAC and CAC risk categories with the FRS and PCE risk categories parallels the generally poor correlation of calcified plaque with risk factor-based algorithms. The striking difference between the mean FRS (5.0%) and PCE (12.6%) 10-year CAD risk assessments reflects the well-described overestimation of risk, particularly in women, that has marred the acceptance of the PCE (19,20). Of critical importance is the equivalence of BAC to both risk factor-based paradigms for the identification of women with CAC, with borderline additive value to PCE. The substantial differences in AUC for additive value (0.72 to 0.77 for FRS, and 0.71 to 0.76 for PCE) may have been significant in a larger cohort including patients with a higher likelihood of disease, as suggested by the significant additive value to both FRS and PCE in the 325-patient cohort that included 33 patients with established CAD by chart review (Online Figure 1, Online Table 1). There are no other diagnostic tests (21) or inflammatory markers, such as high-sensitivity C-reactive protein (22), that are comparable or additive to standard risk factor-based estimates.

MECHANISMS. It is important to realize that the locations of BAC and CAC are different. BAC is a manifestation of Mönckeberg arteriosclerosis, and as indicated by its alternative name, calcific medial sclerosis, is medial in location, as opposed to the intimal location of CAC (23,24). The mammary arteries are branches of the posterior intercostal arteries, the lateral thoracic and thoracoacromial arteries, and perforating branches of the internal mammary arteries; these arteries are thought not to be susceptible to conventional atherosclerosis. There are some shared associations with risk factors. Prior studies have demonstrated significant consistent associations for age, diabetes, chronic kidney disease, and multiparity, but there are no relationships of BAC to the conventional CAC risk factors of hyperlipidemia and smoking and a variable relationship to hypertension (4–14). In the current study (**Table 1**), BAC was significantly more prevalent in older patients and those with hypertension and those with chronic kidney disease but not with hyperlipidemia and diabetes, and was less prevalent in smokers. Increased arterial stiffness from medial calcification may increase risk, but the shared risk factors discussed previously provide the most likely explanation for the highly significant correlation of BAC and CAC, which requires further investigation. The OR of 3.2 for BAC 4 to 12 independent of age indicates that the association with CAC is more than just the aging process.

ORDINAL CAC AND BAC SCORING. The validity of this paper is based on comparison of BAC with CAC ordinal scores derived from nongated CT angiography scans, rather than conventional Agatston scored gated scans. The prognostic power of ordinal CAC has been confirmed (17,25), as has the strong correlation between gated and nongated Agatston scores (26) and between ordinal scores and nongated Agatston scores (27). On the basis of the previously mentioned data, an ordinal CAC of 4 to 12 was designated as high risk similar to Agatston CAC >400 and an ordinal CAC of 0 was designated as low risk equating to Agatston 0 CAC, with ordinal CAC of 1 to 3 classified as intermediate risk.

The ordinal BAC score was devised to reflect increasing severity and arbitrarily scaled 0 to 12 to conform to the CAC ordinal scale. The highly significant correlation of increasing BAC with increasing CAC validates its structure.

CLINICAL RELEVANCE. This study strongly suggests that BAC warrants further investigation. Pending confirmation of its predictive power in an outcomes study, it is reasonable to recommend further risk assessment of BAC-positive women, preferably with a gated CAC scan, with subsequent adjustment or institution of therapy as indicated by the CAC score. In younger women age 39 to 59, the greatest value may be the high negative predictive value for CAC of 81%. The sensitivity of 50% and positive predictive value of 53% in this group, although low, uncovers one-half of the women who are CAC-positive, almost all of whom would have been considered low risk by virtue of their age. Nonetheless, the absence of BAC cannot be viewed as reassurance of low risk. In the older age group (70 to 92) the higher sensitivity of

75% and positive predictive value of 86% confirm the higher risk status of the BAC-positive women and the need for further risk assessment by a gated CAC scan and treatment tailored to the results. In the BAC-negative older women, the absence of BAC cannot be reassurance of low risk, with a negative predictive value of only 36%. In the 60 to 69 age group, the intermediate accuracies should be balanced against their risk factor-based scores (FRS or PCE) to determine the need for further evaluation. Formal incorporation into the cardiac risk assessment of peri- and post-menopausal women is premature, but in the meantime, the opportunity to significantly improve the identification of high-risk women by further simple analysis of a broadly used screening tool should be intensively evaluated in larger patient cohorts. Further refinement of the BAC cutpoints will likely be necessary to develop clinical algorithms for recommendations.

STUDY LIMITATIONS. Ordinal scoring of nongated CT scans, rather than conventional Agatston scoring of gated scans, was used. However, the prognostic value of ordinal scoring has been well validated, as noted previously (17,25). This was a retrospective study of women who had mammography and chest CT scans within a specified time period, rather than a prospective evaluation of consecutive patients, and is therefore subject to many selection biases, including coexisting conditions for which CT evaluation was requested. Consequently, caution must be exercised in applying the results to the general population. Moreover, it is not an event-based outcome study; rather, CAC was used as a surrogate. Nonetheless, the strikingly positive correlations and AUC equivalencies serve to establish the quantitative relationship between BAC and CAC and set the stage for the prospective, bias-free outcome trial that is required before BAC can be routinely incorporated into the prevention paradigm.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Harvey S. Hecht, Mount Sinai Saint Luke's Medical Center, 1111 Amsterdam Avenue, New York, New York 10025. E-mail: harvey.hecht@mountsinai.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is a strong quantitative association between BAC and CAC, and BAC is superior to standard cardiovascular risk factors for the prediction of CAC.

TRANSLATIONAL OUTLOOK: Additional studies are needed to validate the ability of BAC to predict cardiac events in large prospective population-based studies, similar to CAC. Pending these studies, consideration may be given to including BAC in mammography reports.

REFERENCES

1. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). 2nd ed. Geneva, Switzerland: World Health Organization, 2004.

2. Wider J. Women Most Fear Breast Cancer, but Heart Disease Is the Top Killer. Society for Women's Health Research. Society for Women's Health Research, 14 July 2005. Available at: http://www.womenshealthresearch.org/site/News2?page=NewsArticle&id=361&news_iv_ctrl=0&abbr=press_. Accessed November 12, 2014.

3. Pace LE, He Y, Keating NL. Trends in mammography screening rates after publication of the 2009 US Preventive Services Task Force recommendations. Cancer 2013;119:2518–23.

4. Dale PS, Mascarhenas C, Richards M, Mackie G. Mammography as a screening tool for coronary artery disease. J Surg Res 2008;148:1–6.

5. Topal U, Kaderli A, Topal NB, et al. Relationship between the arterial calcification detected in mammography and coronary artery disease. Eur J Radiol 2007;63:391–5.

6. Schnatz PF, Marakovits KA, O'Sullivan DM. The association of breast arterial calcification and coronary heart disease. Obstet Gynecol 2011;117:233–41.

7. Pecchi A, Rossi R, Coppi F, Ligabue G, Modena MG, Romagnoli R. Association of breast arterial calcifications detected by mammography and coronary artery calcifications quantified by multislice CT in a population of post menopausal women. Radiol Med 2003;106:305–12.

8. Maas AH, van der Schouw YT, Atsma F, et al. Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different. Eur J Radiol 2007;63:396–400.

9. Matsumura ME, Maksimik C, Martinez MW, et al. Breast artery calcium noted on screening mammography is predictive of high risk coronary calcium in asymptomatic women: a case control study. VASA Zeitschrift fur Gefasskrankheiten 2013;42:429–33.

10. Shah N, Chainani V, Delafontaine P, Abdo A, Lafferty J, Abi Rafeh N. Mammographically detectable breast arterial calcification and atherosclerosis: a review. Cardiol Rev 2014;22:69–78.

11. Hendriks EJE, de Jong PA, van der Graaf Y, et al. Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events. Atherosclerosis 2015;239:11–20.

12. Zgheib MH, Buchbinder SS, Abi Rafeh N, et al. Breast arterial calcifications on mammograms do not predict coronary heart disease at coronary angiography. Radiology 2010;254:367–73.

13. Penugonda N, Billecke SS, Yerkey MW, Rebner M, Marcovitz PA. Usefulness of breast arterial calcium detected on mammography for predicting coronary artery disease or cardiovascular events in women with angina pectoris and/or positive stress tests. Am J Cardiol 2010;105:359–61.

14. Moradi M, Adibi A, Abedi M. Relationship between breast arterial calcification on mammography with CT calcium scoring and coronary CT angiography results. Adv Biomed Res 2014;3:79.

15. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.

16. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic

cardiovascular risk in adults. J Am Coll Cardiol 2014;63:2889–934.

17. Shemesh J, Henschke CI, Shaham D, et al. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. Radiology 2010;257:541–8.

18. U.S. Food and Drug Administration. MQSA National Statistics. Available at: http://www.fda.gov/radiation-emittingproducts/mammographyqualitystandardsactandprogram/facilityscorecard/ucm113858.htm. Accessed April 1, 2015.

19. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. JAMA Intern Med 2014;174:1964–71.

20. Nasir K, Bittencourt M, Blaha MJ, et al. Eligibility for lipid lowering therapy based on AHA/ACC Risk Score, coronary artery calcification, and CVD events: national implications for the appropriate use of preventive pharmacotherapy. Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2014;130:A15615.

21. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012;308:788–95.

22. Rana JS, Gransar H, Wong ND, et al. Comparative value of coronary artery calcium and multiple blood biomarkers for prognostication of cardiovascular events. Am J Cardiol 2012;109:1449–53.

23. Kim H, Greenberg JS, Javitt MC. Breast calcifications due to Monckeberg medial calcific sclerosis. Radiographics 1999;19:1401–3.

24. Proudfoot D, Shanahan CM. Biology of calcification in vascular cells: intima vs media. Herz 2001;26:245–51.

25. Shemesh J, Morag-Koren N, Goldbourt U, et al. Coronary calcium by spiral computed tomography predicts cardiovascular events in high-risk hypertensive patients. J Hypertens 2004;22:605–10.

26. Xie X, Zhao Y, de Bock H, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography systematic review and meta-analysis. Circ Cardiovasc Imaging 2013;6:514–21.

27. Htwe Y, Cham M, Henschke C, et al. Coronary artery calcification on low-dose non gated computed tomography: comparison of Agatston and ordinal scores. Clin Img 2015;39:799–802.

KEY WORDS breast arterial calcification, coronary artery calcium, risk assessment

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