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Prediction of Subclinical Coronary Artery Disease With Breast Arterial Calcification and Low Bone Mass in Asymptomatic Women

Registry for the Women Health Cohort for Breast, Bone, and Coronary Artery Disease Study

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ABSTRACT

OBJECTIVES This study sought to determine whether evaluations of breast arterial calcification (BAC) and low bone mass (LBM) could improve the ability to predict subclinical coronary artery disease (CAD) in asymptomatic women.

BACKGROUND An improved risk stratification strategy beyond the measurement of conventional risk factors is needed to identify women at high risk of CAD.

METHODS The BBC (Women Health Registry Study for Bone, Breast, and Coronary Artery Disease) enrolled 2,100 asymptomatic women who underwent dual-energy X-ray absorptiometry, digital mammography, and coronary computed tomography angiography. We assessed the predicted 10-year atherosclerotic cardiovascular disease (ASCVD) risk and evaluated the presence and severity of BAC, LBM, coronary artery calcification (CAC), and coronary atherosclerotic plaque (CAP).

RESULTS CAC and CAP were found in 11.2% and 15.6% of participants, respectively. In women with CAC or CAP, increasing trends in the presence and severity of both BAC and LBM were observed. Both BAC and LBM were found to be associated with the presence of CAC (unadjusted odds ratios [OR]: 3.54 and 2.22, respectively) and CAP (unadjusted OR: 3.02 and 1.91, respectively). However, in multivariate analysis, only the presence of BAC and BAC score remained as independent predictors. For the prediction of CAC and CAP, addition of the BAC presence to the 10-year ASCVD risk significantly increased the areas under the curve (area under the curve: 0.71 to 0.72; $p = 0.016$; and area under the curve: 0.66 to 0.68; $p = 0.010$; respectively) and resulted in net reclassification index improvements (area under the curve: 0.304; $p < 0.001$; and area under the curve: 0.245; $p < 0.001$; respectively).

CONCLUSIONS The presence and severity of BAC and LBM were significantly associated with the risk of subclinical CAD in asymptomatic women. BAC evaluation especially provides an independent and incremental value over conventional risk algorithms. (Women Health Cohort for Breast, Bone and Coronary Artery Disease [BBC]; NCT03235622.) (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BAC = breast arterial calcification

BBC = bone, breast, and coronary artery disease

BMD = bone mineral density

CAC = coronary arterial calcification

CAD = coronary artery disease

CAP = coronary atherosclerotic plaque

CCTA = coronary computed tomography angiography

LBM = low bone mass

Despite recent advances in the field of cardiovascular medicine, the rate of coronary artery disease (CAD)-related mortality has not significantly changed in women, in contrast to the dramatic declines seen among men (1). Although atherosclerotic cardiovascular disease (ASCVD) risk prediction algorithms currently play an important role in identifying high-risk patients who may benefit from preventive intervention (2), they are not adequate by themselves, especially in women. Therefore, additional strategies beyond the measurement of conventional risk factors are needed to identify women who may benefit from medical therapy (3).

Although the usefulness of a routine screening for CAD in the asymptomatic population remains the subject of intense debate, women are commonly screened for breast cancer by using mammography (4) and for osteoporosis by using dual-energy X-ray absorptiometry (DXA) (5). There has been growing interest in whether the presence of breast arterial calcification (BAC), which is easily detected on standard mammography, could improve cardiovascular risk assessments (6). At the same time, increasing biological and epidemiological evidence has provided support for a link between decreased bone mineral density (BMD) and ASCVD (7,8). Given that millions of women undergo mammography and DXA, a significant relationship between CAD and measurements available for these modalities would provide the opportunity to improve risk stratification without additional cost and radiation exposure. With this in mind, we sought to investigate whether evaluations of BAC using mammography and low bone mass (LBM) using DXA could predict subclinical CAD on coronary computed tomography angiography (CCTA) in asymptomatic women. We also tried to evaluate the potential utility of those parameters for refining risk assessment in asymptomatic women based on the 10-year ASCVD risk.

METHODS

STUDY PARTICIPANTS AND DESIGN. This cross-sectional study (BBC [Women Health Registry Study for Bone, Breast, and Coronary Artery Disease]) consecutively enrolled self-referred women ≥40 years of age who underwent digital mammography, DXA, and CCTA as part of a general health evaluation at the Health Promotion Center, Seoul National University Bundang Hospital, between March 2011 and February 2013. A total of 2,113 women who underwent all 3 tests on the same day were reviewed. From the initial cohort, we excluded 1 woman with a history of coronary revascularization and 12 women with a history of breast surgery or procedure. None of the participants demonstrated a serum creatinine level >1.4 mg/dl or uninterpretable imaging data. Therefore, 2,100 women were included in the final analysis. The Institutional Review Board approved this retrospective study and waived the requirement for written informed consent. None of the authors had ever been involved in recommending CCTA during health checkups, and there are no financial relationships to disclose regarding this work.

ASCERTAINMENT OF RISK FACTORS. During the health checkup, a detailed interview regarding sociodemographic factors and risk profiles was administered, and all participants underwent clinical examinations. The predicted 10-year ASCVD risk was estimated using the pooled cohort equation (PCE) (2) and the Korean Risk Prediction Model (KRPM) which is recalibration of the PCE specifically for the Korean population (9). Study participants were divided into groups according to the ASCVD risk at 10 years as follows: <5%, ≥5% but <7.5%, and ≥7.5% (10).

DIGITAL MAMMOGRAPHY. All women underwent standard 2-view (craniocaudal and mediolateral oblique) screening mammography, using a full-field digital mammography system (Brestige, Medifuture, Seongnam, Korea). A breast radiologist with 8 years of experience, blinded to the clinical information and DXA and CCTA results, performed the retrospective review of the mammograms, using a 5-megapixel monitor and a picture-archiving and communication system (Infinitt PACS, Infinitt Healthcare, Seoul, Korea). The number, length, and density of BACs were evaluated as previously described (11) (**Figure 1A**). These 3 scores were summed for each woman, and the total BAC score was divided into 3 grades: none (0), mild (1 to 6), and severe (7 to 12). We evaluated the interobserver variability in 100 randomly selected women (4.8%), using a second reader (a breast radiologist with 13 years of experience). The kappa value for BAC presence was

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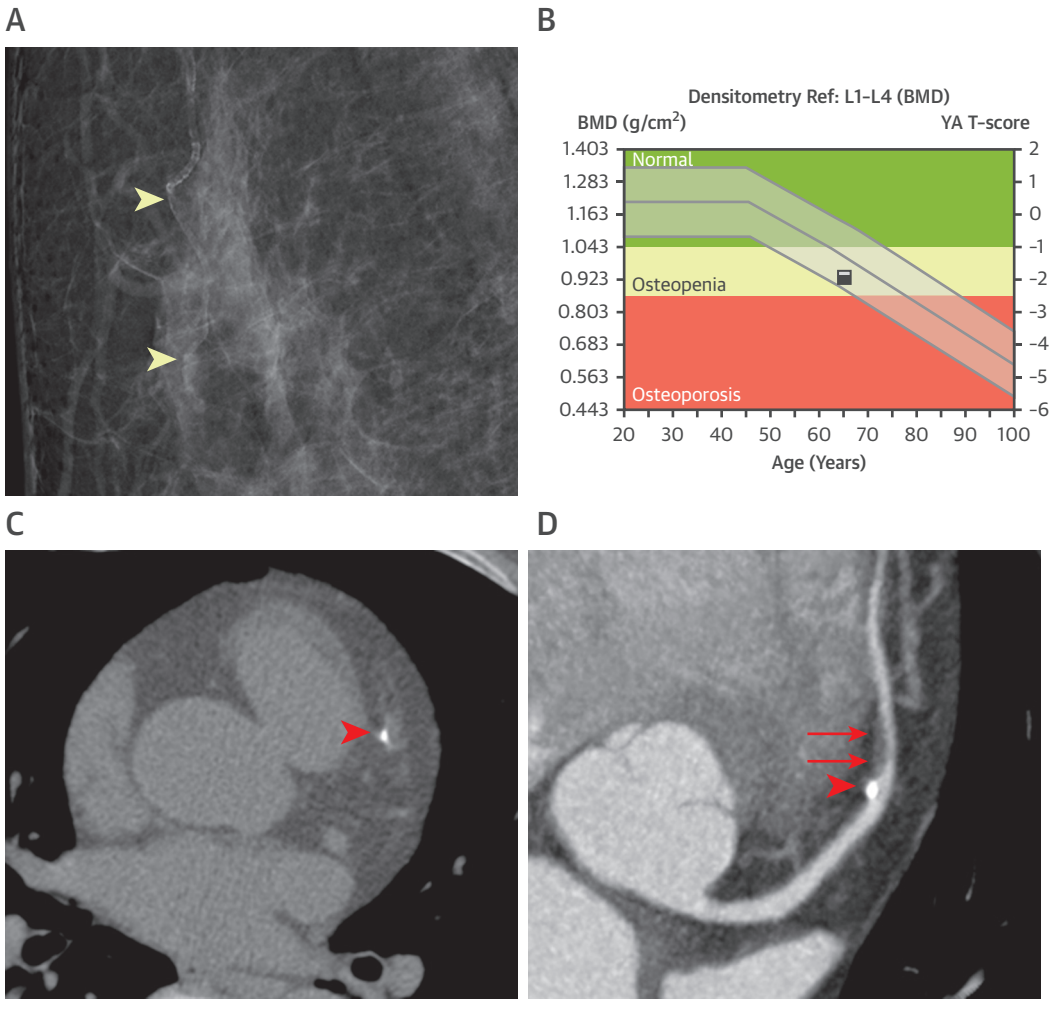
FIGURE 1 A Patient With BAC, Osteopenia, and Subclinical CAD



(A) Mammograph in a 65-year-old woman with BAC **(yellow arrowheads)**; the BAC score was 7. **(B)** Lumbar spine T score is −1.9, which is in the range of osteopenia. **(C)** CAC **(red arrowhead)** with a CAC score of 33.5, and **(D)** CAP **(red arrows)**, with stenosis of 50% at the mid-left anterior descending artery. BAC = breast arterial calcification; BMD = bone mineral density; CAC = coronary artery disease; CAP = coronary atherosclerotic plaque.

0.76 ($p < 0.001$), and the intraclass correlation coefficient for the BAC score was 0.71 (95% confidence interval [CI]: 0.60 to 0.79).

BONE MINERAL DENSITY. Lumbar spine BMD was measured by certified radiological technologists using a single DXA scanner (DXA; GE Lunar Prodigy, Madison, Wisconsin). The entire lumbar spine was scanned in the posteroanterior projection, and the BMD at the lumbar spine was calculated for the first to fourth vertebrae by using densitometric software (Figure 1B). Osteopenia was defined as a BMD T score below -1.0 and osteoporosis as a BMD T score below -2.5. The LBM group was defined as participants with osteopenia or osteoporosis. T scores were calculated using the reference ranges for Asian populations provided by the manufacturer.

CCTA ACQUISITION AND ANALYSIS. Unenhanced and contrast-enhanced computed tomography (CT) angiograms were performed using a 64-detector row CT scanner (Brilliance 64, Philips Medical Systems, Best, the Netherlands), in accordance with established guidelines (12), and the institutional protocols at the time of the scan. CCTA images were transferred to an offline 3-dimensional (3D) workstation

and independently analyzed by a cardiac radiologist with more than 10 years of experience, blinded to the clinical information and mammography and DXA results. The coronary arterial calcification (CAC) score was measured using the Agatston scoring system (13), and the presence of CAC was defined as a CAC score >0. Coronary atherosclerotic plaque (CAP) was defined as the presence of any clearly discernible atherosclerotic plaque lesion >1 mm^2 that could be distinguished from the coronary artery in at least 2 independent image planes (14) (**Figures 1C and 1D**).

STATISTICAL ANALYSIS. All statistical analyses were performed using STATA version 14.0 software (Stata Corp., College Station, Texas). Continuous variables are mean ± SD, and categorical variables are proportions. Quantitative data were compared using Student' *t*-test, chi-square test, and Fisher exact test, as appropriate. The chi-square test for trends was used to analyze the differences in the proportions of mild and severe BAC, and osteopenia and osteoporosis according to the presence of CAC or CAP. Univariate logistic analyses were performed to examine the effects of various characteristics on the presence of CAC and CAP. Multivariate analyses using the enter method were performed to evaluate whether BAC- and LBM-related variables maintained independent associations with the presence of CAC and CAP with adjustment for conventional risk factors. Results are odds ratio (OR) and corresponding 95% CI. Tests for an interaction between BAC presence and LBM on CAC or CAP were performed using regression models with an interaction term as well as the main effects of these 2 factors. To evaluate the incremental value of BAC over the 10-year ASCVD risk, calculated either by the PCE or KRPM, receiver-operator characteristic (ROC) curves were constructed, and areas under the curves (AUCs) were compared using the DeLong method (15). The reclassification improvement was assessed by calculating the category-free and categorical versions of net reclassification improvement (cfNRI and cNRI, respectively), and integrated discrimination improvement indices. For all analyses, a 2-sided p value of <0.05 was considered a statistically significant difference.

RESULTS

Table 1 lists baseline characteristics of the 2,100 study participants (median age: 52 years; range: 40 to 80 years). BAC and LBM were found in 199 (9.5%) and 716 (34.1%) women, respectively. CAC was present in 235 women (11.2%), with a score of 1 to 100 in 188 women (9.0%), 101 to 400 in 39 women (1.9%), and >400 in 8 women (0.4%). CAP was present in 328 women (15.6%), with ≥50% diameter stenosis in 37 women (1.8%) and involving >4 segments in 18 women (0.9%). Women with CAC or CAP showed higher proportions of cardiovascular risk factors and a higher 10-year ASCVD risk (Online Table 1), with increasing proportions of both mild and severe BAC (**Figure 2A**) and osteopenia and osteoporosis (**Figure 2B**) than women without CAC or CAP.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of BAC

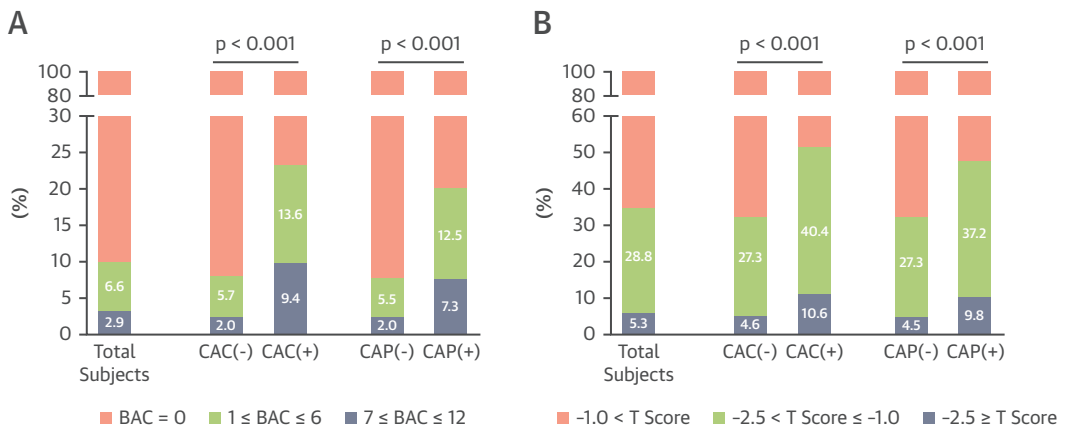
TABLE 1 Baseline Characteristics (N = 2,100)

Age, yrs	52 ± 7
Postmenopausal women	1,321 (62.9)
Number of parity	1.9 ± 1.0
Hypertension	319 (15.2)
Hyperlipidemia	1,156 (55.0)
Diabetes mellitus	87 (4.1)
Current smoking	70 (3.9)
Family history of CAD	247 (20.6)
Antihypertensive medication	260 (12.4)
Antihyperlipidemic medication	152 (7.2)
Antidiabetic medication	69 (3.3)
Body mass index, kg/m^2	22.7 ± 3.0
Systolic blood pressure, mm Hg	110 ± 16
Diastolic blood pressure, mm Hg	64 ± 10
Hemoglobin, g/dl	13.3 ± 1.2
Serum creatinine, mg/dl	0.7 ± 0.1
Fasting blood glucose, mg/dl	89 ± 16
% HbA_{1c}	5.6 ± 0.6
Total cholesterol, mg/dl	202 ± 35
Triglyceride, mg/dl	92 ± 58
High-density lipoprotein, mg/dl	60 ± 14
Low-density lipoprotein, mg/dl	124 ± 32
% of PCE-based 10-yr ASCVD risk	2.1 ± 2.7
10-yr ASCVD risk <5%	1,915 (91.2)
5% ≤10-yr ASCVD risk <7.5%	110 (5.2)
7.5% ≤10-yr ASCVD risk	75 (3.6)
% KRPM-based 10-yr ASCVD risk	3.3 ± 2.9
10-yr ASCVD risk <5%	1,701 (81.0)
5% ≤ 10-yr ASCVD risk <7.5%	231 (11.0)
7.5% ≤ 10-yr ASCVD risk	168 (8.0)
Presence of BAC	199 (9.5)
BAC score	0.5 ± 1.8
Lumbar spine BMD	1.120 ± 0.167
Lumbar spine T score	−0.34 ± 1.35
Low bone mass, T score ≤−1.0	716 (34.1)
Presence of CAC	235 (11.2)
CAC score	10.1 ± 95.3
Presence of CAP	328 (15.6)
CAP ≥50% stenosis	37 (1.8)
CAP involving >4 segments	18 (0.9)

Values are mean ± SD or n (%).

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CAP = coronary atherosclerotic plaque; KRPM = Korean Risk Prediction Model; PCE = pooled cohort equation.

FIGURE 2 Proportions of BAC Grades and Osteopenia and Osteoporosis



Proportions of **(A)** each BAC grade and **(B)** osteopenia and osteoporosis according to the presence of CAC or CAP. CAC (−) = absence of CAC; CAC (+) = presence of CAC; CAP (−) = absence of CAP; CAP (+) = presence of CAP. Abbreviations are as in **Figure 1**.

and LBM for the identification of CAC and CAP are presented in **Table 2**. As the ASCVD risk increased, the sensitivity and PPV increased and the specificity and NPV decreased (Online Table 2).

Univariate analyses demonstrated that the presence and severity of BAC were significant predictors of the presence of both CAC and CAP, and increasing BAC severity demonstrated gradual associations with CAC (unadjusted OR: 2.84 and 5.50, respectively) and CAP (unadjusted OR: 2.61 and 4.15, respectively) (**Table 3**). LBM was also significantly associated with CAC and CAP, and progression to osteopenia and osteoporosis demonstrated graded associations with the presence of CAC (unadjusted OR: 2.06 and 3.21, respectively) and CAP (unadjusted OR: 1.76 and 2.82, respectively). However, in the interaction analysis, BAC presence was the dominant factor for the prediction of CAC and CAP; thus, the full model, including both BAC presence and LBM, did not show additional value over the model using only BAC presence (Online Table 3).

In multivariate analysis (**Table 4**), the presence and severity of BAC, lumbar spine BMD, and T score maintained significant associations with CAC and CAP, after adjustment for the 10-year ASCVD risk as assessed by either the PCE or KRPM. However, after adjustment for conventional risk factors, only the presence and severity of BAC maintained significant associations with the presence of CAC and CAP, whereas BMD, T score, and LBM did not.

In the ROC curve analyses of the models for the predictions of CAC and CAP, the AUCs of the KRPM-based 10-year ASCVD risk were significantly higher than those of the PCE-based 10-year ASCVD risk (AUC: 0.71 vs. 0.64, respectively; p for difference <0.001; and AUC: 0.66 vs. 0.61, respectively; p for difference <0.001). The AUCs of the KRPM-based 10-year ASCVD risk were significantly increased with the addition of BAC presence (AUC: 0.71 vs. 0.72, respectively; p for difference = 0.016; AUC: 0.66 vs. 0.68, respectively; p for difference = 0.010). The addition of BAC presence to the KRPM-based 10-year ASCVD risk resulted in significant improvements in the cfNRI for the detection of CAC (AUC: 0.304; p < 0.001) and CAP (AUC: 0.245, p < 0.001). Similarly, the integrated discrimination improvement for the addition of BAC presence to the KRPM-based 10-year ASCVD risk indicated significantly improved detections of CAC (AUC: 0.0114; p < 0.001) and CAP (AUC: 0.0087; p = 0.004). When we reclassified women by adding BAC presence to a KRPM-based 10-year ASVD risk ≥7.5% (Online Table 4), cNRI values for the detection of CAC and CAP were 0.0516 (p = 0.019) and 0.0468 (p = 0.011), respectively.

DISCUSSION

Although BAC and BMD are expected to be potential risk markers of CAD, they have never been evaluated in the same cohort. In this cross-sectional study, we provide the first insight into the relationships among BAC, BMD, and subclinical CAD, including CAC and CAP, in a large cohort of consecutive asymptomatic women.

BAC, observed as an incidental finding on screening mammography, represents degenerative

TABLE 2 Accuracy of 10-yr ASCVD risk, BAC, and BMD Data for Predicting the Presence of CAC and CAP

	% of Presence of CAC (95% CI)	% of Presence of CAP (95% CI)
PCE-based 10-yr ASCVD risk ≥7.5%		
Sensitivity	17.2 (12.6-22.6)	13.4 (10.0-17.7)
Specificity	98.1 (97.4-98.7)	98.3 (97.5-98.8)
PPV	53.3 (41.5-64.8)	58.7 (46.7-69.7)
NPV	90.4 (89.0-91.6)	86.0 (84.4-87.4)
KRPM-based 10-yr ASCVD risk ≥7.5%		
Sensitivity	28.9 (23.2-35.2)	24.4 (19.8-29.4)
Specificity	94.6 (93.5-95.6)	95.0 (93.9-96.0)
PPV	40.5 (33.0-48.3)	47.6 (39.9-55.5)
NPV	91.4 (90.0-92.6)	87.2 (85.6-88.6)
Presence of BAC (BAC score >0)		
Sensitivity	23.0 (17.8-29.0)	19.8 (15.7-24.6)
Specificity	92.2 (91.0-93.4)	92.4 (91.1-93.6)
PPV	27.1 (21.2-34.0)	32.7 (26.3-39.7)
NPV	90.5 (89.2-91.7)	86.1 (84.5-87.7)
Severe BAC (BAC score >6)		
Sensitivity	9.36 (5.9-13.8)	7.3 (4.8-10.8)
Specificity	98.0 (97.2-98.6)	98.0 (97.2-98.6)
PPV	36.7 (24.9-50.2)	40.0 (27.8-53.5)
NPV	63.3 (49.8-75.1)	85.1 (83.5-86.6)
Low bone mass (T score ≤ −1.0)		
Sensitivity	51.1 (44.5-57.6)	46.9 (41.5-52.5)
Specificity	68.0 (65.9-70.1)	68.3 (66.1-70.4)
PPV	16.8 (14.1-19.7)	21.5 (18.6-24.7)
NPV	91.7 (90.1-93.1)	87.4 (85.5-89.1)
Osteoporosis (T score ≤ −2.5)		
Sensitivity	10.6 (4.4-6.3)	9.7 (6.9-13.6)
Specificity	95.4 (94.3-96.2)	95.5 (94.4-96.4)
PPV	22.5 (15.4-31.6)	28.8 (20.8-38.3)
NPV	89.4 (88.0-90.7)	85.1 (83.4-86.6)

Values are % (95% CI).

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; other abbreviations are as in Table 1.

calcific changes occurring in the mammary arteries. Given that population-based mammography screening is currently recommended in asymptomatic women (16) (although the recommended age may vary, depending on the medical resources and demographic characteristics [17]), a significant relationship between BAC and CAD would provide an opportunity to improve risk stratification without additional cost and exposure to radiation. Although the relationship between BAC and CAD risk factors, such as hypertension, diabetes, and hyperlipidemia, remain inconclusive (18-22), longitudinal studies have consistently demonstrated increased hazards for ASCVD among women with BAC (23-26). Nonetheless, the relationship between BAC and CAD has only been studied in a limited number of studies, which have produced inconsistent results (21,27-30). Furthermore, it should be noted that, as these studies were performed in women who received clinically indicated invasive coronary angiography, the study populations were limited to patients who were suspected of having CAD and were very small in size. Recently, Margolies et al. (11) studied 292 women with mammography who also underwent nongated chest CT within a year and determined CAC in a semiquantitative way. In a previous study, BAC demonstrated a quantitative association with CAC and was superior to standard cardiovascular risk factors for the prediction of CAC. However, the investigators failed to demonstrate a statistically significant incremental value of BAC to the conventional risk stratification algorithm, potentially due to the limited number of study participants. To our knowledge, the present study is the first and largest study to evaluate the association between BAC and subclinical CAD, including both CAC and CAP, as shown by CCTA. BAC remained a strong and independent predictor of subclinical CAD after adjustment for all significant covariates, including age, and demonstrated incremental value over that for a conventional risk stratification algorithm. These results suggest that atherosclerosis imaging allows a more direct visualization of the cumulative effects of all risk determinants in an individual patient.

Several epidemiological studies, including cross-sectional and longitudinal studies, have reported that lower BMD and atherosclerosis are significantly associated. However, in the present study, unlike BAC, LBM did not maintain significant associations with the presence of CAC and CAP after the adjustment for conventional risk factors. It is conceivable that the association between vasculature systems, namely the breast and coronary arteries, is stronger than that between the bone and vessels. However, presently, given the accumulating evidence regarding the shared pathogenesis between the bones and vasculature in given individuals (31,32), it is premature to conclude that BMD does not provide added value for risk stratification. Moreover, the present findings may be associated with the characteristics of the BBC registry. For example, the current study cohort was composed of significantly younger women than those in the previous study by Margolies et al. (11) (mean age: 52 ± 7 years vs. 62 ± 11 years, respectively), and the prevalence of CAC was significantly lower in the present study (11.1% vs. 47.6%, respectively). Given that the diagnostic ability of BAC, and LBM changed according to the 10-year ASCVD risk subgroup, the predictive value of BAC and LBM must be viewed in the context of the study population and should be interpreted carefully. In addition, the relatively low prevalence of LBM in our

TABLE 3 Univariate Analyses To Determine Factors Associated With CAC and CAP

	Presence of CAC			Presence of CAP		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.16	1.13–1.19	<0.001	1.13	1.11–1.15	<0.001
Postmenopausal women	6.62	4.22–10.36	<0.001	4.45	3.20–6.18	<0.001
Number of parity	1.34	1.12–1.533	<0.001	1.30	1.16–1.46	<0.001
Hypertension	4.54	3.37–6.11	<0.001	3.50	2.66–4.59	<0.001
Hyperlipidemia	2.39	1.77–3.23	<0.001	2.38	1.84–3.08	<0.001
Diabetes mellitus	3.46	2.13–5.63	<0.001	4.61	2.96–7.17	<0.001
Current smoking	1.03	0.46–2.17	0.949	0.90	0.46–1.77	0.755
Family history of premature CAD	1.09	0.71–1.66	0.708	1.30	0.91–1.86	0.145
Antihypertensive medication	4.96	3.63–6.76	<0.001	3.72	2.79–4.97	<0.001
Antihyperlipidemic medication	4.04	2.77–5.89	<0.001	3.71	2.61–5.28	<0.001
Antidiabetic medication	4.29	2.55–7.22	<0.001	5.74	3.52–9.35	<0.001
Body mass index	1.13	1.09–1.18	<0.001	1.11	1.07–1.15	<0.001
Systolic blood pressure per 10 mm Hg	1.45	1.37–0.53	<0.001	1.38	1.30–1.46	<0.001
Diastolic blood pressure per 10 mm Hg	1.58	1.47–1.70	<0.001	1.52	1.40–1.64	<0.001
Hemoglobin	1.10	0.97–1.24	0.124	1.15	1.03–1.28	0.010
Serum creatinine	2.29	0.61–8.60	0.221	1.78	0.56–5.64	0.328
Fasting blood glucose per 10 mg/dl	1.14	1.08–1.20	<0.001	1.15	1.09–1.21	<0.001
HbA_{1c}	1.75	1.47–2.09	<0.001	1.90	1.59–2.28	<0.001
Total cholesterol per 10 mg/dl	1.08	1.04–1.12	<0.001	1.08	1.04–1.12	<0.001
Triglyceride, per 10 mg/dl	1.05	1.03–1.07	<0.001	1.05	1.03–1.07	<0.001
High-density lipoprotein per 10 mg/dl	0.86	0.76–0.96	0.005	0.90	0.83–0.98	0.023
Low-density lipoprotein, per 10 mg/dl	1.09	1.05–1.13	<0.001	1.08	1.04–1.12	<0.001
% of PCE-based 10-yr ASCVD risk	1.40	1.33–1.48	<0.001	1.37	1.30–1.44	<0.001
10-yr ASCVD risk <5%	1.00	–	–	1.00	–	–
5% ≤ 10-yr ASCVD risk <7.5%	6.19	4.06–9.46	<0.001	4.86	3.24–7.27	<0.001
7.5% ≤10-yr ASCVD risk	12.9	7.96–20.84	<0.001	9.95	6.16–16.1	<0.001
% of KRPM-based 10-yr ASCVD risk	1.38	1.31–1.44	<0.001	1.33	1.28–1.39	<0.001
10-yr ASCVD risk <5%	1.00	–	–	1.00	–	–
5% ≤ 10-yr ASCVD risk <7.5%	6.19	4.06–9.46	<0.001	3.62	2.63–5.00	<0.001
7.5% ≤10-yr ASCVD risk	12.89	7.96–20.87	<0.001	7.73	5.50–10.86	<0.001
BAC presence	3.54	2.50–5.01	<0.001	3.02	2.19–4.18	<0.001
BAC score	1.22	1.16–1.29	<0.001	1.20	1.13–1.26	<0.001
BAC score = 0	1.00	–	–	1.00	–	–
BAC score = 1–6	2.84	1.86–4.34	<0.001	2.61	1.77–3.84	<0.001
BAC score = 7–12	5.50	3.18–9.61	<0.001	4.15	2.44–7.07	<0.001
Lumbar spine BMD	0.07	0.03–0.18	<0.001	0.11	0.05–0.23	<0.001
Lumbar spine T score	0.72	0.61–0.81	<0.001	0.76	0.69–0.83	<0.001
Low bone mass (T score ≤ −1.0)	2.22	1.69–2.92	<0.001	1.91	1.50–2.42	<0.001
Normal (−1.0 < T score)	1.00	–	–	1.00	–	–
Osteopenia (−2.5 < T score ≤ −1.0)	2.06	1.54–2.75	<0.001	1.76	1.36–2.27	<0.001
Osteoporosis (T score ≤ −2.5)	3.21	1.98–5.21	<0.001	2.82	1.81–4.38	<0.001

OR = odds ratio; other abbreviations are as in Tables 1 and 2.

study population might also have contributed to a lack of statistical power after adjusting for all covariates. Therefore, further studies in the general population, with a larger number of patients, are required to better clarify the association between LBM, and subclinical CAD, beyond the effects of common confounders.

Being able to predict the presence of CAC or CAP in an individual patient based on the presence and severity of BAC in addition to the use of conventional risk stratification algorithms may help clinicians decide when to recommend further cardiac tests and how aggressive interventions to prescribe in order to prevent the onset of clinical CAD. However, before the use of the BAC to facilitate personalized decision making in terms of whether to treat with aspirin or statins, randomized controlled trials of an integrated screening and targeted prevention strategy are required. In addition, the value of BAC for refining risk assessment compared to that achieved using

TABLE 4 Multivariate Analyses of Factors Associated With CAC and CAP

	Adjusted for PCE-Based 10-yr ASCVD Risk			Adjusted for KRPM-Based 10-yr ASCVD Risk			Adjusted for All Covariates*		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Presence of CAC									
BAC presence (BAC score >0)	2.53	1.72–3.71	<0.001	2.18	1.48–3.21	<0.001	2.87	1.67–4.93	<0.001
BAC score	1.15	1.08–1.22	<0.001	1.12	1.06–1.19	<0.001	1.20	1.10–1.31	<0.001
Lumbar spine BMD	0.18	0.07–0.46	<0.001	0.37	1.15–0.93	0.035	0.52	0.14–2.00	0.515
Lumbar spine T score	0.81	0.72–0.91	<0.001	0.88	0.79–0.99	0.033	0.92	0.78–1.09	0.322
Low bone mass (T score ≤−1.0)	1.73	1.29–2.32	<0.001	1.38	1.02–1.87	0.035	1.05	0.69–1.61	0.809
Presence of CAP									
BAC presence (BAC score >0)	2.26	1.60–3.21	<0.001	2.00	1.41–2.85	<0.001	2.52	1.53–4.18	<0.001
BAC score	1.13	1.07–1.20	<0.001	1.11	1.05–1.17	<0.001	1.18	1.08–1.29	<0.001
Lumbar spine BMD	0.23	0.11–0.49	<0.001	0.39	0.18–0.86	0.02	0.46	0.15–1.46	0.188
Lumbar spine T score	0.83	0.76–0.91	<0.001	0.89	0.81–0.98	0.018	0.91	0.79–1.04	0.172
Low bone mass (T score ≤−1.0)	1.54	1.20–1.99	0.001	1.29	0.99–1.68	0.056	0.98	0.68–1.42	0.916

*Adjusted for age, parity number, hypertension, diabetes mellitus, family history of premature CAD, current smoking, body mass index, systolic blood pressure, fasting blood glucose, cholesterol, triglyceride, and high-density lipoprotein cholesterol. Collinearity among all potential confounders was tested using variance inflation factors, and a cutoff of less than 2.0 was defined as a lack of colinearity.

ASCVD = atherosclerotic cardiovascular disease; BAC = breast arterial calcification; BMD = bone mineral density; CAC = coronary artery calcification; CAD = coronary artery disease; CAP = coronary atherosclerotic plaque; CI = confidence interval; KRPM = Korean Risk Prediction Model; OR = odds ratio; PCE = pooled cohort equation.

more direct noninvasive imaging tests of the cardiovascular system needs to be evaluated as part of the preparation for a population-based screening for cardiovascular disease (33,34).

STUDY LIMITATIONS. The design of our study introduced several limitations. First, all participants in the present study were self-referred and underwent digital mammography, DXA, and CCTA as part of a general health evaluation. Although Koreans may undergo a health checkup once every 2 years that is fully covered by the insurance system, if they wish, they can undergo a health checkup at a specialized health checkup center, such as that in the present study, at their own expense. Therefore, even though CCTA is not currently indicated in the absence of symptoms (35), the study participants were able to undergo CCTA through a self-referral mechanism. The present study cohort of self-referred, healthy women may not be fully representative of the general population, and the risk of selection bias must be considered. In addition, we are far from recommending CCTA screening in asymptomatic women and agree with concerns that CCTA may be associated with a non-negligible risk of cancer, especially in women. Therefore, we attempted to evaluate the predictive value of BAC and LBM for the presence of subclinical CAD. Second, although the BBC registry included consecutive patients in our health checkup program, the present study was performed in a retrospective manner and was not an event-based outcome study. Instead, CAC and CAP were used as surrogate markers. Therefore, presently, it is impossible to evaluate whether refining the risk stratification algorithm by addition of BAC and BMD improves the prediction of future cardiovascular risk. However, the present results set the stage for an outcome trial, which is required to evaluate whether the identification of BAC and LBM in asymptomatic women will translate into long-term clinical benefits. We hope to report the results of this trial in the near future.

CONCLUSIONS

Evaluation of the presence of BAC and LBM provides predictive value for the presence of subclinical CAD. BAC especially provides an independent and incremental value over that of conventional risk algorithms based on clinical risk factors. Further studies are warranted to evaluate whether the evaluation of BAC and LBM in asymptomatic women translates into long-term clinical benefits.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence and severity of BAC and LBM are significantly associated with the risk of subclinical CAD. BAC provides an independent and incremental predictive value over conventional risk factors.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The evaluation of BAC in addition to the use of conventional risk algorithms may be helpful in predicting subclinical CAD in asymptomatic women.

TRANSLATIONAL OUTLOOK: Further studies are warranted to determine whether the evaluation of BAC and LBM in asymptomatic women translates into long-term clinical benefits.

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KEY WORDS breast arterial calcification, coronary artery calcification, coronary artery disease, osteopenia, osteoporosis

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