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EDITORIAL COMMENT

# My AI-Assisted Mammography Report Says "Breast Artery Calcifications"

## Should I See a Preventive Cardiologist?

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Biennial screening mammography is recommended by the U.S. Preventive Services Task Force for asymptomatic women between 50 and 74 years of age, with individual consideration for screening initiation at age 40 or earlier in women with elevated breast cancer risk.[1] Breast artery calcifications (BACs) may often be seen as incidental findings on screening mammograms, in particular among older women, with overall prevalence varying from 3% to >40% depending on the population studied.[2-4]

BACs represent a specific type of vascular calcifications found in the medial part of the vascular wall (*tunica media*) of the small- to medium-sized breast arteries. They are characterized by the circumferential, nonocclusive calcium deposits that occur in absence of inflammatory cells or lipid accumulation, in contrast to coronary artery calcifications which primarily affect the endothelial layer (*tunica intima*) and reflect coronary plaque burden, driven by the traditional atherosclerotic processes. BACs are associated with cardiovascular (CV) risk factors, prevalent coronary artery calcifications and both prevalent and incident atherosclerotic CV disease (ASCVD),[2-6] however, the pathophysiology underlying elevated CV risk remains to be elucidated. Among the risk factors, the strongest associations have been reported with aging, diabetes, and chronic kidney disease (CKD), and increased vascular stiffening may represent a potential mediator.[2,7]

Despite growing evidence of BAC as marker of CVD risk, at present time there are no recommended standards for measuring or reporting BACs on routine mammograms. A survey by the American College of Radiology found that a minority of responding radiologists consistently reported BAC and when included, BAC was most often reported in a binary fashion.[8] This may in part reflect some of active challenges in the field, including the lack of objective, standardized, and quantitative approach to BAC measurement, as well as limited contemporary data using digital mammography that has higher sensitivity for BAC detection compared to older techniques.[2]

In this issue of *JACC: Advances*, Allen et al[9] present an elegant analysis of more than 18,000 screening digital mammograms performed between 2007 and 2016 at a single health care center. They utilize a proprietary, investigational, previously validated artificial intelligence (AI)-software to create a patient-level BAC score, representing the mean of the threshold image-level scores across 4 standard views of the individual participant's index mammogram. BACs were analyzed in 3 ways: as a binary variable (with BAC presence defined as BAC score ≥5), continuous variable (BAC score 0-100), and as quartile groups with increasing BAC score severity (1st quartile including the score 0-25, 2nd: 26-50, 3rd: 51-75, and 4th: 76-100). Clinical variables, all-cause mortality (primary outcome), and secondary outcomes including CV composite outcome (myocardial infarction, stroke, heart failure, and all-cause mortality) were collected via electronic health records and International Classification of Diseases-10 codes.

Prevalence of AI-detected BAC was 23% in the setting of mean age of 57 years and prevalent CV risk factors, diabetes (13%), hypertension (36%), and hyperlipidemia (40%). This is comparable to the

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recent study that utilized a different quantification method (densitometry of digital mammograms) and found BAC presence in 26.5% among women with a mean age of 67.[6] Also similar to prior reports,[2] there was a higher prevalence of AI-detected BAC among women who were older, Black or Hispanic, had diabetes, hypertension, history of CKD or history of CV disease, or were taking statins or antihypertensives. Finally, BACs were less prevalent among current smokers, confirming prior published reports of this counterintuitive finding.[2,7]

Over a median follow-up of 4.8 years, 642 (3.6%) of participants died and 1,082 (6.1%) experienced CV composite outcome. The analysis demonstrated significant associations between AI-generated BAC values and all-cause mortality as well as the composite CV outcome which persisted after the adjustment for traditional CV risk factors. The results were consistent when BACs were analyzed as a binary or quantitative variable with the latter showing increased mortality risk with each 10-point BAC score and with increasing BAC quartiles. Some of the most clinically relevant findings of this study come from age- and risk factor-stratified analysis: women in the youngest age group (40-59 years) had the highest residual risk associated with BACs (after accounting for CV risk factors) with adjusted HR of 1.51, and 95% CI of 1.22 to 1.87. Among women aged 60 to 74 elevated BAC also independently predicted mortality risk, while the associations between BAC and mortality among women 75 and older were not significant after adjusting for CV risk factors. When stratified by the presence of risk factors, BAC was associated with mortality among subgroups traditionally not deemed to be high risk, such as nonsmokers, women without diabetes, hypertension, or hyperlipidemia, as well as women without known prior CKD or known CVD. This reinforces the concept that BAC represents an independent measure that captures additional risk beyond conventional risk factors and can serve as an early biomarker of underlying ASCVD risk.

Limitations of the study include lack of available data on cause-specific mortality, in particular CV mortality, and absence of data about the CV interventions such as coronary revascularization. The International Classification of Diseases-10 codes from electronic health records were used to ascertain outcomes which might increase the risk of misclassification. Finally, most women in this study were White indicating the need for further validation in more diverse cohorts.

Relevant to clinical practice, the study by Allen et al adds an important tool to our quest of utilizing BAC as an early marker of CVD and a potential guide of CV prevention efforts. Its AI-based quantitative BAC score, generated using the routine screening mammogram images, represents a step forward toward an objective and standardized BAC measurement which is not labor intensive and could be implemented into structured radiology reporting. At present time, ASCVD risk prediction algorithms, such as pooled cohort equations, are recommended as screening strategies despite their limitations in women where a large proportion of CV events occurs among individuals with 10-year estimated ASCVD risk of $<$7.5%.[10] With many millions of women undergoing mammography each year in the United States alone, the potential impact of adding BAC as a personalized, sex-specific CVD screening tool is major. Importantly, this information comes without additional radiation or testing which has led to calls to radiology professional associations to recommend inclusion of BAC into structured mammogram reporting.[2,11] Availability of an automated algorithm such as proposed by Allen et al may facilitate the reporting uptake by the radiologists and the use of standardized BAC quantification may allow critical comparisons and validation in different populations in the future.

While technology is bringing us closer to universal reporting of the presence and burden of BAC, multiple challenges remain to be addressed including the clinical response and plan for intervention when BACs are found. From patients' perspective, detection of BAC during mammography could lead to increased anxiety if they are informed of their CV risk without clear guidelines on subsequent steps or management. While mammograms are generally covered by insurance for breast cancer screening, the inclusion of BAC assessment might not be covered, leading to potential out-of-pocket costs. Therefore, clinical algorithms for personalized CV risk evaluation and management need to be developed for individuals with BAC findings and aligned with the overall CV prevention strategies in women. These are likely to evolve and improve over time as we increase our understanding of BAC relevance and identify subgroups of women who may benefit the most from this assessment. Finally, training will be needed for clinicians, in particular radiologists, primary care doctors, gynecologists, and preventive cardiologists to assure effective implementation, coordinate appropriate referrals, and guide the patient toward improved care.

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