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Review

Screening mammography beyond breast cancer: breast arterial calcifications as a sex-specific biomarker of cardiovascular risk

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ABSTRACT

Purpose: To highlight the importance of quantitative breast arterial calcifications (BAC) assessment for an effective stratification of cardiovascular (CV) risk in women, for whom current preventive strategies are inadequate. BAC, easily detectable on mammograms, are associated with CV disease and represent a potential imaging biomarker for CV disease prevention in women.

Method: We summarized the available evidence on this topic.

Results: Age, parity, diabetes, and hyperlipidemia were found to positively correlate with BAC. Women with BAC have a higher CV risk than those without BAC: the relative risk was reported to be 1.4 for transient ischemic attack/stroke, 1.5 for thrombosis, 1.8 for myocardial infarction; the reported hazard ratio was 1.32 for coronary artery disease (CAD), 1.52 for heart failure, 1.29 for CV death, 1.44 for death from CAD. However, BAC do not alarm radiologists; when reported, they are commonly mentioned as "present", not impacting on CV decision-making. Of 18 published studies, 9 reported only presence/absence of BAC, 4 used a semi-quantitative scale, and 5 a continuous scale (with manual, automatic or semiautomatic segmentation). Various appearance, topological complexity, and vessels overlap make BAC quantification difficult to standardize. Nevertheless, machine learning approaches showed promising results in BAC quantification on mammograms.

Conclusions: There is a strong rationale for mammography to become a dual test for breast cancer screening and CV disease prevention. However, robust and automated quantification methods are needed for a deeper insight on the association between BAC and CV disease, to stratifying CV risk and define personalized preventive actions.

1. Introduction

Cardiovascular (CV) disease represents a major public health issue and the first cause of death for men and women, accounting for more than 30% of cases worldwide [1]. Over the last fifty years, increasing attention has been paid to primary prevention, through the identification and control of risk factors and a progressive improvement in phenotyping CV risk. The complex biological pathway leading to CV events encompasses functional and structural changes of heart and vessels that develop over the years with a variable progression rate. Hence, there is a chance for these changes to be identified long before CV events occur and for a preventive strategy to be effective. In the last years, several attempts have been made for improving the performance of traditional CV risk scores with the help of improved algorithms including alternative blood-based risk markers and also imaging biomarkers [2] such as the coronary artery calcium score in asymptomatic individuals at intermediate-risk [3].

Notably, a substantial sex-related difference in CV risk factors has been repeatedly emphasized and studied [4]. Based on population-based registries, the mortality rate for coronary heart disease (CHD) did not fall in young women (aged 55 years or less) as it did for male and in elderly populations [5]. Up to 20% of all coronary events occur in the absence of traditional CV risk factors [6], whereas many women with traditional risk factors do not experience coronary events [7]. One possible reason behind this fact is the occurrence of non-traditional risk factors unique to women. Indeed, pregnancy complications,

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contraceptive, fertility and menopausal hormonal therapies, and systemic autoimmune disorders [8] are not included in current CV risk algorithms for women, which are not tailored and are basically the same as 30 years ago.

Moreover, the awareness of CV risk among young women is poor, as they perceive hearth diseases as a "male problem". This reflects in the failure of basic preventive actions, such as lifestyle modifications or appropriate screening tests. Breast cancer campaigns have been building women awareness for more than 20 years, stressing on the importance and efficacy of early diagnosis. In Europe, half of organized mammographic screening programmes achieves a participation rate higher than 70%, demonstrating that women education is the first step to call for action [9]. These different and somewhat paradoxical trends certainly reflect inadequate prevention strategies [5].

Breast arterial calcifications (BAC) have been recently described among *"the top five women's health issues in preventive cardiology, at the forefront of recent and ongoing research",* together with coronary microvascular dysfunction, hormone replacement therapy, calcium and vitamin D supplementation as well as metabolic considerations during pregnancy [4]. BAC are easily recognizable on routine mammograms that women periodically undergo spontaneously or through organized population-based programmes for breast cancer screening from 40, 45 or 50 years of age, according to different national or local policies. Thus, there is a strong rationale for mammography to serve as a preventive test beyond breast cancer screening, spotlighting on the heart and more comprehensively on CV risk. The reported association of BAC with coronary artery disease (CAD) also in middle age [10] strongly suggests their potential as an additional risk factor when traditional CV risk assessment is somewhat inadequate and does not impact on CV mortality [5]. In this light, efforts should be made aiming at: i) improving the awareness of BAC by physicians providing preventive care to women, including radiologists, cardiologists, and general practitioners; ii) implementing the estimation of BAC to be easily applicable in clinical prevention.

2. BAC as a biomarker for CV risk

BAC appear on mammograms [11] as linear, parallel opacities, typically showing a "tram-track" appearance [12,13] (Fig. 1). They express Monckeberg's calcification, a non-atheromatous vascular lesion developing in the internal elastic or in the medial layer of muscular arteries, different from atherosclerotic calcification, involving the intima layer of large and medium sized elastic arteries. Monckeberg's calcification contains hydroxyapatite crystal deposition in the plaques, while accumulation of calcium phosphate salts in the vascular tissue is seen in advanced atherosclerosis [14].

A systematic review and meta-analysis by Hendriks et al. [11] assessed the available evidence on the associations between BAC and CV risk factors (Table 1). Pooled BAC prevalence resulted to be 12.7% among women attending screening programmes. A higher BAC prevalence was associated with increasing age, diabetes, and parity as opposed to nulliparity, while smoking was associated with lower BAC prevalence. No associations were found with other well-known CV risk factors such as hypertension, obesity, or dyslipidemia. Although longitudinal studies (n = 3) were scarce, BAC appeared to be associated with an increased risk of CV disease events (adjusted hazard ratios for CHD ranging from 1.32 to 1.44). The authors concluded that *BAC appear to be associated with an increased risk of CV disease events, and with some of the known CV risk factors, illustrating that medial arterial calcifications might contribute to CV disease through a pathway distinct from the intimal atherosclerotic process.*

The association between BAC, merely reported as "present" at mammographic images, and CV risk was investigated in several studies [15–18], summarized in Table 2.

It is well-known that the transition to menopause is associated with an increase in CV risk due to dysregulation of glucose and lipid metabolism and consequently of estrogens. Indeed, early menopause and premature ovarian insufficiency increase CV risk (1.5–2 folds). According to the literature, hormonal therapy has a positive impact on CV risk factors, with beneficial effects on both CV morbidity and mortality in women at early menopausal age [19]. In this light, the association between BAC and hormonal therapy was investigated by Schnatz et al. [18]. The study demonstrated that BAC prevalence was higher (eight times) in menopausal women than in pre-menopausal ones, thus highlighting the role of estrogenic regulation in BAC development. Moreover, even when adjusting for age, past hormonal therapy was significantly associated to a lower prevalence of BAC. This study highlights the role of BAC as a potential biomarker of sex-specific CV risk due to the close link between CV risk factor and hormonal balance in women during and after transition to menopause.

When evaluating the interaction between BAC and CV disease, woman's age plays as a major confounder. To investigate the potential role of BAC as a biomarker of CV risk beyond the ageing progress, Moshyedi et al. [10] investigated the association between BAC, CAD and diabetes mellitus, adjusting for patient age. Their results showed that BAC may still indicate an additional risk factor for CAD in women with less than 59 years of age (positive predictive value [PPV] of BAC for CAD was 0.88, negative predictive value was 0.65), particularly in diabetic patients (PPV of diabetes mellitus for CAD increased from 0.62 when BAC was absent to 1.00 when BAC was present) [10].

Later on, also Schnatz et al [20] investigated the association between BAC and hormonal therapy in 1,919 women undergoing screening mammography. As expected, the higher was the age, the higher the prevalence of BAC. Nevertheless, the prevalence of atherosclerotic cardiovascular disease and CAD remained higher in women with BAC stratified for age. Indeed, CAD prevalence was always greater in women with BAC than in women without BAC, in women under 55 (10.4% *versus* 3.8%), in women from 55 to 64 (6.7% *versus* 1.1%), and in women over 64 (18.9% *versus* 10.1%), confirming that BAC correlated con CV risk factors even in women aged less than 55 years, when it is especially important to detect CV risk factors [20].

The same research group investigated on the same cohort [18] whether mammography could predict the development of CAD. Among women who did not have CAD at baseline, women with BAC were significantly more likely to develop a heart disease or a stroke than those without BAC (6.3% *versus* 2.3%, $p = 0.003$; 58.3% *versus* 13.3%, $p < 0.001$), respectively. These results remained significant even when adjusting for age. BAC together with hypertension, hypercholesterolemia, and family history contributed to the 5-year incidence of CAD and BAC had the highest odds ratio for predicting CHD after 5 years.

Thus, identifying and consistently reporting BAC presence and severity on mammography is paramount at all ages, in particular in women under 65, where traditional risk factors may not be so prevalent due to the later onset of CV events in women and actual CV risk may be underestimated. BAC are not only an imaging biomarker for CV risk, but represent a predictive factor for CV events. This strength the potential of their application in preventing but also in monitoring the progression of the disease over time and the impact of any preventive measures.

3. What is missing?

Although BAC can be easily detected on routine mammograms, their assessment represents a crucial challenge. Various appearance patterns (bright tubular, single or parallel linear structures, or sporadic bright spots), topological complexity, and vessels overlap on two-dimensional projections make both identification and quantification of BAC difficult to standardize [12].

Currently, screening mammography readers leave BAC aside since they are not suspect for an underlying cancer, *i.e.* they do not "alarm". While parenchymal calcifications, potentially associated with cancer, were extensively analyzed also using computer-aided detection tools

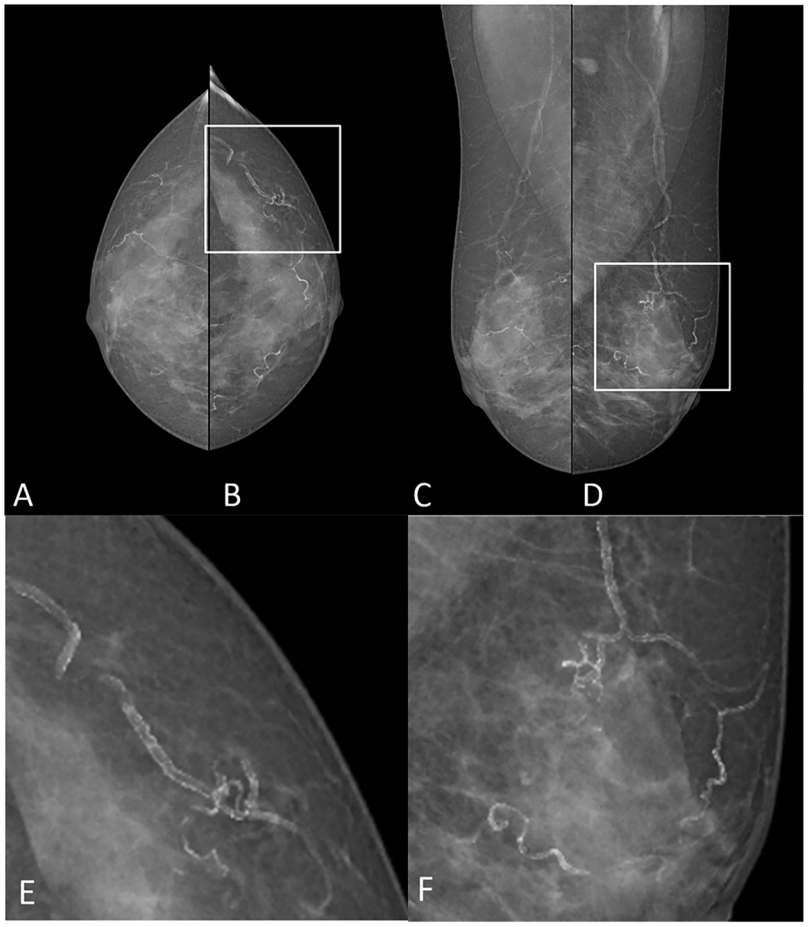

Fig. 1. Screening mammography (A, B cranio-caudal and C, D mediolateral oblique views) of a 65-year old woman showing bilateral breast arterial calcifications (BAC), more prominent on the left side (B, D). Morphology of these calcifications can be appreciated in the magnifications (E, F) of the squared regions of the left breast.

Table 1
Odds ratios (OR), 95% confidence interval (CI) and heterogeneity (I^2) of the risk and reproductive factors as determinants of BAC.

Determinant	OR	95% CI	I^2 (%)
Risk factor			
Age*	2.98	2.31–3.85	87.02
Reproductive factors			
Parity	3.43	2.23–5.47	0
HRT	0.56	0.37–0.84	88.23
Cardiovascular risk factors			
Hypertension	1.08	0.98–1.19	0
Smokers	0.48	0.39–0.60	45.58
Hyperlipidemia	1.72	0.95–3.09	63.87
BMI	0.99	0.95–1.04	27.5
Diabetes	1.88	1.36–2.59	79.53

OR = odds ratio; 95% CI = 95% confidence interval; I^2= heterogeneity; HRT = hormone replacement therapy; BMI = body mass index. *For every 10 years of increasing age. Data are adapted from Hendriks et al [11].

Table 2
Risk of death and cardiovascular outcomes associated with BAC.

Variable	Risk	95% CI
a)		
Transient ischemic attack/stroke	1.4 (RR)	1.01–1.08
Thrombosis	1.5 (RR)	1.00–2.20
Myocardial infarction	1.8 (RR)	1.01–2.90
b)		
Death (all causes)	1.29 (HR)	1.06–1.58
With diabetes	1.74 (HR)	1.19–2.56
Cardiovascular deaths (total)	1.29 (HR)	1.01–1.66
With diabetes	1.71 (HR)	1.00–2.94
Death from CHD	1.44 (HR)	1.02–2.05
c)		
CHD	1.32 (HR)	1.08–1.60
Ischemic stroke	1.41 (HR)	1.11–1.78
Heart failure	1.52 (HR)	1.18–1.98
d)		
Any CHD	3.54 (OR)	2.28–5.50

CHD = coronary heart disease (https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease/coronary-artery-disease); BAC = breast arterial calcifications; 95% CI = 95% confidence interval; RR = relative risk; HR = hazard ratio; OR = odds ratio. a) Data adapted from van Noord et al [15]; b) Data adapted from Kemmeren et al [16]; c) Data adapted from Iribarren et al [17]; d) Data adapted from Schnatz et al [18].

[21], BAC, when detected, are generally just reported as “present” but not interpreted according a CV risk preventive perspective [22–25].

It is unlikely that all subjects with BAC may benefit from the same preventive intervention. To express BAC with a dichotomic assessment (*i.e.*, as present or absent), allows only to classify women into two CV risk classes. However, even at an early research stage, the binary classification hinders the identification of women with intermediate CV risk, who may mostly benefit of a tailored and personalized CV disease prevention. Personalized medicine may be based on the identification of quantitative biomarkers, even blood-based or imaging-based, ideally expressed on a continuous scale. This issue opens the challenge of expressing BAC as a quantitative (or at least semi-quantitative) scale that will allow to stratify patients into multiple CV risk levels.

Recently, few attempts have been made for improving BAC assessment using semi-quantitative scales [26–29]. In dedicated studies, BAC grading ranges from four-level Likert scale [29] to complex scores based on number and maximum length of involved vessels and calcium density [27]. Nevertheless, the heterogeneity among grading scales reflects

Table 3
Methods of BAC assessment reported in original studies and retrieved for this review.

Assessment scale	Authors	Year	Measure
Dichotomic scale	Moshyedi et al. [10]	1995	Present/absent
	Van Noord et al. [15]	1996	Present/absent
	Kemmeren al. [16]	1998	Present/absent
	Kataoka et al. [22]	2006	Present/absent
	Schnatz et al. [18]	2011	Present/absent
	Bae et al. [23]	2013	Present/absent
	Newallo et al. [24]	2015	Present/absent
	Chadashvili et al. [25]	2016	Present/absent
	Schnatz et al. [20]	202007	Present/absent
Semi-quantitative scale	Mostafavi et al. [26]	2015	4 levels visual scale[+]
	Margolies et al. [27]	2016	12 levels scale*
	Kelly et al. [28]	2018	4 levels visual scale[+]
	Ružičić et al. [29]	2018	4 levels visual scale[+]
Continuous scale	Molloi et al. [30]	2008	Manual segmentation
	Molloi et al. [31]	2009	Manual segmentation
	Cheng et al. [12]	2012	Automatic segmentation
	Wang et al. [32]	2017	Automatic segmentation
	Trimboli et al. [2]	2018	Semi-automatic segmentation

[+] Based on BAC severity; *Based on number of vessels, max length and calcium density.

the lack of standardized criteria for BAC burden estimation. However, to the best of our knowledge, there are no studies that stratify CV risk by means of continuous BAC assessment. When quantified, BAC are manually identified by radiologists [30,31], through a time consuming, operator-dependent process, far to be applied in a daily clinical workflow. Only a minority of studies tried to quantify BAC on a continuous scale 2,12, 30–32].

Operator-dependency in BAC quantification is crucial, representing the major source of bias during BAC estimation. Indeed, the few studies that focused on the development of automatic methods for BAC segmentation and quantification employed more than one reader to establish the reference standard for algorithm validation [12,32]. Moreover, a recent original research highlighted this issue comparing the performance of two adequately trained observers in BAC segmentation on a multivendor image dataset of 212 mammographic views from routine practice. In this study, each reader placed rectangular ROIs on both CC and MLO views, separately, then BAC were automatically segmented using an adaptive thresholding algorithm. Reader performance were compared using Bland-Altman analysis, which proved the existing disagreement among manual delineations, with an intraobserver and interobserver reproducibility of only 55% and 3%, respectively [2].

A reliable and automated quantification of BAC is indispensable and could be the solution for contributing to the stratification of CV risk. To this aim, efforts have been put in the development of BAC quantification tools [12,32]. Cheng et al. [10] proposed an automatic algorithm for the delineation of calcified vessels based on a tracking with uncertainty scheme and validated it on 63 mammograms by comparison with manual delineations from two experts. The overall detection performance of their algorithm in terms of sensitivity and specificity reached 92.6 ± 2.2% and 83.9 ± 3.6%, respectively when compared to the first expert and 91.3 ± 3.5% and 82.7 ± 4.1% when compared to the second one. These promising results demonstrated that manual segmentation may be replaced by automatic detection tools. However, the need of stratifying algorithm parameters depending on breast density keeps the path open for further improvements. [12].

More recently, due to the promising performance of artificial intelligence systems in medical image analysis, a recent study [32] investigated the potential of deep learning for BAC detection on mammograms. In their study, Wang et al. proposed a deep convolutional neural network (CNN) that discriminates between BAC and non-BAC pixels [32]. The performance of the proposed CNN was compared with manual delineations performed on 210 cases (840 images) by three expert readers in a two-round reader study. The proposed solution reached detection performances comparable to human experts at free-response receiver operating characteristic analysis and good results also in calcium mass quantification (determination coefficient 96.2%). These results proved the promising application of deep CNN for BAC detection. Nevertheless, further large scale studies are needed to improve and test model generalization across different experimental setup [32]. Table 3 shows different attempts of BAC assessment reported in the literature.

4. Future perspectives

BAC may become an important sex-specific biomarker for CV risk stratification, potentially guiding CV preventive programs in the female population. Women entering screening program for breast cancer and otherwise not considered for CV risk will benefit doubly from mammography, aiming at cancer secondary prevention and CV primary and/or secondary prevention. Although evidence supports a strong association between BAC prevalence and CV risk, this association, *per se*, is not enough for a clinical use. In fact, while in a low-risk population a preventive intervention is likely to be not cost-effective, in a population at increased risk, a preventive treatment could be cost-effective [3]. In the context of a consolidated breast cancer screening, BAC assessment may enable subjects at increased CV risk to be identified and to be offered with tailored preventive and possibly therapeutic interventions.

Recently, several papers pointed out the need to move from the evidence of the association between BAC and CV events to a medical action [33–35]. However, the lack of validated BAC quantification methods that overcome the intrinsic limitation of the dichotomous assessment is a strong factor limiting this action. Only through the stratification into multiple risk classes, BAC on mammography may exploit their potential. Breast radiologists have to support BAC reporting, although this is not recommended by guidelines, and promote the awareness of their significance by women and general practitioners.

Of note, a recent study demonstrated an overwhelming preference of patients to be informed on their BAC status [36]. More than 95% of 397 responding women declared to prefer to have BAC reported; all 107 women who were unaware of a personal history of CV disease wanted to have information about their BAC and, in case of BAC presence, to further investigate atherosclerosis. Coronary artery computed tomography was the preferred option for decision-making in 87% of women.

5. Conclusions

To summarize, mammography allows to identify the presence of

BAC, turning on an alarm bell on woman's CV status. In Europe, about 64 million women aged 50–69 years access screening mammography every two or three years [37] and about 8 million of these women may have BAC identified. A similar rough estimation is for the United States [38,39] where spontaneous screening starts at 40 years of age and about 45 million women yearly access screening mammography with 6 million having BAC potentially identified. This enormous potential needs to be exploited and awareness campaigns have to be promoted. A preventive action could be initiated over a threshold defined by retrospective and prospective studies. BAC represent the added value of an ongoing and consolidated cancer screening to act for preventing the main cause of death among women in which traditional CV risk scores do not adequately perform. We need high-quality research for this, the first step being to make a reliable and user-friendly BAC quantification tools available.

Preventive campaigns usually require huge efforts, both social and economic, to be implemented. In a historical phase of great attention to the healthcare expenditure, to work in favor of using BAC for CV prevention in women, using the infrastructure of an already existing screening, implies that important results could be obtained with relatively limited costs.

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Declaration of Competing Interest

All Authors declare no conflict of interest.

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