In recent years, there have been substantial efforts by the medical community to reduce the cardiovascular disease (CVD) burden in women, as it remains a leading cause of mortality and morbidity in women worldwide. In developed nations such as the United States and Canada, the decline in cardiovascular mortality for women has stagnated since 2017, with mortality rates now increasing. Reasons for this trend are not clear, but may be related to disparities in identification, diagnosis, treatment, and underrepresentation of women in clinical trials. As our understanding of the sex differences in CVD deepens, a generic clinical approach is no longer adequate to properly assess a woman’s cardiovascular risk profile. Failing to recognise female-specific risk factors throughout the reproductive lifespan could lead to an underestimation of a woman’s CVD risk, thereby missing crucial opportunities for primary preventive strategies.

One such sex-specific CVD indicator that is gaining traction is that of breast arterial calcification (BAC), which has historically been considered to be an incidental finding on mammography. BAC is a type of medial arterial calcification that involves nonocclusive, circumferential thickening of the media in small- to medium-size arteries. BAC manifests as radiopaque calcifications arranged linearly, reminiscent of a railroad track. This is distinct from intimal calcification, which is traditionally associated with coronary artery disease and plaque formation. In contrast, medial calcifications are believed to cause arterial stiffness and may increase CVD through microvascular disease and hypertension.

Past research has linked BAC with cardiovascular risks such as diabetes and hypertension, which are especially prevalent in older women. The relationship between BAC and hypertension is intricate; while hypertension promotes calcification, medial calcification may contribute to the development of hypertension by reducing arterial elasticity, leading to arterial stiffening. In addition, arterial calcification is closely correlated with arterial stiffness, an independent predictor of adverse cardiovascular events.

Recent literature offers mixed findings on the association between BAC and CVD risk, with many studies limited by cross-sectional designs. In the study by Koh et al. in this issue of the Canadian Journal of Cardiology, a systematic review and meta-analysis was undertaken to assess the longitudinal relationship of BAC with the primary outcome of cardiac death and secondary cardiovascular outcomes of ischemic/hemorrhagic stroke, ischemic stroke, peripheral vascular disease, heart failure, and acute coronary syndrome. In summary, the analysis incorporated 5 longitudinal studies, encompassing a total of 87,865 female patients ranging in age from 55 to 69 years, with a follow-up duration of up to 19 years. Women with findings of BAC had a 2-fold increased risk for cardiac death (relative risk [RR] 2.06; P < 0.00001) relative to women without BAC. Moreover, BAC was associated with a heightened risk for ischemic/hemorrhagic stroke (RR 1.51; P = 0.003), ischemic stroke (RR 1.82; P < 0.00001), peripheral vascular disease (RR 1.24; P = 0.003), and heart failure (RR 1.84; P < 0.00001), but not myocardial infarction (MI). Because strokes and heart failure in women are mediated to a significant degree by hypertension, these findings support the hypothesis for an alternate pathway to CVD in women.

Whether there is indeed a relationship between BAC and acute MI remains unresolved. Among the 2 negative studies featured in the systematic review and meta-analysis, one used clinical criteria (Penugonda et al., 2020), and the other study (Iribarren et al., 2022) used International Classification of Diseases, Ninth and Tenth Revision codes to determine the incidence of acute MI. Neither study included myocardial infarction with nonobstructive coronary arteries (MINOCA), which can represent 5% to 15% of troponin-positive acute coronary syndrome cases and is more prevalent in younger women with fewer traditional cardiac risk factors. Despite often being reassured and offered no specific treatment, the prognosis for patients with MINOCA is far from benign, with 1- and 5-year mortality rates of 5% and 10%, respectively. To date, there has been incomplete understanding of the heterogeneous causes of MINOCA, including...
spontaneous coronary artery dissection, plaque disruption, thromboembolism, coronary vasospasm, and coronary microvascular dysfunction.\textsuperscript{17} It is possible that included studies in the systematic review missed cases of MINOCA, which could explain the absence of a higher MI incidence in patients with BAC compared with those without. However, with the recent additions to the ICD-10 codes that account for coronary microvascular dysfunction, future studies utilising administrative databases could address this limitation. Specifically, code I21.B is designated for MI associated with coronary microvascular disease, coronary microvascular dysfunction, and MINOCA accompanied by microvascular disease.\textsuperscript{22}

Given this perspective, we advocate for additional research to better understand the relationship between BAC and microvascular dysfunction, a central theme of this editorial to explain the findings in Koh et al.’s paper. In the context of arterial stiffness and hypertension, aortic stiffening is linked with alterations in microcirculatory structure and function.\textsuperscript{23} Research indicates that aortic stiffness correlates with microvascular dysfunction in patients who have nonobstructive coronary artery disease.\textsuperscript{24} Microvascular dysfunction is thought to be a multisystem disorder affecting the architecture and function of small arteries, arterioles, venules, and capillaries across organs such as the heart, brain, kidneys, lungs, and retina.\textsuperscript{25,26} The presence of BAC in small- to medium-size arteries might indicate microvascular dysfunction,\textsuperscript{16} which could be the key underlying mechanism driving the heightened cardiovascular risks observed in women (Fig. 1).

Overall, the authors are commended for their efforts in this study, which sought to clarify the longitudinal relationship between BAC and CVD. It is increasingly evident that the cardiovascular assessment for a woman needs to go beyond just traditional risk scores and factors to integrate female-specific risk enhancers for a more comprehensive evaluation of her risk profile.

In the near future, screening mammography may serve a dual purpose: as a cost-effective method for detecting breast cancer and potentially as a tool for risk-stratifying women through the identification of BAC. Although BAC is often detected incidentally, its documentation remains inconsistent.\textsuperscript{27} Further research is vital to determine if the presence of BAC requires a cardiovascular assessment and whether such an approach can identify women in need of early preventative interventions.

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