Title
Breast arterial calcification is associated with incident atrial fibrillation among older but not younger post-menopausal women

Journal
European Heart Journal Open, 3(2)

ISSN
2752-4191

Authors
Iribarren, Carlos
Chandra, Malini
Parikh, Rishi V
et al.

Publication Date
2023-03-02

DOI
10.1093/ehjopen/oead017

ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–9
https://doi.org/10.1093/ehjopen/oead017

ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Breast arterial calcification is associated with incident atrial fibrillation among older but not younger post-menopausal women

Carlos Iribarren [1,*], Malini Chandra[1], Rishi V. Parikh[1], Gabriela Sanchez[1], Danny L. Sam[2], Farima Faith Azamian[3], Hyo-Min Cho[4], Huanjun Ding[3], Sabee Molloi[3], and Alan S. Go[1,5]

[1]Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, USA; [2]Kaiser Permanente Santa Clara Medical Center, 700 Lawrence Expy, Santa Clara, CA 95051, USA; [3]Department of Radiological Sciences, University of California Irvine School of Medicine, 1001 Health Sciences Rd, Irvine, CA 92617, USA; [4]Medical Measurement Team, Korea Research Institute of Standards and Science, 267 Gajeong-ro, Yuseong-gu, Daejeon 34113, South Korea; and [5]Departments of Epidemiology, Biostatistics and Medicine, University of California at San Francisco, 505 Parnassus Ave, San Francisco, CA 94143, USA

Received 15 December 2022; revised 23 February 2023; accepted 26 February 2023; online publish-ahead-of-print 28 February 2023

Handling Editor: Magnus Bäck

Aims

The goal of this study was to examine the association of breast arterial calcification (BAC) presence and quantity with incident atrial fibrillation (AF) in a large cohort of post-menopausal women.

Methods and results

We conducted a longitudinal cohort study among women free of clinically overt cardiovascular disease and AF at baseline (between October 2012 and February 2015) when they attended mammography screening. Atrial fibrillation incidence was ascertained using diagnostic codes and natural language processing. Among 4908 women, 354 incident cases of AF (7%) were ascertained after a mean (standard deviation) of 7 (2) years of follow-up. In Cox regression adjusting for a propensity score for BAC, BAC presence vs. absence was not significantly associated with AF [hazard ratio (HR) = 1.12; 95% confidence interval (CI), 0.89–1.42; $P = 0.34$]. However, a significant (a priori hypothesized) age by BAC interaction was found ($P = 0.02$) such that BAC presence was not associated with incident AF in women aged 60–69 years (HR = 0.83; 95% CI, 0.63–1.15; $P = 0.26$) but was significantly associated with incident AF in women aged 70–79 years (HR = 1.75; 95% CI, 1.21–2.53; $P = 0.003$). No evidence of dose–response relationship between BAC gradation and AF was noted in the entire cohort or in age groups separately.

Conclusion

Our results demonstrate, for the first time, an independent association between BAC and AF in women over age 70 years.

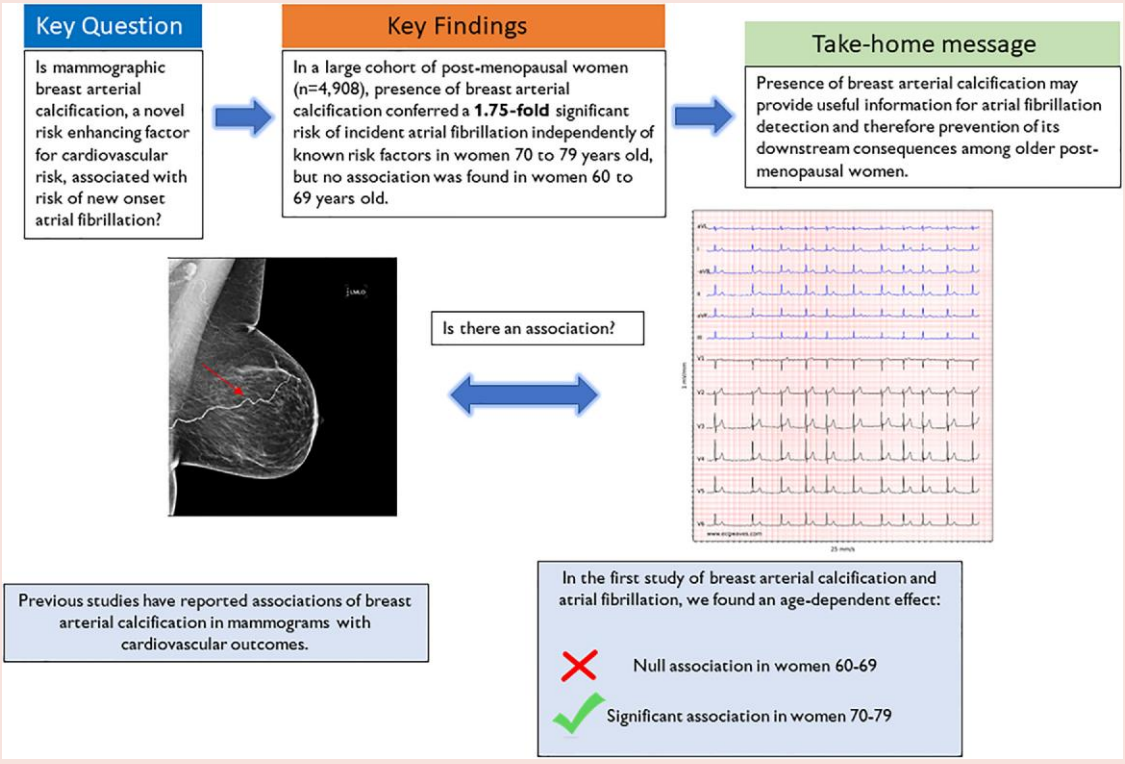
Lay summary

Epidemiological studies have shown that women with breast arterial calcification (BAC) in their mammograms are at increased risk of cardiovascular diseases including heart disease and stroke. However, it is not known at this time whether BAC is associated or not with development of atrial fibrillation, the most common type of heart rhythm abnormality.

We recruited and followed over 7 years a cohort of 4908 postmenopausal women after they attended mammography screening. A total of 354 (7%) women went on to develop new-onset atrial fibrillation. When we considered the entire cohort, we did not find a significant association between the presence of BAC and atrial fibrillation, but when we examined the cohort according to the decade of age, we found that older women (70–79 years old) with BAC were at increased risk of atrial fibrillation (by ~75%), whereas women 60–69 years old with BAC were not. These findings raise the possibility that BAC in mammograms can inform who to screen for atrial fibrillation in women 70 and older.

* Corresponding author. Tel: 1-510-8913554; Fax: 1-510-8913606, Email: Carlos.Iribarren@kp.org

Graphical Abstract



Keywords Breast arterial calcification • Atrial fibrillation/flutter • Women's health • Cohort study

Introduction

Atrial fibrillation (AF) is a common heart rhythm disorder whose incidence and prevalence are rapidly increasing due to aging of the population and improved survival of those with chronic predisposing conditions. Currently, between 3 and 6 million persons have AF in the USA, and this figure is expected to reach 6–16 million in 2050.[1] Since about one-third of the AF cases are thought to be asymptomatic ('silent AF'), and the downstream consequences of AF can be devastating (stroke, dementia, and heart failure),[1] methods to detect AF earlier in life are of paramount importance and the topic of high-priority research.[2]

Epidemiological studies have identified non-modifiable (age, race/ethnicity, and genetic predisposition) and modifiable risk factors for AF including body mass index, hypertension, diabetes mellitus, smoking, obstructive sleep apnoea, myocardial infarction, heart failure, smoking, alcohol, and psychological stress.[1] Recent data from the Multi-Ethnic Study of Atherosclerosis (MESA) study demonstrate that the presence, amount, and progression of coronary artery calcification (CAC, a marker of atherosclerotic burden) are independently associated with risk of incident AF.[3,4]

Breast arterial calcification (BAC) is commonly seen in mammograms and is currently not considered a clinically actionable incidental finding. However, there is mounting evidence that BAC correlates with angiographically defined coronary artery disease (CAD)[5,6] and portends increased risk of CVD outcomes.[7–10] Several studies also support associations of BAC with subclinical CVD including carotid intimal media thickness[11] and coronary artery calcification (CAC).[12,13] However, no studies to date have examined whether BAC is associated with AF. To fill this knowledge gap, we set out to examine the relationship of BAC presence and quantity with incident AF in a large cohort of post-menopausal women.

Methods

Cohort description

MINERVA (**M**ult**I**eth**N**ic study of br**E**ast a**R**terial calcium gradation and cardio**VA**scular disease) is a large, racially, and ethnically diverse cohort of post-menopausal women. Details of recruitment, study procedures, and baseline characteristics can be found elsewhere.[14] In brief, eligible participants were female members of Kaiser Permanente of Northern California (KPNC) who were 60–79 years old when they attended mammography screening between 24 October 2012 and 13 February 2015. Women attending mammography for diagnostic purposes were not eligible. Those with a prior history of myocardial infarction, coronary revascularization, stroke, heart failure, peripheral vascular disease, breast cancer, mastectomy or breast implants, Alzheimer's disease/dementia, chronic dialysis/renal transplant, or not having an assigned primary care provider were also excluded. A total of 5145 women with available digital, uncompressed mammograms were recruited. Of those, 86 had one or more missing covariates of interest, resulting in a final sample of 5059. We retained (using dummy variables) those participants with missing values on age at menarche, breast feeding, hs-CRP, e-GFR, level of stress, or sleep apnoea. Among the 5059, we identified 151 cases of prevalent AF; thus, the at-risk

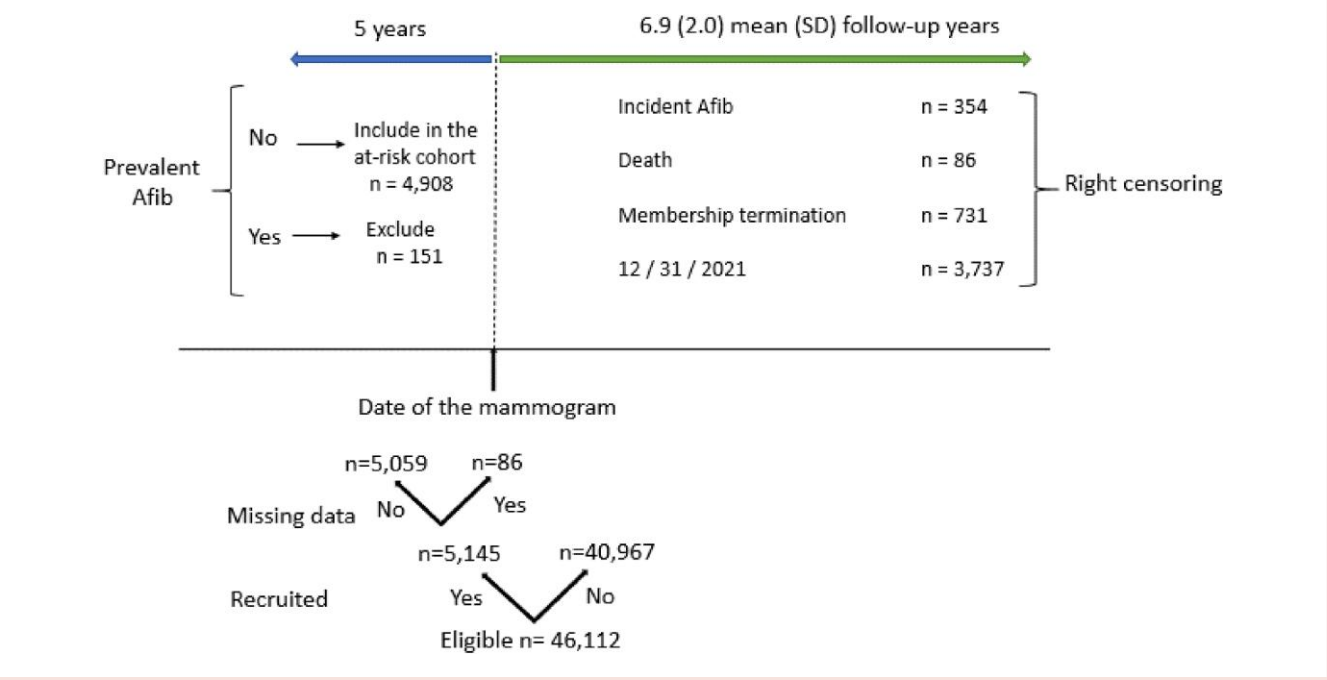


Figure 1 Diagram of study design.

cohort free of AF at baseline was 4908 (*Figure 1*). The study was approved by the Institutional Review Boards of the participating institutions and all participants signed an informed consent. The data underlying this article will be shared on reasonable request to the corresponding author.

BAC assessment

All images were acquired using full-field digital mammography units (Senographe 2000D, General Electric Medical Systems, Milwaukee, WI or Selenia Hologic, Hologic Inc., Malborough, MA). Standard full-field digital mammograms were acquired from mediolateral oblique (MLO) and craniocaudal (CC) projections. A validated densitometry method was used to estimate a continuous BAC mass [in milligrams (mg)] score using raw (uncompressed) digital mammograms prospectively acquired and transmitted to the BAC Reading Center at UC Irvine Department of Radiological Sciences.[15] Intra- and inter-machine variability has been addressed before.[16]

Atrial fibrillation assessment

Prevalent (up to 5 years prior to the baseline visit) and incident (post-baseline and through 12/31/2021) AF were ascertained using a two-pronged approach. We first implemented a code-based approach using at least one hospital discharge diagnosis code or at least two outpatient *ICD-9* (427.31) or *ICD-10* (I48.0, I48.1, I48.11, I48.2, I48.21, and I48.91) codes. The first approach was then augmented by a rule-based natural language processing (NLP) strategy to identify positive mentions of AF within any available progress note from outpatient clinical encounters or electrocardiogram results extracted from the electronic health record (EHR). We derived and validated NLP queries using the I2E software, version 6.2.0 (Linguamatics, Cambridge, UK), an ontology-based interactive information extraction system.[17] A validation study in a separate sample of 105 patients achieved a positive predictive value (PPV) of 90.3% and a negative predictive value (NPV) of 75% among clinical notes and a PPV and NPV of 100% among electrocardiogram notes.

Covariates

Age, ethnicity, education attainment, smoking, reproductive history (menarche, age at menopause, menopausal hormone therapy, number of live births, and breast feeding), perceived level of stress, and physician-diagnosed sleep apnoea were ascertained with a questionnaire self-administered during the clinic visit ($n = 4400$) or administered by phone for those not attending clinic visit ($n = 659$). Clinic visits or phone interviews took place, on average, 3.2 months (SD = 3.0) after the screening mammography. Active prescription at baseline for cholesterol-lowering agents, beta blockers, calcium channel blockers, and antiarrhythmics was ascertained using the Pharmacy Information Management System (PIMS). Details of clinic procedures and laboratory methods can be found elsewhere.[14] Diabetes was defined as self-report of diagnosis, self-report of treatment, fasting glucose ≥ 126 mg/dL, or HbA1c $> 6.5\%$. Hypertension was defined as self-report of hypertension and/or self-report of treatment for hypertension and/or SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Laboratory analyses were performed for a selected panel of blood analytes in non-fasting state at a CLIA-approved regional health plan laboratory. Analytes included total cholesterol, direct low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol (Sekisui Diagnostics LLC, Lexington, MA), haemoglobin A1$_C$ (by immunoturbidimetric assay, Roche Diagnostics, Indianapolis, IN), and high-sensitive C-reactive protein (by chemiluminescent assay, Siemens-Immulite 2000XPi, Tarrytown, NY). Serum creatinine levels measured up to 5 years prior to baseline were extracted from the EHR and glomerular filtration rate was estimated using the 2009 CKD-Epi equation.[18]

Statistical methods

We first assessed the distribution of demographic, behavioural, and clinical factors according to BAC status. Differences were compared across groups using *t*-tests for continuous variables and χ^2 tests for categorical variables. We examined the survival free of AF by BAC status using Kaplan–Meier plots. We estimated a propensity score for any BAC presence using the methodology proposed by Cheng *et al.*[19] Hazard ratios (HR) and 95% confidence intervals (CI) for BAC presence and quantity were estimated using Cox proportional hazards models.[20] Right censoring was applied at death ($n = 86$), termination of health plan membership ($n = 731$), or end of follow-up ($n = 3737$) (*Figure 1*). We fitted unadjusted models and then a model adjusted for the BAC propensity score. Given the results of the MESA study, where progression of coronary artery calcification (CAC) was stronger in younger than in older participants,[4] we tested a priori

the interaction of BAC status (absence vs. presence) and (continuous) age as determinants of AF and performed analyses stratifying by age (60–69 and 70–69 years old) and applied age-specific median BAC cutoff points. To assess improvement of clinical risk prediction, we estimated the change in Harrell's C-statistics after adding BAC status (absence vs. presence) to a model already containing individual AF risk factors (i.e. age, race/ethnicity, BMI, hypertension, diabetes, use of lipid-lowering medications, hs-CRP level, eGFR, presence of sleep apnoea, and early menopause), first in the entire sample and then separately in age strata (60–69 and 70–79). To assess influence of missing data, sensitivity analysis was performed among cohort members with complete data on all covariates ($n = 2,862$, 233 AF events). All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and P-value < 0.05 was used as criterium for statistical significance.

Results

Descriptive analysis

A total of 354 cases of incident AF (7% of the cohort) were ascertained after a mean (SD) of 7 (2) years of follow-up. Four cases were ascertained by codes alone, 206 by NLP alone, and 144 by both methods. As can be seen in *Table 1* women with BAC were significantly older, more likely to be White or Hispanic/Latina, had lower educational attainment, higher HDL cholesterol, higher systolic blood pressure, more likely to be hypertensive, lower e-GFR, higher parity, and lower level of stress.

Survival analysis

As shown in *Figure 2*, the survival free from AF did not differ by BAC status among women 60–69 years old ($P = 0.59$) but was different by BAC status among women 70–79 years old ($P = 0.001$). In unadjusted analysis in the entire cohort, BAC presence was associated with 1.33 increased hazard of incident AF ($P = 0.01$) (*Table 2*). However, adjustment for the BAC propensity score rendered the association not statistically significant (HR = 1.12; 95% CI, 0.89–1.42; $P = 0.34$). In the analysis applying median split among those with BAC, we found a statistically significant association in unadjusted analysis among those at or above the median (HR = 1.37; 95% CI, 1.02–1.82; $P = 0.03$), but adjustment for the propensity score abolished the association. When the cohort was stratified by decades of age, no associations were observed between BAC presence or BAC gradation and AF in the 60–69 years old women. By contrast, among those 70–79 years old, we found statistically significant associations in both unadjusted (HR = 1.77; 95% CI, 1.24–2.52; $P = 0.002$) and propensity score-adjusted models (HR = 1.75; 95% CI, 1.21–2.53; $P = 0.003$). No evidence for dose–response association between BAC and AF was found in women aged 70–79 years old. In a model adjusted for the propensity score, the interaction of BAC status with continuous age was statistically significant ($P = 0.02$). In sensitivity analysis excluding women with missing data, the pattern of results was consistent with the analysis in the entire cohort, although there was loss of statistical power (see Supplementary material online, *Table S1*). The Δ-Harrell's C was 0.003 (0.67–0.67; $P = 0.50$) in the entire cohort, −0.0003 (0.66–0.66; $P = 0.79$) in women 60–69 years old, and 0.02 (0.64–0.66; $P = 0.37$) in women 70–79 years old. The factors that emerged as independently associated with incident AF were age, race/ethnicity (Asian and Hispanic/Latina race inversely related), BMI, hypertension, and early menopause.

Discussion

Main findings

This is the first report examining the association of BAC and extent of BAC with incident AF among post-menopausal women. The relation of BAC with incident AF was modified by age such that no association was seen among women 60–69 years old, and a statistically significant association was noted among women 70–79 years. Consistent with these findings, a (not statistically significant) trend toward improvement in the Harrell's C-statistic noted only in the 70–79 age stratum. Furthermore, the association between BAC and incident AF in women over age 70 was more apparent in those with BAC below the median, arguing against a dose–response relationship.

Interpretation and potential mechanisms

Coronary artery calcification and BAC and two vascular calcification phenotypes with different pathophysiology and aetiology: whereas CAC represents intimal calcium deposits related to the atherosclerotic process (and is related to smoking and hyperlipidaemia), BAC represents medial calcium deposits leading to vascular stiffness and is related to diabetes and hypertension.[21,22]

The association between BAC and AF that we saw in women 70–79 could be due to chance, residual confounding by unmeasured factors. Conversely, it could be real, although our observational data do not imply causality. What are the potential mechanisms linking BAC with AF in women 70–79 years old? Both conditions share risk factors, most notably age, diabetes, hypertension, renal dysfunction, and low-grade inflammation.[1,23] However, in our data, adjusting for these factors did not explain away the association. Hence, other common pathways such as fibrosis, oxidative stress, arterial stiffness, and atrial/arterial remodelling may be involved in both processes.[24,25] Another hypothetical player is the phosphate-regulatory hormone fibroblast growth factor (FGF)-23, which has been implicated in adverse cardiovascular outcomes, endothelial dysfunction, left ventricular hypertrophy, and AF as well as in development of vascular calcification.[26,27] Whatever the mechanism, our results suggest that the potential pathological steps linking BAC and AF do not become apparent until age 70.

Literature review

Recent studies have shown that the burden of coronary artery calcification is higher in patients with AF.[28,29] Data from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrate that CAC progression during 5 years of follow-up is associated with an increased risk for AF at follow-up.[4] Moreover, MESA authors reported an interaction by age with the association of CAC progression with AF being stronger for younger (<61 years: HR = 3.5, 95% CI = 1.3, 9.7) compared with older (≥61 years: HR = 1.4, 95% CI = 0.99, 2.0) participants (P interaction = 0.04), which is at odds with our findings of a BAC–AF association in older (70–79) but not younger (60–69) women. Since MINERVA did not have participants under age 60, we were unable to examine the BAC–AF relation in a comparable cohort of younger women. The MESA investigators speculated that patients with CAC are more prone to have structural heart disease (i.e. enlarged left atria and pulmonary veins) that in turn predisposes to arrhythmogenesis and AF.[4] It is unknown at this time whether BAC or BAC progression is associated with structural heart disease. Coronary artery calcification and BAC and two vascular calcification phenotypes with different pathophysiology and aetiology: whereas CAC represents intimal calcium deposits related to the atherosclerotic process (and is closely related to smoking and hyperlipidaemia), BAC represents medial calcium deposits leading to vascular stiffness and is related more closely to diabetes and hypertension.[21]

Several studies have shown that vitamin K antagonists, the cornerstone of AF treatment, are associated with vascular calcification.[30,31] However, the likelihood of the BAC–AF association being explained by vitamin K antagonists is very low because

Table 1 Baseline cohort characteristics by breast arterial calcification status ($n = 4908$)

	BAC = 0 $n = 3629$ (73.9%)	BAC > 0 $n = 1279$ (26.1%)	*P*
Age (years), mean ± SD	65.2 ± 4.2	67.1 ± 4.8	<0.0001
Race/ethnicity, *n* (%)			<0.0001
White	1848 (50.9%)	738 (57.7%)	
Black	576 (15.9%)	166 (13.0%)	
Hispanic/Latina	421 (11.6%)	182 (14.2%)	
Asian	729 (20.1%)	178 (13.9%)	
Other or unknown race	55 (1.5%)	15 (1.2%)	
Educational attainment, *n* (%)			0.006
Less than completed high school or GED	131 (3.6%)	60 (4.7%)	
Completed high school or GED	652 (18.0%)	267 (20.9%)	
At least some college or completed college	1784 (49.2%)	628 (49.1%)	
Graduate school or professional degree	1062 (29.3%)	324 (25.3%)	
Smoking status, *n* (%)			0.75
Never	2275 (62.7%)	797 (62.3%)	
Former	1206 (33.2%)	435 (34.0%)	
Current	148 (4.1%)	47 (3.7%)	
BMI (kg/m^2), mean ± SD	27.7 ± 6.1	27.8 ± 6.0	0.64
Total cholesterol (mg/dL), mean ± SD	207 ± 37	208 ± 38	0.38
LDL-C (mg/dL), mean ± SD	121 ± 32	120 ± 33	0.67
HDL-C (mg/dL), mean ± SD	65 ± 16	66 ± 17	0.01
Hs-CRP (mg/dL), *n* (%)			0.07
< 1 mg/dL	1086 (29.9%)	378 (29.6%)	
1 to 3 mg/dL	978 (27.0%)	371 (29.0%)	
> 3 mg/dL	839 (23.1%)	357 (27.9%)	
Missing	726 (20.0%)	173 (13.5%)	
Diabetes mellitus[a], *n* (%)			0.07
No	437 (12.0%)	179 (14.0%)	
Yes	3192 (88.0%)	1100 (86.0%)	
Systolic blood pressure (mmHg), mean ± SD	123 ± 16	124 ± 15	0.007
Diastolic blood pressure (mmHg), mean ± SD	69 ± 11	68 ± 10	0.21
Hypertension[b], *n* (%)			0.002
No	1654 (45.6%)	520 (40.7%)	
Yes	1975 (54.4%)	759 (59.3%)	
Cholesterol-lowering drugs, *n* (%)			0.24
No	1001 (27.6%)	331 (25.9%)	
Yes	2628 (72.4%)	948 (74.1%)	
Beta blockers, *n* (%)	19 (0.5%)	13 (1.0%)	0.06
Calcium channel blockers, *n* (%)	19 (0.5%)	8 (0.6%)	0.67
Class IC antiarrhythmics, *n* (%)	1 (0.03%)	0 (0.0%)	0.55
e-GFR (mL/min per 1.73 m^2)[c]			0.003
< 60	189 (5.2%)	100 (7.8%)	
60–90	1901 (52.4%)	744 (58.2%)	
≥ 90	829 (22.8%)	274 (21.4%)	
Missing	710 (19.6%)	161 (12.6%)	
Age at menarche (years)[c], *n* (%)			0.11
< 12	713 (19.7%)	287 (22.4%)	
12–13	1907 (52.6%)	650 (50.8%)	
≥ 14	948 (26.1%)	323 (25.3%)	
Missing	61 (1.7%)	19 (1.5%)	
Early menopause[c], *n* (%)			0.51
No	3034 (83.6%)	1059 (82.8%)	

Continued

Table 1 *Continued*

	BAC = 0 n = 3629 (73.9%)	BAC > 0 n = 1279 (26.1%)	P
Yes	595 (16.4%)	220 (17.2%)	
Menopausal hormone therapy[c], *n* (%)			0.06
No	3211 (88.5%)	1156 (90.4%)	
Yes	411 (11.3%)	121 (9.5%)	
Missing	7 (0.2%)	2 (0.2%)	
History of breast feeding[c], *n* (%)			0.41
No	513 (14.1%)	233 (18.2%)	
Yes	1666 (45.9%)	702 (54.9%)	
Missing	1450 (40.0%)	344 (26.9%)	
Number of live births, *n* (%)			<0.0001
0	1608 (44.3%)	431 (33.7%)	
1–2	1370 (37.8%)	443 (34.6%)	
≥ 3	651 (17.9%)	405 (31.7%)	
Parental history of premature CAD, *n* (%)			0.16
No	3432 (94.6%)	1196 (93.5%)	
Yes	197 (5.4%)	83 (6.5%)	
Self-report of stress, *n* (%)			0.04
No stress at all	358 (9.9%)	140 (11.0%)	
A little bit/moderate	2555 (70.4%)	925 (72.3%)	
Quite a bit/extremely high	712 (19.6%)	212 (16.6%)	
Missing	4 (0.1%)	2 (0.2%)	
Self-report of sleep apnoea, *n* (%)			0.88
No	2747 (75.7%)	1041 (81.4%)	
Yes	298 (8.2%)	111 (8.7%)	
Missing	584 (16.1%)	127 (9.9%)	
Propensity score, mean ± SD	0.24 ± 0.11	0.32 ± 0.14	<0.0001

[a]Self-report or diabetes or HbA1c > 6.5% or fasting glucose ≥ 126 or self-report of treatment.
[b]Self-report of hypertension or self-report of treatment for hypertension or SBP > 140 mmHg or DBP > 90 mmHg.
[c]*P*-value calculated after excluding those with missing values.

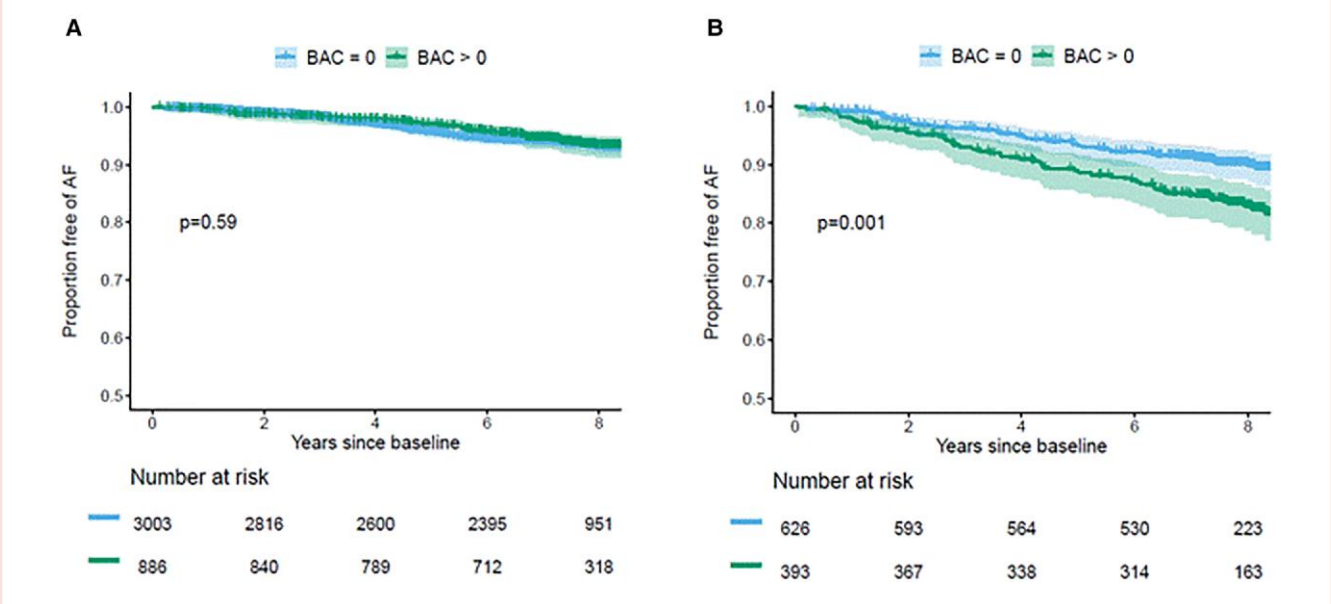


Figure 2 Kaplan–Meier survival plots by breast arterial calcification status and age. Panel (*A*): women 60–69 years old; Panel (*B*): women 70–79 years old.

Table 2 Multivariate association of breast arterial calcification status and gradation with incident atrial fibrillation in the entire cohort and by age groups

Incident atrial fibrillation	Num events	Model 1		Model 2	
		HR (95% CI)	P	HR (95% CI)	P
Age 60–79 years ($n = 4908$)					
BAC presence vs. absence					
> 0 mg vs. 0 mg	240/114	1.33 (1.07–1.66)	0.01	1.12 (0.89–1.42)	0.34
BAC gradation					
0 mg	240	1	—	1.00	—
BAC > 0 mg below median	57	1.30 (0.97–1.73)	0.08	1.16 (0.87–1.55)	0.32
BAC > 0 mg at or above median	57	1.37 (1.02–1.82)	0.03	1.08 (0.80–1.47)	0.60
Age 60–69 years ($n = 3889$)					
BAC presence vs. absence					
> 0 mg vs. 0 mg	181/50	0.92 (0.67–1.25)	0.59	0.83 (0.63– 1.15)	0.26
BAC gradation					
0 mg	181	1	—	1.00	—
BAC > 0 mg below median	26	0.94 (0.62–1.41)	0.76	0.87 (0.58–1.32)	0.52
BAC > 0 mg at or above median	24	0.90 (0.59–1.37)	0.61	0.79 (0.51–1.23)	0.30
Age 70–79 years ($n = 1019$)					
BAC presence vs. absence					
> 0 mg vs. 0 mg	59/64	1.77 (1.24–2.52)	0.002	1.75 (1.21–2.53)	0.003
BAC gradation					
0 mg	59	1	—	1.00	—
BAC > 0 mg below median	36	1.94 (1.28–2.93)	0.002	1.91 (1.26–2.91)	0.03
BAC > 0 mg at or above median	28	1.59 (1.01–2.49)	0.044	1.55 (0.97–2.49)	0.07

Model 1: unadjusted.
Model 2: adjusted for propensity score.

anticoagulant treatment follows AF diagnosis, and we modelled newly developed AF. Moreover, a sensitivity analysis excluding participants that received vitamin K antagonist before the mammogram ($n = 207$), which could have influenced the extent of BAC, did not alter the results (data not shown).

Strengths and limitations

Strengths of the MINERVA cohort include the large size, deep rigorous phenotyping of risk factors, lifestyle and reproductive factors, ethnic diversity, availability of 7 years of follow-up, and objective quantitative assessment of BAC quantity using contemporary digital mammography and thorough ascertainment of incident AF with NLP as well as diagnostic outpatient and inpatient codes. We also recognize limitations. First, our findings may not be generalizable to uninsured populations or to women younger than 60. Second, we were unable to examine types of AF (paroxysmal vs. persistent) or provide distinction between valvular and non-valvular aetiology.

Conclusion

Although further research is warranted to replicate our findings and comparative effectiveness trials are required, BAC assessment and reporting may have utility on who to screen for AF among women 70 and older and thus prevent its downstream consequences.

Lead author biography

Carlos Iribarren MD, MPH, PhD, is a Research Scientist-III at the Kaiser Permanente Northern California Division of Research and an adjunct Assistant Professor in the Department of Epidemiology and Biostatistics at the University of California, San Francisco (UCSF). He joined the Division of Research in 1997, and started at UCSF in 1998. A clinical epidemiologist, Dr. Iribarren's current research interests include risk stratification in the primary prevention setting, including genomic, imaging (particularly breast arterial calcification), and blood biomarkers (particularly high-sensitive troponin I), and the epidemiology of ECG traits (particularly QT interval) and chronic lung disease (COPD, asthma, interstitial pulmonary fibrosis). Dr. Iribarren was a standing member and co-chair of the NIH Cardiovascular, Heart and Sleep Study Section (CHS-B) from 2017-2021 and has participated in numerous other study sections, such as the American Heart Association Behavioral Science, Epidemiology, and Prevention Study Section. He is a Consultant for the Health Care Advisors and for Abbott Diagnostics. He was a Fulbright Fellow at the University of Southern California, Los Angeles, from 1989 through 1994. Dr. Iribarren has published over 220 peer-reviewed articles.

Highlighted publication

Iribarren C, Chandra M, Lee C, Sanchez G, Sam DL, Azamian FF, Cho HM, Ding H , Wong ND, Molloi S. Breast Arterial Calcification: a Novel Cardiovascular Risk Enhancer Among Postmenopausal Women. *Circ Cardiovasc Imaging* 2022;15(3):e013526.

This paper reports the main results of the MINERVA Study (RO1HL106-043; multiple PIs Iribarren, Molloi) indicating that BAC has potential utility for primary CVD prevention and supporting the notion that BAC ought to be considered a risk-enhancing factor for ASCVD among postmenopausal women.

Notable accomplishments

1989-93: Fulbright Scholarship

1993: American Heart Association Jeremiah Stamler Research Award for New Investigators

Data availability

The data used in this article are available upon reasonable request to the PI's of the MINERVA study, Drs. Carlos Iribarren and Sabee Molloi.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

None.

Funding

MINERVA is an investigator-initiated cohort study funded by the National Heart, Lung, and Blood Institute (RO1HL106-043; multiple PIs Iribarren and Molloi).

Conflict of interest: None declared.

Author contributions

Carlos Iribarren: 1) conception and design; 2) drafting of the manuscript; 3) final approval of the manuscript submitted.

Malini Chandra: 1) analysis and interpretation of data; 2) final approval of the manuscript submitted.

Rishi V. Parikh: 1) data pull using NLP; 2) final approval of the manuscript submitted.

Gabriela Sanchez: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Danny L. Sam: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Farima Faith Azamian: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Hyo-Min Cho: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Huanjun Ding: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Sabee Molloi: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

Alan S. Go: 1) revising the manuscript critically for important intellectual content; 2) final approval of the manuscript submitted.

References

1. Kornej J, Borschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. *Circ Res* 2020;**127**:4–20.
2. Khurshid S, Healey JS, McIntyre WF, Lubitz SA. Population-based screening for atrial fibrillation. *Circ Res* 2020;**127**:143–154.
3. O'Neal WT, Efird JT, Dawood FZ, Yeboah J, Alonso A, Heckbert SR, Soliman EZ. Coronary artery calcium and risk of atrial fibrillation (from the multi-ethnic study of atherosclerosis). *Am J Cardiol* 2014;**114**:1707–1712.
4. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, Nazarian S, Soliman EZ. Coronary artery calcium progression and atrial fibrillation: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging* 2015;**8**:8–23.
5. Kelly BS, Scanl OE, Heneghan H, Redmond CE, Healy GM, Mc Dermott E, Heffernan EJ, Prichard R, Mc Nally S. Breast arterial calcification on screening mammography can predict significant coronary artery disease in women. *Clin Imaging* 2018;**49**:48–53.
6. Ruzicic D, Dobric M, Vukovic M, Hrncic D, Dordevic S, Ruzicic M, Aleksandric S, Dordevic-Dikic A, Beleslin B. The correlation of SYNTAX score by coronary angiography with breast arterial calcification by digital mammography. *Clin Radiol* 2018;**73**:454–459.
7. Hendriks EJ, de Jong PA, van der Graaf Y, Mali WP, van der Schouw YT, Beulens JW. Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events. *Atherosclerosis* 2015;**239**:11–20.
8. Iribarren C, Chandra M, Lee C, Sanchez G, Sam DL, Azamian FF, Cho HM, Ding H, Wong ND, Molloi S. Breast arterial calcification: a novel cardiovascular risk enhancer among postmenopausal women. *Circ Cardiovasc Imaging* 2022;**15**:e013526.
9. Iribarren C, Go AS, Tolstykh I, Sidney S, Johnston SC, Spring DB. Breast vascular calcification and risk of coronary heart disease, stroke, and heart failure. *J Womens Health (Larchmt)* 2004;**13**:381–389.
10. Schnatz PF, Marakovits KA, O'Sullivan DM. The association of breast arterial calcification and coronary heart disease. *Obstet Gynecol* 2011;**117**:233–241.
11. Sedighi N, Radmard AR, Radmehr A, Hashemi P, Hajizadeh A, Taheri AP. Breast arterial calcification and risk of carotid atherosclerosis: focusing on the preferentially affected layer of the vessel wall. *Eur J Radiol* 2011;**79**:250–256.
12. Chadashvili T, Litmanovich D, Hall F, Slanetz PJ. Do breast arterial calcifications on mammography predict elevated risk of coronary artery disease? *Eur J Radiol* 2016;**85**:1121–1124.
13. Newallo D, Meinel FG, Schoepf UJ, Baumann S, De Cecco CN, Leddy RJ, Vliegenthart R, Mollmann H, Hamm CW, Morris PB, Renker M. Mammographic detection of breast arterial calcification as an independent predictor of coronary atherosclerotic disease in a single ethnic cohort of African American women. *Atherosclerosis* 2015;**242**:218–221.
14. Iribarren C, Sanchez G, Husson G, Levine-Hall T, Quesenberry C, Sam DL, Maier J, Chaudhary RS, Patel M, Sadeghi B, Javan H, Cho HM, Ding H, Molloi S. MultlethNic Study of BrEast ARterial Calcium Gradation and CardioVAscular Disease: cohort recruitment and baseline characteristics. *Ann Epidemiol* 2018;**28**:41–47.e12.
15. Molloi S, Xu T, Ducote J, Iribarren C. Quantification of breast arterial calcification using full field digital mammography. *Med Phys* 2008;**35**:1428–1439.
16. Molloi S, Mehraien T, Iribarren C, Smith C, Ducote JL, Feig SA. Reproducibility of breast arterial calcium mass quantification using digital mammography. *Acad Radiol* 2009;**16**:275–282.
17. Milward D, Bjareland M, Hayes W, Maxwell M, Oberg L, Tilford N, Thomas J, Hale R, Knight S, Barnes J. Ontology-based interactive information extraction from scientific abstracts. *Comp Funct Genomics* 2005;**6**:67–71.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Int Med* 2009;**150**:604–612.
19. Cheng YJ, Wang MC. Estimating propensity scores and causal survival functions using prevalent survival data. *Biometrics* 2012;**68**:707–716.
20. Cox DR. Regression models and life tables. *J Roy Statist Soc B* 1972;**2**:187–202.
21. Lanzer P, Hannan FM, Lanzer JD, Janzen J, Raggi P, Furniss D, Schuchardt M, Thakker R, Fok PW, Saez-Rodriguez J, Millan A, Sato Y, Ferraresi R, Virmani R, St Hilaire C. Medial arterial calcification: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:1145–1165.
22. Sakata N, Noma A, Yamamoto Y, Okamoto K, Meng J, Takebayashi S, Nagai R, Horiuchi S. Modification of elastin by pentosidine is associated with the calcification of aortic media in patients with end-stage renal disease. *Nephrol Dial Transplant* 2003;**18**:1601–1609.
23. Iribarren C, Molloi S. Breast arterial calcification: a new marker of cardiovascular risk? *Curr Cardiovasc Risk Rep* 2013;**7**:126–135.
24. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011;**91**:265–325.
25. Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. *Trends Cardiovasc Med* 2015;**25**:475–484.
26. Chen JM, Zhong YT, Tu C, Lan J. Significance of serum fibroblast growth factor-23 and miR-208b in pathogenesis of atrial fibrillation and their relationship with prognosis. *World J Clin Cases* 2020;**8**:3458–3464.
27. Mathew JS, Sachs MC, Katz R, Patton KK, Heckbert SR, Hoofnagle AN, Alonso A, Chonchol M, Deo R, Ix JH, Siscovick DS, Kestenbaum B, de Boer IH. Fibroblast growth factor-23 and incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). *Circulation* 2014;**130**:298–307.

28. Chen LQ, Tsiamtsiouris E, Singh H, Rapelje K, Weber J, Dey D, Kosmidou I, Levine J, Cao JJ. Prevalence of coronary artery calcium in patients with atrial fibrillation with and without cardiovascular risk factors. *Am J Cardiol* 2020;**125**: 1765–1769.
29. Nous FMA, Budde RPJ, van Dijkman ED, Musters PJ, Nieman K, Galema TW. Prognostic value of subclinical coronary artery disease in atrial fibrillation patients identified by coronary computed tomography angiography. *Am J Cardiol* 2020;**126**: 16–22.
30. Peeters F, Dudink E, Kimenai DM, Weijs B, Altintas S, Heckman LIB, Mihl C, Schurgers LJ, Wildberger JE, Meex SJR, Kietselaer B, Crijns H. Vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, and vascular calcification in patients with atrial fibrillation. *TH Open* 2018;**2**:e391–e398.
31. Weijs B, Blaauw Y, Rennenberg RJ, Schurgers LJ, Timmermans CC, Pison L, Nieuwlaat R, Hofstra L, Kroon AA, Wildberger J, Crijns HJ. Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients. *Eur Heart J* 2011;**32**:2555–2562.