Arteriosclerotic Calcification and Atrial Fibrillation in the General Population: The Rotterdam Study

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Limited population-based data on the gender differences and association between arteriosclerotic calcification at different sites and atrial fibrillation (AF) exist. We aimed to investigate the (gender-specific) associations between arteriosclerotic calcification at different sites with the risk of AF in the general population. Arteriosclerotic calcification was quantified using computed tomography examinations between 2003 and 2006 in 2,259 participants free of AF from the population-based Rotterdam Study. Cox proportional hazards models, adjusted for cardiovascular risk factors, were used to assess the associations of volumes of coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial and intracranial carotid arteries, vertebrobasilar arteries, and the aortic valve with incident AF. During a median follow-up of 8.6 years, 182 incident AF cases occurred. A larger CAC was associated with incident AF (hazard ratio [HR], 95% confidence interval [CI] 1.25 1.09 to 1.44, p = 0.0019). The gender-stratified analyses showed that larger CAC in men (HR 1.43, 95% CI 1.10 to 1.86, p = 0.0068) and larger AAC in women were associated with incident AF (HR1.44, 95% CI 1.04 to 2.01, p = 0.0299). In conclusion, CAC in the general population, especially in men, and AAC in women were significantly associated with new-onset AF. Our findings imply that interventions to lower arteriosclerotic calcification, particularly, CAC, carry potential for the prevention of AF in the general population, especially in men. **(Am J Cardiol 2024;231:62−69)**

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Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with significant morbidity and mortality risk.[1−4] The exact pathophysiology of AF is not yet completely understood; however, it has been suggested by previous observational studies that arteriosclerotic calcification may play a role in the pathogenesis of AF.[5−7] Arteriosclerotic calcification increases the systolic cardiac afterload through arterial stiffness, which, in turn, gives rise to ventricular and atrial remodeling of the heart and may thereby increase AF susceptibility.[8,9]

Although arteriosclerotic calcification may occur systemically throughout the arterial system, important location and gender differences in its burden have been reported, which also translate to differential risks of clinical events according to the location of arteriosclerotic calcification.[10−13] If this location-specific arteriosclerotic calcification burden translates to a differential risk of AF that also differs between men and women remains to be elucidated. Accumulating evidence also indicates differences between men and women with regard to AF burden, pathophysiology, and prognosis.[14,15] However, previous studies on the relation between arteriosclerotic calcification and AF are limited.[6,16−19] Another recent study showed that arteriosclerotic calcification volume rather than calcification density is more important in AF development.[18] More specifically, previous studies have primarily been limited to CAC and did not take into account the burden of arteriosclerotic calcification throughout the body at other vascular sites (extracoronary) and its potential effect on AF risk.[6,16−19] Moreover, gender differences were mostly also not evaluated in the previous studies.[6,16−19]

We, therefore, aimed to investigate the (gender-specific) association between coronary and extracoronary arteriosclerotic calcification at various locations, including arteriosclerotic calcification of the coronary, aortic arch,

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See page 67 for Declaration of Competing Interest.

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extracranial and intracranial carotid, vertebrobasilar arteries, and the aortic valve, with the risk of new-onset AF in participants from the large population-based Rotterdam Study.

Methods

This investigation was embedded in the Rotterdam Study, a population-based prospective cohort study. During 1990 to 1993, all inhabitants of the Ommoord district in the city of Rotterdam in The Netherlands aged ≥55 years were invited for the study. A total of 7,983 (78% of all invitees) agreed to participate (RS-I). In 2000, the cohort was extended with 3,011 participants (67% of all invitees) who had become aged ≥55 years or had migrated into the research area (RS-II). The study design has been described in detail elsewhere.[20] In short, participants were interviewed at home and examined at the research center to obtain baseline measurements at study entry. The examination of the participants was repeated every 3 to 5 years. Between 2003 and 2006, 2,524 participants from the fourth visit of the original cohort (RS-I-4) and the second visit of the extended cohort (RS-II-2) underwent a computed tomography (CT) to assess arteriosclerotic calcification at various locations.[13,21] From the 2,524 participants who underwent the CT scan, we excluded participants with prevalent AF at the date of the CT scan (n = 92), no written informed consent for follow-up data collection (n = 4), no follow-up time (n = 2), or no data on calcification measures at any location (n = 167). A total of 2,259 participants were included in the present study.

The Rotterdam Study adheres to the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license No. 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration No. EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (https://www.trialregister.nl/trials) and into the World Health Organization (WHO) (Geneva, Switzerland) International Clinical Trials Registry Platform (https://apps.who.int/trialsearch/) under shared catalog No. NL6645/NTR6831. All participants provided written informed consent to participate, before inclusion, in the study and to have their information obtained from treating physicians.

Methods on the assessment of coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial carotid artery calcification (ECAC), intracranial carotid artery calcification (ICAC), vertebrobasilar artery calcification (VBAC) and aortic valve calcification (AVC) have been described in detail previously.[13] In short, noncontrast CT imaging was obtained using 16-slice (n = 674) or 64-slice (n = 1,585) multidetector CT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany). An electrocardiogram (ECG)-gated cardiac scan and a scan that reached from the aortic root to the circle of Willis (1 cm above the sella turcica) was used to scan the following locations: coronary arteries, aortic arch, extracranial internal carotid arteries, intracranial internal carotid arteries, vertebrobasilar arteries, and the aortic valve.[13] The estimated radiation dosage was <2.1 mSv for the cardiac scan and 2.8 mSv for the extracardiac scan. CAC, AAC, and ECAC were quantified in cubic millimeters using commercially available software (Syngo CalciumScoring, Siemens). For ICAC and VBAC, a semiautomated scoring method was used. This method allows to manually delineate calcification in each consecutive slice. The number of pixels above 130 Hounsfield units was then calculated and multiplied by the number of pixels, pixel size, and the increment to calculate the calcification volume.[13]

AF was defined in accordance with the European Society of Cardiology guidelines.[4] Methods on the assessment and definition of prevalent and incident AF have been described in detail previously.[3,4,22] In short, to assess AF at baseline and follow-up examinations, a 10-second 12-lead ECG was recorded with an ACTA Gnosis IV ECG recorder (Esaote; Biomedica, Florence, Italy). The ECG recordings were stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[23] Subsequently, 2 research physicians, blind to the MEANS diagnosis, validated the diagnosis of AF. In case of disagreement, a cardiologist was consulted.[3,22] Additional follow-up data were obtained from medical files of participating general practitioners, hospitals, outpatient clinics, national registration of all hospitals discharge diagnoses, and follow-up examinations at the research center. The date of incident AF was defined as the date of the first occurrence of symptoms suggestive of AF, with subsequent ECG verification obtained from the medical records. Participants were followed up from the date of enrollment in the Rotterdam Study until the date of onset of AF, date of death, loss to follow-up, or to January 1, 2014, whichever occurred first.

Detailed information on current health status, medical history, and medication use was collected by interview, physical examination, and blood sampling.[19,21] Body mass index (BMI) was calculated based on weight in kilograms, divided by the square of the height in meters. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were obtained through blood sampling and measured using an automatic enzymatic procedure. Blood pressure was measured twice at the right upper arm with a random-zero mercury sphygmomanometer in the sitting position, and the average of the 2 consecutive measurements was calculated. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication with indication for hypertension. Smoking information was derived from baseline questionnaires and categorized into never, former, and current smokers. Diabetes mellitus was defined as fasting serum glucose levels ≥7.0 mmol/L (126 mg/100 ml) (or nonfasting serum glucose levels ≥11.1 mmol/L [200 mg/100 ml] if fasting samples were unavailable) or the use of antidiabetic therapy. The methods for assessment and definition of prevalent coronary heart disease (CHD), and heart failure have been described in detail previously.[19,21] Left ventricular hypertrophy (LVH) was diagnosed on ECG using the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction and repolarization. Medication

use was derived from baseline questionnaires and pharmacy data and categorized and defined according to the WHO Anatomical Therapeutic Chemical classifications. More specifically, cardiac medication, antihypertensive medication, and lipid-lowering medication were defined according to the WHO Anatomical Therapeutic Chemical categories c01, c02, and c10, respectively.

The participant characteristics are presented as mean with SD or number (n) with percentages, as appropriate.[24] Differences between men and women were examined by Student's *t* test (normal distribution) or the Mann−Whitney *U* test (skewed distribution) for continuous variables and chi-square test for categorical variables.[25] The distribution of the different calcification volumes were skewed. Therefore, a natural logarithmic transformation was performed to obtain a more normal distribution.[25] To deal with calcification volumes of 0, we added 1.0 mm^3 to the nontransformed values [ln(calcification volume+1.0)].

Competing risk analyses were performed using Cox proportional hazards models to investigate the relation between arteriosclerotic calcification at baseline (CAC, AAC, ECAC, ICAC, VBAC, and AVC), with incident AF and mortality as a competing risk.[26] Cause-specific hazard ratios (HRs) with their 95% confidence intervals (CIs) were calculated to quantify the associations.[25] For the continuous exposure variables, an examination of the shape of the relation with incident AF was performed using natural cubic splines. No deviation from linearity was found. The proportional hazards assumptions were tested by Schoenfeld residual testing in models 1 and 2 for all calcifications measures and found to be satisfied.[26] The natural logarithmic transformed calcification volumes were standardized in the total study sample to obtain the HRs per 1-SD increase in calcification volumes. In the gender-stratified analyzes, the natural logarithmic transformed calcification volumes were standardized in men and women separately to obtain the HRs per 1-SD gender-specific increase in calcification volumes.

Analyses were performed in the total study population and for men and women separately.[26] In addition, we tested the interaction of gender in models 1 and 2 with the different calcification measures in the total population. All models were adjusted for age; gender (if applicable); cohort and type of scanner (model 1); and cardiovascular risk factors, including BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, smoking status, history of diabetes mellitus, history of CHD, history of heart failure, LVH on the ECG, use of cardiac medication, use of antihypertensive medication, and use of lipid-lowering medication (model 2). We considered the aforementioned variables as potential confounders while studying the association between arteriosclerotic calcification and AF because most of these variables are considered as potential risk factors for AF.[1−4] Time was measured in years after baseline and the variables from models 1 and 2 were treated as covariates in the subsequent models. Missing baseline covariate values were imputed under the assumption of missing at random and were imputed using Bayesian linear regression ("norm"), binary logistic regression ("logreg"), and a proportional odds model ("polyr") for continuous, binary, and ordered categorical covariates, respectively, from the "mice" package in R.[27] Missing values for various covariates were as follows: BMI (0.4%), total cholesterol (1.5%), HDL cholesterol (1.5%), systolic blood pressure (0.8%), diastolic blood pressure (0.8%), smoking status (2.5%), LVH on the ECG (8.7%), cardiac medication (1.5%), and lipid-lowering medication (1.5%).

Because these are sensitivity analyses, we examined the associations using complete-case analyses, that is, based on nonimputed data. Furthermore, we examined the associations after exclusion of participants with prevalent CHD and incident CHD during follow-up and before the onset of AF to evaluate if this would attenuate the results. Finally, we also calculated the cause-specific HRs for mortality to evaluate the competing risk of mortality with incident AF.

Statistical significance was considered at 2-sided $p < 0.05$. Data management was done using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, New York). The statistical analyses were performed using the R packages "survival"[28] and "mice"[27] in R software (R 4.0.2: R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2,259 participants free of AF, 1,054 men (46.7%) and 1,205 women (53.3%), were eligible for the analyses. The baseline characteristics for the total study population and for the study population stratified by gender are listed in Table 1. The mean age for the total study population was 69.3 ± 6.6 years and 53.3% were women. The median volumes of CAC, AAC, ECAC, ICAC, VBAC, and AVC were 50.1, 246.4, 21.1, 40.5, 0.0, and 0.0 mm^3, respectively.

During a median follow-up of 8.6 years (interquartile range 8.0 to 9.2), 182 incident AF cases (8.1%) (105 in men and 77 in women) and 309 mortality cases (13.7%) occurred (171 in men and 138 in women). The incidence rate of AF was 10.0 per 1,000 person-years in the total population (in men: 12.7 per 1,000 person-years, in women: 7.8 per 1,000 person-years) and the incidence rate of mortality was 17.0 per 1,000 person-years in the total population (in men: 20.7 per 1,000 person-years, in women: 13.9 per 1,000 person-years).

The Cox proportional hazards models showed significant associations between a larger CAC volume (HR1.31, 95% CI 1.10 to 1.55, p = 0.0019) and a larger VBAC volume (HR1.17, 95% CI 1.04 to 1.32, p = 0.0089), with an increased risk of new-onset AF in the total population in model 1. After adjusting for additional cardiovascular risk factors in model 2, the effect estimates slightly attenuated and only CAC remained significantly associated with the risk of new-onset AF in the total population (HR1.26, 95% CI 1.05 to 1.51, p = 0.0126). Table 2 lists more details. The results of the gender interaction testing in model 1 for CAC, AAC, ECAC, ICAC, VBAC, and AVC in the total population were p = 0.3116, p = 0.0208, p = 0.0141, p = 0.0026, p = 0.0209, p = 0.0097, respectively. In model 2, the results of the gender interaction testing for CAC, AAC, ECAC, ICAC, VBAC, and AVC in the total population were p = 0.4245, p = 0.0158, p = 0.8749, p = 0.8034, p = 0.5523, and p = 0.8303, respectively.

In the gender-stratified analyses, statistically significant associations with new-onset AF in model 1 were observed

Table 1
Baseline characteristics of the total study population and stratified by sex

Baseline Characteristics*	Total study population n=2,259	Men n=1,054	Women n=1,205	$p^{\dagger}$
Age, years	69.3 ± 6.6	69.4 ± 6.4	69.3 ± 6.8	0.868
Women, n (%)	1,205 (53.3)	NA	1,205 (100)	NA
Body mass index, kg/m^2	27.6 ± 4.0	27.4 ± 3.4	27.8 ± 4.4	0.012
Total cholesterol, mmol/L[‡]	5.7 ± 1.0	5.4 ± 0.9	5.9 ± 1.0	<0.001
High-density lipoprotein cholesterol, mmol/L[‡]	1.5 ± 0.4	1.3 ± 0.3	1.6 ± 0.4	<0.001
Systolic blood pressure, mmHg	146.7 ± 19.9	146.2 ± 19.5	147.2 ± 20.3	0.220
Diastolic blood pressure, mmHg	80.4 ± 10.7	81.7 ± 10.9	79.2 ± 10.5	<0.001
Hypertension, n (%)	1665 (73.7)	778 (73.8)	887 (73.6)	0.912
Smoking status, n (%)				<0.001
Never	641 (29.1)	147 (14.3)	494 (42.0)	
Former	1,213 (55.1)	695 (67.7)	518 (44.0)	
Current	348 (15.8)	184 (17.9)	164 (13.9)	
History of diabetes mellitus, n (%)	311 (13.8)	160 (15.2)	151 (12.5)	0.068
History of coronary heart disease, n (%)	144 (6.4)	106 (10.1)	38 (3.2)	<0.001
History of heart failure, n (%)	51 (2.3)	27 (2.6)	24 (2.0)	0.363
Left ventricular hypertrophy, n (%)	122 (5.9)	81 (8.4)	41 (3.7)	<0.001
Cardiac medication, n (%)	130 (5.8)	57 (5.5)	73 (6.1)	0.519
Antihypertensive medication, n (%)	891 (39.4)	419 (39.8)	472 (39.2)	0.777
Lipid lowering medication, n (%)	509 (22.9)	232 (22.4)	277 (23.3)	0.605
CAC volume, mm^3[§]	50.1 (1.7-263.1)	124.5 (18.0-469.8)	15.9 (0.0-117.6)	<0.001
AAC volume, mm^3[§]	248.5 (42.6-806.0)	271.6 (49.0-837.7)	217.7 (38.5-783.2)	0.068
ECAC volume, mm^3[§]	21.1 (0.0-107.0)	40.0 (1.5-145.8)	11.7 (0.0-73.9)	<0.001
ICAC volume, mm^3[§]	40.7 (6.2-134.3)	47.5 (8.4-159.0)	34.7 (5.2-116.0)	<0.001
VBAC volume, mm^3[§]	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.004
AVC volume, mm^3[§]	0.0 (0.0-20.2)	0.0 (0.0-40.0)	0.0 (0.0-6.1)	<0.001

AAC = aortic arch calcification; AVC = aortic valve calcification; CAC = coronary artery calcification; ECAC = extracranial internal carotid artery calcification; ICAC = intracranial internal carotid artery calcification; NA = not applicable; VBAC = vertebrobasilar artery calcification.

* Values are mean (SD) for continuous variables or number (percentages) for categorical variables.

† Statistical significance for continuous data was tested using the Student's *t* test (normal distribution) or the Mann−Whitney *U* test (skewed distribution) and for categorical data was tested using the chi-square test.

‡ SI conversion factor: to convert cholesterol to mg/dl divide by 0.0259.

§ Nontransformed median volume with interquartile range.

Values are shown before imputation and therefore not always add up to 100%.

for CAC in men (HR1.42, 95% CI 1.13 to 1.78, p = 0.0025) and for AAC in women (HR1.52, 95% CI 1.11 to 2.06, p = 0.0086). The associations did not change substantially after additional adjustment for cardiovascular risk factors (CAC in men: HR1.40, 95% CI 1.10 to 1.79, p = 0.0068 and AAC in women: HR1.45, 95% CI 1.04 to 2.03, p = 0.0299) (Table 2).

In our sensitivity analyses, the results from the nonimputed data analysis were similar to the imputed data set analysis (Supplementary Table 1). We also examined the associations after excluding prevalent CHD and incident CHD cases before AF during follow-up. This analysis also yielded similar results to our original findings (Supplementary Table 2). Lastly, we evaluated the competing risk of mortality with incident AF, and larger calcification volumes of CAC, AAC, ECAC, and ICAC were all significantly associated with mortality in models 1 and 2, which confirms that mortality is a potential competing risk for incident AF, especially in men (Supplementary Table 3).

Discussion

In this study, we assessed the association between coronary and multiple extracoronary arteriosclerotic calcification measures and incident AF in the general population. We found that a larger burden of CAC was significantly associated with an increased risk of new-onset AF in the general population. The gender-stratified analyses indicated that CAC in men and AAC in women were significantly associated with an increased risk of new-onset AF in our study. Our findings imply that interventions to lower arteriosclerotic calcification, particularly, CAC, carry the potential for the prevention of AF in the general population, especially in men. Furthermore, our results could make clinicians more aware of the gender-specific deleterious impact of arteriosclerotic burden on AF risk. It could further broaden the ongoing debate regarding gender differences within AF research.

The exact biologic mechanisms linking arteriosclerotic calcification and AF are not yet fully understood. It has been suggested that the association between coronary and extracoronary arteriosclerotic calcification and AF is caused by hypoperfusion and ischemia of the atria and subsequent atrial fibrosis.[29,30] Furthermore, arteriosclerotic calcification increases the systolic cardiac afterload through aortic stiffness that is caused by adaptive wall thickening and calcification of the aorta.[8,9,31−33] This leads to subsequent ventricular wall hypertrophy, increased ventricular filling pressure, increased atrial pressure, atrial enlargement, and, eventually, AF. Other possible mechanisms include the shared cardiovascular risk factors for arteriosclerotic calcification and AF.[7] It has also been suggested that the

Table 2
Association of coronary and extracoronary arteriosclerotic calcification with the risk of new-onset atrial fibrillation in the total study population and stratified by sex

Arteriosclerotic calcification measures	Total study population		Men		Women	
	Cause-specific HR (95% CI) per 1-SD					
	Model 1*	Model 2†	Model 1*	Model 2†	Model 1*	Model 2†
CAC‡	1.31 (1.10-1.55), p=0.0019	1.26 (1.05-1.51), p=0.0126	1.42 (1.13-1.78), p=0.0025	1.40 (1.10-1.79), p=0.0068	1.14 (0.91-1.44), p=0.2610	1.05 (0.82-1.35), p=0.6913
AAC‡	1.19 (0.99-1.42), p=0.0613	1.15 (0.95-1.38), p=0.1538	1.03 (0.83-1.28), p=0.8107	1.03 (0.82-1.29), p=0.8296	1.52 (1.11-2.06), p=0.0086	1.45 (1.04-2.03), p=0.0299
ECAC‡	1.14 (0.97-1.33), p=0.1140	1.08 (0.92-1.28), p=0.3454	1.18 (0.96-1.45), p=0.1201	1.16 (0.93-1.44), p=0.1940	1.06 (0.84-1.34), p=0.6240	0.94 (0.72-1.22), p=0.6177
ICAC‡	1.04 (0.89-1.22), p=0.6150	1.01 (0.86-1.20), p=0.8900	1.04 (0.85-1.28), p=0.6894	1.05 (0.84-1.30), p=0.6952	1.01 (0.78-1.29), p=0.9540	0.91 (0.70-1.18), p=0.4652
VBAC‡	1.17 (1.04-1.32), p=0.0089	1.12 (0.99-1.27), p=0.0637	1.18 (1.00-1.38), p=0.0526	1.13 (0.95-1.34), p=0.1560	1.16 (0.97-1.38), p=0.1020	1.09 (0.90-1.31), p=0.3850
AVC‡	1.14 (0.99-1.31), p=0.0723	1.11 (0.96-1.28), p=0.1486	1.20 (0.99-1.45), p=0.0639	1.17 (0.96-1.42), p=0.1271	1.06 (0.86-1.30), p=0.6110	1.07 (0.86-1.33), p=0.5639

AAC = aortic arch calcification; AVC = aortic valve calcification; CAC = coronary artery calcification; CI = confidence interval; ECAC = extracranial internal carotid artery calcification; HR = hazard ratio; ICAC = intracranial internal carotid artery calcification; NA = not applicable; SD = standard deviation; VBAC = vertebrobasilar artery calcification.

* Adjusted for age, sex (if applicable), cohort, and type of scanner.

† Adjusted for age, sex (if applicable), cohort, type of scanner, body mass index, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking status, history of diabetes mellitus, history of coronary heart disease, history of heart failure, left ventricular hypertrophy on the electrocardiogram, use of cardiac medication, use of antihypertensive medication, and use of lipid lowering medication.

‡ ln(calcification volume + 1.0)—standardized transformed volumes to obtain HR per 1-SD increase. The per 1-SD increase in the total population is computed by using the total study sample where the per 1-SD sex-specific increase in men is computed by using the men study sample and the per 1-SD sex-specific increase in women is computed by using the women study sample. Hazard ratios represent 1-SD increase in ln(calcification volume + 1.0) with the risk of new-onset atrial fibrillation.

association between arteriosclerotic calcification and AF is mediated through CHD.[7] In our study, the associations between arteriosclerotic calcification with incident AF indeed attenuated but remained significant after adjustment for traditional cardiovascular risk factors. Furthermore, excluding participants with prevalent and incident CHD during follow-up and before AF diagnosis did not change our results. It seems plausible that a combination of the aforementioned mechanisms underlie the association between arteriosclerotic calcification and AF; however, future studies to unravel the underlying mechanisms are warranted.

In addition to investigation of arteriosclerotic calcification at multiple sites, our results extend previous evidence[16,17] by reporting the gender differences in the association of arteriosclerotic calcification with new-onset AF. Our results showed that CAC in men and AAC in women were associated with incident AF. Arteriosclerotic calcification occurs at an earlier age in men than in women.[34] The gender difference in the prevalence of arteriosclerotic calcification seen under 55 years narrows at older ages, as the prevalence of AAC in women exceeds that of men.[34] At older age, AAC is more prevalent in women, even in the absence of CAC.[35–37] Compared with men, women also have more severe CAC when they have severe AAC.[38] Differences in gender hormones could, at least partly, explain such patterns. Although women might benefit from the antiatherosclerotic characteristics of higher estrogen levels during their reproductive life span, this protection is rapidly lost after menopause, giving rise to increased arteriosclerotic calcification and various forms of cardiovascular disorders. It has been demonstrated that estrogen affects the coronary, mesenteric, aortic, and cerebral arteries of animals differently depending on the artery that is being involved.[39] Furthermore, the potentially deleterious effect of testosterone is also noteworthy, although the exact relation between androgens and CHD remains to be further elucidated.[40,41] Moreover, the absence of the cardioprotective effects of estrogen in men might also, at least in part, explain the observed gender differences.[40] One could, therefore, hypothesize that the higher estrogen levels before menopause in women may have a larger protective impact on calcification at the coronary arteries than the aortic arch or that men lack the cardioprotective effects of estrogen on calcification at the coronary arteries.[39] Furthermore, previous studies have suggested competing risk of mortality as a plausible explanation for these gender differences.[32,33] Because AF is strongly associated with age, there may be a possibility that men die of other (cardiovascular) diseases before development of AF and this hypothesis was supported by our competing risk analyses which showed that CAC, AAC, ECAC, and ICAC were significantly associated with mortality, especially in men. Nevertheless, we found a higher incidence of AF in men than in women in our study. The stronger association of CAC with AF in men might also be an indication of larger ischemic heart disease burden in men and its contribution to AF.[21,36] However, excluding prevalent and incident CHD events before the diagnosis of AF in our analyses yielded similar results as our original findings. This result, together with the plausibility of the underlying mechanisms described

previously, may link arteriosclerotic calcification and AF. Furthermore, our gender-stratified results could further inform the ongoing debate regarding gender differences within AF research.

Major strengths of this study are its population-based nature, availability of CT-assessed arteriosclerotic calcification measures at multiple sites within the same participants, extensive adjustment for potential confounders, long follow-up time with detailed meticulous adjudication of AF events, multiple sensitivity analyses including complete-case analyses, excluding prevalent and incident CHD before AF events, and the use of competing risk analyses to compute cause-specific hazards. Taken together, we believe that this led to valid and reliable results.

Some limitations should be considered when interpreting these results. We could not distinguish between paroxysmal and permanent AF because Holter monitoring was not performed within the Rotterdam Study (information bias). This potential misclassification is inherent to our study design, although we believe that our assessment of AF was adequate because we relied on 12-lead ECGs to diagnose AF at baseline/inclusion and during the follow-up of our study, which is in accordance with the European Society of Cardiology guidelines for AF diagnosis. In addition, our prevalence and incidence of AF are comparable to other population-based studies, which is reassuring. More specifically, missed paroxysmal AF cases during follow-up would mean that our observed association and effect estimates are an underestimation of the true underlying association between arteriosclerotic calcification and AF. Despite extensive adjustment for cardiovascular risk factors, the possibility of residual confounding of other unmeasured risk factors cannot be entirely ruled out in our analyses as with any observational study (confounding); however, this will be a limited concern given the large number of covariates for which we adjusted. Also, the study population consisted of mainly older persons of European descent (selection bias), which is also inseparable from our study design. Therefore, our results might not be generalizable to younger populations and other ethnicities.

In conclusion, a larger burden of CAC was significantly associated with new-onset AF in the general population. The gender-stratified analyses showed that CAC in men and AAC in women were significantly associated with an increased risk of new-onset AF in our study. Our findings imply that interventions to lower arteriosclerotic calcification, particularly, CAC, carry the potential for the prevention of AF in the general population, especially in men. Furthermore, our results could inform clinicians of the potential gender-specific deleterious effects of arteriosclerotic calcification on AF risk. Our findings could also further feed the ongoing debate regarding gender differences within AF research.

Declaration of competing interest

Dr. Ikram reports consulting fees from Biogen Inc. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Sven Geurts: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maxime M. Bos:** Data curation, Investigation, Validation, Writing – review & editing. **Janine E. van der Toorn:** Data curation, Investigation, Validation, Writing – review & editing. **Bruno H. C. Stricker:** Investigation, Writing – review & editing. **Mohsen Ghanbari:** Investigation, Writing – review & editing. **Jan A. Kors:** Investigation, Writing – review & editing. **M. Arfan Ikram:** Funding acquisition, Investigation, Resources, Writing – review & editing. **Daniel Bos:** Investigation, Resources, Writing – review & editing. **Maryam Kavousi:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft.

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Data Availability

Data can be obtained upon request. Requests should be directed toward the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of the restrictions based on privacy regulations and written informed consent of the participants, data cannot be made freely available in a public repository.

Ethical Standards

The Rotterdam Study adheres to the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license No. 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration No. EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (http://www.trialregister.nl/trials) and into the WHO International Clinical Trials Registry Platform (https://apps.who.int/trialsearch/) under shared catalog No. NL6645/NTR6831. All participants provided written informed consent to participate, before inclusion, in the study and have their information obtained from treating physicians.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.09.002.

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