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Density of Calcified Coronary Artery Plaque and Risk of Incident Atrial Fibrillation (from the Multiethnic Study of Atherosclerosis)

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Abstract

Elevated coronary artery calcium (CAC) score, as assessed by the Agatston method, is associated with incident atrial fibrillation (AF). We aimed to evaluate the associations of CAC volume and density with incident AF. Participants from the Multiethnic Study of Atherosclerosis without baseline AF and CAC >0 were included. The associations between baseline and progression (average annual change) of CAC measures and incident AF were evaluated using Cox proportional hazards models. CAC volume and Agatston scores were natural log (ln)-transformed, and hazard ratios (HRs) were calculated per standard deviation increment. The baseline analysis included 3,332 participants; 2,643 were included in the progression analysis. In multivariable models adjusted for cardiovascular risk factors, volume (HR 1.24, 95% confidence interval [CI] 1.14 to 1.36), density (HR 1.14, 95% CI 1.05 to 1.25), and Agatston score (HR 1.24, 95% CI 1.14 to 1.35) were associated with increased risk of incident AF. In models including both volume and density, the magnitude of association between volume and incident AF was unchanged, whereas the density association was eliminated (HR 0.99, 95% CI 0.89 to 1.11). Median time to follow-up CAC assessment was 1.9 (interquartile range 1.3, 3.0) years. Similar results were observed for the association of incident AF with annual change in volume and Agatston score. CAC volume, but

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Author Contributions

Harpreet Bhatia: conceptualization, methodology, formal analysis, data curation, writing original draft.
Robyn McClelland: methodology, writing review and editing
Susan Heckbert: conceptualization, methodology, writing review and editing.
Michael Criqui: conceptualization, supervision, writing review and editing.
Parveen Garg: conceptualization, methodology, supervision, writing original draft.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

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not density, is associated with risk for incident AF when adjusting for both. In conclusion, our findings suggest that, although CAC may be a risk marker for AF, the association between CAC and AF appears to be independent of plaque density.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, affecting over 30 million people worldwide,[1,2] leading to poor quality of life, higher health care costs, and higher mortality rates compared with those without AF.[3–5] However, over 40% of risk for AF remains unexplained after accounting for established risk factors.[6] Coronary artery calcium (CAC) scoring is a well-established clinical tool for cardiovascular disease (CVD) risk prediction.[7] The use of CAC volume and density scores is more predictive of CVD events than the standard Agatston score because the Agatston score is weighted upward for density, although increased density is associated with reduced CVD events.[8] AF and atherosclerosis appear to be closely related.[9] Higher CAC and CAC progression, using the Agatston score, are associated with an increased risk for AF in patients without known clinical CVD.[10–12] Although the underlying mechanisms of this association remain unclear, these findings suggest that subclinical atherosclerosis is predictive of the development of AF, and CAC may improve our ability to identify patients who are predisposed to AF. Whether accounting for plaque density modifies this association has not been previously studied. We aimed to evaluate the association of CAC density and volume with the risk of incident AF.

Methods

Data from participants from the Multi-Ethnic Study of Atherosclerosis (MESA) were used for this study. Details of the design of MESA have been reported previously.[13] In brief, MESA is a prospective cohort study of 6,814 participants who were free of clinical CVD at baseline. Recruitment occurred at 6 centers across the United States from 2000 to 2002. The study was approved by the institutional review boards at each center, and all participants provided written informed consent. For this study, we excluded those without baseline CAC (because of the need for CAC to calculate a density score), with history of AF, or without long-term follow-up. For the analysis of progression of CAC, we excluded participants with AF before follow-up computed tomography (CT) examination (exam), those without a follow-up CT, and those without CAC on follow-up CT.

All participants in MESA underwent CAC scoring at baseline and at follow-up (half at exam 2, 2002 to 2004 and half at exam 3, 2004 to 2005) by either electron-beam CT or multidetector CT, depending on study location. All studies were cardiac-gated, phantom-adjusted, and read centrally at the MESA CT reading center by 2 trained analysts, yielding high-quality CAC measurements with high reproducibility and comparability between scanner types.[14–16] Agatston and volume scores were reported.[16] The density score was not calculated as part of the original MESA dataset. Using a previously described method,[8] the density score was calculated by dividing the Agatston score by the area score. Progression in CAC (Agatston, volume, density) was calculated as the average annual change between the baseline and visit 2/3 exams.

After the baseline exam, participants were followed up every 9 to 12 months by telephone to obtain information on hospitalizations and medical records, including discharge diagnoses. Incident AF, including atrial flutter, through December 2015 was identified from study electrocardiograms (ECGs) verified for AF at visit 5 (2010 to 2012), International Classification of Diseases, Ninth Revision hospital discharge diagnoses consistent with AF (427.31 or 427.32), and, for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data.[17]

Standardized questionnaires were used at baseline to obtain demographic information, highest level of education, physical activity, smoking history, alcohol use, and medication use, including antihypertensive and antidiabetic use. Physical activity was recorded as participant-reported number of intentional exercise metabolic equivalent in minutes per week of moderate or vigorous activity. Cigarette smoking was calculated in pack-years and also defined as current, former, or never. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressures were taken in seated participants at rest and reported as the average of the last 2 of 3 measurements taken. Total and high-density lipoprotein cholesterol and glucose were measured from fasting blood samples. Low-density lipoprotein cholesterol was calculated by the Friedewald equation in those with triglycerides <400 mg/100 ml. Diabetes was defined as a fasting glucose >125 mg/100 ml or use of antidiabetic medications. Left ventricular hypertrophy was defined by the Cornell ECG criteria.[18]

Baseline characteristics were compared across quartiles of baseline volume and density using analysis of variance testing for continuous variables and chi-square tests for categoric variables. Median follow-up time was compared using the Kruskal–Wallis test. AF incidence rates were calculated across quartiles of volume and density. Kaplan–Meier curves for freedom from AF by quartile of volume and density were created. We performed a time-to-event analysis using Cox proportional hazards models to compare the association between CAC measures (Agatston score, volume alone, density alone, and volume + density), per SD increment, and the risk of incident AF, with time of risk defined as follow-up until first AF event, death, or last follow-up exam. Volume and Agatston scores were natural log (ln)-transformed because of a previously noted log-linear association between CAC and cardiovascular events.[19] Model 1 adjusted for age, race/ethnicity, gender, and highest level of education completed. Model 2 adjusted for model 1 and height, BMI, cigarette smoking status, diabetes mellitus, systolic and diastolic blood pressures, use of antihypertensive medications, moderate/vigorous physical activity, total cholesterol, high-density lipoprotein cholesterol, and left ventricular hypertrophy. As a sensitivity analysis to account for the possibility of interim ischemic events influencing development of AF, we performed an additional analysis which adjusted for model 2 and coronary heart disease events before the development of AF or last known follow-up.

A similar time-to-event analysis was performed to evaluate the association between CAC progression (Agatston change, volume change alone, density change alone, and volume + density change) and incident AF. For this analysis, time at risk began with the follow-up CT exam (exam 2 or 3) and continued until first AF event, death, or last follow-up exam.

Models were adjusted as described previously. A third model was created (model 3) to additionally adjust for baseline CAC measures.

To assess for potential effect modification, interaction terms for race/ethnicity, gender, scanner type, age, diabetes mellitus, antihypertensive medication use, and BMI were evaluated in the previously mentioned models for the baseline CAC analyses only. To further explore risk of AF in those who newly developed CAC at the follow-up CT exam, we performed an additional analysis comparing the risk of incident AF according to CAC Agatston score and CAC volume for these patients with those without evident CAC at baseline or follow-up exams.

Analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics v26.0 (IBM, Armonk, New York). A 2-tailed $p < 0.05$ was considered statistically significant.

Results

The MESA cohort contains 6,814 participants, including 3,398 with baseline CAC. There were 3,332 participants included in the analyses involving baseline CAC measures only and 2,643 participants for analyses involving CAC progression (58 participants were excluded for AF before follow-up CT; Figure 1). In the entire cohort with available data (n = 5,550), the incidence of AF was 13.4% (n = 743). The incidence of AF was higher in those with CAC at baseline (19.8%, n = 524 of 2,645) than in those with no CAC at baseline but with CAC at follow-up (12.0%, n = 56 of 467) and those without CAC at baseline or follow-up (6.7%, n = 163 of 2,438, $p < 0.001$). Characteristics of study participants according to baseline CAC volume and density quartiles are shown in Table 1. Overall, the cohort was 43.8% White, 24.2% Black, 20.0% Hispanic, and 12.0% Chinese. Participants with higher volume were older, were less likely to be women, were more likely to be White, to have hypertension, to have diabetes, and to smoke, and had higher N-terminal brain natriuretic peptide levels. Similar results were noted across higher density quartiles. Alcohol use (for volume quartile), diabetes (for density quartile), and cigarette smoking (for both density and volume), demonstrated significant but nonmonotone relationships. Additionally, total cholesterol and BMI were lower with higher density quartile, whereas high-density cholesterol was higher in the highest density quartile than in the lowest quartile.

Increasing quartile of volume and density were associated with higher incidence of AF (Figure 2). In the multivariable adjusted analyses, baseline ln volume (hazard ratio [HR] per SD increment 1.25, 95% confidence interval [CI] 1.14 to 1.36) and density (HR per SD increment 1.14, 95% CI 1.05 to 1.24) were each associated with increased risk for AF (Table 2). However, when volume and density were assessed together, the association with volume was similar, whereas the association with density was eliminated (HR per SD increment 0.99, 95% CI 0.89 to 1.11). The lack of association of density with incident AF was also seen across quartiles of volume (Supplementary Table 1). The Agatston score was associated with increased risk for AF with a similar magnitude of association as volume (Table 2). No significant interactions were detected between baseline CAC measurements and age, gender, race/ethnicity, or scanner type for model 1 or between baseline CAC measurements

and BMI, diabetes, or hypertensive medication use for model 2. Results were similar with additional adjustment for interim coronary heart disease events (HR per ln volume SD increment 1.26, 95% CI 1.13 to 1.41; HR per density SD increment 0.98, 95% 0.88 to 1.10).

Median time to follow-up CT was 1.9 (interquartile range 1.3 to 3.0) years. An increase in volume was positively associated with incident AF risk (HR per SD increment 1.19, 95% CI 1.11 to 1.28), whereas increased density was not (HR per SD increment 0.98, 95% CI: 0.89 to 1.08; Table 3). Similar results were seen when volume and density were assessed separately. Increase in Agatston score was associated with increased risk for AF (HR per SD increment 1.19, 95% CI 1.11 to 1.27). There was slight attenuation of the HRs for volume change and Agatston change when baseline volume and density or baseline Agatston, respectively, were included (model 3). When change in density was stratified by quartile of volume score at baseline, no association was noted with incident AF (Supplementary Table 2).

There were 2,438 participants (43.9%) with CAC of 0 at baseline and follow-up, 467 with CAC of 0 at baseline and CAC >0 at follow-up (8.4%), and 2,645 with CAC>0 at both exams (47.7%), using either CAC Agatston score or CAC volume score. In a multivariable Cox model (adjusting for similar covariates to Model 2 as previously mentioned), having CAC at both exams was associated with increased risk for incident AF (HR 1.52, 95% CI 1.24 to 1.85) with a nonsignificant trend toward increased risk among those with CAC at follow-up but not at baseline (HR 1.28, 95% CI 0.94 to 1.74).

Discussion

In a multi-ethnic cohort of participants with CAC and without baseline CVD or AF, greater CAC volume was associated with increased risk for incident AF that was similar in magnitude to the Agatston score. Greater CAC density, however, was not associated with incident AF when simultaneously adjusting for volume. Similar results were observed when measures of CAC progression were assessed. Our findings redemonstrate that CAC is associated with risk for incident AF and that the association appears to be related to total atherosclerotic burden, independent of plaque density.

Previous studies have suggested an association between AF and atherosclerosis. Endothelial dysfunction may be associated with the development of AF, and AF may be associated with systemic inflammation affecting plaque stability.[9] CAC, measured by the Agatston score, is associated with risk for AF. Patients with CAC often have multiple underlying AF risk factors. Additionally, calcified coronary arteries are associated with enlarged pulmonary veins and left atria, which are both associated with AF,[20] and CAC is highly prevalent in patients with AF.[21,22] In a previous study of MESA participants, higher CAC score was associated with increased risk of incident AF, with Agatston score >300 associated with a more than twofold increase compared with CAC of 0.[10] Similarly, a study of CAC, using the Western Denmark Heart Registry, demonstrated increased risk of developing AF with higher CAC scores, with a 67% increased relative risk with CAC ≥1,000 compared with no CAC.[12] A follow-up MESA study demonstrated that annual progression of the CAC

score was also associated with increased risk of AF (HR 3.23 for >300 per year increase in Agatston score).[11]

Previous CAC and AF studies used the Agatston method. However, recent studies have shown that the volume/density method provides improved predictive value for CVD events because the Agatston score is weighed upward for density, although increased density is inversely associated with risk.[8] Our study adds to this existing knowledge by demonstrating that the volume score provides similar value for predicting AF risk, and that plaque density is not associated with AF risk when also adjusting for volume. Given that both volume and density represent different measures of atherosclerosis, both were expected to be associated with AF risk. In contrast, the association of volume with AF, without an additional association with density, may suggest that the association between AF and atherosclerosis reflects shared risk factors rather than the direct impact of atherosclerosis on AF risk. Further study is needed to clarify the underlying mechanisms that explain the association between CAC volume, but not density, and AF.

Further study is needed to understand the clinical implications of this study. CAC is a predictor for the development of AF and may provide an opportunity for identifying people at risk for AF. Plaque density is not protective against AF risk, as it is for CVD events, and total atherosclerotic burden is a more important predictor. Taken together, the CAC volume or Agatston score can likely be used interchangeably for the purpose of AF risk. Many traditional cardiovascular risk factors, such as age, male gender, hypertension, diabetes, BMI, and family history, are associated with risk for both incidence and progression of CAC.[23] Modification of risk factors, such as low-density lipoprotein cholesterol with statin use, is associated with stabilization or even reduction in CAC.[24] Statin use has also been associated with reduced incident AF.[25] Further investigation is needed to determine whether modification of risk factors for the incidence and progression of CAC is also associated with reduced incidence of AF.

Our study has some limitations. Density was not reported in the MESA data and was calculated for this study; thus, it is treated categorically and not continuously, which may decrease power. Data regarding alcohol consumption were not available for the whole study cohort. Given that AF may not be associated with symptoms and is often paroxysmal, it is likely that many cases of AF were not captured through hospitalization and billing codes. Additionally, reliance on billing codes without objective evidence of AF is subject to errors in diagnosis. Finally, as an observational study, our results are subject to residual confounding.

In conclusion, baseline CAC volume and progression of volume are associated with incident AF to a similar degree as Agatston scoring. CAC density, when adjusting for volume, is not associated with risk for incident AF. Our findings suggest that, although CAC may be a risk marker for AF, the association between CAC and AF appears to be independent of plaque density. Further study is needed to address the therapeutic implications of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–847. [PubMed: 24345399]
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in atrial fibrillation (ATRIA) Study. JAMA 2001;285:2370–2375. [PubMed: 11343485]
3. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011;4:313–320. [PubMed: 21540439]
4. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 2016;354: i4482. [PubMed: 27599725]
5. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med 2006;119. 448.e1–448.19.
6. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123:1501–1508. [PubMed: 21444879]
7. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–165. [PubMed: 15992651]
8. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311:271–278. [PubMed: 24247483]
9. Liang F, Wang Y. Coronary heart disease and atrial fibrillation: a vicious cycle. Am J Physiol Heart Circ Physiol 2021;320:H1–H12. [PubMed: 33185113]
10. 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. [PubMed: 25282316]

11. 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:e003786. [PubMed: 26659375]
12. Vinter N, Christesen AMS, Mortensen LS, Urbonaviciene G, Lindholt J, Johnsen SP, Frost L. Coronary artery calcium score and the long-term risk of atrial fibrillation in patients undergoing non-contrast cardiac computed tomography for suspected coronary artery disease: a Danish registry-based cohort study. Eur Heart J Cardiovasc Imaging 2018;19:926–932. [PubMed: 28977363]
13. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. [PubMed: 12397006]
14. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary artery Risk Development in Young Adults (CARDIA) study. Radiology 2005;234:35–43. [PubMed: 15618373]
15. Detrano RC, Anderson M, Nelson J, Wong ND, Carr JJ, McNitt-Gray M, Bild DE. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility–MESA study. Radiology 2005;236:477–484. [PubMed: 15972340]
16. Nelson JC, Kronmal RA, Carr JJ, McNitt-Gray MF, Wong ND, Loria CM, Goldin JG, Williams OD, Detrano R. Measuring coronary calcium on CT images adjusted for attenuation differences. Radiology 2005;235:403–414. [PubMed: 15858082]
17. Heckbert SR, Wiggins KL, Blackshear C, Yang Y, Ding J, Liu J, McKnight B, Alonso A, Austin TR, Benjamin EJ, Curtis LH, Sotoodehnia N, Correa A. Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study. Obesity (Silver Spring) 2017;25:1115–1121. [PubMed: 28452401]
18. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the reference standard. Comparison of standard criteria, computer diagnosis and physician interpretation. J Am Coll Cardiol 1984;3:82–87. [PubMed: 6228571]
19. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–1345. [PubMed: 18367736]
20. Pan NH, Tsao HM, Chang NC, Lee CM, Chen YJ, Chen SA. Dilated left atrium and pulmonary veins in patients with calcified coronary artery: a potential contributor to the genesis of atrial fibrillation. J Cardiovasc Electrophysiol 2009;20:153–158. [PubMed: 18803575]
21. 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. [PubMed: 32336536]
22. Wang TKM, Chan N, Cremer PC, Kanj M, Baranowski B, Saliba W, Wazni OM, Jaber WA. Incorporating coronary calcification by computed tomography into CHA2DS2-VASc score: impact on cardiovascular outcomes in patients with atrial fibrillation. Europace 2021;23:1211–1218. [PubMed: 33585883]
23. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–2730. [PubMed: 17502571]
24. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA Reductase Inhibitors on coronary artery disease as assessed by electron-beam computed tomography. N Engl J Med 1998;339:1972–1978. [PubMed: 9869668]
25. Peña JM, Macfadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. Eur Heart J 2012;33:531–537. [PubMed: 22187510]

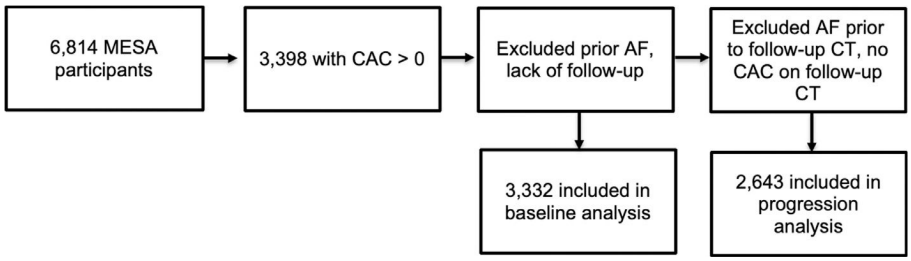

Figure 1.
Study flow diagram.

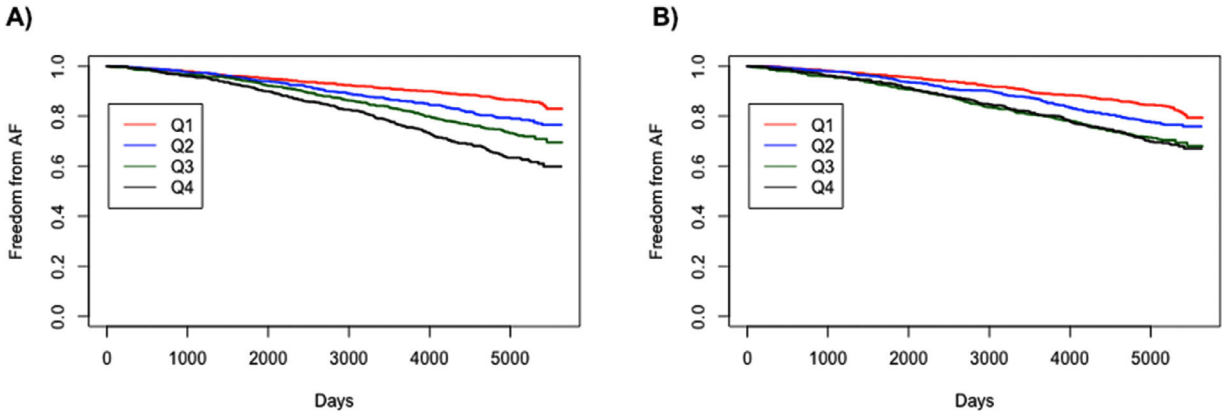

Figure 2.

Freedom from incident atrial fibrillation by Q of (*A*) CAC volume and (*B*) CAC density p <0.001 for comparison of incident AF among both volume and density Qs. Q = quartile.

Table 1

Baseline characteristics of study cohort by CAC volume and density quartiles

Variable	Overall (n = 3332)	CAC volume (mm^3)					CAC density (unitless)				
		Q1 (0–24.53)	Q2 (24.54–84.82)	Q3 (84.83–270.86)	Q4 (>270.86)	*p*	Q1 (1.00–2.47)	Q2 (2.48,3.11)	Q3 (3.12,3.49)	Q4 (>3.49)	*p*
Age (years)	66.2 (9.5)	62.3 (9.8)	65.2 (9.3)	67.4 (9.1)	70.1 (8.2)	<0.001	62.8 (10.1)	66.3 (9.4)	67.7 (8.7)	68.2 (9.0)	<0.001
Female	1401 (42.0%)	421 (50.5%)	386 (46.3%)	330 (39.7%)	264 (31.7%)	<0.001	396 (47.5%)	352 (42.3%)	305 (36.6%)	348 (41.8%)	<0.001
Race / ethnicity						<0.001					<0.001
White	1460 (43.8%)	334 (40.1%)	315 (37.8%)	382 (45.9%)	429 (51.5%)		340 (40.8%)	339 (40.7%)	374 (44.9%)	407 (48.9%)	
Chinese	399 (12.0%)	103 (12.4%)	121 (14.5%)	105 (12.6%)	70 (8.4%)		102 (12.2%)	90 (10.8%)	109(13.1%)	98(11.8%)	
Black	805 (24.2%)	217 (26.1%)	218 (26.1%)	184 (22.1%)	186 (22.3%)		191 (22.9%)	215 (25.8%)	205 (24.6%)	194 (23.3%)	
Hispanic	668 (20.0%)	179 (21.5%)	180 (21.6%)	161 (19.4%)	148 (17.8%)		200 (24.0%)	189 (22.7%)	145 (17.4%)	134(16.1%)	
Height (cm)	167.3 (10.0)	166.5 (10.2)	166.9 (10.3)	167.4 (10.0)	168.5 (9.5)	<0.001	166.6 (10.4)	167.3 (10.0)	168.0 (9.7)	167.3 (9.8)	0.060
BMI (kg/m^2)	28.4 (5.3)	28.4 (5.5)	28.2 (5.3)	28.4 (5.3)	28.5 (5.0)	0.751	28.6 (5.3)	28.8 (5.7)	28.3 (5.3)	27.7 (4.9)	<0.001
SBP (mmHg)	130.8 (21.7)	126.5 (20.7)	130.4 (21.6)	131.7 (21.6)	134.6 (22.0)	<0.001	128.1 (21.1)	131.8 (21.1)	130.9 (21.5)	132.3 (22.7)	<0.001
DBP (mmHg)	72.6 (10.2)	72.9 (10.2)	73.0 (10.4)	72.4 (9.9)	73.3 (10.3)	0.039	72.8 (10.2)	73.0 (10.2)	72.6 (9.7)	72.1 (10.8)	0.341
Hypertension	1825 (54.8%)	379 (45.5%)	427 (51.2%)	474 (57.0%)	545 (65.4%)	<0.001	396 (47.5%)	481 (57.7%)	480 (57.6%)	468 (56.2%)	<0.001
Diabetes	526 (15.8%)	99 (11.9%)	111 (13.3%)	139 (16.7%)	177 (21.4%)	<0.001	116(13.9%)	138 (16.6%)	158(19.0%)	114(13.7%)	0.008
Cigarette smoking						<0.001					0.023
Never	1484 (44.6%)	412 (49.6%)	385 (46.3%)	358 (43.0%)	329 (39.6%)		392(47.1%)	378 (45.4%)	367 (44.2%)	347 (41.8%)	
Former	1412 (42.5%)	300(36.1%)	343 (41.2%)	373 (44.8%)	396 (47.7%)		315 (37.9%)	360 (43.3%)	367 (44.2%)	370 (44.5%)	
Current	429 (12.9%)	118 (14.2%)	104 (12.5%)	101 (12.1%)	106 (12.8%)		125 (15.0%)	94(11.3%)	96(11.6%)	114(13.7%)	
Current alcohol use	1833 (55.0%)	468 (56.6%)	412 (49.6%)	469 (56.9%)	484 (58.4%)	0.001	480 (57.9%)	441 (43.3%)	463 (56.1%)	449 (54.2%)	0.354

Variable	Overall (n = 3332)	CAC volume (mm^3)					CAC density (unitless)				
		Q1 (0–24.53)	Q2 (24.54–84.82)	Q3 (84.83–270.86)	Q4 (>270.86)	*p*	Q1 (1.00–2.47)	Q2 (2.48,3.11)	Q3 (3.12,3.49)	Q4 (>3.49)	*p*
Treatment for hypertension	1512(45.4%)	299 (35.9%)	353 (42.3%)	398 (47.8%)	462 (55.5%)	<0.001	331 (39.7%)	390 (46.8%)	409 (49.1%)	382 (45.9%)	0.001
Total cholesterol (mg/dL)	194.6 (36.4)	196.8 (35.1)	193.7 (37.2)	195.0 (35.6)	193.0(37.7)	0.146	197.6 (36.7)	195.8 (37.6)	192.6 (35.0)	192.5 (36.2)	0.009
HDL (mg/dL)	49.4 (14.5)	49.7 (12.8)	49.7 (14.8)	49.3 (14.8)	48.9 (14.5)	0.588	49.1 (14.0)	49.1 (14.3)	48.3 (14.3)	51.0(15.0)	0.001
NT-proBNP (pg/mL)	121.3 (308.2)	95.1 (287.6)	106.1 (197.6)	122.0(195.5)	162.1 (467.0)	<0.001	102.4 (322.0)	103.9 (154.0)	141.1 (445.1)	137.8 (230.6)	0.009
Physical activity (MET-MIN/week)	5515.6 (5983.2)	5874.1 (7096.4)	5464.0 (5915.6)	5479.8 (5392.6)	5244.8 (5255.1)	0.189	5860.4 (6434.7)	5619.0 (5643.4)	5251.7 (6078.7)	5330.5 (5735.0)	0.143
Left ventricular hypertrophy	50 (1.5%)	8 (1.0%)	12 (1.4%)	13 (1.6%)	17 (2.1%)	0.333	8 (1.0%)	12 (1.5%)	15 (1.8%)	15 (1.8%)	0.432
CAC measurements											
Volume score (mm^3)						<0.001	30.1 (41.0)	146.0 (193.0)	359.4 (437.7)	501.9 (683.3)	<0.001
Density score (unitless)	2.9 (0.7)	2.2 (0.8)	2.9 (0.6)	3.2 (0.4)	3.4 (0.3)	<0.001					
Agatston score (unitless)	294.5 (547.6)	10.4 (7.6)	51.4 (23.0)	176.6 (67.2)	939.6 (790.3)	<0.001	22.1 (32.8)	141.5 (191.3)	399.6 (494.0)	614.7(841.0)	<0.001
Incident AF	709 (21.3%)	106 (12.7%)	159 (19.1%)	197 (23.7%)	247 (29.7%)	<0.001	124 (14.9%)	162 (19.4%)	207 (24.8%)	216 (25.9%)	<0.001

Values are presented as mean (standard deviation), median (interquartile range), or n (%).

AF = atrial fibrillation; BMI = body mass index; CAC = coronary artery calcium; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET-MIN = metabolic equivalent task minutes; NT-proBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure.

Table 2

Association between baseline CAC measures and incident atrial fibrillation

	HR	95% CI	*p*
Model 1 (n = 3324)			
ln volume, per SD	1.31	1.17, 1.45	<0.001
Density, per SD	0.98	0.87, 1.09	0.640
ln volume alone, per SD	1.29	1.18, 1.40	<0.001
Density alone, per SD	1.15	1.06, 1.26	<0.001
ln Agatston alone, per SD	1.28	1.18, 1.40	<0.001
Model 2 (n = 3284)			
ln volume, per SD	1.25	1.12, 1.40	<0.001
Density, per SD	0.99	0.89, 1.11	0.868
ln volume alone, per SD	1.24	1.14, 1.36	<0.001
Density alone, per SD	1.14	1.05, 1.24	0.002
ln Agatston alone, per SD	1.24	1.14, 1.35	<0.001

Results of Cox Proportional Hazards models are shown. Volume and Agatston scores were natural log(ln)-transformed. All hazard ratios are presented per SD increment. Model 1 = age + race + sex + education + CAC measurement (volume and density, volume or density alone, Agatston alone); model 2 = model 1 + height + body mass index + smoking + alcohol use + diabetes + systolic blood pressure + diastolic blood pressure + medications for hypertension + physical activity + total cholesterol + high density lipoprotein + left ventricular hypertrophy + NT-proBNP.

Abbreviations as per Table 1.

Table 3

Association between measures of CAC progression and incident atrial fibrillation

	HR	95% CI	*P*
Model 1 (n = 2638)			
Volume change, per SD	1.23	1.15, 1.32	<0.001
Density change, per SD	0.97	0.88, 1.07	0.579
Volume change alone, per SD	1.23	1.15, 1.32	<0.001
Density change alone, per SD	0.98	0.89, 1.07	0.602
Agatston change alone, per SD	1.23	1.15, 1.31	<0.001
Model 2 (n = 2606)			
Volume change, per SD	1.19	1.11, 1.28	<0.001
Density change, per SD	0.98	0.89, 1.08	0.709
Volume change alone, per SD	1.19	1.11, 1.28	<0.001
Density change alone, per SD	0.98	0.89, 1.08	0.751
Agatston change alone, per SD	1.19	1.11, 1.27	<0.001
Model 3 (n = 2606)			
Volume change, per SD	1.14	1.04, 1.23	0.003
Density change, per SD	1.00	0.88, 1.13	0.974
Volume change alone, per SD	1.14	1.05, 1.23	0.002
Density change alone, per SD	1.06	0.94, 1.19	0.339
Agatston change alone, per SD	1.14	1.05, 1.23	0.002

Results of Cox Proportional Hazards models are shown. All hazard ratios are presented per SD increment. Model 1 = age + race + sex + education + CAC measurement change (volume and density, volume or density alone, Agatston alone); model 2 = model 1 + height + body mass index + smoking + alcohol use + diabetes + systolic blood pressure + diastolic blood pressure + medications for hypertension + physical activity + total cholesterol + high density lipoprotein + left ventricular hypertrophy + NT-proBNP; model 3 = model 2 + baseline CAC measurements (volume and density, volume or density alone, Agatston alone).

Abbreviations as per Table 1.