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ORIGINAL ARTICLE

The Prognostic Implication of Coronary Artery Calcification in Patients with Atrial Fibrillation

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Background: Coronary artery calcification (CAC) is a well-validated parameter reflecting the extent of subclinical atherosclerosis. Atherosclerosis manifestations are commonly presented in atrial fibrillation (AF) patients. Nevertheless, the long-term cardiovascular risks in AF patients with concomitant CAC are limited. **Aim:** The aim of this study is to identify the prognostic impact of CAC in patients with AF. **Methods:** A total of 646 eligible patients who underwent noncontrast coronary computed tomography (nCCT) from January 2012 to December 2018 were evaluated and retrospectively followed up for 2 years. The patients were assessed for cardiovascular outcomes, including nonfatal myocardial infarction, nonfatal stroke, late coronary revascularization, major adverse cardiovascular event (MACE), and total coronary and total composite events, by a multivariable Cox regression hazards model with adjusting for significant confounding factors. **Results:** AF patients with severe CAC (CAC score [CACS] >400 Agatston units) had significantly higher risks of composite cardiovascular outcomes, including MACEs (adjusted hazard ratio [HR]: 57.18, 95% confidence interval [CI]: 2.28–1434.41, $P = 0.014$), total coronary events (adjusted HR: 16.48, 95% CI: 1.21–224.15, $P = 0.035$), and total composite events (adjusted HR: 26.35, 95% CI: 2.45–283.69, $P = 0.007$), than sinus rhythm patients without CAC. Moreover, severe CAC in AF patients was a significant predictor of total composite events (adjusted HR: 59.1, 95% CI: 2.16–1616.33, $P = 0.016$). **Conclusion:** Severe CAC in AF patients may cause significantly higher cardiovascular risks, highlighting the role of nCCT in determining CACs for early risk evaluation to facilitate aggressive risk modification and thereby to prevent subsequent cardiovascular events. Further, large, prospective studies are needed to validate the impact of CAC in patients with AF.

Key words: Atrial fibrillation, coronary artery calcification, noncontrast coronary computed tomography

INTRODUCTION

Atherosclerotic cardiovascular disease contributed to a major economic and public health issue and one of the leading causes of death in adults worldwide.[1] Atherosclerotic plaque development involves a lengthy incubation period, during which biological risk factors interact with genetic and environmental factors.[2] Advanced obstructive coronary artery disease (CAD) can exist with minimal or no symptoms but can also progress suddenly or rapidly to acute cardiac events.[3,4] Early detection of CAD with intensive methods to identify asymptomatic or subclinical stages may prompt consideration of aggressive risk modification and improve the prognosis of

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those individuals at a high risk of such events.[5] Low-dose, noncontrast multidetector computed tomography (nCCT) for the detection and quantification of coronary artery calcification (CAC) has been shown to be superior to traditional risk factors for the prediction of CAD events.[5,6]

CAD is the most common cardiovascular disease, whereas atrial fibrillation (AF) is the most common cardiac arrhythmia.[7,8] AF imposes a significant burden on patients, physicians, and health-care systems globally. It may increase the risk of thromboembolic complications, including stroke and extracranial systemic embolic events, which warrant therapeutic prophylaxis with oral anticoagulation.[8] Previous studies demonstrated that AF seems to be associated with increased risks of subsequent myocardial infarction, all-cause mortality, and heart failure in patients with or without CAD.[8-10] Moreover, the prevalence of CAD in patients with AF ranges from 15% to 45%.[11,12] Therefore, patients with concomitant AF and CAD may bring about higher risks of cardiovascular events than those with AF or CAD alone.

Approximately 5%–15% of patients with AF are estimated to present with CAD, with a mild sizeable proportion of these patients requiring revascularization using percutaneous coronary intervention (PCI) and stent implantation.[13,14] In the Framingham Heart Study, the presence and extent of CAC were associated with an increased risk for major adverse cardiovascular events (MACEs).[15] Since early evaluation and detection of underlying CAD is important, an effective, rapid, and noninvasive imaging tool to assess the risks of CAD in AF patients is needed. However, the prognostic impact of the CAC score (CACS) in AF patients remains limited. In this study, we enrolled patients undergoing nCCT to quantify the CACs and investigated cardiovascular events over 2 years in patients with AF compared to patients with sinus rhythm (SR) with different extents of CACs.

MATERIALS AND METHODS

Study design and setting

A single-center, retrospective, comparative cohort study was conducted at Tri-Service General Hospital, National Defense Medical Center, and was ethically approved by the Institutional Review Board of the center under a protocol number of C202005121 since August 19, 2020. The informed consent requirement was waived due to the retrospective design of the study. This study involved screening consecutive adults with no symptoms or Grade I–II angina pectoris according to the Canadian Cardiovascular Society classification who underwent nCCT at the Outpatient Department from January 2012 to December 2018.[16]

Study population and data collection

Medical records and a 12-lead electrocardiogram (ECG) were fully evaluated by chart review. To establish baseline covariates, individuals meeting any of the following criteria were excluded: extremely advanced age (≥90 years old), missing medical records 3 months before nCCT or loss of follow-up, prior AMI or CAD treated with PCI with stent implantation or coronary artery bypass grafting (CABG), and a history of severe valvular heart disease or a prosthetic heart valve. Medical records and laboratory tests were reviewed and collected to extract baseline characteristics, including demographic data, underlying comorbidities such as diabetes mellitus (DM), hypertension, hyperlipidemia, chronic kidney disease (CKD), congestive heart failure, CAD, cerebrovascular disease (CVD), chronic obstructive pulmonary disease, and malignancy; baseline medication use; and laboratory data.

Coronary artery calcification score measurement

CACs was measured using ECG-gated nCCT and the Agatston score method.[6,17] Coronary calcium lesions were defined as having a threshold ≥130 Hounsfield units (HUs) and an area ≥1 mm^2. The products of the area of each calcified plaque and the peak HU, defined as 1 (130–199 HUs), 2 (200–299 HUs), 3 (300–399 HUs), or 4 (≥400 HUs), were summed for the left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery to determine the total CACs. A Philips Brilliance 256-slice MDCT scanner was used for CAC measurement. nCCT was conducted at the discretion of the ordering physicians, and the results were stored and reported in the picture archiving and communication system and electronic health record system for routine clinical care. All patients received a final written report describing their CAC results with instructions to consult with their physicians.

Ascertainment of atrial fibrillation

The diagnosis of AF, defined as the absence of P-waves and irregular ventricular activity on an entire 12-lead ECG or lasting for more than 30 s on an ECG strip, was confirmed by physicians. The 12-lead ECGs from the study patients were reviewed. Patients were assigned to the AF group depending on the medical history records or evidence on a 12-lead ECG irrespective of the type of AF.[8] Additionally, three types of AF including paroxysmal, persistent, and permanent types were clarified in the AF group.

Outcome measurement

Subjects were assessed for primary cardiovascular outcomes, including MACE (defined as the combination of nonfatal MI, nonfatal stroke, or cardiovascular death), total

coronary event (defined as the combination of nonfatal MI and late coronary revascularization), and total composite events (defined as the combination of nonfatal MI, nonfatal stroke, and late coronary revascularization).[18] A subspecified outcome including nonfatal MI, nonfatal stroke, and late coronary revascularization (defined as PCI or CABG 90 days after nCCT) was explored as an outcome of interest. Mortality data, including the cause of death, were confirmed by death note records. The follow-up period for each patient was 2 years after nCCT.

Statistical analysis

Statistical analyses were performed using the SPSS software package (version 20.0; SPSS, Chicago, IL, USA), and differences were considered statistically significant when the $P < 0.05$. Continuous variables are presented as mean and standard deviation. Categorical variables are presented as the number of patients and the corresponding percentage. The differences in the characteristics of the groups were assessed using the unpaired two-tailed Student's *t*-test or one-way analysis of variance (ANOVA) for continuous variables and the Chi-square and Fisher's exact tests for nominal variables, as appropriate. A multivariate Cox proportional hazards model was used to compare the time to events. For this model, significant confounding factors, which were selected based on the criteria of being associated with exposure and outcomes, were adjusted.

RESULTS

Baseline data

A total of 711 patients were screened. Of these patients, 3 patients with extremely advanced age, 21 patients with missing medical records or loss of follow-up, 29 patients with prior AMI or CAD treated with PCI or CABG, and 12 patients with marked valvular disease were excluded, resulting in 646 patients remaining for analysis. Patients were divided into three groups with different extents of CAC of 0, 0–400 (mild), and ≥400 (severe) Agatston units, and each group was further subdivided into SR and AF groups. A flowchart of study population enrollment is shown in Figure 1.

Among the study population, the prevalence of AF was 10.4%, and the prevalence of severe CAC was 10.7%. The

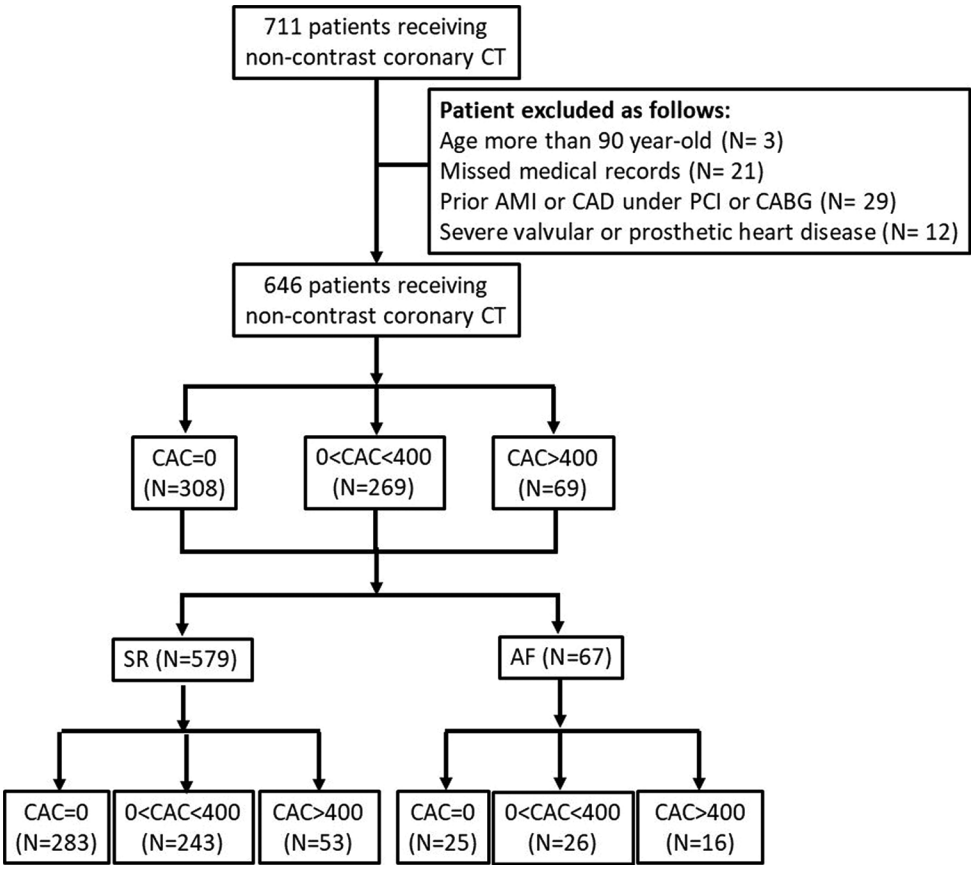

Figure 1: A flowchart of the enrollment of the study population

Table 1: Baseline characteristics in patients with sinus rhythm and atrial fibrillation

	Sinus rhythm				Atrial fibrillation			
	CS: 0 (***n***=283)	CS: 1-400 (***n***=243)	CS: >400 (***n***=53)	***P***	CS: 0 (***n***=25)	CS: 1-400 (***n***=26)	CS: >400 (***n***=16)	***P***
Demography								
Sex (male), *n* (%)	149 (52.7)	175 (72.0)	50 (94.3)	<0.001	16 (64.0)	6 (23.1)	3 (18.8)	0.002
Age (years)	53.4±9.1	58.9±8.3	64.9±9.7	<0.001	56.9±8.9	64.3±7.5	68.8±7.7	<0.001
BMI (kg/m^2)	24.1±3.3	25.2±3.0	26.0±3.2	<0.001	24.9±3.5	24.4±3.2	24.9±2.7	0.913
SBP (mmHg)	125.0±11.6	127.7±11.67	128.8±12.6	0.011	124.9±13.4	130.5±10.8	126.8±21.2	0.252
DBP (mmHg)	75.8±11.1	76.6±10.2	78.2±9.5	0.285	74.6±13.4	76.6±7.1	77.0±8.8	0.665
Heart rate (bpm)	71.7±9.1	72.1±8.3	70.9±7.6	0.634	77.7±8.3	73.3±9.9	71.3±9.9	0.062
Type of AF, *n* (%)								
Paroxysmal	-	-	-		16 (64.0)	14 (53.8)	7 (43.8)	0.438
Persistent	-	-	-		8 (32.0)	10 (38.5)	6 (37.5)	0.879
Permanent	-	-	-		1 (4.0)	2 (7.7)	3 (18.8)	0.315
Smoke, *n* (%)								
Smoking	26 (9.2)	34 (14.0)	11 (20.8)	0.035	2 (8.0)	2 (7.7)	4 (25.0)	0.225
Ever	17 (6.0)	15 (6.2)	7 (13.2)	0.158	3 (12.0)	3 (11.5)	1 (6.2)	1.000
Disease history, *n* (%)								
DM	17 (6.0)	25 (10.3)	17 (32.1)	<0.001	5 (20.0)	6 (23.1)	3 (18.8)	1.000
HTN	52 (18.4)	83 (34.2)	32 (60.4)	<0.001	6 (24.0)	12 (46.2)	11 (68.8)	0.017
HLP	30 (10.6)	62 (25.5)	18 (34.0)	<0.001	6 (24.0)	8 (30.8)	9 (56.2)	0.093
CKD	3 (1.1)	4 (1.6)	5 (9.4)	0.004	0	3 (11.5)	3 (18.8)	0.090
CHF	2 (0.7)	2 (0.8)	0	1.000	0	0	2 (12.5)	0.054
CAD	2 (0.7)	7 (2.9)	15 (28.3)	<0.001	0	1 (3.8)	7 (43.8)	<0.001
Stroke	1 (0.4)	4 (1.6)	2 (3.8)	0.060	0	2 (7.7)	1 (6.2)	0.450
COPD	6 (2.1)	8 (3.3)	2 (3.8)	0.522	3 (12.0)	1 (3.8)	1 (6.2)	0.630
Malignancy	21 (7.4)	15 (6.2)	3 (5.7)	0.805	3 (12.0)	4 (15.4)	1 (6.2)	0.890
Medications, *n* (%)								
Bokey/Aspirin	12 (4.2)	50 (20.6)	21 (39.6)	<0.001	3 (12.0)	7 (26.9)	2 (12.5)	0.366
Clopidogrel	13 (4.6)	25 (10.3)	16 (30.2)	<0.001	3 (12.0)	2 (7.7)	6 (37.5)	0.036
OAC	2 (0.7)	4 (1.6)	3 (5.7)	0.038	2 (8.0)	12 (46.2)	9 (56.2)	0.002
CCB	38 (13.4)	56 (23.0)	17 (32.1)	0.001	2 (8.0)	9 (34.6)	9 (56.2)	0.003
BB	21 (7.4)	38 (15.6)	20 (37.7)	<0.001	8 (32.0)	11 (42.3)	7 (43.8)	0.675
RAS blockade	28 (9.9)	56 (23.0)	24 (45.3)	<0.001	4 (16.0)	4 (15.4)	7 (43.8)	0.094
Statin	47 (16.4)	90 (37.0)	33 (62.3)	<0.001	4 (16.0)	15 (57.7)	14 (87.5)	<0.001
Lab								
Fasting glucose	99.3±16.4	102.89±20.6	112.9±31.2	<0.001	105.5±36.4	105.5±18.0	122.4±34.7	0.042
Total cholesterol	190.6±33.4	188.4±32.2	192.0±26.5	0.637	187.0±33.1	177.7±40.4	181.1±28.6	0.566
LDL	115.4±31.9	118.1±27.5	124.6±25.3	0.106	111.5±34.1	107.6±31.0	111.6±22.9	0.868
HDL	49.4±14.52	43.9±12.9	42.2±18.6	<0.001	49.8±16.9	48.9±14.2	41.7±13.0	0.265

CS=Calcium score; BMI=Body mass index; BP=Blood pressure; SBP=Systolic BP; DBP=Diastolic BP; DM=Diabetes mellitus; HTN=Hypertension; HLP=Hyperlipidemia; CKD=Chronic kidney disease; CHF=Chronic heart failure; CAD=Coronary artery disease; COPD=Chronic obstructive pulmonary disease; OAC=Oral anticoagulants; CCB=Calcium channel blocker; BB=Beta-blocker; RAS=Renin–angiotensin system; LDL=Low-density lipoprotein cholesterol; HDL=High-density lipoprotein cholesterol; AF=Atrial fibrillation

baseline characteristics of the groups are shown in Table 1. In AF groups, no CAC had relative more paroxysmal type (64%) than mild (53.8%) and severe CAC (43.8%) groups. In contrast, severe CAC had relative more permanent

type (18.8%) than mild (7.7%) and no CAC (4%) groups. No significant difference of the AF types between different CACS groups in AF population. In SR patients, the severe CAC group had more males, older age, higher body mass index (BMI), more smoking, more comorbidities, more antiplatelet use, more antihypertensive agent use, more statin use, higher fasting glucose, and lower high-density lipoprotein. In AF patients, the severe CAC group had more males, older age, more hypertension, more CAD, more calcium channel blocker use, more oral anticoagulants, and more statin use. The mean CHA_2DS_2-VASc score was 1.76.

Clinical outcomes

No deaths were noted during the 2-year follow-up. In the SR group, severe CAC tended to be associated with higher crude rates of nonfatal MI (0.4%, 0.8%, and 3.8%, $P = 0.07$) and nonfatal stroke (0.4%, 0.8%, and 1.9%, $P = 0.296$) and significantly higher crude rates of late revascularization (0.4%, 2.1%, and 9.4%, $P < 0.01$), MACE (0.7%, 1.6%, and 5.7%, $P < 0.01$), total coronary events (0.7%, 2.9%, and 13.2%, $P < 0.01$), and total composite events (1.1%, 3.7%, and 15.1%, $P < 0.01$). Likewise, in the AF group, severe CAC showed a trend toward poor outcomes, including MACE, total coronary events, and total composite events without meeting statistical significance, as shown in Table 2.

Risk analysis between rhythm and coronary artery calcification

Event rates for three components of the different composite outcomes by Kaplan–Meier estimate were conducted, as shown in Figure 2. AF with severe CACs had lower event-free rates and higher risks in MACE, total coronary events, and total composite events. Regarding the correlations between the rhythm status, severity of CAC, and clinical outcomes, a multivariate Cox proportional hazards model was applied. The significant variables associated with cardiovascular outcomes, including sex, age, BMI, total CACs, DM, HTN, CAD, CKD, smoking, and antiplatelet agents; anticoagulant agents; and statin use, were selected and adjusted. Compared with SR without CAC, AF with mild CAC and severe CAC was associated with a significantly higher risk of nonfatal stroke (adjusted hazard ratio [HR]: 47.9, 95% confidence interval [CI]: 2.0–1146.6, $P = 0.017$; adjusted HR: 186.80, 95% CI: 4.1–8582.8, $P = 0.007$); AF with severe CAC was associated with a significantly higher

Table 2: Crude rates of outcomes in patients with sinus rhythm and atrial fibrillation

	Sinus rhythm				Atrial fibrillation			
	CS: 0 (*n*=283, *n* (%))	CS: 1-400 (*n*=243), *n* (%)	CS: >400 (*n*=53), *n* (%)	*P*	CS: 0 (*n*=25), *n* (%)	CS: 1-400 (*n*=26), *n* (%)	CS: >400 (*n*=16), n (%)	*P*
Nonfatal MI	1 (0.4)	2 (0.8)	2 (3.8)	0.070	1 (4.0)	1 (3.8)	1 (6.2)	1.000
Nonfatal stroke	1 (0.4)	2 (0.8)	1 (1.9)	0.296	0 (0.0)	1 (3.8)	2 (12.5)	0.242
Late revascularization	1 (0.4)	5 (2.1)	5 (9.4)	<0.001	0 (0.0)	1 (3.8)	2 (12.5)	0.242
MACE	2 (0.7)	4 (1.6)	3 (5.7)	<0.001	1 (4.0)	2 (7.7)	3 (18.8)	0.315
Total coronary events	2 (0.7)	7 (2.9)	7 (13.2)	<0.001	1 (4.0)	2 (7.7)	3 (18.8)	0.315
Total composite events	3 (1.1)	9 (3.7)	8 (15.1)	<0.001	1 (4.0)	3 (11.5)	5 (31.2)	0.055

CS=Calcium score; MI=Myocardial infarction; MACE=Major adverse cardiovascular event

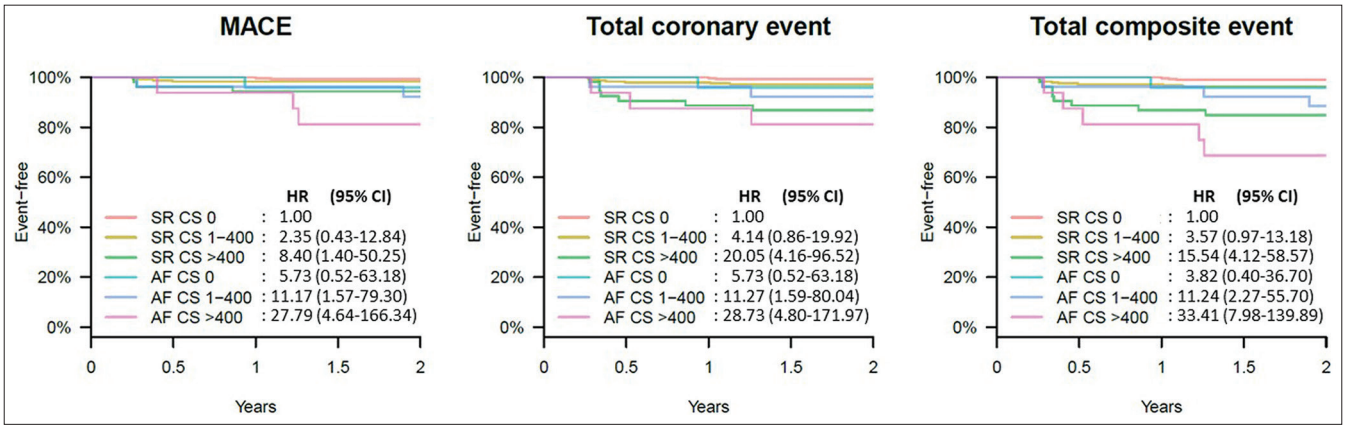

Figure 2: Event-free rates of the different composite outcomes by Kaplan–Meier estimate

risk of late revascularization (adjusted HR: 54.20, 95% CI: 1.3–2198.0, P = 0.035); and SR with severe CAC and AF with mild CAC and severe CAC were associated with significantly higher risks of MACE (adjusted HR: 14.80, 95% CI: 1.45–150.60, P = 0.023; adjusted HR: 22.61, 95% CI: 2.21–231.40, P = 0.009; adjusted HR: 57.18, 95% CI: 2.28–1434.41, P = 0.014), total coronary events (adjusted HR: 12.28 95% CI: 1.69–89.09, P = 0.013; adjusted HR: 9.73, 95% CI: 1.09–86.56, P = 0.041; adjusted HR: 16.48, 95% CI: 1.21–224.15, P = 0.035), and total composite events (adjusted HR: 12.75, 95% CI: 2.31–70.24, P = 0.003; adjusted HR: 13.94 95% CI: 2.34–83.16, P = 0.004; adjusted HR: 26.35, 95% CI: 2.45–283.69, P = 0.007), as shown in Table 3. In the AF group, despite the small sample size, severe CAC was a significant predictor of total composite events in both unadjusted (HR: 11.56, 95% CI: 1.35–99.24, P < 0.05) and adjusted analyses (adjusted HR: 33.94, 95% CI: 1.16–991.83, P < 0.05), as shown in Table 4.

Effects of baseline medications on outcomes

To evaluate the effects of baseline antiplatelets, anticoagulants, and statin use on outcomes, the Cox proportional hazards model was adjusted for significant confounding factors, and the results revealed that only antiplatelets tended to reduce MACEs and total composite events in the SR group (adjusted HR: 0.09, 95% CI: 0.01–1.02, P = 0.052; adjusted HR: 0.33, 95% CI: 0.10–1.14, P = 0.080) but not in the AF group, as shown in Table 5.

DISCUSSION

In this retrospective study evaluating the prognostic implications of CAC in AF patients at a relative low to intermediate risk of cardiovascular events, we demonstrated that AF patients with mild and severe CAC had higher risks of adverse cardiovascular outcomes, including MACEs (adjusted HR: 22.61, 95% CI: 2.21–231.40, P = 0.009; adjusted HR: 57.18, 95% CI: 2.28–1434.41, P = 0.014), total coronary events (adjusted HR: 9.73, 95% CI: 1.09–86.56, P = 0.041; adjusted HR: 16.48, 95% CI: 1.21–224.15, P = 0.035), and total composite events (adjusted HR: 13.94 95% CI: 2.34–83.16, P = 0.004; adjusted HR: 26.35, 95% CI: 2.45–283.69, P = 0.007), than SR subjects without CAC. Moreover, the severity of CAC in the AF group was a significant predictor of total composite

Table 3: Risk analysis by hazard ratio of calcium score and rhythm status

	Sinus rhythm			Atrial fibrillation		
	CS: 0	CS: 1-400	CS: >400	CS: 0	CS: 1-400	CS: >400
Nonfatal MI						
Unadjusted HR	1	2.31 (0.21-25.53)	10.40 (0.94-114.82)	11.30 (0.71-180.72)	11.69 (0.73-187.20)	22.50 (1.39-365.31)
Adjusted HR	1	2.61 (0.21-31.97)	7.98 (0.30-214.75)	18.93 (0.95-376.19)	7.46 (0.21-269.64)	12.91 (0.16-1049.45)
Nonfatal stroke						
Unadjusted HR	1	2.39 (0.22-26.35)	5.49 (0.34-87.71)	-	11.03 (0.69-176.35)	38.79[b] (3.50-429.87)
Adjusted HR	1	3.58 (0.29-43.49)	12.46 (0.40-383.63)	-	47.90[a] (2.00-1146.63)	186.76[b] (4.06-8582.78)
Late revascularization						
Unadjusted HR	1	5.73 (0.67-49.11)	32.50[b] (3.78-279.53)	-	12.59 (0.78-203.09)	50.10[b] (4.49-558.80)
Adjusted HR	1	4.18 (0.45-38.40)	16.53 (1.00-274.24)	-	13.22 (0.69-253.70)	54.20[a] (1.34-2198.00)
MACE						
Unadjusted HR	1	2.35 (0.43-12.84)	8.40[a] (1.40-50.25)	5.73 (0.52-63.18)	11.17[a] (1.57-79.30)	27.79[c] (4.64-166.34)
Adjusted HR	1	3.14 (0.53-18.54)	14.80[a] (1.45-150.60)	10.47 (0.88-124.38)	22.61[b] (2.21-231.40)	57.18[a] (2.28-1434.41)
Total coronary events						
Unadjusted HR	1	4.14 (0.86-19.92)	20.05[c] (4.16-96.52)	5.73 (0.52-63.14)	11.27[a] (1.59-80.04)	28.73[c] (4.80-250.54)
Adjusted HR	1	3.13 (0.62-15.68)	12.28[a] (1.69-89.09)	8.89 (0.79-100.56)	9.73[a] (1.09-86.56)	16.48[a] (1.21-224.15)
Total composite events						
Unadjusted HR	1	3.57 (0.97-13.18)	15.54[c] (4.12-58.57)	3.82 (0.42-36.70)	11.24[b] (2.27-55.70)	33.41[c] (7.98-139.89)
Adjusted HR	1	3.29 (0.85-12.69)	12.75[b] (2.31-70.24)	6.41 (0.65-62.95)	13.94[b] (2.34-83.16)	26.35[b] (2.45-283.69)

[a]<0.05; [b]<0.01; [c]<0.001 significance; Multivariable analysis: sinus rhythm and CS: 0 as reference, adjusting by sex, age, BMI, total CS, smoking, diabetes, HTN, CAD, CKD, antiplatelets, oral anticoagulants, and statin. CS=Calcium score; HR=Hazard ratio; MI=Myocardial infarction; MACE=Major adverse cardiovascular event; BMI=Body mass index; HTN=Hypertension; CAD=Coronary artery disease; CKD=Chronic kidney disease

events. Furthermore, antiplatelet agents might have a preventive effect in patients with SR but not in patients with AF.

AF seems to be associated with an increased risk of subsequent stroke and MI, whereas CAC is associated with atherosclerotic cardiovascular events. The coexistence of AF and CAD may worsen subsequent cardiovascular outcomes. Previous studies reported that severe CAC led to an 18.9-fold higher risk of late revascularization and a more than 72.1-fold higher risk of total coronary events compared with no CAC.[19,20] In the Multi-Ethnic Study of Atherosclerosis cohort, patients with severe CAC (CACs >300) had a 9.67-fold higher risk of any coronary events than patients with no CAC.[21] In consistent with prior studies, our data showed that severe CAC was associated with higher risks of late revascularization and total coronary events (adjusted HR: 16.5, 95% CI: 1.0–274.2, P = 0.050; adjusted HR: 16.48, 95% CI: 1.21–224.15, P = 0.035) than no CAC. Notably, the risks of cardiovascular outcomes may be doubled for patients with AF and severe CAC compared with patients with SR and no CAC. Therefore, it demonstrated that AF with severe CAC contributed to a worse prognosis.

Table 4: Risk analysis by hazard ratio of calcium score in atrial fibrillation

	Atrial fibrillation		
	CS: 0	CS: 1-400	CS: >400
MACE			
Unadjusted HR	1	1.79 (0.16-19.81)	1.88 (0.11-31.07)
Adjusted HR	1	5.52 (0.57-53.33)	127.77 (0.73-22495.77)
All coronary events			
Unadjusted HR	1	2.34 (0.21-26.09)	2.96 (0.07-129.27)
Adjusted HR	1	10.59 (0.91-123.17)	2.10 (0.05-96.86)
Total composite events			
Unadjusted HR	1	3.06 (0.32-29.43)	11.56* (1.35-99.24)
Adjusted HR	1	2.93 (0.23-36.51)	33.94* (1.16-991.83)

*P<0.05 significance; Multivariable analysis: Atrial fibrillation with CS: 0 as reference, adjusting by sex, age, total CS, HTN, CAD, antiplatelets, oral anticoagulants, and statin. CS=Calcium score; HR=Hazard ratio; MACE=Major adverse cardiovascular event; CAD=Coronary artery disease; CS: Calcium score; HTN=Hypertension

Routine application of nCCT for the evaluation of CAC in AF patients has rarely been addressed. According to guideline recommendations, CT coronary angiography (CTA) can be performed in select AF patients who also have a higher CAD risk.[8] Although CTA can evaluate the coronary anatomy in detail, it requires contrast injection, more radiation exposure, and higher costs. We consider the CACs to be a reasonable tool that may help guide decisions regarding preventive interventions in selected individuals and clinician–patient risk discussions. In the current study, AF with severe CAC was associated with a significantly higher risk of total composite events (adjusted HR: 36.9, 95% CI: 3.3–408.8, P = 0.003) than AF without CAC. nCCT might play an important role in the prediction of future cardiovascular events in AF patients. Therefore, nCCT might be recommended to early detect CAC in AF patients and to prompt aggressive intervention to prevent subsequent cardiovascular events.

Table 5: Risk analysis by hazard ratio of baseline medication in different rhythm status

Baseline	Sinus rhythm (***n***=579)				Atrial fibrillation (***n***=67)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	***P***	HR (95% CI)	***P***	HR (95% CI)	***P***	HR (95% CI)	***P***
MACE								
APL	0.93 (0.19-4.50)	0.042	0.09 (0.01-1.02)	0.052	0.86 (0.16-4.69)	0.859	0.19 (0.01-3.79)	0.277
OAC	8.67 (1.08-69.38)	0.042	5.21 (0.19-142.32)	0.328	1.08 (0.20-5.91)	0.929	1.03 (0.07-15.71)	0.985
Statin	1.22 (0.30-4.87)	0.780	0.21 (0.03-1.57)	0.129	1.10 (0.22-5.44)	0.908	0.75 (0.07-7.99)	0.815
Coronary events								
APL	1.55 (0.54-4.48)	0.413	1.55 (0.54-4.48)	0.413	2.10 (0.42-10.59)	0.367	1.41 (0.13-15.54)	0.777
OAC	4.88 (0.64-37.10)	0.126	1.76 (0.14-22.43)	0.663	1.44 (0.24-8.63)	0.689	1.03 (0.06-16.84)	0.981
Statin	4.29 (1.56-11.80)	0.005	1.38 (0.41-4.64)	0.601	7.89 (0.88-70.75)	0.065	6.56 (0.12-349.47)	0.354
Composite events								
APL	1.46 (0.56-3.80)	0.438	0.33 (0.10-1.14)	0.080	1.44 (0.39-5.37)	0.585	1.19 (0.23-6.19)	0.836
OAC	0.33 (0.10-1.14)	0.080	1.76 (0.14-22.43)	0.663	1.11 (0.28-4.43)	0.885	0.28 (0.03-2.84)	0.284
Statin	1.76 (0.14-22.43)	0.663	1.26 (0.42-3.80)	0.682	2.49 (0.62-9.97)	0.197	1.06 (0.15-7.33)	0.954

*P<0.05 significance; Multivariable analysis: Adjusting by sex, age, total CS, HTN, CAD as well as antiplatelets; oral anticoagulants; and statin. HR=Hazard ratio; MACE=Major adverse cardiovascular event; APL=Antiplatelets; OAC=Oral anticoagulants; CAD=Coronary artery disease; CS: Calcium score; HTN=Hypertension; CI=Confidence interval

Antiplatelet and lipid-lowering therapies appear to have a net clinical benefit in patients with a relatively high CACs >100 Agatston units regardless of ASCVD risk category. Moreover, anticoagulant therapy is the mainstay treatment for stroke prevention in AF patients. At present, the evidence of anticoagulants or antiplatelets alone, or anticoagulant plus antiplatelet, or statin use for primary medical prevention in AF patients with CAC is still lacking. In our data, outcome analysis for baseline medications demonstrated that antiplatelet use resulted in relatively reduced risks of MACEs and total composite events compared to no antiplatelets use in the SR group but not in the AF group. Physicians need to evaluate the severity or activity of both AF and CAD and carefully weigh whether the potential benefits of adding these medications are worth the risks.

The severity of CAC is also associated with a high risk of subsequent AF development.[22,23] O'Neal *et al*. noted an increased risk of AF according to the HRs for each CAC category: A CACs of 0 as a reference, a CACs of 1–100: adjusted HR: 1.4, 95% CI: 1.01–2.0; and a CACs >300, adjusted HR: 2.1, 95% CI: 1.4–2.9.[23] In the current study, the prevalence of AF was twofold higher (23.12%) in patients with severe CAC (CACs >400) than in those with mild (9.67%) and no CAC (8.11%). Considering all these results together, the clinical application of nCCT might facilitate not only the assessment of CAC for risk assessment but also the prediction of subsequent AF development, demonstrating potential value for guiding future follow-ups for early AF detection based on the severity of CAC severity.

Limitations

Limitations to this study should be considered. First, this was a single-center, retrospective cohort study that relied on accurate documentation, restricting the external validity of our results. Second, the sample size was small, especially in the AF population, which may reduce the power to evaluate the impact of CAC on cardiovascular outcomes. Furthermore, we could not evaluate the detailed association between outcomes and the different ranges of CAC. Third, in the current study, LV function was not available. The impact of LV function on the outcome of interest could not be investigated. Fourth, the effects of posttest preventive therapies such as statins, antiplatelets, or anticoagulants are of significant interest but were beyond the scope of the current analysis. Finally, blinding to the participants' clinical information was not applied during CACs quantification. However, computer-based CACs calculations were confirmed by radiologists, which reduces our concern for scoring bias.

CONCLUSION

In the present study, AF may lead to significantly higher risks of cardiovascular events for patients with severe and mild CAC, highlighting the role of nCCT in early evaluations of CACs and corresponding cardiovascular risks, which may facilitate the application of early risk modification or aggressive medical prevention for this high-risk AF population. However, further large-scale prospective studies are needed to validate the impact of CACs in AF patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart disease and stroke statistics-2020 update: A report from the American Heart Association. Circulation 2020;141:e139-596.
2. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, *et al.* Atherosclerosis. Nat Rev Dis Primers 2019;5:56.
3. Yeung AC, Barry J, Orav J, Bonassin E, Raby KE, Selwyn AP. Effects of asymptomatic ischemia on long-term prognosis in chronic stable coronary disease. Circulation 1991;83:1598-604.
4. Deedwania PC. Silent ischemia predicts poor outcome in high-risk healthy men. J Am Coll Cardiol 2001;38:80-3.
5. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.
6. Mitchell JD, Paisley R, Moon P, Novak E, Villines TC. Coronary artery calcium and long-term risk of death, myocardial infarction, and stroke: The Walter Reed Cohort Study. JACC Cardiovasc Imaging 2018;11:1799-806.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2020;41:407-77.

8. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
9. Capodanno D, Huber K, Mehran R, Lip GY, Faxon DP, Granger CB, *et al.* Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;74:83-99.
10. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. Eur J Prev Cardiol 2017;24:1555-66.
11. Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease – Double trouble. Adv Med Sci 2018;63:30-5.
12. Akao M. Atrial fibrillation and coronary artery disease: Resembling twins? J Cardiol 2014;63:169-70.
13. Lokshyn S, Mewis C, Kuhlkamp V. Atrial fibrillation in coronary artery disease. Int J Cardiol 2000;72:133-6.
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016;50:e1-88.
15. Ferencik M, Pencina KM, Liu T, Ghemigian K, Baltrusaitis K, Massaro JM, *et al.* Coronary artery calcium distribution is an independent predictor of incident major coronary heart disease events: Results from the Framingham heart study. Circ Cardiovasc Imaging 2017;10:e006592.
16. Smith ER. The angina grading system of the Canadian Cardiovascular Society. Can J Cardiol 2002;18:439, 442.
17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
18. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: Mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005;46:807-14.
19. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, *et al.* 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation 2018;137:961-72.
20. LaMonte MJ, FitzGerald SJ, Church TS, Barlow CE, Radford NB, Levine BD, *et al.* Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421-9.
21. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, *et al.* Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336-45.
22. Vinter N, Christesen AM, Mortensen LS, Urbonaviciene G, Lindholt J, Johnsen SP, *et al.* 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;19:926-32.
23. O'Neal WT, Efird JT, Dawood FZ, Yeboah J, Alonso A, Heckbert SR, *et al.* Coronary artery calcium and risk of atrial fibrillation (from the multi-ethnic study of atherosclerosis). Am J Cardiol 2014;114:1707-12.