Prognostic Value of Subclinical Coronary Artery Disease in Atrial Fibrillation Patients Identified by Coronary Computed Tomography Angiography

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Identifying coronary artery disease (CAD) in atrial fibrillation (AF) patients improves risk stratification and defines clinical management. However, the value of screening for subclinical CAD with cardiac CT in AF patients is unknown. Between 2011 and 2015, 94 consecutive patients without known or suspected CAD (66 (57−73) years, 68% male), who were referred for AF evaluation, underwent a noncontrast-enhanced coronary calcium scan and a coronary computed tomography angiography (CCTA) at our center. We retrospectively evaluated the coronary calcium score, the prevalence of obstructive CAD (≥50% stenosis) determined by CCTA, compared clinical management and 5-year outcome in patients with and without obstructive CAD on CCTA, and examined the potential impact of a coronary calcium score and obstructive CAD on CCTA as a manifestation of vascular disease on the CHA2Ds2VASc score and for the cardiovascular risk stratification of AF patients. The median coronary calcium score was 57 (0−275) and 24 patients (26%) had obstructive CAD on CCTA. At baseline, patients with obstructive CAD more often used statins than those without obstructive CAD (54% vs 26%, p = 0.011). After a median clinical follow-up of 2.4 (0.5−4.5) years, patients with obstructive CAD more frequently used oral anticoagulant and/or antiplatelet drugs, statins, angiotensin-II-receptor blockers and/or angiotensin-converting-enzyme inhibitors, and less often used class I antiarrhythmic drugs than patients without obstructive CAD (all p <0.050). After a median follow-up of 5.7 (4.8−6.8) years, mortality was higher in patients with obstructive CAD than in those without obstructive CAD (29% vs 11%, log-rank test: p = 0.034). Implementation of a coronary calcium score and/or obstructive CAD on CCTA elevated the CHA2Ds2VASc score and cardiovascular risk stratification in 42 patients (p <0.001) and 47 patients (p = 0.006), respectively. In conclusion, we observed a high prevalence of obstructive CAD on CCTA in AF patients without known or suspected CAD. AF patients with obstructive CAD were managed differently and had a worse prognosis than those without obstructive CAD. Cardiac CT could enhance cardiovascular risk stratification of AF patients. **(Am J Cardiol 2020;00:1−7)**

Atrial fibrillation (AF) is the most common arrhythmia, with gradually increasing prevalence worldwide.[1] The mortality of patients with AF is nearly twice higher compared with individuals without AF.[2] Partially, this can be explained by the high prevalence of concomitant diseases such as coronary artery disease (CAD), heart failure, and valvular heart disease.[3] Identification and management of these conditions have been recommended by international guidelines to improve AF burden and outcome.[4] Previous myocardial infarction increases the risk for thromboembolic and coronary events of AF patients, and is incorporated in the risk stratification algorithm for stroke (eg, CHA2Ds2-VASc score) and cardiovascular events (eg, SCORE).[5,6] However, early detection of CAD in AF patients has shown to be prognostic valuable with a substantial potential impact on clinical management, including initiation of anticoagulation therapy, statins, and the choice of antiarrhythmic drugs.[4,7−10] Coronary computed tomography angiography (CCTA) has emerged as a valuable diagnostic tool to evaluate CAD in patients with stable chest pain.[11] In this study, we investigated the prevalence of CAD by CCTA in AF patients without known or suspected CAD, compared clinical management and outcome in AF patients with and without obstructive CAD, and examined the potential value of a noncontrast-enhanced calcium scan and CCTA on the stroke and cardiovascular risk stratification in AF patients of whom the majority were referred by their primary physicians.

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Methods

From January 2011 to January 2015, a total of 94 consecutive patients without known or suspected CAD were referred to a dedicated AF outpatient clinic at our center and underwent a cardiac CT as part of routine clinical management. The large majority of patients were referred by primary or internal medicine physicians with recently diagnosed AF. The clinical evaluation consisted of a comprehensive clinical examination, blood tests, a transthoracic echocardiogram, and a noncontrast-enhanced coronary calcium scan with a CCTA to identify subclinical CAD. CCTA exclusion criteria were pregnancy, renal failure with a glomerular filtration rate <60 ml/min/1.73 m^2, and known allergy to contrast agents. The absence of known or suspected CAD was defined as the absence of a history of ischemic heart disease, heart failure, severe valvular disease, electrocardiogram abnormalities (ie, pathologic q waves), or angina pectoris. AF was defined according to the European guidelines for management of AF.[4] The study was conducted in accordance with Declaration of Helsinki and with research ethics committee approval. The need for informed consent was waved on the basis of the retrospective nature of the study.

All CT scans were performed on second- (96%) or third-generation (4%) dual-source CT scanners (Somatom Definition Flash or Force, Siemens Healthineers, Forchheim, Germany). Ninety-three out of 94 patients underwent a noncontrast-enhanced scan to determine a coronary calcium score according to the Agatston method.[12] Multi-Ethnic Study of Atherosclerosis percentiles were calculated according to the coronary calcium score distribution by age, gender, and ethnicity.[13] CCTA was performed in all patients using a retrospectively electrocardiogram-gated spiral (48%), prospectively electrocardiogram-triggered axial (50%), or prospectively electrocardiogram-triggered high-pitch spiral (2%) scan mode depending on the heart rate and heart rate variability. The heart rhythm during CCTA in those who were scanned in a retrospectively electrocardiogram-gated spiral scan mode was sinus rhythm in 5 patients (11%), AF or other arrhythmia in 29 patients (64%), and was not reported in 11 patients (24%). The heart rhythm during CCTA in those who were scanned with a prospectively electrocardiogram-triggered axial or high-pitch spiral scan mode was sinus rhythm in 37 patients (76%), AF and other arrhythmia in 2 patients (4%), and was not reported in 10 patients (20%). The image quality was scored based on a 4-point Likert score and was excellent in 48 patients (51%), good in 36 patients (38%), impaired in 10 patients (11%), and nondiagnostic in none of the patients. The median radiation dose of the entire cardiac CT examination was 7.3 (4.2−12.1) mSv using a conversion coefficient of 0.014 mSv/ (mGy*cm); a median radiation dose of 11.4 (7.7−17.2) mSv for those who were scanned with a retrospectively electrocardiogram-gated spiral scan mode and a median radiation dose of 4.5 (2.8−7.0) mSv for those who were scanned with a prospective electrocardiogram-gated axial or high-pitch scan mode. Patients received sublingual nitroglycerin before CCTA and beta-blockers if indicated (heart rate >65/min) and clinically safe. The cardiac CT scans were interpreted as part of routine clinical care by radiologists with extensive experience in cardiac imaging, in accordance with international guidelines.[14] Obstructive CAD was defined as the presence of at least 1 stenosis ≥50%.

Medication use and therapeutic procedures were collected from medical records at the time of the first clinical visit when also the cardiac CT was performed and at the time of the last known clinical outpatient visit at our center. All-cause mortality was determined at time of the data collection using the Dutch National Mortality Registry. The medication use, the number of previous cardiac interventions, and deaths were compared between AF patients with and without obstructive CAD on CCTA.

The CHA2Ds2VASc (Congestive heart failure, Hypertension, Age 65−74 or ≥75 years, diabetes mellitus, stroke or systemic embolism, vascular disease [peripheral arterial disease, previous myocardial infarction or aortic plaque], and gender category [ie, female gender]) score was calculated in each patient at the first clinical visit. Based on the published observations that a calcium score >100 and obstructive CAD (≥50% stenosis) predict stroke,[9,15,16] we tested the potential impact of a calcium score and CCTA findings on the CHA2Ds2VASc score by considering a calcium score >100 and/or the presence of ≥50% stenosis on CCTA as a manifestation of vascular disease which adds 1 point to the CHA2Ds2VASc score. The CHA2Ds2VASc score was re-calculated first with the calcium score alone and second with both the calcium score and CCTA findings to investigate the potential value of the calcium score alone and the additional value of CCTA findings on the CHA2Ds2-VASc score. We determined the number of patients with an increase in CHA2Ds2VASc score and who would potentially be reclassified to oral anticoagulation for stroke prevention with the findings of the noncontrast-enhanced scan alone and with the findings of both the noncontrast-enhanced scan and the CCTA.

To investigate the potential clinical impact of the calcium score and CCTA on the cardiovascular risk stratification of AF patients and the utilization of statin therapy, we reassessed the cardiovascular risk stratification according to the European guidelines of cardiovascular disease prevention in clinical practice with (1) a calcium score alone and with (2) both a calcium score and CCTA findings.[7] A reclassification rate was calculated as a proportion of patients who were reclassified after the implementation of the coronary calcium score and CCTA findings. In accordance to European guidelines patients were classified as very high-risk, high-risk, moderate-risk, and low-risk (Table 1). Subsequently, patients were reassessed based on the clinical characteristics and coronary calcium score. A coronary calcium score of 0 reclassified the patient to a lower risk category. Patients with a calcium score of ≥300 or ≥75th percentile were reclassified to a higher risk category. Finally, patients were assessed based on the clinical characteristics, coronary calcium score, and CCTA findings. Obstructive CAD (≥50% stenosis) on CCTA reclassified patients to the very high-risk category.

Absolute variables are represented as totals with percentages and continuous variables as means ± standard deviations or median with 25th−75th percentiles. Chi-square test, Fisher's exact test, and McNemar's test were used to

Table 1
Cardiovascular risk categories: Anyone in each category

Very high-risk	- A prior stroke, aortic aneurysm, peripheral artery disease, or chronic kidney disease with a globular filtration rate <30 mL/min/1.73 m^2. - Diabetes mellitus with a major cardiovascular risk factor (hypertension, hypercholesterolemia or smoking). - A calculated SCORE (10-year risk of fatal cardiovascular disease) of ≥10%.
High-risk	- Diabetes mellitus without major risk factors. - Chronic kidney disease with a globular filtration rates 30−59 mL/min/1.73m2. - A calculated SCORE of ≥5% and <10%.
Moderate-risk	Defined as a calculated SCORE of ≥1 and <5%
Low-risk	Defined as a calculated SCORE of <1%

test the differences in categorical variables. Wilcoxon signed-rank test was used to test the differences in continuous variables. The survival probability was estimated by Kaplan-Meier survival analysis and log-rank test was used to compare the survival distribution of AF patients with and without obstructive CAD on CCTA. A 2-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 25, IBM Corp, Armonk, NY).

Table 2
Baseline characteristics (N = 94)

Age (years)	66 (57−73)
Men	64 (68%)
Symptomatic atrial fibrillation*	51 (54%)
Atrial fibrillation type	
Paroxysmal	65 (69%)
Persistent	18 (19%)
Permanent	11 (12%)
Ablation in history	1 (1%)
CHA2Ds2VASc score†	2 (1−3)
HAS-BLED score‡	1 (0−1)
Body mass index ≥30 kg/m^2	24 (26%)
Hypertension§	44 (47%)
Hypercholesterolemia§	27 (28%)
Diabetes mellitus§	13 (14%)
Prior stroke	13 (14%)
Peripheral artery disease or aortic aneurysms	4 (4%)
Chronic kidney disease‖	2 (2%)
Thyroid dysfunction#	7 (7%)
Smoking (current and previous)	44 (47%)
Alcohol ≥2 units/day	23 (24%)
Transthoracic echocardiogram	
Left ventricular ejection fraction <45%	10 (11%)
Abnormal left atrial diameter**	46 (49%)
Valvular heart disease††	5 (5%)

Continuous data are presented as median (25th to 75th percentile).Categorical data are presented as absolute numbers and percentage (%).

* Defined as an EHRA score ≥2: 1 = no symptoms, 2 = mild symptoms, 3 = severe symptoms, 4 = disabling symptoms.

† CHA2Ds2VASc score: 1 point for congestive heart failure, hypertension, age 65 to 74, diabetes mellitus, vascular disease, and female gender, and 2 points for previous stroke or thromboembolism and age ≥75.

‡ HAS-BLED score: 1 point for hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition to bleeding, labile international normalized ratio, age >65 years, medication usage predisposing bleeding, severe alcohol use.

§ Based on medication use.

‖ Based on eGFR <60 ml/min/1.73m^2.

Based on history of thyroid dysfunction or thyroid medication.

** Defined as left atrial diameter >38 mm for females and >40 mm for males.

†† Defined as moderate to severe valvular heart disease (9 missing values).

Results

The study population consisted of 94 consecutive patients (66 [57−73] years, 68% male) with predominately paroxysmal AF (69%) and a median CHA2Ds2VASc score of 2 (1−3; Table 2). Twenty-two patients had a CHA2Ds2-VASCs of 0 and 20 patients (4 females and 16 males) had a CHA2Ds2VASCs of 1. Thirteen patients (14%) had diabetes mellitus, 13 patients (14%) had a previous history of stroke, 4 patients (4%) had peripheral artery disease (n = 2) or an aortic aneurysm (n = 2), and 2 patients (2%) had chronic kidney disease. The transthoracic echocardiogram showed an ejection fraction <45% in 10 patients (11%) and moderate to severe valvular heart disease in 5 patients (5%).

The median Agatston score was 275 (57−1564), and 31 patients (33%) had a score of 0 indicating no detectable coronary calcium (Table 3). The calcium score was >100 in 40 patients (42%) and ≥300 and/or Multi-Ethnic Study of Atherosclerosis percentile ≥75 in 38 patients (40%). CCTA showed obstructive CAD (≥50% stenosis) in 24 patients (26%), including 12 patients (13%) with high-risk CAD (left main stenosis, proximal left anterior descending stenosis or 3-vessel disease [all ≥50% stenosis]).

Table 3
Cardiac computed tomography findings (N = 94)

Coronary calcium scan	
Agatston calcium score*	57 (0−275)
0	31 (33%)
1−100	22 (23%)
101−400	19 (20%)
≥400	21 (22%)
Coronary computed tomography angiography	
Coronary artery disease†	
None	26 (28%)
None obstructive	44 (47%)
Low-risk obstructive	12 (13%)
High-risk obstructive‡	12 (13%)

Categorical data are presented as absolute numbers and percentage (%).

* 1 missing value.

† Obstructive coronary artery disease defined as a stenosis ≥50%.

‡ High-risk coronary artery disease defined as 3-vessel disease, obstructive stenosis in left main or obstructive stenosis in left anterior descending.

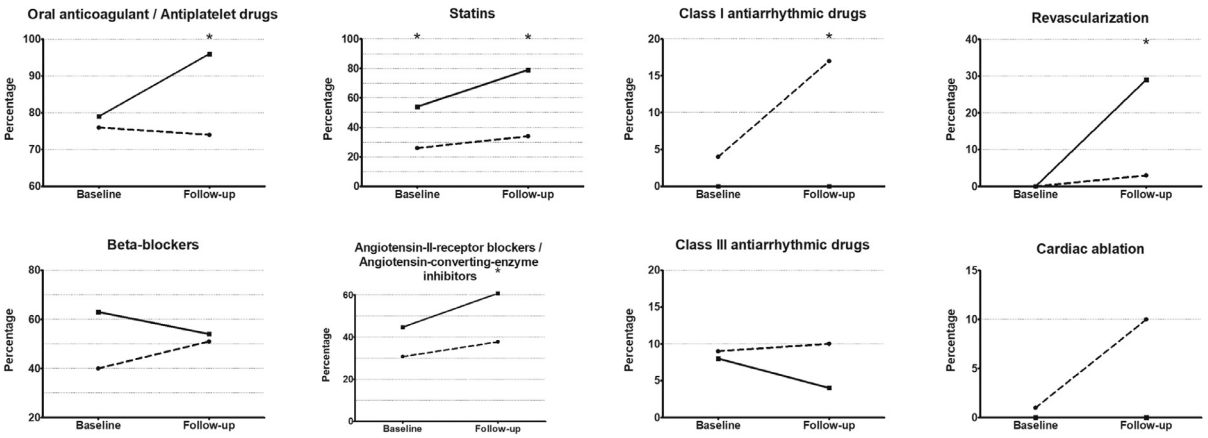

Figure 1. The medication use and therapeutic interventions of AF patients with (continuous line) and without (dashed line) CAD at the time of the first visit with cardiac CT (baseline) and at the last outpatient clinic visit (follow-up). Chi-square test and Fisher's exact test were used to test the differences between obstructive and nonobstructive AF patients with *p <0.05. AF = atrial fibrillation; CAD = coronary obstructive CAD; CT = computed tomography.

The median time between the first visit with cardiac CT and the last outpatient clinic visit was 2.4 (0.5−4.5) years. At the first visit, patients with obstructive CAD already used statins more often than patients without obstructive CAD (54% vs 26%, respectively, p = 0.011; Figure 1). At the last outpatient clinic visit, patients with obstructive CAD more frequently used oral anticoagulant and/or antiplatelet drugs, statins, angiotensin-II-receptor blockers and/or angiotensin-converting-enzyme inhibitors, and less often used class I antiarrhythmic drugs than patients without obstructive CAD (all p <0.050).Patients with obstructive CAD (29%) more often underwent revascularization than those without obstructive CAD (3%, p <0.001). After a median follow-up of 5.7 (4.8 −6.9) years, the all-cause mortality in AF patients with and without obstructive CAD was 29% versus 11% (p = 0.055), respectively. The log-rank test for pairwise comparisons of the Kaplan-Meier survival curves showed a significant different between AF patients with and without obstructive CAD (p = 0.034; Figure 2).

If a coronary calcium score >100 would be considered as manifestation of vascular disease (in addition to myocardial infarction, peripheral artery disease, aortic plaque), the CHA2Ds2VASc score increased in 38 patients (40%, p <0.001), including in 3 patients from 0 to 1 and in 1 female patient from 1 to 2 who would have been reclassified to oral anticoagulant drug use (p = 0.125). The addition of obstructive CAD on CCTA would have increased the CHA2Ds2-VASc score in an additional 4 patients (4%, p = 0.046), of which 1 patients increased from 0 to 1 who would have been reclassified to oral anticoagulant therapy (p = 1.000).

The risk stratification based on clinical risk factors classified 11 patients (12%) as low-risk, 34 patients (36%) as moderate-risk, 18 patients as high-risk (19%), and 31 patients (33%) as very high-risk (Figure 3). The addition of

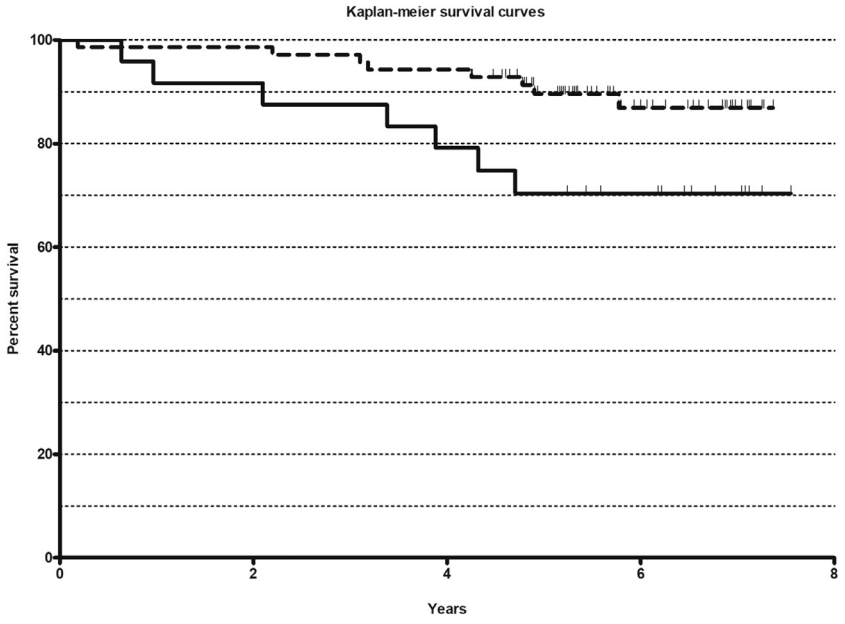

Figure 2. Kaplan-Meier survival curves of AF patients with obstructive (continuous line) and nonobstructive CAD (dashed line). A log-rank test for pairwise comparisons of the survival curves was performed to compare both groups (p = 0.034). AF = atrial fibrillation; CAD = coronary obstructive CAD.

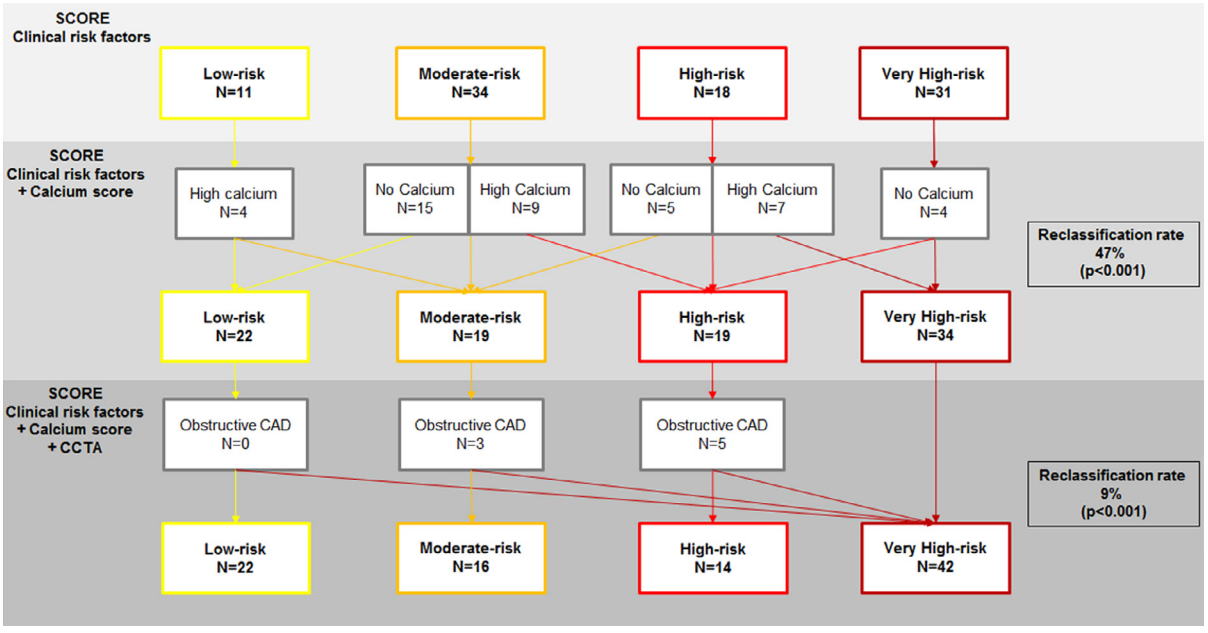

Figure 3. Cardiovascular risk stratification of AF patients based on clinical patient characteristics, calcium score, CCTA findings. A reclassification rate was calculated as a proportion of patients who were reclassified after the implementation of the coronary calcium score and CCTA findings and statistically tested by chi-square tests. AF = atrial fibrillation; CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

the coronary calcium score reclassified 47% of the patients ($p = 0.040$) of whom 24 patients were reclassified to a lower risk classification based on a calcium of 0 and 20 patients to a higher risk classification based on a calcium score ≥300 and/or Multi-Ethnic Study of Atherosclerosis percentile ≥75. The addition of the CCTA findings reclassified 8 patients to very high-risk (reclassification rate 9%, $p = 0.018$). Overall, the cardiovascular risk was reclassified in 47 patients (50%) with calcium score and CCTA ($p = 0.006$). Six out of 15 patients (40%) who did not survive would have been reclassified to a different cardiovascular risk classification of which 5 patients would have been classified to a higher cardiovascular risk classification and 1 patient to a lower cardiovascular risk classification (from very high-risk to high-risk).

Discussion

In this study, we demonstrate a high prevalence of obstructive CAD in AF patients without known or suspected CAD as well as differences in medical management and mortality rate in AF patients with and without obstructive CAD. Additionally, we demonstrated the potential clinical implications of both calcium imaging and CCTA for the stroke and cardiovascular risk stratification in AF patients.

CAD is associated with the development and recurrence of AF, the presence of AF symptoms, and an increased risk of death.[17–20] Multiple studies have shown a high prevalence of CAD (~30% to 40%) in AF patients based on reported medical history, angina symptoms, and electrocardiogram abnormalities.[18,19] Our current study shows a high prevalence of CAD (26%) in AF patients without known or suspected CAD and underlines the hypothesis of AF as a marker of advanced coronary atherosclerosis. Furthermore, 3-vessel, left main, and/or proximal left anterior descending disease was identified in 13% of our study population. However, the underlying pathophysiologic mechanism between CAD and AF is not completely understood. Inflammation and ischemia have been suggested to cause atrial damage subsequently stimulating electrical and structural remodeling, resulting in AF.[21] Additionally, CAD has shown to be an independent risk factor for ischemic stroke, which may be caused by an elevated protrombotic state in the presence of a high atherosclerosis burden.[16]

Cardiac CT is an accurate technique for CAD detection both in patients with and without AF.[22,23] However, only a few studies have addressed the clinical role of calcium imaging and CCTA in the management of AF patients.[8,24] Chaikriangkrai et al performed coronary imaging in AF patients without known or suspected CAD and found a higher prevalence of CAD (calcium score >0) compared with patients in sinus rhythm.[8] A calcium score >0 was identified in 74% of the study population, which is similar to our cohort (67%). Nucifora et al investigated the prevalence of CAD in AF patients using CCTA and found obstructive CAD in 41%, significantly more than in a matched control group without AF (27%).[24] In their cohort, more than half of the AF patients with obstructive CAD had left main and/or proximal LAD disease. We also observed that half of the patients with coronary obstructions had high-risk obstructive CAD. However, the overall prevalence of obstructive CAD in their AF population was higher than in our study due to a more high-risk/angina study population. These observations stress the potential clinical relevance of subclinical CAD in AF patients and may explain the increased risk of cardiovascular events in AF patients.[25] Moreover, we show that the mortality rates in patients with obstructive CAD are higher than in those without obstructive CAD.

Currently, only previous myocardial infarction is considered a risk factor in the risk stratification for stroke.[4] However, recent studies have shown that CAD without clinical manifestation of myocardial infarction independently predicts thromboembolic events.[9,16] Moreover, AF is an independent risk factor for the development of new cardiovascular events, which suggests that cardiovascular risk stratification based on clinical cardiovascular risk factors alone may be insufficient.[7,25] Both the coronary calcium score and CCTA can improve risk stratification for stroke and other cardiovascular events.[13,15,26] Chaikriangkrai et al evaluated the clinical implications of a calcium score in AF patients without known or suspected CAD and identified 19% of the patients as new potential candidates for oral anticoagulation by adding a calcium score >100 to the CHA2DsVASc scores and 12% of the patients (calcium score ≥300) as new potential candidates for statin therapy.[8] We found a much lower prevalence of new potential candidates for oral anticoagulation with calcium score (4%) and CCTA (1%), but did find significant reclassification of cardiovascular risk after the implementation of a calcium score and CCTA in AF patients with known or suspected CAD. More research is needed to prospectively demonstrate the incremental clinical value of a coronary calcium score or CCTA for risk stratification of AF patients and the impact of therapeutic decision and clinical outcome.

Class I antiarrhythmic drugs are recommended for rhythm control therapy in AF patients without structural heart disease.[4] It is advised to evaluate for CAD in patients with cardiovascular risk factors before administrating class I antiarrhythmic drugs, considering that recurrent or chronic ischemia can lead to impaired left ventricular conduction and thereby cause proarrhythmic effects of class IC antiarrhythmic drugs.[10] For this reason, the presence of CAD has been a contraindication for the use of class I antiarrhythmic drugs.[4] In our study, none of the patients with obstructive CAD received class I antiarrhythmic drugs. However, whether the presence of CAD on CCTA has the same consequence as CAD on conventional angiography requires further investigation. Furthermore, we show a high prevalence of high-risk obstructive CAD in our study population.[24] Although routine screening in asymptomatic patients is currently not recommended, early detection of CAD by CCTA may be valuable in AF patients to identify patients who might benefit from preventive or therapeutic therapy.[27,28]

This study has several limitations that should be acknowledged. The retrospective, observational nature and the cohort size do not allow drawing of causal relationships between cardiac CT findings and clinical outcomes. Finally, the observed radiation dose of cardiac CT was still high in this population, which might limit the clinical use in asymptomatic AF patients. However, the use of more recent generation scanners and the implementation of dose-saving algorithms are likely to result in substantial dose reduction, without degradation of image quality. Whether identification and treatment of AF patients with occult coronary disease improves clinical outcome will require further research.

In conclusion, the prevalence of obstructive CAD is high in AF patients without known or suspected CAD. AF patients with obstructive CAD on CCTA had a more intensified medical treatment and a worse clinical outcome than patients without obstructive CAD. Cardiac CT could be a valuable tool for the risk stratification of AF patients.

Author Contribution

F.M.A. Nous: Data curation, Formal analysis, Investigation, Methodology, Formal analysis, Writing − Original draft preparation, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

R.P.J. Budde: Data curation, Resources, Supervision, Writing − Reviewing and Editing, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

E.D. van Dijkman: Investigation, Writing − Original draft preparation, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

P.J. Musters: Project administration, Resources, Writing − Reviewing and Editing, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

K. Nieman: Conceptualization, Methodology, Resources, Supervision, Writing − Reviewing and Editing, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

T.W. Galema: Conceptualization, Data curation, Methodology, Resources, Supervision, Writing − Reviewing and Editing, Final approval of the manuscript and agreed to be accountable for all aspects of the work.

Disclosures

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