Thromboembolic Risk of Imaging-Confirmed Coronary Artery Disease Without Myocardial Infarction in Patients With Nonvalvular Atrial Fibrillation

Min Soo Cho, MD[a,1], Kyusup Lee, MD[a,1], Kee-Joon Choi, MD, PhD[a,*], Jung-bok Lee, PhD[b], Ungjung Do, MD[a], Yu Na Kim, MD[a], Jun Kim, MD[a], Gi-Byoung Nam, MD[a], and You-Ho Kim, MD[a]

The implication of coronary artery disease (CAD) without the clinical manifestation of myocardial infarction (non-MI-CAD) on thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF) is not well evaluated. We hypothesized that non-MI-CAD would have a similar risk of future thromboembolism as MI-CAD. Clinical data for 17,073 consecutive patients (mean age, 64.3 years; males, 64.9%) diagnosed with NVAF at our center were analyzed. CAD was defined as stenosis of ≥50% stenosis of major coronary arteries identified using coronary artery angiography or coronary computed tomographic angiography. The main outcome of the present study was the rate of thromboembolic events (ischemic stroke and systemic embolism) during the follow-up period (3.1 ± 2.4 years). A total of 1,011 patients (5.9%) were diagnosed with CAD without clinical manifestation of MI (non-MI-CAD) and 708 (4.1%) had a history or diagnosis of MI-CAD. Thromboembolic events occurred in 1,007 patients (5.9%) during follow-up. The groups were at high risk of future thromboembolic events determined using univariate (hazard ratio [HR] 1.55; 95% confidence interval [CI] 1.25 to 1.91; p <0.001 for non-MI-CAD and HR 2.14; 95% CI 1.70 to 2.69; p <0.001 for MI-CAD) and multivariate analysis adjusted for CHA_2DS_2-VASc score components and relevant variables (HR 1.42; 95% CI 1.15 to 1.77; p = 0.001 for non-MI-CAD and HR 1.62; 95% CI 1.28 to 2.06; p <0.001 for MI-CAD); this trend was consistent in patients who did not receive anticoagulants during follow-up (n = 8,032, 47.0%). In conclusion, non-MI-CAD is an important predictor of thromboembolic events in patients with NVAF. **(Am J Cardiol 2019;123:1287−1292)**

In recent years, cardiac imaging techniques such as coronary computed tomography angiography (CCTA) have been developed for noninvasive assessment of the presence and severity of coronary artery disease (CAD).[1,2] Subsequently, managing patients with nonvalvular atrial fibrillation (NVAF) with CAD has become an important clinical issue. The most critical step in managing patients has both NVAF and CAD is prescribing proper anticoagulation therapy for stroke prevention. The CHA_2DS_2-VASc scoring system defines vascular disease as previous myocardial infarction (MI), peripheral vascular disease, and aortic plaque, and does not incorporate stable CAD not presenting as MI (non-MI-CAD).[3] However, considering that progressive atherosclerosis is a common pathophysiology of the wide clinical spectrum of CAD,[4−6] non-MI-CAD patients could have significant risk of thromboembolic events as well. We tested whether non-MI-CAD has a similar risk of future thromboembolism as CAD manifesting as MI (MI-CAD), and whether it may serve as a component of vascular disease in the CHA_2DS_2-VASc system.

Methods

The present study is a retrospective observational review of consecutive NVAF patients managed in our center. A total of 20,889 patients were diagnosed with AF from 2006 to 2016 in Asan Medical Center, Seoul, Korea. Patients with (1) prosthetic valve and mitral stenosis and (2) who were lost to follow-up after initial presentation were excluded from analysis. Patients were divided into 3 groups according to the presence of significant CAD and MI: (1) MI-CAD group (patients with a previous MI event); (2) non-MI-CAD group (patients with significant CAD confirmed by imaging studies but without previous MI), and (3) control group (those without any history of CAD or MI). The study was approved by the institutional review board of Asan Medical Center, which waived the need for informed consent from patients based on the retrospective nature of the study.

Data on the study subjects were extracted from the Asan BiomedicaL research Environment (ABLE) system, which included demographic characteristics, baseline thromboembolic risks, and previous history of CAD, MI or revascularization. Baseline thromboembolic risk was calculated using the CHA_2DS_2-VASc scoring system.[3] MI was diagnosed based on the evidence of myocardial necrosis reflected by an elevation in the cardiac enzyme levels, combined with

[a]Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; and [b]Division of Biostatistics, Center for Medical Research and Information, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. Manuscript received October 17, 2018; revised manuscript received and accepted January 7, 2019.

[1]Min Soo Cho and Kyusup Lee contributed equally to this article.

See page 1291 for disclosure information.

*Corresponding author: Tel: +82-2-3010-3167; fax: +82-2-475-6898.
E-mail address: kjchoi@amc.seoul.kr (K.-J. Choi).

0002-9149/© 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjcard.2019.01.023

additional information regarding the patient's symptoms, electrocardiogram changes, and imaging evidences. The definition of MI was limited to type 1 of its third universal definition (spontaneous MI).[7] If a patient was diagnosed with MI at another center, a pathologic Q wave on electrocardiogram, myocardial scar, or akinesia on imaging study was required to confirm MI. CAD diagnosis was primarily based on imaging findings, either by CCTA or coronary artery angiography. CAD was defined as stenosis of ≥50% of major coronary arteries.[8–10]

The primary outcome was the incidence of new-onset ischemic stroke or systemic embolism during follow-up. Ischemic stroke was diagnosed primarily based on imaging findings and clinical presentations.[11] An ischemic stroke event was diagnosed by an independent neurologist blinded to the presence of CAD in patients. Systemic embolism was defined as a sudden loss of perfusion in a limb or organ, assessed using vascular imaging, ankle-brachial index, procedural findings, and laboratory findings along with clinical presentation.[12] The incidence of hemorrhagic stroke was assessed as a separate outcome.

Categorical variables are shown as frequencies with percentages, and continuous variables as median and interquartile range or mean and standard deviation. Categorical variables were compared using the chi-square test, and continuous variables were compared using analysis of variance with posthoc analysis with Tukey's method or Wilcoxon rank-sum test as appropriate. The Kaplan-Meier method was used to calculate the unadjusted event rates, which were then compared using log-rank test. The Cox proportional hazards model was used to assess the relative risk of each variable on study outcomes. Variables with clinical relevance or a p ≤0.1 in univariate analyses were included in the multivariable model. The proportional hazards assumption was tested by examining log [−log survival] curves and partial (Schoenfeld) residuals. We established a 3-step Cox proportional hazards model. (Model 1: unadjusted; Model 2: adjusted for components of the CHA_2DS_2-VASc score; Model 3: adjusted for CHA_2DS_2-VASc score, body mass index, and chronic kidney disease) The same procedure was repeated in the anticoagulation naïve patients for sensitivity analysis. All statistical analyses were performed using R software version 3.3.1. All p values were 2-sided, and p values <0.05 were considered statistically significant.

Results

Among the 20,889 AF patients treated at our center, 17,073 patients met inclusion and exclusion criteria (Figure 1), who were divided into 3 groups (MI-CAD, n = 708, 4.1%; non-MI-CAD, n = 1,011, 5.9%; control, n = 15,354, 90.0%). Baseline characteristics of the patients are summarized in Table 1. Non-MI-CAD and MI-CAD groups had higher age, prevalence of male sex, and prevalence of baseline co-morbidities. As such, the CHA_2DS_2-VASc scores tended to be higher in the non-MI-CAD and even higher in the MI-CAD than in control. Baseline echocardiography data showed that the MI-CAD group had larger left atrial and left ventricular (LV) diameters and lower LV ejection fraction (EF) compared with control. As for baseline medications, antiplatelets use without anticoagulant use was more prevalent in the MI or non-MI CAD groups compared with control. When the patients were divided by their baseline anticoagulation status, anticoagulation-naïve population showed lower prevalence of previous stroke, other co-morbidities, and lower CHA_2DS_2-VASc score (Supplementary Table).

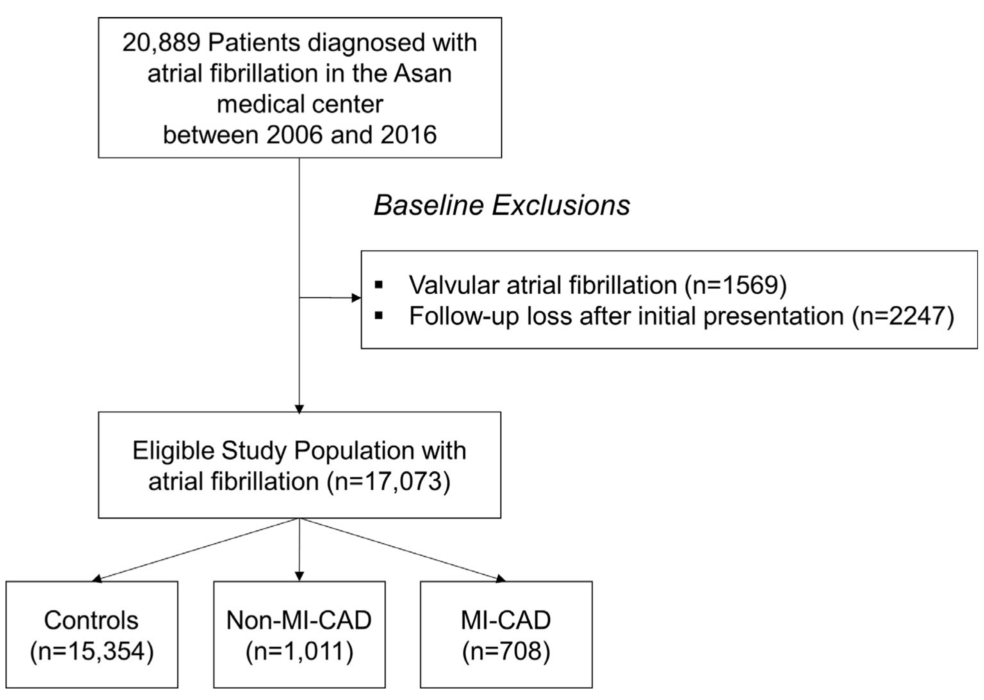

Figure 1. Flow diagram of the study.

Table 1
Baseline characteristics

Variables	Controls (n = 15,354)	MI-CAD No (n = 1,011)	MI-CAD Yes (n = 708)	p Value
Age (years)	63.8 ± 12.8	68.6 ± 9.4	71.1 ± 9.9	<0.001
Men	9,850 (64.2%)	721 (71.3%)	509 (71.9%)	<0.001
BMI (kg/m^{2})	24.3 ± 3.3	24.6 ± 3.2	24.0 ± 3.4	0.038
Hypertension	9,466 (61.7%)	856 (84.7%)	615 (86.9%)	<0.001
Diabetes mellitus	3,039 (19.8%)	405 (40.1%)	316 (44.6%)	<0.001
Previous stroke/TIA	1,558 (10.1%)	129 (12.8%)	146 (20.6%)	<0.001
Chronic lung disease	626 (4.1%)	54 (5.3%)	53 (7.5%)	<0.001
Chronic kidney disease	4,782 (32.9%)	451 (44.8%)	409 (58.1%)	<0.001
Vascular disease*	674 (4.4%)	118 (11.7%)	96 (13.6%)	<0.001
Congestive heart failure	2,090 (13.6%)	161 (15.9%)	231 (32.6%)	<0.001
CHA_2DS_2-VASC score	2.3 ± 1.5	2.8 ± 1.6	4.3 ± 1.6	<0.001
CHA_2DS_2-VASC score ≥2	10,084 (65.7%)	803 (79.4%)	686 (96.9%)	<0.001
$CHADS_2$ score	1.9 ± 1.3	2.4 ± 1.4	3.0 ± 1.5	<0.001
$CHADS_2$ score ≥2	8,439 (55.0%)	743 (73.5%)	589 (83.2%)	<0.001
HAS-BLED score	2.1 ± 1.3	3.5 ± 1.1	3.2 ± 1.2	<0.001
HAS-BLED score ≥3	5,879 (38.3%)	726 (71.8%)	573 (80.9%)	<0.001
Left atrial diameter (mm)	44.4 ± 9.6	45.4 ± 7.6	45.1 ± 8.0	<0.001
LV ejection fraction (%)	56.2 ± 11.2	55.1 ± 11.8	47.7 ± 14.1	<0.001
LV end-diastolic diameter (mm)	50.1 ± 7.4	50.6 ± 7.8	52.5 ± 8.5	<0.001
Anticoagulants	8,101 (52.8%)	594 (58.8%)	346 (48.9%)	<0.001
Aspirin	6,036 (39.3%)	821 (81.2%)	623 (88.0%)	<0.001
Plavix	1,276 (8.3%)	599 (59.2%)	450 (63.6%)	<0.001
Dual antiplatelet	1,003 (6.5%)	573 (56.7%)	432 (61.0%)	<0.001
Triple therapy	456 (3.0%)	251 (24.8%)	174 (24.6%)	<0.001
Combination therapy†	2,501 (16.3%)	403 (39.9%)	278 (39.3%)	<0.001
Beta-blocker	4,937 (32.2%)	590 (58.4%)	477 (67.4%)	<0.001
Calcium channel blocker	3,128 (20.4%)	503 (49.8%)	352 (49.7%)	<0.001
Digoxin	3,308 (21.5%)	226 (22.4%)	211 (29.8%)	<0.001
Amiodarone	943 (6.1%)	106 (10.5%)	104 (14.7%)	<0.001
Anti-arrhythmics‡	3,765 (24.5%)	148 (14.6%)	39 (5.5%)	<0.001

BMI = body mass index; LV = left ventricle.
* Peripheral artery disease or aortic plaque.
† Any combination of anticoagulants and antiplatelet agents.
‡ Antiarrhythmics other than amiodarone.

Of all patients without previous MI (n = 16,345), coronary imaging studies were conducted in 2,897 patients (17.7%, Table 2). Majority of imaging studies were performed for clinically diagnosing stable angina pectoris (81.8%, n = 2,370) and the remnant were for unstable angina (9.1%) or general health check-up (9.4%). CCTA (83.4%) was performed more frequently than coronary angiography (22.3%), and both modalities were performed in 5.7% of patients. In patients who underwent coronary imaging study, significant CAD was diagnosed in 1,011 (38.0%, Table 3). More than half of the patients had high-risk CAD, such as a multivessel disease (59.3%) or left main CAD (9.6%). Subsequently, half of the patients with significant non-MI-CAD underwent percutaneous coronary intervention and 15.4% underwent bypass grafting. Remaining 1/3 patients received medical treatment.

Table 2
Characteristics of patients without myocardial infarction who underwent coronary imaging evaluation (n = 2,897)

Variables	No (%)
Imaging study performed	
Coronary angiography	646 (22.3%)
Coronary computed tomographic angiography	2,415 (83.4%)
Obstructive coronary artery disease	
Presence	1,011 (38.0%)
Absence	1,886 (62.0%)
Indication for imaging study	
Unstable angina pectoris	265 (9.1%)
Stable angina pectoris	2,370 (81.8%)
General health check-up	262 (9.4%)

The crude incidence of subsequent ischemic stroke or systemic embolism following an NVAF diagnosis is depicted in Figure 2. Ischemic stroke or systemic embolism occurred in 1,007 (5.9%) patients during median a follow-up of 3.1 ± 2.4 years. MI-CAD group had the highest rate of thromboembolic events, followed by non-MI-CAD and control groups (Figure 2). The incidence of primary outcome was statistically higher in the non-MI-CAD group than that in the control group, and this trend was consistent even when analysis was confined to the anticoagulation-naive population (Figure 2). This result remained consistent when the analysis was confined to the imaging-confirmed cases in MI-CAD, non-MI-CAD, and control groups (Supplementary Figure 1). The incidence of

Table 3
Imaging characteristics of coronary artery disease in patients with atrial fibrillation without history or presentation of myocardial infarction (n = 1,011)

Variables	No (%)
No. of coronary arteries narrowed	
1	411 (40.7%)
2	267 (26.4%)
3	236 (23.3%)
Left main + 1	33 (3.3%)
Left main + 2	29 (2.9%)
Left main + 3	35 (3.5%)
Diagnosis	
Unstable angina pectoris	91 (9.0%)
Stable angina pectoris	880 (87.0%)
Asymptomatic coronary artery disease	40 (4.0%)
Management of coronary artery disease	
Bypass grafting*	156 (15.4%)
Stenting*	505 (50.0%)
Medication	356 (35.2%)

CAD = coronary artery disease.
* 6 patients underwent both stenting and bypass grafting.

hemorrhagic stroke event was higher in the MI-CAD group compared with the non-MI CAD or control groups, albeit without statistical significance (Supplemental Figure 2).

The relative risk of non-MI-CAD and MI-CAD in each multivariable mode is summarized in Table 4. Both groups were at higher risk of thromboembolic events in the unadjusted model. A higher risk was prevalent in patients with non-MI-CAD and MI-CAD in model 2, which adjusted for components of the CHA_2DS_2-VASc score, and model 3, which was adjusted for all clinically relevant factors. This trend of higher risk was consistent when analysis was confined to an anticoagulation naïve population.

When non-MI-CAD was regarded as a vascular disease, the proportion of patients with vascular score components increased from 8.8% (n = 1,500) to 14.0% (n = 2,393). Subsequently, the percentage of patients requiring anticoagulation therapy (CHA_2DS_2-VASc score ≥2 points) also increased from 67.8% (n = 11,573) to 68.6% (n = 11,713).

Discussion

The following is the major findings of the present study: (1) Non-MI-CAD was found to be more prevalent in a considerable proportion of patients with NVAF. (2) The patients with NVAF in the non-MI-CAD group were at a higher risk of subsequent thromboembolic events than patients in the control group and comparable to the MI-CAD group. (3) A higher embolic risk was consistent even after multivariable adjustment and in the subset of anticoagulation-naive patients. (4) Adding non-MI-CAD to the CHA_2DS_2-VASc scoring system increased the number of patients requiring anticoagulation.

The current scoring system did not include non-MI-CAD as a major component. The CHA_2DS_2-VASc score used from 2010 ESC guideline incorporates only MI-CAD as a component of vascular disease, and does not acknowledge non-MI-CAD.[3] Furthermore, non-MI-CAD is not included in the anticoagulation and risk factors in atrial fibrillation scoring model owing to the loss of statistical significance in the multivariable model.[13] Meanwhile, a modified CHA_2DS_2-VASc score, in which stable coronary disease was substituted for MI, showed excellent performance in Japanese patients.[14] In our opinion, this discrepancy might be related to the vague nature of symptom-based diagnosis, namely angina pectoris, which would inevitably be associated with many false-positive cases. Traditionally, only 1/10 of patients with angina pectoris have a true coronary lesion[15,16]; this was consistent with our data, as only 37% of clinically stable angina has true coronary lesions. Hence, we believe that the mere clinical presentation of angina pectoris or diagnosis code-based diagnosis of stable angina cannot determine anticoagulation therapy. However, different approaches should be used to reach an imaging-confirmed diagnosis of non-MI-CAD because these patients confirmed to have a significant burden of atherosclerosis. We thought that non-MI-CAD and MI-CAD should be managed in the same manner, since they share the common pathophysiology of progressive atherosclerosis in coronary artery. In our study, both groups of CAD patients were more commonly treated with dual antiplatelet or triple therapy than with standard anticoagulation therapy, which reflects the practice patterns before the introduction of

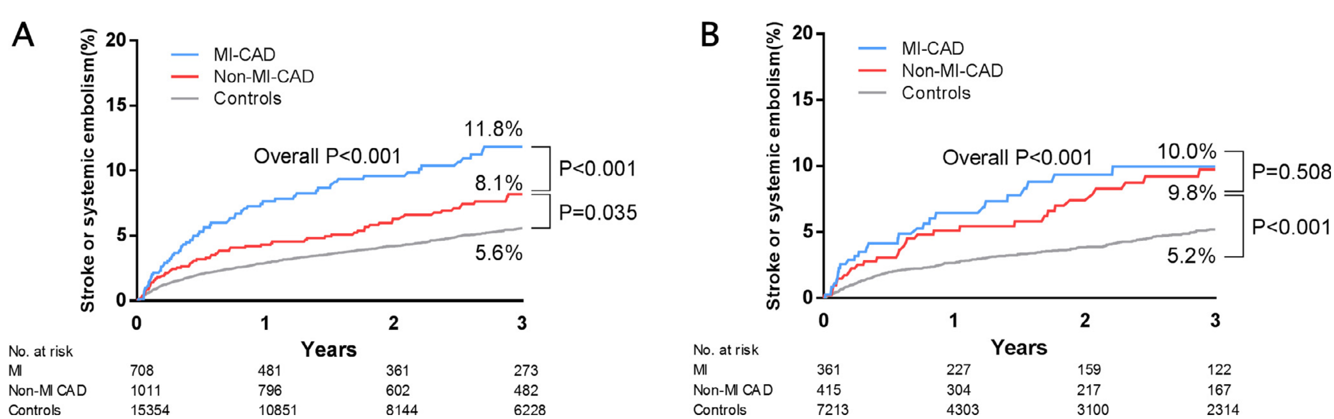

Figure 2. Incidence of ischemic stroke or systemic embolism in patients with myocardial infarction and nonmyocardial infarction coronary artery disease in the overall population (*A*) and anticoagulation-naive population (*B*).

Table 4
Predictive function of coronary artery disease on future embolic events

Variable	Non-MI-CAD HR	95% CI	p Value	MI-CAD HR	95% CI	p Value
Overall population (n = 17,073)						
Model 1: Unadjusted	1.55	1.25−1.91	<0.001	2.14	1.70−2.69	<0.001
Model 2: Adjusted for components of CHA_2DS_2-VASc score*	1.44	1.16−1.79	<0.001	1.69	1.33−2.14	<0.001
Model 3: Adjusted for relevant variables†	1.42	1.15−1.77	0.001	1.62	1.28−2.06	<0.001
Anticoagulation-naïve population (n = 8,032)						
Model 1: Unadjusted	1.59	1.19−2.12	0.002	2.63	1.93−3.59	<0.001
Model 2: Adjusted for components of CHA_2DS_2-VASc score*	1.56	1.07−2.26	0.019	1.58	1.12−2.24	0.010
Model 3: Adjusted for relevant variables†	1.46	1.01−2.13	0.044	1.58	1.12−2.24	0.010

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.
* Adjusted for age, sex, hypertension, congestive heart failure, diabetes, prior stroke or transient ischemic accident.
† Adjusted for age, sex, body mass index, hypertension, congestive heart failure, diabetes, prior stroke or transient ischemic accident, chronic kidney disease.

nonvitamin K antagonist oral anticoagulants, which were fully reimbursed in Korea since 2015. However, with the results of recent landmark trials such as PIONEER AF-PCI and RE-DUAL PCI, nonvitamin K antagonist oral anticoagulants have become the back-bone of the therapeutic strategy for AF and CAD.[17,18] The reproducibility of these trial results in clinical practice should be assessed in a large prospective registry-based study.

In our study, the discriminating performance of the CHA_2DS_2-VASc system was not enhanced upon addition of non-MI-CAD, which may be due to the small number of patients who were reclassified from low to high thromboembolic risk (n = 140, 0.8%). The clinical implication of the present study is relatively limited because non-MI-CAD or MI patients had other types of vascular disease and co-morbidities, thereby diluting the effect of non-MI-CAD. However, clinical relevance of risk stratification still prevails; for example, if the CHA_2DS_2-VASc score criteria were to be strictly applied on our registry data, underestimation of thromboembolic risk would occur in approximately 5.2% of the overall patients and 0.8% would not be indicated for anticoagulation. From a practical standpoint, if a patient is confirmed with CAD on imaging studies, a meticulous search for co-morbidities should be performed to avoid underestimation, and standard anticoagulation therapy should be actively considered in those with relatively low CHA_2DS_2-VASc scores (0−1).

The mechanism connecting obstructive CAD to thromboembolic risk in AF was partially explained in the following ways. Coronary atherosclerosis and thromboembolism in AF share risk factors such as age, hypertension, diabetes, heart failure, and metabolic syndrome,[19,20] which were suggested in the baseline characteristics of our data. Systemic inflammatory status of AF is associated with hypercoagulability as well as progression of atherosclerosis[21−23]; therefore, the risks of thromboembolic event and atherosclerosis may be closely interlinked in AF patients.[24] In our data, the MI-CAD group had a higher rate of thromboembolic events than did the non-MI-CAD group, which may be due to the higher number of baseline risk factors of the MI-CAD group, or the structural changes (lower LV EF or larger left atrial diameter) brought forth by MI. However, non-MI CAD still has clinical relevance, as evidenced by the fact that the adjusted hazard of non-MI-CAD was similar to that of MI-CAD and significantly higher than those of controls, and that non-MI-CAD shared common pathophysiology of progressive atherosclerosis with MI-CADs.[5] Therefore, our data supports the inclusion of all imaging-confirmed CADs rather than only including previous MIs into the risk stratification scheme. Considering the growing use of noninvasive coronary imaging studies, we suggest that risk stratification for those with confirmed non-MI CAD be included in future guidelines.

Our study is limited in that it was a retrospective review of a single-center registry, which carries the possibility of selection bias. Because coronary imaging was performed in 1/5 of the study population, subclinical CAD may have existed in patients who did not undergo coronary imaging. As the study period was over 10 years, indication for anticoagulation or antiplatelet went through changes over time. For the same reason, the preventive role of standard anticoagulation was difficult to be evaluated. The long study period also led to the relatively low prescription rate of anticoagulants in overall population.

In conclusion, non-MI-CAD should be considered an important predictor of thromboembolic events in patients with NVAF. These patients should be meticulously evaluated for unrecognized risk factors, and therapeutic interventions for stroke prevention should be warranted in these patients.

Disclosure

All the authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2019.01.023.

1. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324–2336.
2. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, de Vos AM, Pugliese F, Rensing B, Jukema JW, Bax JJ, Prokop M, Doevendans PA, Hunink MG, Krestin GP, de Feyter PJ. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135–2144.

3. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–272.
4. Fayad ZA, Fuster V. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res* 2001;89:305316.
5. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242–250.
6. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011;473:317–325.
7. Bax JJ, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581–1598.
8. Investigators BARI. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217–225.
9. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961–972.
10. Detre K, Hultgren H, Takaro T. Veterans administration cooperative study of surgery for coronary arterial occlusive disease: III. Methods and baseline characteristics, including experience with medical treatment. *Am J Cardiol* 1977;40:212–225.
11. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). *J Am Coll Cardiol* 2015;66:403–469.
12. Bekwelem W, Connolly SJ, Halperin JL, Adabag S, Duval S, Chrolavicius S, Pogue J, Ezekowitz MD, Eikelboom JW, Wallentin LG, Yusuf S, Hirsch AT. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation* 2015;132:796–803.
13. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;2:e000250.
14. Okumura K, Inoue H, Atarashi H, Yamashita T, Tomita H, Origasa H. J-RHYTHM Registry Investigators. Validation of CHA2DS2-VASc and HAS-BLED Scores in Japanese patients with nonvalvular atrial fibrillation. *Circ J* 2014;78:1593–1599.
15. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. *J Fam Pract* 1994;38:345–352.
16. Bosner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, Karatolios K, Schaefer JR, Seitz G, Baum E, Donner-Banzhoff N. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract* 2009;15:141–146.
17. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F, Wildgoose P, van Eickels M, Lip GY, Cohen M, Husted S. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *Am Heart J* 2015;169:472–478. e475.
18. Cannon CP, Bhatt DL, Oldgren J, Lip GY, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513–1524.
19. Davì G, Gresele P, Violi F, Basili S, Catalano M, Giammarresi C, Volpato R, Nenci GG, Ciabattoni G, Patrono C. Diabetes mellitus, hypercholesterolemia, and hypertension but not vascular disease per se are associated with persistent platelet activation in vivo. *Circulation* 1997;96:69–75.
20. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, Aizawa Y. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation* 2008;117:1255–1260.
21. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012;60:2263–2270.
22. Perri L, Pastori D, Pignatelli P, Violi F, Loffredo L. Flow-mediated dilation is associated with cardiovascular events in non-valvular atrial fibrillation patients. *Int J Cardiol* 2015;179:139–143.
23. Masanauskiene E, Naudziunas A. Comparison of ankle-brachial index in patients with and without atrial fibrillation. *Medicina (Kaunas)* 2011;47:641–645.
24. Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. *J Am Heart Assoc* 2016;5:e003347.