Pharmacotherapy for Patients with Atrial Fibrillation and Cerebral Microbleeds

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Background: Patients with cerebral microbleeds have increased risk of intracranial hemorrhage and ischemic stroke. No trial specifically informs antithrombotic therapy for patients with cerebral microbleeds and atrial fibrillation. We investigated the safety of anticoagulation versus no anticoagulation with regard to cerebrovascular outcomes and mortality. *Methods:* All consecutive atrial fibrillation patients from 2015 to 2018 with MRI evidence of ≥1 cerebral microbleed at time of imaging were reviewed. Patients were treated with warfarin, direct oral anticoagulants, or neither. Primary outcome was all-cause mortality informed by National Death Registry and the composite of ischemic and hemorrhagic stroke. All statistical tests were 2-sided and significant at $P < .05$. *Results:* The median interval from patient identification until the end of electronic health record surveillance was 9.93 months (interquartile range, 2.83-19.17 months). We identified 308 atrial fibrillation patients with cerebral microbleeds; 128(41.6%) were on warfarin, 88(28.6%) on direct oral anticoagulants, and 92(29.9%) on neither. Over the surveillance interval, 87 deaths, 51 ischemic strokes, and 14 hemorrhagic strokes occurred. The estimated likelihoods of the composite stroke outcome and ischemic stroke only did not differ significantly among the 3 groups. However, patients taking direct oral anticoagulants had a significantly smaller likelihood of all-cause mortality than patients who were not anticoagulated (adjusted hazard ratio: .44[.23, .83], P=.012). *Conclusions:* In patients with coprevalent atrial fibrillation and cerebral microbleeds, we did not detect differences in subsequent ischemic stroke, hemorrhagic stroke, or both, comparing warfarin, direct oral anticoagulants, or neither. Patients treated with direct oral anticoagulants had better survival than nonanticoagulated patients.

Key Words: Cerebral microbleed—atrial fibrillation—anticoagulation—stroke—DOAC—warfarin

Introduction

Cerebral microbleeds (CMBs) are round or ovoid areas of signal void detected on brain MRI with associated blooming on hemosiderin-sensitive sequences (T2*-weighted gradient echo and susceptibility-weighted imaging) with at least half of the lesion surrounded by brain parenchyma.[1,2] Pathologically, they correspond to focal clusters of hemosiderin-laden macrophages in the perivascular space thought to be due to leakage from small vessel damage.[2] CMBs are also recognized as a biomarker for cerebral small vessel disease (CSVD) with 2 major subtypes distinguished by their corresponding spatial distributions: hypertensive microangiopathy (deep CMBs) and cerebral amyloid angiopathy (CAA) (lobar CMBs).[3]

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CMB prevalence increases with age, ranging from 6.5% in patients 45-50 years to 35.7% in patients 80 years and older.[4] Other significant risk factors for CMBs include arterial hypertension, atrial fibrillation (AF), and obstructive sleep apnea.[5] Clinically, CMBs are associated with increased risk of hemorrhagic and ischemic stroke.[6,7]

AF is the most common sustained cardiac arrhythmia and an independent risk factor for ischemic stroke. The CHA_2DS_2-VASc score is a validated risk stratification tool that predicts yearly stroke risk in patients with AF based on readily available clinical variables.[8] Current guidelines suggest that patients with CHA_2DS_2-VASc score greater than or equal to 2 should be anticoagulated with a vitamin K antagonist or a direct oral anticoagulant (DOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban), to achieve optimal risk reduction (relative risk reduction = 60%).[9,10] The validated HAS-BLED score (range, 0-9) has been used to predict the risk of major hemorrhage with oral anticoagulation.[11] A HAS-BLED score of greater than or equal to 3 is associated with increased risk of bleeding,[10] but has not been incorporated into guidelines.[11] Additionally, the presence of CMBs in patients with AF has been shown to increase the risk of all-cause mortality, and intracerebral hemorrhage independent of HAS-BLED score.[12-14] We sought to investigate the safety of anticoagulation in AF patients with CMBs by comparing the outcomes of ischemic stroke, hemorrhagic stroke, and mortality in patients anticoagulated (with warfarin, or DOACs) and those not anticoagulated.

Methods

This study used deidentified patient data, and the protocol was approved by the Mayo Clinic Institutional Review Board.

Study Design and Eligibility Criteria

We conducted a retrospective study using clinical data from electronic health records (EHR) at Mayo Clinic Florida. We included all inpatients and outpatients aged greater than or equal to 18 documented to have newly diagnosed or chronic AF and at least one CMB on the latest brain MRI performed at or after AF diagnosis.

Patient Selection

We used a clinical data repository tool called the Advanced Cohort Explorer (ACE) supported by the Unified Data Platform[15] which is a Mayo Clinic-implemented data warehouse that normalizes and consolidates data from 3 Mayo Clinic campuses in Phoenix, AZ; Rochester, MN; and Jacksonville, FL. Integrated data from Unified Data Platform is accessed using ACE, a data finding software, containing patient demographics, diagnoses, procedures, laboratory flow sheets, clinical notes, radiology notes, and pathology reports with the ability to search via text-based queries.[16]

ACE was used to identify adult patients from February 2015 to May 2018 using the following keywords and acronyms in various conjunction and disjunction combinations: AF, atrial fibrillation, nonvalvular atrial fibrillation or NVAF, MR brain or brain magnetic resonance imaging. In radiology reports we searched for the terms: CMB, cerebral microbleeds, microbleed, microhemorrhage, cerebral microhemorrhage, hemosiderosis, and petechial hemorrhage in the radiology reports. All identified MRIs were then reviewed individually to exclude patients who had CMB mimics.[17] Our final patient cohort consisted of 308 patients (Fig 1) with concurrent newly diagnosed or chronic AF plus CMB. Patients with a date of last follow-up before their composite AF and CMB date were excluded.

Baseline Clinical Data

We abstracted the following data prior to the date of the composite AF and CMB date: demographic characteristics, vascular risk factors, uncommon CMB risk factors (infective endocarditis and obstructive sleep apnea),[5] and AF-related treatments (antiplatelets, anticoagulants [DOACs, warfarin], and left-atrial appendage device [LAAD]). CHA_2DS_2-VASc and HAS-BLED scores were calculated for each patient; and whether they satisfied the modified Boston criteria for probable CAA.[1]

Baseline MRI Assessment

All MRI images were independently read by 2 trained investigators (M.K.B., G.K.V.), and CMBs were identified using the recommended criteria.[1] The identified CMBs were counted and scored in lobar, deep, and infratentorial regions using standardized definitions (Microbleed Anatomical Rating Scale).[1,12,17] We also captured the magnetic field strength, the MRI sequence (either susceptibility-weighted imaging or gradient echo), and the presence of a focal area of restricted diffusion consistent with acute cerebral infarction. They were then independently reviewed by a neuroradiologist (V.G.) with more than 10 years of experience, blinded to clinical and outcome data.

Outcomes

The primary outcome was a composite of ischemic stroke (defined by imaging findings of cerebral infarction with corresponding focal symptoms) and hemorrhagic stroke (defined as nontraumatic intracerebral hemorrhage identified on brain imaging) reported after the date of composite AF and CMB diagnosis, extracted from the EHR using international classification of diseases (ICD)-9, ICD-10 and medicare health identification codes (HICs), and all-cause mortality from the US National Death

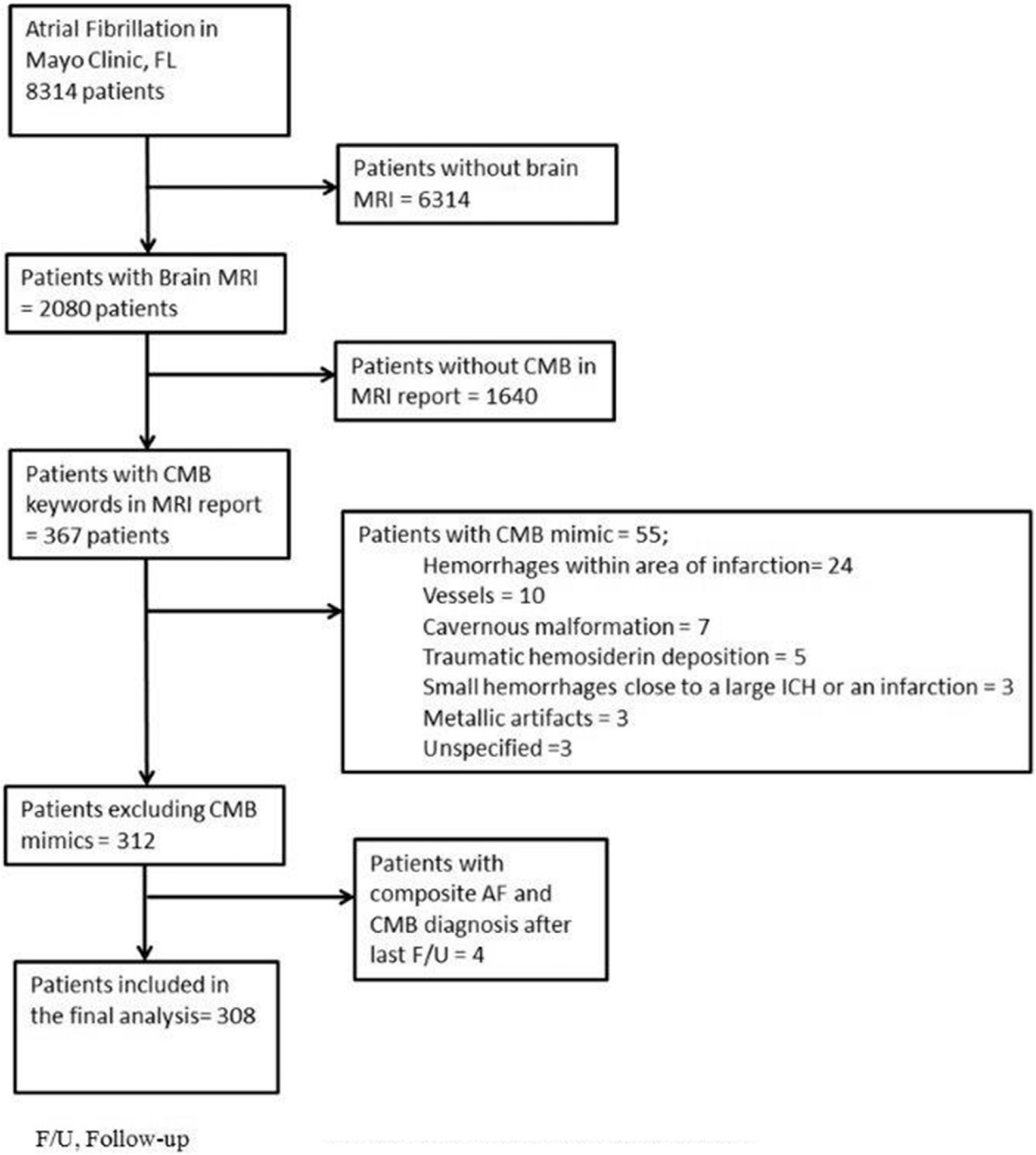

Figure 1. *Flowchart of patient selection.*

Registry until May 30, 2018. We then validated each outcome individually through EHR after the date of the composite AF and CMB diagnosis.

Statistical Analysis

The median and range were used to summarize continuous characteristics, and the frequency and percent were used to summarize categorical characteristics. The Wilcoxon Rank Sum test was used to compare continuous characteristics, and the chi-square test was used to compare proportion differences among anticoagulated patients (warfarin and DOAC). The median time interval from patient identification until the end of medical record surveillance was approximately 9.9 months with an interquartile range of about 2.4-19.2 months. Overall outcome

rates were estimated using the Kaplan-Meier method. To address the outcomes, likelihood of the composite outcome and all-cause mortality were evaluated using unadjusted (single variable) and adjusted (multivariable) Cox Proportional Hazard models.

To reduce possibility of confounding with a limited number of events, characteristics were first considered for adjustment if they were different between anticoagulation groups with $P \leq .05$. Of those, if the characteristics were further associated with the outcome of interest with $P \leq .05$, they were adjusted for in the final models. Multivariable model adjustments for the composite outcome of ischemic and hemorrhagic stroke include MRI sequence, vascular disease, and Labile international normalized ratio.

Adjustments for all-cause mortality involve the CHA_2DS_2-VASc score, serum bilirubin (≥2 times the normal), and Labile international normalized ratio. Ischemic stroke multivariable models were adjusted for vascular disease and MRI sequence. Hazard ratios (HR) and their 95% confidence intervals (CI) were estimated. All tests were 2-sided and performed at the .05 significance level.

Results

From February 2015 to May 2018, we identified 367 patients with AF and greater than or equal to 1 CMB reported in their MRI. We excluded 55 patients with CMB mimics, and 4 patients who had a composite date after their last hospital follow-up. The final cohort used for analysis included 308 patients (Fig 1).

Table 1 describes the baseline characteristics of the study population at the composite AF and CMB diagnosis date. The median age was 76 years (range, 31.8-96.4), 64.9% (200/308) were males and 32.5% (100/308) had greater than or equal to 5 CMBs. Regarding anticoagulant use, 29.9% (92/308) were not on any anticoagulant, whereas, of the 70.1% (216/308) on anticoagulant therapy, 41.6% (128/308) were on warfarin and 28.6% (88/308) were on DOACs. Those not on any anticoagulant were younger (73.9 years [range, 40.6-94.4]) compared to those on warfarin or DOACs (77.3 years [range 34.1, 94.8] and 75.5 years [range, 31.8-96.4], respectively). Of the 308 patients in our cohort, 88.9 % (274/308) had no change in their anticoagulation status over the observation period. From the time of MRI, 42.8% (9/21) of patients taking warfarin stopped all anticoagulants and 52.4% (11/21) started a DOAC over the period of observation. Figure 2A shows the distribution of the timing of the changes from warfarin. From the time of MRI, 7.6% (1/13) of patients taking DOAC stopped all anticoagulants and 7.6% (1/13) started warfarin over the period of observation. Figure 2B shows the distribution of the timing of the changes from DOACs. The median CHA_2DS_2-VASc score was 6 (range, 2-9) (Table I in the Supplement) and median HAS-BLED score was 5 (range, 1-8) (Table II in the Supplement). Despite having a CHA_2DS_2-VASc score of greater than or equal to 2, a third of our study population (92/308) were not on anticoagulants; for that group, the median CHA_2DS_2-VASc and HAS-BLED scores were significantly lower when compared to those anticoagulated ($P < .001$; Table 1).

Additionally, of the 68.2% (210/308) on antiplatelet therapy, 66.9% (206/308) were on aspirin and 17.2% (53/308) were on clopidogrel (Table 1). A total of .6% (2/308) of patients was treated with a LAAD. In addition, we identified 53.2% (164/308) who satisfied the modified Boston criteria for probable CAA diagnosis (Table 1).

In our cohort, indications for brain MRI included: evaluation for stroke (38.6% [119/308]) and evaluation for tumor (14.6% [45/308]) (Table III in the Supplement). Regarding CMB distribution, 84% (259/308) of patients had greater than or equal to 1 CMB in a lobar distribution; 26.9% (83/308) had greater than or equal to 1 CMB in a deep distribution; and 47.7% (147/308) had greater than or equal to 1 CMB in a lobar distribution. (Table 2). A subset of patients with acute cerebral infarction at the time of the composite diagnosis (52/308) had a prevalence of lobar, deep and infratentorial CMBs of 90.4% (47/52), 30.8% (16/52), and 42.3% (22/52), respectively.

Over the surveillance period, 51 ischemic strokes, 14 hemorrhagic strokes, and 87 deaths occurred. The differences in the composite outcome of ischemic stroke and hemorrhagic stroke were not significant when comparing the warfarin group or DOAC group with patients who were not anticoagulated (HR .64, CI 95% .36-1.13, $P = .13$, and HR .75, CI 95% .40-1.40, $P = .36$, respectively) as seen in Table 3 (Figure I in the Supplement). Correspondingly, the difference in the ischemic stroke outcome between anticoagulated and nonanticoagulated groups was not significant (HR .65, CI 95% .34-1.27, $P = .21$, and HR .96, CI 95% .49-1.91, $P = .91$, for warfarin and DOAC, respectively) (Table IV in the Supplement).

There was no significant difference in all-cause mortality between patients on warfarin and nonanticoagulated patients (HR .67, 95% CI .42, 1.06, $P = .086$). However, all-cause mortality was significantly lower for patients treated with DOACs compared to that of nonanticoagulated patients in single variable analysis (HR .41, 95% CI .22-.77, $P = .005$). This difference in all-cause mortality was also detected by the multivariable analysis (HR .44, 95% CI .23, .83, $P = .012$) as shown in Table 4 (Fig 3A). CMB burden did not independently affect all-cause mortality (HR 1.23 [95% CI .79, 1.90], $P = .36$) (Fig 3B) (Table V in the Supplement).

Discussion

Our retrospective single-center study of AF patients with CMB shows that a third of the study population was not on any anticoagulant despite having a CHA_2DS_2-VASc greater than or equal to 2, median score of 5 (range,

Table 1. *Demographic and clinical characteristics for the cohort overall and by anticoagulation therapy*

	All patients (n = 308)	No anticoagulant (n = 92)	Warfarin (n = 128)	DOAC (n = 88)	All groups *P* value	None vs anticoagulation *P* value
Demographics						
Age, years	76 (31.8, 96.4)	73.9 (40.6, 94.4)	77.3 (34.1, 94.8)	75.5 (31.8, 96.4)	.036	.032
Sex, male	200 (64.9)	59 (64.1)	88 (68.8)	53 (60.2)	.43	.85
Ethnicity, Hispanic	2 (.7)	1 (1.1)	0 (.0)	1 (1.1)	.49	.54
Race					.66	.63
White	280 (91.8)	85 (92.4)	113 (89.7)	82 (94.3)		
Black or African American	18 (5.9)	6 (6.5)	9 (7.1)	3 (3.4)		
Other	7 (2.3)	1 (1.1)	4 (3.2)	2 (2.3)		
Risk of thromboembolism						
CHA_2DS_2-Vasc score	6 (2, 9)	5 (2, 9)	6 (2, 9)	6 (2, 9)	.001	<.001
Risk of bleeding						
HAS-BLED score	5 (1, 8)	4 (2, 7)	5 (2, 8)	5 (1, 8)	<.001	<.001
Medication						
Antiplatelet use	210 (68.2)	56 (60.9)	92 (71.9)	62 (70.5)	.19	.072
Aspirin	206 (66.9)	53 (57.6)	91 (71.1)	62 (70.5)	.078	.024
Clopidogrel	53 (17.2)	16 (17.4)	20 (15.6)	17 (19.3)	.78	.96
Aspirin and clopidogrel	51 (16.6)	15 (16.3)	20 (15.6)	16 (18.2)	.88	.94
Statin use	213 (69.2)	52 (56.5)	99 (77.3)	62 (70.5)	.004	.002
Smoking status					.036	.006
Current	13 (4.2)	9 (9.8)	3 (2.3)	1 (1.1)		
Former	156 (50.6)	43 (46.7)	67 (52.3)	46 (52.3)		
Pack-years	20.8 (1, 110)	25 (2.5, 82)	23 (2, 110)	15 (1, 68)	.22	.88
Medical history						
Hypertension	267 (86.7)	78 (84.8)	116 (90.6)	73 (83.0)	.22	.52
Congestive Heart Failure	120 (39.0)	25 (27.2)	60 (46.9)	35 (39.8)	.012	.006
Diabetes mellitus	170 (55.2)	43 (46.7)	77 (60.2)	50 (56.8)	.13	.051
Hyperlipidemia	223 (72.4)	63 (68.5)	100 (78.1)	60 (68.2)	.17	.32
Vascular disease	251 (81.5)	64 (69.6)	112 (87.5)	75 (85.2)	.002	<.001
Stroke/TIA	131 (42.5)	33 (35.9)	59 (46.1)	39 (44.3)	.29	.12
Obstructive sleep apnea	99 (32.1)	19 (20.7)	41 (32.0)	39 (44.3)	.003	.005
History of bleeding	36 (11.7)	8 (8.7)	19 (14.8)	9 (10.2)	.33	.29
Labile INR	72 (23.4)	2 (2.2)	56 (43.8)	14 (15.9)	<.001	<.001
Bilirubin	36 (11.7)	14 (15.2)	18 (14.1)	4 (4.5)	.046	.21
CSS presence	20 (6.5)	10 (10.9)	7 (5.5)	3 (3.4)	.11	.042
Probable CAA*	164 (53.2)	48 (52.2)	72 (56.2)	44 (50.0)	.64	.81

(*Continued*)

Table 1 (*Continued*)

	All patients (n = 308)	No anticoagulant (n = 92)	Warfarin (n = 128)	DOAC (n = 88)	All groups *P* value	None vs anticoagulation *P* value
MRI characteristics						
Sequence, SWI	234 (76.0)	74 (80.4)	87 (68.0)	73 (83.0)	.02	.23
Strength, 1.5 T	275 (89.3)	88 (95.6)	117 (91.4)	70 (79.5)	.001	.018
Cerebral microbleeds						
Greater than or equal to 5	100 (32.5)	27 (29.3)	45 (35.2)	28 (31.8)	.66	.45

Abbreviations: CAA, cerebral amyloid angiopathy; cSS, cortical superficial siderosis; DOAC, direct oral anticoagulant; INR, international normalized ratio; T, tesla;TIA, transient ischemic attack. The sample median (minimum, maximum) is given for continuous variables. *P* values result from a chi-square test or a Wilcoxon rank sum test. Two patients chose not to disclose race and one patient's race was unknown. Two patients chose not to disclose ethnicity and one patient's ethnicity is unknown. All tests were 2-sided and performed at the .05 significance level.
*Calculated using modified Boston criteria for probable CAA.

2-9). Although we found no evidence for an adverse effect on cerebrovascular outcomes in this population, the use of DOACs in the anticoagulated group was associated with a significant reduction in all-cause mortality compared to all-cause mortality in the nonanticoagulated group. Our results are consistent with recent meta-analyses of trials comparing warfarin versus DOACs.[18,19]

Current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend the use of anticoagulants for AF patients with a CHA_2DS_2-VASc score greater than or equal to 2.[10] This recommendation, however, does not take into account the presence of CMBs. Moreover, it is uncertain if CMB presence influenced the decision to anticoagulate or influenced the choice of anticoagulant in this population, as suggested in the recent CROMIS-2 study.[12] There is a growing body of evidence advising caution when deciding to anticoagulate AF patients with CMBs.[20] Expert opinion favors individualizing anticoagulation decisions by considering the patient as a whole.[21,22]

Anticoagulated patients did not have better neurological outcomes than the third of patients that were not treated with any anticoagulant. One can speculate that HAS-BLED scores played a role in the decision to not anticoagulate. Indeed, it has been suggested that there is a misuse of bleeding risk scores to withhold anticoagulants despite higher net clinical benefit compared to risk.[23,24] We compared treatment groups after controlling for CHA_2DS_2-VASc and HAS-BLED scores, implying that there may be no reason to withhold anticoagulant therapy in this patient population.

Our study has some important strengths. We studied a relatively well-defined sample of patients with a composite CMB and AF diagnosis after ruling out CMB mimics. We analyzed both for baseline thrombo-embolic risk and bleeding risk profiles using the CHA_2DS_2-VASc score and HAS-BLED scores, respectively, to study comparable risk groups. We also accounted for technical confounders that influence CMB detection, like MRI magnetic field strength, and blood-sensitive sequences, which is novel in our study.

We also acknowledge study limitations. First, the retrospective nature of the study introduces possible selection bias, which may limit the generalizability of our data to all AF patients with CMBs. Second, the composite date of diagnosis was considered the latest date of MRI as recorded in the EHR; however, it is plausible that a number of outside brain imaging studies were not documented. We attempted to address this by including all outside studies interpreted in our institution. Third, the data on composite outcomes have been abstracted from a database from a single institution, potentially underreporting the actual number of outcomes. Fourth, all-cause mortality was assessed using national death registry, as opposed to EHR review for abstracting ischemic stroke and hemorrhagic stroke outcomes. It is possible that patients

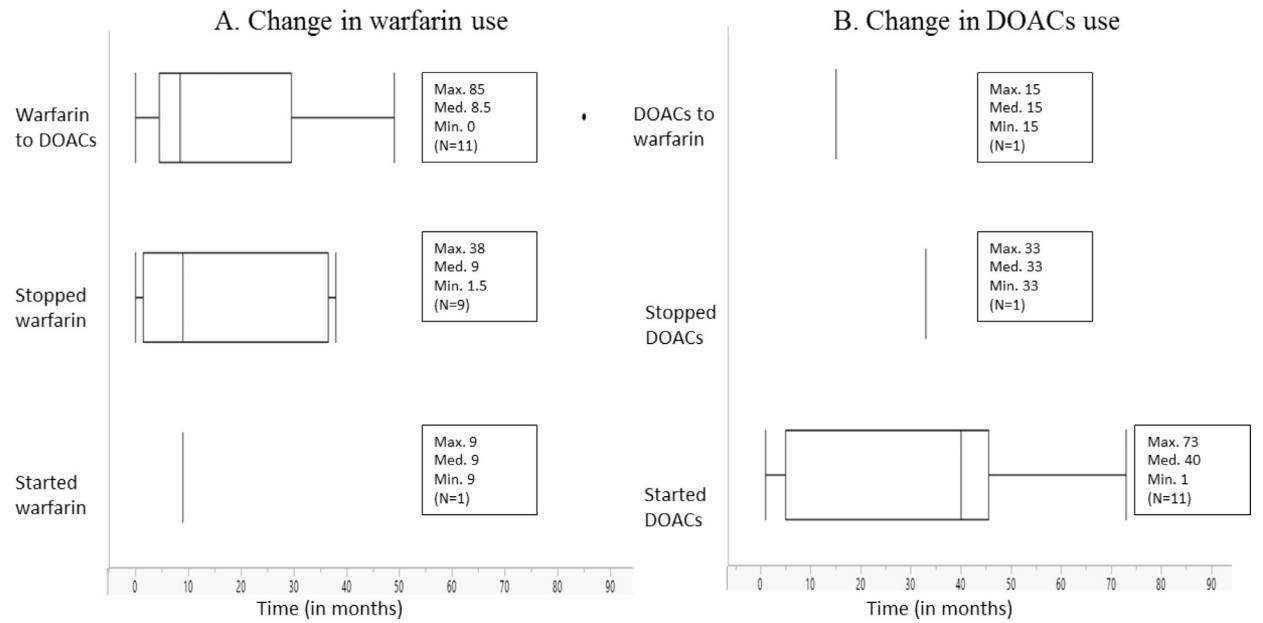

Figure 2. *Change in anticoagulation from time of MRI to last clinical follow-up. Changes in anticoagulation use at and following baseline brain MRI. (A) Shows the distribution of the timing of changes in the use of warfarin during the period of observation following baseline MRI. (B) Shows the distribution of the timing of changes in the use of DOACs during the period of observation from baseline MRI. Abbreviations: DOAC, direct oral anticoagulant; MRI, magnetic resonance imaging.*

could have had fatal ischemic or hemorrhagic stroke outside the institution and not available in the institutional EHR, which could possibly explain the apparent lack of association between DOACs and stroke outcomes. Fifth, analysis on LAAD is lacking due to the very low number of LAAD-treated patients.

Table 2. *Regional and structural distribution of cerebral microbleeds and MRI field strength and sequence for all the patients and by acute cerebral infarction status (presence of a focal area of restricted diffusion on brain MRI)*

	All patients (n = 308)	Patients without acute cerebral infarction (n = 256)	Patients with acute cerebral infarction (n = 52)	*P* value
Presence of CMBs by region − n (%)				
Lobar	259 (84.1)	212 (82.8)	47 (90.4)	.17
Deep	83 (26.9)	67 (26.2)	16 (30.8)	.50
Infratentorial	147 (47.7)	125 (48.8)	22 (42.3)	.39
Presence of CMBs by structure − n (%)				
Frontal	150 (48.7)	124 (48.4)	26 (50.0)	.84
Temporal	99 (32.1)	81 (31.6)	18 (34.6)	.68
Parietal	127 (41.2)	105 (41.0)	22 (42.3)	.86
Occipital	106 (34.4)	82 (32.0)	24 (46.2)	.051
Insular	7 (2.3)	5 (2.0)	2 (3.8)	.40
Thalamus	40 (13.0)	29 (11.3)	11 (21.2)	.06
Basal ganglia	24 (7.8)	21 (8.2)	3 (5.8)	.55
Corpus callosum	0 (0)	0 (0)	0 (0)	1.00
Internal capsule	9 (2.9)	8 (3.1)	1 (1.9)	.64
Cerebellum	124 (40.3)	106 (41.4)	18 (34.6)	.36
Brainstem	40 (13.0)	30 (11.7)	10 (19.2)	.14
MRI field strength - n (%)				
1.5T	275 (89.3)	226 (88.3)	49 (94.2)	.21
3T	33 (10.7)	30 (11.7)	3 (5.8)	
MRI sequence − n (%)				.60
GRE	74 (24.0)	63 (24.6)	11 (21.2)	
SWI	234 (76.0)	193 (75.4)	41 (78.8)	

DWI, diffusion-weighted imaging; GRE, gradient-echo; SWI, susceptibility-weighted imaging; T, tesla.

Table 3. *The effect of anticoagulant treatment on the composite outcome of hemorrhagic stroke and ischemic stroke in all patients*

Anticoagulant treatment	N (%)	Single variable		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
No anticoagulants	23 (25.0)	Reference	N/A	Reference	N/A
Anticoagulants (Warfarin or DOAC)	41 (19.0)	.68 (.41, 1.13)	.14	.92 (.53, 1.60)	.78
Warfarin	24 (18.8)	.64 (.36, 1.13)	.13	.98 (.52, 1.84)	.94
DOAC	17 (19.3)	.75 (.40, 1.40)	.36	.88 (.46, 1.66)	.68

Abbreviations: CI, confidence interval; N/A, not applicable.

Hazard ratios (HR) are interpreted as increase in likelihood. Multivariable analysis is adjusted for CHA_2DS_2Vasc score, Bilirubin, and Labile INR. All tests were 2-sided and performed at the .05 significance level.

Table 4. *The effect of anticoagulant treatment on all-cause mortality in all patients*

Anticoagulant treatment	N (%)	Single variable		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
No anticoagulants	33 (35.9)	Reference	N/A	Reference	N/A
Anticoagulants (Warfarin or DOAC)	54 (25.0)	.57 (.37, .88)	.012	.61 (.38, .98)	.041
Warfarin	40 (31.2)	.67 (.42, 1.06)	.086	.74 (.44, 1.24)	.25
DOAC	14 (15.9)	.41 (.22, .77)	.005	.44 (.23, .83)	.012

Abbreviations: CI, confidence interval; N/A, not applicable.

Hazard ratios (HR) are interpreted as increase in likelihood. Multivariable analysis is adjusted for CHA_2DS_2Vasc score, Bilirubin, and Labile INR. All tests were 2-sided and performed at the .05 significance level.

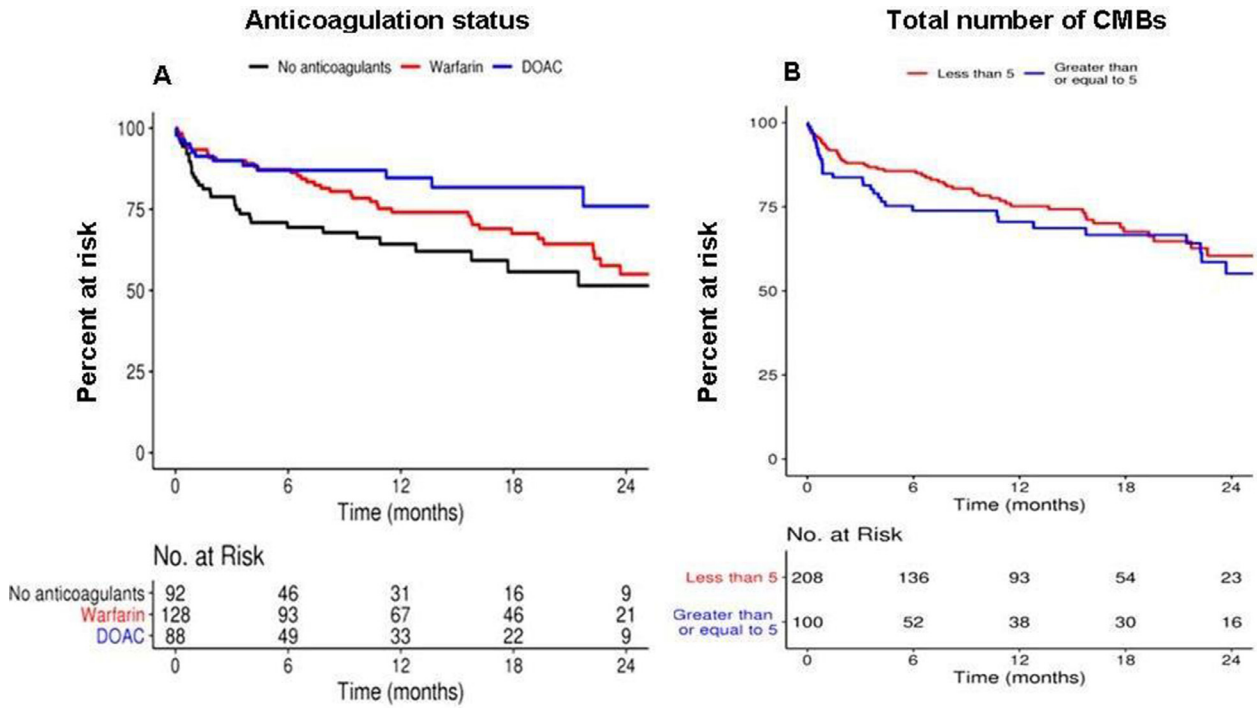

Figure 3. *The effect of anticoagulant treatment and CMB burden on all-cause mortality in all patients. Abbreviation: CMB, cerebral microbleeds.*

Conclusions

The effect of CMBs in therapeutic decisions for stroke prevention in AF remains uncertain, and evidence-based guidelines are not available. Although physicians may be dissuaded from using anticoagulants in patients with AF and CMB the observed reduction in all-cause mortality with the use of DOACs deserves further study in other populations.

Authors' Contributions

Drs. Badi and Vilanilam contributed equally to the study, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Badi, Vilanilam, Gupta, Barrett, Brott, Meschia.

Acquisition, analysis, or interpretation of data: Badi, Vilanilam, Gupta, Lesser, Cochuyt, Hodge, Meschia.

Drafting of the manuscript: Badi, Vilanilam, Barrett, Brott, Meschia.

Critical revision of the manuscript for important intellectual content: Badi, Vilanilam, Gupta, Barrett, Lesser, Hodge, Brott, Meschia.

Statistical analysis: Badi, Vilanilam, Lesser, Cochuyt, Hodge.

Disclosures

The authors have no conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.027.

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