RESEARCH ARTICLE

Impact of Cerebral Microbleeds in Stroke Patients with Atrial Fibrillation

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Objectives: Cerebral microbleeds are associated with the risks of ischemic stroke and intracranial hemorrhage, causing clinical dilemmas for antithrombotic treatment decisions. We aimed to evaluate the risks of intracranial hemorrhage and ischemic stroke associated with microbleeds in patients with atrial fibrillation treated with vitamin K antagonists, direct oral anticoagulants, antiplatelets, and combination therapy (i.e. concurrent oral anticoagulant and antiplatelet).
Methods: We included patients with documented atrial fibrillation from the pooled individual patient data analysis by the Microbleeds International Collaborative Network. Risks of subsequent intracranial hemorrhage and ischemic stroke were compared between patients with and without microbleeds, stratified by antithrombotic use.
Results: A total of 7,839 patients were included. The presence of microbleeds was associated with an increased relative risk of intracranial hemorrhage (adjusted hazard ratio [aHR] = 2.74, 95% confidence interval = 1.76–4.26) and ischemic stroke (aHR = 1.29, 95% confidence interval = 1.04–1.59). For the entire cohort, the absolute incidence of ischemic stroke was higher than intracranial hemorrhage regardless of microbleed burden. However, for the subgroup of patients taking combination of anticoagulant and antiplatelet therapy, the absolute risk of intracranial hemorrhage exceeded that of ischemic stroke in those with 2 to 4 microbleeds (25 vs 12 per 1,000 patient-years) and ≥ 11 microbleeds (94 vs 48 per 1,000 patient-years).
Interpretation: Patients with atrial fibrillation and high burden of microbleeds receiving combination therapy have a tendency of higher rate of intracranial hemorrhage than ischemic stroke, with potential for net harm. Further studies are needed to help optimize stroke preventive strategies in this high-risk group.

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Stroke prevention with oral anticoagulants is the mainstay of treatment for patients with atrial fibrillation (AF). Treatment decisions require carefully balancing the benefit in reduction of ischemic stroke (IS) versus the potential increase in risk of intracranial hemorrhage (ICH) associated with antithrombotic drugs. As the risk of ICH remains the most serious complication of anticoagulation, a number of clinical risk scores have been developed to aid risk prediction for bleeding in patients with AF, for instance, HEMORR$_2$AGES, ATRIA, ORBIT, and HASBLED.[1] Unfortunately, these scores have only moderate performance in predicting ICH and none could reliably discriminate patients at net risk of ICH than IS.[1–4]

In recent years, cerebral microbleeds (CMBs) have evolved to be a useful radiological marker which improves risk prediction for ICH. As part of the spectrum of small vessel disease, CMBs are dot-like hypointense signals detected by heme-sensitive magnetic resonance imaging (MRI) sequences (eg, T2*gradient-echo or susceptibility-weighted imaging [SWI]).[5,6] They are perivascular hemosiderin deposits indicating previous asymptomatic leakage from bleeding-prone microangiopathy. Deep CMBs are commonly associated with hypertensive arteriopathy, whereas pure lobar CMBs are classically associated with cerebral amyloid angiopathy (CAA), which has 4-fold increased risk of warfarin-associated ICH.[7,8] Several studies have shown that the addition of this biomarker to conventional clinical risk scores could improve the predictive value of ICH.[9–13]

To help individualize antithrombotic decision among patients with CMBs, a large-scale global pooled individual patient data analysis was performed by the Microbleeds International Collaborative Network (MICON) which included 20,322 participants from 38 cohorts with previous IS or transient ischemic attack and baseline CMB evaluation.[14] The burden of CMBs was found to have stronger associations with subsequent ICH than IS. However, as the absolute rate of IS was consistently higher than that of ICH irrespective of CMB burden and distribution, withholding antithrombotics routinely for all patients with CMBs is therefore not justified. In this study, the analysis was performed irrespective of stroke subtypes involved in the index event. It remains uncertain if variation in risk-to-benefit ratio may exist among patients with different stroke etiologies and antithrombotic therapies, particularly patients with AF on anticoagulants, which may have a higher risk of ICH than antiplatelets,[15] but better efficacy in prevention of IS.[16]

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We performed a subanalysis among patients with AF from the MICON cohort. We aimed to evaluate the risks of subsequent ICH and IS associated with CMBs among patients with AF, and stratify the stroke risks by 4 antithrombotic treatments: (1) vitamin K antagonist (VKA); (2) direct oral anticoagulants (DOACs); (3) antiplatelets (single or dual agents); and (4) combination therapy (i.e. concurrent oral anticoagulant and antiplatelet drugs).

Methodology

Study Design

The MICON cohort consists of patients from 18 countries in North America, Europe, the Middle East, Asia, and Australia. Inclusion criteria of the MICON collaboration were cohorts with (i) prospectively recruited adult participants with IS or transient ischemic attack, (ii) documented number and anatomical distribution of CMBs evaluated by MRI T2* or SWI, (iii) collected data on outcome events, including IS, ICH, vascular, and non-vascular death, and (iv) a follow-up period of at least 3 months.[14] In this subanalysis, we included 37 cohorts who agreed to participate. We included patients with known or newly diagnosed AF. Patients who had unknown status for AF were excluded.

The MICON project was approved by the Health Research Authority of the UK (REC reference: 8/HRA/0188). Included cohorts obtained ethical and regulatory approvals according to local requirements. As this study involved only fully anonymized data which have been published, individual consent was not required for this subanalysis. The MICON study protocol is registered on PROSPERO, CRD42016036602.

Outcome Parameters

The primary outcomes were subsequent time to ICH alone and IS alone; and the secondary outcome was time to vascular death. All events were adjudicated according to individual cohort protocols. ICH was confirmed radiologically and included ICH, subdural, and subarachnoid hemorrhage. ICH attributed to intravenous thrombolysis or trauma were excluded. IS included acute and subacute symptoms lasting > 24 hours attributed to cerebral ischemia, diagnosed clinically, with or without radiological confirmation. Vascular death included deaths attributed to ICH, IS, systematic embolism, or myocardial infarction.

Statistical Analysis

Baseline demographic, risk factor profiles, and radiological features were compared between patients with and without CMBs as well as patients with and without outcome events. Mann–Whitney test was used for continuous variables not normally distributed and *t* test for normally distributed variables. Categorical variables between groups were compared with the χ^2 test or Fisher's exact test when appropriate.

We calculated absolute rates of outcome events per 1,000 patient-years and constructed 95% confidence intervals for the mean of the Poisson distribution based on the number of observed events. We investigated the association between presence of CMBs, predefined CMB burden categories (0, 1, 2–4, 5–10, and ≥ 11 CMBs) and distribution of CMBs (pure deep, pure lobar, and mixed deep-lobar) in all outcome events by Cox regression adjusted for prognostic and confounding variables based on biological relevance, which included age, sex, history of hypertension, ischemic heart disease, diabetes mellitus, previous ischemic stroke, previous ICH, and type of MRI sequence used to detect CMBs (T2*-weighted Gradient Echo [GRE] or SWI). Patients with missing variables required for Cox regression analyses were excluded from the model. Interaction between presence of CMBs and ethnicity for risk of outcome parameters were investigated. Further analyses were performed to investigate the effect of probable CAA (defined by modified Boston Criteria) and white matter hyperintensities (ie, Fazekas scale ≥ 2) on risk of ICH for patients who have these variables available.

To investigate the influence of CMB burden in outcome events among patients on different antithrombotic treatments, we also performed interaction analyses by adding interaction terms between CMB burden categories and antithrombotic treatments. In addition, we repeated the adjusted multivariable Cox regression separately in patients on VKA, DOACs, antiplatelet, and combination therapy. Patients on unknown antithrombotic therapy were excluded from the model.

All analyses were done in SPSS 25 and R 3.4.5. The alpha level was set at 0.05.

Results

Of the 38 cohorts in MICON, 37 cohorts agreed to participate, and 7,839 patients with documented AF were included in this subanalysis. The mean age was 75.7 ± 10.0 years, and 47.5% were women. Ethnicity was available in 6,386 patients, including 3,394 White patients, 2,973 Asian patients, and 19 Black patients. The median follow-up period was 23.5 months (interquartile range [IQR] = 9.9, 26.6 months), 35.6% of the patients had a follow-up period of less than 1 year.

Characteristics of Patients with CMBs

CMBs were present in 2,142 (27.3%) patients and the exact CMB burden was available in 2,026 patients. Among patients with CMBs, the median number of CMBs was 2 (IQR = 2), including 970 patients with one

CMB, 675 patients with 2 to 4 CMBs, 210 patients with 5 to 10 CMBs, and 171 patients with ≥ 11 CMBs. Information of CMB distribution was available in 1,960 patients. Six hundred ninety-eight patients (35.6%) had pure lobar CMBs, 689 (35.1%) had pure deep CMBs, and 573 (29.3%) had mixed deep-lobar CMBs.

Compared to patients without CMBs, patients with CMBs were older, more likely to have hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure, peripheral vascular disease, prior ischemic stroke, prior ICH, and previous antithrombotic use (Table 1). Furthermore, there were less patients who were scanned with MRI T2* sequence than SWI, and median Fazekas scores was higher in patients with CMBs (see Table 1).

Intracranial Hemorrhage

Eighty-seven patients developed ICH over 13,741 patient-years of follow-up, with 50 (57.5%) ICH occurring within the first year of follow-up. There were 70 patients with ICHs, 3 subarachnoid hemorrhages, 13 subdural hemorrhages, and 1 patient with more than 1 type of ICH. Patients with ICH had a significantly higher prevalence of diabetes mellitus, peripheral vascular disease, and prior ICH (Table 2). The median CMB number was higher in patients with ICH (1 [IQR = 2]) than those without (0 [IQR = 1]), $p < 0.001$. The proportion of patients with ≥ 5 CMBs was higher in patients with ICH (15.7%) than those without (5.0%), $p < 0.001$ (see Table 2).

The incidence of ICH in patients with CMBs was 12 per 1,000 patient-years compared to 4 per 1,000 patient-years in those without CMBs, an absolute increase of 8 per 1,000 patient-years (Table S1A). The incidence rate of ICH increased with higher CMB burden but was consistently lower than that of IS in all CMB categories (Fig 1A). The presence of CMBs was associated with ICH with an adjusted hazard ratio (aHR) of 2.74 [1.76–4.26]. Increased aHR for ICH was also observed with higher CMB burden (Fig 2A), deep CMBs (aHR = 4.39 [2.51–7.67]) and mixed deep-lobar CMBs (aHR = 3.07 [1.48–6.38]; see Table S1A, Fig 2A). Status of Modified Boston Criteria was available in 2,124 patients, whereas Fazekas score was available in 4,301 patients. There was no increase in risk of ICH in those with probable CAA (aHR = 1.35 [0.17–10.48]) nor Fazekas score ≥ 2 (aHR = 0.67 [0.32–1.41]).

Ischemic Stroke

Four hundred twelve patients developed IS over 13,521 patient-years of follow-up, with 273 (66.3%) cases of IS occurring within the first year of follow-up. Patients with recurrent IS were significantly older and had higher prevalence of diabetes mellitus, ischemic heart disease, peripheral artery disease, prior IS, and previous use of anticoagulants compared to patients without IS (Table 3). CMBs were more commonly present in patients with IS than those without (33.7% with IS vs 27.0% without IS, $p = 0.003$) and the proportion of patients with ≥ 5 CMBs was higher in patients with IS (7.9%) than those without (4.9%), $p = 0.009$ (see Table 3).

The incidence of IS was 33 per 1,000 patient-years in patients with CMBs compared to 24 per 1,000 patient-years in those without, an increase by 9 per 1,000 patient-years (aHR = 1.29 [1.04–1.59]; see Table S1A). The presence of mixed deep-lobar CMBs was associated with increased aHR for IS (aHR = 1.57 [1.11–2.22]; see Fig 2B). However, a higher burden of CMBs had no influence on incidence of IS (see Table S1A, Fig 2B). Interaction was noted between presence of CMBs with an asian population for IS (aHR = 1.61 [1.01–2.58], $p_{\text{interaction}} = 0.046$). No interaction was detected between CMBs and other ethnic groups for other outcome events.

Vascular Death

Vascular death occurred in 330 patients over 13,494 patient-years follow-up. The incidence of vascular death was 26 per 1,000 patient-years in patients with CMBs compared to 22 per 1,000 patient-years in patients without CMBs, an increase by 4 per 1,000 patient-years (aHR = 0.93 [0.73–1.19]). There was no association between presence nor burden of CMBs with risk of vascular death in patients with AF overall (see Table S1A, Fig 2C).

Subgroup Analyses of Patients on Different Antithrombotics

After an index event of IS or transient ischemic attack, 7,379 patients received antithrombotic therapy (3,244 patients received a VKA, 1,981 patients received a DOAC, 626 patients received antiplatelet, and 1,528 patients received combination therapy). Twenty-one patients on unknown antithrombotic drugs were excluded from this subanalysis. Interaction for ICH risk was detected between CMB burden categories and VKA ($p_{\text{interaction}} = 0.04$), antiplatelet ($p_{\text{interaction}} < 0.001$) and combination therapy ($p_{\text{interaction}} < 0.001$), but not DOACs. Interaction for IS risk was detected between CMB burden and antiplatelet therapy ($p_{\text{interaction}} < 0.001$) but not with other antithrombotics. No interaction was noted between CMB burden and antithrombotic treatments for vascular death risk.

Patients on VKA and DOACs. For patients on VKA, patients with CMBs had higher incidence of ICH compared to patients without CMBs (12 per 1,000 patient-years with CMBs versus 6 per 1,000 patient-years without

TABLE 1. Characteristics of Patients with Atrial Fibrillation with and without Cerebral Microbleeds

	No. of patients with data available	With CMB (n = 2,142)	Without CMB (n = 5,697)	*p*
Demography				
Mean age ± SD, yr	7,821	77.1 ± 9.6	75.2 ± 10.1	< 0.001
Female, n (%)	7,839	994 (46.4)	2730 (47.9)	0.231
Race, n (%)	6,386			0.317
Whites		940 (51.7)	2454 (53.7)	-
Asian		874 (48)	2,099 (46)	-
Black		5 (0.3)	14 (0.3)	-
Clinical risk factors				
Current smoker, n (%)	6,812	222 (12)	623 (12.6)	0.497
Current drinker, n (%)	5,121	187 (13.7)	592 (15.8)	0.067
Hypertension, n (%)	7,813	1,735 (81.3)	4,290 (75.5)	< 0.001
Dyslipidemia, n (%)	7,539	836 (40.8)	2180 (39.7)	0.413
Diabetes mellitus, n (%)	7,665	524 (25)	1247 (22.4)	0.016
Ischemic heart disease, n (%)	7,561	446 (21.6)	890 (16.2)	< 0.001
Congestive heart failure, n (%)	5,599	201 (13.7)	437 (10.6)	0.001
Peripheral vascular disease, n (%)	4,381	284 (24.8)	558 (17.2)	< 0.001
History of ischemic stroke, n (%)	7,809	505 (23.6)	943 (16.6)	< 0.001
History of ICH, n (%)	7,247	64 (3.2)	56 (1.1)	< 0.001
Previous antiplatelet, n (%)	6,334	726 (42.8)	1830 (39.4)	0.015
Previous anticoagulants, n (%)	6,335	356 (21.0)	734 (15.8)	< 0.001
Medication at baseline, n (%)	7,839			0.058
None		304 (5.3)	135 (6.3)	-
VKA		2,344 (41.1)	900 (42.0)	-
DOAC		1,438 (25.2)	543 (25.4)	-
Antiplatelet		447 (7.8)	179 (8.4)	-
Combination therapy		1145 (20.1)	383 (17.9)	-
Unknown oral anticoagulant		19 (0.3)	2 (0.1)	-
Radiological features				
MRI T2*, n (%)	7,803	1,363 (63.6)	3,906 (69.0)	< 0.001
Median Fazekas score (IQR)	4,301	3 (3)	2 (2)	< 0.001

Abbreviations: CMB = cerebral microbleed; DOAC = direct acting oral anticoagulant; ICH = intracranial hemorrhage; IQR = interquartile range; MRI = magnetic resonance imaging; SD = standard deviation; VKA = vitamin K antagonist.

CMBs, aHR = 1.92 [1.06–3.49]). The association was mostly driven by patients with 5 to 10 CMBs who had significantly higher aHR for ICH (aHR = 4.04 [1.19–13.66]; see Table S1B). Furthermore, presence of CMBs was associated with a trend of increased incidence of IS (aHR = 1.37 [0.99–1.89]), whereas patients with

TABLE 2. Characteristics of Patients with Atrial Fibrillation with and without Intracranial Hemorrhage

	No. of patients with data available	With ICH (n = 87)	Without ICH (n = 7,752)	*p*
Demography				
Mean age ± SD, yr	7,821	77.1 ± 8.9	75.7 ± 10.0	0.206
Female, n (%)	7,839	42 (48.3)	3682 (47.5)	0.885
Race, n (%)	6,386			0.397
Whites		46 (60.5)	3,348 (53.1)	-
Asian		30 (39.5)	2,943 (46.6)	-
Black		0 (0)	19 (0.3)	-
Clinical risk factors				
Current smoker, n (%)	6,812	7 (9.6)	838 (12.4)	0.463
Current drinker, n (%)	5,121	6 (9.8)	773 (15.3)	0.240
Hypertension, n (%)	7,813	69 (79.3)	5,956 (77.1)	0.624
Dyslipidemia, n (%)	7,539	36 (42.9)	2,980 (40.0)	0.592
Diabetes mellitus, n (%)	7,665	29 (34.1)	1,742 (23.0)	0.015
Ischemic heart disease, n (%)	7,561	20 (23.8)	1,316 (17.6)	0.138
Congestive heart failure, n (%)	5,599	8 (11.1)	630 (11.4)	0.939
Peripheral vascular disease, n (%)	4,381	19 (35.2)	823 (19.0)	0.003
History of ischemic stroke, n (%)	7,809	20 (23.3)	1,428 (18.5)	0.258
History of ICH, n (%)	7,247	7 (8.2)	113 (1.6)	< 0.001
Previous antiplatelet, n (%)	6,334	35 (46.1)	2,521 (40.3)	0.308
Previous anticoagulants, n (%)	6,335	15 (19.5)	1,075 (17.1)	0.585
Medication at baseline, n (%)	7,839			0.148
None		2 (2.3)	437 (5.6)	-
VKA		48 (55.2)	3,196 (41.2)	-
DOAC		16 (18.4)	1,965 (25.3)	-
Antiplatelet		7 (8.0)	619 (8.0)	-
Combination therapy		14 (16.1)	1,514 (19.5)	-
Unknown oral anticoagulant		0 (0)	21 (0.3)	-
Radiological features				
MRI T2*, n (%)	7,803	31 (35.6)	2,503 (32.4)	0.527
CMB presence, n (%)	7,839	45 (51.7)	2,097 (27.1)	< 0.001
Median CMB number (IQR)	7,497	1 (2)	0 (1)	< 0.001
≥ 5 CMBs, n (%)	7,497	13 (15.7)	368 (5.0)	< 0.001
Probable cerebral amyloid angiopathy, n (%)	2,124	1 (3.7)	64 (3.1)	0.845
Median Fazekas score (IQR)	4,301	2 (3)	2 (2)	0.899

Abbreviations: CMB = cerebral microbleed; DOAC = direct acting oral anticoagulant; ICH = intracranial hemorrhage; IQR = interquartile range; MRI = magnetic resonance imaging; SD = standard deviation; VKA = vitamin K antagonist.

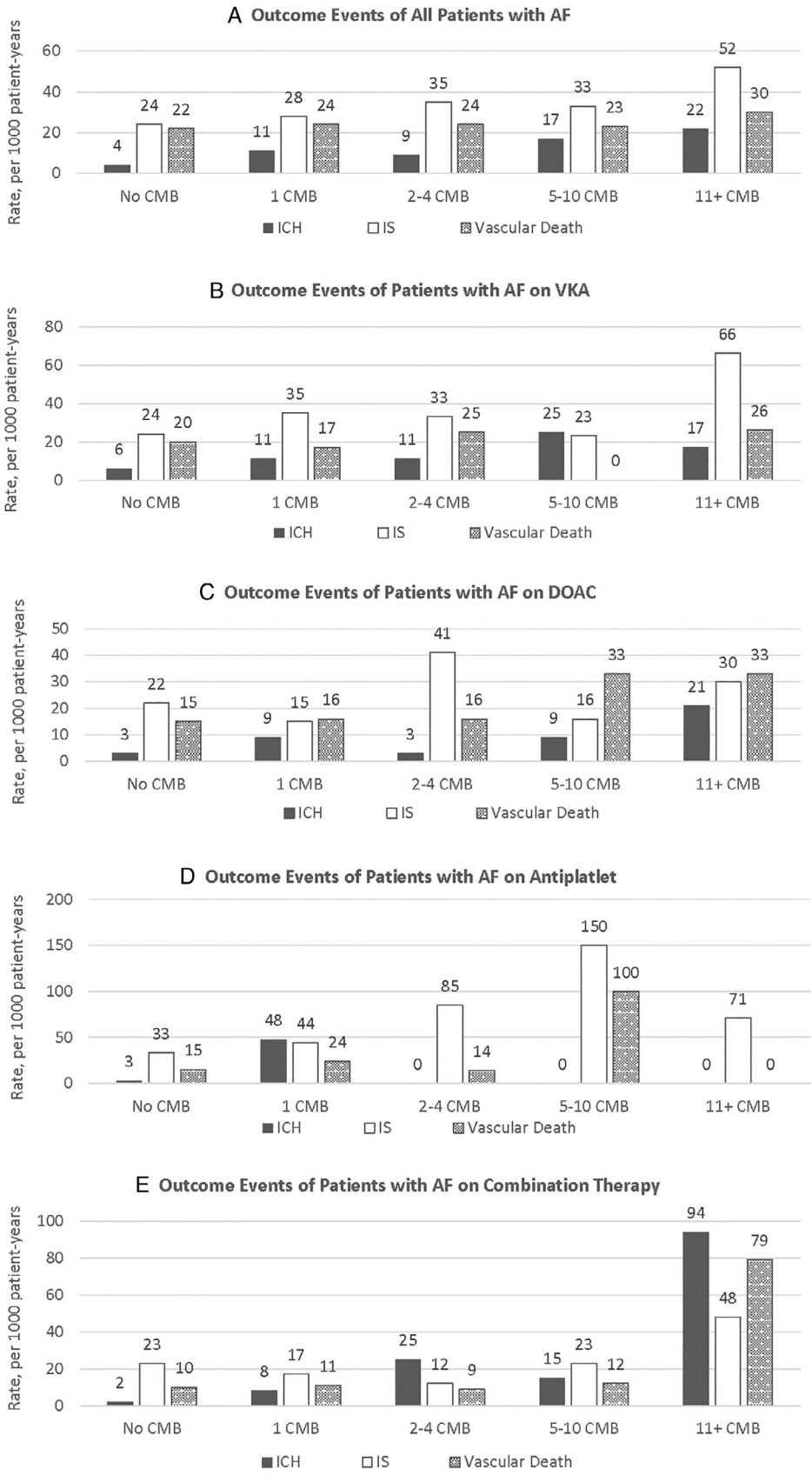

FIGURE 1: Incidence rate of ICH, IS, and vascular death during follow-up in patients with atrial fibrillation in general (A), on VKA (B), on DOAC (C), on antiplatelet (D) and on combination therapy (E). AF = atrial fibrillation; CMB = cerebral microbleed; DOAC = direct oral anticoagulant; ICH = intracranial hemorrhage; IS = ischemic stroke; VKA = vitamin K antagonist.

TABLE 3. Characteristics of Patients with Atrial Fibrillation with and without Ischemic Stroke

	No. of patients with data available	With IS (n = 412)	Without IS (n = 7,427)	*p*
Demography				
Mean age ± SD, yr	7,821	77.1 ± 91	75.7 ± 10.1	0.001
Female, n (%)	7,839	210 (51.0%)	3,514 (47.3%)	0.148
Race, n (%)	6,386			< 0.001
Whites		131 (41.1%)	3,263 (53.8%)	-
Asian		184 (57.7%)	2,789 (46.0%)	-
Black		4 (1.3%)	15 (0.2%)	-
Clinical risk factors				
Current smoker, n (%)	6,812	32 (9.8%)	813 (12.5%)	0.152
Current drinker, n (%)	5,121	38 (12.8%)	741 (15.4%)	0.223
Hypertension, n (%)	7,813	331 (80.3%)	5,694 (76.9%)	0.109
Dyslipidemia, n (%)	7,539	163 (41.8%)	2,853 (39.9%)	0.459
Diabetes mellitus, n (%)	7,665	120 (30.0%)	1,651 (22.7%)	0.001
Ischemic heart disease, n (%)	7,561	90 (22.2%)	1,246 (17.4%)	0.014
Congestive heart failure, n (%)	5,599	49 (14.5%)	589 (11.2%)	0.064
Peripheral vascular disease, n (%)	4,381	84 (29.7%)	758 (18.5%)	< 0.001
History of ischemic stroke, n (%)	7,809	125 (30.5%)	323 (17.9%)	< 0.001
History of ICH, n (%)	7,247	11 (2.7%)	109 (1.5%)	0.119
Previous antiplatelet, n (%)	6,334	147 (44.7%)	2,409 (40.1%)	0.100
Previous anticoagulants, n (%)	6,335	85 (25.8%)	1,005 (16.7%)	< 0.001
Medication at baseline, n (%)	7,839			0.004
None		26 (6.3%)	413 (5.6%)	-
VKA		171 (41.5%)	3,073 (41.4%)	-
DOAC		92 (22.3%)	1,889 (25.4%)	-
Antiplatelet		53 (12.9%)	573 (7.7%)	-
Combination therapy		70 (17.0%)	1,458 (19.6%)	-
Unknown oral anticoagulant		0 (0%)	21 (0.3%)	-
Radiological features				
MRI sequence-T2*, n (%)	7,803	260 (63.7%)	5,009 (67.7%)	0.092
CMB presence, n (%)	7,839	139 (33.7%)	2,003 (27.0%)	0.003
Median CMB number (IQR)	7,497	0 (1)	0 (1)	< 0.001
≥ 5 CMBs, n (%)	7,497	31 (7.9%)	350 (4.9%)	0.009

Abbreviations: CMB = cerebral microbleeds; DOAC = direct acting oral anticoagulant; ICH = intracranial hemorrhage; IQR = interquartile range; MRI = magnetic resonance imaging; SD = standard deviation; VKA = vitamin K antagonist.

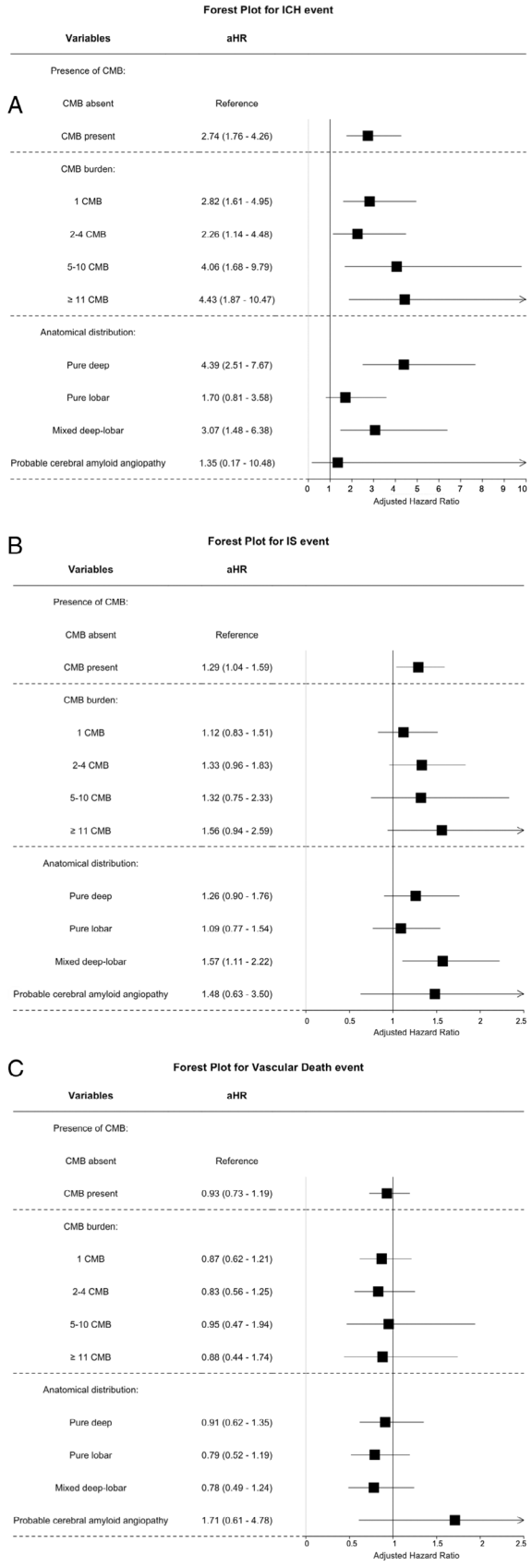

FIGURE 2: Forest plots of associations for (A) ICH, (B) IS, and (C) vascular death during follow-up. aHR = adjusted hazard ratio; CMB = cerebral microbleed; ICH = intracranial hemorrhage; IS = ischemic stroke.

≥ 11 CMBs had significantly higher incidence of IS compared to patients without CMBs (66 per 1,000 patient-years with ≥ 11 CMBs vs 24 per 1,000 patient-year without CMBs, aHR = 2.37 [1.13–5]). Neither presence of CMBs nor their burden influenced risk of vascular death (see Table S1B).

For patients on DOACs, neither the presence nor burden of CMBs influenced the risk of ICH, IS and vascular death (see Table S1C).

Patients on Antiplatelet Drugs. Compared to patients without CMBs, presence of CMBs in patients on antiplatelet drugs was associated with a significantly higher incidence of IS (72 per 1,000 patient-years with CMBs vs 33 per 1,000 patient-years without CMBs, aHR = 2.43 [1.34–4.43]). The association was mostly driven by patient with 5 to 10 CMBs (aHR = 7.27 [2.76–19.15]) who also had increased incidence for vascular mortality (aHR = 6.05 [1.44–25.45]; see Table S1D).

For patients on antiplatelet drugs, no statistically significant association between presence of CMBs and risk of ICH was observed (21 per 1,000 patient-years with CMBs vs 3 per 1,000 patient-years without CMBs, aHR = 4.93 [0.81–30.18]). The small number of ICHs in patients on antiplatelet drugs (n = 5) precluded further multivariate analyses for CMB burden on risk of ICH.

Patients on Combination Therapy. For patients on combination therapy, the incidence of ICH was higher among patients with CMBs (18 per 1,000 patient-years) compared to patients without CMBs (2 per 1,000 patient-years; aHR = 7.92 [2.43–25.82]). The association was most significant among patients with 2 to 4 CMBs (aHR = 10.23 [2.41–43.37]) and ≥ 11 CMBs (aHR = 27.97 [5.57–140.55]). In this treatment group, neither the presence nor burden of CMBs was associated with increased incidence of IS, whereas the presence of ≥ 11 CMBs was associated with increased risk of vascular death (aHR = 4.76 [1.31–17.26]; see Table S1E).

Given the above findings in this treatment group, we did a more detailed post hoc analysis on patients receiving combination treatment; these patients had a higher proportion of dyslipidemia (43.4% vs 39.2%, $p < 0.001$), ischemic heart disease (22.7% vs 16.4%, $p < 0.001$), and peripheral vascular disease (23.1% vs 18.1%, $p < 0.001$) compared to patients receiving either anticoagulant or antiplatelet alone.

Absolute Incidence of Outcome Events Stratified by Antithrombotic Use. The number of patients in each treatment group and the incidence of outcome events among different CMB categories are shown in Table S1B–E and

Figure 1B–E. The absolute incidence rate of IS was higher than ICH for the majority of the patients except for (i) patients on VKA with 5 to 10 CMBs whose rate of ICH was comparable to that of IS (25 per 1,000 patient-years for ICH vs 23 per 1,000 patient-years for IS); (ii) patients on antiplatelet with 1 CMB whose rate of ICH was comparable to IS (48 per 1,000 patient-years for ICH vs 44 per 1,000 patient-years for IS), and (iii) patients on combination therapy with 2 to 4 CMBs and ≥ 11 CMBs who had a rate of ICH almost double that of IS (25 per 1,000 patient-years for ICH vs 12 per 1,000 patient-years for IS in patients with 2 to 4 CMBs and 94 per 1,000 patient-years for ICH vs 48 per 1,000 patient-years for IS in patients with ≥ 11 CMBs; see Fig 1B–E). Among all the treatment groups, the highest rate of ICH was observed among patients on combination therapy with ≥ 11 CMBs (94 per 1,000 patient-years; see Table S1E).

Discussion

In this subanalysis of the MICON pooled individual patient data cohort among patients with AF who had a stroke, the presence of CMBs was associated with increased risk of subsequent ICH and IS but not vascular death; the burden of CMBs had a stronger association with risk of ICH than IS. The absolute rate of subsequent stroke, however, varied among different antithrombotic treatments according to CMB burden. For most patients, the absolute rate of IS was higher than that of ICH. However, for patients on combination therapy with multiple CMBs, the absolute rate of ICH exceeded that of IS, with potential for net clinical harm. Among all antithrombotic treatments, DOAC was the only one which was not associated with an increased risk of ICH, IS, or vascular death among patients with CMBs.

In recent years, the addition of CMBs to clinical scores in stroke risk stratification has been shown to improve the predictive power for ICH versus IS.[9,10,13] In addition, in patients with AF on anticoagulation, high lesion load of overall small vessel disease, including the presence of perivascular spaces, CMBs, white matter hyperintensities, and lacunes[17] was found to be associated with ICH.[18]

Regarding the distribution of CMBs in predicting outcome events, subsequent ICH was strongly associated with presence of deep CMBs, either as pure deep CMBs or mixed deep-lobar CMBs, suggesting that deep perforator arteriopathy (arteriolosclerosis) is an important factor contributing to the development of ICH in these patients.[19] In contrast to our understanding that CAA is associated with 4-fold increased risk of anticoagulant-related ICH,[20] we did not find an increased risk of ICH in the subset of patients rated as probable CAA. This could be accounted by the small number of patients with probable CAA in our study, however, it might also suggest that pure lobar CMBs may be related to etiologies other than CAA in patients with AF who had a stroke.

Despite the stronger association of CMBs with ICH than IS, the absolute rate for IS was higher than ICH in the overall AF subcohort irrespective of the CMB burden (see Table S1), which is consistent with the findings in the main MICON study on patients with different stroke etiologies and antithrombotic treatments. Interestingly, the absolute rate of IS in our present study was lower compared to the main study for both patients with CMBs (33 vs 46 per 1,000 patient-years) and those without CMBs (24 vs 30 per 1,000 patient-years). The lower incidence rate of IS in the AF subcohort may be related to the high efficacy of anticoagulants for prevention of cardioembolic ischemic stroke. The rate of ICH was similar among patients with CMBs (12 per 1,000 patients-years in both studies) and those without CMBs (4 per 1,000 patients-years in both studies). Despite a higher proportion of patients on oral anticoagulant in the AF subcohort (86.1%) than in the main study (38.1%), the same absolute rate of ICH in these 2 studies suggests that factors other than antithrombotic use (eg, blood pressure variability), might also influence the risk of ICH.[14]

Few randomized controlled studies included MRI imaging substudies.[21,22] In the NAVIGATE ESUS trial, the presence of CMBs was associated with recurrent IS, ICH, and death but the numbers of outcome events were too small to draw conclusions about the ICH risk depending on the antithrombotic treatment (ie, rivaroxaban vs aspirin).[22] More importantly none of these trials included patients on combination therapy leading to a lack of randomized data in this high-risk group.

To the best of our knowledge, we have conducted the largest study evaluating the risk–benefit ratio of different antithrombotic treatments in patients with AF who had a stroke and CMBs. Comparing the 4 observed antithrombotic treatments for AF in a real-world setting, DOAC monotherapy appeared to be the safest antithrombotic regimen, which was not associated with IS, ICH, or vascular death across all CMB burden categories. For patients on VKA, comparable rates of ICH (25 per 1,000 patient-years) and IS (23 per 1,000 patient-years) were observed among patients with 5 to 10 CMBs but not among the other CMB categories. The net-benefit of DOACs over VKA observed in our study was in line with recent publications on dependent and elderly patients with AF with stroke, who are also at high risk of having multiple CMBs.[23,24]

Our analysis of stroke risks in patients on combination therapy provides additional insight to this understudied high-risk group. In the recently defined risk score models derived from the MICON cohort for prediction of

ICH (MICON-ICH) and IS (MICON-IS), patients on combination therapy were not specifically captured and were categorized under the treatment category of anticoagulants. Our analysis of the subset of patients on concurrent anticoagulant and antiplatelet allows us to better delineate the relative risks of ICH and IS, which may be different from the rest of the cohort due to the increased risk of ICH from additional antithrombotic treatments as well as higher risk of IS from the increased comorbidities of these patients.[25] With more than 1,500 subjects on combination therapy in our AF-cohort (19.5% among patients with AF vs 2.6% in the MICON patients without AF), this treatment seems to be of clinical relevance in patients with AF who had a stroke. In our study, there was a 2-fold higher absolute rate of ICH than IS in patients on combination therapy with 2 to 4 and ≥ 11 CMBs. This reflects the importance of including detailed antithrombotic information when individualizing stroke risk in patients with AF and CMBs. Our study suggests that concomitant antiplatelet use in anticoagulated patients for AF may be an important component for further risk stratification and could be of added valued to the established risk scores.[13]

From our post hoc analysis, patients on combination therapy more often had ischemic heart and peripheral vascular diseases. Other possible indications for combination therapy include recent acute coronary syndrome, angioplasty or stenting of coronary, carotid or peripheral arteries, which unfortunately were not captured in our cohort. Nevertheless, after adjusting for relevant cardiovascular risk factors in the Cox regression model, the presence of 2 to 4 and ≥ 11 CMBs remained independent predictors for ICH but not IS. Further randomized controlled trials are warranted to determine the best treatment strategy for stroke prevention in patients with AF and multiple CMBs with indications for combination therapy. More importantly, a pre-emptive approach is important to mitigate the risk of ICH in these patients. General measures include stringent blood pressure control, frequent monitoring of International Normalized Ratio (INR) for patients on VKA and renal function for patients on DOACs. Indications for combination therapy should be verified continuously,[26,27] whereas duration of a therapy should be minimized according to the latest guidelines.[28–30] Moreover, agents with lower risk of ICH (ie, DOACs instead of VKA) should be considered.

Limitations of this study include (1) the non-randomized design using prospective collected observational data. We aimed to minimize the risk of confounding with comprehensive adjustment for known stroke risk factors, nevertheless, multiplicity of testing as well as potential unaccounted confounding factors may have influenced our observations and thus our results should be interpreted with caution; (2) limited numbers of patients with ≥ 5 CMBs which did not allow us to detect a potentially linear increase in ICH risk in patients on different antithrombotic agents, particularly in patients under antiplatelets; (3) missing information on the specific indication and duration of the combination therapy as well as possible changes of antithrombotic treatments and patients' compliance; (4) missing information on the Modified Boston Criteria in over two-third of the patients which may lead to underestimation of probable CAA in our cohort; (5) the study population is mainly based on European and Asian cohorts, thus lowering the generalizability to other ethnic groups; (6) data regarding the etiological classification of recurrent IS during the follow-up period were not assessed systematically in all MICON cohorts; and (7) the median follow-up period of our study was 23.5 months thus we cannot determine long-term risks and benefits of different antithrombotic treatments beyond 2 years.

To the best of our knowledge, this is the largest study so far investigating the impact of CMBs in patients with AF. Our study has the following additional strengths (1) we used well characterized pooled individual patient data from MICON with prospective data for CMBs evaluation and outcome events from different ethnic groups; and (2) a detailed analysis of the stroke risk associated with different CMB burden, stratified by observed antithrombotic treatments, which pragmatically helps with decision making in daily clinical practice.

In conclusion, among patients with AF on antithrombotic therapy for secondary prevention after IS or transient ischemic attack, presence of CMBs was associated with increased risk of both subsequent ICH and IS, with stronger association with the former. Among the 4 antithrombotic treatments in this study which reflects a real-world treatment setting, DOAC was the only agent which was not associated with IS, ICH, or vascular death in the presence of CMBs. Although the absolute incidence of IS was higher than ICH regardless of CMB burden for most patient, patients under combination therapy with multiple CMBs might have an absolute risk of ICH exceeding that of IS. As the findings are hypothesis generating, further randomized controlled trials are needed to determine the best strategy for stroke prevention in this high-risk group.

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Authors Contributions

Y.S., A.Z., and N.P. contributed to the conception and design of the study, acquisition and analysis of data, and drafting the text or preparing the figures. B.Y., S.F.T., V.M., A.P., D.S., G.A., D.W., T.L., S.T., W.C., J.A., K.L., J.L., M.S.; M.K., H.C., M.H., D.W., H.M., R.C., S.I., K.Y., E.A., S.H., J.P., B.L., A.W., Y.K., T.S., R.L., S.E., T.G., E.U., D.D., N.B., E.A., H.H., J.M., M.N., J.T., S.C., L.K., R.S., R.J., G.L., M.G., L.P., J.M., L.L., C.K., T.P., M.F., F.C., S.M., D.H., D.W., D.D., P.N., C.B., S.B., K.W., A.T., D.K., C.Y., A.M., S.K., R.O., Y.Z., C.X., S.H., B.G. C.C., M.L., J.S., R.B., N.K., F.L., R.S., J.H., P.K., J.W., F.F. V.S., D.C., S.J., V.K., E.S., H.H., Y.Y., D.O., F.F., V.T., J.H., R.V., H.A., T.I., G.L., E.J., K.T., H.B., J.F., L.P., P.L., J.B., D.W., and S.E. contributed to the acquisition and analysis of data.

Potential Conflict of Interest

Nothing to report.

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