Brain microbleeds, anticoagulation, and hemorrhage risk

Meta-analysis in stroke patients with AF

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ABSTRACT

Objectives: To assess the association between cerebral microbleeds (CMBs) and future spontaneous intracerebral hemorrhage (ICH) risk in ischemic stroke patients with nonvalvular atrial fibrillation (AF) taking oral anticoagulants.

Methods: This was a meta-analysis of cohort studies with >50 patients with recent ischemic stroke and documented AF, brain MRI at baseline, long-term oral anticoagulation treatment, and ≥6 months of follow-up. Authors provided summary-level data on stroke outcomes stratified by CMB status. We estimated pooled annualized ICH and ischemic stroke rates from Poisson regression. We calculated odds ratios (ORs) of ICH by CMB presence/absence, ≥5 CMBs, and CMB topography (strictly lobar, mixed, and strictly deep) using random-effects models.

Results: We established an international collaboration and pooled data from 8 centers including 1,552 patients. The crude CMB prevalence was 30% and 7% for ≥5 CMBs. Baseline CMB presence (vs no CMB) was associated with ICH during follow-up (OR 2.68, 95% confidence interval [CI] 1.19–6.01, $p = 0.017$). Presence of ≥5 CMB was related to higher future ICH risk (OR 5.50, 95% CI 2.07–14.66, $p = 0.001$). The pooled annual ICH incidence increased from 0.30% (95% CI 0.04–0.55) among CMB-negative patients to 0.81% (95% CI 0.17–1.45) in CMB-positive patients ($p = 0.01$) and 2.48% (95% CI 1.2–6.2) in patients with ≥5 CMBs ($p = 0.001$). There was no association between CMBs and recurrent ischemic stroke.

Conclusions: The presence of CMB on MRI and the dichotomized cutoff of ≥5 CMBs might identify subgroups of ischemic stroke patients with AF with high ICH risk and after further validation could help in risk stratification, in anticoagulation decisions, and in guiding randomized trials and ongoing large observational studies. *Neurology*® 2017;89:2317–2326

GLOSSARY

AF = atrial fibrillation; **AVERROES** = A Phase III Study of Apixaban in Patients With Atrial Fibrillation; **CHADS2** = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke; **CI** = confidence interval; **CMB** = cerebral microbleed; **GRE** = gradient-recalled echo; **ICH** = intracerebral hemorrhage; **NOAC** = non–vitamin K oral anticoagulant; **OR** = odds ratio; **SWI** = susceptibility-weighted imaging; **TOAST** = Trial of ORG 10172 in Acute Stroke Treatment.

Long-term oral anticoagulation with warfarin and non–vitamin K oral anticoagulants (NOACs) is highly effective for ischemic stroke prevention in patients with nonvalvular atrial fibrillation (AF).[1] However, the concern about intracerebral hemorrhage (ICH), the most catastrophic of all bleeding complications in terms of mortality and morbidity,[2] is a principal driving force in anticoagulation decision making. Risk stratification schemes have been used to gauge

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anticoagulation benefits and hemorrhage risk, but ICH is not specifically addressed in the commonly used scores.

Growing evidence suggests a link between cerebral microbleeds (CMBs) on MRI and increased future ICH risk,[3] leading to clinical concerns. This is particularly relevant in the setting of new symptomatic stroke in AF.[4] CMBs, detected on T2*-weighted gradient-recalled echo (T2*-GRE) and susceptibility-weighted imaging (SWI) MRI sequences, are neuroimaging markers of hemorrhagic small vessel disease in the brain.[5] CMBs are common in populations who might require anticoagulation therapy, being found in at least a quarter of patients with ischemic stroke.[4,6] However, limited data are available on the effect of CMBs on ICH risk specifically in the setting of anticoagulation after AF-related ischemic stroke.

We sought to address this gap by undertaking a collaborative (International META-MICROBLEEDS Initiative[7]) aggregate data meta-analysis of cohorts including ischemic stroke patients with AF treated with warfarin or NOACs. Our primary analysis focused on the association between the presence of any CMBs and ≥5CMBs (prespecified before the beginning of the current project on the basis of available evidence[8,9]) and risk of future ICH during follow-up.

METHODS

Study design. This systematic review and meta-analysis was undertaken on the basis of a summary protocol finalized on June 2015 and approved by the collaborators with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Individual Patient Data and the *Cochrane Handbook for Systematic Reviews of Interventions*. Two independent raters used electronic search strategies to search PubMed for eligible cohorts between January 1, 1999, and September 1, 2015, using several combinations of MeSH terms and text words: ([microbleed] OR [microhemorrhag] OR [microhemorrhag] OR [dot-like]) AND (MRI OR SWI OR T2* OR suscept OR hemosid) AND (brain OR cerebr OR [cerebral small vessel disease] OR [vascular dementia] OR Alzheimer disease OR Alzheimer's disease OR cognit*). Bibliographies of studies and authors' own files (including abstracts of European Stroke Organisation Conference and International Stroke Conference in 2015 to 2016) were also screened.

Studies (published as full articles or identified from authors records) were eligible for inclusion regardless of language if they (1) included at least 50 adult patients with recent (within 1 week) acute ischemic stroke (confirmed on routine brain imaging in each center, i.e., CT or MRI) in the setting of any type of nonvalvular AF[10] (documented by baseline ECG or clinical history based on ECG at each center); (2) included patients who had routinely acquired clinical T2*-GRE/SWI MRI at baseline and were discharged on oral anticoagulation (warfarin or NOACs, regardless of CMB status); (3) assessed CMBs with standardized ratings; (4) had at least 6 months of follow-up (including a combination of regular patient visits complemented by systematic review of prospective databases, medical and hospital records review, and telephone follow-up according to local policies); and (5) assessed the risk of symptomatic spontaneous ICH (primary outcome) and ischemic stroke during follow-up with valid definitions. Baseline ischemic strokes were classified as presumed cardioembolic on the basis of Trial of ORG 10172 in Acute Stroke Treatment (TOAST), allowing competing causes of stroke to be present.

Standard protocol approvals, registrations, and patient consents. No additional ethics approval was required for this meta-analysis.

Data collection and outcomes. Using a prespecified data collection proforma, collaborating centers provided summary-level data at baseline (sex, mean age, hypertension, CHADS2 [congestive heart failure, hypertension, age ≥75 years, diabetes, stroke] score, previous warfarin use, history of ICH, and presence of moderate to severe while matter hyperintensities with the Fazekas scale[11]), details on MRI sequence parameters, and follow-up information (use of warfarin or NOACs, aspirin, patient-years of follow-up, and outcome events of interest). Spontaneous symptomatic ICH was defined as acute or subacute onset of symptoms of hemorrhage confirmed on CT or MRI. Trained investigators in each center rated CMBs using currently recommended consensus criteria.[12] They provided data on outcome events (ICH and recurrent ischemic stroke) and patient-years of follow-up, stratified by CMB presence, ≥5 CMBs, and location (lobar [in the cortex or subcortical areas of the cerebral hemispheres], deep, or mixed in line with definitions used in visual rating scales[13,14]). The 5-CMB cutoff was predefined on the basis of the totality of available literature on CMB burden and risk of stroke in different patient cohorts.[8,9,15]

Assessment of risk of bias. We assessed the risk of bias of each cohort according to an 8-item tool published by the Cochrane Methods Bias group (Tool to Assess Risk of Bias in Cohort Studies) [16] and the Newcastle-Ottawa Scale for assessing the quality of cohort (nonrandomized) studies.

Statistical analysis. For the primary outcomes, we meta-analyzed data for ICH and ischemic stroke across studies using the DerSimonian and Laird[17] random-effects model with weights calculated by the inverse variance method. Our main analysis quantified the strength of any association with outcomes of interest using odds ratios (ORs) and 95% confidence intervals (CIs) in patients with any CMB, ≥5 CMBs, and <5 CMBs (vs no CMBs as the reference group for all analyses). As prespecified, for comparisons with zero events in both groups, we added 0.5 to each group, considered OR = 1, and calculated the standard error, log OR, and standard error log OR by using the 2-variable input method.

To provide evidence of absolute risks, often useful for clinicians, we additionally estimated annualized symptomatic ICH and recurrent ischemic stroke rates (percent per year) and corresponding 95% CIs for each study from a Poisson regression model and exact Poisson intervals. We calculated pooled rates using the inverse variance method.

We assessed heterogeneity by I^2 and χ^2 statistics and visually through inspection of the forest plot. We explored publication bias with funnel plots and the Egger regression tests. Furthermore, we undertook meta-regression of confounding covariates of potential biological and significance with outcome.

All meta-analyses were performed with Stata 13.0 (StataCorp LP, College Station, TX). A 2-tailed value of $p < 0.05$ was considered a criterion for statistical significance.

RESULTS Eight groups provided clinical data on 9 hospital-based cohorts involving 1,552 patients for inclusion in this meta-analysis (figure 1 and table 1). Data from one of these cohorts (Australian population, 2010–2015, n = 359) were previously unpublished (published only as a conference abstract). A ninth cohort included AF patients without stroke at baseline[18] and was pooled with the rest of the cohorts in a post hoc sensitivity analysis. The risk of bias in the cohorts was moderate to low (table 2). Estimation of publication bias via the Egger test and the Begg test returned nonsignificant results (all $p > 0.20$). Follow-up was both retrospective and prospective, done face to face, and supplemented by telephone follow-up and patient record review as appropriate in all studies. All included studies had >90% completeness of clinical follow-up. Cohorts had some variation in baseline characteristics and rates of concurrent aspirin use during follow-up (table 1). In 3 studies, a proportion of patients were using NOACs during follow-up; however, there was no difference in warfarin vs NOAC use based on CMBs. Seven studies used T2*-GRE MRI at 1.5T and 2 studies used SWI MRI at 1.5T or 3T to detect CMBs at baseline (table 1). The crude random-effects pooled prevalence of CMBs was 30% (95% CI 25%–36%), and the pooled prevalence of ≥5 CMBs was 7% (95% CI 4%–10%).

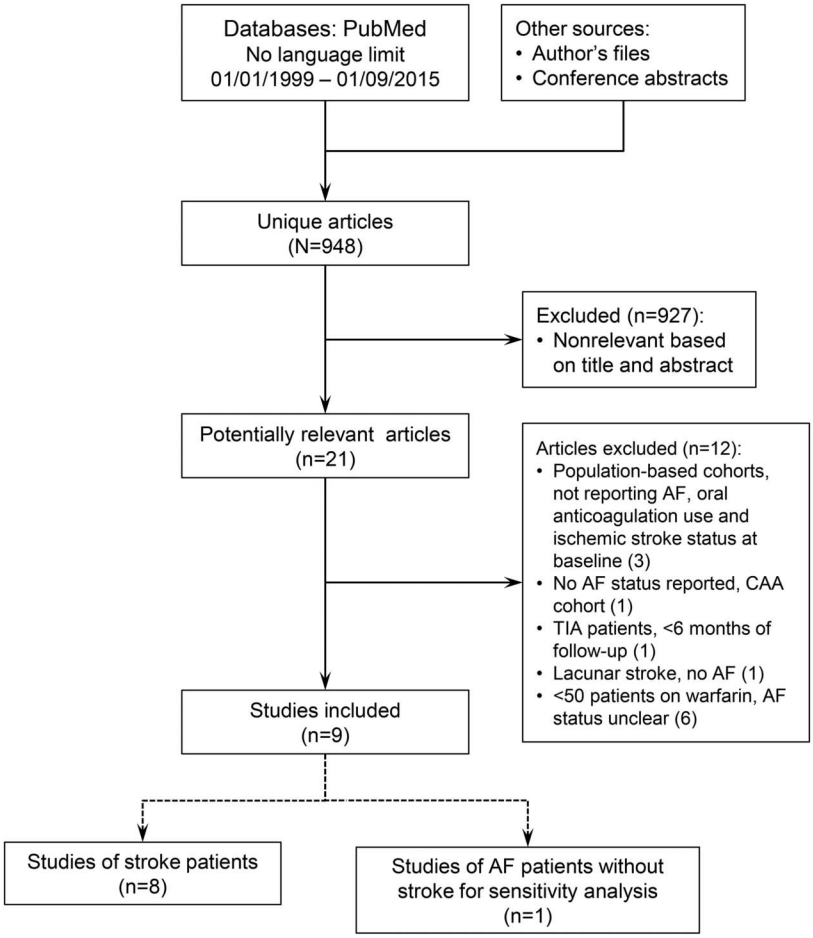
A total of 22 patients had a symptomatic ICH and 81 patients had a recurrent ischemic stroke during follow-up. The pooled annual risk of ICH was 0.49% (95% CI 0.24%–0.745%) per year compared with a higher annual risk of ischemic stroke (2.22%, 95% CI 1.26%–3.18%) ($p = 0.001$) but with moderate heterogeneity (figure 2). The pooled annual risk of ICH increased from 0.30% (95% CI 0.04%–0.55%) per year among those without CMBs to 0.81% (95% CI 0.17%–1.45%) per year in patients with any CMBs ($p = 0.01$) and 2.48% (95% CI 1.2%–6.2%) in patients with ≥5 CMBs ($p = 0.001$). The annual pooled risk in patients with <5 CMBs was 0.49% (95% CI 0%–1.09%).

In the meta-analysis, CMB presence on MRI was associated with a higher risk of symptomatic ICH during follow-up compared with patients without CMBs (OR 2.68, 95% CI 1.19–6.01, $p = 0.017$, figure 3A). This risk was particularly high for patients harboring ≥5 CMBs (OR 5.50, 95% CI 2.07–14.66, $p = 0.001$), with some evidence of heterogeneity across studies, but not for those with <5 CMBs (figure 3, B and C). There was no evidence for substantial heterogeneity in any of the analyses. The pooled risk of recurrent ischemic stroke in the patient group with ≥5 CMBs was 0.29% (95% CI 0%–2.77%) per year and for patients with <5 CMBs was 0.02% (95% CI 0%–0.36%).

No significant heterogeneity was noted between studies for the main outcome (i.e., ICH) according to age, sex, hypertension, median CHADS2 score, ICH history, percentage of warfarin-naive patients, prevalence of white matter hyperintensities, concurrent aspirin use, percentage of NOAC use, and MRI imaging parameters for CMB detection (all $p > 0.1$). Separate sensitivity analyses including only patients taking warfarin during follow-up were consistent and of an effect size similar to the main results presented here. The estimates did not change when the studies with zero cells in both groups were excluded post hoc.

Secondary analyses: CMBs distribution. In secondary analyses of CMBs distribution (vs no CMBs as the reference group), strictly lobar CMBs (OR 2.88, 95% CI

Figure 1 Flowchart of literature search and study selection



The search of electronic databases, authors' own files, and abstract books from recent conferences yielded 948 publications. After initial screening, 21 reports were identified for full-text review. Of these reports that were reviewed in full text, 9 independent studies were identified as potentially eligible. Supplementary EMBASE searches over the same time period did not yield any extra articles. One included center also provided data on an additional new cohort (n = 72), which was later published as a full article (Charidimou et al.[35]). AF = atrial fibrillation; CAA = cerebral amyloid angiopathy.

Table 1 Characteristics of included cohorts

Cohort	Country (study period)	Patients (M), n	Mean age, y	Hypertension, %	CHADS2 score, median (IQR)	Warfarin naive, %	History of ICH, %	WMH, %	Aspirin, %	NOAC, %	MRI parameters			CMB, %	Mean FU, y
											Sequence (echo time, ms)	Field strength, T	ST, mm		
Charidimou et al.[35]	Japan (2008–2014)	72 (60)	74	74	4 (3–4)	93	1	24	19	38	T2*-GRE (ET 26)	1.5	6.5	26	2.1
Srikanth et al.[41]	Australia (2010–2015)	359 (52)	75	79	4 (3–4)	91	1.7	54	8	11	SWI[b]	1.5/3	2/ 1.7	42	1.7
Haji et al.[36]	US (2008–2014)	90 (58)	80	87	4 (3–4)	80	0	60	67	0	T2*-GRE[a] (ET 20/15/24)	1.5	4–5	22	2.9
Horstmann et al.[6]	Germany (2009–2012)	70 (59)	75	90	4 (3–4)	67	0	71	31	50	SWI	3	3	30	0.6
Song et al.[37]	Korea (2005–2011)	477 (60)	69	76	2 (1–3)	74	1.9	40	45	0	T2*-GRE (ET 16)	1.5	5	29	3.5
Orken et al.[38]	Turkey (2009–2015)	204 (57)	67	16	4 (3–4)	100	0	53	28	0	T2*-GRE (ET 15)	1.5	6	17	3.3
Imaizumi et al.[39]	Japan (2004–2010)	68 (71)	70	69	3 (2–4)	71	2	10	29	0	T2*-GRE (ET 26)	1.5	6.5	32	2.5
Thijs et al.[40]	Belgium (2003–2006)	99 (56)	75	71	2 (1–3)	95	1	41	51	0	T2*-GRE (TE 35/26/16)	1.5/3	7	28	2
Soo et al.[8]	Hong Kong (1999–2004)	60 (55)	72	75	3 (2–4)	63	3	52	32	0	T2*-GRE (ET 30)	1.5	5	35	2.1
Saito et al.[18,c]	Japan (2012–2014)	53 (72)	71	62	2 (2–2)	NA	0	36	17	43	T2*-GRE (ET 18–20)	1.5	5.5	43	2.7

Abbreviations: CHADS2 = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke; CMB = cerebral microbleed; ET = echo time; FU = follow-up; GRE = gradient-recalled echo; ICH = intracerebral hemorrhage; IQR = interquartile range; NA = not applicable; NOAC = non-vitamin K oral anticoagulant; ST = slice thickness; SWI = susceptibility-weighted imaging; WMH = white matter hyperintensities.

[a] More than 90% of the cases.

[b] Ninety-five percent patients had SWI; 20 patients had T2*-GRE (ET 15 milliseconds, slice thickness 7 mm).

[c] Study including patients with atrial fibrillation without ischemic stroke.

Table 2 Assessment of the 10 cohorts against each of 8 risks of bias of the Cochrane "Tool to Assess Risk of Bias in Cohort Studies"[a] and the Newcastle-Ottawa Scale[b]

Risks of bias	Charidimou et al.[35]	Srikanth et al.[41]	Haji et al.[36]	Horstmann et al.[6]	Song et al.[37]	Orken et al.[38]	Imaizumi et al.[39]	Thijs et al.[40]	Soo et al.[8]	Saito et al.[18]
Was selection of exposed and nonexposed patients drawn from the same population? (Criterion: all were adults diagnosed with recent symptomatic ischemic stroke and AF and had T2*-GRE/SWI MRI for CMBs status)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	NA
Can we be confident in the assessment of exposure? (Criteria: T2*-GRE/SWI MRI was used to establish CMBs status per current consensus criteria)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Can we be confident that outcome of interest was not present at start of study? (Criterion: ICH was described during follow-up)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Did the study match exposed and unexposed for all variables that are associated with the outcome of interest, or did the statistical analysis adjust for these prognostic variables? (Not applicable because of study design and sample size in each study)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Can we be confident in the assessment of the presence or absence of prognostic factors? (Criteria: T2*-GRE/SWI MRI was used for CMBs; other basic clinical variables noted as well)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Can we be confident in the assessment of outcome? (Criterion: ICH was defined as symptomatic and confirmed by brain imaging)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Was the follow-up of cohorts adequate? (Criterion: median follow-up was ≥2 y)	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Were cointerventions similar between groups? (Criterion: aspirin use, risk factor modifications, etc)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Selection (Newcastle-Ottawa Scale)	***	***	***	***	***	**	***	***	***	**
Comparability (Newcastle-Ottawa Scale)	*	—	—	—	*	—	—	*	*	—
Outcome (Newcastle-Ottawa Scale)	**	**	**	**	***	*	**	***	***	**

Abbreviations: AF = atrial fibrillation; CMB = cerebral microbleed; GRE = gradient-recalled echo; ICH = intracerebral hemorrhage; NA = not applicable; SWI = susceptibility-weighted imaging.

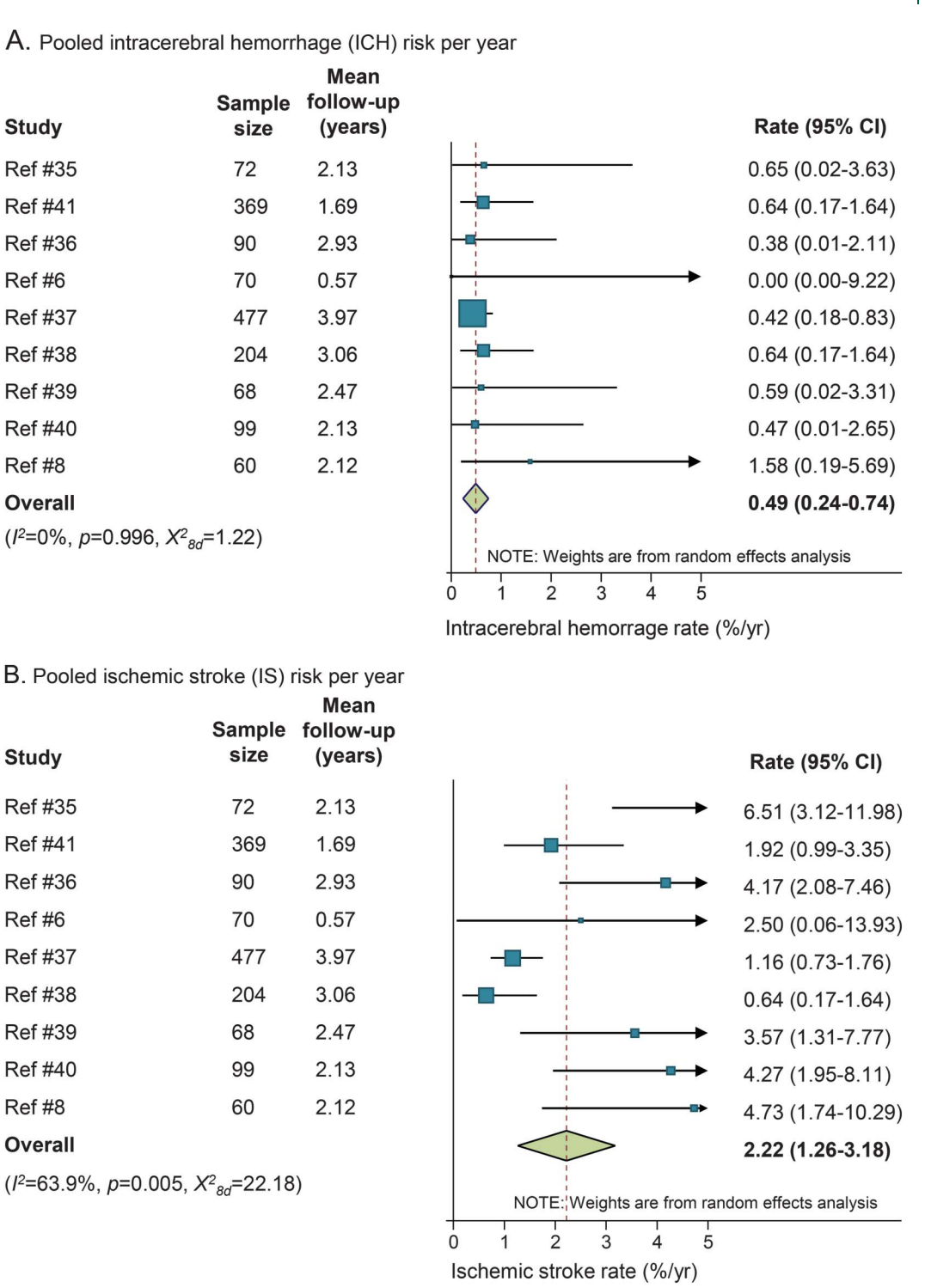
[a] An 8-item tool published by the Cochrane Methods Bias group: http://bmg.cochrane.org/sites/bmg.cochrane.org/files/uploads/Tool%20to%20Assess%20Risk%20of%20Bias%20in%20Cohort%20Studies.pdf.

[b] Ratings for the Newcastle-Ottawa Scale: a study can be awarded a maximum of 1 star for each numbered item within the selection (maximum 4 stars) and outcome (maximum 3 stars) categories. A maximum of 2 stars can be given for comparability. For details, see Wells GA, Shea B, O'Connell D, et al. The Newcastle- Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

1.14–7.23, $p = 0.025$) and mixed CMB pattern (OR 2.91, 95% CI 0.99–8.54, $p = 0.052$), but not strictly deep CMBs (OR 2.43, 95% CI 0.83–7.14, $p = 0.107$), were associated with the risk of ICH. CMB presence, burden, and distribution were not associated with recurrent ischemic stroke (all ORs ≈1.00).

DISCUSSION This is a large-scale meta-analysis of the significance of CMBs in ischemic stroke patients with AF treated with oral anticoagulation (mainly warfarin), a lingering question of clinical relevance.[9,19,20] In this study, we brought together group-level data from >1,500 patients. The most important new finding is that the presence of ≥5 CMBs, regardless of their topographical distribution, identifies a patient group at particularly high risk for ICH. The risk of subsequent ICH in these patients of 2.8%/y may be high enough to be considered in the decision making for anticoagulation, at least in patients with characteristics similar to those of the included cohorts, after validation in international collaborative efforts.[7,21]

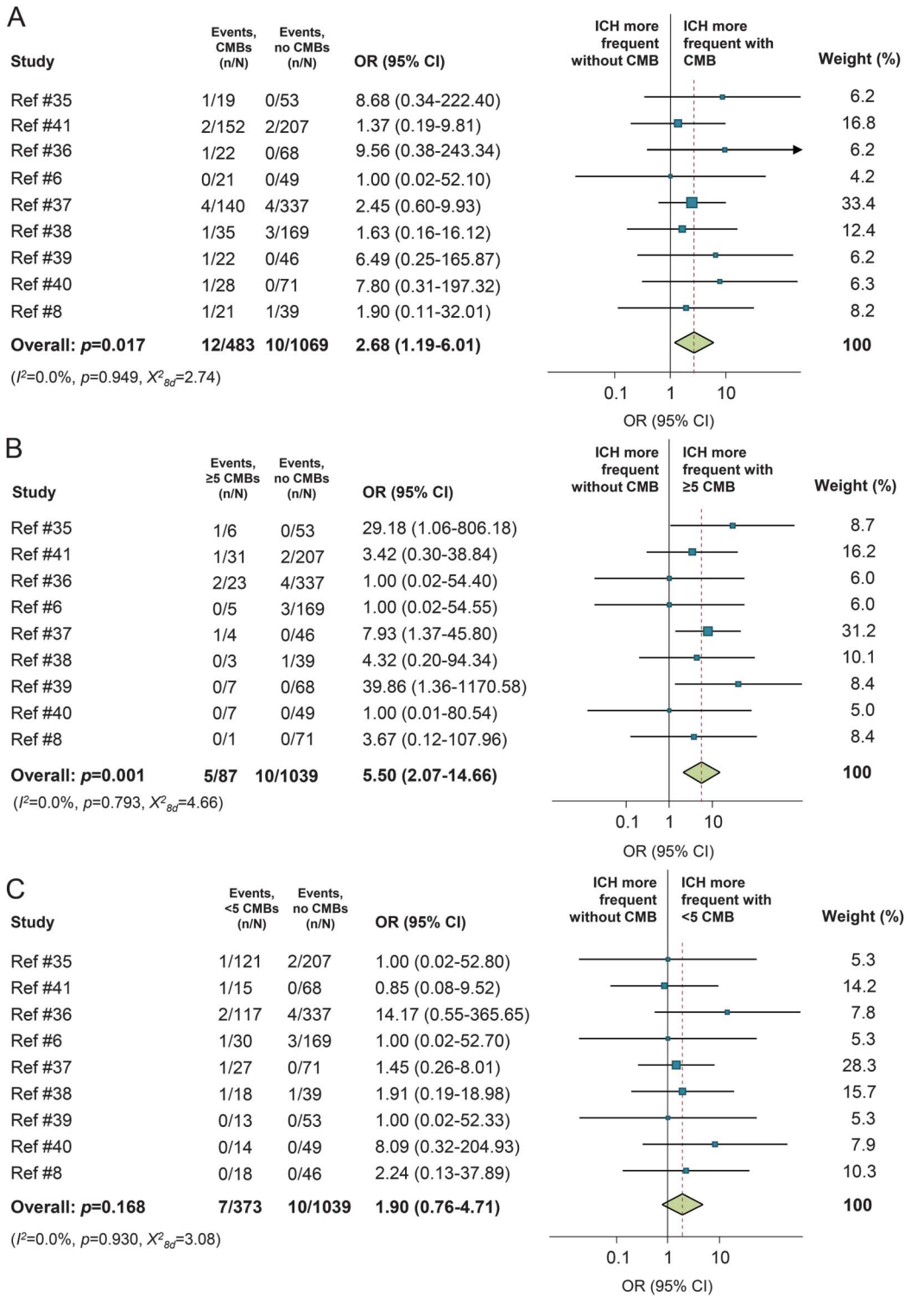
Figure 2 Annual absolute risk of stroke in included cohorts



Pooled annual rates of (A) incident symptomatic intracerebral hemorrhage and (B) recurrent ischemic stroke during follow-up in included studies. Weights are shown by the point estimate area. CI = confidence interval.

These results are largely in line with previous meta-analyses on CMBs in stroke.[3,22,23] A cross-sectional meta-analysis of stroke patients showed that CMBs are more common in warfarin- or antiplatelet-related ICH than spontaneous ICH without previous antithrombotic drug use.[23] A recent meta-analysis of 10 prospective ischemic stroke or TIA cohorts (n = 3,067) demonstrated that the presence of any CMB is associated with a higher risk of ICH.[22] These results were extended by a more recent meta-analysis (n = 5,068) including similar cohorts, demonstrating that with increasing CMB burden (compared with no CMBs), the risk of ICH increases more steeply than that of ischemic stroke.[3] However, the majority of

Figure 3 Meta-analyses of CMBs and risk of future ICH in included studies



Forest plots of associations between (A) CMB presence, (B) ≥5 CMBs, and (C) <5 CMBs and the risk of symptomatic ICH (main outcome) during follow-up. Plots show cohort-level and pooled estimates of these associations with no CMBs as the reference group in all analyses. The area of each shaded box is proportional to the weight of the cohort it represents. CI = confidence interval; CMB = cerebral microbleed; ICH = intracerebral hemorrhage; OR = odds ratio.

these patients did not have AF and were treated with antiplatelet agents.

Our analysis shows that the overall annual risk for ICH in anticoagulant ischemic stroke patients with AF is 0.24% to 0.74%, consistent with subgroup analyses for secondary prevention in randomized trials of vitamin K antagonist vs NOAC in stroke.[24–26] In contrast, patients with ≥5 CMBs are at increased

risk of ICH. Because of the devastating outcome of anticoagulation ICH and despite the effectiveness for preventing stroke due to AF, warfarin might carry more harm than benefit for those AF patients at greatest ICH risk.[9,19] A high burden of CMBs may thus tip the balance in favor of risk rather than benefit for the decision to anticoagulate. In a hypothetical decision analysis model, an AF patient with typical risk for ischemic stroke (i.e., 4.5%/y if untreated) and previous ICH should not be anticoagulated if the (untreated) risk for future recurrent ICH exceeds 1.4%/y.[27] Of note, the ischemic stroke risk might be even higher in patients with a previous ischemic stroke (similar to our meta-analysis population) if untreated. For this patient subgroup, greater emphasis on the newer anticoagulants appears to be in order because of their generally lower risk of hemorrhagic side effects and ischemic outcomes.[28] In the rapidly evolving anticoagulation landscape, it is important to keep in mind that there are no data indicating whether the reduced ICH risk conferred by NOACs compared to warfarin extends to patients with multiple CMBs at high risk for future ICH or to patients with lobar ICH.[29] Because of the class effect of all NOACs in reducing ICH rates, these findings await replication in cohorts treated with NOACs.

In addition, no study to date has directly measured the additive effect of anticoagulation on ICH risk in CMB-positive patients.[19] Percutaneous occlusion of the left atrial appendage may be considered an another alternative stroke prevention therapy in patients with ≥5 CMBs, but evidence for its safety in these patients with multiple CMBs or lobar ICH is very limited, and the effect of antithrombotic regimens required for the procedure remains to be defined.[30,31] Removal or modification of additional risk factors for ICH should include controlling blood pressure, stopping concurrent aspirin, replacing nonsteroidal anti-inflammatory drugs with Cox inhibitors, and restricting alcohol intake as plausible strategies.[19]

Our study has notable strengths, including a large sample size from multiple cohorts and the homogeneity of effect size direction across studies, all pointing to the validity of the results. We have included analyses based on a prespecified CMB cutoff based on previous data, presented secondary analyses based on CMBs distribution, and explored heterogeneity. Our meta-analysis has limitations that deserve careful consideration, especially methodological differences across studies. For example, studies had a small sample size, variable and rather short follow-up (<3 years in general), and hence few outcome events (especially given the rarity of ICH as an outcome), leading to wide CIs around risk estimates. The MRI protocols for CMB detection were similar (including mainly T2*-GRE at 1.5T, with echo times within a reasonable range) but not completely harmonized, potentially affecting the detection of CMBs.[32] In addition, in our study, CMBs were determined by local investigators and not by central readers, although all centers used trained raters and standardized definitions according to Standards for Reporting Vascular Changes on Neuroimaging criteria. Although treating clinicians in participating centers have not taken into account CMBs in routine clinical decision making for anticoagulation, this possibility cannot be completely excluded, especially for patients with very high CMB burden.

A potential important limitation of this study-level data approach is confounding of these estimates by other baseline variables related to future stroke risk in AF, including age, history of stroke, concurrent aspirin use, timing of starting oral anticoagulation after the baseline acute stroke, patient adherence to anticoagulation, and time in range. In addition, data on stroke severity and functional status at baseline were not available, although patients were fit enough to undergo MRI, were discharged on oral anticoagulation, and were to be followed up clinically. Despite our best efforts to adjust for certain available confounding factors in meta-regression analyses, this is unlikely to have accounted for the full range of interactions between different variables. Hence, the present analyses do not adequately account for potential confounding by vascular risk factors or other variables. None of the included cohorts were specifically designed to answer the specific questions explored in the present analysis. Moreover, all cohorts used clinical data, introducing some bias, and data were not collected with same accuracy or did not include the full range of covariates as research data. However, all studies showed a consistent direction of association between CMBs and ICH risk. Further stratified analyses are needed to explore the risk of future stroke and CMBs in Asian vs non-Asian patients and according to anticoagulation strategy, e.g., warfarin vs NOACs. Of relevance, the MRI substudy of A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES) showed that patients on apixaban and patients on aspirin had a similar number of incident CMBs.[33]

Our secondary analyses based on CMB distribution were not powerful enough to fully disentangle the role of different predominant small vessel disease pathologies in increasing the risk of ICH. This is due partly to confounding by CMB number across different topographical categories. Determining patients' underlying small vessel disease subtype on the basis of CMB distribution would be a key next step for future analyses. Bleeding in other intracranial compartments (including subdural and rarely subarachnoid), especially in the

elderly, should also be investigated in further studies and meta-analyses. There might be a selection bias because not all AF patients with stroke undergo an MRI with blood-sensitive MRI sequences in clinical practice. Finally, although AF was defined by ECGs, either they were done at baseline stroke presentation or information was based on clinical history documentation of ECG findings. Presumed cardioembolic strokes (confirmed on either MRI or CT) in the setting of AF were included in our analysis but with potential competing causes. Both can affect the generalizability of our estimates.

Our data suggest that MRI could identify a specific subgroup of patients with ischemic stroke and AF (treated mainly with warfarin), namely those with ≥5 CMBs, who are at high risk for ICH events. Although MRI screening for CMBs is not needed before antithrombotic therapies initiation,[34] in this patient subgroup, the modification of anticoagulation strategy for stroke prevention might be relevant and in line with recent recommendations[34] and should be explored in future studies and trials.[9,20,34] Given the limitations discussed, these results can be generalized only to patient populations with overall characteristics similar to those of the patients included in our study, i.e., patients with generally mild strokes who are fit enough to undergo MRI at baseline and have CHADS2 scores between 2 and 4. Large international efforts in the field are underway to validate and expand these findings.[7,21]

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. A. Charidimou. A. Charidimou: study concept and design, systematic review, data analysis, write-up. Christopher Karayiannis, Tae-Jin Song, Dilek Necioglu Orken, Vincent Thijs, Robin Lemmens, Jinkwon Kim, Su Mei Goh, Thanh G. Phan, Cathy Soufan, Ronil V. Chandra, Lee-Anne Slater, Shamir Haji, Vincent Mok, Solveig Horstmann, Kam Tat Leung, Yuichiro Kawamura, Nobuyuki Saito, Naoyuki Hasebe, Tsukasa Saito, Lawrence K.S. Wong, Yannie Soo, Roland Veltkamp, Kelly D. Flemming, Toshio Imaizumi, Velandai Srikanth, and Ji Hoe Heo: data acquisition, critical revisions.

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DISCLOSURE

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