Impact of Cerebral Microbleeds in Stroke Patients with Atrial Fibrillation

Soo Yannie OY (Orcid ID: 0000-0002-3489-3201)
Polymeris Alexandros A (Orcid ID: 0000-0002-9475-2208)
Seiffge David J (Orcid ID: 0000-0003-3890-3849)
Koga Masatoshi (Orcid ID: 0000-0002-6758-4026)
Chabriat Hugues (Orcid ID: 0000-0001-8436-6074)
Kim Young Dae (Orcid ID: 0000-0001-5750-2616)
Gattringer Thomas (Orcid ID: 0000-0002-6065-6576)
Göldlin Martina Béatrice (Orcid ID: 0000-0001-5800-116X)
Wiegertjes Kim (Orcid ID: 0000-0001-7480-1482)
Tuladhar Anil M (Orcid ID: 0000-0002-4815-2834)
Zhou Ying (Orcid ID: 0000-0003-3577-4527)
Kandiah Nagaendran (Orcid ID: 0000-0001-9244-4298)
Wardlaw Joanna M. (Orcid ID: 0000-0002-9812-6642)
Heo Ji Hoe (Orcid ID: 0000-0002-6112-2939)
Jouvent Eric (Orcid ID: 0000-0001-7797-2236)
Toyoda Kazunori (Orcid ID: 0000-0002-8346-9845)
Yoshimura Sohei (Orcid ID: 0000-0002-4751-3538)
Martí - Fàbregas Joan (Orcid ID: 0000-0001-9229-8649)

Impact of Cerebral Microbleeds in Stroke Patients with Atrial Fibrillation

Yannie Soo MB ChB[1*], Annaelle Zietz MMed[2*], Brian Yiu BBA[1], Vincent C.T. Mok MD[1,3], Alexandros A Polymeris MD, PhD[2], David Seiffge MD[4], Gareth Ambler PhD[5], Duncan Wilson MD, PhD[6], Thomas Wai Hong Leung MD[1], Suk Fung Tsang MPhil[1], Winnie Chu MD[7], Jill Abrigo MD[7], Cyrus Cheng MB ChB[1], Keon-Joo Lee MD[8], Jae-Sung Lim MD[9], Masayuki Shiozawa MD[10], Masatoshi Koga MD PhD[10], Hugues Chabriat MD[11], Michael Hennerici MD[12], Yuen Kwun Wong PhD[13], Henry Mak MD[14], Roger Collet MD[15], Shigeru Inamura MD[16], Kazuhisa Yoshifuji PhD[16], Ethem Murat Arsava MD[17], Solveig Horstmann MD[18], Jan Purrucker MD[18], Bonnie YK Lam PhD[1,3], Adrian Wong PhD[3], Young Dae Kim MD[19], Tae-Jin Song MD,PhD[20], Robin Lemmens PhD[21], Sebastian Eppinger MD[22, 23], Thomas Gattringer MD[22, 23], Ender Uysal MD[24], Derya Selçuk Demirelli, MD[25], Natan M Bornstein MD[26], Einor Ben Assayag PhD[26], Hen Hallevi MD[26], Jeremy Molad MD[26], Masashi Nishihara MD[27], Jun Tanaka MD[28], Shelagh B. Coutts MD[29], L. Jaap Kappelle MD[30], Rustam Al-Shahi Salman PhD[31], Rolf Jager MD[32], Gregory Y.H. Lip MD[33,34], Martina B Goeldlin MD[4], Leonidas D Panos MD[4], Jean-Louis Mas MD[35], Laurence Legrand PhD[36], Chris Karayiannis MD, PhD[37], Thanh Phan MD[38], Maximilian Bellut MD[39], Francesca Chappell PhD[40], Stephen Makin MBChB, PhD[41], Derek Hayden MD, MRCPI[42], David Williams PhD[43], Dianne H.K. van Dam-Nolen MD[44], Paul J. Nederkoorn MD PhD[45], Carmen Barbato MD, PhD[46], Simone Browning BSc[47], Kim Wiegertjes MD[48], Anil Man Tuladhar MD[48], Anne-Marie Mendyk RN[50], Sebastian Köhler PhD[51], Robert van Oostenburgge MD, PhD[52], Ying Zhou PhD[53], Chao Xu MD[53], Hilal Saima MPH, MD, PhD[54], Bibek Gyanwali MD, PhD[55], Christopher Chen FRCP[55], Min Lou MD PhD[53], Julie Staals MD, PhD[52], Regis Bordet MD[50], Nagaendran Kandiah FRCP[49], Frank-Erik de Leeuw MD[48], Robert Simister PhD[47], Jeroen Hendrikse MD PhD[56], Joanna Wardlaw MD FRCR[57], Peter Kelly MD[58], Felix Fluri MD[39], Velandai Srikanth PhD[59], David Calvet MD[35], Simon Jung MD[4], Vincent, I.H. Kwa MD, PhD[60], Eric E. Smith MD MPH, FAHA[29], Hideo Hara MD, PhD[61], Yusuke Yakushiji MD, PhD[62], Dilek Necioglu Orken MD[63], Franz Fazekas MD[22], Vincent Thijs MD[64], Ji-Hoe Heo MD[19], Roland Veltkamp MD[65], Hakan Ay MD[66], Toshio Imaizumi MD[67], Kui Kai Lau DPhil[68], Eric Jouvent MD[69], Kazunori Toyoda MD, PhD[10], Sohei Yoshimura MD[10], Hee-Joon Bae MD, PhD[70], Joan Martí-Fàbregas PhD[15], Luis Prats-Sánchez MD, PhD[15], Philippe Lyrer MD[2], Jonathan Best MD[47], David Werring PhD[47], Stefan T Engelter MD[2,71], Nils Peters MD[2,71,72] on behalf of the Microbleeds International Collaborative Network

[*]Equally contributing first authors

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[1]Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
[2]Department of Neurology and Stroke Centre, University Hospital Basel and University of Basel, Switzerland
[3]Gerald Choa Neuroscience Institute, Margaret K.L. Cheung Research Centre for Management of Parkinsonism, Therese Pei Fong Chow Research Centre for Prevention of Dementia, Lui Che Woo Institute of Innovative Medicine, Li Ka Shing Institute of Health Science, Lau Tat-chuen Research Centre of Brain Degenerative Diseases in Chinese, The Chinese University of Hong Kong, Hong Kong SAR
[4]Department of Neurology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland
[5] Department of Statistical Science, University College London, Gower Street, London, UK
[6] Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK; New Zealand Brain Research Institute, Christchurch,
[7] Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
[8] Department of Neurology, Korea University Guro Hospital, Seoul, Republic of Korea
[9]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[10]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Centre, Suita, Osaka 564-8565, Japan
[11]APHP, Lariboisière Hospital, Translational Neurovascular Centre, F-75475 Paris, France; FHU NeuroVasc, Université de Paris and INSERM U1141, Paris, France
[12] Department of Neurology, University of Heidelberg/Mannheim Hospital, Mannheim, Germany
[13]Division of Neurology, Department of Medicine, The University of Hong Kong, Hong Kong
[14]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong
[15] Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute, Barcelona, Spain
[16] Department of Neurosurgery, Kushiro City General Hospital, Kushiro, Japan
[17]Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA
[18] Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
[19] Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea
[20] Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul, South Korea
[21] Experimental Neurology, Department of Neurosciences, KU Leuven – University of Leuven; VIB Center for Brain & Disease Research; Department of Neurology, University Hospitals
[22] Department of Neurology, Medical University of Graz, Graz, Austria
[23] Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology, Medical University of Graz, Graz, Austria
[24] University of Health Sciences Turkey, Antalya Teaching and Research Hospital, Department of Radiology
[25] University of Health Sciences Turkey, Sisli Hamidiye Etfal Teaching and Research Hospital, Department of Neurology
[26] Department of Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[27] Department of Radiology, Saga University Faculty of Medicine, 5-1-1, Nabeshima, Saga, Japan
[28] Department of Cerebrovascular Medicine, St. Mary's Hospital, Kurume, Japan
[29] Calgary Stroke Program, Department of Clinical Neurosciences, Radiology and Community Health Sciences, Hotchkiss Brain Institute, University of Calgary
[30] Department of Neurology and Neurosurgery, University Medical Centre Utrecht and Utrecht University, Utrecht, The Netherlands
[31] Centre for Clinical Brain Sciences, School of Clinical Sciences, University of Edinburgh, Edinburgh, UK
[32] Lysholm Department of Neuroradiology and the Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK
[33] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[34] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[35] GHU-Paris Psychiatrie et Neurosciences, Neurology Department and Stroke Unit, Sainte-Anne Hospital, and Université de Paris Cité, INSERM U1266, Institute of Psychiatry and Neuroscience of Paris, France
[36]GHU-Paris Psychiatrie et Neurosciences, Neuroradiology Department, Sainte-Anne Hospital, and Université Paris Cité, INSERM U1266, Institute of Psychiatry and Neuroscience of Paris, France
[37] Peninsula Clinical School, Peninsula Health, Monash University, Melbourne, Australia

[38] Stroke and Ageing Research Group, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia
[39] Department of Neurology, University Hospital of Würzburg, Josef-Schneider Strasse 11, 97080, Würzburg, Germany
[40]Centre for Clinical Brain Sciences, Edinburgh Imaging; and UK Dementia Institute at the University of Edinburgh, Edinburgh, UK
[41] Centre for Rural Health, Institute for Applied Health Sciences, University of Aberdeen, UK
[42] Acute Medical Unit and Department of Age-related Healthcare, Tallaght University Hospital, Dublin, Ireland
[43] Department of Geriatric and Stroke Medicine, RCSI University of Medicine and Health Sciences Dublin, Ireland and Beaumont Hospital Dublin, Ireland
[44] Department of Radiology and Nuclear Medicine, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands
[45] Department of Neurology, Amsterdam University Medical Centers, Amsterdam, The Netherlands
[46] Department of Neurology, University of Florence, Italy
[47] Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK; Comprehensive Stroke Service, University College London Hospitals NHS Trust, London, UK
[48]Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Donders Centre for Medical Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands
[49] Dementia Research Centre (Singapore), Lee Kong Chian School of Medicine, Singapore
[50]University of Lille, Inserm, CHU de Lille. Lille Neuroscience & Cognition. F-59000 Lille
[51] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNs), Maastricht University, The Netherlands
[52] Department of Neurology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, The Netherlands
[53] Department of Neurology, The Second Affiliated Hospital of Zhejiang University, School of Medicine
[54] Saw Swee Hock School of Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[55] Memory Aging & Cognition Centre, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[56] Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[57]Division of Neuroimaging Sciences, Edinburgh Imaging; UK Dementia Research Institute, University of Edinburgh and NHS Lothian, Edinburgh, UK
[58] The Neurovascular Research Unit and Health Research Board, Stroke Clinical Trials Network Ireland, University College Dublin, Dublin
[59] Peninsula Clinical School, Peninsula Health, Monash University, Melbourne, Australia; National Centre for Healthy Ageing, Melbourne, Australia.
[60] Department of Neurology, OLVG, Amsterdam, The Netherlands
[61] Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine, Saga, Japan.
[62] Department of Neurology, Kansai Medical University, Hirakata, Osaka, Japan
[63] Istanbul Arel University, Department of Neurology
[64] Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg; Department of Neurology, Austin Health, Heidelberg, Australia
[65] Department of Brain Sciences, Imperial College London, London, UK; Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
[66] A.A. Martinos Center for Biomedial Imaging, Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; Taked
[67] Department of Neurosurgery, Kushiro City General Hospital, Kushiro, Japan
[68] Division of Neurology, Department of Medicine, The University of Hong Kong, Hong Kong; State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong
[69]Université de Paris - Assistance Publique Hôpitaux de Paris, Paris, France; Département de neurologie, Hôpital Lariboisière, FHU NeuroVasc, INSERM NeuroDiderot U1141, Paris, France
[70] Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea
[71] Neurology and Neurorehabilitation, University Department of Geriatric Medicine FELIX PLATTER, University of Basel, Basel, Switzerland.
[72] Stroke Center, Klinik Hirslanden, Zürich, Switzerland

Corresponding author:

Nils Peters, MD
Stroke Center, Klinik Hirslanden Zürich
and
Department of Neurology and Stroke Center
University Hospital Basel
University of Basel
Switzerland
Email: nils.peters@unibas.ch

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2. **What is the current knowledge on the topic?**

   Cerebral microbleeds, an MRI marker of bleeding-prone microangiopathy, are associated with both ischemic stroke and intracranial hemorrhage. In patients at risk of ischemic stroke, the presence of cerebral microbleeds causes clinical dilemmas in stroke prevention using antithrombotic drugs which may also increase the risk of intracranial hemorrhage.

3. **What question did this study address?**

   We aimed to evaluate the risks of subsequent intracranial hemorrhage and ischemic stroke associated with cerebral microbleeds among patients with atrial fibrillation treated with various antithrombotic treatments - Vitamin K antagonist, Direct Oral Anticoagulants, antiplatelets and combination therapy (i.e. concurrent oral anticoagulant and antiplatelet).

4. **What does this study add to our knowledge?**

   To our knowledge, this is the largest study evaluating risk of ischemic stroke and intracranial hemorrhage associated with cerebral microbleeds in patients with atrial fibrillation treated with different antithrombotic treatments. We found that patients with multiple microbleeds taking both anticoagulants and antiplatelets may have risk of subsequent intracranial hemorrhage exceeding that of ischemic stroke.

5. **How might this potentially impact on the practice of neurology?**

   The findings of this study illustrate how CMB could help identify patients with atrial fibrillation who are at excess risk of antithrombotics-associated intracranial hemorrhage which may outweigh the intended benefit in ischemic stroke prevention. This calls for further studies to evaluate safer stroke preventive strategies and measures to mitigate risk of intracranial hemorrhage in patients with atrial fibrillation on combination antithrombotic therapy.

Abstract

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 (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 microbleeds 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 2-4 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.

Introduction

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 (CMB) have evolved to be a useful radiological marker which improves risk prediction for ICH. As part of the spectrum of small vessel disease, CMB are dot-like hypointense signals detected by heme-sensitive MRI sequences, e.g. T2*gradient-echo or susceptibility-weighted imaging (SWI).[5,6] They are perivascular hemosiderin deposits indicating previous asymptomatic leakage from bleeding-prone microangiopathy. Deep CMB are commonly associated with hypertensive arteriopathy, while pure lobar CMB 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 CMB, 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 CMB 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 CMB 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 etiology and antithrombotic therapies, particularly patients with atrial fibrillation (AF) on anticoagulants which may have a higher risk of ICH than antiplatelets,[15] but better efficacy in prevention of IS.[16]

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 CMB among patients with AF, and stratify the stroke risks by four antithrombotic treatments - Vitamin K antagonist (VKA), Direct Oral Anticoagulants (DOAC), antiplatelets (single or dual agents) and 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 CMB 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 sub-analysis. The MICON study protocol is registered on PROSPERO, CRD42016036602.

Outcome parameters

The primary outcomes were subsequent time to ICH alone and IS alone; the secondary outcome was time to vascular death. All events were adjudicated according to individual cohort protocols. ICH was confirmed radiologically and included intracerebral hemorrhage, 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 CMB 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 interval for the mean of the Poisson distribution based on the number of observed events. We investigated the association between presence of CMB, predefined CMB burden categories (0, 1, 2-4,

5-10, ≥11 CMB) and distribution of CMB (pure deep, pure lobar, 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 CMB (T2*-weighted GRE or SWI). Patients with missing variables required for Cox regression analyses were excluded from the model. Interaction between presence of CMB 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 (i.e. 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, DOAC, antiplatelet and combination therapy. Patients on unknown antithrombotic 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, 47.5% were female. Ethnicity was available in 6386 patients, including 3394 Whites, 2973 Asian and 19 Black. The median follow-up period was 23.5 (IQR 9.9, 26.6) months, 35.6% of the patients had follow-up period of less than one year.

Characteristics of patients with CMB

CMB were present in 2,142 (27.3%) patients and the exact CMB burden was available in 2,026 patients. Among patients with CMB, the median number of CMB was 2 (IQR 2), including 970 patients with 1 CMB, 675 patients with 2-4 CMB, 210 patients with 5-10 CMB, and 171 patients with ≥11 CMB. Information of CMB distribution was available in 1960 patients. Six hundred and ninety-eight patients (35.6%) had pure lobar CMB, 689 (35.1%) had pure deep CMB and 573 (29.3%) had mixed deep-lobar CMB.

Compared to patients without CMB, patients with CMB 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 CMB. (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 intracerebral hemorrhages, 3 subarachnoid hemorrhages, 13 subdural hemorrhages and 1 patient with more than one 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 (0 [IQR 2]) than those without (0 [IQR 1]), p<0.001. The proportion of patients with ≥5 CMB was higher in patients with ICH (15.7%) than those without (5.0%), p < 0.001. (Table 2)

The incidence of ICH in patients with CMB was 12 per 1,000 patient-years compared to 4 per 1,000 patient-years in those without CMB, an absolute increase of 8 per 1,000 patient-years. (Table 3A) 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 CMB 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 2), deep CMB (aHR 4.39 [2.51-7.67]) and mixed deep-lobar CMB (aHR 3.07 [1.48 - 6.38]).(Table 3A, Fig 2) Status of Modified Boston Criteria was available in 2,124 patients, while Fazekas score was available in 4301 patients. There was no increase in risk of ICH in those with probable CAA (aHR1.35 [0.17 - 10.48]) nor Fazekas score ≥2 (aHR 0.67 [0.32 - 1.41]).

Ischemic stroke

Four hundred and twelve patients developed IS over 13,521 patient-years of follow-up, with 273 (66.3%) 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, previous use of anticoagulants compared to patients without IS. (Table 4) CMB 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 CMB was higher in patients with IS (7.9%) than those without (4.9%), $p = 0.009$.(Table 4)

The incidence of IS was 33 per 1,000 patient-years in patients with CMB 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]). (Table 3A) The presence of mixed deep-lobar CMB was associated with increased aHR for IS (aHR1.57 [1.11-2.22]).(Fig 2B) However, a higher burden of CMB had no influence on incidence of IS.(Table 3A, Fig

2B) Interaction was noted between presence of CMB with Asian for IS (aHR 1.61 [1.01-2.58], $P_{interaction}$ = 0.046). No interaction was detected between CMB and other ethnic groups for other outcome events.

Vascular death

Vascular death occurred in 330 patients over 13,949 patient-years follow-up. The incidence of vascular death was 26 per 1,000 patient-years in patients with CMB compared to 22 compared to patients without CMB, 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 CMB with risk of vascular death in patients with AF overall. (Table 3A, 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 sub-analysis. Interaction for ICH risk was detected between CMB burden categories and VKA ($P_{interaction}$ = 0.04), antiplatelet ($P_{interaction}$ <0.001) and combination therapy ($P_{interaction}$ <0.001), but not DOAC. Interaction for IS risk was detected between CMB burden and antiplatelet therapy ($P_{interaction}$ <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 DOAC

For patients on VKA, patients with CMB had higher incidence of ICH compared to patients without CMB (12 per 1,000 patient-years with CMB vs 6 per 1,000 patient-years without CMB, aHR 1.92 [1.06 - 3.49]). The association was mostly driven by patients with 5-10 CMB who had significantly higher aHR for ICH (aHR 4.04 [1.19 - 13.66]). (Table 3B) Furthermore, presence of CMB was associated with a trend of increased incidence of IS (aHR 1.37 (0.99-1.89), while patients with ≥11 CMB had significantly higher incidence of IS compared to patients without CMB (66 per 100 patient-years with ≥11 CMB vs 24 per 1,000 patient-year without CMB, aHR 2.37 [1.13 – 5]). Neither presence of CMB nor their burden influenced risk of vascular death. (Table 3B).

For patients on DOACs, neither the presence nor burden of CMB influenced the risk of ICH, IS and vascular death. (Table 3C).

Patients on antiplatelet drugs

Compared to patients without CMB, presence of CMB in patients on antiplatelet drugs was associated with a significantly higher incidence of IS (72 per 1,000 patient-years with CMB vs 33 per 1,000 patient-years without CMB, aHR 2.43 [1.34-4.43]). The association was mostly driven by patient with 5-10 CMB (aHR 7.27 [2.76-19.15]) who also had increased incidence for vascular mortality (aHR 6.05 [1.44-25.45)]). (Table 3D)

For patients on antiplatelet drugs, no statistically significant association between presence of CMB and risk of ICH was observed (21 per 1000 patient-years with CMB vs 3 per 1,000 patient-years without CMB, aHR 4.93 [0.81-30.18]). The small number of ICH in patients on antiplatelet (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 CMB (18 per 1,000 patient-years) compared to patients without CMB (2 per 1,000 patient-years) (aHR 7.92 [2.43-25.82]). The association was most significant among patients with 2-4 CMB (aHR 10.23 [2.41-43.37]) and ≥11 CMB (aHR 27.97 [5.57 - 140.55]). In this treatment group, neither the presence nor burden of CMB was associated with increased incidence of IS, while the presence of ≥ 11 CMB was associated with increased risk of vascular death (aHR 4.76 [1.31–17.26]). (Table 3E)

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 were shown in Table 3B to E and Fig 1B to E. The absolute incidence rate of IS was higher than ICH for majority of the patients except for (i) patients on VKA with 5-10 CMB 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 2-4 CMB and ⩾11 CMB 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 2-4 CMB and 94 per 1,000 patient-years for ICH vs 48 per 1,000 patient-years for IS in patients with ⩾11 CMB). (Fig 1B to E) Among all the treatment groups, the highest rate of ICH was observed among patients on combination therapy with ≥11 CMB (94 per 1,000 patient-years). (Table 3)

Discussion

In this sub-analysis of the MICON pooled individual patient data cohort among stroke patients with AF, the presence of CMB was associated with increased risk of subsequent ICH and IS but not vascular death; the burden of CMB 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 CMB, 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 increased risk of ICH, IS or vascular death among patients with CMB.

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

Regarding the distribution of CMB in predicting outcome events, subsequent ICH was strongly associated with presence of deep CMB, either as pure deep CMB or mixed deep-lobar CMB, 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 CMB may be related to etiologies other than CAA in stroke patients with AF.

Despite the stronger association of CMB with ICH than IS, the absolute rate for IS was higher than ICH in the overall AF subcohort irrespective of the CMB burden (Table 3), 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 CMB (33 vs 46 per 1000 patient-years) and those without CMB (24 vs 30 per 1000 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 CMB (12 per 1000 patients-years in both studies) and those without CMB (4 per 1000 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 two studies suggests that factors other than antithrombotic use, e.g. blood pressure variability, might also influence the risk of ICH.

Few randomized controlled studies included MRI imaging substudies.[21,22] In the NAVIGATE ESUS trial, the presence of CMB 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 (i.e. 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 stroke patients with AF and CMB. Comparing the four observed antithrombotic treatments for AF in a real-world setting, DOAC monotherapy appeared to be the safest antithrombotic, 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 1000 patient-years) and IS (23 per 1000 patient-years) were observed among patients with 5-10 CMB but not among the other CMB categories. The net-benefit of DOAC over VKA observed in our study was in line with recent publications on dependent and elderly stroke patients with AF, who are also at high risk of having multiple CMB. [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.[13] 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 AF patients vs 2.6% in the MICON patients without AF), this treatment seems to be of clinical relevance in stroke patients with AF. In our study, there was a 2-fold higher absolute rate of ICH than IS in patients on combination therapy with 2-4 and ≥11 CMBs. This reflects the importance of including detailed antithrombotic information when individualizing stroke risk in patients with AF and CMB. 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 for 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 2-4 and ≥11 CMB 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 CMB with indications for

combination therapy. More importantly, a preemptive approach is important to mitigate the risk of ICH in these patients. General measures include stringent blood pressure control, frequent monitoring of INR for patients on VKA and renal function for patients on DOAC. Indications for combination therapy should be verified continuously,[26,27] while duration of a therapy should be minimized according to the latest guidelines.[28–30] Moreover, agents with lower risk of ICH (i.e. DOAC instead of VKA) should be considered.

Limitations of this study include (i) 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; (ii) limited numbers of patients with ≥5 CMB 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; (iii) missing information on the specific indication and duration of the combination therapy as well as possible changes of antithrombotic treatments and patients' compliance (iv) 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; (v) the study population is mainly based on European and Asian cohorts, thus lowering the generalizability to other ethnic groups; (vi) data regarding the etiological classification of recurrent IS during the follow up period were not assessed systematically in all MICON cohorts; (vii) 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 CMB in patients with AF. Our study has the following additional strengths (i) we used well characterized pooled individual patient data from MICON with prospective data for CMB evaluation and outcome events from different ethnic groups; (ii) 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 CMB was associated with increased risk of both subsequent ICH and IS, with stronger association with the former. Among the four 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 CMB. Although the absolute incidence of IS was higher than ICH regardless of CMB burden for most patient, patients under combination therapy with multiple CMB 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:

YS, AZ and NP contributed to the conception and design of the study, acquisition and analysis of data and drafting the text or preparing the figures. BY, SFT, VM, AP, DS, GA; DW, TL, ST, WC; JA, KL, JL, MS; MK, HC; MH, DW; HM, RC, SI, KY, EA; SH, JP, BL, AW, YK, TS, RL; SE; TG, EU, DD, NB; EA, HH, JM, MN, JT; SC, LK; RS, RJ, GL; MG; LP; JM; LL; CK; TP; MF; FC; SM; DH; DW, DD; PN; CB; SB; KW; AT; DK; CY; AM; SK; RO; YZ; CX; SH; BG; CC; ML; JS; RB; NK; FL; RS; JH; PK; JW; FF; VS; DC; SJ; VK; ES; HH; YY; DO; FF; VT; JH; RV; HA; TI; GL; EJ; KT; HB; JF; LP; PL; JB; DW SE contributed to the acquisition and analysis of data.

Potential Conflict of Interest:

Nothing to report.

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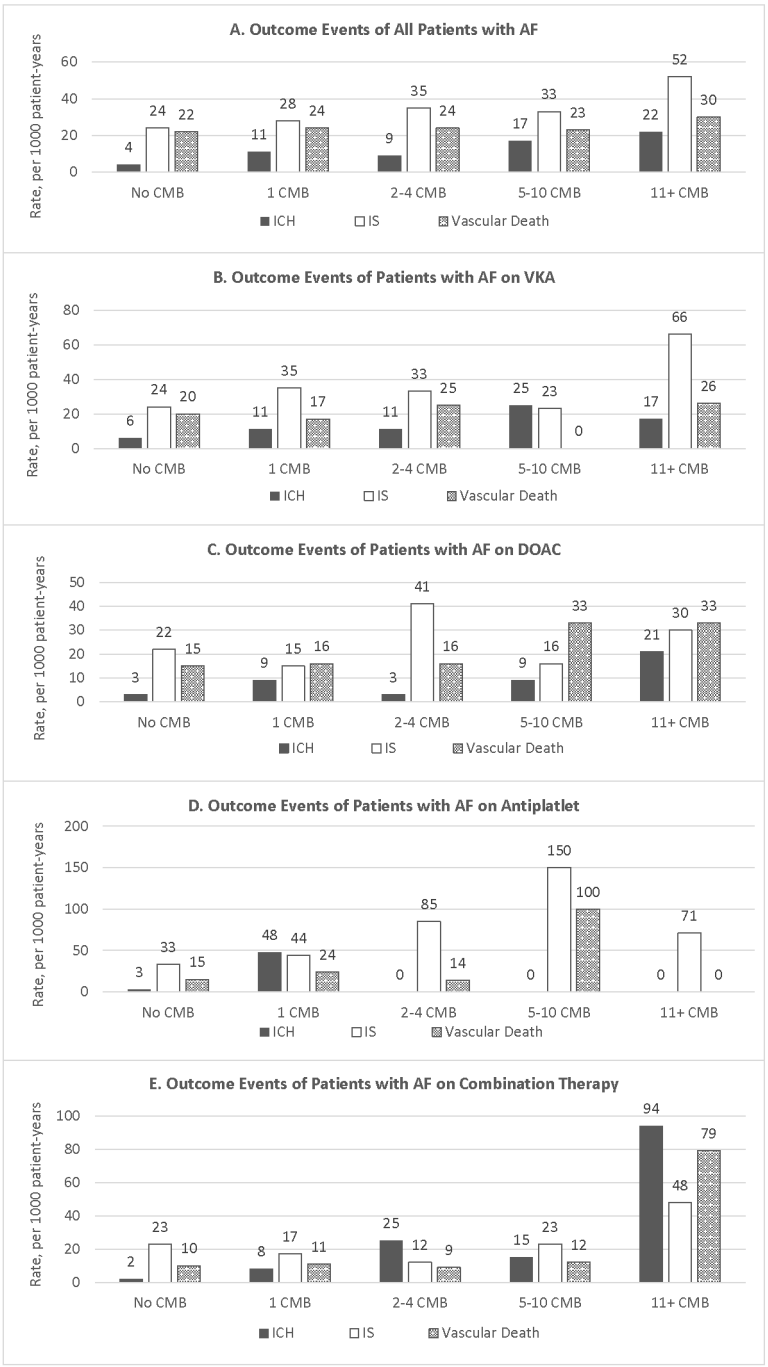

Fig 1 Bar charts combined 300.tiff

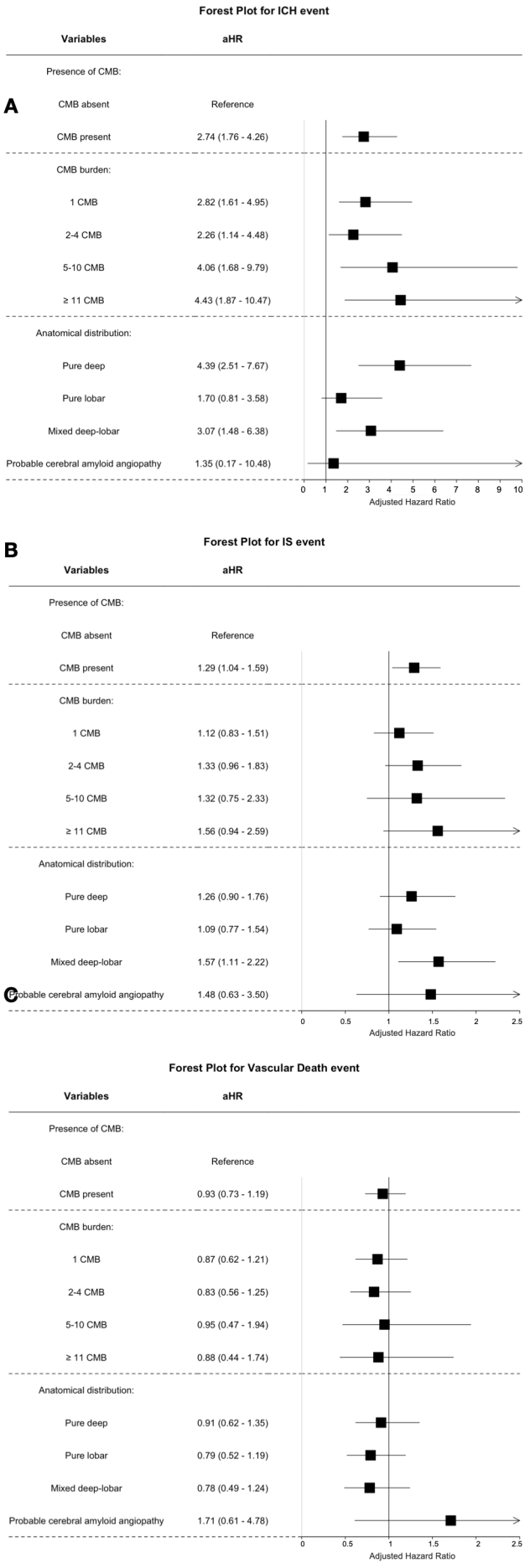

Fig 2 Forest plot combined vertical 300.tiff

Fig 1. Incidence rate of intracranial hemorrhage, ischemic stroke 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).

Fig 2. Forest plots of associations for (A) intracranial hemorrhage, (B) ischemic stroke and (C) vascular death during follow-up.

Table 1. Characteristics of patients with atrial fibrillation with and without cerebral microbleeds.

	No. of patients with data available	With CMB (n=2142)	Without CMB (n=5697)	p
Demography				
Mean age ± SD (years)	7821	77.1 ± 9.6	75.2 ± 10.1	<0.001
Female, n (%)	7839	994 (46.4%)	2730 (47.9%)	0.231
Race, n (%)	6386			0.317
Whites	6386	940 (51.7%)	2454 (53.7%)	-
Asian	6386	874 (48%)	2099 (46%)	-
Black	6386	5 (0.3%)	14 (0.3%)	-
Clinical risk factors				
Current smoker, n (%)	6812	222 (12%)	623 (12.6%)	0.497
Current drinker, n (%)	5121	187 (13.7%)	592 (15.8%)	0.067
Hypertension, n (%)	7813	1735 (81.3%)	4290 (75.5%)	<0.001
Dyslipidemia, n (%)	7539	836 (40.8%)	2180 (39.7%)	0.413
Diabetes mellitus, n (%)	7665	524 (25%)	1247 (22.4%)	0.016
Ischemic heart disease, n (%)	7561	446 (21.6%)	890 (16.2%)	<0.001
Congestive heart failure, n (%)	5599	201 (13.7%)	437 (10.6%)	0.001
Peripheral vascular disease, n (%)	4381	284 (24.8%)	558 (17.2%)	<0.001
History of ischemic stroke, n (%)	7809	505 (23.6%)	943 (16.6%)	<0.001
History of ICH, n (%)	7247	64 (3.2%)	56 (1.1%)	<0.001
Previous antiplatelet, n (%)	6334	726 (42.8%)	1830 (39.4%)	0.015
Previous anticoagulants, n (%)	6335	356 (21.0%)	734 (15.8%)	<0.001
Medication at baseline, n (%)				0.058
None	7839	304 (5.3%)	135 (6.3%)	-
VKA	7839	2344 (41.1%)	900 (42.0%)	-
DOAC	7839	1438 (25.2%)	543 (25.4%)	-
Antiplatelet	7839	447 (7.8%)	179 (8.4%)	-
Combination therapy	7839	1145 (20.1%)	383 (17.9%)	-
Unknown oral anticoagulant	7839	19 (0.3%)	2 (0.1%)	-
Radiological features				
MRI T2*, n (%)	7803	1363 (63.6%)	3906 (69.0%)	<0.001
Median Fazekas score (IQR)	4301	3 (3)	2 (2)	<0.001

CMB = Cerebral microbleeds; SD = Standard deviation; ICH = Intracranial hemorrhage; VKA = Vitamin K antagonist; DOAC = Direct Acting Oral Anticoagulants; IQR = Interquartile range.

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=7752)	p
Demography				
Mean age ± SD (years)	7821	77.1 ± 8.9	75.7 ± 10.0	0.206
Female, n (%)	7839	42 (48.3%)	3682 (47.5%)	0.885
Race, n (%)	6386			0.397
Whites	6386	46 (60.5%)	3348 (53.1%)	-
Asian	6386	30 (39.5%)	2943 (46.6%)	-
Black	6386	0 (0%)	19 (0.3%)	-
Clinical risk factors				
Current smoker, n (%)	6812	7 (9.6%)	838 (12.4%)	0.463
Current drinker, n (%)	5121	6 (9.8%)	773 (15.3%)	0.240
Hypertension, n (%)	7813	69 (79.3%)	5956 (77.1%)	0.624
Dyslipidemia, n (%)	7539	36 (42.9%)	2980 (40.0%)	0.592
Diabetes mellitus, n (%)	7665	29 (34.1%)	1742 (23.0%)	0.015
Ischemic heart disease, n (%)	7561	20 (23.8%)	1316 (17.6%)	0.138
Congestive heart failure, n (%)	5599	8 (11.1%)	630 (11.4%)	0.939
Peripheral vascular disease, n (%)	4381	19 (35.2%)	823 (19.0%)	0.003
History of ischemic stroke, n (%)	7809	20 (23.3%)	1428 (18.5%)	0.258
History of ICH, n (%)	7247	7 (8.2%)	113 (1.6%)	<0.001
Previous antiplatelet, n (%)	6334	35 (46.1%)	2521 (40.3%)	0.308
Previous anticoagulants, n (%)	6335	15 (19.5%)	1075 (17.1%)	0.585
Medication at baseline, n (%)				0.148
None	7839	2 (2.3%)	437 (5.6%)	-
VKA	7839	48 (55.2%)	3196 (41.2%)	-
DOAC	7839	16 (18.4%)	1965 (25.3%)	-
Antiplatelet	7839	7 (8.0%)	619 (8.0%)	-
Combination therapy	7839	14 (16.1%)	1514 (19.5%)	-
Unknown oral anticoagulant	7839	0 (0%)	21 (0.3%)	-
Radiological features				
MRI T2*, n (%)	7803	31 (35.6%)	2503 (32.4%)	0.527
CMB presence, n (%)	7839	45 (51.7%)	2097 (27.1%)	<0.001
Median CMB number (IQR)	7497	0 (2)	0 (1)	<0.001
≥5 CMBs, n (%)	7497	13 (15.7%)	368 (5.0%)	<0.001
Probable cerebral amyloid angiopathy, n (%)	2124	1 (3.7%)	64 (3.1%)	0.845
Median Fazekas score (IQR)	4301	2 (3)	2 (2)	0.899

ICH = Intracranial hemorrhage; SD = Standard deviation; VKA = Vitamin K antagonist; DOAC = Direct Acting Oral Anticoagulants; CMB = Cerebral microbleed, IQR = Interquartile range.

Table 3. Cox-regression of outcome events during follow-up among patients with atrial fibrillation on different antithrombotics.

	Intracranial Hemorrhage					Ischemic Stroke					Vascular Death				
	No. of patients	No. of events	Rate, per 1000 patient-years*	Absolute rate increase, per 1000 patient-years	Adjusted hazard ratio	No. of patients	No. of events	Rate, per 1000 patient-years*	Absolute rate increase, per 1000 patient-years	Adjusted hazard ratio	No. of patients	No. of events	Rate, per 1000 patient-years*	Absolute rate increase, per 1000 patient-years	Adjusted hazard ratio
A. All AF patients															
Follow-up period	13,741 patient-years					13,521 patient-years					13,494 patient-years				
CMB absent	4844	39	4 (3 - 6)	*Reference*	*Reference*	5355	257	24 (21 - 27)	*Reference*	*Reference*	4977	217	22 (19 - 25)	*Reference*	*Reference*
CMB present	1816	44	*12 (9 - 16)*	8 (6 - 11)	2.74 (1.76 - 4.26)	2044	136	33 (28 - 39)	9 (7 - 12)	1.29 (1.04 - 1.59)	1874	96	26 (21 - 31)	4 (2 - 6)	0.93 (0.73 - 1.19)
1 CMB	813	19	11 (7 - 18)	7 (4 - 13)	2.82 (1.61 - 4.95)	923	52	28 (21 - 37)	4 (0 - 10)	1.12 (0.83 - 1.51)	855	41	24 (17 - 33)	2 (-2 - 8)	0.87 (0.62 - 1.21)
2-4 CMB	565	11	9 (5 - 17)	5 (2 - 12)	2.26 (1.14 - 4.48)	644	45	35 (26 - 47)	11 (4 - 20)	1.33 (0.96 - 1.83)	574	27	24 (16 - 34)	2 (-4 - 9)	0.83 (0.56 - 1.25)
5-10 CMB	169	6	17 (7 - 39)	13 (4 - 33)	4.06 (1.68 - 9.79)	197	13	33 (18 - 57)	9 (-4 - 29)	1.32 (0.75 - 2.33)	176	8	23 (10 - 45)	1 (-9 - 20)	0.95 (0.47 - 1.94)
>10 CMB	152	7	22 (9 - 47)	18 (6 - 42)	4.43 (1.87 - 10.47)	164	17	52 (30 - 83)	28 (9 - 56)	1.56 (0.94 - 2.59)	152	9	30 (14 - 56)	8 (-6 - 31)	0.88 (0.44 - 1.74)
B. AF patients on VKA															
Follow-up period	6,370 patient-years					6,272 patient-years					6,469 patient-years				
CMB absent	2087	25	6 (4 - 9)	*Reference*	*Reference*	2165	105	24 (20 - 29)	*Reference*	*Reference*	2016	82	20 (16 - 25)	*Reference*	*Reference*
CMB present	807	20	12 (8 - 19)	6 (4 - 10)	1.92 (1.06 - 3.49)	836	59	35 (27 - 46)	11 (7 - 16)	1.37 (0.99 - 1.89)	765	32	21 (14 - 30)	1 (-2 - 4)	0.94 (0.62 - 1.42)
1 CMB	364	8	11 (5 - 22)	5 (1 - 13)	1.69 (0.76 - 3.78)	376	26	35 (23 - 51)	10 (3 - 21)	1.32 (0.85 - 2.03)	354	12	17 (9 - 30)	-3 (-7 - 4)	0.72 (0.39 - 1.33)
2-4 CMB	266	6	11 (4 - 25)	6 (0 - 16)	1.73 (0.7 - 4.24)	275	18	33 (19 - 52)	8 (0 - 22)	1.21 (0.73 - 2.01)	241	12	25 (13 - 43)	5 (-3 - 18)	1.14 (0.62 - 2.11)
5-10 CMB	59	3	25 (5 - 74)	20 (1 - 65)	4.04 (1.19 - 13.66)	66	3	23 (5 - 66)	-2 (-15 - 37)	1.03 (0.32 - 3.25)	54	0	0 (0 - 34)	-20 (-16 - 9)	
>10 CMB	60	2	17 (2 - 60)	11 (-2 - 51)	3.02 (0.67 - 13.51)	61	8	66 (28 - 129)	41 (8 - 100)	2.37 (1.13 - 5)	58	3	26 (5 - 76)	6 (-11 - 50)	1.47 (0.46 - 4.74)
C. Patients on DOAC															
Follow-up period	3,188 patient-years					3,159 patient-years					3,228 patient-years				
CMB absent	1358	8	3 (1 - 6)	*Reference*	*Reference*	1401	62	22 (17 - 28)	*Reference*	*Reference*	1378	40	15 (10 - 20)	*Reference*	*Reference*
CMB present	512	8	8 (3 - 15)	5 (2 - 10)	2.54 (0.91 - 7.07)	535	29	27 (18 - 39)	5 (1 - 11)	1.14 (0.73 - 1.8)	523	20	19 (12 - 30)	5 (1 - 10)	1.09 (0.63 - 1.89)
1 CMB	214	4	9 (3 - 24)	7 (1 - 18)	3.62 (1 - 13.11)	226	7	15 (6 - 32)	-7 (-11 - 4)	0.66 (0.3 - 1.46)	220	7	16 (6 - 33)	1 (-4 - 13)	0.89 (0.39 - 2)

2-4 CMB	152	1	3 (0 - 18)	0 (-1 - 13)	1.34 (0.15 - 11.81)	157	13	41 (22 - 71)	19 (5 - 42)	1.78 (0.95 - 3.32)	156	5	16 (5 - 37)	2 (-5 - 18)	0.83 (0.31 2.18)
5-10 CMB	58	1	9 (0 - 48)	6 (-1 - 42)	3.11 (0.34 - 28.29)	61	2	16 (2 - 59)	-6 (-15 - 31)	0.62 (0.15 - 2.57)	61	4	33 (9 - 84)	18 (-1 - 64)	1.46 (0.51 4.17)
≥ 11 CMB	47	2	21 (3 - 77)	18 (1 - 71)	5.32 (0.87 - 32.42)	50	3	30 (6 - 88)	8 (-11 - 59)	1.32 (0.41 - 4.32)	46	3	33 (7 - 95)	18 (-4 - 76)	1.69 (0.5 - 5.69)
D. Patients on antiplatelet															
Follow-up period	582 patient-years					555 patient-years					688 patient-years				
CMB absent	288	2	3 (0 - 13)	*Reference*	*Reference*	394	26	33 (22 - 48)	*Reference*	*Reference*	328	10	15 (7 - 28)	*Reference*	*Reference*
CMB present	117	5	21 (7 - 50)	17 (7 - 37)	4.93 (0.81 - 30.18)	166	24	72 (46 - 108)	39 (25 - 59)	2.43 (1.34 - 4.43)	133	7	26 (11 - 54)	11 (3 - 26)	1.95 (0.7 - 5.47)
1 CMB	52	5	48 (16 - 112)	45 (15 - 100)	NA	79	7	44 (18 - 91)	11 (-4 - 43)	1.77 (0.74 - 4.23)	63	3	24 (5 - 70)	9 (-2 - 42)	1.9 (0.47 - 7.59)
2-4 CMB	33	0	0 (0 - 56)	-3 (0 - 43)	NA	47	8	85 (37 - 168)	52 (15 - 119)	2.1 (0.92 - 4.77)	37	1	14 (0 - 75)	-2 (-7 - 47)	0.86 (0.1 - 7.13)
5-10 CMB	14	0	0 (0 - 132)	-3 (0 - 119)	NA	20	6	150 (55 - 326)	117 (33 - 278)	7.27 (2.76 - 19.15)	15	3	100 (21 - 292)	85 (13 - 264)	6.05 (1.44 25.45)
≥ 11 CMB	18	0	0 (0 - 102)	-3 (0 - 90)	NA	21	3	71 (15 - 209)	38 (-7 - 160)	1.84 (0.48 - 7.05)	18	0	0 (0 - 102)	-15 (-7 - 74)	
E. Patients on combination therapy															
Follow-up period	2,543 patient-years					2,495 patient-years					2,861 patient-years				
CMB absent	866	4	2 (1 - 6)	*Reference*	*Reference*	1096	50	23 (17 - 30)	*Reference*	*Reference*	1044	21	10 (6 - 15)	*Reference*	*Reference*
CMB present	269	10	18 (9 - 34)	16 (8 - 28)	7.92 (2.43 - 25.82)	376	14	19 (10 - 31)	-4 (-7 - 1)	0.82 (0.45 - 1.5)	358	11	15 (8 - 27)	5 (1 - 12)	1.32 (0.63 2.77)
1 CMB	129	2	8 (1 - 28)	6 (0 - 22)	3.5 (0.62 - 19.61)	180	6	17 (6 - 36)	-6 (-11 - 6)	0.79 (0.33 - 1.85)	174	4	11 (3 - 29)	1 (-3 - 14)	0.99 (0.34 2.91)
2-4 CMB	80	4	25 (7 - 64)	23 (6 - 58)	10.23 (2.41 - 43.37)	121	3	12 (3 - 36)	-10 (-14 - 6)	0.58 (0.18 - 1.9)	113	2	9 (1 - 32)	-1 (-5 - 17)	0.75 (0.17 3.24)
5-10 CMB	33	1	15 (0 - 84)	13 (0 - 79)	4.03 (0.41 - 39.88)	43	2	23 (3 - 84)	0 (-14 - 54)	0.92 (0.22 - 3.86)	41	1	12 (0 - 68)	2 (-6 - 53)	1.03 (0.14 7.65)
≥ 11 CMB	16	3	94 (19 - 274)	92 (19 - 268)	27.97 (5.57 - 140.55)	21	2	48 (6 - 172)	25 (-11 - 142)	1.6 (0.38 - 6.78)	19	3	79 (16 - 231)	69 (10 - 215)	4.76 (1.31 17.26)

Table 4. Characteristics of patients with atrial fibrillation with and without ischemic stroke.

	No. of patients with data available	With IS (n=412)	Without IS (n=7427)	p
Demography				
Mean age ± SD (years)	7821	77.1 ± 91	75.7 ± 10.1	0.001
Female, n (%)	7839	210 (51.0%)	3514 (47.3%)	0.148
Race, n (%)	6386			<0.001
Whites	6386	131 (41.1%)	3263 (53.8%)	-
Asian	6386	184 (57.7%)	2789 (46.0%)	-
Black	6386	4 (1.3%)	15 (0.2%)	-
Clinical risk factors				
Current smoker, n (%)	6812	32 (9.8%)	813 (12.5%)	0.152
Current drinker, n (%)	5121	38 (12.8%)	741 (15.4%)	0.223
Hypertension, n (%)	7813	331 (80.3%)	5694 (76.9%)	0.109
Dyslipidemia, n (%)	7539	163 (41.8%)	2853 (39.9%)	0.459
Diabetes mellitus, n (%)	7665	120 (30.0%)	1651 (22.7%)	0.001
Ischemic heart disease, n (%)	7561	90 (22.2%)	1246 (17.4%)	0.014
Congestive heart failure, n (%)	5599	49 (14.5%)	589 (11.2%)	0.064
Peripheral vascular disease, n (%)	4381	84 (29.7%)	758 (18.5%)	<0.001
History of ischaemic stroke, n (%)	7809	125 (30.5%)	323 (17.9%)	<0.001
History of ICH, n (%)	7247	11 (2.7%)	109 (1.5%)	0.119
Previous antiplatelet, n (%)	6334	147 (44.7%)	2409 (40.1%)	0.100
Previous anticoagulants, n (%)	6335	85 (25.8%)	1005 (16.7%)	<0.001
Medication at baseline, n (%)				0.004
None	7839	26 (6.3%)	413 (5.6%)	-
VKA	7839	171 (41.5%)	3073 (41.4%)	-
DOAC	7839	92 (22.3%)	1889 (25.4%)	-
Antiplatelet	7839	53 (12.9%)	573 (7.7%)	-
Combination therapy	7839	70 (17.0%)	1458 (19.6%)	-
Unknown oral anticoagulant	7839	0 (0%)	21 (0.3%)	-
Radiological features				
MRI sequence - T2*, n (%)	7803	260 (63.7%)	5009 (67.7%)	0.092
CMB presence, n (%)	7839	139 (33.7%)	2003 (27.0%)	0.003
Median CMB number (IQR)	7497	0 (1)	0 (1)	<0.001
≥5 CMBs, n (%)	7497	31 (7.9%)	350 (4.9%)	0.009

ICH = Intracranial hemorrhage; SD = Standard deviation; VKA = Vitamin K antagonist; DOAC = Direct Acting Oral Anticoagulants; CMB = Cerebral microbleeds, IQR = Interquartile range.