Accepted: 6 March 2018

DOI: 10.1111/ane.12934

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Microbleeds in ischemic vs hemorrhagic strokes on novel oral anticoagulants

J. C. Purrucker[1] | M. Wolf[2] | K. Haas[3] | T. Siedler[3] | T. Rizos[1] | S. Khan[1] | P. U. Heuschmann[3,4] | R. Veltkamp[1,5,6] | for the RASUNOA Investigators

[1]Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany

[2]Department of Neuroradiology, Heidelberg University Hospital, Heidelberg, Germany

[3]Institute of Clinical Epidemiology and Biometry, University Würzburg, Würzburg, Germany

[4]Comprehensive Heart Failure Center, and Clinical Trial Center, University Hospital Würzburg, Würzburg, Germany

[5]Department of Stroke Medicine, Imperial College London, London, UK

[6]NIHR Imperial Biomedical Research Center, London, UK

Correspondence
R. Veltkamp, Department of Stroke Medicine, Imperial College London, London, UK.
Email: r.veltkamp@imperial.ac.uk

Funding information
Investigator-initiated, without commercial funding.

Objectives: To identify differences in clinical characteristics and severity of cerebral small vessel disease (CSVD) including cerebral microbleeds (CMBs), between patients suffering ischemic stroke (IS) or intracerebral hemorrhage (ICH) while taking novel (non-vitamin K antagonists) oral anticoagulants (NOACs).

Methods: Multicenter, prospective, observational cohort study performed at 38 centers between 2012 and 2015. We compared demographics, comorbidity, and functional status (before and after stroke) between NOAC-IS and NOAC-ICH patients. Extent of white matter lesions (WML), and location and counts of CMBs were analyzed in a subgroup of patients for whom MRI including hemorrhage-sensitive sequences was available.

Results: A total of 351 patients were included (290 NOAC-IS, 61 NOAC-ICH). Functional status was worse in NOAC-ICH patients before and after stroke. No significant differences were found for demographic variables and cardiovascular comorbidity. In the subgroup with available MRI (n = 116), the proportion of patients with at least one CMB was higher in NOAC-ICH than in NOAC-IS (15/19 [79%] vs 36/97 [37%], $P < .001$), as was the absolute number of CMBs (median 5 [IQR 1-24] vs 0 [0-1], $P < .001$). WML were more extensive in NOAC-ICH than in NOAC-IS patients. Adjusted for WML, logistic regression analysis showed higher odds of NOAC-ICH in patients with CMB than without (OR 5.60 [1.64-19.14], $P = .006$).

Conclusions: Patients with NOAC-ICH have similar clinical characteristics but a higher prevalent burden of CSVD compared to NOAC-IS. The role of neuroimaging in selection of patients for anticoagulation with NOAC requires further investigation in longitudinal studies.

KEYWORDS
anticoagulation, intracerebral hemorrhage, microbleeds, small vessel disease, stroke

1 | INTRODUCTION

Stroke prevention in patients with atrial fibrillation (AF) using anticoagulants must balance the benefit of reducing ischemic stroke (IS) against the increased risk of major bleeding including intracerebral hemorrhage (ICH).[1] Better distinction between patients who are primarily at risk of suffering either IS or ICH is desirable but the items in the most widely used clinical risk scores for thromboembolism and major bleedings overlap considerably.[2,3] Longitudinal studies, on the manifestations of cerebral small vessel disease (CSVD), focusing on white matter lesions (WML) and cerebral microbleeds (CMBs), indicate an increased risk of both ischemic and hemorrhagic events in patients with CSVD.[4,5] To which extent patients who experience IS or an ICH during anticoagulation treatment differ in

terms of manifestation of CSVD is under intense investigation. It has been suggested that the extent of CSVD may have to be taken into account before starting anticoagulation.[6,7] Available evidence for the effect of anticoagulation and CSVD on bleeding risk is limited to studies using vitamin K antagonists (VKA), which suggest an increased risk of bleeding in patients with multiple CMBs.[7-10] It is unknown whether the implications of CSVD are similar in patients treated with novel (non-VKA) oral anticoagulants (NOACs), which are associated with half the risk of ICH compared to VKA.[11-13] To our knowledge, no study has examined yet whether the extent of CSVD differs between patients on treatment with NOACs who experience IS or ICH. In the present cross-sectional analysis of data generated in the prospective multicenter Registry of Acute Stroke Under Novel Oral Anticoagulants (RASUNOA), we therefore explored whether acute IS patients treated with NOAC at the time of the event differ from patients with acute NOAC-related ICH in terms of clinical characteristics and signs of CSVD.

2 | METHODS

2.1 | Study design and population

We conducted an investigator-initiated, multicenter, prospective, observational cohort study (clinicaltrials.gov, NCT01850797). Patients with acute ischemic or hemorrhagic stroke were prospectively enrolled at 38 Departments of Neurology with certified stroke units across Germany between February 2012 and February 2015. The inclusion criteria were age over 18 years and current therapy with a NOAC (ie, apixaban, dabigatran or rivaroxaban; edoxaban was not yet approved) at the time of stroke onset. For the subanalysis of radiological differences between IS and ICH, only patients with available gradient recalled echo pulse sequences (ie, T2*- or susceptibility-weighted imaging [SWI]) on MRI were included. This study was approved by the ethics committee of the Medical Faculty of Heidelberg, Heidelberg, Germany, as well as by the ethics committees of each participating center. Each patient or legal representative gave written informed consent. For patients who deceased early after the event and had no legal guardian at the time of death, informed consent for participation in the study was waived by the ethics committee and local investigators had to consider the putative wish of the deceased patient.

2.2 | Data acquisition

All diagnostic and treatment decisions, including the selection of imaging modalities, were at the discretion of the treating physicians. Observational data including baseline characteristics, cardiovascular risk factors, clinical observations, and laboratory findings were reported on prespecified case report forms. Double data entry was performed by 2 independent staff members of the Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany. Neurological status was assessed at admission using the NIH stroke scale. Disability was determined using the modified Rankin scale (mRS) score before the index stroke, at discharge, and during 3-month follow-up. The CHA_2DS_2VASc score (Cardiac Failure or Dysfunction, Hypertension, Age ≥75 Years [Doubled], Diabetes, Stroke [Doubled], Vascular Disease, Age 65-74 Years, and Sex Category [Female]) and the HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR [international normalized ratio], Elderly, Drugs/Alcohol Concomitantly) were calculated, excluding the index event.[2,3] The HAS-BLED score item "labile INR" was set to zero. Follow-up was performed via a structured telephone interview by trained mRS raters 3 months after the index event. The interview was performed with the patient or, if the patient could not be contacted in person, a close relative, legal representative, or family physician familiar with the current functional and medical status of the patient.

2.3 | Imaging analysis

Brain MRI examinations were performed as part of local routine on 1.5 T or 3 T MRI systems. Only scans obtained within a maximum of 7 days after the index event were considered. Due to the multicenter observational character of the study, no specific protocol parameters were predefined. Regarding hemorrhage-sensitive sequences, images were acquired in an axial plane with the following parameters: T2* (median repetition [TR]/echo time [TE] interquartile range [IQR] 814 [740-900]/25 [24-26] ms) and SWI (TR/TE 27 [27-27]/19.7 [19.7-20.0] ms) at a median slice thickness of 5 (3-5) mm. For evaluation of white matter changes, standard T2 and fluid-attenuated inversion recovery (FLAIR) sequences were assessed (available in all but one patient, in whom a diffusion weighted imaging b0 sequence had to be used instead). Central imaging analysis was performed following recommendations of the standards for reporting vascular changes on neuroimaging.[14]

Cerebral microbleeds were rated on T2* or SWI sequences using the Microbleed Anatomical Rating Scale (MARS) Rating Form.[15] Accordingly, CMBs were defined as small, round, well-defined, hypointense lesions with a diameter of 2-10 mm that were not seen on T2. In order to exclude mixing of potential CMBs with vessels, adjacent slices of T2*/SWI as well as T2 and Time-of-Flight(TOF)-images/MR-A were carefully analyzed. Trying not to overestimate the number of CMBs, a conservative rating was performed (in case of doubt, rating was "no CMB"). Rating was performed independently by 2 experienced raters (JCP, MW), who were blinded to patient characteristics. There was no access to the original radiological description. To avoid potential interactions as well as masking of CMBs in proximity to acute stroke lesions, rating was performed contralateral to the index lesion. If no lesion could be identified, the left hemisphere was rated. For example, if only 1 CMB was found and no infarct or other CMB was detected in the contralateral hemisphere, we registered "0.5." Agreement between raters was excellent regarding number of CMBs (intraclass correlation coefficient 0.95, 95% CI 0.93-0.97). However, in 25 cases, there was initial disagreement between 0 or 1 CMB, which was resolved via consensus

finding. These cases were particularly addressed as this dichotomization (CMB 0 vs 1) was considered specifically important for further analyses. Counts were subsequently doubled for each region to get an estimate for both hemispheres, and the arithmetic mean of the estimates obtained by the two raters was used for further analysis. There was good interrater agreement for the <5 vs ≥5 CMBs dichotomization (kappa = 0.74, 95% CI 0.57-0.89).[5,7] The presence of cortical superficial siderosis was rated in accordance with consensus recommendations.[16] ICH patients with intraventricular extension were excluded from rating of cSS because traces of intraventricular blood might extend to the subarachnoid space.

For evaluation of white matter changes, two different rating scales were applied: (i) The Age-Related White Matter Changes (ARWMC) rating scale, according to which a score of 0 (no lesions) to 3 (confluent lesions, or diffuse involvement of the entire region) was attributed to white matter and basal ganglia lesions in five predefined brain regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). White matter lesions were defined as hyperintense lesions ≥5 mm on T2 or FLAIR sequences.[17] Non-acute (DWI-negative) lacunes were included. Acute lesions were masked. Again, rating was performed contralateral to the index lesion; scores were then doubled as WMC were distributed symmetrically. The arithmetic mean of the two raters' assessments was used for further analysis. The intraclass correlation coefficient was good (0.72, 95% CI 0.61-0.79). (ii) The Fazekas score was rated for periventricular hyperintensities and deep white matter hyperintense signals, with 0 (no hyperintensity) to 3 (irregular periventricular hyperintensity extending into the deep white matter or large confluent lesions).[18] There was a very good interrater correlation (0.84, 95% CI 0.77-0.88).

2.4 | Statistical analysis

Continuous variables are described as mean (SD) or median (IQR). For categorical variables, absolute and relative frequencies are reported. Distribution of data was ascertained with the Shapiro-Wilk test. Depending on the skewness of the data, nonparametric tests were used. To compare proportions of patients with ischemic vs hemorrhagic stroke, and with or without CMBs, the Fisher exact test and Mann-Whitney *U* test were used. A sensitivity analysis excluding patients with previous IS or ICH was performed. To evaluate the reliability of the two raters' scorings, the intraclass correlation coefficient was calculated (two-way mixed, single-measure). Interrater agreement (Cohen's kappa) was calculated for dichotomous CMB counts (<5 vs ≥5/patient). Univariate logistic regression was used to estimate odds ratio (OR) and 95% CI due to patient characteristics. Multivariate logistic regression analysis was performed to adjust for white matter lesions while investigating the influence of CMB counts. However, due to the small number of cases we had to limit our model rigorously. A two-tailed *P* value of <.05 was considered significant. Statistical analyses were performed using SPSS (V24, IBM, USA). This study was performed consistent with the STROBE guidelines for observational studies.

3 | RESULTS

Of 351 prospectively enrolled patients with IS or ICH occurring during NOAC therapy, 290 had an IS and 61 had an ICH (Figure 1). There were no statistically significant differences in demographic variables and cardiovascular comorbidity between IS and ICH patients (Table 1). NOAC-ICH patients more often had a history of previous intracranial hemorrhage and had a worse functional status before stroke, at admission and after stroke (Table 1). Differences in functional status remained significant in a sensitivity analysis excluding patients with previous ischemic or hemorrhagic stroke (Table S1).

For the analysis of CSVD and CMBs, 116 patients with available MRI including SWI/T2* sequences were included (IS, n = 97, ICH, n = 19) (Figure 1). Patients with MRI were younger and had more frequently peripheral artery disease (Table S2). There were no differences between field strength (1.5 T, n = 60, 3 T, n = 56) or use of T2* (n = 67) and SWI (n = 49) sequences with regard to the stroke type (*P* = .8 and *P* = .7, respectively). ICH location did not differ in patients with MRI and without (MRI, deep 10/19, lobar 6/19, cerebellar 2/19, brainstem 1/19; no MRI, deep 13/42, lobar 19/42, cerebellar 8/42, brainstem 2/42; *P* = .408). FLAIR images were available in 111/116 (96%) of the patients.

There was no significant difference in demographic variables and cardiovascular comorbidity between IS and ICH patients in the MRI subgroup (Table S3). The proportion of patients with at least one CMB was higher in the ICH than in the IS group (79% vs 37%, *P* < .001, Table 2). Moreover, ICH patients had more CMBs than IS patients (median 5 [IQR 1-24] vs 0 [0-1], *P* < .001). Results remained unchanged in a sensitivity analysis that excluded the five patients with previous ICH (Table S4). More NOAC-ICH than IS patients met the modified Boston criteria[19,20] for probable cerebral amyloid angiopathy (CAA) (56% vs 21%, *P* = .005), but no difference was found for possible CAA. Cortical superficial siderosis tended to be more frequent in NOAC-ICH compared to IS (Table 2).

White matter lesions were more extensive in ICH than in IS patients according to both the ARWMC rating scale and the Fazekas score (Table 2). Adjusted for WML according to the ARWMC score, logistic regression analysis revealed higher odds of ICH in patients with CMB than without CMBs (OR 5.60 [1.64-19.14], *P* = .006; after exclusion of patients with previous ICH, OR 7.8 [1.98-30.75], *P* = .003). Association of NOAC-ICH and CMBs became stronger after dividing groups into patients with CMB count <5 vs ≥5 (OR 5.88 [1.87-18.48], *P* = .002; Table S5).

The topographic distribution of CMBs was different in IS and ICH patients. Strictly lobar CMBs were found more frequently in IS patients, while ICH patients had mostly mixed deep and lobar locations (Table 2). A similar distribution pattern was found for ICH locations in the 15 CMB-positive ICH patients (n = 9 deep, 3 lobar, 2 cerebellar, and 1 brainstem).

4 | DISCUSSION

The major findings from our study are (i) that the clinical characteristics in patients experiencing ICH on NOACs are similar to those in

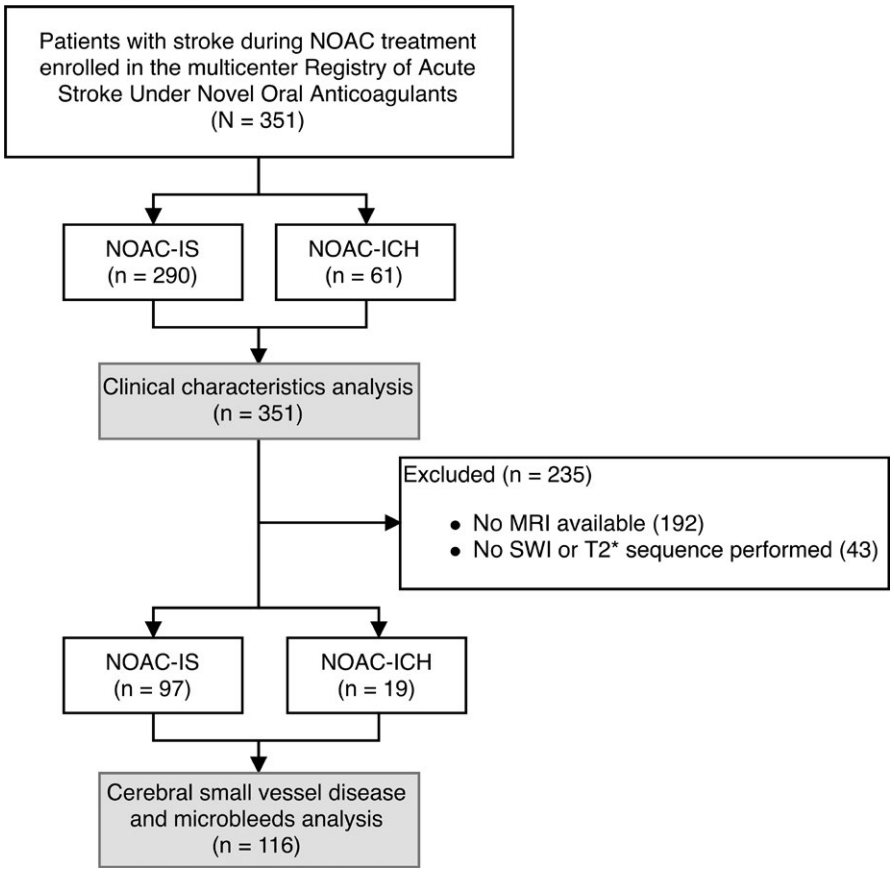

FIGURE 1 Flowchart of study population. ICH, intracerebral hemorrhage; IS, ischemic stroke; MRI, magnetic resonance imaging; NOAC, non-Vitamin K antagonist oral anticoagulants; SWI, susceptibility-weighted imaging

patients suffering NOAC-IS. (ii) NOAC-ICH patients are more likely to have more extensive WML and more CMBs than patients treated with NOACs who experience an IS.

Previous observational studies suggested a higher risk of future ICH than of IS in patients with CMBs.[5,7] Consequently, there is an ongoing debate about whether the benefits of anticoagulation, which itself increases the risk of ICH, hold true for patients with CMBs and an indication for primary or secondary prevention of thromboembolism.[12,13] Data from the VKA era are heterogeneous. Some studies report no relation of microbleeds with use of VKA,[21,22] while others found a higher prevalence of CMBs with previous anticoagulation, predominantly located in the lobar region,[23] suggestive of cerebral amyloid angiopathy.[9] Moreover, warfarin use is an independent predictor of ICH risk in patients with CMBs.[24,25] As NOACs reduced the risk of ICH by about 50% compared to warfarin in patients with atrial fibrillation,[11] they may neither increase the number of incident CMBs nor increase the ICH risk in patients with CMBs. However, data to support this concept are sparse. In a small longitudinal study, warfarin, but not NOACs, was associated with the development of CMBs after 1 year.[26] Our analysis suggests an association of the burden of CMBs with the occurrence of NOAC-ICH compared to IS. Even after adjusting for the extent of WML, there was still a sixfold higher likelihood of having suffered ICH than IS in patients with 5 or more CMBs. Similarly, in a recent meta-analysis including patients with IS, higher numbers of CMBs were both associated with increased risk of IS and ICH, but the risk of ICH increased more rapidly.[5] However, most patients in that study were treated with antiplatelets and only 15% received anticoagulants.[5] Intriguingly, we found CMBs being more often in a mixed than in a strictly lobar location in NOAC-ICH compared to IS. This finding might lead to a switch in the future ICH-risk stratification algorithms, focusing not on the detection of lobar (cortical) CMBs alone, but on the identification of those patients with the presence of both age-related hypertensive vasculopathy and CAA. Furthermore, the higher percentage of superficial siderosis in NOAC-ICH patients compared to IS in our study warrants further investigation in larger cohorts as superficial siderosis might be a useful additional imaging marker to identify patients at high risk for subsequent re-bleeding.

The incidence of CMBs was higher compared to previously reported data from ICH patients.[27] Inclusion of patients irrespective of their functional status and outcome, as well as a higher median age, and use of more sensitive SWI sequences for some patients, might have contributed to this finding. Nevertheless, we cannot rule out a selection bias and confounding by indication.

We observed a lower median HAS-BLED score in the ICH compared to the IS group. Calculation of the HAS-BLED score differed from the originally proposed standard because in NOAC receiving patients, the item "labile INR" had to be set to zero, and the modified score is not yet validated for NOAC-treated patients. Clinical and demographic differences between IS and ICH patients were non-significant except for the mRS, a functional scale that can also

TABLE 1 Clinical patient characteristics and functional outcome

Variables	IS (N = 290)	ICH (N = 61)	*P* value
Age, y	78.6 (72.4-83.4)	76.3 (72.1-84.2)	.604
Women	140 (48)	25 (41)	.325
NOAC			.003
Apixaban	48 (17)	5 (8)	
Dabigatran	76 (26)	7 (12)	
Rivaroxaban	166 (57)	49 (80)	
Antiplatelet therapy	31 (11)	6 (10)	.844
Dual platelet therapy	3 (1)	1 (2)	.686
Medical history			
Previous IS	124 (43)	24 (39)	.670
Previous intracranial hemorrhage	6 (2)	5 (8)	.03
Atrial fibrillation	262 (91)	59 (97)	.858
Hypertension	245 (85)	53 (87)	.844
Diabetes mellitus	78 (27)	19 (31)	.530
Hyperlipidemia	100 (35)	20 (33)	.882
Heart failure	67 (23)	13 (21)	.867
Peripheral artery disease	18 (6)	2 (3)	.547
CHA_2DS_2VASc	4 (3-6)	5 (4-6)	.352
HAS-BLED	3 (3-4)	2 (2-3)	<.001
Renal function			
Creatinine level, mg/dL	1 (0.8-1.3)	1 (0.7-1.2)	.133
GFR <60 mL/min	103 (40)	15 (26)	.07
NIHSS at admission	4 (1-8)	10 (4-18)	<.001
Modified Rankin scale score			
Before stroke	1 (0-2)	2 (0-3)	<.001
At admission	3 (1-4)	5 (4-5)	<.001
At discharge	2 (1-3)	4 (3-5)	<.001
At 3 mo	2 (1-4)	4 (2-6)	<.001
Mortality at 3 mo	33 (13)	17 (28)	.005

CHA_2DS_2VASc, Chronic Heart Failure, Hypertension, Age ≥75 Y [Doubled], Diabetes, Stroke [Doubled], Vascular Disease, Age 65-74 Y, and Sex Category [Female] score; GFR, glomerular filtration rate; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR [international normalized ratio], Elderly, Drugs/Alcohol Concomitantly score; NIHSS, NIH stroke scale; NOAC, non-Vitamin K antagonist oral anticoagulants; IS, ischemic stroke; TIA, transient ischemic attack.
Data are n (%) or median (IQR).

reflect multi-morbidity. The mRS was higher before and after stroke in NOAC-ICH than in NOAC-IS patients. Although specific cardiovascular risk factors such as diabetes and hypertension did not differ between groups, the mRS may indicate differences in underlying but not defined diseases.

Limitations of our study include the low number of patients with MRI especially in the ICH subgroup which largely precluded multivariate testing. MRI protocols were different among centers, and a slight majority used lower-field scanners (1.5 T) and T2* sequences which reduces sensitivity for CMBs. Although balanced between ICH and IS groups, this might have influenced the overall CMB counts. Indication for MRI may have been biased but patients with and without MRI did not differ substantially. We assessed CMBs and WML contralateral to the lesion side, because no prelesion MRIs were available and the presence of CMBs and WML especially in ICH areas could not be determined. Furthermore, the actual lesions, including perifocal edema zones, might influence the occurrence of CMBs and WML. Based on findings in patients with bilaterally assessable images showing symmetrical distributions, we assumed a symmetrical CMB and WML distribution in all other patients, but cannot exclude underlying asymmetrical distribution patterns in some patients with large lesions.

TABLE 2 Radiological findings

Variables	IS (N = 97)	ICH (N = 19)	*P* value
CMB-positive (%)	36 (37)	15 (79)	<.001
CMB count (median)	0 (0-1)	5 (1-24)	<.001
CMB category			
CMB 1	12 (13)	1 (5)	<.001
CMB 2-4	10 (10)	3 (16)	
CMB >= 5	13 (14)	11 (58)	
CMB distribution			
Strictly Lobar	15 (42)	2 (13)	.015
Strictly Deep	5 (14)	0 (0)	
Strictly Infratentorial	2 (6)	0 (0)	
Mixed	14 (39)	13 (87)	
ARWMC, total score	6 (4-10)	10 (9-16)	.001
Fazekas	3 (2-4)	4 (3-6)	.006
Probable CAA	20 (21)	9/16 (56)	.005
Possible CAA	17 (18)	3/16 (19)	>.99
Cortical superficial siderosis	6 (6)	3/16 (19)	.12
Focal (≤3 sulci)	3	1	
Disseminated (≥4 sulci)	3	2	

ARWMC, age-related white matter changes; CAA, cerebral amyloid angiopathy (according to the modified Boston criteria; excluding patients with acute intraventricular hemorrhage); CMB, cerebral microbleed.
Data are n (%) or median (IQR).

Another limitation is that information on the duration of OAC treatment before the index event was not collected. Our study was not intended to detect potential differences among different agents or classes of agents (ie, direct thrombin inhibitors vs factor Xa inhibitors); thus, the observed difference of the type of NOAC used between IS and ICH patients remains subject of further research.

Finally, due to the cross-sectional study design, the limited sample size, and a potential selection bias, firm conclusions regarding the absolute risk of NOAC use in CMB-positive patients cannot be drawn. Longitudinal observational studies (CROMIS-2, clinicaltrials.gov, NCT02513316; and HERO, NCT02238470) as well as imaging substudies of randomized clinical trials in patients with embolic stroke of undetermined source are expected to further clarify the benefit-risk ratio of oral anticoagulation in individual patients with CSVD.[28-31]

ACKNOWLEDGMENTS

We thank all principal investigators of the RASUNOA study and participating hospitals (see Supporting information).

CONFLICT OF INTEREST

J. C. Purrucker received travel and congress participation support from Pfizer, and personal fees from Boehringer Ingelheim. M. Wolf has nothing to disclose. T. Siedler has nothing to disclose. T. Rizos received consulting honoraria, speakers' honoraria and travel support from BMS Pfizer, Boehringer Ingelheim, Bayer HealthCare and Daichii Sankyo. Shujah Kahn has nothing to disclose. Kirsten Haas has nothing to disclose. Peter U. Heuschmann reports grants from BMBF, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, German Heart Foundation, Charité–Universitätsmedizin Berlin (within MonDAFIS; supported by an unrestricted research grant to the Charité from Bayer), University of Göttingen (within FIND-AF randomised, supported by an unrestricted research grant to the University of Göttingen from Boehringer-Ingelheim), and University Hospital Heidelberg (within RASUNOA-prime; supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo). Roland Veltkamp has received speaker fees, consulting honoraria and research support from Bayer, Boehringer Ingeleim, BMS, Pfizer, Daiichi Sankyo, CSL Behring, Morphosys, Amgen, Biogen, AZT Therapeutics, MSD, and Portola.

ORCID

J. C. Purrucker http://orcid.org/0000-0003-2978-4972

REFERENCES

1. Veltkamp R, Rizos T, Horstmann S. Intracerebral bleeding in patients on antithrombotic agents. *Semin Thromb Hemost*. 2013;39:963-971.
2. Lip GYH, Lane DA, Buller H, Apostolakis S. Development of a novel composite stroke and bleeding risk score in patients with atrial fibrillation: the AMADEUS Study. *Chest*. 2013;144:1839-1847.
3. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57:173-180.
4. Akoudad S, Portegies ML, Koudstaal PJ, et al. Cerebral microbleeds are associated with an increased risk of stroke: the rotterdam study. *Circulation*. 2015;132:509-516.
5. Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: a meta-analysis. *Neurology*. 2016;87:1501-1510.
6. Haley KE, Greenberg SM, Gurol ME. Cerebral microbleeds and macrobleeds: should they influence our recommendations for antithrombotic therapies? *Curr Cardiol Rep*. 2013;15:425.
7. Wilson D, Jager HR, Werring DJ. Anticoagulation for atrial fibrillation in patients with cerebral microbleeds. *Curr Atheroscler Rep*. 2015;17:47.
8. Lovelock CE, Cordonnier C, Naka H, et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. *Stroke*. 2010;41:1222-1228.
9. Charidimou A, Shakeshaft C, Werring DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. *Front Neurol*. 2012;3:133.
10. Ueno H, Naka H, Ohshita T, et al. Association between cerebral microbleeds on T2*-weighted MR images and recurrent hemorrhagic stroke in patients treated with warfarin following ischemic stroke. *AJNR Am J Neuroradiol*. 2008;29:1483-1486.

11. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-962.
12. Diener HC, Selim MH, Molina CA, Greenberg SM. Embolic stroke, atrial fibrillation, and microbleeds: is there a role for anticoagulation? *Stroke*. 2016;47:904-907.
13. Selim M, Diener HC. Atrial fibrillation and microbleeds. *Stroke*. 2017;48:2660-2664.
14. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838.
15. Gregoire SM, Chaudhary UJ, Brown MM, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology*. 2009;73:1759-1766.
16. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain*. 2015;138(Pt 8):2126-2139.
17. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318-1322.
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351-356.
19. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74:1346-1350.
20. Yamada M. Cerebral amyloid angiopathy: emerging concepts. *J Stroke*. 2015;17:17-30.
21. Akoudad S, Darweesh SK, Leening MJ, et al. Use of coumarin anticoagulants and cerebral microbleeds in the general population. *Stroke*. 2014;45:3436-3439.
22. Song TJ, Kim J, Lee HS, et al. The frequency of cerebral microbleeds increases with CHADS(2) scores in stroke patients with nonvalvular atrial fibrillation. *Eur J Neurol*. 2013;20:502-508.
23. Horstmann S, Mohlenbruch M, Wegele C, et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. *Eur J Neurol*. 2015;22:1355-1362.
24. van Etten ES, Auriel E, Haley KE, et al. Incidence of symptomatic hemorrhage in patients with lobar microbleeds. *Stroke*. 2014;45:2280-2285.
25. Lee SH, Ryu WS, Roh JK. Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage. *Neurology*. 2009;72:171-176.
26. Saito T, Kawamura Y, Sato N, et al. Non-vitamin k antagonist oral anticoagulants do not increase cerebral microbleeds. *J Stroke Cerebrovasc Dis*. 2015;24:1373-1377.
27. Pasquini M, Benedictus MR, Boulouis G, Rossi C, Dequatre-Ponchelle N, Cordonnier C. Incident cerebral microbleeds in a cohort of intracerebral hemorrhage. *Stroke*. 2016;47:689-694.
28. Diener HC, Easton JD, Granger CB, et al. Design of randomized, double-blind, evaluation in secondary stroke prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *Int J Stroke*. 2015;10:1309-1312.
29. Charidimou A, Wilson D, Shakeshaft C, et al. The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): rationale, design, and methods. *Int J Stroke*. 2015;10(Suppl A100):155-161.
30. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. *Int J Stroke*. 2017;12:985-990.
31. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: design of the NAVIGATE ESUS randomized trial. *European Stroke J*. 2016;1:146-154.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Purrucker JC, Wolf M, Haas K, et al. Microbleeds in ischemic vs hemorrhagic strokes on novel oral anticoagulants. *Acta Neurol Scand*. 2018;138:163–169. https://doi.org/10.1111/ane.12934