

NEWLY IDENTIFIED CEREBRAL MICROBLEEDS IN PATIENTS ON ANTICOAGULATION FOR SECONDARY STROKE PREVENTION

Tereza Šrámková MD¹, Tomáš Vaňásek MD², Martin Šrámek MD PhD^{1,3}, Petr Janský MD¹,
Kateřina Benešová MD¹, Anna Olšerová MD¹, Silvia Kmetonyová MD¹, Jaroslava Paulasová-
Schwabová MD PhD¹, Michal Klíma MD^{1,4}, Lukáš Michal MSc⁵, David Kala MEng PhD⁵, Jakub
Otáhal MD PhD⁵, Lukáš Mikšík MD², Aleš Tomek MD PhD¹

*1 Department of Neurology, Second Faculty of Medicine, Charles University and Motol University
Hospital Motol, Prague, Czech Republic,*

*2 Department of Radiology, Second Faculty of Medicine, Charles University and Motol University
Hospital Motol, Prague, Czech Republic,*

3 Department of Neurology, Military University Hospital Prague, Czech Republic,

4 Department of Neurology, Jihlava Hospital, Czech Republic,

*5 Department of Pathophysiology, Second Faculty of Medicine, Charles University and Motol
University Hospital Motol, Prague, Czech Republic,*

Author email address (in order of list above): terez.ruzickova@gmail.com,
vanastomas@seznam.cz, martin.sramek@gmail.com, petr.jansky@mybox.cz,
katerinabican@gmail.com, a.olserova@gmail.com, silvia.kmetony@gmail.com,
schwabova@gmail.com, mickey.klima@gmail.com, lukasmichal1998@gmail.com,
davidkala@seznam.cz, jakub.otahal@lfmotol.cuni.cz, lukas.miksik@fnmotol.cz,
ales.tomek@gmail.com

Conflicts of Interest: None declared.

Source of Funding:

Supported by Ministry of Health of the Czech Republic, grant nr. NU21-02-00289.

Correspondence to:

Aleš Tomek MD PhD¹, *Department of Neurology, Second Faculty of Medicine, Charles University
and Motol University Hospital Motol, V Uvalu 84, Prague, 15006, Czech Republic,*
email: ales.tomek@gmail.com

34 **List of abbreviations**

35 DOACs, direct oral anticoagulants;

36 MBs, cerebral microbleeds;

37 SWI, susceptibility-weighted imaging;

38 MRI, magnetic resonance imaging;

39 IQR, interquartile range;

40 NIHSS, National Institutes of Health Stroke Scale;

41 OR, odds ratio

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

Abstract

Introduction

Patients with cardioembolic ischemic stroke are commonly prescribed direct oral anticoagulants (DOACs), such as dabigatran (a direct thrombin inhibitor) and factor Xa inhibitors (e.g., apixaban and rivaroxaban), or warfarin to reduce the risk of recurrent stroke. A major concern in anticoagulant therapy is the risk of intracerebral hemorrhage, which is associated with a high mortality rate. Cerebral microbleeds (MBs), small asymptomatic brain hemorrhages detectable by susceptibility-weighted imaging (SWI) on MRI, are associated with increased hemorrhagic stroke risk.

Aim

This study evaluated the incidence of new MBs during one year of anticoagulation therapy in patients after cardioembolic stroke.

Materials and Methods

Patients indicated for anticoagulant therapy after cardioembolic stroke and monitored in the cerebrovascular outpatient clinic of our department underwent brain MRI at baseline and after one year of therapy. The occurrence of new MBs was assessed using susceptibility-weighted imaging (SWI) sequences. MBs were categorized based on location into three groups: deep (dMBs), lobar (lMBs), and infratentorial (iMBs).

Results

A total of 79 patients were included, 53 of whom were male (67.1%), with a median age of 71 years (IQR 64–76). The majority of patients (n = 50, 63.3%) were treated with apixaban, 16 patients (20.3%) with dabigatran, and 13 patients (16.5%) with warfarin. Baseline MRI revealed MBs in 17 patients (21.5%), including dMBs in 2, lMBs in 16, and iMBs in 2 patients. Follow-up MRI showed new MBs in 8 patients (10.1%), with new dMBs in 1, lMBs in 5, and iMBs in 4 patients. No statistically significant differences were observed in MBs the incidence of new MBs between anticoagulant groups ($p = 0.912$).

Conclusion

Over one year of anticoagulant therapy, new MBs were detected in 10.1% of patients, predominantly in lobar and infratentorial regions. No differences in the incidence of new MBs were identified between the different anticoagulant groups.

Key Words: stroke; microbleeds; anticoagulation

Introduction

Patients who have experienced cardioembolic ischemic stroke are predominantly prescribed direct oral anticoagulants (DOACs), such as dabigatran (a direct thrombin inhibitor) and factor Xa inhibitors (such as apixaban and rivaroxaban), as part of secondary prevention, in accordance with current clinical guidelines to minimize the risk of recurrent stroke ¹. One of the major concerns in anticoagulant therapy is the increased risk of intracerebral haemorrhage, a complication that carries a high mortality rate ². Increasing evidence suggests that the presence of small, asymptomatic microbleeds (MBs) detectable by magnetic resonance imaging (MRI), particularly in susceptibility-weighted imaging (SWI) sequences, is associated with an increased risk of subsequent haemorrhagic stroke ³⁻⁶. Cerebral microbleeds are often associated with small vessel pathology⁷ and their prevalence increases with age, rising from 6.5% in patients aged 45-50 years to 28.9% in those aged 70-79⁸. Furthermore, the risk of haemorrhagic stroke correlates with the number of MBs ^{9,10}. Numerous studies have examined factors influencing the incidence of new MBs¹¹, particularly the role of anticoagulants. Findings indicate that both warfarin and DOAC therapy can lead to the development of new MBs, with warfarin generally associated with a higher incidence. For instance, Zhuang et al. reported new MBs in 20.9% of warfarin treated patients compared to 3.4% of those on DOACs¹², while Saito et al. (2015) observed a similar disparity, with 23.8% of warfarin-treated patients developing new MBs compared to none in the DOAC group ¹³. Research specifically evaluating individual DOACs remains limited. The AVERROES-MRI assessment substudy evaluated 931 patients with atrial fibrillation over a median follow-up of one year and reported baseline MBs in 10.5% of patients treated with apixaban, with 7% developing new MBs on follow-up MRI. ¹⁴ Data for dabigatran come from a much smaller sample. For dabigatran, the DECISIVE trial, observed new MBs in 4% of the 57 patients who underwent follow-up MRI ¹⁵.

Aim

The primary aim of this study was to evaluate the the incidence of new MBs over one year of anticoagulation therapy in patients with a history of cardioembolic ischemic stroke. Furthermore, we sought to determine whether the incidence of new MBs differed based on the type of anticoagulant used and to analyse the distribution of newly developed MBs within specific brain regions.

Material and Methods

This prospective study was conducted at the comprehensive stroke centre affiliated with the Department of Neurology, 2nd Faculty of Medicine, Charles University, and Motol University Hospital in Prague, Czech Republic, between November 2015 and March 2020, with approval from the Institutional Review Board. The study adheres to the STROBE guidelines. Participants were recruited from a consecutive series of consenting cardioembolic ischemic stroke patients, and informed consent was obtained from all individuals before entering the study. The choice of anticoagulant therapy was determined by the attending physician. Warfarin therapy was initiated using a dose calculated through a pharmacogenetic algorithm¹⁶. Patients identified as having a genotype associated with an increased bleeding risk during warfarin treatment (i.e., three or more variant alleles of *CYP2C9* or *VKORC1*) were instead prescribed a direct oral anticoagulant (DOAC)¹⁷.

Clinical data

Data were collected from inpatient and outpatient medical records as well as directly from patients during their hospital stay and regular follow-up visits, with a particular focus on ischemic and bleeding complications. Baseline clinical and medical history information included elevated systolic blood pressure, a detailed history of vascular, renal, and hepatic diseases, diabetes mellitus, and concomitant medications. Patients underwent a comprehensive range of diagnostic evaluations, including ultrasound of extracranial and intracranial cerebral vessels, CT angiography, brain MRI, transesophageal echocardiography, and ECG monitoring for at least 72 hours. The aetiology of ischemic stroke was determined using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system.¹⁸

Brain MRI acquisition

MRI imaging was performed using a Philips Ingenia 1.5T machine (Philips Medical Systems, Netherlands). The protocol included the following sequences with specified parameters: 3D T2-weighted (repetition time (TR)/ echo time (TE) = 3200/263ms), FLAIR (TR/TE = 4800/342ms), DWI (TR/TE = 3751/93ms, slice thickness 5mm), SWI (TR/TE = 35/50ms, slice thickness 2mm), 3D T1-weighted (TR/TE = 25/4.6ms) and post-contrast 3D T1-weighted, which used the same parameters as the initial 3D T1-weighted sequence. The total scan duration ranged from 25 to 30 minutes. MRI scans were performed 7 to 12 days after symptom onset. Follow-up MRI examinations were conducted 12 months after the ischemic event using the same imaging protocol.

MRI evaluation

The severity of white matter lesions was evaluated using the Fazekas scale¹⁹. The presence and location of MBs were assessed on SWI sequences by a trained radiologist who was blinded to both laboratory and clinical data. MBs were classified according to their location as deep (basal ganglia, thalamus, internal or external capsule), lobar (cortex, subcortical white matter), or infratentorial (brainstem, cerebellum)^{20–22}. New MBs were identified by comparing MRI findings between baseline and follow-up scans.

Statistical analysis

The study cohort was divided into three groups based on the oral anticoagulant used: direct factor Xa inhibitors (apixaban or rivaroxaban), direct thrombin inhibitors (dabigatran), and vitamin K antagonists (warfarin). Baseline characteristics were compared between the patient groups using χ^2 -tests for categorical variables and independent samples Kruskal-Wallis test for continuous variables as appropriate. Logistic regression was used to assess categorical outcomes. A two-sided P value <0.05 was considered statistically significant. All of the statistical analysis were done using IBM SPSS Statistics 27 for Windows (IBM, USA) software.

Results

Of the 300 consenting patients with recent ischemic stroke screened for the study, 108 were eligible for oral anticoagulation therapy. Among these, 21 patients did not attend the follow-up MRI after 12 months, and 10 were excluded due to changes in anticoagulant medication during the study period. Ultimately, 79 patients were included in the final analysis.

The cohort comprised 53 men (67.1%) with a median age of 71 years (IQR 64–76). The majority of patients (n = 50, 63.3%) were treated with apixaban, while 16 patients (20.3%) received dabigatran and 13 patients (16.5%) were on warfarin. Basic demographic and clinical characteristics are summarized in Table 1.

At baseline, microbleeds (MBs) were detected in 17 patients (21.5%): 1 in the warfarin group, 12 in the apixaban group and 4 in the dabigatran group. Among these, 2 patients had deep MBs, 16 patients presented with lobar MBs, and 2 patients exhibited infratentorial MBs. Among patients in the warfarin group, no deep or infratentorial MBs were observed, while 1 patient had lobar MBs. In the apixaban group, 2 patients had deep MBs, 11 had lobar MBs, and 1 had infratentorial MBs. In

the dabigatran group, no deep MBs were detected, while 4 patients had lobar MBs and 1 patient had infratentorial MBs.

After one year of treatment, an increase in the number of MBs was observed in 8 patients (10.1%). This included 1 patient (7.7%) in the warfarin group, 5 patients (10%) in the apixaban group, and 2 patients (12.5%) in the dabigatran group. Of these, only 2 patients (on apixaban and 1 on dabigatran) had MBs at baseline. Specifically, one patient on apixaban developed a new deep MB, while five patients developed new lobar MBs (1 on warfarin, 2 on apixaban, and 2 on dabigatran). Additionally, four patients developed new infratentorial MBs (1 on warfarin, 2 on apixaban, and 1 on dabigatran). The maximum increase was observed in a patient on dabigatran, who developed 5 new MBs (4 lobar and 1 infratentorial). Another patient on warfarin developed 2 new MBs (1 lobar and 1 infratentorial), while 6 other patients developed 1 new MB each.

Logistic regression analysis identified the Fazekas score as the only statistically significant risk factor for development of new MBs, with an odds ratio of 3.66 (95% CI 1.18–11.37, $p = 0.025$), especially for scores ≥ 2 (OR 16.36, 95% CI 2.92–91.8, $p = 0.001$). Neither the presence of baseline MBs ($p = 0.801$) nor the type of oral anticoagulant ($p = 0.912$) reached statistical significance, indicating that the choice of anticoagulant did not significantly influence the development of MBs during the study period (Table 2).

New ischaemic lesions were detected in 2 patients in the apixaban group and 1 patient in the dabigatran group, with none observed in the warfarin group. Importantly, no clinically significant intracerebral haemorrhages occurred during the study period. The only bleeding complication was a bilateral subdural hematoma in a 71-year-old male on warfarin, an incidental finding identified on follow-up MRI. The patient reported experiencing mild intermittent headaches only after the MRI was conducted.

Discussion

Anticoagulation therapy is a cornerstone in preventing recurrent ischemic strokes in patients with cardioembolic origins. However, its use is accompanied by a recognized risk of haemorrhagic complications, including intracerebral haemorrhages. Cerebral microbleeds (MBs), though often clinically silent, represent subclinical haemorrhagic events and potential predictors of future symptomatic haemorrhages.^{4,5}

In this study, cerebral MBs were detected in 17 patients (21.5%), consistent with the prevalence reported in the Rotterdam study, which identified MBs in 16.8% of patients aged 60–69 years and 28.9% of those aged 70–79 years.⁸

In our cohort, 10.1% of patients experienced an increase in MBs after one year of anticoagulation therapy. This rate is lower than the 22.2% reported by Umemura et al.²³, likely due to differences in follow-up duration (12 months in our study compared to a median interval of 34 months in their work). Conversely, Orken et al.²⁴ reported a 10% rate of new MBs in ischemic stroke patients on warfarin therapy over a two-year follow-up, a finding that closely mirrors our results. Yokoyama et al.²⁵ evaluated ischemic stroke patients with nonvalvular atrial fibrillation who had at least one baseline MB, reporting that 28.6% of patients on NOACs and 66.7% of those on warfarin developed new MBs after 12 months of treatment. Our findings, which demonstrate lower progression rates, may reflect differences inclusion criteria and ethnic origin of the patients, as both MBs and hemorrhagic stroke are more frequent in patients of Asian origin^{26,27}. Similarly, Zhuang et al.¹² observed a trend toward a higher prevalence of new MBs after one year of anticoagulant treatment in the warfarin group compared to the NOAC group (20.9% vs. 3.4%, respectively; $p = 0.08$). However, it is noteworthy that Zhuang et al.'s cohort included all patients with atrial fibrillation, not exclusively stroke survivors. Unlike our findings, their study identified baseline MBs as a strong predictor of development of new MBS ($p = 0.03$, OR 6.37, 95% CI 1.15–35.36). Concerning the incidence of new microbleeds in patients on DOACs, we observed higher incidence in the dabigatran group than previously reported – 12.5% vs 4%¹⁵ and 10% incidence in the apixaban group, consistent with the findings of the AVERROES-MRI assessment sub-study¹⁴. In our cohort, new MBs were most commonly observed in lobar and infratentorial regions, consistent with findings from the meta-analysis by Cheng et al.²⁸, which associated anticoagulant use with a higher prevalence of strictly lobar MBs. The main limitations of our study include a limited sample size and a monocentric design, which focused exclusively on patients of Caucasian descent. As a result, the findings may not be generalizable to individuals of other ethnic backgrounds.

Conclusion

After one year of anticoagulation therapy in patients with prior cardioembolic ischemic stroke, 10.1% showed new MBs, primarily in lobar and infratentorial regions, without any clinically significant haemorrhagic events. No significant differences the incidence of new MBs were observed between patients treated with warfarin, apixaban, or dabigatran. Warfarin-treated patients were preselected based on pharmacogenetic profiles, excluding those with high bleeding risk genotypes. This may explain the comparable safety of warfarin to DOACs in this

study. These results suggest that pharmacogenetically guided warfarin therapy can align with DOACs in safety regarding the development of new MBs.

References

1. Dawson J, Béjot Y, Christensen LM, et al. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J*. 2022;7(3):I-II. doi:10.1177/23969873221100032
2. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. *Volume of Intracerebral Hemorrhage A Powerful and Easy-to-Use Predictor of 30-Day Mortality*. <http://ahajournals.org>
3. Wilson D, Ambler G, Shakeshaft C, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. *Lancet Neurol*. 2018;17(6):539-547. doi:10.1016/S1474-4422(18)30145-5
4. Bokura H, Saika R, Yamaguchi T, et al. Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals. *Stroke*. 2011;42(7):1867-1871. doi:10.1161/STROKEAHA.110.601922
5. Van Etten ES, Auriel E, Haley KE, et al. Incidence of symptomatic hemorrhage in patients with lobar microbleeds. *Stroke*. 2014;45(8):2280-2285. doi:10.1161/STROKEAHA.114.005151
6. Charidimou A, Karayiannis C, Song TJ, et al. *Brain Microbleeds, Anticoagulation, and Hemorrhage Risk Meta-Analysis in Stroke Patients with AF*; 2017. <https://www.neurology.org>
7. Wadi LC, Grigoryan MM, Kim RC, et al. Mechanisms of cerebral microbleeds. *J Neuropathol Exp Neurol*. 2021;79(10):1093-1099. doi:10.1093/JNEN/NLAA082
8. Poels MMF, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: An update of the rotterdam scan study. In: *Stroke*. Vol 41. ; 2010. doi:10.1161/STROKEAHA.110.595181
9. Choi KH, Kim JH, Lee C, et al. Microbleeds and Outcome in Patients With Acute Ischemic Stroke and Atrial Fibrillation Taking Anticoagulants. *Stroke*. 2020;51(12):3514-3522. doi:10.1161/STROKEAHA.120.030300
10. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2019;18(7):653-665. doi:10.1016/S1474-4422(19)30197-8
11. Gregoire SM, Brown MM, Kallis C, Jäger HR, Yousry TA, Werring DJ. MRI detection of new microbleeds in patients with ischemic stroke: Five-year cohort follow-up study. *Stroke*. 2010;41(1):184-186. doi:10.1161/STROKEAHA.109.568469
12. Zhuang L, Zhai L, Qiao S, et al. New cerebral microbleeds in AF patients on non-vitamin K oral anticoagulants or warfarin: One-year follow-up. *Medicine (United States)*. 2022;101(7):E25836. doi:10.1097/MD.00000000000025836
13. Saito T, Kawamura Y, Sato N, et al. Non-vitamin K antagonist oral anticoagulants do not increase cerebral microbleeds. *Journal of Stroke and Cerebrovascular Diseases*. 2015;24(6):1373-1377. doi:10.1016/j.jstrokecerebrovasdis.2015.02.018
14. O'Donnell MJ, Eikelboom JW, Yusuf S, et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. *Am Heart J*. 2016;178:145-150. doi:10.1016/j.ahj.2016.03.019
15. Cho MS, Kim M, Lee S ah, et al. Comparison of Dabigatran Versus Warfarin Treatment for Prevention of New Cerebral Lesions in Valvular Atrial Fibrillation. *American Journal of Cardiology*. 2022;175:58-64. doi:10.1016/j.amjcard.2022.03.050
16. Tomek A, Růžicková T, Kaplan V, et al. Pharmacogenetic algorithm for predicting daily dose of warfarin in Caucasian patients of Czech origin. *Drug Metab Pers Ther*. 2020;0(0). doi:10.1515/DMDI-2020-0171
17. Tomek A, Máoška V, Kolářová T, et al. The bleeding risk during warfarin therapy is associated with the number of variant alleles of CYP2C9 and VKORC1 genes. *Cardiology*. 2013;125(3):182-191. doi:10.1159/000350407

18. Adams HP, Bendixen BH, Kappelle L Jaap, et al. Classification of Subtype of Acute Ischemic Stroke Definitions for Use in a Multicenter Clinical Trial. *Stroke*. 1993;24(1):35-41. doi:10.1161/01.str.24.1.35
19. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR Signal Abnormalities at 1.5 T in Alzheimer's Dementia and Normal Aging. *American Journal of Roentgenology*. 1987;149(2):351-356. doi:10.2214/ajr.149.2.351
20. Cordonnier C, Potter GM, Jackson CA, et al. Improving interrater agreement about brain microbleeds: Development of the Brain Observer MicroBleed Scale (BOMBS). *Stroke*. 2009;40(1):94-99. doi:10.1161/STROKEAHA.108.526996
21. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8(2):165-174. doi:10.1016/S1474-4422(09)70013-4
22. 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(8):822-838. doi:10.1016/S1474-4422(13)70124-8
23. Umemura T, Mashita S, Kawamura T. Oral anticoagulant use and the development of new cerebral microbleeds in cardioembolic stroke patients with atrial fibrillation. *PLoS One*. 2020;15(9 September). doi:10.1371/journal.pone.0238456
24. Orken DN, Uysal E, Timer E, Kuloglu-Pazarci N, Mumcu S, Forta H. New cerebral microbleeds in ischemic stroke patients on warfarin treatment: Two-year follow-up. *Clin Neurol Neurosurg*. 2013;115(9):1682-1685. doi:10.1016/j.clineuro.2013.03.004
25. Yokoyama M, Mizuma A, Terao T, et al. Effectiveness of Nonvitamin K Antagonist Oral Anticoagulants and Warfarin for Preventing Further Cerebral Microbleeds in Acute Ischemic Stroke Patients with Nonvalvular Atrial Fibrillation and At Least One Microbleed: CMB-NOW Multisite Pilot Trial. *Journal of Stroke and Cerebrovascular Diseases*. 2019;28(7):1918-1925. doi:10.1016/j.jstrokecerebrovasdis.2019.03.050
26. Koennecke HC. *Cerebral Microbleeds on MRI Prevalence, Associations, and Potential Clinical Implications*. Vol 66.; 2006.
27. Mehndiratta MM, Khan M, Mehndiratta P, Wasay M. Stroke in Asia: Geographical variations and temporal trends. *J Neurol Neurosurg Psychiatry*. 2014;85(12):1308-1312. doi:10.1136/jnnp-2013-306992
28. Cheng Y, Wang Y, Song Q, Qiu K, Liu M. Use of anticoagulant therapy and cerebral microbleeds: a systematic review and meta-analysis. *J Neurol*. 2021;268(5):1666-1679. doi:10.1007/s00415-019-09572-x