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New cerebral microbleeds in AF patients on non-vitamin K oral anticoagulants or warfarin

One-year follow-up

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Abstract

Anticoagulant treatment increases the risk of intracerebral hemorrhage (ICH), but whether the treatment, more specifically non-vitamin K oral anticoagulants (NOACs), increases the risk of cerebral microbleeds (CMBs) remains uncertain. We performed this study to investigate the development of new CMBs due to NOACs or warfarin treatment in patients with atrial fibrillation (AF).

We prospectively recruited AF patients before anticoagulation from June 2016 to June 2018. We performed susceptibility-weighted imaging (SWI) examinations on all enrolled AF patients and re-examined SWI 1 year later. We compared demographic features and new CMBs between the NOACs group and the warfarin group. Univariate analysis of clinical factors was performed according to the development of new CMBs; and age, a HAS-B(L)ED score, warfarin use, and the presence of baseline CMBs were then selected for inclusion in the multivariate logistic regression model.

A total of 72 AF patients were recruited, 29 of whom were assigned to the NOACs group and 43 to the warfarin group. Finally, 1 patient in the NOACs group (3.4%) and 9 patients (20.9%) in the warfarin group developed new CMBs after 1 year follow-up ($P = .08$). Univariate analysis showed that age, a HAS-B(L)ED score ≥4, the presence of baseline CMBs were associated with the development of new CMBs ($P < .05$). And multivariate regression analysis showed baseline CMBs ($P = .03$, odds ratio = 6.37, 95% confidence interval 1.15–35.36) was independently related to the increase in new CMBs.

AF patients treated with NOACs may have a decreased trend in the development of new CMBs compared with those treated with warfarin. Baseline CMBs increased the frequency of new CMBs during anticoagulant treatment. The development of new CMBs in AF patients with anticoagulation requires further longitudinal studies with longer follow-up in larger samples.

Abbreviations: AF = atrial fibrillation, CMBs = cerebral microbleeds, FLAIR = fluid-attenuated inversion recovery, ICH = intracerebral hemorrhage, INR = international standard ratio, LA = leukoaraiosis, NOACs = non-vitamin K oral anticoagulants, SWI = susceptibility-weighted imaging.

Keywords: atrial fibrillation, cerebral microbleeds, non-vitamin K oral anticoagulants, warfarin

1. Introduction

Atrial fibrillation (AF) is a common type of cardiac arrhythmia, with an incidence that increases with age.[1] The prevalence rate of older people over 80 years is about 7.5%.[2] Furthermore, AF is a strong risk factor for ischemic strokes. The risk of AF-related stroke is 5 times that of the general population, and about 25% of ischemic stroke originates from AF.[3,4] Oral anticoagulation can effectively reduce the incidence of ischemic stroke in AF patients, and various guidelines recommend prompt utilization of anti-coagulation therapy to prevent ischemic stroke in AF patients.[5,6] Nowadays, warfarin and non-vitamin K antagonist oral anti-coagulants (NOACs) are the 2 main kinds of anticoagulants used for cardiogenic embolism prevention. The latter are novel oral anticoagulants and are used widely for their efficacy and convenience. However, oral anticoagulants increase the risk of bleeding, including minor bleeding of the skin or gums, as well as severe bleeding, such as intracranial hemorrhages (ICHs). ICH complications from anticoagulation cause death or disability in 75% of ICH patients.[7] Therefore, the prevention of ICH in patients on anticoagulation is important. Furthermore, it is also necessary to identify the risk factors of bleeding.

Cerebral microbleeds (CMBs) appear as small, round or ovoid, hypointense lesions on T2*gradient-recalled echo-weighted or susceptibility-weighted imaging and have been proven to be

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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associated with future intracranial hemorrhage.[8] Studies in ICH patients with MRI showed that the prevalence of CMBs ranged from 23% to 90%.[9,10] Moreover, it was observed that the presence of more than 5 CMBs was closely related to the development of ICH,[11] and CMBs were seen as a risk factor for subsequent ICH among patients. A meta-analysis showed CMBs increased more in warfarin users than in non-antithrombotic users,[12] and the presence of CMBs was associated with a subsequent ICH in warfarin users.[13] Some large sample-based studies have confirmed that the incidence of ICH during NOACs treatment was lower than that during warfarin treatment.[14,15] However, we know little about the CMBs in NOACs users with AF. A small sample study that utilized gradient echo T2*weighted imaging (T2*WI) suggested that NOACs do not increase CMBs in AF patients.[16] Recently, the CMB-NOW Study showed that the proportion of increase in the number of CMBs with NOACs treatment was lower than that in warfarin treatment.[17] However, the patients recruited in these studies were mainly afflicted with ischemic stroke, and the development of CMBs in non-ischemic stroke patients was not investigated. Moreover, CMB was detected by T2*WI in these studies, and there is evidence reporting that susceptibility-weighted imaging is more sensitive than T2*WI in a number of different patient cohorts with CMBs.[18] The association between the use of anticoagulant drugs and the risk of development of CMBs remains uncertain. Thus, in this study, we aimed to investigate the development of new CMBs in NOACs patients compared with warfarin users.

2. Methods

2.1. Patient enrollment

AF patients who were admitted to the Neurology or Cardiovascular department of Zhejiang Hospital who needed anticoagulation were enrolled consecutively from June 2016 to June 2018. AF was defined as a pre-existing AF or one that was newly detected on an electrocardiogram or by continuous cardiac rhythm monitoring. The inclusion criteria were:

(1) age over 40 years;
(2) met the diagnostic criteria for AF;
(3) CHA_2DS_2-VASc score ≥ 2;
(4) never had anticoagulant therapy.

Exclusion criteria were:

(1) patients diagnosed with valvular AF;
(2) anticoagulant contraindications, such as coagulation dysfunction, gastrointestinal bleeding, amyloidosis, and so on.
(3) patients who refused anticoagulation therapy;
(4) patients that were unable to undergo MRI scan due to metal implants, claustrophobia, or some other reason;
(5) patients with no baseline CMBs, as the development of new CMBs was confirmed by comparing follow-up CMBs to baseline CMBs, and baseline CMBs may also be a confounding factor that should be excluded or adjusted in 2 groups.
(6) patients refused to participate in the study.

A baseline MRI assessment was performed before anticoagulation. Warfarin or NOACs were prescribed according to the patient's liver and kidney function, economic conditions, and personal will. Patients in the warfarin group were treated with an adjusted dose of warfarin that made the INR (international standard ratio) between 2 and 3, while patients taking dabigatran or rivaroxiban were assigned into the NOACs group. A second MRI assessment was performed after anticoagulation at around 1 year $\pm$ 1 month. The number of CMBs that changed after anticoagulation was analyzed in the enrolled patients who had AF. A total of 207 patients were eligible for inclusion, while 93 patients were excluded as they fit the exclusion criteria. Among the remaining 114 patients, 10 patients discontinued anticoagulant therapy, 25 patients were lost to follow-up, and 7 patients did not undergo a second MR after 1 year. Finally, 72 patients completed the study (Fig. 1), and all patients signed the informed consent for the study. The entire study was approved by the Ethical Review Board (No. 2016-C-42) of the Zhejiang Hospital.

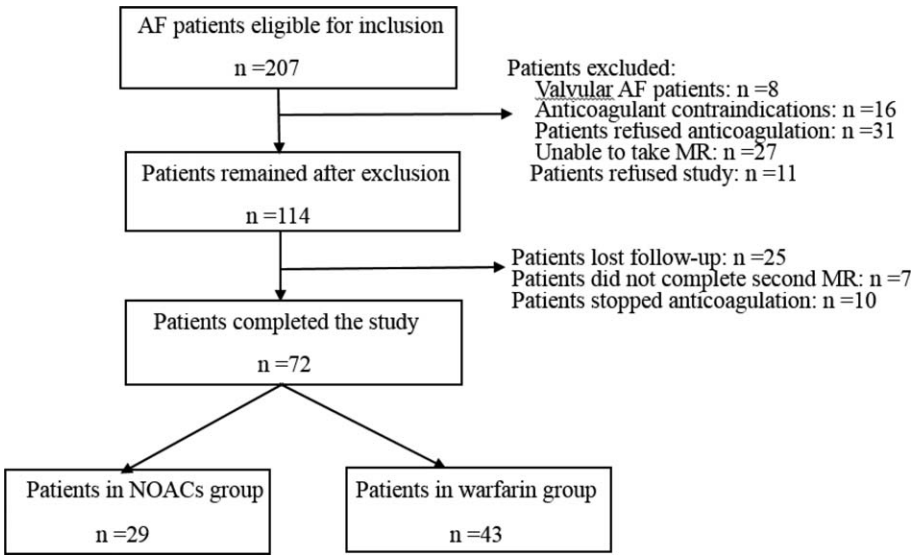

Figure 1. Flow chart of the study population.

2.2. Definition of variables

Hypertension was defined as having a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or the current use of antihypertensive agents based on the WHO hypertension definition. Diabetes mellitus was defined as having a twice fasting plasma glucose levels >126 mg/dL (7.0 mmol/L), a random plasma glucose >200 mg/dL (11.1 mmol/L), or the current use of anti-diabetic agents based on the ADA guidelines. Hypercholesterolemia was defined as having a total cholesterol level >240 mg/dL or the current use of a lipid-lowering medication. Chronic kidney disease was defined as having an estimated glomerular filtration rate level of less than 60 mL/min/1.73 m^2 and/or overt albuminuria continuing longer than 3 months. Stroke was defined as a history of ischemic or hemorrhage stroke with neurological deficits. Coronary disease was defined as a history of myocardial infarction or acute coronary syndrome. Congestive heart failure was defined as previously diagnosed by a cardiovascular specialist. A history of smoking was coded if the patient was a current smoker or an ex-smoker who had quit smoking within 5 years of admission. Alcohol was set as current consumption that reached 300 g/week. Antiplatelet treatment was defined as aspirin or clopidogrel treatment. HAS-B(L)ED score was a cumulative score, including hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile INR (if on warfarin), elderly age, use of drugs (antiplatelet or NSAIDs), and/or excessive alcohol intake.[19]

2.3. MRI protocol

Imaging of the brain was performed on 3.0T MRI scanners (Siemens, Skyra) with a standard head coil. The image protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted imaging (SWI). The T1-weighted sequence parameters were as follows: TR, 1600 ms; TE, 9 ms; field of view, 220 mm; matrix, 240 × 320; slice thickness, 5 mm; interslice gap, 1.5 mm. The T2-weighted sequence parameters were as follows: TR, 4210 ms; TE, 89 ms; field of view, 220 mm; matrix, 384 × 384; slice thickness, 5 mm; interslice gap, 1.5 mm. The fluid-attenuated inversion recovery sequence parameters were as follows: TR, 8000 ms; TE, 97 ms; field of view, 220 mm; matrix, 240 × 320; slice thickness, 5 mm; interslice gap, 1.5 mm. SWI sequence parameters were as follows: sequence, TR, 27 ms; TE, 20 ms; flip angle, 15°; field of view, 220 mm; matrix, 223 × 256; slice thickness, 1.5 mm; interslice gap, 0.3 mm. Minimum intensity projection (MinIP) was used on post processing of SWI.

CMBs were defined as punctuate, hypointense lesions <10 mm in size located in the lobar (cortex, subcortex, and white matter), deep (basal ganglia and thalamus), or infratentorial (brain stem and cerebellum) regions on SWI. Hypointense lesions considered as iron or calcium deposits, bone, or vessel flow were excluded. The number of CMBs over the whole brain was counted separately by 2 trained observers who were blinded to the clinical information. Leukoaraiosis (LA) in our study was assessed based on the FLAIR imaging according to the Fazekas' scale.[20]

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 21.0 software (Chicago, IL). Chi-squared ($\chi 2$) tests or Fisher's exact tests were used to analyze categorical variables, and continuous variables were analyzed using *t* tests or Mann–Whitney tests for group comparisons. The odds ratio (OR) and 95% confidence interval (CI) of the development of CMBs was obtained using logistic regression analysis. Age, sex, vascular risk factors, a HAS-B(L)ED score ≥4, leukoaraiosis, warfarin use, and the presence of baseline CMBs were tested by univariate analysis. Then age, a HAS-B(L)ED score ≥4, warfarin use, and the presence of baseline CMBs with *P* value less than .1 were entered into multivariate logistic regression analysis. A *P* value of <.05 was set as the threshold of statistical significance.

3. Results

A total of 72 patients were recruited into this study, with 45 males (62.5%). A total of 29 AF patients were in the NOAC group including 2 who were treated with dabigatran 300 mg/day, 19 with dabigatran 220 mg/day, 5 with rivaroxaban 15 mg/day, and 3 with rivaroxaban 10 mg/day. The other 43 patients in the warfarin group and the dose of warfarin administered depended on the INR of each patient. The mean follow-up time was 373 ± 12 days. Baseline CMBs was detected by SWI scanning in 18 patients (25%) before anticoagulation. Among these patients, 10 (13.9%) developed new CMBs after 1 year (Fig. 2), while 7 of them already had CMBs before anticoagulation. No patient developed symptomatic intracranial hemorrhage.

The demographic, evaluating score, and clinical and radiological characteristics of the patients in the NOACs and warfarin groups are presented in Table 1. There were no significant differences between the 2 groups in terms of age, sex, antiplatelet treatment, and baseline CMBs numbers. There were also no statistical differences in risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, coronary heart disease, congestive heart failure, alcohol, smoking, ischemic stroke or hemorrhage history, and chronic kidney disease. Among all the risk factors, hypertension was the most common in both groups (62.1% vs 55.8%, *P* = .597). HAS-B(L)ED scores in these 2 groups were also not significantly different. A total of 9 (20.9%) patients developed new CMBs in the warfarin group, which was greater than in the NOACs group (1; 3.4%). However, no significant difference was observed in these 2 groups (*P* = .08).

Univariate and multivariate logistic regression analysis regarding the development of the CMBs are presented in Table 2. The *P* value of age ≥75 years, HAS-B(L)ED score ≥4, and warfarin and baseline CMBs were <.1. A multivariate regression analysis with these 4 factors above showed that the baseline CMBs (*P* = .034, OR 6.37, 95% CI 1.15-35.36) were independently related to the new development of CMBs.

4. Discussion

This is a longitudinal prospective study of the risk of occurrence of CMBs as influenced by the administration of NOACs or warfarin in patients with NVAF. In our study, the rate of development of new CMBs of patients undergoing anticoagulant treatment was 13.9%. This is similar to some longitudinal studies that have reported a rate of 10.5% to 13%.[16,21] Compared to patients without anticoagulant treatment in a community-based Rotterdam study,[22] the incidence of new CMBs was higher in the patients in this study. Postmortem histological analyses found focal effusions of intact erythrocytes in the CMBs that were detected on MRI.[23] Thus, we hypothesize that anticoagulants may accelerate red blood cell extravasation by disrupting

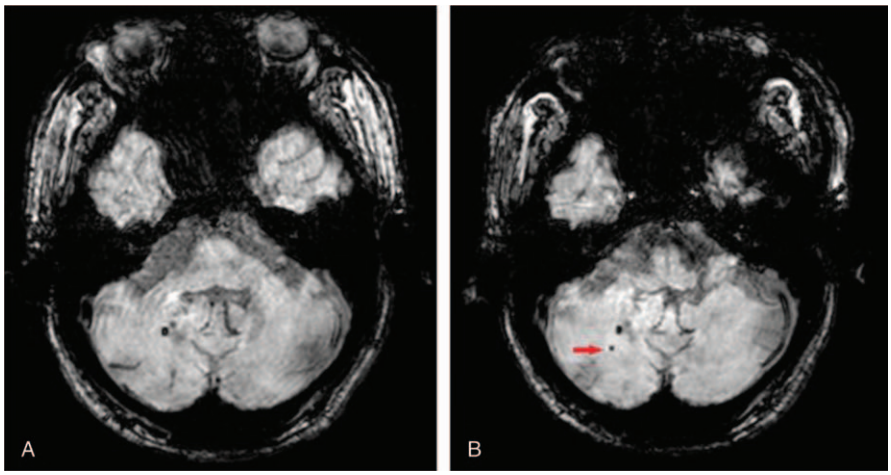

Figure 2. A 72-year-old AF patient with CMB in the right cerebellum before anticoagulant treatment (A). A new CMB had developed after 1 year of warfarin use (B).

hemostatic mechanisms, contributing to the formation and accumulation of CMBs among anticoagulant patients.[24] However, the mechanism of how CMBs are affected by anticoagulants remains unclear; therefore, more studies, especially animal studies, are needed.

Furthermore, we found that the rate of development of new CMBs in the NOACs group (3.4%) was lower than in the warfarin group (20.9%). However, no observable differences were found between these 2 groups. This may be due to the small sample size in our study. Soo et al[25] reported that there was no significant correlation between the duration of NOAC exposure and the quantity of CMBs. Furthermore, Lioutas et al[26] found that the median CMB number was significantly lower in patients who developed a NOACs-related ICH than in warfarin-related cases (2 vs 7). A meta-analysis regarding anticoagulants and CMBs also found no association for NOACs.[27] However, these studies were mainly retrospective studies, and more longitudinal studies on how new CMBs develop are still needed. The CMB-NOW study,[17] as one of the longitudinal studies, reported the proportion of AF patients with an increased number of CMBs were 28.6% and 66.7% in NOACs and warfarin groups, respectively. Although this study lacked statistical comparisons between the 2 groups because of the small sample size and the presence of recruited patients who had at least 1 CMB, the trend of development of new CMBs was consistent with our study. Moreover, another study[16] reported that CMBs did not develop in 23 patients with NOACs for 1 year, and that the rate of new CMBs was significantly lower than in patients treated with warfarin (23.8%). Thus, we speculate that NOACs may have less effect on the development of CMBs. However, we still need further studies with a larger-sample size for confirmation.

Table 1

AF patients' characteristics in the NOAC group compared with the warfarin group.

Characteristic	NOACs (n = 29)	Warfarin (n = 43)	*P*
Age (mean ± SD, yr)	71.93 ± 13.47	73.14 ± 9.14	.651
Female	10 (34.5%)	17 (39.5%)	.664
Hypertension	18 (62.1%)	24 (55.8%)	.597
Diabetes mellitus	5 (17.2%)	10 (23.3%)	.538
Hypercholesterolemia	12 (41.4%)	14 (32.6%)	.445
Coronary heart disease	15 (51.7%)	18 (41.9%)	.410
Congestive heart failure	4 (13.8%)	9 (20.9%)	.440
Alcohol	7 (24.1%)	13 (30.2%)	.571
Smoking	8 (27.6%)	16 (37.2%)	.396
Ischemic stroke history	16 (55.2%)	23 (53.5%)	.888
Hemorrhage history	4 (13.8%)	1 (2.3%)	.160
Chronic kidney disease	6 (20.7%)	7 (16.3%)	.633
Leukoaraiosis	8 (27.6%)	15 (34.9%)	.515
Antiplatelets	7 (24.1%)	14 (32.6%)	.441
HAS-B(L)ED (median)	3	3	.091
Baseline CMBs	6 (20.7%)	12 (27.9%)	.488
New CMBs	1 (3.4%)	9 (20.9%)	.079

CMBs = cerebral microbleeds, HAS-B(L)ED = hypertension, abnormal renal and/or liver function, previous stroke, bleeding history, or predisposition, labile INR, elderly age, drugs and/or alcohol excess, NOACs = non-vitamin K oral anticoagulants.

In the present study, the baseline CMBs of AF patients before anticoagulation was 25%. This is significantly associated with the development of CMBs according to multivariate logistic regression analysis. CMBs are the radiological manifestation of hemosiderin deposits that had leaked from damaged small vessels[28] and are highly associated with small vessel disease, intracranial hemorrhage, and dementia.[29] In previous longitudinal studies, patients with CMBs at baseline were at risk of developing new CMBs, but these studies mainly investigated patients with stroke, dementia, and cerebral amyloid angiopathy.[30–32] There was 1 study that found that AF patients with CMBs at baseline developed significantly more new CMBs than patients without CMBs at baseline during warfarin treatment.[21] Thus, baseline CMBs may have an important influence on the development of subsequent CMBs in anticoagulant patients. Clinicians need to pay more attention to baseline CMBs before anticoagulation treatment, and CMBs should be screened by SWI may be beneficial for AF patients before anticoagulation treatment.

Our study expounds the roles of warfarin and NOACs in the development of CMBs and provides new evidence for the bleeding risk of anticoagulant therapy. However, our study has several limitations. First, our study is a single-center study comprising a few participants; thus, generalizing the results to all anticoagulant patients with AF must be done with caution. Moreover, we will continue to recruit more AF patients for future

Table 2

Univariate and multivariable logistic regression analyses for new CMBs.

Variates	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Age ≥75 yr	.020	12.46 (1.49–104.51)	.189	5.08 (0.45–57.39)
Female	.383	1.82 (0.47–6.97)		
Hypertension	.151	3.29 (0.65–16.78)		
Diabetes mellitus	.944	0.94 (0.18–4.99)		
Hypercholesterolemia	.330	1.95 (0.51–7.51)		
Coronary heart disease	.111	3.23 (0.76–13.68)		
Congestive heart failure	.485	0.46 (0.05–4.01)		
Alcohol	.358	1.92 (0.48–7.67)		
Smoking	.124	0.19 (0.02–1.58)		
Ischemic stroke history	.287	2.19 (0.52–9.25)		
Hemorrhage history	.685	1.61 (0.16–16.09)		
Chronic kidney disease	.299	2.23 (0.49–10.11)		
Leukoaraiosis	.196	2.44 (0.63–9.48)		
HAS-B(L)ED ≥4	.022	5.14 (1.27–20.82)	.317	2.45 (0.42–14.13)
Warfarin	.065	7.41 (0.89–62.10)	.077	7.81 (0.80–76.08)
Baseline CMBs	.002	10.82 (2.41–48.55)	.034	6.37 (1.15–35.36)

CMBs = cerebral microbleeds, HAS-B(L)ED = hypertension, abnormal renal and/or liver function, previous stroke, bleeding history, or predisposition, labile INR, elderly age, drugs and/or alcohol excess.

studies. Second, the NOACs and warfarin groups were not divided randomly, and patients in the NOACs group received either dabigatran or rivaroxaban. These factors may all lead to selection bias and may have influenced the outcome. Because of the small sample size, we are currently unable to reduce this bias through subgroup analysis; however, it can be achieved by increasing the sample size in future studies. Third, the follow-up time in our study was 1 year, and it remains uncertain if a longer duration of NOAC or warfarin treatment may affect the development of CMBs in AF patients; hence, we will follow up patients in further studies for longer periods.

In conclusion, AF patients treated with NOACs may have a decreased rate of development of new CMBs compared with those treated with warfarin. The presence of baseline CMBs was associated with an increased number of new CMBs during anticoagulant treatment. Larger longitudinal studies with longer follow-up are needed to confirm the development of new CMBs in AF patients with anticoagulation.

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References

[1] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5.
[2] Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006; 114:119–25.
[3] Lip G, Freedman B, De Caterina R, et al. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost 2017;117:1230–9.
[4] Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36:1115–9.
[5] Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart 2014;100:396–405.
[6] Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2160–236.
[7] Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120:700–5.
[8] Lee SH, Bae HJ, Kwon SJ, et al. Cerebral microbleeds are regionally associated with intracerebral hemorrhage. Neurology 2004;62:72–6.
[9] Offenbacher H, Fazekas F, Schmidt R, et al. MR of cerebral abnormalities concomitant with primary intracerebral hematomas. AJNR Am J Neuroradiol 1996;17:573–8.
[10] Wilson D, Jager HR, Werring DJ. Anticoagulation for atrial fibrillation in patients with cerebral microbleeds. Curr Atheroscler Rep 2015;17:47–61.
[11] Greenberg SM, Eng JA, Ning M, et al. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke 2004;35:1415–20.
[12] 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;41:1222–8.
[13] Soo Y, Abrigo JM, Leung KT, et al. Risk of intracerebral haemorrhage in Chinese patients with atrial fibrillation on warfarin with cerebral microbleeds: the IPAAC-Warfarin study. J Neurol Neurosurg Psychiatry 2019;90:428–35.
[14] Lee SR, Choi EK, Kwon S, et al. Oral anticoagulation in Asian patients with atrial fibrillation and a history of intracranial hemorrhage. Stroke 2020;51:416–23.
[15] 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;383:955–62.

[16] Saito T, Kawamura Y, Sato N, et al. Non-vitamin k antagonist oral anticoagulants do not increase cerebral microbleeds. J Stroke Cerebrovasc Dis 2015;24:1373–7.
[17] 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. J Stroke Cerebrovasc Dis 2019;28:1918–25.
[18] Shams S, Martola J, Cavallin L, et al. SWI or T2*: which MRI sequence to use in the detection of cerebral microbleeds? The Karolinska Imaging Dementia Study. AJNR Am J Neuroradiol 2015; 36:1089–95.
[19] Dzeshka MS, Lane DA, Lip GY. Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS2, CHA2 DS2 -VASc, R2 CHADS2, HAS-BLED, ATRIA, and more). Clin Cardiol 2014;37:634–44.
[20] Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987; 149:351–6.
[21] Orken DN, Uysal E, Timer E, et al. New cerebral microbleeds in ischemic stroke patients on warfarin treatment: two-year follow-up. Clin Neurol Neurosurg 2013;115:1682–5.
[22] Poels MM, Ikram MA, van der Lugt A, et al. Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. Stroke 2011;42:656–61.
[23] De Reuck J, Deramecourt V, Cordonnier C, et al. Detection of microbleeds in post-mortem brains of patients with frontotemporal lobar degeneration: a 7.0-Tesla magnetic resonance imaging study with neuropathological correlates. Eur J Neurol 2012;19:1355–60.
[24] Wilson D, Werring DJ. Antithrombotic therapy in patients with cerebral microbleeds. Curr Opin Neurol 2017;30:38–47.
[25] Soo Y, Abrigo J, Leung KT, et al. Correlation of non-vitamin K antagonist oral anticoagulant exposure and cerebral microbleeds in Chinese patients with atrial fibrillation. J Neurol Neurosurg Psychiatry 2018;89:680–6.
[26] Lioutas VA, Goyal N, Katsanos AH, et al. Microbleed prevalence and burden in anticoagulant-associated intracerebral bleed. Ann Clin Transl Neurol 2019;6:1546–51.
[27] Cheng Y, Wang Y, Song Q, et al. Use of anticoagulant therapy and cerebral microbleeds: a systematic review and meta-analysis. J Neurol 2021;5:268–281.
[28] Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis 2011; 32:528–34.
[29] Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. Neurology 2017;89:820–9.
[30] Gregoire SM, Brown MM, Kallis C, et al. MRI detection of new microbleeds in patients with ischemic stroke: five-year cohort follow-up study. Stroke 2010;41:184–6.
[31] Graff-Radford J, Lesnick T, Rabinstein AA, et al. Cerebral microbleed incidence, relationship to amyloid burden: the Mayo Clinic Study of Aging. Neurology 2020;94:e190–9.
[32] Goos JD, Henneman WJ, Sluimer JD, et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology 2010;74:1954–60.