Risk of intracerebral haemorrhage in patients with cerebral microbleeds taking warfarin for atrial fibrillation: a prospective study

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KEY MESSAGES

1. In Chinese patients with atrial fibrillation, the presence of ≥5 cerebral microbleeds on magnetic resonance imaging is associated with an increased risk of warfarin-related intracerebral haemorrhage.
2. Evaluation of cerebral microbleeds in patients with atrial fibrillation may help identify patients at higher risk of warfarin-related intracerebral haemorrhage, who may benefit from alternative treatment options with lower bleeding risk.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. Irregular heartbeats can induce the formation of blood clots in the heart that dislodge and occlude arteries in the brain, accounting for a five-fold increase in the risk of ischaemic stroke. Oral anticoagulants can reduce the stroke risk in patients with AF by 68%. However, anticoagulant use is often limited by the potential risk of intracerebral haemorrhage (ICH). Over the past 15 years, there has been an almost three-fold increase in AF-related stroke in Hong Kong.[1]

To optimise use of anticoagulants, better risk stratification of patients is needed for appropriate treatment. Cerebral microbleeds (CMBs) detected by magnetic resonance imaging are radiological markers that can predict future ICH.[2] CMBs are tiny old blood residues in brain, indicating previous silent mild leakage from fragile small vessels. CMBs are present in one-third of patients with AF[3]; this raises concerns about safety of anticoagulation in patients with CMBs, who may have higher risk of ICH that may outweigh the expected treatment benefit. A study explored whether CMBs could guide treatment decisions in AF,[3] but the exact risk of ICH remains uncertain.

This prospective study aimed to evaluate the risk of ICH in Chinese patients taking warfarin for AF with concomitant CMBs.

Methods

This was a prospective multicentre observational study. Chinese patients who took warfarin for AF were recruited from eight public hospitals in Hong Kong. 3T magnetic resonance imaging (Achieva TX; Philips Medical Systems, Best, Netherlands) was performed to evaluate CMBs. The standard stroke scanning protocol included 3D venous BOLD and axial FLAIR for detection of CMBs and white matter hyperintensities, respectively. A CMB was defined as an old, silent focus of signal loss in the susceptibility weighted imaging sequence, measuring 2 to 10 mm in diameter. White matter changes indicating underlying leukoaraiosis were visually rated using age-related white matter changes scale.

Primary outcome was ICH. Secondary outcomes were recurrent ischaemic stroke, systemic embolism, mortality of all causes, and mobility level. Patients were followed up for 2 years. Those with and without CMBs were compared.

Independent *t* test or non-parametric Mann-Whitney U test was used for comparison of continuous variables. The Chi-squared test was used for categorical variables. The Fisher's exact test was used when the expected count in any of the 2×2 table was <5. Multivariate regression model was used to determine predictors of ICH. Potential predictors were first tested using the univariate logistic regression model. Significant variables were further tested in the multivariate model using the stepwise-forward method and then adjusted by age. Statistical analyses were performed using SPSS (Windows version 24; IBM Corp, Armonk [NY], US). A P value of <0.05 was considered statistically significant.

Results

Of 290 patients recruited, 53 were excluded based on pre-defined exclusion criteria and 237 were included in analysis. The mean follow-up period was 22.7±10.2

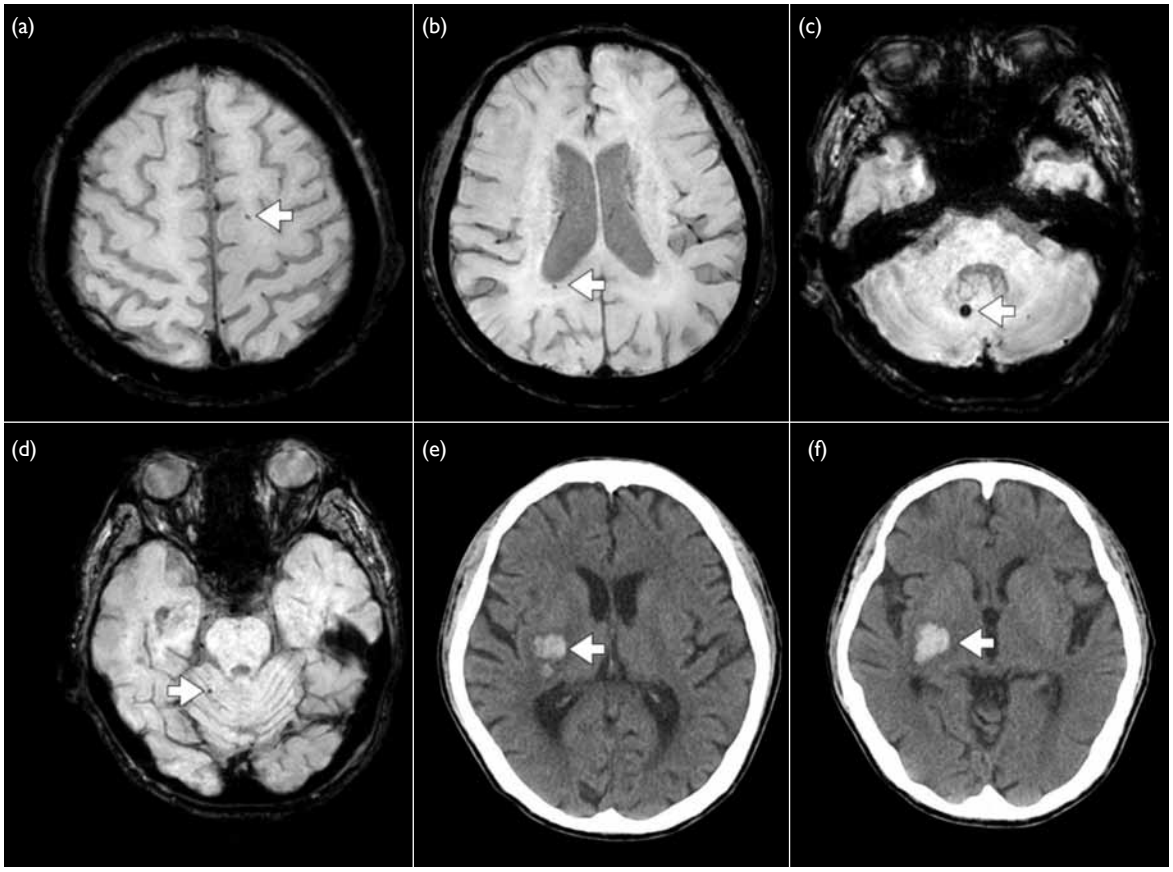

FIG. 68-year-old patient with a history of ischaemic stroke and atrial fibrillation treated with warfarin. Susceptibility-weighted magnetic resonance imaging of the brain at baseline showing a total of 5 cerebral microbleeds over the (a) left frontal lobe, (b) right parietal lobe, and (c, d) right cerebellum. (e, f) Computed tomography of the brain showing intracerebral haemorrhage over the right putaminal region after the patient had sudden onset of left leg weakness 4 months after recruitment.

months.

CMBs were observed in 83 (35.0%) of patients. The mean number of CMBs was 3.1±6.4 (range, 1-54); 9 (3.8%) patients had ≥5 CMBs (Fig). Patients with CMBs were more likely to have non-valvular AF, lower renal function level, and higher age-related white matter score. Those with and without CMBs were comparable in terms of the proportion of patients with a history of ischaemic stroke and other risk factors.

During the 2-year follow-up, there were more events of ischaemic stroke (n=12) and systemic embolism (n=2) than ICH (n=4) [Table 1]. Of the four patients with ICH, three had ≥5 CMBs and one had no CMB. Compared with patients without CMBs, patients with CMBs had a trend towards higher prevalence of ICH (3.6% vs 0.6%, P=0.091) and systemic embolism (2.4% vs 0%, P=0.053) at 2-year follow-up (Table 1). Compared with patients without ICH, patient with ICH were more likely to have underlying ischaemic heart disease or ≥5 CMBs (Table 2).

In multiple logistic regression, after adjusting for age, independent predictors for ICH were ≥5 CMBs (odds ratio [OR]=18.53, 95% confidence interval [CI]=1.501-228.864, P=0.023) and ischaemic heart disease (OR=14.228, 95% CI=1.433-207.136, P=0.025).

TABLE 1. Comparison of outcomes in patients with and without cerebral microbleeds (CMBs) at 2-year follow-up*

	Total no. of events	Patients with CMBs (n=83)	Patients without CMBs (n=154)	P value
Intracerebral haemorrhage	4	3 (3.6)	1 (0.6)	0.091
Ischaemic stroke	12	6 (7.2)	6 (3.9)	0.264
Systemic embolism	2	2 (2.4)	0 (0.0)	0.053
Mortality of all causes	17	6 (7.2)	11 (7.1)	0.980
Modified Rankin Scale score	1.21±1.94	1.3±2.0	1.1±1.9	0.412

* Data are presented as mean ± standard deviation or No. (%) of patients

Discussion

This is the first prospective study evaluating the risk of ICH in Chinese patients taking warfarin for AF with CMBs. A trend of higher prevalence of ICH at 2-year follow-up was observed in patients with CMBs. And

TABLE 2. Comparison of clinical and radiological outcomes in patients with and without intracerebral haemorrhage (ICH) at 2-year follow-up*

Outcome	Patients with ICH (n=4)	Patients without ICH (n=233)	P value
Clinical			
Age, y	71.0±8.8	71.9±8.8	0.933
Baseline modified Rankin Scale score	0.5±0.6	0.6±1.1	0.336
Male	2 (50.0)	138 (59.2)	0.710
Smoker	1 (25.0)	75 (32.2)	0.760
Drinker	1 (25.0)	29 (12.4)	0.454
Hypertension	3 (75.0)	190 (81.5)	0.739
Diabetes mellitus	2 (50.0)	84 (36.1)	0.565
Hyperlipidaemia	3 (75.0)	119 (51.1)	0.342
Congestive heart failure	1 (25.0)	51 (21.9)	0.881
Ischaemic heart disease	2 (50.0)	23 (9.9)	0.010
Newly diagnosed atrial fibrillation	1 (25.0)	29 (12.4)	0.454
Non-valvular atrial fibrillation	2 (100.0)	134 (86.5)	0.576
History of ischaemic stroke or transient ischaemic attack	3 (75.0)	128 (54.9)	0.424
History of ICH	0 (0.0)	1 (0.4)	0.896
Modification of diet in renal disease study equation	51.7±32.0	68.3±21.9	0.139
CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischaemic attack/ thrombo-embolism, vascular disease, age 65-74 years, sex category) score	5.3±2.2	4.2±1.6	0.224
HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile INRs, elderly (age >65 years), drugs and alcohol) score	3.0±1.8	2.7±1.1	0.586
Prior use of aspirin	1 (25.0)	11 (4.7)	0.067
Prior use of non-vitamin K antagonist oral anticoagulants	0 (0.0)	1 (0.4)	0.896
Time within therapeutic range (international normalised ratio of 2 to 3)	35.3±31.4	52.6±20.8	0.102
Patients with time within therapeutic range of <60%	3 (75.0)	147 (63.1)	0.624
Radiological			
Age-related white matter change	6.3±5.9	4.7±3.3	0.361
Patients with cerebral microbleeds (CMBs)	3 (75.0)	80 (34.3)	0.091
No. of CMBs	22.3±27.5	2.4±3.1	0.337
Patients with ≥5 CMBs	2 (50.0)	7 (3.0)	<0.001
Patients with pure lobar CMBs	0 (0.0)	37 (15.9)	0.386
Patients with pure deep CMBs	0 (0.0)	7 (3.0)	0.725
Patients with mixed lobar CMBs	2 (50.0)	21 (9.0)	0.006
Patients with infratentorial CMBs	2 (50.0)	30 (12.9)	0.031

* Data are presented as mean ± standard deviation or No. (%) of patients

the presence of ≥5 CMBs and ischaemic heart disease were independent predictors for ICH.

Patients with ≥5 CMBs had a higher risk of warfarin-related ICH (3.6%). This appears to offset its benefit in patients with low CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischaemic attack/ thrombo-embolism, vascular disease, age 65-74 years, sex category) score of 1 to 2, whose expected stroke risk is 1.3% to 2.2% per year.[4] Nevertheless, patients with CMBs should not be excluded from anticoagulation as they are also at increased risk of thromboembolism as shown in our study. Alternative treatment option with non-vitamin K antagonist oral anticoagulants, which have 50% less ICH risk than warfarin, is a safer alternative. However, the risk of non-vitamin K antagonist oral anticoagulant–related ICH in patients with CMBs remains unknown. Further studies with larger sample size are needed before CMBs evaluation can be incorporated into clinical use. Meta-analysis of pooled patient data through international collaboration can increase the statistical power. Collaboration with The Microbleeds International Collaborative Network is underway to address this question.[5]

Conclusion

The presence of ≥5 CMBs is associated with an increased risk of warfarin-related ICH and thromboembolism in Chinese patients with AF.

Acknowledgements

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Results of this study have been published in: 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.

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