**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.

---

**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,\(^4\) 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
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).

**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
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. 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.

### Conclusion

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

### Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#01120136). We acknowledge Hong Kong Health Check in providing imaging support.

Some patients in this study have been used as controls in: 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.


### References