Risk of Intracerebral Haemorrhage in Chinese Patients Taking Oral Anticoagulants for Atrial Fibrillation with Cerebral Microbleeds. A Prospective Study in Warfarin. (The IPAAC-Warfarin Study)

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Background Risk of devastating intracerebral haemorrhage (ICH) is the main factor limiting use of anticoagulants in atrial fibrillation (AF). MRI detection of cerebral microbleeds (CMBs), which predicts future ICH, may help guide anticoagulant decisions and improve stroke prevention. This is of particular relevance in Chinese population, who have higher risk of ICH compared with Caucasians.

Aims In this prospective multicenter observational study, we aim to evaluate the risk of warfarin-associated ICH in Chinese AF patients with CMBs.

Methods

- Patients were recruited from 6 hospitals in Hong Kong.
- **Inclusion criteria** were Chinese AF patients aged over 18 years old, who required warfarin for stroke prevention.
- **Exclusion criteria** included contra-indications for MRI, patients with bleeding tendency, concurrent treatment with other anti-coagulants or anti-platelet agents.
- **3T MRI brain** was performed for evaluation of CMBs and Age Related White Matter Changes (ARWMC) scale.
- Patients were followed-up clinically for 2 years.
- **Primary outcome** was clinical ICH.
- **Secondary outcome** were ischaemic stroke, systemic embolism, mortality of all causes and modified Rankin Scale ≥3.

Results

- We included 237 patients in final analysis.
- CMBs were present in 84 (35.4%) of patients, 11 patients had ≥5 CMBs.
- Pure lobar CMBs were observed in 36 (42.9%) of patients, mixed lobar CMBs in 25 (29.8%) patients, pure deep CMBs in 7 (8.3%) patients.

Example of a patient with CMBs (red arrows) detected by MRI susceptibility-weighted images.

- The mean follow-up period was 22.7 ± 10.3 months.
- Mean time within therapeutic range (TTR) was 52.3 ± 21.1 %.
- **Patients with CMBs** had significantly higher ARWMC (median score 5.0 ± 6 with CMBs vs 4.0 ± 3 without CMBs, p = 0.001), a trend towards more non-valvular AF (95.5% vs 83.2%, p=0.065) and worse renal function calculated by the MDRD (median 49.0 ± 20.5 with CMBs vs 52.0 ± 26.0 without CMBs, p=0.070).

Patients with CMBs have numerically higher rate of all primary and secondary outcomes.

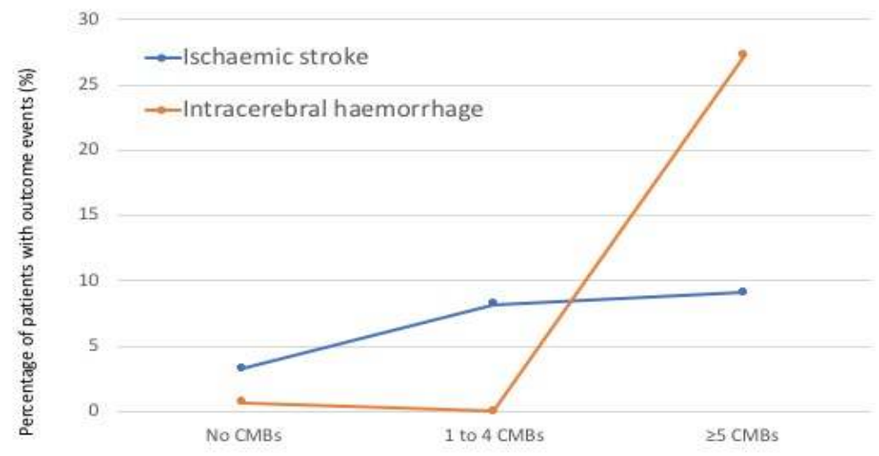
	Patients with CMBs (n = 84)		Patients without CMBs (n = 153)		
	No. of events (%)	Rate per 1000 patient years (95% CI)	No. of events (%)	Rate per 1000 patient years (95% CI)	*p*-value
Primary Outcome					
ICH	3 (3.6%)	18.5 (0 to 39.2)	1 (0.7%)	3.5 (0 to 10.2)	0.129
Secondary Outcome					
Ischaemic stroke	7 (8.3%)	43.1 (11.9 to 74.3)	5 (3.3%)	17.3 (2.3 to 32.3)	0.121
Systemic embolism	2 (2.4%)	12.3 (0 to 29.3)	0 (0.0%)	0.0 (0 to 0)	0.125
Mortality of all causes	6 (7.2%)	36.9 (7.9 to 66.0)	10 (6.5%)	34.6 (13.5 to 55.7)	1.000
Patients with mRS ≥ 3	27 (32.1%)	166.3 (109.0 to 223.5)	34 (22.2%)	117.6 (80.5 to 154.8)	0.095

- **Univariate logistic regression** showed that ischaemic heart disease (OR 9.13, 95% CI 1.23-67.92), percentage of time with INR ≥3 (OR 1.05, 95% CI 1.01-1.10) and ≥5 CMBs (OR 32.29, 95% CI 3.96-263.48) were significant variables predicting ICH.
- **Multiple logistic regression** was not performed due to small number of ICH which risks over-fitting of statistical model.

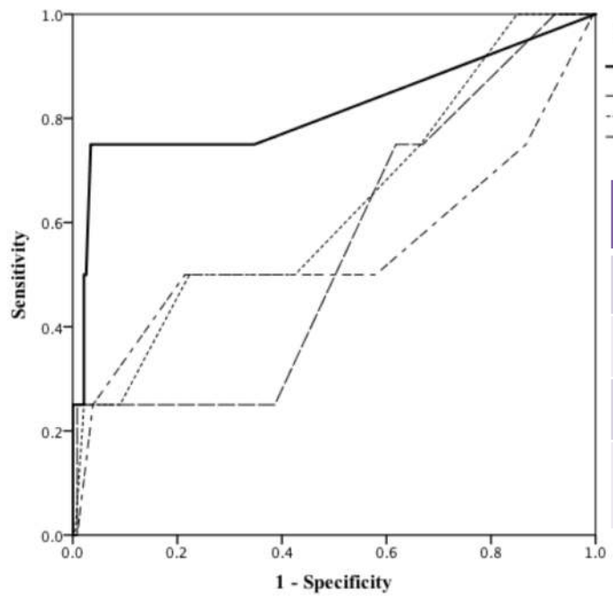
In this study, the rate of ICH among Chinese patients with CMBs (18.5 per 1000 patients years) was much higher than that reported in other Caucasians cohorts, e.g.:

- 9.8 per 1000 patient years in CROMIS-2 study
- 2.4 per 1000 patient years in ROCKET study

During follow-up, patients with 0 to 4 CMBs were associated with more ischaemic stroke than ICH . However, patients with ≥5 CMBs were associated with more ICH than ischaemic stroke.

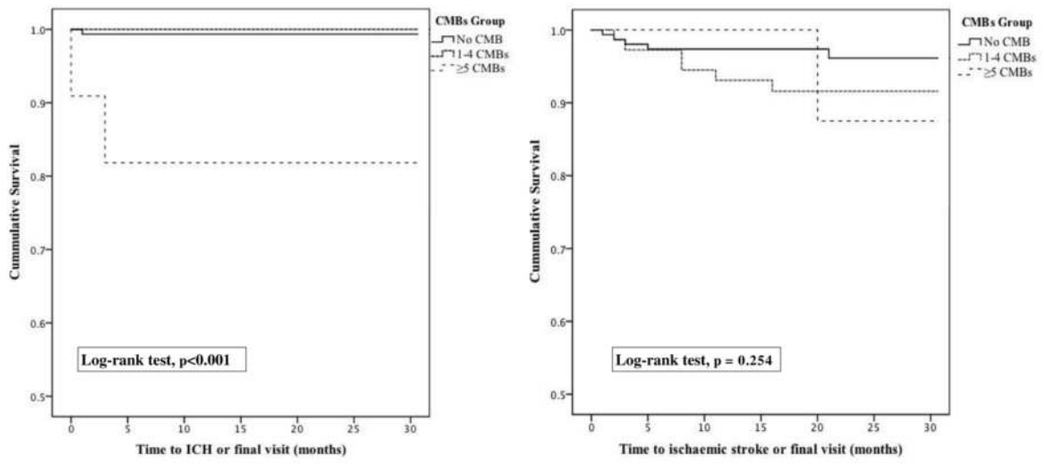


CMBs are more sensitive than HAS-BLED, CHA2DS2-VASc and ARWMC in predicting ICH at follow-up.



Predictors for ICH	C- Index
CMBs	0.82
ARWMC	0.55
HAS-BLED	0.55
CHA2DS2-VASc	0.63

Survival analysis showed patients with ≥5 CMBs were more likely to develop ICH during follow-up, but not ischaemic stroke.



Conclusions

- This is the first study evaluating risk of warfarin-associated ICH in Chinese AF patients with CMBs.
- Chinese patients with multiple CMBs may be associated with higher risk of warfarin-associated ICH than Caucasians.
- Adding CMBs evaluation to conventional clinical scores can help improve the sensitivity for prediction of anticoagulant-related ICH in AF patients.
- Larger studies through international collaboration are needed to increase the sample size for more precise evaluation of risk-to-benefit ratio of warfarin in AF patients with CMBs of different ethnic origin.