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Cerebral microbleeds and intracranial haemorrhage risk in patients with atrial fibrillation after acute ischaemic stroke or transient ischaemic attack: multicentre observational cohort study

D. Wilson, C. Shakeshaft, G. Ambler, M. Brown, A. Charidimou, R. Al-Shahi Salman, G. Lip, H. Cohen, G. Banerjee, H. Houlden, M. White, T. Yousry, K. Muir, H. Jäger, **D. Werring**
on behalf of the CROMIS-2 collaborators

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A common clinical dilemma

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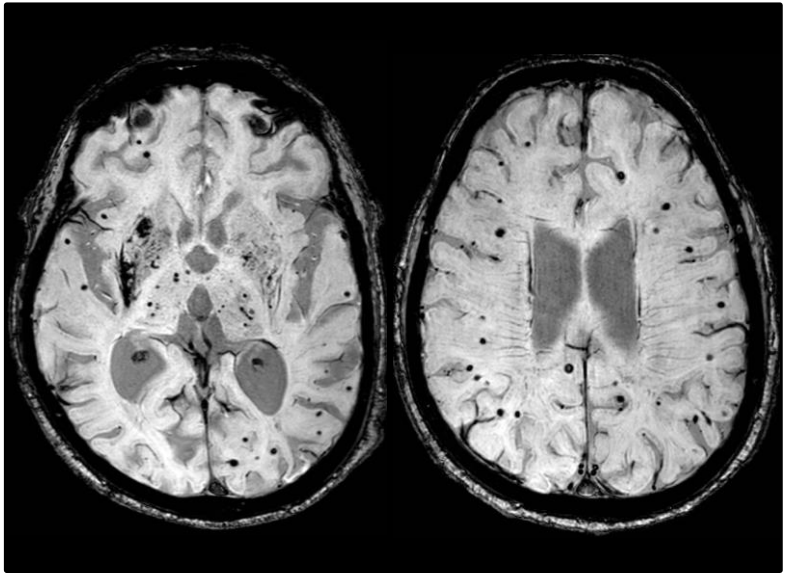
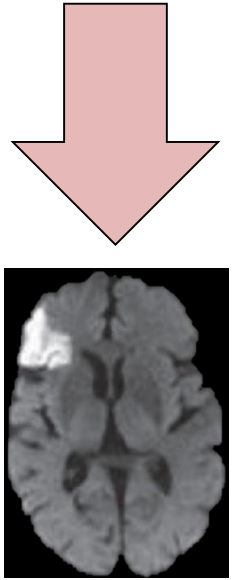
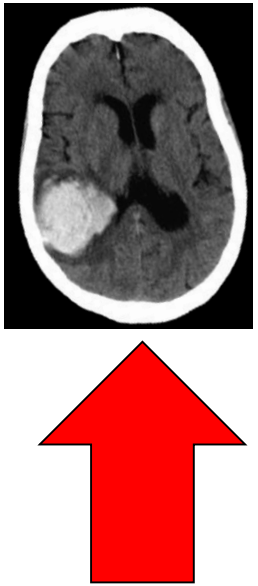
- Ischaemic stroke or TIA with atrial fibrillation
- MRI scan with blood-sensitive imaging shows cerebral microbleeds







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Hypothesis

Curr Opin Neurol. 2017 Feb;30(1):38-47.

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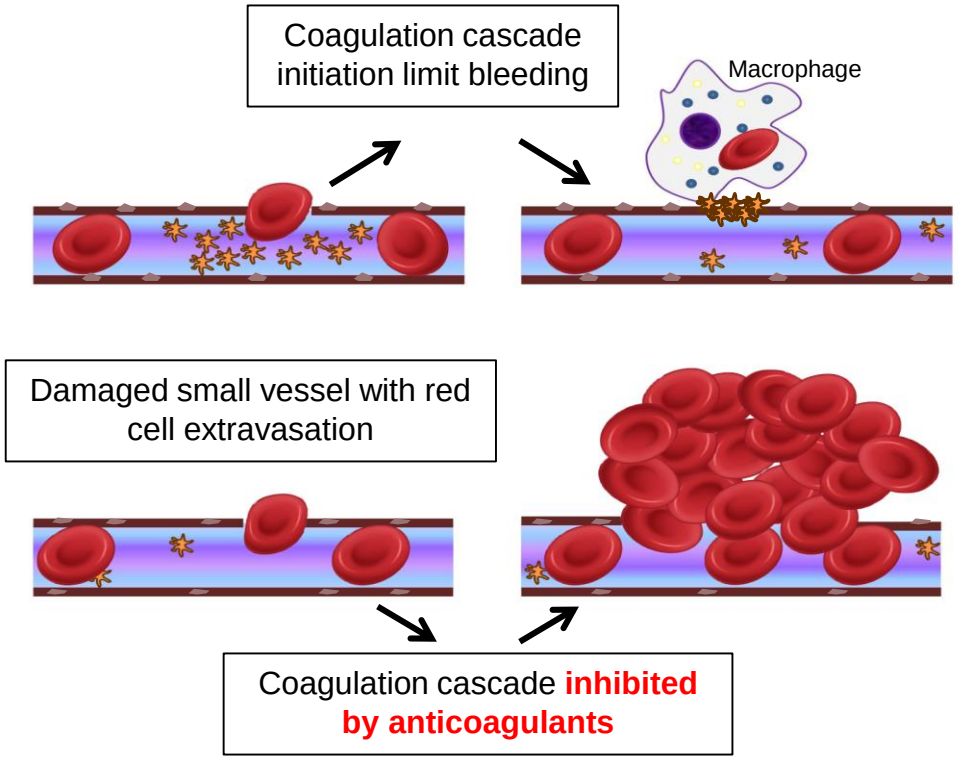
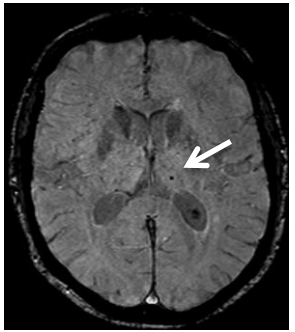
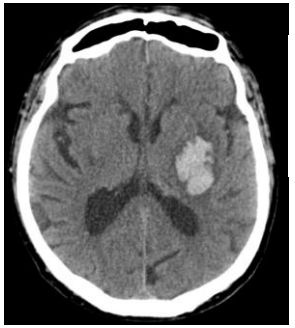




Cerebral microbleed



Macroscopic intracerebral haemorrhage

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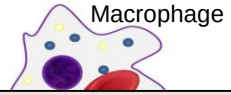
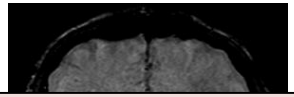
Hypothesis

Coagulation cascade initiation limit bleeding





WHAT IS THE CLINICAL RELEVANCE OF CEREBRAL MICROBLEEDS?

SHOULD THEY AFFECT MY DECISION TO ANTICOAGULATE?

by anticoagulants

Study design and participants

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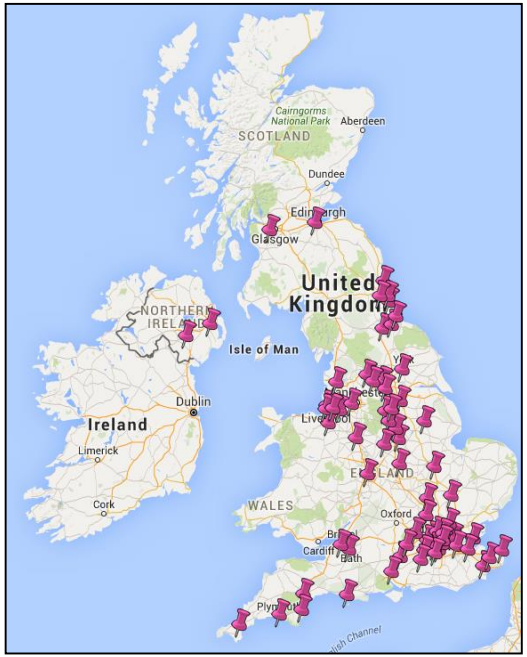
- Prospective observational multicentre observational inception cohort study
- 79 centres throughout UK (and one in the Netherlands)
- Recent ischaemic stroke or TIA with proven atrial fibrillation
- Treated with VKA or DOAC
- Patients followed up for 2 years.
- Multiple overlapping ascertainment methods
  - GP and patient questionnaires
  - Telephone interviews
  - NHS information centre data
  - Hospital visits and records



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Neuroimaging

Int J Stroke. 2015 Oct;10 Suppl A100:155-61.

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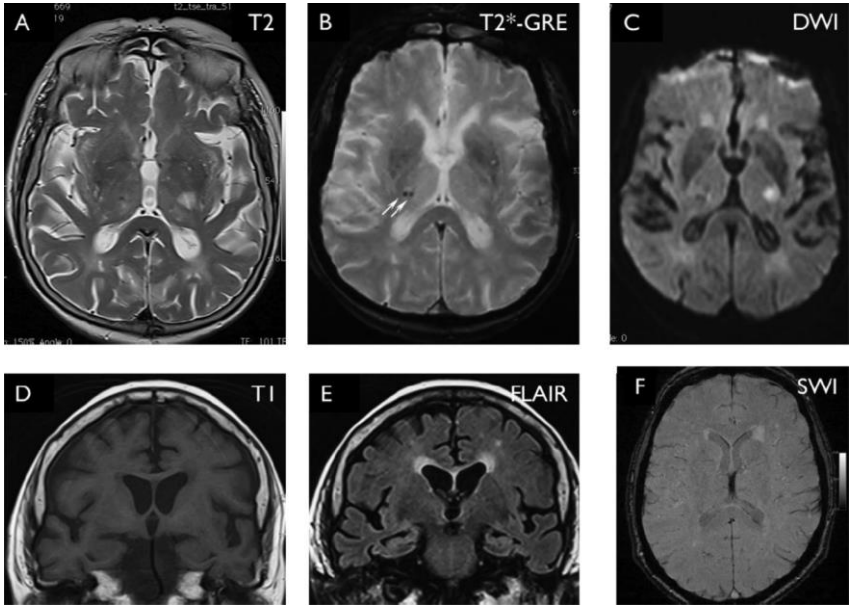
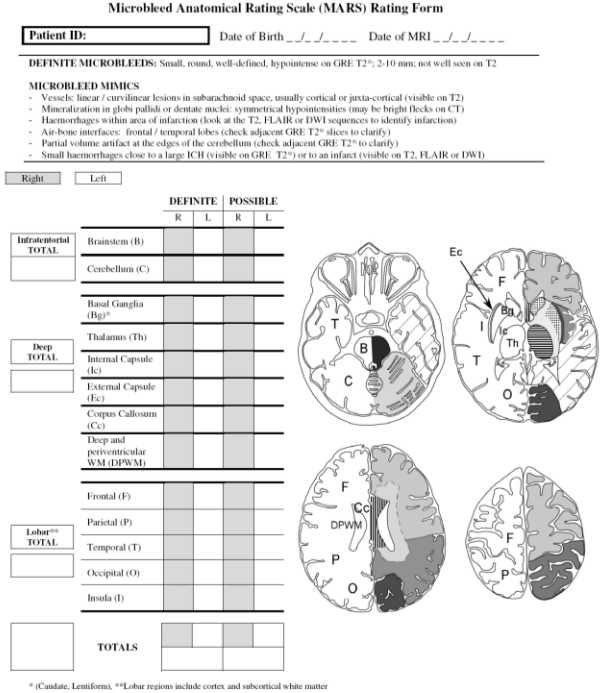
- Patients underwent MRI brain using a pre-defined protocol parameter range, designed to detect markers of cerebrovascular disease
- Analysed using consensus criteria and validated scales





Microbleed Anatomical Rating Scale (MARS) Rating Form

Patient ID: Date of Birth _ _/_ _/_ _ _ _ Date of MRI _ _/_ _/_ _ _ _

DEFINITE MICROBLEEDS: Small, round, well-defined, hypointense on GRE T2*; 2-10 mm; not well seen on T2

MICROBLEED MIMICS
- Vessels: linear / curvilinear lesions in subarachnoid space, usually cortical or juxta-cortical (visible on T2)
- Mineralization in globi pallidi or dentate nuclei: symmetrical hypointensities (may be bright flecks on CT)
- Haemorrhages within area of infarction (look at the T2, FLAIR or DWI sequences to identify infarction)
- Air-bone interfaces: frontal / temporal lobes (check adjacent GRE T2* slices to clarify)
- Partial volume artifact at the edges of the cerebellum (check adjacent GRE T2* to clarify)
- Small haemorrhages close to a large ICH (visible on GRE T2*) or to an infarct (visible on T2, FLAIR or DWI)

Right | Left

		DEFINITE R	DEFINITE L	POSSIBLE R	POSSIBLE L
Infratentorial TOTAL	Brainstem (B)				
	Cerebellum (C)				
Deep TOTAL	Basal Ganglia (Bg)*				
	Thalamus (Th)				
	Internal Capsule (Ic)				
	External Capsule (Ec)				
	Corpus Callosum (Cc)				
	Deep and periventricular WM (DPWM)				
Lobar** TOTAL	Frontal (F)				
	Parietal (P)				
	Temporal (T)				
	Occipital (O)				
	Insula (I)				
TOTALS					

* (Caudate, Lentiform), **Lobar regions include cortex and subcortical white matter

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Outcomes

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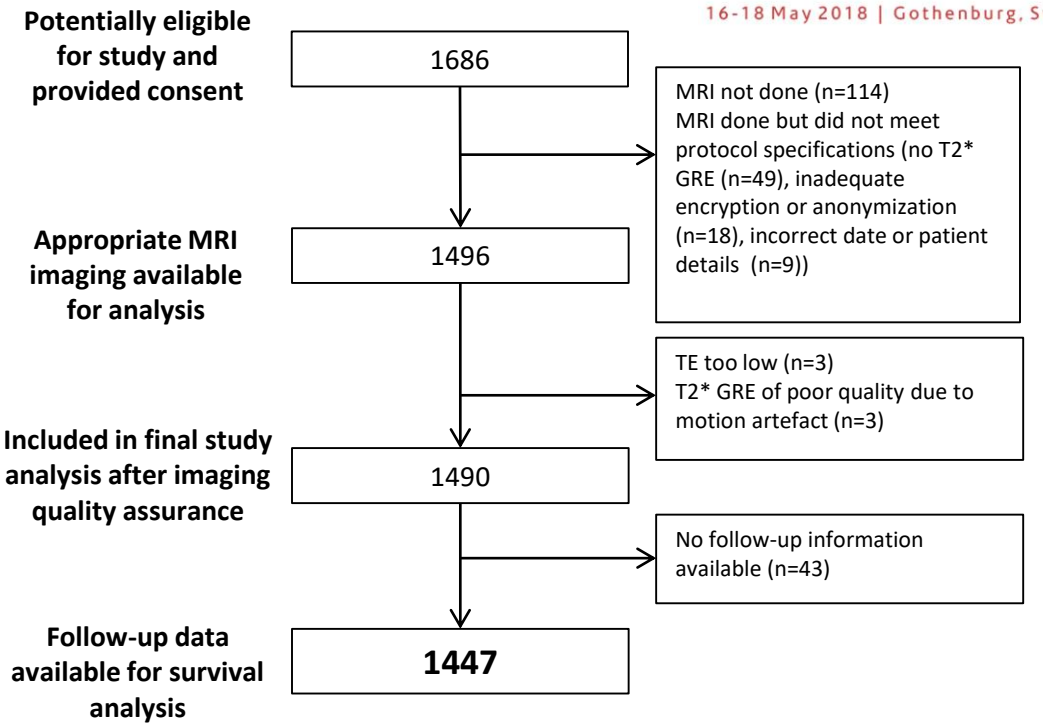
PRE-SPECIFIED STATISTICAL ANALYSIS PLAN

- **Primary outcome: symptomatic intracranial haemorrhage**
- Secondary outcomes:
  - Symptomatic ischaemic stroke
  - Death
  - Intracerebral haemorrhage
  - Composite outcome (death Ischaemic stroke, Symptomatic intracranial haemorrhage)
- All outcomes adjudicated blinded to baseline imaging

Results

- 1490 patients included
- **1447 (97%) had follow-up data and were included in survival analysis**
- Mean age 76 years (SD 10)
- 631 (42%) female
- 311 (21%) patients had CMBs



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Results

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- Intra-rater and inter-rater reliability for the presence of CMBs were excellent
  - Kappas 0·93 (95% CI 0.86 to 1.00) and 0.85 (95% CI 0.74 to 0.96)
- CMB distribution
  - **Strictly lobar** 116 patients
  - **Strictly non-lobar (deep)** 120 patients
  - **Mixed** 75 patients
  - **Modified Boston criteria for CAA** 46 patients

Results: primary outcome

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- The 1447 patients provided 3366 patient-years of follow-up data (mean follow-up 850 (SD 373) days
- During follow-up there were:
  - **14 symptomatic intracranial haemorrhages**
    - 11 intracerebral
    - Two subdural
    - One subarachnoid

Variable		Patients with symptomatic intracranial haemorrhage (n=14)	Patients without symptomatic intracranial haemorrhage (n=1433)	p value
Age, years median (IQR)		79 (10)	76 (10)	0·32
Sex, female, n (%)		5 (36)	606 (42)	0·62
Hypertension n (%)		8 (57)	898 (64)	0·62
Hyperlipidaemia n (%)		8 (57)	653 (45)	0·36
Diabetes mellitus n (%)		**6 (43)**	**236 (17)**	**0·0086**
Ischaemic heart disease		1 (7)	238 (17)	0·34
Previous ischaemic stroke n (%)		2 (15)	138 (10)	0·50
Previous intracerebral haemorrhage n (%)		0 (0)	8 (0·6)	1·00
Alcohol use >14 units/week n (%)		1 (8)	212 (15)	0·50
Ethnicity	White n (%)	14 (100)	1356 (97)	
	Asian n (%)	0 (0)	29 (2)	
	Black n (%)	0 (0)	17 (1)	
Platelet count median (IQR)		212 (167 to 225)	220 (185 to 264)	0.25
CHA_2DS_2VASc score median (IQR)		6 (4 to 6)	5 (4 to 6)	0·23
HAS-BLED score median (IQR)		2 (2 to 3)	3 (2 to 3)	0·14
Anticoagulation started n (%)		14 (100)	1385(97)	0.49
DOAC use n (%)		**2 (14)**	**510 (37)**	**0·081**
Concurrent antiplatelets n (%)		1 (7)	56 (4)	0.54
Poor therapeutic time in range n (%)		0 (0)	133/862 (15)	0.145
Total white matter hyperintensity (ARWMC) score median (IQR)		1·5 (0 to 5)	1 (0 to 3)	0·97
CMB presence n (%) CMB median (IQR) CMB range		**7 (50)** **0.5 (0 to 3)** 0 to 12	**297 (21)** **0 (0 to 0)** 0 to 107	**0·0075** **0·0036** N/A
cSS presence n (%)		**1 (7)**	**4 (0·3)**	<0·0001

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Primary outcome

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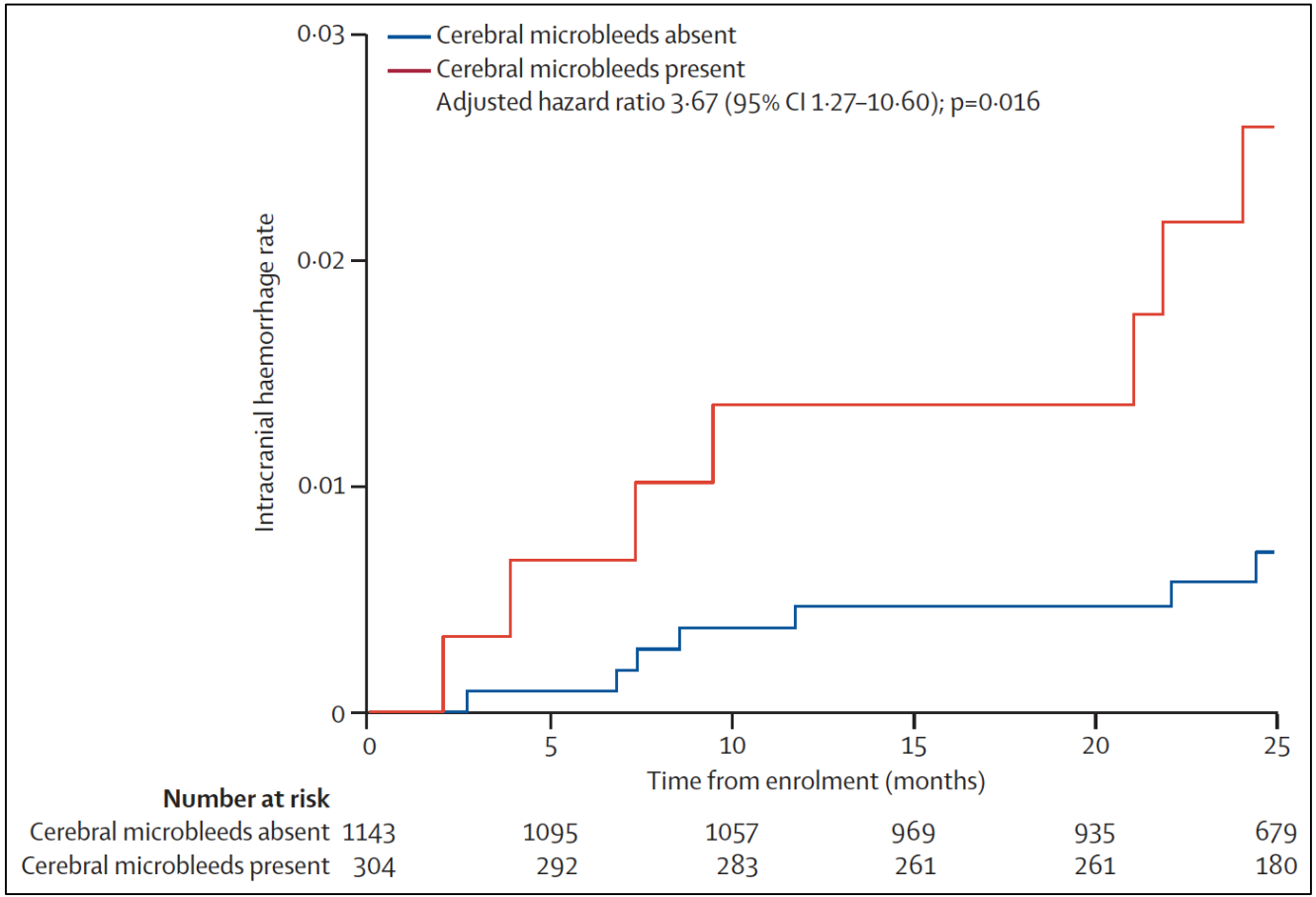
- The symptomatic intracranial haemorrhage event rates were:
  - **10 per 1000 patient-years (95% CI 4 to 20)** in patients with CMBs
  - **3 per 1000 patient-years (95% CI 1 to 5)** in patients without CMBs
- The **absolute rate increase** associated with CMBs was **7 per 1000 patient-years (95% CI 3 to 15)**



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Intracranial haemorrhage rates according to CMB status

Pre-specified model adjusted for age and hypertension

Lancet Neurology 2018. In press

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Secondary outcomes: ischaemic stroke

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- There were 56 recurrent ischaemic strokes during 3312 patient-years of follow-up.
- The recurrent ischaemic stroke rates were:
  - **24 per 1000 patient-years (95% CI 14 to 39)** in patients with CMBs
  - **15 per 1000 patient-years (95% CI 11 to 20)** in patients without CMBs
- The **absolute rate increase** associated with CMBs was 9 per 1000 patient-years (95% CI 3 to 19)

Secondary outcome: ischaemic stroke

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- CMB presence was not significantly associated with recurrent ischaemic stroke in regression analyses:
  - univariable (HR 1·62 95% CI 0·92 to 2·87)
  - multivariable (HR 1·53; 95% CI 0·85 to 2·76)

    (adjusted for age, sex, hypertension, diabetes, previous ischaemic stroke prior to study entry, and age-related white matter hyperintensities score)

Intracranial haemorrhage and ischaemic stroke rates

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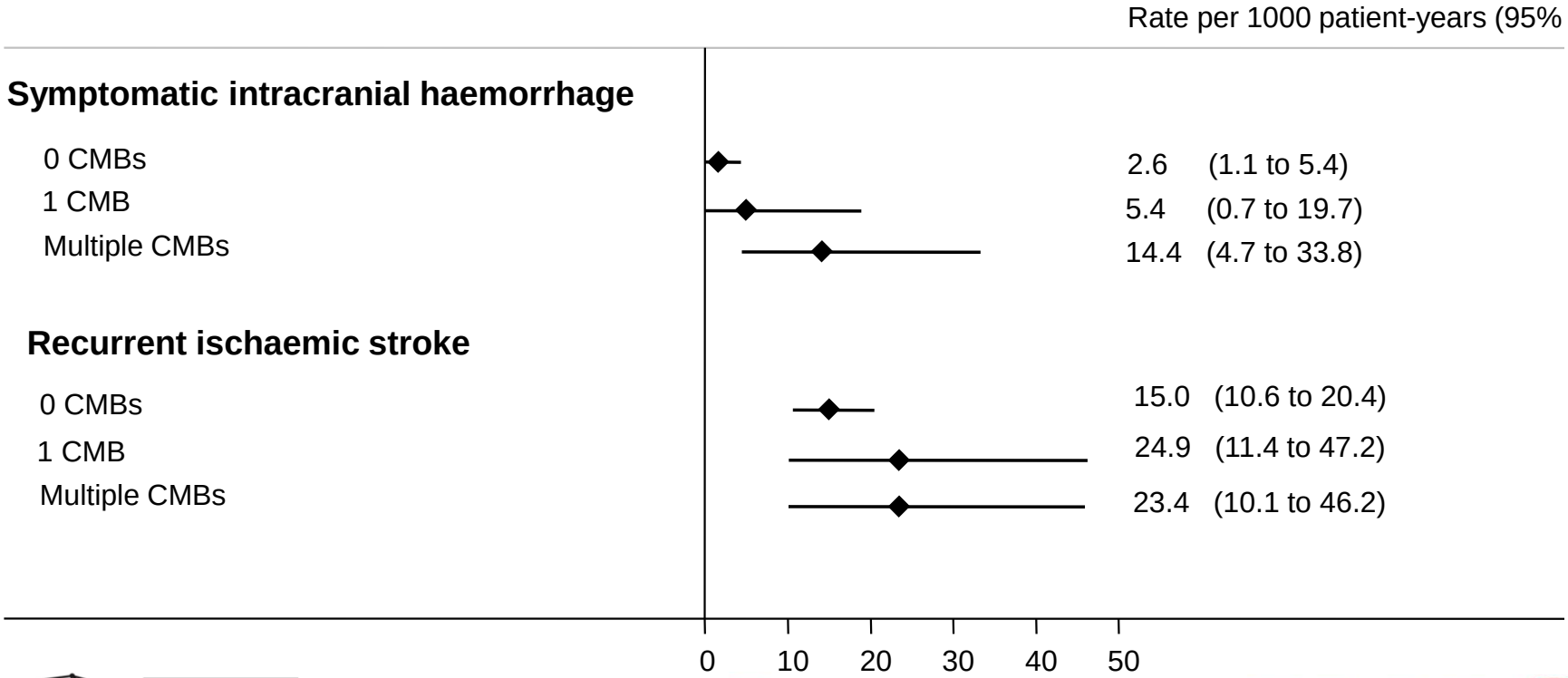

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Prediction models for intracranial haemorrhage

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- **HASBLED only** (**C-index 0·41** (95% CI 0·29-0·53)
- **Model 1**: HASBLED + CMBs (**C-index 0·66** (95% CI 0·53-0·80)
- **Model 2**: HASBLED+DM+OAC+CMBs (**C-index 0·74** (95% CI 0·60-0·88)

- Models including CMBs predicted symptomatic intracranial haemorrhage significantly better compared to HAS-BLED score alone
  - **C index (diff) model 1: 0·25** (95% CI 0·07-0·43, p=0·007)
  - **C index (diff) model 2: 0·33** (95% CI 0·14-0·51, p=0·00059)

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Conclusions

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- CMB presence is associated with an **increased hazard of symptomatic intracranial haemorrhage** but not recurrent ischaemic stroke
- Including CMB presence as a neuroimaging biomarker improves the predictive value of a commonly used bleeding risk score based on clinical data alone (the HAS-BLED score)
- However, even in patients with CMBs the absolute incidence of symptomatic intracranial haemorrhage was lower than that of recurrent ischaemic stroke
- Large international pooled analyses are needed to confirm our findings, validate risk scores including CMBs (including burden), and establish whether CMBs can identify patients at risk of net harm from OAC

Acknowledgements

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NHS
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