

## **SUPPLEMENTAL MATERIAL**

### **Proportion of intracerebral haemorrhage due to cerebral amyloid angiopathy in the East and West**

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## **Supplemental Methods**

### ***Definition of other clinical variables***

Patients who were current smokers at the time of their index haemorrhagic stroke were considered current smokers. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg persistent for  $\geq 7$  days from admission, and/or use of antihypertensive drug(s) before the onset, and/or having had confirmed hypertension on at least two occasions by a healthcare professional before intracerebral haemorrhage (ICH) onset. Diabetes mellitus was defined as ongoing use of anti-hypoglycaemic drug(s). Dyslipidaemia was defined as ongoing use of anti-dyslipidaemia drug(s), including 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins), fibrates, niacin/nicotinic acid, or bile acid-binding resins.

### ***Definition and classification of haemorrhagic findings on blood-sensitive magnetic resonance imaging (MRI)***

Cerebral microbleeds (CMBs) were defined on blood-sensitive MRI as rounded areas of signal loss,  $\leq 10$  mm in diameter [1,2]. CMBs were categorized into different anatomical regions (lobar, deep, or infratentorial areas) using the validated rating scale [3]. Cortical superficial siderosis (cSS) were defined as linear residues of chronic blood products in the superficial layers of the cerebral cortex showing a characteristic “gyriform” pattern of low signal intensity on blood-sensitive MRI, without corresponding hyperintense signal on T1-weighted or FLuid-Attenuated Inversion Recovery (FLAIR) images [4]. We did not include cSS if it was contiguous with any ICH.

## Supplemental References

- [1] Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165-174. [https://doi:10.1016/S1474-4422\(09\)70013-4](https://doi:10.1016/S1474-4422(09)70013-4)
- [2] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822-838. [https://doi:10.1016/s1474-4422\(13\)70124-8](https://doi:10.1016/s1474-4422(13)70124-8)
- [3] Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jager HR, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology* 2009;73:1759-1766. <https://doi:10.1212/WNL.0b013e3181c34a7d>
- [4] Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346-1350. <https://doi:10.1212/WNL.0b013e3181dad605>

**Table S1: The details of the MRI scanners and protocols in each centre**

|               | Western centres |         |       |          |         |          | Eastern centre |                          |          |         |
|---------------|-----------------|---------|-------|----------|---------|----------|----------------|--------------------------|----------|---------|
|               | NHNN            |         |       | UCH      |         |          | UCLH           | Saga University Hospital |          |         |
| MRI Equipment | MAGNETOM        |         |       | MAGNETOM |         |          | Achieva        | Achieva                  | MAGNETOM |         |
|               | Avanto          | TrioTim | Skyra | Avanto   | Esprea  | Symphony |                |                          | Avanto   | TrioTim |
| Manufacturer  | SIEMENS         |         |       | SIEMENS  |         |          | Philips MS     | Philips MS               | SIEMENS  |         |
| MFS, tesla    | 1.5             | 3.0     | 3.0   | 1.5      | 1.5     | 1.5      | 3.0            | 3.0                      | 1.5      | 3.0     |
| GE-T2*WI, n   | 6               | 1       | 1     | 13       | 2       | 1        | 2              | 4                        | 12       | 29      |
| TR, ms        | 780-881         | 625     | 630   | 439-865  | 881     | 719      | 832.5-928      | 700.3-802.3              | 650-656  | 532-585 |
| TE, ms        | 26              | 20      | 19.9  | 25.5-26  | 25.5    | 26       | 16             | 16.0-16.1                | 25       | 15      |
| FA, degree    | 20              | 20      | 20    | 20       | 20      | 20       | 20             | 20                       | 20       | 15      |
| ST / Gap, mm  | 5/1.0-1.5       | 5/1.5   | 5     | 5        | 5       | 5        | 4              | 5                        | 6        | 6       |
| Gap, mm       | 1.0-1.5         | 1.5     | 1.5   | 1.5-1.6  | 1.0-1.5 | 1.5      | 1.0            | 1.0                      | 1.0-1.2  | 1.0-1.2 |
| SWI, n        | 30              | 12      | 4     | 6        | 9       | 0        | 0              | 0                        | 14       | 71      |
| TR, ms        | 49              | 27      | 27    | 49       | 49      | N/A      | N/A            | N/A                      | 49       | 27      |
| TE, ms        | 40              | 20      | 20    | 40       | 40      | N/A      | N/A            | N/A                      | 50       | 20      |
| FA, degree    | 15              | 15      | 15    | 15       | 15      | N/A      | N/A            | N/A                      | 15       | 15      |
| ST, mm        | 2.0             | 1.8     | 1.5   | 1.6-2.0  | 2.0     | N/A      | N/A            | N/A                      | 3        | 3       |
| Gap, mm       | 0               | 0       | 0     | 0        | 0       | N/A      | N/A            | N/A                      | 0        | 0       |

Abbreviations: FA: flip angle; GE-T2\*WI: gradient-echo T2\*-weighted imaging; MFS: magnetic field strength; MS: Medical Systems; N/A.: Not Applicable; NHNN: National Hospital for Neurology and Neurosurgery; ST: slice thickness; SWI: susceptibility weighted imaging; TE: echo time; TR: repetition time; UCH: University College Hospital; UCLH: University College London Hospital

**Table S2: Ethnicities in Eastern centre origin and Western centre origin in CT-based cohort.**

|                   | Western centre origin<br>n= 240 | Eastern centre origin<br>n= 193 |
|-------------------|---------------------------------|---------------------------------|
| Ethnicity, n (%)  |                                 |                                 |
| White             | 144 (60)                        | 0 (0)                           |
| East Asian        | 4 (2)                           | 193 (100)                       |
| Other ethnicities |                                 |                                 |
| Any other Asian   | 17 (7)                          | 0 (0)                           |
| African           | 10 (4)                          | 0 (0)                           |
| Caribbean         | 4 (2)                           | 0 (0)                           |
| Other             | 39 (16)                         | 0 (0)                           |
| Not available     | 22 (9)                          | 0 (0)                           |

**Table S3: The details of inter-rater reliability and intra-rater reliability**

|  | Inter-rater reliability testing  | Intra-rater reliability testing  |
|--|--|--|
| Haematoma on CT  | Performed with 50 randomly selected scans rated by 2 clinical neurologists (D.W. and Y.Y.)   | Determined from 20 randomly selected scans scored twice by 2 clinical neurologists (D.W. and Y.Y.) |
| Lobar ICH  | 0.94   | 0.79-1.00  |
| Deep ICH   | 0.91   | 0.88-0.90  |
| Infratentorial ICH                                       | 0.88   | 0.64-1.00  |
| CMBs and cSS on MRI                                      | Performed with 50 randomly selected scans rated by 2 clinical neurologists (D.W. and Y.Y.)   | Determined from 20 randomly selected scans scored twice by 2 clinical neurologists (D.W. and Y.Y.) |
| Any CMBs   | 0.77   | 0.86-1.00  |
| Lobar CMBs   | 0.76   | 0.90-1.00  |
| Deep CMBs  | 0.76   | 0.89-1.00  |
| Infratentorial CMBs                                      | 0.83   | 1.00-1.00  |
| Any cSS  | 0.65   | 0.77-1.00  |
| Specific CT findings of Edinburgh CT diagnostic criteria | Performed with 20 randomly selected scans rated by 2 raters (a clinical neurologist [J.B.] and a certificated neuroradiologist [M.N.]) | Determined from 20 randomly selected scans scored twice by 2 raters (J.B. and M.N.).               |
| SAH  | 0.80   | 0.69-0.90  |
| FLPs   | 0.78   | 0.63-0.88  |

Abbreviations: CMBs: cerebral microbleeds; cSS: cortical superficial siderosis; CT: computed tomography; FLPs= finger-like projections; ICH: intracerebral haemorrhage; MRI: magnetic resonance imaging; SAH = subarachnoid haemorrhage

**Table S4: Sensitivity analysis: ethnicities according to Eastern and Western centre origin (CT and MRI-based cohort).**

|                   | Western centre origin<br>n= 91 | Eastern centre origin<br>n= 126 |
|-------------------|--------------------------------|---------------------------------|
| Ethnicity, n (%)  |                                |                                 |
| White             | 53 (58)                        | 0 (0)                           |
| East Asian        | 2 (2)                          | 126 (100)                       |
| Other ethnicities |                                |                                 |
| Any other Asian   | 9 (10)                         | 0 (0)                           |
| African           | 5 (6)                          | 0 (0)                           |
| Caribbean         | 2 (2)                          | 0 (0)                           |
| Other             | 9 (10)                         | 0 (0)                           |
| Not available     | 11 (12)                        | 0 (0)                           |

**Table S5: Sensitivity analysis - clinical characteristics and neuroimaging findings according to Eastern and Western centre origin (CT and MRI based cohort).**

| Variables                                  | Western centre origin | Eastern centre origin | p Value |
|--|-----------------------|-----------------------|---------|
|  | n=91 (42%)            | n= 126 (58%)          |         |
| On-set to Admission, days                  | 0 (0-0)               | 0 (0-0)               | 0.330   |
| Age, years                                 | 68 (52-76)            | 71 (60-78)            | 0.112   |
| Sex, male                                  | 47 (52)               | 67 (53)               | 0.824   |
| Current smoker                             | 11 (12)               | 24 (20)               | 0.147   |
| Previous stroke                            | 7 (8)                 | 31 (25)               | 0.001   |
| Antithrombotic drug(s) use                 | 28 (31)               | 26 (21)               | 0.109   |
| Hypertension                               | 70 (77)               | 93 (74)               | 0.601   |
| Diabetes mellitus                          | 11 (12)               | 19 (15)               | 0.499   |
| Dyslipidaemia                              | 35 (38)               | 20 (16)               | <0.001  |
| Hematoma volume, ml                        | 7.7 (3.0-20.6)        | 8.6 (4.1-23.9)        | 0.297   |
| Strictly lobar ICH                         | 44 (48)               | 25 (20)               | <0.001  |
| Admission to MRI > 30 days after ICH onset | 21 (23)               | 9 (7)                 | 0.001   |
| Admission to MRI, day                      | 9 (4-27)              | 9 (6-13)              | 0.412   |
| 3.0 T use                                  | 24 (26)               | 100 (79)              | <0.001  |
| SWI use                                    | 61 (67)               | 85 (67)               | 0.947   |
| Echo time, ms                              | 40 (20-40)            | 20 (20-20)            | <0.001  |
| Strictly lobar CMBs                        | 15 (16)               | 14 (11)               | 0.251   |
| Other CMBs                                 | 34 (37)               | 79 (63)               | <0.001  |
| Cortical superficial siderosis             | 17 (19)               | 12 (10)               | 0.050   |
| CAA-related ICH *                          | 21 (23)               | 10 (8)                | 0.002   |

Data presented as median (interquartile range) for continuous variables and number (percentages) for categorical variables.

Abbreviations: CAA = cerebral amyloid angiopathy; CMBs = cerebral microbleeds; ICH= intracerebral haemorrhage;

IQR = interquartile range; MRI = magnetic resonance imaging; SWI = susceptibility-weighted imaging

All data was <5% missing.

\* defined by the modified Boston criteria



**Table S6: Sensitivity analysis - differences in patient characteristics according to CAA status defined by the modified Boston criteria.**

| Variables                               | Other ICH<br>n=186 (86%) | CAA-related ICH<br>n=31 (14%) | p Value |
|---|--------------------------|-------------------------------|---------|
| Age, years                              | 68 (56-77)               | 74 (68-81)                    | 0.001   |
| Sex, male                               | 106 (57)                 | 8 (26)                        | 0.001   |
| Eastern centre origin                   | 116 (62)                 | 10 (32)                       | 0.002   |
| Current smoker <sup>a</sup>             | 32 (17)                  | 3 (10)                        | 0.277   |
| Previous stroke                         | 33 (18)                  | 5 (16)                        | 0.827   |
| Antithrombotic drug(s) use <sup>b</sup> | 44 (24)                  | 10 (32)                       | 0.330   |
| Hypertension                            | 143 (77)                 | 20 (65)                       | 0.140   |
| Diabetes mellitus <sup>c</sup>          | 22 (12)                  | 8 (26)                        | 0.040   |
| Dyslipidaemia <sup>d</sup>              | 44 (24)                  | 11 (35)                       | 0.172   |

Data presented as median (interquartile range) for continuous variables and number (percentages) for categorical variables.

All data was <5% missing.

**Table S7: Sensitivity analysis - multivariable logistic regression analyses of associations of geographical location and ethnicity with CAA-related ICH defined by the MRI-based modified Boston criteria.**

| <b>Geographical location</b> | Model I          | Model II         | Model III        |
|------------------------------|------------------|------------------|------------------|
| Eastern centre origin        | 0.29 (0.13-0.65) | 0.22 (0.09-0.53) | 0.31 (0.10-0.93) |
| <b>Ethnicity</b>             | Model IV         | Model V          | Model VI         |
| East Asian                   | 0.20 (0.08-0.47) | 0.19 (0.08-0.49) | 0.24 (0.07-0.82) |
| Other ethnicities            | 0.20 (0.04-0.96) | 0.30 (0.06-1.55) | 0.38 (0.07-2.11) |

Odds ratios (95% confidence intervals) for CAA-related ICH according to geographical location (Eastern vs. Western centre origin [Reference]) are presented in models I, II and III. Odds ratios (95% confidence intervals) for CAA-related ICH according to ethnicity (East Asian and other ethnicities vs. White [Reference]) are presented in models IV, V and VI.

Abbreviations: CAA: cerebral amyloid angiopathy; CI: confidence interval; CT: computed tomography; ICH: intracerebral haemorrhage; MRI: magnetic resonance imaging; OR: odds ratio.

Model I: unadjusted; included all patients from the full CT or MRI-based cohort (n=217).

Model II: adjusted for age and sex (n=217).

Model III: further adjusted for previous stroke, antithrombotic use, hypertension, 3T use, and echo time (n=214).

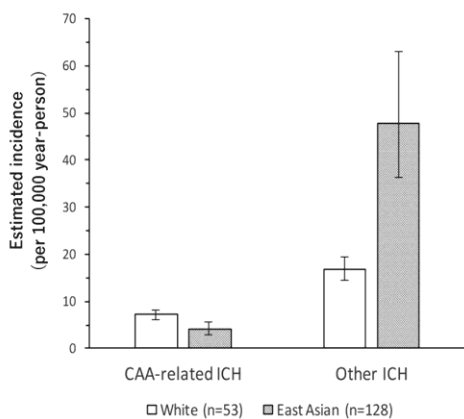
Model IV: unadjusted; included all patients from the full CT or MRI-based cohort with available data (n=206)

Model V: adjusted for age and sex (n=206)

Model VI: further adjusted for previous stroke, antithrombotic use, hypertension, 3T use, and echo time (n=203)

## Figure S1

**Estimated incidence and its 95%CI of each type of ICH by White and East Asian ethnicity (using the CT/MRI-based classifications of ICH types)**



Abbreviations: CAA: cerebral amyloid angiopathy; CI: confidence interval; ICH: intracerebral haemorrhage

White represents estimated incidence of each type of ICH (per 100,000 person-year) in White ethnicity. Grey represents that in East Asian ethnicity.

The error bars indicated 95% CI.

In the result of CT/MRI-based cohort (CAA-related ICH, 30.2% in White ethnicities; 7.8% in East Asian ethnicities), the incidence of CAA-related ICH of East Asian ethnicity (4.0 ([3.0-5.4]) was about half (0.55-fold) of that of White ethnicity (7.3 [6.3-8.5]), while the rate of other ICH was 2.8-fold higher in those of East Asian [46.5 (34.8-62.2)] compared to White ethnicity [18.4 (15.9-21.4)].