**LONGER-TERM STROKE RISK IN INTRACEREBRAL HAEMORRHAGE SURVIVORS**

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**ABSTRACT**

**Objective:**

To evaluate the influence of intracerebral haemorrhage (ICH) location on stroke outcomes.

**Methods:**

We included patients recruited to a UK hospital-based, multicentre observational study of adults with imaging confirmed spontaneous ICH. The outcomes of interest were occurrence of a cerebral ischaemic event (either stroke or transient ischaemic attack, TIA) or a further ICH following study entry. Haematoma location was classified as lobar or non-lobar.

**Results:**

All 1094 patients recruited to the CROMIS-2 ICH study were included (mean age 73.3 years; 57.4% male). There were 45 recurrent ICH events (absolute event rate, AER, 1.88 per 100 patient-years); 35 in patients presenting with lobar ICH (n=447, AER 3.77 per 100 patient-years), and 9 in patients presenting with non-lobar ICH (n=580, AER 0.69 per 100 patient-years). Multivariable Cox regression found that lobar ICH was associated with ICH recurrence (HR 8.96, 95% CI3.36 to 23.87***,*** p<0.0001); similar results were found in multivariable completing risk analyses.

There were 70 cerebral ischaemic events (AER 2.93 per 100 patient-years); 29 in patients presenting with lobar ICH (AER 3.12 per 100 patient-years) and 39 in patients with non-lobar ICH (AER 2.97 per 100 patient-years). Multivariable Cox regression found no association with ICH location (HR 1.13***,*** 95% CI 0.66 to 1.92***, p=***0.659). Similar results were seen in completing risk analyses.

**Conclusions:**

In ICH survivors, lobar ICH location was associated with a higher risk of recurrent ICH events than non-lobar ICH; ICH location did not influence risk of subsequent ischaemic events.

**Trial Registration**

https://clinicaltrials.gov; NCT02513316

### INTRODUCTION

Intracerebral haemorrhage (ICH) is associated with high rates of mortality (1 year and 5 year survival estimated at 46% and 29% respectively1), and consequently data on subsequent stroke events in ICH survivors are limited. Recent data2 3 has challenged the prevailing view4 that antiplatelet and anticoagulant medications increase the risk of further ICH to an extent that outweighs any potential benefits with regard to ischaemic risk, suggesting that the risk of ischaemic events is underestimated in this population.

One baseline feature which might help stratify future stroke risk is the dominant underlying cerebral small vessel disease. Lobar ICH has a higher recurrence rate1, which is thought to reflect its association with the bleeding-prone cerebral amyloid angiopathy (CAA)5 6. Hypertensive arteriopathy, also termed deep perforator arteriopathy, is thought to be responsible for non-lobar or “deep” ICH; it is associated with cardiovascular risk factors and lacunar infarction5 and therefore might confer greater ischaemic risks, in addition to lower ICH risks. Data for relative ischaemic and haemorrhagic risks based on index ICH location could therefore also be useful for future decision making, but there are limited data available1 7.

Our aim was to provide new data on stroke risk following spontaneous ICH in a large cohort of ICH survivors (i.e. patients with ICH who survived the index event for a period of time that allowed for study enrolment). The specific objectives are: (1) to describe the incidence of recurrent ICH and cerebral ischaemic events in the longer term (up to 3 years) following ICH, and (2) to evaluate the influence of ICH location on stroke outcomes.

### 

### METHODS

**Standard Protocol Approvals, Registrations, and Patient Consents**

We included patients recruited to a multicentre observational cohort study of adults with imaging-confirmed symptomatic ICH (CROMIS-2 ICH; https://clinicaltrials.gov; NCT02513316). The study was approved by the National Research Ethics Service (IRAS reference 10/H0716/61). Patients with capacity gave informed written consent; in those without capacity, written consent was obtained from a proxy, as defined by relevant local legislation.

#### Participants

Full details of the CROMIS-2 ICH study protocol have been published previously8. Briefly, participants were adults (aged 18 years or above) with spontaneous ICH confirmed on brain imaging (CT or MRI) within the preceding month, with or without a history of anticoagulant use prior to the index event. Patients with ICH secondary to a known structural cause or major head trauma were excluded. Patients were considered to have pre-existing cognitive impairment if they had a formal diagnosis of dementia or cognitive impairment at study entry, or if they scored more than 3.3 on the 16-item IQCODE, in accordance with previous data9. History of coronary artery disease was defined as a prior history of angina, myocardial infarction or cardiac revascularisation (percutaneous coronary intervention or coronary artery bypass grafting).  *APOE* genotype was established from peripheral blood samples; the method for this has been previously described10.

#### Outcomes

#### For the first 6 months after the index event, outcomes were collected using multiple ascertainment methods, as detailed in the previously published study protocol8. Briefly, these methods included postal questionnaires sent to patients and their general practitioners, and notifications from NHS Digital (previously the Health and Social Care Information Centre)8. NHS Digital is a national centralised body that collects data on health and social care in the United Kingdom, including “hospital episode statistics” (HES; records of all NHS patient admissions) and information on registered deaths from the Office of National Statistics (death registration is a legal requirement in the United Kingdom).

#### Outcome data from 6 months to 3 years were compiled from notifications from NHS Digital. Hospital episode statistics for all admitted patient care (APC) events were reviewed using the NHS Digital HES Data Dictionary for APC episodes11. An “admission” was defined as one or more individual episodes, which ended with the patient being discharged to a “home destination” (DISDEST codes 19, 29, 30, 49, 50, 54, 65, 85) or hospice (DISDEST code 88), or with the death of the patient (DISDEST code 79). The primary diagnosis (DIAG\_01 code) was determined using the online version of the World Health Organisation International Statistical Classification of Diseases and Related Health Problems12. A cerebrovascular event was defined as an admission due to a cerebral ischaemic event (G459, I632, I633, I634, I635, I638, I639, I663), ICH (I610, I611, I612, I614, I615, I616, I618, I619), other non-traumatic intracranial bleeding events (I609, I620, I629), or unspecified stroke event (I64X, I678). Outcome events were diagnosed locally and not adjudicated centrally.

#### The outcomes of interest were occurrence of a cerebral ischaemic event (either stroke or TIA) or a further ICH following study entry. Follow up time was defined as time to first cerebrovascular event, and for those patients who did not have a subsequent cerebrovascular event, follow up time was defined as time to death. For patients who did not have a cerebrovascular or mortality event, follow up time was defined as either 3 years following the index event, or at the time of the study’s last notification from NHS Digital (March 31, 2017), with the earlier date used in these cases. For each analysis (except for competing risk analyses), patients were considered censored if they did not have the event of interest.

#### Imaging

#### Brain CT imaging was acquired acutely at the time of the index event as part of the patient’s routine clinical care. Imaging analysis was carried out by a clinical research associate (DW) trained in neuroimaging rating and blinded to the participant clinical details. Haematoma location was classified using the CHARTS scale13 as lobar (including convexity subarachnoid haemorrhage), deep (involving the basal ganglia or thalamus), cerebellar or brainstem. Non-lobar was defined as the presence of either deep or brainstem haemorrhage; cerebellar haemorrhage was excluded from this definition as this does not have a clear small vessel disease association. CT images were also rated for the presence of lacunes, which were defined in accordance with STRIVE criteria as a “round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole”14. White matter changes were rated on CT images using the Van Swieten score; the highest scores for anterior and posterior regions were combined in order to generate a “total” score (range 0 to 4)15. Haematoma volume was rated using a previously described semi-automated planimetric method16 17.

#### Statistics

#### Statistical analysis was performed using Stata (Version 11.2). Univariable Cox regression was used to investigate which clinical and imaging variables were associated with the occurrence of an outcome of interest. Multivariable Cox regression analysis was then performed; adjustments were made for all variables with p<0.10 in univariable analyses, in addition to the primary variable of interest (ICH location). The proportional-hazards assumption test based on Schoenfeld residuals was applied to all Cox models (univariable and multivariable). Univariable and multivariable competing risk analyses (using the Fine-Gray subdistribution hazard model18 19) were also performed; subdistribution hazard ratios (SHR) are provided. Figures for the cumulative incidence of outcome events were generated using Kaplan-Meier survival analyses.

**Data availability**

Analyses for the CROMIS-2 study are ongoing; once all of these analyses are completed, the CROMIS-2 Steering Committee will consider applications from other researchers for access to anonymised source data.

### RESULTS

All 1094 patients recruited to CROMIS-2 ICH were included (baseline characteristics are shown in Table 1); 447 (40.9%) were lobar ICH, 546 (50.0%) were deep, 65 (6.0%) were cerebellar, and 34 (3.1%) occurred in the brainstem. Follow up was for a total of 2391 patient-years (median 3.00 years, IQR 1.48 to 3.00 years).

**Table 1: Baseline characteristics**

Percentage values were calculated using the total number of patients for whom data was available as the denominator.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | **All** | **Lobar ICH** | **Non-lobar ICH** |
| n | | 1094 | 447 | 580 |
| Age, years, mean (SD) | | 73.3 (12.5) | 75.4 (10.9) | 71.5 (13.3) |
| Sex, male, n (%) | | 628 (57.4) | 241 (53.9) | 356 (61.4) |
| Hypertension, n (%) | | 718 (66.7) | 278 (63.2) | 389 (68.0) |
| Hypercholesterolaemia, n (%) | | 467 (44.0) | 202 (46.9) | 241 (42.6) |
| Diabetes mellitus, n (%) | | 202 (18.6) | 84 (18.9) | 103 (17.9) |
| AF, n (%) | | 375 (37.4) | 162 (39.7) | 181 (34.1) |
| Smoking, n (%) | |  |  |  |
| Never | | 523 (49.7) | 221 (51.6) | 271 (48.3) |
| Ex-smoker | | 416 (39.5) | 173 (40.4) | 218 (38.9( |
| Current | | 114 (10.8) | 34 (7.9) | 72 (12.8) |
| Alcohol use, n (%) | | 604 (58.9) | 230 (55.3) | 338 (61.9) |
| Coronary artery disease, n (%) | | 174 (16.2) | 75 (17.0) | 90 (15.8) |
| Chronic liver disease, n (%) | | 5 (0.5) | 2 (0.5) | 2 (0.4) |
| Chronic renal disease requiring dialysis, n (%) | | 5 (0.5) | 0 (0.0) | 5 (0.9) |
|  | |  |  |  |
| Pre-existing cognitive impairment, n (%) | | 251 (39.8) | 116 (43.9) | 115 (35.3) |
| Previous cerebral ischaemic event, n (%) | | 241 (22.9) | 96 (22.6) | 126 (22.4) |
| Previous ICH, n (%) | | 46 (4.3) | 21 (4.9) | 21 (3.7) |
|  | |  |  |  |
| ApoE ε2, presence, n (%) | | 189 (20.7) | 92 (24.9) | 90 (18.4) |
| ApoE ε4, presence, n (%) | | 256 (28.1) | 113 (30.6) | 125 (25.6) |
|  | |  |  |  |
| **Medications** | | | | |
| Antiplatelet use prior to ICH, n (%) | | 267 (24.6) | 111 (25.0) | 143 (25.0) |
| Anticoagulant use prior to ICH, n (%) | | 436 (40.1) | 190 (42.8) | 208 (36.1) |
| None, n (%) | | 650 (59.9) | 254 (57.3) | 367 (63.7) |
| Warfarin, n (%) | | 402 (37.0) | 175 (39.5) | 191 (33.2) |
| NOAC (dabigatran, factor Xa inhibitor), n (%) | | 27(2.5) | 10 (2.3) | 15 (2.6) |
| Heparin (LMWH, UFH), n (%) | | 7 (0.6) | 4 (0.9) | 3 (0.5) |
| Antiplatelet at discharge, n (%) | | 65 (6.4) | 27 (6.5) | 35 (6.5) |
| Anticoagulant at discharge, n (%) | | 113 (10.7) | 44 (10.2) | 57 (10.2) |
| None, n (%) | | 954 (93.3) | 391 (93.1) | 505 (93.9) |
| Warfarin, n (%) | | 27 (2.6) | 13 (3.1) | 9 (1.7) |
| NOAC (dabigatran, factor Xa inhibitor), n (%) | | 8 (0.8) | 2 (0.5) | 6 (1.1) |
| Heparin (LMWH, UFH), n (%) | | 34 (3.3) | 14 (3.3) | 18 (3.4) |
|  | |  |  |  |
| **Clinical features at study entry** | | | | |
| NIHSS, median (IQR) | | 7 (3 to 13) | 6 (2 to 13) | 8 (4 to 14) |
| GCS, median (IQR) | | 15 (14 to 15) | 15 (14 to 15) | 15 (14 to 15) |
|  | |  |  |  |
| **Imaging features at study entry** | | | | |
| Lacunes, presence, n (%) | | 98 (9.0) | 27 (6.1) | 65 (11.3) |
| Van Swieten Score, median (IQR) | | 0 (0 to 2) | 0 (0 to 2) | 1 (0 to 2) |
| ICH volume, n (%) | < 30ml | 886 (85.9) | 304 (72.6) | 523 (94.8) |
| 30 - 60ml | 99 (9.6) | 75 (17.9) | 22 (4.0) |
| >60ml | 47 (4.6) | 40 (9.6) | 9 (1.3) |
|  | |  |  |  |
| ICH location | |  |  |  |
| Lobar | | 447 (40.9) | - | - |
| Deep | | 546 (50.0) | - | - |
| Cerebellar | | 65 (6.0) | - | - |
| Brainstem | | 34 (3.1) | - | - |
|  | |  |  |  |
| Discharge mRS, median (IQR) | | 3 (2 to 4) | 3 (2 to 4) | 4 (2 to 4) |

#### Recurrent ICH events

#### There were 45 recurrent ICH events (absolute event rate 1.88 per 100 patient-years, 95% CI 1.41 to 2.52 per 100 patient-years); 35 were in patients whose index event was lobar and 9 in patients presenting with non-lobar ICH. Absolute event rates are provided in Table 2.

#### In univariable Cox regression analyses (Table 3; Supplementary Table 1), the following predictors showed associations with recurrent ICH events (p <0.10): increasing age, history of previous cerebral ischaemic events, ICH prior to study entry, presence of at least one APOE ε2 allele and antiplatelet use prior to study entry. There were also associations with the severity of white matter disease (as measured by increasing Van Swieten score), ICH volume and lobar ICH location on baseline imaging (Figure 1A). In univariable competing risk regression for recurrent ICH events (Supplementary Table 1), where occurrence of an ischaemic event or death was the competing risk, a similar association with lobar ICH location was observed.

**Table 2: Absolute rates for recurrent ICH and cerebral ischaemic events**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Location of index ICH** | **Number of patients** | **Total follow up time (patient-years)** | **Recurrent ICH events** | | | **Subsequent cerebral ischaemic events** | | |
| **Number of events** | **Absolute Event Rate (per 100 patient-years)** | **95% Confidence Interval (per 100 patient-years)** | **Number of events** | **Absolute Event Rate (per 100 patient-years)** | **95% Confidence Interval (per 100 patient-years)** |
| Lobar | 447 | 929 | 35 | 3.77 | 2.70 to 5.24 | 29 | 3.12 | 2.17 to 4.49 |
| Non-lobar | 580 | 1311 | 9 | 0.69 | 0.36 to 1.32 | 39 | 2.97 | 2.17 to 4.07 |
| *Deep* | 546 | 1228 | 9 | 0.73 | 0.38 to 1.41 | 37 | 3.01 | 2.18 to 4.16 |
| *Brainstem* | 34 | 83 | 0 | - | - | 2 | 2.40 | 0.60 to 9.61 |
| Cerebellar | 65 | 144 | 1 | 0.69 | 0.01 to 4.92 | 2 | 1.38 | 0.35 to 5.54 |

Table 3: Cox regression analyses for recurrent ICH events

Multivariable results for ICH volume >60ml not shown as only 1 event in this group (HR <0.0001).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Univariable** | | | **Multivariable** | | |
| **HR** | **95% CI** | **p value** | **HR** | **95% CI** | **p value** |
| ICH location, lobar (vs non-lobar) | | 5.40 | 2.60 to 11.24 | <0.0001 | 8.96 | 3.36 to 23.87 | <0.0001 |
| Age, per year increase | | 1.03 | 1.00 to 1.06 | 0.039 | 1.02 | 0.98 to 1.06 | 0.349 |
| Previous cerebral ischaemic event | | 2.32 | 1.25 to 4.34 | 0.008 | 2.86 | 1.37 to 5.96 | 0.005 |
| Previous ICH | | 5.00 | 2.22 to 11.24 | <0.0001 | 4.86 | 1.41 to 16.67 | 0.012 |
| *APOE* ε2 | | 1.84 | 0.93 to 3.65 | 0.080 | 1.37 | 0.65 to 2.90 | 0.415 |
| Antiplatelet use prior to ICH | | 2.24 | 1.24 to 4.04 | 0.008 | 2.22 | 1.09 to 4.50 | 0.028 |
| Van Swieten Score, per point increase | | 1.29 | 1.07 to 1.55 | 0.008 | 1.22 | 0.97 to 1.53 | 0.084 |
| ICH volume | < 30ml | Reference Group | | | Reference Group | | |
| 30 - 60ml | 2.14 | 0.95 to 4.82 | 0.068 | 1.06 | 0.40 to 2.81 | 0.911 |
| >60ml | 0.78 | 0.11 to 5.68 | 0.804 | - | - | - |

#### Multivariable Cox regression including variables of interest identified in univariable Cox analyses (listed above) found that lobar ICH location at presentation remained associated with subsequent ICH occurrence (HR 8.96, 95% CI 3.36 to 23.87, p<0.0001; Table 3). A history of cerebral ischaemic events (HR 2.86, 95% CI 1.37 to 5.96, p=0.005), previous ICH (HR 4.86, 95% CI 1.41 to 16.67, p=0.012), and antiplatelet use (HR 2.22, 95% CI 1.09 to 4.50, p=0.028) prior to the index event were also associated with subsequent ICH occurrence. Multivariable completing risk analyses (including the same variables as the adjusted Cox regression) with either subsequent cerebral ischaemic events or death as the competing risk, showed similar results for the association with lobar ICH location (Supplementary Table 2).

#### Cerebral ischaemic events

#### There were 70 cerebral ischaemic events (absolute event rate 2.93 per 100 patient-years, 95% CI 2.32 to 3.70 per 100 patient-years), of which 29 occurred in patients presenting with lobar ICH and 39 in patients with non-lobar ICH. Absolute event rates are provided in Table 2.

#### In univariable Cox regression analyses (Table 4; Supplementary Table 3), subsequent cerebral ischaemic events were associated with increasing age, hypercholesterolaemia, AF, alcohol use at study entry, history of previous cerebral ischaemic events, anticoagulant use prior to ICH, and increasing Van Swieten score; there was no association with ICH location (Figure 1B). Univariable competing risk regression for subsequent ischaemic events, with occurrence of recurrent ICH or death as the competing risk, found similar results (Supplementary Table 3); the association with age was no longer observed.

#### Multivariable Cox regression (Table 4) found significant associations with age (HR 1.04, 95% CI 1.01 to 1.06, p=0.016), alcohol use at study entry (HR 2.16, 95% CI 1.20 to 3.91, p=0.011) and a history of previous ischaemic events (HR 2.17, 95% CI 1.24 to 3.79, p=0.007). There was no association with ICH location (HR 1.13, 95% CI 0.66 to 1.92, p=0.659). Similar results were seen in multivariable completing risk analyses with recurrent ICH or death as the competing event (Supplementary Table 4).

**Table 4: Cox regression analyses for subsequent cerebral ischaemic events**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Univariable** | | | **Multivariable** | | |
| **HR** | **95% CI** | **p value** | **HR** | **95% CI** | **p value** |
| ICH location, lobar (vs non-lobar) | 1.04 | 0.64 to 1.69 | 0.856 | 1.13 | 0.66 to 1.92 | 0.659 |
| Age | 1.03 | 1.01 to 1.05 | 0.004 | 1.04 | 1.01 to 1.06 | 0.016 |
| Hypercholesterolaemia | 1.69 | 1.05 to 2.73 | 0.031 | 1.22 | 0.71 to 2.09 | 0.479 |
| AF | 2.92 | 1.77 to 4.82 | <0.0001 | 1.04 | 0.48 to 2.26 | 0.918 |
| Alcohol use | 1.63 | 0.96 to 2.78 | 0.071 | 2.16 | 1.20 to 3.91 | 0.011 |
| Previous cerebral ischaemic event | 2.97 | 1.83 to 4.82 | <0.0001 | 2.17 | 1.24 to 3.79 | 0.007 |
| Anticoagulant use prior to ICH | 2.56 | 1.58 to 4.15 | <0.0001 | 1.95 | 0.90 to 4.26 | 0.093 |
| Van Swieten Score, per point increase | 1.24 | 1.06 to 1.44 | 0.006 | 1.11 | 0.93 to 1.33 | 0.265 |

### DISCUSSION

Our main findings are: (1) at 3 year follow up, there were fewer ICH events than cerebral ischaemic events (45 vs 70); (2) there was a difference in absolute event rates for recurrent ICH events for patients with lobar and non-lobar ICH (3.77 vs 0.69 per 100 patient-years), and lobar ICH location was independently associated with a higher risk of recurrent ICH events; and (3) absolute event rates for subsequent cerebral ischaemic events were similar for lobar and non-lobar groups (3.12 vs 2.97 per 100 patient-years), and there was no association between ICH location and the risk of subsequent cerebral ischaemic events. In addition to ICH location, recurrent ICH events were associated with a history of previous ischaemic events, previous ICH, and antiplatelet use prior to study entry, whereas cerebral ischaemic events were associated with age, alcohol use at study entry and a history of previous ischaemic events.

Our results support two recent studies that challenge the idea that the risks of antiplatelet and anticoagulant medications in ICH patients outweigh the benefits. An individual patient data meta-analysis2 of 1012 patients who resumed treatment with oral anticoagulant therapy following spontaneous ICH, found that resumption was associated with reduced mortality and all-cause stroke incidence, as well as more favourable outcomes, at 1 year. RESTART3 was a prospective multicentre randomised trial of patients taking antiplatelet or anticoagulant medications at the time of their ICH; patients were randomised to either restart or discontinue antiplatelet medications following their ICH. RESTART did not find significant changes in either ICH or major vaso-occlusive events with antiplatelet treatment, even in subgroup analyses where these events were considered by index ICH location20. Our finding that cerebral ischaemic events are more frequent than ICH events suggests that the ischaemic risk in patients with ICH, particularly those with lobar ICH, is underestimated. These data support the argument for further randomised trials of antiplatelet or anticoagulant treatments in ICH patients; there has previously been little appetite for this, due to a perceived lack of clinical equipoise.

The finding that lobar ICH is associated with a higher ICH recurrence rate is in keeping with previous work1 5 6, and this is believed to reflect the association of lobar ICH with CAA. We also observed an association between APOE ε2 and recurrent ICH events, and although this association did not reach statistical significance in univariate analyses, it was of reasonable magnitude (HR 1.84); this association was less apparent in the multivariable analysis. This association could reflect the association of APOE ε2 with lobar ICH and CAA, and in particular CAA with vasculopathic “haemorrhagic” changes21-23. However, lobar haemorrhage is not only due to CAA, with one recent study observing that of 62 patients with lobar ICH, 26 had absent or mild CAA24. Given that CAA frequently co-exists with other small vessel pathologies in patients with lobar ICH (the same study found that of 36 patients with moderate or severe CAA, 26 also had evidence of deep perforator arteriopathy24), the increased recurrent ICH risk in these patients might represent more “severe” small vessel disease – be it CAA, or deep perforator arteriopathy, or both. We also found an association with a prior history of ICH was associated with subsequent ICH occurrence, suggesting that some individuals are particularly “bleeding-prone”, independent of ICH location. The observed association with previous cerebral ischaemic events might reflect that these events (in particular lacunar infarction) are associated with more severe small vessel disease (specifically, deep perforator arteriopathy); the association with prior antiplatelet use might be a surrogate marker for this (although other explanations are possible; this observation could also reflect that those taking antiplatelet medications prior to ICH are more likely to be restarted on them, following discharge). When considering subsequent cerebral ischaemic risk, we did not see an increased number of events in those with non-lobar ICH, which might suggest that the ischaemic risk of deep perforator arteriopathy is overestimated. Taken together, this suggests that factors beyond ICH location are important for identifying those at highest risk of subsequent stroke events, and that severe small vessel disease, regardless of subtype, is important.

The strengths of this study are its large size, its multicentre design and the detailed clinical and imaging data available for participants. Limitations include those inherent to the coding of hospital episodes (with regard to accuracy) and the lack of central adjudication of events. This method of ascertainment could result in some events being missed, for example if patients were treated in non-NHS facilities (such as those outside the UK or private hospitals), or in the case of minor events, which might not have resulted in a hospital attendance. New neurological symptoms in ICH survivors can represent a recrudescence of previous stroke symptoms, which could be misdiagnosed as a new cerebrovascular event, particularly in the absence of appropriate investigations including MRI brain with diffusion-weighted sequences25. Additionally, in order to complete competing risk analyses, only the first cerebrovascular event was considered; this work did not explore repeated events, and in patients who had both ischaemic and haemorrhagic events, only the first event was included. The number of outcome events was relatively low, and as a consequence we were unable to explore the role of ICH location in further detail (i.e. in those with cerebellar or brainstem ICH); additionally, we were unable to comment on the clinical severity of the outcome events, as this information was not available. MR data was not available for all patients, and as a consequence we were unable to provide more detailed information on the nature and severity of any underlying cerebral small vessel disease (including the number, presence and distribution of cerebral microbleeds) ; we acknowledge that CT-based quantification methods of white matter changes and lacunes are less sensitive than equivalent MR measures. We also acknowledge that our results might be subject to selection bias, as our cohort only included ICH survivors. We also acknowledge that our cohort is older and has a higher rate of pre-event anti-platelet and anticoagulant use than other cohorts26 (likely to reflect higher rates of comorbidities in our cohort, including atrial fibrillation), which again might limit its generalisability. Finally, as noted above, we did not have information on the prescription of antiplatelet or anticoagulant medications following discharge, or the indications for their use on discharge, which could have influenced our results.

In conclusion, in this large cohort study, there were fewer ICH events than cerebral ischaemic events at 3 years in ICH survivors. Lobar ICH location is associated with a higher risk of recurrent ICH events than non-lobar ICH, as are some features that may reflect cerebral small vessel disease severity. Outstanding questions remain about whether these associations with lobar ICH occur reflect a single small vessel pathology or the severity of small vessel disease more generally. Further work is needed to disentangle the complex interaction between these small vessel diseases, and their impact on an individual’s future stroke risk.

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**Competing interests**

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**FIGURES**

**Figure 1**

Unadjusted Kaplan-Meier failure estimates, comparing patients with lobar and non-lobar ICH, for (A) recurrent ICH and (B) subsequent cerebral ischaemic events. p values are from univariable Cox regression analyses.