

Longer term stroke risk in intracerebral haemorrhage survivors

Banerjee, Gargi; Wilson, Duncan; Ambler, Gareth; Hostettler, Isabel Charlotte; Shakeshaft, Clare; Cohen, Hannah; Yousry, Tarek; Al-Shahi Salman, Rustam; Lip, Gregory Y.H.; Houlden, Henry; Muir, Keith W.; Brown, Martin M.; Jäger, Hans Rolf; Werring, David J.

Published in:

Journal of Neurology, Neurosurgery and Psychiatry

DOI (link to publication from Publisher):

[10.1136/jnnp-2020-323079](https://doi.org/10.1136/jnnp-2020-323079)

Publication date:

2020

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Banerjee, G., Wilson, D., Ambler, G., Hostettler, I. C., Shakeshaft, C., Cohen, H., Yousry, T., Al-Shahi Salman, R., Lip, G. Y. H., Houlden, H., Muir, K. W., Brown, M. M., Jäger, H. R., & Werring, D. J. (2020). Longer term stroke risk in intracerebral haemorrhage survivors. *Journal of Neurology, Neurosurgery and Psychiatry*, 91(8), 840-845. <https://doi.org/10.1136/jnnp-2020-323079>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Take down policy

If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

LONGER-TERM STROKE RISK IN INTRACEREBRAL HAEMORRHAGE SURVIVORS

Gargi Banerjee¹, Duncan Wilson^{1,2}, Gareth Ambler³, Isabel C Hostettler¹, Clare Shakeshaft¹, Hannah Cohen⁴, Tarek Yousry⁵, Rustam Al-Shahi Salman⁶, Gregory Y H Lip⁷, Henry Houlden⁸, Keith W Muir⁹, Martin M Brown¹, Hans Rolf Jäger⁵, David J Werring¹; on behalf of the CROMIS-2 collaborators.

¹Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

²New Zealand Brain Research Institute, Christchurch, New Zealand

³Department of Statistical Science, University College London, London, UK

⁴Haemostasis Research Unit, Department of Haematology, University College London, London, UK

⁵Lysholm Department of Neuroradiology and the Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK

⁶Centre for Clinical Brain Sciences, School of Clinical Sciences, University of Edinburgh, Edinburgh, UK

⁷Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

⁸Department of Molecular Neuroscience, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

⁹Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK

Corresponding author:

Professor David J Werring

Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, Russell Square House, 10 - 12 Russell Square, London WC1B 5EH, UK.

Tel: +44 (0)20 3108 7493; Fax: +44 (0)20 7833 8613; Email: d.werring@ucl.ac.uk

Abstract word count: 247 words

Manuscript word count: 2905 words

Number of references: 26

Key words:

Cerebral small vessel disease; Intracerebral haemorrhage; Ischaemic stroke; Prognosis

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% CI 3.36 to 23.87, $p<0.0001$); similar results were found in multivariable competing 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 data^{2 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 available^{1 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](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 method^{16 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 model^{18 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)	523 (94.8)
	30 - 60ml	99 (9.6)	22 (4.0)
	>60ml	47 (4.6)	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* $\epsilon 2$ 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
<i>Deep</i>	546	1228	9	0.73	0.38 to 1.41	37	3.01	2.18 to 4.16
<i>Brainstem</i>	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 competing 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 competing 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 work^{1 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.

Acknowledgements

We would like to acknowledge Surabhika Lunawat for her assistance in quantifying ICH volumes for this study.

Funding

The CROMIS-2 study is funded by the Stroke Association and British Heart Foundation. GB holds an NIHR Academic Clinical Fellowship, and received funding from the Rosetrees Trust. GA receives funding from the National Institute for Health Research University College London Hospitals Biomedical Research Centre. MMB's Chair in Stroke Medicine is supported by the Reta Lila Weston Trust for Medical Research. DJW receives research support from the Stroke Association, the British Heart Foundation and the Rosetrees Trust. This work was undertaken at UCLH/UCL which receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme.

Competing interests

HC has received institutional research support from Bayer; honoraria for lectures and an Advisory Board from Bayer, diverted to a local charity; and travel/accommodation expenses for participation in scientific meetings covered by Bayer. GYHL acts as a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim,

Novartis, Verseon and Daiichi-Sankyo, and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo; no fees are directly received personally. DJW has received honoraria for consultancy and lectures from Bayer, Portola and Alnylam. The remaining authors report no disclosures or conflicts of interest relevant to the manuscript.

REFERENCES

1. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *Journal of neurology, neurosurgery, and psychiatry* 2014;85(6):660-7. doi: 10.1136/jnnp-2013-306476 [published Online First: 2013/11/23]
2. Biffi A, Kuramatsu JB, Leasure A, et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. *Annals of neurology* 2017;82(5):755-65. doi: 10.1002/ana.25079 [published Online First: 2017/10/14]
3. Collaboration R. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet (London, England)* 2019;393(10191):2613-23. doi: 10.1016/S0140-6736(19)30840-2 [published Online First: 2019/05/28]
4. Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015;46(7):2032-60. doi: 10.1161/STR.0000000000000069 [published Online First: 2015/05/30]
5. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology* 2010;9(7):689-701. doi: 10.1016/S1474-4422(10)70104-6 [published Online First: 2010/07/09]
6. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Annals of neurology* 2011;70(6):871-80. doi: 10.1002/ana.22516 [published Online First: 2011/12/23]

7. Weimar C, Benemann J, Terborg C, et al. Recurrent stroke after lobar and deep intracerebral hemorrhage: a hospital-based cohort study. *Cerebrovascular diseases (Basel, Switzerland)* 2011;32(3):283-8. doi: 10.1159/000330643 [published Online First: 2011/09/07]
8. Charidimou A, Wilson D, Shakeshaft C, et al. The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): rationale, design, and methods. *International journal of stroke : official journal of the International Stroke Society* 2015;10 Suppl A100:155-61. doi: 10.1111/ijss.12569 [published Online First: 2015/08/04]
9. Harrison JK, Fearon P, Noel-Storr AH, et al. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a secondary care setting. *Cochrane Database Syst Rev* 2015;3(3):CD010772. doi: 10.1002/14651858.CD010772.pub2 [published Online First: 2015/03/11]
10. Crook R, Hardy J, Duff K. Single-day apolipoprotein E genotyping. *Journal of neuroscience methods* 1994;53(2):125-7. [published Online First: 1994/08/01]
11. HES Data Dictionary: Admitted Patient Care 2017. <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary>.
12. World Health Organisation International Statistical Classification of Diseases and Related Health Problems 10th Revision World Health Organisation; [updated 23/04/2018. Available from: <http://apps.who.int/classifications/icd10/browse/2016/en>.
13. Charidimou A, Schmitt A, Wilson D, et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability.

- Journal of the neurological sciences* 2017;372:178-83. doi:
10.1016/j.jns.2016.11.021 [published Online First: 2016/12/27]
14. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology* 2013;12(8):822-38. doi:
10.1016/S1474-4422(13)70124-8 [published Online First: 2013/07/23]
15. van Swieten JC, Hijdra A, Koudstaal PJ, et al. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry* 1990;53(12):1080-3.
16. Volbers B, Staykov D, Wagner I, et al. Semi-automatic volumetric assessment of perihemorrhagic edema with computed tomography. *Eur J Neurol* 2011;18(11):1323-8. doi: 10.1111/j.1468-1331.2011.03395.x [published Online First: 2011/04/05]
17. Wilson D, Charidimou A, Shakeshaft C, et al. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. *Neurology* 2016;86(4):360-6. doi: 10.1212/WNL.0000000000002310 [published Online First: 2016/01/01]
18. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94(446):496-509. doi:
10.1080/01621459.1999.10474144
19. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Statistics in medicine* 2017;36(27):4391-400. doi: 10.1002/sim.7501 [published Online First: 2017/09/16]
20. Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and

- cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *The Lancet Neurology* 2019;18(7):643-52. doi: 10.1016/S1474-4422(19)30184-X [published Online First: 2019/05/28]
21. Greenberg SM, Vonsattel JP, Segal AZ, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. *Neurology* 1998;50(4):961-5. doi: 10.1212/wnl.50.4.961 [published Online First: 1998/05/05]
22. Charidimou A, Martinez-Ramirez S, Shoamanesh A, et al. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. *Neurology* 2015;84(12):1206-12. doi: 10.1212/WNL.0000000000001398 [published Online First: 2015/02/27]
23. Charidimou A, Zonneveld HI, Shams S, et al. APOE and cortical superficial siderosis in CAA: Meta-analysis and potential mechanisms. *Neurology* 2019;93(4):e358-e71. doi: 10.1212/wnl.00000000000007818 [published Online First: 2019/06/28]
24. Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *The Lancet Neurology* 2018;17(3):232-40. doi: 10.1016/S1474-4422(18)30006-1 [published Online First: 2018/01/15]
25. Topcuoglu MA, Saka E, Silverman SB, et al. Recrudescence of Deficits After Stroke: Clinical and Imaging Phenotype, Triggers, and Risk Factors. *JAMA neurology* 2017;74(9):1048-55. doi: 10.1001/jamaneurol.2017.1668 [published Online First: 2017/08/08]

26. Arima H, Tzourio C, Butcher K, et al. Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. *Stroke* 2006;37(6):1497-502. doi: 10.1161/01.STR.0000221212.36860.c9 [published Online First: 2006/04/22]

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.