JAMA Neurology | Original Investigation

Location and Timing of Recurrent, Nontraumatic Intracerebral Hemorrhage

Martina B. Goeldlin, MD, PhD; Simon Fandler-Höfler, MD, PhD; Alessandro Pezzini, MD; Anusha Manikantan, MMed; Janis Rauch, MD; Stine Munk Hald, MD, PhD; Mona Løgtholt Kristensen, MD; Lena Obergottsberger, MD; Jochen A. Sembill, MD; David Haupenthal, MD; Kristin Tveitan Larsen, MD; Nikolaos S. Avramiotis, MD; Alexandros A. Polymeris, MD, PhD; Charlotte Periole, MD; Kitti Thiankhaw, MD; Ida Rangus, MD; Laurent Puy, MD, PhD; Marco Pasi, MD, PhD; Andrea Morotti, MD; Giorgio Silvestrelli, MD; Giacomo Giacalone, MD, PhD; Maurizio Paciaroni, MD; Marialuisa Zedde, MD; Elisa Giorli, MD; Rossana Tassi, MD; Marc Delgado-Romeu, MD; Urs Fischer, MD; Bastian Volbers, MD; Arsany Hakim, MD; Werner J. Z'Graggen, MD; Christian H. Nolte, MD; David J. Werring, PhD; Nicolas Raposo, MD, PhD; Stefan T. Engelter, MD; Espen S. Kristoffersen, MD, PhD; Joji Kuramatsu, MD; Thomas Gattringer, MD; David Gaist, MD, PhD; David J. Seiffge, MD; for the EURECA collaborators

IMPORTANCE : The spatial and temporal distribution of intracerebral hemorrhage (ICH) recurrence are largely unknown.

OBJECTIVE To assess timing and location of recurrent ICH events in relation to the index ICH event (adjacent ICH [adjICH] vs remote ICH [remICH]).

DESIGN, SETTING, AND PARTICIPANTS This cohort study was a pooled analysis of individual cohort studies from 2002 to 2021 among hospital-based European cohorts. Patients with 2 or more clinically distinguishable (≥1 recurrent) small vessel disease–related ICH events were included. Data analysis was performed from December 2023 to December 2024.

EXPOSURES ICH location and underlying small vessel disease type.

MAIN OUTCOMES AND MEASURES The primary outcome was adjICH, defined by anatomical ICH location and side, and the secondary outcome was time to recurrence. Multivariable regression analyses were conducted adjusting for ICH location, cerebral amyloid angiopathy according to Boston 2.0 or simplified Edinburgh criteria, convexity subarachnoid hemorrhage extension, hypertension, and antihypertensive treatment, including an interaction term for hypertension and antihypertensive treatment.

RESULTS Among 733 patients (median [IQR] age, 72.4 [65.2 to 79.0] years; 346 female [47.2%]), there were 1616 ICH events, including 733 index and 883 recurrent ICH events (range, 1 to 6 recurrences) over a median (IQR) follow-up of 2.53 (0.66 to 4.92) years. There were 340 patients (46.4%) with adjICH and 393 patients (53.6%) with remICH. Among recurrent ICH events, there were 476 adjICH events and 407 remICH events. In multivariable regression analyses, lobar index ICH (adjusted odds ratio [aOR], 2.08; 95% CI, 1.32 to 3.27) and cerebral amyloid angiopathy at index ICH (aOR, 2.21; 95% CI, 1.57 to 3.11) were associated with higher odds of adjICH, while cerebellar index ICH was associated with lower odds of adjICH (aOR, 0.25; 95% CI, 0.07 to 0.89). The median (IQR) time to recurrence was 1.25 (0.36 to 3.38) years for adjICH and 2.21 (0.66 to 4.85) years for remICH. Previous lobar or convexity subarachnoid hemorrhage (coefficient, −0.75; 95% CI, −1.25 to −0.25; P = .003), adjICH (coefficient, −0.60; 95% CI, −1.02 to −0.18; P = .005), and the number of previous ICH events (coefficient per 1-event increase, −0.62; 95% CI, −0.93 to −0.32; P < .001) were independently associated with a shorter time to recurrence.

CONCLUSIONS AND RELEVANCE This study found that early recurrence and cerebral amyloid angiopathy were associated with adjICH. These findings suggest that regional, tissue-based factors may facilitate recurrence and that identifying and targeting local vasculopathic changes may represent potential novel treatment targets.

JAMA Neurol. doi:10.1001/jamaneurol.2025.0026
Published online March 3, 2025.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EURECA collaborators appear at the end of the article.

Corresponding Authors: Martina B. Goeldlin, MD, PhD, Department of Neurology, Inselspital Bern University Hospital and University of Bern, Rosenbühlgasse 25, 3010 , Bern, Switzerland (martinabeatrice.goeldlin@insel.ch); David J. Seiffge, MD, Department of Neurology, Inselspital Bern University Hospital and University of Bern, Rosenbühlgasse 25, 3010, Bern, Switzerland (david.seiffge@insel.ch).

Intracerebral hemorrhage (ICH) is a disease causing significant morbidity and mortality.[1,2] The incidence of ICH is projected to increase significantly in Europe by 2050.[3]

Cerebral small vessel disease is the major cause of nontraumatic ICH in older individuals,[4,5] likely responsible for more than 80% of cases. There are 2 major types of small vessel diseases, cerebral amyloid angiopathy (CAA) and hypertension-associated deep perforator arteriolopathy, which may be concomitantly present in many patients with ICH based on findings from histopathology[6] and magnetic resonance imaging (MRI) studies.[7] Each of the 2 types of small vessel diseases affects different areas of the brain, and local and regional disease burden may vary. Survivors of ICH are at risk of recurrent ICH.[8] Historical data of unselected patients with ICH found annualized rates of recurrence between 1.7% and 7.4%,[8] while contemporary cohorts reported the highest recurrence rates in CAA.[7,9,10] However, exact mechanisms associated with frequent or early recurrences remain largely unknown.

In our clinical practice, we often observe patients with recurrent ICH in spatial or temporal proximity to a previous ICH event. The primary aim of this study was to investigate the frequency of recurrent ICH events in brain regions adjacent to an index ICH event (adjICH) compared with ICH located in other brain regions (ie, remote ICH [remICH]). Secondary aims were to assess time to recurrence and identify factors associated with adjICH.

Key Points

Question What is the spatial and temporal distribution of recurrent intracerebral hemorrhage (ICH) events?

Findings In this cohort study among 733 patients with 1616 ICH events, 46.4% of patients had recurrent ICH located adjacent to a previous ICH (adjICH), and features of cerebral amyloid angiopathy were associated with adjICH. Time to recurrence was shorter in patients with adjICH compared with patients who had recurrent ICH remote to a previous ICH.

Meaning This study found that early recurrence and features of cerebral amyloid angiopathy were associated with adjICH. Spatial and temporal clustering findings suggest that regional tissue-based factors may play a role.

Methods

Ethical Board Review

For this cohort study, we collected data from investigator-initiated ICH cohorts. Informed consent and study procedures followed local regulations at the time of individual patient inclusion. Primary cohorts and data transfer were approved by a local review board, legal entity, or both if required.

Study Setting

The European Intracerebral Hemorrhage Recurrence Alliance (EURECA) is a multicenter collaboration of local registries or cohort studies. Cohorts for the EURECA collaboration were identified through existing networks and prior collaborations. We pooled individual patient data of patients with recurrent, nontraumatic ICH and convexity subarachnoid hemorrhage (cSAH). A detailed overview of all 14 participating cohorts, including data from 20 centers, is available in eTable 1 in Supplement 1. Patients were eligible if they had imaging-documented, recurrent, nontraumatic ICH or cSAH with available clinical and imaging information about index and recurrent ICH events. We defined *recurrent ICH* as a new, clinically apparent ICH detected on follow-up brain imaging that was independent from the index ICH event in time and space. Clinical deterioration due to secondary hematoma expansion of the index ICH does not fulfill the criteria for recurrent ICH. Diagnostic workup was performed according to international guidelines[11,12] and a commonly used prediction score[13] to identify macrovascular causes of ICH, including noninvasive computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography, if deemed necessary by local investigators. We excluded patients with ICH due to a secondary cause (eg, macrovascular or structural brain lesion). The manuscript was prepared in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, including the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement.[14]

Data Collection

Clinical Data Collection

All data were collected as part of the respective primary cohort by local investigators. Anonymized data from all cohorts were sent to the coordinating center (Inselspital Bern, Switzerland). We assessed clinical and neuroimaging data, including demographics (age, sex, and date of event), cerebrovascular risk factors and comorbidities (history of hypertension, diabetes, dyslipidemia, and atrial fibrillation), medication on admission (antiplatelet treatment, anticoagulants, antihypertensive treatment, glucose-lowering treatment, and lipid-lowering treatments), and clinical presentation on admission (National Institutes of Health Stroke Scale, Glasgow Coma Scale, and systolic and diastolic blood pressure). The total follow-up period was defined as the time from the index ICH to the last documented follow-up ICH.

Neuroimaging Data Collection

For every event, local investigators assessed ICH locations in their cohort according to the Cerebral Hemorrhage Anatomical Rating Instrument (CHARTS), which has been shown to have excellent interrater reliability.[15] We determined the presence of CAA according to the simplified Edinburgh CT criteria (high probability of CAA based on the presence of fingerlike projections and subarachnoid hemorrhage)[6] or the Boston MRI criteria (definite or probable CAA based on the criteria of version 1.5 or 2.0, depending on the time of data collection).[16,17] If a patient had multiple hemorrhages at the same time, we considered the largest hematoma as the epicenter and used this location for analysis.

Outcomes

The prespecified primary outcome was adjICH, defined as ICH in the same brain region and side using the CHARTS[15] classification tool, vs remICH, defined as recurrent ICH in brain

regions distant from a previous ICH. That is, if a patient had more than 1 recurrence with at least 1 recurrent ICH adjacent to a previous one (not necessarily the index ICH), we grouped this patient into the adjICH group. Secondary outcomes were time to recurrence from the previous to the next ICH and ICH location according to CHARTS.[15]

Statistical Analysis

Data management and statistical analysis were performed by M.B.G. using Stata/MP statistical software version 16.0 (StataCorp). The statistical analysis plan, including the selection of covariables, was developed by M.B.G. and D.J.S. prior to receiving any data from collaborators. For descriptive analyses, we grouped patients according to the presence or absence of the primary outcome, adjICH, and compared groups using appropriate descriptive statistics. We reported percentages and 95% CIs for binary and categorical variables and median and IQR for continuous, nonnormally distributed outcomes. Given that this was an exploratory analysis, there was no formal hypothesis testing and we did not adjust for multiple testing. All regression analyses were performed using listwise deletion (cases with missing values were excluded from regression models). Data analysis was performed from December 2023 to December 2024.

Primary Outcome Analysis

We performed logistic mixed-effects regression analyses on characteristics present at the first event to determine associations with the primary outcome, including random intercepts for the individual patient and cohort. We adjusted for the following covariables present at baseline, which were selected based on literature review[7,10,18,19] and clinical plausibility prior to data collection: ICH location, CAA (present at index ICH), cSAH, hypertension, and antihypertensive treatments, including an interaction term for hypertension and antihypertensive treatment to account for potentially uncontrolled hypertension. To account for collinearity among ICH location, cSAH, and CAA, we built 2 different models, one including ICH location and cSAH but not CAA and the other including CAA but not cSAH or location.

Secondary Outcome and Sensitivity Analyses

For secondary outcomes, we performed a mixed-effects linear regression, including random intercepts for the individual patient and cohort. We determined the association of the following, prespecified covariables with time to recurrence: ICH location, number of previous ICH events, any adjacent ICH, hypertension known at previous ICH, anticoagulation on admission for the respective ICH (as a surrogate for anticoagulation pretreatment given that medication was not assessed in the interval between 2 ICH events), and sex. Results are reported as nonstandardized coefficients and 95% CIs. We plotted the time to recurrence using a Kaplan-Meier curve. To further investigate potentially underlying pathophysiological mechanisms, we performed a sensitivity analysis in which we restricted our analysis population to patients in whom CAA was diagnosed at any time (at baseline or during follow-up).

Results

The cohorts consisted of 13 429 patients with ICH, of whom we included 733 patients with at least 1 recurrent ICH event (median [IQR] age, 72.4 [65.2-79.0] years; 346 female [47.2%]), resulting in a total of 1616 events, including 733 index ICH and 883 recurrent ICH events (range, 1-6 recurrent ICH events). There were 392 patients (53.5%) with at least 1 MRI during the study period, 538 patients (73.4%) with at least 1 CT or magnetic resonance angiography, and 95 patients (13.0%) who underwent digital subtraction angiography. In total, 409 patients (55.8%) were reported to have CAA (107 patients [26.2%] according to Edinburgh CT-based criteria[6] and 215 patients [52.6%] according to Boston criteria; for the remaining patients, information about diagnostic criteria was missing).[16,17] The respective version depended on the time of imaging assessment, including patients who had a diagnosis of CAA prior to their first ICH and did not undergo further MRI. Information about contributing cohorts is summarized in eTable 1 in Supplement 1, and eFigure 1 in Supplement 1 displays the study flowchart.

Patient Characteristics at Index ICH

Among all patients, 393 patients (53.6%) had remICH and 340 patients (46.4%) had adjICH. The **Table** displays baseline characteristics of patients overall and by the location of the recurrent ICH event (remICH vs adjICH). The median (IQR) follow-up period was 2.53 (0.66-4.92) years and did not differ between patients who had adjICH (2.69 [0.61-4.71] years) vs those with remICH (2.45 [0.68-5.08] years; $P = .90$). During this time, patients with adjICH had a greater number of recurrent ICH events than those with remICH (median [IQR; range], 1 [1-2; 1-6] recurrences vs 1 [1-1; 1-3] recurrences). Patients with adjICH had a higher prevalence of lobar location as the index ICH event (261 of 330 patients with data [79.1%] vs 223 of 389 patients with data [57.3%]; $P < .001$) and subarachnoid expansion (120 of 284 patients with data [42.3%] vs 95 of 346 patients with data [27.5%]; $P < .001$) compared with patients with remICH, while deep index ICH was more frequent in patients with remICH than adjICH (108 of 389 patients with data [27.8%] vs 51 of 330 patients with data [15.5%]) (Table).

Spatial Distribution

Information on the location of index and recurrent ICH was available in all patients (100%). Among recurrent ICH events, there were 476 adjICH events (53.9%) and 407 remICH events (46.1%). **Figure 1** displays hematoma location at index and recurrent ICH for patients with adjICH compared with those with remICH. Among 484 patients with a lobar index ICH, adjICH were more likely than remICH events (261 patients [53.9%] vs 223 patients [46.1%]), while among 203 patients with ICH in deep structures or the cerebellum, adjICH was less frequent than remICH (58 patients [28.6%] vs 145 patients [71.4%]; $P < .001$). Both adjICH and remICH recurred most frequently in the frontal and parietal lobe. However, frontal, parietal, and occipital recurrences were significantly more prevalent in patients with adjICH. While the index ICH more frequently

Table. Clinical and Neuroimaging Characteristics at Index ICH in Patients With Recurrent ICH

Characteristic	Patients, No. (%)[a]			P value
	Total (N = 733)	remICH recurrence (n = 393)	adjICH recurrence (n = 340)	
Clinical				
Age, median (IQR), y	72.4 (65.2-79.0)	72 (64-79.0)	72.7 (67.0-79.0)	.19
Total ICH events, median (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	<.001
Sex				
Female	346 (47.2)	191 (48.6)	155 (45.6)	.42
Male	387 (52.8)	202 (51.4)	185 (54.4)	
CAA diagnosed at any time	409 (56.0)	188 (47.8)	221 (65)	<.001
CAA present at index ICH	278 (43.2)	119 (33.5)	159 (55.2)	<.001
Hypertension	450 (66.2)	242 (65.6)	208 (66.9)	.72
Dyslipidemia	218 (31.6)	118 (31.6)	100 (31.7)	.96
Diabetes	132 (18.9)	76 (20.1)	56 (17.5)	.38
Atrial fibrillation	94 (13.3)	48 (12.5)	46 (14.3)	.50
Antiplatelet therapy	220 (33.9)	117 (32.4)	103 (35.8)	.50
Anticoagulation	83 (11.9)	48 (12.6)	35 (11.1)	.55
Antihypertensives	346 (54.2)	188 (53.6)	158 (55.1)	.71
Antidiabetics	108 (15.7)	65 (17.4)	43 (13.8)	.20
Lipid-lowering drugs	180 (28.3)	96 (27.5)	84 (29.4)	.60
Blood pressure, median (IQR), mm Hg				
Systolic	160 (136.5-180)	161.5 (139-180)	154.5 (135-180)	.08
Diastolic	84 (76-97)	85 (79-99)	81.5 (72-95)	.06
Neuroimaging				
Hematoma epicenter at index ICH				
Lobar	484 (67.3)	223 (57.3)	261 (79.1)	<.001
Deep	159 (22.1)	108 (27.8)	51 (15.5)	
Brain stem	12 (1.7)	10 (2.6)	2 (0.6)	
Cerebellum	32 (4.5)	27 (6.9)	5 (1.5)	
Isolated IVH	1 (0.1)	1 (0.3)	0 (0.0)	
Isolated cSAH	28 (3.9)	18 (4.6)	10 (3.0)	
Uncertain location	3 (0.4)	2 (0.5)	1 (0.3)	
Side of hematoma at index ICH				
Right	319 (44.2)	175 (44.6)	144 (43.6)	.047
Left	385 (53.3)	202 (51.5)	183 (55.5)	
Midline or central	7 (1.0)	7 (1.8)	0 (0.0)	
Bilateral	11 (1.5)	8 (2.0)	3 (0.9)	
Intraventricular hemorrhage	114 (17.5)	64 (17.9)	50 (16.9)	.74
Subarachnoid expansion	215 (34.1)	95 (27.5)	120 (42.3)	<.001

Abbreviations: adjICH, adjacent intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; remICH, remote intracerebral hemorrhage.

[a] Percentages are indicated among patients with available information on the respective variable. Denominators therefore vary.

occurred on the left side in patients with adjICH, there was no difference for recurrent ICH. Most index ICH events were located in lobar brain areas in patients with CAA (352 of 405 patients with data [86.9%]). Among 321 patients with non-CAA ICH, the index location was lobar in 130 patients (41.8%) and 131 patients (42.1%) of 311 patients with data had a deep supratentorial ICH.

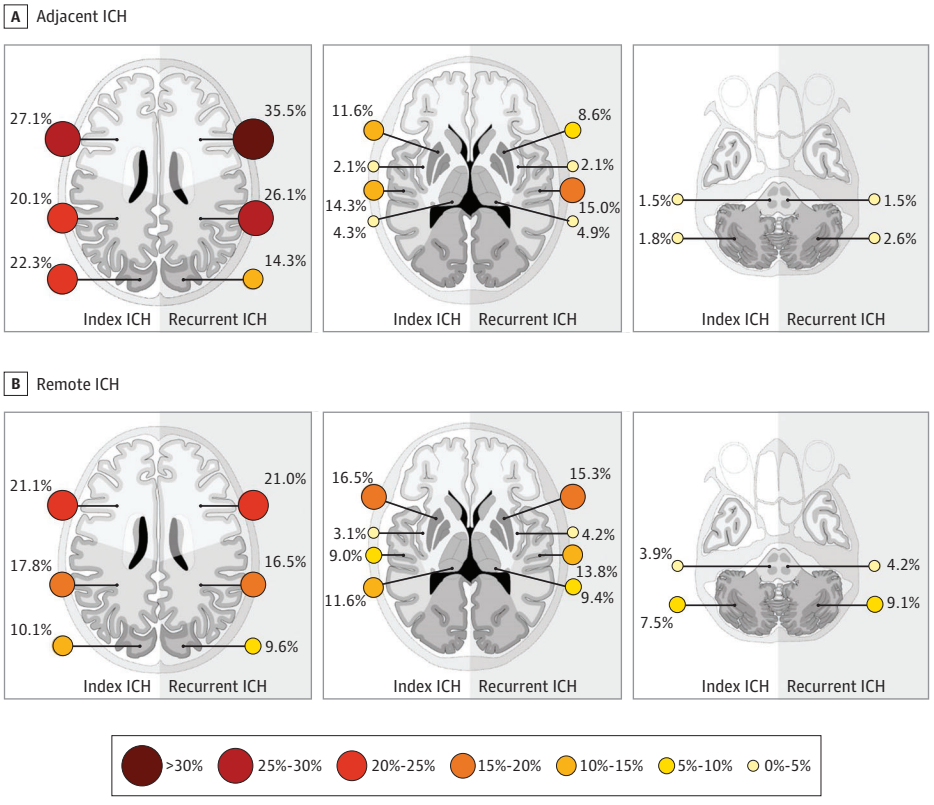
Factors Associated With adjICH

In the multivariable regression analysis (full model listed in eTable 2 in Supplement 1) including ICH location and cSAH extension (597 patients with complete information), we found a positive association of lobar hematoma location (adjusted odds ratio [aOR], 2.08; 95% CI, 1.32-3.27) with adjICH, while cerebellar ICH was inversely associated with adjICH (aOR, 0.25; 95% CI, 0.07-0.89). In the model including CAA (611 patients with complete information), CAA at index ICH was associated with adjICH (aOR, 2.21; 95% CI, 1.57-3.11). We did not observe associations for hypertension or antihypertensive treatment even when adjusting for potential interactions (**Figure 2**).

Time to Recurrence

Time to recurrence was available for 873 recurrent events (98.9%), among which 808 events were included in the mixed linear regression. The median (IQR) time to recurrence was 1.25 (0.36-3.38) years for patients with adjICH and 2.21 (0.66-4.85) years for those with remICH. Previous lobar or cSAH location (coefficient, −0.75; 95% CI, −1.25 to −0.25; P = .003),

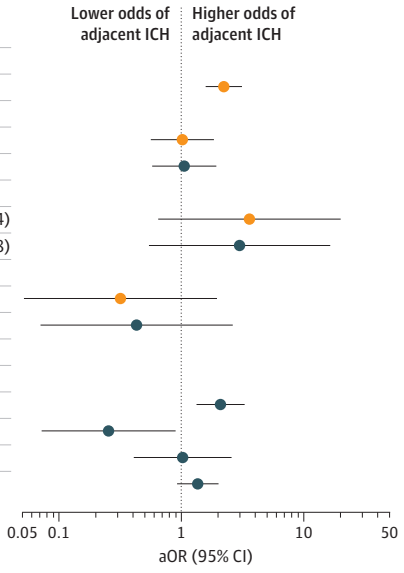
Figure 1. Locations in Adjacent vs Remote Intracerebral Hemorrhage (ICH)



Locations of ICH are displayed according to adjacent vs remote ICH. The left, white-shaded part displays the distribution of index ICH locations, while the right, gray-shaded part displays the distribution of ICH recurrences.

Figure 2. Factors Associated With Adjacent vs Remote Recurrent Intracerebral Hemorrhage (ICH)

	aOR (95% CI)
CAA at index ICH	
Model including CAA	2.21 (1.57-3.11)
Hypertension	
Model including CAA	1.01 (0.56-1.84)
Model including hematoma characteristics	1.05 (0.57-1.92)
Antihypertensives	
Model including CAA	3.58 (0.64-19.94)
Model including hematoma characteristics	2.98 (0.54-16.38)
Hypertension and antihypertensives interaction	
Model including CAA	0.32 (0.05-1.95)
Model including hematoma characteristics	0.43 (0.07-2.62)
Hematoma epicenter	
Model including hematoma characteristics	
Lobar	2.08 (1.32-3.27)
Cerebellum	0.25 (0.07-0.89)
Isolated cSAH	1.02 (0.41-2.56)
Subarachnoid extension	1.36 (0.92-2.00)



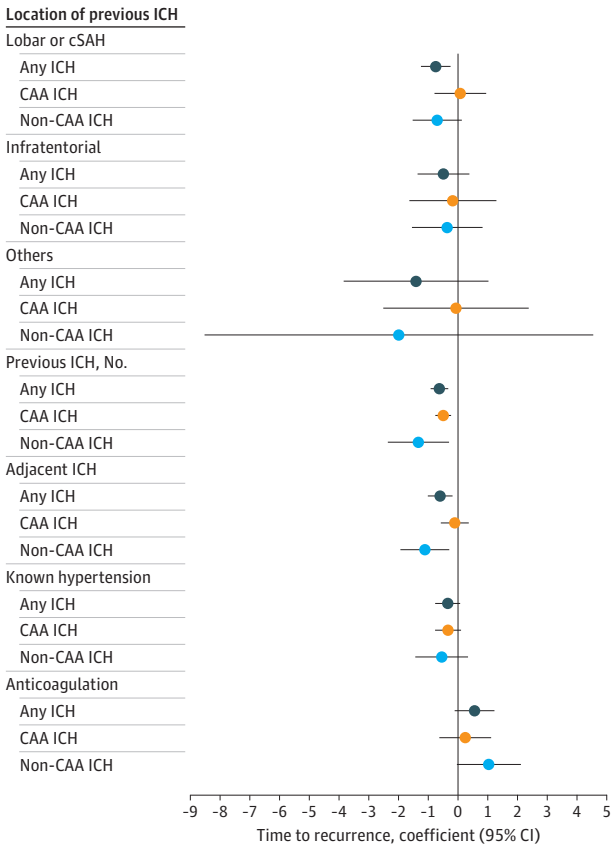
This coefficient plot displays adjusted odds ratios (aORs) for all covariables included in the 2 models for the primary outcome (adjacent ICH), including the interaction term for hypertension and antihypertensives. CAA indicates cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage.

adjICH (coefficient, −0.60; 95% CI −1.02 to −0.18, $P = .005$), and the number of previous ICH events (coefficient per 1-event increase, −0.62; 95% CI, −0.93 to −0.32; $P < .001$) were independently associated with a shorter time to recurrence (**Figure 3**).

Sensitivity Analysis Restricted to Patients With CAA

Information about CAA status was available for at least 1 time in 730 patients (99.6%) (eTable 3 in Supplement 1). Of all included patients, 409 individuals (56.0%) fulfilled the neuroimaging-based Edinburgh or Boston criteria at any time. Among

Figure 3. Associations With Time to Recurrence



Association of covariables with the time to recurrence (event-based analysis) is presented. CAA indicates cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage.

patients diagnosed with CAA, 278 patients (73.0%) had CAA diagnosed already at the index ICH. Patients with CAA (ie, on either index or recurrent ICH) were older than those with non-CAA ICH (median [IQR] age, 74.0 [68.0-80.0] years vs 70.0 [62.8-78.0] years).

Spatial Distribution

Among 538 CAA-associated recurrences, 475 of 536 recurrences with data (88.6%) were in a lobar area, predominantly in the frontal and parietal lobes. In patients with CAA, lobar hematoma location at index ICH (aOR, 9.82; 95% CI, 2.80-34.43) but not cSAH was independently associated with experiencing an adjICH. Among 335 of 342 events with non-CAA ICH with available information for exact ICH location, recurrences were in deep structures (141 events [42.1%]), particularly the basal ganglia (91 events [27.2%]), and in lobar areas (127 events [37.9%]), and cerebellar ICH was associated with a lower odds of adjICH.

Time to Recurrence in Patients With CAA

In patients with CAA, the median (IQR) time to recurrence was significantly shorter (1.23 [0.34-3.36] years) compared with patients without CAA (2.50 [0.81-5.11] years; $P < .001$). When restricting the regression model to patients with CAA, the number of previous ICH events (coefficient per 1-event increase, −0.49; 95% CI, −0.77 to −0.22) was associated with a shorter time to recurrence, while hematoma location and adjICH were not. In patients with non-CAA ICH, adjICH (coefficient, −1.12; 95% CI, −1.94 to −0.29) and the number of previous ICH events (coefficient per 1-event increase, −1.33; 95% CI, −2.42 to −0.24) were associated with a shorter time to recurrence.

Discussion

This cohort study was a large, multicohort collaboration analysis including 14 European cohorts and yielded the following main findings: In half of all patients with recurrent ICH, recurrent events occurred anatomically adjacent to a previous ICH. The time to recurrence was significantly shorter in patients with adjICH compared with remICH. CAA was associated with adjICH.

Recurrent ICH is a significant burden for individuals, next of kin, carers, and hospital personnel. However, no disease-specific treatment exists that effectively reduces this burden. Therefore, understanding ICH recurrence is a major, yet unmet medical need. Previous studies have identified traditional risk factors associated with recurrent ICH, including uncontrolled hypertension,[18] the presence of cerebral microbleeds,[19] lobar ICH location,[20,21] and multifocal cortical superficial siderosis.[22] While this information is suggestive for the most prevalent pathology associated with recurrent ICH (CAA),[7,10,19] specific mechanisms leading to recurrence remain poorly understood. Our study goes beyond classical systemic risk factors given that we assessed temporal and spatial distribution of ICH recurrence following a tissue-based hypothesis.

The main finding of our study was that we identified a common subgroup of patients who had recurrent ICH events adjacent to the index ICH (approximately 50% of all recurrent ICH events), a shorter time to recurrence, and frequently features of CAA. We can only speculate about the reasons that underlie our observations. One potential explanation is that regional disease-related processes (disease progression,[23] significant local disease burden, or disease-related inflammation[24,25]) may play a role.

The association of CAA with shorter time to recurrence suggests that pathological processes observed in CAA, including vessel remodelling,[26,27] perivascular compartment-related fluid flow disturbance,[28] blood-brain barrier breakdown, and related inflammation, may play a role.[29] However, most observations were made in postmortem studies of patients deceased after ICH with advanced stages of CAA. Processes in patients with milder forms of CAA or lobar ICH without CAA[6] who survive the index ICH and have the time to experience a recurrent ICH (as in our study) may differ.

Observational data from 2024 reported a high frequency of early (within 90 days) ICH recurrence in patients with CAA,[30] in line with findings of our study; however, the number of patients with recurrent ICH was small in this study. Inflammation and its role in the pathology of CAA-related ICH have gained recent interest.[28,31] Small studies associated postcontrast leakage

and enhancement with progression of CAA,[32,33] and individual case reports described beneficial outcomes of immunosuppression counteracting inflammatory activity in a case of CAA-related recurrent subarachnoid hemorrhage.[34] These reports may point toward vasculopathy-related inflammation as a potential driver of the observations made in our study.

Spatial and temporal clustering of ICH recurrence were assessed in 2 previous small studies,[35,36] but these were limited by small sample sizes (both including 24 recurrent ICH events) or restricted to patients with CAA and also including asymptomatic hemorrhagic lesions (ie, cerebral microbleeds).[36] A 2022 study[37] assessed spatial and temporal clustering in a sample of 72 patients with hereditary CAA and found that 34% of recurrent ICH events occurred in the same lobe as the index ICH, which is in line with our findings. Our study has advantages over those studies given its large sample size, multicenter setting, and inclusion of all small vessel disease-related ICH events, providing a more comprehensive picture and allowing us to investigate associations with CAA.

Results of our study do not have immediate clinical implications but suggest the existence of a particularly high-risk subgroup of patients requiring dedicated prevention of recurrence who may benefit from novel management options of ICH (eg, tissue-based treatments). Our findings were robust in different sensitivity analyses and models but should be validated in an unselected ICH cohort including patients with 1 or more than 1 ICH. Future studies need to further characterize this patient group by including findings from advanced neuroimaging (ie, MRI) studies and histopathology. These studies need to clarify which mechanisms ultimately lead to early and locally adjacent recurrent ICH and whether disease burden, disease progression, or inflammation play critical roles.

Limitations

This study has several limitations. First, this is a pooled analysis from Western European cohorts that had different recruitment and follow-up strategies, with a possibility of selection bias. Pooling was done retrospectively. Thus, our findings should be considered as hypothesis generating. Second, patients who died were excluded from further follow-up, resulting in a bias toward patients with less severe neurological status. This may lead to an overrepresentation of patients with lobar ICH, who have a better functional outcome.[38] Third, our analysis did not adjust probabilities of adjICH or remICH for the relative size of regions, and we did not further differentiate cerebellar ICH location. Fourth, neuroimaging assessment was performed by local investigators and not by a central imaging core lab, and the definition for CAA was based on neuroimaging (Boston or Edinburgh criteria). For most patients, neither histopathological nor genetic data were available. Thus, patients with smaller CAA-associated hematomas may have been missed when applying Edinburgh CT-based criteria.[39] Additionally, CAA diagnosis is no longer possible according to Boston criteria in patients with deep hemorrhagic manifestations, leading to a potential underrepresentation of patients with mixed CAA–deep perforator arteriolopathy phenotypes in the CAA-positive group. Fifth, patients with a non-CAA pathology may still have had heterogeneous underlying diseases. Sixth, due to time and regional differences in guidelines, homogeneous data regarding etiological assessment, classification,[7,40] and outcomes throughout the 14 cohorts were not available.

Conclusions

This cohort study identified a particularly high-risk subgroup of patients with early recurrent adjICH. This subgroup was substantial in size, making up approximately 50% of all patients with recurrent ICH, and CAA and its imaging markers were associated with adjICH. Our findings offer novel insights into the potential pathophysiological mechanisms of recurrent ICH and suggest a role of tissue-related factors. Based on our findings, we suggest that future studies should further investigate disease activity, including neuroinflammation, neurodegeneration, and local disease burden. A deeper understanding may help to identify patients at a particularly high risk for early recurrence and foster the development of new treatments for this population.

ARTICLE INFORMATION

Accepted for Publication: January 6, 2025.

Published Online: March 3, 2025. doi:10.1001/jamaneurol.2025.0026

Author Affiliations: Department of Neurology, Inselspital Bern University Hospital and University of Bern, Bern, Switzerland (Goeldlin, Manikantan, Rauch, Fischer, Volbers, Z'Graggen, Seiffge); Department of Neurology, Medical University of Graz, Graz, Austria (Fandler-Höfler, Obergottsberger, Gattringer); Stroke Research Centre, Department of Brain Repair & Rehabilitation, UCL Queen Square Institute of Neurology, London, United Kingdom (Fandler-Höfler, Thiankhaw, Werring); Department of Medicine and Surgery, University of Parma, Parma, Italy (Pezzini); Stroke Care Program, Department of Emergency, Parma University Hospital, Parma, Italy (Pezzini); Research Unit for Neurology, Odense University Hospital and University of Southern Denmark, Odense, Denmark (Hald, Gaist); Department of Radiology, Odense University Hospital and University of Southern Denmark, Odense, Denmark (Kristensen); Department of Neurology, University Hospital Erlangen, Germany (Sembill, Haupenthal, Kuramatsu); Department of Neurology, Akershus University Hospital, Lørenskog, Norway (Larsen, Kristoffersen); Department of Clinical Research and Department of Neurology, University Hospital and University of Basel, Basel, Switzerland (Avramiotis, Polymeris, Engelter); Department of Neurology, Hôpital Pierre-Paul Riquet, CHU Toulouse, Toulouse, France (Periole, Raposo); Department of Neurology with experimental Neurology, Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany (Rangus, Nolte); University Lille, Inserm, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, Lille, France (Puy); Department of Neurology, University Hospital of Tours, Inserm U1253, CIC-IT 1245, Tours, France (Pasi); ASST-Spedali Civili, Brescia, Italy (Morotti); Stroke Unit, Department of Neuroscience, ASST Mantova, Mantova, Italy (Silvestrelli); Neurology Unit and Stroke Unit, IRCCS S. Raffaele Hospital, Milano, Italy (Giacalone); Department of Neurosciences and Rehabilitation, Azienda Ospedaliero-Universitaria di Ferrara, Italy (Paciaroni); Neurology and Stroke Unit, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy (Zedde); Neurology Unit, S. Andrea Hospital, La Spezia, Italy (Giorli); Stroke Unit, AOU Senese, Siena, Italy (Tassi); Stroke Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (Delgado-Romeu); Institute of Diagnostic and Interventional Neuroradiology, Stroke Research Center Bern, Inselspital, Bern University Hospital, University of Bern, Switzerland (Hakim); Department of Neurosurgery, Inselspital

University Hospital and University of Bern, Switzerland (Z'Graggen); Berlin Institute of Health, Charité–Universitätsmedizin Berlin, Berlin, Germany (Nolte); NeuroImaging Center, Université de Toulouse, Inserm, UPS, Toulouse, France (Raposo); Neurology and Neurorehabilitation, University Department of Geriatric Medicine Felix Platter, University Hospital and University of Basel, Basel, Switzerland (Engelter); Department of Neurology, RoMed Klinikum, Rosenheim, Germany (Kuramatsu).

Author Contributions: Drs Goeldlin and Seiffge had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Goeldlin, Fischer, Kristoffersen, Seiffge.
Acquisition, analysis, or interpretation of data: Goeldlin, Fandler-Höfler, Pezzini, Manikantan, Rauch, Hald, Kristensen, Obergottsberger, Sembill, Haupenthal, Larsen, Avramiotis, Polymeris, Periole, Thiankhaw, Rangus, Puy, Pasi, Morotti, Silvestrelli, Giacalone, Paciaroni, Zedde, Giorli, Tassi, Delgado Romeu, Volbers, Hakim, Z'Graggen, Nolte, Werring, Raposo, Engelter, Kristoffersen, Kuramatsu, Gattringer, Gaist, Seiffge.
Drafting of the manuscript: Goeldlin, Obergottsberger, Seiffge.
Critical review of the manuscript for important intellectual content: Fandler-Höfler, Pezzini, Manikantan, Rauch, Hald, Kristensen, Sembill, Haupenthal, Larsen, Avramiotis, Polymeris, Periole, Thiankhaw, Rangus, Puy, Pasi, Morotti, Silvestrelli, Giacalone, Paciaroni, Zedde, Giorli, Tassi, Delgado Romeu, Fischer, Volbers, Hakim, Z'Graggen, Nolte, Werring, Raposo, Engelter, Kristoffersen, Kuramatsu, Gattringer, Gaist.
Statistical analysis: Goeldlin, Puy, Kristoffersen, Seiffge.
Obtained funding: Periole, Seiffge.
Administrative, technical, or material support: Goeldlin, Obergottsberger, Larsen, Periole, Thiankhaw, Rangus, Delgado Romeu, Hakim, Nolte, Raposo, Kristoffersen, Kuramatsu, Seiffge.
Supervision: Pezzini, Polymeris, Silvestrelli, Paciaroni, Tassi, Z'Graggen, Raposo, Kristoffersen, Seiffge.

Conflict of Interest Disclosures: Dr Goeldlin reported receiving grants from Inselgruppe AG, Swiss Stroke Society, Bangerter-Rhyner-Foundation/Swiss Academy of Medical Sciences, and European Stroke Organisation; congress registration and hotel from the European Academy of Neurology; and a travel grant from Pfizer to Inselspital Bern outside the submitted work. Dr Fandler-Höfler reported receiving personal fees from AstraZeneca outside the submitted work. Dr Puy reported receiving personal fees from Novo Nordisk outside the submitted work. Dr Morotti reported receiving personal fees from the Emergency Cardiac Research and Education Group and AstraZeneca outside the submitted work. Dr Fischer reported receiving grants from Medtronic, Stryker, Penumbra, Phenox, Rapid Medical, Boehringer Ingelheim, Swiss National Science Foundation, and Swiss Heart Foundation to Inselspital Bern outside the submitted work and personal fees from Medtronic, AstraZeneca (formerly, Alexion/Portola), Bayer, Boehringer Ingelheim, Biogen, AbbVie, and Siemens to Inselspital Bern and serving as a member of a clinical event committee of the COATING study (Phenox) and data and safety monitoring committee of the TITAN, LATE_MT, IN EXTREMIS, and RapidPulse trials and president of the Swiss Neurological Society and president-elect of the European Stroke Organisation. Dr Volbers reported receiving personal fees from Pfizer AG/Bristol Myers Squibb SA, Bayer AG, Ipsen Pharma, CSL Behring, and AstraZeneca and education and training from AbbVie outside the submitted work. Dr Werring reported receiving personal fees from Bayer, Alnylam, and AstraZeneca outside the submitted work. Dr Engelter reported receiving grants from Daiichi Sankyo to Felix Platter Spital Basel and grants from Bayer and Boehringer Ingelheim during the conduct of the study. Dr Kuramatsu reported receiving personal fees from Boehringer Ingelheim and AstraZeneca outside the submitted work. Dr Gattringer reported receiving grants from the Austrian Science Fund and personal fees from Bayer, Bristol Myers Squibb-Pfizer, Boehringer Ingelheim, Novartis, and AstraZeneca outside the submitted work. Dr Gaist reported receiving personal fees from Pfizer and Bristol Myers Squibb and participating in research funded by Bayer paid to Odense University Hospital outside the submitted work. Dr Seiffge reported receiving grants from AstraZeneca, Swiss National Science Foundation, Swiss Heart Foundation, and Bangerter Rhyner Foundation outside the submitted work and personal fees from AstraZeneca, Bayer AG, Bioxodes, and VarmX to Inselspital Bern.
No other disclosures were reported.

Group Information: The EURECA collaborators appear in Supplement 2.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We would like to thank Anja Giger (Inselspital), for providing technical support with Figure 1 and Mattia Branca, PhD, and Lukas Bütikofer, PhD (Clinical Trials Unit, University of Berne), and Lorin Begré, MD, PhD (Department of Infectious Diseases, Inselspital Bern University Hospital and University of Berne), for providing statistical consulting. These individuals were not compensated for these contributions. We thank the Bangerter-Rhyner foundation provided funding for the Bernese intracerebral hemorrhage cohort and the Novo Nordisk Foundation for partly financing the acquisition of the Danish cohort data.

REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0

2. Seiffge DJ, Fandler-Höfler S, Du Y, et al. Intracerebral haemorrhage—mechanisms, diagnosis and prospects for treatment and prevention. *Nat Rev Neurol*. 2024;20(12):708-723. doi:10.1038/s41582-024-01035-w

3. Wafa HA, Marshall I, Wolfe CDA, et al; PRESTIGE-AF consortium. Burden of intracerebral haemorrhage in Europe: forecasting incidence and mortality between 2019 and 2050. *Lancet Reg Health Eur*. 2024;38:100842. doi:10.1016/j.lanepe.2024.100842

4. Goeldlin M, Stewart C, Radojewski P, Wiest R, Seiffge D, Werring DJ. Clinical neuroimaging in intracerebral haemorrhage related to cerebral small vessel disease: contemporary practice and emerging concepts. *Expert Rev Neurother*. 2022;22(7):579-594. doi:10.1080/14737175.2022.2104157

5. van Asch CJ, Velthuis BK, Rinkel GJ, et al; DIAGRAM Investigators. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ*. 2015;351:h5762. doi:10.1136/bmj.h5762

6. 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. *Lancet Neurol*. 2018;17(3):232-240. doi:10.1016/S1474-4422(18)30006-1

7. Goeldlin MB, Mueller M, Siepen BM, et al; for Swiss Stroke Registry Investigators and SIGNAL Investigators. CADMUS: a novel MRI-based classification of spontaneous intracerebral hemorrhage associated with cerebral small vessel disease. *Neurology*. 2024;102(1):e207977. doi:10.1212/WNL.0000000000207977

8. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85(6):660-667. doi:10.1136/jnnp-2013-306476

9. Goeldlin MB, Mueller A, Siepen BM, et al; SSR Investigators. Etiology, 3-month functional outcome and recurrent events in non-traumatic intracerebral hemorrhage. *J Stroke*. 2022;24(2):266-277. doi:10.5853/jos.2021.01823

10. Fandler-Höfler S, Obergottsberger L, Ambler G, et al. Association of the presence and pattern of MRI markers of cerebral small vessel disease with recurrent intracerebral hemorrhage. *Neurology*. 2023;101(8):e794-e804. doi:10.1212/WNL.0000000000207510

11. Hemphill JC III, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. 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):2032-2060. doi:10.1161/STR.0000000000000069

12. Steiner T, Al-Shahi Salman R, Beer R, et al; European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9(7):840-855. doi:10.1111/ijs.12309

13. Hilkens NA, van Asch CJJ, Werring DJ, et al; DIAGRAM study group. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. *J Neurol Neurosurg Psychiatry*. 2018;89(7):674-679. doi:10.1136/jnnp-2017-317262

14. Benchimol EI, Smeeth L, Guttmann A, et al; RECORD Working Committee. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885

15. Charidimou A, Schmitt A, Wilson D, et al. The cerebral haemorrhage anatomical rating instrument (CHARTS): development and assessment of

reliability. *J Neurol Sci*. 2017;372:178-183. doi:10.1016/j.jns.2016.11.021

16. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21(8):714-725. doi:10.1016/S1474-4422(22)00208-3

17. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74(17):1346-1350. doi:10.1212/WNL.0b013e3181dad605

18. Biffi A, Anderson CD, Battey TW, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. 2015;314(9):904-912. doi:10.1001/jama.2015.10082

19. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. *Neurology*. 2017;89(8):820-829. doi:10.1212/WNL.0000000000004259

20. Banerjee G, Wilson D, Ambler G, et al; CROMIS-2 collaborators. Longer term stroke risk in intracerebral haemorrhage survivors. *J Neurol Neurosurg Psychiatry*. 2020;91(8):840-845. doi:10.1136/jnnp-2020-323079

21. Li L, Poon MTC, Samarasekera NE, et al. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *Lancet Neurol*. 2021;20(6):437-447. doi:10.1016/S1474-4422(21)00075-2

22. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: a prospective study. *Neurology*. 2017;89(21):2128-2135. doi:10.1212/WNL.0000000000004665

23. Koemans EA, Chhatwal JP, van Veluw SJ, et al. Progression of cerebral amyloid angiopathy: a pathophysiological framework. *Lancet Neurol*. 2023;22(7):632-642. doi:10.1016/S1474-4422(23)00114-X

24. Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry*. 2011;82(1):20-26. doi:10.1136/jnnp.2009.204180

25. Charidimou A, Martinez-Ramirez S, Reijmer YD, et al. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy: an imaging-pathologic study of concept validation. *JAMA Neurol*. 2016;73(8):994-1001. doi:10.1001/jamaneurol.2016.0832

26. van Veluw SJ, Kuijf HJ, Charidimou A, et al. Reduced vascular amyloid burden at microhemorrhage sites in cerebral amyloid angiopathy. *Acta Neuropathol*. 2017;133(3):409-415. doi:10.1007/s00401-016-1635-0

27. van Veluw SJ, Scherlek AA, Freeze WM, et al. Different microvascular alterations underlie microbleeds and microinfarcts. *Ann Neurol*. 2019;86(2):279-292. doi:10.1002/ana.25512

28. Kozberg MG, Yi I, Freeze WM, et al. Blood-brain barrier leakage and perivascular inflammation in cerebral amyloid angiopathy. *Brain Commun*. 2022;4(5):fcac245. doi:10.1093/braincomms/fcac245

29. Bown CW, Carare RO, Schrag MS, Jefferson AL. Physiology and clinical relevance of enlarged perivascular spaces in the aging brain. *Neurology*. 2022;98(3):107-117. doi:10.1212/WNL.0000000000013077

30. Fandler-Höfler S, Ambler G, Banerjee G, et al. Temporal and spatial clustering of intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2024;103(5):e209770. doi:10.1212/WNL.0000000000209770

31. Ohashi SN, DeLong JH, Kozberg MG, et al. Role of inflammatory processes in hemorrhagic stroke. *Stroke*. 2023;54(2):605-619. doi:10.1161/STROKEAHA.122.037155

32. Jolink WM, Lindenholz A, van Etten ES, et al. Contrast leakage distant from the hematoma in patients with spontaneous ICH: a 7 T MRI study. *J Cereb Blood Flow Metab*. 2020;40(5):1002-1011. doi:10.1177/0271678X19852876

33. van Nieuwenhuizen KM, Hendrikse J, Klijn CJM. New microbleed after blood-brain barrier leakage in intracerebral haemorrhage. *BMJ Case Rep*. 2017;2017:bcr2016218794. doi:10.1136/bcr-2016-218794

34. Schreiber S, John AC, Werner CJ, et al. Counteraction of inflammatory activity in CAA-related subarachnoid hemorrhage. *J Neurol*. 2023;270(2):1159-1161. doi:10.1007/s00415-022-11437-9

35. Neau JP, Ingrand P, Couderq C, et al. Recurrent intracerebral hemorrhage. *Neurology*. 1997;49(1):106-113. doi:10.1212/WNL.49.1.106

36. Rosand J, Muzikansky A, Kumar A, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. *Ann Neurol*. 2005;58(3):459-462. doi:10.1002/ana.20596

37. Voigt S, Amlal S, Koemans EA, et al. Spatial and temporal intracerebral hemorrhage patterns in Dutch-type hereditary cerebral amyloid angiopathy. *Int J Stroke*. 2022;17(7):793-798. doi:10.1177/17474930211057022

38. Sreekrishnan A, Dearborn JL, Greer DM, et al. Intracerebral hemorrhage location and functional outcomes of patients: a systematic literature review and meta-analysis. *Neurocrit Care*. 2016;25(3):384-391. doi:10.1007/s12028-016-0276-4

39. van Etten ES, Kaushik K, van Zwet EW, et al. Sensitivity of the Edinburgh criteria for lobar intracerebral hemorrhage in hereditary cerebral amyloid angiopathy. *Stroke*. 2020;51(12):3608-3612. doi:10.1161/STROKEAHA.120.031264

40. Raposo N, Zanon Zotin MC, Seiffge DJ, et al. A Causal classification system for intracerebral hemorrhage subtypes. *Ann Neurol*. 2023;93(1):16-28. doi:10.1002/ana.26519