Association between the Edinburgh CT and genetic diagnostic criteria for cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage and recurrent intracerebral haemorrhage: an individual patient data meta-analysis

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See **Comment** page 803

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Summary

Background Patients with lobar intracerebral haemorrhage and MRI biomarkers of cerebral amyloid angiopathy have a greater risk of recurrent intracerebral haemorrhage than patients without these biomarkers. However, access to MRI is limited. We aimed to determine whether the Edinburgh CT-only and CT-*APOE* diagnostic criteria for cerebral amyloid angiopathy-related lobar intracerebral haemorrhage are associated with recurrent intracerebral haemorrhage.

Methods We did a meta-analysis of individual patient data from cohort studies identified at the 2018 International cerebral amyloid angiopathy conference in Lille, France, assessing patients with lobar intracerebral haemorrhage with available diagnostic CT imaging that had been, or could be, rated for the Edinburgh cerebral amyloid angiopathy criteria imaging features, and with follow-up data for recurrent intracerebral haemorrhage and death. Eligible patients were aged 16 years or older with first or recurrent spontaneous lobar intracerebral haemorrhage diagnosed by non-contrast brain CT, with no evidence of an underlying cause other than cerebral small vessel disease. Collaborators provided individual patient-level data. The primary outcome was first recurrent intracerebral haemorrhage occurring at least 30 days after the index event, analysed using primary two-stage (cohort-level) and secondary one-stage (pooled) meta-analyses with multivariable regression models with a competing risk of death, adjusted for age, sex, and CT small vessel disease score. Pooled analyses were adjusted for previous intracerebral haemorrhage, dementia, hypertension, and cohort clustering. All analyses were done in R Project for Statistical Computing (version 4.5.0).

Findings We included eight cohorts from Austria, France, Germany, Italy, the UK, and the USA, with 1705 eligible patients for the CT-only criteria. In the primary two-stage meta-analysis of the CT-only criteria (562 patients from three European cohorts, median age 76 years [IQR 68–82], 282 [50%] female and 280 [50%] male), 69 patients had a recurrent intracerebral haemorrhage over 1381 person-years' follow-up. The proportion with recurrent intracerebral haemorrhage during 5-year follow-up in the intermediate-risk and high-risk CT-only cerebral amyloid angiopathy criteria group was 48 (16%) of 307 patients compared with 21 (8%) of 255 patients in the low-risk group (adjusted sub-distribution hazard ratio [HR] 1·79, 95% CI 1·05–3·05, p=0·032). In the one-stage meta-analysis of the CT-only criteria (1620 patients with lobar intracerebral haemorrhage from eight cohorts, median age 73 years [IQR 62–80], 763 [47%] female and 857 [53%] male), 171 patients had a recurrent intracerebral haemorrhage over 3208 person-years' follow-up. Cumulative 5-year incidence of recurrent intracerebral haemorrhage in the low-risk CT-only cerebral amyloid angiopathy criteria group was 45 (12%) of 727 patients compared with 54 (16%) of 513 patients in the intermediate-risk group (adjusted sub-distribution HR 1·68, 95% CI 1·21–2·32; p=0·0018), and 72 (26%) of 380 patients in the high-risk group (adjusted sub-distribution HR 2·97, 1·50–5·89, p=0·0018). We included six cohorts with 1021 eligible patients for the CT-*APOE* criteria; 15 patients with missing baseline data were excluded. There were insufficient outcomes in individual CT-*APOE* cohorts to do the two-stage meta-analysis. In the one-stage meta-analysis of the CT-*APOE* criteria (1006 patients, median age 71 years [IQR 58–79, 477 [47%] female and 529 [53%] male), 74 patients had a recurrent intracerebral haemorrhage over 1495 person-years' follow-up. Cumulative 3-year incidence of recurrent intracerebral haemorrhage was 34 (15%) of 320 patients in the high-risk CT-*APOE* cerebral amyloid angiopathy criteria group versus 14 (8%) of 322 patients in the low-risk group (adjusted sub-distribution HR 2·22 [95% CI 1·36–3·61], p=0·0014).

Interpretation The Edinburgh CT-only and CT-*APOE* diagnostic criteria for cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage were associated with a greater incidence of recurrent intracerebral haemorrhage. These findings could aid personalised prediction and targeted secondary prevention in standard clinical practice where brain CT is available.

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See Online for appendix

Introduction

Spontaneous (non-traumatic) intracerebral haemorrhage attributed to cerebral small vessel disease, mainly cerebral amyloid angiopathy or arteriolosclerosis, caused 3·4 million strokes worldwide in 2021.[1] Survivors are at risk of recurrent intracerebral haemorrhage, which is more frequent after intracerebral haemorrhage in supratentorial lobar locations (about 5% per year) than in non-lobar locations (about 2% per year).[2,3]

The heightened risk of recurrent lobar intracerebral haemorrhage might be explained by the occurrence of cerebral amyloid angiopathy in these locations, in addition to arteriolosclerosis.[4] This notion is supported by the association between MRI biomarkers of cerebral amyloid angiopathy alone[5,6] or mixed cerebral amyloid angiopathy and arteriolosclerosis,[7] and a higher risk of intracerebral haemorrhage.

Since the 1990s, non-invasive diagnosis of cerebral amyloid angiopathy in clinical practice has required application of the Boston cerebral amyloid angiopathy criteria to brain MRI with susceptibility-weighted sequences.[8,9] However, many patients with intracerebral haemorrhage cannot undergo MRI because of comorbidities, contraindications, or limited availability, especially in low-income and middle-income countries where 90% of incident intracerebral haemorrhages occur.[1]

To promote widespread identification of cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage, in 2018 we proposed the Edinburgh CT and *APOE*-diagnostic criteria for cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage, which uses two diagnostic CT features (subarachnoid haemorrhage and finger-like projections from the haematoma) and *APOE* genotype, or the Edinburgh CT-only criteria, which uses the two CT features only.[4] The rule-in and rule-out diagnostic criteria had excellent discrimination in the derivation cohort.

A greater risk of intracerebral haemorrhage recurrence has been associated with subarachnoid extension[10–13] and *APOE* genotype[14,15] individually, as well as with subarachnoid extension and finger-like projections in a small study,[16] but the associations with the Edinburgh CT-only and CT-*APOE* cerebral amyloid angiopathy

Research in context

Evidence before this study

We searched for studies assessing the associations between one or more components of the Edinburgh cerebral amyloid angiopathy diagnostic criteria and recurrent intracerebral haemorrhage in Ovid MEDLINE (from 1946), bibliographies of relevant publications, and backward citation searching in Google Scholar on July 22, 2025 (appendix p 5). We identified four published studies assessing the association between convexity subarachnoid haemorrhage accompanying lobar intracerebral haemorrhage and recurrent intracerebral haemorrhage. Three studies used overlapping data from the same single hospital-based cohort while the other was a multicentre study. Two studies assessed convexity subarachnoid haemorrhage on CT, one on MRI, and one used either CT or MRI. All studies included only cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage according to Boston criteria and had small sample sizes ranging from 197 to 292, with 17 to 54 outcome events. All studies showed that convexity subarachnoid haemorrhage was independently associated with recurrent intracerebral haemorrhage in multivariable analyses; however, they adjusted for different confounders and were at risk of overfitting. One multicentre study found significantly greater incidence of recurrent intracerebral haemorrhage in patients with subarachnoid haemorrhage with or without finger-like projections than in those with neither subarachnoid haemorrhage or finger-like projections. Two studies (involving 787 patients and 108 recurrent intracerebral haemorrhage outcomes) found that APOE ε4 allele possession was associated with recurrent intracerebral haemorrhage. None of the studies examined associations between the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria and clinical outcomes.

Added value of this study

We attained a larger sample size and number of outcomes than existing studies of individual components of the diagnostic criteria. A collaborative individual patient data approach enabled us to harmonise datasets, perform consistent adjustment of study-level estimates, and use different approaches to meta-analysis and risk estimation to confirm an association between the Edinburgh cerebral amyloid angiopathy diagnostic criteria and recurrent intracerebral haemorrhage.

Implications of all the available evidence

These findings aid personalised prediction of recurrent intracerebral haemorrhage using the high-risk and intermediate-risk versus low-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria, or the CT-*APOE* cerebral amyloid angiopathy criteria, focussing attention on secondary prevention interventions (such as intensity of blood pressure lowering) for high-risk groups.

diagnostic criteria are unclear. If these associations exist, they could help personalise risk prediction after lobar intracerebral haemorrhage worldwide and support the construct validity of the Edinburgh cerebral amyloid angiopathy criteria.

We aimed to investigate the association between the Edinburgh CT-only and CT-*APOE* cerebral amyloid angiopathy diagnostic criteria and recurrent intracerebral haemorrhage in survivors of lobar intracerebral haemorrhage, using the largest sample size we could achieve by collaborating with investigators of cohort studies that had applied these recent diagnostic criteria.

Methods

Search strategy and selection criteria

There were no published studies of the Edinburgh CT-only and CT-*APOE* cerebral amyloid angiopathy diagnostic criteria and recurrent intracerebral haemorrhage when the criteria were published in March, 2018. Therefore, we approached the leads of published cerebral amyloid angiopathy-intracerebral haemorrhage cohorts that might have suitable non-contrast brain CT and follow-up data and were willing to review their brain CT imaging for the rating of Edinburgh cerebral amyloid angiopathy criteria, who were present at the International cerebral amyloid angiopathy conference in September, 2018 in Lille, France.

We included cohort studies that assessed patients with lobar intracerebral haemorrhage; collected diagnostic CT imaging that had been, or could be, rated for the imaging features in the Edinburgh cerebral amyloid angiopathy criteria; and included follow-up data for recurrent intracerebral haemorrhage and death (appendix p 6). *APOE* genotype was a desirable, but not essential inclusion criterion. We excluded two cohorts due to small sample sizes (n=75 and n=10). We assessed the risk of bias using the Quality in Prognosis Studies tool (appendix pp 7–8).[17]

We included adults aged 16 years or older who had a first-ever or recurrent lobar intracerebral haemorrhage diagnosed by non-contrast brain CT. We excluded patients with exclusively extra-axial intracranial haemorrhage, with intracerebral haemorrhage secondary to an underlying cause other than cerebral small vessel disease (trauma, macrovascular causes, structural causes, or haemorrhagic transformation of cerebral infarction) after standard clinical workup, or without a diagnostic quality non-contrast brain CT. To assess recurrent haemorrhage in survivors of lobar intracerebral haemorrhage and to minimise the high early impact of death as a competing event,[18] we excluded those who died or had a recurrent intracerebral haemorrhage within the first 30 days after the index intracerebral haemorrhage.

The study protocol was designed by investigators from the University of Edinburgh, Edinburgh, Scotland, with input from collaborators at University College London, London, UK in September, 2018.[19]

Data analysis

Investigators at participating centres collected demographic data, date of index intracerebral haemorrhage symptom onset, admission Glasgow Coma Scale score, presence of pre-intracerebral haemorrhage comorbidities, and medication use at the time of intracerebral haemorrhage and on hospital discharge (or at 30 days after intracerebral haemorrhage), by interviewing patients or their families or carers at the time of presentation and by reviewing primary care and hospital records.

Investigators at participating centres underwent online training[20] and rated brain CTs blinded to clinical, genetic, and outcome information. We assessed the location of the largest acute intracerebral haematoma,[21] the volume of the largest acute intracerebral haematoma,[22] and the presence or absence of extra-axial haemorrhage (in subarachnoid, subdural, or intraventricular spaces) and finger-like projections arising from the largest acute haematoma on the diagnostic brain CT.[4] We calculated the CT small vessel disease burden score[23] on the basis of the presence and severity of white matter lucencies and leukoaraiosis,[24] lacunes,[25] and cortical and central cerebral atrophy.[26]

We classified all patients according to the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria[4] (low risk=lobar intracerebral haemorrhage with no finger-like projections or subarachnoid haemorrhage; intermediate risk=lobar intracerebral haemorrhage with either finger-like projections or subarachnoid haemorrhage; and high risk=lobar intracerebral haemorrhage with both finger-like projections and subarachnoid haemorrhage).

Where available, investigators did *APOE* genotyping on DNA extracted from peripheral venous blood or brain tissue using standard techniques, blinded to radiological, clinical, and outcome data. We classified patients as carriers of *APOE* ε2 and *APOE* ε4 if they possessed at least one copy of these alleles.

We classified patients with *APOE* genotyping according to the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria[4] (low risk=lobar intracerebral haemorrhage with no finger-like projections, subarachnoid haemorrhage, or *APOE* ε4 possession; intermediate risk=lobar intracerebral haemorrhage with one of finger-like projections, subarachnoid haemorrhage, or *APOE* ε4 possession; and high risk=lobar intracerebral haemorrhage with two or more of finger-like projections, subarachnoid haemorrhage, or *APOE* ε4 possession).

Investigators followed up patients in their cohort for recurrent intracerebral haemorrhage and death using combinations of primary care and hospital records, hospital appointments, telephone interviews with survivors and caregivers, questionnaires, and death certificates according to the study design of the cohort (appendix p 6).

Outcomes

The primary outcome was the first recurrent intracerebral haemorrhage occurring at least 30 days after the index intracerebral haemorrhage, which we defined as the onset of new neurological deficits or worsening of pre-existing deficits, anatomically referable to evidence of new intracerebral haemorrhage on brain imaging. Death from any other cause occurring at least 30 days after the index intracerebral haemorrhage was used as a competing event because it was frequent and precluded the occurrence of the primary event. Both the primary outcome and the competing event were adjudicated by trained investigators at the participating centres using all available clinical and imaging information.

Statistical analysis

The study estimand is the association between the Edinburgh CT-only and CT-*APOE* cerebral amyloid angiopathy diagnostic criteria and the rate of recurrent intracerebral haemorrhage in survivors of lobar intracerebral haemorrhage attributed to small vessel disease. Relevant intercurrent events include death, blood pressure control, and antithrombotic use during follow up.

The study estimator is a competing risk analysis for recurrent intracerebral haemorrhage, described below and in the appendix, to account for death as an intercurrent event or competing risk.

The estimates include the sub-distribution and cause-specific hazard functions. The sub-distribution hazard function represents the instantaneous risk of failure in patients who have not yet experienced the event type of interest. This includes those who are currently free of both the primary event (recurrent intracerebral haemorrhage) and competing event, as well as those who have experienced the competing event (death). The cause-specific hazard function represents the instantaneous rate of occurrence of an event type in those who have not yet experienced any of the event types.

We sought missing data from investigators at participating centres. We did complete case analyses without imputation and report missing data where applicable. We described baseline clinical characteristics, diagnostic brain CT features, and *APOE* genotypes in the cohorts.

Traditional methods for survival analysis, such as Kaplan–Meier method and the Cox proportional hazards model, assume competing risks are absent. Their use in the presence of a competing event, such as death, results in an overestimation of outcome incidence and misestimation of magnitude of relative effects of predictors.[27] Therefore, we did time to event analyses with first recurrent intracerebral haemorrhage as the outcome and treated death from any other cause as a competing risk (appendix p 9). All analyses were done in R Project for Statistical Computing (version 4.5.0).

For the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria, we censored follow-up data 5 years after the index intracerebral haemorrhage because of the duration of follow-up that was available in most cohorts.

In the primary analysis, we included patients with first-ever lobar intracerebral haemorrhage as the index event to standardise the inception point (appendix pp 10–11). We used the cumulative incidence function to estimate incidence of recurrent intracerebral haemorrhage in individual cohorts, stratified by prespecified variables (sex, CT small vessel disease score [0 *vs* 1, 2, or 3], Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories [low vs intermediate or high]), and accounting for the competing risk of death. We constructed univariable sub-distribution and cause-specific hazard models with death as a competing risk in individual cohorts using these prespecified variables. We did multivariable regression with death as a competing risk using the Fine-Gray sub-distribution hazard[28] and cause-specific hazard models, adjusting for pre-specified variables (Edinburgh CT-only cerebral amyloid angiopathy diagnostic category [low *vs* intermediate or high], age [per 10-year increase], sex, CT small vessel disease score [0 *vs* 1, 2, or 3]) in cohorts with at least 20 outcomes. The variance inflation factor values confirmed no evidence of multicollinearity between variables. We did a primary two-stage (cohort-level) meta-analysis of the sub-distribution hazard models using a random effects model with DerSimonian-Laird weights to account for differences in study design and baseline characteristics between the cohorts.[29,30]

In the secondary analysis, we pooled data from all cohorts to maximise power and included patients with either first-ever or recurrent intracerebral haemorrhage as the index event (appendix pp 10–11). We used the cumulative incidence function to estimate incidence of recurrent intracerebral haemorrhage stratified by the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria (low *vs* intermediate *vs* high) accounting for the competing risk of death. We did one-stage (pooled) multivariable regression meta-analyses using sub-distribution and cause-specific hazard models for the Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories (low *vs* intermediate *vs* high) and the individual components of the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria (subarachnoid haemorrhage or finger-like projections) separately. We adjusted all models for age, sex, CT small vessel disease score (0 *vs* 1, 2, or 3), history of previous intracerebral haemorrhage, pre-existing hypertension or dementia, and cohort clustering. The variance inflation factor values confirmed no evidence of multicollinearity between variables.

We did post-hoc sensitivity analyses excluding CT small vessel disease from the primary and secondary Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria multivariable models.

For the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria, we censored data 3 years after the index intracerebral haemorrhage due to the low number of outcomes and the loss of proportional hazards after this timepoint.

We did not do the primary statistical analyses in individual cohorts due to the small numbers of outcomes in each cohort.

Instead, we pooled data from all cohorts to maximise power and included patients with *APOE* genotyping with either first-ever or recurrent intracerebral haemorrhage as the index event (appendix pp 39–40). We used the cumulative incidence function to estimate incidence of recurrent intracerebral haemorrhage stratified by the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic categories (low *vs* intermediate *vs* high), and accounting for the competing risk of death. We did one-stage (pooled) multivariable regression meta-analyses using sub-distribution and cause-specific hazard models for the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic categories (low *vs* intermediate *vs* high) and the individual components of the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria (subarachnoid haemorrhage, finger-like projections, or *APOE* ε4 allele possession) separately. We adjusted all models for age, sex, CT small vessel disease score (0 *vs* 1, 2, or 3), history of previous intracerebral haemorrhage, pre-existing hypertension or dementia, *APOE* ε2 allele possession, and cohort clustering. The variance inflation factor values confirmed no evidence of multicollinearity between variables.

We did a post-hoc assessment of the added value of *APOE* ε4 allele possession in the Edinburgh criteria (appendix p 9).

	LATCH (n=120)	CROMIS-2 (n=340)	Magdeburg (n=102)
Age, years	78 (70–82)	76 (68–83)	74 (67–77)
Sex			
Female	73 (61%)	157 (46%)	52 (51%)
Male	47 (39%)	183 (54%)	50 (49%)
Comorbidities			
Hypertension	66 (55%)	214 (63%)	70/99 (71%)
Hypertension unknown	0	6 (2%)	3 (3%)
Dementia	19 (16%)	33 (10%)	8/56 (14%)
Dementia unknown	0	5 (1%)	46 (45%)
Subarachnoid haemorrhage	78 (65%)	130 (38%)	48 (47%)
Finger-like projections	20 (17%)	78 (23%)	52 (51%)
Edinburgh CT-only cerebral amyloid angiopathy criteria			
Low risk	42 (35%)	177 (52%)	36 (35%)
Intermediate risk	58 (48%)	118 (35%)	32 (31%)
High risk	20 (17%)	45 (13%)	34 (33%)
CT small vessel disease score			
0	50 (42%)	193 (57%)	37 (36%)
1	40 (33%)	102 (30%)	48 (47%)
2	26 (22%)	44 (13%)	16 (16%)
3	4 (3%)	1 (<1%)	1 (1%)
Follow up, days	976 (285–1826)	1048 (646–1094)	897 (321–1818)
Outcome			
Recurrent intracerebral haemorrhage	22 (18%)	25 (7%)	22 (22%)
Death	56 (47%)	65 (19%)	24 (24%)
Censored	42 (35%)	250 (74%)	56 (55%)

Data are n (%), n/N (%), or median (IQR). CROMIS-2=The Clinical Relevance of Microbleeds in Stroke study. LATCH=The Lothian Audit for the Treatment of Cerebral Haemorrhage.

Table 1: **Baseline characteristics of individuals included in the primary Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria two-stage (cohort-level) meta-analysis**

Role of the funding source

The funders of the study had no role in study design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit.

Results

Eight intracerebral haemorrhage cohorts from Europe (Austria, France, Germany, Italy, UK) and the USA contributed data to the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria analyses (appendix pp 10–11). Key baseline characteristics for included and excluded patients are shown in the appendix (pp 12–13).

Most cohorts had a moderate risk of bias for study participation because they were retrospective studies or were susceptible to selection bias (appendix pp 7–8). The Boston cohort had high risk of bias for study attrition due to large amounts of missing outcome data. All had moderate risk for study confounding as data on blood pressure control during follow-up were not available.

The eight cohorts included 1568 patients with first-ever small vessel disease-associated lobar intracerebral haemorrhage with complete key baseline and outcome data (appendix pp 14–17). Median age was 73 years (IQR 61–80). 826 (53%) of 1568 patients were male and 742 (47%) were female. During 3156 person-years of follow-up (median 1·16 years, IQR 0·89–3·00), 144 patients had a recurrent intracerebral haemorrhage and 321 died from causes other than recurrent intracerebral haemorrhage.

The cumulative incidence of death exceeded that of recurrent intracerebral haemorrhage in the individual cohorts, confirming that death was a substantial competing event although there was some variation in the absolute events between cohorts (appendix pp 18–23). In univariable sub-distribution hazard models in individual cohorts, stratified by sex, CT-small vessel disease score, and Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories, two cohorts found a significant increase in the relative incidence of recurrent intracerebral haemorrhage with intermediate or high risk of cerebral amyloid angiopathy (appendix pp 24–27).

Four cohorts (LATCH, CROMIS-2, Magdeburg, and Reggio Emilia) had enough outcomes to permit multivariable regression. However, the CT-small vessel disease score variable showed complete separation

between the outcome groups in the Reggio Emilia cohort. Therefore, we included 562 patients with first-ever lobar intracerebral haemorrhage from the LATCH, CROMIS-2, and Magdeburg cohorts in the primary multivariable analysis (table 1). The median age of patients in these cohorts was 76 years (IQR 68–82), which was slightly higher than the excluded patients from the remaining five cohorts (median 70 years, 58–79; appendix p 13). 280 (50%) of 562 patients were male and 282 (50%) were female. During a total follow-up of 1381 person-years (median 2·74 years, IQR 1·41–3·01), 69 patients had recurrent intracerebral haemorrhage and 145 died. In all three cohorts, patients in intermediate or high-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories had a numerically greater relative incidence of recurrent intracerebral haemorrhage compared with the low-risk category, although the difference was not statistically significant (appendix pp 28–29).

In the primary two-stage (cohort-level) meta-analysis, there was a statistically significant association between the intermediate or high-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories and a greater relative incidence of recurrent intracerebral haemorrhage compared with the low-risk category (48 [16%] of 307 *vs* 21 [8%] of 255 patients, adjusted sub-distribution HR 1·79, 95% CI 1·05–3·05; p=0·032, figure 1). These associations remained similar in a post-hoc sensitivity analysis excluding the CT-small vessel disease variable (appendix pp 30–31).

In the prespecified secondary analysis, we pooled data from 1620 patients with first-ever or recurrent intracerebral haemorrhage from the eight cohorts after excluding those with missing baseline and outcome data (appendix pp 10, 32–33). Median age was 73 years (IQR 62–80), 857 (53%) of 1620 patients were male and 763 (47%) were female. During a total follow-up of 3208 person-years (median 1·16, IQR 0·82–3·00), 171 patients had a recurrent intracerebral haemorrhage and 343 died from causes other than recurrent intracerebral haemorrhage.

The 5-year cumulative incidence rate for recurrent intracerebral haemorrhage increased with the Edinburgh CT-only cerebral amyloid angiopathy diagnostic categories (low risk 11·9%, 95% CI 8·3–16·1; intermediate risk 16·2%, 12·0–21·0; high risk 25·5%, 20·0–31·4; p<0·0001, figure 2; appendix pp 34–35). The presence of subarachnoid haemorrhage and finger-like projections individually, and history of intracerebral haemorrhage and CT small vessel disease score 1–3, were also associated with an increased 5-year cumulative incidence rate for recurrent intracerebral haemorrhage in univariate analyses (appendix p 35).

In the prespecified one-stage (pooled) multivariable regression analysis, both the intermediate-risk (54 [16%] of 513 patients, adjusted sub-distribution HR 1·68; 95% CI 1·21–2·32, p=0·0018) and high-risk categories (72 [26%] of 380 patients, 2·97; 1·50–5·89, p=0·0018) on the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria were associated with an increased relative incidence of recurrent intracerebral haemorrhage compared to the low-risk category (45 [12%] of 727 patients; table 2), which were consistent in cause-specific hazard models. These associations remained similar in a post-hoc sensitivity analysis excluding the CT-small vessel disease variable (appendix p 36).

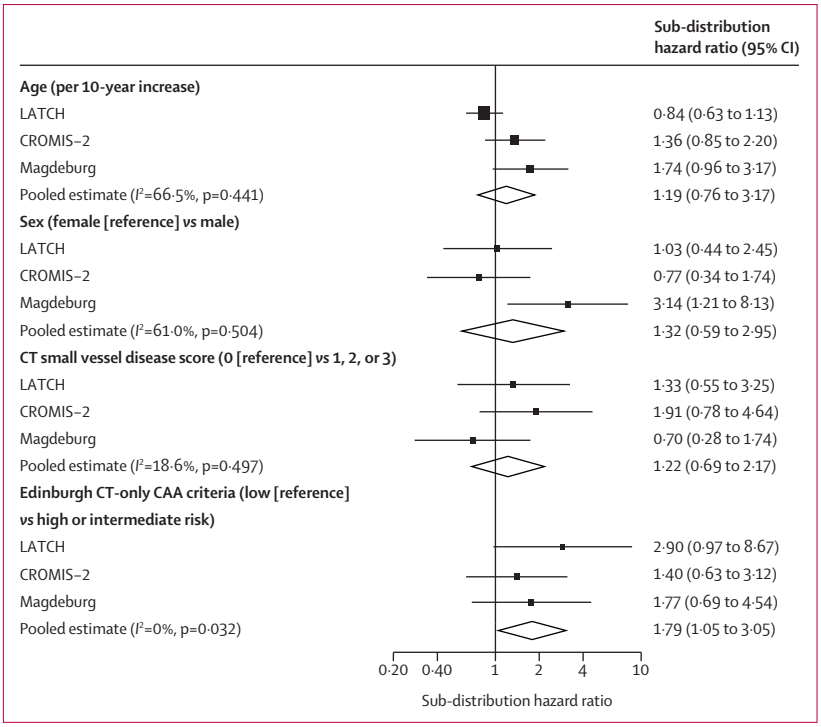

Figure 1: **Forest plot of relative incidence of recurrent intracerebral haemorrhage by age, sex, CT cerebral small vessel disease score, and Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria category**
CAA=cerebral amyloid angiopathy. CROMIS-2=The Clinical Relevance of Microbleeds in Stroke study. LATCH=The Lothian Audit for the Treatment of Cerebral Haemorrhage.

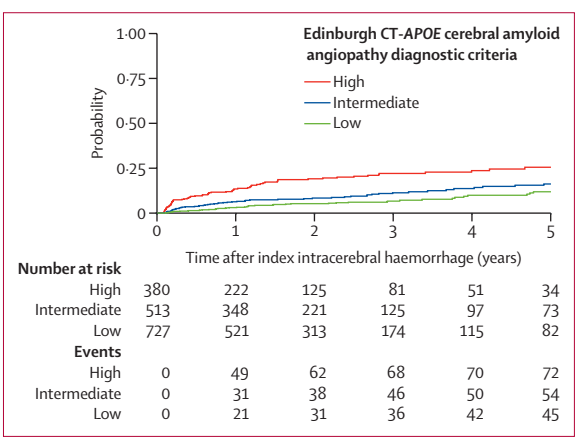

Figure 2: **Cumulative incidence of recurrent intracerebral haemorrhage stratified by Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria category**

	Sub-distribution hazard model				Cause-specific hazard model			
	Recurrent intracerebral haemorrhage		Death		Recurrent intracerebral haemorrhage		Death	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (per 10-year increase)	1·13 (0·97–1·31)	p=0·12	1·71 (1·47–2·00)	p<0·0001	1·21 (1·07–1·37)	p=0·0029	1·72 (1·46–2·03)	p<0·0001
Sex								
Female	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Male	1·20 (0·97–1·48)	p=0·10	1·08 (0·95–1·24)	p=0·24	1·21 (0·97–1·52)	p=0·088	1·11 (0·95–1·29)	p=0·21
History of intracerebral haemorrhage								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	2·99 (2·05–4·37)	p<0·0001	1·17 (0·84–1·63)	p=0·36	3·16 (2·10–4·75)	p<0·0001	1·36 (0·98–1·90)	p=0·068
History of dementia								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	1·04 (0·64–1·70)	p=0·87	1·63 (1·22–2·17)	p=0·0009	1·19 (0·74–1·90)	p=0·474	1·70 (1·34–2·16)	p<0·0001
History of hypertension								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	0·99 (0·60–1·62)	p=0·95	1·01 (0·68–1·49)	p=0·97	1·01 (0·64–1·59)	p=0·98	1·03 (0·72–1·48)	p=0·86
CT cerebral small vessel disease score								
0	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
1, 2, 3	1·56 (0·92–2·65)	p=0·10	1·20 (0·98–1·46)	p=0·075	1·57 (0·95–2·61)	p=0·079	1·25 (1·01–1·53)	p=0·039
Edinburgh CT-only CAA criteria								
Low risk	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Intermediate risk	1·68 (1·21–2·32)	p=0·0018	1·08 (0·93–1·26)	p=0·30	1·74 (1·24–2·44)	p=0·0014	1·13 (0·98–1·31)	p=0·10
High risk	2·97 (1·50–5·89)	p=0·0018	1·15 (0·80–1·64)	p=0·45	3·10 (1·62–5·96)	p=0·0007	1·34 (1·04–1·73)	p=0·021

Data are hazard ratio (95% CI) adjusted for cohort clustering. CAA=cerebral amyloid angiopathy.

Table 2: **Multivariable sub-distribution and cause-specific hazard models for recurrent intracerebral haemorrhage and death in the secondary Edinburgh CT-only criteria one-stage (pooled) meta-analysis**

In a post-hoc one-stage (pooled) multivariable regression analysis, the combined intermediate-risk and high-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria had an adjusted sub-distribution HR of 2·23 (95% CI 1·37–3·64, p=0·0013) relative to the low-risk category (appendix p 37).

In a separate prespecified one-stage (pooled) multivariable regression model including the individual components of the Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria, the presence of subarachnoid haemorrhage was associated with an increased relative incidence of recurrent intracerebral haemorrhage (108 [22%] of 694 patients with subarachnoid haemorrhage *vs* 63 [12%] of 926 patients without subarachnoid haemorrhage, adjusted sub-distribution HR 1·92; 95% CI 1·38–2·67, p=0·0001) while there was no evidence of an association with the presence of finger-like projections (90 [22%] of 579 patients with finger-like projections *vs* 81 [14%] of 1041 patients without finger-like projections, adjusted sub-distribution HR 1·56; 0·95–2·59, p=0·082; appendix p 38).

Six cohorts from the UK, Germany, Italy, and the USA contributed data to the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria study (appendix pp 39–40). Most cohorts had a moderate or high risk of bias for study participation due to large numbers of patients with missing *APOE* data resulting in selection bias. Many studies were also retrospective (appendix pp 7–8). All had moderate risk for study confounding as data on blood pressure control during follow-up were not available.

Only one cohort (CROMIS-2) had enough outcomes to permit multivariable regression. Therefore, we did not perform statistical analyses in individual cohorts.

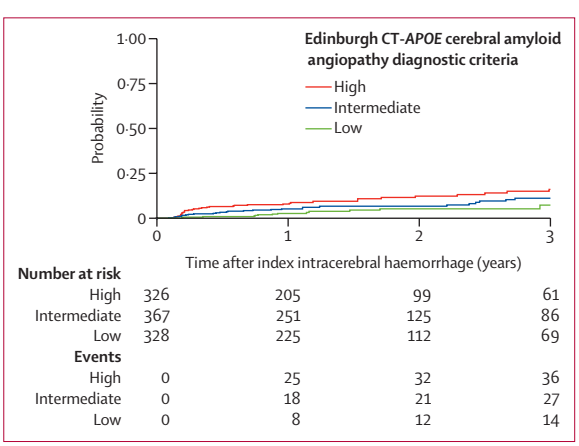

Figure 3: **Cumulative incidence of recurrent intracerebral haemorrhage stratified by Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria category**

The six cohorts included 1021 patients with either first-ever or recurrent intracerebral haemorrhage as the index event, *APOE* genotyping, and complete key baseline and outcome data (appendix pp 41–44). Median age was 71 years (IQR 59–79). 537 (53%) of 1021 patients were male and 484 (47%) were female. During a total follow-up of 1528 person-years (median 1·11 years, IQR 0·96–2·62), 77 patients had a recurrent intracerebral haemorrhage and 133 died from causes other than recurrent intracerebral haemorrhage.

The 3-year cumulative incidence rate for recurrent intracerebral haemorrhage increased with increasing risk of cerebral amyloid angiopathy according to the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic categories (low risk 7·3%, 95% CI 3·9–12·2%; intermediate risk 11·1%, 7·2–16·0; high risk 16·1%, 11·0–22·0; p=0·0035, figure 3; appendix pp 45–46). The presence of subarachnoid haemorrhage, finger-like projections, history of intracerebral haemorrhage, history of dementia, CT small vessel disease score 1–3, and *APOE* ε2 allele possession were associated with a higher 3-year cumulative incidence rate for recurrent intracerebral haemorrhage in univariate analyses (appendix p 45).

We included 1006 patients in the prespecified secondary one-stage (pooled) multivariable regression analyses after excluding 15 patients with missing baseline data (appendix pp 47–48). Median age was 71 years (IQR 58–79). 529 (53%) of 1006 patients were male and 477 (47%) were female. During a total follow-up of 1495 person-years (median 1·11, IQR 0·96–2·61), 74 patients had a recurrent intracerebral haemorrhage and 132 died.

The high-risk Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic category was associated with an increased relative incidence of recurrent intracerebral haemorrhage compared with the low-risk category (34 [15%] of 320 patients versus 14 [8%] of 322 patients, adjusted sub-distribution HR 2·22; 95% CI 1·36–3·61, p=0·0014), whereas there was only very weak evidence to support an association between intermediate-risk and recurrent intracerebral haemorrhage (28 [8%] of 334 patients, adjusted sub-distribution HR 1·63 0·98–2·70; p=0·059. table 3), which were consistent in cause-specific hazard models.

In a separate pooled multivariable regression model assessing the individual components of the Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria, the presence of subarachnoid haemorrhage was

	Sub-distribution hazard model				Cause-specific hazard model			
	Recurrent intracerebral haemorrhage		Death		Recurrent intracerebral haemorrhage		Death	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (per 10-year increase)	1·09 (0·91–1·30)	p=0·35	1·77 (1·21–2·59)	p=0·0032	1·11 (0·93–1·32)	p=0·24	1·75 (1·19–2·57)	p=0·0042
Sex								
Female	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Male	1·11 (0·67–1·84)	p=0·69	0·92 (0·75–1·14)	p=0·47	1·06 (0·63–1·77)	p=0·83	0·91 (0·71–1·16)	p=0·43
History of intracerebral haemorrhage								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	2·98 (1·92–4·61)	p<0·0001	1·36 (0·86–2·16)	p=0·19	3·06 (2·10–4·56)	p<0·0001	1·57 (1·00–2·47)	p=0·052
History of dementia								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	1·48 (0·94–2·33)	p=0·091	1·40 (1·01–1·94)	p=0·041	1·54 (0·99–2·40)	p=0·054	1·44 (1·06–1·97)	p=0·019
History of hypertension								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	0·96 (0·53–1·74)	p=0·90	1·58 (0·80–3·12)	p=0·19	1·01 (0·57–1·81)	p=0·96	1·60 (0·81–3·15)	p=0·18
APOE ε2 possession								
No	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Yes	1·92 (1·48–2·48)	p<0·0001	0·77 (0·65–0·92)	p=0·0038	1·85 (1·46–2·35)	p<0·0001	0·78 (0·66–0·93)	p=0·0042
CT small vessel disease score								
0	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
1, 2, 3	2·08 (1·12–3·86)	p=0·021	1·26 (0·97–1·63)	p=0·085	2·16 (1·19–3·94)	p=0·012	1·33 (1·04–1·70)	p=0·021
Edinburgh CT-*APOE* CAA criteria								
Low risk	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..	1·00 (reference)	..
Intermediate risk	1·63 (0·98–2·70)	p=0·059	0·82 (0·66–1·01)	p=0·062	1·58 (0·92–2·70)	p=0·094	0·84 (0·68–1·03)	p=0·096
High risk	2·22 (1·36–3·61)	p=0·0014	0·94 (0·62–1·41)	p=0·75	2·15 (1·30–3·57)	p=0·0030	1·00 (0·70–1·41)	p=0·99

Data are also adjusted for cohort clustering. CAA=cerebral amyloid angiopathy.

Table 3: **Multivariable sub-distribution and cause-specific hazard models for recurrent intracerebral haemorrhage and death in the secondary Edinburgh CT-*APOE* criteria one-stage (pooled) meta-analysis**

associated with an increased relative incidence of recurrent intracerebral haemorrhage (44 [15%] of 429 patients *vs* 30 [8%] of 577 patients, adjusted sub-distribution HR 1·42; 95% CI 1·11–1·82, p=0·0061), finger-like projections had only very weak evidence of an association (32 [15%] of 329 patients *vs* 42 [10%] of 684 patients, adjusted sub-distribution HR 1·45; 95% CI 0·99–2·13, p=0·057) and *APOE* ε4 allele possession was not associated with an increased relative incidence of recurrent intracerebral haemorrhage (30 [13%] of 342 patients *vs* 44 [11%] of 664, adjusted sub-distribution HR 1·21; 0·78–1·90, p=0·40; appendix p 49).

In both pooled multivariable models *APOE* ε2 allele possession was independently associated with an increased relative incidence of recurrent intracerebral haemorrhage (27 [20%] of 206 patients *vs* 47 [8%] of 800 patients, table 3; appendix p 49).

We assessed the added value of including *APOE* genotype by comparing nested models post hoc (appendix p 51–54). The addition of *APOE* ε4 allele possession did not significantly improve the sub-distribution (p=0·79) or cause-specific (p=0·83) hazard models above the base models that included subarachnoid haemorrhage and finger-like projections, nor the base models that also included *APOE* ε2 allele possession (sub-distribution hazard (p=0·73) or cause-specific hazard (p=0·78) models). The addition of *APOE* ε4 allele possession into the cause specific hazard models did not improve model discrimination or calibration (appendix pp 51–54).

Discussion

In survivors of lobar intracerebral haemorrhage, intermediate-risk or high-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria were associated with an increased relative incidence of recurrent intracerebral haemorrhage compared with the low-risk criteria over 5-year follow up, and this hazard was highest for high risk of cerebral amyloid angiopathy. We found that the high-risk Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic category was associated with an increased relative incidence and cause-specific hazard of recurrent intracerebral haemorrhage compared with the low-risk category.

The association between the intermediate-risk and high-risk Edinburgh CT-only cerebral amyloid angiopathy diagnostic criteria and high-risk Edinburgh CT-*APOE* cerebral amyloid angiopathy diagnostic criteria and recurrent intracerebral haemorrhage is consistent with previous MRI studies that showed survivors of lobar intracerebral haemorrhage with MRI biomarkers of cerebral amyloid angiopathy have a greater risk of recurrent intracerebral haemorrhage than those without these biomarkers.[6,7] The intermediate-risk and high-risk Edinburgh cerebral amyloid angiopathy diagnostic criteria were associated with increasing frequency of moderate to severe cerebral amyloid angiopathy on research autopsy in the derivation study,[4] which probably accounts for the greater risk of recurrent intracerebral haemorrhage in these patients. Furthermore, these dose-dependent prognostic associations of the intermediate-risk and high-risk criteria add construct validity to the Edinburgh cerebral amyloid angiopathy diagnostic criteria in survivors of lobar intracerebral haemorrhage, who were younger and with smaller and less severe intracerebral haemorrhages than those who died before inclusion in the derivation study.[4]

The CT-only and CT-*APOE* criteria secondary analyses showed a consistent independent association between the presence of subarachnoid haemorrhage on CT and the relative incidence and cause-specific hazard of recurrent intracerebral haemorrhage, after adjusting for important confounders such as age and *APOE* genotype. This finding is consistent with the previous smaller studies assessing convexity subarachnoid haemorrhage and recurrent intracerebral haemorrhage risk.[10–13,16] It also supports the MRI studies showing a strong independent association between cortical superficial siderosis, which is thought to represent the chronic breakdown of acute convexity subarachnoid haemorrhage in cerebral amyloid angiopathy,[31] and recurrent intracerebral haemorrhage risk.[6,7]

Finger-like projections from the intracerebral haematoma showed only very weak evidence of an association with relative incidence and cause-specific hazard of recurrent intracerebral haemorrhage in both the Edinburgh CT-only and CT-*APOE* diagnostic criteria secondary analyses, which probably reflects the limited power of the studies. The presence of finger-like projections appears to have an additive predictive effect with subarachnoid haemorrhage given the dose-dependent association of intermediate-risk and high-risk Edinburgh CT-only criteria and recurrent intracerebral haemorrhage, which is consistent with a smaller published study.[16]

APOE ε2 was independently associated with recurrent intracerebral haemorrhage in the CT-*APOE* diagnostic criteria secondary analyses, whereas no association was found with *APOE* ε4. Indeed, the inclusion of *APOE* ε4 did not improve model performance. *APOE* ε2 has been associated with increased lobar intracerebral haemorrhage severity,[32] possibly mediated through more severe vasculopathy in cerebral amyloid angiopathy.[33] The associations of *APOE* ε2 and ε4 with recurrent intracerebral haemorrhage have varied in previous studies, which might reflect methods of adjustment and study power.[14,15] Further research in larger sample sizes is needed to clarify the association of *APOE* alleles and recurrent intracerebral haemorrhage.

This study's strengths include the use of data from several intracerebral haemorrhage cohorts from Europe and the USA, which increases generalisability. To minimise information bias, we used standardised definitions for baseline data and outcomes. Collaborators

underwent specific training for rating the Edinburgh criteria and rated the diagnostic non-contrast brain CT scans using a standardised proforma, blinded to baseline data and outcome information. We adjusted for the substantial competing risk of death in our time-to-event analyses and did pre-specified primary and secondary analyses.

However, our study has some limitations. All patients were from European or North American intracerebral haemorrhage cohorts, which limits the generalisability of the results to other geographical regions, such as low-income and middle-income countries. However, a Chinese study found that the risk of recurrent intracerebral haemorrhage is associated with subarachnoid haemorrhage, and this risk is greater still if there are also finger-like projections.[16] The number of outcomes in individual cohorts was modest, especially in the CT-*APOE* study, which limited the number of cohorts that could be included in the primary analyses and the number of variables included in those models. However, the prespecified secondary one-stage (pooled) individual patient data meta-analyses allowed us to maximise the power and adjust for more potential confounders. The prespecified multivariable analyses might be over-adjusted, which could result in an underestimation of the magnitude of associations (appendix p 50). Post-hoc sensitivity analyses excluding the CT small vessel disease burden score were in the same direction and had similar magnitude and statistical significance as the prespecified models including CT-small vessel disease score. We were unable to adjust for some key confounders of recurrent intracerebral haemorrhage, such as blood pressure control and antithrombotic drug use during follow-up because accurate data on these were not available. In some cohorts, *APOE* genotyping was not offered to all patients and the decision to do it might have been influenced by patient factors or imaging findings, resulting in selection bias. There were methodological differences between the cohorts. For example, we did not have central formal adjudication of outcome events, although we used standardised outcome definitions to help mitigate this effect. Non-contrast CT brain scans were assessed independently by collaborators in each cohort. There was no assessment of inter-rater agreement, which might account for differences in the frequency of CT-based variables between the cohorts. We tried to minimise the effect of this approach using standardised CT rating training tools and data collection proformas. Nonetheless, this approach reflects real world practice, making the results more generalisable. There were differences in baseline clinical characteristics and outcome events between the cohorts, which probably reflects underlying differences in cohort populations and study design. We used two-stage (cohort level) meta-analysis using a random effects model to assess the relative risk separately in each cohort to help account for the differences in absolute risks between cohorts. The use of a 30-day landmark period might have introduced a selection bias if cerebral amyloid angiopathy severity influences early mortality; however, we wanted to minimise the impact of the high early competing risk of death.[18] The association between the Edinburgh criteria and recurrent intracerebral haemorrhage might be greater if we had included these patients given the early increased risk of recurrent intracerebral haemorrhage in patients with MRI biomarkers of cerebral amyloid angiopathy.[34] Modelling survival analysis in the presence of competing events, such as death, is difficult. Traditional approaches to time-to-event analysis, such as the Kaplan–Meier method and the Cox proportional hazards model, assume that competing events are absent and result in misestimation of the magnitude of relative effects of predictors on incidence of the event. The competing risk models we used help to address this but provide less intuitive causal interpretation because they reflect both indirect effects through the competing event (death) and the direct effect on the primary outcome (recurrent intracerebral haemorrhage). The Fine-Gray model assumes censoring is independent of both the primary outcome and the competing event, which might not be true across all cohorts. Also, they are limited to first events and ignore subsequent events. Multistate models can accommodate multiple transitions between difference states, such as multiple recurrent intracerebral haemorrhages, allowing better modelling of the disease trajectory and dynamic risks overtime, but the necessary detailed longitudinal data were not available. These data would be particularly valuable given the temporal changes in recurrent intracerebral haemorrhage rate in patients with cerebral amyloid angiopathy biomarkers, which appears highest in the first months after the index intracerebral haemorrhage (figure 2).[34]

The main implication of our findings for clinical practice is that two simple CT features can help predict the incidence of recurrent intracerebral haemorrhage for survivors of lobar intracerebral haemorrhage and identify a high-risk group for targeted secondary prevention with blood pressure lowering. This might be particularly useful in parts of the world in which MRI is scarce, or unavailable, and has the advantage of basing prediction on the diagnostic CT, without the need for further imaging resulting in financial and environmental benefits.

Further research is needed to validate our findings in other cohorts, particularly in middle-income and low-income countries. Future studies could adjust for time-dependent covariates, such as blood pressure control and antithrombotic drug use during follow-up. Comparison of the rate of recurrent haemorrhage between the Edinburgh cerebral amyloid angiopathy criteria for lobar intracerebral haemorrhage and deep intracerebral haemorrhage would be of interest. Comparison of the prognostic value of the Edinburgh cerebral amyloid angiopathy criteria against the Boston

criteria[9] for recurrent intracerebral haemorrhage risk would be valuable. The Edinburgh cerebral amyloid angiopathy criteria could also be used in randomised controlled trials to use a statistically efficient approach to explore heterogeneity of treatment effect according to predicted risk of recurrent intracerebral haemorrhage,[35] as was done in RESTART.[36]

In summary, in our international, multicentre, patient-level meta-analysis of lobar intracerebral haemorrhage survivors, we have shown that the Edinburgh CT-only and CT-*APOE* cerebral amyloid angiopathy diagnostic criteria are associated with recurrent intracerebral haemorrhage.

Contributors

MAR, DS, DJW, and RASS conceived the study. MAR and RASS wrote the protocol with input from DS and DJW. TJM did the literature search. MAR, DS, NS, TJM, JMW, SS, TPB, VK, RJS, VV, DW, MZ, RP, AC, AW, SMG, SE, TG, BC, CC, DJW, and RASS provided or curated the data, or both. MAR and RASS accessed and verified the data. MAR performed the statistical analysis with input from DS, DJW, and RASS. MAR and RASS wrote the original draft of the manuscript, and all coauthors subsequently reviewed the manuscript and provided comments. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MAR reports a grant paid to their institution from The Wellcome Trust. DS reports grants from the Swiss Medical Science Foundation and Bangerter-Rhyner Foundation. TJM reports grants paid to their institution from the Chief Scientist Office, Scotland, and Scottish Heart and Arterial Risk Prevention. JMW reports grants paid to their institution from UK Dementia Research Institute funded by UK Medical Research Council, Alzheimer's Society, and Alzheimer's Research UK. RJS reports a grant paid to their institution from the National Institutes for Health (NIH). DW reports a grant paid to their institution from NIH. TG reports a grant paid to their institution from the Austrian Science Fund. BC reports grants from Regional GIRCI Méditerranée funding, Nice University Hospital, Acticor Biotech, Bayer, and Agence Nationale de la Recherche; honoraria from ACTICOR Biotech, University of Bern, Sanofi-Aventis France, and AMGEN; and support from European Stroke Organisation, French Neurovascular Society, Belgium Stroke Council, and French Neurology Society for attending meetings. CC reports grants from the French Ministry of Health and Agence Nationale de la Recherche and is on the International Trial Steering committee (ongoing) for Biogen (CHARM trial) and International Trial Steering committee (ongoing) for Bayer (Oceanic Stroke trial). DJW reports consulting fees from NovoNordisk, National Institute for Health and Clinical Excellence, and Alnylam; honoraria from NovoNordisk, Bayer, and AstraZeneca; participation on OXHARP trial data safety monitoring board; participation on MACE-ICH and PLINTH Steering Committee Chairs; and is President of British and Irish Association of Stroke Physicians. RASS reports grants paid to their institution from the Medical Research Council, The Stroke Association, British Heart Foundation Clinical Study Grant and Chief Scientist Office Health Improvement, Protection and Services Research Committee Project Grant; consulting fees paid to their institution from Recursion Pharmaceuticals; honoraria paid to their institution from European Stroke Masters (European Stroke Organisation); participation on Novo Nordisk NN9931-4553 and NN9931-4554 endpoint adjudication committee; and is clinical director of UK Clinical Research Collaboration network of registered Clinical Trials Units. NS, SS, TPB, VK, MZ, RP, AC, AW, SMG, SE declare no competing interests.

Data sharing

Contributing studies shared data on the condition that the data recipient (University of Edinburgh) shall not sub-license, transfer, disclose, or otherwise make available the data in whole or part to any third party except with specific previous written consent from the data provider. Written proposals will be assessed by representatives of the contributing studies and a decision made about the appropriateness of re-use of data. A data-sharing agreement will be put in place before any data are shared. Please contact the corresponding author about data access.

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