1 **TITLE**

2 **Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic**
3 **attack: a pooled analysis of individual patient data from cohort studies**

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SUMMARY

Background Cerebral microbleeds (CMBs) are a neuroimaging biomarker ('biological marker') of stroke risk. A crucial clinical question is whether CMBs identify patients with recent ischaemic stroke or TIA in whom the risk of future intracranial haemorrhage exceeds that of recurrent ischaemic stroke when treated with antithrombotic drugs. We therefore aimed to determine whether a large burden of CMBs, or particular anatomical patterns, can identify ischaemic stroke or TIA patients at higher absolute risk of intracranial haemorrhage than ischaemic stroke.

Methods In a pooled analysis of individual patient data from cohort studies in adults with recent ischaemic stroke or TIA, we determined associations of baseline CMBs with stroke risks using multivariable Cox regression, adjusted for pre-specified prognostic variables. We registered this study (CRD42016036602).

Findings Among 20,322 patients from 38 cohorts (over 35,225 patient-years [median 1·98 years] follow-up), CMBs were associated with the composite risk of intracranial haemorrhage and ischaemic stroke (adjusted hazard ratio[aHR], 95%CI 1·39, 1·24-1·56), intracranial haemorrhage (2·56, 1·89-3·47), and ischaemic stroke (1·27, 1·10-1·45). As CMB burden increased, there was a greater increase in the aHR for intracranial haemorrhage than for ischaemic stroke (for ≥5 CMBs, aHR 4·55[3·08-6·72] vs. 1·47[1·19-1·80]; for ≥10 CMBs, aHR 5·52[3·36-6·72] vs. 1·43[1·07-1·91]; for ≥20 CMBs, aHR 8·61[4·69-15·81] vs. 1·86[1·23-1·82], respectively). Even with high CMB burden, the absolute rate of ischaemic stroke exceeded that of intracranial haemorrhage (for ≥10 CMBs, rate 64[48-84] per 1000 patient-years vs. 27[17-41] per 1000 patient-years, respectively; for ≥20 CMBs, rate 73[46-108] per 1000 patient-years vs. 39[21-67] per 1000 patient-years, respectively). Hazard ratios for all outcomes were similar

regardless of CMB anatomical distribution. Similar patterns were seen in patients taking antiplatelet drugs or oral anticoagulants.

Interpretation In patients with recent ischaemic stroke or TIA, CMBs are associated with a greater aHR for intracranial haemorrhage than for ischaemic stroke, but the absolute risk of ischaemic stroke is consistently higher than that of intracranial haemorrhage; CMB presence, burden or distribution do not identify patients at higher absolute risk of intracranial haemorrhage than recurrent ischaemic stroke.

Funding

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RESEARCH IN CONTEXT

Evidence before this study

We searched Medline and EMBASE (search strategy: cerebral adj2 micro* OR CMB OR microbleed.mp AND [stroke.mp OR stroke/ OR intracerebral h?emorr* OR intracranial h?emorr* OR isch?emic stroke OR isch?emic infarct*]). An aggregate level meta-analysis (n=5068) showed that CMBs were associated with both intracranial haemorrhage (risk ratio [RR] 3.8, 95% CI 3.5-11.4) and ischaemic stroke (RR 1.8, 95% CI 1.4-2.5); this pooled analysis, and another recent study in two cohorts (one mainly Chinese [n=1003], the other mainly white Caucasian [n=1080]) reported that five or more CMBs were associated with similar absolute risks of intracranial haemorrhage and ischaemic stroke. However, limited sample sizes and intracranial haemorrhage outcome events in previous studies did not provide enough statistical power and precision to determine whether a large CMB burden or distribution pattern is associated with a higher absolute risk of intracranial haemorrhage than ischaemic stroke in patients with recent ischaemic stroke or TIA treated with antithrombotic drugs.

Added value of this study

Our pooled analysis of individual data from 20,322 patients with recent ischaemic stroke or TIA confirms that CMBs are associated with a higher adjusted hazard ratio (aHR) for intracranial haemorrhage than ischaemic stroke; with increasing CMB burden the aHR for intracranial haemorrhage rises more steeply than that of ischaemic stroke. Regardless of the number or distribution of CMBs, or the type of antithrombotic treatment received (antiplatelet drugs or oral anticoagulants), the absolute rate of ischaemic stroke substantially exceeded that of intracranial haemorrhage.

Implications of all the available evidence

Although CMBs can inform hazard for intracranial haemorrhage in patients with recent ischaemic stroke or TIA treated with antithrombotic drugs, the absolute risk of ischaemic stroke is consistently much higher than that of intracranial haemorrhage, regardless of CMB presence, burden, or pattern.

INTRODUCTION

A central challenge in stroke prevention after ischaemic stroke or TIA is to predict the risk of intracranial haemorrhage, and to differentiate this from the risk of recurrent ischaemic stroke, in patients treated with antithrombotic therapy - usually antiplatelet agents or, in patients with atrial fibrillation, oral anticoagulants (OAC)[1]. Cerebral microbleeds (CMBs) are a radiological finding of small (<10mm), hypointense (black) ovoid or rounded regions on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI)[2]. CMBs mostly correspond pathologically to haemosiderin-laden macrophages close to arterioles affected by small vessel diseases[3,4]; strictly lobar CMBs suggest cerebral amyloid angiopathy (CAA), while deep or mixed patterns probably indicate arteriolosclerosis or mixed pathologies, respectively[5-8]. It is hypothesised that CMBs result from red blood cell leakage from arterioles and capillaries, raising clinical concerns that they herald an increased risk of potentially devastating intracranial haemorrhage, particularly in patients treated with antithrombotic drugs[9]. However, CMBs signal small vessel diseases that can also cause ischaemic stroke, and might result from non-haemorrhagic mechanisms[10-13]. In ischaemic stroke cohorts, CMBs are associated with the risks of both subsequent intracranial haemorrhage and recurrent ischemic stroke[14-28]. As the number of CMBs increases, the risk of intracranial haemorrhage seems to rise more steeply than that of ischaemic stroke, and ≥5 CMBs have been reported to be associated with similar absolute risks of intracranial haemorrhage and ischaemic stroke [28,29].

Because previous studies had limited sample sizes and few intracranial haemorrhage outcome events, they could not reliably answer the crucial clinical question of whether many CMBs, or particular CMB patterns, predict a higher risk of intracranial haemorrhage than recurrent ischaemic stroke. We established the Microbleeds International Collaborative Network[30] to undertake large-scaled pooled analyses of prospective observational cohort

studies. We tested the hypothesis that a large burden of CMBs, or particular anatomical patterns, can identify ischaemic stroke or TIA patients at higher absolute risk of intracranial haemorrhage than ischaemic stroke.

METHODS

The Microbleeds International Collaborative Network protocol and statistical analysis plan were registered with PROSPERO on 5th April 2016 (36602) (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=36602).

Study design and participants

We identified cohorts by searching Medline and EMBASE (search strategy: cerebral adj2 micro* OR CMB OR microbleed.mp AND stroke.mp OR stroke/ OR intracerebral h?emorr* OR intracranial h?emorr* OR isch?emic stroke OR isch?emic infarct*), clinical trial databases (clinicaltrials.gov, strokecenter.org), and scientific meeting abstracts. We invited members of METACOHORTS[31]; an international database of over 90 studies in small vessel disease, including 660,000 patients. Two authors (DW and DJW) independently did the search and reviewed all titles and abstracts; DW and DJW also did an independent risk of bias assessment for all included studies. Cohorts were eligible for inclusion if they: prospectively recruited adult participants with ischaemic stroke or TIA; included at least 50 participants; collected data on stroke events over at least three months follow up; used an appropriate MRI sequence sensitive to magnetic susceptibility (GRE or SWI); and documented the number and distribution of CMBs reliably using consensus criteria and validated scales. Each patient was only included in one cohort.

Risk of bias and study quality

We assessed all studies for risk of bias (including selection bias) and quality using the Cochrane Collaboration tool[32].

Ethical approval

All cohorts obtained ethical approval as required by local regulations to allow data sharing. All data reviewed by the co-ordinating centre was fully anonymised. The project was approved by the Health Research Authority United Kingdom (REC reference: 8/HRA/0188).

Outcome events

Our pre-specified primary outcome events were: a composite of any symptomatic intracranial haemorrhage (confirmed radiologically, including subdural, extradural and subarachnoid haemorrhage, and excluding intracranial haemorrhages attributed to intravenous thrombolysis or trauma) or ischaemic stroke (acute or subacute neurological symptoms lasting >24 h, and attributed to cerebral ischaemia, diagnosed clinically, with or without radiological confirmation); symptomatic intracranial haemorrhage; and symptomatic ischaemic stroke. Secondary outcome events were death (all cause) and vascular death. All events were adjudicated according to individual cohort protocols.

Statistical analysis

As per our prespecified protocol, a single dataset was created by combining individual participant data from the 38 cohorts. We compared baseline demographic and risk factor

profiles between patients with and without CMBs, and between patients with and without outcome events, using the Mann-Whitney test if not normally distributed, or the t-test if normally distributed; we compared categorical variables between groups with the Chi-squared test or Fisher's exact test. We censored patients at the last available follow-up (truncated to five years) or at the time of the pre-specified outcome. In instances where patient had multiple events of the same type, we censored follow up at the first event. We calculated absolute event rates per 1000 patient-years for primary outcomes in patients with and without CMBs. We assessed the proportional hazards assumption through visual inspection of (log-log) plots of log cumulative hazard against time and tested for a non-zero slope in a regression of scaled Schoenfeld residuals against time. We calculated univariate Kaplan-Meier survival probabilities in patients with and without CMBs to estimate event rates, and used the log-rank test to compare groups. We performed multivariable Cox regression adjusting for the following prognostic and confounding variables (selected by consensus, based upon availability, biological plausibility and known associations with CMBs and outcomes): age; sex; presentation with TIA or ischaemic stroke; history of hypertension; previous stroke; known atrial fibrillation; antithrombotic use after index event; and type of MRI sequence used to detect CMBs [T2*-weighted GRE, or SWI]). We investigated the effect of predefined CMB burden categories (1, 2-4, ≥5, ≥10 and ≥20). When investigating CMB distribution, we adjusted for total CMB number. We added a shared frailty term[33] to account for patients being nested in individual studies (thus potentially having correlated data). We performed sub-analyses for patients treated with OAC and antiplatelet drugs and added interaction terms between antithrombotic therapy and CMB presence. We categorised ethnicity (when available) as White Caucasian or Asian (Japanese, Chinese, Malays, Indian, Pakistani, Korean) to investigate the interaction between ethnicity and CMB presence. We performed two pre-specified sensitivity analyses: first, exploring time-varying risks within the Cox model to investigate later events

(beyond the first year) accounting for death as a competing risk (using the Fine-Gray subdistribution hazard model), calculating subdistribution hazard ratios (SHR); and second, a two-stage individual patient meta-analysis to quantify between-study heterogeneity using the inverse-variance method (which fits a separate survival model for each cohort, then pools and displays estimates in a forest plot). We performed three post-hoc analysis: first adding white matter hyperintensities (WMH; another common marker of cerebral small vessel disease, rated using the Fazekas scale[34] and considered severe if ≥2 in the periventricular or deep white matter) into our multivariable model; second, including only intracerebral haemorrhage, convexity subarachnoid haemorrhage and subdural haemorrhage, as these bleeding events are the most likely to be associated with CMBs; and third, investigating the interaction between CMB and age, dichotomised as less than or greater than 80 years. If a variable was not sufficiently available across all cohorts for the final multivariable model, it was excluded. In sensitivity analyses, if a variable of interest was not sufficiently available in a cohort, the cohort was excluded. We undertook all statistical analysis using STATA version 15 (StataCorp LP, TX).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis or data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We included 20,322 participants from 38 cohorts including 23 published studies and 15 unpublished studies (study flow chart shown in figure 1; demographics, risk factors and outcome events for each cohort are shown in table 1). Although more than one-half of participants and outcome events came from the six largest cohorts, there was no major risk of bias for any included cohort (appendix table 1). The mean age was 70 years (SD 13); 8593 (42%) were female. CMBs were present in 5649 (28%) of patients (characteristics shown in appendix table 2), including 2,145 (12%) with 1 CMB, 1,990 (10%) with 2-4 CMB, and 1,244 (6%) with ≥5 CMBs. Over 35,225 patient-years of follow-up (median 1.34 years, IQR 0.19 to 2.44), there were 1,474 composite events: 189 intracranial haemorrhages; 1,113 ischaemic strokes; and 172 composite events of unknown type from one cohort (total n=3,355 participants) that did not subclassify composite outcomes as intracranial haemorrhage or ischaemic stroke. Characteristics between patients with and without events are presented in the appendix tables 2 to 4. Visual assessment of the log-log plots and the results of testing the Schoenfeld residuals suggest that the proportional hazards assumption was not violated in any of the following analyses.

Survival estimates according to baseline CMBs

The composite of any intracranial haemorrhage or ischaemic stroke ($p<0{\cdot}0001$; log-rank test), symptomatic intracranial haemorrhage ($p<0{\cdot}0001$) and symptomatic ischaemic stroke ($p<0{\cdot}0001$) were more frequent in patients with CMBs compared to those without. Kaplan-Meier curves for CMB presence and burden categories are shown in figure 2, and for different CMB distributions in the appendix figure 1.

Multivariable Cox regression for outcome events according to CMB presence, burden and distribution

Composite of ischaemic stroke and intracranial haemorrhage

1,461 of 20,332 patients had 1,474 composite outcome events during 35,225 patient-years of follow up. The incidence of all composite events in patients with any CMB was 59 per 1000 patient-years (95% CI 54-64) compared to 35 per 1000 patient-years (95% CI 33-38) in those without CMBs, an absolute increased incidence of 24 outcomes per 1000 patient-years. Table 2 shows the incidence of a composite event for each CMB burden and distribution category. The risk of a composite event was 1·35 (95% CI 1·20-1·50) times higher for patients with CMBs than those without and rose with increasing CMB burden (table 2), p trend <0.0001). Mixed, deep, lobar, and strictly lobar CMBs were associated with similar hazards (table 2).

Intracranial haemorrhage

189 patients had a symptomatic intracranial haemorrhage during 32,847 patient-years of follow up (151 intracerebral haemorrhages, 31 subdural haemorrhages, 8 subarachnoid haemorrhages [4 cortical], and 3 extradural haemorrhages; 4 patients had more than 1 type of intracranial haemorrhage). The incidence of intracranial haemorrhage was 12 per 1000 patient-years (95% CI 10-14) in those with CMBs compared to 4 per 1000 patient-years (95% CI 3-5) in those without CMBs, an absolute increased incidence of 8 intracranial haemorrhages per 1000 patient-years. Table 2 shows the incidence of intracranial haemorrhage for each CMB burden and distribution category. The risk of symptomatic intracranial haemorrhage was 2·45 (95% CI 1·82-3·29) times higher for patients with CMBs than patients without CMBs and rose with

increasing CMB burden (table 2), p trend <0.0001. The presence of mixed, deep, and lobar CMBs were associated with similar hazards (table 2). Patients with multiple strictly lobar CMBs (fulfilling the Boston criteria[5] for probable CAA) did not have a significantly higher risk for symptomatic intracranial haemorrhage than those without (HR 1·29, 95% CI 0·60-2·77) (Table 2). There was no interaction between CMBs and antiplatelet medication (p-interaction=0·358), OAC (p-interaction=0·717) or combined OAC and antiplatelet medication (p-interaction=0·163) for intracranial haemorrhage risk.

Ischaemic stroke

1113 patients had a symptomatic ischaemic stroke during 32,293 patient-years of follow up. The incidence of symptomatic ischaemic stroke in patients with CMBs was 46 per 1000 patient-years (95% CI 42-51) compared to 30 per 1000 patient-years (95% CI 28-33) in those without CMBs, an absolute increased incidence of 16 strokes per 1000 patient-years. Table 2 shows the incidence of ischaemic stroke for each CMB burden and distribution category. The risk of symptomatic ischaemic stroke was 1·23 (95% CI 1·08-1·40) times higher for patients with CMBs than patients without CMBs, and rose with increasing CMB burden (table 2), p trend =0.0053. CMB distribution had little effect on ischaemic stroke risk (table 2). There was no interaction between CMBs and antiplatelet medication (p-interaction=0.943) or OAC (p-interaction=0.408) for ischaemic stroke risk.

Secondary outcomes: death and vascular death

There were 2418 deaths, 484 of which were vascular. In multivariable analyses, CMB presence was not associated with all-cause death (aHR 1·03, 95% CI 0·94-1·12) or vascular death (aHR 0·97, 95% CI 0·79-1·19).

Ethnicity

There was no interaction between CMB and ethnicity (n=15123; 6743 white, 8380 Asian) for the risks of: the composite outcome of intracranial haemorrhage or ischaemic stroke (p-interaction=0·707); intracranial haemorrhage (p-interaction=0·537); or ischaemic stroke (p-interaction=0·654).

Age

There was no interaction between CMB and older age (4376 patients aged >80 years) for the risk of the composite outcome of intracranial haemorrhage or ischaemic stroke (p-interaction=0·538); intracranial haemorrhage (p-interaction=0·219); or ischaemic stroke (p-interaction=0·286).

Sensitivity analysis to quantify heterogeneity

Using a two-stage meta-analysis, the estimated risks associated with CMB presence were consistent with our main model for: the composite of intracranial haemorrhage or ischaemic

stroke (heterogeneity (I^2=31.7%); intracranial haemorrhage (I^2=0%); and ischaemic stroke (I^2=24.2%). The forest plots are shown in the appendix (appendix Figure 2)

Sensitivity analysis including white matter hyperintensities

23 cohorts, including 10,235 patients, provided ratings for WMH, which were moderate to severe (Fazekas grade≥2) in 3,105 (30%). Including WMH in multivariable models did not substantially change the aHR associated with the presence of CMBs for the composite outcome (aHR 1.30, 95% CI 1.12-1.52), intracranial haemorrhage (aHR 2.44, 95% CI 1.68-3.53) or for ischaemic stroke (aHR 1.16, 95% CI 0.98-1.37).

Sensitivity analysis including only intracerebral, convexity subarachnoid and subdural intracranial haemorrhage

183 patients had a symptomatic intracranial haemorrhage during 32,847 patient-years of follow up. The risk of symptomatic intracranial haemorrhage was 2·59 (95% CI 1·91-3·50) times higher for patients with CMBs than patients without CMBs and rose with increasing CMB burden. Compared to no CMBs, aHRs were: 1·92 (95% CI 1·25-2·94) for 1 CMB; 2.02 (95% CI 1·30-3·16) for 2-4 CMBs; 4·88 (95% CI 3·29-7·25) for ≥5 CMBs; 5·87 (95% CI 3·56-9·66) for ≥ 10 CMBs; and 9·32 (95% CI 5·06-17·16) for ≥20 CMBs. These results are consistent with our primary findings.

Incidence of outcome events beyond the first year and change in risks over time

There were 102 intracranial haemorrhage events over 12,794 patient-years of follow up within the first year, and 87 symptomatic intracranial haemorrhages over 31,059 patient-years of follow-up after the first year. In patients with CMBs, the incidence of intracranial haemorrhage (per 1000 patients-years) was 18 (95% CI 14-23) within the first year, and 5 (95% CI 3-6) after the first year.

There were 696 ischaemic strokes over 12,873 patient -years of follow up within the first year, and 417 symptomatic ischaemic strokes during 30447 patient-years of follow up after the first year. In patients with CMBs the incidence of symptomatic ischaemic stroke within the first year was 70 (95% CI 62-80), and 18 (95% CI 15-21) after the first year. Accounting for death as a competing risk, we found no evidence for a change in risk over time associated with CMB presence for intracranial haemorrhage (subdistribution Hazard Ratio [SHR] 4·96, 95% CI 3·18-7·74 at day 0 vs. 4·81, 95% CI 3·15-7·35 after 1 year) or ischaemic stroke. (SHR 1·46, 95% CI 1·23-1·73 at day 0 vs. 1·49, 95% CI 1·27-1·75 after 1 year).

Patients treated with oral anticoagulants

In those treated with OAC after their index ischaemic stroke or TIA (n=7737; VKA=5253, NOAC=2484) there were 91 intracranial haemorrhages during 13,942 patient-years of follow up, and 384 ischaemic strokes during 13,737 patient-years of follow up. For those with CMBs, the incidence of intracranial haemorrhage was 12 per 1000 patient-years (95% CI 9-16); the incidence of ischaemic stroke was 32 per 1000 patient-years (95% CI 26-39). The incidence of ischaemic stroke was much higher than that of intracranial haemorrhage for all CMB burden

and distribution categories (table 2); the risk of intracranial haemorrhage associated with CMBs (vs. those without) rose more steeply with increasing CMB burden (table 2). Mixed and deep CMB distributions had similar aHRs for intracranial haemorrhage, but patients with lobar CMBs had a lower risk of intracranial haemorrhage (table 2). CMBs were not statistically associated with ischaemic stroke risk. We found no evidence of an interaction between OAC type (vitamin K antagonist vs. direct oral anticoagulant) and CMB presence for intracranial haemorrhage (p-interaction=0·4) or ischaemic stroke (p-interaction=0·61).

Patients treated with antiplatelet drugs

In patients treated with antiplatelet drugs only (n=11520) there were 93 intracranial haemorrhages during 18059 patient-years of follow up and 664 ischaemic strokes during 17731 patient-years of follow up. The incidence of ischaemic stroke remained higher than the incidence of intracranial haemorrhage for all CMB burden and distribution categories (table 2). The adjusted risks of intracranial haemorrhage and ischaemic stroke were similar to those in the full cohort, with little variation according to CMB distribution (table 2).

Patients not treated with antithrombotic medication

Compared to patients who received antithrombotic treatment (OAC or antiplatelets), those not treated with antithrombotic drugs (n=1065) were older (median age 72 vs. 70), and more likely to be female (46% vs. 42%), to have presented with ischaemic stroke (91% vs. 83%), to have had a previous intracranial haemorrhage (6% vs. 2%), or to have atrial fibrillation (44% vs. 37%). There was no difference in the prevalence of CMBs in those not receiving antithrombotic treatment (29% vs. 28%). In those not treated with any antithrombotic drugs there were 5

intracranial haemorrhages over 846 patient-years, and 65 ischaemic strokes over 825 patient-years. The aHRs associated with CMB presence were 1.10 (95% CI 0·17-7·34) for intracranial haemorrhage and 1·51 (95% CI 0·87-2·65) for ischaemic stroke.

DISCUSSION

Our large-scale pooled analysis of individual patient data confirms that, in patients with recent ischaemic stroke or TIA treated with antithrombotic drugs, CMBs are associated with the subsequent risks of symptomatic intracranial haemorrhage and ischaemic stroke; as CMB burden increases, the relative risk (aHR) of intracranial haemorrhage rises more steeply than that of ischaemic stroke. Our most important new finding is that, regardless of CMB burden and distribution (i.e. mixed, deep, or lobar), or the type of antithrombotic treatment received (OAC or antiplatelet therapy), the absolute risk of ischaemic stroke is consistently substantially higher than that of intracranial haemorrhage.

As well as confirming the association with CMBs and both recurrent ischaemic stroke and symptomatic intracranial haemorrhage found in smaller cohorts of patients with ischaemic stroke and TIA treated with antiplatelet agents[28] or OACs,[27,35,36] the large number of participants has improved the precision of our estimates of stroke recurrence rates and risks, while allowing adjustment for potential confounding factors. Our study also adds new data on important subgroups of patients with many (e.g. ≥20) CMBs, which cause most clinical concern and could not be addressed by any of the previously published meta-analyses. Moreover, only our study has undertaken individual patient data pooled analyses to allow adjustment for important potential confounding factors. The association of CMBs with a consistently higher absolute risk of ischaemic stroke than intracranial haemorrhage suggests

that CMBs are a marker for cerebral small vessel diseases that can cause not only intracranial haemorrhage, but also ischaemic stroke. Although it has been inferred that CMBs are a marker of direct extravasation of red blood cells from arterioles and capillaries damaged by "bleeding-prone arteriopathies", alternative non-haemorrhagic mechanisms include ischemia-mediated iron store release by oligodendrocytes[10] or phagocytosis of red cell micro-emboli into the perivascular space[11]. A recent report of haemorrhagic transformation of small acute "microinfarcts" into CMBs provides direct evidence that CMBs can result from ischaemic mechanisms[13]. These varied mechanisms underlying CMBs might explain why even patients at highest risk of intracranial haemorrhage still have a higher absolute risk of ischaemic stroke. Indeed, patients with CMBs often have multiple vascular risk factors, so are at risk of not only small vessel ischemic stroke but also other ischaemic stroke subtypes[37]. Patients with CMBs usually also have WMH - themselves associated with the risk of recurrent stroke, death and poor functional outcome after ischaemic stroke[38] - which might also contribute to the increased risk of ischaemic stroke associated with CMBs.

We found no evidence that a strictly lobar pattern of CMBs (fulfilling the Boston criteria for probable CAA[5], causing particular clinical concern for intracranial bleeding risk[36]) is associated with the risk of intracranial haemorrhage or ischaemic stroke. These findings might reflect limited diagnostic accuracy when using CMBs for diagnosis of CAA in patients without intracerebral haemorrhage or dementia[39], rather than a true lack of any association of CAA with intracranial haemorrhage. Furthermore, the HRs for intracranial haemorrhage associated with lobar CMBs (when compared to patients without lobar CMBs [including none]) were closer to those associated with deep or mixed CMBs (when compared to patients without deep or mixed CMBs [including none]).

Our results differ from some previous observations in smaller cohorts. First, in contrast to a smaller two-centre study[29], we did not find that the risk of intracranial haemorrhage approached the risk of ischaemic stroke after one year. Rather, we found the risk associated with CMB for both ischaemic stroke and intracranial haemorrhage remained stable over time. Second, our data indicate a smaller increase in the relative risk of intracranial haemorrhage for patients with ≥5 CMBs than reported in a previous smaller meta-analysis[28], but our much larger individual participant sample size allowed us to investigate high CMB burdens (≥5, ≥10 and ≥20) with adjustment for confounders and greater statistical precision and power.

The comparatively low frequency of symptomatic intracranial haemorrhage after ischaemic stroke or TIA, and the consistently higher risk of recurrent ischaemic stroke, make randomised controlled trials of antithrombotic treatment (themselves proven in large randomised trials) guided by CMBs challenging. However, ongoing and future randomised controlled trials should provide further insights. The MRI sub-study in the RESTART trial[40] of antiplatelet therapy after intracerebral haemorrhage identified reassuring effects in patients with CMB, but also illustrates how very large sample sizes are likely to be required to identify statistically significant interactions in CMB sub-groups in current (e.g. the MRI sub-study of NAVIGATE ESUS [NCT02313909]), and future, randomised controlled trials. Nevertheless, our large collaborative pooled analysis provides the best available evidence on the associations of CMBs with intracranial haemorrhage and ischaemic stroke after ischaemic stroke or TIA.

Our study has strengths. We included data from a worldwide collaborative network, making our results globally generalisable. The large individual patient dataset provides high statistical power and precision for risk estimates, allowing us to explore associations with several clinically important primary outcomes, while adjusting for important prognostic variables to

minimise confounding. The large number of events allow us to add new data on important subgroups of patients with a large number of CMBs (e.g. ≥20 CMBs) which are those patients who cause most clinical concern; this issue could not be addressed by any of the previously published meta-analyses. Included cohorts used validating rating instruments for CMBs, and in our analyses we accounted for the use of different MRI sequences (T2* GRE or SWI) to detect CMBs which accounts for the higher sensitivity of SWI for detecting CMBs when compared with T2* GRE[41]. Finally, we followed a published statistical analysis plan and confirmed our findings in a two-stage meta-analysis indicating the robustness of our results.

We also acknowledge limitations. Our observational study design has potential for selection bias and confounding of antithrombotic therapy by indication or unmeasured physician factors; thus, the hazard ratios for intracranial haemorrhage and ischaemic stroke must be interpreted with caution. To definitively determine whether CMBs modify the net clinical benefit of antithrombotic drugs would require a randomised controlled trial. Many of the included studies did not undertake formal adjudication of events. The requirement for MRI suitable patients probably led to the inclusion of less severe strokes than an unselected ischaemic stroke population. Even with a large number of individual patients, we could not precisely estimate risks associated with an extremely large number of CMBs (e.g. ≥50), but such patients are very rare in clinical practice. Although we adjusted for known prognostic variables, it is possible that residual confounding secondary to unknown or uncontrolled factors such as stroke mechanism could still have affected our results. Furthermore, we were unable to include some candidate variables in our multivariable models because they were not sufficiently widely available across all participating cohorts (e.g, white matter hyperintensities, MRI field strength, diabetes, ischaemic heart disease, renal function, statin use on discharge). Our analyses did not

formally assess net clinical benefit, accounting for the greater severity of intracranial haemorrhage compared to recurrent ischaemic stroke.

In summary, our large-scale pooled analysis in patients with recent ischaemic stroke or TIA found that the absolute risk of ischaemic stroke is consistently higher than that of intracranial haemorrhage, regardless of the number or anatomical distribution of CMBs. However, CMBs are associated with a greater adjusted hazard ratio for intracranial haemorrhage than ischaemic stroke; further studies are needed to establish the value of neuroimaging biomarkers, including CMBs, in improving risk prediction scores for intracranial haemorrhage and ischaemic stroke.

CONTRIBUTIONS

DJW, DW, GA and JM-F drafted the initial protocol, which was reviewed with critical revisions and approval by all authors. DW and GA undertook the statistical analysis. DW, DJW and GA wrote the first draft of the manuscript. All authors contributed to data acquisition, management, and brain imaging analyses. All authors contributed to critical revision of the manuscript and approved the final manuscript for submission.

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Table 1: Demographics, risk factors and events for each included cohort

Cohort	Total n	OAC n	TIA (%)	Age mean, years (SD)	Sex female (%)	HTN (%)	AF (%)	Prior stroke (%)	IHD (%)	Any CMB (%)	SWI (%)	Median follow up, days (IQR)	Patients with composite events (n)	Patients with ICH Events (n)	Patients with ischaemic stroke events (n)
CROMIS-2[27]	1490	1436	16	76 (10)	42	63	100	10	16	21	0	774 (705-974)	70	14	56
HBS	660	114	9	69 (15)	44	75	29	24	21	15	0	90 (90-90)	4	0	4
Bern[42]	392	74	0	68 (14)	43	64	46	15	18	23	100	93 (5-106)	16	0	16
CU-STRIDE[43]	536	24	15	67 (11)	42	70	7	15	7	23	44	524 (472-557)	17	2	15
TABASCO[44]	436	33	28	67 (9)	43	59	8	0	14	15	0	1825 (1164-1825)	57	0	57
Graz	460	78	10	67 (13)	39	78	25	22	21	19	0	117 (87-973)	65	13	54
PERFORM-MRI[45]	1056	0	12	68 (8)	35	84	2	11	7	36	0	774 (701-1042)	104	10	94
PARISK[46]	228	0	56	71 (9)	29	68	0	29	22	27	0	786 (757-819)	10	0	10
SAMURAI NVAF[47]	1103	1039	4	78 (10)	44	93	100	22	9	24	74	723 (758-818)	82	10	72
RUNDMC[48]	179	19	50	65 (9)	35	81	10	26	17	20	0	1825 (1825-1825)	25	2	23
Wuerzburg	358	122	22	71 (13)	44	80	37	25	11	24	45	95 (89-103)	22	1	21
Monash Stroke[49]	359	356	15	75 (11)	48	79	100	28	34	43	94	530 (280-898)	14	7	9
Basel TIA[18]	192	33	100	69 (13)	38	71	14	7	20	11	0	90 (90-90)	26	0	26
Yonsei[50]	504	487	6	70 (11)	57	78	100	20	22	31	0	849 (393-1398)	56	7	49

SNUBH Stroke Cohort[51,52]	3355	625	11	67 (13)	40	69	19	15	8	35	0	355 (340-365)	172	N/A	N/A
BIOSTROKE/TIA[53]	260	73	62	68 (13)	37	59	31	8	22	9	0	90 (90-365)	14	0	14
Kushiro City[54]	784	63	0	72 (11)	42	64	13	18	11	41	0	1008 (105-1825)	139	22	119
Soo[55]	81	81	20	72 (9)	49	69	100	31	10	30	88	737 (641-794)	8	3	5
CASPER[56]	135	18	0	66 (11)	29	71	10	7	21	59	100	453 (444-465)	3	0	3
HERO	937	933	13	78 (7)	52	74	92	27	16	26	0	737 (641-794)	49	18	32
HAGAKURE	426	157	8	74 (13)	41	76	32	18	11	37	9	748 (350-1040)	34	9	25
Leuven[14]	487	133	27	72 (9)	39	64	21	13	23	26	0	804 (686-968)	36	4	32
NOACISP	306	286	10	73 (19)	45	79	100	20	27	28	98	735 (417-836)	28	10	19
Min Lou[57]	126	14	0	65 (13)	37	75	20	14	3	33	100	92 (87-218)	2	0	2
MICRO[21]	397	40	91	65 (12)	42	55	8	9	6	18	0	1212 (579-1825)	30	11	21
Orken[58]	454	454	4	72 (12)	51	79	65	27	32	30	55	575 (228-1825)	11	3	8
CATCH[59]	416	67	42	67 (14)	39	54	6	0	N/A	16	0	88 (80-100)	14	1	13
MSS2[60]	263	26	0	67 (12)	41	72	10	12	20	16	95	368 (253-403)	31	0	31
Sainte-Anne	385	302	0	80 (11)	53	72	100	16	19	26	0	440 (163-733)	25	5	23
STROKDEM	181	48	0	64 (13)	38	55	7	11	9	13	0	1150 (420-1820)	17	0	17
Singapore	45	15	0	67 (10)	29	76	24	7	9	56	100	1057 (703-1199)	6	0	6
FUTURE Study	19	0	37	44 (6)	53	42	0	0	0	5	100	164 (131-242)	4	0	4
Heidelberg[61]	650	119	16	64 (14)	37	76	18	17	N/A	24	100	1534	34	4	30

												(1271-1825)			
NNI	184	32	0	58 (11)	31	78	15	15	N/A	27	0	251 (86-477)	0	0	0
OXVASC[29]	1080	118	52	68 (14)	48	55	15	19	13	15	0	1271 (681-1825)	90	11	79
HKU[29]	1003	104	0	69 (12)	40	66	13	19	9	45	100	1005 (599-1549)	112	20	92
IPAAC Warfarin[36]	182	173	15	73 (9)	46	87	98	20	9	37	100	738 (191-812)	7	1	6
SIGNaL	213	18	10	72 (14)	41	61	32	28	23	44	68	225 (202-249)	27	1	26
TOTAL	**20322**	**7737**	**761**	**70 (13)**	**42**	**71**	**38**	**16**	**14**	**28**	**39**	**534 (243-928)**	**1461**	**189**	**1113**

Footnote: OAC -oral anticoagulant; TIA -transient ischaemic attack; HTN -hypertension; AF- Atrial fibrillation; IHD- ischaemic heart disease; SWI – susceptibility-weighted imaging; ICH (intracranial haemorrhage).

Table 2. Incidence and risk of outcome events according to baseline CMBs

ALL PATIENTS (n=20322)												
	Composite of intracranial haemorrhage and ischaemic stroke (n=19816 for multivariable model)				**Symptomatic Intracranial haemorrhage (n=16447 for multivariable model)**				**Symptomatic ischaemic stroke (n=16464 for multivariable model)**			
CMB category	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**
No CMB	919/25997	35 (33 to 38)	*Reference*	*Reference*	91/24496	4 (3 to 5)	*Reference*	*Reference*	733/24094	30 (28 to 33)	*Reference*	*Reference*
CMB present	542/9228	59 (54 to 64)	24 (21 to 26)	1·35 (1·20 to 1·50)	98/8351	12 (10 to 14)	8 (7 to 9)	2·45 (1·82 to 3·29)	380/8200	46 (42 to 51)	16 (14 to 18)	1·23 (1·08 to 1·40)
1 CMB	190/4095	46 (40 to 53)	11 (7 to 15)	1·21 (1·03 to 1·42)	30/3691	8 (5 to 12)	4 (2 to 7)	1·87 (1·23 to 2·84)	134/3635	37 (31 to 44)	7 (3 to 11)	1·14 (0·94 to 1·37)
2-4 CMBs	184/3166	58 (50 to 67)	23 (17 to 29)	1·25 (1·06 to 1·47)	27/2853	9 (6 to 14)	5 (3 to 9)	1·89 (1·22 to 2·93)	133/2797	48 (40 to 56)	18 (12 to 23)	1·17 (0·97 to 1·42)
≥5 CMBs*	168/1967	85 (73 to 99)	50 (40 to 61)	1·74 (1·46 to 2·06)	41/1807	23 (16 to 31)	19 (13 to 26)	4·55 (3·08 to 6·72)	113/1767	64 (53 to 77)	34 (25 to 43)	1·47 (1·19 to 1·80)
≥10 CMBs*	82/898	91 (73 to 113)	56 (40 to 75)	1·82 (1·44 to 2·29)	22/818	27 (17 to 41)	23 (14 to 36)	5·52 (3·36 to 9·05)	52/809	64 (48 to 84)	34 (20 to 51)	1·43 (1·07 to 1·91)
≥20 CMBs*	42/363	118 (86 to 160)	83 (53 to 122)	2·61 (1.90 to 3·57)	13/332	39 (21 to 67)	35 (18 to 62)	8·61 (4·69 to 15·81)	24/331	73 (46 to 108)	43 (18 to 75)	1·86 (1·23 to 1·82)
Mixed CMBs	160/1991	80 (68 to 94)	45 (35 to 56)	1·28 (1·06 to 1·54)	35/1721	20 (14 to 28)	16 (11 to 23)	2·38 (1·55 to 3·65)	101/1677	60 (49 to 73)	30 (21 to 40)	1·12 (0·88 to 1·41)
Deep CMBs	307/4202	73 (65 to 82)	38 (32 to 44)	1·29 (1·12 to 1·48)	59/3468	17 (13 to 22)	13 (10 to 17)	2·57 (1·78 to 3·70)	194/3398	57 (49 to 66)	27 (21 to 33)	1·14 (0·96 to 1·36)
Lobar CMBs	278/4532	60 (53 to 67)	25 (20 to 29)	1·22 (1·06 to 1·41)	51/4071	13 (9 to 16)	9 (6 to 9)	1·87 (1·29 to 2·71)	193/3983	48 (42 to 56)	18 (14 to 23)	1·17 (0·99 to 1·40)
Probable CAA	45/821	55 (40 to 73)	20 (7 to 35)	1·21 (0·90 to 1·64)	7/789	9 (4 to 18)	5 (1 to 13)	1·29 (0·60 to 2·77)	37/767	48 (34 to 66)	18 (6 to 33)	1·31 (0·94 to 1·83)

PATIENTS TREATED WITH ORAL ANTICOAGULANTS (+/- antiplatelet drugs) (n=7737)												
	Composite of intracranial haemorrhage and ischaemic stroke (n=7582 for multivariable model)				**Symptomatic Intracranial haemorrhage (n=6942 for multivariable model)**				**Symptomatic ischaemic stroke (n=6958 in multivariable models)**			
	n/time at risk (years)	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**
No CMB	332/10591	31 (28 to 35)	*Reference*	*Reference*	47/10383	5 (3 to 6)	*Reference*	*Reference*	271/10221	27 (23 to 30)	*Reference*	*Reference*
CMB present	168/3671	46 (39 to 53)	15 (11 to 18)	1·30 (1·07 to 1·57)	44/3559	12 (9 to 16)	7 (6 to 10)	2·49 (1·64 to 3·79)	113/3515	32 (26 to 39)	5 (3 to 9)	1·07 (0·86 to 1·35)
1 CMB	65/1689	38 (30 to 49)	7 (2 to 14)	1·19 (0.91 to 1·56)	17/1641	10 (6 to 17)	5 (3 to 11)	2·15 (1·23 to 3·75)	42/1624	26 (19 to 35)	-1 (-4 to 5)	0·96 (0·69 to 1·33)
2-4 CMBs	61/1307	47 (36 to 60)	16 (8 to 25)	1·23 (0·93 to 1·62)	14/1267	11 (6 to 19)	6 (3 to 13)	2·22 (1·21 to 4·06)	45/1245	36 (26 to 48)	11 (3 to 18)	1·10 (0·80 to 1·52)
≥5 CMBs*	42/675	62 (45 to 84)	31 (17 to 49)	1·69 (1·22 to 2·35)	13/651	20 (11 to 34)	15 (8 to 28)	3·91 (2·08 to 7·34)	26/650	40 (26 to 59)	13 (3 to 29)	1·27 (0·84 to 1·91)
≥10 CMBs*	20/266	75 (46 to 116)	44 (18 to 81)	2·15 (1·35 to 3·43)	6/261	23 (8 to 50)	18 (5 to 44)	4·63 (1·92 to 11·22)	12/260	46 (24 to 81)	19 (1 to 51)	1·52 (0·84 to 2·67)
Mixed CMBs	46/793	58 (42 to 77)	27 (14 to 42)	1·43 (1·02 to 2·00)	11/751	15 (7 to 26)	10 (4 to 20)	2·21 (1·09 to 4·47)	31/737	42 (29 to 60)	15 (6 to 30)	1·28 (0·85 to 1·94)
Deep CMBs	91/1763	52 (42 to 63)	21 (14 to 28)	1·43 (1·11 to 1·84)	24/1665	14 (9 to 21)	9 (6 to 15)	2·71 (1·61 to 4·59)	58/1661	35 (27 to 46)	8 (4 to 16)	1·16 (0·85 to 1·59)
Lobar CMBs	80/1969	41 (32 to 51)	10 (4 to 16)	1·13 (0·87 to 1·47)	20/1905	10 (6 to 16)	5 (3 to 10)	1·63 (0·94 to 2·83)	54/1877	29 (22 to 38)	2 (-1 to 8)	1·00 (0·73 to 1·38)
Probable CAA	11/415	27 (13 to 47)	-4 (-15 to 12)	0·76 (0·41 to 1·39)	4/413	10 (3 to 25)	5 (0 to 19)	1·29 (0·47 to 3·57)	7/407	17 (7 to 35)	-10 (-16 to 5)	0·64 (0·30 to 1·37)

PATIENTS TREATED WITH ANTIPLATELET DRUGS ONLY (n=11520)												
Composite of intracranial haemorrhage and ischaemic stroke (n=11312 in multivariable models)					**Symptomatic intracranial haemorrhage (n=8670 in multivariable models)**				**Symptomatic ischaemic stroke (n=8670 in multivariable models)**			
	n/time at risk (years)	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**	**n/time at risk (years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/ 1000 patient years (95% CI)**	**Adjusted Hazard ratio (95% CI)**
No CMB	544/14798	37 (34 to 40)	*Reference*	*Reference*	41/13518	3 (2 to 4)	*Reference*	*Reference*	424/13290	32 (29 to 35)	*Reference*	*Reference*
CMB present	343/5301	65 (58 to 72)	28 (24 to 32)	1·38 (1·19 to 1·59)	52/4541	11 (9 to 15)	8 (7 to 11)	2·59 (1·68 to 4·00)	240/4442	54 (47 to 61)	22 (18 to 26)	1·32 (1·11 to 1·56)
1 CMB	114/2340	49 (40 to 59)	12 (6 to 19)	1·20 (0.97 to 1·47)	12/1984	6 (3 to 11)	3 (1 to 7)	1·60 (0·83 to 3·08)	82/1951	42 (33 to 52)	10 (4 to 17)	1·22 (0·96 to 1·55)
2-4 CMBs	111/1759	63 (52 to 76)	26 (18 to 36)	1·25 (1·02 to 1·55)	13/1487	9 (5 to 15)	6 (3 to 11)	1·82 (0·95 to 3·47)	78/1457	54 (42 to 67)	22 (13 to 32)	1·20 (0·94 to 1·55)
≥5 CMBs*	118/1203	98 (81 to 117)	61 (47 to 77)	1·85 (1·50 to 2·28)	27/1069	25 (17 to 37)	22 (15 to 33)	5·69 (3·36 to 9·65)	80/1034	77 (61 to 96)	45 (32 to 61)	1·63 (1·27 to 2·09)
≥10 CMBs*	59/593	99 (76 to 128)	62 (42 to 88)	1·82 (1·38 to 2·40)	16/519	31 (18 to 50)	28 (16 to 46)	6·81 (3·67 to 12·63)	37/511	72 (51 to 100)	40 (22 to 65)	1·47 (1·04 to 2·07)
≥20 CMBs*	30/221	136 (92 to 194)	99 (58 to 154)	2·86 (1·97 to 4·96)	11/194	57 (28 to 101)	54 (26 to 97)	15·71 (7·69 to 32·11)	16/192	83 (48 to 135)	51 (19 to 100)	2·00 (1·20 to 3·32)
Mixed CMBs	102/1121	91 (74 to 110)	54 (40 to 70)	1·21 (0·96 to 1·52)	24/896	27 (17 to 40)	24 (15 to 36)	2·90 (1·64 to 5·13)	60/867	69 (53 to 89)	37 (21 to 54)	1·03 (0·76 to 1·39)
Deep CMBs	193/2320	83 (72 to 96)	46 (38 to 56)	1·22 (1·02 to 1·47)	34/1692	20 (14 to 28)	17 (12 to 24)	2·63 (1·54 to 4·47)	116/1647	70 (58 to 84)	38 (29 to 49)	1·11 (0·88 to 1·40)
Lobar CMBs	180/2423	74 (64 to 86)	37 (30 to 46)	1·26 (1·05 to 1·52)	31/2029	15 (10 to 22)	12 (8 to 18)	2·44 (1·44 to 4.15)	123/1973	62 (52 to 74)	30 (23 to 39)	1·26 (1·01 to 1·57)
Probable CAA	32/372	86 (59 to 121)	49 (25 to 81)	1·52 (1·07 to 2·18)	3/340	9 (2 to 26)	6 (0 to 22)	1·43 (0·44 to 4·59)	28/326	86 (57 to 124)	54 (28 to 89)	1·79 (1·21 to 2·63)

Footnote: CMB location HRs are compared to patients without CMBs in each location and are adjusted for CMB number in addition to our pre-specified variables, *overlapping categories

Figure 1 legend

Kaplan-Meier estimates for the primary outcomes: (A) All patients (n=20,322); (B) Patients treated with oral anticoagulants (with or without antiplatelet drugs) (n=7,737); and (C) Patients treated with antiplatelet drugs only (n=11,520).