Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1212/WNL.0000000000004259</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:34492029">http://nrs.harvard.edu/urn-3:HUL.InstRepos:34492029</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds
A meta-analysis

ABSTRACT
Objective: We evaluated recurrent intracerebral hemorrhage (ICH) risk in ICH survivors, stratified by the presence, distribution, and number of cerebral microbleeds (CMBs) on MRI (i.e., the presumed causal underlying small vessel disease and its severity).

Methods: This was a meta-analysis of prospective cohorts following ICH, with blood-sensitive brain MRI soon after ICH. We estimated annualized recurrent symptomatic ICH rates for each study and compared pooled odds ratios (ORs) of recurrent ICH by CMB presence/absence and presumed etiology based on CMB distribution (strictly lobar CMBs related to probable or possible cerebral amyloid angiopathy [CAA] vs non-CAA) and burden (1, 2–4, 5–10, and >10 CMBs), using random effects models.

Results: We pooled data from 10 studies including 1,306 patients: 325 with CAA-related and 981 CAA-unrelated ICH. The annual recurrent ICH risk was higher in CAA-related ICH vs CAA-unrelated ICH (7.4%, 95% confidence interval [CI] 3.2–12.6 vs 1.1%, 95% CI 0.5–1.7 per year, respectively; p = 0.01). In CAA-related ICH, multiple baseline CMBs (versus none) were associated with ICH recurrence during follow-up (range 1-3 years): OR 3.1 (95% CI 1.4–6.8; p = 0.006), 4.3 (95% CI 1.8–10.3; p = 0.001), and 3.4 (95% CI 1.4–8.3; p = 0.007) for 2–4, 5–10, and >10 CMBs, respectively. In CAA-unrelated ICH, only >10 CMBs (versus none) were associated with recurrent ICH (OR 5.6, 95% CI 2.1–15; p = 0.001). The presence of 1 CMB (versus none) was not associated with recurrent ICH in CAA-related or CAA-unrelated cohorts.

Conclusions: CMB burden and distribution on MRI identify subgroups of ICH survivors with higher ICH recurrence risk, which may help to predict ICH prognosis with relevance for clinical practice and treatment trials. Neurology® 2017;89:820–829

GLOSSARY
CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; GRE = gradient-recalled echo; ICH = intracerebral hemorrhage; OR = odds ratio.

Spontaneous (nontraumatic) primary intracerebral hemorrhage (ICH) presumed due to cerebral small vessel disease1 is a catastrophic form of stroke associated with high morbidity and mortality2 and a substantial recurrence risk.2 ICH location is associated with the risk of subsequent ICH recurrence,3 probably because of the type and severity of the underlying small vessel diseases (microangiopathies), which include arteriosclerosis, lipohyalinosis, and cerebral amyloid angiopathy (CAA).4 The arteriopathy associated with systemic arterial hypertension affects...
small deep perforating arteries supplying the basal ganglia and deep white matter, resulting in ICH in deep and lobar brain regions. By contrast, CAA causes progressive vascular deposition of β-amyloid in small cortical and leptomeningeal arterial walls, and is associated with lobar (but not deep) ICH, especially in the elderly. Some studies suggest that CAA-related lobar ICH carries a significantly higher risk for recurrence compared to deep ICH due to hypertensive arteriopathy.

Cerebral microbleeds (CMBs), seen on blood-sensitive MRI sequences (e.g., T2*-weighted gradient-recalled echo [T2*-GRE] and susceptibility-weighted imaging), are a radiologic biomarker of cerebral small vessel disease, present in 52% of patients with first-ever ICH and 83% of those with recurrent ICH. Since CMBs sometimes represent blood leakage from hemorrhage-prone small vessels, and their prevalence is higher in recurrent vs first-ever ICH, CMB have been hypothesized to predict increased recurrent ICH risk. Moreover, the distribution of CMBs can reflect the likely underlying microangiopathy: a strictly lobar distribution (alongside other clinical factors) is highly specific for CAA diagnosis within the Boston criteria. If the risk of ICH recurrence is related to the underlying microangiopathies and their severity, CMB distribution and burden may help to identify patients at high risk of recurrence.

Therefore, we sought published prospective ICH cohorts with MRI (including blood-sensitive sequences) at baseline, to investigate the association of CMB burden and distribution with recurrent ICH in a meta-analysis of aggregate summary-level data, stratified by the presumed underlying microangiopathy (CAA vs CAA-unrelated ICH).

METHODS This systematic review and meta-analysis was undertaken using an in-house developed protocol (A.C. and D.J.W.).

Search strategy, selection criteria, and data extraction. Two authors (A.C. and D.J.W.) searched PubMed between January 1, 1999, and October 1, 2015, using several combinations of medical subject heading terms and text words: (microbleed* or microhemorrhag* or microhemorrhage) and (intracerebral hemorrhage) or (intracerebral haemorrhage) or (brain bleed*) and (MRI or MR imaging) and (recurrence* or outcome or survival or predict*). Reference lists from all included articles, relevant review articles, and the authors’ own files were also searched. Studies were eligible if they included adult patients with spontaneous symptomatic ICH confirmed by imaging and presumed due to sporadic cerebral small vessel disease; had a prospective design, with at least 3 months of follow-up; assessed the risk of recurrent symptomatic spontaneous ICH (main outcome) during follow-up; had data for the presence of CMBs on baseline T2*-GRE MRI; and were published in English. In cases of multiple publications from the same or overlapping cohorts, only the most recent comprehensive results from the report with the largest sample size were used in the analysis. We excluded case-control and cross-sectional studies, case reports, and case series. Two reviewers (A.C. and Y.Y.) determined study eligibility, resolving any disagreements or uncertainties with a third reviewer (D.J.W.) by consensus.

For each study, we extracted data on the country of the study; time period; clinical setting; population size; demographic data (including mean age, sex, and vascular risk factors); use of antithrombotic agents; T2*-GRE MRI parameters; number of participants with at least one CMB at baseline; method and duration of follow-up; and the number of participants with the outcome event of interest. The outcome event of interest was recurrent symptomatic ICH assessed using clear, predefined criteria: namely, symptomatic stroke syndrome associated with neuroimaging evidence of a corresponding ICH. For included cohorts, we sought information from the authors on total person-years of follow-up and outcome events (recurrent ICH) stratified by CMB burden (1, 2–4, 5–10, and >10 CMBs) and distribution (lobar [in the cortex or subcortical areas of the cerebral hemispheres], deep, or both [mixed]).

We classified the study cohorts and subcohorts as CAA-related ICH (including probable and possible CAA, based on the presence of strictly lobar macrobleeds and microbleeds, according to the original Boston criteria) or CAA-unrelated ICH (i.e., including patients with a strictly deep or mixed pattern of CMBs not fulfilling the original Boston criteria) based on published information and correspondence with authors.

The risk of bias of each included study was assessed against 6 key quality indicators: clearly defined populations, standardized MRI measures, CMB clearly defined per criteria, standardized rating scale used for CMBs rating, standardized definition of outcome (ICH), and completion of follow-up (>90%).

Statistical analysis. We estimated recurrent symptomatic ICH (%/year) and corresponding 95% confidence intervals (CIs) for each study from a Poisson regression model and exact Poisson intervals. We calculated pooled rates using the inverse variance method, stratified by study population (CAA-related ICH vs CAA-unrelated ICH). We compared the log (incidence) of recurrent ICH events between these groups using a significance test with the appropriate degrees of freedom.

We meta-analyzed recurrent ICH risks across studies, using a random effects model with DerSimonian-Laird weights, quantifying the strength of any association using odds ratios (OR) and 95% CI in patients without CMBs vs different CMB burden categories. We analyzed the association between CMBs and ICH recurrence using OR rather than hazard ratios because individual patient data including follow-up time were not available for this meta-analysis. To maximize the power of our analyses, for comparisons with zero events in both groups, we added 0.5 to each group, considered OR = 1, and calculated the SE, logOR, and SE logOR by using the 2-variable input method. We assessed heterogeneity by P and χ² statistics and also visually through inspection of the forest plot and checking for overlapping CIs. We explored publication bias with funnel plots and the Harbord regression tests for funnel plot asymmetry. We stratified all
analyses by baseline ICH presumed cause (CAA-related vs CAA-unrelated ICH). We used meta-regression to explore whether certain confounders could have affected our results.

All meta-analyses were performed using Stata 11.2 (StataCorp, College Station, TX). We prepared this report with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

RESULTS 

Ten unique hospital-based studies and 1 population-based study with a total of 1,306 ICH patients met our predefined inclusion criteria (figure 1).20–29 The studies comprised 5 CAA-related ICH cohorts (n = 325)20,23,24,28,29—3 of which were unselected, and also included CAA-unrelated ICH24,28,29—and 5 CAA-unrelated ICH cohorts (n = 981).21,22,25–27 Studies had slightly different inception points, variation in the proportion of patients with first-ever vs recurrent ICH, and different prospective and retrospective methods of follow-up (table 1). The risk of bias assessment is summarized in table e-1 at Neurology.org. All studies used T2*-GRE MRI at 1.5T to detect CMBs at baseline, although imaging measures, including echo time and slice thickness, varied slightly. Differences in demographic, clinical, and imaging characteristics between the subgroups with and without CMB are also described in table 1. Overall, compared to CAA-unrelated ICH patients, CAA-related ICH patients in general were older, more often had a prior ICH, and had greater prevalence of white matter hyperintensities (table 1).

Patients with CAA-related ICH had a higher pooled annual risk of recurrent ICH compared to those with CAA-unrelated ICH (7.39%, 95% CI 3.2–12.6 vs 1.1%, 95% CI 0.5–1.7 per year, respectively; p = 0.01), but with considerable statistical heterogeneity (figure 2).

In the CAA-unrelated ICH cohorts, among patients with CMBs, 30/656 (4.6%, 95% CI 3.1%–6.5%) experienced recurrent ICH, compared to 4/325 (1.2%, 95% CI 0.3%–3.1%) patients without CMBs. The presence of CMBs was associated with an increased risk of recurrent ICH (OR 2.48, 95% CI 1.0–5.9; p = 0.04) (figure 3). Although ICH risk seemed to increase with increasing CMB burden, only patients with >10 CMBs had a statistically significant increase in risk compared to patients without CMB (OR 5.6, 95% CI 2.1–15; p = 0.001) (figure 3). When we pooled data based on CMBs location, the presence of mixed CMBs (but not strictly lobar or strictly deep) was associated with higher risk of recurrent ICH (data not shown). The results were consistent from study to study (test for heterogeneity p > 0.10).

In the CAA-related ICH cohorts, 55/192 (28.7%, 95% CI 22.4%–35.6%) patients with CMBs and 15/133 (11.3%, 95% CI 6.5%–17.9%) patients without CMBs had a prior ICH.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/setting</th>
<th>T2* GRE MRI measures (field strength/TE/ST)</th>
<th>Mean age, y (SD)</th>
<th>HTN, %</th>
<th>Previous ICH, %</th>
<th>Antithrombotic users</th>
<th>Advanced WMC (grade ≥2), %</th>
<th>CMB prevalence, %</th>
<th>Significant differences, CMB+ vs CMB− groups</th>
<th>Patient-years of follow-up methods*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAA-unrelated ICH cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PITCH study</td>
<td>France, single-center</td>
<td>1.5T/22.8 ms/5 mm</td>
<td>65 (13)</td>
<td>66</td>
<td>5</td>
<td>24</td>
<td>10</td>
<td>58.5</td>
<td>60.5</td>
<td>Age: 66.4 vs 60.6, (p = 0.004)</td>
</tr>
<tr>
<td>Samarasekera et al.</td>
<td>United Kingdom, population-based</td>
<td>1.5T/15 ms/5 mm</td>
<td>66 (2)</td>
<td>60.4</td>
<td>6.3</td>
<td>27.1</td>
<td>12.5</td>
<td>25</td>
<td>60.4</td>
<td>No</td>
</tr>
<tr>
<td>Kang et al.</td>
<td>South Korea, multicenter</td>
<td>1.5T/30, 20, 23 ms/1-2 mm</td>
<td>59 (12)</td>
<td>84.5</td>
<td>5.2</td>
<td>14.4</td>
<td>0</td>
<td>42.2</td>
<td>76.3</td>
<td>Age: 62 (26-81) vs 53 (38-77), (p = 0.059), advanced WMH 52.7% vs 8.7%, (p &lt; 0.001)</td>
</tr>
<tr>
<td>Imaizumi et al.</td>
<td>Japan, single-center</td>
<td>1.5T/26 ms/7.5 mm</td>
<td>68 (12)</td>
<td>67.4</td>
<td>9.1</td>
<td>5.9</td>
<td>3.2</td>
<td>28.9</td>
<td>71.1</td>
<td>No</td>
</tr>
<tr>
<td>Jeon et al.</td>
<td>South Korea, single-center</td>
<td>1.5T/30 ms/2 mm</td>
<td>58 (range 38-81)</td>
<td>96.8</td>
<td>NA</td>
<td>6.4</td>
<td>0</td>
<td>NA</td>
<td>68.3</td>
<td>Hypcholesterolemia 37.2% vs 5%, (p = 0.013)</td>
</tr>
<tr>
<td>Naka et al.</td>
<td>Japan, single-center</td>
<td>17T/26 ms/5 mm</td>
<td>64 (12)</td>
<td>83.1</td>
<td>18.1</td>
<td>2.4</td>
<td>2.4</td>
<td>28.9</td>
<td>48.2</td>
<td>Advanced WMH 45% vs 14%, (p = 0.002)</td>
</tr>
<tr>
<td>Imaizumi et al.</td>
<td>Japan, single-center</td>
<td>1.5T/26 ms/8 mm</td>
<td>66 (11)</td>
<td>84.4</td>
<td>9.1</td>
<td>1</td>
<td>0</td>
<td>NA</td>
<td>77.4</td>
<td>Age: 67.3 ± 10.8 vs 61.4 ± 11.2, (p = 0.0013)</td>
</tr>
<tr>
<td><strong>CAA-related ICH cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PITCH study</td>
<td>France, single-center</td>
<td>1.5T/22.8 ms/5 mm</td>
<td>74 (7)</td>
<td>46.9</td>
<td>6.1</td>
<td>46.9</td>
<td>20.4</td>
<td>71.4</td>
<td>49</td>
<td>No</td>
</tr>
<tr>
<td>Samarasekera et al.</td>
<td>United Kingdom, population-based</td>
<td>1.5T/15 ms/5 mm</td>
<td>74 (2)</td>
<td>39.3</td>
<td>10.7</td>
<td>21.4</td>
<td>14.3</td>
<td>35.7</td>
<td>32.1</td>
<td>No</td>
</tr>
<tr>
<td>Charidimou et al.</td>
<td>United Kingdom/Belgium, multicenter</td>
<td>1.5T/15-70 ms/5 mm</td>
<td>71 (10)</td>
<td>59</td>
<td>28.9</td>
<td>20</td>
<td>2</td>
<td>44.1</td>
<td>65.4</td>
<td>No</td>
</tr>
<tr>
<td>Dominguez- Montanari et al.</td>
<td>Spain, single-center</td>
<td>1.5T/29 ms/7</td>
<td>75 (7)</td>
<td>43.6</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
<td>51.3</td>
<td>70</td>
<td>Previous ICH: 53.6% vs 16.7%, (p = 0.041)</td>
</tr>
<tr>
<td>Biffi et al.</td>
<td>United States, single-center</td>
<td>1.5T/50 ms/5-6 mm</td>
<td>73 (8)</td>
<td>58.2</td>
<td>7.7</td>
<td>15.4</td>
<td>10.6</td>
<td>71.2</td>
<td>60.6</td>
<td>HTN: 63.4% vs 36.6%, (p = 0.007)</td>
</tr>
</tbody>
</table>

Abbreviations: CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; HTN = hypertension; ICH = intracerebral hemorrhage; NA = not available; OAC = oral anticoagulation; PITCH = Prognosis of Intracerebral Hemorrhage cohort study; ST = slice thickness; T2* GRE = T2*-weighted gradient recalled echo; TE = echo time; WMC = white matter changes; WMH = white matter hyperintensity.

*Multiple sources of follow-up denotes a combination of overlapping ascertainment methods including patient records review, follow-up imaging review, patient interview, and hospital registry review.
CMBs had recurrent ICH during follow-up. CMB presence was associated with recurrent ICH risk (OR 2.7, 95% CI 1.4–5.1; \( p = 0.003 \)) (figure 4). The presence of a single CMB was not associated with a higher risk of recurrence compared to CAA patients without any CMBs. However, there was a substantial risk of recurrent ICH with greater CMB burden categories (figure 4).

We used meta-regression to see whether certain confounders could have affected our results. No significant difference was noted in our estimates when we included age, sex, hypertension at baseline, history of previous ICH, white matter hyperintensities, or prior use of antithrombotic medication (antiplatelets or anticoagulants) in the model for our main outcomes. Sensitivity analyses involving sequential removal of each individual study in turn yielded very similar results for all comparisons. Estimation of publication bias via the Egger test and the Begg test returned nonsignificant results (all analyses \( p > 0.20 \)).

**DISCUSSION** In this meta-analysis of 10 cohorts involving more than 1,300 survivors of symptomatic spontaneous ICH who underwent blood-sensitive MRI, pooled estimates demonstrated a 7-fold increase in the risk of recurrent ICH after CAA-related ICH compared to CAA-unrelated ICH. We found a consistent association between CMB presence at baseline and future ICH recurrence, but the strength of the association of CMBs and the magnitude of recurrent ICH risk differed according to underlying microangiopathy.

Our finding of high ICH risk in probable CAA-related ICH is in line with most previous studies and systematic reviews that found ICH recurrence is more common following lobar ICH (whether related to CAA or not) than nonlobar ICH. However, few previous studies of ICH prognosis have used MRI to systematically phenotype the likely underlying small vessel arteriopathy. MRI has emerged as the most useful noninvasive method to diagnose the microangiopathies associated with spontaneous ICH. Our data suggest that MRI may also be valuable in assessing prognosis.

The differential stroke risks in ICH survivors have implications for prognosis and secondary prevention decisions, especially antithrombotic treatment, an increasingly common clinical dilemma. Our data suggest that MRI could identify a specific subgroup of patients with ICH at highest risk for further hemorrhagic events. A decision analysis based on a 69-year-old survivor of a lobar CAA-related ICH and newly diagnosed nonvalvular atrial fibrillation suggested that such patients should not be anticoagulated with...
Figure 3  Meta-analysis of the associations between cerebral microbleeds (CMBs) presence or burden and the risk of recurrent symptomatic spontaneous intracerebral hemorrhage (ICH) in cerebral amyloid angiopathy (CAA)—unrelated ICH cohorts

<table>
<thead>
<tr>
<th>CAA-unrelated ICH cohorts (study reference)</th>
<th>CMBs burden</th>
<th>OR (95% CI)</th>
<th>Events, CMBs (n/N)</th>
<th>Events, no CMBs (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMBs presence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 27</td>
<td></td>
<td>3.25 (0.18, 59.96)</td>
<td>5/155</td>
<td>0/44</td>
</tr>
<tr>
<td>Ref 26</td>
<td></td>
<td>10.73 (0.56, 205.89)</td>
<td>4/40</td>
<td>0/43</td>
</tr>
<tr>
<td>Ref 25</td>
<td></td>
<td>2.47 (0.11, 53.85)</td>
<td>2/43</td>
<td>0/20</td>
</tr>
<tr>
<td>Ref 24</td>
<td></td>
<td>2.17 (0.22, 21.62)</td>
<td>3/61</td>
<td>1/43</td>
</tr>
<tr>
<td>Ref 21</td>
<td></td>
<td>0.96 (0.04, 24.35)</td>
<td>1/74</td>
<td>2/23</td>
</tr>
<tr>
<td>Ref 22</td>
<td></td>
<td>2.34 (0.50, 10.95)</td>
<td>11/133</td>
<td>2/54</td>
</tr>
<tr>
<td>Ref 28</td>
<td></td>
<td>2.05 (0.08, 53.05)</td>
<td>1/29</td>
<td>0/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td></td>
<td>1.98 (0.20, 19.41)</td>
<td>3/121</td>
<td>1/79</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.040 (I²=0.0%, p=0.986, X² pool=1.38)</strong></td>
<td></td>
<td>2.48 (1.04, 5.90)</td>
<td>30/656</td>
<td>4/325</td>
</tr>
<tr>
<td><strong>1 CMB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 27</td>
<td></td>
<td>1.00 (0.02, 51.80)</td>
<td>0/00</td>
<td>0/44</td>
</tr>
<tr>
<td>Ref 26</td>
<td></td>
<td>1.00 (0.02, 59.80)</td>
<td>0/3</td>
<td>0/43</td>
</tr>
<tr>
<td>Ref 25</td>
<td></td>
<td>4.92 (0.19, 130.38)</td>
<td>1/13</td>
<td>0/20</td>
</tr>
<tr>
<td>Ref 24</td>
<td></td>
<td>2.63 (0.23, 30.24)</td>
<td>2/24</td>
<td>1/43</td>
</tr>
<tr>
<td>Ref 21</td>
<td></td>
<td>1.00 (0.02, 53.17)</td>
<td>0/15</td>
<td>0/23</td>
</tr>
<tr>
<td>Ref 22</td>
<td></td>
<td>2.26 (0.30, 17.05)</td>
<td>2/25</td>
<td>2/54</td>
</tr>
<tr>
<td>Ref 28</td>
<td></td>
<td>1.00 (0.02, 55.40)</td>
<td>0/7</td>
<td>0/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td></td>
<td>1.28 (0.05, 32.50)</td>
<td>0/20</td>
<td>1/79</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.257 (I²=0.0%, p=0.997, X² pool=0.87)</strong></td>
<td></td>
<td>1.87 (0.63, 5.54)</td>
<td>5/147</td>
<td>4/325</td>
</tr>
<tr>
<td><strong>2-4 CMBs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 27</td>
<td></td>
<td>2.45 (0.10, 61.62)</td>
<td>1/55</td>
<td>0/44</td>
</tr>
<tr>
<td>Ref 26</td>
<td></td>
<td>15.00 (0.68, 330.97)</td>
<td>2/16</td>
<td>0/43</td>
</tr>
<tr>
<td>Ref 25</td>
<td></td>
<td>4.56 (0.17, 120.28)</td>
<td>1/14</td>
<td>0/20</td>
</tr>
<tr>
<td>Ref 24</td>
<td></td>
<td>0.91 (0.04, 23.64)</td>
<td>0/15</td>
<td>1/43</td>
</tr>
<tr>
<td>Ref 21</td>
<td></td>
<td>1.00 (0.02, 52.29)</td>
<td>0/31</td>
<td>0/23</td>
</tr>
<tr>
<td>Ref 22</td>
<td></td>
<td>1.96 (0.30, 11.63)</td>
<td>3/45</td>
<td>2/54</td>
</tr>
<tr>
<td>Ref 28</td>
<td></td>
<td>1.00 (0.02, 54.93)</td>
<td>0/8</td>
<td>0/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td></td>
<td>2.11 (0.13, 34.64)</td>
<td>1/38</td>
<td>1/79</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.114 (I²=0.0%, p=0.943, X² pool=2.28)</strong></td>
<td></td>
<td>2.30 (0.82, 6.45)</td>
<td>8/222</td>
<td>4/325</td>
</tr>
<tr>
<td><strong>5-10 CMBs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 27</td>
<td></td>
<td>9.47 (0.44, 205.44)</td>
<td>2/25</td>
<td>0/44</td>
</tr>
<tr>
<td>Ref 26</td>
<td></td>
<td>1.00 (0.02, 54.63)</td>
<td>0/7</td>
<td>0/43</td>
</tr>
<tr>
<td>Ref 25</td>
<td></td>
<td>1.00 (0.02, 53.60)</td>
<td>0/13</td>
<td>0/20</td>
</tr>
<tr>
<td>Ref 24</td>
<td></td>
<td>1.67 (0.06, 44.48)</td>
<td>0/8</td>
<td>1/43</td>
</tr>
<tr>
<td>Ref 21</td>
<td></td>
<td>1.00 (0.02, 53.44)</td>
<td>0/13</td>
<td>0/23</td>
</tr>
<tr>
<td>Ref 22</td>
<td></td>
<td>2.05 (0.33, 12.89)</td>
<td>3/41</td>
<td>2/54</td>
</tr>
<tr>
<td>Ref 28</td>
<td></td>
<td>1.00 (0.02, 55.40)</td>
<td>0/7</td>
<td>0/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td></td>
<td>1.11 (0.04, 28.25)</td>
<td>0/23</td>
<td>1/79</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.278 (I²=0.0%, p=0.980 X² pool=1.56)</strong></td>
<td></td>
<td>1.83 (0.61, 5.44)</td>
<td>5/137</td>
<td>4/325</td>
</tr>
<tr>
<td><strong>&gt;10 CMBs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 27</td>
<td></td>
<td>5.11 (0.24, 109.63)</td>
<td>2/45</td>
<td>0/44</td>
</tr>
<tr>
<td>Ref 26</td>
<td></td>
<td>17.40 (0.78, 386.56)</td>
<td>2/14</td>
<td>0/43</td>
</tr>
<tr>
<td>Ref 25</td>
<td></td>
<td>1.00 (0.02, 60.55)</td>
<td>0/3</td>
<td>0/20</td>
</tr>
<tr>
<td>Ref 24</td>
<td></td>
<td>14.00 (0.69, 283.78)</td>
<td>1/4</td>
<td>1/43</td>
</tr>
<tr>
<td>Ref 21</td>
<td></td>
<td>4.86 (0.19, 127.52)</td>
<td>1/15</td>
<td>0/23</td>
</tr>
<tr>
<td>Ref 22</td>
<td></td>
<td>4.11 (0.64, 26.50)</td>
<td>3/22</td>
<td>2/54</td>
</tr>
<tr>
<td>Ref 28</td>
<td></td>
<td>9.00 (0.32, 249.30)</td>
<td>1/7</td>
<td>0/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td></td>
<td>4.11 (0.36, 46.70)</td>
<td>2/40</td>
<td>1/79</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.001 (I²=0.0%, p=0.970 X² pool=1.80)</strong></td>
<td></td>
<td>5.57 (2.07, 14.99)</td>
<td>12/150</td>
<td>4/325</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

ICH more frequent
without CMB
ICH more frequent
with CMB

Weights are shown by the point estimate area. I² is used to test statistical heterogeneity between the subgroup pooled estimates across the different studies. CI = confidence interval; OR = odds ratio.
warfarin across the spectrum of thromboembolic and hemorrhagic risks. However, the value of MRI in stratifying patients according to their risks for recurrent ICH and ischemic events needs to be tested in randomized controlled trials.

We did not find a significantly elevated risk for recurrent ICH associated with the presence of a single CMB relative to the absence of CMB in any of the cohorts. The pathophysiologic significance of a single CMB is unclear as it might indicate a less severe

### Meta-analysis of the associations between cerebral microbleeds (CMBs) presence or burden and the risk of recurrent spontaneous intracerebral hemorrhage (ICH) in cerebral amyloid angiopathy (CAA)-related ICH cohorts

<table>
<thead>
<tr>
<th>CAA-related ICH cohorts (study reference): CMBs burden</th>
<th>OR (95% CI)</th>
<th>Events, CMBs (n/N)</th>
<th>Events, no CMBs (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMBs presence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 23</td>
<td>5.77 (1.06, 31.27)</td>
<td>15/28</td>
<td>2/12</td>
</tr>
<tr>
<td>Ref 24</td>
<td>2.81 (0.99, 6.84)</td>
<td>22/63</td>
<td>7/41</td>
</tr>
<tr>
<td>Ref 20</td>
<td>2.46 (0.76, 8.02)</td>
<td>10/68</td>
<td>4/36</td>
</tr>
<tr>
<td>Ref 28</td>
<td>0.65 (0.02, 17.51)</td>
<td>0/9</td>
<td>1/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td>2.18 (0.18, 25.77)</td>
<td>2/24</td>
<td>1/25</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.003</strong> (I²=0.0%, p=0.817, X²_ad=1.55)</td>
<td>2.69 (1.41, 5.14)</td>
<td>55/192</td>
<td>15/133</td>
</tr>
<tr>
<td><strong>1 CMB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 23</td>
<td>3.33 (0.32, 34.83)</td>
<td>2/5</td>
<td>2/12</td>
</tr>
<tr>
<td>Ref 24</td>
<td>0.86 (0.20, 3.74)</td>
<td>3/20</td>
<td>7/41</td>
</tr>
<tr>
<td>Ref 20</td>
<td>3.00 (0.56, 16.19)</td>
<td>3/11</td>
<td>4/36</td>
</tr>
<tr>
<td>Ref 28</td>
<td>1.76 (0.06, 52.71)</td>
<td>0/3</td>
<td>1/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td>3.00 (0.17, 53.71)</td>
<td>1/9</td>
<td>1/25</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.201</strong> (I²=0.0%, p=0.768, X²_ad=1.71)</td>
<td>1.81 (0.73, 4.52)</td>
<td>9/48</td>
<td>15/133</td>
</tr>
<tr>
<td><strong>2-4 CMBS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 23</td>
<td>7.50 (1.04, 54.12)</td>
<td>6/10</td>
<td>2/12</td>
</tr>
<tr>
<td>Ref 24</td>
<td>3.40 (0.96, 12.02)</td>
<td>7/17</td>
<td>7/41</td>
</tr>
<tr>
<td>Ref 20</td>
<td>2.11 (0.50, 8.82)</td>
<td>5/24</td>
<td>4/36</td>
</tr>
<tr>
<td>Ref 28</td>
<td>1.12 (0.04, 31.61)</td>
<td>0/5</td>
<td>1/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td>2.40 (0.14, 42.26)</td>
<td>1/11</td>
<td>1/25</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.006</strong> (I²=0.0%, p=0.835, X²_ad=1.45)</td>
<td>3.05 (1.38, 6.75)</td>
<td>19/67</td>
<td>15/133</td>
</tr>
<tr>
<td><strong>5-10 CMBS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 23</td>
<td>6.67 (0.79, 56.22)</td>
<td>4/7</td>
<td>2/12</td>
</tr>
<tr>
<td>Ref 24</td>
<td>5.55 (1.51, 20.37)</td>
<td>8/15</td>
<td>7/41</td>
</tr>
<tr>
<td>Ref 20</td>
<td>2.40 (0.46, 12.56)</td>
<td>3/13</td>
<td>4/36</td>
</tr>
<tr>
<td>Ref 28</td>
<td>4.11 (0.11, 151.56)</td>
<td>0/1</td>
<td>1/19</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td>3.27 (0.10, 103.42)</td>
<td>0/2</td>
<td>1/25</td>
</tr>
<tr>
<td><strong>Subtotal: p=0.001</strong> (I²=0.0%, p=0.937, X²_ad=0.81)</td>
<td>4.33 (1.82, 10.28)</td>
<td>15/38</td>
<td>15/133</td>
</tr>
<tr>
<td><strong>&gt;10 CMBS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref 23</td>
<td>5.00 (0.55, 45.39)</td>
<td>3/6</td>
<td>2/12</td>
</tr>
<tr>
<td>Ref 24</td>
<td>2.78 (0.64, 12.11)</td>
<td>4/11</td>
<td>7/41</td>
</tr>
<tr>
<td>Ref 20</td>
<td>2.67 (0.63, 11.38)</td>
<td>5/20</td>
<td>4/36</td>
</tr>
<tr>
<td>Ref 28</td>
<td>12.00 (0.53, 273.03)</td>
<td>(Excluded)</td>
<td>0/0</td>
</tr>
<tr>
<td>PITCH study (Ref 29)</td>
<td>3.40 (1.39, 8.33)</td>
<td>13/40</td>
<td>15/133</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.

Weights are shown by the point estimate area. I² is used to test statistical heterogeneity between the subgroup pooled estimates across the different studies. CI = confidence interval; OR = odds ratio.
Spontaneous ICH originates from a variety of cerebral microangiopathies with potentially distinct future stroke risks (including recurrent ICH and ischemic stroke). Our findings suggest that using MRI to determine the presumed microangiopathies underlying spontaneous ICH can improve estimation of future recurrent ICH risk. This is important to inform patients and caregivers, plan clinical services, and design clinical trials. Our data suggest that the presence and burden of CMBs on blood-sensitive MRI sequences are important for stratifying patients more prone to recurrent ICH, but their role in identifying patients at higher risk for ischemic stroke could not be addressed. Whether the balance of risk of recurrent ICH and ischemic stroke after ICH changes over time, and how antithrombotic drugs (antiplatelet and anticoagulant agents) influence this, remain important questions for randomized controlled trials, such as the ongoing RESTART (registered ISRCTN71907627) and APACHE-AF (EudraCT number: 2014-000112-33) trials testing whether a policy of starting antiplatelet or anticoagulant drugs results in a beneficial net reduction of serious vascular events compared with a policy of avoiding antithrombotic drugs.
REFERENCES


