Microbleeds, cerebral hemorrhage and functional outcome after stroke thrombolysis: individual patient data meta-analysis

Cover title: Microbleeds and thrombolysis in acute stroke

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Keywords: cerebral microbleeds, thrombolysis, intracerebral haemorrhage, cerebral small vessel disease

Total word count: 4985

Abstract word count: 249

Abstract

Background-and-Purpose: we assessed whether the presence, number and distribution of cerebral microbleeds (CMBs) on pre-IV thrombolysis acute ischaemic stroke MRI scans are associated with an increased risk of intracerebral haemorrhage (ICH), or poor functional outcome.

Methods: We performed an individual patient data meta-analysis including prospective and retrospective studies of acute ischaemic stroke treated with IV tPA. Using multilevel mixed-effects logistic regression, we investigated associations of pre-treatment CMB presence, burden (1, 2-4, ≥5 and >10) and presumed aetiology (cerebral amyloid angiopathy (CAA) defined as strictly lobar CMBs; and non-CAA) with symptomatic ICH (sICH), parenchymal haematoma (within (PH) and remote from the ischaemic area (PHr)); and poor 3-6 month functional outcome (modified Rankin Score (mRS) >2).

Results: In 1973 patients from eight centres, the crude prevalence of CMBs was 526/1973 (26.7%). 77/1973 (3.9%) patients suffered sICH; 210/1806 (11.6%) PH, and 56/1720 (3.3%) PHr. In adjusted analyses, patients with CMBs (compared to those without CMBs) had increased risk of PH (OR: 1.50; 95%CI: 1.09-2.07; p=0.013), and PHr (OR: 3.04; 95%CI: 1.73-5.35; p<0.001) but not sICH. Both CAA and non-CAA patterns of CMBs were associated with PH and PHr. Increasing CMB burden category was associated with the risk of sICH (p=0.014), PH (p=0.013) and PHr (p<0.00001). Five or more, and >10 CMBs predicted poor 3-6 month outcome (OR:1.85(95% CI 1.10-3.12, p=0.020; and OR:3.99 (95%CI: 1.55-10.22, p=0.004, respectively).

Conclusions: Increasing CMB burden is associated with increased risks of ICH (including PHr) and poor 3-6 month functional outcome after intravenous thrombolysis for acute ischaemic stroke.

Introduction

Intravenous thrombolysis with recombinant tissue plasminogen activator (IV tPA) has benefit in acute ischaemic stroke,[1] but some patients are harmed by early symptomatic intracerebral haemorrhage (sICH), associated with poor outcome.[2, 3] Inceasing age, stroke severity, blood pressure, early ischaemic change and hyperglycaemia are associated with increased sICH risk,[2-4] but have not led to robust prediction scores.[5]

Patterns of ICH after thrombolysis include haemorrhage within the infarct and remote bleeding.[4] Cerebral microbleeds (CMBs), detected on blood-sensitive MRI, are a marker of haemorrhage-prone small vessel pathology,[6] which might contribute, particularly to remote ICH. In a recent meta-analysis, pre-treatment CMBs increased the odds of sICH (pooled OR: 2.87; 95% CI: 1.76–4.69; p<0.0001),[7] but could not investigate CMB burden, distribution, or key confounders.[7]

We performed a large-scale pooled individual patient data meta-analysis of quality observational studies to test the following hypotheses: (1) there is a relationship between increasing CMB burden and ICH risk;[8, 9] (2) strictly lobar CMBs (reflecting possible or probable cerebral amyloid angiopathy [CAA]) and mixed or strictly deep CMBs (likely associated with hypertensive arteriopathy) have different effects on ICH risk; (3) CMBs are associated more strongly with the risk of remote ICH than other ICH types;[10] and (4) CMBs are associated with worse functional outcome.

Methods

Study design and inclusion criteria

We identified prospective or retrospective studies which assessed pre-treatment MRI-defined CMBs, ICH, and 3-6 month functional outcome after acute ischaemic stroke, treated solely with IV tPA, from a systematic review prepared according to PRISMA[11, 7] (updated 1st August 2015). We searched: PubMed for "micro(-)bleed*", or "micro(-)h(a)emorrhag*, or "gradient-echo", or "susceptibility-weighted" in association with "thromboly*" or "tPA", or "tissue plasminogen activator";[7] reference lists; and authors' own files. Supplementary Figure 1 shows a flow diagram.

We collected anonymised individual patient detailed clinical data, and CMB counts in lobar, deep and infratentorial regions according to standardised definitions[6, 12, 13] using

standardised report forms. A pre-specified protocol was circulated to collaborators, but not published.

Outcomes

We defined ICH according to European Cooperative Acute Stroke Study II (ECASS-2)[14, 15] including: haemorrhagic infarction (HI); parenchymal haemorrhage (PH); and symptomatic ICH[16] (sICH, acute intracerebral blood and associated increase in NIHSS ≥4 points, except one study[17] which used the definition in the PROACT-II trial).[18] Remote parenchymal haemorrhage (PHr) was defined as ICH remote from the symptomatic ischaemic area.[10] We defined poor outcome at 3-6 months as mRS>2.

Assessing the risk of bias

We critically appraised all studies against quality indicators,[9, 19, 20] with reference to the STROBE statement and ideal characteristics.[21] [7]

Statistical analysis

Using one-stage meta-analysis[22] and mixed-effects logistic regression (modelling different centres as random effects), we investigated the associations of CMBs presence, burden (pre-specified as 1, 2-4, 5-10 and >10 CMBs categories, clinically relevant for ICH risk[9]), number (log-transformed for normality, +1 to account for zero cells), and location, with ICH subtypes (sICH, PH, PHr) and functional outcome, using no CMBs as a reference group. The overall p-value for CMBs as a categorical predictor was obtained and reported for each ICH outcome. CMB distribution was classified as "CAA-related" (strictly lobar, including possible and probable CAA), and "non-CAA-related" (mixed or strictly deep). We adjusted all models for sICH risk factors available in all patients (treatment delay, age, and baseline NIHSS, as continuous variables, log transformed as appropriate);[1] and for MRI sequence characteristics (T2*-GRE/SWI and field strength) which influence CMBs detection.[23] In post-hoc sensitivity analyses, we also adjusted for sex, hypertension, atrial fibrillation, and admission systolic and diastolic blood pressures. We used a similar approach to investigate CMBs as a predictor of poor 3-6 month functional outcome (mRS>2). We used Stata 13 (StataCorp LP, Texas) and prepared this report with reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD)[24] (supplemental Table I) and the Cochrane Handbook.

Results

We obtained data for 2048 participants from eight centres [8, 17, 25-28]. Individual patient data was not available from the BRASIL multicenter study (n=570)[29, 30] with similar quality and characteristics to studies included.[7] We excluded one study of mainly IV and intra-arterial treatment.[31] We included 1973 (96%) participants in ICH analyses and 1894 (93%) in functional outcome analysis. One study (n=253) did not provide PHr[32] or CMB distribution data;[32] another (n=167)[17] did not provide HT/PH data, resulting in different numbers in outcome analyses (Supplemental Figure I and Supplemental Table II). Details of the cohorts included are provided in Tables 1 and 2.

Crude prevalence rates were as follows: any CMBs 526/1973 (26.7%); sICH 77/1973 (3.9%); PH 210/1806 (11.6%); PHr 56/1720 (3.3%); and HI 338/1806 (18.7%; symptomatic in 9 cases). In adjusted analyses (Table 3), patients with any CMBs (compared to those without CMBs) had a higher risk of PH (OR: 1.50; 95%CI: 1.09-2.07), and PHr (OR: 3.04; 95%CI: 1.73-5.35), but not sICH (OR: 1.42; 95%CI: 0.86-2.35;) or HI. In the overall full 'categorical' model, increasing CMBs burden (1, 2-4, 5-10, and >10) was associated with sICH, PH and PHr (overall p-values: 0.014, 0.013 and <0.00001 respectively); effect estimates for different CMBs burden categories and log CMBs number are shown in Table 3.

CAA-related CMB increasing burden category was associated with the risk of PHr (overall p=0.001), and marginally with PH (overall p=0.06) (Table 4). Increased burden category of non-CAA CMBs was associated with the risk of PH (overall p=0.006) and PHr (overall p=0.003); effect estimates of different CMBs distribution and burden categories and log CMBs number are shown in Table 4.

Results were similar in sensitivity analyses also adjusted for sex, hypertension, atrial fibrillation and admission systolic and diastolic blood pressure. The main fully adjusted model for CMB burden is summarised in Supplemental Table III.

746 of 1894 (39%; 95%CI: 37-42%) patients had poor outcome (mRS>2) at 3–6 months, which was associated with ≥5 and >10 CMBs (OR:1.85 (95% CI 1.10-3.12, p=0.020; and OR:3.99 (95%CI: 1.55-10.22, p=0.004, respectively). Non-CAA-related CMBs (but not CAA-related CMBs) predicted poor outcome; CMBs were not associated with 3-6 month mortality (Table 5).

Discussion

Our individual patient data meta-analysis shows that pre-thrombolysis CMBs are independently associated with increased risk of ICH and poor functional outcome after acute ischaemic stroke. CMBs might be most strongly associated with PHr than PH, but the odds ratio 95% confidence intervals overlapped. Although CMB presence was not related to an increased risk of sICH as suggested by previous meta-analyses[7] (perhaps due to the inclusion of slightly different cohorts and model adjustments),[25, 30] increasing CMB category burden was associated with increased risk of sICH, PH and PHr. More than 5 CMBs was associated with a doubling, and >10 CMBs with a four-fold increase in the odds of poor functional outcome.

Most ICHs after thrombolysis occur within the acute ischemic area, but a minority occur remotely.[4, 10] While ICH within the ischaemic area results from reperfusion and vascular injury in the territory of an occluded vessel, PHr is plausibly due to widespread pre-existing bleeding-prone cerebral small vessel diseases.[4, 10, 33] We observed a strong association between PHr and CMBs, supporting this hypothesis, consistent with an association between 'previous vascular pathology' and PHr.[10] CMBs develop rapidly in acute ischemic stroke, a process which could be aggravated by thrombolysis.[34] Increasing CAA-related CMBs burden was associated with PHr (p=0.001) but only marginally with PH (p=0.06) while non-CAA-related CMB burden was linked to PH and PHr. Five or more CAA-related CMBs had the highest PHr risk, but with very wide confidence intervals. Previous neuropathological data directly link CAA to thrombolysis-related ICH,[33] as does an amyloid-β PET study.[35] Although the effect sizes in our study suggest a possible stronger relationship for CMBs with PHr, we did not definitively demonstrate this statistically, so this should be investigated further in future studies.

Multiple CMBs (≥5 or >10) were associated with increased risk of poor outcome, though only 35/20143 (2%) of patients had >10 CMBs; some clinicians might already exclude similar patients from IV tPA. Worse functional outcome with multiple CMBs might be explained by vulnerability to acute ischaemia (through impaired microcirculation or collateral function), or poorer functional recovery due to impaired cerebral connectivity.

Our study has strengths: large-scale individual patient data gave statistical power to test hypotheses about CMB burden and distribution,[7, 9, 20] using standardized classification and adjustment for confounding factors.

We acknowledge limitations. Heterogeneous study characteristics might still partly account for some reported associations: MRI parameters could affect CMBs category; not all patients undergo MRI; and patient characteristics, treatment, and follow-up protocols varied.[7] We could not include some potential confounders, e.g. infarct volume, acute thrombus, clinical syndrome, concomitant treatments (antiplatelets, anticoagulants, statins), early ischaemic changes, hyperglycaemia, leukoaraiosis, or pre-stroke mRS.

We confirm that CMBs are associated with an increased risk of ICH after IV thrombolysis. Although some CMB subgroups had higher risk of poor functional outcome, our data do not establish the risk vs. benefit ratio of IV tPA in relation to CMBs so treatment should not be witheld from otherwise eligible patients solely because of CMBs. However, clinicians might consider many CMBs a risk factor for ICH or poor outcome, to inform clinical decisions and prognosis; randomized trials of pre-treatment CMB evaluation versus standard imaging might be justified.

Acknowledgements:

Author contributions

AC and DJW designed the study. All authors contributed to original acquisition or collation of data. AC, ZF, DJW and GA designed the statistical analysis plan. AC created the combined dataset and performed the statistical analysis (independently replicated and checked by GA and DW). AC and DJW wrote the first draft. All authors contributed to interpretation of results, critical revisions, and approved the manuscript.

Disclosures:

GWA has undertaken consultancy for iSchemaView, with an equity interest; and consultancy for Medtronic.

CC is a member of the Institut Universitaire de France.

CHN received funding from the German Federal Ministry of Education and Research via the grant Center for Stroke Research Berlin (01 EO 0801).

JFS participates in the Charité Clinical Scientist Program funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health.

JLS has consulted on stroke prevention clinical trial design and conduct for Boehringer Ingelheim.

DJW has received funding from Bayer, Allergan and Ixico. This work was partly undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.

Tables

Table 1. Baseline characteristics of patients

	Turc et al.[25] (Lille cohort)	**Turc et al.[25] (Paris cohort)**	**Kakuda et al[27]**	**Yan et al [26]**	**Dannenberg et al [8]**	**Gratz et al [17]**	**Moriya et al [28]**	**Kimura et al [32]**	**TOTAL**
Patient number (% men)	375 (42%)	342 (56%)	70 (57%)	433 (66%)	326 (51%)	167 (64%)	71 (70%)	257 (56%)	2048 (56%)
Age (yrs) median (IQR)	77 (63 to 85)	70 (58 to 80)	75 (66 to 82)	67 (58 to 75)	76 (68 to 84)	71 (63 to 79)	75 (66 to 81)	77 (69 to 83)	73 (62 to 81)
Treatment delay (hours) median (IQR)	2.5 (2 to 3.2)	2.7 (1.2 to 2.1)	5.4 (5.2 to 5.8)	3.6 (2.7 to 4.5)	2.3 (1.8 to 3.4)	3.2 (2.6 to 3.8)	2.5 (2.1 to 2.7)	2.5 (2.1 to 2.9)	2.8 (2.1 to 3.7)
Stroke severity (NIHSS) median (IQR)	9 (5 to 16)	13 (8 to 19)	12 (8 to 16)	10 (5 to 15)	8 (5 to 14)	6 (5 to 9)	14 (9 to 20)	13 (7 to 19)	10 (6 to 16)
History of hypertension	255 (68%)	197 (58%)	42 (60%)	295 (68%)	277 (85%)	124 (71%)	-	176 (68%)	1366/1977 (69%)
History of diabetes mellitus	62 (17%)	51 (15%)	18 (26%)	92 (21%)	74 (23%)	34 (20%)	-	62 (24%)	393/1976 (20%)
History of previous ischaemic stroke	42 (11%)	29 (8%)	14 (20%)	68 (16%)	80 (25%)	22 (13%)	-	N/A	255/1720 (15)
History of atrial fibrillation	82 (22%)	84 (25%)	30 (43%)	164 (38%)	128 (39%)	54 (38%)	40 (56)	126 (49%)	708 (35%)
Systolic blood pressure on admission (mmHg) median (IQR)	157 (140 to 170)	155 (141 to 170)	150 (135 to 164)	154 (138 to 170)	157 (140 to 172)	162 (140 to 178)	166 (140 to 190)	152 (140 to 166)	155 (140 to 170)
Diastolic blood pressure on admission (mmHg) median (IQR)	80 (70 to 90)	83 (73 to 93)	76 (64 to 86)	86 (77 to 96)	85 (74 to 95)	87 (74 to 100)	-	83 (72 to 94)	83 (74 to 94) *1959 observations
Any symptomatic ICH	28 (7%)	13 (4%)	7 (10%)	9 (2%)	10(3%)	6 (3%)	5 (7%)	6 (2%)	84 (4%)
PH	65 (17%)	27 (8%)	13 (19%)	40 (9%)	24 (7%)	-	7 (10%)	47 (18%)	223 (12%)
PHr	20 (5%)	4 (1%)	0 (0%)	14 (3%)	8 (2%)	13 (7%)	2 (3%)	-	58/1733 (3%)
mRS median (IQR)	2 (1-4)	2 (1 to 4)	2.5 (1 to 4)	2 (1 to 4)	2 (1 to 4)	2 (1 to 3)	4 (3 to 6)	4 (1 to 5)	2 (1 to 4)
mRS>2 at 3-6 months n (%)	169 (45%)	160 (47%)	35 (50%)	179 (41%)	158 (49%)	48 (30%)	24 (89%)	157 (65%)	930/1968 (47%)
CMBs presence n (%)	80 (21%)	70 (21%)	11 (16%)	166 (38%)	80 (25%)	38 (22%)	14 (20%)	82 (32%)	541 (26%)

Single CMB, n (%)	46 (12%)	46 (14%)	8 (11%)	72 (17%)	52 (16%)	21 (12%)	6 (8%)	33 (13)	284 (14%)
≥2 CMBs, n (%)	34 (9%)	24 (7%)	3 (4%)	94 (22%)	28 (9%)	17 (10%)	8 (11%)	49 (19)	257 (13%)
2-4 CMBs, n (%)	22 (6%)	11 (3%)	2 (3%)	52 (12%)	19 (6%)	14 (8%)	6 (8%)	38 (15)	164 (8%)
≥5 CMBs, n (%)	12 (3%)	13 (4%)	1 (1%)	42 (10%)	9 (3%)	3 (2%)	2 (3%)	11 (4)	93 (5%)
5-10 CMBs, n (%)	9 (2%)	11 (3%)	1 (1%)	23 (5%)	5 (2%)	1 (1%)	0 (0%)	8 (3)	58 (3%)
>10 CMBs, n (%)	3 (1%)	2 (1%)	0 (0%)	19 (4%)	4 (1%)	2 (1%)	2 (3%)	3 (1)	35 (2%)
CAA-related CMBs (i.e. strictly lobar), n (%)	31 (8%)	38 (11%)	0 (0%)	61 (14%)	41 (12%)	16 (9%)	1 (1%)	-	188/1790 (11%)
Non-CAA-related CMBs (i.e. mixed or strictly deep), n (%)	49 (13%)	32 (9%)	11 (16%)	105 (24%)	39 (12%)	22 (13%)	13 (18%)	-	271/1790 (15%)

Categorical data presented as n (%).

Table 2. Risk of bias and quality indicators

Study	Study size (>100)	Selection of exposed and non-exposed cohorts from the same population	CMB criteria clearly defined	ICH criteria clearly defined	Standardised rating scale or trained inter/intra-observer agreement reported	Classification of CMB distribution	Assessments of CMB and ICH independent	Adjusted results for other risk factors	No. of quality indicators fulfilled
Turc et al.	✓	✓	✓	✓	✓	✓	✓	✓	8/8
Kakuda et al.	x	✓	✓	✓	✓	x	✓	✓	6/8
Yan et al.	✓	✓	✓	✓	✓	✓	✓	✓	8/8
Dannenberg et al.	✓	✓	✓	✓	✓	✓	✓	✓	8/8
Gratz et al.	✓	✓	✓	✓	✓	✓	?	✓	7/8
Moriya et al.	x	✓	x	✓	x	x	?	✓	3/8
Kimura et al.	✓	✓	x	✓	x	x	✓	✓	5/8

✓ = Yes; x = No; ? = not reported; CMB=cerebral microbleeds; ICH=intracerebral haemorrhage

Table 3. Adjusted odds ratios (95% CI) for associations between cerebral microbleed (CMB) presence and burden and the risk of ICH after IV thrombolysis. Overall p-values for the main model including CMBs as a single categorical variable are shown in the right column for each outcome. Asterisks next to CMBs burden categories denote statistical significance

	Symptomatic ICH (per ECASS-2 definition) OR (95% CI); p-value (N=1973)		**Any HT (vs. no ICH) (per ECASS-2 definition) OR (95% CI); p-value (N=1806)**		**PH (vs. no or non-PH ICH)† (per ECASS-2 definition) OR (95% CI); p-value (N=1806)**		**PHr (remote parenchymal ICH, vs. no or non-remote ICH) OR (95% CI); p-value (N=1720)**	
A. CMBs presence Model	1.42 (0.86-2.35)		0.94 (0.70-1.25)		1.50 (1.09-2.07) *		3.04 (1.73-5.35) ***	
B. Main Model (CMBs categorised according to burden)								
Single CMB	0.84 (0.39-1.82)	Overall p=0.014	0.98 (0.68-1.40)	Overall p=0.239	1.15 (0.75-1.79)	Overall p=0.013	1.75 (0.80-3.86)	Overall p<0.00001
2-4 CMBs	2.46 (1.26-4.80) *		1.13 (0.71-1.79)		1.60 (0.98-2.61)		3.99 (1.86-8.54) ***	
5-10 CMBs	0.47 (0.06-3.48)		0.85 (0.40-1.82)		2.06 (1.02-4.18) *		3.59 (1.16-11.19) *	
>10 CMBs	3.65 (1.17-11.42)*		0.13 (0.02-0.98)*		3.20 (1.40-7.29) *		9.09 (3.25-25.40) ***	
C. Log CMBs number Model	1.36 (1.01-1.84)*		0.87 (0.70-1.08)		1.42 (1.17-1.74) **		2.07 (1.57-2.74) ***	

All models are adjusted for the following co-variates: treatment delay (log transformed for normality), age, baseline stroke severity, MRI sequence (T2*-GRE vs. SWI) and field strength (1.5T vs. 3T) and stratified by centre. The 'No CMBs' group is the reference group for all analyses.

*p<0.05; **p<0.005; ***p<0.001 †Results similar for PH vs. no ICH

Table 4. Adjusted odds ratios (95% CI) for cerebral microbleed (CMB) distribution and the risk of ICH after IV thrombolysis. Overall p-values for the Main model including CMBs as a single categorical variable are shown on the right column for each outcome. Asterisks next to CMBs burden categories denote statistical significance

	Symptomatic ICH (per ECASS-2 definition) OR (95% CI)		**PH (vs. no or non-PH ICH)† (per ECASS-2 definition) OR (95% CI)**		**PHr (remote parenchymal ICH, vs. no or non-remote ICH) OR (95% CI)**	
A. CAA-related CMBs Models	N=1458		N=1311		N=1458	
i. CAA-related CMBs presence Model	1.14 (0.49-2.67)		1.78 (1.05-3.00) *		3.26 (1.54-6.91) **	
ii. Main Model (CAA-related CMBs categorised by burden)						
Single CMB	0.65 (0.19-1.19)	Overall p=0.113	1.42 (0.75-2.68)	Overall p=0.06	2.18 (0.85-5.61)	Overall p=0.001
2-4 CMBs	2.67 (0.74-9.66)		2.39 (0.91-6.27)		4.89 (1.51-15.82) *	
≥5 CMBs	2.31 (0.24-22.19)		4.77 (1.03-22.05) *		16.40 (2.87-93.58) **	
iii. Log CMBs number Model	1.49 (0.74-2.98)		2.06 (1.32-3.21) **		3.77 (2.12-6.71) ***	
B. Non-CAA-related CMBs Models	N=1538		N=1386		N=1538	
i. Non-CAA-related CMBs presence Model	1.62 (0.89-2.96)		1.77 (1.55-2.70) *		2.99 (1.56-5.72) **	
ii. Main Model (Non-CAA-related CMBs categorised by burden)						
Single CMB	1.20 (0.46-3.15)	Overall p=0.123	0.94 (0.45-1.97)	Overall p=0.006	1.35 (0.40-4.60)	Overall p=0.003
2-4 CMBs	2.79 (1.23-6.34)*		2.06 (1.06-4.01) *		3.62 (1.48-8.84) *	
5-10 CMBs	0.58 (0.08-4.38)		3.16 (1.45-6.86) **		3.95 (1.24-12.56) *	
>10 CMBs	1.87 (0.41-8.51)		2.63 (0.99-7.01)		5.61 (1.71-18.36) **	
iii. Log CMBs number Model	1.25 (0.88-1.76)		1.47 (1.16-1.87) **		1.85 (1.37-2.50) ***	

All models are adjusted for the following co-variates: treatment delay (log transformed for normality), age, baseline stroke severity, MRI sequence (T2*-GRE vs. SWI) and field strength (1.5T vs. 3T) and stratified by centre. * Results similar for PH vs. no ICH. The 'No CMBs' group is the reference group for all analyses.

*p<0.05; **p<0.005; ***p<0.001

†Results similar for PH vs. no ICH

Table 5. Adjusted odds ratios (95% CI) for cerebral microbleeds (CMBs) and functional outcome after IV thrombolysis.

	Poor outcome (mRS>2) at 3-6 months OR (95% CI) (n=1894)	**Death at 3-6 months OR (95% CI)**
A. CMBs presence Model	1.26 (0.98-1.63)	0.86 (0.60-1.24)
B. Main Model (CMBs categorised by burden)		
Single CMB	1.19 (0.86-1.64)	0.75 (0.45-1.21)
2-4 CMBs	1.13 (0.76-1.70)	1.00 (0.56-1.78)
5-10 CMBs	1.28 (0.69-2.39)	0.47 (0.16-1.39)
>10 CMBs	3.99 (1.55-10.22)**	2.44 (0.92-6.49)
C. Log CMBs number Model	1.28 (1.08-1.53)*	1.05 (0.82-1.34)
CMBs distribution/presumed underlying aetiology		
CAA-related CMBs Log CMBs number Model ≥5 CMBs Model †	 1.18 (0.81-1.75) 4.18 (0.42-41.21)	-
Non-CAA-related CMBs Log CMBs number Model >10 CMBs Model	 1.30 (1.06-1.58)* 3.39 (1.29-8.89)*	-

All models are adjusted for the following co-variates: treatment delay (log transformed for normality), age, baseline stroke severity, sex, hypertension, atrial fibrillation, MRI sequence (T2*-GRE vs. SWI and 1.5T vs. 3T). and stratified by centre. The 'No CMBs' group is the reference group for all analyses.

*p<0.05; **p<0.005

†Effect sizes not calculated for >10 CMBs due to the small number of patients.

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