Brain microbleeds as a potential risk factor for antiplatelet-related intracerebral haemorrhage: hospital-based, case—control study

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ABSTRACT

Background Intracerebral haemorrhage (ICH) is an uncommon but devastating complication of regular antiplatelet use: identifying high-risk patients before treatment could potentially reduce this hazard. Brain microbleeds on gradient-recalled echo (GRE) T2*-weighted MRI are considered a biomarker for bleeding-prone small-vessel diseases. The authors hypothesised that microbleeds are a risk factor for antiplatelet-related ICH, and investigated this in a hospital-based matched case—control study.

Methods Cases of spontaneous ICH were ascertained, using overlapping methods, from a prospective database of 1017 consecutive unselected patients referred to our stroke unit and associated clinics. For each case of antiplatelet-related ICH, two controls matched for age, sex and hypertension without history of ICH on antiplatelet therapy were selected. Microbleeds were identified by a trained observer blinded to clinical details.

Results Microbleeds were more frequent in antiplatelet users with ICH than in matched antiplatelet users without ICH (13/16 (81%) vs 6/32 (19%), $p=0.004$) and patients with non-antiplatelet-related ICH (13/16 (81%) vs 15/33 (45%), $p=0.03$). The frequency of lobar microbleeds was 11/16 (69%) in antiplatelet-related ICH versus 11/33 (33%) in non antiplatelet-related ICH ($p=0.032$). Microbleeds were more numerous in antiplatelet users with ICH compared with controls ($p=0.016$). The number of microbleeds was associated with the risk of antiplatelet-related ICH (adjusted OR 1.33 per additional microbleed, 95% CI 1.06 to 1.66, $p=0.013$).

Conclusions Brain microbleeds are associated with antiplatelet-related ICH. In patients with a large number of lobar microbleeds, the risk of ICH could outweigh the benefits of antiplatelet therapy. Larger prospective studies to investigate the prognostic significance of microbleeds in regular antiplatelet users are warranted.

Antiplatelet agents, especially aspirin, are widely used for the primary and secondary prevention of ischaemic stroke (IS) and cardiovascular diseases. Intracerebral haemorrhage (ICH) is an uncommon but often fatal or disabling complication of long-term antiplatelet use,^{1 2} for which effective treatment remains limited. A meta-analysis of 16 randomised, placebo-controlled clinical trials showed that treatment with aspirin was associated with an RR of haemorrhagic stroke of 1.84 ($p=0.001$).³ In patients at high cardiovascular risk, the benefit of aspirin in preventing vascular events outweighs the risk of ICH.^{2 4} However, in those with a lower cardiovascular risk (eg, healthy elderly individuals who take

aspirin because of a widespread perception of overall benefit), the benefits of aspirin are minimal⁵ and could be offset by even a small increase in the risk of ICH.^{3 6} A clinical decision about the use of antiplatelet treatment must weigh the benefits of treatment against the risks, including ICH. If patients at high risk of ICH could be identified prior to treatment, they could potentially be spared this potentially devastating hazard. This is especially important, since the increasing use of anticoagulants and antiplatelet drugs in an ageing population has led to a dramatic increase in antithrombotic-related ICH in the past two decades.⁷

Clinical factors associated with an increased ICH risk during anticoagulation include age, previous stroke and severe hypertension.² Brain-imaging studies using CT suggest that leucoaraiosis is a risk factor for ICH in patients taking Warfarin ($RR \sim 7$),^{8 9} but there have been few studies of imaging risk factors for aspirin-related ICH. Microbleeds detected on MRI of the brain are considered a biomarker of bleeding-prone small-vessel diseases (in particular hypertensive small-vessel arteriopathy and cerebral amyloid angiopathy (CAA)), and several studies in patients with stroke suggest that they increase the future risk of ICH.^{10 11} They are very common in patients with stroke or TIA¹² and in healthy elderly individuals (up to 40%).¹³ Recent studies have suggested an association between microbleeds and antiplatelet use,¹⁴ and between microbleeds and the risk of antithrombotic-related ICH with a dose-dependent effect.¹⁵ In patients with CAA, this risk could be particularly high, especially in older people.⁷ Since CAA is radiologically characterised by microbleeds in a lobar distribution in the brain,¹³ we hypothesised that brain microbleeds—especially lobar—are associated with antiplatelet-related ICH. We used a case—control study design to compare microbleed prevalence and distribution in antiplatelet users with symptomatic ICH compared with matched ICH-free antiplatelet users. Because microbleeds are known to be associated with ICH regardless of antiplatelet use, we also conducted a case—case comparison study between antiplatelet users with ICH and patients with spontaneous ICH unrelated to antiplatelets.

METHODS

Subjects

We studied a population of 1017 unselected consecutive patients referred to the Stroke Unit and associated neurovascular clinics at the National Hospital for Neurology and Neurosurgery (NHNN) from December 2000 to February 2008. The Stroke

Unit takes all patients with suspected stroke admitted from the surrounding district and has a policy of performing MRI with gradient-recalled echo (GRE) T2* sequence in all patients with ICH and IS unless contraindicated, allowing us to minimise selection bias. MRIs are performed within 5 days of admission or on the day of the clinic. All patients have standard questions including questions about antithrombotic use recorded onto a written proforma.

Cases were patients with spontaneous symptomatic ICH occurring during regular antiplatelet treatment. All patients with ICH were ascertained with overlapping methods including MRI images, reports and medical records. The intake and duration of antiplatelet treatment at the time of admission or visit were ascertained from hospital and GP records. For each antiplatelet user with ICH, two controls matched for age, sex and hypertension and without any history of ICH were selected randomly (blinded to other clinical details or microbleed ratings) from prospective databases of consecutive patients admitted to the stroke unit and associated neurovascular clinics. Controls were patients using antiplatelet agents admitted to the department due to suspected IS or TIA.

We recorded the blood pressures taken at the time of admission or visit. Patients were considered hypertensive when they were on antihypertensive drugs or when their blood pressure was $\geq 140/90$ for more than 7 days after admission. We compared baseline demographics, prevalence of leucoaraiosis and presence, number and distribution of microbleeds between cases and controls. We also performed a case–case comparison between antiplatelet users and non-antiplatelet users with ICH. The study received ethics approval by The NHNN & Institute of Neurology Joint Research Ethics Committee.

Imaging analysis

MRIs were carried out at 1.5 T field strength. GRE T2* sequences were obtained in the axial plane on a Genesis Signa Scanner (repetition time (TR) 300 ms, echo time (TE) 40 ms, flip angle (FA) 20°, FoV 24×18, matrix 256×160, slice thickness 5 mm, slice gap 1.5 mm, NEX 1). A minority of patients were scanned on a Siemens Avanto Scanner (TR 800 ms, TE 26 ms, FA 20°, FoV 24×18, matrix 512×448, slice thickness 5 mm, slice gap 1.5 mm, NEX 1). Microbleeds were identified by a neurologist trained in microbleed identification (SG) and blinded to all clinical information, who rated microbleed presence, number and distribution on GRE T2* images using the microbleed anatomical rating scale (MARS), a validated scale for microbleed reporting in all brain locations.¹⁶ Leucoaraiosis was defined as the presence of early confluent or confluent white-matter lesions, corresponding to a Wahlund score equal or above 2.¹⁷ Lacunes were defined as brain infarcts measuring between 3 and 20 mm in size and mostly present in the deep brain structures.¹⁸ According to previous descriptions, they were characterised as being hypointense in T1-weighted and FLAIR images, and surrounded by a hyperintense rim in FLAIR images.^{19–20} ICHs were classified as deep, lobar and posterior fossa. According to MARS, microbleed distribution was classified as deep, lobar and posterior fossa.

Statistical analysis

Blinded analysis of the data was performed with the Data Analysis and Statistical Software STATA Intercooled version 8.0 and the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS, Chicago, Illinois). Conditional logistic regression analysis was used for the comparison of characteristics between the case group (antiplatelet users with ICH) and matched control group (antiplatelet users without ICH). A two-

sided independent groups t test was used for variables that are normally distributed in each group, the Fisher exact test for comparison of proportions and the Mann–Whitney U test for comparison of variables that are not normally distributed in at least one of the two groups. We investigated the effects of the number of microbleeds in predicting antiplatelet-related ICH, with adjustment for leucoaraiosis. For the case–case comparison study, we used two-sided independent t test, the Fisher exact tests and non-parametric Mann–Whitney U tests to compare demographics and radiological features between the two groups. Statistical significance was declared if $p < 0.05$.

RESULTS

Demographics

We identified a total of 164 subjects (N=164) with ICH admitted during the study period. Of these, we excluded patients with structural and secondary causes of ICH (aneurysms, tumours, cavernomas, arteriovenous malformations, coagulation disorders or use of oral anticoagulants, venous thrombosis or head injuries) (N=69). We then excluded patients in whom the MRI images were not of satisfactory quality (N=3), did not include a GRE T2* sequence (N=8) or were not performed (N=35). Of the remaining 49 patients (30%), we identified 16 cases (patients on regular antiplatelet therapy) and 33 non-antiplatelet users with ICH (figure 1). Patients included in the study were slightly older than patients excluded due to a lack of MRI ($p=0.043$). However, there was no significant difference between the two groups for any of the other vascular risk factors: hypertension, systolic blood pressure, diastolic blood pressure, statin use, median cholesterol total, smoking history, diabetes, previous history of stroke, history of atrial fibrillation, ischaemic heart disease and antithrombotic use. The proportion of patients scanned on the Siemens Avanto scanner was small: antiplatelet-related ICH (N=1, 6%), controls (N=2, 6%), non-antiplatelet-related ICH (N=3, 9%).

We selected 32 matched controls from the database of antiplatelet users without ICH. Cases and controls were well matched for all clinical characteristics and potential confounding factors including previous history of IS, ischaemic heart disease, lacunar infarcts, median dose of aspirin and duration on antiplatelets (table 1). Antiplatelet agents used by patients and controls were: aspirin (N=43), clopidogrel (N=3), aspirin plus dipyridamole (N=1) or clopidogrel plus aspirin (N=1).

Figure 1 Patient flow diagram. GRE, gradient-recalled echo; ICH, intracerebral haemorrhage.

Table 1 Characteristics of antiplatelet users with and without history of intracerebral haemorrhage

	With intracerebral haemorrhage (N=16)	Without intracerebral haemorrhage (N=32)	p Value
Clinical characteristics†			
Mean age in years (range)	70±10.5 (52–86)	67.25±9.9 (53–94)	NS
Men, N (%)	10 (62.5)	20 (62.5)	NS
Hypertension (%)	12 (75)	24 (75)	NS
Systolic blood pressure (mm Hg)	165±26	154.85±25	NS
Diastolic blood pressure (mm Hg)	87±12	81.5±15.51	NS
Diabetes (%)	4 (25)	7 (22)	NS
Cholesterol total >6 mmol/l (%)	1 (6)	3 (9)	NS
Statin use (%)	5 (31)	14 (52)	NS
Ischaemic heart disease (%)	6 (37.5)	13 (40.6)	NS
Atrial fibrillation (%)	2 (12.5)	6 (18.7)	NS
Previous stroke (%)	8 (50)	16 (50)	NS
Smoking (%)	10 (62.5)	17 (53)	NS
Duration, months (%)	41.6±48.4	37.7±43.4	NS
No taking aspirin (%)	15 (94)	30 (94)	NS
Median dose of aspirin in aspirin users in mg (range)	75 (75–300)	75 (75)	NS
Median interval stroke-MRI in days (range)	11 (2–115)	17 (0–131)	NS
Imaging characteristics			
Microbleeds			
Presence (% range)	13 (81.2, 0–28)	6 (18.8, 0–15)	0.004*
Median (range)	6.0 (0–28)	0 (0–15)	0.016*
Lobar			
Presence (%)	11 (69)	5 (15.6)	0.004*
Median (range)	3.0 (0–15)	0 (0–8)	0.016*
Deep (basal ganglia and thalamus)			
Presence (%)	9 (56.2)	3 (9.4)	<0.001*
Median (range)	1.0 (0–11)	0 (0–3)	NS
Posterior fossa (brainstem and cerebellum)			
Presence (%)	6 (37.5)	4 (12.5)	NS
Median (range)	0 (0–2)	0 (0–5)	NS
Lacunae			
Presence (%)	12 (80)	27 (84)	NS
Median (range)	2.0 (0–9)	2.5 (0–10)	NS
Leucoaraiosis			
Presence (%)	8 (50)	7 (22)	NS

*p<0.05.

†Plus–minus values are mean±SD.

NS, not significant.

Among patients with ICH related and unrelated to antiplatelet agents, the groups were similar for most clinical characteristics (table 2), but as expected, previous ischaemic heart disease and stroke were more prevalent among antiplatelet than among non-antiplatelet users (p=0.003 and <0.001).

Incidence and location of ICHs

The majority of subjects had single ICHs (N=14 (87.5%) and N=28 (85%) in antiplatelet users and non-antiplatelet users). The ICHs were most often located in the cerebral lobes (table 2). Multiple acute ICHs were seen in two antiplatelet users (12%) and five non-antiplatelet users (18%). Two patients had prior ICH, one on long-term antiplatelet therapy (6%) and one non-antiplatelet user (3%). Examples of GRE T2* images of an antiplatelet user who developed two acute lobar haemorrhages are shown in figure 2.

Comparison between cases and controls

Thirteen (81.2%) antiplatelet users with symptomatic ICH had microbleeds compared with six (18.8%) antiplatelet users without any history of ICH (p=0.004) (table 1). Microbleeds

were more numerous in subjects with ICH compared with controls (median: 6.0, range 0–28, vs median: 0, range 0–15; p=0.016). In both groups, microbleeds were more common in the lobes than in the deep or posterior fossa regions. The prevalence of leucoaraiosis was higher in antiplatelet users with ICH compared with controls (50% vs 22%, p=0.069).

Factors associated with the risk of antiplatelet-related ICH

In a conditional logistic regression, the total number of microbleeds was a significant predictor of antiplatelet-related ICH (OR 1.27, 95% CI 1.04 to 1.55, p=0.016), even after adjusting for the presence of leucoaraiosis (OR 1.33, 95% CI 1.06 to 1.66, p=0.013) (table 3). Lobar microbleeds were significantly associated with antiplatelet-related ICH after adjusting for the presence of leucoaraiosis (OR 1.42, 95% CI 1.07 to 1.89, p=0.016), whereas deep microbleeds were not (OR 5.69, 95% CI 0.95 to 34.22, p=0.057). However, the OR for the association between antiplatelet-related ICH and deep microbleeds was greater than that of lobar microbleeds (albeit with wide CIs) and approached statistical significance.

Table 2 Characteristics of subjects with symptomatic spontaneous intracerebral haemorrhage

	Antiplatelet users (N = 16)	Non-antiplatelet users (N = 33)	p Value
Clinical characteristics†			
Mean age in years (range)	70 ± 10.5 (52–86)	66 ± 10.6 (41–87)	NS
Men, N (%)	10 (62.5)	18 (54.5)	NS
Hypertension (%)	12 (75)	27 (81.8)	NS
Systolic blood pressure (mm Hg)	165 ± 26	151 ± 32	NS
Diastolic blood pressure (mm Hg)	87 ± 12	83 ± 16	NS
Diabetes (%)	4 (25)	2 (6.1)	NS
Cholesterol total >6 mmol/l (%)	1 (6)	2 (6)	NS
Statin use (%)	5 (31)	4 (13)	NS
Ischaemic heart disease (%)	6 (37.5)	1 (3)	0.003*
Atrial fibrillation (%)	2 (12.5)	3 (9.1)	NS
Previous stroke (%)	8 (50)	2 (6.1)	<0.001*
Smoking (%)	10 (62.5)	10 (30.3)	NS
Median interval stroke-MRI in days (range)	11 (2–115)	7 (0–222)	NS
Imaging characteristics			
Microbleeds			
Presence (% range)	13 (81.2, 0–28)	15 (45.4, 0–31)	0.030*
Median (range)	6.0 (0–28)	0.0 (0–31)	0.012*
Lobar			
Presence (%)	11 (69)	11 (33)	0.032*
Median (range)	3.0 (0–15)	0 (0–12)	0.016*
Deep (basal ganglia and thalamus)			
Presence (%)	9 (56.2)	9 (27.3)	NS
Median (range)	1.0 (0–11)	0 (0–17)	0.032*
Posterior fossa (brainstem and cerebellum)			
Presence (%)	6 (37.5)	5 (15)	NS
Median (range)	0 (0–2)	0 (0–8)	NS
Lacunes			
Presence (%)	12 (80)	24 (75)	NS
Median (range)	2.0 (0–9)	2.0 (0–7)	NS
Leucoaraiosis			
Presence (%)	8 (50)	8 (24)	NS

*p<0.05.

†Plus-minus values are mean ± SD.

NS, not significant.

Comparison between cases of ICH differing in the use of antiplatelets

Microbleeds were more frequent in antiplatelet users with ICH compared with patients with non-antiplatelet-related ICH (13/16 (81.2%) vs 15/33 (45.4%); p=0.030). Microbleeds were more

numerous in antiplatelet users (range 0–28, median 6.0 vs range 0–31, median 0; p=0.012), and lobar microbleeds more prevalent (69% vs 33%, p=0.032). Both deep and lobar microbleeds were more numerous in antiplatelet users than in non-antiplatelet users (p=0.032 for deep and p=0.016 for lobar microbleeds).

Figure 2 Gradient-recalled echo (GRE) T2* MRI of an antiplatelet user who developed two lobar intracerebral haemorrhages. GRE T2*-weighted axial images of a patient with antiplatelet-related intracerebral haemorrhage (ICH) demonstrating numerous lobar microbleeds (small white arrows) and three lobar haemorrhages (temporal left, parietal right, frontal right, large grey arrows). Cerebral amyloid angiopathy is likely to be the underlying cause of the microbleeds and multiple ICHs in this patient.

Table 3 Logistic regression analyses testing the factors predicting the likelihood of intracerebral haemorrhage in antiplatelet users with intracerebral haemorrhage and antiplatelet users without intracerebral haemorrhage matched for age, sex and hypertension

	OR	95% CI for OR	p Value
Presence and no of microbleeds			
Total no of microbleeds	1.27	1.04 to 1.55	0.016*
Total no of microbleeds adjusted for leucoaraiosis	1.33	1.06 to 1.66	0.013*
Distribution of microbleeds			
No of lobar microbleeds	1.35	1.06 to 1.72	0.016*
No of lobar microbleeds adjusted for leucoaraiosis	1.42	1.07 to 1.89	0.016*
No of deep microbleeds	5.86	0.96 to 35.69	0.055
No of deep microbleeds adjusted for leucoaraiosis	5.69	0.95 to 34.22	0.057

*p<0.05.

Finally, leucoaraiosis was more prevalent in antiplatelet users with ICH compared with subjects with ICH unrelated to antiplatelets, but the difference was not statistically significant (50% vs 24%, $p=0.106$).

DISCUSSION

In this case–control study, we found that microbleeds were more prevalent and numerous in antiplatelet users who developed symptomatic ICH compared with matched antiplatelet-users who did not develop ICH. The microbleed number was strongly associated with ICH risk, even after controlling for the presence of leucoaraiosis and other potential confounding factors. Our study suggests that the association of ICH with microbleeds may be more powerful than that with leucoaraiosis, although microbleeds and leucoaraiosis may reflect similar pathological damage to small vessels.²⁰ In separate regression analyses adjusted for the presence of leucoaraiosis, lobar (but not deep) microbleeds were a statistically significant predictor of antiplatelet-related ICH. These data support a potential role for brain microbleeds, particularly in a lobar distribution, as a risk factor for antiplatelet-associated ICH.

We have confirmed previous observations of a predominance of lobar microbleeds in patients with ICH;^{21–22} we also found that lobar microbleeds were more common in antiplatelet-associated ICH than in ICH unrelated to antiplatelet agents ($p=0.032$). Moreover, regression analyses indicated that lobar microbleeds were significantly associated with antiplatelet-related ICH. These observations suggest that lobar microbleeds may be more strongly related to antiplatelet-related bleeding than deep microbleeds, although our sample size is too small to confirm this hypothesis, which requires confirmation in larger studies. Previous autopsy and MRI studies suggest that lobar microbleeds are related to CAA.^{23–24} In CAA, amyloid β -protein is deposited in the walls of superficial cortical and leptomeningeal vessels, causing them to become brittle and prone to bleeding. CAA may account for a large proportion of spontaneous ICH in older people²⁵ and has been suggested as a risk factor for ICH associated with warfarin²⁴ and aspirin,²⁵ as well as with ICH after thrombolysis for IS.²⁶ These data are consistent with the hypothesis that CAA is an important risk factor for ICH related to antiplatelet use, and suggest that patients with clinical and imaging findings suggestive of CAA should be treated with antiplatelet agents only if there are compelling reasons to treat to reduce their overall risk of ischaemic vascular events.

Very few previous studies have investigated the association between microbleeds and antiplatelet-associated haemorrhage.^{27–28}

Moreover, these were in Chinese patients in whom hypertension and microbleeds are more common than in Europeans and so may not be generalisable to all stroke populations. Nevertheless, Wong *et al* found microbleeds in 19 of 21 aspirin users with symptomatic ICH, compared with seven of 21 matched aspirin users without ICH, a result consistent with our findings. In contrast with our study, no cases of ICH unrelated to aspirin were included, and no adjustment was made for the presence of leucoaraiosis, a potentially important confounding factor. A recent randomised trial comparing the new antiplatelet drug cilostazol to aspirin found that in the six patients who developed ICH, all had previous microbleeds in the location of the ICH;²⁸ this observation is also consistent with the hypothesis that microbleeds could be used to identify patients at the highest risk of antiplatelet-associated ICH, but the small number of outcome events makes it difficult to draw firm conclusions.

Our study has a number of methodological strengths. First, these data were prospectively collected, with standardised clinical data and MRI imaging sequences; because of our policy of performing routine GRE MRI on all patients unless contraindicated, we were able to minimise selection bias. Second, we used a case–control design, which is the most powerful way to identify risk factors for rare outcome events. Given the very low absolute risk of antiplatelet-associated ICH (about 0.1–0.2% per year), prospective studies would require a large number of patients and long follow-ups: indeed, the few prospective studies available so far failed to reach definite conclusions because of small sample sizes and low statistical power.^{20–29–30} Third, we were able to investigate specifically the independent effect of microbleeds on ICH risk because important known confounding factors (age, sex, hypertension, duration on antiplatelets, previous history of stroke and presence of leucoaraiosis) were controlled for in the matching process and logistic regression analysis. We adjusted for leucoaraiosis, which is a risk factor for warfarin-associated ICH and is associated with microbleeds.^{8–9–21–31–32} Fourth, we used a reliable anatomical microbleed rating scale with good intra- and interobserver agreement.¹⁶ Finally, we included patients with ICH unrelated to antiplatelet treatment, ascertained from the same population as our main case group, making it less likely that our finding is confounded by the well-described association of microbleeds with ICH overall. However, in this case–case ICH comparison, a greater proportion of patients with ICH taking antiplatelet agents had a history of previous IS, which could contribute to the higher microbleed prevalence in this group.

The main limitations of our study include the small cohort and retrospective design. We obtained large CIs in the estimation

of ICH risk for the number of deep microbleeds, likely to be due to the small number of deep microbleeds in our cohort overall. We could only include patients who had MRI, which biased the study towards including slightly older cases of ICH. Our overall prevalence of microbleeds could therefore be overestimated, but this should not affect the case–control and case–case comparisons that we have reported. Another limitation comes from the fact that our ‘controls’ presented with non-ICH stroke symptoms, and therefore were not ‘true’ controls. However, this should not have biased our study towards positive results, as our controls are likely to have more microbleeds than ‘true’ controls. Finally, like all case–control studies, ours can only provide evidence of an association between microbleeds and antiplatelet-related ICH, and not that microbleeds are causally associated. For these reasons, our results need to be confirmed in other prospective studies.

In summary, we have demonstrated a strong independent association between brain microbleeds and antiplatelet-related ICH. The predominance of lobar microbleeds in patients on antiplatelets who develop an ICH suggests that CAA may be an important underlying risk factor for ICH in patients taking antiplatelets. Our findings suggest that patients with numerous microbleeds, particularly in a lobar distribution, may be at higher risk of ICH, which could outweigh the benefits of antiplatelet therapy in these patients.¹⁵ Therefore, microbleed screening may be an important component in the design of future antiplatelet trials. Large prospective studies and systematic analyses are needed to further clarify the risks and benefits of antiplatelet therapy in patients with microbleeds.

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Competing interests HRJ serves as a consultant to Biogen Idec and GlaxoSmithKline. TAY served on a scientific advisory board for UCB and serves on the editorial board of European Radiology. MMB serves as a Section Editor for Stroke; serves as a consultant to Pfizer Inc. and AGA Medical Corporation, and serves on a Data and Ethics Monitoring Committee for Bayer Schering Pharma.

Ethics approval Ethics approval was provided by the Joint Institute of Neurology and National Hospital for Neurology and Neurosurgery Research Ethics Committee.

Contributors SMG was responsible for the data acquisition, analyses, interpretation and writing of the manuscript. DJW and SMG contributed to the conception and design of the study. DJW also contributed to the data analysis, interpretation and review of the manuscript and supervised the whole project. HRJ helped with the review of the manuscript. TAY provided useful feedback on the manuscript. CK, statistician at the London School of Hygiene and Tropical Medicine, was responsible for the statistics. All authors revised and approved the final version of the manuscript.

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