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

S M Gregoire,1 H R Jäger,2 T A Yousry,2 C Kallis,3 M M Brown,1 D J Werring1

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.5 Brain-imaging studies using CT suggest that leukoaraisis is a risk factor for ICH in patients taking Warfarin (RR ~ 7.1 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 17 They are very common in patients with stroke or TIA17 and in healthy elderly individuals (up to 40%).18 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,10 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 (NHHNN) 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. MRls 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 antplatelet treatment. All patients with ICH were ascertained with overlapping methods including MRI images, reports and medical records. The intake and duration of antplatelet treatment at the time of admission or visit were ascertained from hospital and GP records. For each antplatelet 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 antplatelet 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 ≥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 antplatelet users and non-antplatelet users with ICH. The study received ethics approval by The NHNN & Institute of Neurology Joint Research Ethics Committee.

**Imaging analysis**

MRls 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 hypo-intense in T1-weighted and FLAIR images, and surrounded by a hyperintense rim in FLAIR images.19 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 (antplatelet users with ICH) and matched control group (antplatelet 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 antplatelet-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=16%) 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 antplatelet therapy) and 33 non-antplatelet users with ICH (figure 1). Patients included in the study were slightly older than patients excluded due to a lack of MRI (p=0.045). 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: antplatelet-related ICH (N=1, 6%), controls (N=2, 6%), non-antplatelet-related ICH (N=3, 9%).

We selected 32 matched controls from the database of antplatelet 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 antplatelets (table 1). Antplatelet agents used by patients and controls were: aspirin (N=45), clopidogrel (N=5), aspirin plus dipyridamole (N=1) or clopidogrel plus aspirin (N=1).

![Figure 1](http://jnnp.bmj.com/)

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

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=0.015) (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 1 Characteristics of antiplatelet users with and without history of intracerebral haemorrhage

<table>
<thead>
<tr>
<th>Clinical characteristics†</th>
<th>With intracerebral haemorrhage (N=16)</th>
<th>Without intracerebral haemorrhage (N=32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>70±10.5 (52–86)</td>
<td>67.25±9.9 (53–94)</td>
<td>NS</td>
</tr>
<tr>
<td>Men, N (%)</td>
<td>10 (62.5)</td>
<td>20 (62.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>12 (75)</td>
<td>24 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165±26</td>
<td>154.85±25</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>87±12</td>
<td>81.5±15.5</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4 (25)</td>
<td>7 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol total &gt;6 mmol/l (%)</td>
<td>1 (6)</td>
<td>3 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>5 (31)</td>
<td>14 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>6 (37.5)</td>
<td>13 (40.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>2 (12.5)</td>
<td>6 (18.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8 (50)</td>
<td>16 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>10 (62.5)</td>
<td>17 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration, months (%)</td>
<td>41.6±48.4</td>
<td>37.7±43.4</td>
<td>NS</td>
</tr>
<tr>
<td>No taking aspirin (%)</td>
<td>15 (94)</td>
<td>30 (94)</td>
<td>NS</td>
</tr>
<tr>
<td>Median dose of aspirin in aspirin users in mg (range)</td>
<td>75 (75–300)</td>
<td>75 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Median interval stroke-MRI in days (range)</td>
<td>11 (2–115)</td>
<td>17 (0–131)</td>
<td>NS</td>
</tr>
<tr>
<td>Imaging characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%; range)</td>
<td>13 (81.2, 0–28)</td>
<td>6 (18.8, 0–15)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.0 (0–28)</td>
<td>0 (0–15)</td>
<td>0.016*</td>
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<tr>
<td>Lobar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%)</td>
<td>11 (69)</td>
<td>5 (15.6)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.0 (0–15)</td>
<td>0 (0–8)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Deep (basal ganglia and thalamus)</td>
<td>9 (56.2)</td>
<td>3 (8.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Presence (%)</td>
<td>1.0 (0–11)</td>
<td>0 (0–3)</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior fossa (brainstem and cerebellum)</td>
<td>6 (37.5)</td>
<td>4 (12.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Presence (%)</td>
<td>0 (0–2)</td>
<td>0 (0–5)</td>
<td>NS</td>
</tr>
<tr>
<td>Lacunes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%)</td>
<td>12 (80)</td>
<td>27 (84)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (0–9)</td>
<td>2.5 (0–10)</td>
<td>NS</td>
</tr>
<tr>
<td>Leucoaraiosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%)</td>
<td>8 (50)</td>
<td>7 (22)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*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 (\( p = 0.052 \) for deep and \( p = 0.016 \) for lobar microbleeds).

**Table 2**

Characteristics of subjects with symptomatic spontaneous intracerebral haemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Antiplatelet users (N = 16)</th>
<th>Non-antiplatelet users (N = 33)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>70.0 ± 10.5 (52–86)</td>
<td>66.0 ± 10.6 (41–87)</td>
<td>NS</td>
</tr>
<tr>
<td>Men, N (%)</td>
<td>10 (62.5)</td>
<td>18 (54.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>12 (75)</td>
<td>27 (81.8)</td>
<td>NS</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165.0 ± 26</td>
<td>151.0 ± 32</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>87.0 ± 12</td>
<td>83.0 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4 (25)</td>
<td>2 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol total &gt;6 mmol/l (%)</td>
<td>1 (6)</td>
<td>2 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>5 (31)</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>6 (37.5)</td>
<td>1 (3)</td>
<td>0.003*</td>
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<td>Atrial fibrillation (%)</td>
<td>2 (12.5)</td>
<td>3 (9.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8 (50)</td>
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<td>&lt;0.001*</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>10 (62.5)</td>
<td>10 (30.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Median interval stroke-MRI in days (range)</td>
<td>11 (2–115)</td>
<td>7 (0–222)</td>
<td>NS</td>
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<td><strong>Imaging characteristics</strong></td>
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<td></td>
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<tr>
<td>Microbleeds</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%, range)</td>
<td>13 (81.2, 0–28)</td>
<td>15 (45.4, 0–31)</td>
<td>0.030*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.0 (0–28)</td>
<td>0.0 (0–31)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Lobar</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Presence (%)</td>
<td>11 (69)</td>
<td>11 (33)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Median (range)</td>
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<td>0 (0–12)</td>
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<td>9 (56.2)</td>
<td>9 (27.3)</td>
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<td>Median (range)</td>
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<td>0 (0–17)</td>
<td>0.032*</td>
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<td>6 (37.5)</td>
<td>5 (15)</td>
<td>NS</td>
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<tr>
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<td>12 (80)</td>
<td>24 (75)</td>
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<td>Median (range)</td>
<td>2.0 (0–9)</td>
<td>2.0 (0–7)</td>
<td>NS</td>
</tr>
<tr>
<td>Lacunes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Presence (%)</td>
<td>8 (50)</td>
<td>8 (24)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \).
†Plus–minus values are mean ± SD.
NS, not significant.

**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.
is deposited in the walls of super
ich in older people25 and has been suggested as a risk factor for
neural vessels, causing them to become brittle and prone to
deep microbleeds were a statistically signi
cifications adjusted for the presence of leucoaraiosis, lobar (but not
factor for antiplatelet-associated ICH.

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 people23 and has been suggested as a risk factor for
ICH associated with warfarin27 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
these patients with ICH taking antiplatelet agents had a history of previous IS, which
indicated, 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

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

Finally, leucoaraiosis was more prevalent in antiplatelet users
with ICH compared with subjects with ICH unrelated to anti-
platelets, 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 devel-
oped 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 fac-
tors. 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.

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

<table>
<thead>
<tr>
<th>Presence and no of microbleeds</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of microbleeds</td>
<td>1.27</td>
<td>1.04 to 1.55</td>
<td>0.016*</td>
</tr>
<tr>
<td>Total no of microbleeds adjusted for leucoaraiosis</td>
<td>1.33</td>
<td>1.06 to 1.66</td>
<td>0.013*</td>
</tr>
<tr>
<td>Distribution of microbleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of lobar microbleeds</td>
<td>1.35</td>
<td>1.06 to 1.72</td>
<td>0.016*</td>
</tr>
<tr>
<td>No of lobar microbleeds adjusted for leucoaraiosis</td>
<td>1.42</td>
<td>1.07 to 1.89</td>
<td>0.016*</td>
</tr>
<tr>
<td>No of deep microbleeds</td>
<td>5.66</td>
<td>0.96 to 35.69</td>
<td>0.055</td>
</tr>
<tr>
<td>No of deep microbleeds adjusted for leucoaraiosis</td>
<td>5.69</td>
<td>0.95 to 34.22</td>
<td>0.057</td>
</tr>
</tbody>
</table>

*p<0.05.

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,25
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 contra-
indicated, 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

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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–control 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 prevalence of lobar microbleeds on 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. 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 IHU serves as a consultant to Bogen Idee and GlaxoSmithKline. TAY served on a scientific advisory board for UCBC and serves on the editorial board of European Radiology. MMV 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. IHU 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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