Antithrombotic Drug Use, Cerebral Microbleeds, and Intracerebral Hemorrhage
A Systematic Review of Published and Unpublished Studies

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Background and Purpose—Cerebral microbleeds (MB) are potential risk factors for intracerebral hemorrhage (ICH), but it is unclear if they are a contraindication to using antithrombotic drugs. Insights could be gained by pooling data on MB frequency stratified by antithrombotic use in cohorts with ICH and ischemic stroke (IS)/transient ischemic attack (TIA).

Methods—We performed a systematic review of published and unpublished data from cohorts with stroke or TIA to compare the presence of MB in: (1) antithrombotic users vs nonantithrombotic users with ICH; (2) antithrombotic users vs nonusers with IS/TIA; and (3) ICH vs ischemic events stratified by antithrombotic use. We also analyzed published and unpublished follow-up data to determine the risk of ICH in antithrombotic users with MB.

Results—In a pooled analysis of 1460 ICH and 3817 IS/TIA, MB were more frequent in ICH vs IS/TIA in all treatment groups, but the excess increased from 2.8 (odds ratio; range, 2.3–3.5) in nonantithrombotic users to 5.7 (range, 3.4–9.7) in antiplatelet users and 8.0 (range, 3.5–17.8) in warfarin users (P difference=0.01). There was also an excess of MB in warfarin users vs nonusers with ICH (OR, 2.7; 95% CI, 1.6–4.4; \( P<0.001 \)) but none in warfarin users with IS/TIA (OR, 1.3; 95% CI, 0.9–1.7; \( P=0.33 \); P difference=0.01). There was a smaller excess of MB in antiplatelet users vs nonusers with ICH (OR, 1.7; 95% CI, 1.3–2.3; \( P<0.001 \)), but findings were similar for antiplatelet users with IS/TIA (OR, 1.4; 95% CI, 1.2–1.7; \( P<0.001 \); P difference=0.25). In pooled follow-up data for 768 antithrombotic users, presence of MB at baseline was associated with a substantially increased risk of subsequent ICH (OR, 12.1; 95% CI, 3.4–42.5; \( P<0.001 \)).

Conclusions—The excess of MB in warfarin users with ICH compared to other groups suggests that MB increase the risk of warfarin-associated ICH. Limited prospective data corroborate these findings, but larger prospective studies are urgently required. (Stroke. 2010;41:1222-1228.)

Key Words: antiplatelet agents ■ intracerebral hemorrhage ■ microbleeds ■ stroke ■ warfarin

Increasing use of gradient-recalled echo (GRE) MRI has highlighted the association between cerebral microbleeds (MB) and ischemic stroke (IS) and transient ischemic attack (TIA).1-6 MB appear as small hypointense lesions on GRE imaging,7 and correspond histologically to hemosiderin deposition in the perivascular space in association with severe microangiopathy.8 MB appear to predict future intracerebral hemorrhage (ICH) in prospective observational studies of patients with either ICH9,10 or IS.2,11 This has led to concerns over the safety of antithrombotic drug use in patients with MB, and some clinicians already regard MB as a relative contraindication to warfarin use.12 However, there is no clear evidence that MB further increase the risk of antithrombotic-associated ICH. The number of outcomes in existing prospec-
been produced from the same group, these were carefully reviewed and the proportion of patients with MB. When several articles had premorbid antithrombotic drug use, prevalence of previous stroke, details of the imaging protocol, demographic data, prevalence of disease. For each study we recorded inclusion and exclusion criteria, on application to the authors. We excluded studies of patients with stroke and TIA who had undergone GRE MRI to detect MB. Further studies were identified by hand-searching the bibliographies of retrieved articles and reviews. We included studies of patients who were also enrolled in the Oxford Vascular study. The Oxford Vascular study is a prospective population-based study of all vascular events in which all patients are followed-up at regular intervals after their index event. In addition, all recurrent events in the population are identified through multiple overlapping methods of ascertainment.

Materials and Methods
We conducted a Medline search on September 31, 2009, using the terms “microbleed,” “micro(a)hemorrhage,” “haemorrhagic lacune,” and “stroke” or “TIA” to identify cohort studies of patients with stroke and TIA who had undergone GRE MRI to detect MB. Further studies were identified by hand-searching the bibliographies of retrieved articles and reviews. We included studies of patients who had presented with an acute stroke or TIA, those that identified MB in ≥10 subjects, and those presented data on premorbid antithrombotic drug use according to the presence or absence of MB. We separated cases with IS/TIA and ICH or these data were provided on application to the authors. We excluded studies of patients with vascular dementia, “chronic cerebrovascular disease,” orBinswanger disease. For each study we recorded inclusion and exclusion criteria, details of the imaging protocol, demographic data, prevalence of premorbid antithrombotic drug use, prevalence of previous stroke, and the proportion of patients with MB. When several articles had been produced from the same group, these were carefully reviewed to ensure that cohorts did not overlap. When it was not possible to determine this, data from the largest available cohort were taken.

We also obtained previously unpublished data from 6 cohorts with recent stroke or TIA from the Oxford Regional Neurosciences Centres Cohort, the Prognosis of Intracerebral Cerebral Hemorrhage study, the Institute of Neurology Cohort, the Edinburgh Stroke Study, the Nishi-cho Hospital Cohort, and the Suiseikai Kajikawa Hospital Cohort. Details of the methods of these studies including the imaging protocols are shown in Table 1. Those cohorts that included patients with ICH excluded hemorrhages secondary to tumor, trauma, aneurysmal bleeds, cavernous malformations, and vasculitis. Patients in each cohort were assessed by a neurologist, and demographic and clinical data including premorbid medication were recorded. Scans were reviewed by at least 2 observers who were either neurologists or neuroradiologists and experienced in examining GRE MRI. MB were defined as hypointense lesions on GRE imaging protocol, demographic data, prevalence of premorbid antithrombotic drug use, prevalence of previous stroke, and the proportion of patients with MB. When several articles had been produced from the same group, these were carefully reviewed to ensure that cohorts did not overlap. When it was not possible to determine this, data from the largest available cohort were taken.

Using available prospective data on the risk of subsequent ICH in patients treated with antithrombotic medications who had undergone GRE MRI, MB were defined as hypointense lesions on GRE T2*-weighted MRI images measuring <10 mm, with the exception of the Nishi-cho Hospital Cohort, in which MB measured 2 to 5 mm. All images were assessed blind to clinical data.

Finally, we examined available prospective data on the risk of subsequent ICH in patients treated with antithrombotic medications who had undergone GRE MRI after an index stroke or TIA. Prospective data were identified from the literature search and were available for 248 patients in the Oxford Neurosciences Centre Cohort who were also enrolled in the Oxford Vascular study. The Oxford Vascular study is a prospective population-based study of all vascular events in which all patients are followed-up at regular intervals after their index event. In addition, all recurrent events in the population are identified through multiple overlapping methods of ascertainment.

Table 1. Methods of Previously Unpublished Cohort Studies of Patients With Recent TIA and Stroke

<table>
<thead>
<tr>
<th>Region</th>
<th>Oxford Regional Neurosciences Centre</th>
<th>Prognosis of Intracerebral Cerebral Hemorrhage Study, Lille University</th>
<th>Institute of Neurology</th>
<th>Edinburgh Stroke Study, Western General Hospital</th>
<th>Nishi-cho Hospital</th>
<th>Suiseikai Kajikawa Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>770</td>
<td>235</td>
<td>52</td>
<td>275</td>
<td>94</td>
<td>1398</td>
</tr>
<tr>
<td>Event</td>
<td>All stroke and TIA</td>
<td>ICH, Warfarin users with IS</td>
<td>ICH</td>
<td>All stroke and TIA</td>
<td>ICH</td>
<td>All stroke</td>
</tr>
<tr>
<td>Consecutive recruitment</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes (from Oct 2007)</td>
</tr>
<tr>
<td>Magnet strength (T)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>TR (ms)/TE (ms)</td>
<td>4000/95 and 530/14</td>
<td>800/22</td>
<td>300/40</td>
<td>620/15</td>
<td>675/15</td>
<td>800/26</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Gap thickness (mm)</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Median delay (interquartile range) to scan (days)</td>
<td>20 (10–41)</td>
<td>6 (3–9)</td>
<td>27 (0–219)</td>
<td>22 (8–37)</td>
<td>All scanned ≤28 days</td>
<td>…</td>
</tr>
</tbody>
</table>

*Excludes September 2007. T indicates Tesla; TR, recall time; TE, echo time.
combination of antiplatelet agents and warfarin, then they were included in the group using anticoagulation and not in the group using antiplatelet agents.

**Results**

Results from the previously unpublished cohorts, including numbers of patients with ICH and ischemic events, numbers of patients with MB stratified by stroke type, and baseline demographic and risk factor data, are presented in Table 2. The frequency of MB ranged from 11% to 38% in cohorts with IS/TIA, and from 36% to 64% in cohorts with ICH. The frequency of premorbid antiplatelet and warfarin use also varied between studies, ranging from 5% to 42% and 0% to 17%, respectively.

The electronic search identified 174 articles. Of 70 potentially relevant cohort studies, 12 studies1,5,15–24 including 6 cohorts with ICH and 8 cohorts with ischemic cerebrovascular events, met our inclusion criteria. Details of these studies are shown in Table 3. Patients were recruited and scanned within 24 hours of stroke onset in 3 studies,1,5,6 and within 90 days in another 7 studies.15–19,21,24 Three studies did not specify the delay between symptom onset and imaging.20,22,23 All studies used GRE MRI to identify MB, although magnet strength, imaging sequences, and slice thickness varied. The definition of MB size also varied: MB measured \( \geq 10 \) mm in 4 studies,19,22–24 \( \geq 7 \) mm in 2 studies,1,15 \( \leq 5 \) mm in 6 studies,6,16–18,20,21 and size was not defined in 1 study.5

### Table 2. Numbers (%) of Subjects With Risk Factors and Using Premorbid Antithrombotic Agents in Previously Unpublished Cohorts With TIA and Stroke

<table>
<thead>
<tr>
<th>Region</th>
<th>Ischemic Stroke/TIA, N=715 (348 TIA/367 TIA)</th>
<th>ICH, N=55</th>
<th>Ischemic Stroke/TIA, N=265 (10 TIA/255 Stroke)</th>
<th>ICH, N=10</th>
<th>Ischemic Stroke, ICH, N=1064</th>
<th>ICH, N=332</th>
<th>ICH, N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>70 (12)</td>
<td>74 (10)</td>
<td>67 (13.6)</td>
<td>70 (17)</td>
<td>72 (12)</td>
<td>68 (13)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>397 (56)</td>
<td>34 (61)</td>
<td>126 (57)</td>
<td>56 (50)</td>
<td>651 (61)</td>
<td>186 (56)</td>
<td>58 (62)</td>
</tr>
<tr>
<td>N with MB (%)</td>
<td>80 (11)</td>
<td>20 (36)</td>
<td>119 (54)</td>
<td>60 (60)</td>
<td>379 (200)</td>
<td>200 (60)</td>
<td>60 (64)</td>
</tr>
</tbody>
</table>

**Risk factors**

- Hypertension (%): 404 (57) 40 (71) 140 (63) 44 (85) 138 (52) 4 (40) 708 (67) 296 (89) 93 (99)
- Diabetes (%): 93 (13) 8 (14) 34 (15) 6 (12) 22 (8) 1 (10) 290 (27) 73 (22) 10 (11)
- Hyperlipidemia (%): 285 (40) 6 (11) 68 (31) 22 (43) 21 (8) 1 (10) 400 (38) 92 (28) 1 (1)
- Previous stroke (%): 69 (10) 8 (14) 28 (13) 6 (12) 35 (13) 2 (20) 47 (18) 2 (20)
- Previous TIA (%): 30 (4) 9 (14) 14 (6) 6 (12) 30 (11) 1 (10) 35 (11) 1 (10) 1 (1)
- IHD (%) 118 (17) 7 (13) 30 (14) 9 (17) 62 (23) 3 (30) 5 (21) 0 (0) 2 (2)
- AF (%) 51 (7) 13 (23) 21 (10) 7 (13) 55 (21) 0 (0) 379 (36) 200 (60) 60 (64)

**Previous antithrombotic use**

- Warfarin (%): 25 (4) 9 (16) 25 (11) 2 (4) 10 (4) 0 (0) 118 (11) 56 (17) 2 (2)
- Antiplatelet (%): 238 (33) 16 (29) 62 (28) 17 (33) 112 (42) 30 (30) 279 (26) 15 (5) 9 (10)

IHD indicates ischemic heart disease; AF, atrial fibrillation.

### Table 3. Summary of Published Studies Included in Systematic Review

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Region</th>
<th>N and Stroke Type</th>
<th>Mean Age, yr</th>
<th>Male %</th>
<th>MB %</th>
<th>Antiplatelet Users %</th>
<th>Warfarin Users %</th>
<th>Previous Stroke %</th>
<th>MRI Strength TR (ms)/TE (ms)</th>
<th>Mean (SD) Follow-Up, mo</th>
<th>N With Subsequent ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaizumi15</td>
<td>Hokkaido, Japan</td>
<td>202 ICH, 135 LI</td>
<td>66, 66</td>
<td>51, 65</td>
<td>77, 46</td>
<td>6, 13</td>
<td>1, 5</td>
<td>5, 13</td>
<td>1.5 T, 450/26</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lee16–18</td>
<td>Seoul, Korea</td>
<td>149 ICH, 143 IS</td>
<td>62, 65</td>
<td>50, 52</td>
<td>68, 35</td>
<td>22, 12</td>
<td>16, none</td>
<td>25, 28</td>
<td>1.5 T, 200–500/15</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Nishikawa22</td>
<td>Osaka, Japan</td>
<td>106 ICH</td>
<td>67</td>
<td>62</td>
<td>55</td>
<td>11</td>
<td>None</td>
<td>18</td>
<td>1.5 T, 889/23</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Jeong20</td>
<td>Ilos, Korea</td>
<td>107 ICH</td>
<td>62</td>
<td>59</td>
<td>70</td>
<td>24</td>
<td>3</td>
<td>25</td>
<td>1.5 T, 284/20</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Copenhagen19</td>
<td>Washington, DC</td>
<td>87 ICH</td>
<td>68</td>
<td>46</td>
<td>57</td>
<td>9</td>
<td>14</td>
<td></td>
<td>1.5 T and 3.0 T, 800/20 and 875/11</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Alemany21</td>
<td>Uppsala, Sweden</td>
<td>45 ICH, 45 IS</td>
<td>67, 67</td>
<td>53, 53</td>
<td>64, 18</td>
<td>27</td>
<td>7</td>
<td>19</td>
<td>1.5 T, 500/14</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sook22</td>
<td>Hong Kong, China</td>
<td>908 IS</td>
<td>68</td>
<td>58</td>
<td>28</td>
<td>27</td>
<td>3</td>
<td>20</td>
<td>1.5 T, 350/30</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Schonewille24</td>
<td>Utrecht, Netherlands</td>
<td>42 LI</td>
<td>NR</td>
<td>21</td>
<td>43</td>
<td>12</td>
<td>31</td>
<td></td>
<td>1.5 T, 600/30–40</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Boulanger25</td>
<td>Calgary, Canada</td>
<td>236 IS/TIA</td>
<td>NR</td>
<td>55</td>
<td>19</td>
<td>24</td>
<td>NR</td>
<td>41</td>
<td>3 T, 500/20</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Oubiabete16</td>
<td>Los Angeles, CA</td>
<td>164 IS/TIA</td>
<td>71</td>
<td>48</td>
<td>35</td>
<td>22</td>
<td>6</td>
<td>18</td>
<td>1.5 T, 800/15</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Nighogossian26</td>
<td>Lyon, France</td>
<td>100 IS</td>
<td>60</td>
<td>58</td>
<td>20</td>
<td>27</td>
<td>NR</td>
<td>26</td>
<td>1.5 T, 800/26</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Prospective studies

- Örken25        | Istanbul, Turkey     | 141 IS           | 66           | 58     | 22    | None               | 100              | 18                  | 1.5 T, 640/15           | 46.5                     | 2                   |
- Naka11          | Hiroshima, Japan     | 183 IS, 83 ICH   | 67           | 63     | 35    | 66                  | None             | NR                  | 1 T, 4500/112           | 18.6                     | 10                  |
- Fan2            | Hong Kong, China     | 121 IS           | 68           | 68     | 36    | 80                  | 6                | 41                  | 1.5 T, 300/30           | 27.5                     | 5                   |
The pooled data set included 1460 patients with ICH and 3817 patients with IS/TIA. Eight of the cohorts, contributing half the patients in this analysis, were recruited from Asian populations, and the remaining studies were based in North American and European centers. The majority of data for patients with ICH came from Asian cohorts.

Results from the pooled analysis of published and unpublished data are shown in Figure 1, stratified by event type. MB were more frequent in warfarin users with ICH compared to nonantithrombotic users (OR, 2.7; 95% CI, 1.6–4.4; \( P < 0.001 \)) but were not more frequent in warfarin users with IS/TIA (OR, 1.3; 95% CI, 0.9–1.7; \( P = 0.33 \); \( P \) difference between pooled OR, 0.01). In comparisons involving antiplatelet users, the relationship between MB frequency and antiplatelet-associated ICH was similar but weaker. MB were more frequent in antiplatelet users vs nonusers with ICH (OR, 1.7; 95% CI, 1.3–2.3; \( P = 0.001 \)), but the excess of MB was not significantly different in the analysis of IS/TIA (OR, 1.3; 95% CI, 0.9–1.7; \( P = 0.33 \); \( P \) difference between pooled OR, 0.01). In comparisons involving antiplatelet users, the relationship between MB frequency and antiplatelet-associated ICH was similar but weaker. MB were more frequent in antiplatelet users vs nonusers with ICH (OR, 1.7; 95% CI, 1.3–2.3; \( P = 0.001 \)), but the excess of MB was not significantly different in the analysis of IS/TIA (OR, 1.3; 95% CI, 0.9–1.7; \( P = 0.33 \); \( P \) difference between pooled OR, 0.01). However, once again, there was significant heterogeneity in the comparison involving antiplatelet users (\( P = 0.02 \)), largely driven by the cohort from Hiroshima, and when this was removed from the analysis the difference in MB frequency between antiplatelet users with ICH and antiplatelet users with ischemic events decreased (OR, 2.6; 95% CI, 1.4–4.9) and was no different from the result seen in nonantithrombotic users (difference, \( P = 0.83 \)).

Prospective data were available for 241 patients (135 males; mean age, 67 years) with IS/TIA in the Oxford Neurosciences Centre cohort; 208 patients (34 with MB) were started or continued on antiplatelet agents, and 16 patients (2 with MB) were started or continued on warfarin after their index event. The follow-up period was censored at September 30, 2009, providing a mean follow-up of 27 (SD, 13) months. During this time, 2 patients who had MB on their baseline scans had ICH on follow-up; 1 was an antiplatelet user and the other was a warfarin user. Published prospective data were also available from 3 other cohorts7,11,25; details are included in Table 3. The pooled prospective data set included 768 patients with stroke or TIA (90 ICH, 123 TIA, 555 IS), with a mean follow-up period of 27.7 months. Of these, 482 were prescribed antiplatelet agents after their index event and 164 were prescribed warfarin. Among all antithrombotic users, the odds of a subsequent ICH in patients with MB vs patients without MB was 12.1 (95% CI, 3.4–32.5; \( P < 0.001 \)); Figure 3), and among warfarin users it was 3.0 (95% CI, 0.5–17.5; \( P = 0.23 \)), although this latter analysis was limited by having only 5 cases of recurrent stroke attributable to ICH in warfarin users.

**Discussion**

To our knowledge, this is the first systematic evidence of an association between warfarin-associated ICH and MB. In a pooled analysis of 3817 patients with IS/TIA and 1460
patients with ICH, we have shown an excess of MB in warfarin-associated ICH that was not found in warfarin-associated IS/TIA. Although there were relatively few data on warfarin users, these preliminary results indicate that warfarin may be hazardous in patients with MB. Similar but weaker associations between MB frequency and antiplatelet-associated ICH were also seen, but these results have to be interpreted with caution because there was significant heterogeneity between cohorts in analyses involving antiplatelet-associated ICH. The limited available prospective data also support the hypothesis that the presence of MB increases the risk of future ICH as a complication of antithrombotic drug use. Whereas we do not advise avoiding antithrombotic drugs in patients with MB who are at high risk for future thromboembolic events, these data suggest that more prospective data on the safety of antithrombotic drugs in such patients are urgently required.

There are a number of caveats regarding our interpretation of the cross-sectional data. First, comparisons in this study are not adjusted for all potential confounders. For example, warfarin users are more likely to have a history of hypertension or past stroke than nonusers,26 and both risk factors are associated with an increased frequency of MB.27 However, we did not find an excess of MB in warfarin users vs nonusers with IS/TIA, although similar differences in risk factors might be expected between these groups. In comparisons of MB frequency in ICH vs IS/TIA within treatment groups, cases were probably better matched. In this analysis, we expected to find an excess of MB in cases with ICH vs cases with IS/TIA in all treatment groups,4,16,21 but the relative frequency of MB in warfarin-associated ICH was higher than the relative frequency in nonantithrombotic-associated ICH. This, again, is consistent with the hypothesis that MB are markers of increased bleeding risk with warfarin. Second, it is possible that warfarin causes MB, and this is the reason for the excess of MB in warfarin users with ICH. However, if this

![Figure 2. Proportions of ICH events vs infarct/TIA events with visible MB stratified by premorbid antithrombotic medication use.](image)

![Figure 3. Frequency of ICH on follow-up in antithrombotic users with MB vs antithrombotic users with no MB.](image)
were true, then we also should have seen a similar excess of MB in warfarin users with IS/TIA.

Our results are more difficult to interpret for antiplatelet users. There was a weak association between MB and antiplatelet use among patients with ICH in particular, which was similar in magnitude to that reported recently in a cohort of predominantly healthy elderly individuals.28 However, this association was largely driven by the results of 1 large Japanese cohort and disappeared when the results of this cohort were excluded from the analysis. Heterogeneity between cohorts of antiplatelet users was perhaps not entirely unexpected because there may be groups of antiplatelet users at higher risk for future ICH. There is evidence that the risk of future ICH increases with the number of MB identified on a baseline scan.9,10 Moreover, lobar MB may be a marker for cerebral amyloid angiopathy, an increasingly recognized cause of antithrombotic-related ICH; therefore, it is possible that multiple lobar MB increase the risk of antplatelet-related ICH. We were unable to stratify our findings by the number of antiplatelet agents used or the number and location of MB present, but we are continuing to collect data to perform these subgroup analyses.

Prospective studies can provide more direct evidence about whether or not MB increase the risk of antithrombotic-associated ICH but so far have been limited by few warfarin users, relatively short follow-up periods, and insufficient numbers of outcome events to provide a reliable estimate of the risks of antithrombotic drug use in the presence of MB.2,11,23,25 However, the limited prospective data that are available appear to show that MB do increase the risk of ICH as a complication of antithrombotic use. These results are also unadjusted for potential confounders but are nevertheless consistent with the results of the pooled analysis of cross-sectional data and together make a compelling argument for the need for a collaborative prospective study of warfarin users with MB in particular.

Our review presents data on MB frequency in the largest number of antithrombotic users with stroke to date but does have some limitations. As mentioned, there are still few data on the prevalence of MB in warfarin users with ICH, and although MB are more frequent in these cases compared to other subgroups, the confidence limits for these estimates are wide. Second, more data are required on ICH in non-Asian cohorts. The risk of antithrombotic-associated ICH appears to be highest in Asian patients,29 and so the apparent risk of antithrombotic-associated ICH in the presence of MB may also differ between ethnic groups. Third, our analysis might have underestimated the association between MB and warfarin-associated ICH. Average hematoma volumes and case fatality rates are higher in warfarin-associated ICH compared to spontaneous ICH,26 potentially reducing MB detection rates in this group because patients are too clinically unstable to be scanned, and because MB might be obscured by larger hematomas associated with increased edema and distortion of brain parenchyma. Furthermore, our analysis is not limited to cases with incident ICH. Recurrent ICH is associated with a higher prevalence of MB than incident ICH,3 and cases with recurrent ICH are less likely to be using warfarin before the recurrent stroke.

In some of the Oxford cohort, the imaging technique was not always optimal for highlighting MB. Hybrid imaging techniques incorporating gradient and spin echo such as Turbo Gradient Spin Echo have the advantage of being fast and therefore useful in busy neurovascular clinics but are less sensitive than GRE imaging for detecting MB.30 Imaging sequences used by other studies in the systematic review also varied, and this also might have contributed to differences in the observed frequency of MB.27,31 However, these issues are more relevant to interstudy comparisons and should not have affected case–case comparisons between subgroups within each study.

ICH is the most feared complication of warfarin use and is associated with very poor outcomes.26 Warfarin-associated ICH comprises 14% of all ICH,32 and given the increasing prevalence of atrial fibrillation and greater use of warfarin, its incidence is expected to increase.33 Therefore, any means of better-identifying patients at risk for warfarin-related complications is vital. Our study provides further evidence that MB are likely to indicate an increased risk of ICH associated with warfarin use and highlights the urgent need for more prospective studies of the safety of warfarin in patients with MB. Data on the association between MB and antiplatelet-associated ICH are less consistent, but addition of future observational studies to the meta-analyses published here might provide more reliable estimates.

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Disclosures

None.

References


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