Topical Review

Cerebral Microbleeds

Is Antithrombotic Therapy Safe to Administer?

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Growing evidence suggests a link between cerebral microbleeds (CMBs) and increased risk of intracerebral hemorrhage (ICH), leading to concerns on the safety of administering antithrombotic drugs in patients with CMBs. This review summarized studies on the association among CMBs, ICH, and antithrombotic therapy (defined as antiplatelet and anticoagulant agents). Recommendations for future studies on this topic were also proposed.

CMBs are small perivascular hemosiderin deposits (usually with macrophages) from leakage through cerebral small vessels, which can be visualized as small, rounded, homogeneous, and hypointense lesions on T2*-weighed gradient-recalled echo or susceptibility-weighted imaging MRI. CMBs indicate hemorrhage-prone pathological states, and studies have shown that the presence of CMBs is associated with increased risk of future ICH (odds ratio [OR], 8.52; 95% confidence interval [CI], 4.23–17.18), which is also the most feared complication associated with antithrombotic drugs. Thus, it is natural to wonder whether antithrombotic therapy should be averted in patients with CMBs. Different perspectives should be considered to address this question. In this review, we will seek to clarify this topic by answering the following questions: (1) What is the pathophysiology of CMBs? (2) Are CMBs common in populations who might require antithrombotic therapy? (3) Do patients taking antithrombotic therapy develop more CMBs? (4) Under antithrombotic therapy, do patients with CMBs have an increased risk of future ICH compared with patients without CMBs? (5) Does the increased risk of ICH outweigh the benefit of antithrombotic therapy in patients with CMBs?

What Is the Pathophysiology of CMBs?

Figure 1 illustrates our current understanding on the pathophysiology of CMBs. At least 2 pathological mechanisms may lead to CMBs: cerebral amyloid angiopathy (CAA) and hypertensive microangiopathy. CAA, characterized by amyloid-β deposition in vessel walls, is related to apolipoprotein E genotype. Amyloid-β, especially inflammatory amyloid, induces local inflammation ranging from mild changes to a granulomatous angiitis with apoptosis of vascular smooth muscle cells. Hypertensive microangiopathy, characterized by fibrohyalinosis and arteriolosclerosis, is related to vascular risk factors (eg, age, hypertension, diabetes mellitus). Both CAA and hypertensive microangiopathy would damage the blood–brain barrier and neurovascular unit, leading to blood leakage and hemosiderin deposition, resulting in CMBs. Recent studies found that CMBs accumulate over time. Pathogenetically, this accumulation is most likely caused by the progression of CAA and hypertensive microangiopathy, which can be accelerated by age, hypertension, diabetes mellitus, genetic factors, and so on. Antithrombotic therapy may also accelerate blood leakage, contributing to the formation and accumulation of CMBs, or even macrobleeds. In addition, 1 study found that some CMBs could disappear at >12 months of follow-up. The disappearance of CMBs might depend on the clearance of hemosiderin-laden macrophages. Given the lack of animal model and autopsy study for CMBs, the exact pathophysiology and mechanisms explaining the progression or disappearance of CMBs are still largely unknown.

Are CMBs Common in Populations That Might Require Antithrombotic Therapy?

As a main population taking antithrombotic therapy, patients with ischemic stroke/transient ischemic attack (TIA) have a high prevalence of CMBs, ranging from 18% to 68% in previous studies. A systematic review concluded a 23% of prevalence in patients with first-ever ischemic stroke (ie, presumably majority are naive to antithrombotic drugs) and 44% in patients with recurrent ischemic stroke. One study found CMBs are more common in ischemic stroke compared with TIA patients. Studies investigating CMB prevalence among different stroke subtypes observed a lower prevalence of CMBs in cardioembolic stroke than in atherothrombotic or lacunar stroke. One study found that the frequency of CMBs increased with the burden of vascular risk factors (using congestive heart failure, hypertension, age, diabetes, prior stroke/TIA [CHADS, score] in ischemic stroke patients with nonvalvular atrial fibrillation. In subjects without a history of cerebrovascular disease, the prevalence of CMBs was reported to be ≥5%. Besides, CMBs are also common in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts

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and leukoencephalopathy (25%–69%), which is a hereditary cerebrovascular disease that may benefit from antiplatelet therapy.10

Few studies investigated the frequency of CMBs in patients with myocardial infarction or peripheral arterial diseases, which are other common indications for antithrombotic therapy. A Dutch study found that hemosiderin deposition (including both hemorrhagic lacunes and CMBs) was less frequent among patients with myocardial infarction (4%) or peripheral arterial disease (13%) compared with patients with ischemic stroke (26%).17

In patients with CMBs, the number of CMBs is usually positively skewed with a wide range (1–93 per person in ischemic stroke cohort),18 meaning that the majority of people have only 1 or 2 CMBs and only a small portion of patients have ≥5 CMBs (17.4% in ischemic stroke patients with CMBs).19

Overall, CMBs are not uncommonly found in subjects with ischemic stroke/TIA, who require antithrombotic therapy. At least about a quarter of these subjects harbor CMBs. With this high prevalence, understanding the safety of administering antithrombotic therapy in these subjects with CMBs is thus of high clinical relevance.

Do Patients Taking Antithrombotic Therapy Develop More CMBs?

Whether antithrombotic therapy increases the development of CMBs remains controversial. Table 1 shows some major cross-sectional studies addressing this potential association. The community-based Rotterdam study with a large sample size found that CMBs were more prevalent among antiplatelet users as a whole (OR, 1.71; CI, 1.21–2.41) or clopidogrel users (OR, 1.55; CI, 1.01–2.37), instead of anticoagulant users, compared with nonusers.20,21 In patients with ischemic stroke, both a French and a Chinese study showed the association between antithrombotic use as a whole or aspirin use and the presence of CMBs.22,23 A Japanese study found that antiplatelet use was associated with the presence of CMBs in 412 patients with ICH (OR, 2.418; CI, 1.236–4.730) but not in 1502 patients with ischemic stroke.24 In patients with ICH, aspirin (OR, 2.160; CI, 1.050–4.443), but not clopidogrel, cilostazol, or ticlopidine, was associated with CMBs, especially deep CMBs.24

However, several studies revealed no association between antithrombotic therapy and the risk of CMBs. Most of these studies had small sample sizes, except a Korean study with 1452 asymptomatic elderly patients,26 as shown in Table 1. A Japanese study found a significant association between aspirin use and CMB presence in the crude analysis, but not after adjusting for hypertension.25

A pooled systematic review including 1460 ICH and 3817 ischemic stroke/TIA found that patients with ICH had more CMBs than patients with ischemic stroke/TIA, and the excess (OR) went up from 2.8 (CI, 2.3–3.5) in nonantithrombotic users to 5.7 (CI, 3.4–9.7) in antplatelet users and 8.0 (CI, 3.5–17.8) in warfarin users (P difference=0.01).29 In patients with ICH, instead of patients with ischemic stroke, warfarin or antplatelet users had more CMBs than non-antithrombotic users.29

Recent longitudinal studies show that CMBs accumulate over time, but antithrombotic therapy does not seem to be related to this accumulation, based on only 4 available studies.8,9,30,31 Baseline CMBs, age, baseline blood pressure, and presence of small vessel diseases were risk factors for the generation of new CMBs.8,9,30 More large prospective studies are urgently needed to address the causal relationship between antithrombotic use and development of CMBs. To our knowledge, 3 randomized clinical trials are currently underway to explore the longitudinal changes of CMBs in patients with different antithrombotic treatments, providing a clue about the impact of different antithrombotic agents on CMB accumulation (Safety Study of Dabigatran in CADASIL, ClinicalTrials.gov Identifier: NCT01361763; Efficacy Study of Cilostazol and Aspirin on Cerebral Small Vessel Disease, ClinicalTrials.gov Identifier: NCT01932203; Left Ventricular Thrombus After Acute Myocardial Infarctions, ClinicalTrials.gov Identifier: NCT0155665).


Table 1. Studies Regarding the Association of Antithrombotic Therapy With Presence of CMBs

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Sample, Size</th>
<th>CMB Presence</th>
<th>Total Number of Antithrombotic Agent Users</th>
<th>Various Antithrombotic Agents and Number of Respective Users</th>
<th>Association of Antithrombotic Therapy With CMBs, OR (CI), if Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darwesh et al²⁶ (2013)</td>
<td>Stroke-free, Rotterdam study, 4408</td>
<td>828</td>
<td>121</td>
<td>Clopidogrel 121</td>
<td>Yes, 1.55 (1.01–2.37)</td>
</tr>
<tr>
<td>Naka et al²⁴ (2013)</td>
<td>AIS, 1502</td>
<td>542</td>
<td>455</td>
<td>Aspirin 295; clopidogrel 95; cilostazol 70; ticlopidine 74; multiple antiplatelet 78</td>
<td>No</td>
</tr>
<tr>
<td>Naka et al²⁴ (2013)</td>
<td>ICH, 412</td>
<td>232</td>
<td>82</td>
<td>Aspirin 58; clopidogrel 14; cilostazol 11; ticlopidine 15; dual antiplatelet 16</td>
<td>Yes, * 2.418 (1.236–4.730)</td>
</tr>
<tr>
<td>Yamashiro et al²⁵ (2013)</td>
<td>Patients with ischemic lesions, 220</td>
<td>71</td>
<td>148</td>
<td>Aspirin 93; thienopyridine 62; dual use NA</td>
<td>No</td>
</tr>
<tr>
<td>Kim et al²⁷ (2012)</td>
<td>Asymptomatic elderly, 1452</td>
<td>138</td>
<td>412</td>
<td>Aspirin 383; warfarin 29</td>
<td>No</td>
</tr>
<tr>
<td>Ge et al²² (2011)</td>
<td>IS/TIA, 300</td>
<td>78</td>
<td>150</td>
<td>Aspirin 150 (use &gt;1 y)</td>
<td>Yes, 4.889 (2.707–8.802)</td>
</tr>
<tr>
<td>Nishikawa et al²² (2009)</td>
<td>AIS, 106</td>
<td>58</td>
<td>12</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Orken et al²³ (2009)</td>
<td>AIS, 246</td>
<td>48</td>
<td>141</td>
<td>Warfarin 141</td>
<td>No</td>
</tr>
<tr>
<td>Vernooij et al²¹ (2009)</td>
<td>Elderly, Rotterdam study, 1062</td>
<td>250</td>
<td>363</td>
<td>Antiplatelet 245; anticoagulant 61; antiplatelet plus anticoagulant 57</td>
<td>Yes, † 1.71 (1.21–2.41)</td>
</tr>
<tr>
<td>Nighoghossian et al²⁷ (2002)</td>
<td>AIS, 100</td>
<td>20</td>
<td>27</td>
<td>NA</td>
<td>Yes, 3.9 (1.0–15.8)</td>
</tr>
</tbody>
</table>

AIS indicates acute ischemic stroke; CI, 95% confidence interval; CMBs, cerebral microbleeds; ICH, intracranial hemorrhage; IS, ischemic stroke; NA, data not available; OR, odds ratio; and TIA, transient ischemic attack.

*Aspirin was the only agent associated with CMBs, especially deep/infratentorial CMBs.
†Antiplatelet agents, not anticoagulants, were associated with CMBs. Aspirin was associated with strictly lobar CMBs, instead of deep/infratentorial CMBs.

Under Antithrombotic Therapy, Do Patients With CMBs Have an Increased Risk of Future ICH Compared With Patients Without CMBs?

Case-control studies found that CMBs were more numerous in antiplatelet or warfarin users with ICH than in antiplatelet or warfarin users without ICH, and there was a 83-fold increased risk of warfarin-associated ICH in patients with CMBs.²²,²³ Several longitudinal studies have also shown an increased risk of future ICH in healthy population, acute ischemic stroke, or ICH patients with CMBs, although controversy still exists (a recent cohort study observed a significant association of CMBs with future stroke in general, but not with recurrent ICH, among ischemic stroke/TIA patients receiving antithrombotic therapy).²⁴ as shown in Table 2.

In a pooled analysis of 768 antithrombotic users (including both antiplatelet users and anticoagulant users) with stroke or TIA, presence of CMBs at baseline was related with a greatly increased risk of future ICH (OR, 12.1; CI, 3.4–32.5).²⁹ When stratified by antithrombotic agents, CMBs were somehow not related to future ICH in 164 warfarin users. However, this latter analysis should be carefully interpreted because of a small number of recurrent ICH (5 cases).²⁹ Actually, no large prospective studies of CMBs in ischemic stroke cohorts treated with anticoagulants have been completed to date. The Clinical Relevance of Microbleeds in Stroke (CROMIS-2) study with 1000 participants in Europe and risk of Intracerebral Hemorrhage in Patients Taking Oral Anticoagulant for Atrial Fibrillation With Cerebral Microbleeds (IPAAC)—Warfarin study in Hong Kong are currently underway to explore whether CMBs predict recurrent ICH in patients with cardioembolic ischemic stroke receiving warfarin. The parallel Novel Oral Anticoagulants (IPAAC-NOAC) study in Hong Kong assesses CMB-related future ICH in patients with stroke taking novel oral anticoagulants.

The most recent meta-analysis pooled data from 10 prospective cohorts, including 3067 ischemic stroke/TIA patients, and found that the risk of ICH increased ≤8.52-fold (OR, 8.52; CI, 4.23–17.18) in those with CMB versus those without, whereas the ischemic stroke risk and overall stroke risk were 1.55× (OR, 1.55; CI, 1.12–2.13) and 2.25× (OR, 2.25; CI, 1.70–2.98) greater, respectively, indicating a higher risk of recurrent ICH than recurrent ischemic stroke.¹ After stratification by study population ethnicity (Asian versus Western cohorts), the association of CMBs with ICH was significant in Asian (OR, 10.43; CI, 4.59–23.72) but borderline significant with a lower magnitude in Western cohorts (OR, 3.87; OR=3.87; CI, 0.91–16.4; P=0.066). In contrast, CMBs were related with recurrent ischemic stroke in Western but not Asian cohorts.¹ These findings suggest an ethnic difference in the relationship between CMBs and the risk of ICH.

Meta-analyses pooling 5 studies also showed similar results in 790 patients with acute ischemic stroke after thrombolysis.⁴⁶ The presence of CMBs tended to be related with an increased risk of post-thrombolysis symptomatic ICH (OR, 2.29; CI, 1.01–5.17; P=0.05), whereas the quantity of CMBs was significantly associated with symptomatic ICH (P=0.0015). This risk was most dominant in patients with >10 CMBs.⁴⁸
Table 2. Longitudinal Studies Regarding the Association of CMBs With Recurrent ICH

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Sample, Size</th>
<th>Follow-Up Time</th>
<th>CMB Presence</th>
<th>Various Antithrombotic Agents and Number of Respective Users</th>
<th>Recurrent ICH</th>
<th>Association of CMBs With Recurrent ICH OR/HR (CI), if Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaizumi et al** (2013)</td>
<td>Stroke patients with deep CMBs, 347</td>
<td>31.6 mo</td>
<td>347</td>
<td>Aspirin 89; clopidogrel 51; ticlopidine 20; warfarin 35</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>Kwa et al** (2013)</td>
<td>TIA or minor IS, 397</td>
<td>3.8-year</td>
<td>48</td>
<td>Antiplatelet 357; anticoagulants 40</td>
<td>5</td>
<td>No*</td>
</tr>
<tr>
<td>Takahashi et al** (2013)</td>
<td>AIS, 187</td>
<td>2 –d</td>
<td>63</td>
<td>Antiplatelet 51; anticoagulant 136</td>
<td>27 (HT)</td>
<td>No</td>
</tr>
<tr>
<td>Huang et al** (2012)</td>
<td>AIS, 44</td>
<td>7 d</td>
<td>14</td>
<td>Aspirin 21; clopidogrel 19; heparin 1; dipyridamole 1</td>
<td>20 (HT)</td>
<td>Yes</td>
</tr>
<tr>
<td>Soo et al** (2012)</td>
<td>Patients with stenting, 133</td>
<td>12 wk</td>
<td>23</td>
<td>All received aspirin and clopidogrel</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Bokura et al** (2011)</td>
<td>Elderly, 2102</td>
<td>3.6 –y</td>
<td>93</td>
<td>NA</td>
<td>10 ICH, 4 SAH</td>
<td>Yes, 50.2 (16.7–150.9)</td>
</tr>
<tr>
<td>Biffi et al** (2010)</td>
<td>Lobar ICH, 104</td>
<td>34.3 –mo</td>
<td>63</td>
<td>Antiplatelet 88; warfarin NA</td>
<td>29</td>
<td>Yes,† 4.12 (1.6–9.3) in ≥5 CMBs</td>
</tr>
<tr>
<td>Thijss et al** (2010)</td>
<td>AIS/TIA, 487</td>
<td>2.2 y</td>
<td>129</td>
<td>Antiplatelet NA; anticoagulant 130</td>
<td>2</td>
<td>No‡</td>
</tr>
<tr>
<td>Lee et al** (2008)</td>
<td>AIS because of LAA or CE, 377</td>
<td>6 d</td>
<td>109</td>
<td>Antiplatelet 146; anticoagulant 208; thrombolysis 39</td>
<td>74 (HT)</td>
<td>No</td>
</tr>
<tr>
<td>Soo et al** (2008)</td>
<td>AIS, 908</td>
<td>26.6 mo</td>
<td>252</td>
<td>Single antiplatelet 840; coumadin 39; switch 29</td>
<td>15</td>
<td>Yes, 9.81 (2.76–34.83) in ≥5 CMBs</td>
</tr>
<tr>
<td>Fiehler et al** (2007)</td>
<td>AIS with tPA, 570</td>
<td>10 d</td>
<td>86</td>
<td>All IPA</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>Jeon et al** (2007)</td>
<td>ICH, 63</td>
<td>23.3 mo</td>
<td>43</td>
<td>Antiplatelet 6</td>
<td>7</td>
<td>Yes§</td>
</tr>
<tr>
<td>Boulanger et al** (2006)</td>
<td>AIS/TIA, 236</td>
<td>14 mo</td>
<td>45</td>
<td>Antiplatelet 56; anticoagulant NA</td>
<td>2</td>
<td>No†</td>
</tr>
<tr>
<td>Naka et al** (2006)</td>
<td>Acute stroke, 266</td>
<td>564.8 d</td>
<td>94</td>
<td>NA</td>
<td>10</td>
<td>Yes, 85.6 (6.3–1155.6)</td>
</tr>
<tr>
<td>Fan et al** (2003)</td>
<td>AIS, 121</td>
<td>27 mo</td>
<td>43</td>
<td>Antiplatelet 97; anticoagulant 7</td>
<td>5</td>
<td>Yes</td>
</tr>
<tr>
<td>Nighoghossian et al** (2002)</td>
<td>AIS, 100</td>
<td>7 d</td>
<td>20</td>
<td>tPA 27; aspirin or thienopyridine 8; heparin or warfarin 39; LMWH 26</td>
<td>26</td>
<td>Yes, 7.2 (1.9–28.2)</td>
</tr>
</tbody>
</table>

AIS indicates acute ischemic stroke; CE, cardioembolism; CI, 95% confidence interval; CMBs, cerebral microbleeds; HR, hazard ratio; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; IS, ischemic stroke; LAA, large artery atherosclerosis; NA, data not available; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; and IPA, tissue-type plasminogen activator.

* CMBs were related with future stroke in general.
** The number of lobar CMBs was related with recurrence of lobar ICH.
† Lobar CMBs or combined lobar and deep CMBs were independent predictors of recurrent stroke.
‡ The number of CMBs predicted recurrent ICH.
§ ICMBs were related with recurrent disabling and fatal strokes. This risk was mainly assumed by recurrent ischemic strokes.

Does the Increased Risk of ICH Outweigh the Benefit of Antithrombotic Therapy in Patients With CMBs?

From a clinical perspective, the major concern is whether the increased risk of ICH in patients with CMBs, if any, outweighs the benefit of antithrombotic therapy. So far, few studies investigated this risk–benefit ratio. Soo et al** compared the risk of future ICH with the benefit of antithrombotic agents in 908 patients with acute ischemic stroke treated with a single antithrombotic agent (840 antiplatelet users, 39 coumadin users, and 29 users switching between antiplatelet and coumadin) during 26 months of follow-up. Percentage of subsequent ICH increased significantly from 0.6% (4/656) among those without CMBs to 4.4% (11/252) among those with CMBs (P<0.001). Risk of subsequent ICH increased significantly with quantity of CMBs: 0.6% (no CMBs), 1.9% (1 CMBs), 4.6% (2–4 CMBs) and 7.6% (≥5 CMBs; P<0.001). There was also a significant increase in mortality from ICH with quantity of CMBs: 0.6%, 0.9%, 1.5%, and 3.8%, respectively (P=0.054). Rate of recurrent cerebral infarction was 9.6%, 5.6%, 21.5%, and 15.2%, respectively, in those 4 groups based on CMB quantity (P=0.226). Comparing with the modest benefit of antithrombotic agents in secondary stroke prevention (absolute risk reduction of 0.69%–2.49% for aspirin and 6% for warfarin), the extra bleeding risk when there were ≥5 CMBs (7.6%) seems to outweigh the benefit of treatment. In addition, in patients with ≥5 CMBs, the mortality from recurrent ICH (3.8%) also outweighs the mortality from recurrent ischemic stroke (1.5%).

In a decision analysis exploring warfarin therapy in patients with nonvalvular atrial fibrillation, using a conservative estimate of a 2-fold increased risk of ICH for patients with CMBs, anticoagulant therapy still would be superior to aspirin for patients at average risk for thromboembolic stroke (4.5%/y). However, if the risk of ICH is assumed to be >16-fold in patients at average risk for thromboembolic stroke or 3.2-fold in patients at a low risk for thromboembolic stroke (1.5%/y), anticoagulants should be withheld. The lack of longitudinal studies of incident ICH in patients with CMBs limited this decision making. In Asia, a randomized controlled study Prevention of Cardiovascular Events in Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage (PICASSO;
ClinicalTrials.gov Identifier: NCT01013532) is ongoing to investigate the risk of recurrent ICH, ischemic stroke, cardiovascular events, and death in ischemic stroke patients with CMBs taking cilostazol versus aspirin. This trial will provide important data about antithrombotic-related risk versus benefit in patients with different burden of CMBs.

**Recommendations and Future Directions**

Although several studies investigated the association among CMBs, ICH, and antithrombotic therapy, several questions remained unanswered, and attention should be paid to the following points in future studies.

First, most of the current studies mainly investigated aspirin, clopidogrel, and warfarin. Other antithrombotic agents, such as dipyridamole, cilostazol, new oral anticoagulants, or double antiplatelet regime, are less studied. In addition, most studies did not evaluate CMB-related ICH by stratifying patients according to antithrombotic agents, ignoring different bleeding risks among different agents. Prior studies and clinical experience have demonstrated a general safety profile for bleeding risk as follows: combined therapy of antiplatelet plus anticoagulant > single anticoagulant or dual antiplatelet therapy (ie, aspirin plus clopidogrel) > antiplatelet monotherapy. Even for single antithrombotic therapy, the bleeding risk varies from one agent to another (ie, aspirin>cilostazol; warfarin>new oral anticoagulants). Patients with CMBs might have an unacceptable risk–benefit ratio under warfarin treatment, but not necessarily under new oral anticoagulants. Stratification by antithrombotic agents is necessary in future studies.

Second, whether CMB-related ICH depends on CMB locations is unclear. The cause of CMBs is presumed to differ according to CMB locations, with strictly lobar CMBs mainly caused by CAA and deep or infratentorial CMBs mainly caused by hypertensive microangiopathy. Although these 2 pathologies may interact/coexist in clinical practice, and further pathological studies are required to support this assertion. Recurrent ICH was more common in survivors of lobar hemorrhage compared with survivors of deep hemorrhage. Aspirin users are more likely to have lobar ICH or lobar CMBs. Antiplatelet-related ICH patients had more lobar CMBs than nonantiplatelet-related ICH patients. Longitudinal studies show that lobar CMBs predict recurrent lobar ICH or recurrent stroke. In contrast, some studies discovered the association between aspirin or clopidogrel use and a higher prevalence of deep/infratentorial CMBs, instead of strictly lobar CMBs. Definitive data about the impact of CMBs location on recurrent ICH are lacking.

Third, there may be a threshold number for CMBs that tip the risk–benefit balance in favor of avoiding antithrombotic therapy. The risk of antiplatelet/warfarin-related ICH increases with quantity of CMBs, and the risk of ICH may outweigh the benefit in patients with ≥5 CMBs detected on gradient-recalled echo.

Fourth, the risk of ICH and ischemic stroke in the presence of CMBs might vary across ethnic groups. CMBs are more related to recurrent ICH in Asians but more related to recurrent acute ischemic stroke in whites. Most CMBs are located in lobar regions in whites, suggesting CAA as a dominant cause. In contrast, deep CMBs, mainly representing hypertensive microangiopathy, predominate in Asian cohorts.

Fifth, before randomized controlled trials, which can ultimately provide definitive guidance about the use or withholding of antithrombotic therapy in patients with CMBs, prospective studies, with large sample size, are essential in establishing the risk–benefit ratio of antithrombotic agents. Confounding factors, including age, hypertension, and white matter hyperintensities, should be adjusted with enough statistical power.

Sixth, personalized antithrombotic therapy may be necessary. Recently, Dr Mark Fisher proposed an algorithm, suggesting that warfarin should be avoided, but new oral anticoagulants would be acceptable in atrial fibrillation patients with lobar CMBs or ≥5 subcortical CMBs. This seems logical but needs validation. Although efforts are dedicated to explore whether CMBs can be a potential radiological marker that guide antithrombotic therapy, treatment decision should always take into account other underlying risk factors. A reliable risk model, incorporating imaging hemorrhagic markers (CMBs, white matter hyperintensities, cortical superficial siderosis, etc), genetic factors (apolipoprotein E, vitamin K epoxide reductase complex subunit 1, cytochrome P450 2C9, etc), and clinical risk factors (age, hypertension, diabetes mellitus, end-stage renal disease, etc) may be helpful for decision making on specific patients. Some existing risk scores might have an unacceptable risk–benefit ratio under warfarin treatment, but not necessarily under new oral anticoagulants. Stratification by antithrombotic agents is necessary in future studies.

**Figure 2.** The seesaw when making antithrombotic treatment decision. Decision making depends on the risk–benefit ratio associated with antithrombotic treatment. From a clinical perspective, decreased risk of ischemic stroke is the main benefit, whereas increased risk of intracerebral hemorrhage (ICH) is the main risk. This figure shows factors that may increase the risk of ischemic stroke or ICH, assisting physicians to evaluate the risk–benefit ratio. Note that ischemic stroke and ICH may share similar risk factors (eg, age and hypertension are included in ABCD2, CHA2DS2-VASc score, and HAS-BLED score). Note that meta-analysis shows that CMBs predict a higher risk of recurrent ICH (odds ratio [OR], 8.52) than recurrent ischemic stroke (OR, 1.55). Some CMBs were listed in factors associated with increased risk of ICH. ABCD2 indicates age, blood pressure, clinical features, duration of transient ischemic attack (TIA), diabetes mellitus; AF, atrial fibrillation; CAA, cerebral amyloid angiopathy; CHA2DS2-VASc score, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, and prior stroke or TIA (doubled), vascular disease, age 65 to 74 years, and sex category; and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly.
(eg, age, blood pressure, clinical features, duration of transient ischemic attack, diabetes mellitus [ABCD2]; congestive heart failure, hypertension, age >75 years (doubled), diabetes mellitus, and prior stroke or TIA (doubled), vascular disease, age 65–74 years, and sex category [CHA2DS2-VASc]; and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly [HAS-BLED])57,58 may be helpful to assess the bleeding/ischemia risk. Figure 2 listed some factors that may increase the risk of ischemic stroke or ICH, assisting physicians to weigh risks versus benefits when making antithrombotic treatment decisions.

Seventh, most of the current studies used T2-weighted gradient-recalled echo technique on 1.5-T MR to detect CMBs. Whether more advanced techniques, such as susceptibility-dendent-recalled echo technique on 1.5-T MR to detect CMBs,59 can change the clinical relevance in terms of making antithrombotic treatment decisions. ICH, assisting physicians to weigh risks versus benefits when taking antithrombotic therapy must weigh against the risk–benefit ratio, and the principle of primum non nocere should be applied in antithrombotic therapy might increase the risk of ICH. Advanced age, Asian ethnicity, who have a significantly heightened risk of ICH. Other risk factors of ICH, including advanced age, uncontrolled hypertension, diabetes mellitus, renal function, and presence of small vessel diseases, should be taken into account for decision making, as well. Selection of antithrombotic therapy must weigh against the risk–benefit ratio, and the principle of primum non nocere should be applied in patients with highest risk.

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