Risk of Intracerebral Hemorrhage in Patients With Cerebral Microbleeds Undergoing Endovascular Intervention

Yannie O.Y. Soo, MD; Deyond Y.W. Siu, MD; Jill Abrigo, MD; Simon Yu, MD; Nick Ng, MSc; Anil T. Ahuja, MD; Lawrence K.S. Wong, MD; Thomas W. Leung, MD

Background and Purpose—Cerebral microbleeds (CMBs) on MRI gradient echo images are hemosiderin deposits, which may predict intracerebral hemorrhage (ICH). The risk of ICH in patients with CMBs could be exacerbated by the use of antithrombotics. The purpose of our study is to prospectively evaluate the risk of ICH in patients with ischemic stroke who receive dual antiplatelet therapy for endovascular intervention.

Methods—We analyzed MRI of 133 patients admitted consecutively for intra- and extracranial stenting for symptomatic large artery atherosclerosis who received aspirin and clopidogrel. Quantity and location of CMBs were recorded by neuroradiologists independent from the angioplasty team. The primary end point was symptomatic ICH as evident in CT of the brain within 12 weeks of procedure.

Results—CMBs were identified in 23 patients. Mean number of CMBs was 2.3±1.6. Four patients had >5 CMBs. Forty-seven patients had intracranial stents, 84 patients had extracranial stents, and 2 patients had both intracranial and extracranial stents. There was no difference in risk of symptomatic ICH between those with (4.3%) and without CMBs (5.5%) patient with CMBs (P=1.000).

Conclusions—The presence of a small number of CMBs does not cause a large increase in the short-term risk of symptomatic ICH in patients with ischemic stroke who undergo endovascular intervention with dual antiplatelet therapy. The risk of ICH in patients with ≥5 CMBs, however, remains unclear. Further studies with a larger sample size of patients with multiple CMBs are needed. 

Key Words: cerebral microbleeds ■ endovascular intervention ■ hemorrhage ■ stroke ■ stenting

Cerebral microbleeds (CMBs) are hemosiderin deposits in macrophages related to bleeding-prone microangiopathy, which appear as dot-like hypointense signals on gradient echo MRI.1 CMBs are associated with aging, hypertension, small vessel disease, spontaneous intracerebral hemorrhage, and cerebral amyloid angiopathy2-7 and may predict intracerebral hemorrhage (ICH) in both patients with ischemic and hemorrhage stroke.8-12 In addition, a population-based study suggested that CMBs are more frequently observed in antiplatelet users.13 This led to concerns over the safety of antithrombotics in patients with stroke with CMBs. A prospective study showed that patients with ischemic stroke treated with long-term aspirin could be at risk of ICH in parallel with the number of CMBs. For patients with ≥5 CMBs, the risk of future ICH was 7.6%, compared with 0.6% in patients without CMBs.12

Stent-assisted angioplasty is an emerging treatment option for patients with refractory ischemic strokes attributed to large artery atherosclerosis. Dual antiplatelet agents, commonly aspirin and clopidogrel, are prescribed for at least 4 weeks for prevention of stent thrombosis. However, ICH may occur in up to 5% of patients receiving stent-assisted angioplasty in association with the use of antithrombotics or hyperperfusion syndrome.14,15 The purpose of this study is to evaluate the short-term risk of ICH in patients with ischemic stroke with CMBs who received dual antiplatelet therapy for endovascular intervention.

Methods

Study Population
We recruited consecutive patients admitted to Prince of Wales Hospital for ischemic stroke attributed to large artery atherosclerosis who require intracranial or extracranial stent-assisted angioplasty from April 2004 to October 2009. Each participant provided an informed consent. Recruited patients underwent a 1.5-T MRI brain scan (T1-weighted, T2-weighted, and gradient echo imaging) before the endovascular procedure. They all received dual antiplatelet...
therapy (80 mg aspirin daily and 75 mg clopidogrel daily). Patients who had a bleeding tendency or required additional antithrombotics apart from periprocedural heparin were excluded.

One hundred forty-five patients met the eligibility criteria and were enrolled into the study. All patients followed a standardized management protocol in the perioperative period. To prevent hyper-perfusion syndrome, systolic blood pressure was aimed <140 mm Hg postoperatively in the absence of any untreated high-grade stenosis. In general, dual antiplatelets therapy was begun at least 3 days before until 6 to 12 weeks after the procedure. Primary end points were symptomatic fatal and nonfatal ICH within 12 weeks from the endovascular procedure as evident on CT brain scan.

### Image Analysis

The MRI examinations were performed with a 1.5-T scanner (Sonata; Siemens Medical System, Erlangen, Germany). The gradient-echo sequence was performed with the following parameters: TR = 350 ms, TE = 30 ms, excitations = 2, flip angle = 30°, slice thickness = 5 mm, gap = 0.5 mm, field of view = 230 mm, matrix = 256×256, acquisition time = 5 minutes 4 seconds. Axial spin echo T1-weighted images and turbo spin echo T2-weighted images were acquired. The MRI films were evaluated by neuroradiologists (D.Y.W.S., J.A.) and neurologist (Y.O.Y.S.) who are experienced in reading CMBs. A CMB was defined as an old, silent focus of signal loss or hypointensity in the gradient-echo sequence measuring 2 to 10 mm in diameter. Lesions within an acute infarct or hypertensitivities on conventional T1 sequence were excluded. Symmetrical signal loss or hypointensities in the globus pallidum, which may represent calcification, was also excluded. Flow void artifacts of the pial blood vessels were distinguished from CMB by their morphology and correlation with T1- and T2-weighted images. The number and distribution of CMBs were documented according to the Brain Observer MicroBleed Scale (BOMBS). White matter change was defined as presence of periventricular punctate or confluent hyperintense signals on MRI fluid-attenuated inversion recovery sequence. Severity of vascular stenosis was defined from digital subtraction angiograms according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.

### Statistical Analysis

We assumed CMBs in 20% of the cohort and risk of symptomatic ICH in patients without CMBs to be 5%. Based on these assumptions, a study to rule out OR of 5.5 for increased risk of symptomatic ICH in patients with CMBs versus those without would require a total sample of 120 patients (α=0.05, 80% power at 95% CI). One hundred forty-five potentially eligible patients met the inclusion criteria and were recruited into the study during the study period.

An interrater reliability analysis using the κ statistic was performed to determine consistency among CMB raters. In all analyses, nonparametric Mann-Whitney test was used for comparison of continuous variables and χ² test was used for categorical variables. The Fisher exact test was used when the expected count in any of the 2×2 table was <5. To investigate for predictors of ICH, survival analysis using the Cox proportional hazards regression model was used. We first performed a univariate model for each potential candidate variable as exploratory analyses. Because there were no significant variables in the univariate model, multivariate analysis was not performed. Statistical analyses were performed using SPSS Version 13.0. Alpha was set at 0.05.

### Results

One hundred forty-five patients were recruited. During the study period, a total of 12 patients was excluded from the study, including 2 patients with movement artifacts on MRI, 7 patients who needed other antithrombotic agents, 2 patients with no significant stenosis on digital subtraction angiogram, and 1 patient who had gastrointestinal bleeding before procedure, who therefore did not receive intervention. Finally, 133 patients were enrolled into the study for analysis. Mean age was 67.3 years. CMBs were identified in 23 (17.3%) patients. The mean number of CMBs was 2.3 in patients with CMBs versus those without would require a total sample of 120 patients (α=0.05, 80% power at 95% CI). One hundred forty-five potentially eligible subjects met the inclusion criteria and were recruited into the study during the study period.

### Table 1. Baseline Characteristics of Patients With and Without CMBs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CMBs (-)</th>
<th>CMBs (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
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<tr>
<td>Median age (interquartile range, y)</td>
<td>67.4±14</td>
<td>67.0±17</td>
<td>0.869</td>
</tr>
<tr>
<td>Smoker</td>
<td>46 (41.8%)</td>
<td>12 (52.2%)</td>
<td>0.362</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (30.0%)</td>
<td>8 (34.8%)</td>
<td>0.651</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (73.6%)</td>
<td>20 (87.0%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>93 (84.5%)</td>
<td>20 (87.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18 (16.4%)</td>
<td>6 (26.1%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Prior ischemic stroke or transient</td>
<td>43 (39.1%)</td>
<td>12 (52.2%)</td>
<td>0.247</td>
</tr>
<tr>
<td>ischemic attack before index stroke</td>
<td></td>
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<tr>
<td>Prior intracerebral hemorrhage</td>
<td>0</td>
<td>0</td>
<td>. . .</td>
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<tr>
<td>Imaging characteristics</td>
<td></td>
<td></td>
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<tr>
<td>White matter change</td>
<td>33 (30.0%)</td>
<td>9 (39.1%)</td>
<td>0.392</td>
</tr>
<tr>
<td>Severity of stenosis, %</td>
<td>80.0±20.0</td>
<td>77.0±13.3</td>
<td>0.265</td>
</tr>
<tr>
<td>median±interquartile range</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment received</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment duration of dual</td>
<td>61.0±42.0</td>
<td>52.5±40.0</td>
<td>0.389</td>
</tr>
<tr>
<td>antiplatelet agents, d,</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>median±interquartile range</td>
<td></td>
<td></td>
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<tr>
<td>Patients maintained on aspirin after</td>
<td>105 (95.5%)</td>
<td>21 (91.3%)</td>
<td>0.288</td>
</tr>
<tr>
<td>dual antiplatelet therapy</td>
<td></td>
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<tr>
<td>Patients maintained on clopidogrel</td>
<td>5 (4.5%)</td>
<td>2 (8.7%)</td>
<td>0.365</td>
</tr>
<tr>
<td>after dual antiplatelet therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage of aspirin, median, mg/d</td>
<td>80±0</td>
<td>80±0</td>
<td>0.834</td>
</tr>
<tr>
<td>Dosage of clopidogrel, median, mg/d</td>
<td>75±0</td>
<td>75±0</td>
<td>0.306</td>
</tr>
<tr>
<td>Intracranial stent</td>
<td>38 (34.5%)</td>
<td>9 (39.1%)</td>
<td>0.676</td>
</tr>
<tr>
<td>Extracranial stent</td>
<td>71 (64.5%)</td>
<td>13 (56.6%)</td>
<td>0.468</td>
</tr>
</tbody>
</table>

CMBs indicates cerebral microbleeds.
patient with CMBs. Among the patients without CMBs, ICH occurred Day 1 after stenting in 2 patients, the others on Days 3, 10, 12, 68, and 78. For the patient with CMB, ICH developed on the same day after stenting (Figure). There was no significant difference in risk of fatal and nonfatal ICH between the 2 groups (Table 2). ICH occurred within the territory of stented vessel in 5 patients. None of the ICHs occurred within areas of prior strokes. No patients had ICH during the period of prestent dual antiplatelet therapy. None of the 12 nonenrolled patients had ICH before or within 12 weeks of the procedure.

By Cox regression analysis, presence of CMBs, stroke severity, severity of angiographic stenosis, duration between stroke onset and stent, and location of stent were not predictive of ICH (Table 3).

Discussion

This is the first prospective study to evaluate the risk of symptomatic ICH in patients with ischemic stroke with CMBs who undergo stent-assisted angioplasty. In the study, all patients received aspirin and clopidogrel for the prevention of stent thrombosis. Among patients with CMBs, there was no large increase in risk of ICH within the period of dual antiplatelet treatment or 12 weeks from the procedure. There has been growing interest in CMBs as a radiological predictor of ICH. Gradient echo and susceptibility-weighted imaging can sensitively detect hemosiderin deposits as small as a few millimeters arising from previous silent vascular leakage. Supported by histological evidence of its high association with bleeding-prone microangiopathy,1 these asymptomatic tiny CMBs were associated with future spontaneous and aspirin-associated ICH in prospective and cross-sectional studies.8,9,12,18–20 Because CMBs are frequently observed in patients with ischemic stroke and antiplatelet users, there is a growing concern on the clinical significance of this radiological marker and the safety of thrombolytic and antithrombotic therapies in patients with CMBs. The Bleeding Risk Analysis in Stroke Imaging Before Thrombolysis (BRASIL) study analyzed MRIs of 570 patients acquired within 6 hours of stroke onset and detected no significant increase in risk of symptomatic ICH with intravenous thrombolysis in the 86 patients with CMBs (5.8% in the CMBs group versus 2.7% in the control group, P=0.17).21 However, in a large prospective cohort of 908 patients with ischemic stroke, of whom 252 had CMBs, the risk of subsequent ICH in patients with CMBs treated with aspirin increased significantly with the number of CMBs: 0.6% with no CMB, 1.9% with 1 CMB, 4.6% with 2 to 4 CMBs, and 7.6% with ≥5 CMBs.12 When compared with the benefit of aspirin in secondary stroke prevention (absolute risk reduction 0.69%–2.49%),12,22 the associated hemorrhagic risk seems to outweigh its benefit for patients with ≥5 CMBs. Currently, due to the modest benefit of aspirin in secondary stroke prevention, many patients seek alternative treatment options, for example, a combination of antiplatelet agents or endovascular intervention. In theory, these aggressive treatments could potentially lead to an even higher risk of ICH in patients with CMBs, although no data are available in these patients.

For patients with stroke undergoing stent-assisted angioplasty, ICH related to cerebral hyperperfusion syndrome most commonly occurs 5 to 7 days after the procedure.23–25 After this period, the risk of ICH will then be attributed mainly to dual antiplatelet agents.26 In this study, we monitor this adverse outcome up to 12 weeks after an endovascular procedure. During the study period, 5 of the 7 incidents of ICH occurred in the territories of stented vessels. Many factors may play a role in hyperperfusion-related ICH, including a sudden change in perfusion pressure, impaired cerebral autoregulation, uncontrolled hypertension, ischemia–reperfusion injury, baroreceptor dysfunction, and intraoperative ischemia. In patients with a high-grade stenosis and impaired flow, cerebral blood flow is maintained at a normal level at the expense of maximal arteriolar vasodilatation. With impaired autoregulation, cerebral blood flow is directly dependent on the systemic blood pressure. Recanalization with endovascular stenting, thus, causes an immediate, rapid surge in cerebral blood flow predisposing the patients to disruption of blood–brain barrier and ICH. In this study, 2 of the ICHs occurred at territories without prior vascular intervention. With the small sample size, it remains uncertain if

| Table 2. Intracerebral Hemorrhage Within 12 Wk of Endovascular Intervention |
|-----------------------------|-----------------------------|-----------------------------|
| CMBs (−) (n=110) | CMBs (+) (n=23) | P Value |
| All ICH | 6 (5.5%) | 1 (4.3%) | 1.000 |
| Nonfatal ICH | 4 (3.6%) | 0 (0%) | 0.429 |
| Fatal ICH | 2 (1.8%) | 1 (4.3%) | 0.437 |

CMBs indicates cerebral microbleeds; ICH, intracerebral hemorrhage.
stent-associated ICH or antithrombotics-associated ICH is more dependent on the presence of CMBs.

In this study, the sample size was powered to exclude a large increase in risk of ICH (OR, 5.5) in patients with CMBs versus those without CMBs. Hence, a moderate increase in the risk of ICH cannot be excluded, particularly for those with ≥5 CMBs, which were not well represented in this study. McCabe et al and Chamorro et al suggested that the presence of microangiopathy represented by leukoaraiosis on CT of the brain might be associated with an elevated risk of hyperperfusion injury.27,28 Given the close association of CMBs and leukoaraiosis, it remains plausible that CMBs, which reflect an advanced stage of bleeding-prone microangiopathy, may predispose to ICH in patients undergoing endovascular intervention. As illustrated in the case in the Figure, the hematoma developed at the site of CMB (right parietal lobe) contralateral to the acute infarct (left corona radiata). The ICH could have happened due to a sudden surge in perfusion pressure after the right carotid stenting causing a rupture of the leaky arterioles with underlying microangiopathy. This may suggest that advanced-stage microangiopathy as indicated by the presence of CMBs may portend a higher risk of ICH during or after endovascular intervention.

When considering for endovascular intervention, its benefit in preventing further strokes should always be weighed against the risk of ICH associated with the procedure. Although the efficacy of carotid intervention has been well established in the NASCET trial,29 long-term benefit of intracranial stenting remains uncertain. Without a thorough understanding of the effectiveness of these treatments, it is uncertain if a moderate risk of ICH should alter the decision for intervention, in which otherwise recurrent stroke risk could be up to 25%.70,30 Further research in exploring both the risk and benefit of endovascular intervention in patients with CMBs is clearly needed to help physicians in evaluating the safety of this emerging treatment in the presence of CMBs. Further studies with a large sample size are needed. Additional analysis of signs of blood–brain barrier damage, for example on postinterventional contrast-enhanced CT images, will be helpful in understanding the pathophysiology of ICH in these patients.31

The strength of our study is the homogeneity of our patients in terms of stroke mechanism (ie, large artery disease) and the standardized dual antiplatelet treatment. Because different antithrombotic agents may have different bleeding potentials,32,33 a possible confounding effect from various antithrombotics was minimized by excluding patients with other antithrombotics, for example, dipyridamole, cilostazol, and Coumadin. Furthermore, we also controlled the dosage of antiplatelet therapy between the 2 groups and standardized perioperative blood pressure management.

However, the interpretation of our study is limited by its small sample size and the small number of patients with ≥5 CMBs. Because previous studies showed that risk of ICH are significantly higher when there are >5 CMBs, it remains possible that patients with ≥5 CMBs may stand a higher risk of ICH with endovascular intervention. Finally, our study was carried out in a Chinese population in which the result may not be generalizable to other ethnic groups.

In conclusion, in this prospective cohort of patients with stroke with CMBs undergoing endovascular intervention for symptomatic large artery atherosclerosis with dual antiplatelet therapy, the presence of a small number of CMBs does not lead to a large increase in the short-term risk of ICH significantly. However, a moderate increase in risk of ICH cannot be excluded. Further studies with a larger sample size, particularly in patients with ≥5 CMBs, are needed to evaluate the bleeding risk in this high-risk group.

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Disclosures
None.

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