Quantity of Cerebral Microbleeds, Antiplatelet Therapy, and Intracerebral Hemorrhage Outcomes: A Systematic Review and Meta-analysis

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Background and purpose: Cerebral microbleeds (CMBs) increase future intracerebral hemorrhage (ICH) risk after ischemic stroke (IS) or transient ischemic attack (TIA). However, whether CMB-related ICH risk depends on CMB quantity, CMB location, or antithrombotic agents is unclear. We performed a systematic review and meta-analysis to investigate CMB-related ICH risk, stratifying patients according to the quantity of CMB, the location of CMB, and the type of antithrombotic therapy used. *Methods:* Literature databases were searched for prospective cohorts reporting ICH outcomes in patients with IS or TIA with baseline CMB evaluation. We calculated pooled relative ratios (RRs) for ICH among patients with and without CMBs. Pooled RRs of CMB-related ICH were further calculated in subgroups stratified by CMB quantity, CMB location, and antithrombotic therapy. *Results:* Among the 10 included studies, the pooled RR of future ICH was 7.73 (95% confidence interval [CI], 4.07-14.70; $P < .001$) in CMB versus non-CMB patients. Subgroup analysis revealed that compared with non-CMB patients, multiple-CMB patients were at an increased risk for future ICH (RR = 8.02; 95% CI, 3.21-20.01; $P < .001$), whereas single-CMB patients did not incur this risk (RR = 2.33; 95% CI, .63-8.63; $P = .205$). A strong association was found between CMB presence and subsequent ICH in antiplatelet users (RR = 16.56; 95% CI, 3.68-74.42; $P < .001$). Studies on CMB-related ICH according to CMB locations and in anticoagulant users are lacking for subgroup analysis. *Conclusion:* Our study revealed that patients with IS or TIA with multiple CMBs may incur a higher risk of future ICH, and the presence of CMBs in patients with IS or TIA using antiplatelet agents may significantly increase the subsequent ICH risk. **Key Words:** Cerebral microbleeds—antiplatelet therapy—intracerebral hemorrhage—stroke—magnetic resonance imaging—secondary prevention.

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Introduction

Cerebral microbleeds (CMBs) are small hemosiderin depositions resulting from blood leakage caused by damaged small blood vessels. CMBs are related mainly to age, vascular risk factors, and cerebral amyloid angiopathy. CMBs are already present by middle age, and their prevalence increases with age.[1] Compared with neurologically healthy elderly persons, patients with ischemic stroke (IS) may be prone to CMBs[2] and may develop new CMBs rapidly after acute IS.[3] Recently, a meta-analysis of prospective cohorts showed that patients with IS or transient ischemic attack (TIA) with baseline CMBs have an increased risk of spontaneous intracerebral hemorrhage (ICH), especially Asian patients.[4] These findings suggest that clinicians should reconsider the balance between the benefits of antithrombotic therapy and the increased risk of future ICH in patients with IS or TIA with baseline CMBs. However, whether CMB-related ICH depends on the quantity and location of CMBs is still unknown. One study revealed that future ICH risk increased with the quantity of CMBs,[5] whereas some studies have shown that the risk was unrelated to CMB quantity.[6-8] In one study,[5] a mixed cortical–subcortical CMB location was an independent predictor of future ICH, whereas in another study results showed that both lobar and mixed lobar–deep locations might predict recurrent stroke.[7] Additionally, few systematic reviews have evaluated CMB-related ICH by stratifying patients according to various antithrombotic therapies. A previous systematic review and meta-analysis based on cross-sectional studies provided stronger evidence that, compared to nonantithrombotic users, CMBs were more frequent either in warfarin users or in antiplatelet users with ICH.[9] However, the systematic review is based on cross-sectional studies with inadequate evidence of a cause-and-effect relationship. To the best of our knowledge, no systematic review and meta-analysis based on prospective studies had evaluated the CMB-related ICH risk in patients with IS/TIA according to various antithrombotic therapies. As different antithrombotic agents have various effects on the risk of bleeding, it is important to determine CMB-related ICH risk among patients with IS or TIA who undergo antiplatelet and anticoagulant therapies, respectively. We therefore performed a systematic review and meta-analysis of the relationship between CMB presence and the risk of future ICH in patients after IS or TIA and further investigated the CMB-related ICH by stratifying patients according to quantity of CMB, location of CMB, and type of antithrombotic therapy.

Methods

The Medline, Cochrane Library, and China National Knowledge Infrastructure databases were searched for all relevant studies from inception to August 2014. The following free words were used: ("stroke" or "cerebral infarction" or "TIA") and ("microbleed*" or "microhaemorrhage*" or "microhemorrhage*"). In addition, meta-analyses and references of reviews were also screened to identify relevant studies. The reference lists of each available article were manually searched to identify relevant citations.

The titles and abstracts of all obtained articles were screened, and eligible studies were independently selected for further evaluation by two reviewers. Studies were eligible for inclusion based on the following criteria: (1) The design was a prospective cohort study; (2) patients were 18 years of age or older with IS or TIA; (3) patients underwent a baseline magnetic resonance imaging (MRI), including a T2*-weighted gradient echo sequence or susceptibility-weighted imaging to detect the presence of CMBs; (4) the follow-up time was 3 months or more, and the study included the assessment of symptomatic ICH outcomes during the follow-up period; and (5) the study evaluated the risk of symptomatic ICH according to the presence of CMBs in the baseline MRI.

Studies were excluded if they (1) were case–control studies, cross-sectional studies, review articles, letters, commentaries, or case reports; (2) enrolled patients with IS who received endovascular intervention or intravenous thrombolysis; (3) did not describe the symptomatic ICH outcomes after the baseline event; (4) did not report the risk of symptomatic ICH outcomes related to the presence of CMBs in the baseline MRI; or (5) had an inadequate follow-up interval (less than 3 months).

Data Extraction

Two authors independently recorded data from each included study using a data collection form. The following basic data were extracted: author of the study, year of publication, country of study population, number of patients, disease type, demographic characteristics (mean age and sex), CMB prevalence, antithrombotic users, numbers of antithrombotic users in the CMB (+) and CMB (–) groups, baseline MRI, and follow-up period. We extracted detailed data regarding spontaneous symptomatic ICH outcomes stratified by CMB presence. The outcomes of symptomatic ICH were further extracted according to the following subgroups: studies that described CMB quantity were stratified into non-CMB, single-CMB, and multiple-CMB subgroups; and studies that described CMB location were classified as lobar region, nonlobar region, and mixed region. Moreover, we restricted the patients to antiplatelet or anticoagulant users and extracted spontaneous symptomatic ICH outcomes stratified by CMB presence in these two groups. In the meta-analysis of the subgroups, published data with any miscalculation were excluded.