# Predictors of New Cerebral Microbleeds in Patients with Antiplatelet Drug Therapy

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*Background:* Cerebral microbleeds (CMB) are associated with an increased risk for ischemic and especially hemorrhagic stroke. The aim of the present study is to identify patients at high risk for the development of new CMB after initiation of an antiplatelet drug therapy. *Methods:* Patients received magnetic resonance imaging (MRI) within 1 week after initiation of an antiplatelet drug treatment due to a first ischemic stroke (n = 58) and after a follow-up period of 6 months (n = 40). We documented the presence and the number of CMB at baseline and follow-up and analyzed the influence of possible risk factors including vascular risk factors, stroke etiology, and number of CMB at baseline using stepwise logistic regression and Spearman's correlation coefficient. We compared progression rates of CMB in relation to each risk factor using the Mann–Whitney *U*-test. *Results:* The logistic regression model could correctly predict the presence of CMB in 70.7% of patients at baseline and 80% at follow-up. The model correctly identified 85% of patients with new CMB. We observed progression of CMB in 40% of the patients. The overall progression rate was .8 CMB per patient. The progression rate was significantly influenced by age more than 70 years and atherothrombotic stroke. The number of new CMB correlated significantly with the number of CMB at baseline. *Conclusions:* We found several predictors of CMB after initiation of antiplatelet drug therapy. The results help to identify patients who need closer monitoring and thorough control of risk factors in order to lower the risk of new CMB and associated complications. **Key Words:** Cerebral microbleeds—CMB—antiplatelet drug therapy—ischemic stroke—vascular risk factors—hemorrhagic stroke.


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## Introduction

Cerebral microbleeds (CMB) are small (<10 mm) hemosiderin deposits caused by small vessel blood leakage and are considered a magnetic resonance imaging (MRI) marker of vascular brain disease.[1] They are related to cerebral amyloid angiopathy (CAA) when located in cortical or subcortical lobar brain regions[1-4] and to hypertensive vascular pathology when located in deep or infratentorial brain regions.[1-3] Their prevalence increases with increasing age.[4,5] Microbleeds are associated with an increased risk for first or recurrent stroke, especially hemorrhagic stroke,[6,7] but also ischemic stroke of microangiopathic or atherothrombotic origin.[7,8] They are present in 5% of healthy adults, one third of patients with ischemic stroke, and 50% and 80% of patients with first or recurrent intracranial hemorrhage, respectively.[9] The presence and the number of CMB are also associated with an increased mortality, especially mortality related to cardiovascular causes.[4]

Patients usually receive an antiplatelet drug therapy for secondary prevention after an ischemic stroke. However, several studies have shown a higher prevalence and number of CMB in patients taking antiplatelet drug therapy as compared to nonusers,[5,7,10] and a higher risk and mortality of intracerebral hemorrhage in these patients.[9,11,12] Furthermore, previous studies also revealed an association between the development of new deep microbleeds after a first stroke and overall stroke recurrence and deep intracerebral hemorrhage, even after adjusting for preexisting microbleeds and other risk factors.[7,13] Therefore, clinicians need to weigh the risk associated with the development of new microbleeds against the benefits of antiplatelet drug therapy.

The present study investigates the possible predictors for the development of new microbleeds after the initiation of antiplatelet therapy in order to identify patients at high risk for microbleeds and subsequent complications. Possible predictors include the number of microbleeds at baseline,[8] vascular risk factors such as older age, male sex, hypertension, diabetes mellitus, and hyperlipidemia,[1,4,7,13] as well as microangiopathic or atherothrombotic stroke etiology.[7,8,13]

## Patients and Methods

### *Patients*

We recruited patients from the stroke unit of the University Hospital Marburg, Germany, between September 2009 and September 2010. Inclusion criteria were the diagnosis of ischemic stroke or transient ischemic attack (TIA) and the initialization of antiplatelet agents such as aspirin or clopidogrel. We excluded patients with a history of stroke or TIA, previous treatment with antithrombotic medication, aphasia or disability to consent, need for intensive care monitoring, or contraindications for MRI (including cardiac pacemaker, metal plates or medication pumps, and claustrophobia). In addition, we excluded patients if they received anticoagulation. All patients gave written informed consent to participate in the study. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the local institutional review board (AZ 47/10).

### *Methods*

For all patients, we recorded vascular risk factors such as age more than 70 years, male sex, hypertension, hyperlipidemia, or diabetes mellitus. Stroke etiology was classified into 5 subtypes (atherothrombotic, cardioembolic, microangiopathic, other known reasons, and unknown reason) according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) score.[14] Relevant data were obtained from the stroke unit patients' charts and discharge letters. We assessed stroke severity with the National Institutes of Health Stroke Scale (NIHSS).

### *MRI Acquisition*

One to seven days after stroke onset, patients underwent a 3T MRI (Tim Trio, Siemens Medical Solutions, Erlangen, Germany). Besides T1- and T2-weighted imaging and diffusion-weighted imaging, the MRI protocol included a susceptibility-weighted imaging (SWI) sequence (TR/TE = 28/20.0 ms, FoV 230 mm, slice thickness 1.20 mm, flip angle = 15°), which was used for quantification and localization of CMB. Patients received the same MRI protocol during the follow-up scan after 6 months. A neuroradiologist (C.M.) and a neurologist with extensive neuroimaging experience (S.K.) counted the CMB for each patient and documented their localization. CMB could be localized in deep (basal ganglia, thalamus, internal or external capsule), infratentorial (cerebellum, brain stem), and lobar (cortical, subcortical[15]) brain regions. Both investigators were blinded for the symptoms and medication of the patients as well as for the order of the MRI (initial MRI versus follow-up MRI).

### *Statistical Methods*

The statistical analysis was performed with SPSS software version 22.0 (SPSS, IBM Company, Chicago, IL).

At baseline, we calculated the probability for the *presence* of CMB using a stepwise logistic regression model with vascular risk factors (male sex, age >70 years, hypertension, hyperlipidemia, and diabetes mellitus; step 1) and atherothrombotic or microangiopathic stroke etiology (step 2) as predictors. In addition, we analyzed the correlation of vascular risk factors and stroke etiology with the *number* of CMB using the Pearson correlation coefficient.