Incidence, Locations, and Longitudinal Course of Cerebral Microbleeds in European Moyamoya

Holger Wenz, MD*; Ralf Wenz, MSc*; Máté Maros, MD; Gregory Ehrlich, MD; Mansour Al-Zghoul, MD; Christoph Groden, MD; Alex Förster, MD

Background and Purpose—Cerebral microbleeds (cMBs) have previously been linked with especially high incidence in Asian patients with moyamoya together with high tendency to bleed. This, presumably, is characteristic of patients with moyamoya. Herein, we, therefore, investigate retrospectively the frequency, location, and longitudinal course of cMBs in a large German cohort.

Methods—We included all patients with moyamoya who underwent standard magnetic resonance imaging, including T2* -weighted images, in our department between 1998 and 2015. Two independent readers evaluated magnetic resonance imaging scans to determine the occurrence of cMBs according to the Brain Observer Microbleed Scale. Demographics, initial symptoms leading to hospitalization, and associated diseases were obtained by chart review.

Results—Overall, there was a total of 242 T2* studies of 101 included moyamoya patients available with a strong female predominance (69.3%). Eight patients (7.9%) were ≤18 years of age. We detected 25 cMBs within 13 patients (12.9%). One patient <18 of age was presented with a cMB; 2 of 3 patients with an intracranial hemorrhage as initial event demonstrated cMB(s). In 72 of 101 cases, there were 1719 person months of follow-up, with 3 adult patients showing 3 de novo cMBs in the course. The majority of cMBs (64.0%) were located at the cortex/gray–white junction.

Conclusions—Although the frequency of cMBs herein is much higher than the expected age-specific incidence, it is still much lower compared with previous reports on cMBs in moyamoya patients of Asian descent. These results might reflect another ethnic-specific difference in patients diagnosed with moyamoya. (Stroke. 2017;48:307-313. DOI: 10.1161/STROKEAHA.116.014335.)

Key Words: adult ■ brain ■ cerebrovascular disorder ■ Down syndrome ■ moyamoya disease

Moyamoya disease (MMD) is a rare idiopathic occlusive cerebrovascular disorder characterized by progressive stenosis or occlusion of the distal internal carotid artery or its proximal branches and an extensive network of collateral vessels at the base of the brain.1 All unilateral cases or those found in association with systemic disorders (such as trisomy 21 or neurofibromatosis) are defined as moyamoya syndrome (MMS), whereas patients with no known associated risk factors are said to have MMD.1 Although MMD was originally considered to affect predominantly people of Asian descent, the disease has been observed all over the world in people with different origins.1,2 Among different ethnic groups, there is a vast heterogeneity of incidence, prevalence, clinical course, and clinical features.1,2 For example, the typical bimodal incidence with one peak in childhood, typical for most Asian patients (Korean, Japanese, and Chinese),1,2 could not be found in larger cohorts in Europe and the United States.5-6 Furthermore, MMD in adult patients of Asian descent (except Taiwan and Nanjing) have much higher rates of intracerebral hemorrhage as initial symptomatic event than adult moyamoya patients in Europe and the United States.2,5 Recent studies demonstrated that the incidence of cerebral microbleeds (cMBs) is higher in Asian patients with MMD in comparison to healthy controls.7-11 Furthermore, cMBs are a predictor of future intracerebral hemorrhage.10,12,13 Although there are several studies, which analyzed the frequency, localization, and association of cMBs with intracerebral hemorrhage in Asian patients with moyamoya, there are no equivalent studies of patients outside of Asia.7-13

The present study attempts to provide additional information about the incidence, distribution pattern, and longitudinal course of cMBs in a German cohort based on a retrospective analysis of magnetic resonance imaging (MRI) studies.

Received July 7, 2016; final revision received November 12, 2016; accepted November 15, 2016.

From the University Medical Center Mannheim, Department of Neuroradiology (H.W., R.W., M.M., M.A.-Z., C.G., A.F.) and Department of Neurosurgery (G.E.), University of Heidelberg, Mannheim, Germany.

*Dr H. Wenz and R. Wenz contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014335/-/DC1.

Correspondence to Holger Wenz, MD. Department of Neuroradiology, Universitätsmedizin Mannheim, Theodor-Kutzer-Ufer 1–3, 68137 Mannheim, Germany. E-mail holger.wenz@ummed.de

© 2017 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.014335
Methods

Patients
From a prospectively maintained report database (Syngo Data Manager), we identified all patients with conventionally catheter angiographically verified MMD or MMS who were referred to our hospital for diagnosis and treatment between 1998 and 2015. Patients with pathognomonic angiographic findings (Figure 1) who also had well-recognized associated conditions, such as trisomy 21, neurofibromatosis, or unilaterally affected vessels, were classified as having MMS. Patients with no known associated risk factors and bilateral presentation were considered to have MMD. Demographic data such as age, sex, initial clinical presentation, and comorbidities were prospectively tabulated in the database. Only patients who underwent MRI including T2*-weighted images and for whom detailed clinical information was available were included. Patients of Asian descent were excluded. Initially, a total of 155 patients with MMD/MMS were included. Of these, 28 patients (18.1%) were excluded because of missing MRI and 26 patients (16.8%) because of lacking T2*-weighted images. The remaining 101 MMD/MMS patients (65.2%) were included and formed the study cohort.

The study was approved by the local institutional review board. Patient consent was not required by our institutional review board for this analysis because of the retrospective nature of the study and the lack of patient interaction.

MRI Studies
MRI was performed on a 1.5-T MR system (Magnetom Sonata or Avanto; Siemens Medical Systems, Erlangen, Germany) or a 3-T MR system (Magnetom Trio; Siemens Medical Systems). The standardized protocol consisted of at least (1) transverse, coronal, and sagittal localizing sequences followed by transverse oblique contiguous images aligned with the inferior borders of the corpus callosum (applied on sequences 2–5); (2) T1-weighted images; (3) T2-weighted images; (4) diffusion-weighted images; (5) fluid attenuated inversion recovery images; (6) T2*-weighted images; and (7) a 3D time-of-flight magnetic resonance angiography. Parameters of T2*-weighted images are displayed in the Tables I and II in the online-only Data Supplement. Overall, 72 patients (71.3%) underwent follow-up MRI examinations (median: 2.0; SD: 1.6). In 46 patients (45.5%), at least one MRI scan was available before revascularization surgery and in 76 patients (75.2%), at least one MRI scan was available after revascularization surgery. In 18 patients (17.8%), at least one MRI was performed before and after surgery. Altogether, there were 250 T2*-weighted images available. Of these, 214 images were acquired on a 1.5 magnetic resonance system and 36 T2*-weighted images on a 3-T MR system.

MRI Analysis
cMBs were diagnosed according to the proposed guidelines and the topographical distribution noted according to Brain Observer Microbleed Scale (BOMBS) and its user guide for BOMBS. For a thematic illustration, see Figure 2. All viewing and analysis of the acquired data sets were electronically performed on a DICOM workstation using OsiriX Imaging Software (http://www.osirix-viewer.com/index.html). To distinguish cMBs from potential differential diagnosis, T2*-weighted images were compared with the other images. Presence and location of cMBs and intracerebral hemorrhage were independently reviewed by 2 neuroradiologists (H.W. and A.F.) who were blinded to all clinical data. Follow-up images were used to check for de novo microbleeds. Cases with discrepancies were reviewed by both readers and discussed until a consensus was reached.

Statistical Analysis
The statistical analyses were descriptive and performed using SPSS software (Statistical Package for the Social Sciences version 19.0;
IBM Corporation). Data were summarized with mean±SD or median with lower quartiles and upper quartiles respective to their distributions; the absolute value and proportion (%) of cMBs were calculated. We used the nonparametric test of equal or given proportions (stats package, R environment for statistical computing, version 3.2.2) to check the hypothesis whether the proportions of cMBs in our central European collective and in the referenced Japanese cohorts are sampled from populations with the same true/underlying cMB proportion. Because of the descriptive nature of the analyses, no multiplicity correction was applied. P values <0.05 were considered significant.

For evaluation of intrarater agreement, the Cohen κ statistic for the presence of cMBs was applied.18,19

### Results

#### Baseline Characteristics and Clinical Presentation

In the final analysis, 101 patients with MMS/MMD were included (mean age: 37.1; SD: 14.9; Table 1). Among these, 31 patients (30.7%) were men and 70 patients (69.3%) were women. There were 8 patients (7.9%) <18 years of age. There was no peak incidence of moyamoya in early childhood. Within the whole cohort, 83 patients (82.2%) were categorized as having MMD and 18 patients (17.8%) as having MMS. In case of MMS, there were 3 underlying associated systemic diseases in 4 different patients: one patient had Down syndrome, a second experienced multifocal cranial germinoma with consecutive cranial irradiation, and 2 patients presented with pronounced arteriosclerosis. Only 14 patients (13.9%) out of 101 showed unilaterally affected vessels. The majority of patients (92.0%) initially presented with transient ischemic attack or acute ischemic infarction, whereas only 3 patients (3.0%) had an intracerebral hemorrhage.

#### Incidence and Topographical Patterns of cMBs

The weighted κ statistics18,19 for the interrater agreement has shown an extremely good intrarater agreement20 of 0.97 (95% confidence interval, 0.93–1.00).

In total, we detected 25 cMBs within 13 moyamoya patients (12.9%) (mean: 1.86; SD: 2.07; Figures 3 and 4). Only 1 patient <18 years of age demonstrated a cMB. The remaining 88 patients (87.1%) had no cMBs. In detail, 1 patient had 9 cMBs, 1 patient 3 cMBs, 2 patients 2 cMBs, and 9 patients 1 cMB. Two of 3 patients with intracerebral hemorrhage as initial symptomatic event demonstrated cMB(s). With regard to the anatomic distribution, 16 out of 25 cMBs (64%) were located at the lobar cortex/gray–white junction (Table 2).

#### Longitudinal Course

There were 1719 person months of follow-up between the first and last MRI examination. The median follow-up period of patients with multiple imaging was 17 months (lower–upper quartile: 0–28.5 months). During follow-up periods, no de novo microbleeds were observed in pediatric patients, whereas 3 adult MMD/MMS patients showed 3 new cMBs (4.2%; Figure 3).

#### Comparison of cMB Proportion With Asian Moyamoya Cohorts

Previous studies reported the prevalence of cMBs in the Asian moyamoya collectives to range from 12% to 44%.8,12 As for the upper range, the proportion of cMBs in our cohort (12.9%;13/101) was significantly smaller in comparison to the study of Kikuta et al8 with 44% of cMBs (11/25; $\chi^2=10.656; df=1; P=5.49\times10^{-4}$). However, one should note that the patient collective of Kikuta et al8 was comparably small.

As for the lower range, Kazumata et al12 reported 23 cMBs (12.0%) in 191 moyamoya patients including both pediatric and adult cases and 14.4% cMBs in the adult subgroup.

---

**Table 1. Demographics and Clinical Characteristics of Moyamoya Patients**

<table>
<thead>
<tr>
<th>Moyamoya patients, n=101</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyamoya disease</td>
<td>83 (82.2)</td>
</tr>
<tr>
<td>Moyamoya syndrome</td>
<td>18 (17.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Mean age at the time of diagnosis (range)</td>
<td>37.1 (7–64)</td>
</tr>
<tr>
<td>Patients &lt;18 y</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>70 (69.3)</td>
</tr>
<tr>
<td>Men</td>
<td>31 (30.6)</td>
</tr>
<tr>
<td>Women:Men ratio</td>
<td>2.26:1</td>
</tr>
<tr>
<td>Affection of vessels</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>87 (86.1)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>14 (13.9)</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>51 (50.5)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>42 (41.6)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

Figure 2. The distribution of cerebral microbleeds in moyamoya disease/syndrome were noted according to the Brain Observer Microbleed Scale.
Compared with their collective, there was no relevant difference \((P=0.9857)\) of the cMB prevalence in our cohort.

However, when comparing our data with pooled data from a recent meta-analysis\(^{13}\) of 5 publications (of Asian/Japanese populations),\(^{7,10,11,13,21}\) rather than single studies, a different picture emerges. The pooled number of cMBs in these studies was 76 patients (30.8%) in 246. Using the test for equality of proportions showed that there is a highly significant difference between the Asian and European cohort \((\chi^2=13.536; \text{df}=1; P=0.000234)\). Therefore, this suggests that the 2 patient populations are in fact markedly different.

**Discussion**

We investigated the incidence and distribution of cMB in the largest cohort of European patients with MMD/MMS to date. cMBs are first and foremost a radiological construct describing small foci of blood degradation products in normal (or near normal) brain tissue after extravasation of blood. According to the consensus criteria published in 2009, they are small, rounded, or ovoid (rather than linear or curvilinear), blooming, homogeneous hypointense lesions (signal voids), which can be solely identified on susceptibility-weighted sequences.\(^{14}\) They correlate with specific histopathologic findings, such as perivascular hemosiderin deposits.\(^{14}\) Detection rate of cMBs depends on the used sequence, magnetic field strength, and echo time.\(^{14,22,23}\) Higher field strengths are associated with higher detection rates, whereas susceptibility weighted imaging promises superiority over T2*-weighted imaging.\(^{22,23}\)

The first description of cMBs in Asian patients with MMD revealed a detection rate of 44% of patients at 3 Tesla with T2* sequence versus 28% at 1.5 Tesla.\(^{8}\) Although the incidence of cMBs in Asian adult MMD patients ranges\(^{7-13}\) from 14%\(^{12}\) to 44%\(^{8}\) depending on the study design, the prevalence in healthy middle-aged Japanese has been shown to be much lower (3.1%).\(^{24}\) The Rotterdam Scan study reported the age-specific prevalence of cMBs as 5.4% for the age group of 60 to 69 years rising to 23.3% for the age group of 80 to 97 years.\(^{25}\)

Furthermore, the pooled estimate of the proportion of cMBs in the meta-analysis of Qin et al\(^{13}\) (one of which was an update of the aforementioned Kikuta study\(^{8}\)) in Asian moyamoya patients was \(\approx 30\%). Our moyamoya collective has significantly less cMB, supporting the alternative hypothesis that they come from substantially different moyamoya populations. However, the studies’ sample sizes in the meta-analysis ranged from 27

<table>
<thead>
<tr>
<th>Cerebral Hemisphere</th>
<th>Supratentorial</th>
<th>Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar</td>
<td>Basal ganglia gray matter(^1)</td>
</tr>
<tr>
<td></td>
<td>Number of cMBs &lt;5 mm (%)</td>
<td>Number of cMBs 5–10 mm (%)</td>
</tr>
<tr>
<td>Right</td>
<td>4 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Left</td>
<td>10 (40)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Number of cMBs 5–10 mm (%)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Number of cMBs &gt;5 mm (%)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Subcortical white matter(^1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Internal and external capsule</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of cMBs &lt;5 mm (%)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Number of cMBs 5–10 mm (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2. Microbleeds According to the Modified BOMBS Rating Scale**

BOMBS indicates Brain Observer Microbleed Scale; and cMB, cerebral microbleed.

\(^*\)Includes subcortical cMBs that touch the gray–white matter junction.

\(^1\)Includes periventricular white matter and deep portions of the centrum semi-ovale.

\(^\dagger\)Caudate and lentiform nuclei.
to 78 (median n=50). Such relatively small cohorts can provide potentially biased estimates of cMB proportions and are prone to publication bias.

On the contrary, the results of Kazumata et al\textsuperscript{12} of a larger (n=191) moyamoya collective showed no significant difference compared with our data. However, their proportion of pediatric patients was high (38.2%; 73/191).\textsuperscript{12} In the meta-analysis of Qin et al,\textsuperscript{13} it also varied substantially between 0% and 80%, whereas in our sample it was just 8%. Taken together, these somewhat contradictory results underscore the importance of further research in this field. From a clinical perspective, the abovementioned findings are particularly noteworthy.

Studies that prospectively followed up survivors of lobar intracerebral bleeding\textsuperscript{26} and ischemic stroke\textsuperscript{27} show that cMBs might serve as a predictor for future risk of symptomatic intracerebral hemorrhage. Furthermore, some investigators conclude that cMBs represent an independent risk factor for antiplatelet-related\textsuperscript{28} and warfarin-related\textsuperscript{29} intracranial bleedings. The latter is an especially clinically relevant issue as some physicians treat moyamoya patients with antiplatelet agents to prevent emboli from microthrombi formed at sites of arterial stenosis.\textsuperscript{30} Likewise, studies of Asian moyamoya patients indicate that cMBs represent an important risk factor for future hemorrhagic stroke events.\textsuperscript{10,12,13} This is concomitant with the fact that moyamoya in adult patients of Asian descent (except Taiwan and Nanjing) have much higher rates of intracerebral hemorrhage as initial symptomatic event than adult moyamoya patients in Europe and the United States.\textsuperscript{2,4,5} In our cohort, only 3 patients (3%) experienced an intracerebral hemorrhage as initial symptomatic event, whereas 2 of these 3 patients (67%) had cMBs as underlying MRI finding.

Figure 3. Chart demonstrating patient age, sex, diagnosis, clinical course, time of magnetic resonance imaging, follow-up interval, and number of cerebral microbleeds (cMBs) and de novo cMBs. MMD indicates moyamoya disease; MMS, moyamoya syndrome; N/A, not applicable; post-OP, post-operation; and pre-OP, pre-operation.

Figure 4. The distribution of cerebral microbleeds (cMBs; circles) in moyamoya disease (MMD)/moyamoya syndrome (MMS) patients as compared with the results of the study of Kazumata et al. The right hemisphere reflects the results of Kazamata et al with 30 cMBs in 20 adult MMD/MMS patients (red circles). The left hemisphere displays the results of the present study with (A) 16 cMBs in 12 moyamoya patients (yellow circles) and (B) 9 cMBs in 1 moyamaya patient (yellow circles), respectively. The illustrative separation in (A) and (B) was implemented attributable to the relatively high incidence of cMBs in 1 patient.
Although a reasonable statistical analysis based on the limited available data is not yielding, these findings are still important as they could add weight to the previously suggested hypothesis that microbleeds might promote intracerebral bleedings in moyamoya.\textsuperscript{12,13} Furthermore, the low rate of intracerebral hemorrhages in our cohort might support the theory that it is an expression of ethnic-specific difference.\textsuperscript{5}

In light thereof, cMBs lead to higher risk of intracerebral hemorrhages that are—in contrast to our central European cohort—much more frequent in adult Asian moyamoya patients. Consequently, the low rate of cMBs in central European moyamoya patients might represent another key difference between moyamoya forms that might be reflected in the different expression of initial symptoms of the disease.

Furthermore, we could show that cMBs in Asian and non-Asian patients with moyamoya have a different distribution. Qin et al reported that about half (49.7\%) of the cMBs were localized within the periventricular white matter in their study, which was confirmed by several other studies.\textsuperscript{10–12} The frequency of cMBs within the periventricular white matter in moyamoya patients was even higher in the studies of Kikuta et al\textsuperscript{10} and Sun et al.\textsuperscript{31} This pattern of distribution is well exemplified in the article by Kazumata et al.\textsuperscript{12} In great contrast to these observations in Asian moyamoya patients, we show that cMBs in central European moyamoya patients are mainly (64\%) localized within the lobar cortex/grey–white junction. Follow-up MRI revealed 3 de novo cMBs in 3 adult moyamoya patients (4.2\%) in the present study. Likewise, Kuroda et al\textsuperscript{11} found newly developed cerebral cMBs in 4 adults (6.9\%) in a cohort of 78 patients with a mean follow-up period of 43.1 months. In contrast, Sun et al\textsuperscript{31} did not find any new cMBs, although this was within a shorter follow-up time of \textapprox{}23 months.

Nonetheless, the present study has some limitations: First, the evaluation of cMBs is based on different rating systems. Qin et al,\textsuperscript{13} Sun et al,\textsuperscript{31} and Kazumata et al\textsuperscript{12} used the Microbleed Anatomical Rating Scale,\textsuperscript{32} whereas we used the BOMBS.\textsuperscript{33} Regrettably, Microbleed Anatomical Rating Scale does not specify the location of cMBs that are located within the cortex/grey–white junction. This anatomical information, however, is important and would have skewed our results if missing. Therefore, we intentionally chose the BOMBS classification. Second, this is a retrospective study of moderate size. However, to our knowledge, this is the first study focusing on cMBs in European moyamoya patients. Third, the study was performed with different MRI scanners and different imaging sequences; mostly on a 1.5 MR system and only a minority on a 3-T MR system (36 scans). This is important to highlight as a higher magnetic field strength can lead to increased numbers of detectable cMBs (because of a more pronounced blooming effect).\textsuperscript{22,23} Accordingly, this might bias our results of detected de novo cMBs. However, all patients with a new lesions were exclusively examined on a 1.5 Tesla MRI, thus indicating that the de novo lesions are not because of possible detection by higher field strength but rather lesions that are truly new.

Furthermore, it has to be stressed that all MRI sequences, especially the T\textsuperscript{2*}-weighted sequences, have been customized for optimal comparability in daily clinical routine and consequently are generally comparable. Finally, moyamoya is a rare disease in Germany.\textsuperscript{2} As a consequence, our study has insufficient statistical significance because of the small number of patients and the low incidence of cMBs.

Fourth, because the definition of MMD includes idiopathic pathology, there are semantic distinctions in the terminology of patients with unilateral vessel affection and patients in association with various disease entities (such as atherosclerosis, autoimmune diseases, Down syndrome, etc.). According to the guidelines, definitive MMD (82\% of our cases) is generally characterized by pathognomonic bilateral steno-occlusive affection of vessels and no association of underlying disease.\textsuperscript{34–36} In contrast, patients with unilateral involvement are termed probable moyamoya disease patients (14\% of our cases), and patients with underlying disease and unilateral or bilateral affection are known as quasi-moyamoya disease patients (4\% of our cases).\textsuperscript{34–36}

Keeping with the study by Scott and Smith,\textsuperscript{1} we applied the term moyamoya syndrome for all unilateral affected patients and for patients with underlying disease. This poses a problem because >40\% of unilateral affected patients might progress to bilateral MMD,\textsuperscript{37–39} which might lead to a lack of conceptual clarity and inhomogeneity within the group of MMS. Nonetheless, recent imaging findings could show that even the group of quasi-moyamoya disease is heterogeneous and overlaps the MMD group.\textsuperscript{36}

In conclusion, cMBs and intracerebral hemorrhages as initial symptomatic event in European moyamoya patients are much less common in comparison to Asian moyamoya patients. Furthermore, cMB distribution differs significantly. Further studies with larger number of patients and longer follow-up periods should follow to reconfirm our results.

\section*{Disclosures}
None.

\section*{References}
Cerebral Microbleeds in European Moyamoya

Wenz et al

Incidence, Locations, and Longitudinal Course of Cerebral Microbleeds in European Moyamoya
Holger Wenz, Ralf Wenz, Máté Maros, Gregory Ehrlich, Mansour Al-Zghoul, Christoph Groden and Alex Förster

Stroke. 2017;48:307-313; originally published online January 6, 2017;
doi: 10.1161/STROKEAHA.116.014335
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/2/307

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2017/01/06/STROKEAHA.116.014335.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
I. Supplemental Table - Supplementary table of the number of imaging studies stratified by the number of cMBs.

<table>
<thead>
<tr>
<th>Number of cMBs</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Sum</th>
<th>Median Follow-up time (days)</th>
<th>Cumulative FU (days)</th>
<th>Avg. days of FU/person</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>26</td>
<td>16</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>88</td>
<td>519</td>
<td>44383</td>
<td>504.4</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>675</td>
<td>4780</td>
<td>531.1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1972</td>
<td>1972</td>
<td>1972</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sum</td>
<td>31</td>
<td>32</td>
<td>16</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>101</td>
<td>-</td>
<td>51136</td>
<td>-</td>
</tr>
</tbody>
</table>

Median-, average follow-up (FU; [days]), and the total/cumulative FU by number of cMBs are given.

II. Supplemental Table 2 - Sequence parameters of T2*-weighted images at the department’s MRI scanners.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MRI scanner</th>
<th>1.5-T Siemens</th>
<th>1.5-T Siemens</th>
<th>3-T Siemens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sonata</td>
<td>Avanto</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td>FOV</td>
<td>240</td>
<td>230</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Number of slices</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Flip angle</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>ST</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td>670</td>
<td>814</td>
<td>620</td>
<td></td>
</tr>
<tr>
<td>TE</td>
<td>16</td>
<td>26</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Legend: FOV = field of view (mm x mm), ST = slice thickness (mm), TR = repetition time (ms), TE = echo time (ms).