Risk of Recurrent Stroke in Patients With Silent Brain Infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Imaging Substudy

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Background and Purpose—Silent brain infarctions are associated with an increased risk of stroke in healthy individuals. Risk of recurrent stroke in patients with both symptomatic and silent brain infarction (SBI) has only been investigated in patients with cardioembolic stroke in the European Atrial Fibrillation Trial. We assessed whether patients with recent noncardioembolic stroke and SBI detected on MRI are at increased risk for recurrent stroke, other cardiovascular events, and mortality.

Methods—The prevalence of SBI detected on MRI was assessed in 1014 patients enrolled in the imaging substudy of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial. The primary outcome was first recurrence of stroke in patients with both symptomatic stroke and SBI in comparison with age- and sex-matched patients with stroke without SBI. Secondary outcomes were a combined vascular end point, other vascular events, and mortality. The 2 groups were compared using conditional logistic regression.

Results—Silent brain infarction was detected in 207 (20.4%) of the 1014 patients. Twenty-seven (13.0%) patients with SBI and 19 (9.2%) without SBI had a recurrent stroke (OR, 1.42; 95% CI, 0.79–2.56; P = 0.24) during a mean follow-up of 2.5 years. Similarly, there was no statistically significant difference for all secondary outcome parameters between patients with SBI and matched patients without SBI.

Conclusions—The presence of SBI in patients with recent mild noncardioembolic ischemic stroke could not be shown to be an independent risk factor for recurrent stroke, other vascular events, or a higher mortality rate.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00153062.

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Key Words: cerebral infarction ■ ischemic stroke ■ magnetic resonance imaging ■ mortality ■ silent brain infarction

B rain infarction is classified as silent if it lacks clinically overt stroke-like symptoms. The prevalence of silent brain infarction (SBI) defined on MRI in the general population ranges from 8% to 28% with a higher prevalence with increasing age.1–3 Patients with SBI are at increased risk of stroke in population-based studies of healthy elderly people.4,5 There is little information, however, on the prevalence of SBI among patients with ischemic stroke. In studies of consecutive patients with patients with ischemic stroke, the prevalence of SBI ranged from 13% in young adults aged 15 to 49 years with first-ever stroke up to 57% in a cohort of Japanese patients with a mean age of 72 years.6–9 The risk of recurrent stroke in patients with both symptomatic and silent ischemic stroke (identified on CT) has only been investigated in the European Atrial Fibrillation Trial in the early 1990s, which found a nonsignificant increased risk of recurrent stroke and vascular events in patients with SBI.10 However, medical secondary stroke prevention treatment has substan-
tially improved since this time and CT was used as the imaging modality, which has a lower sensitivity for the detection of SBI compared with MRI. No study to date has evaluated the risk of recurrent stroke and other cardiovascular events in patients with noncardioembolic ischemic stroke and SBI. The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial is the largest trial to date that has investigated the prevention of recurrent stroke in 20,332 patients with a recent ischemic stroke and compared, in a factorial design, the combination of aspirin and extended-release dipyridamole with clopidogrel.\textsuperscript{11,12} The PROFESS Imaging Substudy was designed to assess the prevalence of SBI detected on MRI in a subset of patients with a recent noncardioembolic ischemic stroke enrolled in the main PROFESS trial and subsequently whether patients with SBI are at increased risk for recurrent stroke and other cardiovascular events.

Methods

Patients and Sample Size Calculation

The PROFESS trial protocol and primary results have been published elsewhere.\textsuperscript{11–13} In brief, 20,332 patients who were at least 50 years of age with recent ischemic stroke within 120 days of study entry were randomized to either aspirin (25 mg twice a day) plus extended-release dipyridamole (200 mg twice a day) or clopidogrel (75 mg daily) and telmisartan (80 mg daily) or placebo in a 2×2 factorial design and treated for 2 years. Mean duration of follow-up was 2.5 years. All patients received best medical care independent of treatment assignment. Apart from previous clinical stroke symptoms before the qualifying ischemic stroke as an exclusion criterion, and an MRI after the qualifying stroke as an additional inclusion criterion, patient inclusion and exclusion criteria were the same as for the main PROFESS trial. We hypothesized that patients with both symptomatic and SBI had a higher risk of recurrent stroke compared with patients without evidence of SBI on MRI. All analyses in this imaging substudy were predefined. We estimated a prevalence of 30% of SBI in our study population and calculated with a sample size of 300 patients with SBI and 300 age- and sex-matched control subjects without SBI. Male and female patients with SBI were matched with patients of the same gender without evidence of SBI with dates of birth that were closest together chronologically. If a direct age match was not found, patients were matched if their ages were within 5 years of each other. If this resulted in >1 match, then the 2 patients with dates of birth that were closest together chronologically were matched.

The Imaging substudy of the PROFESS trial was approved in global amendment No. 3 by the ethics committees of the participating centers. Participating patients signed the informed consent form for the main PROFESS trial as well as a separate consent form for the imaging substudy.

MRI Analysis and Definition of SBI

MRI data were sent to the Clinical Adjudication Center of the University Duisburg-Essen and each case was independently rated by 2 experienced neuroradiologists blinded for treatment allocation. SBI were defined as a focal hyperintense lesion on T2-weighted images and/or fluid-attenuated inversion recovery with no corresponding symptoms in the clinical history of the patient that could be attributed to the lesion. SBI were distinguished from nonspecific subcortical and periventricular white matter lesions by the presence of a corresponding hypointense lesion on T1-weighted images. All ischemic strokes (the qualifying symptomatic stroke and SBI) were classified according to location. Lacunar infarcts were defined as a hypointense lesion that were ≥3 mm on T1-weighted images. Cortical border zone infarctions were defined as infarctions of the cortex located at the border zones between the anterior, middle, and posterior cerebral arteries and separated from hemodynamic lesions in the roof of the lateral ventricles or the centrum semiovale.\textsuperscript{14} Subcortical infarctions were defined as infarctions in the basal ganglia and subcortical white matter supplied by the anterior cerebral, middle cerebral, posterior cerebral, lenticulostriate/choroidal, and thalamic arteries. Information regarding stroke symptoms of the qualifying ischemic stroke was elicited using baseline case report forms from the main PROFESS trial.

Statistical Analysis

The primary outcome variable was first recurrence of stroke of any type. Secondary outcomes were a composite end point of vascular events (stroke, myocardial infarction, vascular death), other vascular events (pulmonary embolism, retinal vascular accidents that were not a retinal arterial occlusion, deep vein thrombosis, central venous thrombosis, peripheral arterial occlusion, or transient ischemic attack), and death. The primary and secondary outcomes were adjudicated by a central committee.

The 2 groups (presence/absence of SBI at study entry) were compared using conditional logistic regression. This analysis was confirmed by logistic regression with age (in years) as a continuous covariate and sex (male/female). Statistical significance was set at \(P<0.05\). Analyses were performed with SAS Version 8.2.

Results

A total of 1057 patients who were randomized in the PROFESS study had given consent to enter the imaging substudy of which 1014 (95.9%) patients had an evaluable MRI scan performed within 120 days of their qualifying stroke. Mean age was 66.1 years, and 63.9% of the patients were male. T1-weighted images were available for evaluation in 928 (91.5%), T2-weighted images in 954 (94.1%), fluid-attenuated inversion recovery images in 926 (91.3%), diffusion-weighted images in 887 (87.5%), T1-weighted contrast-enhanced images in 186 (18.3%), and gradient echo MRI in 204 (20.1%) of these patients. Mean time from qualifying ischemic stroke to baseline MRI scan was 8.0 (±15.7) days. Mean time from baseline MRI to study drug randomization was 18.4 (±24.1) days in 956 patients. Fifty-eight patients got their baseline MRIs after study drug randomization with a mean delay of 15.7 (±24.6) days, but none of these patients experienced a recurrent stroke between study drug randomization and MRI.

An ischemic stroke on MRI attributable to the clinical presentation of the qualifying ischemic stroke was detected in 821 (81.0%) patients. A SBI was detected in 207 (20.4%) patients. The mean age of patients with a SBI was 66.2 years and 150 (72.5%) were males. These patients were age- and sex-matched with 207 patients without evidence of SBI. Baseline demographic characteristics, vascular risk factors, and treatment are shown in the Table. There were no significant differences between patients with SBI and matched patients without SBI except for a significantly higher rate of current smokers and a higher proportion of qualifying strokes classified as small-artery occlusion. The frequency of cerebral microbleeds did not differ between patients with and without SBI in the 82 patients in whom gradient echo MRI was available (41 patients with and 41 patients without SBI). Eight patients in the SBI group and 7 patients in the non-SBI group had evidence of cerebral microbleeds.

A total of 501 ischemic brain infarctions (symptomatic and silent) were diagnosed in the 207 patients with SBI on the
### Table. Patient Characteristics at Enrollment in 414 Patients With Stroke With and Without Silent Brain
Infarction on MRI and Comparison With the Patient Population in the PRoFESS Imaging Substudy and the
Whole Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Silent Brain Infarction (n=207)</th>
<th>No Silent Brain Infarction (n=207)</th>
<th>MRI Substudy (n=1014)</th>
<th>Whole Trial (n=20,332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>66.2 (8.5)</td>
<td>66.2 (8.5)</td>
<td>66.1 (8.4)</td>
<td>66.1 (8.6)</td>
</tr>
<tr>
<td>Age group, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75 y</td>
<td>173 (83.6)</td>
<td>173 (83.6)</td>
<td>862 (85.0)</td>
<td>17,114 (84.2)</td>
</tr>
<tr>
<td>&gt;75 y</td>
<td>34 (16.4)</td>
<td>34 (16.4)</td>
<td>152 (15.0)</td>
<td>3218 (15.8)</td>
</tr>
<tr>
<td>Sex, male, no. (%)</td>
<td>150 (72.5)</td>
<td>150 (72.5)</td>
<td>648 (63.9)</td>
<td>13,022 (64.0)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>131 (63.3)</td>
<td>134 (64.7)</td>
<td>644 (63.5)</td>
<td>6,660 (32.8)</td>
</tr>
<tr>
<td>White</td>
<td>55 (26.6)</td>
<td>53 (25.6)</td>
<td>264 (26.0)</td>
<td>11,697 (57.5)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (1.0)</td>
<td>8 (3.9)</td>
<td>30 (3.0)</td>
<td>816 (4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (9.1)</td>
<td>12 (5.8)</td>
<td>76 (7.5)</td>
<td>1,159 (5.7)</td>
</tr>
<tr>
<td>Clinical history, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>19 (9.2)</td>
<td>25 (12.1)</td>
<td>97 (9.6)</td>
<td>1762 (8.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>162 (78.3)</td>
<td>155 (74.9)</td>
<td>774 (76.3)</td>
<td>15,048 (74.0)</td>
</tr>
<tr>
<td>Hypertension, treated</td>
<td>90 (43.5)</td>
<td>88 (42.5)</td>
<td>428 (42.2)</td>
<td>9,553 (47.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (3.9)</td>
<td>6 (2.9)</td>
<td>28 (2.8)</td>
<td>540 (2.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (32.4)</td>
<td>63 (30.4)</td>
<td>320 (31.6)</td>
<td>5,743 (28.2)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>99 (47.8)</td>
<td>111 (53.6)</td>
<td>502 (49.5)</td>
<td>9,493 (46.7)</td>
</tr>
<tr>
<td>Smoker*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>67 (32.4)</td>
<td>41 (19.8)</td>
<td>245 (24.2)</td>
<td>4,308 (21.2)</td>
</tr>
<tr>
<td>Former</td>
<td>68 (32.9)</td>
<td>89 (43.0)</td>
<td>331 (32.6)</td>
<td>7,352 (36.2)</td>
</tr>
<tr>
<td>Never</td>
<td>72 (34.8)</td>
<td>77 (37.2)</td>
<td>438 (43.2)</td>
<td>8,663 (42.6)</td>
</tr>
<tr>
<td>Clinical details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS score, median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>25.6 (4.2)</td>
<td>26.1 (3.8)</td>
<td>26.0 (4.3)</td>
<td>26.8 (5.0)</td>
</tr>
<tr>
<td>TOAST classification of qualifying stroke, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>69 (33.3)</td>
<td>82 (39.6)</td>
<td>327 (32.2)</td>
<td>5,805 (28.6)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>5 (2.4)</td>
<td>3 (1.4)</td>
<td>17 (1.7)</td>
<td>369 (1.8)</td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>114 (55.1)</td>
<td>94 (45.4)</td>
<td>539 (53.2)</td>
<td>10,578 (52.0)</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>1 (0.5)</td>
<td>8 (3.9)</td>
<td>18 (1.8)</td>
<td>416 (2.0)</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>18 (8.7)</td>
<td>20 (9.7)</td>
<td>112 (11.0)</td>
<td>3,148 (15.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>16 (0.1)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinded antiplatelet therapy during treatment, no. (%)</td>
<td>108 (52.2)</td>
<td>91 (44.0)</td>
<td>510 (50.3)</td>
<td>10,181 (50.1)</td>
</tr>
<tr>
<td>Aspirin/ER-DP</td>
<td>99 (47.8)</td>
<td>116 (56.0)</td>
<td>504 (49.7)</td>
<td>10,151 (49.9)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>97 (46.9)</td>
<td>95 (45.9)</td>
<td>466 (46.0)</td>
<td>10,526 (51.8)</td>
</tr>
<tr>
<td>Antihypertensive therapy, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open-label</td>
<td>105 (50.7)</td>
<td>113 (54.6)</td>
<td>516 (50.9)</td>
<td>10,146 (49.9)</td>
</tr>
</tbody>
</table>

Data for the imaging substudy and whole PRoFESS trial are given for comparison. Comparison of matched patients with and without silent brain infarction were based on the \(\chi^2\) test for qualitative variables and Student \(t\) test for quantitative variables.

PRoFESS indicates Prevention Regimen for Effectively Avoiding Second Strokes; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; ER-DP, extended-release dipyridamole.

* \(P\)-values for all comparisons between patients with silent brain infarction and matched patients without silent brain infarction were >0.05 except for smoking status (\(P=0.01\)).
qualifying MRI. The localization of these ischemic brain infarctions are shown in Figure 1.

Although the rate of recurrent stroke was slightly increased among patients with SBI on baseline MRI compared with patients without SBI, the difference was not significant. Twenty-seven (13.0%) patients with SBI and 19 (9.2%) without SBI had a recurrent stroke (adjusted OR, 1.42; 95% CI, 0.79–2.56; $P=0.24$) during mean follow-up of 2.5 years (Figure 2). The results of this analysis were consistent with the confirmatory model. Recurrent ischemic stroke occurred in 24 (11.6%) patients with SBI and 17 (8.2%) matched patients without SBI. A hemorrhagic stroke occurred in 3 (1.4%) patients with SBI and 2 (1%) matched patients without SBI. There was no apparent difference in stroke recurrence between Asian (17 [13.0%] of 131 patients) and non-Asian (10 [13.2%] of 76 patients) patients with SBI.

Similarly, there was no statistically significant difference for all secondary outcome parameters between patients with SBI and matched patients without SBI. The combined vascular end point occurred in 33 patients (15.9%) with SBI compared with 24 (11.6%) in the matched group (OR, 1.38; 95% CI, 0.81–2.33; $P=0.24$). Other vascular events occurred in 8 patients (3.9%) with SBI compared with 9 (4.3%) in the matched group (OR, 0.88; 95% CI, 0.32–2.41; $P=0.80$). Fourteen patients with SBI (6.8%) died compared with 6 (2.9%) in the group without SBI (OR, 2.33; 95% CI, 0.90–6.07; $P=0.08$).

In comparison with the total number of 788 patients included in the PRoFESS imaging substudy who had no evidence of SBI on MRI, the 207 patients with SBI had a significantly higher stroke recurrence rate (13.0% versus 8.0%; OR, 0.58; 95% CI, 0.36–0.94; $P=0.03$) and mortality rate (6.8% versus 3.2%; OR, 0.45; 95% CI, 0.23–0.89; $P=0.02$).

**Discussion**

Patients with both symptomatic and silent ischemic brain infarction detected on MRI had a numerically higher risk of recurrent stroke, other vascular events, and a higher mortality compared with patients with stroke without evidence of SBI in this imaging substudy of the ProFESS trial. The differences were not statistically significant in age- and sex-matched patients.

Two previous population-based studies and 1 study in 933 neurologically normal Japanese adults had consistently found a significantly increased risk of symptomatic stroke in patients with SBI on MRI who did not have a history of symptomatic stroke at study entry.4–5,15 Symptomatic stroke occurred in 7.3% of 923 patients with SBI compared with...
3.8% of 2401 patients without evidence of SBI (hazard ratio, 1.5; 95% CI, 1.1–2.1) during a 4-year follow-up period in the Cardiovascular Health Study.6 Similar to this study, we found a nonsignificant OR for recurrent stroke of 1.42 in patients with SBI. In the Rotterdam Scan Study, SBI at baseline MRI was associated with an increased risk of both a new SBI and a symptomatic infarct during a mean interval of 3.4 years. Presence of SBI increased the risk of stroke >3-fold independently of other stroke risk factors (adjusted hazard ratio, 3.9; 95% CI, 2.3–6.8).3 Both aforementioned population-based studies reported a 30% to 40% higher prevalence of SBI among women compared with men, whereas 72.5% of patients with SBI in our patient cohort were male. Furthermore, most of the participants in the population-based studies were white, whereas the majority of our patients were Asians. Thus, we cannot rule out a bias by selection of patients with stroke in our study. There was, however, no difference in stroke recurrence between Asian and non-Asian patients with stroke with SBI in our patient cohort.

Data from a retrospective cohort study in 104 patients with acute ischemic stroke who underwent initial MRI within 24 hours of symptom onset and subsequent MRI on Day 5 and between 30 and 90 days suggested that patients with late SBI recurrence between 30 and 90 days (22.1%) had a significantly increased risk of recurrent symptomatic ischemic stroke during a mean follow-up of 19.3±9.0 months (OR, 6.55; 95% CI, 1.09–39.55).16 The combined vascular end point of recurrent symptomatic ischemic stroke, transient ischemic attack, and vascular death was independently predicted by both early (OR, 3.10; 95% CI, 1.02–10.00) and late (OR, 8.09; 95% CI, 1.29–50.91) SBI recurrences.

The only prospective study that investigated the risk of stroke recurrence in patients with both symptomatic and silent stroke was the European Atrial Fibrillation Trial.10 Nine hundred eighty-five patients with nonrheumatic atrial fibrillation with a mean age of 73 years who had a transient ischemic attack or nondisabling ischemic stroke were included for this analysis. Fourteen percent had evidence of SBI on CT and these patients had a nonsignificantly increased risk for recurrent stroke (hazard ratio, 1.18; 95% CI, 0.79–1.77) and recurrent vascular events (hazard ratio, 1.2; 95% CI, 0.9–1.6) compared with patients without SBI.

In addition, there was a slightly higher mortality in patients with symptomatic and silent stroke in our study. Likewise, 3-year mortality was increased in a population-based study in 239 85-year-old stroke-free individuals,17 whereas there was no effect on 1-year mortality in patients with SBI in a study of 755 consecutive patients with first-ever stroke.6

Due to the lower than expected prevalence of SBI in patients with recent ischemic stroke, our study was underpowered to detect a significantly increased cardiovascular risk or mortality in patients with stroke with SBI when compared with age- and sex-matched patients with stroke without SBI. The low prevalence of SBI can be explained by the mean age of 66.2 years in our patient group, whereas the prevalence of SBI has been shown to be strongly age-dependent in population-based studies.4 The mean age of 66.1 years in the main study PRoFESS was almost identical to the mean age in this study. An almost identical prevalence of 20% SBI in 226 Asian patients with first-ever stroke and a similar age distribution (mean age, 68.8 years) was reported by Ong et al.18 In contrast, the prevalence of SBI in 171 Japanese patients with acute first-ever ischemic stroke with a mean age of approximately 72 years was as high as 56.7%.7 Furthermore, mean duration of follow-up was 2.5 years in our study, which is substantially lower compared with the follow-up period in the Cardiovascular Health Study (4 years) and the Rotterdam Scan Study (3.4 years). These studies also had larger sample sizes compared with our study. Increasing the study sample size by comparing the 207 patients with SBI with the total number of 788 nonmatched patients without evidence of SBI resulted in a statistically significantly higher rate of symptomatic stroke recurrence and mortality rate in patients with SBI.

There is a wide variation in classification, detection, and discrimination of SBI, especially lacunar ischemic lesions, and white matter lesions on brain imaging.19 Strengths of our study include the blinded assessment of MRI scans by 2 experienced neuroradiologists and the use of multimodal MRI. The combination of T1-, T2-weighted, and fluid-attenuated inversion recovery images, which was available in >90% of our included patients, has been shown to accurately discriminate between small white matter infarction and non-specific white matter lesions in a multicenter observer performance study.20 Furthermore, diffusion-weighted images, which allow differentiation of the acute qualifying stroke from chronic stroke and white matter lesions,21 were also available for evaluation in 87.5% of patients.

In summary, the presence of SBI in patients with recent mild noncardioembolic ischemic stroke could not be shown to be an independent risk factor for recurrent stroke, other vascular events, or a higher mortality.

Sources of Funding
Boehringer Ingelheim sponsored and funded the PRoFESS trial and this imaging substudy.

Disclosures
C.W. received honoraria for participation in clinical trials and contribution to advisory boards or oral presentations from Boehringer Ingelheim, Bristol-Myers Squib, Daiichi Asubio, Novartis, Novo-Nordisk, and Sanofi-Aventis. J.B. and K.H. are employees of Boehringer Ingelheim. A.M.D. received honoraria for contribution to advisory boards or oral presentations from Boehringer Ingelheim and Merck. R.L.S. received grants from the National Institute of Neurological Disorders and Stroke for the Northern Manhattan Study. He served as a consultant to Boehringer Ingelheim during the conduct of the PRoFESS trial. J.L.S. is an employee of the University of California, which received payments based on clinical trial contracts for the number of subjects enrolled from Boehringer Ingelheim and AGA Medical and received payments for faculty participation on scientific advisory boards from AGA Medical. H.C.D. received honoraria for participation in clinical trials and contribution to advisory boards or oral presentations from Abbott, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, D-Pharm, Frese-nius, GlaxoSmithKline, Janssen-Cilag, MSD, MindFrame, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi. He also received financial support for research projects provided by Astra/ Zeneca, GSK, Boehringer Ingelheim, Novartis, Janssen-Cilag, and Sanofi-Aventis. A.D. received honoraria for contribution to advisory
boards or oral presentations from Boehringer Ingelheim and Bristol-Myers-Squibb.

References
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SUPPLEMENTAL MATERIAL

Site representatives at investigative sites of the PROFESS Imaging Substudy where at least one patient was recruited:

Argentina (Conrado Estol, Miguel Garrote, María Esnaola y Rojas, Sebastián Ameriso, Raúl Rey, Pablo Leonardo Ioli, Juan José Cirio, Gustavo Angel Saredo), Australia (Christopher Bladin, Stephen Davis) Canada (David Howse, James Scott, Jaime Silva), China (Xiaojiang Sun, Ling Miao, Wei Li, Liying Cui, Haibo Chen, Weiwei Zhang, Lijuan Wang, En Xu, Qing Di, Yan Liu), Germany (Jörg Glahn, Dietmar Schneider, Peter Ringleb, Wolfgang Steinke, Lutz Harms, Andreas Hetzel, Michael Rosenkranz), Mexico (Carlos Cantu, Jorge Villarreal), South Korea (Byung Woo Yoon, Byung Chul Lee, Ki Hyun Cho, Ji Hoe Heo, Joung Ho Rha, Hyo Suk Nam, Sun Uck Kwon), Taiwan (Sien-Tsong Chen, Jiann-Shing Jeng, Helen L Po, Ming-Hong Chang, Ku-Chou Chang, Li-Ming Lien, Chung Y. Hsu), USA (Clinton Wright, Daniel Hanley, Jeffery Kramer, Donald Tamulonis, Joseph Weissman, Bret Haake, Steve Moon, Scott Silliman, Pierre Fayad, Erfan Albakri).
PRoFESS 画像サブスタディにおける無症候性脳梗塞患者の脳卒中再発リスク

Risk of Recurrent Stroke in Patients With Silent Brain Infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Imaging Substudy

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Abstract

背景および目的: 無症候性脳梗塞 (SBI) は健常者における脳卒中リスクの増加と関連している。症候性および無症候性脳梗塞の両方を有する患者における脳卒中再発リスクは、これまで、European Atrial Fibrillation Trial 試験において心原性脳塞栓症患者を対象に検討されたのみである。我々は、最近非心原性脳塞栓症を発症し、MRI で SBI が検出された患者は、脳卒中再発、その他の心血管イベント、および死亡のリスクが高いかどうかを評価した。

方法: Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) 試験の画像サブスタディに登録された 1,014 例の患者を対象に、MRI で検出される SBI の有病率を評価した。主要評価項目は、年齢および性別を対応させた SBI を伴わない脳卒中患者との比較で、症候性脳卒中と SBI の両方を有する患者における脳卒中の初回再発とした。副次的評価項目は、複合血管エンドポイント、その他の血管イベント、および死亡とした。条件付きロジスティック回帰を用いて両群を比較した。

結果: 1,014 例の患者のうち 207 例 (20.4%) に SBI が検出された。SBI 患者 27 例 (13.0%) および SBI を伴わない患者 19 例 (9.2%) で、平均追跡調査期間 2.5 年以内に脳卒中が再発した (OR = 1.42, 95% CI: 0.79 ~ 2.56, p = 0.24)。同様に、すべての副次的評価項目パラメータについて、SBI 患者と SBI を伴わない対応する患者との間に統計学的有意差は認められなかった。

結論: 最近軽度の非心原性虚血性脳卒中を発症した患者における SBI の存在が、脳卒中再発、その他の心血管イベント、または死亡率上昇の独立した危険因子であるとは実証することができなかった。

臨床試験登録: URL:http://clinicaltrials.gov。識別番号:NCT00153062。

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図2

MRI で無症候性脳梗塞の証拠が認められた 207 例の患者および年齢と性別を対応させた無症候性脳梗塞を伴わない 207 例の患者における脳卒中の初回再発までの時間の Kaplan-Meier 推定値。ゼロ時点はベースラインの MRI の日を示す。ベースラインの MRI は脳卒中後の 24 時間以内に撮像した。