Silent Brain Infarcts in Patients With Manifest Vascular Disease

Janneke L.P. Giele, MsC; Theo D. Witkamp, MD; Willem P.T.M. Mali, MD, PhD; Yolanda van der Graaf, MD, PhD; for the SMART Study Group

Background and Purpose—Silent infarcts are frequently found on MRIs of brains of healthy elderly persons (aged ≥ 60 years). The purpose of this study was to investigate the prevalence and determinants of silent infarcts in a population of patients with clinically manifest vascular disease.

Methods—To detect silent infarcts, MR images were made in 308 participants of the Second Manifestations of ARTerial disease (SMART) study (mean age, 58 years) without prior stroke or transient ischemic attack. These are patients referred to the University Medical Center Utrecht because of atherosclerotic vascular disease. Risk factors were assessed by questionnaire and by physical, ultrasonographic, and laboratory examinations.

Results—Silent infarcts were found in 51 patients (17%). Most infarcts (62%) were located in white matter, 20% in basal ganglia, 14% in brain stem and cerebellum, and 4% in cortical area. Categorical determinants for presence of silent infarct(s) that remained (borderline) significant after adjustment for age were hypertension (odds ratio [OR] = 2.2; 95% CI, 1.2 to 4.2), abdominal aortic aneurysm (OR = 2.4; 95% CI, 0.9 to 6.4), severe renal failure (OR = 7.3; 95% CI, 2.1 to 25.2), and hyperhomocysteinemia (OR = 2.6; 95% CI, 1.1 to 5.9).

Conclusions—Patients with manifest vascular disease are at risk for silent infarcts at a younger age. In particular, patients with the aforementioned risk factors should be considered for treatment or (secondary) prevention. (Stroke. 2004;35:742-746.)

Key Words: cerebral infarction • epidemiology • magnetic resonance imaging

Silent brain infarcts, focal ischemic lesions in the brain without any previous symptoms of stroke, are frequently found on MRIs of apparently healthy elderly persons. In the Rotterdam Scan Study, a prevalence of 20% was found in a normal, healthy population aged 60 to 90 years.¹ The prevalence depended strongly on age and increased from 8% in the participants aged 60 to 64 years to 35% in the oldest group (aged 85 to 90 years). These numbers correspond well with other studies when differences in design (scanning protocol) and study population are taken into account.²–⁵

Although asymptomatic, these silent infarcts are not innocuous. In people with 1 or more silent infarcts, the risk of stroke increased 2- to 10-fold during a mean follow-up time of 2 to 4 years.²,⁶,⁷ The prognosis of the stroke (morbidity, mortality) is not influenced by the presence of silent infarcts.⁸,⁹ Furthermore, there are indications that silent infarcts are associated with decreased cognitive functioning.⁵,¹⁰,¹¹ The prospective Rotterdam Scan Study showed that the presence of silent infarcts more than doubled the risk of dementia. People with silent infarcts at baseline had a steeper decline in cognitive function during follow-up than those without silent infarcts; this decline was restricted to people who had new silent infarcts during follow-up.¹² Several studies on children with sickle cell disease also showed a relationship between silent infarcts and decreased cognitive function.¹³,¹⁴

Risk factors for silent infarcts are thought to be comparable to those for stroke. Therefore, cardiovascular patients may be at high risk for silent infarcts as well. The objectives of this study were to investigate the prevalence of silent infarcts in a high-risk population of patients with clinically manifest vascular disease (coronary artery disease, peripheral vascular disease, abdominal aortic aneurysm [AAA]) and to investigate its determinants.

Subjects and Methods

Patients

All patients in this study were participants of the Second Manifestations of ARTerial disease (SMART) study. This is an ongoing single-center, prospective cohort study among patients (aged 18 to 79 years) referred to the University Medical Center Utrecht for the first time because of atherosclerotic vascular disease (peripheral arterial disease, transient ischemic attack [TIA] or stroke, internal carotid artery stenosis, angina pectoris, myocardial infarction, diabetic foot disorder, AAA, renal failure, or renal artery stenosis) or for treatment of atherosclerotic risk factors (hypertension, hyperlipidemia, diabetes mellitus).¹⁴ The objectives of the SMART study are to determine the prevalence of additional vascular disease and risk and to study predictors for future cardiovascular events in these patients.
The study was approved by the ethics committee of the University Medical Center Utrecht, and written informed consent was obtained from all participants. Since May 2001 the SMART protocol has been extended with an MRI of the brain performed for all patients with clinically manifest vascular disease. Contraindications for MRI are claustrophobia, pregnancy, pacemaker implants, and some metal prostheses.

For the study described here, we selected SMART patients for whom an MRI was available. Patients who were referred to the University Medical Center Utrecht for cerebrovascular disease (TIA, stroke, amaurosis fugax, retinal infarction) were excluded. Furthermore, patients were excluded who reported that they had ever had a stroke or TIA to distinguish silent from symptomatic brain infarction (Figure 1).

Cardiovascular Risk Factors

At inclusion, data were collected about risk factors and (a)symptomatic vascular disease by means of an extensive questionnaire and physical, ultrasonographic, and laboratory examinations. Details about the exact methods and definitions used are published elsewhere. In addition to age and sex, the following risk factors were assessed: Smoking habits of the patients were categorized as current smoker or recent cessation (≤1 year), past smoker, and never smoker. The amount of smoked cigarettes was expressed in pack-years [(mean number of cigarettes each day/20) × number of years smoked]. Alcohol consumption was also questioned (current drinker or recent cessation, past, or never).

History of myocardial infarction was defined as positive when patients reported that they had ever had a myocardial infarction or were included in the SMART study with this diagnosis. History of stroke and neurological symptoms, which could indicate TIA, was queried in the questionnaire. Of the patients who reported any of these symptoms, the full questionnaire, diagnoses, and medical letters were reviewed to categorize them into the following classifications: probable or certain history of TIA (excluded), probably no history of TIA, or certainly no history of TIA, when the reported symptoms could be explained otherwise. Patients who reported that they had ever had a stroke were excluded.

Systolic and diastolic blood pressures were measured with a sphygmomanometer, and the mean of 3 measurements was used in the analysis. Hypertension was defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or reported treatment of hypertension. Peripheral arterial disease was considered present when the ankle-brachial index was <0.90. Height and weight were measured, from which the body mass index was calculated: body mass index = weight (kg)/height (m)^2.

A fasting venous blood sample was taken to determine glucose, lipid, creatinine, and homocysteine levels. Diabetes mellitus was defined as glucose ≥7.0 mmol/L or reported treatment of diabetes. Hyperlipidemia was defined as total cholesterol ≥5.0 mmol/L, LDL cholesterol ≥3.2 mmol/L, or reported treatment of elevated cholesterol. Hyperhomocysteinemia was defined as homocysteine ≥16.3 μmol/L in women and ≥18.8 μmol/L in men. Renal failure was defined with the use of Cockcroft’s formula for creatinine clearance, weighting for age, sex, height, and weight. Cutoff values for no and severe renal failure were ≥80.0 and ≤50.0, respectively.

Ultrasonography was performed to measure stenosis of the internal carotid arteries. Carotid artery stenosis was defined as >70% diameter reduction of 1 or both internal carotid arteries. Furthermore, the intima-media thickness (IMT) was measured in the left and right common carotid arteries. This was represented by the mean value of 6 measurements. Ultrasonography of the abdomen was performed to screen for an AAA.

Magnetic Resonance Imaging

MRI examination was performed at 1.5 T with a Philips Gyroscan ACS-NT 15 whole-body system (Philips Medical Systems). The scanning protocol included a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time 6000 ms, echo time 100 ms, inversion time 2000 ms) and a turbo spin-echo T2-weighted sequence (repetition time 2200 ms, echo time 100 ms). Images were obtained of 19 transaxial slices per scan. Slice thickness was 4 mm, with no interstice gap. These MRIs were read on hard copies.

Infarcts

The whole brain, including cortex, brain stem, and cerebellum, was searched for silent infarcts. Infarcts were defined as focal lesions of at least 3 mm in diameter, with signal intensity corresponding to liquor: hyperintense on T2-weighted images and low signal on the FLAIR image. Often they were surrounded by a hyperintense gliotic rim on the FLAIR sequence. They were differentiated from white matter lesions on FLAIR, which were of high signal intensity. Dilated perivascular spaces were distinguished from silent infarcts on the basis of their location (along perforating or medullary arteries, often symmetrical bilaterally, usually in the lower third of the basal ganglia or in the centrum semiovale), form (round/oval), and the absence of gliosis (Figure 2).

Presence, number, and location(s) of infarcts were scored. An infarct in the cortex, even if it involved the subcortical white matter, was termed cortical. The infaracts were scored in consensus between the investigator (J.L.P.G.) and a neuroradiologist (T.D.W.). Both were blinded for the history and diagnosis of the patient.

Statistical Analyses

Univariate analyses were performed to compare baseline characteristics between patients with and without silent infarcts. Differences were tested with χ² tests for categorized variables; for continuous variables, Student t tests or Mann-Whitney U tests were performed. Analyses were done separately with and without the patients who were in the category of “probably no history of TIA.” Next, age-adjusted odds ratios (ORs) and 95% CIs were calculated for significant risk factors with the use of logistic regression.

Results

A total of 308 SMART patients were included in this study. Mean age was 58.4 years (SD 10.2; range, 34 to 82 years), and the majority (86%) was male. Diagnosis at inclusion in the SMART study was coronary heart disease (70%), peripheral vascular disease (19%), AAA (10%), or others (1%). From the screening, it was found that 39% of the patients had hypertension, 77% had hyperlipidemia, and 19% had diabetes. Furthermore, in 7 patients (2.3%) carotid artery stenosis was detected, 22 patients (7.1%) appeared to have AAA, and peripheral artery disease was present in 61 (20%) of the patients.
Ninety patients reported symptoms that could indicate TIA. Included in this study were the 65 patients who were categorized as probably (n=48) or certainly (n=17) having no TIA.

Silent infarcts were found in 51 patients (16.6%). Thirty-four patients had a single infarct; the number of infarcts in the other patients ranged from 2 to 8. Together, they had 90 infarcts. Most infarcts (62%) were located in the white matter (internal capsule, corona radiata, centrum semiovale, and subcortical frontal and temporal lobes), and 20% were located in the basal ganglia and thalamus (Figure 3). By definition, these are all lacunar infarcts.16 A silent cortical infarct was found in 4 patients. These silent cortical infarcts occurred in all 4 lobes: frontal, temporal, parietal, and occipital. The silent infarcts were distributed evenly over the left and right hemispheres.

### Table 1. Baseline Characteristics of Patients With and Without Silent Infarct(s)

<table>
<thead>
<tr>
<th>Silent Infarcts</th>
<th>No (n=257)</th>
<th>Yes (n=51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.6 (10.0)</td>
<td>62.0 (10.0)</td>
<td>0.004‡</td>
</tr>
<tr>
<td>Sex, M</td>
<td>223 (87)</td>
<td>43 (84)</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (3.3)</td>
<td>26.7 (3.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92 (38)</td>
<td>29 (59)</td>
<td>0.007‡</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>199 (83)</td>
<td>39 (67)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (20)</td>
<td>12 (25)</td>
<td>0.4</td>
</tr>
<tr>
<td>Carotid artery stenosis &gt;70%</td>
<td>6 (2.4)</td>
<td>1 (2.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>14 (5.5)</td>
<td>8 (16)</td>
<td>0.009‡</td>
</tr>
<tr>
<td>Peripheral artery disease, ABI =90</td>
<td>49 (19)</td>
<td>12 (24)</td>
<td>0.5</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>81 (32)</td>
<td>15 (29)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pack-years*</td>
<td>20.8 (27.0)</td>
<td>18.2 (25.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>42 (16)</td>
<td>11 (22)</td>
<td>0.5</td>
</tr>
<tr>
<td>Past</td>
<td>151 (59)</td>
<td>26 (51)</td>
<td></td>
</tr>
<tr>
<td>Current/quit recently</td>
<td>64 (25)</td>
<td>14 (28)</td>
<td></td>
</tr>
<tr>
<td>Status alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40 (16)</td>
<td>7 (14)</td>
<td>0.9</td>
</tr>
<tr>
<td>Past</td>
<td>25 (9.8)</td>
<td>5 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Current/quit recently</td>
<td>191 (75)</td>
<td>39 (77)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133.9 (18.0)</td>
<td>142.3 (17.1)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.2 (9.5)</td>
<td>81.4 (10.2)</td>
<td>0.030†</td>
</tr>
<tr>
<td>Mean IMT,* mm</td>
<td>0.85 (0.26)</td>
<td>0.93 (0.40)</td>
<td>0.014†</td>
</tr>
<tr>
<td>Creatinine,* μmol/L</td>
<td>86.0 (20.0)</td>
<td>95.0 (22.0)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Homocysteine,* μmol/L</td>
<td>11.9 (4.6)</td>
<td>14.3 (5.8)</td>
<td>0.000‡</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are n (%). BMI indicates body mass index; ABI, ankle-arm index; BP, blood pressure; IMT, intima-media thickness. Dichotomous and categorical variables: χ² test; Continuous variables: mean (SD) and t test.

*Nonparametric variables: median (IQR) and Mann-Whitney U tests.
†P<0.05, ‡P<0.01.

Univariate relations between presence of silent infarct and baseline characteristics are listed in Table 1. Patients with silent infarcts were older and more often had hypertension. Both systolic and diastolic blood pressures were significantly elevated. More patients with silent infarcts had an AAA, and the intima-media of their common carotid arteries was thicker. Serum creatinine and homocysteine were significantly higher in patients with silent infarcts.

Exclusion of the 48 patients who were categorized as having “probably no history of TIA” did not change these relationships or the prevalence of silent infarcts.

Table 2 shows ORs for the categorical variables that remained (borderline) significant after adjustment for age. AAA was borderline significant (P<0.10). Increased systolic and diastolic blood pressures, as well as elevated creatinine and homocysteine levels, were also associated with a higher prevalence of silent infarcts, independent of age (P<0.05).

### Discussion

In this population of patients with manifest vascular disease (mean age, 58 years), the prevalence of silent infarcts was...
TABLE 2. Age-Adjusted Odds Ratios (OR) for Presence of Silent Infarct(s)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.2</td>
<td>1.2–4.2</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>2.4</td>
<td>0.9–6.4</td>
</tr>
<tr>
<td>Renal failure*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.6</td>
<td>0.7–3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>7.3</td>
<td>2.1–25.2</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2.6</td>
<td>1.1–5.9</td>
</tr>
</tbody>
</table>

*Renal failure was defined using Cockcroft’s formula for creatinine clearance, weighting for age, sex, length and weight.

17%. This is high in view of the relatively young age. Comparable prevalences were found in population studies with healthy elderly persons in the age group 65 to 69 years.1,5 Thus, patients with manifest vascular disease, especially AAA, are at risk for silent infarcts at a younger age. In another relatively young (aged 40 to 79 years) high-risk population for stroke and silent infarcts (patients with asymptomatic carotid artery stenosis), a prevalence of 15% was also found.13 The number of patients with carotid artery stenosis in our study, however, was too small to find an association.

In this study significant risk factors for presence of silent infarct(s) were age, hypertension, systolic and diastolic blood pressure, AAA, elevated creatinine, renal failure, elevated homocysteine, and increased IMT. In the literature, age and hypertension are the most consistent determinants for silent infarcts. Other candidate determinants, although they did not appear in this study, are diabetes, smoking, female sex, and coronary heart disease. AAA was not previously investigated in relation to silent infarcts. Some investigators found that AAA is strongly associated with cerebral vascular disease in women.18 AAA is also known to be associated with hypertension, although not all studies confirm this.19 In our study correction for hypertension did not essentially change the OR of AAA and silent infarcts.

Creatinine in relation to silent infarcts was previously investigated only in the Cardiovascular Health Study; they too found a significant association.10 Elevated creatinine level could be a marker for subtle renal impairment caused by hypertension or an independent risk factor for cerebrovascular diseases through a still unknown mechanism. Patients with severe renal failure had silent infarcts 7 times more often. Elevated total plasma homocysteine also reflects renal impairment or, alternatively, nutritional deficiencies (folate/B12) or genetic defects (N5,N10-methylenetetrahydrofolate reductase) (MTHFR).20 Elevated total plasma homocysteine is an independent risk factor for vascular disease, as well as silent cerebral infarcts,21,22 although MTHFR polymorphism was significantly associated only with symptomatic lacunar infarcts.23 Elevated homocysteine can be reduced by vitamin supplementation.20 Further research will be needed on the interaction and pathological mechanisms of hypertension, renal failure, creatinine, homocysteine, and silent infarcts.

IMT is seen as a marker for atherosclerosis. Significant associations have been found between IMT and silent infarcts,10,24,25 although in this study the relationship was no longer significant after adjustment for age. This supports the hypothesis that atherosclerosis may be a causative factor for silent infarcts, next to hypertension, which is thought to be the most important etiological risk factor for small-vessel disease and lacunar infarcts.

Most silent infarcts were located in the white matter (62%); 20% were located in the basal ganglia and thalamus. Previous research indicated the basal ganglia as the most important location.1,10 One possible explanation for our different finding is a difference in the definition of the area of the basal ganglia. Including the internal capsule and corona radiata in the area of the basal ganglia may be justified; this would then result in the majority of silent infarcts occurring in the basal ganglia. Another possibility is misclassification of enlarged perivascular spaces in the basal ganglia as silent infarcts. In the lower third of the putamen, most hyperintense foci on T2-weighted images are known to represent perivascular spaces,26–28 and in the remainder of the basal ganglia most hyperintense foci are perivascular spaces.29 Some investigators differentiated lacunar infarcts from perivascular spaces on proton-density scans principally by their size, by only counting lesions >3 or 5 mm.1,6 Indeed, perivascular spaces usually do not exceed 5 mm, and many investigators found them to be significantly smaller than infarcts.28,29 However, perivascular spaces can attain large sizes, up to 2 to 3 cm.30 Therefore, the size of the foci alone is not the correct criterion to differentiate between lacunar infarcts and perivascular spaces and may lead to overestimation of the number of infarcts in the basal ganglia and the total prevalence of silent infarcts.

A limitation of this study is the possibility of misclassification of silent infarcts. This may have occurred in 2 ways. First, we did not have pathological information to confirm the infarcts on the MRIs. In addition, to determine whether the infarcts were silent, we relied heavily on patient’s self-reports of their history of TIA or stroke. Because of doubts concerning the specificity of the questions about past TIA, history of TIA was checked by reviewing medical letters of the patients who reported any of these symptoms. Separate analyses without those patients who were categorized as having “probably no TIA” indicated that these patients were classified correctly. However, a study of residents of Rochester, Minn, suggested that self-reports may underestimate the number of people who had TIA or stroke.31 Therefore, some patients may have been incorrectly included in this study, and some infarcts may have been misjudged as silent.

In conclusion, silent infarcts were present in 17% of the patients with manifest vascular disease. In particular, older patients and patients with hypertension, elevated creatinine, elevated homocysteine, AAA, or increased IMT are at high risk. Because of the risk of stroke and cognitive decline associated with silent infarcts, these people should be treated, for example, to lower blood pressure or homocysteine levels or with antithrombotic agents.

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References

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