

# Silent Brain Infarcts in 755 Consecutive Patients With a First-Ever Supratentorial Ischemic Stroke

## Relationship With Index-Stroke Subtype, Vascular Risk Factors, and Mortality

Arthur Boon, MD; Jan Lodder, MD; Lisette Heuts-van Raak, MD; Fons Kessels, MD

**Background and Purpose** We wanted to establish independent associations of various clinical variables, computed tomographic (CT) scan features, presenting stroke subtypes, and outcome with the presence of silent infarcts on CT.

**Methods** We studied 755 consecutive patients in a prospective registration of patients with first-ever supratentorial atherothrombotic, cardioembolic, or lacunar stroke or stroke of undetermined cause by multiple logistic regression analysis.

**Results** Two hundred six patients (27%) with a first symptomatic territorial or small deep ischemic stroke had one or more silent infarcts on CT. Of all silent lesions, 169 (82%) were small and deep. Silent infarcts were significantly more strongly associated with a lacunar than atherothrombotic (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.02 to 2.47;  $P=.039$ ) or cardioembolic (OR, 1.89; 95% CI, 1.2 to 2.99;  $P=.005$ ) index stroke. Silent territorial lesions were more strongly associated with cardioembolic than with lacunar stroke but not with atherothrombotic stroke. In this respect, no differences were found between the atherothrombotic and undetermined-cause group. Advanced age and hypertension were the only risk factors that were significantly associated with silent infarcts (OR, 1.76; 95% CI, 1.14 to 2.71;  $P=.011$ ; and OR, 1.58; 95% CI, 1.13 to 2.21;  $P=.007$ ; respectively), mainly because of a strong independent association of these risk factors with silent small deep infarcts (OR, 1.75; 95% CI,

1.10 to 2.79;  $P=.018$ ; and OR, 1.57; 95% CI, 1.09 to 2.24;  $P=.014$ ; respectively). A cardioembolic source or atrial fibrillation in specific was not independently associated with any type or number of silent infarcts. Significant carotid stenosis (diameter reduction  $>50\%$ ) was not significantly associated with any type of silent lesion. Initial severe handicap (Rankin Scale score  $>3$ ), 30-day case fatality rate, and 1-year mortality were not affected by the presence of silent infarcts.

**Conclusions** The strong association of silent small deep lesions with first symptomatic small deep infarcts suggests a common underlying mechanism (presumably small-vessel vasculopathy), whereas cardiogenic embolism and large-vessel thromboembolism are the most likely causes in both silent and first symptomatic territorial infarcts. Single or multiple silent infarcts do not predict a cardioembolic stroke mechanism in first symptomatic supratentorial brain infarcts. As silent infarcts do not predict the cause of carotid embolic stroke in first symptomatic brain infarcts, their presence should not influence the decision on carotid surgery. Silent infarcts do not affect the degree of initial handicap, 30-day case fatality, or 1-year mortality. The significance of silent infarcts for predicting possible future cognitive decline and risk of recurrent stroke deserves further study. (*Stroke*. 1994;25: 2384-2390.)

**Key Words** • cerebral infarction • infarcts, silent • lacunar infarction • mortality • risk factors

Computed tomographic (CT) scanning of the brain may detect one or more hypodense lesions compatible with brain infarction without a history of prior stroke. Such lesions are often called silent brain infarcts.<sup>1-15</sup> Their presence has been associated with worse stroke outcome,<sup>4,16-25</sup> vascular risk factors,<sup>3,6,12,26</sup> a cardiac source of embolism (especially atrial fibrillation),<sup>4,19-23,27-32</sup> carotid obstructive lesions,<sup>33-37</sup> an increased risk of recurrent stroke, and the development of vascular dementia.<sup>12,23,38-45</sup> However, most studies on silent brain infarcts were done in selected patients, such as those with a carotid stenosis or with atrial fibrillation only, thereby not allowing

conclusions on the significance of silent infarcts for stroke patients in general.<sup>20,21,31,33,35,36,46,47</sup> One large study included a control group for comparison but selected only transient ischemic attack or minor stroke patients without atrial fibrillation, restricting conclusions to this subgroup.<sup>12</sup> Some studies of unselected stroke patients were small or retrospective, not allowing any firm conclusions.<sup>31,48,49</sup> There are five prospective studies that analyzed different aspects of silent brain infarcts in consecutive stroke patients.<sup>1-3,6,7</sup> However, these studies can be criticized for several reasons: two were rather small,<sup>3,6</sup> early generation CT scanners may have missed silent infarcts,<sup>2,3</sup> approximately 25% of patients or more did not undergo CT,<sup>2,3,6</sup> a cohort of only a certain age was included,<sup>3</sup> a subgroup was selected based only on whether certain ancillary investigations were performed,<sup>7</sup> patients with transient ischemic attack were included in a stroke series,<sup>7</sup> and multiple logistic regression analysis allowing for collinearity between factors associated with silent infarct was not performed.<sup>2,3,7</sup> No studies included subgroup analy-

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From the Department of Neurology, St-Anna Hospital, Geldrop (A.B.), the Department of Neurology, University Hospital (J.L., L.H.-van R.), and the Department of Epidemiology, University of Limburg, Maastricht (F.K.), Netherlands.

Correspondence to A. Boon, MD, Department of Neurology, St-Anna Hospital, PO Box 90, 5660 AB, Geldrop, Netherlands.

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sis. One prospective series of 500 stroke patients had a high rate (85%) of CT scanning and performed multivariate comparisons. However, risk factors could not be studied in all patients; infarct and hemorrhages were not considered separately, and no prospectively well-defined separation of different infarct subtypes was performed.<sup>1</sup> One prospective study established a significant association between carotid stenosis and silent infarction (lesions  $\geq 5$  mm) on magnetic resonance imaging in 117 patients free of stroke, increasing the a priori chance of such an association by excluding all patients with a potential cardioembolic source and possibly some with small deep silent infarcts.<sup>34</sup> Studying separate brain-infarct subgroups could be relevant because they may differ in stroke cause, clinical presentation, and outcome.<sup>9,50,51</sup> Thus, the significance of finding silent brain infarcts may differ between index-stroke subtypes. Also, similarity in silent and symptomatic brain-infarct type may point to a consistency in the underlying cause of stroke. These considerations led us to conclude that so far several aspects of silent brain infarcts have not been fully clarified. Therefore, in a prospective study of 755 consecutive patients with first-ever supratentorially located ischemic stroke, we studied independent associations of various clinical and CT scan features with the presence of silent brain infarcts. In particular, we wondered whether silent infarcts influence stroke outcome in terms of 30-day case fatality rate and 1-year mortality and whether they are small and deep or territorial in symptomatic small deep strokes and territorial strokes, respectively.

### Subjects and Methods

Patients were registered between July 1987 and August 1992 in an ongoing prospective registry at the University Hospital of Maastricht, including all patients with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours. Twenty-five of 813 consecutive patients were excluded because of rare causes such as fibromuscular dysplasia, carotid dissection, vasculitis, etc, leaving 788 patients; 755 underwent CT and were included in the study. The University Hospital is the only hospital in the Maastricht region with an adherent population of approximately 190 000 people. All patients were examined as soon as possible after admission or at the first outpatient clinic visit. They had routine investigations including standard blood and urine tests, electrocardiography (ECG), chest radiography, carotid studies, and CT scan. Echocardiography, 24-hour ECG monitoring, and cerebral angiography were performed in selected cases.

A brain infarct was defined as rapidly developing clinical signs of focal disturbance of cerebral function, lasting longer than 24 hours or leading to death, with no other apparent cause than that of vascular origin; CT scan showed an area of low attenuation compatible with the clinical signs and symptoms or was without specific lesion. For symptomatic infarcts, when no CT was available, we used the Guy's Hospital Stroke Diagnostic Score (Allen Score) that predicts with a probability of more than 90% whether the stroke was due to infarction when the score is lower than 4.<sup>52</sup>

A small deep infarct was defined as a CT-identified lesion compatible with the occlusion of a single perforating artery (ie, a subcortical, small, sharply marginated, hypodense lesion with a diameter  $< 20$  mm) or as a clinically identified lacunar syndrome if no specific lesion was visible<sup>53</sup> on CT. A patient with a cortical syndrome and a lacunar infarct on CT was classified as having a symptomatic lacunar infarct, unless symptoms were completely incompatible,<sup>26,53</sup> but cortical syndrome and lacunar infarct were also analyzed separately. We

distinguished four lacunar syndromes: pure motor stroke, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis including dysarthria-clumsy hand cases.

A territorial infarct was defined as CT findings compatible with infarction involving the cortex or a clinically identified cortical syndrome such as unilateral motor or sensory deficit, or both, in combination with signs of cortical dysfunction (eg, aphasia, visual field deficit, visuospatial disturbances, apraxia, neglect, or agnosia) if no specific lesion was visible on CT. Patients with a large subcortical infarct were included in this group because of similar pathogenesis.<sup>54</sup> Territorial infarcts were divided into three groups by presumed cause: atherothrombotic, cardioembolic, or undetermined cause.

Infarcts were considered of undetermined origin in the absence of carotid studies (duplex ultrasonographic scan, continuous-wave Doppler, multigate pulse Doppler, or angiography), any compatible carotid lesion (more than 5% to 15% stenosis on multigate pulse Doppler, duplex scanning, or angiography or more than 15% to 50% stenosis on continuous-wave Doppler), or cardiac source of embolism.

A cardioembolic infarct was defined as a territorial infarct in the presence of one or more of the following cardiac sources of embolism: chronic and paroxysmal atrial fibrillation, myocardial infarction less than 6 weeks before infarct, prosthetic aortic or mitral valve, endocarditis, cardiomyopathy, mitral stenosis, left ventricular aneurysm, and intraventricular thrombus. Four patients with a cardioembolic cause of stroke but with significant ipsilateral carotid stenosis were included in this group. Atherothrombotic infarction was defined as a territorial infarct with no other apparent cause than presumed large-vessel disease, ie, atherothrombosis or artery-to-artery embolism, fulfilling the criteria of compatible carotid lesions as mentioned above.

A silent brain infarct was defined as a low-density area seen on CT and compatible with infarction but without a history of stroke as determined from the patient's history, the family, or any other accessible information. Identification of silent lesions was based on the incompatibility of the lesion and index-stroke symptoms, such as location in a different hemisphere or other anatomic incompatibility (eg, a small deep infarct in the anterior leg of the internal capsule on CT in a patient with sudden hemianopia). Furthermore, old lesions are more hypodense or may show signs of surrounding tissue loss such as retraction of brain structures toward the lesion. Sometimes a repeated CT scan showed the recent infarct. We distinguished two types of silent brain infarcts: small deep lesions and silent territorial infarcts, defined by CT findings as described above. In addition to age and sex, the following risk factors were recorded: hypertension (known hypertension treated with antihypertensive medication, two or more blood pressure recordings  $> 160/90$  mm Hg before stroke or at least 1 week after stroke), diabetes mellitus (known diabetes treated with diet and/or medication or either a fasting serum glucose  $> 7$  mmol/L or a postprandial serum glucose level  $> 11$  mmol/L measured on at least two separate occasions before or after stroke but not in the acute phase [the first 72 hours]), a history of ischemic heart disease (myocardial infarction, angina pectoris), and carotid stenosis of  $> 50\%$  on carotid tests. Handicap on admission was measured using the modified Rankin Scale.<sup>55</sup> Categorical variables were analyzed in a univariate analysis by means of  $\chi^2$  test and crude odds ratios (cOR) with 95% confidence intervals (CI).<sup>56</sup>

Subsequent multiple logistic regression analysis determined the independent association of age, sex, hypertension, diabetes mellitus, a history of ischemic heart disease, significant carotid stenosis ( $> 50\%$  stenosis), and stroke subtypes (lacunar, atherothrombotic, cardioembolic, or undetermined cause) with any type of silent infarct, silent small deep infarct, or silent territorial infarct as dependent variables. Statistical analysis was performed with ORs adjusted (aORs) for age, sex, hypertension, diabetes mellitus, ischemic heart disease, atrial

TABLE 1. Numbers of Patients With Silent Infarcts Among Index Stroke Types

Type of Infarct	Index Brain Infarct				Total
	Atherothrombotic	Undetermined Cause	Cardioembolic	Small Deep	
One small infarct	21	20	21	42	104
Two or more small infarcts	8	6	6	34	54
One territorial infarct	10	6	13	6	35
Two or more territorial infarcts	0	0	1	1	2
Small and territorial infarcts	4	1	3	3	11
No silent infarcts	133	112	134	170	549
Total	176	145	178	256	755

fibrillation, carotid stenosis, and symptomatic stroke subtype with 95% CI. Risk-factor profiles for silent infarcts were also determined with symptomatic-stroke subtypes added to the model. Models with different subsets of variables in subgroups of patients were tested to determine collinearity; only relevant results are reported.

### Results

There were 398 men (53%) and 357 women (47%), with a median age of 71 years (range, 24 to 96 years). The median delay until CT scan was 5 days (range, 0 to 912 days); 490 CT scans (65%) were performed within the first week, 638 (85%) within 2 weeks, and 681 (90%) within 3 weeks after stroke onset. There were 210 stroke patients with infarcts that were not confirmed on CT; of these, 34 infarcts were atherothrombotic, 46 cardioembolic, 95 lacunar, and 35 of undetermined cause. Two hundred six patients (27%; 95% CI, 24 to 30) had one or more silent infarcts on CT. There were 145 patients with undetermined stroke cause. These patients had a frequency of CT-confirmed infarcts and silent infarct subtypes similar to that of the atherothrombotic group. Therefore, because of the absence of any specific stroke cause and given the patients' ages (mean, 71 years), the most likely cause was considered to be generalized atherosclerosis, but undetermined stroke cause was analyzed separately.

Table 1 shows the frequency of patients with silent infarcts among the four presenting stroke subtypes. One hundred thirty-nine patients had one silent infarct, and 67 had more than one. One hundred sixty-nine patients had one or more silent small deep infarcts, and 48 had

one or more silent territorial infarcts. Of all silent lesions, 164 (49%) were right hemispheric; 22 of these, and 30 of 169 left hemispheric silent lesions, were territorial. In the patients with multiple silent infarcts, 177 lesions were small and deep (83 in the right hemisphere), and 17 were territorial (7 in the right hemisphere). Multiple silent infarcts did not occur more often in patients with (10/178) than in those without (57/577) a cardioembolic stroke (cOR, 0.54; 95% CI, 0.26 to 1.15;  $P=.11$ ).

Multiple logistic regression comparison (Table 2) showed that silent infarcts were significantly more prevalent in patients with a small deep index stroke than in those with an atherothrombotic or cardioembolic index stroke. This association was due mainly to a significant preponderance of silent small deep infarcts in patients with a small deep index stroke compared with those with an atherothrombotic or cardioembolic index stroke. Silent infarcts were equally prevalent in atherothrombotic or cardioembolic index-stroke groups. Silent territorial infarcts were associated significantly less strongly with small and deep than cardioembolic infarcts. The association with silent infarcts of the undetermined-cause group was similar to that of the atherothrombotic group when compared with the other index-stroke groups. Because the type of index stroke in patients who had a cortical syndrome but showed a small deep infarct on CT may be uncertain, in a separate analysis we also looked at this group of patients. This group was much more strongly associated with silent small deep infarcts than with atherothrom-

TABLE 2. Comparison of Index Brain Infarct Subtypes Among Patients With Silent Infarcts by Means of Multivariate Logistic Regression

Index Stroke Subtypes	All Silent Infarcts			Small Deep Silent Infarcts			Territorial Silent Infarcts		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Small deep vs atherothrombotic	1.59	1.02-2.47	.039	1.97	1.23-3.16	.005	0.46	0.20-1.07	NS
Small deep vs cardioembolic	1.89	1.20-2.99	.005	2.71	1.64-4.48	.000	0.43	0.19-0.99	.04
Cardioembolic vs atherothrombotic	0.84	0.50-1.40	NS	0.73	0.41-1.29	NS	1.08	0.49-2.35	NS
Unknown cause vs atherothrombotic	0.81	0.47-1.38	NS	0.89	0.50-1.59	NS	0.53	0.20-1.38	NS
Unknown cause vs small deep	0.51	0.32-0.83	.006	0.45	0.27-0.75	.002	1.14	0.42-3.12	NS
Unknown cause vs cardioembolic	0.97	0.57-1.63	NS	1.23	0.69-2.20	NS	0.49	0.20-1.23	NS

OR indicates odds ratio; CI, confidence interval. ORs adjusted for age, sex, hypertension, ischemic heart disease, and diabetes mellitus.

TABLE 3. Univariate Comparison of Risk Factors and Outcome in Different Types of Silent Infarcts

Risk Factor	All Silent Infarcts				Small Deep Silent Infarcts				Territorial Silent Infarcts			
	n	OR	95% CI	P	n	OR	95% CI	P	n	OR	95% CI	P
65 < Age ≤ 75 vs age ≤ 65	78/44	1.69	1.09-2.62	.02	66/37	1.66	1.04-2.66	.03	17/9	1.62	0.60-4.39	.3
Age > 75 vs age ≤ 65	84/44	1.85	1.20-2.84	.005	66/37	1.63	1.02-2.62	.04	22/9	2.12	0.89-5.04	.09
Men vs women	110/96	1.03	0.58-1.83	.92	88/81	0.96	0.55-1.67	.89	27/21	1.16	0.50-2.70	.74
Hypertension	113	1.58	1.13-2.19	.007	94	1.59	1.12-2.27	.01	23	1.06	0.05-2.12	1.00
Ischemic heart disease	61	1.30	0.91-1.86	.17	50	1.28	0.85-1.93	.24	14	1.14	0.41-3.15	.8
Atrial fibrillation	53	1.14	0.74-1.75	.54	38	0.90	0.54-1.49	.68	18	2.00	1.05-3.84	.04
Diabetes mellitus	39	1.24	0.78-1.98	.36	31	1.16	0.67-2.00	.59	11	1.53	0.66-3.54	.32
Any carotid stenosis	29	0.74	0.46-1.21	.23	20	0.59	0.35-1.02	.06	12	1.70	0.78-3.69	.18
Rankin score > 3	108	1.12	0.78-1.61	.53	82	0.91	0.60-1.37	.65	32	2.06	1.08-3.95	.03

OR indicates crude odds ratio; CI, confidence interval; and OR > 1, more frequent in silent infarct.

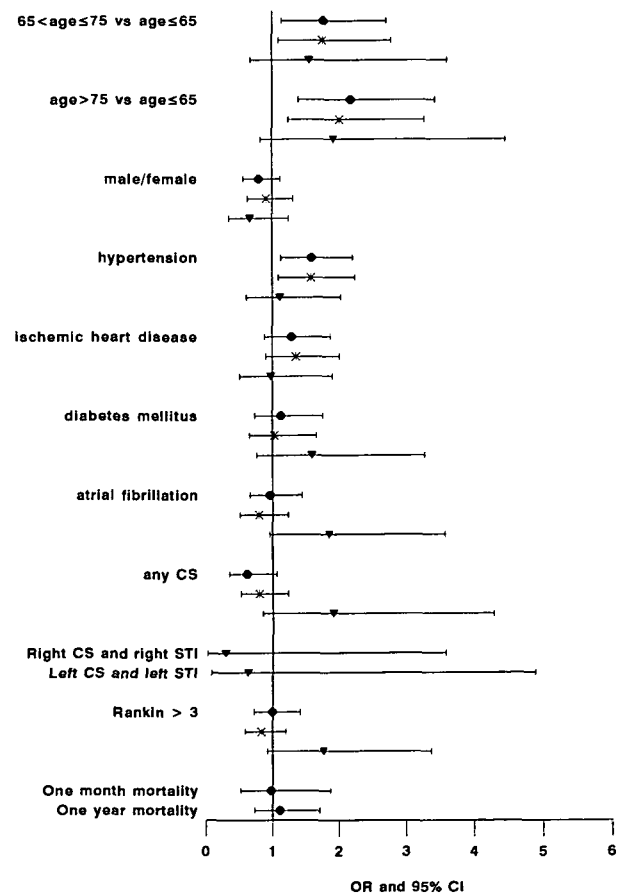
botic (aOR, 5.12; 95% CI, 2.30 to 11.4; P=.0000), lacunar (aOR, 3.06; 95% CI, 1.42 to 6.56; P=.003), or cardioembolic strokes (aOR, 6.95; 95% CI, 3.08 to 15.7; P=.0000) or strokes with undetermined cause (aOR, 5.68; 95% CI, 2.50 to 12.9; P=.0000). Associations of this group with silent territorial infarcts were the same as in the other stroke groups.

Table 3 shows the frequencies of risk factors among patients with a silent infarct, which were compared between the different groups by cORs. Higher age and hypertension were significantly more frequent in patients with one or more silent (small deep) infarcts. Atrial fibrillation and a more severe initial handicap (Rankin score > 3) were significantly more frequent in patients with than without a silent territorial lesion. Significant carotid stenosis on either side was less frequent in patients with than without a silent small deep infarct. The Figure displays the association of risk factors, also shown in Table 4, with the presence of one or more silent infarcts as demonstrated by multiple logistic regression analysis. Age above 65 years and hypertension were significantly associated with the presence of a silent small deep infarct, or with the presence of any type of silent brain infarct, but not with silent territorial infarcts. Only when small deep index strokes were excluded from the analysis with silent territorial infarcts as a dependent variable did atrial fibrillation become significant (aOR, 2.11; 95% CI, 1.01 to 4.40; P=.046). Diabetes mellitus was significantly associated with silent territorial infarcts only when the analysis was restricted to patients with noncardioembolic territorial index strokes (aOR, 3.31; 95% CI, 1.10 to 9.95; P=.03). Restricting the analysis to other stroke subtypes did not significantly change associations. A tendency for silent territorial cortical infarcts to be associated with a significant carotid stenosis either ipsilateral or contralateral to the silent infarct was not significant; this tendency was lost when analyzing only carotid stenosis ipsilateral to the silent territorial lesion (right carotid stenosis: aOR, 0.29; 95% CI, 0.02 to 3.58; P=.45; left carotid stenosis: aOR, 0.62; 95% CI, 0.08 to 4.88; P=.87). Thirty-day case fatality rate and 1-year mortality did not significantly differ between patients with or without a silent infarct (aOR, 0.97; 95% CI, 0.51 to 1.87; P=.11; and aOR, 1.11; 95% CI, 0.73 to 1.70; P=.63; respectively). A more severe initial handicap (Rankin score > 3) was not significantly

associated with the presence of one or more silent infarcts (aOR, 0.96; 95% CI, 0.71 to 1.40).

Discussion

The 27% of patients with one or more silent brain infarcts is more than has been reported by others.<sup>2,3,8</sup>



Graph shows factors associated with silent infarcts. Comparison is between patients with and those without silent infarct by multiple logistic regression analysis. OR indicates adjusted odds ratio; CI, confidence interval; OR > 1, more strongly associated with silent infarct; lower limit 95% CI > 1, value of P < .05; CS, carotid stenosis; STI, silent territorial infarct; ●, all silent infarcts; \*, silent small deep infarcts; and ▼, silent territorial infarcts.

TABLE 4. Potential Risk Factors for Silent Infarcts

Risk Factor	All Silent Infarcts			Small Deep Silent Infarcts			Territorial Silent Infarcts		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
65 < Age ≤ 75 vs age ≤ 65	1.76	1.14-2.71	.01	1.75	1.10-2.79	.02	1.55	0.67-3.61	.30
Age > 75 vs age ≤ 65	2.18	1.39-3.43	.0007	2.01	1.24-3.27	.005	1.92	0.82-4.46	.13
Men vs women	0.79	0.56-1.12	.19	0.90	0.66-1.31	.59	0.66	0.35-1.25	.20
Hypertension	1.58	1.13-2.21	.007	1.57	1.09-2.24	.01	1.11	0.60-2.03	.74
Ischemic heart disease	1.29	0.89-1.87	.18	1.35	0.90-2.01	.14	0.98	0.50-1.90	.46
Atrial fibrillation	0.96	0.65-1.43	.85	0.79	0.50-1.23	.29	1.85	0.96-3.57	.066
Diabetes mellitus	1.13	0.73-1.75	.58	1.03	0.647-1.65	.89	1.58	0.76-3.27	.22
Any carotid stenosis	0.61	0.35-1.06	.08	0.80	0.52-1.23	.31	1.91	0.85-4.28	.11
Rankin score > 3	0.99	0.71-1.40	.9	0.83	0.58-1.20	.32	1.76	0.92-3.37	.09

OR indicates odds ratios adjusted for age, sex, hypertension, diabetes mellitus, ischemic heart disease, carotid stenosis, atrial fibrillation, and index stroke subtype; CI, confidence interval; and OR > 1, more strongly associated with silent infarct. Multiple logistic regression analysis with different subtypes of silent infarcts as dependent variables.

The CT scanning rate in our study was higher compared with other series. Especially for very elderly patients not admitted to the hospital, CT may be less easily accessible. Because higher age is related to the presence of silent infarcts, both our high CT scanning rate and the more advanced age of our patients may explain the higher frequency of silent infarcts in our study.<sup>1</sup> Advanced age might explain the even higher percentage (38%) in the community-based SEPIVAC.<sup>6,9,10</sup>

As in other studies, we found most silent infarcts to be small deep lesions.<sup>1-3,7,12,20</sup> Depending on the lesion site, a small deep infarct may more often go unnoticed by the patient than infarction involving the cortex.<sup>57</sup> None of the prospective studies on consecutive patients with ischemic stroke reported multivariate analysis accounting for collinearity between features related to silent infarcts<sup>2,3,6,7</sup> except a recent study<sup>1</sup> in which different index-stroke subtypes were not distinguished. Although predominant in all of our four index-stroke subgroups, silent small deep infarcts were significantly more frequent in first-ever lacunar stroke. Silent territorial infarcts, on the other hand, were underrepresented in lacunar index stroke. These findings suggest a similarity in the type of underlying mechanism in symptomatic and silent infarcts: small-vessel vasculopathy in most small deep infarcts and cardiogenic embolism or large-vessel thromboembolism in territorial infarcts.<sup>57</sup> Some patients may suffer from both because silent small infarcts are common among stroke patients with cardiogenic or large-vessel thromboembolism. This may reflect hypertension-related small-vessel vasculopathy because, other than age, hypertension was the only risk factor significantly associated with silent small deep but not territorial infarcts. This small-vessel vasculopathy may be small-vessel hyalinosis rather than small-vessel atherothrombosis, as was argued before.<sup>26</sup> In contrast, the Copenhagen Stroke Study<sup>1</sup> reported lower mean symptomatic infarct size in a crude comparison of patients with and without silent infarcts, concluding that the underlying stroke mechanism might be different. However, our study indicates that those findings merely reflected differences in the frequency of silent small infarcts among symptomatic stroke subtypes. It should

be kept in mind that some lesions considered as silent infarcts may be sequelae of small hemorrhages. Also, some patients with a lacunar syndrome but without a visible compatible lesion on CT may have an infarct in the brain stem; we recently discussed CT-negative cases that resemble those with visible symptomatic lacunar infarctions.<sup>53</sup> We found that the presumed lacunar index strokes with a cortical syndrome resembled the lacunar strokes. The likelihood that a lacunar stroke might be erroneously diagnosed as a territorial infarct increases in the presence of one or more silent small deep infarcts, as we discussed elsewhere.<sup>53</sup> As have others, we found increasing age strongly related to the presence of silent brain infarcts, mainly due to age dependency of the silent small deep lesions. Thus, with increasing age, hypertensive patients may be at increased risk for silent small deep infarcts probably due to hypertension-related small-vessel lipohyalinosis.<sup>51</sup>

As in the Copenhagen study but opposed to other studies (most of which lacked noncardioembolic stroke patients for comparison), neither a cardiac source of embolism in general nor atrial fibrillation in specific were significantly associated with any type of silent stroke in our series.<sup>4,19-23,27-32,47,58,59</sup> Only when small deep index strokes were excluded from the analysis with silent territorial infarcts as a dependent variable did atrial fibrillation become significant. That concurs with the above-mentioned consistency in an underlying stroke mechanism in prior silent and first symptomatic stroke. However, our data and those of Jorgensen et al<sup>1</sup> do not concur with the general statement that the presence of silent brain infarcts increases the likelihood that the symptomatic stroke was caused by cardiogenic embolism. Other studies of consecutive stroke patients also did not find atrial fibrillation to be associated with silent infarcts<sup>3,6</sup> as opposed to studies restricted to patients with atrial fibrillation.<sup>20-22,32</sup>

The Framingham study found glucose intolerance to be the only risk factor for silent infarcts.<sup>3</sup> We found diabetes mellitus to be an independent associated factor only with silent territorial infarcts and only when we restricted the analysis to the atherothrombotic index-stroke subgroup. There was a tendency for carotid

stenosis to be associated with silent territorial lesions, but this was not statistically significant. Our findings do not confirm suggestions by others of the significance of carotid obstructive lesions for the presence of silent infarcts, even when our analysis was restricted to the atherothrombotic subgroup or included stenosis compatible with the side of the silent lesion or side of the index stroke. The relation of silent infarcts to carotid stenosis in other studies may be explained by the lack of adjusting for collinearity with other associated factors<sup>35,36</sup> or by selection bias.<sup>34</sup> Therefore, in our view the decision to undertake carotid surgery should not be influenced by the presence of prior silent infarcts.

Prior silent infarcts may increase functional deficit when a symptomatic stroke occurs.<sup>12</sup> However, more severe initial handicap as indicated by a Rankin score of 4 or 5 was not associated with silent infarcts in our study. Also, 30-day case fatality rate and 1-year mortality were not affected by the presence of silent infarcts. Obviously, silent brain infarcts do not have a deleterious effect on stroke outcome, a finding that contrasts with the suggestions of others. These other studies, however, were mostly based on data from series of selected patients.<sup>4,16-25</sup> In the SEPIVAC, the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank, and the Copenhagen Stroke studies, the presence of silent infarcts also did not affect stroke outcome.<sup>12-6</sup> An increased risk of cognitive decline or even dementia has often been related to the presence of silent brain infarcts. However, this view was more often based on flawed inferences than on the results of prospective evaluation of patients being compared with those without silent brain infarcts.<sup>47-50</sup> Patients with multiple asymptomatic lesions in the NINDS study were "free of overt symptoms in cognitive or behavioural spheres."<sup>2-45</sup> Jorgensen et al<sup>1</sup> found silent infarcts to have no effect on Mini-Mental State Examination ratings. Until there is a follow-up evaluation of prospectively included stroke patients that compares those with and without silent lesions and also accounts for a collinearity of factors that may influence cognitive decline such as leukoaraiosis or brain atrophy, it will remain unclear whether silent lesions present an independent factor threatening stroke patients' cognition or indicate an increased risk for future (silent) stroke.

Our study illustrates that the significance of silent brain infarcts may depend on silent infarct subtype and on index-infarct subtype. Evaluating the brain using imaging techniques in patients at risk, especially those with hypertension, should be considered to document the degree of cerebral "end organ damage" in terms of silent infarcts, although the precise significance of these detected lesions for future risk of stroke and cognitive decline deserves further study.

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A Boon, J Lodder, L Heuts-van Raak and F Kessels

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