Two Types of Lacunar Infarcts:
Further Arguments From a Study on Prognosis
G. de Jong, MD, PhD; F. Kessels, MD, MSc; J. Lodder, MD, PhD

Background and Purpose—Earlier, we found that lacunar stroke patients with ≥1 asymptomatic lacunar infarcts on CT had leukoaraiosis and hypertension significantly more often than patients without such lesions, and we hypothesized that 2 types of small-vessel disease could be distinguished during life: arteriolosclerosis and microatheromatosis, respectively. Differences in prognosis might sustain this hypothesis of 2 lacunar stroke entities. Therefore, we performed a follow-up in 333 patients with first lacunar stroke, distinguishing those with ≥1 asymptomatic lacunar lesions (LACI+) from those without such lesions (LACI−).

Methods—Cross-sectional follow-up was performed after 785±479 days (mean±SD) in 104 LACI+ patients and 865±545 days in 229 LACI− patients.

Results—Mortality at the end of follow-up was 33% in LACI+ and 21% in LACI− patients [odds ratio (OR), 1.74; 95% confidence interval (CI), 1.01 to 3.01]. Stroke recurrence rate was 21% in LACI+ and 11% in LACI− (OR, 2.09; 95% CI, 1.08 to 4.06). Forty percent of LACI+ and 26% of LACI− patients had unfavorable outcome at the end of follow-up (OR, 1.95; 95% CI, 1.17 to 3.26). Kaplan-Meier curves showed less favorable survival in LACI+ (log-rank test, P=0.0218) and survival free of stroke (log-rank test, P=0.0121) than in LACI−. When we restricted the analysis to patients with both silent lesions and leukoaraiosis (n=63) compared with those without (n=196), differences were even more pronounced.

Conclusions—Prognosis for mortality, recurrent stroke, and overall functional outcome in lacunar stroke patients with ≥1 silent lacunar lesions is more unfavorable than in patients without such lesions. These findings sustain the idea of 2 lacunar stroke entities.

Key Words: arterioli • arteriolosclerosis • lacunar infarction • prognosis • small-vessel disease

Lacunar infarcts are caused mainly by small-vessel disease occluding a small perforating artery. At autopsy, Fisher1 distinguished 2 types of underlying vascular pathology: lipohyalinosis and microatheromatosis. Lipohyalinosis was present mainly in patients who had hypertension during life, whereas the lacunes Fisher found were small, multiple, and asymptomatic. Microatheromatosis was found mainly in patients with single, larger, symptomatic lacunes. Periventricular white-matter hypodensities on CT, or so-called leukoaraiosis (LA), is also caused by lipohyalinosis of white matter perforating small arteries.2 LA has also been associated with hypertension.3 Earlier, we found that lacunar stroke patients with ≥1 asymptomatic lacunar infarcts on CT had LA and hypertension significantly more often than patients without asymptomatic small deep infarcts.4 Moreover, we found that the symptomatic lacunar infarcts were larger than the asymptomatic ones. These data concurred with Fisher’s pathological findings. From these data, we hypothesized that the 2 types of underlying small-vessel pathology (lipohyalinosis and microatheromatosis) could be distinguished during life and that hypertension, especially severe hypertension, is more strongly related to lipohyalinosis.4 Pathological studies suggested that the term “arteriolosclerosis” would be more appropriate than lipohyalinosis, although the reasons behind this preference differed between studies.2,5

Results from clinical studies,6,7 studies on cerebrovascular reactivity5,8,9 or cerebral blood flow,10,11 and studies in neurologically normal people12,13 concur with our hypothesis. Further evidence that a similar small-vessel vasculopathy underlies both LA and multiple small deep infarcts came from a follow-up CT study that showed marked progression of both phenomena, mainly in lacunar stroke patients.14 Two other studies also showed progression of white-matter lesions in lacunar stroke.15,16 Some investigators found no evidence in favor of the hypothesis on 2 different types of lacunar strokes17,18 or stated earlier that similar underlying pathology in silent lacunar stroke and LA remains unclear.19 It is unknown how lesion progression influences prognosis after a first lacunar stroke. If patients with a single symptomatic lacunar stroke would have better prognosis over time than those with concomitant silent lacunar lesions, this would provide further arguments in favor of 2 distinct types of...
lacunar stroke. To test this hypothesis, we performed a follow-up study in 339 patients with first lacunar stroke.

Patients and Methods

Patients were registered in the Maastricht Stroke Registry, which is a prospective registry at the University Hospital of Maastricht of all stroke patients >18 years of age with symptoms lasting >24 hours. Patients were registered prospectively and consecutively between July 1987 and March 1992. Last follow-up was completed in May 1995.

All patients were examined as soon as possible after admission or at the first outpatient clinic visit. Routine investigations included standard blood and urine analyses, a 12-lead ECG, a chest X-ray, ultrasound studies, and a cerebral CT scan or MRI. At the time of patient inclusion in this study, MRI was not available for regular use, so neuroimaging data were based on CT. Echocardiography, 24-hour (Holter) monitoring, and cerebral angiography were performed in selected patients. Data were registered on standard forms.

Lacunar infarct was defined as an acute stroke syndrome with a CT lesion compatible with the occlusion of a single perforating artery, consisting of a subcortical (basal ganglia, internal capsule, brainstem), small, sharply demarcated hypodense lesion with a diameter <15 mm. If no such lesion was visible or if no CT was performed, we used the established criteria of unilateral motor and/or sensory signs that involved the whole of at least 2 of the 3 body parts (face, arm, leg) without disturbance of consciousness, visual fields, language, or other cortical functions. We distinguished 4 lacunar syndromes: pure motor stroke, sensorimotor stroke, pure sensory stroke, and atactic hemiparesis/dysarthria clumsy hand syndrome.20

Two neurologists with knowledge of the type and likely site of stroke but who were blinded for outcome data examined the CT scans separately and independently, as described earlier.4 In case of disagreement, we tried to reach consensus by argument. If consensus could not be obtained, CT was considered negative for that particular item. A silent brain infarct was defined as described elsewhere.21 We distinguished patients with ≥1 asymptomatic lacunar lesions on CT (LACI+) from patients without such lesions (LACI−). To contrast both types further, we compared lacunar patients with at least 1 asymptomatic lacunar lesions and LA (LACI+/+) versus patients with neither of these features (LACI−/−).

In addition to age and sex, the following vascular risk factors were recorded: hypertension (known hypertension, treated or not, or at least 2 blood pressure recordings >160/90 mm Hg before stroke or >1 week after stroke), diabetes mellitus (DM; known diabetes, treated or not; fasting serum glucose >7 mmol/L; or a postprandial level >11 mmol/L on at least 2 separate occasions before or at least 3 days after stroke), ischemic heart disease (known or treated angina pectoris, the presence of an old (>6 weeks) myocardial infarction, or typical ECG changes), and old arterial wall disease (a diameter reduction of >50% of the ipsilateral internal carotid artery documented on noninvasive investigation with ultrasound or angiography). Handicap was assessed with the modified Rankin score.22 We also used the modified Rankin score to measure initial stroke severity. Although we realized that the Rankin scale was not designed to measure the degree of functional handicap in the acute stroke phase, we decided to use this scale because of its familiarity and convenience in application. We dichotomized the Rankin score into 2 categories, functionally independent (Rankin score of 0, 1, 2, or 3) and functionally dependent (Rankin score of 4 or 5).

Statistical Analysis

For both lacunar subtypes, we calculated and compared baseline characteristics (univariate analysis, χ², odds ratio (OR) with 95% confidence interval (CI)). Using the same tests, we compared 30-day, 1-year, and total mortality: 30-day, 1-year, and total stroke recurrence; and ultimate functional outcome between stroke subtypes. Some associations were tested with multivariate logistic regression analysis. Cox regression analyses for survival and stroke recurrence were done with lacunar subtype added to the standard model; later, LA was added to look for significant predictors in a time-dependent analysis. We constructed Kaplan-Meier curves for survival and for survival free of recurrent stroke with lacunar subtype as the different strata and with log-rank tests for significance. For the comparison of recurrent stroke subtypes, we used univariate χ² analysis.

Results

Of the 339 lacunar strokes, 6 had no CT at the time of first stroke and were left out of the analysis. Of the 333 remaining LACI, 104 had at least 1 symptomatic, small, deep ischemic lesion on CT, and these were compared with the 229 without such lesions. Hypertension was more frequent in the LACI+ group, but this difference was not statistically significant (49% and 39%, respectively; OR, 1.46; 95% CI, 0.88 to 2.41). LA was highly statistically significant more frequent among LACI+ than LACI− (61% and 14%, respectively; OR, 9.13; 95% CI, 5.48 to 15.21; P<0.001). The remaining characteristics did not differ between groups. A logistic regression analysis
LACI/H11001. Log-rank, 5.26; \( P = 2.08; 95\% \text{ CI}, 1.12 \text{ to } 3.88; \) statistically significant. Cox regression detected DM (OR, \( P = 95\% \text{ CI}, 3.14 \text{ to } 11.06; \)) follow-up (Table 1). Cox regression showed age (OR, 5.94; \( P = 95\% \text{ CI}, 1.00 \text{ to } 2.61; \) \( P = 0.05 \)) to be independent predictors of death, whereas LACI+ versus LACI− (OR, 1.40; 95% CI, 0.89 to 2.18) and LA (OR, 1.74; 95% CI, 0.72 to 2.15) were not. As the Kaplan-Meier survival curves in Figure 1 show, LACI+ had less favorable survival than LACI− (log-rank test, \( P = 0.0218 \)).

### Mortality

More patients in the LACI+ group had died at the end of follow-up (Table 1). Cox regression showed age (OR, 5.94; 95% CI, 3.14 to 11.06; \( P < 0.0001 \)) and DM (OR, 1.62; 95% CI, 1.00 to 2.61; \( P = 0.05 \)) to be independent predictors of death, whereas LACI+ versus LACI− (OR, 1.40; 95% CI, 0.89 to 2.18) and LA (OR, 1.74; 95% CI, 0.72 to 2.15) were not. As the Kaplan-Meier survival curves in Figure 1 show, LACI+ had less favorable survival than LACI− (log-rank test, \( P = 0.0218 \)).

### Recurrent Stroke

There were twice the number of recurrent strokes in the LACI+ group (Table 1) at the end of follow-up. Although the point estimate of the OR for 30-day stroke recurrence rate in LACI+ versus LACI− was 4.08, the difference was not statistically significant. Cox regression detected DM (OR, 2.08; 95% CI, 1.12 to 3.88; \( P = 0.021 \)) and LACI+ versus LACI− (OR, 1.94; 95% CI, 1.08 to 3.48; \( P = 0.025 \)) as independent predictors of stroke recurrence. Six recurrent strokes were intracranial hemorrhages, and 5 of these occurred in the LACI+ group, constituting a quarter of all recurrences in this group, whereas only 4% of recurrences were hemorrhages in the LACI− group (Table 2). Of the 14 nonlacunar recurrent infarcts, 9 occurred in the LACI− group. Kaplan-Meier curves of survival free of recurrent stroke are shown in Figure 2. LACI+ had less favorable survival free of stroke than LACI− (log-rank test, \( P = 0.0121 \)).

### Functional Outcome at the End of Follow-Up

LACI+ survivors had worse functional outcome (Rankin, 4 or 5), but this was not statistically significant (Table 1). Prognosis for major handicap or death (Rankin, 4 through 6) was significantly more unfavorable for LACI+. In a separate logistic regression analysis with a Rankin score of 4 through 6 as an end of follow-up outcome measure and with sex, age, DM, ischemic heart disease, hypertension, and LA in the regression model, age (OR, 8.85; 95% CI, 4.39 to 17.84; \( P < 0.0001 \)), DM (OR, 2.33; 95% CI, 1.21 to 4.14; \( P = 0.004 \)), and LA (OR, 3.02; 95% CI, 1.95 to 5.75; \( P = 0.0008 \)) were independent predictors.

### Restricted Analysis of LACI+/+ and LACI−/−

There were 63 LACI+/+ and 196 LACI−/−, 19% and 59% of all 333 LACIs, respectively. Hypertension (OR, 2.21; 95% CI, 1.18 to 4.15) and age (age group 2 versus 1: OR, 2.25; 95% CI, 1.06 to 4.77; age group 3 versus 1: OR, 6.81; 95% CI, 3.09 to 15.03) were associated with LACI+/+ in a logistic regression analysis. At the end of follow-up, there were 27 deaths (43%) and 7 severely handicapped patients (11%) in the LACI+/+ group and 37 deaths (19%) and 4 severely handicapped patients (2%) in the LACI−/− group (OR, 5.79; 95% CI, 1.60 to 20.95; and OR, 3.22; 95% CI, 1.73 to 6.02, respectively).

There were 16 (stroke recurrences, 25%) in the LACI+/+ group (LACI, 6; atherothrombotic, 5; primary intracerebral

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**TABLE 1. Mortality and Stroke Recurrence Rates at 30 Days and 1 Year and Functional Outcome at the End of Follow-up in LACI+ Versus LACI−**

<table>
<thead>
<tr>
<th></th>
<th>LACI+, n (%)</th>
<th>LACI−, n (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>1 (1)</td>
<td>5 (2)</td>
<td>0.43</td>
<td>0.00–58.97</td>
</tr>
<tr>
<td>1 y</td>
<td>15 (14)</td>
<td>28 (12)</td>
<td>1.09</td>
<td>0.11–10.53</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>34 (33)</td>
<td>50 (22)</td>
<td>1.74</td>
<td>1.01–3.01†</td>
</tr>
<tr>
<td><strong>Stroke recurrence rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>2 (2)</td>
<td>1 (0.5)</td>
<td>4.08</td>
<td>0.05–347.0</td>
</tr>
<tr>
<td>1 y</td>
<td>9 (11)</td>
<td>11 (6)</td>
<td>1.71</td>
<td>0.54–5.38</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>22 (21)</td>
<td>26 (11)</td>
<td>2.09</td>
<td>1.08–4.06†</td>
</tr>
<tr>
<td><strong>Unfavorable outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin score, 4 or 5 (n=70 and 159, respectively)</td>
<td>8 (11)</td>
<td>9 (5)</td>
<td>2.31</td>
<td>0.72–7.40</td>
</tr>
<tr>
<td>Rankin score, 4 through 6</td>
<td>42 (40)</td>
<td>59 (26)</td>
<td>1.95</td>
<td>1.17–3.26†</td>
</tr>
</tbody>
</table>

*Censored for follow-up <30 d.
†Significant difference.
‡Censored for follow-up <1 y.

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**Figure 1.** Kaplan-Meier survival in days. Top, LACI−, bottom, LACI+. Log-rank, 5.26; \( P = 0.0218 \).

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hemorrhage, 5) and 19 (10%) in the LACI−/− group (LACI, 9; atherothrombotic, 4; primary intracerebral hemorrhage, 1; cardioembolism, 3; undetermined, 2) (OR, 3.17; 95% CI, 1.48 to 6.81). Notice that 5 of the 6 PICH occurred in the LACI+/+ group, which constitutes almost one third of stroke recurrences in this subgroup. DM (OR, 2.31; 95% CI, 1.12 to 4.78) and LACI+/+ type (OR, 2.78; 95% CI, 1.33 to 5.83) were significantly associated with recurrent stroke in the Cox analysis. The time interval between the first and recurrent stroke was longer in the LACI+/+ group (mean, 495 days) than in the LACI−/− type (mean, 340 days).

**Discussion**

In this rather large, well-defined group of lacunar stroke patients, we found hypertension and LA to be associated with lacunar stroke with ≥1 silent, deep, small ischemic lesions on CT. This finding concurs with that from our initial, smaller series.4 Pathological studies found that medullary small-vessel arteriolosclerosis was the underlying vasculopathy in LA.2,5 Therefore, we hypothesized that small-vessel arteriolosclerosis may be the main underlying vasculopathy in lacunar stroke patients with concomitant small, deep, silent lesions, with hypertension as a major risk factor, perhaps with more severe hypertension being even more important.4 Some authors found no evidence in favor of this hypothesis, but their study design did not allow reliable conclusions in this respect.17,18 Others, however, sustained the idea of 2 different types of lacunar stroke.6–8,10,12,13 A CT follow-up study supported the hypothesis and showed that lesions progressed over time despite customary secondary stroke prevention treatment.14 In contrast to our findings, Corea et al14 did not detect a relationship between the presence of silent lesions and prognosis, but their series was almost 5 times smaller than ours.

Our present results add evidence to the idea of 2 different lacunar stroke types because prognosis differed between the 2 groups, with a more unfavorable prognosis for the patients with ≥1 silent lesions on CT. The difference in prognosis was even more pronounced when we contrasted the groups more sharply by comparing LACI+/+ patients with LACI−/− patients. Therefore, because risk factors differ, the associations with LA differ, lesion progression differs, and prognoses differ, one may well speak of 2 lacunar stroke entities with different underlying vasculopathies: small-vessel arteriolosclerosis in most patients with a single symptomatic lacunar stroke and arteriolosclerosis in those with ≥1 silent lacunar lesions. Arteriolosclerosis is also the most frequent underlying vasculopathy in primary intracerebral hemorrhage, with hypertension being the most significant risk factor.25,26 Lacunar infarction and hypertension are predictors of primary intracerebral hemorrhage, whereas white-matter lesions are also related to primary intracerebral hemorrhage.27 Samuelsson et al28 found 15% of stroke recurrences in first lacunar infarction to be hemorrhage. The fact that one quarter of all recurrent strokes in our patients with ≥1 silent lesions and one third of the more selected group were primary intracerebral hemorrhage further sustains the idea of arteriolosclerosis as the underlying vasculopathy in those patients.

Earlier, we found that most first-ever symptomatic lacunar infarcts are located in the area supplied by the anterior choroidal artery, whereas most asymptomatic lesions were located in the area supplied by the lenticulostriate penetrating.4,29 Besides being heterogeneous in terms of the pathological vessel wall reaction to hypertension, these 2 different vascular systems differ in susceptibility to hypertension: More severe hypertension may be required for the development of arteriolosclerosis. Absence of diminished nocturnal blood pressure dipping may play a role because it was related to the presence of LA.30,31 This, however, remains for further study. Another possibility is that severe hypertension and cerebral arteriolosclerosis have a common, still unknown, cause.

It is obvious that the 2 types of lacunar stroke are not mutually exclusive. More than 1 pathophysiological mechanism may be present in the various ischemic stroke subtypes.32 Cupini et al33 recently found a strong link between impaired cerebrovascular reactivity and the presence of silent subcortical infarcts, which points to a role of hemodynamic factors in this patient group. Hypertension is an especially important primary or attributing risk factor for stroke in general.

**Figure 2.** Kaplan-Meier survival free of stroke in days. Top, LACI−, bottom, LACI+. Log-rank, 6.30; P = 0.0121.

**Table 2.** Recurrent Stroke Type in the Lacunar Subtypes at End of Follow-Up

<table>
<thead>
<tr>
<th>Recurrent Stroke Type</th>
<th>LACI+, n (%)</th>
<th>LACI−, n (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar</td>
<td>12 (55)</td>
<td>14 (58)</td>
<td>1.03</td>
<td>0.82–1.29</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>4 (18)</td>
<td>6 (25)</td>
<td>0.74</td>
<td>0.00–7.03</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>1 (5)</td>
<td>3 (13)</td>
<td>0.12</td>
<td>0.00–10.40</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>5 (23)</td>
<td>1 (4)</td>
<td>7.35</td>
<td>0.57–94.27</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0</td>
<td>2 (8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Undetermined were not included in the analysis.
Trying to distinguish different ischemic stroke subgroups is more than just epidemiological hair splitting. Pinpointing well-defined separate stroke entities may facilitate research into the underlying causes of the disease on a cell-molecular level. Although various genetic abnormalities that increase the risk of stroke are known, the molecular basis of atherosclerotic cerebrovascular disease in general remains elusive. In addition, the screening of measurable genomic polymorphisms has so far not led to a substantial increase in insight into the cell-biological abnormalities underlying the disease. The “lumping side” of the spectrum of how to study diseases has led to considerable insight into the pathogenesis and treatment possibilities of stroke. The “splitting side” may just be a timely, additional route to follow to obtain further insights into the basic abnormalities underlying ischemic brain infarction.

References

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