A Dark Side of Subcortical Diffusion-Weighted Lesions?
Characteristics, Cause, and Outcome in Large Subcortical Infarction:
The Bergen Norwegian Stroke Cooperation Study

Christopher Elnan Kvistad, MD; Halvor Oygarden, MD; Nicola Logallo, MD, PhD; Gunnar Moen, MD; Lars Thomassen, MD, PhD; Ulrike Waje-Andreassen, MD, PhD; Halvor Naess, MD, PhD

Background and Purpose—Diffusion-weighted imaging (DWI) is highly accurate in identifying and locating ischemic stroke injury. Few studies using DWI have investigated large subcortical infarctions (LSIs). We aimed to study clinical characteristics, cause, and outcome in patients with ischemic stroke with LSI diagnosed on DWI and compare these with those who had lacunar DWI lesions or DWI lesions located elsewhere.

Methods—Patients with stroke admitted between February 2006 and July 2013 were prospectively registered in a stroke database and examined with DWI. Patients with DWI lesions classified as LSI (subcortical, ≥15 mm) were compared with those with lacunar lesions (subcortical, <15 mm, lacunar infarction [LIs]), cortical lesions (cortical infarction [CIs]), or no LSI, which included LIs, CIs, mixed cortical–subcortical, cerebellar, brain stem, and combined lesion locations.

Results—A total of 1886 patients with ischemic stroke were included, of which 128 patients (6.8%) had LSI, 317 (16.8%) LIs, and 544 (28.8%) CI. The no LSI group included 1758 patients. Occlusive pathology in the proximal middle cerebral artery was more frequent in patients with acute stroke with LSI. Lacunar syndrome was associated with LSI when compared with CI and no LSI. Unknown cause was frequent in the LSI group (60.4%) and independently associated with LSI in the LSI versus LI (P<0.001), LSI versus CI (P=0.002), and LSI versus no LSI population (P<0.001). LSI was independently associated with unfavorable outcome, whether compared with LI (P=0.002), CI (P<0.001), or no LSI (P=0.002).

Conclusions—LSI is associated with distinct clinical characteristics, unknown cause, and unfavorable outcome, which separates this stroke entity from patients with lacunar subcortical DWI lesions or DWI lesions located elsewhere. (Stroke. 2014;45:2710-2716.)

Key Words: cerebral infarction • diffusion-weighted MRI • subcortical vascular lesion

Ischemic stroke affecting subcortical regions is frequent and often occurs as small infarcts caused by small-vessel disease. This stroke subgroup named lacunar infarction (LIs) is well studied and has been associated with pre-existing diseases such as hypertension and diabetes mellitus. Most studies have shown a high rate of favorable outcome after LIs, although increasing evidence suggests a worse prognosis with time. There are, however, several patients presenting with subcortical infarction who do not fall under the category of LI. These lesions are larger than lacunar lesions and may not be caused by small-vessel disease. Our knowledge of these large subcortical infarctions (LSIs) is limited. Clinical characteristics and cause have mostly been studied in smaller series performed in the 1980s or 1990s and often without being compared with other stroke subtypes or locations. One exception was a Dutch trial, where no differences were found regarding clinical features or risk factor profiles in patients with LSIs as compared with lacunar (LIs) or cortical infarctions (CIs) diagnosed with computed tomography (CT). Because several patients with stroke are without sign of infarction on CT, stroke localization and classification may be inaccurate. Diffusion-weighted imaging (DWI) has proved to be highly sensitive and specific in detecting and locating ischemic injury and has revolutionized the concept of neuroimaging within stroke research. In this study, we aimed to identify clinical characteristics, cause, and outcome in patients with LSI on DWI and compare these with patients who had lacunar subcortical DWI lesions or lesions located elsewhere.

Methods and Patients
All patients with ischemic stroke admitted to the Stroke Unit, Department of Neurology, Haukeland University Hospital in Bergen,
Norway, between February 2006 and July 2013 were prospectively registered in a database (The Bergen Norwegian Stroke Cooperation Registry). MRI and MR angiography were in general performed <1 day after admission unless any contraindications were present. Contraindications included pacemaker, none-consenting, or unstable patient. CT angiography was performed in patients potentially eligible for recanalization treatment. Patients with DWI lesions because of ischemic stroke were included in the study after informed consent had been obtained. The study was approved by the local ethics committee. Clinical characteristics, medical history, and stroke cause were registered by a stroke neurologist <1 day after admission. Cause was determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.12 Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). NIHSS score was measured on admission, repeatedly during the first 24 hours and at discharge. NIHSS was measured by certified stroke neurologists or stroke nurses. Progressive neurological symptoms were defined as a worsening of ≥2 NIHSS points at any time within the first 24 hours after hospital admission. ΔNIHSS was defined as the difference between NIHSS on admission and at discharge. Based on presenting symptoms, patients were classified according to the Oxford Community Stroke Project classification.13 An additional retrospective analysis was performed to compare rates of the most common lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis) in patients with LSI and LI.14 Symptomatic extracranial internal carotid artery stenosis was defined as ≥70% stenosis based on percentage of area reduction at duplex ultrasonography. Outcome was defined by the modified Rankin Scale (mRS) score at day 7 or at discharge, if discharged earlier. Favorable outcome was defined as mRS 0 to 1 and good outcome as mRS 0 to 2. Patients were also scored with the Barthel Index on day 7 or at discharge, if discharged earlier.

**Statistical Analyses**

Univariate analyses were performed with clinical characteristics, cause, and outcomes where patients in the LSI group were compared with the LI group, CI group, and no LSI group. Student t test or Mann–Whitney U test was used for continuous variables when appropriate. χ² test was used for categorical variables. Logistic regression analyses were performed to identify clinical characteristics and cause associated with LSI within the 3 different patient populations: LSI versus LI, LSI versus CI, and LSI versus no LSI. Analyses were performed by stepwise backward elimination where first step included all parameters that turned out significant (P<0.05) in the univariate analyses. Logistic regression analyses were also performed with favorable outcome (mRS 0–1) versus unfavorable outcome (mRS 2–6) as dependent variable to assess the relationship between LSI and clinical outcome within the patient populations LSI versus LI, LSI versus CI, and LSI versus no LSI. Analyses were performed by stepwise backward elimination where potential confounders for favorable or unfavorable outcome were included in first step analyses. Age and sex were forced into each regression analysis to adjust for these potentially confounding factors.

**Results**

In total, 2412 patients had ischemic stroke during the study period. MRI was performed in 1979 (82.1%) of these patients. Patients without MRI examination were older (79.4 versus 69.0 years; P<0.001), had higher NIHSS scores on admission (11.4 versus 4.9; P<0.001), and a lower proportion of favorable outcome (84 [19.4%] versus 874 [44.3%]; P<0.001). A total of 1886 patients examined with MRI had DWI lesions and were included in the study.

There were 128 patients (6.8%) with LSI, 317 (16.8%) with LI, 544 (28.8%) with CI, 484 (25.7%) with mixed cortical–subcortical infarction, 98 (5.2%) with cerebellar infarction, 136 (7.2%) with brain stem infarction, and 179 (9.5%) with a combination of >1 infarct location. Accordingly, 128 patients were included in the LSI group, 317 in the LI group, 588 in the CI group, and 1758 in the no LSI group. In patients with LSI, 61 patients (47.7%) had DWI lesions in lenticulostriate territory, 29 (22.7%) in anterior choroidal artery territory, 8 (6.3%) in thalamic territory, and 30 (23.4%) in white matter medullary branches territory.

**Clinical Characteristics**

Univariate analyses of clinical characteristics are presented in Table 1. Distribution of age and sex were similar between the LSI group and the other 3 groups. Prior medical history was similar between the groups, except fewer smokers (P=0.014) and more patients with atrial fibrillation (P=0.003) in the LSI group than in the LI group. Median admission stroke severity as measured by the NIHSS score was higher in patients with LSI as compared with patients with LI (P<0.001), CI (P<0.001), and no LSI (P=0.025). Higher NIHSS score on admission (odds ratio [OR], 1.13; P<0.001), clinical presentation as partial anterior circulation infarct (OR, 3.02; P<0.001), and symptomatic internal carotid artery stenosis (OR, 7.98; P=0.004) were independently associated with LSI as compared with LI (Table 2). Patients with LSI had a higher NIHSS score (OR, 1.11; P<0.001) and systolic blood pressure (OR, 1.01; P<0.001) on admission and more frequently presented as lacunar infarct (LACI; OR, 2.56, P<0.001)) when compared with patients with CI. Similarly, LSI was associated with higher NIHSS score (OR, 1.04; P=0.005) and systolic
Table 1. Univariate Analyses of Clinical Characteristics, Cause, and Outcome in Patients With Ischemic Stroke With LSI as Compared With Patients With LI, CI, and No LSI

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>LSI (n=128)</th>
<th>LI (n=317)</th>
<th>CI (n=544)</th>
<th>No LSI (n=1758)</th>
<th>P1 (LSI vs LI)</th>
<th>P2 (LSI vs CI)</th>
<th>P3 (LSI vs No LSI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>69.3 (13.0)</td>
<td>67.5 (13.7)</td>
<td>70.8 (14.1)</td>
<td>69.0 (14.7)</td>
<td>0.110</td>
<td>0.136</td>
<td>0.415</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>74 (57.8)</td>
<td>183 (57.7)</td>
<td>334 (61.4)</td>
<td>1060 (60.3)</td>
<td>0.987</td>
<td>0.455</td>
<td>0.580</td>
</tr>
<tr>
<td>Time from symptom onset to admission, min, median (IQR)</td>
<td>210 (101–1131)</td>
<td>589 (162–1291)</td>
<td>163 (90–464)</td>
<td>195 (93–754)</td>
<td>0.007</td>
<td>0.228</td>
<td>0.781</td>
</tr>
<tr>
<td>Definite time of symptom onset, %</td>
<td>66 (51.6)</td>
<td>178 (56.2)</td>
<td>348 (64.0)</td>
<td>998 (56.8)</td>
<td>0.379</td>
<td>0.009</td>
<td>0.251</td>
</tr>
<tr>
<td>Woke up with stroke, %</td>
<td>24 (18.8)</td>
<td>77 (24.3)</td>
<td>73 (13.4)</td>
<td>268 (15.2)</td>
<td>0.207</td>
<td>0.123</td>
<td>0.290</td>
</tr>
<tr>
<td>Prior functional status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Living in own residence, independent</td>
<td>120 (93.8)</td>
<td>281 (88.6)</td>
<td>489 (89.9)</td>
<td>1559 (88.7)</td>
<td>0.102</td>
<td>0.178</td>
<td>0.076</td>
</tr>
<tr>
<td>Living in own residence or nursery home, dependent</td>
<td>7 (5.5)</td>
<td>31 (9.8)</td>
<td>44 (8.1)</td>
<td>167 (9.5)</td>
<td>0.141</td>
<td>0.314</td>
<td>0.128</td>
</tr>
<tr>
<td>Prior medical history, %</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>72 (56.3)</td>
<td>168 (53.0)</td>
<td>263 (48.4)</td>
<td>897 (51.1)</td>
<td>0.533</td>
<td>0.112</td>
<td>0.261</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (12.5)</td>
<td>44 (14.0)</td>
<td>78 (14.4)</td>
<td>244 (14.0)</td>
<td>0.674</td>
<td>0.580</td>
<td>0.641</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>27 (21.1)</td>
<td>102 (32.9)</td>
<td>123 (23.3)</td>
<td>469 (28.1)</td>
<td>0.014</td>
<td>0.824</td>
<td>0.090</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27 (21.1)</td>
<td>33 (10.4)</td>
<td>156 (26.7)</td>
<td>447 (25.4)</td>
<td>0.003</td>
<td>0.083</td>
<td>0.275</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>14 (10.9)</td>
<td>18 (5.7)</td>
<td>79 (14.5)</td>
<td>230 (13.1)</td>
<td>0.052</td>
<td>0.291</td>
<td>0.485</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11 (8.6)</td>
<td>32 (10.4)</td>
<td>73 (13.6)</td>
<td>206 (11.9)</td>
<td>0.574</td>
<td>0.124</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Clinical features on presentation

| NIHSS score, median (IQR) | 4 (1–8) | 3 (1–4) | 2 (0–5) | 3 (1–6) | <0.001 | <0.001 | 0.025 |
| Progressive neurological symptoms, % | 39 (30.5) | 65 (20.5) | 70 (12.9) | 370 (21.1) | 0.025 | <0.001 | 0.013 |
| Progressive neurological symptoms in those admitted <6 h after onset, % | 15 (38.5) | 19 (27.9) | 30 (12.6) | 146 (24.5) | 0.261 | <0.001 | 0.052 |
| Systolic blood pressure, mm Hg, mean (SD) | 170.6 (28.5) | 175.4 (30.9) | 159.8 (28.9) | 163.6 (29.6) | 0.066 | <0.001 | 0.005 |
| Diastolic blood pressure, mm Hg, mean (SD) | 89.4 (16.9) | 92.8 (18.8) | 86.2 (17.3) | 86.9 (17.8) | 0.039 | 0.030 | 0.059 |

OCSP, %

| TACI | 16 (12.5) | 1 (0.3) | 30 (5.5) | 207 (11.8) | <0.001 | 0.005 | 0.806 |
| PACI | 59 (46.1) | 73 (23.0) | 358 (65.8) | 731 (41.6) | <0.001 | <0.001 | 0.318 |
| LACI | 45 (35.2) | 200 (63.1) | 95 (17.5) | 402 (22.9) | <0.001 | <0.001 | 0.002 |
| POCI | 8 (6.3) | 42 (13.3) | 60 (11.0) | 412 (23.4) | 0.034 | 0.107 | <0.001 |

Intracranial occlusions and recanalization, %

| Performed CT angiography on admission | 46 (35.9) | 63 (19.9) | 187 (34.5) | 564 (32.2) | <0.001 | 0.759 | 0.377 |
| Complete M1 occlusion | 8 (17.4) | 0 (0) | 7 (3.7) | 68 (12.1) | 0.001 | 0.001 | 0.292 |
| Partial M1 occlusion | 10 (21.7) | 1 (1.6) | 8 (4.3) | 29 (5.1) | 0.001 | <0.001 | <0.001 |
| Complete/partial M1 occlusion | 18 (39.1) | 1 (1.6) | 15 (7.9) | 97 (17.1) | <0.001 | <0.001 | <0.001 |
| Performed MR angiography on d 1 | 121 (94.5) | 290 (91.8) | 492 (90.4) | 1571 (89.4) | 0.315 | 0.141 | 0.065 |
| Complete recanalization after complete M1 occlusion | 2 (25.0) | 0 | 6 (85.7) | 24 (37.5) | N/A | 0.019 | 0.488 |
| Complete recanalization after partial/complete M1 occlusion | 5 (27.8) | 0 | 8 (53.3) | 33 (35.9) | 0.539 | 0.135 | 0.509 |

(Continued)
blood pressure (OR, 1.01; P=0.042) on admission and clinical presentation as LACI (OR, 1.89; P=0.002) when compared with patients with no LSI.

CT angiography on admission was performed in 46 (35.9%) patients with LSI, of which 27 (58.7%) had normal findings, 8 (17.4%) had complete M1 occlusion, 10 (21.7%) had partial M1 occlusion, and 1 (2.2%) had complete M2 occlusion (Table 1). Occlusive pathology in M1 (complete or partial occlusion) was more frequent in patients with LSI (18; 39.1%) as compared with those with LI (1 [1.6%]; P<0.001), CI (15 [7.9%]; P<0.001), or no LSI (97 [17.1%]; P<0.001). The rate of recanalization on MR angiography in patients with complete M1 occlusion was lower in patients with LSI as compared with patients with CI (P=0.019).

**Cause**

More patients in the LSI group (17; 13.3%) had large artery disease as compared with the LI group (5 [1.6%]; P<0.001; Table 1). Cardioembolism was also more frequent in patients with LSI (30; 23.4%) than in patients with LI (13 [4.1%]; P<0.001), yet less frequent than in patients with CI (206 [37.9%]; P=0.002).

A total of 78 patients (60.9%) had unknown stroke cause in the LSI group, which was higher than the proportion in the LI (104 [32.8%]; P<0.001), CI (231 [42.5%]; P<0.001), and no LSI group (672 [38.2%]; P<0.001). There were no differences in proportions of large artery disease (P=0.554), cardioembolism (P=0.103), or unknown cause (P=0.238) among the different territories in patients with LSI. Cause with TOAST classification was similar in patients with LSI and occlusive pathology versus LSI and no occlusive pathology, except a borderline significant increase of large-vessel disease in patients with occlusion (5 [27.8%] versus 12 [10.9%]; P=0.051).

Unknown cause was independently associated with LSI in the LSI versus LI (OR, 3.75; P=0.001), LSI versus CI (OR, 1.95; P=0.002), and LSI versus no LSI population (OR, 2.69; P<0.001; Table 2).

**Outcome**

Progressive neurological symptoms was more frequent in patients with LSI (39 [30.5%]) as compared with patients with LI (65 [20.5%]; P=0.025), CI (70 [12.9%]; P=0.001), and no LSI (370 [21.1%; P=0.013; Table 1). LSI was independently associated with unfavorable outcome when adjusted for confounders in the LSI versus LI (OR, 2.31; P=0.002), LSI versus CI (OR, 4.33; P=0.001), and LSI versus no LSI (OR, 2.08; P=0.002) population (Table 3). Unfavorable outcome was particularly high in patients with LSI and DWI lesions in anterior choroidal artery territory. A total of 27 patients (93.1%) in this group had unfavorable outcome as compared with 44 (72.1%) in lenticulostriate territory, 4 (50.0%) in thalamic territory, and 16 (53.3%) in white matter medullary branches territory (P=0.004).

**Discussion**

Prior studies of LSI have mainly used CT for infarct localization without having compared LSI with other stroke subtypes or locations.3-6 In our study, all patients included were

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**Table 1. Continued**

<table>
<thead>
<tr>
<th>Ultrasound ICA, %</th>
<th>LSI (n=128)</th>
<th>LI (n=317)</th>
<th>CI (n=544)</th>
<th>No LSI (n=1758)</th>
<th>P1 (LSI vs LI)</th>
<th>P2 (LSI vs CI)</th>
<th>P3 (LSI vs No LSI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70% symptomatic stenosis</td>
<td>10 (8.3)</td>
<td>3 (1.0)</td>
<td>45 (9.0)</td>
<td>146 (9.3)</td>
<td>&lt;0.001</td>
<td>0.827</td>
<td>0.726</td>
</tr>
<tr>
<td>Trombolytic treatment, %</td>
<td></td>
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<tr>
<td>IV-tPA</td>
<td>17 (13.3)</td>
<td>22 (6.9)</td>
<td>107 (19.7)</td>
<td>304 (17.3)</td>
<td>0.032</td>
<td>0.094</td>
<td>0.243</td>
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<tr>
<td>Cause by TOAST, %</td>
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</tr>
<tr>
<td>Large artery</td>
<td>17 (13.3)</td>
<td>5 (1.6)</td>
<td>89 (16.4)</td>
<td>228 (13.0)</td>
<td>&lt;0.001</td>
<td>0.371</td>
<td>0.919</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>30 (23.4)</td>
<td>13 (4.1)</td>
<td>260 (37.9)</td>
<td>545 (31.0)</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.073</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>1 (0.8)</td>
<td>193 (60.9)</td>
<td>1 (0.2)</td>
<td>253 (14.4)</td>
<td>&lt;0.001</td>
<td>0.264</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.6)</td>
<td>1 (0.3)</td>
<td>16 (2.9)</td>
<td>54 (3.1)</td>
<td>0.146</td>
<td>0.385</td>
<td>0.331</td>
</tr>
<tr>
<td>Unknown</td>
<td>78 (60.9)</td>
<td>104 (32.8)</td>
<td>231 (42.5)</td>
<td>672 (38.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Outcome</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–1, %</td>
<td>37 (28.9)</td>
<td>166 (52.4)</td>
<td>331 (60.9)</td>
<td>776 (44.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>mRS 0–2, %</td>
<td>65 (50.8)</td>
<td>244 (77.0)</td>
<td>433 (79.6)</td>
<td>1148 (65.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>NIHSS at discharge, median (IQR)</td>
<td>3 (1–7)</td>
<td>1 (0–3)</td>
<td>1 (0–2)</td>
<td>2 (0–5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔNIHSS improvement at admission and discharge, median (IQR)</td>
<td>0 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>1 (0–2)</td>
<td>0.175</td>
<td>0.015</td>
<td>0.116</td>
</tr>
<tr>
<td>Barthel score at discharge, median (SD)</td>
<td>75.3 (30.4)</td>
<td>90.6 (19.5)</td>
<td>91.5 (20.6)</td>
<td>82.3 (29.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
</tbody>
</table>

CI indicates cortical infarction; CT, computed tomography; ICA, internal carotid artery; IQR, interquartile range; IV-tPA, intravenous tissue-type plasminogen activator; LACI, lacunar infarct; LI, lacunar infarction; LSI, large subcortical infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; no LSI, all infarctions except LSI; OCSP, Oxford Community Stroke Project; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.
examined with DWI. We showed that patients with LSI differed from patients with lacunar subcortical DWI lesions or patients with DWI lesions located elsewhere as to clinical characteristics, cause, and outcome, emphasizing the distinctive features of this specific ischemic stroke subtype.

There were several clinical characteristics associated with LSI, such as neurological worsening. Prior studies have reported that 20% to 30% of patients with lacunar stroke experience neurological worsening within the first hours or days after stroke onset.16,17 The exact pathophysiology behind this mechanism is uncertain, but explanations based on hemodynamic factors, inflammation, and extension of thrombosis have been proposed.18 Our study may add new insights into this phenomenon because neurological worsening was more frequent in patients with LSI as compared with the other groups, including LI. Because major occlusion seems to be a frequent cause of LSI, this could suggest that neurological worsening may be because of other mechanisms than those directly associated with lacunar stroke.

Clinical presentation of patients with LSI as classified by the Oxford Community Stroke Project scale also differed from the other groups. Oxford Community Stroke Project is a widely used stroke classification system, which categorizes neurological deficits into 4 different stroke syndromes and may assist in predicting arterial occlusion location and clinical outcome.19,20 Our study showed that LSI was associated with LACI when compared with patients with CI or no LSI, and partial anterior circulation infarct when compared with patients with LI. This is in line with another study that showed that ≈16% of those with lacunar syndrome did not have LI. A high proportion of these patients had atherotrombotic or cardioembolic infarction, indicating that lacunar syndromes could be caused by more extensive nonlacunar infarctions, such as LSI.21 In concordance with a prior study, we found a lower rate of pure sensory stroke in LSI as compared with LI.22 Nevertheless, our findings indicate that several patients presenting with LACI have larger subcortical lesions and not lacunar lesions, which often is caused by small-vessel disease. This highlights the importance of performing DWI in patients presenting with LACI.

Our study showed that a majority of patients with LSI either had normal CT angiography findings on admission or occlusive pathology in the proximal middle cerebral artery. The high rate of normal angiographic findings may suggest that several patients with LSI experience recanalization before admission. Alternatively, it suggests that LSI may occur because of other mechanisms than major occlusions, similar to the pathophysiology behind smaller LIs such as in situ atheroma or lipohyalinosis.2,23 However, the high frequency of middle cerebral artery occlusions in patients with LSI suggests other contributing mechanisms than that of lacunar stroke. These findings are also in conformity with prior transcranial Doppler studies that have shown a relatively high frequency of middle cerebral artery occlusions in patients with large striatocapsular infarctions.3,8 Our study showed that complete recanalization on day one was achieved in relatively few patients with LSI with middle cerebral artery occlusion. This is in contrast to another study that showed that persistent middle cerebral artery occlusion frequently leads to CI.24 A developed collateral circulation may have prevented CI in our patients with LSI and middle cerebral artery occlusion.

Stroke cause is important because different causes are treated differently for secondary stroke prevention.25 In our study, large artery disease, cardioembolism, and unknown stroke cause were more frequent in LSI than in LI, showing that larger subcortical lesions may have other causes than smaller lacunar lesions. More than half of the patients with LSI had unknown stroke cause, and LSI was also associated with unknown stroke cause when compared with CI and no LSI. These findings are in concordance with another study that investigated the association of DWI lesion patterns with TOAST stroke subtypes.26 The authors reported that nearly half (11 of 23) of the patients with large subcortical lesions were classified with an unknown TOAST cause. As in our study, a possible explanation may be that several of these patients actually may have had small-vessel disease. However, as the definition of this specific TOAST subtype has a cutoff size limit of <15 mm, they cannot be defined as small-vessel disease by using the TOAST classification. Recent studies have, however, questioned the validity of using a 15-mm limit in DWI lesions, because the original TOAST classification lesions were based on CT findings and not DWI.26-28

### Table 2. Relationship Between LSI and Clinical Characteristics in Logistic Regression Analyses Among Different Patient Populations (LSI vs LI, LSI vs CI, and LSI vs No LSI)

<table>
<thead>
<tr>
<th>LSI vs LI (n=445)</th>
<th>OR</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
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<td>Sex</td>
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<td>0.62–1.74</td>
<td>0.888</td>
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<tr>
<td>NIHSS on admission</td>
<td>1.13</td>
<td>1.06–1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic ICA stenosis ≥70%</td>
<td>7.98</td>
<td>1.92–33.11</td>
<td>0.004</td>
</tr>
<tr>
<td>PACI</td>
<td>3.02</td>
<td>1.82–5.01</td>
<td>&lt;0.001</td>
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<tr>
<td>Unknown stroke cause</td>
<td>3.75</td>
<td>2.28–6.18</td>
<td>&lt;0.001</td>
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<table>
<thead>
<tr>
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<th>95% Confidence Interval</th>
<th>P Value</th>
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<td>0.96–0.99</td>
<td>0.007</td>
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<tr>
<td>Sex</td>
<td>1.07</td>
<td>0.69–1.64</td>
<td>0.776</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td>1.11</td>
<td>1.07–1.16</td>
<td>&lt;0.001</td>
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<td>Systolic BP on admission</td>
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<table>
<thead>
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<th>LSI vs no LSI (n=1886)</th>
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<td>Sex</td>
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<tr>
<td>Unknown cause</td>
<td>2.69</td>
<td>1.84–3.94</td>
<td>&lt;0.001</td>
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</table>

For stepwise backward selection procedure, see Table I in the online-only Data Supplement. BP indicates blood pressure; CI, cortical infarction; ICA, internal carotid artery; LACI, lacunar infarct; LI, lacunar infarction; LSI, large subcortical infarction; NIHSS, National Institutes of Health Stroke Scale; no LSI, all infarctions except LSI; OR, odds ratio; and PACI, partial anterior circulation infarct.
Our study showed an independent association between LSI and unfavorable outcome as compared with patients with LI, CI, and no LSI. In support of these findings, patients with LSI also performed worse on Barthel Index at discharge. This may partly be explained by the larger size of DWI lesions in the LSI group, resulting in increased baseline stroke severity and consequently worse outcomes. However, associations between LSI and unfavorable outcome were sustained when adjusting for initial stroke severity, indicating other contributing mechanisms as well. Such a mechanism may rely on the large number of axons concentrated in subcortical white matter tracts, including the pyramid. Large infarctions affecting these areas may thus cause worse outcomes as compared with cortical lesions of similar size. Cortical functions are spread out over larger regions, and unaffected cortical areas may compensate for damaged cortical areas.29,36 Studies have also shown an ability of perilesional reorganization in cortical lesions resulting in improved chances of recovery.31 These mechanisms may not be present in LSIs, leading to more damage caused by infarction. Prior studies have also shown an association between subcortical infarcts and focal cortical thinning with neuropsychological impairment.32–34 In theory, this could contribute to a worse long-term prognosis with cognitive decline in patients with subcortical infarcts, which may be worse in patients with larger subcortical infarcts considering the potentially larger number of disrupted axons as compared with smaller lacunar infarcts. Differences in cortical atrophy and cognitive deficits between LSI and LI could be a relevant topic for future studies.

Our findings are in contrast to 2 other studies of LSI.9,35 A Dutch trial reviewed patients with LSI of presumed non-cardioembolic origin on CT.9 Clinical features and risk factor profiles were similar in patients with LSI as compared with those with LIs or CIs. Clinical outcomes were not assessed, but stroke recurrence rates were similar. In contrast to our study, patient recruitment was limited to patients with transient ischemic attack or minor ischemic attack, and neuroimaging was performed by CT and not MRI. These factors may partly explain the different results from our study. Another study investigated outcomes of patients with LSI on MRI or CT as compared with patients with lacunar, atherothrombotic, and cardioembolic infarctions.35 Short-term outcome was worse in patients with LSI than that of LIs, but better than atherothrombotic or cardioembolic infarction. Unlike our study, patients with LSI were mainly compared with other stroke causes and not with other stroke locations.

There are some limitations in our study. We only included patients where MRI had been performed and 18% of the total ischemic stroke population registered was thus excluded. Contraindications to MRI included nonconsenting, which is more frequent in severe ischemic stroke. This is also supported by the more severe neurological deficits on admission in patients not examined with MRI. The generalizability of our results may, therefore, be limited. Second, size of DWI lesions was not measured, except subcortical DWI lesions, which were differentiated between LSI (≥15 mm) and LI (<15 mm). However, prior studies have shown a strong association between DWI lesion size and neurological deficits as measured by NIHSS on admission.29,36 We adjusted for NIHSS score on admission in all logistic regression analyses with favorable outcome as dependent variable. It, therefore, seems unlikely that patients with LSI solely had worse outcomes because of larger DWI lesions. Third, only short-term outcome was registered and not outcome after 90 days. Short-term outcomes are, however, highly relevant in acute ischemic stroke, because long-term outcome also encompasses other factors such as rehabilitation and secondary infections. Short-term outcome is, therefore, more related to the stroke as such.37

Strengths of the study include stroke location classification exclusively with MR DWI and the use of prospectively included patients in a stroke registry.

In conclusion, LSI is associated with distinct clinical characteristics, unknown cause, and unfavorable outcome, which separates this stroke entity from patients with lacunar DWI lesions or DWI lesions located elsewhere.

### Sources of Funding

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### Disclosures

None.
References


A Dark Side of Subcortical Diffusion-Weighted Lesions?: Characteristics, Cause, and Outcome in Large Subcortical Infarction: The Bergen Norwegian Stroke Cooperation Study

Christopher Elnan Kvistad, Halvor Oygarden, Nicola Logallo, Gunnar Moen, Lars Thomassen, Ulrike Waje-Andreassen and Halvor Naess

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Supplemental table I: Stepwise-backwards multiple regression analysis with LSI vs. LI, CI and No-LSI as dependent variables and clinical characteristics as independent variables.

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<td>p-value</td>
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_Last step (multivariate R²=0.115)_

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_LSI vs. no-LSI, N= 1886_

_Last step (multivariate R²=0.054)_

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_Last step (multivariate R²=0.054)_

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LSI, large subcortical infarction; LI, lacunar infarction; CI, cortical infarction; AI, all infarctions (includes lacunar infarction, cortical infarction, mixed cortical- and subcortical infarction, cerebellar infarction, brain stem infarction and infarctions on multiple locations); NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; PACI, partial anterior circulation infarct; LACI, lacunar infarct; ICA, internal carotid artery.

*We did not include other etiological variables in this regression analysis due to strong association between LI and small vessel disease.*
Supplemental table II: Stepwise backwards multiple regression analysis with favorable outcome (mRS 0-1) vs. unfavorable outcome (mRS 2-6) as dependent variable among patients with LSI as compared to LI, CI and No-LSI.

<table>
<thead>
<tr>
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<td>Atrial fibrillation</td>
<td>1.15</td>
<td>0.56-2.35</td>
<td>0.708</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.47</td>
<td>0.50-2.50</td>
<td>0.156</td>
</tr>
<tr>
<td>Prior independency</td>
<td>5.20</td>
<td>1.69-16.07</td>
<td>0.004</td>
</tr>
<tr>
<td>Iv treatment with tPA</td>
<td>1.37</td>
<td>0.53-3.55</td>
<td>0.522</td>
</tr>
<tr>
<td><strong>LSI</strong></td>
<td><strong>0.46</strong></td>
<td><strong>0.27-0.78</strong></td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Last step (multivariate R²=0.231)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96</td>
<td>0.94-0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.88</td>
<td>0.55-1.40</td>
<td>0.595</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td>0.74</td>
<td>0.67-0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose on admission</td>
<td>0.90</td>
<td>0.80-1.02</td>
<td>0.096</td>
</tr>
<tr>
<td>Prior independency</td>
<td>5.53</td>
<td>1.81-16.90</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>LSI</strong></td>
<td><strong>0.43</strong></td>
<td><strong>0.26-0.73</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td><strong>LSI vs. CI, N=672</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First step (multivariate R²=0.278)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96</td>
<td>0.95-0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.78</td>
<td>0.52-1.16</td>
<td>0.219</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>0.75</td>
<td>0.70-0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose on admission</td>
<td>0.96</td>
<td>0.89-1.04</td>
<td>0.300</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.85</td>
<td>0.84-1.32</td>
<td>0.463</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.84</td>
<td>0.52-1.32</td>
<td>0.475</td>
</tr>
</tbody>
</table>
Prior independency & 4.03 & 1.89-8.61 & <0.001  
Iv treatment with tPA & 1.49 & 1.89-2.62 & 0.170  
**LSI** & **0.23** & **0.14-0.38** & **<0.001**  

**Last step (multivariate R2=0.276)**

| Age | 0.96 | 0.94-0.98 | <0.001  
| Sex | 0.81 | 0.55-1.20 | 0.297  
| NIHSS on admission | 0.76 | 0.72-0.81 | <0.001  
| Prior independency | 3.78 | 1.83-7.82 | <0.001  
| **LSI** | **0.23** | **0.14-0.38** | **<0.001**  

**LSI vs. No-LSI**  
N= 1886

**First step (multivariate R2=0.214)**

| Age | 0.98 | 0.97-0.99 | <0.001  
| Sex | 0.93 | 0.74-1.18 | 0.551  
| NIHSS score on admission | 0.75 | 0.72-0.78 | <0.001  
| Serum glucose on admission | 0.96 | 0.91-1.00 | 0.59  
| Atrial fibrillation | 1.04 | 0.78-1.38 | 0.795  
| Smoking | 0.94 | 0.73-1.21 | 0.629  
| Prior independency | 3.82 | 2.37-6.17 | <0.001  
| Iv treatment with tPA | 1.75 | 1.24-2.47 | 0.001  
| **LSI** | **0.48** | **0.30-0.75** | **0.001**  

**Last step (multivariate R2=0.223)**

| Age | 0.98 | 0.98-0.99 | <0.001  
| Sex | 0.94 | 0.75-1.18 | 0.576  
| NIHSS score on admission | 0.75 | 0.72-0.78 | <0.001  
| Serum glucose on admission | 0.95 | 0.91-1.00 | 0.045  
| Prior independency | 3.75 | 2.33-5.96 | <0.001  
| Iv treatment with tPA | 1.82 | 1.30-2.55 | <0.001  
| **LSI** | **0.48** | **0.31-0.76** | **0.002**  

**LSI**, large subcortical infarction; **LI**, lacunar infarction; **CI**, cortical infarction; **No-LSI**, all infarctions except **LSI** (includes **LI**, **CI**, mixed cortical- subcortical infarction, cerebellar infarction, brain stem infarction and infarctions on multiple locations); **Iv**, intravenous; **tPA**, tissue plasminogen activator; **mRS**, modified Rankin Scale.