Clinical Diagnosis of Lacunar Stroke in the First 6 Hours After Symptom Onset
Analysis of Data From the Glycine Antagonist In Neuroprotection (GAIN) Americas Trial

Stephen J. Phillips, MBBS; Dingwei Dai, PhD; Arnold Mitnitski, PhD; Gordon J. Gubitz, MD; Karen C. Johnston, MD; Walter J. Koroshetz, MD; Karen L. Furie, MD; Sandra Black, MD; Darell E. Heiselman, DO; on behalf of the GAIN Americas Investigators

Background and Purpose—Although the pathophysiological heterogeneity of stroke may be highly relevant to the development of acute-phase therapies, discriminating between ischemic stroke subtypes soon after onset remains a challenge. We conducted a study of the accuracy of a clinical diagnosis of lacunar stroke in the first 6 hours after symptom onset.

Methods—We analyzed data from 1367 patients in the Glycine Antagonist In Neuroprotection (GAIN) Americas trial. The Trial of ORG10172 in Acute Stroke Treatment (TOAST) category “small vessel (lacunar)” disease at day 7 or at hospital discharge was used as the reference standard to determine the accuracy of a diagnosis of a lacunar stroke made within 6 hours of symptom onset using the Oxfordshire Community Stroke Project (OCSP) classification “LACS.” Outcome was analyzed by comparing the proportions of patients classified as “LACS” at baseline or “small vessel (lacunar)” at 7 days who were dead or dependent at 3 months.

Results—The positive predictive value of an OCSP diagnosis of a lacunar stroke was 76% (95% CI: 69% to 81%; sensitivity 64% [95% CI: 58% to 70%]; specificity 96% [95% CI: 95% to 97%]; negative predictive value 93% [95% CI: 92% to 94%]; accuracy 91% [95% CI: 89% to 92%]). The 3-month outcomes of patients classified as either OCSP “LACS” within 6 hours of onset or TOAST “small vessel (lacunar)” at 7 days were not significantly different.

Conclusions—An OCSP LACS diagnosis made within 6 hours of stroke onset is reasonably predictive of a final diagnosis of “small vessel (lacunar)” disease made using TOAST criteria and has a similar relationship to outcome at 3 months. (Stroke. 2007;38:2706-2711.)

Key Words: lacunar infarction stroke assessment stroke classification stroke outcome

A n acute stroke may be described in several different ways. Although there is much contemporary interest in the use of imaging techniques such as perfusion-weighted and diffusion-weighted MRI, clinical descriptors will continue to be important because: (1) MRI is not feasible in a substantial minority of patients; (2) the narrow time window for intervention restricts the application of MRI and other time-consuming special investigations; (3) the relatively long scanning time for MRI is associated with hypoxia in medically unstable patients with severe strokes; (4) small vessel infarcts, particularly those located in the brainstem, may not be detected by diffusion-weighted MRI in the early hours after onset; and (5) MRI is not widely available.

Stroke treatments with most impact will be delivered soon after symptom onset and will be available to the majority of patients. To facilitate uptake of new treatments in clinical practice, potential interventions must be studied in the settings in which they will be used. Because most therapies under development are likely to be only modestly beneficial, clinical trials have to be large to ensure that random error (the play of chance) does not mask a true treatment effect. The requirement for treatment trials to be large, streamlined, and pragmatic highlights the need for a clinical classification of ischemic stroke that can be applied easily within the first few hours after symptom onset and which reliably distinguishes between stroke subtypes with substantially different

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From the Queen Elizabeth II Health Sciences Centre (S.J.P., G.J.G.) and the Departments of Medicine (S.J.P., A.M., G.J.G.) and Community Health and Epidemiology (D.D.), Dalhousie University, Halifax, Nova Scotia, Canada.; the University of Virginia (K.C.J.), Charlottesville, Va.; the National Institutes of Neurological Disorders and Stroke (W.J.K.), Bethesda, Md.; Massachusetts General Hospital (K.L.F.), Boston, Mass.; the University of Toronto and Sunnybrook Health Sciences Centre (S.B.), Toronto, Ontario, Canada.; and Akron General Medical Centre (D.E.H.), Akron, Ohio. Current affiliation for D.D.: Health Core Inc, Wilmington, Del. Current affiliation for D.E.H.: Cuyahoga Falls General Hospital-Summa Health Systems, Akron, Ohio.
Correspondence to Stephen J. Phillips, MBBS, Division of Neurology, Halifax Infirmary Room 3831, 1796 Summer Street, Halifax, Nova Scotia, Canada B3H 3A7. E-mail stephen.phillips@dal.ca

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outcomes. Such a classification system may be used in stratification and minimization algorithms to ensure that important prognostic factors are balanced between the treatment groups of a clinical trial.

The pathophysiological heterogeneity of ischemic stroke may be relevant to the development of acute-phase therapies because it is possible that what works for one subtype of stroke may work differently for another. Although no clinical stroke syndrome is absolutely pure with respect to pathophysiology, lacunar syndromes are the most homogeneous. Lacunar syndromes are usually due to a small subcortical infarct in the territory of a penetrating artery caused by in situ microatheroma or lipohyalinosis. Neurochemical studies suggest that subcortical ischemia may respond differently to hyperacute intervention than cortical ischemia. The Oxfordshire Community Stroke Project (OCSP) classification of ischemic stroke subtypes (including lacunar stroke [LACS]) has reasonable interrater reliability, provides information about the topography and vascular pathology of the stroke; and is reasonably predictive of death, dependency, and stroke recurrence during the first year poststroke. Although most of our knowledge of the prognostic power of the OCSP classification is derived from the original population-based study in which patients were first assessed days after stroke onset, the OCSP classification also lends itself for use within the first few hours after stroke onset because it depends only on the clinical findings and a CT scan (to exclude hemorrhage and stroke mimics).

The Trial of ORG10172 in Acute Stroke Treatment (TOAST) investigators defined criteria for distinguishing between the pathophysiological mechanisms of ischemic stroke, including “small vessel (lacunar)” disease, that have since become widely used in clinical stroke studies. The TOAST criteria are based on a combination of clinical and imaging findings and the results of ancillary investigations and so cannot be easily applied within the first few hours after stroke onset.

GAIN Americas used the OCSP and TOAST classifications, as well as other evaluation tools, to describe the trial subjects. We analyzed the GAIN Americas data to describe the relationships between these tools, focusing on the accuracy of the OCSP classification in the early diagnosis of a lacunar stroke syndrome.

Methods

Study Population
Analyses were performed on the primary efficacy (nonhemorrhagic) population (n=1367) of the GAIN Americas trial, which was a randomized, double-blind, placebo-controlled trial of gavestinel, an antagonist of the glycine site of the N-methyl-D-aspartate receptor and putative neuroprotective agent for acute ischemic stroke when administered within 6 hours after stroke onset. This substudy used data from both arms of the trial because there was no statistically significant difference in outcome between gavestinel- and placebo-treated patients. Patients were eligible for enrollment in GAIN Americas if they were aged 18 years or older, previously functionally independent, and within 6 hours after the onset of a stroke that caused a predefined level of limb weakness but no major reduction in level of consciousness. Baseline evaluation included assessment of stroke severity using the National Institutes of Health Stroke Scale.

Figure 1. Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram.
(NIHSS)²⁹ and ischemic stroke subtype according to the OCSP classification.²⁶,²⁸ Participating investigators were certified in the use of the NIHSS and oriented to the use of the OCSP at the start of the trial.

Brain imaging was performed using either CT within 18 hours of stroke onset or MRI within 6 hours. A committee of 3 independent neuroradiologists blinded to all clinical data read the scans, but the imaging findings were not linked with the neurological findings on scan. Repeat scanning was performed in the first 6 hours after stroke onset. Outcome was analyzed by comparing the proportions of patients classified as “LACS” at baseline or “small vessel (lacunar)” at 7 days who were dead or (unknown), ischemic stroke of other etiology.

Atrial fibrillation 59 (12.5) 265 (62.1) 15 (6.5) 12 (6.3) 0 2 (10.0) 0.02

Current smoker 194 (14.2) 20 (1.9) 7 (5.0) 5 (4.2–5.7) 5.0 (4.0–5.9) <0.0001

Time to treatment,* h 5.5 (4.6–5.9) 5.2 (4.4–5.8) 5.7 (5.0–5.9) 5.1 (4.2–5.7) 5.0 (4.0–5.9) <0.0001

NIHSS score* 6 (5–9) 10 (7–15) 9 (6–12) 18 (12–21) 8.5 (6–11) <0.00001

Stroke risk factors, no. (%) Hypertension 134 (69.1) 397 (67.0) 37 (78.7) 351 (69.2) 18 (69.2) 0.54

Diabetes 63 (32.5) 128 (26.1) 13 (27.7) 125 (24.7) 8 (30.8) 0.03

Atrial fibrillation 23 (11.9) 147 (24.8) 9 (19.2) 171 (33.7) 3 (11.5) <0.0001

Previous myocardial infarction 37 (19.1) 139 (23.4) 7 (14.8) 116 (22.8) 6 (23.1) 0.52

Hypercholesterolemia 62 (31.8) 193 (32.5) 18 (38.3) 135 (26.6) 5 (19.2) 0.10

Current smoker 27 (13.9) 110 (25.3) 13 (27.7) 96 (19.4) 6 (23.1) 0.17

Hypercholesterolemia 160 (34.0) 112 (26.2) 74 (32.1) 56 (29.4) 3 (10.3) 8 (40.0) 0.02

Current smoker 134 (28.5) 74 (17.3) 57 (24.8) 51 (26.8) 8 (27.6) 4 (20.0) <0.01

Heavy alcohol (>2/d) 46 (9.7) 52 (11.9) 17 (7.3) 15 (7.8) 3 (10.3) 2 (10.0) 0.32

*Data expressed as median (interquartile range). P values reflect global comparisons.

PACS indicates partial anterior circulation stroke; POCS, posterior circulation stroke; TACS, total anterior circulation stroke; Unknown, nonischemic/not stroke.

### Table 2. Baseline Characteristics of the Primary Efficacy (nonhemorrhagic) Population of the GAIN Americas Trial Described According to the TOAST Classification at 7 Days or at Discharge From the Hospital

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Large Vessel</th>
<th>Cardioembolic</th>
<th>Small Vessel</th>
<th>Infarct (unknown)</th>
<th>Infarct (other)</th>
<th>Noninfarct</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>471 (34.5)</td>
<td>427 (31.2)</td>
<td>230 (16.8)</td>
<td>190 (13.9)</td>
<td>29 (2.1)</td>
<td>20 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Age,* y</td>
<td>72 (62–78)</td>
<td>75 (67–82)</td>
<td>69 (60–77)</td>
<td>70 (57–77)</td>
<td>64 (48–79)</td>
<td>66 (60–77)</td>
<td></td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>275 (58.4)</td>
<td>196 (45.9)</td>
<td>120 (52.2)</td>
<td>96 (50.5)</td>
<td>16 (55.2)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Time to treatment,* h</td>
<td>5.1 (4.2–5.7)</td>
<td>5.2 (4.4–5.8)</td>
<td>5.5 (4.7–5.9)</td>
<td>5.2 (4.3–5.8)</td>
<td>5.2 (4.4–5.8)</td>
<td>5.1 (4.3–5.4)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score*</td>
<td>14 (9–19)</td>
<td>15 (10–19)</td>
<td>6 (5–9)</td>
<td>10 (7–16)</td>
<td>11 (7–15)</td>
<td>9 (7.5–15)</td>
<td></td>
</tr>
<tr>
<td>Stroke risk factors, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>314 (66.7)</td>
<td>315 (73.8)</td>
<td>158 (88.7)</td>
<td>123 (64.7)</td>
<td>14 (48.3)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>105 (22.3)</td>
<td>111 (26.0)</td>
<td>75 (32.6)</td>
<td>40 (21.1)</td>
<td>1 (3.4)</td>
<td>5 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>59 (12.5)</td>
<td>265 (62.1)</td>
<td>15 (6.5)</td>
<td>12 (6.3)</td>
<td>0</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>108 (22.9)</td>
<td>119 (27.8)</td>
<td>38 (16.5)</td>
<td>32 (16.8)</td>
<td>3 (10.3)</td>
<td>5 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>160 (34.0)</td>
<td>112 (26.2)</td>
<td>74 (32.1)</td>
<td>56 (29.4)</td>
<td>3 (10.3)</td>
<td>8 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>134 (28.5)</td>
<td>74 (17.3)</td>
<td>57 (24.8)</td>
<td>51 (26.8)</td>
<td>8 (27.6)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol (&gt;2/d)</td>
<td>46 (9.7)</td>
<td>24 (5.6)</td>
<td>17 (7.3)</td>
<td>15 (7.8)</td>
<td>3 (10.3)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Data expressed as median (interquartile range). P values reflect global comparisons.

Large vessel indicates large vessel atherothromboembolic; Small vessel, small vessel (lacunar); Infarct (unknown), infarct of unknown cause; Infarct (other), acute ischemic stroke of other etiology.
dependent (defined using different cut points on the MRS and BI) at 3 months. The relationship among the NIHSS, BI, and MRS at 3 months was analyzed using the Spearman rank order correlation statistic. Group characteristics were compared using parametric and nonparametric statistics, as appropriate. Confidence intervals were estimated by using the exact binomial procedure with continuity corrections. All statistical testing was performed at the 2-tailed alpha level of 0.05. The data were analyzed using SAS software (SAS Institute Inc, Version 9.1).

**Results**

Figure 1 summarizes the study in the format of a Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram. Table 1 describes the primary efficacy (nonhemorrhagic) population (n=1367) of the GAIN Americas trial according to OCSP classification at baseline. Fewer than 2% of patients were unclassified. The timing of the neurological examination was not recorded, but the median time from stroke onset to treatment was 5.2 hours. Stroke severity was greatest for total anterior circulation strokes and lowest for LACS (P<0.0001).

Table 2 describes the study population according to the TOAST classification at 7 days or at the time of discharge from the hospital. Small vessel (lacunar) strokes were the least severe (P<0.0001). The median NIHSS scores for the other TOAST subtypes differed by only 5 points.

Table 3 compares the OCSP and TOAST classifications. The positive predictive value of an OCSP diagnosis of a lacunar stroke syndrome was 76% (95% CI: 69% to 81%; sensitivity 64% [95% CI: 58% to 70%]; specificity 96% [95% CI: 95% to 97%]; negative predictive value 93% [95% CI: 92% to 94%]; accuracy 91% [95% CI: 89% to 92%]). At 3 months poststroke, there was no significant difference in the likelihood of death, dependency, or the proportion of patients living at home for patients classified as either OCSP “LACS” within 6 hours of onset or TOAST “small vessel (lacunar)” at 7 days (Table 4).

Patients with an acute LACS diagnosis not classified as small vessel (lacunar) on day 7 were equally distributed among large vessel (14 patients), cardioembolic (16 patients), and infarct of unknown cause (14 patients). Of the 230 patients with a small vessel (lacunar) TOAST diagnosis at 7 days, 83 were not diagnosed as LACS initially. The majority of these (50 patients) were called partial anterior stroke. Of the 47 patients acutely classified as posterior circulation stroke, 30% were assigned a final diagnosis of small vessel (lacunar) stroke.

Figure 2 summarizes the NIHSS, BI, and MRS scores of the patients who survived 3 months as well as the proportions living at home displayed according to OCSP subtype at baseline and TOAST subtype at 7 days (or at time of discharge from hospital). “Small vessel (lacunar)” strokes had better outcomes than the other TOAST subtypes, but the TOAST classification system did not clearly distinguish differences in outcomes between the other subtypes.

Table 4. Three-Month Outcomes of Patients Classified as OCSP ‘LACS’ or TOAST ‘Small Vessel (lacunar)’

<table>
<thead>
<tr>
<th></th>
<th>LACS (n=194)</th>
<th>Small Vessel (n=230)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead, no. (%)</td>
<td>11 (5.7)</td>
<td>15 (6.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>BI, median (IQR)</td>
<td>95 (80–100)</td>
<td>100 (85–100)</td>
<td>0.37</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>2 (0–5)</td>
<td>1.5 (0–4)</td>
<td>0.25</td>
</tr>
<tr>
<td>mRS, median (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dead or dependent (mRS &gt;1), no. (%)</td>
<td>110 (56.9)</td>
<td>124 (53.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Dead or dependent (mRS &gt;2), no. (%)</td>
<td>75 (38.7)</td>
<td>76 (33.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Dead or dependent (BI &lt;95), no. (%)</td>
<td>93 (47.9)</td>
<td>117 (50.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Dead or dependent (BI &lt;55), no. (%)</td>
<td>31 (15.9)</td>
<td>34 (14.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Residence at home, % (no./No.)</td>
<td>84.5 (153/181)</td>
<td>86.5 (180/208)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
(r = −0.75; P < 0.001) at 3 months. For each one-point increase in the MRS, the NIHSS increased by approximately 3 points. For each decile increase in the BI, the NIHSS decreased by approximately 2 points.

**Discussion**

The main findings of this study are that an OCSP LACS diagnosis made within 6 hours of stroke onset is reasonably predictive of a final diagnosis of “small vessel (lacunar)” disease made using TOAST criteria and that both diagnoses have a similar relationship to better outcome at 3 months when compared with the other ischemic stroke subtypes. We also demonstrated the overlap in 3-month MRS and BI scores for all OCSP and TOAST subtypes and quantified the correlation between the NIHSS and MRS and BI.

The 76% positive predictive value of a clinical diagnosis of lacunar stroke in GAIN Americas is similar to that found in a prospective population-based cohort of patients with ischemic stroke in the Northern Manhattan Stroke Study (NOMASS). Among the 195 patients who presented with a lacunar syndrome (diagnosed within 1 week after stroke onset) and had a lacunar infarct on CT or MRI, 147 (positive predictive value = 75%) were caused by small vessel disease as determined by a modified Stroke Data Bank scheme (a forerunner of TOAST).

There are a number of limitations to the work presented here. The GAIN Americas cohort was selected and so the findings may not apply to all strokes in general. Lacunar strokes not causing limb weakness were excluded; this may have biased our findings in the conservative direction as pure sensory stroke had a positive predictive value of 100% for detecting a lacunar infarct on brain imaging in NOMASS.

Our analyses did not include any information derived from brain imaging. Although this is of some concern because studies using MRI have shown that not all lacunar stroke syndromes are caused by solitary, small, deep, infarcts, our findings demonstrate the pragmatic use of distinguishing lacunar strokes from other stroke syndromes. In NOMASS in which 74% of patients had 2 or more CT or MRI scans, a lacunar syndrome had a positive predictive value of 87% for detecting a lacunar infarct on brain imaging.

We were unable to assess the extent to which brain imaging at baseline influenced the diagnosis of OCSP subtype, but very few patients had an MRI before randomization and acute infarcts are not well seen on CT performed within 6 hours after stroke onset. The TOAST criteria for “small vessel (lacunar)” stroke include the clinical findings of a lacunar stroke syndrome, and we were unable to assess how repeat brain imaging and other investigations influenced the investigators’ TOAST categorization.

Despite these limitations, our study suggests that lacunar strokes, which are relatively pathophysiologically homogeneous, can be identified with reasonable accuracy in the first 6 hours after stroke onset. The use of the OCSP classification in acute treatment trials would allow an important minority of patients to be categorized at the time of randomization on the basis of most likely mechanism as well as stroke severity.

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**Disclosures**

None.

**References**


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