Poststroke Neurological Improvement Within 7 Days Is Associated With Subsequent Deterioration
Stella Aslanyan, MD; Christopher J. Weir, PhD; S. Claiborne Johnston, MD, PhD; Kennedy R. Lees, MD, FRCP; for the GAIN International Steering Committee and Investigators

Background and Purpose—Improvement in the National Institutes of Health Stroke Scale (NIHSS) 24 hours after stroke has been associated with subsequent neurological deterioration. We hypothesized that a similar association would be apparent for events occurring after 7 days, when acute changes from edema and herniation are less common. We evaluated the degree of NIHSS improvement at 7 days (recovery) as a predictor of subsequent neurological deterioration from day 7 to day 90.

Methods—We studied all patients of the Glycine Antagonist (gavestinel) In Neuroprotection (GAIN) International Trial with ischemic stroke alive at day 7, excluding patients with hemorrhagic events and deaths from nonstroke-related causes. The GAIN International Trial was a randomized, double-blind, placebo-controlled, and parallel-group trial; because the study drug had no effect on stroke outcome, treatment groups were combined for this analysis. Neurological deterioration was assessed by the combined measure, including: (1) stroke-related events recorded as “serious adverse events,” (2) recurrent stroke recorded on a separate case report form, and (3) any NIHSS worsening.

Results—Among 1187 patients included, 25% had ≥65% recovery. Deterioration was more prevalent in the group with >65% early recovery (15.5% versus 10.3%; P=0.01). Logistic regression modeling indicated that recovery was associated with subsequent neurological deterioration (odds ratio, 1.2; 95% CI, 1.1 to 1.3, per 10% recovery) after adjusting for age, NIHSS at 7 days, and stroke subtype.

Conclusions—Substantial neurological recovery at 7 days is associated with subsequent neurological deterioration.
(Stroke. 2004;35:2165-2170.)

Key Words: cerebral infarction ■ disease progression ■ recovery of function ■ recurrence

Several studies have suggested that short-term stroke risk after transient ischemic attack (TIA) is greater than after stroke. For example, in a cohort of patients diagnosed with TIA in the emergency department, 10.5% had a stroke during the first 3 months after the index event. Stroke risk after a completed stroke has been reported to be lower in clinical trials, with recurrence rates ranging from 3% to 6% at 6 months. Observational studies suggest stroke recurrence rates of 3% to 6% at 1 month and 7% at 3 months. Direct comparisons of those studies are confounded by differences in study design.

The recurrent stroke rate within 3 months was substantially higher after hemispheric TIA than after completed stroke (20.1% versus 2.3%) in the medical arm of the North American Symptomatic Carotid Endarterectomy Trial. Patients of the National Institute of Neurological Diseases and Stroke t-PA Trial and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) with TIA were at greater risk of subsequent neurological deterioration, defined as worsening of National Institutes of Health Stroke Scale (NIHSS) score from day 1 to day 90 resulting from causes other than hemorrhage, than those with completed stroke. Further, the risk of subsequent neurological deterioration extended to acute substantial but incomplete recovery of 50% to 100% in NIHSS at 24 hours from baseline.

In studies evaluating a 24-hour time point for recovery, early changes attributable to factors other than new ischemia could account for subsequent deterioration, including worsening edema and reperfusion injury. This should be less evident ≥1 week after the initial stroke; deterioration after the first week may be more indicative of new ischemia. In fact, patients with reversible ischemic neurological deficit with symptom resolution by 3 weeks and TIA had similar subsequent stroke event rates (38%) in contrast to patients with completed stroke (23%) during the mean follow-up of 2 years. Further, patients with TIA and those in whom symptoms resolve within 7 days have significantly higher rates of subsequent ischemic stroke compared with those with a longer duration of initial symptoms. These time factors and definitions of complete symptom resolution in distin-

Received January 7, 2004; final revision received March 10, 2004; accepted April 13, 2004.
From the Division of Cardiovascular and Medical Sciences (S.A., C.J.W., K.R.L.) and the Robertson Centre for Biostatistics (C.J.W.), University of Glasgow, Scotland; and the Departments of Neurology and Epidemiology (S.C.J.), University of California, San Francisco, Calif.
Correspondence to Dr S. Aslanyan, Division of Cardiovascular and Medical Sciences, University of Glasgow, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, United Kingdom. E-mail 0110768a@student.gla.ac.uk
© 2004 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000136554.03470.9d

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guising between TIA, reversible neurological deficits, and stroke are arbitrary.\textsuperscript{13,15,17}

In this study, we investigated whether the degree of ischemic stroke recovery at 7 days is associated with risk of neurological deterioration occurring between days 7 and 90 after stroke. We analyzed data from the Glycine Antagonist (gavestinel) In Neuroprotection (GAIN) International Trial\textsuperscript{18} to test the hypothesis that stroke recovery at 7 days is associated with increased risk of subsequent neurological deterioration.

**Subjects and Methods**

GAIN International was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted to test the effectiveness of gavestinel for acute stroke treatment. The trial was approved by regulatory and ethics committees of each participating institution. Written or witnessed verbal informed consent was obtained for all patients. The trial included previously independent patients with symptoms of acute stroke who were \( \geq 18 \) years of age and who presented within 6 hours of stroke onset. Subjects had limb weakness (drift within 10 s for the arm or 5 s for the leg; if mild, both should have been affected). Exclusion criteria were reported previously.\textsuperscript{18} Standard stroke care was accompanied by gavestinel or placebo administration. None of the patients received thrombolytic therapy. The diagnoses were confirmed by imaging. Gavestinel had no effect on stroke outcome or occurrence of serious adverse events. For this study, we selected patients with confirmed cerebral ischemia who were alive at 7 days and had NIHSS recorded at 7 days (postrandomization NIHSS was not recorded before 7 days in this trial) from both treatment groups combined.

Our primary outcome measure was “neurological deterioration” from day 7 to day 90. It included (1) “stroke-related events” after day 7 (serious adverse events related to a new ischemic event or to the original stroke, such as stroke deterioration, evolution, extension, progression, or neurological damage or deterioration resulting from the original stroke); (2) “recurrent stroke” after day 7 (recorded on a separate case report form as one of the prespecified events common to stroke patients); and (3) NIHSS worsening (dichotomized as “worse, by at least 1 point” versus “no change or better” from day 7 to day 90). The main clinical interest in this study is the risk of stroke-related events. Considering the post hoc nature of our study and the difficulties of assessing the cause and extent of poststroke deterioration (and therefore under-reporting of stroke events), the combined neurological deterioration was used as a surrogate. Stroke recovery was assessed by NIHSS percentage change from baseline to day 7.

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**TABLE 1. Comparison of Groups With and Without >65% Recovery and Neurological Deterioration**

<table>
<thead>
<tr>
<th>Variables</th>
<th>&gt;65% Recovery</th>
<th>Neurological Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With (n=303)</td>
<td>Without (n=884)</td>
</tr>
<tr>
<td>Age (y), mean±SD</td>
<td>67±13</td>
<td>70±12</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Treatment, gavestinel (%)</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Systolic BP, mean±SD</td>
<td>157±27</td>
<td>159±27</td>
</tr>
<tr>
<td>Diastolic BP, mean±SD</td>
<td>87±15</td>
<td>86±15</td>
</tr>
<tr>
<td>White cell count, 10(^9)/L, mean±SD</td>
<td>8.8±2.9</td>
<td>8.9±2.8</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Current smoker</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>9.9</td>
<td>10</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>OCSP classification (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Partial anterior</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Total anterior</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Posterior</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>NIHSS score, mean±SD†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.5±5.0</td>
<td>13±6.0</td>
</tr>
<tr>
<td>7 days</td>
<td>1.5±1.5</td>
<td>12±7.0</td>
</tr>
<tr>
<td>90 days</td>
<td>1.3±3.6</td>
<td>8.3±8.3</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>&gt;65% recovery</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

* \( * \) test or \( / \) test.
†Upper quartile-median-lower quartile.
BP indicates blood pressure.
Patients who died as a result of causes other than stroke-related events were excluded, as were patients who had a hemorrhage from day 7 to day 90, to investigate the deterioration purely because of the ischemic neurological events.

**Statistical Analyses**

Means with SDs (for continuous variables) and percentages (for categorical variables) of the baseline factors and NIHSS scores were compared between groups with and without recovery at 7 days and between groups with and without deterioration. Stratification of recovery was based on the best cut point in sensitivity analysis for predicting subsequent neurological deterioration.

Logistic regression was used to investigate the effect of percentage of recovery at 7 days as a continuous variable on neurological deterioration, in univariate analyses, and after adjusting for prognostic factors (NIHSS at 7 days, age and stroke subtype by Oxfordshire Community Stroke Project [OCSP] clinical classification). Using ANOVA, we compared these models with generalized additive modeling to identify a nonlinear relationship of any form between degree of early recovery and outcome. In sensitivity analysis, we used cut points from 0% to 100% by 5% intervals in degree of recovery to predict neurological deterioration after correcting for prognostic factors. The best cut point was chosen on the basis of the highest odds ratio (OR).

Patients were stratified by the quartiles of NIHSS at 7 days. The association between stroke recovery dichotomized by the best cut point and neurological deterioration was investigated in each subgroup. The SAS System V8 and S-PLUS 6.0 statistical software were used for analysis.

**Results**

Of 1455 patients, 1313 were alive at 7 days. Of these, 1 had missing values for NIHSS at 7 days, 3 had a hemorrhagic stroke, and 122 (9.3%) died from noncerebrovascular causes. Thus, our sample comprised 1187 patients.

The best cut point for predicting neurological deterioration was >65% recovery from baseline. Patients with recovery >65% were younger, had lower rates of atrial fibrillation, hypertension, and total anterior circulation infarction, and had higher rates of lacunar stroke compared with patients without recovery (Table 1). They had lower NIHSS scores at baseline, at 7 and 90 days, and had higher rates of neurological deterioration. Patients with deterioration were older, had higher rates of atrial fibrillation and recovery, and higher NIHSS scores at 90 days (Table 1).

Considering the composite nature of our main outcome measure of neurological deterioration, Figure 1 presents the number of events and the overlap of stroke-related events, recurrent stroke, and NIHSS worsening. Thus, 11 cases of only stroke-related events, 4 cases of only recurrent stroke, and 7 cases of stroke-related events and recurrent stroke did not correspond to the NIHSS worsening definition. In 79 patients, the cause of NIHSS worsening was not identified specifically. Figure 2 presents NIHSS change from day 7 to 90 in patients, with the primary outcome of neurological deterioration.

Table 2 presents the ORs per additional 10% recovery predicting neurological deterioration. After adjusting for age, NIHSS at 7 days, and stroke subtype, recovery was associated with neurological deterioration; each 10% increase in recovery was associated with 16% increase in the odds of neurological deterioration (95% CI, 6% to 28%). There was no significant difference between logistic and generalized additive models, indicating no substantial nonlinear relationship between percentage recovery and neurological deterioration.

Along with age, NIHSS at 7 days predicted neurological deterioration (Table 2). In view of this strong association between NIHSS at 7 days and at outcome, we stratified the sample by quartiles of NIHSS at 7 days. In the first group (NIHSS 0 to 2; n=274), 88% of patients had a >65% recovery. In the second group (NIHSS 3 to 8; n=369), only 17% of patients had a >65% recovery. The other 2 groups combined (n=544) did not have any case of recovery >65% (Figure 3). Table 3 presents the rates of neurological deterioration in patients stratified by >65% recovery and NIHSS at 7 days. In the first subgroup, there was a nonsignificant trend toward patients with >65% recovery having a higher rate of subsequent deterioration (14% versus 3%; P=0.07), which
was confirmed in the second subgroup (19% versus 7%; P = 0.004). After correcting for age, stroke subtype, and NIHSS at 7 days, >65% recovery was associated with neurological deterioration in the entire sample (OR, 2.9; 95% CI, 1.7 to 5.0) and in the second subgroup (OR, 3.7; 95% CI, 1.4 to 9.6) but not in the first (OR, 3.6; 95% CI, 0.4 to 30.0).

In additional sensitivity analysis, including all patients alive at 7 days (n = 1313), recovery and absence of neurological deterioration were associated in univariate analysis (OR, 0.9; 95% CI, 0.9 to 0.9 per 10% recovery). However, after correcting for prognostic factors, findings were consistent with those of the main analysis, recovery being associated with neurological deterioration (OR, 1.1; 95% CI, 1.1 to 1.2).

**Discussion**

We found a strong linear association (on the logit scale) between high levels of early stroke recovery and subsequent neurological deterioration after adjusting for age, NIHSS at 7 days and stroke subtype. There was no difference in the recovery and deterioration between randomized treatment groups, justifying the combination of both groups.

We used a composite outcome measure for neurological deterioration. However, when analyzing the components separately (Figure 1), the ORs were similar in direction and significance for stroke-related events and NIHSS worsening (results are not presented for simplicity), suggesting that the choice of the primary outcome measure was appropriate.

The best cut point of early recovery for predicting neurological deterioration was 65%; it had a higher OR in both univariate and corrected models predicting the neurological deterioration and its components. Dichotomizing recovery in this way renders it easier to interpret and aids comparison with previous studies. The relationship between substantial recovery by 7 days and later NIHSS worsening found in our study supports the results published for recovery by 24 hours and 7 days. Complete symptom resolution at day 1 and day 7 does not appear to be required to identify a patient with greater risk of subsequent neurological deterioration.

After 7 days, the cause of deterioration is less likely to be stroke progression or evolution and more likely to be a new ischemic event. However, documentation of deterioration in a clinical trial setting might not relate directly to the underlying pathophysiological phenomena. Elevated risk of new ischemic stroke after initial early recovery from stroke could be an indicator of overall pathophysiological instability: brain tissue being at risk of recurrent ischemic event.

To be able to speculate further on the underlying process, we conducted a subgroup analysis by TOAST classification. The association between >65% recovery and neurological deterioration was stronger in patients with large-vessel atherothromboembolic stroke (n = 327; OR, 4.3; 95% CI, 1.2 to 15.1), confirming that this subtype predisposes to stroke events and makes recovery less stable because of rethromboses. There was no statistically significant association in patients with cardioembolic stroke (n = 331; OR, 1.9; 95% CI, 0.7 to 5.2) or with lacunar stroke (n = 184; OR, 1.3; 95% CI, 0.3 to 4.7). However, ORs presented overlap with each other, indicating that small sample size might contribute to absence of association. Our results confirm that large-vessel atherothrombosis can predispose to stroke events and make recovery less stable because of rethromboses. Cardioembolic strokes may have spontaneous or therapy-induced total or partial thrombolysis and might rethrombose, whereas patients with lacunar stroke have steady slow recovery. Apart from limited sample size, we may have failed to find supportive evidence in the subgroup with cardioembolic strokes because of no thrombolytic treatment and exclusion of patients who died from causes other than stroke-related events who tended to have greater cardiac pathology.

In subgroup analyses, the association was the strongest in the group with a 7 day NIHSS of 3 to 8. No evidence of this

![Figure 3. Recovery of patients stratified by 7 day NIHSS.](image-url)
in the group with an NIHSS of 0 to 2 might be because of small sample size with a univariate analyses $P$ value of 0.07 (Table 3) and wide OR CI after correcting for prognostic factors. Other reasons for presented discrepancies might be the higher rate of lacunar strokes in the group with an NIHSS of 0 to 2 compared with the group with an NIHSS of 3 to 8 (39% versus 28%; $P=0.005$), which have a steadier course of recovery. However, there was no statistically significant interaction between lacunar strokes and $>65\%$ recovery ($P=0.09$).

Although this is the third study to find an association between early recovery and subsequent risk of neurological deterioration, none of the published studies have included a large number of patients with substantial early recovery or have investigated recovery at 7 days. Further studies, which have available recordings of NIHSS at 24 hours and 7 days, are necessary to investigate the relative prognostic values of acute (24 hours) and early (7 days) stroke recovery. The clinical implications are unknown. Secondary prevention interventions should commence in all patients but especially in those with early recovery, regardless of the timing of event resolution and its completeness. We cannot recommend any specific measures of prevention from our observational study. Prospective studies, such as the Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) Trial, will examine this issue further, administering preventive treatment with aspirin and clopidogrel or with aspirin and simvastatin within 12 hours of TIA or acute stroke.20 The Prevention regimen For Effectively avoiding Second Stroke (ProFESS) Trial will investigate the secondary prevention of telmisartan combined with aspirin and dipyridamole or aspirin and clopidogrel, with treatment initiation within 90 days of index stroke.21 Post hoc subset analysis of those trials may reveal differences in therapeutic benefits apparent in those with early recovery but not in those without recovery because the risk of new ischemia may be greater in the former. It might be beneficial to compare the appropriate groups of these 2 trials in combined post hoc analysis to discriminate between early and late initiation of secondary prevention.

Similar results from sensitivity analyses of the sample including all patients alive at day 7 after correction for age and NIHSS scores at day 7 indicate that we did not introduce a bias by excluding patients who died from causes other than stroke-related events. The opposite relationship found in univariate analyses was expected because patients who might die from other causes probably will not have good recovery at 7 days because they will have higher comorbidity, older age, and more severe stroke.

Our study experienced some limitations. First, patients with very early improvement of stroke symptoms were excluded from the trial, and those cases with early recovery that were included may be more unstable than those seen in general practice. Second, we might have introduced a measurement bias because new ischemic events may go unnoticed in the nonrecovery group, in which a neurological deficit may mask the new event. However, this bias is clinically unimportant to the patient. Furthermore, the association persisted after adjustment for and stratification by neurological condition at 7 days. Finally, postrandomization NIHSS was not recorded before 7 days in the GAIN Trial; we could not directly compare the effect of recovery at 24 hours and at 7 days on neurological deterioration.

“Regression to the mean” can bias our results on NIHSS worsening. This is a statistical phenomenon that occurs when there is nonrandom sampling from a population (in this case, patients with recovery at 7 days) and when 2 or more measures are correlated imperfectly (in this case, 3 measurements of NIHSS score: at baseline, at 7 days, and at 3 months). However, separate analyses of the components of neurological deterioration showed a similar association for NIHSS worsening and stroke-related events; the association between stroke-related events and recovery could not be explained by regression to the mean. The mean NIHSS values at 7 days in the $>65\%$ recovery group may also suggest that any NIHSS worsening might be simply attributable to random variability or measurement error; the scores are so low that they can only rise. However, the associations between early recovery and subsequent deterioration were strongest in the group with an NIHSS score of 3 to 8 at 7 days, in which this measurement error should not be an issue.

In conclusion, substantial neurological recovery at 7 days was associated with subsequent neurological deterioration in this cohort study after adjusting for age; NIHSS at 7 days, and stroke subtype.

Acknowledgments

The GAIN International Trial was sponsored by GlaxoSmithKline (GlaxoWellcome). C.J.W. was supported by a UK Medical Research Council career development award. S.A. was supported by a UK universities overseas students’ research award. GAIN International Steering Committee: K. Asplund, A. Carolei, S.M. Davis, H.-C. Diener, M. Kaste, J.-M. Orgogozo, J. Whitehead, K.R. Lees (chair).

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10. Publications Committee for the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparnoid,


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Stroke. 2004;35:2165-2170; originally published online July 8, 2004; doi: 10.1161/01.STR.0000136554.03470.9d

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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