Progression in Acute Stroke
Value of the Initial NIH Stroke Scale Score on Patient Stratification in Future Trials

Thomas J. DeGraba, MD; John M. Hallenbeck, MD; Karen D. Pettigrew, PhD; Andrew J. Dutka, MD; Brian J. Kelly, MD

Background and Purpose—The objective was to determine the occurrence of neurological changes during the first 48 hours after acute stroke as it relates to initial stroke severity.

Methods—The National Institutes of Health Stroke Scale (NIHSS) was performed serially for the first 48 hours on 127 consecutive ischemic stroke patients (129 strokes) admitted to the neuroscience intensive care unit. Incidence of stroke progression (a $\geq 3$-point increase on the NIHSS) was recorded and analysis performed to determine its association with initial stroke severity and other demographic and physiological variables. Deficit resolution by 48 hours, defined as an NIHSS score of 0 or 1, measured the frequency of functional recovery predicted by the initial deficit.

Results—Overall progression was noted in 31% of events (40/129). Applying Bayes’ solution to the observed frequency of worsening, the greatest likelihood of predicting future patient progression occurs with stratification at NIHSS scores of $\leq 7$ and $> 7$. Patients with an initial NIHSS of $\leq 7$ experienced a 14.8% (13/88) worsening rate versus a those with a score of $> 7$ with a 65.9% (27/41) worsening rate ($P<0.000005$). Forty-five percent (40/88) of those with an initial score of $\leq 7$ were functionally normal at 48 hours, whereas only 2.4% (1/41) of those with scores of $> 7$ returned to a normal examination within this period ($\chi^2$, $P<0.000005$).

Conclusions—This study suggests that the early clinical course of the neurological deficit after acute stroke is dependent on the initial stroke severity and that a dichotomy in early outcome exists surrounding an initial NIHSS score of 7. These findings may have significant implications for the design and patient stratification in treatment protocols with respect to primary clinical outcome. (Stroke. 1999;30:1208-1212.)

Key Words: outcome ■ stroke assessment ■ stroke, acute

Demonstration of benefits from the use of neuroprotective agents in acute stroke is predicated on the finding of a measurable clinical outcome that is more favorable than best medical care alone. A large number of trials, however, using various neuroprotective agents in that setting have been unsuccessful in demonstrating benefit in the population receiving the study medication versus placebo. One potential obstacle with these studies is that patients with any stroke severity (generally with a National Institutes of Health Stroke Scale [NIHSS] score of $\geq 4$ or its equivalent$^{1-4}$) are enrolled into a nonstratified group to receive either the treatment medication or the placebo and are anticipated to improve, as part of the “natural course of the disease,” at equal rates, regardless of the initial stroke severity. However, it may well be that strokes of varying severity have a nonlinear profile of recovery and that the early course of improvement may be greater at the lower end of the deficit scale than at the higher end. If this is the case, many more patients will improve regardless of the treatment if enrolled with these lower scores, thus diluting the potential to see a true protective effect. Conversely, there may also be a population of patients who worsen, based on the initial severity of their stroke, resulting in further neuronal injury and less-favorable outcome. Thus, the ability to use “normal outcome” as a primary end point may not optimize the evaluation of the benefit of an agent in patients with severe strokes unless the medication has a profound benefit.$^4$ Therefore, understanding the potential course of worsening and improvement may help with the design of the prestudy randomization schedule and power analysis.

Clinical observations suggest that the first 48 hours after an ischemic stroke are associated with potential instability and...
secondary worsening. Work in the neurosciences has demonstrated that much of the cell death from stroke results from a complex series of biochemical events (often termed the “ischemic cascade”) that occur over a period of hours or even days after the initial stroke. Additionally, components of the inflammatory pathways, thought to be the hallmark of reperfusion injury, can also result in secondary tissue injury and vascular compromise. These ongoing changes represent a compilation of physiological events that expose the compromised brain tissue to further injury early in the course of the disease. The degree to which the initial ischemic injury, the secondary cascade of injurious mediators, and their associated medical or physiological complications play a role in the overall development of brain infarction may be difficult to unravel. A study designed to care for stroke patients in an intensive care unit (ICU) during the period of maximal vulnerability would allow for more uniform management of the physiological parameters, such as blood pressure, fluid status, and oxygenation, that are felt to be influencing variables in neuronal salvage in clinical trials.

The objective of this study was to determine characteristics of patients likely to show neurological changes during the first 48 hours after the onset of acute cerebral ischemia by closely recording worsening and improvement in a monitored ICU setting. Because one of the key criteria for enrollment into acute stroke trials is stroke severity, the NIHSS was one of multiple variables analyzed for its capacity to predict progression and improvement.

Subjects and Methods
All patients older than 18 years presenting to the emergency room at the National Naval Medical Center (NNMC) with the diagnosis of acute ischemic stroke with any level of sustained focal deficit were admitted to the Neuroscience Intensive Care Unit for a minimum of 48 hours in accordance with an NNMC and NINDS IRB–approved protocol to study stroke progression. Noninvasive blood pressure, heart rate, telemetry, and pulse oximetry were monitored and recorded during the initial 48 hours of hospitalization. Complete blood count, cholesterol level, and platelet counts were also obtained on admission. The primary physician determined treatment decisions regarding the use of antiplatelet agents and anticoagulants, and in addition to the research protocol, all patients were treated following the standard of care designated by the treating institution’s stroke critical pathway throughout their hospital stay. The NIHSS was performed on presentation and every 8 hours for 48 hours on all patients. All raters were trained and certified in administering the NIHSS by the criteria used in the NINDS tPA trial. Inclusion criteria for the study included (1) ischemic stroke onset within 24 hours of enrollment, (2) identifiable time of onset, (3) stable deficit lasting longer than 1 hour without rapid improvement, and (4) the ability to obtain informed consent or third-party consent. (Note that all patients with sustained neurological deficit at the time of admission regardless of stroke severity were admitted to the ICU to avoid inclusion bias.) Exclusions were hemorrhagic stroke, prior neurological deficit that obscured the ability to follow the neurological examination from the most recent infarct, coma, inability to perform physiological monitoring for 48 hours, and thrombolytic therapy.

One hundred thirty-two consecutive patients with the admission diagnosis of acute stroke of <24 hours’ duration were entered into the study. Consent was obtained from the patient or a family member to record examination scores, standard laboratory test results, radiographic test results, and physiological parameters for research purposes. Two patients were enrolled twice with separate ischemic events, bringing the total number of acute events studied to 134. Of the 134 patient events, 5 events were excluded from analysis. The reasons for exclusion were encephalopathy (in 2 patients), glioblastoma (1), Mениere’s disease (1), and monitored bed nonavailability (1). The remaining 129 events in 127 patients formed the cohort for analyses. A CT scan or MRI was performed in the first 7 days and used to confirm the location and size of the infarct. Imaging classification of the strokes were divided into the following 5 categories: lacunar (subcortical lesions ≤3 cm), small to moderate cortical or subcortical (>1 cm and ≤1/3 MCA distribution), moderate to large cortical or subcortical infarcts (>1/3 MCA distribution), brain stem, and normal.

Patients were monitored carefully for clinical changes as stated above, and neurological worsening was defined as a 3-point or greater increase on the NIHSS during the first 48 hours. A 3-point or greater decline on the NIHSS was chosen as the definition of “worsening” in this study because it was felt to represent the minimal change that was clinically significant, warranting diagnostic work-up in all such cases. It was also chosen to avoid recording the mild, nonsignificant fluctuations sometimes seen in acute stroke patients. At the time of neurological worsening, studies performed on all patients to determine the possible etiologies included CT scan of the head, blood pressure monitoring, fluid status, arrhythmias, oxygen saturation, and evidence of infection.

Patients were classified as having “improved” if they had a normal examination at the end of 48 hours (NIHSS score of 0 or 1). This definition of improvement has previously been used as an end point in drug trials and was used in this study to demonstrate the number of patients who spontaneously achieve this outcome in the first 2 days.

Statistical Analysis
Given the utility in knowing whether a patient is more likely to improve or to worsen before randomization into a clinical trial, analysis was performed on the distribution of admission NIHSS scores, stratified by the observed frequency of progression. The analysis identified a cutoff value that would optimize the prediction of patients’ clinical course based on their initial neurological deficits; ie, it identified an admission NIHSS score that minimized the probability of a classification error when predicting who would worsen and who would not. Bayes’ solution rule was applied to identify a threshold initial NIHSS score such that the probability of misclassification of patients was minimized, ie, the probability that a patient with a score below the threshold who is predicted to improve in 48 hours actually will not and the probability that a patient with a score above the threshold who is predicted to worsen in 48 hours actually does not. The observed frequency distributions of initial NIHSS scores for the stratified samples were used to estimate the discrete probability distributions. A χ² test was performed to determine whether the rates of worsening and improvement were different between the groups of patients above and below the initial stroke scale threshold.

A stepwise logistic regression analysis was performed to assess which variables were associated with stroke progression. Again, stroke progression was defined by an increase of ≥5 points on the NIHSS at any time during the first 48 hours. The factors tested for associations with stroke progression are listed in Table 1. The demographic data, baseline characteristics, and risk factors for stroke as well as stroke subtypes were compared between those who showed progression and those who did not by the Student t test and Mann-Whitney rank sum as appropriate.

Results
Of the 127 patients admitted, 86 were men and 41 were women. The average patient age was 66.5 years. The average time from onset of stroke symptoms to enrollment into the study was 12.1 hours, and the average initial NIHSS score was 7.1. Overall, progression of neurological deficits occurred in 40 of the 129 events (31.5%). Bayes’ solution rule identified a threshold initial NIHSS score of 7.5, above which


TABLE 1. Demographic Data, Baseline Characteristics, and Risk Factors for Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Neurological Progression</th>
<th>No Progression</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>67.6</td>
<td>66.0</td>
<td>0.467</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>26/14</td>
<td>62/27</td>
<td>0.945</td>
</tr>
<tr>
<td>White</td>
<td>36 (90)</td>
<td>73 (82)</td>
<td>0.847</td>
</tr>
<tr>
<td>Black</td>
<td>3 (7.5)</td>
<td>14 (15.7)</td>
<td>0.394</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.5)</td>
<td>2 (2.3)</td>
<td>0.586</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (67.5)</td>
<td>58 (65.2)</td>
<td>0.954</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (50)</td>
<td>53 (59.6)</td>
<td>0.412</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10 (25)</td>
<td>31 (34.8)</td>
<td>0.366</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (32.5)</td>
<td>20 (22.5)</td>
<td>0.323</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>15 (37.5)</td>
<td>10 (11.2)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>Initial NIHSS*†</td>
<td>12.7</td>
<td>5.0</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>WBC*†</td>
<td>8.812</td>
<td>8.906</td>
<td>0.082</td>
</tr>
<tr>
<td>Platelet*†</td>
<td>225.7</td>
<td>215.1</td>
<td>0.952</td>
</tr>
<tr>
<td>Maximum MAP,* mm Hg</td>
<td>113.9</td>
<td>108.6</td>
<td>0.051</td>
</tr>
<tr>
<td>Minimum MAP,* mm Hg</td>
<td>78.0</td>
<td>77.0</td>
<td>0.710</td>
</tr>
<tr>
<td>Largest change in MAP,* mm Hg</td>
<td>34.2</td>
<td>31.5</td>
<td>0.354</td>
</tr>
<tr>
<td>Minimum O₂ saturation*†</td>
<td>93.1</td>
<td>93.5</td>
<td>0.929</td>
</tr>
</tbody>
</table>

Values in parentheses are percent.†Factors used in regression analysis.‡Significant association with stroke progression.

the probability of incorrectly predicting that a patient would worsen when they actually did not is 0.157. The probability of incorrectly predicting that a patient with a score of ≤7 would not worsen when they actually did is 0.325. Shifting the threshold score in either direction increases the overall probability of a classification error. A χ² test, Yates’ corrected, was performed to determine whether the rates of worsening and improvement were different between the groups of patients above and below the initial stroke scale threshold.

Patients with an NIHSS of >7 worsened in 27 of 41 cases (65.9%) compared with those with an initial score of ≤7, who worsened in only 13 of 88 cases (14.8%) (χ²(1,cor)=31.77, P<0.000005). Additionally, 40 of 88 patients (45.5%) with an initial NIHSS score ≤7 were normal (NIHSS score of 0 or 1) at 48 hours, whereas only 1 of 41 (2.4%) of those with scores >7 were normal at the same time point (χ²(1,cor)=21.93, P<0.000005; Figure). A post hoc analysis of the data was also performed with a 4-point change as the criteria for worsening, a change deemed to be significant in the NINDS tPA acute stroke trial.4 Again, a threshold in the initial score between 7 and 8 was found to correlate with the dichotomy in the clinical course, as noted above. Stepwise logistic regression of the 9 factors tested for association with stroke progression revealed that only the initial neurological score and atrial fibrillation were useful in predicting which patients would worsen and which would not (Table 1). The presence of atrial fibrillation on the initial admission ECG was significantly associated with stroke progression (P=0.001). There was no association between the occurrence of neurological progression and admission white blood cell count, platelet count, or cholesterol level; the maximum or minimum mean arterial blood pressure (MAP); and the minimum O₂ saturation in the first 48 hours. The same applied to the presence of the risk factors hypertension, diabetes, smoking, and hypercholesterolemia. The maximum MAP in the first 48 hours strongly tended toward association with patients who worsened (P=0.051). However, changes in the physiological parameters of MAP, oxygen saturation, evidence of infection, and cardiac output–altering arrhythmias were not identified at the time of worsening. Additionally, relatively lower MAPs were noted in a number of patients at the time of their worsening, but neither the change in pressure nor absolute level of the MAP was different from pressure fluctuations recorded in the nonprogression population. CT scans obtained at the time of worsening revealed hemorrhagic conversion in 5 of the 40 patients. Because a CT scan of the head was only done if the patient deteriorated during the first 48 hours, no comparison with the “nonprogression” group can be made with respect to the incidence of hemorrhagic conversion or degree of edema.

Of the 40 patients who worsened, only 6 (15%) returned to their baseline score, and none improved beyond their baseline score. The remainder had sustained worsening from baseline at 48 hours from admission.

Analysis of stroke subtypes by CT and MRI demonstrated a significantly greater likelihood of progression in patients with large to moderate cortical and subcortical infarcts, whereas patients with lacunes and small subcortical infarcts or normal scans had significantly fewer episodes of neurological deterioration (Table 2). Because the general conception is that lacunar strokes are more likely to improve, stratification of the nonlacunar strokes again revealed that patients with an NIHSS of >7 had a far greater likelihood of
TABLE 2. Stroke Progression Related to Stroke Subtype

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Progression</th>
<th>No Progression</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar/small subcortical infarction</td>
<td>2 (5%)</td>
<td>20 (22.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate to large cortical or subcortical (&gt;1/3 MCA)</td>
<td>25 (62.5%)</td>
<td>15 (16.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small cortical or subcortical (&lt;1/3 MCA)</td>
<td>9 (22.5%)</td>
<td>26 (29.2%)</td>
<td>0.573</td>
</tr>
<tr>
<td>Brain stem</td>
<td>3 (7.5%)</td>
<td>7 (7.9%)</td>
<td>0.776</td>
</tr>
<tr>
<td>Normal</td>
<td>1 (2.5%)</td>
<td>21 (23.6%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

χ² analysis was performed to identify associations between stroke subtypes and clinical changes. A significantly greater number of patients with moderate to large infarcts worsened in the first 48 hours, whereas patients with lacunar infarcts or normal CT scan either remained stable or improved.

significant progression (67.5%) versus those with scores ≤7 (16.4%) (χ²(1)cor=26.35, P<0.001).

The average time to progression was 34.9±13.2 hours from the onset of the stroke, with the median being 34.1 hours. Among the 40 patients who progressed, 22 were on aspirin, 6 were on subcutaneous heparin 5000 U BID, and 5 were on intravenous heparin at the time of progression. This is compared with 89 nonprogression patients who received aspirin (n=45), subcutaneous heparin (n=12), and intravenous heparin (n=18) during the first 48 hours. None of these ratios were significantly different.

Discussion

The ability to predict clinical improvement and deficit progression in patients with acute cerebral ischemic infarcts can be a valuable asset in future attempts to assess the effects of therapeutic intervention. It can provide a guide to expected outcome when considering subject inclusion and sample size in therapeutic trials. Additionally, it may provide insight into potential ongoing mechanisms of injury that occur after the initial ischemic insult. That is, progression that occurs while the patient is in the hospital may represent a new “window of opportunity” to deliver therapies targeting these sequelae of ischemia or even allow for prophylactic treatment before neurological worsening.

Our study demonstrates the potential value of the initial NIHSS score in identifying those patients who are likely to progress as well as those likely to improve over the first 48 hours. The observed frequency of clinical worsening sharply increased above an initial NIHSS score of 7, with the probability of worsening being far greater with a score of >7 (63.4%) than with a score of ≤7 (14.8%). The threshold score of 7.5 was calculated using Bayes’ solution rule and based on the assumption that it is equally advantageous to avoid a misclassification of a patient’s outcome if a patient worsened when improvement was expected and vice versa. Analysis using a score of ≤6 or a score of ≥8 leads to an aggregate misclassification of >50%, becoming progressively larger the farther from 7 that the threshold is set.

A sharp demarcation in the occurrence of improvement was also seen at a threshold of 7. With a score of ≤7 on admission, a patient was 19 times more likely to be normal in 48 hours than those presenting with higher scores. Given the high frequency of excellent outcome in this group, a large number of patients with an initial score of ≤7 enrolled in a randomized investigational drug trial would tend to reduce the potential for identifying a beneficial effect.

Other recent prospective studies of progression in acute stroke have highlighted the high frequency of change in the neurological examination that can occur in the first several hours to days after ischemic injury. Early deterioration has been noted in as many as 22% to 40% of patients in the first 48 hours, and “major neurological improvement” has been reported in 22% to 28% of acute stroke victims during the same time frame.

The importance of understanding the frequency of alterations in the clinical condition after acute stroke is illustrated by the data that show the predictive value of early changes on long-term outcome. Studies reveal that patients with early deterioration have an increased mortality of 35% to 50% and up to an 88% chance of poor long-term outcome (poor function and death). Conversely, patients with early improvement have been reported to have a high frequency of good outcome (79%) at 30 days. In addition, it has been shown that the clinical course of recovery stabilizes beyond day 4, with improvement becoming more linear from that time on.

We found several other parameters that were associated with a change in clinical course. Infarct size was closely associated with neurological changes, as previously noted by some but not all investigators. Patients with lacunar infarcts were 10 times more likely to remain stable or improve than to experience neurological deterioration. Conversely, patients with moderate to large cortical and subcortical infarcts (>1/3 of the MCA territory) were significantly more likely to progress than any other imaging-defined subgroup. Additionally, our study demonstrated that strokes occurring in patients with atrial fibrillation are more likely to progress. Whether this is due to larger strokes (more commonly seen with cardioembolic ischemic events) or reembolization is unknown. It is thought that the latter is less likely, given our clinical observations of a 60% (15/25) worsening rate compared with the 2-week recurrent stroke rate of 4.5% anticipated in patients with atrial fibrillation recently reported. Of those with atrial fibrillation who progressed, 13 of 15 had moderate to large cortical or subcortical infarcts. Of those who did not progress, 50% had small cortical or subcortical infarcts. There was no predilection for worsening in the vertebrobasilar infarct subgroup, as previously reported, though the numbers were too small to be able to draw definitive conclusions. Worsening associated with early hypodensity on CT, elevated admission systolic blood pressure, and elevated glucose levels was not seen or did not reach statistical significance in our study.

The overall design of the study was to identify predictors of neurological change and not particular mechanisms of injury. However, a reasonable conclusion from the data is that delayed edema may play a role in symptom progression. If reembolization were the primary mechanism of stroke progression, we would not have expected such a major difference in the rates between large and small strokes, since these events might be expected to occur at a similar frequency in all strokes. The
average time to worsening of 34.9 hours from stroke onset also fits a temporal profile consistent with edema.

In summary, our study shows a clinical dichotomy based on the initial NIHSS score of 7. It is therefore cautioned that randomization into clinical trials without stratification of stroke severity increases the risk of testing 2 populations of patients with different clinical courses and potentially different mechanisms of secondary injury. The methodology used to determine this dichotomy is a limitation in this study. Given our findings and the previous observations made by other investigators, a need for an expanded and prospective look at the natural history of stroke progression and outcome as it relates to presenting stroke severity is warranted to determine which patients are likely to have the best benefit-to-risk ratio from therapeutic interventions. This is not to imply that patients with lower stroke scale scores at onset would not benefit from neuroprotective agents or that they necessarily should be excluded from randomized trials. Rather, it suggests that severity should be taken into account when determining sample size and stratification of randomization for drug trials. Equally important is the concept that the variance in clinical course implies different mechanisms of secondary injury and should be considered when proposing studies of various “protective” agents as well as further investigations into mechanisms of neuronal injury.

Conclusions
This study strongly suggests that the course of the neurological deficit following acute stroke is dependent on the initial stroke severity and that a dichotomy in early outcome exists with respect to the initial NIHSS scores when patients are stratified to ≤7 and >7. These findings may have significant implications for the design and patient stratification in treatment protocols with respect to primary clinical outcome. In addition, the average time to the onset of neurological worsening and the association with larger strokes may provide clues as to the etiology of secondary functional decline. This may allow therapies targeting the ischemic penumbra to be instituted during the phase of lesion extension in these patient subgroups with greater chances of stroke progression. This same subgroup could constitute a target population for conducting pilot studies of the efficacy of putative therapeutic agents in acute stroke.

Acknowledgments
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References
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