Using Change in the National Institutes of Health Stroke Scale to Measure Treatment Effect in Acute Stroke Trials

Askiel Bruno, MD; Chandan Saha, PhD; Linda S. Williams, MD

Background and Purpose—Outcome measures in acute stroke trials are being refined. Changes in neurological deficits might be useful outcome measures because they can measure the entire spectrum of deficits.

Methods—We analyzed data from the acute stroke treatment trial Trial of Org 10172 in Acute Stroke Treatment (TOAST). Using logistic regression analysis, we modeled the probability of the TOAST predefined very favorable outcome (VFO; both Glasgow Outcome Scale 1 and modified Barthel Index 19 to 20) at 3 months. Within-subject changes (baseline–3 months) on the National Institutes of Health Stroke Scale (NIHSS) was the main predictor of interest.

Results—The baseline median NIHSS for the entire TOAST cohort was 7, and it improved by 4 points (interquartile range 3 to 6) among 603 patient with VFO and by 2 points (interquartile range −1 to 5) among 638 patients without a VFO (P < 0.001). The odds for VFO increased by 2.29 (95% CI, 2.06 to 2.54; P < 0.001) for each 1-point improvement on the NIHSS. In receiver operating characteristic analysis, final NIHSS ≤ 2 was a good predictor of VFO, but no single NIHSS change cut point was a good predictor of VFO.

Conclusions—NIHSS change appears to be a useful outcome measure for acute stroke trials and is not fully comparable to dichotomized functional outcomes. (Stroke. 2006;37:920-921.)

Key Words: outcome ■ recovery of function ■ stroke, acute

The traditional, dichotomized, primary functional outcomes in acute stroke trials may not capture clinically meaningful improvements that fall short of the defined outcomes,1,2 which may lessen the analytical power.1–4 Neurological deficit scales can measure changes from stroke onset through recovery across the entire range of deficits. The National Institutes of Health Stroke Scale (NIHSS) is a popular neurological deficit scale with documented reliability, validity, and outcome predictive ability.5–8 To evaluate NIHSS change over time as a potential marker of treatment effect in acute stroke trials, we analyzed data from a large acute stroke treatment trial, Trial of Org 10172 in Acute Stroke Treatment (TOAST).9 The TOAST trial compared treatment with the anticoagulant Danaparoid to placebo in patients with acute cerebral infarction and showed no treatment benefit.

Patients and Methods

Very favorable outcome (VFO) was predefined in TOAST as having both Glasgow Outcome Scale of 1 and modified Barthel Index 19 to 20 of 20 at 3 months. We defined NIHSS change as the baseline score minus the final 3-month score. Finalized TOAST trial data were provided by the TOAST Data Management Center at the University of Iowa College of Medicine, Iowa City, Iowa.

Logistic regression analysis modeled for VFO. Our primary objective was to assess the effect of within-subject NIHSS change after adjusting for significant covariates. Wilcoxon rank sum test compared NIHSS change between subjects with and without VFO. Subjects who died were assigned the highest possible NIHSS score. We also compared the NIHSS change by treatment group in the TOAST subgroups showing a significant treatment effect in the TOAST trial (Table). Receiver operating characteristic (ROC) analysis assessed sensitivities and specificities of the NIHSS change and the final 3-month NIHSS in predicting VFO.

Results

The TOAST trial enrolled 1281 subjects, and complete data for this analysis were available for 1232. At 3 months, the NIHSS score decreased by a median of 4 points (interquartile range 3 to 6) in subjects with VFO and by 2 points (interquartile range −1 to 5) in subjects without VFO (P < 0.001). In multiple logistic regression analysis, baseline NIHSS, baseline blood glucose, and NIHSS change were significant independent predictors of VFO. With each 1-point improvement in the NIHSS, the odds for VFO increased by 2.29 (95% CI, 2.06 to 2.54; P < 0.001). The Table shows the outcomes by treatment group.

Despite good correlation between NIHSS change and VFO in logistic regression analysis, ROC analysis did not find a specific cut point for NIHSS change with sufficiently high sensitivity and specificity to reliably predict VFO (area under curve 0.65; 95% CI, 0.62 to 0.68). However, analysis of the NIHSS score at 3 months as a predictor of VFO showed that a score of ≤2 is a good predictor of VFO (area under curve 0.91; 95% CI, 0.90 to 0.93; sensitivity 82.8%; specificity 84.6%).

Received November 28, 2005; final revision received December 16, 2005; accepted December 20, 2005.

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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000202679.88377.e4
Discussion

NIHSS change during the first 3 months of stroke and dichotomized functional outcomes convey different information and are not fully comparable. The NIHSS change measures all improvements, including those that stop short of a dichotomized favorable outcome but may nonetheless be clinically significant and may indicate a treatment effect. Theoretically, this method should increase the power of statistical analysis when comparing treatments. The association between NIHSS change and VFO found in this study indicates that the NIHSS change may be a useful addition to the traditional dichotomized outcomes in acute stroke trials.

As to reliably predicting the dichotomized VFO, no single NIHSS change cut point has sufficient sensitivity and specificity. This is because greater NIHSS changes are needed to achieve VFO in severe than in mild strokes. This is indicated by ROC analysis showing that a final 3-month NIHSS score dichotomized at ≤2 is a good predictor of VFO. Thus, to best predict VFO, a patient with a baseline NIHSS of 10 needs to improve by ≥8 points and a patient with a baseline of 5 by ≥3 points.

NIHSS change did not detect the treatment effects seen in secondary analyses in the TOAST trial (Table). At least 2 explanations for this are possible. One, NIHSS change might be a less sensitive outcome measure than the VFO. Alternatively, improvements in subjects with severe strokes who did not reach the VFO may have been such that they countered the result seen in TOAST when tested according to NIHSS change. Several acute stroke treatment trials report NIHSS change as a secondary outcome, largely in agreement with dichotomized functional outcomes.10–15 NIHSS change appears to be a useful outcome measure in acute stroke trials and should be studied further.

References


Very Favorable (functional) Outcomes and Median NIHSS Changes in the TOAST Trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Danaparoid</th>
<th>P Value</th>
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<tr>
<td>Entire TOAST cohort at 3 months (n=615–641)</td>
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<tr>
<td>VFO (%)</td>
<td>47.0</td>
<td>49.5</td>
<td>NS</td>
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<td>NIHSS change (IQ range)</td>
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<td>NS</td>
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<td>Entire TOAST cohort at 7 days (n=615–646)</td>
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<td>VFO (%)</td>
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<td>NIHSS change (IQ range)</td>
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<td>Atherothrombotic stroke subtype at 3 months (n=111–117)</td>
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<tr>
<td>VFO (%)</td>
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<td>NIHSS change (IQ range)</td>
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<td>3 (1–6)</td>
<td>NS</td>
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IQ indicates interquartile.
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Stroke. 2006;37:920-921; originally published online January 26, 2006;
doi: 10.1161/01.STR.0000202679.88377.e4

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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