Confirming tPA Treatment Effect by Baseline Severity-Adjusted End Point Reanalysis of the NINDS-tPA Stroke Trials

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Background and Purpose—Baseline severity-adjusted end point analysis, an emerging approach to the evaluation of primary end points in acute stroke trials, offers a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups, a factor that has complicated interpretation and reception of the results of the pivotal National Institute of Neurological Disorders and Stroke tissue plasminogen activator (NINDS-tPA) trials.

Methods—The sliding scale dichotomy end point responder analysis applied in recent acute ischemic stroke clinical trials was used to analyze NINDS-tPA stroke trials 1 and 2. Good outcomes were: 3-month Rankin scale 0 to 2 if pretreatment NIHSS scores were 0 to 5; 3-month Rankin scale 0 to 1 if pretreatment NIHSS scores were 6 to 14; 3-month Rankin scale 0 to 1 if pretreatment NIHSS scores were 15 versus 14, 0.10), and more extremely mild severity stroke patients were randomized to the placebo group. Among patients with NIHSS scores of 0 to 5, 72% were assigned to the tPA group versus 28% in the placebo group. This difference was particularly pronounced among patients in the 91 to 180 minute time window from onset to treatment.

This study was undertaken to determine whether NINDS-tPA study data indicate a beneficial treatment effect of tPA when a severity-adjusted end point analysis is applied to correct for imbalances in baseline stroke severity.

Methods

The sliding scale dichotomy end point applied in recent acute ischemic stroke clinical trials was used.1,2 Good outcomes were defined as: 3-month Rankin scale 0 if pretreatment NIHSS scores were 0 to 17; 3-month Rankin scale 0 to 1 if pretreatment NIHSS scores were 18 to 24; 3-month Rankin scale 0 to 2 if pretreatment NIHSS scores were >14. Data were obtained from the publicly available dataset of the results of NINDS trials 1 and 2. Analyses were performed on the following data groups: trial 1, trial 2, all patients from trials 1 and 2 combined, 0- to 90-minute

Key Words: acute care ■ acute Rx ■ acute stroke ■ clinical trials ■ emergency medicine ■ stroke ■ stroke care ■ therapy ■ thrombolysis ■ thrombolytic Rx

Baseline severity-adjusted end point analysis is an emerging approach to the evaluation of primary end points in acute stroke trials. Prognosis-adjusted end points allow enrolled patients to be assessed on achievable goals given their presenting stroke severity rather than a fixed target outcome inappropriate for individuals with very mild or very severe presenting stroke deficits.1-3

Severity-adjusted analysis also offers a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups. Baseline imbalance in prognostic factors has complicated interpretation and reception of the results of the pivotal National Institute of Neurological Disorders and Stroke tissue plasminogen activator (NINDS-tPA) trials.4,5 Whereas some baseline imbalances favored the placebo group (eg, younger age), others, particularly aspects of presenting stroke severity, favored the treatment group.4 The median NIHSS stroke severity score at entry showed a trend toward a difference between the tPA and placebo groups (15 versus 14, P=0.10), and more extremely
onset to treatment patients from trials 1 and 2 combined, and 91- to 
180-minute onset to treatment patients from trials 1 and 2 combined.
Analyses were performed on both raw data and on data after 
adjustment for baseline variables predictive of outcome. The follow-
ing 12 variables identified in previous studies, including the NINDS 
study itself, as determinants of prognosis or treatment response in 
acute ischemic stroke were covariates in the adjusted analysis, using 
logistic regression: age, sex, history of hypertension, history of 
diabetes, current smoking, pre-existing disability, mean arterial 
pressure, serum glucose, stroke subtype, baseline CT hypodensity, 
baseline CT intravascular thrombus, and baseline CT mass effect. 
Age, mean arterial pressure, and glucose level were treated as 
continuous variables, and the remaining factors were treated as 
binary variables. In an additional analysis, baseline NIHSS was 
adjusted for in addition to the other 12 predictor variables.

Power to detect a treatment effect was good in the combined 
analysis and moderate in the subgroup analyses. To detect a 
treatment effect that increased the odds ratio of good outcome to 1.8, 
power was 0.94 in the combined analysis, from 0.66 to 0.72 in the 
half population (trial part, time window) subgroup analyses, and 
from 0.29 to 0.69 within each tertile.

**Results**

In unadjusted analyses, both of the NINDS tPA stroke trials 
showed a statistically significant beneficial treatment effect 
of tPA. Among all 624 patients in trials 1 and 2 combined, and 91- to 
180-minute onset to treatment patients from trials 1 and 2 combined.
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included logistic regression analysis, risk adjustment effect analysis, interaction tests, analysis within tertiles and quintiles, and analysis of defined minor stroke categories. All found a beneficial effect of tPA after taking into account imbalances in baseline stroke severity.

Traditional statistical adjustment approaches can generally be conceptualized as adjusting the starting point for each patient based on their stroke severity, and then determining if treatment allows the patient to attain a good outcome state. The sliding scale dichotomy applied in this study can be conceptualized as adjusting the finish line for each patient based on their stroke severity, and then determining if treatment allows the patient to attain a good outcome. That both approaches show congruent findings provides additional confirmation that tPA is beneficial when administered within 3 hours of onset to patients with acute cerebral ischemia.

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**References**
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