Novel End Point Analytic Techniques and Interpreting Shifts Across the Entire Range of Outcome Scales in Acute Stroke Trials

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Background and Purpose—Stroke treatments are generally not curative, but rather alter patient outcome over the entire range of functional measures. Dichotomizing outcome scales reduces computational complexity, but discards substantial outcome information, artificially privileges only a single health state transition as clinically meaningful, and often reduces study power. Newer approaches to endpoint analysis have several advantageous properties.

Summary of Review—The global statistic assesses treatment effects on multiple outcome measures simultaneously. However, translating the global statistic multidimensional vector effect at the population level into benefit or harm expected in the individual patient is problematic. Responder analysis adjusts outcome thresholds to patient stroke severity at study entry, identifying achievable goals for each patient. However, responder analysis still discards substantial outcome information. Shift analysis gauges change in outcome distributions over the full range of ascertained outcomes, incorporating benefit and harm at all health state transitions valued by patients and clinicians, and often increasing study power. Translation of findings of shift analyses into clinically accessible terms may be accomplished using the recently developed joint outcome table specification technique, which yields the following values for the number needed to treat for 1 patient to improve in a clinically important manner: nimodipine in subarachnoid hemorrhage, 6.8; coiling over clipping, 5.9; intra-arterial pro-urokinase in acute cerebral ischemia, 4.8; intravenous tissue plasminogen activator, 3.3.

Conclusions—Dichotomized, global statistic, responder, and shift analyses each offer distinctive benefits and drawbacks. Choice of primary end point analytic technique should be tailored to the study population, expected treatment response, and study purpose. Shift analysis generally provides the most comprehensive index of a treatment’s clinical impact. (Stroke. 2007;38:3055-3062.)

Key Words: cerebral hemorrhage ■ cerebral infarction ■ cerebrovascular accident ■ clinical trials ■ research design

In approximately the year 2000, the field of acute stroke clinical trials experienced a scientific crisis. Over the course of the 20th century, at least 75 promising agents had emerged from animal testing, rich with promise, to undergo clinical study. Although at least 178 randomized clinical trials enrolling >73 000 patients were conducted of these agents, only 3 trials reported positive findings and only 1 agent had been approved by the Food and Drug Administration for use in acute cerebral ischemia.¹ This remarkable record of failure led to a fundamental reassessment of the methodological framework of preclinical and clinical development of pharmacologic agents for acute stroke.²–⁶

In the sphere of clinical trial design, 6 common defects were noted: (1) treatment was initiated too late; (2) dosages of neuroprotective class agents were too low; (3) patients were enrolled who were unable to respond to the study agent mechanism of action; (4) patients with uninformative deficits were enrolled; (5) studies were underpowered; and (6) the endpoints and statistical endpoint analytic techniques discarded substantial outcome information. These designs led to studies that examined infarcts that were already largely completed; failed to attain adequate neuroprotective tissue levels of the study drug; and enrolled inappropriate patients, such as those with pure white matter infarcts for studies of drugs active only at gray matter synaptic terminals or those with deficits too mild or too severe to permit demonstration of a treatment effect. The use of small sample sizes yielded studies insensitive to modest but clinically important benefits of tested agents. Discarding relevant outcomes in primary endpoint analysis reduced study power.

These insights have informed the design many 21st century trials, which have made substantial efforts to accelerate time of treatment start, attain neuroprotective blood levels, enroll only patients with informative conditions, increase samples sizes, and use novel statistical techniques to increase study power.
Perhaps the most exotic of these innovations to clinicians are novel statistical analysis approaches used in recent and current trials. Simple dichotomized analysis of a single end point has virtually disappeared as a primary end point. Nearly all acute stroke clinical trials now use 1 of 3 new approaches to end point statistical assessment: (1) the global statistic; (2) responder analysis; and (3) shift analysis. Hence, the need to understand the advantages, disadvantages, and interpretation of these prevalent statistical analytic techniques takes on great urgency. This review surveys these novel statistical techniques, with special emphasis on shift analysis, as the least familiar of these approaches. Understanding these innovative outcome analysis strategies is facilitated by placing them in perspective against the traditional dichotomized approach to end point analysis.

Traditional Dichotomized End Point Analysis
Stroke treatments are generally not curative, but rather confer improvement to patients along an entire range of functional outcomes. A patient’s final health state may range from full recovery, with no residual symptoms; through mild symptoms without alteration in vocational capacity; varying levels of dependence in activities of daily living; permanent vegetative state; to death. To capture this range of health states, the outcome scales commonly used in stroke trials rate patients across multiple ranks. The modified Rankin Scale (mRS) divides global disability into 7 strata, the Barthel Index rates functional activities of daily living among 20 levels, and the NIHSS assigns patients according to 42 ranks of neurologic deficit severity. Stroke-related quality-of-life scales have even finer gradations, further reducing ceiling and floor effects.

Dichotomized end point analyses convert these ordinal scales, which have a spectrum of outcomes, into binary measures. The dichotomized statistical approach can be thought of as asking, “Does the treatment make more patients achieve a good outcome, defined as better than threshold X?” Binary analysis has the advantage of computational simplicity and straightforward clinical interpretation. Net number needed to treat to benefit (NNT) values are easily derived from dichotomized end points. This derivation allows clinicians to clearly convert trial results into how many patients are needed to achieve one additional net good outcome (where “good” means exceeding the dichotomization threshold).

Binary analysis also has several disadvantages. It requires that trialists privilege as valuable only 1 health state transition among the many that matter to patients and caregivers. The choice regarding which health state transition to value above all others is often made arbitrarily. Moreover, by inspecting only a single health state transition, binary analysis forces trialists to discard substantial amounts of outcome information, which will generally lead to underestimation of treatment benefit or treatment harm or both (Figure 1a).

Figure 1. a, Discarding of outcome information in dichotomized analysis. Top panel, Schematic illustrations of 7-level outcome scale. Top row, A range of potential small step improvements in response to therapy. Lower row, A range of moderate step improvements. Middle panel, 7-level scale converted to a binary measure by dichotomization at 0 to 2 vs 3 to 6. Lower panel, 3 to 2 health state transition improvements measured in the binary analysis (white arrow) and improvements that go unmeasured in the primary analysis (light blue arrows) (©UCLA Stroke Program). b, Worsening at unanalyzed transitions in dichotomized analysis. Top panel, Schematic illustration of a response pattern on a 7-level outcome scale to an agent that benefits patients with mild stroke severities at trial entry but harms patients with moderate to severe strokes at entry (e.g., fibrinolytic drug with high hemorrhagic propensity). Top row, Small step changes. Lower row, Moderate step changes. Bottom panel, After conversion of the 7-level scale to a binary measure by dichotomization at 0 to 1 vs 2 to 6, only at improvements at the 2 to 1 health state transition are counted (white arrows). The binary analysis suggests the agent is beneficial, even though it causes harm to more patients (light blue arrows) than it benefits (©UCLA Stroke Program).
Consider, for example, the most commonly used primary end point in stroke clinical trials, the mRS of global disability (Table 1). When the 7-level mRS is dichotomized as 0 to 2 vs 3 to 6, a traditional breakpoint in binary trial analysis, the resulting analysis examines only 1 important transition in health state, from vocationally impaired, but able to live independently, to requiring assistance in daily living. However, this analysis places absolutely no value on other health state transitions that are pertinent to patients. For example, going from disabled to dead (mRS=6) to moderately disabled and able to walk on one’s own (mRS=3). Binary outcome analyses prioritize only a single health state transition as clinically worthwhile, whereas patients naturally place great value on several health state transitions.

The focus of binary analysis on a single transition in health state is of particular concern when a treatment has beneficial and harmful effects differentially distributed over the range of disease severities. For example, a treatment such as a fibrinolytic drug with a strong hemorrhagic propensity might be beneficial for patients with milder strokes, but harmful for patients with more severe stroke. When a trial of this type of drug is analyzed with a binary primary end point focused on a health state transition to very good outcomes, the statistical analysis might be formally positive for a beneficial effect. Yet the agent could actually be harming more patients in the unanalyzed severe end of the outcome spectrum than it is helping in the analyzed milder end (Figure 1b).

**Newer Approaches to End Point Analysis**

Because of the drawbacks of dichotomization, several new approaches to end point analysis have recently been adopted in acute stroke clinical trials (Figure 2), including the global statistic, responder analysis, and shift analysis.

**Global Statistic**

The global statistic simultaneously looks at multiple outcome measures, each related to an underlying unitary health state, and examines whether treatment is increasing the proportion of patients with good outcomes on each measure. The global statistic can be thought of as asking the question, “Does the treatment make the treated population better as assessed in these several ways?”

The global statistic has several advantageous features. It reflects the reality that many measurement instruments capture desired health states only partially. For example, patients and physicians consider good stroke recovery to include all of the following: having few neurologic deficits, being independent, having a high level of cognitive function, and having a high quality of life. Generalized estimating equations and other mathematical techniques can combine individual statistics, each measuring the association between a treatment and 1 aspect of stroke recovery, into a global statistic that provides a more complete map of outcome. Furthermore, use of the global statistic often improves study power. By combining several different correlated measurements of the same trial population and the same underlying health outcome state, study power is enhanced through the reduction of noise generated by random fluctuations along any single outcome scale.

Nevertheless, the global statistic has drawbacks. Statistical methods for applying the global statistic over all levels of several ordinal scales, rather than only dichotomized end points, are still in development. As a result, acute stroke trialists have combined only multiple dichotomized end points in global statistic analyses, from the landmark NINDS recombinant tissue plasminogen activator trials to the recent IMAGES trial. The resulting hyperdichotomized end point has many of the disadvantages of standard dichotomized end points, including discarding much of the outcome data and failing to reflect beneficial or harmful transitions over the

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**Table 1. Modified Rankin Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to perform all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to perform all previous activities, but able to take care of self without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

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**Figure 2.** Four approaches to end point analysis. Column 1 depicts standard dichotomized analysis, counting only transitions across a single scale threshold. Column 2 shows global statistic analysis, counting transitions on several different outcome scales, eg, mRS, Barthel Index, NIHSS, and Glasgow Outcome Scale. Column 3 depicts sliding dichotomy responder analysis. Patients with mild deficits at study entry must attain level 0 to count as responders; patients with moderate deficits $\leq$ level 1, and patients with severe deficits $\leq$ level 2. Column 4 shows shift analysis, with transitions across all levels of the scale counted (©UCLA Stroke Program).
entire outcome range. When component scales are dichotomized at cut points identifying extreme good outcomes, trial assessment may be unduly driven by responses seen only in mildly affected patients. Perhaps the greatest disadvantage of the global statistic is that it is difficult to express the results in terms intuitively meaningful to the patient and clinician at bedside. Techniques for translating multidimensional vector effects at the population level into benefit or harm to be expected in the individual patient remain undeveloped. For this reason, in the past the Food and Drug Administration and other regulatory agencies have discouraged the use of the global statistic as the primary end point in pivotal acute trials.

**Responder Analysis**

Responder analysis, also known as baseline severity-adjusted analysis, adjusts outcome thresholds according to stroke severity at study entry. Although responder analysis can be applied across several ranks, to date only a sliding dichotomization strategy has been deployed in acute stroke trials. If a patient has a mild deficit at study entry, then only an excellent final outcome is considered a positive treatment response; for a patient with a moderate deficit at entry, a good outcome is judged as positive; and for a patient with a severe deficit at entry, a fair final outcome is considered positive. Responder analysis asks the question, “Does the treatment make patients better, considering where they started?”

Responder analysis has the advantage of analyzing an achievable goal for each patient rather than a fixed uniform outcome that would be inappropriate for very mild or severe stroke patients. As a result, it tends to increase detection of true signals occurring in the data set without increasing noise, thereby improving study power. However, like standard dichotomized assessments, responder analysis collapses outcome categories into binary or other reduced categories, discarding much outcome information and ignoring important disease state transitions. Another substantial drawback is that optimal calibration of the “slide” (demarcating the entry severity categories and outcome thresholds), responder analysis requires that the investigators have foreknowledge of where along the outcome continuum the study treatment is most likely to work. A general advantage of shift analysis compared with other approaches is that it makes the least assumptions about the type of patients who will end up enrolled in a trial, the type of outcomes they will experience, and the treatment effect pattern the study agent will exert. Because it detects all important disease state transitions, shift analysis heightens the recognition of true signal and, therefore, in many situations, can increase study power. Shift analysis will especially enhance trial efficiency compared with collapsed analyses when treatment effects occur at all severities or at unpredictable state transitions.

Shift analysis does have disadvantages, primarily its computational complexity. Although modern statistical software can readily handle the appropriate ranked calculations, investigators may not be fully adept at projecting the population distributions of outcomes required for sample size and power calculations using shift analysis. If polytomization is carried to the extreme, unimportant differences in outcome may enter into the analysis, resulting in detection of treatment effects so small as to be clinically insignificant or in nondifferential misclassification that may reduce analytical power. These problems likely arise when the full 42-level NIHSS is used as an outcome measure; they are less of an issue when using scales of 7 levels or fewer levels, such as the mRS or the Glasgow Outcome Scale. Shift analysis may be less efficient than collapsed analyses when treatment effects cluster at one state transition. Another historical drawback of shift analysis is difficulty expressing the treatment effect measured in terms meaningful to patients and clinicians.

Extensive evidence from both model and actual stroke trial populations show that shift analysis often improves study power to detect a true treatment effect. In the extreme case of a model population in which a drug was postulated to improve the outcome of every enrolled patient to the same small degree, Berge and Barer showed that, compared with dichotomized analysis, shift analysis reduced by >60% the sample size required to demonstrate the true treatment effect. The effect of shift analysis in actual stroke trial populations has been analyzed by the Optimizing Acute Stroke Trials Collaboration. The Optimizing Acute Stroke Trials group collected data from 55 treatment comparison in trials of acute stroke or stroke rehabilitation interventions that the investigators felt likely exerted a biological effect, either beneficial or harmful. The collaborators compared various modes of analysis of final end points, including standard dichotomized analysis, trichotomized analysis, and a variety of forms of ranked analysis. Ordinal shift analyses consistently outperformed dichotomized analysis and other collapsed approaches. These findings confirm empirically the theoretical expectation that for a disease like stroke, which causes a range of functional impairments to develop, shift analysis will often be a more powerful mode of end point analysis than standard dichotomization. Stroke trialists have indeed long been handicapping their studies by use of an inefficient statistical mode of primary end point analysis.

**Clinical Interpretation of Shift Analyses**

The perceived difficulty in translating ranked analyses into meaningful terms at the bedside was the primary reason for...
Because of the need to express a shift treatment effects distributed over a range of outcomes in a manner intuitively meaningful to patients and clinicians, single NNT and NNH values that incorporate health state transitions across the entire range of outcomes are highly desirable. However, deriving NNT values over the entire range of outcomes from randomized clinical trials requires a novel approach to NNT calculation that overcomes 2 statistical barriers.

The first barrier is scale nonlinearity. Nonlinearity refers to the fact that transitions at different points on ordinal scales like the mRS are not necessarily equal in value. A 1-point change from 6 to 5 (dead to persistent vegetative state) is qualitatively different and almost certainly quantitatively different from the 1-point change from 1 to 0 (symptoms without functional impairment to no symptoms at all). However, a useful NNT measure can be derived from noncomparable health state transitions, as long as each transition that is being counted is clinically worthwhile for the patient to attain.

Some transitions are not considered desirable by many individuals. For example, among healthy, elderly Americans, 47% consider a stroke outcome of surviving alive but severely disabled as worse, not better, than death.29 For these individuals, transitioning from an mRS of 6 to 5 is not a better outcome, it is worse. For this reason, it sometimes will make sense to collapse mRS 5 and 6 categories into a single worst outcome group and not count transitions from 6 to 5 as improvements. In contrast, virtually all other single-point transitions on the mRS appear to be clinically valuable. Once nonvaluable transitions are discarded from the analysis, a value can be calculated for the NNT for 1 patient to improve by ≥1 clinically worthwhile steps.

The second statistical barrier, stated technically, is that derivation of an NNT across an ordinal scale requires knowledge of the within-patient correlation, and these data are not specified by parallel group clinical trials, but only by crossover design trials.10,30,31 In nontechnical terms (Figure 3), the challenge is that trial data do not specify if group differences in the distribution of outcomes occur because many individuals each improve a little bit, a few individuals each improve a lot, or a mixture of these outcomes.

This problem can be overcome, however, by using the method of joint outcome table specification.10 This method permits derivation of: (1) the trial data specified minimum possible value for the NNT; (2) the trial data specified maximum possible value for the NNT; (3) individual expert judgment of the biologically most plausible NNT; and (4) individual expert judgment of the biologically most plausible NNH.

Table 2 shows the NNTs for the PROACT 2 Trial for different dichotomizations of the mRS. Each of the dichotomized NNTs provides only an incomplete index of treatment impact and the values range widely depending on the breakpoint used (6.7 to infinity). Proponents of a therapy may highlight only the most favorable NNTs23 and opponents only the least favorable, a reporting emphasis that might be termed “impact bias.” More importantly, all of these dichotomized NNTs underestimate the treatment effect of most relevance to decision-makers, which is benefit over the full range of outcomes rather than just at a single, arbitrarily selected, health state transition.

Table 2. PROACT 2 Trial Number

<table>
<thead>
<tr>
<th>Rankin Transition</th>
<th>NNT, net</th>
</tr>
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<tbody>
<tr>
<td>Dichotomized</td>
<td></td>
</tr>
<tr>
<td>0 vs 1–5</td>
<td>100</td>
</tr>
<tr>
<td>0–1 vs 2–5</td>
<td>11.1</td>
</tr>
<tr>
<td>0–2 vs 3–5</td>
<td>6.7</td>
</tr>
<tr>
<td>0–3 vs 4–6</td>
<td>20</td>
</tr>
<tr>
<td>0–4 vs 5–6</td>
<td>Infinity</td>
</tr>
<tr>
<td>0–5 vs 6</td>
<td>50</td>
</tr>
</tbody>
</table>

Across all transitions of 7-level Rankin scale

| Minimum possible | 2.6 | 25 |
| Maximum possible | 5.9 | 25 |
| Biologically most plausible | 4.8 | 28.4 |

Needed-to-treat values for different 6-level Rankin transitions.

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the final group distribution, the highest possible NNT compatible with the trial data can be derived.\textsuperscript{32,33} Moreover, having disease experts specify the biologically most reasonable distribution of responses specifies within-patient correlation and permits derivation of the biologically most plausible NNT and NNH, reflecting benefits and adverse effects accrued across the entire outcome range. Averaging the NNTs and NNHs independently derived from multiple experts avoids idiosyncratic perspectives and permits derivation of benefit and harm values that represent the best insight from the field.\textsuperscript{10,32}

This method allows derivation of the number needed to treat for 1 additional patient to benefit by improving by \( \geq 1 \) grades of global disability on the mRS.

Tables 2 and 3 demonstrate the results that arise from this analytic method. Table 2 shows that the PROACT 2 trial data indicate the lowest possible NNT for 1 patient to benefit by improving by \( \geq 1 \) grades of global disability on the mRS is 2.6, and the highest possible is 5.9. The expert-derived most plausible NNT is 4.8 (95% CI, 4.1 to 5.5). For every 100 middle cerebral artery occlusion patients treated within 6 hours of onset with intra-arterial pro-urokinase, 21 improve by \( \geq 1 \) grades on the mRS global disability scale and 4 worsen by \( \geq 1 \) grades. Table 3 shows the NNT and NNH across the 6-level version of the mRS for 5 acute stroke interventions with positive phase 3 trials, recombinant tissue plasminogen activator, intra-arterial pro-urokinase, and NXY-059 for acute cerebral
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