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 endpoint 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.

Keywords: 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. 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.

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](http://stroke.ahajournals.org/)

**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 (eg, 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 vocationally impaired (mRS=2) to no symptoms at all (mRS=0) is not counted as a clinically meaningful improvement, nor is going from 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 an 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

<table>
<thead>
<tr>
<th>Table 1. Modified Rankin Scale</th>
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<tr>
<td>Score</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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</table>

**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 ≥level 1, and patients with severe deficits ≥level 2. Column 4 shows shift analysis, with transitions across all levels of the scale counted (©UCLA Stroke Program).
Responder Analysis
Responder analysis, also known as baseline-severity-adjusted analysis, adjusts outcome thresholds according to stroke severity at study entry.\textsuperscript{14,15} Although responder analysis can be applied across several ranks, to date only a sliding dichotomy analysis strategy has been deployed in acute stroke trials.\textsuperscript{16–18} 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 for 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 alter patient status.

Shift Analysis
Shift analysis gauges change in outcome distributions over the full (or nearly full) range of ascertained outcomes. Also known as analysis of distributions, rank analysis, and analysis over levels, shift analysis asks the question, “Does the treatment make the patient better to some degree?” Several recent National Institute of Health, academic, and industry acute stroke clinical trials have used shift analysis.\textsuperscript{19–21}

Shift analysis has several distinct advantages compared with simple dichotomization. It is irreducibly polychotomous, and consequently incorporates benefits and harm seen at all disease state transitions. Like responder analysis, shift analysis evaluates achievable goals for every patient. In addition, shift analysis inspects a greater number of achievable goals than sliding dichotomy implementations of responder analysis and does not require investigator foreknowledge of where in the spectrum of stroke severities an experimental 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 polychotomization 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\textsuperscript{22,23} or in nondifferential misclassification that may reduce analytical power.\textsuperscript{24} 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\textsuperscript{25} showed that, compared with dichotomized analysis, shift analysis reduced by \textgreater 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.\textsuperscript{26} 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 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
across all transitions of 7-level Rankin scale

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

**Table 2. PROACT 2 Trial Number**

**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.

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.

Trial data fully specify the minimum and maximum possible values for the NNT across an ordinal scale, if a treatment does not cause harm or causes a known pattern of harm. By completing joint outcome tables under the extreme assumption that every patient who improves does so by only one step, the lowest possible NNT compatible with the trial data can be derived. By completing joint outcome tables under the extreme assumption that every patient who improves does so by the largest number of steps compatible with
the final group distribution, the highest possible NNT compatible with the trial data can be derived.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.10,32 This method allows derivation of the number needed to treat for 1 additional patient to benefit by improving by ≥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 ≥1 grades of global disability on the mRS is 2.6, and the highest possible is 5.9. For every 100 middle cerebral artery occlusion patients treated within 6 hours of onset with intra-arterial pro-urokinase, 21 improve by ≥1 grades on the mRS global disability scale and 4 worsen by ≥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
ischemia, and nimodipine and coiling (versus clipping) for aneurysmal subarachnoid hemorrhage.

Good judgment comes from experience. Experience comes from bad judgment. One consolation of the many nonpositive stroke trials performed to date is the hope that acute stroke trialists have at last failed often enough to gain sufficient wisdom to devise trials that will be successful. One of the most important lessons we have learned is that we can design and clinically interpret trials that employ primary end point analyses sensitive to treatment effects over the entire range of outcomes. For any individual trial, the selection of primary end point analysis technique should be guided by the study population, expected treatment response, and study purpose; often, though not always, shift analysis will be advantageous. Shift analysis is an important advance in the interpretation, as well the design, of clinical trials, and generally provides the most comprehensive single value summary of a treatment’s clinical impact. As clinicians and as researchers, we seek to help patients afflicted by a disease that cripples as well as kills, and we are deeply interested in detecting all treatment benefits that matter to our patients and their families.

Acknowledgments

The author thanks fellow members of the pro-urokinase NNT and NIH derivation expert panel: Gary Duckwiler, MD, Reza Jahan, MD, David Liebeskind, MD, Sidney Starkman, MD, and Fernando Vinuela, MD.

Sources of Funding

This work was supported in part by NIH-NINDS Awards U01 NS 44364 and P50 NS044378.

Disclosures

Scientific Advisory Boards and Scientific Consulting from: Ambit Biosciences, Quintiles, Nuvemo, Co-Axia, Astellas, Novo Nordisk, Astra Zeneca, FibroGen,Boehringer Ingelheim (secondary prevention), Talairach. Trial site subinvestigator: Takeda, Eli Lilly, Astra Zeneca, Neurobiological Technologies. Trial investigator in NIH supported studies with drug or devices supplied by the following companies: CLEAR Trial, IMS 1–3 Trials, MR RESCUE Trial. Speaker’s Bureau or Speaking Honoraria received from Boehringer Ingelheim (secondary prevention), Concentric Medical.

References


Table 3. Treatment Effect Summary Measures for 5 Positive Acute Stroke Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Source Trials</th>
<th>Mean mRS Difference</th>
<th>Net NNT 0–1 vs 2–6</th>
<th>Net NNT 0–2 vs 3–6</th>
<th>NNH Across 6-Level Scale</th>
<th>NNT Across 6-Level Scale</th>
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<tr>
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<td>8.4</td>
<td>56.6</td>
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<td>PROACT 2</td>
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<td>11.1</td>
<td>6.7</td>
<td>28.4</td>
<td>4.8</td>
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<td>Coiling in SAH</td>
<td>ISAT</td>
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<td>14.3</td>
<td>NH</td>
<td>5.9</td>
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<tr>
<td>NXY-059</td>
<td>SAINT 1</td>
<td>0.13</td>
<td>41.7</td>
<td>47.6</td>
<td>NH</td>
<td>9.8</td>
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<td>Nimodipine in SAH</td>
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<td>9.6</td>
<td>7.6</td>
<td>NH</td>
<td>6.8</td>
</tr>
</tbody>
</table>

GOS indicates Glasgow Outcome Scale; ProUK, pro-urokinase; TPA, tissue plasminogen activator; SAH, subarachnoid hemorrhage; NH, no harm estimated.
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Stroke. published online October 4, 2007;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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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