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Thrombolysis Is Associated With Consistent Functional Improvement Across Baseline Stroke Severity

A Comparison of Outcomes in Patients From the Virtual International Stroke Trials Archive (VISTA)

Nishant K. Mishra, MBBS; Patrick Lyden, MD; James C. Grotta, MD; Kennedy R. Lees, MD, FRCP;
for the VISTA Collaborators

Background and Purpose—Baseline stroke severity predicts outcomes among thrombolysed patients. The baseline National Institutes of Health Stroke Scale (NIHSS) thresholds are sometimes used to select patients for thrombolysis, clinical trial enrollment, or both. Using data lodged with Virtual International Stroke Trials Archive, we compared adjusted outcomes between thrombolysed and nonthrombolysed patients enrolled in neuroprotection trials (1998–2007) to assess the influence of various levels of baseline NIHSS.

Method—We assessed the association of treatment with outcome, measured across the modified Rankin scale score distribution, in patients categorized by baseline NIHSS in increments of 4. We used an age and baseline NIHSS adjusted Cochran-Mantel-Haenszel test followed by proportional odds logistic regression analysis. We report the Cochran-Mantel-Haenszel *P* values and estimated odds ratios (OR) for improved modified Rankin scale score distribution with treatment for patients within each baseline NIHSS category.

Results—Data were available for 5817 patients (1585 thrombolysed and 4232 nonthrombolysed). Baseline severity was greater among thrombolysed than nonthrombolysed (median baseline NIHSS, 14 vs 13; *P*<0.05). An association of treatment with outcome was seen independently and was of similar magnitude within each of the baseline NIHSS categories 5 to 8 (*P*=0.04; OR, 1.25; 95% confidence interval [CI], 1.0–1.6; N=278/934 thrombolysed/nonthrombolysed), 9 to 12 (*P*=0.01; OR, 1.3; 95% CI, 1.1–1.6; N=404/942), 13 to 16 (*P*<0.05; OR, 1.6; 95% CI, 1.3–2.1; N=342/814), 17 to 20 (*P*<0.05; OR, 1.7; 95% CI, 1.3–2.1; N=311/736), and 21 to 24 (*P*<0.05; OR, 1.6; 95% CI, 1.1–2.1; N=178/466). No association was observed within baseline NIHSS categories 1 to 4 (*P*=0.8; OR, 1.1; 95% CI, 0.3–4.4; N=8/161) or ≥ 25 (*P*=0.08; OR, 1.1; 95% CI, 0.7–1.9; N=64/179).

Conclusions—In this nonrandomized comparison, outcomes after thrombolysis were significantly better than in untreated comparators across baseline NIHSS 5 to 24. The significant association was lost only at extremes of baseline NIHSS when sample sizes were small and confidence limits were wide. (*Stroke*. 2010;41:2612-2617.)

Key Words: baseline ■ functional ■ severity ■ stroke ■ thrombolysis

Intravenous thrombolysis with alteplase is a proven therapy for acute ischemic stroke patients presenting before 4.5 hours of symptom onset.¹ However, some patients are denied therapy for fear of poor outcomes.² European guidelines recommend that patients with baseline stroke severity, National Institutes of Health Stroke Scale (NIHSS) ≥ 25 , and minor/rapidly improving strokes should not be thrombolysed,^{2,3} because it is believed that many patients who show rapid improvement/have minor strokes would not display residual deficit, and treatment with thrombolytic therapy would expose them to risk of complications, such as cerebral hemorrhage. Similarly, those patients who present with base-

line NIHSS ≥ 25 are also supposed to have poorer outcomes because of excess symptomatic hemorrhages.²⁻³ Baseline stroke severity (baseline NIHSS) is known to affect outcomes among thrombolysed patients⁴ and therefore was incorporated for patient selection in the ECASS III trial.¹ Although the regulatory authorities have recommended withholding thrombolytic therapy among patients with minor/rapidly improving strokes and for those with severe stroke at baseline, poorer response to therapy in these subgroups has never been demonstrated in randomized, controlled trials.⁵ Post hoc analyses of the NINDS and ECASS-III trials suggest equal efficacy across severity range, although power to examine

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subgroups is inevitably lower than chosen for the primary analyses, and patients at extremes of severity were under-represented.^{6–8} The logistical challenges involved in generating randomized trial evidence for these limited subgroups militate against any prospect for producing a definitive answer in the foreseeable future. Therefore, we must turn to alternative sources of evidence.

The Virtual International Stroke Trials Archive (VISTA) is a repository of data from many rigorously controlled clinical trials.⁹ Although most of these trials examined putative neuroprotectant agents, use of recombinant tissue plasminogen activator was generally recorded. We planned to use data from VISTA, hypothesizing that clinical practice over the past decade would have been sufficiently diverse to allow analysis of existing rigorously collected clinical data lodged in VISTA to examine the influence of baseline stroke severity on outcomes after thrombolytic therapy.

Patients and Methods

Data Source and Patients

We collated the demographics, clinical data, and measures of functional outcome from neuroprotection trials conducted in the period 1998 to 2007, held within VISTA (www.vista.gla.ac.uk).¹⁰ All trials held necessary review board and regulatory approvals, and patients consented to participation; only anonymous data are held by VISTA. We sought VISTA data derived from trials in which the investigational neuroprotection agent was not vasoactive and did not interfere with clotting or from placebo groups. We excluded any patient who had cerebral hemorrhage or stroke of undetermined etiology. To avoid dual publication, we excluded patients who may have been enrolled in SITS-MOST; we determined this from their country and date of enrollment. Finally, we excluded patients lacking our chosen outcome measure, 90-day modified Rankin scale (mRS) score, or secondary outcome, 90-day NIHSS score. Patients who died within 90 days were attributed the mRS score of 6 and categorized separately for NIHSS analysis.

Statistical Analysis

We compared outcome between patients who received thrombolysis and patients who did not receive thrombolysis (controls) among the categories of baseline NIHSS scores (<4, 5–8, 9–12, 13–16, 17–20, 21–24, and ≥ 25). Note that the reason for withholding thrombolysis in each case was not recorded but will include absence of marketing approval in the region at that time, clinical uncertainty over the use of thrombolysis for stroke generally, absence of treatment facilities for thrombolysis in the hospital at that time, and contraindications to thrombolysis for the individual patient. For each contrast, we compared the overall distribution of all 7 categories of day 90 mRS scores of the 2 groups, ie, from 0 (asymptomatic) through 5 (bed-bound and completely dependent) to 6 (dead). The European Medicines Evaluation Agency Points to Consider for reporting trials allow for use of the full distribution of the mRS but suggest that this may be supported by a secondary analysis of a second outcome measure, such as NIHSS.¹¹ For analysis of our supporting end point, NIHSS, we grouped adjacent scores into categories: 0 (no measurable deficit), 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, 21 to 24, and ≥ 25 (most severe neurological deficit) or dead. The distribution of patients across these categories was then compared between the groups as it was for mRS.

To test for a significant association of outcome distribution with thrombolysis exposure, we used the Cochran-Mantel-Haenszel statistic, adjusting for both age and baseline NIHSS as continuous variables.^{12,13} This nonparametric approach avoids invoking an assumption of proportional odds in which there should be a common odds ratio across all cut points on the ordinal outcome scale, and we consider that the Cochran-Mantel-Haenszel test provides the most

conservative estimate of statistical significance. However, it does not express the extent of the association. For this, we applied logistic regression analysis, also adjusted for age and baseline NIHSS, to estimate the odds ratio under the assumption of proportional odds and its associated 95% confidence interval.

Our choice of baseline factors for adjustment was based on 2 influences. First, age and baseline severity are the 2 most powerful prognostic factors for stroke and are usually included in outcome distribution analyses.^{13–17} Second, age and NIHSS data were available for our entire sample, whereas other factors of potential interest were incomplete. However, we also undertook a sensitivity analysis in which we adjusted for ECASS III variables diabetes and previous stroke. In addition, we also undertook an adjusted analysis by combining the variables that differed significantly at baseline; however, if this resulted in excessive diminution of our sample, we reported the limitations.

Our objective was mainly to undertake ordinal distribution or “shift” analysis, which is an efficient end point analytic technique recommended by European Medicines Evaluation Agency.^{11,18–20} Shift analysis is considered better than dichotomization of end point measures, although there are differences of opinion.^{21,22} Dichotomization is criticized for the statistical information it discards, ie, loss of power, and shift analysis is especially useful when the treatment effect is mild and/or uniform across all Rankin categories. Odds ratios in our analysis express the common odds of an improved distribution of outcome in association with alteplase treatment.

Cochran-Mantel-Haenszel and logistic regression analyses were undertaken using SAS 9.2 software (SAS Software Limited, United Kingdom) and other analyses by Stats Direct software (StatsDirect Limited, United Kingdom).

Reliable information on symptomatic hemorrhage was not available because post-treatment imaging was not routinely applied in neuroprotection trials to patients who had not been treated with alteplase.

Results

Patient Sample

We collated data on 9665 patients, of whom 5342 (59%) were enrolled from non-European sites. To avoid dual publication with SITS-MOST, we excluded 2789 patients (28%) enrolled from European sites between 2002 and 2006, and 177 patients for whom we lacked information on country. Complete data were available for analysis of mRS for 5817 patients and data on NIHSS were available for 5715 (Figure 1).

All stroke patients were treated as per institutional practice and stroke guidelines acceptable at the point of trial conduct. Monitoring for protocol compliance was undertaken on behalf of sponsors for these trials. This implies that when thrombolysis was administered, this was in accordance with marketing authorization for the relevant country, ie, that treatment commenced within 3 hours of stroke onset; however, the onset to treatment delay is not recorded for thrombolysis in these trials. Our data derived mainly from North American (60%), European (16%), and Australasian (13%) centers. Baseline characteristics are shown in the Table. Of the 5817 patients with mRS outcome data, 1585 (27.2%) received thrombolysis.

Does Baseline Stroke Severity Influence Stroke Outcomes?

In an ordinal logistic regression analysis, we found that baseline severity ($P < 0.0001$), use of recombinant tissue plasminogen activator, and age were significant predictors of outcomes. Then, in an age-adjusted ordinal logistic regression analysis, we found that baseline stroke severity ($P < 0.0001$) and the interaction between severity and use of alteplase

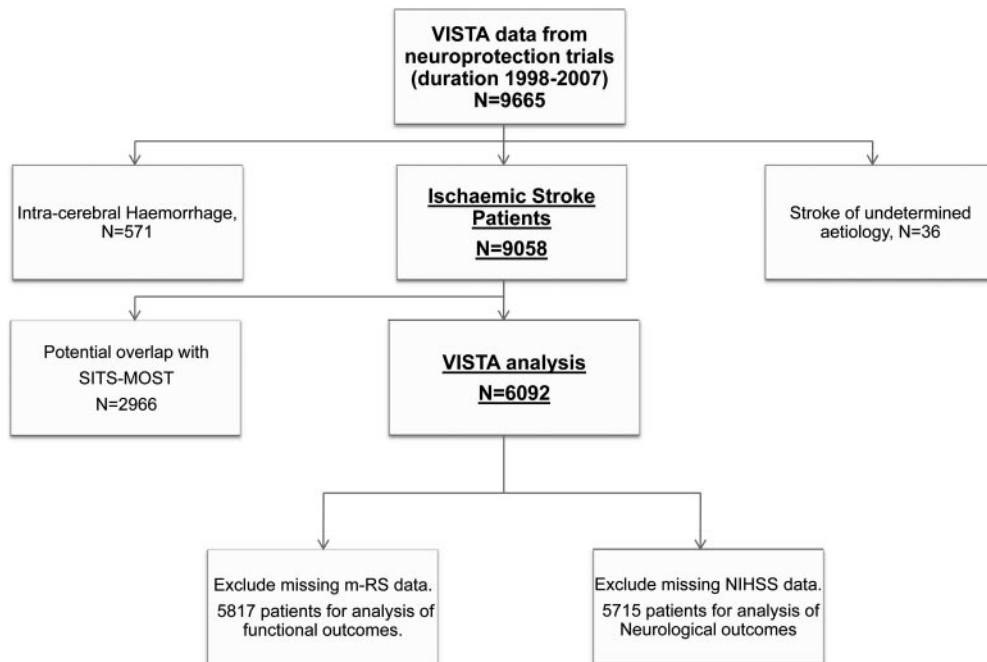


Figure 1. Flow diagram describing selection of data from Virtual International Stroke Trials Archive neuroprotection trials (1998–2007) for the analyses reported.

($P=0.04$) were associated with outcome of stroke, but we did not see an independent effect of alteplase ($P=0.65$).

Supported by this interaction test, we classified the baseline stroke severity into 7 baseline NIHSS score categories: 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, 21 to 24, and ≥ 25 , and undertook tests of association for thrombolysis with outcomes in each of these categories.

Are There Improved Outcomes Across All Baseline Stroke Severity Categories?

Findings from age and baseline NIHSS-adjusted analysis of functional outcomes are shown in Figure 2. This essentially shows a significant association of better outcomes with use of alteplase for patients presenting with baseline NIHSS 5 to 24. The patients with NIHSS <4 at baseline had a mixed distribution of outcomes at 90 days, some Rankin categories appeared to have improved, and others worsened. Patients

with baseline NIHSS >24 showed generally improved Rankin distribution with alteplase; however, proportionality of the treatment effect was maintained.

Findings were consistent for the neurological outcomes (by NIHSS on day 90) and also for the sensitivity analyses (ie, unadjusted analysis and analysis adjusting for age, baseline NIHSS, diabetes, and previous stroke). We could not adjust for onset to treatment time because time to initiation of thrombolytic therapy was not recorded within our source neuroprotection trials. Fifty-nine percent of records lacked coding for the variable “antithrombotic” ($N=3432$), 4.8% lacked coding for atrial fibrillation ($N=278$), and 3.2% lacked coding for patients with previous strokes ($N=186$). This limitation to our sample precluded a reliable analysis that was adjusted for all variables that differed at baseline (age, baseline NIHSS, previous use of antithrombotic drugs, previous stroke, and atrial fibrillation).

Table. Baseline Characteristics of the Patients

	Thrombolysis		Nonthrombolysed Controls		<i>P</i>
Age, median (range)	71 (21–98)	N=1585	72 (21–101)	N=4232	<0.05
Male	880/1585	55.52%	2226/4232	52.6%	0.05
Baseline NIHSS, median (range)	14 (2–32)	N=1585	13 (2–37)	N=4232	<0.05
Previous antiplatelet use	429/1078	39.8%	446/1306	34.2%	<0.05
Previous anticoagulation use	67/1078	6.2%	198/1306	15.2%	<0.05
Previous stroke	319/1555	20.5%	1579/4076	38.7%	<0.05
Congestive heart failure	151/1262	12%	164/1409	11.6%	0.79
Diabetes mellitus	342/1548	22.1%	992/3991	24.9%	0.03
Hypertension	1030/1548	66.5%	2827/3991	70.8%	<0.05
Atrial fibrillation	398/1548	25.7%	1274/3991	31.3%	<0.05
Myocardial infarction	278/1548	18%	691/3991	17.3%	0.57

NIHSS, National Institutes of Health Stroke Scale.

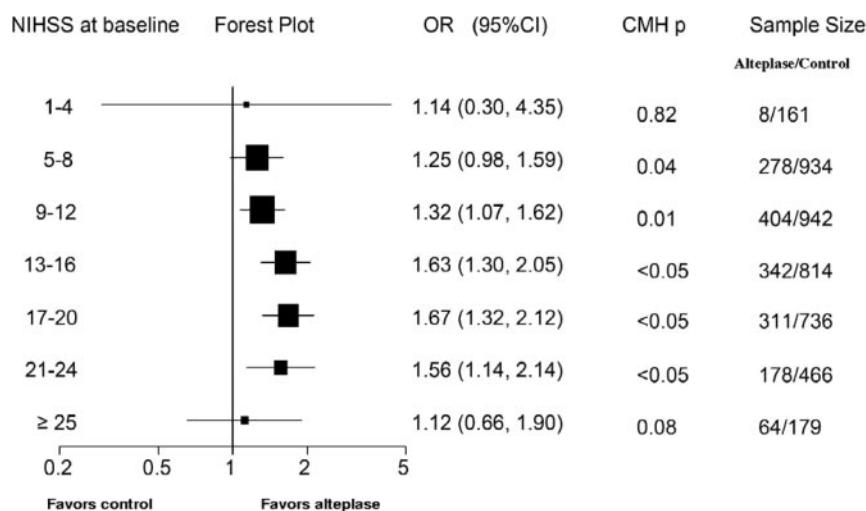


Figure 2. Age and baseline severity-adjusted analyses showing functional outcomes corresponding to various baseline NIHSS categories. Odds ratios are derived from proportional odds logistic regression analyses and refer to proportional (common) odds for shift toward better modified Rankin scale categories for patients who receive alteplase. Cochran-Mantel-Haenszel (CMH) test is a nonparametric test, and it measures the strength of association between alteplase use and better outcomes.

Discussion

Patients with mild and severe strokes are under-represented in randomized trials and post-marketing analyses. As a result, the European Medicines Evaluation Agency marketing authorization for alteplase in acute ischemic stroke lists minor neurological deficit or symptoms rapidly improving before start of infusion and severe stroke as assessed clinically (eg, NIHSS >25) and/or by appropriate imaging techniques as contraindications.^{2,23} Such patients do present to hospital services, however, and this places the physician in a dilemma of whether to offer treatment. Some experienced physicians treat such patients. For example, 12% of patients in the SITS-ISTR thrombolysis registry had a baseline NIHSS score in the range of 0 to 4, and 4% had severe stroke with NIHSS ≥25. Many more patients were probably denied treatment. A Canadian series found that 31% of cases were considered too mild or improving too rapidly for treatment,¹⁹ and a report from the United States indicates that only 1 in 5 patients with NIHSS scores <8 are treated.⁶ This cannot be justified on the basis of observed outcomes. In retrospect, 32% of patients with cases considered too mild to be treated had either died or were disabled 90 days later.¹⁹ Others^{7,20–21} report similar findings. Randomized trials to establish the existence or extent of benefit at extremes of baseline severity may be difficult to conduct and delayed in execution. Other sources of evidence must be examined, and high-quality registry data are the obvious choice.

In our present nonrandomized comparison of data held in VISTA, outcomes after thrombolysis were significantly better than in untreated comparators across baseline NIHSS scores 5 to 24. This significant association was lost only at extremes of baseline NIHSS (ie, 1–4 and ≥25). Although the point estimates for both adjusted and unadjusted odds ratios remain favorable in the extreme groups, they are lower than those observed at other levels of stroke severity.

In these extreme groups, the small sample size seriously undermines the power of the statistical tests and, with wide confidence intervals, the true point estimate is not reliably indicated. There is a second statistical issue to consider relating to the outcome measure that we used. By examining the full distribution of the mRS, we have used a test that is

less dependent on case-mix than dichotomization. We are able to use the same test for patients with mild stroke as is used severe stroke and may still detect benefit. Even so, at the extremes of baseline severity, outcomes are generally so good or so poor that only a few mRS categories are well-represented in the control groups. Both the Cochran-Mantel-Haenszel test and the proportional odds estimations will be compromised if some categories are not contributing to the analysis. Effectively, the test of treatment effect will be diluted by the noncontributing groups. For Cochran-Mantel-Haenszel, this means that it becomes more difficult to reach statistical significance; however, but for the proportional odds tests, the basic assumption has been breached and the effect is not proportional. There is no easy solution to this problem. If case-mix is altered to deliver a significant result, then patients with mild or severe stroke must be excluded, which is the solution used by the trials. Conversely, if the outcome measure is varied according to the sample case-mix (the sliding dichotomy approach discussed by Murray et al²⁴), then interpretation is rendered difficult. Is an odds ratio for achieving mRS 0 vs 1 to 6 equivalent to an odds ratio for achieving mRS 0 to 5 vs 6, ie, is survival free from symptoms equivalent to survival at any cost?

Here, we have chosen to present 1 analytic approach for all severities of stroke, but we also illustrate the range of outcomes at extremes of severity. From these, although the summary statistics show only a nonsignificant but favorable trend, we can draw further conclusions. Among patients with severe stroke, there are evident trends toward benefit across almost all boundaries of mRS. Among patients with mild stroke, all boundaries except 0 to 1 vs 2 to 6 show benefit, but 4 of the mRS categories are entirely unrepresented. Our data show no reason to withhold treatment from either group of patients but are not in themselves sufficient evidence to justify treatment.

Our findings draw validity from the fact that our source clinical trials rigorously reported concomitant treatments and outcomes and had strict on-site data verification procedures. However, the nonrandom allocation to treatment vs control groups is a significant weakness of our design. We could not determine the degree and cause of exclusion of patients from

our database. We can only consider factors known to be associated with prognosis.

We have adjusted statistically for factors that have a large influence on outcome. We can also ‘anchor’ our findings by comparison of treatment associations for patients with moderate stroke severity in our study against known treatment effects in comparable patients from randomized trials. For example, we find an odds ratio for favorable outcome of 1.3 to 1.6 for patients with baseline NIHSS 9 to 12 and 13 to 16; the comparable estimate from treatment within 3 hours of stroke onset in a randomized control trial would be 1.64 and for 3 to 4.5 hours would be 1.34.²⁵ Our estimates are comparable and perhaps conservative.

The decay of benefit across later onset to treatment times raises a second issue. We do not have information on the onset to treatment delay for alteplase in our current analysis. Because the patients were permitted only 1 investigational drug in the participating VISTA trials, with alteplase being used as standard of care, and because these trials were closely monitored by their sponsors, we assume that patients were largely treated within 3 hours of stroke onset. We also assume that the onset-to-treatment time is comparable to those from the CASES and SITS-MOST registries (155 [130–175] minutes and 140 [115–165] minutes, respectively; n=6483). Unfortunately, the latency between stroke onset and recording of initial severity differed between our treatment group (3.7 hours) and controls (5.1 hours). Severity is associated with onset to hospital arrival time: patients with more severe stroke present earlier.²⁶ We adjusted our analyses for stroke severity, but it is conceivable that residual bias persists. Such a bias would cause underestimation of true initial severity among our controls and through the baseline adjustment would lead us to overestimate treatment effect. It will influence all patients across our severity range but may be less evident at extremes of severity: the NIHSS criterion will be responsible for discouraging use of alteplase, and so the proportion of patients who are treated with alteplase will have extremes of NIHSS.

With these caveats, it would be desirable to replicate our findings. Supporting evidence could come from a comparison of SITS-ISTR data against VISTA controls, a collaborative analysis that is underway. We lack data on symptomatic hemorrhages because patients who are not treated with thrombolysis generally do not undergo follow-up cerebral imaging for routine detection of hemorrhagic transformation. However, the outcome measure that we use takes into account effects of hemorrhage or other adverse events on function.

We adjusted for age and baseline severity because these are the established most important variables known to influence outcomes.²⁷ We could not adjust for all age, baseline NIHSS, previous use of antithrombotic drugs, previous stroke, and atrial fibrillation data together because 1 of the contributing trial programs did not record pretreatment medications. However, we were able to undertake an adjusted analysis for the variables that were found significant in ECASS III, namely diabetes and previous stroke, and our estimates remained consistent.

Some of the patients in our study received an investigational medicinal product. Each contributing trial has already

tested for, and excluded, a significant interaction of that product with alteplase, both in vitro and in vivo.

Conclusion

In conclusion, our findings imply that patients with extremes of NIHSS scores recorded at baseline may still benefit from treatment but the supporting evidence remains weak.

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Disclosures

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