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

**In**travenous thrombolysis with alteplase is a proven therapy for acute ischemic stroke patients presenting before 4.5 hours of symptom onset. However, some patients are denied therapy for fear of poor outcomes. 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, 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 baseline NIHSS ≥25 are also supposed to have poorer outcomes because of excess symptomatic hemorrhages. Baseline stroke severity (baseline NIHSS) is known to affect outcomes among thrombolysed patients and therefore was incorporated for patient selection in the ECASS III trial. 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. Post hoc analyses of the NINDS and ECASS-III trials suggest equal efficacy across severity range, although power to examine
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 to patients who had not been treated with alteplase. 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...
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

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<thead>
<tr>
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<th>Thrombolysis</th>
<th>Nonthrombolysed Controls</th>
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<td>71 (21–98)</td>
<td>72 (21–101)</td>
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<td>Male</td>
<td>880/1585</td>
<td>2226/4232</td>
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<td>Baseline NIHSS, median (range)</td>
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<td>13 (2–37)</td>
<td>&lt;0.05</td>
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<td>Previous antiplatelet use</td>
<td>429/1078</td>
<td>446/1306</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Previous anticoagulation use</td>
<td>67/1078</td>
<td>198/1306</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>319/1555</td>
<td>1579/4076</td>
<td>&lt;0.05</td>
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<tr>
<td>Congestive heart failure</td>
<td>151/1262</td>
<td>164/1409</td>
<td>0.79</td>
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<tr>
<td>Diabetes mellitus</td>
<td>342/1548</td>
<td>992/3991</td>
<td>0.03</td>
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<td>Hypertension</td>
<td>1030/1548</td>
<td>2827/3991</td>
<td>&lt;0.05</td>
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<tr>
<td>Atrial fibrillation</td>
<td>398/1548</td>
<td>1274/3991</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>278/1548</td>
<td>691/3991</td>
<td>0.57</td>
</tr>
</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale.
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 Others7–20–21 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 al22), 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

Acknowledgments


Disclosures

The analyses reported in this article were based on a research proposal approved by the VISTA Steering Committee and were undertaken by N.K.M. at University of Glasgow, UK. N.K.M. is supported by a British ORS Scholarship and the University of Glasgow scholarship. VISTA has received financial support from the European Stroke Organisation in the form of an unrestricted grant and contributions toward data extraction and capacity building from the Universities of Glasgow, California San Diego, Nottingham, Edinburgh, Calgary, Texas, and Massachusetts; from commercial groups, including Brainsgate, Novartis, Boehringer Ingelheim, and the Vertical Group; and from grant agencies and charities, including the UK Stroke Association, N.K.M. and K.R.L. designed and interpreted the analyses and drafted the manuscript; both had access to the VISTA data. P.L. and J.G. contributed data, reviewed the outline proposal, commented on the manuscript, and approved the final version. All authors take full responsibility for the content. The manuscript was reviewed and approved by the VISTA steering committee (www.vista.gla.ac.uk). No commercial organization was involved in the origin, execution, or reporting of this work. P.L. has received research support from the American Heart Association, the National Institutes of Health, and the Veteran’s Affairs Medical Research Department; consulting fees from Mitsubishi, Co-Axia, Benechill, and Photothera; and research contracts from Astrazeneca, Bayer, and Innercool. J.G. has received consulting compensation from Lundbeck. K.L. has received honoraria (modest) from Boehringer Ingelheim, Lundbeck, Thrombogenics, and Talecirs.

References


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Stroke. 2010;41:2612-2617; originally published online October 14, 2010;
doi: 10.1161/STROKEAHA.110.589317
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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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 can predict the benefit of thrombolysis. The National Institutes of Health Stroke Scale (NIHSS) threshold has been used to select patients for thrombolysis, for inclusion in clinical trials, or to select patients for inclusion in clinical trials. We conducted a comparison study of outcomes in patients from the Virtual International Stroke Trials Archive (VISTA) primarily evaluating neurological outcomes in patients randomized to thrombolysis or no thrombolysis from neuroprotection trials (1998-2007) with different baseline NIHSS scores.

Methods: Patients were grouped by baseline NIHSS score (increase of 4 points for each group) and compared for treatment outcomes, which were assessed by the modified Rankin score. The age- and baseline NIHSS score-adjusted Cochran-Mantel-Haenszel test was then performed, followed by logistic regression analysis. We reported Cochran-Mantel-Haenszel test P-values, as well as the odds ratio (OR) for different baseline NIHSS score groups.

Results: Data included 5817 patients (1585 in the thrombolysis group, 4232 in the non-thrombolysis group). Thrombolysis patients had worse baseline NIHSS scores compared to non-thrombolysis patients (baseline NIHSS median 14 vs. 13; P<0.05). Treatment outcomes were independent of baseline NIHSS score: within the 5-8 group (P=0.04; OR, 1.25; 95% CI, 1.0-1.6; N=278/934), 9-12 group (P<0.05; OR, 1.3; 95% CI, 1.1-1.6; N=404/942), 13-16 group (P<0.05; OR, 1.6; 95% CI, 1.3-2.1; N=342/814), 17-20 group (P<0.05; OR, 1.7; 95% CI, 1.3-2.1; N=311/736) and 21-24 group (P<0.05; OR, 1.7; 95% CI, 1.3-2.1; N=178/466). Their results were similar and comparable across different baseline NIHSS score categories. In the baseline NIHSS score 1-4 group (P=0.8; OR, 1.1; 95% CI, 0.7-1.9; N=64/179) or >25 group (P=0.08; OR, 1.1; 95% CI, 0.7-1.9; N=64/179) there was no association.

Conclusion: This study, through non-randomized comparisons, compared patients with baseline NIHSS scores 5-24, whose results were significantly better than non-thrombolysis patients. Only when the sample size was small and the confidence interval was wide, would removing thrombolysis influence the results.

Keywords: Baseline, functional, severity, stroke, thrombolysis

(Stroke. 2010;41:2612-2617. 吉林大学第一医院神经内科 金涛 译 吴江 董铭 校)

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some patients with mild or rapid improvement and those with severe stroke at baseline. randomized trials also did not show a worse response in these subgroups. the retrospective analysis of the NINDS and ECASS III trials showed that the effect of thrombolysis was similar across different severity levels of stroke, although the power to detect differences was lower compared to the first analysis and the outcomes of patients at the extremes of stroke severity were underestimated. therefore, we need to conduct randomized trials in specific subgroups to get a clear answer. thus, we must seek alternative sources of evidence.

VISTA (Virtual International Stroke Trials Archive) is a database that includes data from rigorously controlled clinical trials. although most trials have validated the assumed neuroprotective agents, the use of recombinant tissue plasminogen activator (rt-PA) is still common. we plan to use data from VISTA to see if the baseline severity of stroke affects the outcome of thrombolysis. this will be done by comparing patients at different severity levels at baseline with those who received no treatment. we will also include factors such as diabetes and previous stroke history. for sensitivity analysis, we will include other factors that may affect the outcome.

Statistical analysis
We compared patients with different baseline NIHSS scores (<4, 5-8, 9-12, 13-16, 17-20, 21-24, and >25) who received thrombolysis or no treatment. we used a shift analysis, which is a more effective endpoint analysis tool recommended by the EMA. we also compared the results of the second analysis, which includes all patients, to see if there is a significant difference. in our analysis, we found that the treatment effect was consistent across different severity levels and the results were not biased by any other factors.
direct 软件 (StatsDirect Limited, United Kingdom)。关于症状性出血我们缺乏有效的信息，因为在神经保护试验中，未行阿替普酶治疗的患者于治疗后不做常规性影像学检查。

结果

患者样本

我们整理校对了关于 9665 个患者的数据，其中 5342 人 (59%) 来自非欧洲地区。为了避免与 SITS-MOST 发表相同的数据，我们排除了 2002 至 2005 年间收录的来自欧洲地区的 2789 位 (28%) 患者和 177 名缺少所在国家信息的患者。5817 名患者完整的数据可用于 mRS 分析，5715 个患者的 NIHSS 评估数据可以应用 (图 1)。

所有卒中患者接受的治疗措施所依从的每个治疗中心的治疗常规及卒中指南均在试验指导可接受的范围内。试验的赞助商负责监督试验流程图的依从性，这意味着患者接受的溶栓治疗与所属国家的行销许可相一致，就是说，这一治疗在卒中发生 3 小时内展开；但是，在试验中治疗延迟的将不做记录。我们的试验数据 60% 来源于北美试验中心，欧洲 16%，澳大利亚 13%。基线特征列于表中。5817 名有 mRS 数据的患者中，有 1585 名 (27.2%) 接受了溶栓治疗。

卒中基线的严重性影响患者的转归吗？

在顺序的逻辑回归分析中，我们发现基线的严重程度 (P<0.0001)、使用 r-tPA 和年龄是判断预

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<td>高血压</td>
<td>1030/1548</td>
<td>66.5%</td>
<td>2827/3991</td>
</tr>
<tr>
<td>房颤</td>
<td>398/1548</td>
<td>25.7%</td>
<td>1274/3991</td>
</tr>
<tr>
<td>心肌梗死</td>
<td>278/1548</td>
<td>18%</td>
<td>691/3991</td>
</tr>
</tbody>
</table>
后的重要预测因素。然后，在行年龄校正后的顺序逻辑回归分析中，我们发现卒中基线的严重程度（P<0.0001）及卒中病情的严重性与阿替普酶之间的相互作用与卒中预后相关，但是我们没有看到阿替普酶的独立作用（P=0.65）。

依据这一相互作用试验，我们把卒中基线的严重程度分为 7 个 NIHSS 评分等级: 1-4 分, 5-8 分, 9-12 分, 13-16 分, 17-20 分, 21-24 分及 ≥25 分, 并着手验证在每一分级中溶栓治疗和预后的关联。所有卒中基线严重程度分化的预后均有改善吗?

图 2 显示了年龄与基线 NIHSS 评分校正分析后的功能结果。这实质上显示了基线 NIHSS 评分在 5 到 24 分的患者使用阿替普酶后预后好转比较显著。基线期 NIHSS 评分 <4 分的患者在 90 天内有着不同的预后, 某些患者的 Rankin 分级显示有所好转, 而有些则有所恶化。NIHSS 评分 ≥24 分的患者显示使用阿替普酶后 Rankin 分级逐渐改善；但是，总体治疗效果不明显。

结果与神经病学的预后判断（通过 90 天时进行的 NIHSS 评分）及灵敏度分析（包括未校正的数据分析和对年龄、基线期 NIHSS 评分、糖尿病及既往卒中病史校正后的分析）相一致。由于在我们的神经保护治疗试验中，溶栓治疗的开始时间没有记录，所以我们不能校正起病到治疗开始的时间。数据记录中有 59% 基线 NIHSS 评分的变化性数据 (N=3432), 4.8% 缺乏病史数据 (N=278), 还有 3.2% 缺乏既往卒中病史的数据 (N=186)。本研究样本有这样的局限性，不能在基线校正所有不同的变量（年龄，基线 NIHSS 评分，既往抗血栓药物的使用，卒中史和房颤病史），影响了数据的可靠性。

讨论

轻中度卒中患者在药品随机试验及上市后分析中较少被关注。因此，欧洲药品评价局针对急性缺血性卒中，把轻度神经功能受损、在开始静脉用药前症状迅速恢复、以及经临床或适当的成像技术评估为严重卒中的患者都列为阿替普酶使用的禁忌症 [2,23]。这类患者在去医院就医时，是否给其应用阿替普酶常常使医生处于进退两难之地。某些有经验的医师会选择溶栓来治疗这类患者。例如，在卒中治疗安全实施与国际卒中溶栓治疗登记(SITS-ISTR) 记录的溶栓患者中, 12% 患者的基线 NIHSS 评分为 0-4 分，有 4% 的患者卒中较严重, NIHSS 评分 ≥25 分。大多数这类患者采取了非溶栓治疗。加拿大的一系列试验发现有 31% 的患者被认为症状太轻或者症状恢复太快而不适宜溶栓治疗 [19], 而一份美国报道显示, NIHSS 评分 <8 分患者仅有 1/5 选择溶栓 [6]。现有结果表明此种做法不尽合理。而事后观察，被认为症状太轻而不需行溶栓治疗的患者中，有 32% 的患者在 90 天后或者死亡、或者致残 [19]。其他研究也有类似报道 [19,21]。为了明确卒中基线评分最轻与最重时溶栓的益处，开展随机试验可能会比较困难或者是执行起来比较拖延时间。其他的试验数据还有待验证，最好能有高质量的登记数据。

现我们经过对比发现，记录于 VISTA 上的非随机对照试验中，基线 NIHSS 评分在 5 至 24 分时，溶栓的结果明显优于非溶栓患者。而当基线 NIHSS
评分在1-4分与＞25分时，溶栓与否与结果的相关性不具统计学意义。尽管在两极的患者中，校正及非校正的优势比溶栓组倾向于比非溶栓组好，但低于其他卒中严重程度评分患者的改善程度。

处于两极的患者，因样本量小而严重降低了统计检验效力，较宽的可信区间则严重地否定了结论。尽管在两极的患者中，校正及非校正的优势比溶栓组倾向于比非溶栓组好，但低于其他卒中严重程度评分患者的改善程度。处于两极的患者，因样本量小而严重地降低了统计检验的统计学检验效力，较宽的可信区间则严重影响了真实值评估的可信度。在研究mRS的全方位分布时，我们应用检测法比起二分法，更少依赖于案例组合(case-mix)。对于卒中病情较轻或者较重的患者，我们可以应用相同的检验，并且可能仍会检测到溶栓治疗的益处。对于卒中病情较轻或者较重的患者，我们可以应用相同的检验，并且可能仍会检测到溶栓治疗的益处。虽然如此，这两组的改善程度并未达到统计学上的显著性差异，尽管在对照组中，仅有一小部分mRS分组具有代表性。如果分类不能归纳分析，无论Cochran-Mantel-Haenszel检验，还是优势比率评估，检验效率都会大打折扣。那些没有贡献的组群将显著地削弱统计检验的效力。

非统计性分析的五分量表(mRS)上面的患者，由于样本量小而严重地降低了统计检验的统计学检验效力，较宽的可信区间则严重影响了真实值评估的可信度。在研究mRS的全方位分布时，我们应用检测法比起二分法，更少依赖于案例组合(case-mix)。对于卒中病情较轻或者较重的患者，我们可以应用相同的检验，并且可能仍会检测到溶栓治疗的益处。对于卒中病情较轻或者较重的患者，我们可以应用相同的检验，并且可能仍会检测到溶栓治疗的益处。虽然如此，这两组的改善程度并未达到统计学上的显著性差异，尽管在对照组中，仅有一小部分mRS分组具有代表性。如果分类不能归纳分析，无论Cochran-Mantel-Haenszel检验，还是优势比率评估，检验效率都会大打折扣。那些没有贡献的组群将显著地削弱统计检验的效力。

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此，我们仍开展了一项多变量校正分析，如校正在ECASS III试验中发现的重要因素：糖尿病及卒中病史，并且我们的评估保持前后一致。

在本研究中，某些患者仅接受一种调查研究的药物。每个有贡献的试验已经验证或排除了该药品与阿替普酶的重要相互作用，包括体内和体外试验。

结论
总之，我们的发现表明，尽管支持证据尚不够充分，对于NIHSS 评分基线值处于两个极端的患者来说，溶栓治疗仍能使他们受益。

参考文献