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 $\geq 25$ ($P=0.08$; 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. 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) $\geq 25$, 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 $\geq 25$ 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. 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. 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). 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. 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 thrombolyis exposure, we used the Cochran-Mantel-Haenszel statistic, adjusting for both age and baseline NIHSS as continuous variables. 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. 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 endpoint analytic technique recommended by European Medicines Evaluation Agency. Shift analysis is considered better than dichotomization of end point measures, although there are differences of opinion. 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
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 (i.e., 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>
<thead>
<tr>
<th>Table. Baseline Characteristics of the Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
</tr>
<tr>
<td>71 (21–98)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Baseline NIHSS, median (range)</td>
</tr>
<tr>
<td>Previous antiplatelet use</td>
</tr>
<tr>
<td>Previous anticoagulation use</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Myocardial infarction</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 Others7–21 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 odd 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. 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 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.

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, Edmonton, Calgary, Texas, and Massachusetts; from commercial groups, including Braingate, 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 origination, 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 Talerics.

References


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, Patrick Lyden, James C. Grotta and Kennedy R. Lees for the VISTA Collaborators

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
Copyright © 2010 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/41/11/2612

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/04/02/STROKEAHA.110.589317.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Original Contributions

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

背景及目的：卒中基线评分的严重程度可预测溶栓的结果。美国国立卫生研究院卒中量表 (NIHSS) 的基线阈值有时被用来选择可以溶栓的患者，选择临床试验入组人员，或者用于选择临床试验入组的溶栓患者。我们进行了一项对比研究，数据来自于校正后且存储于虚拟国际卒中试验档案 (VISTA) 的试验结果，主要是评估那些被纳入神经保护试验 (1998-2007) 不同基线 NIHSS 评分对溶栓与非溶栓患者治疗结果的影响。

方法：通过基线 NIHSS 评分每增加 4 分为一档将病人分组，评估了治疗与其结果的相关性，其中结果由改良 Rankin 评分测定。应用年龄及基线 NIHSS 校正分层 Cochran-Mantel-Haenszel 检验法，随后进行比例优势逻辑回归分析。我们报道了分层 Cochran-Mantel-Haenszel 检验法 P 值，报道了对不同基线 NIHSS 评分分组病人进行治疗后改良 Rankin 评分分布的优势比 (OR)。

结果：数据包括 5817 例患者 (1585 例为溶栓患者，4232 例为非溶栓患者)，溶栓患者基线的严重程度高于非溶栓患者（基线 NIHSS 中位值，14 比 13；P<0.05）。治疗结果的相关性显示是独立的：在基线 NIHSS 评分 5-8 分组 (P=0.04；OR，1.25；95% 可信区间 [CI]，1.0-1.6；N=278/934[溶栓/非溶栓])，9-12 分组 (P=0.01；OR，1.3；95% CI，1.1-1.6；N=404/942)、13-16 分组 (P<0.05；OR，1.6；95% CI，1.3-2.1；N=342/814)、17-20 分组 (P<0.05；OR，1.7；95% CI，1.3-2.1；N=311/736) 和 21-24 分组 (P<0.05；OR，1.6；95% CI，1.1-2.1；N=178/466)。结其果与基线的严重程度相关且在很大程度上比较相似。在基线 NIHSS 评分 1-4 分组 (P=0.8；OR，1.1；95% CI，0.3-4.4；N=8/161) 或 >25 分组 (P=0.08；OR，1.1；95% CI，0.7-1.9；N=64/179) 则无相关性。

结论：本研究通过非随机比较，对比基线 NIHSS 评分为 5-24 分的患者，其溶栓后结果明显好于非溶栓患者。仅当样本含量很小及可信区间较宽时，即基线 NIHSS 在两个极端 (病情较轻及较重) 的情况下，溶栓与否与结果的相关性无显著性意义。

关键词：基线，功能的，严重程度，卒中，溶栓

(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)
些轻微或快速改善的患者及基线水平严重的卒中患者进行溶栓治疗，但在这些亚组中，并无随机对照试验去证实对治疗的反应确实更差[5]。对 NINDS 及 ECASS III 试验的事后分析显示不同卒中严重程度其溶栓治疗效果相当，尽管检测不同组别的功效不可避免会比第一次分析时低，且通常处于卒中两极的患者溶栓治疗效果被低估[6-8]。需要在有限的亚组中产生随机试验证据，以得到一个明确的答案。因此，我们必须寻求可选择的证据资源。

VISTA(Virtual International Stroke Trials Archive) 是一个数据库，包含的数据都来自经过严格控制的临床试验[9]。尽管大部分试验验证了特定的神经保护剂，但重组组织型纤溶酶原激活剂(r-tPA)的应用还是比较普遍。我们计划应用来自 VISTA 的数据，假定在过去 10 年里的临床试验有足够广泛的各种不同类型的患者，经过严格的筛选且存储于 VISTA 上的临床数据，能够用来检验不同卒中基线评分严重程度对溶栓治疗结果的影响。

患者与方法

数据来源与患者

我们整理校对了自 1998 至 2007 年开展的神经保护剂试验且存储于 VISTA 上的人口统计资料、临床数据及功能测量结果(www.vista.gla.ac.uk) [10]。在所有试验中，审查委员会、注册审批及患者自愿参与这些条件都是必不可少的，来自 VISTA 的数据均为匿名。我们需要的 VISTA 数据来源于试验，在试验中神经保护剂无血管活性并且不被凝血或安慰剂组干扰。我们排除了所有脑出血及病因未明的卒中患者。为了避免重复发表相同的数据，我们根据国家及入组时间排除了入组于 SITS-MOST 试验的患者。最后，排除了那些缺少我们所选择的治疗结果的、缺少 90 天改良 Rankin 评分 (mRS) 的、缺少次要结果的及缺少 90 天 NIHSS 评分的患者。病人在 90 天内死亡的，归为 mRS 评分 6 分，并且在 NIHSS 分析时独自列为一组。

统计分析

我们对比了基线 NIHSS 评分不同组间 (<4, 5-8, 9-12, 13-16, 17-20, 21-24, 及 >25 分) 接受溶栓治疗及非溶栓治疗的患者。值得注意的是，未选择溶栓的原因未被记录，这可能包括当时在那些地区市场上尚无溶栓剂提供、临床上对卒中溶栓疗效的不确定性的影响、在那时医院缺乏溶栓治疗的某些设施及因个人有禁忌症而无法进行溶栓。在每项对比中，我们应用 90 天 mRS 评分对比分析了分成 7 个亚组的所有溶栓及非溶栓患者。欧洲药物评估局指出对试验结果的报道应使用 mRS 的完整分布建议，但这应建立在对第二级结果(如应用 NIHSS) 进行再分析的基础上[11]。为了分析我们支持的终点结果，我们把相邻近的 NIHSS 评分结果进行如下分组：0(无神经功能缺陷), 1-4, 5-8, 9-12, 13-16, 17-20, 21-24 及 >25 分（严重的神经功能缺陷）或死亡。如同对 mRS 进行的分析一样，对不同组间的病人的分布进行对比分析。

为了证实结果分布与溶栓的相关性，我们用分层 Cochran-Mantel-Haenszel 检验来统计数值，把年龄及基线 NIHSS 作为连续变量进行校正[12,13]。这种非参数方法避免引起一种比例优势的假设，这种比例优势就是所有连续评分结果分界点上常见的优势比，我们认为分层 Cochran-Mantel-Haenszel 检测对统计数据的评估是最保守的。尽管如此，也没有表达出相关性的具体程度。为此，我们进行了逻辑回归分析，并且校正了年龄与基线 NIHSS，来评估在假定比例优势下的优势比 (OR) 及其相关的 95% 可信区间 (CI)。我们选择基线因子来校正主要是基于两种原因。首先，年龄及基线的严重水平是卒中最重要重要的预后因子，并且常用于结果分布的分析中 [13-17]。第二，在我们的整个样本中，年龄及 NIHSS 评分的结果都是完整的，而其他令人感兴趣的潜在因素的记录则并不完整。尽管进行了这样的校正，我们还进行了灵敏度分析，校正了 ECASS III 的变量即糖尿病及早先的卒中病史。此外，我们在校正分析的同时还结合了基线水平差异较大的变量；虽然这样会导致样本含量极度减少，不过我们报道了此局限性。

我们的主要目的是进行连续分布或“偏移”分析(“shift” analysis)，此分析是欧洲药物评估局推荐的较有效的终点分析工具[11,18-20]。尽管有不同的观点，在终点测量上偏移分析被认为优于二分法[21,22]。二分法因放弃某些统计数据而不被看好，比如，缺乏统计效率，而在疗效轻微或所有组间 Rankin 评分较一致时，应用偏移分析尤其有效。在我们的分析中，阿替普酶应用后疗效改进的优势比(OR) 在假定比例优势下的优势比 (OR) 及其相关的 95% 可信区间 (CI)。
用于分析的来源于 VISTA 神经保护试验 (1998-2007) 的数据筛选流程图。

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其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

表 患者基线特征

<table>
<thead>
<tr>
<th>项目</th>
<th>溶栓组</th>
<th>非溶栓对照组</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄，中位数 (范围)</td>
<td>71 (21–98)</td>
<td>72 (21–101)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>男性</td>
<td>880/1585</td>
<td>2226/4232</td>
<td>0.05</td>
</tr>
<tr>
<td>基线 NIHSS，中位数 (范围)</td>
<td>14 (2–32)</td>
<td>13 (2–37)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>血糖水平</td>
<td>429/1078</td>
<td>446/1306</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>抗凝药物应用史</td>
<td>67/1078</td>
<td>198/1306</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>充血性心衰</td>
<td>319/1555</td>
<td>1579/4076</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>高血压</td>
<td>42/1548</td>
<td>164/1409</td>
<td>0.79</td>
</tr>
<tr>
<td>糖尿病</td>
<td>342/1548</td>
<td>992/3991</td>
<td>0.03</td>
</tr>
<tr>
<td>高血压</td>
<td>1030/1548</td>
<td>2827/3991</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>房颤</td>
<td>398/1548</td>
<td>1274/3991</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>心肌梗死</td>
<td>278/1548</td>
<td>691/3991</td>
<td>0.57</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作 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类的预后均有改善吗？图 2 显示了年龄和基线严重性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% 缺乏抗血栓治疗的变化性数据（N=3432），48% 缺乏房颤病史的数据（N=278），还有 32% 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），影响了数据结果的可靠性。

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，被认为是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[17,21]。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结果改善程度。

处于两极的患者，因样本量小而严重降低了统计检验效力，较宽的可信区间则更严重影响了真实值评估的可信度。关于我们用的测量结果，有另外的统计方法可以考虑。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。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，在两极的患者，测评结果显示通常不是太好就是太差，因此在对照组中，仅有一小部分mRS分组具代表性。如果分类不能归纳分析，无论Cochran-Mantel-Haenszel检验，还是优势比率估计的检验效果都会打折扣。对于全部卒中类群将会显著地削弱治疗效果的检测。对于分层Cochran-Mantel-Haenszel检验而言，意味着将很难达到统计学上的显著性差异。尽管如此，对于优势比率检验来说，违背了最初的假设，因而产生的影响不成比例。解决此问题并非易事。如果改变case-mix来提供一个有统计学意义的结果，那么轻微的或严重的卒中患者将被排除在外，这是一些试验的解决办法。相反的，如果根据样本case-mix的变化，而相应的测量结果也变化，不同的卒中水平的卒中患者将被排除在外，这是一些试验的解决办法。相反的，如果根据样本case-mix的变化，而相应的测量结果也变化，不同卒中基线水平的卒中程度和卒中程度的两极的影响可能不太明显：应用阿替普酶的大部分患者NIHSS评分可能不采用阿替普酶的原因。

有了这些警示，重复我们的发现将是值得的。一个即将进行的来自SITS-ISTR数据与VISTA对照组的对比协作分析可能成为有力证据。我们缺乏症状性出血患者的数据，因为通常不经历溶栓治疗的患者，在随访中不会常规行影像学检查以检测出血的转归。尽管如此，我们应用的检测指标考虑到了出血或其他不利于神经功能事件的影响。

我们校正了年龄及基线的严重程度，因为这些是比较明确的影响结果的重要变量。我们不能对所有年龄、基线NIHSS、先前应用抗血栓药物史、卒中病史及房颤等数据综合校正，主要是因为其中一个试验项目并没有记录治疗前用药。尽管如
此，我们仍开展了一项多变量校正分析，如校正在ECASS III试验中发现的很重要的变量：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研究药物。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