

A User's Guide to the NINDS rt-PA Stroke Trial Database

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In December 1995, results from the National Institute for Neurological Disorders (NINDS) Recombinant Tissue Plasminogen Activator (rt-PA) Stroke Trial were published [1]. The implications of this trial have been profound, affecting the emergency management of stroke patients as well as any patient with apparent symptoms of an ischemic stroke.

Based on the NINDS findings, the United States Food and Drug Administration approved the use of rt-PA for the treatment of acute ischemic stroke. Subsequent to this approval, both the American Heart Association and the American Academy of Neurology endorsed the use of rt-PA for selected stroke patients [2,3].

The approval and endorsement of rt-PA for stroke therapy has been controversial. Since the publication of the NINDS rt-PA trial, concerns regarding the study's design, results, and ramifications have been published and disseminated. Specific criticisms of the NINDS trial have included: (1) lack of early improvement (within 24 hours) in patients treated with rt-PA; (2) a trial enrollment policy that required half of the participants to be treated within 0–90 minutes of presentation and the remainder at 91–180 minutes—thereby not reflecting a “real world” setting; (3) discrepancies in baseline characteristics of patients favoring those treated with rt-PA; (4) a small sample size with resulting large confidence intervals; and (5) a reported benefit of therapy, a finding inconsistent with previous thrombolytic trials in stroke [4–8].

Additional concerns have been expressed regarding the generalization of the NINDS results to the community hospital setting, the reorientation of emergency medical systems, and an unacceptably high risk of harm with limited benefit to patients. The NINDS authors have attempted to address many of these concerns [9], and supporters have defended and encouraged the increased use of rt-PA in patients with acute stroke [10,11].

In hopes of clarifying many of the issues raised, researchers who were not involved in the NINDS study have made requests for access to the NINDS rt-PA trial data. Access to this data was initially denied, even after petition to the Food and Drug Administration under the Freedom of Information Act, heightening concern and suspicions regarding the trial findings [12]. During this period, the NINDS authors published no less than 27 reports using various permutations of the NINDS dataset [9,13–38].

In October 2003, nearly eight years after the NINDS publication, the original data from the NINDS rt-PA Stroke Trial were made available to the public. Since this time, we are aware of only three reports by non-NINDS researchers that have used the original dataset [39–41].

The Guidelines and Guidance section contains advice on conducting and reporting medical research.

Summary Points

- In 1995, the NINDS rt-PA study documented an improvement in neurologic outcomes at three months for those patients given rt-PA within 3 hours of onset of an acute ischemic stroke.
- This trial has become the sentinel study supporting the use of rt-PA in acute ischemic stroke.
- Questions raised regarding this trial have been difficult to answer, since the raw data have been unavailable to non-NINDS researchers.
- In October 2003, the data from this trial became available for purchase.
- In this report, we describe the process of acquiring and deciphering the dataset from the original trial, provide a detailed description of the dataset, and discuss the implications for potential future research.

We document our efforts to access and decipher the NINDS rt-PA Stroke Trial dataset. By documenting the steps necessary to obtain and organize the data, along with a description of each data point, we hope to assist future researchers and clinicians who desire to further analyze this landmark trial.

Obtaining the NINDS rt-PA Database

A CD-ROM containing the NINDS rt-PA database can be purchased from the National Technical Information Service (<http://www.ntis.gov/>; 1-888-584-8332). The cost is US\$79.00 plus US\$5.00 for shipping and handling, and delivery can be expected within seven to ten business days. However, the data on the CD-ROM are not in a readable format. Multiple conversions are required, which can only be accomplished

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Abbreviations: NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator

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with technical assistance from the software company (SAS Institute,; <http://www.sas.com/>). Once these conversions are completed and the data are placed in an Excel spreadsheet format, no key accompanies the dataset to decode the numeric designations given to the variables.

The steps necessary to obtain the NINDS database, software requirements, necessary conversions, additional instructions, incomplete/missing data, and methods used to decode data variables are documented in Text S1.

Patient Results in the Database

There are 100 separate variables recorded for the 624 patients enrolled in the NINDS study. Text S2 documents each individual variable in the order in which it is displayed in the Excel format.

Patient results can be divided into nine natural groupings: A, baseline characteristics; B, patient demographics; C, baseline vital signs and laboratory values; D, head computerized tomography results; E, treatment randomization and timing of drug delivery; F, deleterious effects (death and hemorrhage); G, neurological outcomes; H, dosing of rt-PA and use of heparin; and I, stroke type and clinical outcomes. Text S3 summarizes the data for each of the above groups and details the location of missing data, inconsistencies with previous reported data, and protocol violations not previously reported. Texts S4 through S12 present the results of every variable in the groups noted above.

Discussion

This report is intended to demonstrate the process for establishing access and analyzing the NINDS rt-PA Stroke Trial dataset. While the purchase of the database is simple, the process of gaining access to the information on the CD-ROM is convoluted and difficult. We have summarized these steps and provided access to the entire database for researchers desiring to analyze the data from this landmark trial for independent research queries.

Some may suggest that a reanalysis of the NINDS rt-PA database is not necessary and that those who review the data are immersed in a futile attempt to topple or tarnish the study's impact. However, the NINDS rt-PA trial has guided the worldwide care of acute ischemic stroke victims since its publication. The study has been referenced over 1,900 times [42] and stands alone as the largest randomized control trial to demonstrate rt-PA's benefit in patients with acute ischemic stroke.

The data from this trial have been incorporated into influential pooled analyses [31] and reviews [43], with the salutary results widely promoted by groups such as the American Heart Association and American Stroke Association as the basis of the "Brain Attack" campaign and the creation of stroke centers. Until the results of future prospective trials such as IST-3 (The Third International Stroke Trial), ECASS-3 (The European Cooperative Acute Stroke Study), and EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) become available, the NINDS rt-PA study will likely continue to provide the primary evidence for the use of thrombolytic therapy in the management of acute ischemic stroke.

Accessing the database as described in this report can lead to future investigation by interested researchers. There have

Box 1. Inclusion and Exclusion Criteria

Measurements Available in Dataset

- Onset of ischemic stroke symptoms
- Deficit measurable on the National Institutes of Health Stroke Scale
- Baseline computerized tomography scan of the brain showing no intracranial hemorrhage
- Systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg
- Patients taking heparin within 48 hours
- Glucose concentration <50 mg per deciliter or >400 mg per deciliter

Measurements Not Available in Dataset

- History of stroke or serious head trauma in the preceding three months
- Major surgery in the past 14 days
- History of intracranial hemorrhage
- Rapidly improving or minor symptoms
- Symptoms suggestive of subarachnoid hemorrhage
- Gastrointestinal hemorrhage or urinary tract hemorrhage within the past 21 days
- Arterial puncture at a noncompressible site in past seven days
- Seizure at onset of stroke
- Patients taking anticoagulants within 48 hours
- Elevated partial thromboplastin time or prothrombin time
- Platelet counts <100,000
- Patients requiring aggressive treatment to reduce their blood pressure to specified limits

been few studies by non-NINDS researchers using the original NINDS data. Published reports include: (1) an analysis of potential baseline imbalances in the NINDS trial, and (2) a review of severity-adjusted end points [39,40]. Both of these studies support the use of rt-PA in acute ischemic stroke. In a more recent reanalysis of the NINDS data, Hoffman and Schriger found similar responses to treatment in the placebo and rt-PA treatment groups [41]. Contradictory opinions and analyses of the original NINDS data such as these have fueled the controversy regarding the risks and benefits of rt-PA therapy in acute ischemic stroke. Our report provides researchers with a method to easily access the NINDS database for independent analysis in the hope that further review of this investigation will yield future insights into the risks and/or benefits of this intervention.

Analysis of patients in this trial with elevated blood pressure [15], elevated glucose levels [16], transient ischemic attacks [26], and minor strokes [36] have been performed by the NINDS researchers. Other subgroups of patients, such as those who received aspirin, those with congestive heart failure, those with prior strokes, and many others can now be analyzed, with the understanding that such subgroup analysis should not guide therapeutic decisions but may allow the creation of new hypotheses for future studies.

While the purchased dataset provides a large amount of data, some data appear to be missing. Documentation of inclusion and exclusion criteria in the dataset is incomplete

(Box 1). This will limit any attempt to analyze protocol violations in this study. This is unfortunate given that protocol violations have been noted to be problematic in other studies, particularly in community hospital settings [44,45]. Other baseline data points that were not recorded (for example, patient's baseline living situation) can also potentially hinder future research queries.

In summary, this report describes the process for researchers to acquire and decipher the dataset from the original NINDS rt-PA trial. A detailed description of the dataset has been provided to assist researchers interested in further evaluating this pivotal trial and for those researchers involved in future trials assessing the role of thrombolytic therapy for acute ischemic stroke. ■

Supporting Information

Text S1. Methods of obtaining and deciphering NINDS database

Found at doi:10.1371/journal.pmed.0050113.sd001 (27 KB DOC).

Text S2. Complete rt-PA NINDS database

Found at doi:10.1371/journal.pmed.0050113.sd002 (105 KB DOC).

Text S3. Results—overview

Found at doi:10.1371/journal.pmed.0050113.sd003 (49 KB DOC).

Text S4. Baseline characteristics (minus blood pressure)

Found at doi:10.1371/journal.pmed.0050113.sd004 (36 KB DOC).

Text S5. Patient demographics: gender, race, weight, and age

Found at doi:10.1371/journal.pmed.0050113.sd005 (20 KB DOC).

Text S6. Baseline blood pressures and laboratory values

Found at doi:10.1371/journal.pmed.0050113.sd006 (23 KB DOC).

Text S7. Computerized tomography results: baseline and post-intervention

Found at doi:10.1371/journal.pmed.0050113.sd007 (37 KB DOC).

Text S8. Randomization and timing

Found at doi:10.1371/journal.pmed.0050113.sd008 (30 KB DOC).

Text S9. Deleterious effects

Found at doi:10.1371/journal.pmed.0050113.sd009 (27 KB DOC).

Text S10. Neurologic outcomes

Found at doi:10.1371/journal.pmed.0050113.sd010 (32 KB DOC).

Text S11. Dosing and heparin use

Found at doi:10.1371/journal.pmed.0050113.sd011 (21 KB DOC).

Text S12. Clinical classification of stroke and clinical outcome

Found at doi:10.1371/journal.pmed.0050113.sd012 (22 KB DOC).

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. *N Eng J Med* 333: 1581-1587.
2. American Heart Association in Collaborator with the International Liaison Committee on Resuscitation (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 7: The era of reperfusion: Section 2: Acute stroke. *Circulation* 102 (suppl 1): 1204-1216.
3. Quality Standards Subcommittee of the American Academy of Neurology, Practice Advisory (1996) Thrombolytic therapy for acute ischemic stroke: Summary statement. *Neurology* 47: 835-839.
4. Hoffman JR (2001) Tissue plasminogen activator for acute ischemic stroke: Is the CAEP Position Statement too negative? *Can J Emerg Med* 3: 183-185.
5. Hoffman JR (2000) Should physicians give tPA to patients with acute ischemic stroke? Against: And just what is the emperor of stroke wearing? *West J Med* 173: 149-150.
6. Hoffman JR (2003) Tissue plasminogen activator (tPA) for acute ischaemic stroke: Why so much has been made of so little. *Med J Aust* 179: 333-334.
7. Mann J (2002) Truths about the NINDS study: Setting the record straight. *West J Med* 176: 192-194.
8. Trotter G (2002) Why were the benefits of tPA exaggerated? The role of interpretation bias. *West J Med* 176: 194-197.
9. Haley EC, Lewandowski C, Tilley B, NINDS rt-PA Stroke Study Group (1997) Myths regarding the NINDS rt-PA Stroke Trial: Setting the record straight. *Ann Emerg Med* 30: 676-682.
10. Robinson DJ (2000) Should physicians give tPA to patients with acute ischemic stroke? For: Thrombolytics in stroke: Whose risk is it anyway? *West J Med* 173: 148-9.
11. Lattimore SU, Chalela J, Davis L, DeGraba T, Ezzeddine M, et al. (2003) Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: The NINDS Suburban Hospital Stroke Center experience. *Stroke* 34: e55-e57.
12. Lenzer J (2002) Alteplase for stroke: Money and optimistic claims buttress the "brain attack" campaign. *BMJ* 324: 723-729.
13. Broderick J, Lu M, Jackson C, Pancioli A, Tilley B, et al. (2001) Apolipoprotein E phenotype and the efficacy of intravenous tissue plasminogen activator in acute ischemic stroke. *Ann Neurol* 49: 736-744.
14. Broderick JP, Lu M, Kothari R, Levine SR, Lyden PD, et al. (2000) Finding the most powerful measures of t-PA's effectiveness in the NINDS t-PA Stroke Trial. *Stroke* 31: 2335-2341.
15. Brott T, Lu M, Kothari R, Fagan SC, Frankel M, et al. (1998) Hypertension and its treatment in the NINDS rt-PA Stroke Trial. *Stroke* 29: 1504-1509.
16. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, et al. (2002) Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology* 59: 669-674.
17. Fagan SC, Morgenstern LB, Petitta A, Ward RE, Tilley BC, et al. (1998) Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. *Neurology* 50: 883-890.
18. Frankel M, Morgenstern LB, Kwiatkowski T, Lu M, Tilley BC, et al. (2000) Predicting prognosis after stroke: A placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology* 55: 952-959.
19. Grotta J, Welch KMA, Fagan S, Lu M, Frankel M, et al. (2001) Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. *Stroke* 32: 661-668.
20. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, et al. (1999) Effects of tissue plasminogen activator for acute ischemic stroke at one year. *N Eng J Med* 340: 1781-1787.
21. Kwiatkowski T, Libman R, Tilley BC, Lewandowski C, Grotta J, et al. (2005) The impact of imbalances in baseline stroke severity on outcome in the NINDS rt-PA Stroke Study. *Ann Emerg Med* 45: 377-384.
22. Lu M, Lyden PD, Brott TG, Hamilton S, Broderick JP, et al. (2005) Beyond subgroup analysis: Improving the clinical interpretation of treatment effects in stroke research. *J Neurosci Methods* 143: 209-216.
23. Lu M, Tilley BC; the NINDS t-PA Stroke Trial Study Group (2001) Use of odds ratio or relative risk to measure a treatment effect in clinical trials with multiple correlated binary outcomes: Data from the NINDS t-PA Stroke Trial. *Stat Med* 20: 1891-1901.
24. Lu M, Tilley BC, Li S (1998) Issues on permutation tests: Applications in analysis of CT lesion volume in the NINDS T-PA Stroke Trial. In: *ASA Proceedings of the Biopharmaceutical Section*. pp. 27-32. Alexandria (VA): American Statistical Association.
25. Lyden L, Lu M, Jackson C, Marler J, Kothari R, et al. (1999) Underlying structure of the NIH Stroke Scale: Results of factor analysis. *Stroke* 30: 2347-2354.
26. Lyden P, Lu M, Kwiatkowski T, Frankel M, Levine S, et al. (2001) Thrombolysis in patients with transient neurologic deficits. *Neurology* 57: 2125-2128.
27. Lyden P, Lu M, Levine S, Brott T, Broderick J, et al. (2001) A modified National Institutes of Health Stroke Scale for use in stroke clinical trials. *Stroke* 32: 1310-1317.
28. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, et al. (2000) Early stroke treatment associated with better outcome. *Neurology* 55: 1649-1655.
29. Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, et al. (2001) Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA* 286: 2830-2838.
30. Tanne D, Levine SR, Brey RL, Lin H, Fagan SC, et al. (2003) Antiphospholipid-protein antibodies and acute ischemic stroke in the NINDS rt-PA Stroke Trial. *Neurology* 61: 1158-1159.
31. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators (2004) Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA Stroke Trials. *Lancet* 363: 768-774.
32. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group (1997) A systems approach to immediate evaluation and management of hyperacute stroke: Experience at eight centers and implications for community practice and patient care. *Stroke* 28: 1530-1540.
33. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group (2000) Effect of intravenous recombinant tissue plasminogen activator on ischemic stroke lesion size measured by computed tomography. *Stroke* 31: 2912-2919.
34. The NINDS t-PA Stroke Study Group (1997) Generalized efficacy of t-PA for acute stroke: Subgroup analysis of the NINDS t-PA Stroke Study. *Stroke* 28: 2119-2125.
35. The NINDS t-PA Stroke Study Group (1997) Intracerebral hemorrhage following intravenous t-PA therapy for ischemic stroke. *Stroke* 28: 2109-2118.
36. The NINDS rt-PA Stroke Study Group (2005) Recombinant tissue plasminogen activator for minor strokes: The National Institute of

- Neurological Disorders and Stroke rt-PA Stroke study experience. *Ann Emerg Med* 46: 243-252.
37. Tilley BC, Marler J, Geller N, Lu M, Legler J, et al. (1996) Use of a global test for multiple outcomes in stroke trials with application to the NINDS t-PA Stroke Trial. *Stroke* 27: 2136-2141.
38. Woo D, Broderick J, Kothari R, Lu M, Brott T, et al. (1999) Does National Institutes of Health Stroke Scale (NIHSS) favor left hemisphere stroke? *Stroke* 30: 2355-2359.
39. Ingall TJ, O'Fallen WM, Asplund K, Goldfrank LR, Hertzberg VS, et al. (2004) Findings from the reanalysis of the NINDS Tissue Plasminogen Activator for Acute Ischemic Stroke Treatment Trial. *Stroke* 35: 2418-2424.
40. Saver JL, Yafeh B (2007) Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA Stroke Trials. *Stroke* 38: 414-416.
41. Hoffman JR, Schriger DL (2007) Impact of treatment on individual patients in the NINDS Trial: A graphic representation based on change in NIHSS Score [abstract]. 38th American College of Emergency Physicians Research Forum; 8-11 October 2007; Seattle, Washington, United States
42. Ioannidis JPA (2005) Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 294: 218-228.
43. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E (2006) Thrombolysis of acute ischemic stroke (Cochrane Review). In: *The Cochrane Library*, Issue 3. Chichester (UK): John Wiley and Sons.
44. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, et al. (2000) Use of tissue-type plasminogen activator for acute ischemic stroke: The Cleveland area experience. *JAMA* 283: 1151-1158.
45. Bravata DM, Kime N, Concato J, Krumholz HM, Brass LM (2002) Thrombolysis for acute stroke in routine clinical practice. *Arch Intern Med* 162: 1994-2001.

