Effect of Intravenous Recombinant Tissue Plasminogen Activator on Ischemic Stroke Lesion Size Measured by Computed Tomography

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group

Background and Purpose—When given within 3 hours of symptom onset, recombinant tissue plasminogen activator (rtPA) improves outcome 3 months after ischemic stroke. Prespecified secondary endpoints of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial were CT lesion volumes in the 2 treatment groups (tPA and placebo) at 24 hours, 7 to 10 days, and 3 months after stroke.

Methods—The trial included 2 independent studies, part I and part II, with identical methods of data collection. Before part I, uniform standards were established for CT scanning. CT images were obtained at baseline, 24 hours, 7 to 10 days, and 3 months after stroke onset and were reviewed centrally by reviewers blinded to treatment group and clinical findings. Since the individual studies were not powered to test for lesion volume differences, data from both parts of the trial were combined for all analyses. The primary analysis was conducted with the use of an intention-to-treat algorithm (including patients who died or were lost to follow-up). Measured lesion volume (excluding deaths and those lost to follow-up) was used as a secondary outcome in an exploratory analysis.

Results—After tPA treatment, there was a trend toward a reduction in 3-month median lesion volume in the tPA group: 15 cm³ (interquartile range, 2 to 87) compared with 24 cm³ (interquartile range, 4 to 101) in the placebo group (P=0.06, log model) with a reduction of 11% in cumulative lesion volume, computed with Smirnov’s D statistic. After exclusion of deaths and those lost to follow-up, similar trends toward positive treatment effects were seen at all time points.

Conclusions—The direction of the effect of tPA on CT lesion volume at all time points was consistent with the observed clinical effects at 3 months. CT lesion volume may not be as sensitive a measure of treatment effect as clinical evaluation, at least as used in this study. An intention-to-treat analysis for the radiographic end point in this acute ischemic stroke clinical trial is a less biased approach to account for missing radiographic data than an analysis that uses only measured radiological data. (Stroke. 2000;31:2912-2919.)

Key Words: cerebrovascular disorders • clinical trials • computed tomography • thrombolysis • tissue plasminogen activator

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous recombinant tissue plasminogen activator (rtPA) for acute ischemic cerebral infarction.1 The trial was conducted in 2 parts. Part I (291 patients) tested the effect of tPA 24 hours after stroke; 3-month outcome data were also collected. Part II (333 patients) tested the effect of tPA 3 months after treatment with the use of 4 clinical assessment scales. The trial demonstrated that tPA given within 3 hours of stroke onset improved clinical outcome at 3 months despite an increased incidence of symptomatic intracerebral hemorrhage.1 Prespecified secondary outcomes included total volume of brain lesions 3 months, 24 hours, and 7 to 10 days after stroke on CT.

As evidence of a beneficial effect of therapy on stroke outcome, final lesion volume as determined pathologically in experimental stroke and radiographically in clinical stroke2–4 has been considered an important surrogate marker. However, measures of neurological function may be more sensitive in demonstrating the effectiveness of a therapy than morphometric measures.5,6 In this report we present analyses of CT measurements from the NINDS rt-PA Stroke Trial1 testing the hypothesis that there would be a difference in total CT lesion volume 3 months, 24 hours, and 7 to 10 days after stroke between tPA- and placebo-treated groups. We also present an analysis of clinical assessments and other factors associated with CT lesion volumes. Data from parts I and II were combined to analyze this secondary outcome with increased statistical power.

Subjects and Methods

The 8 clinical centers enrolled patients at 43 sites (33 community hospitals, 8 teaching hospitals, and 2 Veterans’ Administration

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A list of all NINDS rtPA Stroke Study participants is given in Appendix 1.

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hospitals) within 3 hours of stroke onset. Almost half of the patients (n=302) were treated in 0 to 90 minutes, with 322 treated in 91 to 180 minutes. Before the trial, uniform standards were established for CT scanning. Guidelines for image acquisition and printing were established and disseminated.

CT Data Collection
For the 624 patients in the NINDS rtPA Stroke Trial, CT images were to be obtained at baseline before the treatment, 24 (±6) hours, 7 to 10 (5 to 11) days, and 3 (±0.5) months. Additional CT scans were also obtained when patients developed neurological worsening within the initial hospitalization or had a clinical suspicion of intracerebral hemorrhage within 3 months after stroke.

The CT scans were performed on third- or fourth-generation CT scanners. For rapid patient evaluation, the baseline CT scans were obtained with 10-mm slice thickness. Subsequent CT scans were obtained with a slice thickness of 5 mm. Technical factors included the following: 120 kV, 170 mA, matrix size of 512×512, and scanning time of 3 seconds for posterior cranial fossa and 2 seconds for the supratentorial compartment. All slices were contiguous without interruption, with a display field of view of 20 cm. All the CT scans were to be performed from the level of the foramen magnum to high vertex region.

All the CT scan images were displayed on films (14×17 inches). Window levels and window width for display of images on the films were optimized for adequate display of gray/white matter distinction. All films of CT scans were then sent to the Central Coordinating Center for review. CT scan data also were archived on either magnetic tape or optical disk for a lesion volume calculation in 75% of part I patients. By late in part I, most sites had changed to using optical disk archiving in multiple formats. For scans not stored on magnetic tape or optical disk, the lesion volume was calculated from the CT films by readers at the University of Virginia. All films of CT scans were reviewed by the Central Coordinating Center neuroradiologist (Suresh C. Patel, MD) for the presence of hemorrhage, old infarct (lesion), edema, and mass effect. The Central Coordinating Center neuroradiologist was blinded to the treatment assignment, clinical findings, and other CT scans at different time points for a given patient.

Total Lesion Volume and Measurement
Since scans were initially read independently, blinded to other CT scans at different time points for a given patient, lesion volume after baseline included both new (current stroke) and old (prebaseline) lesions. Any area of parenchymal hemorrhage on the CT scans was included in the measurement of lesion volume. We thereby total lesion volume throughout this analysis rather than new “stroke” volume. It was hypothesized that the thrombolytic properties of rtPA would reduce the total lesion volume at 3 months after stroke. Lesion volume was measured on all available magnetic tapes, optical disks, or films from 2 (tape film) processes, as previously described in detail.46 and in Appendix 2. To assess agreement within and across processes, a sample of scans was read more than once within the same or with different measurement processes. Intraclass correlation coefficients11 were calculated to describe agreements on lesion volume.

Statistical Methods
To test the primary hypotheses, an intention-to-treat algorithm (Appendix 3) was used to compute lesion volume for those patients who died or were lost to follow-up or had incomplete CT images at 3 months. Because of concern that the different lesion measurement process (tape versus film) could influence the treatment effect, we first tested the interactions between treatment and the process on lesion volume. An interaction was considered if the P-value was <0.1. Since no interactions were present (P-value for interactions >0.14), data were combined.

Given the nonnormality of lesion volume or the lesion transformation, we conducted the analysis on regression on a transformed lesion volume using the generalized estimating equation approach, based on the goodness of fit, since the generalized estimating equation provides more robust estimation. The selection of the transformation and the statistical method have been discussed in detail.12 The analysis was performed with adjustment for clinical center, time strata, aspirin, and weight, which were imbalanced between groups. We reported the median and interquartile ranges of the lesion in describing the data. The Smirnov D statistic was calculated13 and interpreted as the percentage of reduction in cumulative lesion volume from the tPA-treated group compared with the placebo-treated group.

To describe the relationship between lesion volume at different time points and 3-month clinical outcomes, we computed Spearman correlation of the lesion volume versus 3-month clinical assessments: scores on National Institutes of Health Stroke Scale (NIHSS),14 Barthel Index,15 modified Rankin Scale,16 and Glasgow Outcome Scale17: point biserial correlation coefficients18 between lesion volume and 3-month favorable/unfavorable outcomes; and Φ correlation coefficients19 among 3-month favorable/unfavorable outcomes. In addition, to assess the variability and efficiency of the outcome in detecting a treatment effect, we calculated the coefficient of variation (the standard error divided by the mean) and conducted a Wilcoxon nonparametric test on the lesion volume as well as on each clinical assessment collected at 3 months.

Multivariable analysis, as described previously,20 was conducted to test the association of baseline variables (including clinical and demographic variables and old lesion volume and presence, number of slices, process type) and treatment interactions with lesion volumes at 3 months. Thirty baseline covariates (Appendix 4), including the presence of an old lesion at baseline and process type used to measure volume, were considered. The final model would include a covariate with P<0.05 and any treatment-covariates or covariate-covariate interactions with P<0.10.

Similar analyses were performed on lesion volume at 24 hours and at 7 to 10 days for consistency. Exploratory analysis was performed using the lesion data without imputation or excluding patients with old lesion at the baseline with awareness of possible bias.

Results
CT Data Quality
Of the 2333 total scans expected, 2255 (97%) were received, including 91% in and 6% out of the study windows. Only 9 patients (1%) had missing baseline CT data, and 7% had missing 3-month CT data in a wider time window. Of 2255 received, 2251 (99%) were readable for hemorrhages and other CT findings, and 2247 (99%) had measurable lesion volumes, in which 34% of the scans were processed using tape/optical disk images, and 66% were processed using images on film. Of those scans received, 56 had motion artifacts, 9 had other artifacts, 13 incomplete scans required use of the algorithm to impute lesion volume, and 74 missing slices in the middle required averaging slices above and below the missing area.

Reliability was assessed within processes and across processes (Appendix 2) on the basis of a sample size of 10 and 46 scans, respectively. The intraclass correlations were close to 90% (with the lowest 95% CI of 80%), suggesting excellent agreement for all pairwise comparisons of processes involved in the lesion volume calculation.

In addition to the baseline characteristics reported earlier,1 28% of patients in the tPA-treated group had the presence of an old lesion compared with 27% in the placebo-treated group (P=0.69); 41% of the tPA-treated patients had at least 1 abnormal acute finding (eg, early CT ischemic changes such as loss of gray-white junction, sulcal effacement, focal hypodensity, or hyperdense artery sign) compared with 42%
in the placebo-treated group with $P=0.56$. There were 12 new (recurrent) strokes detected by CT at 3 months after stroke with 6 in each treatment arm.

### Treatment Effects on Lesion Volumes

The treatment effects on lesion volumes are presented in Table 1 using the intention-to-treat algorithm and Table 2 based on the available lesion measurements. After rtPA treatment, there was a trend toward smaller 3-month lesion volume compared with the placebo group ($P=0.06$), with a reduction of 11% in cumulative lesion volume in the tPA-treated group compared with the placebo-treated group. The time course of CT lesion volume change is depicted in Figure 1. The treatment effects on the intention-to-treat lesion volume at 24 hours or at 7 to 10 days or on the lesion volume without imputation are consistent with the results at 3 months.

With the exclusion of patients who had an old lesion at the baseline, no detectable lesion was seen in 47 of 455 patients at 3 months after stroke: 27 (57%) in the tPA group and 20 (43%) in the placebo group ($P=0.32$). The correlation coefficients between the lesion volume with the exclusion of those who died or were lost to follow-up at each time point and 3-month clinical outcomes are listed in Table 3 (scores) and Table 4 (dichotomized into favorable and unfavorable for each outcome defined earlier, in Reference 1). Correlations at all time points are moderate (in a range of 0.48 to 0.63 regardless of the sign) and reduced by dichotomized outcomes (0.28 to 0.53). However, the correlation among the clinical outcomes is 0.90 to 0.95 on the basis of clinical scores and 0.60 to 0.89 on the basis of dichotomized outcomes.

The coefficients of variation are 149% for actual lesion and 66% for transformed lesion compared with 61% to 120% for clinical scores. Results of Wilcoxon tests showed significant treatment effect on each clinical score ($P<0.01$) and borderline treatment effect on lesion volume.

### Baseline Variables Associated With Lesion Volume (Intention-to-Treat) at 3 Months, 24 Hours, and 7 to 10 Days

Stroke subtype was strongly associated with lesion volume at each time point in the multivariable analyses ($P<0.02$), as presented in Table 5. Eighteen patients with baseline stroke subtypes classified as “others” were excluded from the multivariable analyses.

In the multivariable analyses, we detected an age-by-treatment interaction for the 3-month lesion volume ($P=0.01$;
At 3 months after stroke, patients who were younger and treated with tPA had smaller lesion volumes than patients of comparable age treated with placebo. In contrast, older patients treated with tPA tended to have larger lesion volumes at 3 months than patients of similar age treated with the placebo. We also detected the baseline NIHSS score by the presence of old lesion or the early CT finding interaction for lesion volume at 3 months as well as for lesion volume at 24 hours and 7 days (P<0.002). We found that patients with high baseline NIHSS score alone or with a combination of old lesion and early finding on the baseline CT would have larger lesion volume than other patients.

**Discussion**

Intravenous rtPA, when given within 3 hours of acute ischemic stroke, tends to reduce lesion volume compared with the placebo at 24 hours, 7 to 10 days, and 3 months after stroke in the intention-to-treat analysis. Lesion data without imputation show a consistent treatment effect in the same direction.

We observed a similar variability among the clinical and lesion measures but a statistically significant treatment benefit on each measure and a borderline treatment benefit on the lesion measure using the Wilcoxon nonparametric test, which minimizes the effect of the variability of the data. There are high correlations among the clinical measures (range, 0.90 to 0.95) compared with 0.48 to 0.64 correlation coefficients between lesion volume and the clinical measures. These data suggest that the variability of CT lesion volume is not the single major factor that diminished the statistical significance of treatment benefit on lesion volume. CT lesion volume may

### Table 3. Correlations Between Lesion Volume* and Clinical Scores (Trial Parts I and II Combined)

<table>
<thead>
<tr>
<th>Time After Stroke</th>
<th>NIHSS†</th>
<th>Barthel Index‡</th>
<th>Rankin Scale§</th>
<th>Glasgow Scale¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.62</td>
<td>−0.57</td>
<td>0.61</td>
<td>0.59</td>
</tr>
<tr>
<td>7–10 d</td>
<td>0.63</td>
<td>−0.55</td>
<td>0.61</td>
<td>0.63</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.64</td>
<td>−0.54</td>
<td>0.60</td>
<td>0.61</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.52</td>
<td>−0.48</td>
<td>0.51</td>
<td>0.48</td>
</tr>
<tr>
<td>7–10 d</td>
<td>0.61</td>
<td>−0.56</td>
<td>0.58</td>
<td>0.56</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.62</td>
<td>−0.55</td>
<td>0.55</td>
<td>0.52</td>
</tr>
<tr>
<td>tPA/placebo combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.64</td>
<td>−0.55</td>
<td>0.58</td>
<td>0.57</td>
</tr>
<tr>
<td>7–10 d</td>
<td>0.63</td>
<td>−0.57</td>
<td>0.61</td>
<td>0.60</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.59</td>
<td>−0.54</td>
<td>0.57</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Spearman correlation coefficients differed from zero, with P<0.001.

*Excluding patients who died or had no follow-up CT during the scheduled time intervals.
†0–42, where 0 is the best score.
‡0–100, where 100 is the best score.
§0–5, where 0 is the best score.
¶1–4, where 1 is the best score.

Figure 2) but not for the 24-hour and 7- to 10-day time points. At 3 months after stroke, patients who were younger and treated with tPA had smaller lesion volumes than patients of comparable age treated with placebo. In contrast, older patients treated with tPA tended to have larger lesion volumes at 3 months than patients of similar age treated with the placebo. We also detected the baseline NIHSS score by the presence of old lesion or the early CT finding interaction for lesion volume at 3 months as well as for lesion volume at 24 hours and 7 days (P<0.002). We found that patients with high baseline NIHSS score alone or with a combination of old lesion and early finding on the baseline CT would have larger lesion volume than other patients.

### Table 4. Correlation Between Lesion Volume and Favorable or Unfavorable Clinical Outcome on Parts I and II Combined Data*

<table>
<thead>
<tr>
<th>Time After Stroke</th>
<th>NIHSS (≥1)</th>
<th>Barthel Index (≥95)</th>
<th>Rankin Scale (≥1)</th>
<th>Glasgow Scale (≥1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>−0.38</td>
<td>−0.47</td>
<td>−0.44</td>
<td>−0.46</td>
</tr>
<tr>
<td>7–10 d</td>
<td>−0.39</td>
<td>−0.45</td>
<td>−0.45</td>
<td>−0.49</td>
</tr>
<tr>
<td>3 mo</td>
<td>−0.42</td>
<td>−0.50</td>
<td>−0.51</td>
<td>−0.539</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>−0.28</td>
<td>−0.34</td>
<td>−0.31</td>
<td>−0.35</td>
</tr>
<tr>
<td>7–10 d</td>
<td>−0.30</td>
<td>−0.41</td>
<td>−0.36</td>
<td>−0.40</td>
</tr>
<tr>
<td>3 mo</td>
<td>−0.35</td>
<td>−0.44</td>
<td>−0.39</td>
<td>−0.43</td>
</tr>
<tr>
<td>tPA/placebo combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>−0.34</td>
<td>−0.41</td>
<td>−0.38</td>
<td>−0.41</td>
</tr>
<tr>
<td>7–10 d</td>
<td>−0.35</td>
<td>−0.43</td>
<td>−0.41</td>
<td>−0.45</td>
</tr>
<tr>
<td>3 mo</td>
<td>−0.39</td>
<td>−0.47</td>
<td>−0.46</td>
<td>−0.49</td>
</tr>
</tbody>
</table>

Point biserial correlation coefficient.

*Excluding patients who died or had no follow-up CT during the scheduled time intervals.

### Table 5. Stroke Subtype (as Determined at Baseline) and CT Lesion Volumes by Intention-to-Treat

<table>
<thead>
<tr>
<th>Treatment tPA Placebo Treatment Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic n=136 Placebo n=137 Treatment Combined n=273</td>
</tr>
<tr>
<td>24 h</td>
</tr>
<tr>
<td>7–10 d</td>
</tr>
<tr>
<td>3 mo</td>
</tr>
<tr>
<td>Large vessel</td>
</tr>
<tr>
<td>24 h</td>
</tr>
<tr>
<td>7–10 d</td>
</tr>
<tr>
<td>3 mo</td>
</tr>
<tr>
<td>Small vessel</td>
</tr>
<tr>
<td>24 h</td>
</tr>
<tr>
<td>7–10 d</td>
</tr>
<tr>
<td>3 mo</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).
not be as sensitive (or as precise) a measure of treatment effect as the clinical measures. Location of the lesion, not size of the infarct alone, is critical to eventual clinical outcome. Small discrete CT lesions can have significant clinical effects, and large CT lesions can have minimal clinical effects. The correlation of clinical and radiographic end points at all time points measured is moderately good but not perfect. It is also possible that treatment with tPA does not have as large an effect on lesion volume as it does on clinical outcome measures. Furthermore, even when parts I and II are combined, the trial was not designed or powered to detect CT lesion volume differences between groups.

We have used an intention-to-treat analysis for a radiographic end point in a stroke clinical trial. This intention-to-treat approach to lesion analysis is the standard means to address clinical end points. Potential bias can be introduced by deleting those who die or who are lost to follow-up (eg, systematic bias away from larger lesions).

The effect of tPA on lesion volume at 24 hours and 7 to 10 days is consistent with the clinical benefit seen at 24 hours (median NIHSS of 8 in the tPA-treated patients and 12 in the placebo-treated patients; \( P<0.001 \)) and at 7 to 10 days (median NIHSS of 5 in the tPA-treated patients and 9 in the placebo-treated patients; \( P<0.001 \)). The lesion volume differences between the 2 treatment groups were similar between the 3-month time point and the 7- to 10-day time point. The median lesion volumes for both the tPA-treated and placebo-treated groups were also highest at the 7- to 10-day time point, suggesting that the presence of edema, mass effect, and hemorrhage may play a role in the subacute lesion volumes. The difference in lesion volumes due to treatment was already apparent 24 hours after stroke, supporting a short-term benefit of tPA on reducing ischemic tissue volume.

More than 96% of all CT scans from the trial had measurable CT lesion volumes, and only 7% of the CTs were missing for those alive at 3 months. A relatively small number of CTs were performed outside of the study window. Baseline CT abnormalities were balanced between treatment arms. The frequency, characterization, significance, and reliability of the early CT changes at baseline (such as sulcal effacement, focal hypodensity) will be the subject of forthcoming communications.

Variables that may be important in the final predictive model of 3-month lesion volume include treatment with tPA, age, age×treatment interaction, NIHSS score×early CT scan changes interaction, and stroke subtype determined at baseline. Our data suggest that many variables contribute to the final, 3-month lesion volume in acute ischemic stroke patients, although none of these variables when present should cause the treating physician to withhold tPA treatment. The clinical significance of the age×treatment interaction that was seen at 3 months but not at 24 hours or 7 to 10 days is not clear given the lack of consistency over the 3 time points.

Cerebral infarct volumes on CT can be measured with good interrater agreement by 3 different approaches as assessed by intraclass correlations,\(^{21,22}\) although smaller lesion volumes (<5 mL) tend to have greater interrater variability. Stereological methods for measuring infarct and brain compartment volumes from CT scans provide another approach to quantifying the effects of treatment on lesion size and may reduce interobserver variability.\(^{23}\)

Measurements of stroke determined by CT have some advantages compared with clinical assessments.\(^{14}\) Language-dependent scales introduce measurement bias when applied to patients who may or may not have injury to portions of the brain that are important for language function.\(^{24,25}\) Clinical assessment scales also have the potential for measurement bias related to culture, age, sex, education, and income.\(^{26}\) Numerical expressions of the commonly used clinical outcome scales do not describe a true continuum. For example, the numerical value of 3 on the NIHSS could represent minor findings of weakness in arms and legs or a major language deficit. Thus, scales are often analyzed as broad categories, such as the categorization of favorable and unfavorable outcome used in the trial (\( \leq 1 \) versus \( >1 \) for NIHSS). In contrast, measurement of lesion volume by CT represents a continuum of values. Lesion volume is free of the bias potentially related to factors such as language, culture, and sex. To understand the significance of volumetric measures in relation to clinical outcomes, future analyses need to include location of the lesion (ie, hemispheric versus brain stem). In addition, while it is true that CT measurements are less subject
to bias, errors in CT volume measurements and errors (artifact) introduced into determining the volume of infarction may make it more difficult to detect significant differences.

A remaining question is whether the radiological end point used in this study should be used in future treatment studies, given the high cost of obtaining these data. It is possible that treatment does not have as great an effect on measurable lesion volume as it does on clinical outcome. In other words, CT lesion volumes may be less sensitive in demonstrating the efficacy of a drug. Furthermore, our method of determining lesion volume included the baseline old lesions present in the total lesion volume, thereby lessening the treatment effect, since it is not expected that tPA will reduce old lesion volumes on the baseline CT. In the Randomized Trial of Tiroliazad Mesylate in Patients With Acute Stroke (RANTTAS), subacute CT lesion volumes calculated by operator-assisted computerized planimetry (5-mm slices) at days 6 to 11 after hemispheric stroke in 50% of the eligible subjects correlated only moderately with 3-month clinical outcomes: Barthel Index, \( r = 0.43 \); Glasgow Outcome Scale, \( r = 0.53 \); and NIHSS, \( r = 0.54 \). These investigators concluded that the degree of these correlations limits the use of infarct volume as a surrogate end point in ischemic stroke trials. Our data also support only a moderate correlation of clinical-CT data. These issues should be carefully examined in ongoing and future studies that use MRI lesion size as a surrogate end point. MR lesion size, as assessed by diffusion-weighted imaging, is likely to be a more robust measure of infarct volume than CT when measured within the acute phase of stroke.

Appendix 1

All Personnel in the NINDS rt-PA Stroke Trial (Including CT Personnel Involved in This Project Not Previously Listed)

The following persons and institutions participated in the NINDS rt-PA Stroke Trial. The list represents the location of investigators at the time the trial was conducted. Many of the investigators are now at other locations.

Clinical Centers: University of Cincinnati (150 patients): Principal Investigators: T. Brott, Co-investigators: J. Broderick, R. Rothari, M. O’Donoghue, W. Barsan, T. Tomskich. Study Coordinators: J. Spilker, R. Miller, L. Sauerbeck. Affiliated Sites: St Luke (East), Bethesda North Hospital, University of Cincinnati, J. Farrell, J. Kelly, T. Perkins, R. Miller, University Hospital, McDonald; Bethesda North Hospital, M. Rorick, C. Hickey; St Luke (East), J. Armitage, C. Perry; Providence, K. Thalinger, R. Rhude; The Christ Hospital, J. Armitage, J. Schill; St Luke (West), P.S. Becker, R.S. Heath, D. Adams; Good Samaritan Hospital, R. Reed, M. Klei; St Francis/St George, A. Hughes, R. Rhude; Bethesda Oak, J. Anthony, D. Baudendistel; St Elizabeth (North), C. Zadicoff, R. Miller; St Luke/Kansas City, M. Rymer, I. Bettinger, P. Laubinger; Jewish Hospital, M. Schmerler, G. Meiros.


Appendix 2

Detailed CT Volumetric Analysis Methodology

Method 1 for Reading Tapes and Optical Disk at Henry Ford Health System

At Henry Ford Health System, the initial method was used to read the CT data archived on magnetic tape or readable optical disk. These data were transferred to an independent work station (CAMRA S-200, ISG Technologies, Inc, Toronto, Canada). The CT technologist, trained by the Central Coordinating Center neuroradiologist then analyzed the entire CT scan and inspected the lesion outlined by the CT technologist and
manually made appropriate corrections. The final corrected lesion volume outlined by the Central Coordinating Center neuroradiologist was entered into the CT scan database. Three hundred forty-seven CTs were read by this method.

Method 2 for Reading Tapes and Optical Disks at Henry Ford Health System

The CT scan data archived on magnetic tape or readable optical disk were transferred to a SUN workstation SPARC-10. A physicist trained by the Central Coordinating Center neuroradiologist reviewed the CT scan. Initially, for segmentation of the lesion, proprietary software was used to automatically segment normal and abnormal tissue to calculate lesion volume by computer ("tape process") with the use of preset threshold CT units (Hounsfield units). Segmentation was performed from the histogram of the CT image. The histogram analysis used the spatial and featured domain properties of the CT data. A nonlinear edge-preserving filter was used to suppress noise. After automated segmentation, manual correction to the lesion segmentation was performed. Finally, the Central Coordinating Center neuroradiologist reviewed the entire CT scan, and appropriate corrections were performed manually on each slice of the CT scan before final data entry. Four hundred twenty-seven CTs were read by this method.

Films for CT scans that could not be read from magnetic tape or optical disk were sent to the University of Virginia for lesion measurements. Films were digitized (using a Lumisys model 150 digital scanner set at 100 μm spot size or a Vidar scanner at 8 bits per pixel and 150 dots per inch) and then electronically transferred to the image analysis workstation (a Hewlett Packard Apollo 9000 series computer in a server configuration running proprietary software) for linear and volume measurements ("film process"). Lesion volume was calculated with segmentation performed on each slice. The trained operator manually outlined the lesion on each slice. The outlined data were reviewed by neurosurgery fellows and adjusted as necessary. Lesion volume was calculated from the cross-sectional area of the lesion on each slice multiplied by slice thickness. Lesion volumes on slices from which the lesion was identified were then added for calculation of the final volume. Quality control checks were performed to ensure that all images were properly scanned and available for measurements. Slice thickness and the measurement scale were taken into account for calculations of each lesion volume. Four hundred seventy-three films were read by this method.

Appendix 3

Figure 3. Intention-to-treat algorithm for lesion volume at 3 months. A similar process was used for 24-hour and 7- to 10-day intention-to-treat algorithms.
Appendix 4
Listing of 30 Baseline Variables
Age; Sex; Cigarette smoking in previous year (yes, no); Drinking problems; History of diabetes; Stroke subtype: small-vessel, cardioembolic, and large-vessel; Baseline NIHSS; Early CT findings excluding hyperdense artery sign/thrombus; Percentage of correct dose (ranked data used); Admission mean blood pressure; Baseline mean blood pressure; Admission systolic blood pressure; Baseline systolic blood pressure; Admission diastolic blood pressure; Baseline diastolic blood pressure; Admission pulse pressure; Baseline pulse pressure; Race: white, black, and Hispanic; Weight (ranked data used); History of atherosclerosis; History of hypertension; History of other cardiac disease; History of hepatic disease; Admission temperature; Total dose delivered; Aspirin (NSAID) used before stroke; Time from stroke onset to treatment; Presence of old lesion (yes, no); Number of CT slices; CT process types. (Number of CT slices and CT process types were not baseline variables.)

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Effect of Intravenous Recombinant Tissue Plasminogen Activator on Ischemic Stroke
Lesion Size Measured by Computed Tomography

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