Lack of Clinical Significance of Early Ischemic Changes on Computed Tomography in Acute Stroke

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Context The prevalence and clinical significance of early ischemic changes (EICs) on baseline computed tomography (CT) scan of the head obtained within 3 hours of ischemic stroke are not established.

Objective To determine the frequency and significance of EIC on baseline head CT scans in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA (recombinant tissue plasminogen activator) Stroke Trial.

Design and Setting The original study, a randomized controlled trial, took place from January 1991 through October 1994 at 43 sites, during which CT images were obtained within 3 hours of symptom onset and prior to the initiation of rt-PA or placebo. For the current analysis, detailed reevaluation was undertaken after October 1994 of all baseline head CT scans with clinical data available pretreatment (blinded to treatment arm).

Patients Of 624 patients enrolled in the trial, baseline CT scans were retrieved and reviewed for 616 (99%).

Main Outcome Measures Frequency of EICs on baseline CT scans; association of EIC with other baseline variables; effect of EICs on deterioration at 24 hours (≥4 points increase from the baseline National Institutes of Health Stroke Scale [NIHSS] score); clinical outcome (measured by 4 clinical scales) at 3 months, CT lesion volume at 3 months, death at 90 days; and symptomatic intracranial hemorrhage (ICH) within 36 hours of treatment.

Results The prevalence of EIC on baseline CT in the combined rt-PA and placebo groups was 31% (n = 194). The EIC was significantly associated with baseline NIHSS score (β = 0.23; P < .001) and time from stroke onset to baseline CT scan (β = 0.11; P = .007). After adjusting for baseline variables, there was no EIC × treatment interaction detected for any clinical outcome, including deterioration at 24 hours, 4 clinical scales, lesion volume, and death at 90 days (P ≥ .25), implying that EIC is unlikely to affect response to rt-PA treatment. After adjusting for NIHSS score (an independent predictor of ICH), no EIC association with symptomatic ICH at 36 hours was detected in the group treated with rt-PA (P ≥ .22).

Conclusions Our analysis suggests that EICs are prevalent within 3 hours of stroke onset and correlate with stroke severity. However, EICs are not independently associated with increased risk of adverse outcome after rt-PA treatment. Patients treated with rt-PA did better whether or not they had EICs, suggesting that EICs on CT scan are not critical to the decision to treat otherwise eligible patients with rt-PA within 3 hours of stroke onset.
of symptomatic ICH was increased beyond 6.4% in the 16 (5.2%) rt-PA-treated patients who had clearly visible signs of edema or mass effect on the baseline CT scan and in the 136 (20%) rt-PA-treated patients with severe neurological deficits (National Institutes of Health Stroke Scale [NIHSS] score ≥20 at baseline).\(^1,4\) Despite this increased risk of ICH, patients with signs of edema or mass effect on CT scans or severe neurological deficits at baseline remained more likely to have a favorable clinical outcome if they received rt-PA than if they received placebo.\(^1,3,4\)

The European Cooperative Acute Stroke Study (ECASS)\(^3\) introduced the concept of using baseline head CT studies to exclude patients from rt-PA treatment with ICH and/or major early infarct signs within 5 to 6 hours of stroke onset. Major early infarct or extended infarct signs in the ECASS study included both subtle and clearly visible CT findings of early ischemia such as diffuse swelling of the affected cerebral hemisphere, parenchymal hypodensity, and/or effacement of the cerebral sulci involving more than 33% of the middle cerebral artery (MCA) territory.\(^5,6\) The ECASS investigators chose to exclude these patients suggesting that those eligible for thrombolytic treatment within 5 to 6 hours of stroke onset in whom there was CT scan evidence of early ischemic changes (EICs) in more than one third of the MCA territory have been associated with severe stroke, an excessively high frequency of spontaneous hemorrhagic transformation of the infarct, and poor outcome.\(^5\) Subsequent stroke trials for thrombolytic therapy with rt-PA—ECASS II,\(^7\) ATLANTIS,\(^8\) and PROACT II—used similar CT scan exclusion guidelines as those used in ECASS.

Since the design of the NINDS rt-PA Stroke Trial, additional subtle changes associated with early cerebral ischemia on CT scan within 6 hours of stroke onset have been well described in the literature.\(^10-21\) These subtle EICs include hypodensity/hypoattenuation of the brain parenchyma and/or gray matter including the basal ganglia and lentiform nucleus (obscuration of lentiform nucleus), insular cortex (loss of insular ribbon), and focal and diffuse swelling of the cerebral parenchyma as seen by effacement of the cerebral sulci, the basal cisterns, and compression of the ventricular system.

The NINDS rt-PA Stroke Trial did not use either EICs or visual quantification of EICs on CT scan as an exclusion criterion and did not collect data at the time of randomization on the full range of major infarct signs as defined in ECASS. We therefore undertook a detailed reevaluation of all NINDS rt-PA Stroke Trial baseline CT scans for EICs. We determined the prevalence and evaluated the significance of EICs on the baseline CT scan with respect to treatment response, outcome (including mortality 3 months poststroke), and ICH risk. We tested the following hypotheses: EICs, including both clearly visible and subtle changes on baseline CT scan, are independently associated with (1) response (or lack thereof) to rt-PA therapy; (2) clinical outcome including death; (3) CT scan lesion volume; and (4) the development of symptomatic ICH.

**METHODS**

The NINDS rt-PA Stroke Trial was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rt-PA for acute ischemic stroke, which took place from January 1991 through October 1994.\(^1\) The trial was conducted in 2 parts: (1) 291 patients tested the effect of rt-PA 24 hours following stroke, but clinical data at 3 months were also systematically collected; and (2) 333 patients tested the effect of rt-PA on favorable outcome at 3 months measured by 4 clinical outcome scales: NIHSS,\(^22\) the Barthel Index,\(^23\) the modified Rankin scale,\(^24\) and the Glasgow outcome scale.\(^25\) Treatment included either placebo or rt-PA, 0.9 mg/kg body weight (maximum 90 mg), 10% of which was injected as an initial bolus over 1 minute and the remainder infused over 1 hour. Treatment was initiated within 3 hours of stroke onset.

**Patient Population**

Eight clinical centers enrolled patients at 43 sites (33 community hospitals, 8 teaching hospitals, and 2 Veterans Affairs hospitals). Almost half of the patients (n=302) were treated in 0 to 90 minutes; 322 patients were treated within 91 to 180 minutes. Principal investigators received approval from the respective participating centers’ institutional review boards for obtaining and analyzing the CT scans.

**CT Scanning**

Prior to beginning the NINDS rt-PA Stroke Trial, uniform standards for image acquisition of CT scans and printing of hard copies were established and disseminated to the 8 clinical centers. Images were obtained within 3 hours of symptom onset and prior to the initiation of rt-PA or placebo. The baseline CT scan was used to identify ICH, a major exclusion criterion. All CT scans were performed on either third- or fourth-generation CT scanners. For rapid enrollment of patients, all of the baseline CT scans were obtained with 10-mm slice thickness. Technical factors were 120 kV, 170 mA, matrix size of 512 × 512, and scanning time for 3 seconds for the posterior cranial fossa and 2 seconds for the supratentorial compartment. All slices were contiguous with a display field of view of 20 cm and were performed from the level of the foramen magnum to the high vertex region. All the CT scan images were displayed on hard copies (14” × 17” [36 cm × 43 cm]). Window levels and window width for display of images on the hard copies were to be optimized for adequate display of gray/white matter distinction. All hard copies of the CT scan were sent to the coordinating center for review after they had been examined for evidence of hemorrhage by the on-site investigators. Time of stroke onset to time of CT scan performance was recorded.

As reported in the original communication,\(^1\) all CT scans were reviewed.
centrally by the coordinating center neuroradiologist (S.C.P.) for presence of ICH. Additional information including presence of old infaracts, edema, mass effects, hyperdense artery sign, anatomic location, and arterial distribution of infarct was also obtained. For the initial review of CT scans during the trial, the coordinating center neuroradiologist was blinded to the treatment assignment and clinical findings included time from symptom onset. The main purpose of the original prospective review of the CT scan was for identification of ICH, the principal CT scan exclusion criterion for the trial. Patients with CT scan findings of readily apparent edema or mass effect were not excluded from the study.

Old lesions on the baseline CT scan were recorded on the initial review for the trial. We defined an old lesion on baseline CT scan as a well-circumscribed hypodense area without any mass effect or edema. This definition did not include areas of leukomalacia, leukoariosis, demyelination, or artifacts in the judgment of the interpreting neuroradiologist.

For this study, all baseline CT scans were reevaluated after October 1994 centrally by the coordinating center neuroradiologist (S.C.P.) with clinical information provided by a stroke neurologist (S.R.L.) to simulate the clinical setting of the treatment of acute stroke. The clinical information included patient demographics (age and sex), time of the stroke onset, time from stroke onset to the CT scan, history of prior stroke, presumed localization of the stroke symptoms involving right or left cerebral hemisphere, brain stem, posterior cranial fossa or subcortical location, presumed stroke mechanism provided by the clinical on-site investigator, and the initial individual component scores of the baseline NIHSS.22 No information on treatment assignment was provided to the neuroradiologist or stroke neurologist during this review.

The EICs analyzed on the baseline CT scans were classified into the following 3 categories: (1) loss of gray/white matter distinction (focal or diffuse area in cerebral or cerebellar hemispheres); (2) hypodensity or hypointenuation (focal or diffuse area, which on a visual inspection is less than the white matter density but greater than cerebrospinal fluid (CSF) density, excluding areas of chronic white matter ischemic changes or areas considered chronic or old and closer to CSF density and artifacts); and (3) compression of CSF spaces (focal and/or diffuse brain swelling). The hyperdense artery sign on baseline CT scan was not included as EIC. The CT scan finding of EIC was defined as at least 1 of the CT scan findings of (1) through (3) above. Visual quantification of each of these 3 CT scan findings of EIC was carried out to determine whether the findings involved more or less than one third percentage of the territory of the MCA. Early ischemic change was classified as more than one third of the MCA territory based on visual inspection indicating EIC involvement of 2 or more different lobes of the cerebral hemisphere and basal ganglia plus insular cortex. Data were collected on standardized forms.

**Other Data Collected During the NINDS rt-PA Stroke Trial**

Clinical data were collected at baseline, 24 hours, 7 to 10 days, 3 months, and 1 year after randomization. Adverse events were collected as they occurred, including symptomatic ICH and death. Symptomatic ICH was defined as neurological deterioration thought to be due to hemorrhage on CT scan.4 Hemorrhages within 36 hours of treatment were designated prospectively as being potentially attributable to the study drug. Four clinical outcome scales—NIHSS,22 the Barthel Index,21 the modified Rankin scale,24 and the Glasgow outcome scale25—were assessed at 3 months poststroke. Favorable clinical outcome at 3 months after stroke was defined either as a complete or near complete recovery on the 4 neurological scales as defined in the original trial publication.1 Deaths and all patients with less than complete or near recovery on a particular outcome measure were classified as having an unfavorable outcome on that measure. Deterioration at 24 hours was defined as 4 points or higher increase from the baseline NIHSS score. All deaths were recorded up to 3 months. Additional CT scans were obtained at 24 hours, 7 to 10 days, and 3 months after stroke. The lesion volume on CT scan was measured at these 3 time periods.

**Statistical Analysis**

Accuracy of Identification of EIC by CT Scan. We assessed the accuracy of our identification of EICs on CT scan by assessing the relationship between EICs on the baseline scan and the location and presence of hypodensity on the 24-hour scan. Only the placebo patients were used for this analysis because treatment with rt-PA might reduce the presence of hypodensity at 24 hours. The baseline CT scan data in the placebo group were reviewed with clinical information. We computed the positive predictive value of EICs at baseline for infarction at 24 hours, assuming agreement if a lesion was detected by CT scan at 24 hours in the same region and location as the EICs at baseline. Patients who had baseline CT scans with old lesions were excluded from this analysis.

Association Between EIC and Selected Baseline Variables. The associations between EIC and baseline variables previously found to be associated with clinical outcome2 as well as time from stroke onset to baseline CT scan were assessed using χ² tests for trend (binary baseline variables) and tests of Spearman rank correlation (p) (continuous baseline variables). The baseline variables were age, baseline NIHSS score, diabetes mellitus, admission mean arterial pressure, stroke subtype, old lesions on baseline CT scan, and baseline CT scan findings (edema or mass effect or hyperdense artery sign). All analyses were conducted using an intent-to-treat approach,13 except for the exclusion of 2 patients whose baseline CT scans were performed later than 3 hours from stroke onset (ie, protocol violations).

Association Between EIC and Outcome. We tested the association of EIC with 3-month favorable outcome using
a global statistical test and with deterioration at 24 hours, symptomatic ICH within 36 hours, and death within 90 days using logistic regressions. Multivariable analyses also are reported for each outcome adjusting for the baseline variables listed above, excluding baseline CT scan finding because both baseline CT scan finding and EIC included edema and mass effect. There was no substantive change in results when we included baseline CT scan finding as a variable in the analyses, probably due to the low correlation between baseline CT scan finding and EIC induced by the inclusion of hypodense artery sign as a baseline CT scan finding (a finding not included in EIC).

To determine if EIC affected response to treatment with rt-PA, we tested for EIC and treatment interactions in the multivariable models on both the log and linear scales. Results were similar and are reported only for log scale. Poisson regression analysis was used to analyze the CT scan lesion volume on a transformed scale (cube-root of lesion volume). Consistent with our previous work, an interaction between EIC and treatment was considered to be significant at \( P < .10 \). We had power of greater than 80% to detect an EIC \( \times \) treatment interaction odds ratio (OR) greater than 1.4 when EIC was categorized as yes or no, assuming the proportion of variance explained by the other covariates in the model (\( R^2 \)) ranged from 0.18 to 0.27 and the proportion in the placebo group with the outcome ranged from 0.20 to 0.49. Power could be slightly increased or slightly reduced when testing the interaction with EIC as 3 categories rather than as yes or no. For descriptive purposes, we reported the adjusted OR and 95% confidence interval (CI) limits for each category of EIC, for each outcome, using the placebo group with no EIC as the reference group, and provided a graphic comparison with the treatment/placebo OR within EIC subgroups.

Where a treatment \( \times \) EIC interaction was not detected, we tested for a treatment effect on each outcome adjusting for the other baseline covariates to determine if adjusting for any baseline imbalance in EIC would diminish or enhance the previously reported treatment benefit. Where no interaction was detected, we also reported the adjusted ORs and 95% CIs for favorable and adverse outcomes.

The analysis of symptomatic ICH within 36 hours of treatment was based on rt-PA–treated patients only, because only 2 patients in the placebo group had ICH. We explored the association between each subtype of EIC and the risk of symptomatic ICH within 36 hours of treatment. Statistical analysis was performed using SAS version 6.12 and 8.0 (SAS Institute, Cary, NC).

### RESULTS

From the 624 patients enrolled in the trial (312 randomized to rt-PA treatment and 312 to placebo), 616 (99%) baseline CT scans were reviewed. Eight patients (1%) had a CT scan performed at baseline, but the CT scans were not retrievable from the clinical sites. Two patients with CT scans performed more than 3 hours after stroke onset were subsequently excluded.

#### Accuracy of Identification of EIC on Baseline CT Scan

Of 222 placebo patients who did not have an old lesion on the baseline CT scan, 82 (37%) patients had at least 1 EIC on the baseline CT scan. Of these 82 patients, 71 had at least 1 new lesion on the 24-hour poststroke CT scan that matched the location of the CT findings on the baseline CT scan (positive predictive value, 87%; 95% CI, 79%-94%).

#### Distribution of EIC on Baseline CT Scan

The distributions of the EICs on the baseline CT scan are summarized in Table 1. Those patients who had an old lesion on CT scan are included in Table 1 and in all subsequent analyses. There was no statistically significant difference in the distribution of EICs between rt-PA and placebo groups (28% vs 35%, respectively; \( P = .09 \)).

### Association of EIC With Other Baseline Variables

Table 2 describes the associations of EIC with baseline variables. Early ischemic change was significantly associated with baseline NIHSS score (\( p = .03 \), \( P < .001 \)) and time from stroke onset to baseline CT scan (\( p = .011 \); \( P = .007 \)) but all correlations were low (\( p = .23 \)). Within the EIC subgroups, there appeared to be imbalances in baseline variables between the rt-PA–treated and placebo patients. To take these imbalances into account, we adjusted for any baseline variables shown in previous publications to be associated with treatment outcome.

#### EIC Status Associated With Clinical Outcomes

Table 3 shows the relationship between EIC and clinical outcomes, both unadjusted and adjusted for other baseline variables. After adjusting for other baseline variables, there was no EIC \( \times \) treatment interaction detected for any clinical outcome (\( P > .25 \)) implying that the presence of EIC did not affect response to rt-PA. The adjusted ORs comparing treatment by EIC categories with the reference group (placebo group with no EIC) are also given in Table 3 and suggest that if an interaction was missed, due to potential low power, this interaction would be small.

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shows a different perspective, the ORs for treatment effect within EIC subgroups, again supporting the lack of an EIC×treatment interaction.

After adjusting for the baseline variables shown to be associated with 3-month favorable outcome and treatment, there was a marginal effect of EIC on outcome detected in the combined rt-PA and placebo groups (model 1, Table 3; P = .07), but no effect was detected for neurological deterioration at 24 hours or death at 90 days. The 2 variables, NIHSS score and the NIHSS score × age interaction, had an association with 3-month favorable outcome (P < .001) in model 1 with EIC included. If the NIHSS score and NIHSS score × age interaction terms are omitted from model 1, EIC has a significant effect (P < .001) on 3-month clinical outcome, reflecting the correlation between NIHSS and EIC. If we include the time from stroke onset and the time × treatment interaction in model 1, the effect of EIC on 3-month favorable outcome was unchanged (P = .07). There was an association between EIC and 3-month lesion volume (P ≤ .001).

The treatment effect for rt-PA remained significant for 3-month favorable outcome (OR, 2.0; 95% CI, 1.5-2.8; P < .001) after adjusting for the effect of NIHSS score, other baseline variables, and the presence of EIC. An rt-PA treatment effect could not be detected for deterioration in the first 24 hours (OR, 0.8; 95% CI, 0.5-1.3) or death at 90 days (OR, 0.8; 95% CI, 0.5-1.2) after adjusting for the baseline covariates, including EIC.

In the rt-PA–treated patients, the unadjusted incidence of symptomatic ICH within 36 hours appeared higher in the groups of patients who had EIC extending over more than one third of the MCA territory or EIC covering one third or less than one third of the MCA territory compared with patients without EIC (Table 4). After adjusting for the baseline NIHSS score, which we have already shown to be predictive of ICH risk, EICs were not associated with symptomatic ICH within 36 hours of treatment (P = .22). In the placebo group, the 2 patients who had symptomatic ICH within 36 hours both had EICs on CT scan involving one third or significantly less than one third MCA distribution.

**COMMENT**

Our data demonstrate that subtle CT scan changes of focal cerebral ischemia in patients presenting within 3 hours of ischemic stroke are relatively common. These EICs are correlated with stroke severity as measured by the NIHSS score and time from stroke onset to CT scan. However, we could not detect an association with an increased risk of adverse outcome, independent of the NIHSS score, after rt-PA treatment (ie, we could not detect an EIC×treatment interaction). In our study, after adjusting for baseline variables, patients treated with rt-PA fared better whether or not they had EIC on CT scans. This was true for both one third and less and for greater than one third MCA territory.

### Table 2. Association of Selected Baseline Variables With Extent of Early Ischemic Change*

<table>
<thead>
<tr>
<th>Baseline Computed Tomography (CT) Scan Status</th>
<th>Comparison of Baseline Variables and EIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIC &gt;1/3 MCA</td>
<td>EIC ≤1/3 MCA</td>
</tr>
<tr>
<td>rt-PA</td>
<td>Placebo</td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>Selected baseline variables, No.†</td>
<td></td>
</tr>
<tr>
<td>Edema and mass effect, No. (%)</td>
<td>38</td>
</tr>
<tr>
<td>Edema, mass effect, and/or hyperdense artery sign (baseline CT finding), No. (%)</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>10</td>
</tr>
<tr>
<td>Presence of old lesion, No. (%)</td>
<td>9</td>
</tr>
<tr>
<td>Aspirin prior to treatment, No. (%)</td>
<td>14</td>
</tr>
<tr>
<td>Presumptive stroke type, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Small vessel</td>
<td>0</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>24</td>
</tr>
<tr>
<td>Large vessel</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>NIHSS, median (interquartile range)‡</td>
<td>19</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67</td>
</tr>
<tr>
<td>Admission mean arterial blood pressure, mean (SD), mm Hg</td>
<td>115</td>
</tr>
<tr>
<td>Time from stroke onset to baseline CT scan, mean (SD), min</td>
<td>88</td>
</tr>
</tbody>
</table>

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*EIC (early ischemic change) indicates loss of gray/white matter distinction, presence of hypodensity, or compression of cerebrospinal fluid spaces; MCA, middle cerebral artery; rt-PA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; and NA, not applicable. P values computed from χ² tests for trend (binary variables) or Spearman rank correlation (p) (continuous variables) combining rt-PA and placebo groups.

†Selected baseline variables shown to be associated with at least 1 of the outcomes specified above.‡

‡Higher values indicate greater stroke severity.
third involvement of the MCA territory on the baseline CT scan.

In the analysis presented in Table 3, the placebo group in the “no EIC” category was used as the reference for all other groups since testing for interaction between treatment and EIC required a common placebo reference group. It appears that compared with the reference group, only the group of rt-PA patients with no EIC had an increased likelihood of favorable outcome on all measures with CIs that did not include 1.0. While it makes intuitive biological sense that rt-PA might be most effective in patients without such severe tissue damage as to produce CT scan changes, it is likely that the apparent greater benefit of rt-PA in this group is due to other factors. These include the substantially larger number of patients with no EIC compared with those with EIC, which increases the power to make statistical comparisons in the rt-PA group with no EIC. Comparing the likelihood of favorable outcome within EIC categories (Figure), a greater relative benefit of rt-PA over placebo in patients with EIC in more than one third of the MCA territory is apparent. If there had been a strong harmful interaction, we would expect to see a much smaller OR for

Table 3. Baseline Computed Tomography Scan Status by Treatment Associated With Clinical Outcomes*

<table>
<thead>
<tr>
<th>EIC Type†</th>
<th>rt-PA</th>
<th>Placebo</th>
<th>rt-PA</th>
<th>Placebo</th>
<th>rt-PA</th>
<th>Placebo</th>
<th>rt-PA</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>EIC &gt;1/3 MCA</td>
<td></td>
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<tr>
<td>No EIC</td>
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<tr>
<td>EIC ≤1/3 MCA</td>
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<tr>
<td>No EIC</td>
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<tr>
<td>EIC × Treatment Interaction‡</td>
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<tr>
<td>EIC Effect§</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No. of EIC findings</td>
<td>38</td>
<td>46</td>
<td>49</td>
<td>61</td>
<td>220</td>
<td>202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>0.5 (0.2-1.1)</td>
<td>0.5 (0.2-0.9)</td>
<td>0.9 (0.5-1.7)</td>
<td>0.8 (0.4-1.4)</td>
<td>2.1 (1.5-2.9)</td>
<td>1.0</td>
<td>.40</td>
<td>&lt;.001</td>
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<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.1 (0.4-2.5)</td>
<td>0.5 (0.2-0.9)</td>
<td>1.2 (0.6-2.5)</td>
<td>0.8 (0.5-1.5)</td>
<td>2.1 (1.5-3.1)</td>
<td>1.0</td>
<td>.52</td>
<td>.07</td>
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<td>Rankin score = 0 or 1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome, %</td>
<td>21</td>
<td>15</td>
<td>33</td>
<td>28</td>
<td>48</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>0.7 (0.3-1.5)</td>
<td>0.4 (0.2-1.0)</td>
<td>1.2 (0.6-2.3)</td>
<td>0.9 (0.5-1.8)</td>
<td>2.3 (1.5-3.4)</td>
<td>1.0</td>
<td>.41</td>
<td>&lt;.001</td>
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<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.7 (0.6-4.6)</td>
<td>0.4 (0.2-1.1)</td>
<td>1.7 (0.8-3.7)</td>
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<td>.18</td>
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<td>NIHSS score = 0 or 1</td>
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<tr>
<td>Outcome, %</td>
<td>13</td>
<td>13</td>
<td>22</td>
<td>21</td>
<td>40</td>
<td>22</td>
<td></td>
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<tr>
<td>Unadjusted OR (95% CI)</td>
<td>0.5 (0.2-1.5)</td>
<td>0.5 (0.2-1.3)</td>
<td>1.0 (0.5-2.1)</td>
<td>0.9 (0.5-1.9)</td>
<td>2.3 (1.5-3.5)</td>
<td>1.0</td>
<td>.21</td>
<td>.001</td>
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<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.1 (0.4-3.6)</td>
<td>0.5 (0.2-1.4)</td>
<td>1.3 (0.6-3.0)</td>
<td>1.0 (0.5-2.2)</td>
<td>2.3 (1.4-3.8)</td>
<td>1.0</td>
<td>.59</td>
<td>.13</td>
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<tr>
<td>Barthel Index &gt;50</td>
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<td>Outcome, %</td>
<td>26</td>
<td>26</td>
<td>39</td>
<td>33</td>
<td>59</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>0.5 (0.2-1.1)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.8 (0.4-1.6)</td>
<td>0.6 (0.4-1.2)</td>
<td>1.9 (1.3-2.8)</td>
<td>1.0</td>
<td>.42</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>0.8 (0.3-2.1)</td>
<td>0.4 (0.2-0.9)</td>
<td>1.1 (0.5-2.3)</td>
<td>0.6 (0.3-1.3)</td>
<td>2.1 (1.3-3.3)</td>
<td>1.0</td>
<td>.91</td>
<td>&lt;.003</td>
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<td>Glasgow = 1</td>
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<tr>
<td>Outcome, %</td>
<td>24</td>
<td>17</td>
<td>35</td>
<td>34</td>
<td>51</td>
<td>34</td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted OR (95% CI)</td>
<td>0.6 (0.3-1.4)</td>
<td>0.4 (0.2-0.9)</td>
<td>1.0 (0.5-2.0)</td>
<td>1.0 (0.6-1.9)</td>
<td>2.0 (1.4-3.0)</td>
<td>1.0</td>
<td>.29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.6 (0.6-4.1)</td>
<td>0.4 (0.2-1.0)</td>
<td>1.4 (0.7-3.1)</td>
<td>1.2 (0.6-2.4)</td>
<td>2.1 (1.3-3.4)</td>
<td>1.0</td>
<td>.32</td>
<td>.17</td>
</tr>
<tr>
<td>Model 2: deterioration at 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Outcome, %</td>
<td>21</td>
<td>20</td>
<td>15</td>
<td>11</td>
<td>18</td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.3 (0.5-3.0)</td>
<td>1.1 (0.5-2.5)</td>
<td>1.2 (0.5-2.6)</td>
<td>0.8 (0.4-1.8)</td>
<td>0.6 (0.3-1.0)</td>
<td>1.0</td>
<td>.22</td>
<td>.40</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.3 (0.6-3.1)</td>
<td>1.1 (0.5-2.4)</td>
<td>1.2 (0.6-2.7)</td>
<td>0.8 (0.4-1.8)</td>
<td>0.6 (0.4-1.1)</td>
<td>1.0</td>
<td>.25</td>
<td>.47</td>
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<tr>
<td>Model 3: 3-month lesion volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (interquartile range)</td>
<td>74 (41-159)</td>
<td>81 (29-181)</td>
<td>24 (8-89)</td>
<td>18 (6-121)</td>
<td>8 (1-64)</td>
<td>18 (2-75)</td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.6 (1.3-1.9)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.1 (1.0-1.4)</td>
<td>1.2 (1.0-1.4)</td>
<td>0.9 (0.8-1.0)</td>
<td>1.0</td>
<td>.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.2 (1.1-1.4)</td>
<td>1.4 (1.2-1.6)</td>
<td>1.1 (0.9-1.3)</td>
<td>1.1 (1.0-1.3)</td>
<td>0.9 (0.8-1.1)</td>
<td>1.0</td>
<td>.58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 4: death at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome, %</td>
<td>34</td>
<td>26</td>
<td>18</td>
<td>18</td>
<td>14</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>2.2 (1.0-4.7)</td>
<td>1.4 (0.7-3.0)</td>
<td>0.9 (0.4-2.0)</td>
<td>0.9 (0.4-1.9)</td>
<td>0.7 (0.4-1.1)</td>
<td>1.0</td>
<td>.28</td>
<td>.03</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.2 (0.5-2.9)</td>
<td>1.1 (0.5-2.6)</td>
<td>0.7 (0.3-1.6)</td>
<td>0.8 (0.4-1.8)</td>
<td>0.7 (0.4-1.3)</td>
<td>1.0</td>
<td>.82</td>
<td>.48</td>
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</tbody>
</table>

*EIC (early ischemic change) indicates loss of gray/white matter distinction, presence of hypodensity, or compression of cerebrospinal fluid spaces; MCA, middle cerebral artery; rt-PA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; and CI, confidence interval. Adjusted odds ratios (ORs) are in reference to the placebo-no EIC group. For a favorable 3-month outcome, OR > 1 indicates that patients in the EIC subgroup had lesser odds of a favorable outcome than those given placebo with no EIC; for deterioration and death, an OR > 1 indicates that patients in the EIC subgroup had greater odds of having the event than patients given placebo with no EIC.

†Model 1 includes baseline age, diabetes, NIHSS, admission mean arterial pressure (MAP), age × NIHSS, age × admission MAP. Model 2 includes aspirin use prior to randomization. Model 3 includes old lesion volume, baseline NIHSS, baseline age, NIHSS × old lesion volume, presumptive stroke subtype (small, cardioembolic, and large vessel), age × treatment, and time strata. Model 4 includes baseline age, diabetes, and NIHSS.

‡Adjusted based on models 1-4, including the EIC and treatment main effect, but not the EIC × treatment interaction term.

§The definitions of 3-month favorable outcomes; values >1 indicate unfavorable outcomes for the modified Rankin scale,24 NIHSS,22 and Glasgow outcome scale,25 and values <95 indicate unfavorable outcomes for the Barthel Index.31

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rt-PA compared with the placebo within the group with EIC in more than one third of the MCA territory than within the group with no EIC.

It remains possible that a small EIC × treatment interaction was not detected. The sample size for the EIC greater than one third of the MCA territory is only 84, making detection of interactions more difficult than if the 624 patients had been distributed more evenly over the 3 groups. Given the current distribution of patients we do not have power to detect interactions with ORs less than 1.4.

In a previous analysis we found clearly visible mass effect or edema to be present in 6% of patients and to be associated with an increased risk of ICH. This was not the case for EIC after adjusting for the NIHSS. This may be because the EIC described here includes both those clearly visible findings and more subtle findings; these findings occurred in 31% of patients in the NINDS trial.

The ECASS investigators stated that the use of thrombolytic substances in patients with extended early infarct signs is dangerous because of increased risks of major ICH and death based on their analysis of 52 of the 109 patients who were ineligible for target population analysis because of protocol violations due to extended early infarct signs. Conversely, they reported that patients who had early CT scan findings involving less than one third the MCA territory had a better outcome with rt-PA than with placebo. However, in the same 1997 report on ECASS I data, it does not appear that the investigators adjusted for baseline variables nor did they test directly for an EIC × treatment interaction as was done in this study. In addition, with one exception, the CIs on the ORs for all outcomes included 1.0, suggesting that within subgroups, ECASS investigators could not detect differences between rt-PA and placebo (Figure). The one exception was in the “no disability” category. In the ECASS data, the ORs of no disability for those with small infarcts and more subtle findings; these findings occurred in 31% of patients. The observations from our data on patients treated within 3 hours confirmed this lack of findings in ECASS.

Two recent preliminary presentations also showed that EICs are not associated with increased incidence of ICH and poor outcome when strict inclusion/exclusion criteria for enrollment of the patients were followed within 3 hours of stroke onset using NINDS rt-PA Stroke Trial guide-
lines. Similarly, favorable clinical outcomes and a low rate of symptomatic ICH comparable with our study were achieved using similar guidelines in the STARS study.54

Given the association between baseline NIHSS score and 3-month and 1-year stroke outcome, it seems probable that larger and more severe infarctions are accompanied by more evident EIC on CT scans, which is also supported by larger 3-month CT scan lesion volume in patients with EIC in more than one third of the MCA territory.59 We found an association between the NIHSS score at baseline and the presence of EIC. This relationship between the NIHSS score and EIC is expected from the correlation between the CT scan lesion volume at 3 months and EIC. The NIHSS has been shown to be reliable and reproducible35 while EIC has not.36

We detected only a marginal association between EIC on baseline CT scan and 3-month favorable outcome after adjusting for the baseline NIHSS score and the NIHSS score × age interaction and no association with symptomatic ICH following rt-PA treatment after adjusting for the baseline NIHSS score. Patients treated with rt-PA fared better overall regardless of whether or not they had EICs, based on current or prior definitions,5 and EICs did not significantly add predictive information to the already established predictors of ICH, namely NIHSS score and clearly visible CT scan evidence of edema or mass effect.6 The intent of the initial CT scan analysis for the trial was to emphasize safety by identifying any evidence of hemorrhage; however, data were also collected and reported regarding the presence of clearly visible CT scan changes of ischemia, manifest as definite hypodensity or mass effect, that occurred in only 6% of patients. With improvement in tissue contrast and spatial resolution in newer generation CT scanners, findings of acute cerebral ischemia are increasingly identified.67 This may, in part, explain the positive predictive results of EIC using the Alberta Stroke Programme Early CT Score (ASPECTS) score7 as well as their higher (over 2 times our rate) frequency of EIC seen within 3 hours of symptom onset.

Many factors, such as severity and extension of the ischemic process, collateral circulation, and location and extent of the arterial occlusion, can determine the appearance of early CT scan findings. ECASS II investigators reported “X-ray hypodenuation at CT being highly specific for irreversible brain damage if detected within 6 hours of stroke onset.”50 Whether or not the EICs on CT scans within 3 hours of stroke onset reflect irreversible tissue damage in all cases is not answered by our data and requires further study. Time plays an important role, even within the 3-hour rt-PA treatment window (Table 2). The EICs became increasingly visible in the patients imaged later in the time window of treatment. Also, the patients treated earlier with rt-PA within 90 minutes of stroke onset had favorable outcome compared with those treated from 90 to 180 minutes.31 The association we found between EIC and the time from stroke onset to the baseline CT scan may explain the difference in prevalence of EIC between ECASS data obtained within 6 hours and our data obtained within 3 hours of stroke onset. Also, the detection rate of EIC on CT scan increases with physician training66,78 and the experience of the interpreting physician.38,39

Our retrospective review identified 31% of patients who had baseline CT scans with subtle evidence of an evolving ischemic stroke, despite the variation in CT scan quality across 43 different institutions and the use of scanners from the early part of the last decade. The detection of EIC is greater with the current generation of higher resolution CT scanners.57 However, our data suggest that enhanced detection and quantification of EIC on CT scan is unlikely to improve clinical decision making in patients who meet criteria for treatment with rt-PA.1

We recently demonstrated that the treating physicians’ agreement on identification and quantification of EIC was actually poorer than anticipated.36 Physician education and training in interpreting CT scans of patients for thrombolytic therapy within 3 hours of stroke onset is vitally important especially in the detection of acute ICH.40 The presence of a frank, large area of hypodensity and mass effect should alert the treating physician to reascertain the time of stroke symptom onset for thrombolytic treatment with rt-PA within 3 hours of stroke onset. For these reasons, treating physicians must have the expertise or seek the services of physicians with expertise in the accurate interpretation of CT scan of acute stroke patients especially in the detection of ICH.

In summary, although early subtle CT scan changes of evolving cerebral ischemia within 3 hours of stroke onset are more frequent than previously realized, these findings do not appear to be critical in the decision to treat an otherwise eligible patient with rt-PA within 3 hours of stroke onset, provided the strict eligibility criteria (specifically excluding ICH on CT scan) of the NINDS rt-PA Stroke Trial are followed.

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Author Contributions: Study concept and design: Patel, Levine, Tilley, Grotta, Frankel, Haley, Broderick, Horowitz, Lyden, Marler, Welch. Acquisition of data: Levine, Tilley, Grotta, Lu, Frankel, Haley, Brott, Broderick, Horowitz, Lyden, Marler, Welch. Analysis and interpretation of data: Patel, Levine, Tilley, Grotta, Lu, Frankel, Haley, Broderick, Horowitz, Lyden, Marler, Welch. Drafting of the manuscript: Patel, Levine, Tilley, Grotta, Lu, Frankel, Haley, Horowitz, Lewandowski, Marler. Critical revision of the manuscript for important intellectual content: Patel, Levine, Tilley, Grotta, Frankel, and "EARLY ISCHEMIC CHANGES ON CT IN ACUTE STROKE"
Haley, Brett, Broderick, Horowitz, Lyden, Lewandowski, Welch.

Statistical expertise: Tilley, Lu.

Obtained funding: Tilley, Haley, Brett, Marler.

Administrative, technical, or material support: Patel, Levine, Grotta, Horowitz, Lyden, Marler.

Study supervision: Patel, Levine, Broderick, Horowitz, Lewandowski, Marler, Welch.

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