Computed Tomographic Findings in Patients Undergoing Intra-arterial Thrombolysis for Acute Ischemic Stroke due to Middle Cerebral Artery Occlusion

Results From the PROACT II Trial

Heidi C. Roberts, MD; William P. Dillon, MD; Anthony J. Furlan, MD; Lawrence R. Wechsler, MD; Howard A. Rowley, MD; Nancy J. Fischbein, MD; Randall T. Higashida, MD; Carlos Kase, MD; Gregory A. Schulz, MS; Ying Lu, PhD; Carolyn M. Firszt, MS

Background and Purpose—The purpose of this study was to evaluate the role of noncontrast CT in the selection of patients to receive thrombolytic therapy for acute ischemic stroke and to predict radiological and clinical outcomes.

Methods—One hundred eighty patients with stroke due to middle cerebral artery (MCA) occlusion were randomized 2:1 within 6 hours of onset to receive intra-arterial recombinant prourokinase plus intravenous heparin or intravenous heparin only. Four hundred fifty-four CT examinations were digitized to calculate early infarct changes, infarct volumes, and hemorrhagic changes among the 162 patients treated as randomized (108 recombinant prourokinase–treated patients and 54 control patients). CT changes were correlated with baseline stroke severity, angiographic clot location, collateral vessels, and outcome at 90 days.

Results—Baseline CT scans, 120 (75%) of 159, showed early infarct–related abnormalities. The baseline CT abnormality volume was not correlated with the baseline National Institutes of Health Stroke Scale (NIHSS) score \( (r = -0.11) \) but was correlated weakly with the outcome \( (r = 0.17, P < 0.05) \). Compared with patients with M2 occlusions, patients with M1 MCA occlusions had significantly higher baseline NIHSS scores \( (P < 0.05) \), more basal ganglia involvement on CT, and larger hypodensity volumes on follow-up CTs. Compared with patients with partial or no collateral supply, patients with full collateral supply had lower baseline NIHSS scores, significantly smaller baseline CT infarct volumes, and less cortical involvement \( (P < 0.05) \).

Conclusions—Noncontrast CT is not correlated with baseline stroke severity and does not predict outcome in patients with stroke due to MCA occlusion. However, baseline CT changes, clinical presentation, and the evolution of CT changes are influenced by clot location and the presence of a collateral supply. (Stroke. 2002;33:1557-1567.)

Key Words: stroke, ischemic □ thrombolysis □ tomography, x-ray computed
ischemic stroke of <6-hour duration due to MCA occlusion. In PROACT II, patient selection was based not only on traditional clinical and CT criteria but also on angiographic criteria. Angiography was also used to assess recanalization and collateral circulation. The present report describes the CT findings in PROACT II and their correlation with clinical presentation, angiographic findings, and outcome. The purpose of the present analysis was to establish the value of noncontrast CT in the selection of acute-stroke patients for thrombolytic therapy and to predict radiological and clinical outcome.

Subjects and Methods
The clinical, CT, and angiographic inclusion and exclusion criteria of PROACT II have been previously published in detail.7 Between February 1996 and August 1998, 180 patients were randomized at 43 North American centers to receive either 9 mg intra-arterial recombinant prourokinase (r-proUK) plus low-dose intravenous heparin or control (low-dose intravenous heparin alone) in a ratio of 2:1. All patients received a 2000 U bolus and a 500-U/h infusion of intravenous heparin for 4 hours beginning at the time of angiography. Heparin flush solutions for angiography contained 1 U/mL heparin in 0.9% sodium chloride and were infused at 60 to 120 mL/h. Otherwise, antithrombotic agents were prohibited for the first 24 hours.

The primary efficacy analysis involved the proportion of patients achieving a modified Rankin score (mRS) of ≤2 at 90 days after randomization. The primary efficacy analysis included all randomized patients (ie, intent to treat [n = 180]). However, this retrospective division of the MCA. r-ProUK infusion details in patients randomized to intra-arterial r-proUK are provided elsewhere.7 Another CT exclusion criteria were intracranial tumors, except for small meningioma; hemorrhage of any degree or location; significant mass effect, mass effect, and hyperdense MCA sign. A qualitative reading of the baseline CT scans was performed to assess whether early signs of infarction covered more than one third of the MCA territory (ECASS violators). The extent of early signs of infarction was determined independently by 2 neuroradiologists (W.P.D., N.J.F., or H.A.R.) who subsequently adjudicated any disagreements according to the ECASS I methodology.

On follow-up CT scans, hypodensity, hemorrhagic infarction, and parenchymal hematoma were noted separately. Hemorrhagic infarction was defined as any area of petechial or small confluent hemorrhages within larger regions of hypodense ischemic injury. Parenchymatous hematoma was defined as more homogeneous areas of hemorrhage, with or without mass effect or intraventricular extension.

Computed Tomography
According to the protocol, CT scans were to be obtained at baseline, at 24 hours, and at 7 to 10 days after randomization. Follow-up CT scans were included even if they were not exactly in the protocol time frame; CT scans performed within the windows of 3 hours to 2 days and >2 days were considered for analyses at the 24-hour and 7- to 10-day time points, respectively.

CT scans were from different manufacturers who used similar data acquisition parameters. CT scans were to be acquired without contrast agent; in 1 case, the baseline CT scan was obtained after contrast injection. CT scans were to be acquired with a slice thickness of 5 mm; if technically adequate, a slice thickness of 8 mm or 10 mm was accepted.

CT exclusion criteria were intracranial tumors, except for small meningioma; hemorrhage of any degree or location; significant mass effect with midline shift; acute hypodense parenchymal lesion; or effacement of cerebral sulci in more than one third of the MCA territory (ECASS criteria).2

All CT scans were assessed by the Core Neuroradiology facility at the University of California, San Francisco, by a board-certified member of the American Society of Neuroradiology who was blinded to the clinical presentation, treatment assignment, and outcome. All CT scans from an individual patient were read in a blinded fashion by the core laboratory neuroradiologist. This reading was independently confirmed by a neuroradiologist (W.P.D., N.J.F., or H.A.R.) and by another neuroradiologist (ECASS violators). The extent of early signs of infarction was assessed from the baseline diagnostic angiogram in blinded fashion by the core laboratory neuroradiologist. The presence of collateral vessels was categorized as (1) none, (2) partial (collateral flow to parts of the vascular territory at risk), or (3) full (collateral flow to the entire vascular territory at risk, with the clot visible from the distal side).

Statistical Analysis
Statistical analyses in the present report are based on 162 patients who met all clinical and CT criteria and for whom informed consent was obtained (108 r-proUK patients and 54 control patients); subgroup analyses may be based on smaller numbers if some values are missing. For continuous variables, data are presented as mean±SEM; for categorical data, the median is given. Because of the skewed data distribution, a Wilcoxon rank sum test or Kruskal-Wallis test was performed to compare data from different groups. Correlation between groups was assessed by using the Spearman correlation coefficient.

Results
Available CT Examinations
Baseline CT scans were available in 159 of the 162 patients treated as randomized. CT scans from all 3 time points (baseline, 24 hours, and 7 to 10 days) were available in 132 of 162 patients (87 r-proUK patients and 45 control patients); for 2 of the 30 incomplete cases, 2 time points were missing. Reasons for failure to obtain all 3 follow-up CT scans were as follows: death (15 r-proUK patients and 1 control subject); withdrawal of consent (2 control patients); referral from other hospitals (1 control subject); scan never received by core (4 r-proUK patients and 5 control patients); and no reference scale, so that volume could not be measured (2 r-proUK patients and 2 control patients).

Technical Adequacy and General Assessment
Four hundred fifty-four CT examinations were read and digitized for volumetric measurements (baseline, 159 scans;
24 hours, 160 scans; and 7 to 10 days, 135 scans). Only 2 (0.4%) of the 454 CT scans were technically inadequate. The average time from stroke onset to baseline CT was 139±5 minutes (range from 24 minutes to 5 hours 30 minutes). One hundred twenty (75%) of 159 baseline CT scans showed early infarct–related abnormalities (Table 1); in 14 (11.7%) of the 120 patients, the only early infarct–related abnormality on baseline CT was a hyperdense MCA sign. The overall occurrence of the hyperdense MCA sign was 44% (53 of 120) in patients with pathological baseline CT scans, and 33% (53 of 159) in all patients with baseline CT scans. There was no correlation between the time from stroke onset and the volume of early infarct abnormalities on the baseline CT (r=0.11).

The qualitative reading of the baseline CT scans identified 12 (8%) of 159 individuals (10 r-proUK patients and 2 control patients) with infarcts involving more than one third of the MCA territory (ECASS violators). The average time from symptom onset for the ECASS violators was 152±15 minutes (range from 1 hour 17 minutes to 3 hours 45 minutes).

Early Deaths in All Patients
The 16 individuals (15 r-proUK patients and 1 control patient) who died before the 7- to 10-day CT scan had an average baseline CT abnormality volume 2.5 times greater than the 132 individuals who underwent all follow-up CT scans (28.0±8.8 versus 11.7±1.7 mL, P<0.05). Only 3 of the 16 were ECASS violators. At 24 hours, 15 of 16 had CT hypodensity volumes >120 mL, and 12 of 16 had hemorrhagic infarctions or parenchymal hematomas. The median baseline National Institutes of Health Stroke Scale (NIHSS) score was 18.5 in the 16 patients who died before day 7 to 10 compared with 17 in the 132 patients with CT scans from all time points (P=NS).

Baseline CT: r-ProUK Versus Control
The mean baseline CT abnormality volume was greater in the r-proUK patients for patients treated as randomized (15.5±2.4 mL for r-proUK patients versus 8.8±2.3 mL for control patients) and for patients with all CT follow-up studies (13.9±2.5 mL for r-proUK patients versus 7.3±1.6 mL for control patients). This difference is significant by t test assuming unequal variance (P<0.05), but the data distribution is skewed, and the Wilcoxon test shows no significance.

Baseline CT Scans: Correlation With Clinical Presentation and Outcome
Baseline CT scans were stratified by the volume (in milliliters) of early abnormalities into 5 groups: no abnormalities (n=53), abnormality volume ≤20 mL (n=77), abnormality volume 20 to 40 mL (n=14), abnormality volume 40 to 60 mL (n=7), and abnormality volume >60 mL (n=8). There was no correlation between the volume of baseline CT abnormalities and the baseline NIHSS score (r=−0.11, Figure 1). The 12 ECASS violators had an average baseline CT abnormality volume of 69.5±9.7 mL, compared with a volume of 8.7±1.2 mL in the non-ECASS violators. The median baseline NIHSS score in the 12 ECASS CT violators was 15 compared with 17 in the non-ECASS violators. Patients with a hyperdense MCA sign on their baseline CT scan (n=53) had a baseline CT abnormality volume (15.0±3.5 mL) similar to that in patients without the hyperdense MCA sign (n=107, 104 of whom had a baseline CT scan of 12.6±2.1 mL).

There was a modest, albeit significant, correlation between baseline CT abnormality volume and outcome at 90 days (r=0.17, P<0.05). The best outcomes occurred in patients with a normal baseline CT: no abnormality, 22 (42%) of 53 patients with mRS ≤2; abnormality volume ≤20 mL, 30 (39%) of 77 patients with mRS ≤2; abnormality volume 20 to 40 mL, 1 (29%) of 14 patients with mRS ≤2; abnormality volume 40 to 60 mL, 1 (14%) of 7 patients with mRS ≤2; and abnormality volume >60 mL, 2 (25%) of 8 patients with mRS ≤2. Only 3 (25%) of the 12 ECASS violators had mRS ≤2 at 90 days compared with 56 (38%) of the 147 non-ECASS violators. Patients with a hyperdense MCA sign had a similar rate of good outcome (18 [34%] of 53 with mRS ≤2) compared with those without the hyperdense MCA sign (40 [37%] of 107 with mRS ≤2).

Baseline CT and Outcome: r-ProUK Versus Control
Regardless of the baseline CT abnormality volume, there was a better outcome in r-proUK patients compared with control patients (Figure 2). However, the percentage of patients with mRS ≤2 at 90 days decreased with increasing baseline CT abnormality volume in both groups (Table 2).

Evolution of CT Changes
There was a weak, but significant, correlation between baseline CT abnormality volume and the 24-hour (r=0.51) and 7- to 10-day (r=0.31) CT hypodensity volume. However, there was a correlation between the CT hypodensity volumes
at 24 hours and at 7 to 10 days for all patients ($r=0.87$), for r-proUK patients ($r=0.87$), and for control patients ($r=0.88$).

At 24 hours, 3 r-proUK patients still had a normal CT, whereas none of the control patients had a normal CT. At 7 to 10 days, there was no significant difference in CT hypodensity volume between r-proUK patients and control patients (83.8 ± 9.5 mL versus 68.0 ± 10.8 mL, respectively). At 7 to 10 days, CT hypodensity infarction volume remained constant in the r-proUK patients (85.0 ± 8.8 mL) but increased significantly in the control patients (80.7 ± 12.1 mL, $P<0.05$ compared with 24-hour hypodense volume in control patients).

### Site of Occlusion

One hundred seven patients (66%) had an M1 occlusion, and 48 patients (30%) had an M2 occlusion. Seven patients (4%) had either an M1 occlusion with some proximal extension or MCA flow of more than TIMI grade 1. The baseline median NIHSS was significantly higher in patients with an M1 compared with an M2 occlusion (median NIHSS score of 17 versus 15, respectively; $P<0.05$). There was no significant difference in baseline CT abnormality volume in patients with an M1 occlusion (13.8 ± 2.2 mL, n = 104) versus an M2 occlusion (12.8 ± 3.6 mL, n = 48). However, the basal ganglia were much more frequently involved in patients with M1 occlusions (see below).

Although CT hypodensity volumes were not significantly different at baseline, patients with an M1 MCA occlusion had significantly larger CT hypodensity volumes at 24 hours and at 7 to 10 days ($P<0.05$, Figure 4).

r-ProUK patients with an M1 occlusion had larger baseline CT abnormality volumes compared with control patients with an M1 occlusion (16.7 ± 3.6 versus 6.8 ± 1.8 mL, respectively; $P<0.05$). At 24 hours, the r-proUK patients with an M1 occlusion retained a tendency toward larger hypodensity volume compared with control patients (96.6 ± 13.5 versus 71.6 ± 15.1 mL, respectively; $P=NS$). At 7 to 10 days, no further increase in hypodensity volume in the r-proUK patients with M1 occlusion was seen (98.6 ± 12.4 mL), whereas in control patients, the mean hypodensity volume increased to 83.8 ± 15.7 mL; the hypodensity volumes at 7 to 10 days were not significantly different between treatment groups.

### Table 2: Patients With 90-Day mRS ≤2 in r-ProUK and Control Groups, Calculated for Different Baseline CT Abnormality Volumes

<table>
<thead>
<tr>
<th>No Abnormalities</th>
<th>Abnormality Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20 mL</td>
</tr>
<tr>
<td>Treatment</td>
<td>n</td>
</tr>
<tr>
<td>r-ProUK</td>
<td>17/34</td>
</tr>
<tr>
<td>Control</td>
<td>5/19</td>
</tr>
</tbody>
</table>

Figure 2. Baseline CT abnormality volume plotted against 90-day mRS ≤2 by treatment group. Numbers above bars indicate the number of patients per group. In all of the groups, there was a better outcome in r-proUK patients than in control patients.

Figure 3. CT hypodensity volumes: evolution over time. At 24 hours, there was no significant difference in CT hypodensity volume between r-proUK patients and control patients (83.8 ± 9.5 versus 68.0 ± 10.8 mL, respectively). At 7 to 10 days, CT hypodensity infarction volume remained constant in the r-proUK patients (85.0 ± 8.8 mL) but increased significantly in the control patients (80.7 ± 12.1 mL, $P<0.05$ compared with 24-hour hypodense volume in control patients).
For M2 occlusions, baseline and 24-hour CT hypodensity volumes were similar in r-proUK patients and control patients (at baseline, 8.6±2.5 versus 8.1±3.5 mL, respectively [P=NS]; at 24 hours, 58.3±10.0 versus 59.0±14.2 mL, respectively [P=NS]). At 7 to 10 days, the CT hypodensity volume appeared greater in control patients (59.7±9.9 versus 71.0±21.2 mL for r-proUK versus control patients, respectively), although this difference was not statistically significant.

Collateral Circulation
Fifty patients had no angiographic collaterals, 100 had partial collaterals, and 11 had full collaterals. In 1 patient, collaterals could not be assessed. Patients with full collaterals had infarction volumes on baseline CT (2.0±0.9 mL) that were significantly smaller than those in patients with partial collaterals (12.5±2.1 mL, P<0.05) or patients with no collaterals (17.6±4.0 mL, P<0.05). There was a significant difference in the median baseline NIHSS score among the 3 collateral groups (no collaterals, median NIHSS score 18; partial collaterals, median NIHSS score 16.5; and full collaterals, median NIHSS score 15 [P<0.05]).

Because the number of patients with full collaterals was small, treated patients with no collaterals were compared with those with partial or full collaterals (Figure 5). In patients with no collaterals, the baseline CT abnormality volume was higher in the r-proUK patients compared with control patients at baseline (15.3±3.9 versus 5.8±1.9 mL, respectively; P=NS), 24 hours (134.0±18 versus 61.6±10.3 mL, respectively; P=NS), and 7 to 10 days (133.7±17.4 versus 82.6±16.4 mL, respectively; P=NS). In patients with collaterals, there was also a greater baseline CT abnormality volume in the r-proUK patients compared with control patients (13.5±3.2 versus 7.7±1.9 mL, respectively; P=NS). However, there was a smaller hypodensity volume in the r-proUK patients with collaterals compared with control patients at 24 hours (59.0±9.3 versus 69.7±13.3 mL, respectively; P=NS) and at 7 to 10 days (60.8±8.4 versus 80.2±14.7 mL, respectively; P=NS).

To correct for the chance imbalance in baseline CT abnormality volumes between the r-proUK and control patients, a subset of 22 patients without collaterals (at baseline CT, 6.8±1.2 mL) and a subset of 43 patients with collaterals (at baseline CT, 6.2±1.4 mL) were matched for baseline CT abnormality volume. For the matched subset of r-proUK patients without collaterals, CT abnormality volume increased over time (6.8±1.2 mL at baseline, 112.7±20.8 mL at 24 hours, and 121.1±21.3 mL at 7 to 10 days), as did the volumes of the control patients (5.8±1.9 mL at baseline, 61.6±10.3 mL at 24 hours, and 82.6±16.4 mL at 7 to 10 days; see above). However, in the matched subset of r-proUK patients with collaterals, CT abnormality volume was smaller in the r-proUK patients than in the control patients at 24 hours and at 7 to 10 days (for r-proUK patients, 6.2±1.4 mL at baseline, 46.5±8.3 mL at 24 hours, and 55.3±9.1 mL at 7 to 10 days; for control patients, 7.7±1.9 mL at baseline, 60.8±8.4 mL at 24 hours, and 80.2±14.7 mL at 7 to 10 days).

Infarct Location on CT
Seventy patients had a right-hemispheric infarct, and 92 patients had a left-hemispheric infarct. Patients with an infarct in the right hemisphere had higher NIHSS scores (median 15) that was significantly lower than the score in those with a left-hemispheric infarct (median 19). The outcome at 90 days was not significantly different in the 2 groups: 22 (33%) of the 70 patients with an infarct in the right hemisphere had mRS 2 compared with 37 (40%) of the 92 patients with an infarct in the left hemisphere.

In 77 patients, the basal ganglia and the cortex were involved. In 28 patients, only the basal ganglia were involved, and in 57 patients, only the cortex or insula without the basal ganglia were involved. Baseline NIHSS score was independent of the final infarct location (Table 3).

Infarct location corresponded well with the clot location on angiography. Patients with basal ganglia involvement had a higher percentage of M1 occlusions (61 [79%] of 77 with basal ganglia and cortex and 22 [79%] of 28 with basal ganglia only) compared with patients without basal ganglia involvement (24 [42%] of 57 with M1). Patients with basal ganglia involvement had higher infarct volumes compared with volumes in patients with cortical infarct only, at 24 hours and at 7 to 10 days (for basal ganglia involvement)
involvement, baseline values were 14.0±2.2 mL, 24-hour values were 96.0±9.7 mL, and 7- to 10-day values were 107.3±10.8 mL; for no basal ganglia involvement, baseline values were 10.6±2.9 mL, 24-hour values were 81.1±10.2 mL, and 7- to 10-day values were 87.7±11.1 mL). Patients with both basal ganglia and cortex involvement had the worst outcomes (Table 3).

Patients with a collateral supply were less likely to have cortical infarcts. In patients with a cortical hypodensity at 24 hours and possible angiographic assessment of collateral flow (n=117), 45 (38%) demonstrated no collateral supply on angiography, 70 had some collateral supply, and 2 had full collaterals (ie, there were 62% with at least some collateral supply). In patients without cortical infarct involvement (n=44), only 5 (11%) had no collaterals, whereas 30 had some collateral supply, and 9 had full collateral supply (ie, there were 89% with at least some collateral supply).

**TABLE 3. Clinical Presentation at Baseline (NIHSS Score), Clot Location, and Outcome (Percentage of Patients With mRS <2 at 90 Days) Depending on Final Infarct Location**

<table>
<thead>
<tr>
<th>Clot Location</th>
<th>N</th>
<th>NIHSS Score, n</th>
<th>M1, n/N (%)</th>
<th>M2, n/N (%)</th>
<th>Other, n/N (%)</th>
<th>90-day mRS &lt;2, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia and cortex/insula</td>
<td>77</td>
<td>17</td>
<td>61/77 (79%)</td>
<td>13/77 (17%)</td>
<td>3/77 (4%)</td>
<td>22 (29%)</td>
</tr>
<tr>
<td>Basal ganglia only</td>
<td>28</td>
<td>16</td>
<td>22/28 (79%)</td>
<td>4/28 (14%)</td>
<td>2/28 (7%)</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Cortex/insula only</td>
<td>57</td>
<td>17</td>
<td>24/57 (42%)</td>
<td>31/57 (54%)</td>
<td>2/57 (4%)</td>
<td>25 (44%)</td>
</tr>
</tbody>
</table>

Clot locations are M1, M2, and other (ie, location with proximal extension of the clot or flow of more than TIMI grade 1).
Hemorrhagic CT Changes

No patients had hemorrhagic changes on baseline CT. On the 24-hour CT scans, hemorrhagic infarction was present in 45 (42%) of the 108 r-proUK patients and in 15 (29%) of the 52 control patients. In those patients in whom prolonged contrast agent stasis was present in addition to tissue hemorrhage, these features were distinguished on the basis of the higher density of the contrast agent compared with the interstitial blood deposits. Parenchymatous hemATOMA was present in 18 (17%) of the 108 r-proUK patients and in 1 (2%) of the 52 control patients at 24 hours. Six of the 12 ECASS violators had hemorrhagic infarctions at 24 hours. On the 7–to-10-day CT, hemorrhagic infarction was present in 47 (53%) of the 88 r-proUK patients and in 20 (43%) of the 47 control patients. Parenchymal hemATOMa was present in 12 (14%) of the 88 r-proUK patients and in 2 (4%) of 47 control patients. The mean volume of early infarct abnormalities on baseline CT was 11.6±2.7 mL in r-proUK patients without hemorrhagic complications at 24 hours, 18.8±3.9 mL in r-proUK patients who developed intracerebral hemorrhages and/or parenchymal hemATOMAs, and 23.3±8.9 mL in those patients with intracerebral hemorrhage and clinical deterioration.

Discussion

PROACT II provides a unique opportunity to evaluate the evolution of CT findings in patients with angiographically confirmed acute MCA occlusion with or without intra-arterial thrombolysis. Seventy-five percent of the baseline CT scans in PROACT II showed early signs of infarction, indicating that within 6 hours after symptom onset, CT is sensitive to acute ischemic tissue changes in the majority of patients with MCA occlusion.3,4,11

We failed to demonstrate any correlation between the baseline CT abnormality volume (<6 hours) and baseline stroke severity (NIHSS score). Moreover, noncontrast CT was of limited use as a predictor or surrogate marker of outcome in patients with MCA occlusion in the treated group and in the control group. There was only a weak correlation between the volume of baseline CT abnormality and clinical outcome at 90 days. The weak correlation between the baseline CT abnormality volume and clinical outcome at 90 days is in agreement with some studies6,14 but not others.3 Saver et al found only marginal correlations (0.43 to 0.54) between CT infarction volumes at 6 to 11 days and neurological outcome scales at 3 months and concluded that CT infarct volume is of limited use as a surrogate measure of outcome in clinical trials. Moulin et al11 found that the number of early CT signs was correlated with initial stroke severity and outcome rather than volume. A recent publication by von Kummer et al13 is based on the baseline CT scans from the ECASS II trial. The authors categorized the presence of hypodensity at baseline CT into either no hypodATTenuation, hypodATTenuation involving less than one third of the MCA territory, or hypodATTenuation involving more than one third of the MCA territory. As such, they found that the presence of hypodATTenuation is highly specific for irreversible ischemic brain damage if detection occurs within the first 6 hours.

There are important differences between these studies and PROACT II, which might explain some of the discrepant findings regarding the sensitivity and predictive value of baseline CT findings. Extensive early CT signs of infarction will be more prevalent in populations with large-vessel occlusions, such as the internal carotid artery and, especially, the mainstem MCA, and less prevalent in populations with lacunar strokes. Patients with an acute ischemic stroke have a variety of arterial occlusion sites despite similar clinical presentations, and 20% have no visible occlusion.7,16 Because there was no angiographic confirmation of clot location or recanalization in the intravenous trials,1,2 vascular occlusions other than the MCA as well as lacunar strokes were included in NINDS and ECASS. CT is expected to be less discriminating for baseline stroke severity or outcome in a homogeneous stroke population with M1 or M2 MCA occlusion compared with a mixed stroke population including patients with lacunar infarcts, MCA branch occlusions, or no occlusions. The natural history of MCA occlusion is generally poor. This might explain why the median baseline NIHSS in PROACT II17 was greater than that in either NINDS14 or ECASS II.11

Even confined to patients with MCA occlusion, the precision of CT diagnosis is affected by several variables. The whole MCA territory has a volume of ~300 mL (Tomsick17 and authors’ unpublished data, 2001). However, because of variable vascular patterns of supply, patients might have markedly different MCA territory volumes,18 so that reader interpretation of the “MCA territory” is somewhat arbitrary. This variability was reflected in the range of CT volumes among our ECASS violators and the high interobserver variability in identifying ECASS violators even between neuroradiologists.1 Therefore, it would be more precise to define ECASS CT criteria as a minimum abnormality volume of, for example, 60 mL (which implies a diameter of ~5 cm) rather than one third of the MCA territory. Mainly because of the high interindividual variability of the overall MCA volume, an alternative quantitative scoring system based on anatomic landmarks might replace the volume assessment.19 A minimum hypodensity volume of 100 mL may have an even better predictive value; CT hypodensity volumes >100 mL at 24 hours were almost universally associated with a poor outcome at 90 days regardless of treatment.

The definition of early signs of infarction has also not been completely standardized.17,20,21 ECASS I referred to “major early infarct signs” on CT “such as diffuse swelling of the affected hemisphere, parenchymal hypodensity, and/or effacement of cerebral sulci in more than 33% of the MCA territory.” 2 ECASS II excluded patients if “brain swelling” exceeded 33% of the MCA territory.22 von Kummer23 identified hypodensity (radiolucency) as the key characteristic of the ECASS CT criteria.23 Hypodensity is not always associated with sulcal effacement or other evidence of brain swelling. The NINDS investigators analyzed CT scans for edema, which was defined as a focal or diffuse area of hypodensity, and for mass effect.4 The most consistent definition of early signs of infarction, therefore, is hypodensity with or without brain swelling or mass effect.

Hypodensity and brain swelling on early CT (ie, <6 hours) are not synonymous with irreversible infarction. The physiological cause of early tissue hypodensity on CT corresponds...
to an increase in the water component in brain cells.\textsuperscript{24} This cytotoxic or cellular edema is caused by osmotic and ionic gradients between blood and ischemic brain tissue and by pinocytosis of water in the presence of remaining blood flow.\textsuperscript{25–27} Furthermore, the density on CT scans in patients with acute ischemia reflects not only hypodensity from cytotoxic edema but also hyperdensity due to local increases in blood volume from compensatory vasodilatation in regions of low perfusion pressure.\textsuperscript{3} These simultaneous pathological processes may increase or decrease tissue density and make it difficult to predict the ultimate extent of an infarction with early CT. Recently, diffusion-weighted MRI was shown to be more sensitive than CT for identifying early evidence of infarction in more than one third of the MCA territory; lesion volume on acute DWI, but not on acute CT, was also correlated strongly with final infarct volume.\textsuperscript{28}

The baseline CT appearance is influenced by the clot location, with a higher percentage of basal ganglia involvement in M1 occlusions compared with M2 occlusions. Clot location influences not only the CT appearance at baseline but also the evolution of the infarct over time. Infarct progression on CT between baseline and 24 hours, in particular, is considerably less in M2 occlusions compared with M1 occlusions. Compared with patients with a more proximal M1 occlusion, patients with an M2 occlusion not only have less basal ganglia involvement and smaller follow-up CT hypodensity volumes but also have lower NIHSS scores at baseline. This is not surprising, inasmuch as M1 supplies a larger territory than M2, and tissue survival is dependent on the presence of collateral circulation. Furthermore, an M1 occlusion includes the lenticulostriates, which are end arteries that supply regions of the brain (eg, lentiform nucleus and internal capsule) that do not have collateral supply.\textsuperscript{29} Similar to the ECASS investigators, we found that patients with final basal ganglia involvement on CT had a worse outcome than did patients with only cortical infarction.

Patients with left-hemispheric infarcts had initially higher baseline stroke scale scores than did patients with right-hemispheric infarcts. In part, this reflects some bias for left-hemispheric dysfunction in the NIHSS. However, outcome did not differ significantly between patients with right-versus left-hemispheric infarcts. Hemispheric specific differences in functional outcome might be detected with quality of life assessments or with neurological scales other than the mRS.

Only a crude angiographic estimate of collateral supply was performed in the present study, and angiographic estimates of collateral vessels were not well correlated with cerebral blood flow.\textsuperscript{30} Nonetheless, the presence of collaterals had a powerful effect not only on the CT changes but also on the clinical presentation. Patients with full collaterals had baseline CT abnormalities that were smaller than those in patients with partial collaterals and in patients with no collaterals and lower baseline NIHSS scores. Cortical involvement on CT scans corresponded to little or no collateral flow. Compared with the control patients without collaterals, patients without collateral flow who received r-proUK developed larger infarction volumes. This might be due in part to the larger infarction volume by chance at baseline in the r-proUK patients. However, inasmuch as a matched subgroup with small baseline CT volumes demonstrated an increase in CT hypodensity volume in r-proUK patients, this may reflect reperfusion edema in patients who recanalize but have no collaterals. In patients with collaterals, the nonhemorrhagic infarct volume at 24 hours and at 7 to 10 days was smaller in the treated group than in the control group despite a similar bias in baseline infarction volume. The influence of collateral supply on patient management and the complex interaction between collateral flow with other variables will be published separately.

Although the patients in PROACT II were well matched for baseline NIHSS score, by chance the mean baseline CT early infarct volume was considerably greater in the r-proUK patients. However, it was still possible to assess relative infarct progression on CT between 24 hours and 7 to 10 days. In this time interval, the volume of CT hypodensity in r-proUK patients did not change significantly, whereas in the control group, the hypodensity volume increased significantly so that by 7 to 10 days, the CT hypodensity volumes in the 2 groups did not differ.

A similar trend was observed in the volume of hemorrhagic infarctions. Overall, there was a higher proportion of hemorrhages in the r-proUK patients compared with the control patients. The average volume of hemorrhagic infarction showed little change in the r-proUK patients between 24 hours and 7 to 10 days, whereas there was an increase of the volume of hemorrhagic infarction in the control group. These CT changes may reflect a balance between earlier beneficial recanalization in the r-proUK patients, which may cause early reperfusion hemorrhage and reperfusion edema in some patients with large infarcts and delayed spontaneous recanalization in control patients that are not beneficial but lead to hemorrhagic conversion on CT. A more detailed analysis of the hemorrhagic infarcts in PROACT II can be found in Kase et al.\textsuperscript{31}

Although PROACT II is the largest randomized trial performed to date that is restricted to patients with MCA occlusion, the small numbers often precluded firm statistical conclusions related to CT findings. Nonetheless, other than excluding hemorrhage, the value of noncontrast CT for the assessment of patients with an acute ischemic stroke appears limited. In a mixed stroke population, noncontrast baseline CT may help distinguish patient subgroups, but noncontrast CT appears to have little predictive value within specific subgroups. In patients with MCA occlusion, baseline CT abnormality volume was not correlated with baseline stroke severity and did not predict outcome with the possible exception of patients with baseline infarct volumes of >60 mL. Lack of infarct growth rather than final infarct volume appears to be the best CT indicator of response to thrombolytic therapy. New techniques, including perfusion CT, single-photon emission CT, and diffusion/perfusion magnetic resonance, will be required to advance the imaging analysis of acute stroke.

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Computed Tomography of Hyperacute Infarctions in Relation to Intra-arterial Clot Lysis

The report by Roberts et al1 in this issue of Stroke provides a good summary of the uses of simple noncontrast CT imaging of the brain prior to and following innovative treatment of proximal middle cerebral occlusion by thromboembolic clot causing acute ischemia. The authors provide an insightful summary of their use of CT in these patients. They highlight that CT evolved from being a way to exclude mimickers of acute ischemic infarction to actually demonstrating infarction by recognition of the early signs of infarction in the early hours.

Every practitioner using brain CT in cases of early ischemia has gone through a learning curve of using the signs of hyperacute infarction. At first, one did not look for and therefore did not see those early signs because they seemed too subtle, when everyone knew that early infarction “could
not be seen” in the initial stages. CT was done to exclude other events, and when those were not found, everyone was satisfied. During that time, the observation of identifying clot on CT in major vessels at the base was very exciting. However, review of CT images from the cases illustrated in the report by Gacs et al reveals more than the high density of the blood vessels. The subtle findings of early infarction, some cases within 3 or so hours after infarction, were there but not well highlighted, contributing to a delay of well over another decade in the dissemination of that knowledge. It is so logical that expected findings of infarction well known after 24 hours should be subtly recognizable to varying degrees in the first hours.

Since the importance of identifying the extent of early infarction has been recognized by the various intravenous and intra-arterial trials of thrombolytic treatment with important conclusions from the European Cooperative Acute Stroke Study (ECASS), \textsuperscript{3,4} assessment for infarction early on has become a normal part of urgent investigation. Diffusion-weighted MRI has made the identification of the presence and extent of infarcting and/or infarcted brain very easy for those units and patients who can easily and quickly enter a magnet to be handled in the magnetic environment. There are relatively quick and reasonably thorough MR protocols that can assess for brain mass, hemorrhage, infarction, and even brain perfusion with MR scanning down to a minimum of even 10 minutes. However, even in clinical stroke sites trying hard to cut down the imaging procedural time because of the “Time is Brain” dictum, it is seldom that a 10-minute set of MR image acquisitions takes less than 40 minutes. Certainly this time is important, despite competing with the need to initiate treatment immediately, with a stressful clock ticking all the time. The problems for MR use concern using the magnetic compatibility for necessary pieces of monitoring equipment, as well as verifying the standard safety rules and questionnaires for patients entering high-field magnets, which is especially difficult for incapacitated stroke victims arriving anew to an emergency department.

While sophisticated MR diffusion and perfusion studies for acute stroke have been developed, CT scanning has also advanced. A scan of the head can now be done in a few seconds. Perfusion and angiographic CT studies can be performed in less than a minute. The potential use of CT as the primary modality for hyperacute stroke, including vascular and physiological aspects, is so obvious in its convenience that this article on the relationship of the early CT findings of stroke to lysis therapy is significant. For the past few years, many neuroradiologists have experienced the potential of achieving a rather high level of correlation between early CT infarction recognition and the follow-up CT the next day, or the diffusion study done later. This is an operator-related task.

A program to increase one’s ability to prospectively perceive and interpret subtle early infarction on CT is offered: (1) Careful study of sets of images in hyperacute stroke (5 mm thick is recommended), looking for all the well-known early infarction criteria, and especially seeking subtleties of gray matter density approaching white matter density in deep and superficial locations. \textsuperscript{4} (2) Utilization of clinical information for brain localization of suspected infarction, and a careful “second look,” gyrus by gyrus, of all gray matter areas, especially in clinically suspicious regions. (3) Whatever the interpretation, the reader should document it and compare it with subsequent diffusion MR or follow-up CT with retrospective comparison. The subsequent knowledge of infarction findings and locations allow the initial CT to be closely examined retrospectively to discover any overlooked subtle changes. After a while, with this back-and-forth looking at the first CT with an attitude of trying to do better, a skilled and motivated interpreter can achieve remarkable accuracy, approaching that of diffusion imaging.

The alternative pathway to this type of approach to the subtleties of hyperacute infarction—to be defensive over not having seen findings initially and therefore not see them later—make no attempt to refine one’s skills. Improvement in interpretative abilities can succeed only if one is open to truly finding what was missed initially. This increase of interpretive skill for the subtle findings can succeed even as part of normal radiology residency training with accurate results. However, the goal of working hard at seeing subtle things on CT when diffusion MRI makes it easy is not of universal interest. Because CT interpretation is more difficult and many centers do not provide clinical stroke localization for CT readers, not all are interested to advance this modality as far as it can go. We have competition between an easy test that is difficult to interpret (CT) against a test that is more difficult to perform but easier to interpret (diffusion MR imaging).

Quite surprisingly, the authors have not found that the initial CT findings correlated with the subsequent outcomes or imaging findings. That result goes against expectations of acute stroke. There are a number of questions that arise from this. The first concerns the CT results, not as a measure of evolution of infarction on imaging, but as a test of the images in relation to the effects of the treatment offered, which for this randomized trial consisted of infusion of the thrombolytic intracranially via a microcatheter, and in the other group infusion of heparin saline into the carotid artery for 2 hours. A few patients treated with thrombolysis showed reversal of the hyperacute findings.

Unfortunately, there is no example of the type of hyperacute infarction identified by the readers that is illustrated here, along with an example of “no finding.” A review of numerous publications and presentations of various stroke studies, including at dedicated stroke symposia, in the past 5 years or so reveals a disappointing commentary by many experts in other techniques for identification of hyperacute stroke on CT. This is especially noticeable for those dealing with newer improved stroke imaging studies, especially with physiological and functional components. Many of these first show a noncontrast CT claiming to show nothing wrong, followed by the diffusion or perfusion of some other variant that shows an obvious lesion. However, it is striking how experts in MR imaging, or diffusion, or perfusion of stroke often overlook the subtle, simple, but definitely noncontrast CT findings. There have been multiple times when a group sitting together at a stroke symposium quickly and correctly perceives a subtle infarction, whereas the speaker declares the image “normal.” We cannot presume that the same set of oversights has occurred with the interpretation of hyperacute
stroke CT scans in this PROACT report, with the expert neuroradiologists who are investigators for this report. There is nothing shown here, however, that completely eliminates this possibility.

An important contribution to terminology here is the understanding and highlighting of the variability of distributions of the main cerebral arteries. While the contributions of the lessons of CT findings of ECASS have been pivotal, the expression “one third of the middle cerebral territory” has been difficult for many to use because of both the vagueness and the variability. In the current study, the authors have defined the transition size of an interpreted infarction as a volume of 60 mL, which can be objectively used on CT by the graphics tools that are part of every CT scanner.

On the other hand, the expressions ECASS violators and nonviolators used in this article remind one of the old point about the Holy Roman Empire, which was neither holy nor Roman. Here the ECASS violators were neither part of ECASS (or a similar protocol) nor violators of that trial. These cases are similar to cases from ECASS only in that some were entered because of the oversight of the neurointerventionalists not recognizing what was on the CT prior to treatment, despite exclusion of patients with medium to large infarctions from this trial. That they occurred in only 8% of cases is a testament to the learning that has taken place in the stroke expert community since ECASS, when such violations occurred in about half of the entered cases.

We owe ECASS a lot more than attaching its name to “violator.” The observations of ECASS for the cases with medium or large infarction on CT compared with those with smaller or no infarction are extremely important contributions to the knowledge of the risks of thrombolytics for acute stroke victims. We can, at this point, declare that there were really no violations by patients who entered ECASS. There was a growth curve of understanding of the prevalence of the subtle signs of infarction on hyperacute CT stimulated by ECASS and the criteria of that trial. This meant that central review of the CT images ended up much more accurate than the interpretation of the same CT images out in the field. This is a record of the growth of important knowledge and skill, and the literature should desist in denigrating this important detail by referring to “violations.”

Overall, this report on the CT findings from PROACT II demonstrates a mature use of noncontrast CT for hyperacute stroke. It is unclear why the initial CT tests were not more determinant in predicting and correlating with outcome. The authors predict that diffusion imaging would have been a lot better. It would have been easier to see, but for those who aspire to get the most out of these CT images, there is a goal that is aspired to as well: to do as well with CT as with diffusion. It is uncertain whether that would have made a difference for these treated PROACT cases.

Allan J. Fox, MD, FRCPC, Guest Editor
Department of Medical Imaging
University of Toronto
Neuroradiology
Sunnybrook & Women’s College Health Sciences Centre
Toronto, Ontario, Canada

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Computed Tomographic Findings in Patients Undergoing Intra-arterial Thrombolysis for Acute Ischemic Stroke due to Middle Cerebral Artery Occlusion: Results From the PROACT II Trial


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