Stroke

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Selection of Acute Ischemic Stroke Patients for Intra-Arterial Thrombolysis With Pro-Urokinase by Using ASPECTS

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Background—Previous studies have suggested that baseline computed tomographic (CT) scans might be a useful tool for selecting particular ischemic stroke patients who would benefit from thrombolysis. The aim of the present study was to assess whether the baseline CT scan, assessed with the Alberta Stroke Program Early CT Score (ASPECTS), could identify ischemic stroke patients who might particularly benefit from intra-arterial thrombolysis of middle cerebral artery occlusion.

Methods—Baseline and 24-hour follow-up CT scans of patients randomized within 6 hours of symptoms to intra-arterial thrombolysis with recombinant pro-urokinase or control in the PROACT-II study were retrospectively scored by using ASPECTS. Patients were stratified into those with ASPECTS >7 or ≤7. Independent functional outcome at 90 days was compared between the 2 strata according to treatment assignment.

Results—The analysis included 154 patients with angiographically confirmed middle cerebral artery occlusion. The unadjusted risk ratio of an independent functional outcome, in favor of treatment, in the ASPECTS >7 group was 5.0 (95% confidence interval [CI], 1.3 to 19.2) compared with 1.0 (95% CI, 0.6 to 1.9) in the ASPECTS ≤7 group. After adjustment for baseline characteristics, the risk ratio in the ASPECTS score >7 was 3.2 (95% CI, 1.2 to 9.1). Similar favorable treatment effects were observed when secondary outcomes were used, but these did not reach statistical significance.

Conclusions—Ischemic stroke patients with a baseline ASPECTS >7 were 3 times more likely to have an independent functional outcome with thrombolytic treatment compared with control. Patients with a baseline ASPECTS ≤7 were less likely to benefit from treatment. This observation suggests that ASPECTS can be both a useful clinical tool and an important method of baseline risk stratification in future clinical trials of acute stroke therapy. (***Stroke***. 2003;34:1925-1931.)

Key Words: computed tomography ■ randomized controlled trials ■ stroke, acute ■ stroke, ischemic ■ thrombolysis ■ urokinase

Controversy exists over the interpretation of clinical trials of thrombolysis for acute ischemic stroke[1,2] The National Institute of Neurological Disorders and Stroke (NINDS) tissue-type plasminogen activator (tPA) Stroke Study showed a treatment benefit for the primary outcome of excellent functional and neurologic outcome.[3] Both European Co-operative Acute Stroke Studies (ECASS-1 and ECASS-2)

were negative for the primary analysis,[4,5] but secondary and post hoc analyses with use of the global statistic[6] or independent instead of excellent functional outcome measures suggested a benefit[7,8] The ATLANTIS study, which assessed a 3- to 5-hour time window, was discontinued early because of a lack of demonstrated benefit.[9] Beyond the 3-hour window, the existing data are suggestive of efficacy, but choosing

patients who are likely to benefit from current clinical methods is a difficult art.

The Pro-Urokinase for Acute Cerebral Thromboembolism II (PROACT-II) trial randomized patients to either intra-arterial delivery of recombinant pro-urokinase or control after a middle cerebral artery (MCA) thrombus was demonstrated by emergent angiography.[10] Patients were treated at a mean of just >5 hours from symptom onset. Although PROACT-II yielded positive results for the primary outcome of independent function ($P=0.043$) and showed consistent positive trends for other secondary outcomes, the drug has not been approved for clinical use.

Appropriate patient selection for thrombolysis is important and continues to be refined. One approach is to use the baseline computed tomographic (CT) brain scan. The ECASS investigators suggested that estimating whether more than one third of the MCA territory showed signs of ischemia could be used to select patients who would not benefit from thrombolytic therapy and had a higher risk of intracranial hemorrhage[11–13] The NINDS investigators reported that the one-third MCA rule does not predict benefit from thrombolysis.[14] Poor reproducibility among observers,[15–18] measurement errors, and individual variations in the MCA territory[19] obscure the one-third rule's discriminative ability.

An alternative approach for grading early signs of ischemia on a baseline CT brain scan is the Alberta Stroke Program Early CT Score (ASPECTS)[20,21] (Figure 1). It is a 10-point scale that rates the presence or absence of ischemia in 10 regions of the brain. The ASPECTS has advantages over solely assessing lesion volume, because lesion volume is only weakly correlated with neurologic outcome.[22] The ASPECTS scale has been shown to be reproducible at varying levels of observer expertise and to predict functional outcome and symptomatic intracerebral hemorrhage[20,21] The dichotomized score of ASPECTS 0 to 7 versus 8 to 10 has been previously validated and shown to have prognostic value among patients treated with intravenous alteplase for acute ischemic stroke within 3 hours of onset.[20,21]

The aim of the present study was to assess whether the baseline ASPECTS could discriminate between patients who would and would not particularly benefit from treatment with intra-arterial recombinant pro-urokinase up to 6 hours from symptom onset.

Methods

Detailed methods and primary results from the PROACT-II trial have been reported previously.[10] In brief, the PROACT-II study was a randomized, clinical trial of intra-arterial stroke thrombolysis. Patients with acute stroke syndrome clinically thought to be caused by MCA occlusion and between the ages of 18 and 85 were screened. Patients without evidence of hemorrhage on baseline brain CT, a National Institutes of Health (NIH) Stroke Scale score between 4 and 30, an anticipated stroke-onset-to-treatment time of <6 hours, and no known contraindication to thrombolysis were eligible. Randomization occurred only after emergent cerebral angiography demonstrated an MCA occlusion in the M1 or M2 branches. All patients provided informed consent. Of 474 patients who underwent screening cerebral angiography, 180 were assigned to 9 mg intra-arterial recombinant pro-urokinase or control in a 2:1 randomization ratio, which was stratified by baseline NIH Stroke Scale score into 3 strata: 4 to 10, 11 to 20, and 21 to 30. Treatment assignment was open but outcome assessment was blinded. Recombinant pro-urokinase was delivered
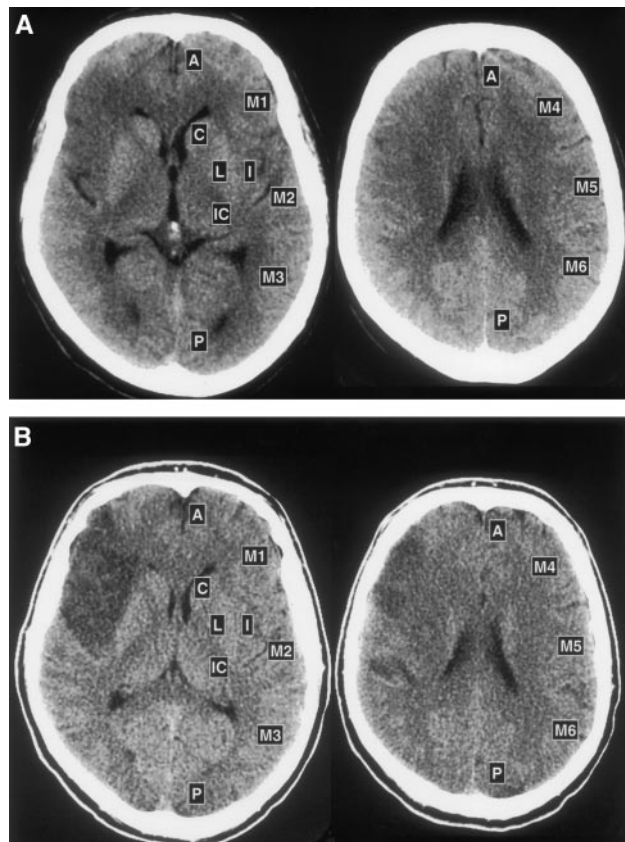

Figure 1. The ASPECTS scoring form and abbreviations. A indicates anterior circulation; P, posterior circulation; C, caudate nucleus; L, lentiform nucleus; IC, internal capsule, genu and posterior limb only; I, insular ribbon; M1, anterior MCA cortex anterior to the sylvian fissure; M2, MCA cortex lateral to the insular ribbon (opercular cortex); M3, posterior inferior MCA cortex (posterior temporal lobe); and M4, M5, and M6 refer respectively to anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3 and rostral to the basal ganglia. The medial boundary of the M4, M5, and M6 regions extends to the midline. a, Baseline ASPECT score was 6. Points were taken off for the insula, M1, M4, and M5 regions. This patient had an M1-MCA segment occlusion and was in the treatment group. He had a partial recanalization. b, Follow-up scan from the same patient, showing an ASPECT of 5. Points were taken off for the insula, M1, M2, M4, and M5.

by 2-hour microcatheter infusion at the face of the thrombus; mechanical disruption was not permitted. All patients additionally received a bolus of 2000 U heparin IV followed by 500 U/h for 4 hours beginning from the time of angiography. Heparin flushes were used during the procedure to maintain catheter patency. Angiography was repeated at the end of the 2-hour infusion. Clinical outcomes were assessed at 90 days.

CT scans were to be acquired with contiguous, noncontrast, axial 5-mm slices. A minority of CT images were acquired with 10-mm axial slices. The power (kV and mA · s) and scan obliquity were not prespecified. Scans were done at baseline, 24 hours after treatment, and at 7 to 10 days. Other CT scans were performed when clinical events warranted. All radiologic studies were reviewed and scored at a core laboratory, blinded to treatment assignment and clinical status. The baseline CT scan was assessed for the presence of ischemic changes involving greater or less than one third of the MCA territory (one-third MCA rule). Hemorrhage on follow-up brain CT scans was divided into hemorrhagic infarction and parenchymal hematoma and was further subclassified as asymptomatic or symptomatic, defined as a clinical worsening of ≥4 points on the NIH Stroke Scale or a 1-point or greater decline on the level-of-consciousness subscale.

Separate from the core laboratory initial CT reading, the baseline and 24-hour follow-up CT scans of the brain were assessed retrospectively with ASPECTS[20,21] (Figure 1). ASPECTS is assessed by systematically scoring each of 10 regions on the CT scan and assigning a score of 1 for a normal region and 0 for a region showing signs of ischemia. Signs of ischemia are defined as x-ray hypoattenuation, loss of the gray-white boundary (which is due to x-ray hypoattenuation of the gray matter), and/or effacement of cortical sulci. Only new areas of acute ischemia are scored. The regions include the subcortical structures that are allotted 3 points (the caudate nucleus, lentiform nucleus, and internal capule, genu and posterior limb only) and the MCA cortex, which is allotted 7 points (insular cortex, M1 through M6). The score combines localization in the brain and volume into a semiquantitative, topographic score. A score of 10 implies no evidence of new early signs of ischemia in the MCA territory, and a progressively lower score indicates more extensive ischemic changes. Scoring is facilitated by high-quality CT brain scanning including 5-mm slices, adequate power, and appropriately narrow window width and center level (80 and 40 Hounsfield units, respectively) before filming. Hyperdense artery signs are recorded but are not components of the score. The anterior cerebral artery territory and posterior cerebral artery territories are not scored but are indicated as an aide memoire. Although 2 representative slices are illustrated, in practice the entire scan is reviewed during scoring.

Patients who were treated on-protocol and whose baseline and 24-hour follow-up CT scans were available for analysis were included in the present study. CT scans were scored from film by using a consensus approach. Each of 3 readers (M.D.H., A.M.B., and H.A.R.) scored the scan simultaneously and discussed the scan to achieve a consensus score, and then the consensus score was recorded for analysis. The baseline scans were read blinded to the follow-up scans. However, follow-up scans were read with the baseline scan present to ensure that only new ischemic changes were scored. All scans were scored with knowledge of the clinical side of symptoms but blinded to treatment assignment, stroke severity, or other clinical details. This analysis was funded by a restricted grant from Abbott Laboratories. This design and analysis were conducted independent of Abbott Laboratories, and the authors had full and unfettered access to the clinical data.

Statistical Analysis

The primary outcome for this study was predefined as a 90-day modified Rankin Scale score of ≤2, indicating functional independence. Secondary outcomes were a 90-day modified Rankin Scale score of ≤1, an NIH Stroke Scale score of ≤1, mortality at 90 days, and symptomatic intracerebral hemorrhage. Before the scans were read, it was decided to dichotomize the ASPECTS at ≥7 (8 to 10) versus ≤7 (0 to 7), based on previous analyses.[20] A further analysis was conducted with the ASPECTS dichotomized at >8 versus ≤8 and >9 versus ≤9. Multiple logistic regression modeling was used to examine the relation between the dichotomized ASPECTS and the primary and secondary outcomes. Unadjusted and adjusted risk ratios (RRs) were used to summarize the relation instead of odds ratios, because it was expected that the proportion of patients achieving a good outcome would be common, and the odds ratio would overestimate the effect size. Variables for inclusion in the model were chosen from clinical knowledge, evidence from the literature, and univariable analysis. Variables that were defined after treatment (eg, recanalization) were not included in the model, because these variables would not influence the decision to treat beyond the inclusion criteria for the trial. The regression-modeling strategy consisted of first testing for treatment-effect modification by using a test of interaction between each baseline patient characteristic listed in Table 1 and the binary variable indicating treatment assignment. Effect modification was considered present when an interaction term reached statistical significant at the 10% level. The presence of confounding factors was assessed by the "change-in-estimate" strategy.[23] A forward stepwise method was used to enter variables into the regression model. The final parsimonious model consisted of all effect modifiers and confounders. Statistical analyses were conducted with STATA 6.0 software (Stata Corp).

Results

Of the 180 patients enrolled in the trial, 162 were treated on-protocol. The quality of 4 baseline CT scans was insufficient to allow interpretation, and an additional 4 were unavailable for review. Therefore, 154 patients with interpretable CT scans were analyzed in the present study, consisting of 105 in the treatment arm and 49 in the control arm. Among the 26 patients excluded from this analysis, 10 were in the control arm and 16 were in the treatment arm. No differences in baseline characteristics or outcome were observed between these 26 patients and the 154 who were included in the present analysis.

The median baseline ASPECTS was 7 (range, 2 to 10), and the distribution of baseline scores was approximately normal. One hundred thirty-seven patients (89%) had an ASPECTS ≤9, indicating some evidence of observable ischemia. Baseline clinical and demographic characteristics are shown in Table 1. Patients with an ASPECTS >7 were more likely to be older, but other baseline characteristics were similar. The baseline ASPECTS were related to clinical stroke severity (Figure 2).

The median 24-hour ASPECTS was 4 (range, 0 to 10). Patients who achieved functional independence at 90 days (modified Rankin Scale ≤2) were more likely to have a higher 24-hour ASPECTS by a median of 3 points ($P<0.001$, Mann-Whitney U test). Similarly, patients who were deceased at 90 days were more likely to have a lower 24-hour ASPECTS by a median of 3 points ($P=0.002$, Mann-Whitney U test). Twelve patients were classified by the core laboratory to have had baseline CT scans showing ischemic change in more than one third of the MCA territory. All of these patients had a baseline ASPECTS ≤7.

To assess the accuracy of scoring ischemic changes with the use of ASPECTS, the 24-hour ASPECTS was compared with the baseline ASPECTS of each patient. The 24-hour ASPECTS was greater than the baseline score in 7 patients, implying that the follow-up scan showed less evidence of ischemic change. Six of these patients were in the treatment arm. Although the baseline ASPECTS in the single control patient was probably overinterpreted (by 1 point, in this case), it is possible that ischemic change among the 6 treated patients was partly reversed with treatment. The proportion of patients with ischemic change (ASPECTS ≤9) at baseline who showed infarction on the 24-hour CT scan (24-hour ASPECTS ≤ baseline ASPECTS) in this cohort was 94.9% (95% confidence interval [CI], 89.8% to 97.9%).

Among the 7 patients who showed improved ASPECTS on the follow-up scan, 1 patient showed a dramatic improvement of 6 ASPECTS points. His baseline ASPECTS was 3 and follow-up ASPECTS was 9. He had complete neurologic and functional recovery at 90 days. He was 59 years old, had a baseline NIH Stroke Scale score of 23, was in the treatment group, and had a large, dominant left M2-MCA occlusion that was reperfused. He had prominent collateral circulation retrograde to the occlusion site.

TABLE 1.   Demographic and Baseline Characteristics

	Baseline ASPECTS >7 (n=66), %	Baseline ASPECTS ≤7 (n=88), %	P
Assigned to proUK	69.7	67.1	0.86
Age >65 years	69.7	40.9	0.001
Male sex, n	54.5	61.4	0.41
Caucasian	83.3	77.3	0.42
NIHSS >15	39.4	39.8	1.00
Left hemisphere, n	59.1	54.5	0.62
Mean glucose (SD), mg/dL	133 (54)	143 (60)	0.28
Mean arterial pressure (SD), mm Hg	101 (14)	100 (17)	0.74
M1 occlusion	69.7	62.5	0.39
Median time [h] to treatment (range)	5.3 (2.9–6.7)	5.2 (2.8–6.6)	0.98
Stroke subtype			0.94
Angiogram complication	1.5	1.1	
Cardiogenic embolism	62.1	55.7	
Carotid atheroembolism	7.6	10.2	
Other	1.5	2.3	
Unknown	27.3	30.7	
History of:			
Aspirin use	30.3	25.0	0.47
Anticoagulation	13.6	19.3	0.39
Diabetes	16.7	19.3	0.83
Heart disease	54.5	56.8	0.87
Hypertension	38.9	44.1	0.70
Previous stroke or TIA	15.2	15.9	1.00
Smoker	43.1	46.6	0.74

ASPECTS indicates Alberta Stroke Program Early CT Score; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale score; M1, M1 segment of the middle cerebral artery.

Heart disease implies history of arrhythmia, ischemic heart disease, or congestive heart failure.

Before adjusting for baseline characteristics, when the baseline ASPECTS was >7, 50% of the treatment group achieved an independent functional outcome at 90 days compared with 10% of the control group (RR, 5.0; 95% CI, 1.3 to 19.2) (Table 2). When the baseline ASPECTS was ≤7, 35.6% and 34.5% of the treatment and control groups, respectively, achieved an independent outcome (RR, 1.0;
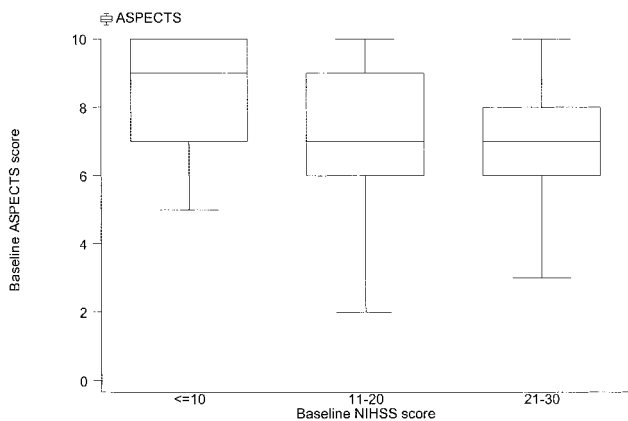

Figure 2. Relation between baseline NIH Stroke Scale score and baseline ASPECTS.

95% CI, 0.6 to 1.9). The treatment effects between the 2 ASPECTS strata were statistically different (P=0.021, likelihood ratio test), implying that the dichotomized ASPECTS was a significant effect modifier. Age showed an important confounding effect on outcome. Older patients (age >65 years) with unfavorable CT scans (ASPECTS ≤7) did uniformly badly without treatment (0% good outcome; RR=∞ in favor of treatment). Younger patients with unfavorable CT scans (ASPECTS ≤7) did equally well with or without treatment: RR=0.9 (95% CI, 0.5 to 1.5). The NIH Stroke Scale score showed only a weak correlation with ASPECTS (r=−0.11, P=0.17).

When these risks were adjusted for baseline characteristics (age >65, baseline NIH Stroke Scale score >15, time to treatment >5 hours, race, presence of comorbid heart disease), the RR (treatment versus control) of a good outcome when the baseline ASPECTS was >7 was 3.2 (95% CI, 1.2 to 9.1) (Table 3). Although confidence limits crossed unity, similar treatment effects were observed for the secondary outcomes (modified Rankin Scale ≤1 and NIH Stroke Scale ≤1), and fewer patients in the ASPECTS >7 group suffered symptomatic intracerebral hemorrhage.

The beneficial effect of treatment was greater when the baseline ASPECTS was >9, with 53.8% of the treatment

TABLE 2.   Unadjusted Risk Ratios for Outcome Stratified by Baseline ASPECTS Score

	Baseline ASPECTS >7				Baseline ASPECTS ≤7			
Outcome	ProUK (n=46), %	Control (n=20), %	Risk Difference, %	RR (95% CI)	ProUK (n=59), %	Control (n=29), %	Risk Difference, %	RR (95% CI)
Primary								
mRS 0–2	50.0	10.0	40.0	5.0 (1.3–19.2)	35.6	34.5	1.1	1.0 (0.6–1.9)
Secondary								
mRS 0–1	37.0	10.0	27.0	3.7 (0.9–14.5)*	20.3	24.1	−3.8	0.8 (0.4–1.9)*
NIHSS 0–1	26.1	5.0	21.1	5.2 (0.7–37.5)*	13.6	17.2	−3.6	0.8 (0.3–2.2)*
BI ≥90	52.2	20.0	32.2	2.6 (1.0–6.5)	35.6	37.9	−2.3	0.9 (0.5–1.7)
Mortality	23.9	35.0	−11.1	0.7 (0.3–1.5)*	27.1	20.7	6.4	1.3 (0.6–3.0)*
Symptomatic ICH	8.7	0	8.7	...†	15.3	6.9	8.4	2.2 (0.5–9.6)†
Partial or complete recanalization at 120 min	58.7	11.1	47.6	5.3 (1.4–20.0)*	69.5	22.2	47.3	3.1 (1.5–6.5)*

ASPECTS indicates Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale score; mRS, modified Rankin Scale score; BI, modified Barthel Index score; ICH, intracerebral hemorrhage.

*There was no difference between the risk ratios in the 2 ASPECTS groups using a test for interaction from logistic regression analysis.

†A test for interaction could not be performed because no patient in the control group with ASPECTS >7 suffered a symptomatic hemorrhage.

group achieving an independent functional outcome at 90 days compared with 0% of the control group (RR=∞). This compares to an RR of 1.5 (95% CI, 0.9 to 2.6) for ASPECTS ≤9. When the baseline ASPECTS was >8, 50.0% of the treatment group achieved an independent functional outcome at 90 days compared with 6.7% of the control group (RR, 7.5; 95% CI, 1.1 to 51.4). This compares with an RR of 1.2 (95% CI, 0.7 to 2.1) when the ASPECTS was ≤8.

Discussion

The results from the present study support the concept that the use of ASPECTS can identify stroke patients with MCA occlusion who will receive particular benefit from intra-arterial thrombolysis. Patients who received treatment did better than with the control only when they had a baseline ASPECTS >7. The magnitude of benefit for these patients was large, with a number needed to treat of 3 to yield functional independence at 90 days. There was consistency of treatment effect at higher ASPECTS.

Careful note should be made of the difference in outcomes between the control groups according to ASPECTS strata. The rate of favorable outcome among the ASPECTS >7 controls was 10% compared with 34.5% in the ASPECTS ≤7 controls. This appears to be a paradoxical result. However, the importance of confounding by age (> 65 years) accounts for this observation and emphasizes the need for multivariable adjustment of the univariable RRs.

Signs of ischemia on CT scan reflect early tissue edema and/or tissue hypoperfusion[11,24] Regions of ischemic brain showing hypoattenuation as a manifestation of tissue edema are probably always irreversibly damaged and therefore, unsalvageable with thrombolysis.[11] Rarely, cortical sulcal

TABLE 3.   Adjusted Risk Ratios for Outcome Stratified by Baseline ASPECT Score

	Baseline ASPECTS >7				Baseline ASPECTS ≤7			
Outcome	ProUK (n=46), %	Control (n=20), %	Risk Difference, %	RR (95% CI)	ProUK (n=59), %	Control (n=29), %	Risk Difference, %	RR (95% CI)
Primary								
mRS 0–2	52.6	16.2	36.4	3.2 (1.2–9.1)	33.6	27.2	6.4	1.2 (0.5–2.7)
Secondary								
mRS 0–1	40.0	16.9	23.1	2.4 (0.8–6.7)	19.0	18.0	1.0	1.1 (0.4–3.3)
NIHSS 0–1	28.9	9.6	19.3	3.0 (0.7–12.4)	13.2	11.6	1.6	1.1 (0.3–4.5)
BI ≥90	53.8	29.1	24.7	1.8 (0.9–3.9)	34.6	30.1	4.5	1.1 (0.5–2.4)
Mortality	23.2	28.7	−5.5	0.8 (0.3–1.9)	28.3	23.6	4.7	1.2 (0.5–3.0)
Symptomatic ICH	7.7	0.0	7.7	...	15.4	7.9	7.5	1.9 (0.4–9.8)

Adjusted risk ratios (RR) were computed using the corrected group prognosis method[23] from a logistic regression model containing the variables: treatment with recombinant pro-urokinase, ASPECTS >7, interaction term treatment by ASPECTS >7, baseline NIH stroke scale score >15, age >65, time to treatment >5 hours, race, heart disease. All other variables listed in Table 1 were not shown to be relevant confounders.[23]

ASPECTS indicates Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale score; mRS, modified Rankin Scale score; BI, modified Barthel Index score; ICH, intracerebral hemorrhage.

effacement or very subtle hypoattenuation due to hypoperfusion scored as ischemic change on a baseline CT scan might reverse (6 cases in our study). When there are minimal or no signs of ischemia on the scan, most neurons and glia in the ischemic region are likely to be intact. Neuronal membrane depolarization occurs as the blood flow falls below 18 mL/100 g brain per minute,[25] making the clinical examination a rough surrogate for the volume, location, and degree of perfusion. Therefore, in the setting where there is a moderate to large clinical deficit, an occluded MCA, and a favorable-looking CT scan, the results of the present study suggest that these patients might receive the greatest benefit when an aggressive interventional approach is taken.

The appearance of ischemic changes on the CT scan is related to a triad of factors: duration of ischemia, severity of ischemia or absolute level of perfusion, and brain susceptibility. Of these, the latter is the least well defined clinically. One surrogate marker for susceptibility might be age. The observation of an interaction effect between age and baseline NIH Stroke Scale score observed by the NINDS tPA Stroke Trialists supports this contention.[26] The appearance of the baseline CT and hence the ASPECTS most likely represents a convergence of underlying biologic variables that determines outcome differentially according to treatment.

The duration of ischemia is a critical factor, because it is the only other variable that has been shown to have a clear effect on the efficacy of treatment.[27] The NINDS investigators reported a low prevalence of ischemic change (31%) among patients in the NINDS tPA Stroke Trial and that ischemic change on the CT scan was not a modifier of the treatment effect.[14] A linear 3-way interaction (treatment by ischemic change by time) was also not evident (B. Tilley, personal communication, 2002), but the power to detect such interactions was low. Combined with results from the present study, 1 hypothesis that arises is that the CT scan appearance is most important as time from stroke onset elapses.

A previous and independently conceived analysis of the PROACT-II trial showed no relation between the volume of ischemic change on the baseline CT scan and treatment effect.[28] Analyses based on simple infarct volumes take no account of the location of the ischemic lesion, thus ignoring the neurologic maxim of the importance of localization. The advantage of ASPECTS is that it combines a semiquantitative estimate of volume with localization by simply weighting smaller volumes in the basal ganglia and internal capsule equally with larger volumes of brain designated M1 through M6.

ASPECTS is an ideal scoring tool because it is a straightforward portable skill, easy to learn, and easy to teach. It allows those who are not expert in CT scan interpretation a framework for assessing the acute stroke CT. Using the cutoff of ASPECTS >7 versus ASPECTS ≤7 would have excluded 100% of patients deemed by the core laboratory to demonstrate the one-third MCA rule. However, ASPECTS is more sensitive to smaller areas of ischemic change than the one-third MCA rule. Additionally, although practical issues restrict the widespread use of acute magnetic resonance imaging, CT scanning is widely available and remains the dominant modality for assessing acute stroke patients. ASPECTS has disadvantages, such as the lack of application to anterior cerebral artery,

posterior cerebral artery, or brainstem strokes. Small, focal infarctions of the internal capsule (eg, anterior choroidal artery syndrome) can be clinically devastating, yet the ASPECTS will be 9. New contrast-enhanced CT techniques, such as blood-pool analysis from CT angiography source images[29] or CT perfusion studies, show promise as tools for patient selection[30,31] and might provide additional useful information in the treatment of acute ischemic stroke patients. However, each additional technique is limited by the extra time required for scanning, and clinicians will need to judge the relative merits of moving directly to therapy compared with gaining more information at the expense of more brain proceeding to irreversible infarction during the imaging time. Tools to better understand the baseline noncontrast CT will continue to be useful.

The implications of this study are potentially broad in 2 ways. Treatment of the acute ischemic stroke patient is restricted by rapid recruitment of the penumbra to irreversible infarction or its surrogate: time. Investigations required to demonstrate an occlusion must occur rapidly and in parallel with the baseline CT scan. Both transcranial Doppler ultrasound examination and CT angiography can be used for rapid assessment of the intracranial circulation before treatment. The demonstration of occlusion could then naturally lead to more aggressive, catheter-based interventions, perhaps in combination with intravenous therapy given up front[32–34] Our results suggest that a subpopulation of thrombolysis candidates can be specifically targeted for inclusion by using ASPECTS rather than exclusion during acute stroke treatment triage. The positive clinical outcomes at treatment times as long as 6 hours from stroke onset provide a basis for considering a tissue window for stroke thrombolysis based on CT criteria alone.

The results must be confirmed in future studies because it is based on a secondary analysis of existing data. Ideally, patients should be randomized to treatment or control after stratification according to ASPECTS to prospectively assess both the utility and feasibility of the tool, as well as its capability for selecting particular patients who would benefit from therapy. In summary, selection of acute ischemic stroke patients with a simple CT scoring tool, ASPECTS, leads to identification of a group of patients who particularly benefit from intra-arterial pro-urokinase treatment beyond the 3-hour time window for intravenous thrombolysis.

Acknowledgments

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