Extent of Early Ischemic Changes on Computed Tomography (CT) Before Thrombolysis
Prognostic Value of the Alberta Stroke Program Early CT Score in ECASS II

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Background and Purpose—The significance of early ischemic changes (EICs) on computed tomography (CT) to triage patients for thrombolysis has been controversial. The Alberta Stroke Program Early CT Score (ASPECTS) semiquantitatively assesses EICs within the middle cerebral artery territory using a 10-point grading system. We hypothesized that dichotomized ASPECTS predicts response to intravenous thrombolysis and incidence of secondary hemorrhage within 6 hours of stroke onset.

Methods—Data from the European-Australian Acute Stroke Study (ECASS) II study were used in which 800 patients were randomized to recombinant tissue plasminogen activator (rt-PA) or placebo within 6 hours of symptom onset. We retrospectively assessed all baseline CT scans, dichotomized ASPECTS at \( \leq 7 \) and \( > 7 \), defined favorable outcome as modified Rankin Scale score 0 to 2 after 90 days, and secondary hemorrhage as parenchymal hematoma 1 (PH1) or PH2. We performed a multivariable logistic regression analysis and assessed for an interaction between rt-PA treatment and baseline ASPECTS score.

Results—We scored ASPECTS \( \leq 7 \) in 557 and \( > 7 \) in 231 patients. There was no treatment-by-ASPECTS interaction with dichotomized ASPECTS (\( P = 0.3 \)). This also applied for the 0- to 3-hour and 3- to 6-hour cohorts. However, a treatment-by-ASPECTS effect modification was seen in predicting PH (0.043 for the interaction term), indicating a much higher likelihood of thrombolytic-related parenchymal hemorrhage in those with ASPECTS \( > 7 \).

Conclusion—In ECASS II, the effect of rt-PA on functional outcome is not influenced by baseline ASPECTS. Patients with low ASPECTS have a substantially increased risk of thrombolytic-related PH. (Stroke. 2006;37:973-978.)

Key Words: brain ischemia ▪ computed tomography ▪ intracranial hemorrhage ▪ stroke ▪ thrombolysis

Noncontrast computed tomography (CT) reliably distinguishes hemorrhagic from ischemic stroke enabling the possibility of intravenous thrombolytic therapy.\(^1,2\) The treatment response is highly time dependent, with the odds for favorable outcome declining rapidly with increasing time from stroke onset. However, the time window is merely an artificial surrogate for biology. Preferably, patient selection for thrombolysis should not rely on a “time window” only\(^3,4\) because this strategy might preclude patients who could still benefit from therapy, include patients who stand little chance for benefit, or fail to reliably identify patients at risk for thrombolysis-related symptomatic hemorrhage.\(^2\) There is ongoing controversy whether the presence of “early ischemic changes” (EICs) on baseline noncontrast CT (NCCT) can help predict benefit from thrombolysis.\(^5,7\) Hypoattenuation on CT reflects a decrease in x-ray attenuation, which is inversely correlated with tissue net water uptake\(^8\) and thereby specifically depicts early ischemic edema as a marker of irreversibly damaged ischemic brain tissue.\(^9,10\) The extent of ischemic edema has been assessed according to the presence of hypoattenuation in less or more than one third of the middle cerebral artery (MCA) territory\(^11\) or using the Alberta Stroke Program Early CT Score (ASPECTS). The ASPECTS is a semiquantitative grading score that subdivides...
the MCA territory into 10 regions of interest\textsuperscript{12} combining information about edema volume and localization. Extensive ischemic edema (ie, in more than one third of the MCA territory or in >2 ASPECTS regions) is associated with poor outcome and might increase risk for thrombolysis-related symptomatic hemorrhage.\textsuperscript{11,12} In patients with MCA occlusion, an ASPECTS >7 predicted beneficial response to intra-arterial thrombolysis.\textsuperscript{13}

In this study, we tested the hypothesis that extensive EICs defined as an ASPECTS of ≤7 predict poor response to intravenous recombinant tissue plasminogen activator (rt-PA) and increased risk of thrombolysis-related hemorrhage in patients treated within 6 hours of stroke onset. Furthermore, we sought to define a subgroup of patients that may be especially likely to benefit from thrombolysis.

Methods

The European-Australian Acute Stroke Study (ECASS) II was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rt-PA for acute ischemic stroke within 6 hours of symptom onset, performed from October 1996 to January 1998, including 800 patients. Methodology and final results of the trial have been published previously.\textsuperscript{14}

An NCCT scan of the brain was mandatory before enrollment. Patients were to be excluded from the trial if baseline NCCT revealed intracranial hemorrhage or if parenchymal hypoattenuation or brain swelling exceeded one third of the MCA territory.

For our study, all baseline NCCT hardcopy images were randomly assigned to 2 teams, with 3 CT scan readers each, and evaluated by consensus using ASPECTS. To ensure uniform rating between the 2 groups, 1 member from each group switched teams midway through the reading. In addition, ASPECTS was applied in the same fashion to 200 randomly selected day 1 follow-up CT scans to estimate diagnostic accuracy. All readers had experience using ASPECTS methodology and underwent a detailed tutorial before initiating reading. Readers were completely blinded to clinical information, including side of symptoms.

ASPECTS was assessed by systematically scoring each of 10 regions on the CT scan, assigning a score of 1 for a normal and a score of 0 for a region showing EIC. Ischemic changes were defined as parenchymal x-ray hypoattenuation (ie, region of abnormally low attenuation of brain structures relative to attenuation of other parts of the same structure or of the contralateral hemisphere) or effacement of cortical sulci. Detailed methodology has been described previously.\textsuperscript{12} ASPECTS is only scored for acute changes. The 10 regions are subdivided into 2 levels. The upper level involves all axial cuts above the ganglionic structures and the lower level all ganglionic and infraganglionic cuts (Figure 1\textsuperscript{13}). The individual regions include subcortical (lentiform and caudate nucleus, posterior limb of internal capsule) and cortical structures (insula, M1 through M6). Signs of ischemia in the anterior cerebral artery and the posterior circulation territory were scored separately. We defined small ischemic changes as ASPECTS >7 and extensive ischemic changes as ASPECTS ≤7.

Data from the ECASS II database were used to assess ischemic damage on day 1 follow-up scans, the one-third-of-MCA-territory rule at baseline scored by the local investigators, and independently by the ECASS expert panel, outcomes, and thrombolysis-related hemorrhage. Hemorrhage was classified as hemorrhagic infarction and parenchymal hematoma (PH); PH was defined as blood clots comprising less (PH1) or more (PH2) than one third of the infarcted area.\textsuperscript{13} Intracerebral hemorrhage was defined as symptomatic (sICH) if the patient’s National Institutes of Health Stroke Scale Score (NIHSS) increased by ≥4 points from baseline and if the hemorrhage was likely the cause of the deterioration.

Statistical Analysis

The primary outcomes were independent functional outcome defined as 90-day modified Rankin Scale (mRS) score ≤2 and the occurrence. Secondary outcomes were excellent neurological recovery (mRS score ≤1, Barthel index ≥95%, and NIHSS ≤1 at 90 days), functional dependency (mRS score >3), bad outcome (mRS score ≥5), death, and sICH. ASPECTS was dichotomized at ≤7 or >7.

The data are described with standard descriptive statistics and stratified analysis. Logistic regression was used to assess whether an ASPECTS by treatment interaction was present for the primary outcomes using a likelihood ratio test.

We determined predictive value of ASPECTS and compared with that of local investigators and ECASS expert panel for detection of any EIC using the ECASS expert panel assessment of day 1 follow-up scans as reference standard. In addition, we correlated baseline ASPECTS with ASPECTS at day 1 in a random sample of 200 patients.

Results

Of 800 patients, 788 baseline CT scans were available and of sufficient quality for reading. Among these, 404 (51%) patients were randomized to t-PA treatment, and 141 (18%) were randomized within 3 hours of stroke onset. The distribution of ASPECTS values was skewed with a median ASPECTS value of 9 (interquartile range 7 to 10; Figure 1). In 47.5% (n=374) of baseline CT scans, the ASPECTS values were 10. None of these patients were judged to show EICs in the other vascular territories. Predictive value for any EICs with ASPECTS (sensitivity 66% and specificity 92%) was similar compared with ECASS expert panel (sensitivity 63% and specificity 84%) but improved when compared with ECASS local investigators (sensitivity 47% and specificity 84%). We observed a close positive correlation between ASPECTS at baseline and day 1 (Figure 2).

We scored ASPECTS >7 in 557 patients and ASPECTS ≤7 in 231 patients. Baseline characteristics and treatment allocation were similar between both ASPECTS groups except for an excess of past myocardial infarction among the ASPECTS >7 group treated with t-PA (Table 1). The median ASPECTS value in patients showing EICs in more than one third of the MCA territory was 4 (interquartile range 3 to 5.5) compared with 8 (interquartile range 6 to 9) in patients with EICs in less than one third of the MCA territory.

In the primary analysis, we did not find an ASPECTS by rt-PA treatment interaction when ASPECTS was dichotomized at ≤7 and >7 (P=0.29). There was no evidence for
masking confounding by age and baseline NIHSS score. This lack of multiplicative interaction was also true for the 0- to 3-hour ($P_{/H11005}=0.89$) and 3- to 6-hour ($P_{/H11005}=0.219$) subgroups and for secondary outcome measures.

However, studying the risk for thrombolysis-related hemorrhage, we found effect modification by ASPECTS in predicting PH that was not confounded by age, baseline NIHSS, and stroke-onset-to-treatment-time ($P_{/H11005}=0.033$). We could not show that baseline NIHSS score, onset-to-treatment time, congestive heart failure, or a history of hypertension were independent predictors of hemorrhage, as has been reported previously. This suggests that ASPECTS is a confounder on congestive heart failure and hypertension. Baseline serum glucose was not available to test within the model.

In an exploratory analysis to define subgroups that might particularly benefit from thrombolysis, we did not find an interaction between dichotomized ASPECTS and rt-PA treatment when studying patients with hyperdense artery sign ($n=188; P=0.43$), NIHSS score $>20$ ($n=68; P=0.43$), or the combination of both ($n=22; P=\text{not calculable}$).

**Discussion**

In our study, we investigated the prognostic value of the extent of EICs on CT before thrombolysis, applying a standardized validated scoring system. Our study shows: (1) that the extent of EICs on the baseline NCCT has prognostic value regardless of thrombolytic therapy; (2) it does not provide evidence that the extent of EICs on the baseline CT

Regardless of thrombolytic treatment, patients with high ASPECTS values achieved better outcomes than patients with low ASPECTS values (Figure 3). In a multivariable logistic regression analysis, we identified baseline ASPECTS as an independent predictor of outcome ($P=0.011$). Other predictors were age ($P=0.002$), and the interaction between acetasalic acid use and rt-PA treatment ($P=0.033$). We could not show that baseline NIHSS score, onset-to-treatment time, congestive heart failure, or a history of hypertension were independent predictors of hemorrhage, as has been reported previously. This suggests that ASPECTS is a confounder on congestive heart failure and hypertension. Baseline serum glucose was not available to test within the model.

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**TABLE 1. Baseline Characteristics for Dichotomized ASPECTS Groups**

<table>
<thead>
<tr>
<th>ASPECTS</th>
<th>Alteplase</th>
<th>Placebo</th>
<th>$P$</th>
<th>Alteplase</th>
<th>Placebo</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;7 (n=557)</td>
<td>(n=280)</td>
<td>(n=277)</td>
<td></td>
<td>(n=124)</td>
<td>(n=107)</td>
<td></td>
</tr>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age±SD</td>
<td>66±11</td>
<td>67±11</td>
<td>0.32</td>
<td>63±11</td>
<td>64±12</td>
<td>0.28</td>
</tr>
<tr>
<td>Female %</td>
<td>39</td>
<td>46</td>
<td></td>
<td>40</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>OTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3 h % (n)</td>
<td>20 (55/279)#</td>
<td>18 (48/274)†</td>
<td>0.52</td>
<td>15 (19/123)#</td>
<td>18 (19/106)#</td>
<td>0.72</td>
</tr>
<tr>
<td>3–6 h % (n)</td>
<td>80 (224/279)</td>
<td>82 (226/274)</td>
<td></td>
<td>85 (104/123)</td>
<td>82 (87/106)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>9</td>
<td>10</td>
<td>0.29</td>
<td>13</td>
<td>14</td>
<td>0.27</td>
</tr>
<tr>
<td>ASA</td>
<td>21%</td>
<td>24%</td>
<td>0.48</td>
<td>18%</td>
<td>26%</td>
<td>0.20</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>22%</td>
<td>24%</td>
<td>0.69</td>
<td>20%</td>
<td>31%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56%</td>
<td>54%</td>
<td>0.61</td>
<td>44%</td>
<td>41%</td>
<td>0.69</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>23%</td>
<td>22%</td>
<td>1.0</td>
<td>13%</td>
<td>14%</td>
<td>0.85</td>
</tr>
<tr>
<td>History of TIA</td>
<td>9%</td>
<td>8%</td>
<td>0.77</td>
<td>6%</td>
<td>6%</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22%</td>
<td>23%</td>
<td>0.76</td>
<td>20%</td>
<td>17%</td>
<td>0.61</td>
</tr>
<tr>
<td>Angina</td>
<td>8%</td>
<td>4%</td>
<td>0.10</td>
<td>6%</td>
<td>7%</td>
<td>0.80</td>
</tr>
<tr>
<td>Previous MI</td>
<td>13%</td>
<td>7%</td>
<td>0.03</td>
<td>15%</td>
<td>8%</td>
<td>0.16</td>
</tr>
<tr>
<td>History of CHF</td>
<td>6%</td>
<td>7%</td>
<td>1.0</td>
<td>8%</td>
<td>6%</td>
<td>0.47</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>5%</td>
<td>6%</td>
<td>0.57</td>
<td>3%</td>
<td>6%</td>
<td>0.52</td>
</tr>
</tbody>
</table>

OTT denotes onset to treatment time; CHF, congestive heart failure; TIA, transient ischemic attack; ASA, acetasalic acid; MI, myocardial infarction.

#1 missing value; †3 missing values.
scan predicts favorable response to intravenous rt-PA treatment within the first 6 hours of stroke onset; (3) it demonstrates a strongly increased risk for thrombolysis-related parenchymal and symptomatic hemorrhage if extensive ischemic changes are present; and (4) an ASPECTS score >7 corresponds well with the “less than one third MCA” rule.

The ECASS I investigators first identified the possible importance of EICs on CT. In contrast to our study, they found that patients presenting with small ischemic damage (ie, hypoattenuation in less than one third of the MCA territory) did benefit from rt-PA treatment, whereas patients with no or extensive damage showed an increased risk for fatal secondary hemorrhage. A secondary analysis of the ECASS II data identified the extent of hypoattenuating brain tissue on baseline NCCT as independent risk factors for sICH and PH. A clear interaction effect between extent of ischemic changes and response to rt-PA or intracerebral hemorrhage was not demonstrated in either study. A recent systematic review assessed reliability of early infarct signs on NCCT and outcome after thrombolysis, showing an increased risk for poor outcome with any early infarct signs but did not find an interaction between infarct signs and response to thrombolysis. In addition, this review highlights the general lack of definitions for early signs of infarction resulting in poor interobserver agreement.

ASPECTS provides a simple, semiquantitative, systematic approach to assessing and improving reliability of EIC identification in regions of the MCA territory. It is a reliable, localization-weighted estimation of ischemic tissue volume that correlates well with functional outcome after rt-PA. Diagnostic accuracy for EICs with ASPECTS in this study was equal to that of the ECASS expert readers but improved compared with local investigators. CT-ASPECTS correlates well with ASPECTS assessed on MRI diffusion-weighted images.

ASPECTS was shown recently to have a treatment-modifying effect in stroke patients with MCA occlusion receiving intra-arterial thrombolysis with prourokinase. The odds for functional independence for these patients were 3-fold increased when the ASPECTS was >7. Patients in both the ECASS II and PROACT II trials were randomized within 6 hours from symptom onset. The main difference between these studies, in addition to the thrombolytic agent and its mode of delivery, was the preselection of MCA occlusions in PROACT II, implying a perfusion deficit and likelihood of salvageable tissue at risk. This difference might explain why the present study failed to reproduce an ASPECTS-by-treatment interaction. Barber et al have recently shown that an ASPECTS of 10 is only associated with intracranial occlusion in 15% of cases, thus patients with a normal CT scan (48% in our study) may not be ideal targets.

### Table 2. Rate of Thrombolysis-Related Hemorrhage for Dichotomized and Trichotomized ASPECTS

<table>
<thead>
<tr>
<th>ASPECTS</th>
<th>Alteplase % (n)</th>
<th>Placebo % (n)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–10</td>
<td>9.3 (26/280)</td>
<td>6.4 (18/280)</td>
<td>2.3 (1.2–4.6)</td>
</tr>
<tr>
<td>0–7</td>
<td>17.7 (22/124)</td>
<td>14.5 (18/124)</td>
<td>18.9 (2.6–138)</td>
</tr>
<tr>
<td>0–3</td>
<td>40.0 (2/5)</td>
<td>40.0 (2/5)</td>
<td>17.5 (2.4–128.0)</td>
</tr>
<tr>
<td>4–7</td>
<td>16.8 (20/119)</td>
<td>13.5 (16/119)</td>
<td>17.5 (2.4–128.0)</td>
</tr>
</tbody>
</table>

**Figure 3.** Relationship between functional outcome at 3 months (mRS) and baseline ASPECTS dichotomized at >7 and ≤7. Clinical 90-day outcome by group. P indicates placebo.
for thrombolysis because the absence of occlusion implies a low probability of penumbral tissue. Other plausible explanations for the lack of effect modification in the current study are lower recanalization rates with intravenous compared with intra-arterial thrombolysis.

Using the ECASS II trial population, we essentially studied patients randomized within a 3- to 6-hour time window. However, our subanalysis of the significance of EICs in the 0- to 3-hour time window is consistent with results of recent work with the NINDS rt-PA Stroke Study population. These did not show an interaction effect between EICs on CT and response to rt-PA or secondary hemorrhage within 3 hours from stroke onset, regardless of whether the one-third-MCA-rule or the ASPECTS was applied. The NINDS analyses as well as our subanalysis do not provide sufficient evidence to recommend that patients be excluded from rt-PA on the basis of EICs on CT within a 3-hour window.

Our study has limitations. As initially proposed, we scored ASPECTS for areas on CT exhibiting brain tissue hypodensity or exclusive tissue swelling. Early hypodensity on CT (eg, loss of cortical ribbon) is highly predictive for irreversible tissue damage, whereas the relatively rarer finding of brain tissue swelling without concomitant hypodensity likely represents reversible change attributable to compensatory hyperperfusion. We have not determined the frequency of this finding in our study, but recent observation by Na et al and an unpublished series from our institution suggest an incidence between 1 to 13%.

In the ECASS II trial population, hypodensity or swelling on CT exceeding more than one third of the MCA territory was an exclusion criterion, thereby introducing possible selection bias to our study. A “real-world” stroke population presenting within 6 hours from onset would likely include a much larger proportion of patients with ASPECTS of 4 to 7 and 0 to 3, implying a substantially higher risk for sICH and possibly poor outcomes with thrombolysis (Table 2). Including those patients in a study looking for ASPECTS-by-thrombolysis interaction might increase statistical power to detect a true effect modification.

What is the clinical significance of assessing the extent of EICs in this cohort? It appears paradoxical that low ASPECTS does not influence treatment effect on functional outcome on one hand but predicts risk of thrombolysis-related PH on the other. A plausible explanation is that the radiological finding of PH (and sICH) in patients with baseline ASPECTS ≤7 might not necessarily be detrimental on long-term outcome. This hypothesis is supported by the lack of ASPECTS-by-treatment interaction in patients with bad functional outcome (mRS ≥5) at 90 days. Any harm caused by treatment in some patients in the low ASPECTS group seems to be balanced by benefit in others. Alternately, as discussed above, it is most likely that the low number of patients with ASPECTS ≤7 resulted in a very low power to find an clinically meaningful interaction effect.

On the basis of our current and previous work, we believe that assessing EIC with ASPECTS adds important information to patient selection for thrombolysis beyond 3 hours from onset. It seems to be reasonably safe to treat patients with ASPECTS >7 up to 6 hours from onset (6.4% ICH) in the presence of a disabling deficit. However, we are currently testing the hypothesis that such patients should only be treated in the presence of a target thrombus as demonstrated by acute vascular imaging.

Acknowledgments

Dr Kent is supported by a Career Development Award from the National Institute for Neurological Disorders and Stroke (K23 NS44929-01). The ASPECTS reading of the ECASS-2 CT-scans was supported, in part, by a grant from the Tufts-New England Medical Center Research Fund.

References


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*Stroke*. 2006;37:973-978; originally published online February 23, 2006;
doi: 10.1161/01.STR.0000206215.62441.56

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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