Clinical Utility of Electronic Alberta Stroke Program Early Computed Tomography Score Software in the ENCHANTED Trial Database

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Background and Purpose—Clinical utility of electronic Alberta Stroke Program Early CT Score (e-ASPECTS), an automated system for quantifying signs of infarction, was evaluated in a large database of thrombolyzed patients with acute ischemic stroke.

Methods—All baseline noncontrast computed tomographic scans of patients with anterior circulation acute ischemic stroke who participated in the alteplase dose arm of the randomized controlled trial ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) were reviewed; poor quality and large (>6 mm) slice thickness were excluded. Included scans had e-ASPECTS scores correlated with baseline neurological severity (National Institutes of Health Stroke Scale scores) and 90-day disability outcomes (modified Rankin Scale scores). Multivariable logistic regression models were used to determine the predictive ability of e-ASPECTS for disability outcomes and symptomatic intracranial hemorrhage.

Results—Of 2426 available computed tomographic images, 1480 (61%) were included in analyses of e-ASPECTS scores (median 9 [interquartile range, 8–10], 77% with good [range, 8–10] scores). Lower e-ASPECTS scores (per 1-point decrease) were significantly associated with increasing baseline National Institutes of Health Stroke Scale scores (r, −0.31; P<0.0001) and 90-day poor outcome (modified Rankin Scale scores, 2–6; r, −0.27; P<0.001). Adjusted odds ratios and 95% confidence intervals for 90-day outcomes were death or disability (modified Rankin Scale scores, 2–6; 0.91 [0.85–0.97]), death and major disability (modified Rankin Scale scores, 3–6; 0.89 [0.83–0.95]), and death (0.86 [0.79–0.95]); and for symptomatic intracranial hemorrhage, according to the Implementation of Thrombolysis in Stroke-Monitoring Study criteria was 0.87 (0.72–1.05).

Conclusions—e-ASPECT scores from thin computed tomographic slices (≤6 mm) were highly correlated with baseline neurological severity and independently predict functional recovery and adverse outcomes in acute ischemic stroke.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01422616.

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Key Words: infarction ■ intracranial hemorrhages ■ stroke ■ tissue-type plasminogen activator ■ tomography, X-ray computed

Noncontrast enhanced computerized tomography (NCCT) is the most widely used imaging modality for the management of patients with suspected acute stroke. In addition to being an inexpensive, fast, and reliably diagnostic tool for excluding intracranial hemorrhage and other mass lesions, NCCT can assist in decisions over the use of reperfusion therapy as the degree of cerebral ischemia can predict chances of recovery and risk of symptomatic intracerebral hemorrhage (sICH).[1–3] The Alberta Stroke Program Early CT Score (ASPECTS) was developed to provide a simple quantification of ischemic changes within 10 regions of the cerebral hemisphere supplied by the middle cerebral artery.[4] The electronic ASPECTS (e-ASPECTS) software has extended this approach to a medical device for automated imaging analysis, designed to aide clinical decision making in patients with suspected acute ischemic stroke (AIS; www.brainomix.com). Based on a machine learning algorithm, e-ASPECTS provides a rapid and standardized automated analysis of NCCT[5] slices, which has

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been shown to be noninferior in the detection of early ischemic changes to that of an experienced neuroradiologist.[6] Moreover, scores on e-ASPECTS can predict death and disability in patients who undergo mechanical thrombectomy for large vessel occlusion.[7] However, validation studies of the performance of e-ASPECTS have to date only been undertaken in small selected series. Herein, we outline an assessment of the clinical utility of e-ASPECTS in a large population of AIS patients with a broad range of characteristics who received thrombolysis treatment according to standard national guidelines as part of the alteplase dose comparison arm of the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke study).[8]

Methods

Study Design

The ENCHANTED is an international, multicenter, quasi-factorial, prospective, randomized, open-label trial with blinded outcome evaluation (PROBE) to compare the effectiveness of 2 doses of alteplase (0.9 versus 0.6 mg/kg, body weight) and 2 intensities of blood pressure control in thrombolysis-eligible adult patients with AIS, as outlined in detail elsewhere.[8] The alteplase dose arm has been completed, with 3310 patients with AIS recruited from 111 centers in 13 countries; and the blood pressure control arm is ongoing. A key inclusion criterion is a clinical diagnosis of AIS confirmed by either NCCT or magnetic resonance imaging; a large ischemic core on baseline imaging was not an exclusion criterion. The study protocol is pragmatic: computed tomographic (CT) scans are required to cover the entire brain from the foramen magnum to the vertex, with 4- to 5-mm thick slices through the posterior fossa and 8 to 10 mm thickness for the cerebral hemispheres, with no slice gap; the window width is 80 Hounsfield Units and a center level of 35 to 40 Hounsfield Units.[8] Clinical outcomes are assessed by a blinded observer: the primary end point is death or any disability, defined by scores 2 to 6 on the modified Rankin Scale (mRS); and secondary end points include death or major disability (mRS scores, 3–6) and death alone. All scans are reviewed centrally for evidence of sICH according to the following definitions: parenchymal hemorrhage type II within the first 36 hours associated with an increase in scores of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) from baseline or leading to death (SITS-MOST [Safe Implementation of Thrombolysis in Stroke-Monitoring Study])[9]; blood at any site in the brain and clinical deterioration with an increase in scores of ≥4 points on the NIHSS compared with the lowest value within the first 7 days or any ICH leading to death (second ECASS II [European-Australasian Cooperative Acute Stroke Study])[10]; any new ICH on follow-up imaging with any clinical deterioration within the first 7 days (NINDS [National Institutes of Neurological Diseases and Stroke study]).[11] The study protocol was approved by the ethics committees at each participating center, and written informed consent was obtained from patients or an appropriate surrogate. Data created for this study are available in accordance with data access and sharing policy of the George Institute for Global Health at www.georgeinstitute.org.

Imaging Analysis

All available baseline NCCT scans in Digital Imaging and Communications in Medicine format for patients with AIS in the anterior circulation that were compatible with the e-ASPECTS software (version 6.0) run on an Intel Core i5-6300U processor were included. Patients were excluded if (1) their baseline scan was magnetic resonance imaging; (2) the final clinical diagnosis was outside the anterior circulation; (3) the CT scans were poor quality, could technically not be processed, or contained artefacts; or (4) the slice thickness was too large for a reliable result from e-ASPECTS (Figure). Briefly, e-ASPECTS consists of 3-dimensional registration, segmentation, and scoring modules that apply rigorous statistical tests to image features to determine whether regions are abnormal.[5,6] In unusual situations where e-ASPECTS detected ischemic damage in both hemispheres but only one side was affected, the clinically correct side was applied, and where there was ischemic in both hemispheres according to the final clinical diagnosis, an e-ASPECTS score was not assigned. Sensitivity analysis was performed in patients whose baseline NCCTs were ≤3 mm in slice thickness because more accurate results from e-ASPECTS are to be expected with thinner slice thickness (optimum is 1 mm).

Statistical Analysis

Continuous variables are presented as mean±SD or median and interquartile range and categorical data as frequencies in percent (%). The correlation between the e-ASPECTS and baseline neurological severity (NIHSS score) was estimated using spearman correlation. The association of e-ASPECTS with death or disability, and sICH, was estimated in logistic regression models with adjustment for baseline covariates chosen based on their clinical relevance or significance at $P<0.05$ on univariate analysis. A sensitivity analysis that only included those with thin slice NCCT was performed. Data are reported as odds ratios (OR) and 95% confidence intervals (CI). Two-sided P values are reported as statistically significant ($P<0.05$). All analyses were undertaken with SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 3310 randomized patients, 2426 NCCTs were available and 1480 patients (61%) met the inclusion criteria and had scans suitable for processing with e-ASPECTS; a more

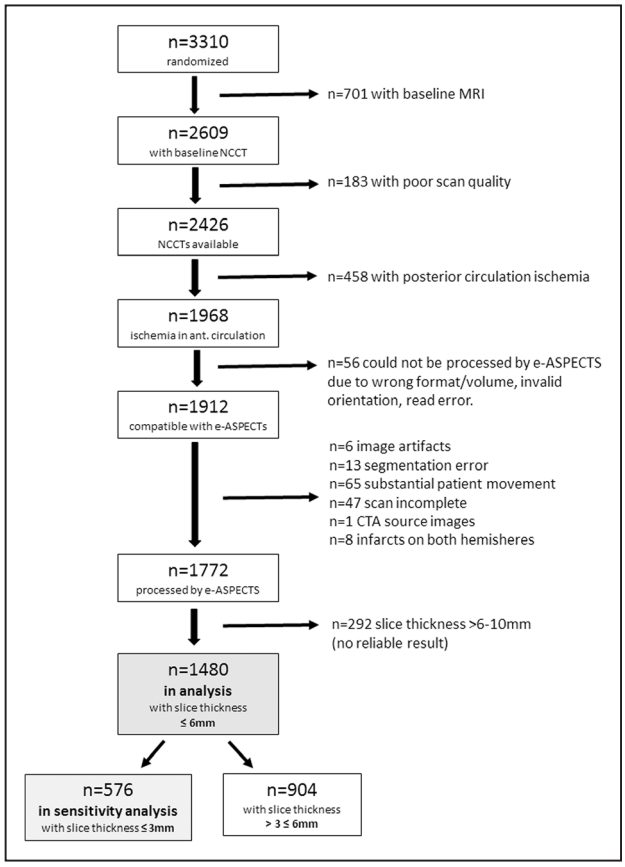

Figure. Flowchart of patients included in analysis. e-ASPECTS indicates electronic Alberta Stroke Program Early CT Score; CTA, computed tomographic angiography; MRI, magnetic resonance imaging, and NCCT, noncontrast enhanced computerized tomography.

selected 576 patients (23.7%) with thin slice NCCTs were included in sensitivity analysis. Of the available NCCT scans with ischemic in the anterior circulation (n=1968), 488 (24.8%) were excluded because of technical incompatibilities from thick (>6 mm) scan slices (292; 14.8%), inaccurate e-ASPECTS data (56; 2.8%), imaging artifacts, patient movement, or bilateral ischemia (79; 4.0%), incomplete imaging data (48; 2.4%), and invalid results (13; 0.7%; Figure).

Table 1 summarizes the baseline demographic, clinical, and radiological details of the included patients with AIS (median NIHSS, 8), where the majority (77.2%) had a good scan (e-ASPECTS scores, 8–10). These patients represented a typical cohort of unselected AIS patients with 11% having a proximal vessel occlusion. In the whole cohort, the primary end point of death or disability (mRS, 2–6) occurred in 52.9% (versus 57.9% in the sensitivity analysis), death or disability (mRS, 3–6) in 37.8% (versus 40.6%), and death in 9.8% (versus 11.8%). The frequencies of various sICH end points were as follows: SITS-MOST 1.5% (versus 1.7%), NINDS 6.5% (versus 6.9%), and ECASS II 4.2% (versus 4%).

Decreasing e-ASPECTS scores were significantly correlated with increasing baseline NIHSS scores (r=–0.31; P<0.0001). The relationships of interquartile range scores on e-ASPECTS and interquartile range scores on NIHSS were as follows: 8 to 10 versus 5 to 12; 5 to 7 versus 7 to 17; and 0 to 4 versus 11 to 20.

In univariate analysis, lower e-ASPECT scores (per 1-point decrease) were significantly associated with worse 90-day clinical outcome: death or disability (mRS, 2–6; OR, 0.81; 95% CI, 0.77–0.86), death or disability (mRS, 3–6; OR, 0.78; 95% CI, 0.74–0.82), and death (OR, 0.76; 95% CI, 0.71–0.82; Table 2). These strong associations were confirmed in the sensitivity analysis albeit with strength (ie, smaller ORs) for all end points (Table 3). In multivariable regression analysis with adjustment for baseline variables, e-ASPECTS remained an independent predictor of all clinical end points: death or disability (mRS, 2–6; OR, 0.91; 95% CI, 0.85–0.97), death or disability (mRS, 3–6; OR, 0.89; 95% CI, 0.83–0.95), and death (OR, 0.86; 95% CI, 0.79–0.95; Table 2). Sensitivity analysis again confirmed associations with smaller ORs (Table 3).

Table 1. Baseline Characteristics of 1480 Patients With Acute Ischemic Stroke in Primary Analysis

Variable	Measure
Age, y	68 (13)
Female	590 (40)
Ethnicity, non-Asian	687 (47)
Clinical features	
Systolic BP, mm Hg	150 (20)
Glucose, mg/dL	117 (101–146)
Creatinine, mg/dL	0.9 (0.7–1.1)
NIHSS score	8.0 (5.0–14.0)
Medical history	
Hypertension	962 (65)
Previous stroke	260 (18)
Coronary artery disease	239 (16)
Atrial fibrillation	327 (22)
Diabetes mellitus	296 (20)
Hypercholesterolemia	278 (19)
Current smoker	336 (23)
Prestroke function without symptoms (mRS score, 0)	1151 (78)
Medication at presentation	
Antihypertensive agent(s)	734 (50)
Warfarin anticoagulation	40 (3)
Aspirin or other antiplatelet agent(s)	378 (26)
Imaging features	
CT angiogram shows proximal occlusion	165 (11)
e-ASPECTS score	9 (8–10)
0–4	97 (7)
5–7	241 (16)
8–10	1142 (77)
Time from stroke onset to randomization, h	2.6 (1.9–3.3)
Randomized to low-dose alteplase treatment	765 (52)
Time from stroke onset to treatment, min	165 (122–210)

Data are n (%), mean (SD), or median (interquartile range). BP indicates blood pressure; CT, computed tomography; e-ASPECTS, electronic Alberta Stroke Program Early CT Score; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Table 2. Clinical Outcomes From Acute Ischemic Stroke at 90 Days (Odds of Outcome per 1-Point Decrease in e-ASPECT Score)

Outcome	OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Death or disability (mRS, 2–6)*	0.81 (0.77–0.86)	<0.001	0.91 (0.85–0.97)	0.006
Death or disability (mRS, 3–6)*	0.78 (0.74–0.82)	<0.001	0.89 (0.83–0.95)	0.001
Death*	0.76 (0.71–0.82)	<0.001	0.86 (0.79–0.95)	0.002
SITS-MOST†	0.81 (0.69–0.94)	0.008	0.87 (0.72–1.05)	0.145
NINDS†	0.78 (0.72–0.84)	<0.001	0.85 (0.78–0.93)	0.001
ECASS II†	0.74 (0.67–0.81)	<0.001	0.80 (0.72–0.89)	<0.001

AOR denotes adjusted odds ratio; CI, confidence interval; CT, computed tomography; e-ASPECTS, electronic Alberta Stroke Program Early CT Score; ECASS II, European-Australian Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institutes of Neurological Diseases and Stroke; OR, odds ratio; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Model 1 adjusted for age, sex, ethnicity (Asian vs non-Asian), baseline NIHSS score, premorbid mRS (0 or 1), premorbid use of aspirin, other antiplatelet agent or warfarin anticoagulant, any history of stroke, hypertension, coronary artery disease, atrial fibrillation, hypercholesterolemia, heart rate, glucose, creatinine, and randomized treatment (low dose vs standard dose).

†Model 2 adjusted for baseline NIHSS score, premorbid use of aspirin, other antiplatelet agent, atrial fibrillation, and randomized treatment (low dose vs standard dose).

Table 3. Major Clinical Outcomes at 90 Days in Acute Ischemic Stroke Patients With Thin (0–3 mm) Baseline CT Slice Thickness

Outcome	OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Death or disability (mRS, 2–6)*	0.74 (0.66–0.84)	<0.001	0.81 (0.70–0.93)	0.003
Death or disability (mRS, 3–6)*	0.74 (0.67–0.82)	<0.001	0.82 (0.72–0.94)	0.003
Death*	0.71 (0.64–0.79)	<0.001	0.77 (0.66–0.9)	0.001
SITS-MOST†	0.76 (0.6–0.95)	0.018	0.71 (0.52–0.97)	0.031
NINDS†	0.80 (0.7–0.92)	0.001	0.89 (0.76–1.03)	0.110
ECASS II†	0.74 (0.63–0.86)	<0.001	0.76 (0.63–0.92)	0.005

AOR indicates adjusted odds ratio; CI, confidence interval; CT, computed tomography; ECASS II, European-Australian Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institutes of Neurological Diseases and Stroke; OR, odds ratio; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Model 1 adjusted for age, sex, ethnicity (Asian vs non-Asian), baseline NIHSS score, premorbid mRS (0 or 1), premorbid use of aspirin, other antiplatelet agent or warfarin anticoagulant, any history of stroke, hypertension, coronary artery disease, atrial fibrillation, hypercholesterolemia, heart rate, glucose, creatinine, and randomized treatment (low dose vs standard dose).

†Model 2 adjusted for baseline NIHSS score, premorbid use of aspirin, other antiplatelet agent, atrial fibrillation, and randomized treatment (low dose vs standard dose).

In univariate analysis, e-ASPECTS scores were significantly associated with sICH across all definitions in the primary and sensitivity analyses (Table 2). In the primary analysis, e-ASPECTS was an independent predictor for sICH on NINDS (OR, 0.85; 95% CI, 0.78–0.93) and ECASS II (OR, 0.8; 95% CI, 0.72–0.89) definitions (Table 2) and in the sensitivity analysis on SITS-MOST (OR, 0.71; 95% CI, 0.52–0.97) and ECASS II(OR, 0.76; 95% CI, 0.63–0.92) definitions (Table 3).

Discussion

This study confirms the clinical utility of e-ASPECTS software in a large cohort of thrombolysis-treated patients with AIS who participated in a pragmatic international randomized controlled trial, where only 3.5% of eligible NCCT scans could not be processed for technical reasons and 4% excluded because of various imaging artifacts. Despite the absence of a stringent imaging protocol, a substantial proportion of trial participants were scanned with slice thickness of 6 mm or smaller. There was a strong association of increased ischemic brain damage, defined by low e-ASPECT scores, with baseline clinical severity as measured by NIHSS scores, and in predicting 90-day disability outcomes. A 1-point decrease in e-ASPECTS score was associated with a 19% higher risk of a poor outcome (death or disability), and a 23% increased risk of death when optimal thin slice NCCT scans were used. Although the prediction of sICH by e-ASPECTS was not as precise as for the clinical outcomes, in part as this end point occurred less frequently, it was nonetheless an independent predictor of this major adverse outcome of alteplase treatment using ECASS II criteria in both our primary and sensitivity analyses.

In their initial study, Barber et al[4] described an association of ASPECTS with functional outcome in a thrombolyzed AIS patient cohort, which Hill et al[12] subsequently confirmed in a larger cohort (n>1000). However, other studies have failed to show ASPECTS as a predictor of outcome in AIS.[13] Application of ASPECTS in the NINDS recombinant tissue-type plasminogen activator study database showed no modification of the treatment effect by baseline ASPECTS score although there was a trend toward reduced mortality and increased benefit of recombinant tissue-type plasminogen activator in those with a favorable (ASPECTS >7) baseline CT scan.[14] Similarly, the effect of recombinant tissue-type plasminogen activator on functional outcome was not influenced by baseline ASPECTS in the ECASS II database although patients with low ASPECTS had substantially increased risk of parenchymal ICH.[15] The manual ASPECTS was applied to NCCTs of participants of the third IST-3 (International Stroke Trial 3),[2] but these analyses were complicated by low statistical power from having a low proportion of patients with extensive ischemic damage (ASPECTS, 0–7). Reasons for the lack of association of ASPECTS with outcome parameters in these trials might be because of (1) less sensitive ASPECTS scoring on scans from older scanners; and (2) scoring by readers using only 2 slices, as originally described in the original publication by Barber et al.[4] Our present analysis, however, confirms that the automated e-ASPECTS is a potentially useful prediction tool for clinical outcome in patients with AIS of the anterior circulation who undergo thrombolysis treatment.

The ASPECTS method is more reliable than the simple visual assessment, 1/3 middle cerebral artery rule,[16] in determining the presence and extent of ischemic change on NCCT. Yet, despite being a simple tool, manual evaluation of ischemic damage on NCCT by a radiologist or stroke physician requires training, and consequently there is considerable variability among experts in scoring on the ASPECTS.[17,18] Thus, e-ASPECTS provides a least biased and standardized assessment of the ASPECTS that could be applied to patients in randomized controlled trials as well as clinical practice. Recent studies demonstrate that the ASPECTS method on NCCT has superior predictive capability for outcomes than clinical scores, and there is comparability in predictive accuracy of CT perfusion core volume and ASPECTS on NCCT.[19,20] Caution should be exercised, however, in making decisions or prognostic estimates in individual patients using ASPECTS or e-ASPECTS alone.[21]

The purpose of our study was not to validate e-ASPECTS against a gold standard performance of radiologists, which has been described elsewhere,[5,6] but to demonstrate that e-ASPECTS can be reliably applied to NCCT scans in a real-world population of patients with AIS managed in healthcare systems with variable resources. Although the study population was from a clinical trial, the large sample of participants and centers is a strength, and e-ASPECTS would likely have greater utility when applied prospectively to scans with 1-mm thickness.

In summary, we have shown that e-ASPECTS could be applied to a considerably high proportion of patients with AIS enrolled into the ENCHANTED trial, with scores from thin CT slices (≤6 mm) reliably predicting clinical outcomes. Optimal CT slice thickness (ideally 1 mm) led to more concise results.

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Disclosures

Dr Nagel has received consulting fees and travel expenses from Brainomix, consulting fees from Bohringer Ingelheim, and travel expenses and lecture fees from Bayer, Medtronic, and Pfizer. Dr Robinson is a National Institute for Health Research Senior Investigator and reports receiving speaking fees from Bayer and Boehringer Ingelheim and fees for Advisory Panels from Bayer. Dr Lindley reports receiving speaking fees from Boehringer Ingelheim, Covidien, and Pfizer. Dr Chalmers reports research grants and lecture fees from Servier for the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and post-trial follow-up. Dr Anderson reports receiving speaking fees from Takeda China. The other authors report no conflicts.

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