Impact of Pretreatment Noncontrast CT Alberta Stroke Program Early CT Score on Clinical Outcome After Intra-Arterial Stroke Therapy

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**Background and Purpose**—The efficacy of intra-arterial treatment remains uncertain. Because most centers performing IAT use noncontrast CT (NCCT) imaging, it is critical to understand the impact of NCCT findings on treatment outcomes. This study aimed to compare functional independence and safety among patients undergoing intra-arterial treatment stratified by the extent of ischemic change on pretreatment NCCT.

**Methods**—The study cohort was derived from multicenter trials of the Penumbra System. Inclusion criteria were anterior circulation proximal occlusion, evaluable pretreatment NCCT, and known time to reperfusion. Ischemic change was quantified using the Alberta Stroke Program Early CT Score (ASPECTS) and stratified into 3 prespecified groups for comparison: 0 to 4 (most ischemic change) versus 5 to 7 versus 8 to 10 (least ischemic change).

**Results**—A total of 249 patients were analyzed: 40 with ASPECTS 0 to 4, 83 with ASPECTS 5 to 7, and 126 with ASPECTS 8 to 10. For ASPECTS 0 to 4, 5 to 7, and 8 to 10, respectively, good outcome (modified Rankin Scale score, 0–2) rates were 5%, 38.6%, and 46% (*P*<0.0001), and mortality rates were 55%, 28.9%, and 19% (*P*<0.0001). The only significant pairwise differences were between ASPECTS 0 to 4 and other groups. Symptomatic hemorrhage was more common with lower ASPECTS (*P*=0.02). Shorter time to reperfusion was significantly associated with better outcomes among patients with ASPECTS 8 to 10 (*P*=0.01). A similar relationship was seen for ASPECTS 5 to 7 but was not statistically significant. No such relationship was seen for ASPECTS 0 to 4.

**Conclusions**—NCCT seems useful for excluding patients with the greatest burden of ischemic damage from futile intra-arterial treatment, which is unlikely to result in patient functional independence and increases the risk of hemorrhage. (*Stroke.* 2014;45:746-751.)

**Key Words:** endovascular procedures ▪ radiography, interventional ▪ tomography, spiral computed ▪ stroke

There has been 1 formally completed, randomized, controlled trial demonstrating the clinical efficacy of intra-arterial treatment (IAT) with thrombolytic drugs. This finding was further supported by a subsequent meta-analysis of intra-arterial thrombolytic trials. Nevertheless, there remains significant uncertainty regarding the benefits of a catheter-based approach, a point recently highlighted by the failure of 3 randomized controlled trials to demonstrate the superiority of IAT over standard medical management alone. To address the poorer-than-expected clinical outcomes after IAT with mechanical thrombectomy, there is a growing emphasis on improving patient selection using neuroimaging. Numerous studies have shown that baseline core infarct size is a powerful predictor of IAT outcomes. Although MR diffusion-weighted imaging is the most accurate method of infarct determination in the hyperacute time window, noncontrast CT (NCCT) remains the most commonly used imaging modality. As such, understanding the prognostic value of NCCT findings regarding the outcomes of catheter-based mechanical thrombectomy treatment is of practical importance for the management of these patients.

It is well known that NCCT suffers from limited sensitivity for early infarct-related changes. The Alberta Stroke Program Early CT Score (ASPECTS) is a semiquantitative grading system that improves user detection of these changes, with lower scores indicating greater infarct burden. Although NCCT ASPECTS has been studied in the setting of IAT, much of this work has focused on the effects of a single score threshold (ie, ASPECTS ≤7 versus >7). More recent data suggest that a substantial number of patients with scores below this threshold may still do well after IAT, and that a lower threshold (ie, ASPECTS <5) may be more appropriate for...
treatment exclusion. Using a large cohort of patients pooled from 2 multicenter trials of the Penumbra Stroke System, we sought to characterize functional outcomes among the following pretreatment ASPECTS strata: 0 to 4 versus 5 to 7 versus 8 to 10. Furthermore, we aimed to test whether patients with higher ASPECTS scores would have a more favorable clinical response to earlier reperfusion.

Subjects and Methods

Study Design and Participants
This study represents a pooled analysis of acute ischemic stroke patients enrolled in the Penumbra Pivotal trial (ClinicalTrials.gov; NCT00334061) and the Penumbra Imaging Collaborative Study (PICS; ClinicalTrials.gov; NCT00785161). The study design and results of the Penumbra Pivotal trial were reported previously. Briefly, this open-label, single-arm trial enrolled 125 patients at 24 centers who were treated with the Penumbra Stroke System, with safety and outcome data up to 90 days. PICS was a postmarket, observational registry of patients treated with the Penumbra Stroke System that aimed to further examine device-related safety and effectiveness as well as the relationship between pretreatment neuroimaging findings and clinical outcomes at 90 days. Between October 2008 and December 2010, PICS recruited 289 patients at 38 centers. Both studies were conducted under the auspices of the Institutional Review Board at each participating center, and patient consent was obtained.

Patient inclusion criteria for the present analysis were as follows: anterior circulation proximal artery occlusion involving the internal carotid artery terminus or proximal middle cerebral artery (MCA); available 90-day modified Rankin Scale (mRS) score; evaluable pretreatment NCCT scan; and reperfusion status and time to reperfusion. Time to reperfusion was defined as the time to procedure completion (ie, termination of Penumbra aspiration). From the Penumbra Pivotal cohort, 42 patients were excluded; 15 had stroke in other vessels, 3 had missing 90-day mRS score, and 24 had missing or unreadable NCCT scans. From the PICS registry, 123 patients were excluded; 22 had stroke in other vessels, 45 had missing 90-day mRS score, 46 had missing or unreadable NCCT scans, 2 had missing reperfusion status, and 8 had missing time to reperfusion. There were no significant differences between patients included versus excluded in the analysis for the baseline variables of age (P=0.88), National Institutes of Health Stroke Scale (NIHSS; P=0.84), occlusion location (P=0.19), rate of intravenous tissue-type plasminogen activator (tPA) treatment (P=0.44), and distribution of 90-day mRS scores (P=0.76).

Imaging Analysis
Baseline NCCT imaging was evaluated by 1 of 3 physicians (A.J.Y., M.G., A.M.D.) highly experienced in stroke imaging and the ASPECTS system. Contrary to the original system that used only 2 brain slices, readers graded early ischemic change in each of the 10 ASPECTS regions (caudate, lentiform, insula, internal capsule, and 6 cortical regions) according to current methodology, which uses all of the scan images. Early ischemic change was defined as tissue hypoattenuation or loss of gray–white matter differentiation, because these changes have been associated with edema and irreversible injury. Isolated cortical swelling, which was part of the original ASPECTS criteria, was not included because of recent work demonstrating that it is associated with increased cerebral blood volume and may represent penumbral (threatened but salvageable) tissue. Window and level settings were adjusted at the discretion of the readers to increase contrast between normal and ischemic brain. ASPECTS was calculated by subtracting the number of affected regions from a total possible score of 10, such that lower scores correspond to larger infarcts. Imaging review was performed blinded to all clinical information except stroke side.

Statistical Analysis
The rate of good outcomes was compared among ASPECTS subgroups using traditional dichotomization (0–7 versus 8–10) as well as using a preplanned trichotomized scheme in which the 0 to 7 group was further subdivided into 0 to 4 and 5 to 7 groups. In addition, the clinical impact of reperfusion and time to reperfusion was evaluated within these ASPECTS groups. Reperfusion was analyzed as a binary variable, with success defined as a Thrombolysis in Myocardial Infarction (TIMI) scale score of 2 to 3 (partial to complete reperfusion). Modified TICI scores 2b to 3 were not used in this analysis. Time from symptom onset to reperfusion was trichotomized at <6 hours (early) versus 6–24 hours (late) versus no reperfusion. Safety end points were compared between ASPECTS groups and included mortality, serious adverse events, and symptomatic intracranial hemorrhage (any hemorrhage with associated NIHSS score worsening of ≥4 points).

Baseline clinical and imaging variables were tested in univariate analysis for the prediction of good outcome, defined as 90-day mRS scores 0 to 2. Student t test was used for normally distributed continuous data; Mann–Whitney test was used for ordinal or nonnormal data; and Fisher exact test was used for categorical data. Variables with a univariate P value <0.1 were further tested in stepwise multivariate logistic regression analysis. Normality was tested with the Kolmogorov–Smirnov test.

All statistical analyses were performed using MedCalc for Windows, version 9.3.9.0 (MedCalc Software, Mariakerke, Belgium). Statistical significance was defined as a 2-tailed P value <0.05.

Results

Angiographic and Clinical Outcomes After IAT Stratified by Pretreatment ASPECTS

The pooled study cohort consisted of 249 patients. The median baseline NCCT ASPECTS was 8 (interquartile range, 6–9). The median time from stroke onset to CT was 2.0 hours (interquartile range, 1.1–3.5 hours). Baseline characteristics for the entire cohort and for trichotomized ASPECTS subgroups are displayed in Table 1. Patients in worse (lower) ASPECTS groups had higher baseline NIHSS scores. There was a trend for higher rates of diabetes mellitus and lower rates of intravenous tissue plasminogen activator treatment with lower ASPECTS.

TIMI 2 to 3 reperfusion was achieved in 84.7% of the study cohort, with early (<6 hours from onset) reperfusion in 27.7% (Table 2). There was no statistically significant difference in TIMI 2 to 3 between trichotomized ASPECTS groups (P=0.15). However, there was a statistical trend toward earlier reperfusion in patients with higher ASPECTS (P=0.08).

In the entire cohort, good outcome (mRS 0–2) was achieved in 36.9%, with a mortality rate of 28.1% at 90 days. Using the traditional ASPECTS dichotomization 0 to 7 versus 8 to 10, good outcomes were significantly more common in the ASPECTS 8 to 10 group (46.0% versus 27.6%; P=0.004). In the trichotomized ASPECTS scheme, good outcomes were seen in 46.0% of ASPECTS 8 to 10, 38.6% of ASPECTS 5 to 7, and 5.0% of ASPECTS 0 to 4 (P<0.0001; Figure 1A).

In pairwise comparison, the only significant differences were between ASPECTS 0 to 4 and other groups.

In the multivariable model, higher trichotomized baseline ASPECTS was an independent predictor of good outcome (odds ratio [OR], 2.46 per step; P=0.0004). Other independent predictors were age (OR, 0.95; P=0.001), time to reperfusion (OR, 2.04 for none versus late versus early; P=0.006), baseline NIHSS score (OR, 0.93; P=0.01), and any intracranial hemorrhage (OR, 0.34; P=0.01).
With regard to safety, death was less common among higher ASPECTS (19% versus 28.9% versus 55% for ASPECTS 8–10 versus 5–7 versus 0–4; P=0.0001; Figure 1A). Only ASPECTS 0 to 4 was significantly different from the other groups. Device-related or procedure-related serious adverse events occurred in 22 (8.8%) patients, with no significant difference in ASPECTS subgroup. These events included hemorrhagic conversion (n=11; 6 symptomatic, 5 asymptomatic), reocclusion (n=2), embolization into a new territory (n=2), vessel perforation (n=3), cerebral vasospasm (n=2), cardiac arrhythmia (n=1), and cerebral vasospasm and right leg hypoperfusion (n=1). Overall, symptomatic hemorrhage occurred in 9.6%, all of whom had a poor outcome (P=0.0002). Symptomatic intracranial hemorrhage was more frequent with lower ASPECTS (4.8% versus 13.3% versus 17.5% for ASPECTS 8–10 versus 5–7 versus 0–4; P=0.02; Figure 1B). In pairwise comparisons, only ASPECTS 8 to 10 was significantly different from other groups.

Impact of Time to Reperfusion on Outcomes Among ASPECTS Subgroups
The relationship between timing of reperfusion (early versus late versus none) and good outcome varied depending on pretreatment ASPECTS group (Figure 2). Earlier reperfusion was significantly associated with higher rates of good outcome among patients with ASPECTS 8 to 10 (P=0.01). In this group, the OR for good outcome with early reperfusion was 6.00 (95% confidence interval, 1.71–21.0; P=0.005) versus no reperfusion; for late reperfusion, the OR was 3.75 (95% confidence interval, 1.14–12.4; P=0.03). A similar relationship (with similar ORs) was found among patients with ASPECTS 5 to 7, although this did not reach statistical significance. There was no relationship between earlier reperfusion and outcome among the worst ASPECTS group.

In a secondary analysis examining individual ASPECTS scores as an ordinal variable, the optimal cutpoint for predicting good outcome was ASPECTS >5 (area under the curve, 0.66; P=0.0001; sensitivity, 96.7%; specificity, 30.6%). This cutpoint remained the same when including only patients who underwent reperfusion.

Discussion
This large study of patients with anterior circulation stroke treated with the Penumbra System confirms the importance of pretreatment NCCT ASPECTS for predicting clinical outcomes after intra-arterial therapy. Higher ASPECTS was
significantly associated with better functional outcomes, reduced mortality, and lower rates of symptomatic intracranial hemorrhage, and was an independent predictor of 90-day independence. A unique aspect of this study was the characterization of clinical and safety outcomes for ASPECTS 0 to 4 and 5 to 7 groups, which were considered as a single group in previous studies. This analysis yielded a finding of immediate relevance to both clinical practice and trial design, namely that very low ASPECTS scores (ie, 0–4) identify a patient subgroup with dismal outcomes (5% independence; 55% mortality) and a high rate of symptomatic hemorrhage after endovascular reperfusion. This finding provides strong support for using a threshold of ASPECTS <5 to exclude patients from treatment.

Previous work has illustrated the importance of traditional ASPECTS dichotomization of >7 versus ≤7 for identifying patients who will benefit from IAT. A post hoc analysis of the Pro-Urokinase for Acute Cerebral Thromboembolism (PROACT) II trial demonstrated a differential treatment effect by baseline ASPECTS, such that only patients with scores >7 demonstrated a benefit from intra-arterial thrombolysis.13 Similarly, a comparison of intravenous–intra-arterial therapy bridging patients from the Interventional Management of Stroke (IMS) I trial with a similar cohort of intravenous tPA–treated patients from the National Institute for Neurological Disorders and Stroke tPA trial revealed that patients with ASPECTS >7 appeared to benefit from the added intra-arterial approach, whereas there was a suggestion of harm among patients with lower scores.14

However, in light of the present findings, excluding patients with ASPECTS ≤7 from catheter-based treatment would exclude some patients who seem to benefit from early endovascular reperfusion, specifically those with ASPECTS 5 to 7. In this subgroup, the ORs for a good outcome with both early and late reperfusion were higher (although similar in magnitude) compared with those for the ASPECTS 8 to 10 group, implying that the lack of statistical significance in the ASPECTS 5 to 7 group was related to its smaller sample size. The rate of good outcomes and mortality were not significantly different between ASPECTS 5 to 7 and 8 to 10, despite more frequent symptomatic hemorrhages in the 5 to 7 group. These results suggest that poor outcomes in the ASPECTS 0 to 4 group may be responsible for the absence of treatment benefit previously reported for ASPECTS ≤7.

Given the recent failure of IMS III, these findings further suggest that rigorous evaluation of NCCT images using ASPECTS may be helpful for patient selection in trials. Although IMS III used NCCT for estimating ischemic brain injury, the imaging criteria were imprecise.20 Patients were excluded if there were “large regions of clear hypodensity on CT scan, such as greater than one-third of the MCA vascular territory.” The one-third MCA rule has been shown to have poor sensitivity for detecting large infarcts21 and also demonstrates poor interobserver agreement.

Figure 1. A, Distribution of modified Rankin Scale scores (labeled boxes) between pretreatment Alberta Stroke Program Early CT Score (ASPECTS) 8 to 10 (top), 5 to 7 (middle), and 0 to 4 (bottom) groups (overall \( P<0.0001 \)). \( P \) values for pairwise comparisons are indicated at the right. B, Rate of symptomatic intracranial hemorrhage stratified by trichotomized pretreatment ASPECTS group (overall \( P=0.02 \)). \( P \) values for pairwise comparisons are indicated at the top. ICH indicates intracranial hemorrhage.
reliability. Unfortunately, using ASPECTS of ≤4 as an exclusion criterion was only suggested as a helpful guideline in IMS III. The idea that ASPECTS may improve reader detection of major ischemic changes on NCCT is supported by the 16% rate of ASPECTS 0 to 4 in this study cohort despite the fact that more than one-third MCA territory involvement was an explicit exclusion criterion in the Penumbra Pivotal trial and a likely clinical exclusion criterion at most, if not all, of the centers participating in the PICS registry. Based on the clinical benefit of early reperfusion seen among patients with higher ASPECTS scores in this study, a randomized controlled trial of IAT based on strict NCCT ASPECTS selection may be warranted. In such a trial, training investigators in the ASPECTS methodology will be critical.

Both the current study and the recently published Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study add to the growing body of evidence that a small core infarct (ie, region of irreversible tissue injury) at presentation predicts a good clinical response to endovascular reperfusion. In DEFUSE 2, which mandated perfusion imaging, the only significant difference among the primary imaging variables between patients with and without a target mismatch (ie, favorable imaging profile) was the core infarct volume on diffusion imaging, not the extent of perfusion abnormality. Core infarct size was an independent predictor of outcome in both DEFUSE 2 and this study. One area of future investigation is to determine which approach to core infarct imaging—MRI diffusion lesion volume or NCCT ASPECTS—is better for IAT selection.

A noteworthy difference between DEFUSE 2 and this study is the impact of time to treatment on clinical outcome. Among DEFUSE 2 patients with a target mismatch, those who were treated late (>6 hours) derived a similar clinical benefit from reperfusion as did those who were treated earlier. In contrast, there was a clear benefit to early reperfusion among patients with ASPECTS 8 to 10 in this study. This disparity may be related to how the time intervals were defined (stroke onset to treatment initiation in DEFUSE 2 versus stroke onset to reperfusion in the present study). Nevertheless, there is controversy in the literature concerning this point. Recent studies have shown that shorter time from stroke onset to revascularization is associated with improved IAT outcomes, whereas others have shown no significant effect of this time interval. Such variability in the impact of stroke duration likely reflects its interdependence with collateral strength for determining the rate of infarct progression. Of note, the studies that revealed a limited time effect used MRI for imaging selection, whereas those finding a strong time dependence used NCCT-based selection. It may be that MRI is superior to NCCT for identifying patients with better collaterals in whom the harm accruing with each passing
minute is reduced. Consistent with this idea, a recent multicenter retrospective study demonstrated that patients treated beyond the traditional 8-hour window based on advanced imaging (MRI or CT perfusion) selection have a similar safety profile and equivalent rates of good outcomes when compared with patients treated at <8 hours based on NCCT.26

A major limitation of this study is the absence of a control group that did not receive IAT. This prevents any definitive conclusions regarding the benefits and risks of catheter-based treatment among patients with ASPECTS 5 to 7 and 8 to 10. However, the recommendation that patients with ASPECTS 0 to 4 should be excluded from IAT remains reasonable given that these patients are not likely to have worse outcomes with medical management alone. The major strength of this study is its use of NCCT imaging, which is performed in a standard fashion in the majority of medical centers that offer endovascular therapy. This renders the present findings highly generalizable to current clinical practice. Additional strengths include large sample size and use of blinded imaging analysis by expert readers.

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The study was sponsored and funded by Penumbra Inc. The sponsor worked with stroke experts to design the trial, control the allocation schedule, and monitor, analyze, interpret, and present the data. The sponsor could not suppress publication of the report even if the results were negative or detrimental to its products.

Disclosures

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References

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