Title

Serial Alberta Stroke Program Early CT Score From Baseline to 24 Hours in Solitaire Flow Restoration With the Intention for Thrombectomy Study

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Serial ASPECTS from Baseline to 24 Hours in SWIFT: A Novel Surrogate Endpoint for Revascularization in Acute Stroke

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Abstract

Background and Purpose—ASPECTS on baseline imaging is an established predictor of acute ischemic stroke outcomes. We analyzed change on serial ASPECTS at baseline and 24-hour imaging in the SOLITAIRE™ FR With the Intention For Thrombectomy (SWIFT) Study to determine prognostic value and to identify subgroups with extensive injury after intervention.

Methods—ASPECTS at baseline and 24 hours was independently scored in all anterior circulation SWIFT cases, blind to all other trial data. ASPECTS at baseline, at 24 hours, and serial changes were analyzed with univariate and multivariate approaches.

Results—139 patients (mean age 67 years (SD 12), 52% female, median NIHSS 18 (IQR 8–28)) with complete data at both time points were studied. Multivariate analyses showed higher 24-hour ASPECTS predicted good clinical outcome (Day 90 mRS 0–2): OR 1.67, p<0.001. Among patients with high baseline ASPECTS (8–10; n=109), dramatic infarct progression (decrease in ASPECTS ≥ 6 points at 24 hours) was noted in 31/109 (28%). Such serial ASPECTS change was predicted by higher baseline SBP (p=0.019), higher baseline blood glucose (p=0.133), and failure to achieve TICI 2b/3 reperfusion (p<0.001), culminating in worse Day 90 mRS outcomes (mean mRS 4.4 vs. 2.7, p<0.001).

Conclusions—24-hour ASPECTS provides better prognostic information than baseline ASPECTS. Predictors of dramatic infarct progression on ASPECTS are hyperglycemia, hypertension and non-reperfusion. Serial ASPECTS change from baseline to 24 hours predicts clinical outcome, providing an early surrogate endpoint for thrombectomy trials.

Clinical Trial Registration-URL—http://clinicaltrials.gov. Unique identifier: NCT01054560.

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Conflict(s) of Interest/Disclosure(s)

Some authors (Liebeskind, Jahan, Saver) were employed by the University of California (UC), which holds a patent on retriever devices for stroke, at the time of this work.

D. Liebeskind: Consultant/Advisory Board; Modest; Stryker and Covidien.

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Keywords

Stroke; revascularization; CT; collaterals

Introduction

The Alberta Stroke Program Early CT Score (ASPECTS) grading system provides a systematic method to quantify and describe the topography of tissue changes in the brain due to acute ischemic stroke in the anterior circulation.[1–3] ASPECTS scoring of baseline imaging with CT or MRI has been established as a reliable predictor of clinical outcome after various therapeutic strategies, including reperfusion strategies.[4–6] Such semi-quantitative information on the extent or number of regions within the brain affected by ischemia rapidly provided by ASPECTS may be used to select optimal candidates for endovascular therapies. This information on baseline imaging may be used to predict outcome, yet follow-up ASPECTS at 24 hours may also provide early estimates of therapeutic effectiveness after endovascular therapy. The change of such serial ASPECTS on imaging from baseline to 24 hours after revascularization may therefore provide an early biomarker of therapeutic success or failure.

We analyzed ASPECTS on baseline and 24-hr imaging in the SOLITAIRE™ FR With the Intention For Thrombectomy (SWIFT) Study to determine the potential prognostic value of this approach and to identify subgroups with extensive injury after intervention.[7] Our primary objective was to establish serial ASPECTS as a novel measure of ischemic evolution and the potential therapeutic effects of reperfusion.

Methods

The SWIFT Study was a randomized safety and efficacy study comparing use of the Merci device with the SOLITAIRE™ FR stentriever for arterial recanalization without hemorrhagic transformation in the setting of acute ischemic stroke.[7] Detailed methods and results of this study have been previously published.[8] In brief, patients were randomized to mechanical thrombectomy with Merci or SOLITAIRE™ FR within 8 hours of symptom onset, following baseline imaging that excluded the presence of hemorrhage. No imaging criteria were used to identify potential study candidates other than absence of extensive ischemia, manifest as CT hypodensity or MR hyperintensity involving greater than 1/3 of the middle cerebral artery (MCA) territory (or in other territories, >100 cc of tissue) at presentation. ASPECTS on baseline imaging was not pre-specified for data extraction in primary or secondary analyses of the trial.

Post hoc evaluation of the baseline CT or MRI was conducted in our study, using the imaging archive established by the core laboratory. Two experienced readers, including a neuroradiologist and vascular neurologist with stroke imaging expertise, reviewed baseline imaging in all cases of anterior circulation stroke enrolled in SWIFT. ASPECTS were independently determined with disagreements resolved by consensus, blind to all other trial data. A DICOM reader was used for image display, using a standard CT window width and center level of 50 HU and 30 HU, respectively. Diffusion-weighted imaging (DWI) sequences were used for ASPECTS scoring on MRI.[9] Cases were reviewed in a routine order, with baseline imaging followed by review of the 24-hour study, as would be encountered in routine clinical practice. ASPECTS was scored using all axial slices available, to reliably identify presence of any ischemia in each topographical region of the MCA territory. Chronic changes, such as leukoaraiosis, established infarcts or atrophy, were not included in generation of ASPECTS so that only acute ischemic changes could be

quantified. ASPECTS was scored on the CT or MRI acquired immediately prior to treatment and on the required 24-hour imaging. Baseline imaging included 132 CT studies and 7 MRI, with 123 CT and 16 MRI studies used for the 24-hour scan.

Statistical analyses were conducted by the SWIFT statisticians utilizing clinical variables obtained from the main dataset with ASPECTS and angiographic reperfusion scores obtained as part of this post hoc study. ASPECTS at baseline, 24 hours, and the corresponding serial changes in each case were recorded. Reperfusion of the corresponding arterial territory was separately scored with the modified Thrombolysis in Cerebral Infarction (TICI) scale, using 2/3 as the threshold for achieving grade 2b reperfusion.[10, 11] Dramatic infarct progression was defined as a decrease in ASPECTS ≥ 6 points between the baseline and 24-hour imaging studies. Angiographic reperfusion was defined as TICI of 2b or 3. Clinical outcomes considered were symptomatic intracranial hemorrhage and functional independence at 90 days, defined as a modified Rankin Scale (mRS) of 0, 1, or 2. ASPECTS was treated as an ordinal variable. Cumulative logit regression was used to model outcome as a function of ASPECTS at each time point and the serial ASPECTS change, using covariates selected by backward selection methodology. Baseline variables potentially associated with outcomes ($p<0.2$) were considered for inclusion in the multivariate model. A significance level of $p<0.05$ was used to identify significant predictors of clinical outcomes.

Results

A total of 139 patients (mean age 67 years (SD 12), 52% female, median NIHSS 18 (IQR 8–28)) with imaging data at baseline and 24 hours were included in our analyses. 5 cases in the 144 patient dataset of the SWIFT study did not have imaging available for our retrospective analyses. ASPECTS were evaluated in a total of 139 SWIFT cases at baseline and 139 cases at 24 hours. Baseline imaging included 132 CT studies and 7 MRI, with 123 CT and 16 MRI at 24 hours. Serial ASPECTS changes were calculated based on 120 CT-CT pairs, 15 CT-MRI pairs, and 4 MRI-MRI pairs, at baseline and 24 hours, respectively.

Baseline ASPECTS was categorized as 0–7, 8, 9, and 10 are illustrated in Figure 1, revealing an even distribution across these categories. Baseline ASPECTS of 0–7 was related to worse NIHSS (OR 1.176, p=0.006) and the absence of coronary artery disease (OR 0.20, p=0.008). Other clinical variables in the trial dataset were unrelated to baseline ASPECTS. ASPECTS on the 24-hour imaging studies depicted in Figure 1 illustrate a relatively even split using categories of 0, 1–4, 5–7 and 8–10. Lower 24-hr ASPECTS was related to worse baseline NIHSS (p=0.003) and higher baseline SBP (p=0.033). Interestingly, baseline ASPECTS was linked with Day 7/discharge NIHSS (p=0.008) and Day 90 mRS (p=0.066), yet not TICI 2b/3 reperfusion or hemorrhage. The 24-hour ASPECTS was closely linked with all of these outcome variables (all $p<0.01$). Multivariate analyses demonstrated that a higher 24-hour ASPECTS best predicted a good clinical outcome (Day 90 mRS 0–2): OR 1.67, $p<0.001$, compared with other variables entered into the model.

Serial changes in ASPECTS from baseline to 24 hours were principally measured by dramatic infarct progression, or a decrease in ASPECTS ≥ 6 points at 24 hours. Figure 2 (B) illustrates a case of dramatic infarct progression from a baseline ASPECTS of 9. Among patients with high baseline ASPECTS (8–10; n=109), dramatic infarct progression (decrease in ASPECTS ≥ 6 points at 24 hours) was noted in 31/109 (28%). Variables associated with dramatic infarct progression were elevated baseline SBP (p=0.019), elevated baseline blood glucose (p=0.133), and failure to achieve TICI 2b/3 reperfusion ($p<0.001$) (Figure 3). Interestingly, a subset of 14/31 cases demonstrated dramatic infarct progression on serial ASPECTS without hemorrhagic transformation despite reperfusion (Figure 2, C). The

patients with dramatic infarct progression measured by serial ASPECTS from baseline to 24 hours had worse Day 90 mRS clinical outcomes (mean mRS 4.4 vs. 2.7, $p<0.001$) compared with cases where such infarct evolution did not evolve.

Discussion

Our findings confirm the utility of ASPECTS as a practical algorithm to quantify ischemic changes in acute stroke that correlate with neurological deficits measured on the NIHSS and subsequent outcomes. Interestingly, we noted that baseline ASPECTS was not predictive of reperfusion or hemorrhagic transformation. More severe baseline NIHSS and elevated SBP predicted more extensive injury at 24 hours, possibly reflecting worse collateral perfusion.[12, 13] At 24 hours, ASPECTS similarly correlated with NIHSS, although the distribution was much wider as it included many patients with extensive lesions throughout the MCA territory and others where minimal or no change was evident from baseline. ASPECTS at 24 hours was the best predictor of clinical outcomes at 3 months after endovascular therapy. This key finding is consistent with previous work demonstrating that final infarct volume is the most important predictor of outcomes after stroke, yet ASPECTS provides a relatively simple measure compared to the more complex quantification of final infarct volume.

The use of serial ASPECTS from baseline to 24 hours following endovascular therapy revealed several interesting facets. Dramatic infarct progression occurred in almost 1/3 of patients. Although the majority (79%) of cases had ASPECTS of 8–10 at baseline, only 31% had ASPECTS of 8–10 at 24 hours. This likely reflects evolving ischemic injury unapparent at baseline, failed or ineffective reperfusion, or alternatively, reperfusion injury.[14] Failed reperfusion was demonstrated to be an influential factor in our analyses, but elevated hypertension and hyperglycemia at baseline suggest impaired collateral flow and also the possibility of reperfusion injury. In fact, a subset of cases exhibited dramatic infarct progression without hemorrhagic transformation after successful reperfusion. Overall, serial ASPECTS within the first 24 hours was a potent predictor of outcomes up to 3 months later.

Our detailed, semi-quantitative analyses of baseline and corresponding 24-hour imaging of patients enrolled in the SWIFT study with the ASPECTS scoring system provide the basis for a novel surrogate endpoint after revascularization. Quantifying the degree of change on serial ASPECTS at these standard imaging time points may reveal the extent of tissue injury and key prognostic information regarding clinical outcomes at 3 months. Such serial changes of tissue injury on routinely acquired imaging such as noncontrast CT are inherently informative as they reveal not only the extent of potential injury, but also the trajectory of expected clinical sequelae in a specific patient. Endovascular strategies have been hampered by the imperfect correlation between arterial recanalization and subsequent clinical outcomes. Potential imaging biomarkers, such as serial ASPECTS, may serve as future surrogate endpoints after revascularization, as improved prediction algorithms are desperately needed for acute stroke therapies.[15] Prediction of subsequent clinical outcomes at 3 months is ideally established during the earliest phases of ischemia, as demonstrated by the change in ASPECTS at 24 hours. Baseline imaging is predominantly used to exclude unfavorable revascularization candidates, as with the malignant profiles on CT or MRI, yet predicting good outcomes remains limited.[16] Serial changes in ASPECTS from baseline to 24 hours may provide critical data on the response of downstream brain tissue to varying degrees of reperfusion that may accompany acute ischemic stroke.

Prognostication at 24 hours, using a tool such as serial ASPECTS to gauge therapeutic response may facilitate early decision-making during the subacute phase of patient care. Our analyses of serial imaging with modalities as simple as noncontrast CT were feasible in a

retrospective fashion, but also easily generalizable to other stroke populations. Although we used serial ASPECTS to ascertain the impact of endovascular therapy using early changes in ischemic injury at the tissue level, this method may be used to evaluate other therapeutic interventions or to simply chronicle the natural evolution of ischemic injury in the brain after stroke. Such surrogate imaging measures, however, remain subsidiary or secondary to clinical outcomes, however, examination findings may be limited during the subacute phase, particularly in the intensive care unit.

The lack of progressive ischemia in patients with successful reperfusion after endovascular therapy enhances enthusiasm for the potential benefit of such strategies that remain to be proven in randomized trials.[17, 18] The marked decline in ASPECTS or dramatic infarct progression despite reperfusion in other cases, however, underscores the need to discern the potential of reperfusion injury in routine clinical care. Voluminous literature in the basic sciences has focused on multiple features of reperfusion injury yet only limited information is available regarding the impact of reperfusion injury within the clinical context of acute stroke patient management.[14] The use of serial imaging, even utilizing relatively gross changes in ASPECTS topography may be a practical tool to measure the extent of reperfusion injury and disclose new areas of investigation to enhance outcomes of acute stroke patients, in parallel with the development of endovascular therapies.

Limitations of our retrospective study include potential issues with image quality, patient motion or other artifacts, the use of both CT and MRI, inherent scale limitations of the ASPECTS and our designation of any abnormality (including hemorrhage) as abnormal that deviates from original use of this score. Further analyses may explore alternative definitions of dramatic infarct progression other than a 6-point decline. Furthermore, ASPECTS may be trichotomized to identify futile revascularization at low scores or to analyze response to particular thrombectomy devices.[19, 20] Prospective studies are needed to validate the use of serial ASPECTS as a novel surrogate measure, particularly by local investigators in real-time decision-making from triage to follow-up after endovascular therapy.

Conclusions

Serial ASPECTS change from baseline to 24 hours after endovascular therapy predicts clinical outcome at 3 months and may therefore serve as a useful, early surrogate endpoint for thrombectomy trials. The extent of ischemic injury quantified by ASPECTS on routinely acquired imaging at 24 hours enhances prediction, illustrating the potential of revascularization to offset evolving infarction and also provides insight on potential untoward effects of reperfusion.

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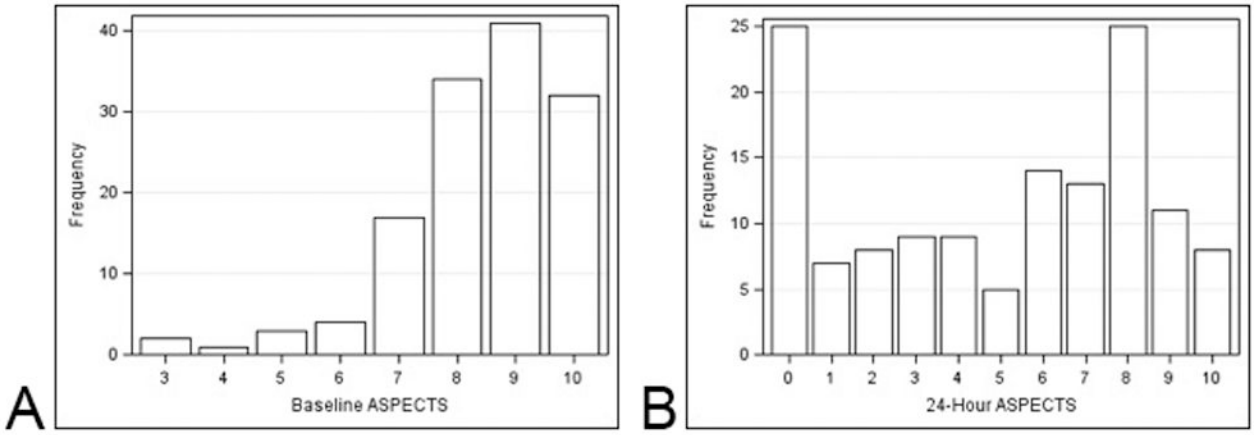

Figure 1.

Changes in ASPECTS from baseline to 24-hour. (A) Bar graph of baseline ASPECTS (n=139), including 0–7 in 30 (22%), 8 in 34 (25%), 9 in 42 (30%) and 10 in 33 (24%). (B) Bar graph of 24-hour ASPECTS (n=139), including 0 in 25 (18%), 1–4 in 35 (25%), 5–7 in 35 (25%) and 8–10 in 44 (31%).

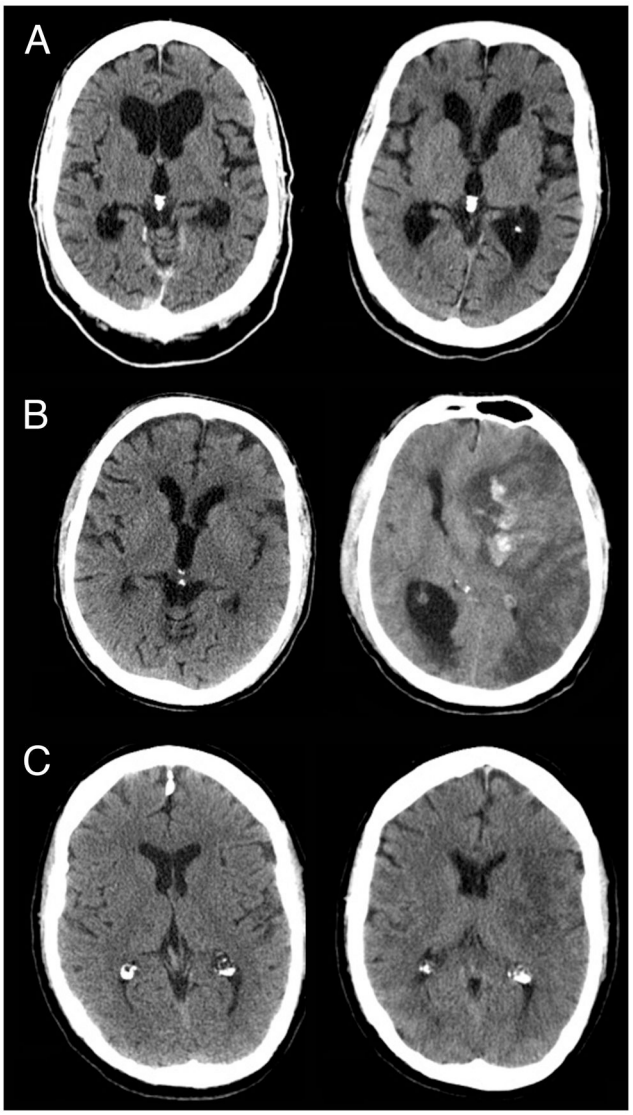

Figure 2.
Serial noncontrast CT in left MCA stroke at baseline (A, left) and 24 hours (A, right), revealing no change in ASPECTS of 10 following successful reperfusion. Serial noncontrast CT studies at baseline (B, left) and 24 hours (B, right) illustrating dramatic infarct progression from ASPECTS of 9 to 0 in left MCA stroke, with extensive ischemia and petechial hemorrhagic transformation. Dramatic infarct progression in a case of left MCA stroke from baseline (C, left) to 24 hours (C, right) on serial noncontrast CT, defined by a drop in ASPECTS from 8 to 3 without hemorrhagic transformation despite reperfusion.

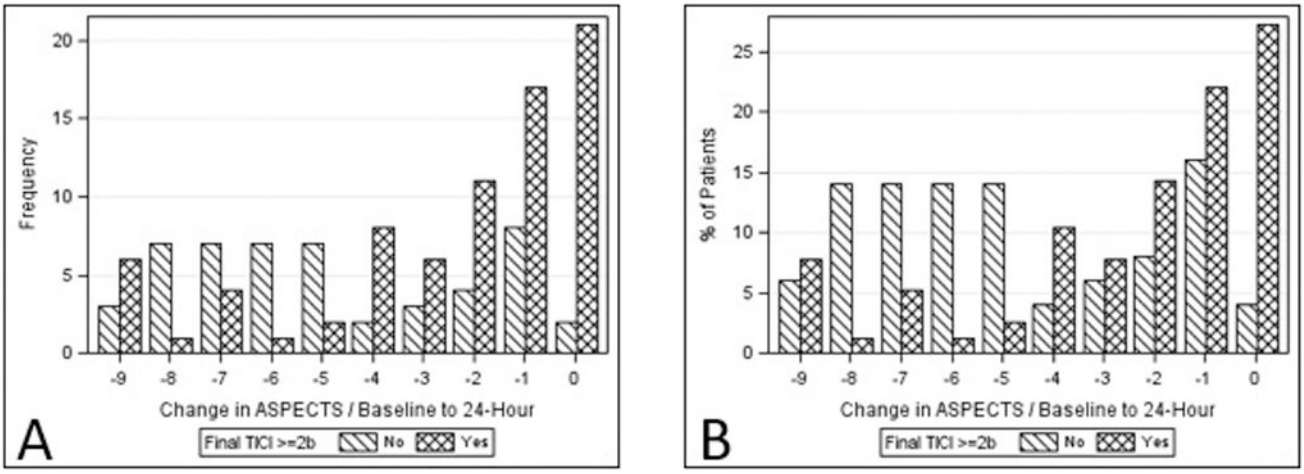

Figure 3.

Graphic illustrating changes by frequency (A) and by percentage of patients (B) in serial ASPECTS from baseline to 24-hour imaging, grouped by reperfusion or non-reperfusion defined as TICI 2b/3.