See related article, p 653.

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 semiquantitative 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-hour imaging in the Solitaire Flow Restoration 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, blinded to all other trial data. ASPECTS at baseline, at 24 hours, and serial changes were analyzed with univariate and multivariate approaches.

Results—One hundred thirty-nine patients (mean age, 67 [SD, 12] years; 52% women; median National Institutes of Health Stroke Scale, 18 [interquartile range, 8–28]) with complete data at both time points were studied. Multivariate analyses showed that higher 24-hour ASPECTS predicted good clinical outcome (day 90 modified Rankin Scale, 0–2; odds ratio, 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 of 109 (28%). Such serial ASPECTS change was predicted by higher baseline systolic blood pressure (\( P = 0.019 \)), higher baseline blood glucose (\( P = 0.133 \)), and failure to achieve Thrombolysis in Cerebral Infarction score of 2b/3 reperfusion (\( P < 0.001 \)), culminating in worse day 90 modified Rankin Scale outcomes (mean modified Rankin Scale, 4.4 versus 2.7; \( P < 0.001 \)).

Conclusions—Twenty-four-hour ASPECTS provides better prognostic information compared with baseline ASPECTS. Predictors of dramatic infarct progression on ASPECTS are hyperglycemia, hypertension, and nonreperfusion. Serial ASPECTS change from baseline to 24 hours predicts clinical outcome, providing an early surrogate end point for thrombectomy trials.

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

Key Word: stroke
arterial recanalization without hemorrhagic transformation in the setting of acute ischemic stroke. Detailed methods and results of this study have been previously published. In brief, patients were randomized to mechanical thrombectomy with Merci or SOLITAIRE FR <8 hours of symptom onset, after 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 more than one third of the middle cerebral artery territory (or in other territories, >100 mL of tissue) at presentation. ASPECTS on baseline imaging was not prespecified for data extraction in primary or secondary analyses of the trial.

Post hoc evaluation of 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 scores were independently determined, with disagreements resolved by consensus, blinded to all other trial data. A DICOM reader was used for image display, using a standard CT window width and center level of 50 and 30 HU, respectively. Diffusion-weighted imaging sequences were used for ASPECTS scoring on MRI. 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 identify the presence reliably of any ischemia in each topographical region of the middle cerebral artery territory. Chronic changes, such as leukoaraiosis, established infarcts, or atrophy, were not included in the generation of ASPECTS so that only acute ischemic changes could be quantified. ASPECTS was scored on the CT or MRI acquired immediately before 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 SWIFT statisticians using clinical variables obtained from the main data set with ASPECTS and angiographic reperfusion scores obtained as part of this post hoc study. ASPECTS at baseline, 24 hours, and 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. Dramatic infarct progression was defined as a decrease in ASPECTS ≥6 points between baseline and 24 hours. 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) score 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 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 [SD, 12] years; 52% women; median National Institutes of Health Stroke Scale [NIHSS], 18 [interquartile range, 8–28]) with imaging data at baseline and 24 hours were included in our analyses. Five cases in the 144-patient data set of the SWIFT study did not have imaging available for our retrospective analyses. ASPECTS scores 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–MRI pairs, 15 CT–MRI pairs, and 4 MRI–MRI pairs, at baseline and 24 hours, respectively.

Baseline ASPECTS was categorized as 0 to 7, 8, 9, and 10 as illustrated in Figure 1, revealing an even distribution across these categories. Baseline ASPECTS of 0 to 7 was related to worse NIHSS (odds ratio, 1.176; P=0.006) and absence of coronary artery disease (odds ratio, 0.20; P=0.008). Other clinical variables in the trial data set were unrelated to baseline ASPECTS. ASPECTS on 24-hour imaging studies depicted in Figure 1 illustrates a relatively even split using categories of 0, 1 to 4, 5 to 7, and 8 to 10. Lower 24-hour ASPECTS was related to worse baseline NIHSS (P=0.003) and higher baseline systolic blood pressure (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 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; odds ratio, 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 2B illustrates a case of dramatic infarct progression from a

Figure 1. Changes in Alberta Stroke Program Early CT Score (ASPECTS) from baseline to 24 h. A, Bar graph of baseline ASPECTS (n=139), including 0 to 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 to 4 in 35 (25%), 5 to 7 in 35 (25%), and 8 to 10 in 44 (31%).
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 of 109 (28%). Variables associated with dramatic infarct progression were elevated baseline systolic blood pressure ($P=0.019$), 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 of 31 cases demonstrated dramatic infarct progression on serial ASPECTS without hemorrhagic transformation despite reperfusion (Figure 2C). 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 versus 2.7; $P<0.001$) compared with cases where such infarct evolution did not evolve.

### Discussion

Our findings confirm the use 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 systolic blood pressure predicted more extensive injury at 24 hours, possibly reflecting worse collateral perfusion. At 24 hours, ASPECTS similarly correlated with NIHSS, although the distribution was much wider as it included many patients with extensive lesions throughout the middle cerebral artery 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 with the more complex quantification of final infarct volume.

The use of serial ASPECTS from baseline to 24 hours after endovascular therapy revealed several interesting facets. Dramatic infarct progression occurred in almost one third of patients. Although the majority (79%) of cases had ASPECTS of 8 to 10 at baseline, only 31% had ASPECTS of 8 to 10 at 24 hours. This likely reflects evolving ischemic injury unapparent at baseline, failed or ineffective reperfusion, or, alternatively, reperfusion injury. Failed reperfusion was demonstrated to be an influential factor in our analyses, but elevated hypertension and hyperglycemia at baseline suggests 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 semiquantitative 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 end point 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 because 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 end points after revascularization, because improved prediction algorithms are desperately needed for acute stroke therapies. 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 malignant profiles on CT or MRI; yet, predicting good outcomes remains limited. 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.

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. 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 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. 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, 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 the 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. 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 end point 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, as well as provides insight on potential untoward effects of reperfusion.

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Disclosures

Drs Liebeskind, Jahan, and Saver were employed by the University of California, which holds a patent on retriever devices for stroke, at the time of this work. Dr Liebeskind: consultant/advisory board (modest)—Stryker and Covidien. Dr Jahan: speakers’ bureau (modest)—Stryker; consultant/advisory board (modest)—Covidien. Dr Nogueira: consultant/advisory board (modest)—Stryker/Concentric Medical, Inc, Covidien/ev3 Neurovascular, Inc, Co-Axia, Inc, Penumbra, Inc, Rapid Medical, Inc, Reverse Medical, Inc, and Neurointervention, Inc. Dr Jovin: consultant/advisory board (modest)—Stryker/Concentric Medical, Inc, Covidien/ev3 Neurovascular, Inc, Co-Axia, Inc, and Neurointervention, Inc. Dr Lutsep: consultant/advisory board (modest)—Stryker/Concentric Medical, Inc, and Co-Axia, Inc. Dr Saver: research grant (significant)—National Institutes of Health/National Institute of Neurological Disorders and Stroke award P50NS044378; consultant/advisory board (significant)—Covidien.

References

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Solitaire Flow Restoration With the Intention for Thrombectomy (SWIFT) 試験における入院時と24時間後の連続Alberta Stroke Program Early CT Score
急性脳卒中における再灌流の新たな代用評価項目

Serial Alberta Stroke Program Early CT Score From Baseline to 24 Hours in Solitaire Flow Restoration With the Intention for Thrombectomy Study
A Novel Surrogate End Point for Revascularization in Acute Stroke

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Abstract

目的一目的は：入院時画像診断によるAlberta Stroke Program Early CT Score（ASPECTS）は、急性脳卒中病状の中の転帰の予測因子として用いられている。本研究では、Solitaire Flow Restoration with the Intention for Thrombectomy（SWIFT）試験における入院時と24時間後の画像診断による連続ASPECTSの変化を解析し、予後予測に関する有用性を判定し、処置後に予後予測の変化を示すサブグループを特定した。

方法：SWIFT研究に登録されたすべての前頭部循環障害症例を対象として、入院時および24時間後のASPECTSを個別に点数化し、その他の試験データはすべて再評価した。多変量解析を多変量解析を用いて、入院時および24時間後のASPECTS、およびその連続的な変化について解析した。

結果：入院時と24時間後の完全なデータが得られた139例（平均年齢67（標準偏差12）歳、女性52%、国立医学研究所脳卒中スコア（NIHSS）の中央値13（四分位範囲：8–28））を検討した。多変量解析により、24時間後の高いASPECTSは良好な臨床転帰を予測することが示された[90日目の変化Rankinスケール（mRS）0～2、オッズ比=1.67，p<0.001]。ベースラインのASPECTSが高かった患者（ASPECTS 8–10, 109例）において、109例中31例（28%）に梗塞の著しい進行（24時間後にASPECTSが6ポイント以上減少）が認められた。このようなASPECTSの連続変化はベースラインの高い収縮期血圧（p=0.019）および高血圧（p=0.133）、血栓溶解（TICI）スコアで2b/3の再灌流の未達成（p<0.001）によって予測され、90日目のmRSの転帰の悪化（mRSの平均値4.4対2.7, p<0.001）に至った。

結論：24時間後のASPECTSは、入院時のASPECTSよりも予後の予測に優れていた。ASPECTSで確認した梗塞の著しい進行の予後因子は、高血糖、高血圧、再灌流未達成であった。入院時から24時間後のASPECTSの変化により臨床転帰が予測され、血栓除去試験の早期・代用評価項目を提供する。

臨床試験登録情報：URL: http://www.clinicaltrials.gov 固有識別子：NCT01054560

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