Impact of Diffusion-Weighted Imaging Alberta Stroke Program Early Computed Tomography Score on the Success of Endovascular Reperfusion Therapy

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Background and Purpose—In acute ischemic stroke patients treated by intravenous thrombolysis, a diffusion-weighted imaging (DWI) Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an independent factor of functional outcomes. Our aim was to assess the impact of pretreatment DWI-ASPECTS on outcomes after endovascular therapy, with a specific emphasis on recanalization.

Methods—We analyzed data collected between April 2007 and March 2013 in a prospective clinical registry of acute ischemic stroke patients treated by endovascular approach. Every patient with a documented internal carotid artery or middle cerebral artery occlusion who underwent an acute DWI-MRI before treatment was eligible for this study. The primary outcome was a favorable outcome defined by modified Rankin Scale of 0 to 2 at 90 days.

Results—Two hundred ten patients were included and median DWI-ASPECTS was 7 (interquartile range, 4–8). DWI-ASPECTS ≥5 was the optimal threshold to predict a favorable outcome (area under the curve=0.69; sensitivity, 90%; specificity, 38%). In a multivariate analysis including confounding variables, the adjusted odds ratio for favorable outcomes associated with a DWI-ASPECTS of ≥5 was 5.06 (95% confidence interval, 1.86–13.77; P=0.002). Nonetheless, the occurrence of a complete recanalization was associated with an increased rate of favorable outcomes in patients with DWI-ASPECTS under 5 (50% versus 3%, P<0.001).

Conclusions—DWI-ASPECTS ≥5 seems to be the optimal threshold to predict favorable outcomes among patients undergoing endovascular reperfusion within 6 hours. Selected patients with a DWI-ASPECTS of <5 may still benefit when a complete reperfusion is achieved. (Stroke. 2014;45:1992-1998.)

Key Words: brain magnetic resonance imaging • diffusion • endovascular therapy • stroke

The size of the acute ischemic lesion is a demonstrated independent prognostic factor in patients undergoing a recanalization therapy for an acute brain infarction.1–3 The Alberta Stroke Program Early Computed Tomography Score (ASPECTS), which evaluates early ischemic signs extension on a noncontrast head computed tomography (CT), has been associated with clinical outcomes in acute ischemic stroke (AIS) patients treated by intravenous and intra-arterial thrombolysis.4,5 Diffusion-weighted imaging (DWI) is far more sensitive than CT in detecting acute ischemia.6 The acute DWI lesion volume has been tested and validated as a major independent predictor after intravenous recombinant tissue-type plasminogen activator (rtPA) or endovascular therapies.3,5 If some groups proposed automated DWI volume measurement in hemispheric strokes, the DWI lesion volume estimation using CT-ASPECTS anatomic landmarks offers an acceptable estimation of critical DWI volumes.10 The direct comparison between CT and DWI-ASPECTS has shown that in contrast to CT-ASPECTS, DWI-ASPECTS >7 did not always reliably predict functional outcomes after intravenous rtPA.11 Therefore, several groups have tested and proposed different DWI-ASPECTS score to assess functional outcomes after intravenous rtPA.10,12–14

The occurrence of an early complete recanalization is also a major independent factor of clinical recovery after AIS.15 We have recently shown that the occurrence of a complete

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recanalization achieved by endovascular treatment may influence the relationships observed between acute DWI lesion volume and functional outcomes.17 Last year, Aoki et al16 showed in an AIS patient cohort with M1 middle cerebral artery occlusion treated by intravenous rtPA that a DWI-ASPECTS of ≥7 was the optimal cutoff to predict a dramatic recovery (>10 points improvement in National Institutes of Health Stroke Scale). The occurrence of a recanalization was associated with an increased rate of favorable outcomes (modified Rankin Scale score 0–2 at 3 months) only in the subgroup of patients with a DWI-ASPECTS of <7. This result suggests that some patients with a DWI-ASPECTS of <7 may still benefit from an early recanalization.

With this as a background, we evaluated in an AIS patients cohort eligible for endovascular therapy which DWI-ASPECTS value will predict a functional outcome and whether the occurrence of a complete reperfusion would have an impact on this relationship.

Methods

Bichat Stroke Program

Patients were identified from a prospective clinical registry of patients with AIS treated between April 2007 and March 2013 at Bichat University Hospital. Detailed material and methods have been previously reported.17 All patients underwent a magnetic resonance angiography or CT angiography before treatment to document arterial occlusion. Patients eligible for intravenous thrombolysis were treated by conventional intravenous thrombolysis in case of no documented arterial occlusion and with a systematic intravenous–intra-arterial approach in case of documented arterial occlusion. Patients with a documented arterial occlusion received an intravenous rtPA dose of 0.6 mg/kg followed by an intra-arterial dose of 0.3 mg/kg (except in case of complete recanalization after intravenous thrombolysis). In case of persistent occlusion after intravenous/intra-arterial rtPA administration, additional mechanical endovascular therapy (MET) was performed using either the snare (eV3) or the Solitaire (Covidien) devices.18 Patients with a documented arterial occlusion who were not eligible for intravenous tissue-type plasminogen activator were treated by intra-arterial tissue-type plasminogen activator (dose 0.5 mg/kg), followed by adjunctive MET if the occlusion persisted. Finally, in patients with a contraindication to tissue-type plasminogen activator, a direct MET approach was considered.19 Endovascular therapy (either intra-arterial rtPA and MET) was performed beyond 6 hours after symptom onset.

Table. Baseline Characteristics According to DWI-ASPECTS

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Overall (n=210)</th>
<th>&lt;6 (n=75)</th>
<th>6–7 (n=60)</th>
<th>&gt;7 (n=75)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>70.4 (16.8)</td>
<td>67.7 (17.7)</td>
<td>69.1 (16.8)</td>
<td>74.2 (15.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>Men</td>
<td>94 (44.8)</td>
<td>27 (36.0)</td>
<td>35 (58.3)</td>
<td>32 (42.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (51.4)</td>
<td>40 (53.3)</td>
<td>34 (56.7)</td>
<td>34 (45.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (10.1)</td>
<td>8 (10.7)</td>
<td>5 (8.6)</td>
<td>9 (10.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>51 (24.8)</td>
<td>19 (25.3)</td>
<td>14 (24.1)</td>
<td>18 (24.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>68 (34.2)</td>
<td>20 (27.8)</td>
<td>23 (40.4)</td>
<td>25 (35.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Antithrombotic medications</td>
<td>80 (38.1)</td>
<td>28 (37.3)</td>
<td>19 (31.7)</td>
<td>33 (44.0)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; MET, mechanical endovascular therapy; NIHSS, National Institutes of Health Stroke Scale; and rtPA, recombinant tissue-type plasminogen activator.
after initiation of treatment. Time from symptom onset to cerebral imaging (MRI), to initiation of therapy (rtPA administration by intravenous or intra-arterial if contraindicated or local thrombectomy device deployment if rtPA is contraindicated) were also recorded. Arterial status of the occluded artery was monitored with conventional angiography during the intra-arterial approach and time to recanalization was noted. Recanalization was measured using the Thrombolysis In Myocardial Infarction (TIMI) score by 2 members of the staff (E.M. and M.M.). Successful recanalization was defined as a complete restoration of blood flow (TIMI 3). All patients had a CT or MRI scan 24 hours after treatment onset to assess hemorrhagic complications. The modified Rankin Scale at 3 months was assessed during face-to-face interviews or telephone calls by a senior vascular neurologist (E.M. or M.M.) certified for modified Rankin Scale scoring.

**DWI Measurements**

DWI volumes were calculated retrospectively by using an automated software program: RApid processing of Perfusion and Diffusion which uses a delay-independent deconvolution approach. DWI-ASPECTS was assessed by 2 stroke neurologists blinded from any clinical information (W.T. and M.I.).

**Clinical Outcome Definitions**

The primary study outcome was the percentage of patients who achieved a favorable outcome at 90 days, defined by a modified Rankin Scale score of 0 to 2. Secondary outcomes included 90-day mortality and symptomatic intracerebral hemorrhage per European-Australasian Acute Stroke Study (ECASS) II definition.

**Statistical Analysis**

Data are presented as mean (SD) or median (interquartile range [IQR]) for continuous variables and percentage (count) for categorical variables. DWI-ASPECTS were divided into tertiles to describe the association with baseline characteristics and outcomes. Comparisons between tertiles were made using the Cochran–Mantel–Haenszel trend test for categorical variables and analysis of variance (nonparametric for skewed baseline data) with linear contrast. Similar results were obtained when DWI-ASPECTS was analyzed as a continuous variable (using the Spearman rank correlation for continuous baseline data and Mann–Whitney U test for categorical variables). For each clinical outcome, we calculated the odds ratios (ORs) of outcomes by using as reference the lowest tertile of DWI-ASPECTS for primary outcome and the highest tertile for secondary outcomes. Heterogeneities in the ORs across patients with prior or no use of intravenous rtPA (ie, comparing the group treated by intravenous/intra-arterial therapy and the group treated by intra-arterial therapy only) and across patients treated or not by MET were tested by introducing an interaction term into logistic regression model. Receiver operating characteristics (ROC) curve analysis was performed to estimate the optimal cutoff value for discriminating outcomes. We determined the optimal thresholds by maximizing the Youden index. Using logistic regression analysis, ORs for tertiles and optimal cutoff values of DWI-ASPECTS were further adjusted for type of treatment (including prior intravenous rtPA use and MET) and for other potential confounding factors selected on the basis of their significance with DWI-ASPECTS in univariate analyses (P<0.20).

Finally, to further evaluate the impact of DWI-ASPECTS on the success of reperfusion therapy, we compared outcomes between patients who achieved a complete recanalization and those who did not according to DWI-ASPECTS subgroups (defined using the optimal cutoff value). Comparisons were done using the χ² test (or Fisher exact test when the expected cell frequency was <5) and a Breslow–Day test for homogeneity was done.

Statistical testing was done at a 2-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

**Results**

During a 5-year study period, 285 consecutive AIS patients complicating an acute internal carotid artery or middle cerebral artery occlusion were treated by endovascular therapy. Of these, 232 patients (81%) underwent MRI before recanalization therapy. Twenty-two patients with no or poor-quality DWI were excluded, resulting in a sample size of 210.
patients with a measure of DWI-ASPECTS (Figure I in the online-only Data Supplement). The baseline characteristics of these patients are shown in the Table, overall and according to DWI-ASPECTS tertiles. The median delay from symptom onset to MRI was 105 minutes (IQR, 75–178) and the median DWI-ASPECTS was 7 (IQR, 4–8). A weak but significant negative correlation between MRI delay and DWI-ASPECTS score was found ($r=-0.18$; $P=0.009$). As shown in Figure II in the online-only Data Supplement, there was a strong correlation between DWI-ASPECTS and DWI lesion volume ($r=-0.85$; $P<0.001$). In addition, there was a negative correlation between DWI-ASPECTS and National Institutes of Health Stroke Scale at admission ($r=-0.33$; $P<0.001$). Age, blood pressure values, prior intravenous rtPA use, and internal carotid artery occlusion presence were also associated with DWI-ASPECTS (Table). Fifteen patients did have a median baseline DWI lesion volume above 100 mL; 14 of them did have a DWI-ASPECTS of $\leq 2$.

**DWI-ASPECTS and Clinical Outcomes**

Lower values of DWI-ASPECTS were associated with increased mortality and intracranial hemorrhage rates (Figure 1). As shown in Figure 2, by comparison with patients with a DWI-ASPECTS of $\geq 5$, patients with a DWI-ASPECTS of $<5$ had a lower rate of favorable outcomes and a higher rate of mortality and symptomatic intracranial hemorrhage (sICH). After categorization of DWI-ASPECTS into tertiles, the upper 2 tertiles of DWI-ASPECTS score were both significantly associated with an increased rate of favorable outcomes, while the lower tertile of DWI-ASPECTS was associated with an increased rate of death and sICH. There was no heterogeneity in the association between DWI-ASPECTS with outcomes according to prior use of intravenous rtPA (all $P$ for heterogeneity $>0.36$) or according to MET use (all $P$ for heterogeneity $>0.47$). These relationships remained unchanged in multivariate analysis including potential confounding factors (Figure 2). ROC analysis (Figure 3) showed that DWI-ASPECTS $\geq 5$ was the optimal threshold to predict a favorable functional outcome with an area under the curve (AUC) of 0.69 (95% confidence interval [CI], 0.62–0.76), a sensitivity of 90% (95% CI, 84–96), and a specificity of 38% (95% CI, 29–47). In addition, the optimal DWI-ASPECTS threshold to predict 90-day mortality (AUC, 0.67 [95% CI, 0.59–0.76]; sensitivity, 47% [95% CI, 35–59]; specificity, 85% [95% CI, 78–91]) and sICH (AUC, 0.72 [95% CI, 0.58–0.85]; sensitivity, 65% [95% CI, 42–88]; specificity, 73% [95% CI, 72–84]) was also $<5$. In multivariate analysis, the adjusted OR of favorable outcomes was 4.70 (95% CI, 1.71–12.89) for DWI-ASPECTS $\geq 5$, the adjusted OR of 90-day mortality was 6.80 (95% CI, 2.61–17.70) for DWI-ASPECTS $<5$, and the adjusted OR of intracranial hemorrhage was 8.10 (95% CI, 2.29–28.66) DWI-ASPECTS $<5$ (Figure 2).

**Figure 2.** Impact of diffusion-weighted imaging (DWI) Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on clinical outcomes. DWI-ASPECTS was categorized into 3 groups of similar sample size and was further dichotomized according to the optimal cutoff calculated from receiver operating characteristics curves. Odds ratios (ORs) were calculated using as reference group, the lowest ASPECTS scores for favorable outcomes and the upper ASPECTS scores for death and symptomatic intracranial hemorrhage (sICH). ORs were adjusted for age, admission systolic and diastolic blood pressure, internal carotid artery occlusion, prior use of intravenous thrombolysis, mechanical endovascular therapy, time from symptom onset to MRI, and admission National Institutes of Health Stroke Scale score. CI indicates confidence interval.
Ninety-eight patients (47%) experienced a complete recanalization (TIMI 3) within a median delay from symptom onset of 248 minutes (IQR, 206–290). Patients with TIMI 3 had a higher median DWI-ASPECTS than patients with TIMI 0 to 2 (no or partial recanalization) (7 [IQR, 5–9] versus 6 [IQR, 3–8], *P*=0.001). As shown in Figure 4, the impact of TIMI 3 on clinical outcomes was stronger in patients with DWI-ASPECTS <5 than in patients with DWI-ASPECTS ≥5 (*P*<0.002) for heterogeneity. Favorable outcomes were more frequent in patients with TIMI 3 than with TIMI 0 to 2 in the subgroup with DWI-ASPECTS ≥5 (67% versus 41%, *P*<0.001) as well as in the subgroup with DWI-ASPECTS <5 (50% versus 3%, *P*<0.001).

The median DWI lesion volume measured among the patients with a DWI-ASPECTS of <5 who did recanalize was not different from the DWI lesion volume measured among the nonrecanalizers (75 mL (43–95) and 70 mL (50–105) among the recanalizers (*P*=0.66). The favorable outcome rate in patients with DWI-ASPECTS <5 and TIMI 3 was comparable with the rate observed among patients with DWI-ASPECTS ≥5 and TIMI 0 to 2. The occurrence of a complete recanalization was associated with a decreased mortality rate at 90 days in the subgroup of patients with a DWI-ASPECTS of <5 (25% versus 73%, *P*=0.001) but not among patients with a higher DWI-ASPECTS (17% versus 28%, *P*=0.10). Finally, the sICH rate was 27% in patients DWI-ASPECTS <5 and TIMI 0 to 2, whereas it was lower than 7% in other subgroups (Figure 4). In ROC curve analyses (Figure III in the online-only Data Supplement), DWI-ASPECTS predicted favorable outcomes in patients with TIMI 0 to 2 (AUC=0.76; optimal cutoff point ≥5 with a sensitivity=97% and specificity=45%), but not in patients with TIMI 3 (AUC=0.57).

**Discussion**

Our results suggest that a DWI-ASPECTS of 5 seems to be in our cohort the optimal cutoff to predict functional outcomes in AIS patients eligible for an endovascular treatment. These findings concur with the results of previous studies, showing that a low ASPECTS on CT or MRI is a strong predictor of functional outcomes after intravenous or intra-arterial thrombolysis.5,12,16 As previously shown, our results demonstrate a strong correlation between DWI-ASPECTS and DWI lesion volume quantified by the RApid processing of PerfusIon and Diffusion software.10,13 For example, 14 of the 15 patients with a large infarction on baseline DWI (>100 mL) did have a DWI-ASPECTS of ≤2.23 We have previously reported in the same cohort that DWI lesion volume had a strong impact on the clinical outcome,3 but were unable to identify a predictive volumetric threshold in this current study. Conversely, ROC curve analyses isolated an optimal cutoff of the ordinal DWI-ASPECTS scale associated with patient outcomes. DWI-ASPECTS <5 predicted 90-day mortality and sICH with specificity values, respectively, of 85% and 73%. These relationships were strong, as illustrated by the adjusted ORs, (associated with a DWI-ASPECTS<5), which was 6.74 (95% CI, 2.63–17.28) for 90-day mortality. In addition, a DWI-ASPECTS of ≥5 predicted a favorable functional outcome with a sensitivity value of 90% and was strongly associated with the occurrence of a favorable outcome 5.06 (95% CI, 1.86–13.77). However, its specificity was only 38%, suggesting that a subset of patients with a DWI-ASPECTS of <5 may still experience a favorable outcome.

**Figure 3.** Receiver operating characteristic curves of diffusion-weighted imaging Alberta Stroke Program Early Computed Tomography Score (ASPECTS) for the prediction of favorable outcomes (A), 90-day mortality (B), and symptomatic intracranial hemorrhage (C). AUC indicates area under the curve; and CI, confidence interval.

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The occurrence of a complete recanalization was associated with an increased rate of clinical recovery and a decreased rate of mortality and sICH. Interestingly, the magnitude of this effect was higher in the subgroup of patients with a DWI-ASPECTS of <5 compared with the rate observed in patients with a DWI-ASPECTS of ≥5. ROC curve analyses confirmed that DWI-ASPECTS >5 was the optimal cutoff to predict outcomes overall and in case of an incomplete recanalization while no cutoff could be isolated among the 99 (47%) patients who experienced a complete recanalization. These results do have several implications. First they support the use of DWI-ASPECTS, an ordinal visual scale, as a default measurement of DWI lesion volume in the absence of any available reliable volumetric measurement. Second, they suggest that a DWI-ASPECTS of 5 may outperform the commonly accepted threshold of 7 to select the patient who may still benefit from revascularization therapy.5,12–14 However, despite this improvement, several patients who did experience clinical recovery after reperfusion would have been excluded by these criteria. As an illustration, 16 of the 32 (50%) patients with a DWI-ASPECTS of <5 and 22 of the 37 patients (56%) with a DWI-ASPECTS of <7 did experience a favorable outcome after a complete recanalization. Second, it is plausible that some patients with a significant DWI lesion may still exhibit a large perfusion deficit. Third, in our study patients were scanned after a median delay of 1.7 hours and revascularized 4.1 hours after symptom onset. By comparison, Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2 study patients were scanned 4.1 hours and endovascular procedure started 6.2 hours after symptom onset, while magnetic resonance rescue patients were enrolled after a median delay of 5.2 hours.3,24 The results of both studies suggested that patients with a large ischemic lesion on DWI did not experience a good outcome after reperfusion. Therefore, our results may not be extrapolated to a time window where DWI lesion has demonstrated a critical impact even among recanalizers.9,24,25 Finally, the retrospective and monocentric design of our study has undoubtedly contributed to selection biases.

In conclusion, a DWI-ASPECTS cutoff of 5 seems to be the optimal cutoff to predict the outcome of patients undergoing endovascular therapy within 6 hours of symptom onset. Complete recanalization may still play a role on favorable outcomes in patients with DWI-ASPECTS <5, suggesting that DWI-ASPECTS is a limited tool for endovascular therapy patient eligibility.

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Disclosures
Dr Olivot reports speaker fees and travel expenses from Boehringer Ingelheim. Dr Mazighi reports travel expenses from Boehringer Ingelheim, Covidiem and Bayer. The other authors report no conflicts.
References


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Supplementary Figures

Supplementary Figure I. Study Flow-Chart.

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CTA = computed tomography angiography; CT scan = computed tomography scan; DWI = diffusion-weighted imaging; IA = intra-arterial therapy; ICA = internal carotid artery; IVT = intravenous thrombolysis; MCA = middle cerebral artery; MRA = magnetic resonance angiography; MET = mechanical endovascular therapy; MRI = magnetic resonance imaging.
Supplementary Figure II. Correlation between DWI-ASPECTS and DWI lesion volume

Spearman's rank correlation coefficient, $r = 0.85$ ($p < 0.0001$)

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; DWI = diffusion-weighted imaging.
Supplementary Figure III. Receiver operating characteristic curves of DWI-ASPECTS for the prediction of Favourable Outcome in patients with no or partial recanalization (TIMI 0-2) and in patients with complete recanalization (TIMI 3).