Extent of Hypoattenuation on CT Angiography Source Images Predicts Functional Outcome in Patients With Basilar Artery Occlusion

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Background and Purpose—Quantification of early ischemic changes (EIC) may predict functional outcome in patients with basilar artery occlusion (BAO). We tested the validity of a novel CT score, the posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS).

Methods—Pc-ASPECTS allocates the posterior circulation 10 points. Two points each are subtracted for EIC in midbrain or pons and 1 point each for EIC in left or right thalamus, cerebellum or PCA-territory, respectively. We studied 2 different populations: (1) patients with suspected vertebrobasilar ischemia and (2) patients with BAO. We applied pc-ASPECTS to noncontrast CT (NCCT), CT angiography source images (CTASI), and follow-up image by 3-reader consensus. We calculated sensitivity for ischemic changes and analyzed the predictivity of pc-ASPECTS for independent (modified Rankin Scale [mRS] score ≥2) and favorable (mRS score ≤3) outcome.

Results—Of 130 patients with suspected vertebrobasilar ischemia, 72% (94) had posterior circulation stroke, 8% (10) transient ischemic attack, and 20% (26) nonischemic etiology. Sensitivity for ischemic changes was improved with CTASI compared to NCCT (65% [95% CI, 57% to 73%] versus 46% [95% CI, 37% to 55%], respectively). Pc-ASPECTS score on CTASI but not NCCT predicted functional independence (OR 1.58; P = 0.005 versus 1.22; P = 0.42, respectively). Of 46 patients with BAO, 52% (12/23) with CTASI pc-ASPECTS score ≥8 but only 4% (1/23) with a score <8 had favorable functional outcome (RR 12.1; 95% CI, 1.7 to 84.9). This difference was consistent in 21 patients with angiographic recanalization (RR 7.7; 95% CI, 1.1 to 52.1).

Conclusion—The CTASI pc-ASPECTS score may identify BAO patients unlikely to have a favorable outcome despite recanalization. (Stroke. 2008;39:2485-2490.)

Key Words: stroke ■ acute ■ CT angiography ■ basilar artery ■ posterior cerebral artery stroke ■ stroke ■ ischemic

Acute occlusion of the basilar artery carries high risk of disabling stroke or death.1,2,3 Intravenous (IV) or intraarterial (IA) thrombolysis is frequently initiated to achieve recanalization of the basilar artery.1–4 However, predicting benefit from this therapy is difficult.

In patients with ischemic stroke in the anterior circulation, quantification of early ischemic changes on pretreatment noncontrast CT (NCCT) predicts treatment response to IV and IA thrombolysis.5,6 CT angiography (CTA) is increasingly performed and can be rapidly obtained with minimal delay after NCCT.7,8 Areas of hypoattenuation on CTA source images (CTASI) delineate regions of brain tissue with ischemic damage.8,9 Applied on the Alberta Stroke Program Early CT Score (ASPECTS), CTASI has improved the prediction of final infarct size and clinical outcome compared to NCCT.7

CTA is frequently used in the assessment of patients with suspected basilar artery occlusion and provides excellent information on vascular status.10–12 The diagnostic and prognostic impact of CTASI in posterior circulation ischemia has not been analyzed. The aim of our study was to determine the validity and reliability of a novel CT score, the posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS), in patients with vertebrobasilar ischemia. We
hypothesized that quantification of hypoattenuation on CTASI would predict functional outcome and treatment response in patients with basilar artery occlusion (BAO).

Methods

Patients

We conducted this retrospective cohort study in 2 parts. In part 1, we tested the diagnostic and prognostic value of CTASI in patients with clinically suspected acute vertebrobasilar ischemia. In part 2, we tested the prognostic value of CTASI in patients with acute BAO.

Part 1

We identified patients from a database containing consecutive patients (04/02 to 08/06) who had CTA for suspected acute ischemic stroke or transient ischemic attack (TIA) at Foothills Medical Centre, Calgary. Inclusion criteria were acute coma at presentation, sudden onset decreased level of consciousness without history of seizures, and various symptoms and signs suggesting brain stem, cerebellar, and posterior cerebral artery ischemia (acute onset vertigo, double vision, dysarthria, homonymous hemianopsia, oculomotor, or other cranial nerve signs and crossed brain stem, cerebellar, or bilateral motor signs). Final clinical diagnosis was established by the stroke neurologist at discharge.

Part 2

We analyzed patients with acute BAO who presented to Foothills Medical Centre, Calgary, or Dresden University Stroke Center and had CTASI available for review. Patients in Calgary were identified from the same database as in part 1. In Dresden, patients with BAO were identified from a database containing consecutive discharge summaries (05/01 to 01/06). Diagnosis was based on acute onset of symptoms referable to the posterior circulation and CTA showing complete occlusion at any level of the basilar artery.

For both parts, we included patients if CTA was performed within 24 hours from symptom onset and NCCT-to-CTA time was ≤2 hours. Clinical baseline variables including National Institute of Health Stroke Scale (NIHSS) score and Glasgow Coma scale (GCS) score and treatment regimens are routinely recorded prospectively in the patient record. In cases where these scores were unavailable, they were derived retrospectively.

Functional outcome was recorded prospectively at 3 months in a stroke follow-up clinic in Calgary. Missing 3 months outcomes were imputed from the discharge modified Rankin scale (mRS) score using the last-score-carried-forward principle. For patients with BAO in Dresden, 3 months functional outcomes were derived from telephone interview with the patients or their relatives. This study was approved by the local institutional ethics committee in Calgary under a waiver of consent. Patients with BAO in Dresden were treated under an institutional protocol approved by the local ethics committee.

Imaging

Standard nonhelical NCCT was performed on a multislice CT scanner (GE Medical Systems or Siemens) using 120 kV, 170 mAs with 5-mm slice thickness. Coverage was from skull base to vertex with continuous axial slices parallel to the orbitomeatal line. NCCT was followed by CTA with a helical scan technique on the same scanner. Acquisitions were obtained after single bolus IV contrast injection of 90 to 120 mL nonionic contrast media into an antecubital vein at 3 to 5 mL/s. Imaging was autotriggered by the appearance of contrast media in the ascending aorta. Minimum coverage was from foramen magnum to centrum semiovale with 0.6-mm to 1.0-mm slice thickness. Source images were reconstructed at 1.25-, 2.5-, or 4.0-mm thickness in axial planes at half-thickness intervals.

Follow-up NCCT or MRI were performed as indicated by the treating stroke neurologist. Follow-up imaging had to be performed between day 1 and 7 after symptom onset to be assessed for final infarct extension.

Image Analysis

We developed a posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS). Pc-ASPECTS allots the posterior circulation 10 points (Figure 1). One point each is subtracted for early ischemic changes (EIC) on NCCT or hypoattenuation on CTASI in left or right thalamus, cerebellum, or posterior cerebral artery (PCA) territory, respectively, and 2 points each for EIC (NCCT) or hypoattenuation (CTASI) in any part of the midbrain or pons. A pc-ASPECTS score of 10 indicates absence of visible posterior circulation ischemia, a score of 0 indicates EIC or hypoattenuation in all pc-ASPECTS territories.

We developed the pc-ASPECTS score a priori based on clinical experience and the following findings from previously published literature. The number of lesions in the posterior circulation correlated with fatal outcome in a study of patients without permanent BAO. Locations most frequently associated with death were pons and midbrain.13 In the New England Medical Center Posterior Circulation Registry, the number of territories involved was associated with functional outcome.14

We independently applied pc-ASPECTS to NCCT, CTASI, and follow-up scan by 3-reader consensus. Raters were blinded to all clinical information except presumed vertebrobasilar ischemia (part 1) or BAO on CTA (part 2). NCCT images were evaluated for focal hypodensity or loss of gray–white differentiation. On CTASI, regions of relatively diminished contrast enhancement were scored as abnormal (Figure 2). On follow-up NCCT, we applied pc-ASPECTS to regions of subacute brain infarction; on follow-up MRI we scored hyperintense regions on diffusion-weighted sequences. If

Figure 1. The posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS). From 10 points, 1 or 2 points each (as indicated) are subtracted for early ischemic changes (NCCT) or hypoattenuation (CTASI) in: left or right thalamus, cerebellum or PCA-territory, respectively (1 point); any part of midbrain or pons (2 points). Pc-ASPECTS=10 indicates a normal scan, pc-ASPECTS=0 indicates early ischemic changes (NCCT) or hypoattenuation (CTASI) in all above territories.
patients had follow-up NCCT and MRI, we used the lower pc-ASPECTS score for analysis.

Reliability for pc-ASPECTS on CTASI was assessed within 6 observers of 3 physician groups: neuroradiologists (M.G., P.S.), stroke neurologists trained to read pc-ASPECTS by reading ≥50 CTASI scans (A.M.D., S.B.C.), and stroke neurologists without this training (P.A.B., M.D.H.). Raters were blinded to clinical data and final diagnosis and scored a sample of 20 randomly selected CTAs of patients with suspected vertebrobasilar ischemia (subgroup of study part 1).

In patients with BAO who had digital subtraction angiography (DSA) completed within 24 hours from symptom onset, we rated perfusion of the entire basilar artery with delayed flow or full perfusion with normal basilar artery flow as stated in the neuroradiology report (according to TIMI 2 to 3 flow grades) as basilar artery recanalization.15

Statistical Analysis
Data are reported using standard descriptive statistics. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of NCCT and CTASI for any ischemic change where follow-up images represented the “Gold Standard”. Interrater reliability was assessed using ANOVA to define an intraclass correlation coefficient.

Primary clinical outcome in patients with suspected vertebrobasilar ischemia (part 1) was independent functional outcome (mRS ≤2), in patients with basilar artery occlusion (part 2) favorable functional outcome (mRS ≤3). Secondary outcome was death.

We performed unadjusted univariate analysis to calculate odds ratios (OR) for functional outcomes. A review of the distribution of the mRS scores according to the CTASI pc-ASPECTS scores in patients with BAO suggested that pc-ASPECTS value in 2 categories (≥8 and <8) discriminated favorable functional outcome from unfavourable functional outcome and death. For analysis, we categorized patients into 2 groups (CTASI pc-ASPECTS score ≥8 versus <8). We compared the distributions of the mRS between the pc-ASPECTS categories with the Mann–Whitney U test and calculated unadjusted risk ratios (RR) for the primary and secondary outcomes.
Table 1. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for any Ischemic Change in Patients With Suspected Vertebrobasilar Ischemia (Study Part 1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NCCT</th>
<th>CTASI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.46</td>
<td>0.37–0.55</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.84</td>
<td>0.77–0.90</td>
</tr>
<tr>
<td>PPV</td>
<td>0.79</td>
<td>0.72–0.87</td>
</tr>
<tr>
<td>NPV</td>
<td>0.53</td>
<td>0.44–0.61</td>
</tr>
</tbody>
</table>

Results

Part 1: Patients With Suspected Vertebrobasilar Ischemia

Baseline Data

We identified 130 patients (93 men, 37 women) with clinically suspected vertebrobasilar ischemia who fulfilled inclusion criteria. Median (interquartile range [IQR]) age was 65 (52 to 75) years, baseline NIHSS score 4.5 (1 to 12), baseline GCS score 15 (14 to 15) onset-to-CFA time 5.0 hours (2.7 to 10.4) and NCCT-to-CFA time 0.1 hours (0 to 1.2). The final clinical diagnosis was posterior circulation stroke in 72% (n=94), TIA in 8% (n=10), and nonischemic in 20% (n=26).

Imaging Data

Compared to NCCT, CTASI had higher sensitivity and a trend toward higher NPV for any ischemic change on follow-up image (Table 1). Specificity and PPV were similar for both modalities. In a substudy of 20 randomly selected cases, interrater reliability for the exact pc-ASPECTS score on CTASI among 6 raters of different physician groups was good (intraclass correlation coefficient 0.72; lower 95% CI, 0.54).16

Functional Outcome

At 3 months, 71% (n=92) of patients were functionally independent (mRS ≤2), 18% (n=24) were functionally dependent (mRS 3 to 5), and 11% (n=14) were deceased. In unadjusted univariate analysis, the pc-ASPECTS score on CTASI predicted independent functional outcome (OR 1.6; 95% CI, 1.1 to 2.2) and death (OR 0.6; 95% CI, 0.5 to 0.9).

Part 2: Patients With Basilar Artery Occlusion

Baseline Clinical and Imaging Data

We identified 46 patients (31 men, 15 women) with acute BAO who had CTA within 24 hours from symptom onset. Overall median (IQR) age was 68 years (55.5 to 77.5), baseline NIHSS score 22 (11 to 30), baseline GCS score 8 (4 to 14.5), and onset-to-CFA time 5.0 hours (3.0 to 10.8). Thirty-six patients were treated with acute thrombolytic or mechanical revascularization therapies: 7 patients with IV tPA only, 7 patients with thrombolytic or mechanical IA therapy only, and 22 patients with various combinations of IV (tPA [n=11] or abciximab [n=11]) and IA therapies, respectively.

Twenty-three patients each had a CTASI pc-ASPECTS score ≥8 and <8, respectively. Baseline clinical data according to categorized CTASI pc-ASPECTS groups (≥8 versus <8) are summarized in Table 2. Compared to patients with a CTASI pc-ASPECTS score ≥8, patients with a score <8 had a higher baseline NIHSS score and lower baseline GCS scores (P<0.001 for both).

Table 2. Baseline Characteristics of 46 Patients With BAO (Study Part 2) Categorized by pc-ASPECTS Score on CTASI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTASI pc-ASPECTS</th>
<th>Value</th>
<th>95% CI</th>
<th>Value</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8–10</td>
<td>0–7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td></td>
<td>23</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>69 (50–78)</td>
<td>67 (59–77)</td>
<td>0.376</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>15 (65)</td>
<td>16 (70)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>13 (6–22)</td>
<td>30 (24–34)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>14 (8–15)</td>
<td>5 (4–8)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset-to-CTA (hrs), median (IQR)</td>
<td>5.0 (2.5–12.2)</td>
<td>5.0 (4.0–8.6)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any thrombolysis, n (%)</td>
<td>16 (70)</td>
<td>20 (87)</td>
<td>0.284</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any IV lysis, n (%)</td>
<td>14 (61)</td>
<td>15 (65)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV tPA, n (%)</td>
<td>10 (43)</td>
<td>9 (39)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV abciximab, n (%)</td>
<td>4 (17)</td>
<td>7 (30)</td>
<td>0.491</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any IA therapy, n (%)</td>
<td>14 (61)</td>
<td>15 (65)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset-to-treatment (hrs), median (IQR)</td>
<td>4.1 (3.0–7.3)</td>
<td>5.1 (3.7–8.3)</td>
<td>0.502</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vascular risk factors, n (%)

- Diabetes mellitus | 3 (13) | 8 (35) | 0.165 |
- Arterial hypertension | 20 (87) | 14 (61) | 0.091 |
- Atrial fibrillation | 7 (30) | 7 (30) | 1.000 |
- Known coronary artery disease | 4 (17) | 7 (30) | 1.000 |
- Smoking (any time) | 7 (30) | 6 (26) | 1.000 |
- Hypercholesterolemia | 6 (26) | 5 (22) | 1.000 |

(tPA [n=11] or abciximab [n=11]) and IA therapies, respectively.

Overall at 3 months, 28% (n=13) of patients had a favorable functional outcome (mRS ≤3), 26% (n=12) had an unfavorable functional outcome (mRS 4 to 5), and 46% (n=21) were deceased. As shown in Figure 3, the distribution of the scores on the mRS according to categorized CTASI pc-ASPECTS groups (≥8 versus <8) differed significantly (P<0.001). As shown in Table 3, 52% (12/23) of patients with a CTASI pc-ASPECTS score ≥8 but only 4% (1/23) of patients with a CTASI pc-ASPECTS score <8 had a favorable functional outcome (RR 12.1; 95% CI, 1.7 to 84.9). In contrast, patients with a CTASI pc-ASPECTS score ≥8 were less likely to die (RR 0.4; 95% CI, 0.2 to 0.9).

Patients with a baseline GCS score <8 had a favorable functional outcome. In patients with a baseline GCS score ≥8, 63% (12/19) of patients with a CTASI pc-ASPECTS score ≥8 but only 14% (1/7) of patients with a CTASI pc-ASPECTS score <8 had a favorable functional outcome (Fisher’s exact test, P=0.073).
The overall functional outcome of patients with BAO in our study is comparable to average outcomes reported in previous studies.17,19 Similarly to anterior circulation stroke, CTASI improved the detection of ischemia in the posterior circulation. We have shown that CTASI provide added information in patients with posterior circulation stroke.20 Demonstration of small DWI lesions or a diffusion-perfusion mismatch has been proposed to identify patients with BAO who potentially benefit from thrombolysis.21,22 This concept has not been validated in a larger series of patients. Feasibility of MRI may be limited in these frequently unstable patients.23 Assessment of early ischemic changes on NCCT did not predict recanalization or functional outcome in patients with BAO in previous studies.17,19 Application of pc-ASPECTS could be useful to identify patients with BAO who potentially benefit from IA therapy, thus validating the concept and feasibility of this approach.26 Finally, our analysis does not address the effects of different thrombolytic treatment regimens. These varied broadly in our study, partly secondary to institutional preferences.24

This study describes the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) which quantifies early ischemic changes on NCCT or hypodensity on CTASI in the posterior circulation. We have shown that CTASI provide added information in patients with posterior circulation ischemia. Applied on CTASI, pc-ASPECTS predicted favorable functional outcome and death in patients with basilar artery occlusion. The prognostic value was consistent in patients who had angiographic recanalization. Application of pc-ASPECTS could be useful to identify patients with basilar artery occlusion who potentially benefit from thrombolysis and to homogenize patient cohorts in this study.

**Table 3. Clinical Outcome for CTASI pc-ASPECTS Categories in Patients With BAO (Study Part 2)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTASI pc-ASPECTS</th>
<th>Risk Difference</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, N</td>
<td>8–10</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>mRS ≤3, % (n)</td>
<td>52.2 (12)</td>
<td>4.3 (1)</td>
<td>47.9%</td>
</tr>
<tr>
<td>Death, % (n)</td>
<td>26.1 (6)</td>
<td>65.2 (15)</td>
<td>−39.1%</td>
</tr>
<tr>
<td>Patients with recanalization ≤24 hours, N</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>mRS ≤3, % (n)</td>
<td>70.0 (7)</td>
<td>9.1 (1)</td>
<td>60.9%</td>
</tr>
<tr>
<td>Death, % (n)</td>
<td>10.0 (1)</td>
<td>63.6 (7)</td>
<td>−53.6%</td>
</tr>
</tbody>
</table>

**Outcome With Angiographic Recanalization**

Of 30 patients who had a diagnostic or therapeutic conventional angiography within 24 hours from onset (median [IQR] 6.3 hours [4.3 to 9.3]), DSA demonstrated recanalization of the basilar artery in 21 patients. Of these, 70% (7/10) with a CTASI pc-ASPECTS score ≥8 but only 9% (1/11) with a CTASI pc-ASPECTS score <8 had a favorable functional outcome (RR 7.7; 95% CI, 1.1 to 52.1; Table 3). In contrast, 10% (1/10) of patients with a score ≥8 compared to 64% (7/11) of patients with a score <8 died despite basilar artery recanalization (RR 0.2; 95% CI, 0.02 to 1.1).

**Discussion**

We have shown that quantification of hypodensity on CT angiography source images predicts functional outcome in patients with posterior circulation stroke. Using a systematic approach with a novel CT score, the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS), CTASI improved the detection of ischemia in the posterior circulation. Applied on CTASI, pc-ASPECTS predicted independent functional outcome and death in patients with clinically suspected vertebrobasilar ischemia. In patients with BAO, extensive hypodensity defined by a CTASI pc-ASPECTS score <8 identified patients extremely unlikely to have a favorable functional outcome despite recanalization of the basilar artery.

MRI with diffusion-weighted imaging (DWI) sequences is considered the diagnostic “Gold standard” in patients with posterior circulation stroke.20 Demonstration of small DWI lesions or a diffusion-perfusion mismatch has been proposed to identify patients with BAO who potentially benefit from thrombolysis.21,22 This concept has not been validated in a larger series of patients. Feasibility of MRI may be limited in these frequently unstable patients.23 Assessment of early ischemic changes on NCCT did not predict recanalization or functional outcome in patients with BAO in previous studies.17,19 CTASI provide added information in patients with posterior circulation stroke.20 Demonstration of small DWI lesions or a diffusion-perfusion mismatch has been proposed to identify patients with BAO who potentially benefit from thrombolysis.21,22 This concept has not been validated in a larger series of patients. Feasibility of MRI may be limited in these frequently unstable patients.23 Assessment of early ischemic changes on NCCT did not predict recanalization or functional outcome in patients with BAO in previous studies.17,19 Similarly to anterior circulation stroke, CTASI improved the detection of ischemia in our study.7 Compared to CTASI, perfusion CT (CTP) better delineates the ischemic core and can identify areas of salvageable brain tissue in anterior circulation stroke.24,25 Similar findings in the posterior circulation are conceivable. Comparison of CTA, CTP and multimodal MRI to predict outcome and treatment response in patients with BAO could be subject of future studies.

Our study has limitations. Clinical outcomes were identified retrospectively based on the chart review and will require prospective validation in another cohort. Furthermore, the inter-rater reliability for pc-ASPECTS on CTASI was good (ie, not excellent). For these reasons, we cannot endorse treatment decision making (eg, withhold thrombolytic therapy) based on the CTASI pc-ASPECTS score in patients with BAO. In a recent study, a similarly designed CTASI score correlated with functional outcomes in vertebrobasilar occlusion patients who underwent IA therapy, thus validating the concept and feasibility of this approach.26 Finally, our analysis does not address the effects of different thrombolytic treatment regimens. These varied broadly in our study, partly secondary to institutional preferences.
future trials comparing IV and IA therapy for basilar artery occlusion.

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Disclosures
None.

References
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