The most widely used imaging technique for acute stroke remains noncontrast CT (NCCT). The reliability of early subtle ischemic sign detection in middle cerebral artery territory is improved with experience, clinical history, stroke window width and level, and the use of the Alberta Stroke Program Early CT Score (ASPECTS). NCCT ASPECTS allows a rapid and reliable assessment of stroke extent and has been shown to correlate with final infarct size. Published thresholds exist for noncontrast CT (NCCT) ASPECTS, which may distinguish outcome/complication risk, but early ischemic signs are difficult to detect. We hypothesized that different ASPECTS thresholds exist for CTP parameters versus NCCT and that these may be superior at predicting clinical and radiologic outcome in the acute setting.

**Materials and Methods:** Thirty-six baseline acute stroke NCCT and CTP studies within 3 hours of symptoms were blindly reviewed by 3 neuroradiologists, and ASPECTS were assigned. Treatment response was defined as major neurologic improvement when a ≥8-point National Institutes of Health Stroke Scale improvement at 24 hours occurred. Follow-up NCCT ASPECTS and 90-day modified Rankin score (mRS) were radiologic and clinical reference standards. Receiver operating characteristic curves derived optimal thresholds for outcome.

**Results:** Cerebral blood volume and NCCT ASPECTS had similar radiologic correlations (0.6 and 0.5, respectively) and best predicted infarct size in the absence of major neurologic improvement. A NCCT ASPECT threshold of 7 and a cerebral blood volume threshold of 8 discriminated patients with poor follow-up scans (P < .0002 and P = .0001) and mRS ≤2 (P = .001 and P < .001). Only cerebral blood volume predicted major neurologic improvement (P = .02). Interobserver agreement was substantial (intraclass correlation coefficient, 0.69). Cerebral blood volume ASPECTS sensitivity, specificity, positive predictive value, and negative predictive value for clinical outcome were 60%, 100%, 100%, and 45%, respectively. No patients with cerebral blood volume ASPECTS <8 achieved good clinical outcome.

**Conclusion:** Cerebral blood volume ASPECTS is equivalent to NCCT for predicting radiologic outcome but may have an additional benefit in predicting patients with major neurologic improvement.

**Materials and Methods**
This was a retrospective study of consecutive tissue plasminogen activator (tPA)–treated patients presenting between January and June 2005. Patients were included if they presented with suspected acute stroke within 3 hours of onset, underwent a CT stroke protocol (including CT angiography [CTA] and CTP), were treated with intravenous thrombolysis, and were followed up at 5–7 days. A standard tPA administration regime was used (0.9 mg/kg dose, 10% bolus, 90% continuous infusion for 1 hour). Recanalization data were variably collected because of differences in practice of clinicians and did not exclude the patient from participation. To determine prediction of presentation perfusion parameters with radiologic outcome, we dichotomized patients into 2 groups: those with a major neurologic improvement and those without. Major neurologic improvement was defined in accordance with previous publications, as ≥8-point National Institutes of Health Stroke Scale (NIHSS) improvement at 24 hours after tPA. Major neurologic improvement was used as a surrogate marker of response to treatment on the basis of the following rationale: Secondary analysis by the National Institute of Neurological Disorders and Stroke investigators demonstrated that this magnitude of improvement discriminated between the treatment and placebo group without overlap in the confidence intervals (CIs). This degree of improvement is an independent predictor of good 90-day outcome. Major neurologic improvement has, therefore, been interpreted in this study and others as a marker of treatment efficacy and has been suggested as a surrogate marker for clinical efficacy and a
possible marker of recanalization.\textsuperscript{8,9} The NIHSS was recorded by an experienced stroke neurologist with NIHSS certification. Thirty-nine patients met the criteria and constituted the study group; 3 were subsequently excluded on the basis of suboptimal CTP image quality. NIHSS at presentation, the change in NIHSS at 24 hours after thrombolysis, and 3-month modified Rankin Scale (mRS) scores were recorded. An mRS ≤2 at 3 months was considered a good clinical outcome. Local institutional review board approval was obtained.

**Imaging**

The CT stroke protocol using a 4-section CT scanner (LightSpeed; GE Healthcare, Milwaukee, Wis) comprised pre- and postcontrast head scans from the skull base to the vertex. Imaging parameters were the following: 120 kVp, 400 mAs, 4 × 5 mm collimation, 1 s/rotation, and table speed of 15 mm/rotation. CTP parameters were the following: 45-second cine scanning (80 kVp, 190 mAs), 3- to 5-second delay, injection of 0.5-mL/kg (30–50 mL) iohexol (300 mg/mL; Omnipaque, Nycomed, Princeton, NJ) at a rate of 4 mL/s. CTP studies covered a 20-mm slab with four 5-mm sections carefully positioned to allow visualization of the sections required for ASPECTS scoring from the basal ganglia to the centrum. This was achievable in all patients (Fig 1). CTA covered carotid bifurcations to the vertex with the following parameters: 0.7-mL/kg iohexol (maximum, 90 mL); 5- to 10-second delay; 120 kVp; 270 mAs; 1 s/rotation; 1.25-mm-thick sections; table speed, 3.75 mm/rotation. For each CTP study, a time attenuation curve was made, displaying the change in Hounsfield units for a specified region for the duration of the scanning. Arterial and venous input functions were obtained from the ipsilateral anterior cerebral artery and from the superior sagittal sinus, respectively. CT Perfusion 3 (GE Healthcare) was used to calculate parametric maps of cerebral blood flow and cerebral blood volume by deconvolution of tissue-enhancement curves and arterial time-attenuation curve in 2 × 2 pixel blocks. Mean-transit-time maps were also calculated. Partial volume averaging of the arterial input curve was corrected by using the venous time-attenuation curve.

**Statistical Analysis**

Data were transferred to and analyzed in Statistical Package for the Social Sciences (Version 10; SPSS, Chicago, Ill). Median ASPECTS for the presentation and follow-up NCCT and CTP parameters were compared by using paired \( t \) tests, dichotomizing patients according to recanalization implied by NIHSS improvement as discussed previously. Pearson correlation coefficients were computed between ASPECTS for NCCT, cerebral blood volume, cerebral blood flow, and mean-transit-time maps; and the affected side was recorded. A delay of 1 week between each sequence read was instituted to avoid recall bias. The final NCCT ASPECTS was scored separately by 2 experienced readers without knowledge of previous imaging.

**Results**

There were 18 female and 18 male patients. The median age was 75 years (range, 35–95 years). Median NIHSS was 15
In the absence of NIHSS improvement, cerebral blood volume ASPECTS were 63%, 89%, 94%, and 44%, respectively. Optimal thresholds were determined and are presented in Table 2. Optimal thresholds were determined and are presented in Table 2. Optimal thresholds were determined and are presented in Table 2.

Table 1: Mean ASPECTS values and 95% CIs for differences in ASPECTS at baseline for NCCT and CTP compared with final NCCT ASPECTS

| MNI (n = 7) | NC-CT | CBV | CBF | MTT | Final NC-CT ASPECTS |
|------------|--------|-----|-----|-----|-------------------|
| Mean       | 8.5    | 9   | 5.166667 | 5 | 9 |
| NCCT       | -2.3–1.4NS | 0.06–3.6S | 0.11–3.88S | -2.1–1.7NS |
| CBV        | 0.5–4.3S  | 0.5–4.4S | -1.8–1.9NS | -4.0 to -0.3S |
| CBF        | -1.8–1.9NS | -4.0 to -0.3S |
| MTT        | -4.0 to -0.3S |
| No MNI (n = 29) | 6.8 | 6.5 | 4.0 | 4.0 | 5.4 |
| NCCT       | -0.4–1.1NS | 1.7–4.0S** | S 1.7–4.0S** | 0.6–2.2S |
| CBV        | 1.3–3.6S*** | S 1.4–3.6S*** | 0.07–2.3S |
| CBF        | -1.3–1.4NS | -2.6–0.05NS |
| MTT        | -2.7–0.01NS |

Note:—MNI indicates major neurologic improvement; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; NS, nonsignificant; S, significant (level of significance determined by paired t test, P < .05, or S**, P < .01).

* In patients with MNI, mean CBV and NCCT were not significantly different from mean final NCCT ASPECTS, whereas in the absence of MNI, CBF, and MTT most closely approximated final NCCT ASPECTS.

Table 2: Performance measures of NCCT, CTP, final ASPECTS, and 24-hour NIHSS change for clinical outcome

| Threshold* | Good Outcome, mRS | RR (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | Accuracy |
|------------|-------------------|-------------|----------------------|----------------------|----------|
| NCCT > 7 vs = 7 | 44 (6) | 8.0 (1.1–57.6) | 0.018 | 0.63 (0.4–0.8) | 0.89 (0.47–0.99) | 0.69 |
| CBV ≥ 8 vs < 8 | 45 (0) | 15.4 (0.96–246) | 0.02 | 0.60 (0.4–0.8) | 100 (0.66–100) | 0.69 |
| Final NCCT > 6 vs ≤ 6 | 47 (0) | 17.1 (1.1–273) | 0.001 | 1.00 (0.7–1) | 0.63 (0.44–0.78) | 0.72 |
| CBF/MTT > 5 vs ≤ 5 | 46 (13) | 3.54 (1.1–11.8) | 0.046 | 0.74 (0.5–0.9) | 0.67 (0.35–0.88) | 0.69 |
| Change NIHSS 24 hours ≥ 8 | 86 (10) | 8 (2.7–25.2) | 0.0001 | 0.96 (0.8–1.0) | 0.67 (0.3–0.9) | 0.89 |

Note:—RR indicates relative risk; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time.

* Dichotomized thresholds were determined by ROC analysis. Percentage of patients presenting with good outcome above and below the selected threshold is illustrated. The best early predictors of clinical outcome were 24-hour NIHSS and presentation CBV.

P value was calculated using Fisher exact test.

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knowledge, and has important clinical implications. Major neurologic improvement is defined as NIHSS improvement ≥8 points. It is usually determined by subtracting the post-tPA treatment NIHSS from the presentation score. Major neurologic improvement is considered a marker of treatment response and thought to reflect recanalization. Major neurologic improvement and 24-hour NIHSS are known to strongly discriminate 90-day outcome with an area under the curve for 24-hour NIHSS of 0.71.8-10 In our study, baseline cerebral blood volume ASPECTS was the only parameter to discriminate patients who showed major neurologic improvement. This improvement was also associated with the highest accuracy for prediction of 3-month clinical outcome. Our findings suggest that ASPECTS scoring of cerebral blood volume may provide additional clinical prognostic information not available on NCCT.

In this series, patients with a cerebral blood volume ASPECTS <8 treated with thrombolysis did not have a good clinical outcome. The prognosis is more guarded when the cerebral blood volume is ≥8, with an outcome of mRS ≥2 in only 45% of patients, and is consistent with a recent report of ASPECTS in the Canadian Alteplase for Stroke Effectiveness Study dataset.10 The rate of patients’ achieving mRS ≤3 was 70%, also consistent with the previously mentioned study with 1 false-negative (6%).

CTP has a spatial resolution (1.5 × 1.5 × 3 cm) similar to that of MR perfusion but is limited by spatial coverage, ionizing radiation, and iodinated contrast injection. Despite limited 2-cm coverage on a 4-section scanner, a carefully positioned slab ensures that the ASPECTS were highly correlated with final infarct volume and clinical outcome. A recent study has evaluated the dose obtained at CTP. With commonly used parameters, the dose of 1.1–1.3 mSV is lower than that in NCCT. The dose was recorded for a 64-section scanner over 2.4 cm, which is greater than the 2 cm achievable on a 4-section scanner.11 In clinical practice, we do not repeat the CTP study if movement occurs. It is often possible for the CTP raw data to be edited and the sections with movement to be eliminated. Nevertheless, 3 studies in this consecutive series were uninterpretable. The score is robust and unaffected by scanning angle or interpretation of extent of middle cerebral artery territory.12 In comparison with more elaborate and time-consuming perfusion threshold or volume measures13-17 for determining final infarct size, the ASPECTS scoring of CTP may seem relatively crude. We believe that this simplicity is its strength, and we have shown that CTP ASPECTS correlated well with final NCCT ASPECTS. The extended coverage that a 64-section scanner or other techniques (such as table toggle18 or double injection19) provide, however, may allow greater final infarct volume correlation.

At acute stroke presentation, limited data are available to guide thrombolysis decision-making or to provide prognostic information. Conflicting data exist as to whether patients with early ischemic signs are at higher risk for poor outcome and thrombolysis-related complications, based on NCCT interpretation.20-28 Although there is a general pattern of worse outcome when the hypoattenuation is widespread (ASPECTS >7 or 1/3 middle cerebral arteries19-21), only 3 studies have looked directly for an association between such patients and thrombolysis treatment and have found no such interac-

<8 had an mRS ≤2 at follow-up. However, the prognosis for patients with cerebral blood volume ≥8 was more variable, with only 45% achieving an mRS ≤2. However, 70% achieved an mRS ≤3 with only 1 false-negative (6%) (Table 3). There was no difference between mean transit time and cerebral blood flow for clinical outcome (P = .008 and .009). The sensitivity and specificity were 67% and 70%, respectively.

**Interobserver Agreement**

The ICC for each CT parameter is given in Table 4. Cerebral blood volume agreement was slightly higher than NCCT agreement, but both demonstrated comparable CIs. The ICC for cerebral blood flow and mean transit time was high, with narrow CIs.

**Discussion**

We demonstrated that a cerebral blood volume ASPECTS threshold of 8 discriminates patients who experience major neurologic improvement and have good clinical outcome at 3 months (mRS ≤2). The ability of a cerebral blood volume ASPECTS threshold at presentation to predict major neurologic improvement has not previously been described, to our
tion.25–27 Early ischemic changes are difficult to detect on NCCT, with low interobserver agreement for presence and extent.29,30 Whereas loss of gray-white differentiation is consistent with infarction,31 cerebral swelling may be intermixed, extending the apparent boundary of infarct. Cerebral swelling is associated with a variable and lower stroke risk32 and may account for overestimation of initial infarct size on NCCT. Use of ASPECTS on CTA signal intensity allows easier detection of the infarct extent and provides additional information.33 When compared with NCCT, the median cerebral blood volume ASPECTS was higher and lower in patients with good and bad outcome, respectively. A single previous study in the neurology literature has looked at ASPECTS interpretation of CTP and reported benefit of cerebral blood volume ASPECTS over NCCT.33 However, a lower threshold of 6–7 was used, resulting in a false-negative rate of 13%–18%.

A limitation of this study is the absence of direct evidence of recanalization; however, the purpose was to investigate what prognostic baseline data the CTP study offers independent of other factors. Furthermore, unless continuous transcranial Doppler is used, the exact moment of recanalization and duration of ischemia cannot be known. A post-thrombolysis NIHSS improvement of ≥8 points (major neurologic improvement) was considered a surrogate marker of recanalization, supported by recent publications.6,8 In support of major neurologic improvement as a marker of treatment response, 86% of patients in this series fulfilling these criteria achieved a good outcome. This is similar for published data of outcome in patients with successful recanalization following intra-arterial therapy44 and in agreement with outcomes in other studies using major neurologic improvement.8

In conclusion, a threshold of 8 applied to the ASPECTS interpretation of cerebral blood volume is equivalent to that of NCCT for radiologic outcome and may confer some advantage over NCCT at predicting 24-hour improvement and final clinical outcome. The results of our series indicate that patients treated with thrombolysis presenting with a cerebral blood volume ASPECTS of <8 have a poor outcome.

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Table 3: Relationship between 3-month functional outcome (mRS) and dichotomized baseline CBV ASPECTS

| Baseline CBV ASPECTS | mRS |
|----------------------|-----|
| 0–2 (%)              | 3 (%) |
| 3 (%)                | 4 (%) |
| 4 (%)                | 5 (%) |
| 5 (%)                | 6 (%) |

Note: CBV indicates cerebral blood volume.

Table 4: Interobserver variability

| ICC       | CI        |
|-----------|-----------|
| NCCT      | 0.65      |
| 0.49–0.78 |
| CBF       | 0.69      |
| 0.54–0.81 |
| CBF       | 0.82      |
| 0.72–0.89 |
| MTT       | 0.81      |
| 0.7–0.89  |

Note: CBV indicates cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time.
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