Relative Influence of Capillary Index Score, Revascularization, and Time on Stroke Outcomes From the Interventional Management of Stroke III Trial

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Background and Purpose—Until recently, acute ischemic stroke (AIS) trials have failed to show a benefit of endovascular therapy compared with standard therapy, leading some authors to recommend decreasing the time from ictus to revascularization to improve outcomes. We hypothesize that improving patient selection using the capillary index score (CIS) may also be a useful strategy.

Methods—CIS was calculated, blinded to outcome, from pretreatment diagnostic cerebral angiograms for 78 subjects in the Interventional Management of Stroke III database with internal carotid artery and middle cerebral artery trunk occlusion. The CIS was dichotomized into favorable (fCIS=2 or 3) and poor (pCIS=0 or 1). Outcomes were categorized based on the modified Rankin Scale score at 90 days (0–2 considered a good outcome). Modified thrombolysis in cerebral infarction score 2b or 3 was considered good revascularization. Multivariable logistic regression was performed to relate CIS, time from ictus to revascularization, modified thrombolysis in cerebral infarction score, and National Institue of Health Stroke Scale score to good outcomes.

Results—Only CIS and modified thrombolysis in cerebral infarction scores were correlated with good outcomes (P<0.01). Patients with fCIS and good revascularization achieved 71% modified Rankin Scale ≤2, compared with 13% for patients with pCIS and good revascularization.

Conclusions—In this subset of patients from the Interventional Management of Stroke III Trial, CIS and modified thrombolysis in cerebral infarction were strong predictors of outcome after endovascular reperfusion. Using the CIS to improve patient selection could be a powerful strategy to improve rate of good outcomes in endovascular therapy. A randomized trial is needed.

Key Words: acute ischemic stroke ■ capillary index score ■ collateral ■ outcome ■ revascularization

Patient selection for endovascular treatment (EVT) in acute ischemic stroke (AIS) typically relies on an absolute, but arbitrary, time window. Prior randomized trials showed no benefit of combined intravenous therapy (IVT) and EVT over IVT alone.1,2 Recently, however, a few trials have demonstrated the benefits of EVT.3–5 To further improve the response to EVT, some authors recommend additional decreases in the time from ictus to revascularization (TIR).6 Based on our prior work, we hypothesize that an alternative approach may be to improve patient selection for endovascular clot removal at the time of intra-arterial angiography using the capillary index score (CIS).7,8

The CIS was first introduced in an analysis of the Borgess Medical Center-Acute Ischemic Stroke Registry and is described in detail elsewhere.7 The CIS has since been shown to be a reliable predictor of patients who will achieve a good clinical outcome (GCO) after EVT.7,8 We retrospectively tested the merit of the CIS as a tool for patient selection in those patients from the Interventional Management of Stroke (IMS) III data set with distal internal carotid artery and middle cerebral artery trunk occlusions who underwent Intravenous-Endovascular treatment (IV-EVT).

Materials and Methods
The IMS III trial was a multicenter, double-arm study evaluating clinical outcomes after IV recombinant tissue plasminogen activator alone versus IV recombinant tissue plasminogen activator combined with...
EVT in patients with AIS. The study included subjects aged 18 to 82 years with initiation of IV recombinant tissue plasminogen activator within 3 hours of onset of stroke symptoms and a National Institute of Health Stroke Scale (NIHSS) score of at least 10 points, or 8 to 9 points with large vessel occlusion confirmed by CT angiography, at the onset of IVT.7 Computed tomography angiography was not required, but allowed in centers where it had become a standard of evaluation and management. The publication committee of the IMS III provided access to deidentified databases. The current analysis was exempt from institutional review board review since the data were deidentified.

Pretreatment diagnostic cerebral angiograms from the 200 IMS III subjects with either internal carotid artery or middle cerebral artery trunk occlusions were evaluated to identify subjects meeting the inclusion criteria to accurately ascribe a CIS: (a) all potential collaterals to the ischemic territory were opacified, (b) images, including the venous phase, were available, and (c) no significant motion artifacts were present. These criteria were necessary to allow clear visualization of the capillary blush. Unfortunately, most patients did not have all their potential collaterals studied. Eighty-one subjects met these criteria (40.5%), but 3 of them did not receive EVT based on operator discretion, leaving 78 patients constituting the CIS substudy cohort.

Based on previously established criteria,7 CIS scoring was dichotomized into favorable (CIS=2 or 3) and poor (CIS=0 or 1). Two authors (F.Ai Ali and T.A. Tomsick) blinded to clinical outcome ascribed the CIS and came to unanimous consensus on the final score. Because the CIS scale is relatively simple and differences between scores imply the presence or absence of capillary blush within one third of the ischemic area, consensus was easily achieved.

Demographic evaluation and outcome measures were collected from the IMS III deidentified databases. Parameters related to pretreatment included baseline NIHSS score, time from stroke to onset of IV recombinant tissue plasminogen activator administration, time to onset of EVT, and site of treated target occlusion. Posttreatment parameters included the modified thrombolysis in cerebral infarction (mTICI) score, TIR, and modified Rankin Scale (mRS) score at the closest time point to 90 days. TIR was based on the time of the final angiogram independent of the final mTICI score. For dichotomization of the primary clinical outcome, a 90-day mRS of 2 or less was considered a good outcome. The mTICI score was dichotomized into poor (0, 1, or 2A) or good (2B or 3) revascularization.

**Statistical Analysis**

Statistical analyses were performed to identify parameters correlated with the good outcomes and fCIS. Analyses were conducted using statistical analysis software (Minitab version 16 and Microsoft Excel). Because of concerns related to multiple evaluations of parameters influencing outcome and fCIS increasing the risk of a type I error (false-positive), a conservative P value of 0.01 was used to determine statistical significance. CIS classification, mTICI score classification, sex, occlusion site, and presence of diabetes mellitus were compared with good outcomes based on the mRS score using a χ² analysis. Categories for mTICI score and CIS were also combined to evaluate the relationship with good outcome using a 4x2 Fisher exact test. Sex, site of occlusion, and presence of diabetes mellitus were compared between the fCIS and pCIS subgroups with a χ² analysis. Baseline characteristics (NIHSS, age, systolic and diastolic blood pressure) and treatment characteristics (time from ictus to start of EVT, to start of EVT, and TIR) were compared between the fCIS and pCIS subgroups using t-tests.

Multivariable logistic regression was used to relate the NIHSS score, CIS classification, TIR, and mTICI classification to good outcomes, with goodness of fit established with a Hosmer–Lemeshow test. Multivariable logistic regression was also performed for 3 subgroups of patients: patients in the fCIS substudy cohort, patients with good revascularization (mTICI 2b, 3), and for patients with an fCIS who achieved good revascularization.

**Results**

A favorable CIS was found in 48 of the 78 subjects (62%). No significant differences in baseline NIHSS, time from ictus to IVT, to EVT, TIR, or systolic or diastolic blood pressure were identified between the fCIS and pCIS subgroups (Table 1). The average age for pCIS patients was 71±28 years, compared with 63±14 years for fCIS patients (P=0.011), which did not meet the predefined significance level of P<0.01. No significant differences were found between proportion of patients with fCIS and sex, presence of diabetes mellitus, or occlusion site (Table 2).

From the χ² analyses, both fCIS and successful revascularization were associated with GCO. Specifically, an mRS of 2 or lower was achieved in 23 of the 48 subjects with a fCIS (48%), but only 3 of the 30 subjects (10%) with a pCIS (P<0.001; Table 2). Similarly, of the 39 subjects who achieved mTICI 2b or 3, 19 had a good outcome (49%), compared with only 7 of 39 (18%) subjects with a poor mTICI (P=0.004). Good outcome was not significantly related to occlusion site, sex, or presence of diabetes mellitus. Of the 7 subjects who achieved a GCO with poor revascularization, 6 had a fCIS. For patients with a combination of fCIS and good revascularization, 71% achieved a good outcome versus 25% for patients with fCIS and poor revascularization, 13% for patients with pCIS and good revascularization, and 7% for patients with pCIS and poor revascularization (Table 2). Using the Fisher exact test, the proportion of GCO was significantly greater for the combination of good revascularization and fCIS than for the other 3 combinations (P<0.001; Table 2).

CIS and revascularization were the primary parameters that correlated with good outcomes. For the multivariable logistic regressions including all patients, the CIS and mTICI classification were significantly correlated with GCO (P=0.005; Table 3). For the logistic regression focused on patients who achieved good revascularization, fCIS was correlated with GCO (P=0.009; Table 3). For the fCIS subgroup, only good revascularization was correlated with outcome (P=0.006). For the subgroup fCIS with good revascularization, no parameter was significantly correlated with GCO. TIR was not significantly correlated with GCO for any of the logistic regressions.

**Discussion**

The PROACT II study showed that 22% of patients with ischemic stroke caused by middle cerebral artery trunk occlusion...
In the current study, 62% of the subpopulation of IMS III patients had a fCIS, a higher percentage than identified with the Borgess Medical Center-Acute Ischemic Stroke Registry registry (42%) and the IMS I-II subgroup analysis (46%).

The figure still, however, hovers around 50%, strengthening our previous hypothesis of the 50% barrier—the notion that approximately half of all patients with AIS will have sufficient collaterals to sustain ischemia until revascularization. The percentage of fCIS for a specific patient cohort will deviate slightly from 50% depending on the selection criteria used. If one accepts this notion, we will be challenged to appreciably exceed 50% GCOs when treating all patients for cerebral ischemia because of large vessel occlusion, no matter how we alter our current treatment strategy.

### Stroke Risk Factors, CIS, and Clinical Outcome

None of the known stroke risk factors studied in the current analysis were significantly correlated with outcome or fCIS, although the sample size limits power to detect potential relationships. Patients with pCIS tended to be older than patients with fCIS, but the level did not reach significance because of the conservative P value set for the current study based on multiple comparisons. In previous studies, age was similar for both CIS groups. A larger prospective study is needed to better characterize the relationship between the CIS and the various stroke risk factors.

### CIS, mTICI, and Clinical Outcome

As in our 2 previous analyses,7,8 fCIS and good revascularization based on mTICI 2b or 3 were strongly correlated with good outcomes based on the mRS score. The fact that subjects with a fCIS who achieved good revascularization did significantly better than those without good revascularization (71% versus 25%) strengthens our previous hypothesis that fCIS identifies patients with viable, but ischemic, cerebral tissue. A fCIS seems to identify tissue at risk that can recover, but does not guarantee that the tissue will recover in the absence of successful intervention. The consistency of the current results with our 2 prior studies, despite differences in patient selection criteria, time window, and methods of treatment, promotes the validity of the CIS as a method of patient selection in AIS-EVT.

It is equally important that patients with a pCIS rarely achieved good outcomes, regardless of revascularization status. In the current analysis, only 2 of 15 patients (13%) with pCIS had GCO after good revascularization, versus 1 of 15 (7%) with GCO in the pCIS group without good revascularization. That the percentages (13% and 7%) are similar and below the estimated 22% for untreated occlusion leads us to think that revascularization in those with pCIS and within the time window of the IMS III trial may not improve outcomes for a large majority of patients. Successful revascularization seems to be the best chance for a patient to achieve GCO for those patients with fCIS.

### Time From Ictus to Revascularization and Clinical Outcome

In the current and previous 2 studies5,8 assessing the CIS, times from ictus to IVT and EVT were similar in the fCIS and pCIS
subgroups. Yet /CIS was, in each of these studies, a critical predictor of a GCO. This observation supports the contention that the relationship between TIR and outcome is not direct and linear, but also depends on the robustness of collateral flow. Shorter TIR does not always guarantee better outcome. The logistic multivariable regression did not find a significant correlation between TIR and good outcomes for the whole group of patients or the subgroups with the higher chance of a good outcome (CIS subgroup, patients with good revascularization, and /CIS patients with good revascularization). CIS and good revascularization were correlated with good outcomes.

Our results support the hypothesis that selecting patients with larger artery occlusions and with /CIS for safe and rapid revascularization may be an effective strategy to maximize the benefit and minimize the risk of EVT. A prospective randomized study is still needed to test this hypothesis.

In a recent IMS III trial publication focusing on the relationship between TIR and outcome in a cohort who reperfused to mTICI ≥2b, six collateral flow as quantified by the American Society of Interventional and Therapeutic Neuroradiology and Society of Interventional Radiology (ASITN/SIR) scale was significantly related to clinical outcome in univariate analyses but fell out in a multivariable model, although time to reperfusion remained significant. Several methodological factors likely underlie this difference between the previous and current analysis. In the prior study, the emphasis was on determining the influence of time to successful reperfusion on outcomes and the model did not include participants who did not reperfuse. The current study treated reperfusion status as a variable that was related to outcomes along with the CIS and TIR. The current study did include a subgroup analysis that included 39 patients with good reperfusion (TICI 2b-3) and found no significant correlation between TIR and outcome. However, the small sample size provides limited power to evaluate TIR. Finally, the current report used the CIS instead of the ASITN/SIR to measure collateral flow and angiographic perfusion, and the differences between the 2 systems have not yet been studied. Challenging the concept of an absolute time window from ictus to treatment is a provocative thought and may extend the treatment window in those patients with /CIS. Support for this concept from previous studies includes a documented lack of correlation between infarct size and time from ictus and excellent GCOs in patients whose treatment window exceeded 18 hours. These results reflect, in our opinion, the presence of robust collaterals in the patient population way beyond the traditional treatment time windows.

We think that the relationship between TIR and clinical outcome in AIS may be logarithmic rather than linear. In patients with poor collaterals (pCIS subgroup), the time to revascularization needed before irreversible ischemia occurs may not be clinically attainable, whereas patients with good collaterals (fCIS subgroup) have a much more gradual decrease in the probability of GCO over time. This hypothesis needs to be tested in a prospective trial and, if proven to be true, would have 2 significant impacts on the indication for EVT. First, treatment may be effective beyond a time window of 6 hours in people with fCIS. Second, costly and potentially harmful treatment could be eliminated in patients with pCIS if it is shown that EVT in these patients does not provide better outcomes than standard medical therapy.

Conclusions

The presence of a /CIS is a major factor in obtaining a GCO in AIS patients treated with EVT and is limited to approximately 50% to 60% of unselected patients: the 50% barrier. Successful revascularization is still needed. EVT outcomes in the setting of pCIS may be no better than no EVT overall. A prospective trial to address the use of EVT in patients with pCIS in early treatment and /CIS outside of the traditional time window is needed.

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Disclosures

Dr Liebeskind has served as a consultant for Covidien and Stryker. Furthermore, the University of California holds a patent on retriever devices for stroke at the time of this work. The University of Cincinnati, Department of Neurology, receives financial support from Genetech for Dr Broderick’s research roles (Executive Committee of a Study of the Efficacy and Safety of Activase [Alteplase] in Patients With Mild Stroke Trial). Dr Broderick has also received materials and supplies from Genentech (study medication for Interventional Management of Stroke III), EKOS Corp, Cordis Neugrovascular, and Concentric Inc (study catheter devices for Interventional Management of Stroke III) and support for travel from Boehringer Ingelheim. Dr Tomsick served as an interventional primary investigator on the National Institutes of Health National Institute of Neurological Disorders and Stroke grant U01NS052220 with his salary from National Institute of Health. The other authors report no conflicts.

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