Capillary Index Score in the Interventional Management of Stroke Trials I and II

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Background and Purpose—The Capillary Index Score (CIS) is a simple angiography-based scale for assessing viable tissue in the ischemic territory. We retrospectively applied it to Interventional Management of Stroke (IMS) trials I and II to evaluate the predictive value for good outcomes.

Methods—CIS was calculated from pretreatment diagnostic cerebral angiograms blinded to outcome. IMS I and II diagnostic cerebral angiogram images of sufficient quality were reviewed and CIS calculated for treated subjects with internal carotid artery or M1 occlusion. CIS scoring (0–3) was dichotomized into favorable (f CIS; 2 or 3) and poor (p CIS; 0 or 1). Modified thrombolysis in cerebral infarction score 2b or 3 was considered good revascularization. CIS and modified thrombolysis in cerebral infarction scores were compared with good outcome, defined as modified Rankin Scale score ≤2 at 90 days.

Results—Twenty-eight of 161 subjects met the inclusion criteria. Thirteen (46%) had f CIS. Good clinical outcome was significantly different between the 2 CIS groups (62% for f CIS versus 7% for p CIS; β=0.004). Good reperfusion correlated to good outcome (β=0.04). No significant differences in time to intravenous or intra-arterial treatment were identified between f CIS and p CIS groups (β>0.25).

Conclusions—A f CIS was found in ≥50% of subjects and was a virtual prerequisite for good outcome in this study subgroup of IMS I and II. We call this the 50% barrier. (Stroke. 2014;45:1999-2003.)

Key Words: collateral circulation — diagnostic imaging — diagnostic techniques, neurological — stroke, acute

The Capillary Index Score (CIS) has been proposed as a metric to identify patients with acute ischemic stroke who have sufficient collateral blood flow for good functional outcomes after good revascularization. The CIS is a simple, 4-point scale ranging from 0 (no angiographic capillary blush) to 3 (the whole ischemic area exhibits capillary blush) developed from the Borgess Medical Center—Acute Ischemic Stroke (BMC-AIS) Registry of patients treated with endovascular revascularization. Capillary blush serves as a marker of residual viable tissue, with absence implying irreversible ischemia. Favorable CIS (f CIS) was found to be a prerequisite for a good clinical outcome, defined as a modified Rankin Scale (mRS) score ≤2 at 90 days. In the original registry, a f CIS was identified in 42% of subjects, suggesting a limitation to potential clinical benefit, or a ceiling effect, of intra-arterial treatment for acute ischemic stroke (IAT-AIS). Because the BMC-AIC Registry population was similar to the general white population, these results may be generalizable, indicating that timely revascularization cannot produce a good functional outcome for ≥50% of patients presenting with AIS (the 50% barrier). To further evaluate the predictive value of the CIS in patient inclusion/exclusion for IAT-AIS and to test the proposed 50% barrier, we retrospectively evaluated the CIS from 2 multicenter, international clinical trials, the Interventional Management of Stroke (IMS) I and II.2,3

Methods

The IMS I and II trials were multicenter, single-arm, pilot studies characterizing outcomes after intravenous treatment (IVT) combined with IAT after ischemic stroke. The studies included subjects aged 18–80 years with initiation of intravenous tissue plasminogen activator <3 hours of onset of stroke symptoms and a National Institutes of Health Stroke Scale (NIHSS) score ≥10 points at the onset of IVT.2,3 Access to deidentified databases was provided by the publication committees of the IMS I and II series. Because of evaluation of previously collected data without subject identifiers, the current analysis was exempt from institutional review board review, although all subjects had provided informed consent for participation in each trial and subsequent analyses.

Pretreatment diagnostic cerebral angiograms (DCAs) from the 161 subjects enrolled in these series were evaluated to identify subjects meeting the inclusion criteria: intracranial internal carotid artery or middle cerebral artery trunk (M1) occlusion; all potential collaterals to the ischemic area injected; delayed images available including the venous phase; and no significant motion artifacts. These criteria allowed for clear visualization of the capillary blush. Thirty-one subjects met these criteria, of which 28 received IAT and comprise the analysis population.
The ischemic area was defined as the area lacking antegrade flow with blood supplied in a retrograde fashion through the pial collaterals. The CIS was calculated from anterior-posterior images after dividing the ischemic area into 3 equal segments (Figure 1). One point was awarded for each segment of identifiable capillary blush. A CIS=0 (no staining) implies no viable tissue in the ischemic area, whereas a score of 3 implies that essentially all tissues may be salvageable. The anterior-posterior images allow distinction between the left and right hemispheres. Based on previous findings, CIS scoring was dichotomized into f CIS (score=2 or 3) and poor CIS (p CIS; score=0 or 1). Three reviewers blinded to all other information simultaneously measured 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 information including age and sex and outcome measures were collected from the IMS I and II deidentified databases. Parameters relating to pre-IAT treatment included site of occlusion, time from stroke to onset of intravenous tissue plasminogen activator administration, time to onset of IAT, and baseline NIHSS score. Post-treatment parameters included the modified thrombolysis in cerebral infarction (mTICI) score, cerebral infarction volume from follow-up computed tomographic scan (Cheshire software, Hayden Image Processing Group, Boulder, CO), and 90-day mRS score. For dichotomization of the primary clinical outcome, a 90-day mRS score of 0 to 2 was considered a good outcome. Other dichotomized parameters included mTICI score (poor=0, 1, or 2a; good=2b or 3) and occlusion site (internal carotid artery versus middle cerebral artery).

Statistical analysis focused on identifying parameters correlated with the mRS score and the CIS. The dichotomized data on CIS and mTICI score were compared with dichotomized clinical outcomes based on the 90-day mRS score ≤2 using the Fisher exact test. Stepwise multivariable linear regression analyses were used to relate infarction volume, time to IVT, time to IAT, NIHSS score, CIS, and mTICI score to mRS score. Only parameters that significantly (P<0.05) contributed to the regression were retained for subsequent analysis. Relationships between CIS and other parameters were also evaluated. Proportions of men and women and good and bad mTICI scores were compared with the f CIS and p CIS groups with a Fisher exact test or with a χ² analysis if the sample size was suitable. Tests were used to compare ages, mRS scores, NIHSS scores, infarction volumes, intravenous times, and intra-arterial times between subjects in the f CIS and p CIS groups. Analyses were conducted using a variety of statistical analyses programs (IBM SPSS Statistics version 20, Minitab version 16, and Microsoft Excel).

Results

Infarction volume and mRS scores were the parameters most strongly associated with CIS. No significant differences in age, baseline NIHSS, and time to IVT or IAT were identified between the f CIS and p CIS groups (P>0.25; Table 1). Proportions related to mTICI score, occlusion site, and sex also did not vary significantly between the f CIS and p CIS groups (P>0.25; Table 2). Mean infarction volume was 60,000±47,000 mm³ for the f CIS group compared with 121,000±72,000 mm³ for the p CIS group (P=0.02). Mean mRS score was 2.8±2.4 for the f CIS group compared with 4.6±1.1 for the p CIS group (P=0.01).

The primary parameters associated with a good outcome were a f CIS and successful reperfusion. A f CIS was identified in 13 of 28 subjects. An mRS score ≤2 was achieved in 8 (62%) of those subjects (Table 2). Only 1 of 15 subjects (7%) with a p CIS had a good outcome, but nevertheless with a relatively large infarction volume (100,000 mm³). Ten subjects achieved mTICI 2b/3 reperfusion, with 6 reaching a mRS 0 to 2, whereas 3 of 18 subjects with a poor mTICI score had a good clinical outcome, all with CIS=2 (f CIS). Three with a good outcome were from a total of 8 subjects with f CIS and poor reperfusion (38%; Table 3). All 5 subjects who presented with f CIS and achieved good reperfusion had a good outcome (100%). The rates of good clinical outcome were significantly related to f CIS (P=0.004) and good mTICI score (P=0.04). Rates of good outcome were not significantly related to dichotomized parameters along the level of significance from comparisons.

| Table 1. Comparisons Between f CIS and p CIS Groups for Continuous Data |
|----------------------|-----------------|----------------|
|                     | f CIS           | p CIS          |
| Age, y              | 61±13           | 63±13          | 0.66 |
| NIHSS score         | 19±4e3          | 20±3           | 0.32 |
| Time to IVT, min    | 120±36          | 133±22         | 0.26 |
| Time to IAT, min    | 218±41          | 218±40         | 0.98 |
| Infarction volume, cm³ | 60±47   | 121±72         | 0.02*|
| mRS score           | 2.8±2.4         | 4.6±1.1        | 0.01*|

CIS indicates Capillary Index Score; f CIS, favorable CIS (2 or 3); IAT, intra-arterial treatment; IVT, intravenous treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and p CIS, poor CIS (0 or 1).

*Indicates a significant difference.

Table 2. Proportions of Subjects With Good Outcomes (mRS Score ≤2) and a Favorable CIS for Dichotomized Parameters Along With the Level of Significance From Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Good mRS/ Total</th>
<th>P Value</th>
<th>f CIS/Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p: 0 or 1</td>
<td>1/15 (7%)</td>
<td>0.004*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f: 2 or 3</td>
<td>8/13 (62%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>mTICI* score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0, 1, or 2a</td>
<td>3/18 (17%)</td>
<td>0.04*</td>
<td>8/18 (44%)</td>
<td>1</td>
</tr>
<tr>
<td>2b or 3†</td>
<td>6/10 (60%)</td>
<td>5/10 (50%)</td>
<td></td>
<td></td>
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<tr>
<td>Occlusion site</td>
<td></td>
<td></td>
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<tr>
<td>ICA</td>
<td>2/12 (17%)</td>
<td>0.22</td>
<td>4/12 (33%)</td>
<td>0.28</td>
</tr>
<tr>
<td>MCA</td>
<td>7/16 (44%)</td>
<td>9/16 (56%)</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>6/15 (40%)</td>
<td>0.43</td>
<td>7/15 (47%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Female</td>
<td>3/13 (23%)</td>
<td>6/13 (46%)</td>
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</tbody>
</table>

CIS indicates Capillary Index Score; f, favorable; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction; and p, poor.

*Indicates a significant difference.

†2b or 3 is considered good revascularization.
occlusion site or sex (P > 0.2). Regression analyses did not find significant relationships between outcome and time to IVT or IAT (P > 0.5; \( r^2 < 0.02 \) for regressions). Stepwise multivariable linear regression indicated that only CIS and mTICI score were significantly correlated with mRS score (P < 0.03). The adjusted \( r^2 \) from multivariable linear regression indicated that the CIS and mTICI score combined to account for 41% of the total variation in the mRS over the study population. The standardized \( \beta \)-coefficients were nearly identical for the CIS and mTICI score (–0.54 for CIS and –0.53 for mTICI score), with a variance inflation factor of 1.04, indicating that the influence on mRS score is similar for the 2 parameters with minimal interdependence.

### Discussion

The current analysis identified the CIS and mTICI score as the primary parameters contributing to good clinical outcomes in this cohort of IMS I and II trials. No significant relationship was established between mTICI score and CIS, indicating that these parameters contribute independently to the likelihood of a good outcome. A previous study based on the BMC-AIS Registry also identified CIS and reperfusion as parameters influencing good outcomes.\(^1\) Neither study showed a significant relationship between time from ictus and CIS, suggesting that early treatment cannot overcome irreversible ischemia for some patients. The current analysis showed no significant association between good clinical outcome and time to intravenous tissue plasminogen activator treatment or IAT, but significant associations were found between clinical outcome and CIS and mTICI scores. The current results, along with those from the BMC-AIS Registry, support the value of the CIS for identifying salvageable tissue. The rates of good clinical outcome for the \( f \) CIS and \( p \) CIS groups were 62% and 7%, respectively, for the current study, compared with 55% and 0%, respectively, for the BMC-AIS Registry. The single exception to a direct relationship of \( f \) CIS to mRS \( \geq 2 \) had a large infarction on follow-up computed tomography (100 000 mm\(^3\)). The overall rate of good outcomes for this cohort of patients was 32%, compared with 31% of all patients from the IMS I and II databases with T or M1 occlusions.\(^5\)

A \( f \) CIS seems to identify viable tissue, but does not seem to guarantee recovery without successful intervention. All 5 subjects with a \( f \) CIS and successful reperfusion had a good outcome (100%), compared with 3 of 8 (38%) subjects with a \( f \) CIS but unsatisfactory reperfusion. Only 1 of the 5 subjects with a \( p \) CIS and successful reperfusion (mTICI 2b) had a good outcome. Although the data do not exclude good outcomes for some patients with \( f \) CIS without treatment, revascularization still seems to provide the best chance for a good outcome in these patients.

Futile recanalization related to treating subjects with poor collaterals (\( p \) CIS) beyond \( t = 1 \) hour after onset of symptoms is a concept that overrides any other conventional understanding of optimal treatment based on patient-specific characteristics or comorbidities. This finding is consistent with a primate model showing that complete reperfusion \( <1 \) to 2 hours from onset of occlusion salvaged only \( \approx 50\% \) of ischemic brain.\(^6\) Although this concept needs verification from a larger prospective clinical trial, if proven, it will lead to substantial changes in the IAT-AIS paradigm. Reperfusion in subjects with \( p \) CIS can also be harmful because reperfusing nonviable tissue could increase the hemorrhagic transformation and vasogenic edema with harmful effects on the residual normal cerebral tissue.

### The \( f \) CIS and the 50% Barrier

The current results and those of the previous evaluation of the CIS\(^1\) imply that a \( f \) CIS is a virtual prerequisite for a good clinical outcome. Agreement between the BMC-AIS Registry\(^1\) and IMS I and II trials concerning the percentage of \( f \) CIS (42% and 46%, respectively), despite differences in methods and time to treatment, strengthen the hypothesis that approximately half of patients do not have sufficiently robust collaterals to sustain ischemia until reperfusion (the 50% barrier). Poor collaterals may account for a success rate of only \( \approx 60\% \) for patients without large vessel occlusion on DCA after intravenous tissue plasminogen activator in IMS I and II (T.A. Tomsick, unpublished data, 2013) and IMS III.\(^7\) Treating all who exhibit large vessel occlusion at DCA is unlikely to provide a significantly higher percentage of good outcomes, further pointing to a ceiling effect for good outcomes in patients with IAT-AIS.

No significant relationships were established between \( f \) CIS and age, sex, occlusion site, time to IVT, or time to IAT, although these comparisons were limited by a small sample size. Based on the effect size noted for the current study, >150 patients would be needed to evaluate the relationship between CIS categorization and time to IVT with a power of 0.8. Similarly, no significant relationships with age or time to reperfusion were noted in the BMC-AIS.\(^1\) With recent reports identifying genes thought to be responsible for poor versus good pial collaterals in mice,\(^4\) the presence of a similar gene in humans is plausible. A trial to search for such a gene is ongoing (Genetic Determinants of Collateral Status in Stroke [GENEDCSS] trial).

### Relationship Between Time and Ischemia: Linear Versus Logarithmic

The data from IMS I and II and BMC-AIS suggest no relationship between CIS and time from ictus. In other words, the CIS of a patient presenting <2 hours of ictus is not necessarily more favorable than the CIS of a patient presenting at 5 hours. Time from ictus to DCA was similar for the \( f \) CIS and \( p \) CIS groups for both the BMC-AIS Registry and current data, and the percentage of subjects with \( f \) CIS was similar for the 2 studies despite the current study only including patients presenting <3 hours of ictus, as opposed to 6 hours for the BMC-AIS Registry.
These data suggest that the proportion of f CIS remains relatively stable ≤6 hours. Previous trials demonstrate a decrease in %mRS 0 to 2 between 3 and 6 hours. Subjects in IMS I and II and in a pre-IMS registry with intra-arterial therapy initiated <3 hours demonstrated >60% good outcomes. Trial subjects with angiograms but no treatable occlusion recovered similarly. Subjects with M1 or M2 occlusion in Prolyse in Acute Cerebral Thromboembolism (PROACT) II achieved 40% mRS 0 to 2 with treatment initiated at mean 5.3 hours, and control subjects achieved 25% good outcomes. Control subject in Mechanical Embolus Removal in Cerebral Ischemia (MERCI) recovered proportionately less well than treated subjects in PROACT II. The ≤20% decrease in proportion of good outcome >2.3 hours from IMS I and II to PROACT II may be attributed to different treatment methods or individual subjects’ ability to maintain collateral viability over time. This ≤50% per hour difference is not applicable to each subject. We hypothesize that those with greater collaterals and higher CIS show less decrease in %mRS 0 to 2 with time than those with a lower CIS. Other authors have demonstrated a statistically significant decrease in the odds ratio of mRS 0 to 2 outcomes within the IMS studies with increasing time from ictus to reperfusion (≤6 hours), also suggesting a linear relationship between good outcomes and time from ictus to reperfusion.

The current data suggest that the decrease in percentage of good outcomes and stable percentage of f CIS are not consistent with a linear relationship between time from ictus and proportion of patients with potentially good outcomes (Figure 2). We do know that a time limit exists before brain tissue becomes irreversibly damaged for a specific patient, depending on residual cerebral blood flow (rCBF). To reconcile this observation, we propose that the linear relationship of time to outcome is a subset of the overall relationship when all AIS patients are taken into account. Analysis of IMS III data regarding odds ratios of good outcomes in CIS 0 to 1 versus CIS 2 to 3 versus time will be of interest in this regard.

When examining the entire population of patients with AIS, the rCBF value of some will be so low that they experience irreversible ischemia within an hour to 2 of ictus (≈50% of all patients, the 50% barrier). These patients are seldom enrolled in studies because of evidence of ischemia on diagnostic imaging or typically do poorly if they are enrolled. A second group of patients are hypothesized to present with intermediate rCBF and will demonstrate a gradual decrease in reversible ischemia with time. A third group of patients with a higher rCBF, but still below the 23 mL/100 g per min threshold established previously, will exhibit a more asymptotic, flat curve (Figure 2), with many typically excluded from studies or treatment because of the artificial time window. Combining these 3 groups, the relationship between time from ictus and reversible ischemia will resemble a more logarithmic function. This logarithmic, rather than linear, fit of time from ictus versus reversible ischemia was actually alluded to in the empirical data available on cerebral ischemia in primates by Jones et al.

When examining the entire population of patients with AIS, the rCBF value of some will be so low that they experience irreversible ischemia within an hour to 2 of ictus (≈50% of all patients, the 50% barrier). These patients are seldom enrolled in studies because of evidence of ischemia on diagnostic imaging.
to measures from perfusion MRI, no other imaging modality currently provides a similar threshold for patient selection.

Conclusions
Although time is brain, our data suggest a logarithmic, rather than linear, relationship. During the traditional time window for IAT-AIS, about 50% of patients may have already sustained irreversible damage before treatment (the 50% barrier). Poor patient selection may explain why the recent IMS III trial and other studies failed to show efficacy of IAT-AIS. Using the CIS for patient selection in future trials should demonstrate the efficacy of IAT-AIS. A large, prospective, multicenter trial is needed.

Acknowledgments
We acknowledge the contribution of Danielle Filipkowski, M.S., in the preparation of the article.

Sources of Funding
Interventional Management of Stroke I and II were funded by the National Institute of Neurological Diseases and Stroke (#NS39160). The other authors report no conflicts.

Disclosures
Dr. Broderick has received compensation for research activities from Genentech; materials and supplies from EKOS, Codman, and Concentric; and support for travel from Boehringer Ingelheim. Dr. Gebel serves as an expert witness related to stroke treatment. Dr. Tomsick serves as an interventional primary investigator on the National Institutes of Health National Institute of Neurological Disorders and Stroke grant U01NS052220. The other authors report no conflicts.

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Stroke. 2014;45:1999-2003; originally published online May 22, 2014;
doi: 10.1161/STROKEAHA.114.005304

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/7/1999

An erratum has been published regarding this article. Please see the attached page for:
/content/45/7/e137.full.pdf

Figures 2 and 3 were replaced together with their legends.

Figure 2 legend read: Theoretical relationship between good outcomes and time. The 50% barrier is caused by a decline in residual cerebral blood flow so steep that early treatment cannot reverse tissue damage. Group 1 denotes patients rarely enrolled in studies because of early signs of irreversible ischemia; Group 2 denotes patient population in most intra-arterial treatment for acute ischemic stroke trials; Group 3 denotes patients excluded from most studies because of artificial time window. MCA indicates middle cerebral artery.

Figure 2 now reads:

Outcome versus time. Theoretical relationship between good outcomes and time. The 50% barrier is caused by a decline in residual cerebral blood flow so steep that ~50% of patients cannot be treated fast enough to prevent irreversible ischemia (due to lack of sufficient collaterals). Time to treatment is irrelevant for these patients. MCA indicates middle cerebral artery.

Figure 3 legend read:

Logarithmic time curve: infarction threshold distinguishing between reversible and irreversible ischemia as a function of residual cerebral blood flow (rCBF) and time from ictus. The vertical lines are an approximation and have not yet been validated.

Figure 3 now reads:

The logarithmic relationship between time to irreversible ischemia and residual cerebral blood flow (rCBF). The overall relationship between time from ictus and irreversible ischemia is not a linear but rather a logarithmic one. The curve consists of three sections, each corresponding to a group of patients. Group I patients experience early irreversible ischemia (50% barrier) and are rarely enrolled in IAT-AIS studies. Group 2 are those in most trials. Those in Group 3 are excluded from most studies due to an artificial time window. MCA indicates middle cerebral artery. Adapted from Jones et al with permission from the publisher. Copyright © 1981, American Association of Neurological Surgeons. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

The authors apologize for this error.

These corrections have been made to the online and print version of the article.