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Relative Influence of Capillary Index Score, Revascularization and Time on Stroke Outcomes from the IMS III Trial

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Abstract

Background and Purpose—Until recently, acute ischemic stroke (AIS) trials have failed to show a benefit of endovascular therapy (EVT) compared to standard therapy, leading some authors to recommend decreasing the time from ictus to revascularization (TIR) 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 pre-treatment diagnostic cerebral angiograms for 78 subjects in the Interventional Management of Stroke (IMS) III database with internal carotid artery (ICA) and middle cerebral artery trunk (M1) occlusion. The CIS was dichotomized into favorable (*f*CIS = 2 or 3) and poor (*p*CIS = 0 or 1). Outcomes were categorized based on the modified Rankin Scale (mRS) score at 90-days (0 to 2 considered a good outcome). Modified thrombolysis in cerebral infarction (mTICI) score 2b or 3 was considered good revascularization. Multivariable logistic regression was performed to relate CIS, TIR, mTICI score, and NIH Stroke Scale score to good outcomes.

Results—Only CIS and mTICI score were correlated with good outcomes ($p < 0.01$). Patients with *f*CIS and good revascularization achieved 71% mRS ≤ 2, compared to 13% for patients with *p*CIS and good revascularization.

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Conflict of Interest/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 Neurovascular 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 NIH. No other authors have any conflicts of interest related to this study.

Conclusions—In this subset of patients from the IMS III Trial, CIS and mTICI 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 EVT. A randomized trial is needed.

Clinical Trial Registration: www.clinicaltrials.gov. Unique identifier: NCT00359424

Keywords

ischemic stroke; revascularization; outcome; collateral; capillary index score; 50% barrier

Introduction

Patient selection for endovascular treatment (EVT) in acute ischemic stroke (AIS) typically relies upon 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 Capillary Index Score (CIS) was first introduced in an analysis of the Borgess Medical Center-Acute Ischemic Stroke Registry (BMC-AIS) 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) following EVT [7, 8]. We retrospectively tested the merit of the CIS as a tool for patient selection in those patients from the IMS III dataset with distal internal carotid artery (ICA) and middle cerebral artery trunk (M1) occlusions who underwent Intravenous-Endovascular treatment (IV-EVT).

Materials and Methods

The IMS III trial was a multicenter, double-arm study evaluating clinical outcomes following IV recombinant tissue plasminogen activator (rtPA) alone versus IV rtPA combined with EVT in patients with acute ischemic stroke. The study included subjects aged 18 through 82 years with initiation of IV rtPA within 3 hours of onset of stroke symptoms and an NIH 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 [1]. CT angiography (CTA) 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 de-identified databases. The current analysis was exempt from IRB review since the data were de-identified.

Pre-treatment diagnostic cerebral angiograms (DCA) from the 200 IMS III subjects with either ICA or M1 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 (*f*CIS = 2 or 3) and poor (*p*CIS = 0 or 1). Two authors (FAA and TT) blinded to clinical outcome ascribed the CIS and came to unanimous consensus on the final score. Since 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 de-identified databases. Parameters related to pre-EVT treatment included baseline NIHSS score, time from stroke to onset of IV rtPA administration, time to onset of EVT, and site of treated target occlusion. Post-treatment parameters included the modified thrombolysis in cerebral infarction (mTICI) score, time from ictus to revascularization (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 ≤ 2 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 *f*CIS. Analyses were conducted using statistical analysis software (Minitab version 16 and Microsoft Excel). Due to concerns related to multiple evaluations of parameters influencing outcome and *f*CIS 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 were compared to good outcomes based on the mRS score using a χ^2 analysis. Categories for mTICI score and CIS were also combined to evaluate the relationship with good outcome using a 4 × 2 Fisher's exact test. Sex, site of occlusion, and presence of diabetes were also compared between the *f*CIS and *p*CIS subgroups with a χ^2 analysis. Baseline characteristics (NIHSS, age, systolic and diastolic blood pressure) and treatment characteristics (time from ictus to start of IVT, to start of EVT, and TIR) were compared between the *f*CIS and *p*CIS 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 three subgroups of patients: patients in the *f*CIS substudy cohort, patients with good revascularization (mTICI 2b, 3), and for patients with a *f*CIS 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 *f*CIS and *p*CIS subgroups (Table 1). The average age for *p*CIS patients was 71 ± 8 years, compared to 63 ± 14 years for *f*CIS patients ($p = 0.011$), which did not meet the pre-defined significance level of $p < 0.01$. No significant differences were found between proportion of patients with *f*CIS and sex, presence of diabetes, or occlusion site (Table 2).

From the χ^2 analyses, both *f*CIS and successful revascularization were associated with GCO. Specifically, an mRS of 2 or lower was achieved in 23 of the 48 subjects with a *f*CIS (48%), but only 3 of the 30 subjects (10%) with a *p*CIS ($p < 0.001$, Table 2). Similarly, of the 39 subjects who achieved mTICI 2b or 3, 19 had a good outcome (49%), compared to 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. Of the 7 subjects who achieved a GCO with poor revascularization, 6 had a *f*CIS. For patients with a combination of *f*CIS and good revascularization, 71% achieved a good outcome vs. 25% for patients with *f*CIS and poor revascularization, 13% for patients with *p*CIS and good revascularization, and 7% for patients with *p*CIS and poor revascularization (Table 2). Using the Fisher exact test, the proportion of GCO was significantly greater for the combination of good revascularization and *f*CIS 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 ($p \leq 0.005$, Table 3). For the logistic regression focused on patients who achieved good revascularization, *f*CIS was correlated with GCO ($p = 0.009$, Table 3). For the *f*CIS subgroup, only good revascularization was correlated with outcome ($p = 0.006$). For the subgroup *f*CIS 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 due to M1 occlusion achieve a GCO when treated with placebo [9, L. Wechsler, unpublished data, 2006]. We consider this a conservative estimate of the likelihood of good outcome with ischemic stroke due to middle cerebral artery occlusion, if left untreated.

In the current study 62% of the subpopulation of IMS III patients had a *f*CIS, a higher percentage than identified with the BMC-AIS registry (42%) [7] and the IMS I–II subgroup analysis (46%) [8]. 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 *f*CIS 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% GCO's when treating all patients for cerebral ischemia due to 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 *f*CIS, although the sample size limits power to detect potential relationships. Patients with *p*CIS tended to be older than patients with *f*CIS, but the level did not reach significance due to the conservative p-value set for the current study based on multiple comparisons. In previous studies age was similar for both CIS groups [7, 8]. 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 two previous analyses [7, 8], *f*CIS 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 *f*CIS who achieved good revascularization did significantly better than those without good revascularization (71% vs. 25%) strengthens our previous hypothesis that *f*CIS identifies patients with viable, but ischemic, cerebral tissue. A *f*CIS 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 two 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 *p*CIS rarely achieved good outcomes regardless of revascularization status. In the current analysis, only 2 of 15 patients (13%) with *p*CIS had GCO following good revascularization, vs. 1 of 15 (7%) with GCO in the *p*CIS group without good revascularization. That the percentages (13% and 7%) are similar and below the estimated 22% for untreated occlusion leads us to believe that revascularization in those with *p*CIS and within the time window of the IMS III trial may not improve outcomes for a large majority of patients. Successful revascularization appears to be the best chance for a patient to achieve GCO for those patients with *f*CIS.

Time from ictus to revascularization and clinical outcome

In the current and previous two studies [7, 8] assessing the CIS, times from ictus to IVT and EVT were similar in the *f*CIS and *p*CIS subgroups. Yet *f*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 upon 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 (*f*CIS subgroup, patients with good revascularization, and *f*CIS patients with good revascularization). *f*CIS and good revascularization were correlated with good outcomes. Our results support the hypothesis that selecting patients with larger artery occlusions and with *f*CIS for safe and rapid revascularization may be an effective strategy to maximize the

benefit and minimize the risk of endovascular therapy. 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 ≥ 2, [6] collateral flow as quantified by the American Society of Interventional and Therapeutic Neuroradiology and Society of Interventional Radiology (ASITN/SIR) scale [10] was significantly related to clinical outcome in univariate analyses but fell out in a multivariable model, while time to reperfusion remained significant. Several methodological factors likely underlie this difference between the previous and current analysis. In the prior study [6] 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 two systems have not yet been studied. Challenging the concept of an absolute time widow from ictus to treatment is a provocative thought and may extend the treatment window in those patients with *f*CIS. Support for this concept from previous studies includes a documented lack of correlation between infarct size and time from ictus [11], and excellent GCOs in patients whose treatment window exceeded 18 hours [12]. 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 [8]. In patients with poor collaterals (*p*CIS subgroup) the time to revascularization needed before irreversible ischemia occurs may not be clinically attainable, while patients with good collaterals (*f*CIS 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 two significant impacts on the indication for EVT. First, treatment may be effective beyond a time window of 6 hours in people with *f*CIS. Second, costly and potentially harmful treatment could be eliminated in patients with *p*CIS if it is shown that EVT in these patients does not provide better outcomes than standard medical therapy.

Conclusion

The presence of a *f*CIS is a major factor in obtaining a good clinical outcome in AIS patients treated with endovascular therapy and is limited to approximately 50–60% of unselected patients: “the 50% barrier”. Successful revascularization is still needed. EVT outcomes in the setting of *p*CIS may be no better than no EVT overall. A prospective trial to address the use of EVT in patients with *p*CIS in early treatment and *f*CIS outside of the traditional time window is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparisons between *f*CIS and *p*CIS groups for continuous data

	***f*CIS**[*]	***p*CIS**[†]	**p-value**
Age (years)	63±14	71±8	0.011
NIHSS[‡] score	18±5	20±4	0.09
Time to IVT[§] (minutes)	123±30	129±34	0.41
Time to EVT[||] (minutes)	237±49	252±57	0.23
TIR (minutes)	332±56	341±56	0.48
Systolic blood pressure (mmHg)	143±30	153±30	0.18
Diastolic blood pressure (mm Hg)	78±19	86±20	0.10

[*] *f*CIS: favorable capillary index score (2 or 3),

[†] *p*CIS: poor capillary index score (0 or 1)

[‡] NIHSS: NIH stroke scale

[§] IVT: intravenous treatment,

[||] EVT: endovascular treatment

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

		good mRS/total	p-value	*f*CIS/total	p-value
CIS*	(*p*) 0 or 1	3/30 (0.10)	**<0.001**		
	(*f*) 2 or 3	23/48 (0.48)			
mTICI† score	0, 1, or 2a	7/39 (0.18)	**0.004**		
	2b or 3	19/39 (0.49)			
Occlusion site	ICA‡	6/21 (0.29)	0.79	9/21 (0.43)	0.07
	M1§	20/57 (0.35)		39/57 (0.68)	
Sex	Male	8/32 (0.25)	0.15	18/32 (0.56)	0.57
	Female	18/46 (0.39)		30/46 (0.65)	
Diabetes	Yes	2/17 (0.12)	0.06	10/17 (0.59)	1
	No	24/60 (0.40)		37/60 (0.62)	
CIS + mTICI	(*p*) + 0–2a	1/15 (0.07)	**<0.001**		
	(*p*) + 2b, 3	2/15 (0.13)			
	(*f*) + 0–2a	6/24 (0.25)			
	(*f*) + 2b, 3	17/24 (0.71)			

*CIS: capillary index score;

p = poor, *f* = favorable

†mTICI: modified thrombolysis in cerebral infarction; 2b or 3 considered good outcome

‡ICA: internal carotid artery,

§M1: middle cerebral artery trunk

Bold p-value indicates a significant difference

Table 3

Results of multivariable logistic regression for odds of a good outcome (mRS* ≤ 2)

	p-value	odds ratio	95% lower limit	95% upper limit
All patients (N = 78)				
mTICI† (0–2a vs 2b–3)	**0.005**	6.0	1.7	21.1
NIHSS‡ (unit scale)	0.044	0.87	0.77	1.00
CIS§ (*f*CIS vs *p*CIS)	**0.003**	9.2	2.2	39.3
TIR‖ (minutes)	0.39	1.00	0.98	1.01
Good reperfusion only (N = 39)				
NIHSS (unit scale)	0.012	0.73	0.56	0.93
CIS (*f*CIS vs *p*CIS)	**0.009**	16.7	2.0	136.7
TIR (minutes)	0.16	0.99	0.97	1
***f*CIS only (N = 48)**				
mTICI (0–2a vs 2b–3)	**0.006**	7.0	1.7	28.0
NIHSS (unit scale)	0.13	0.90	0.78	1.03
TIR (minutes)	0.44	1.00	0.98	1.01
Good reperfusion & *f*CIS (N = 24)				
NIHSS (unit scale)	0.048	0.78	0.61	1.00
TIR (minutes)	0.16	0.99	0.97	1.01

*mRS: modified Rankin Scale,

†mTICI: modified thrombolysis in cerebral infarction,

‡NIHSS: NIH stroke scale,

§CIS: capillary index score,

‖TIR: time from ischemia to revascularization

Bold p-value indicates a statistically significant difference