The iScore Predicts Efficacy and Risk of Bleeding in the National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator Stroke Trial

Gustavo Saposnik, MD, MSc, FAHA, FRCPC,*†‡ Andrew Demchuk, MD, FAHA, FRCPC,§ Jack V. Tu, MD, PhD, FRCPC,†‡ and S. Claiborne Johnston, MD, PhD, FAHA,¶ on behalf of the Stroke Outcomes Research Canada (SORCan) Working Group

The iScore is a validated tool to estimate outcomes after an acute ischemic stroke. A previous study showed the iScore can predict clinical response and risk of intracerebral hemorrhage (ICH) after administration of tissue plasminogen activator (tPA). We applied the iScore (www.sorcan.ca/iscore) to participants in the National Institute of Neurological Disorders and Stroke tPA stroke trials to evaluate its ability to estimate clinical response and risk of ICH after thrombolysis. Based on results from our previous study, patients were stratified a priori into iScore <200 and iScore ≥200. The main outcome measure was ICH. Secondary outcomes included favorable composite outcome (defined as a modified Rankin Scale score of 0 or 1, National Institutes of Health Stroke Scale score ≤1, Barthel Index ≥95, or Glasgow Outcome Scale <1 at 3 months) and functional outcomes. The iScore was calculated in all 624 patients enrolled in the trial. The cohort comprised 507 patients (81%) with an iScore <200 and 117 (19%) with an iScore ≥200. An iScore ≥200 was associated with greater risk of symptomatic ICH in the tPA group compared with the placebo group (15.4% *v* 3.9%; $P = .04$). Similar findings were found for ICH of any type (30.8% *v* 11.5%; $P = .014$), with higher ICH mortality (69.2% *v* 23.8%; $P < .001$). Despite the higher favorable composite outcome of tPA therapy in patients with an iScore <200 (58.7% *v* 41.9%; $P < .001$), this therapy had no benefit in patients with an iScore ≥200 (15.4% *v* 13.4%; $P = .77$). In patients receiving tPA in the National Institute of Neurological Disorders and Stroke trial, the iScore estimated the clinical response and risk of hemorrhagic complications. Further prospective studies are needed before a change in practice can be recommended. **Key Words:** Risk score—tools—thrombolysis—tPA—outcomes—mortality—disability—intracerebral hemorrhage—modified Rankin scale.

From the *Stroke Outcomes Research Unit, Division of Neurology, Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Canada; †Institute for Clinical Evaluative Sciences, Toronto, Canada; ‡Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada; §Calgary Stroke Program, Department of Clinical Neurosciences and Radiology, University of Calgary, Calgary, Canada; and ¶Clinical and Translational Science Institute and Department of Neurology, University of California, San Francisco, California.

Received July 19, 2012; accepted September 5, 2012.

Supported by Distinguished Clinician-Scientist Award from the Heart and Stroke Foundation of Canada (to G.S.) and a Canada Research Chair in Health Services Research and a Career Investigator Award from the Heart and Stroke Foundation of Ontario (to J.T.). The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript. All authors made substantive intellectual contributions to the study conceptualization and design, analyzed and interpreted results, and drafted the manuscript. They all approved the final submitted version.

Address correspondence to Dr Gustavo Saposnik, MD, MSc, FAHA, FRCPC, Director, Stroke Outcomes Research Unit, Department of Medicine, St Michael's Hospital, University of Toronto, 55 Queen St E, Toronto, ON, Canada M5C 1R6. E-mail: saposnikg@smh.ca.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2012.09.001

The decision to administer intravenous (IV) thrombolysis may be challenging, especially in patients with a higher prevalence of comorbid conditions, preadmission dependency, and dementia. Patients and families wonder about the likelihood of a good outcome when tissue plasminogen activator (tPA) is given, especially if the risk of developing hemorrhagic complications is high.

The iScore is a newly developed and validated tool that can be used to estimate the risk of short-term and long-term mortality and clinical outcomes after an acute ischemic stroke.[1,2] The iScore contains variables easily evaluated in the early hours after hospital presentation independent of specialized laboratory tests or imaging evaluations, including age, sex, stroke severity and subtype, serum glucose level on admission, and history of atrial fibrillation, myocardial infarction, cardiac failure, cancer, kidney disease on dialysis, and dependency before the stroke (Table 1). The iScore includes some well-established predictors (eg, age, stroke severity, hyperglycemia) and adds other relevant concomitant conditions associated with poorer clinical response to thrombolysis.[3-5]

Observational data suggest that patients with an iScore >200 derive no apparent benefit from IV tPA and are at an increased higher risk of hemorrhagic complications.[6] The possibility of residual confounding raises questions about the validity of observational studies, however. Consequently, application of the iScore to randomized clinical trials is crucial before changes to clinical practice can be recommended.[2]

The objectives of the present study were to evaluate the ability of the iScore to predict clinical response after tPA administration in participants in the National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study, and to determine whether the iScore is predictive of the risk of hemorrhagic transformation (ie, intracranial hemorrhage [ICH]) after tPA therapy in these patients.

Table 1. *Risk scoring system for the iScore*

Variable	Points	
	30-day score	1-year score
Age, years	+ age (in years)	+ age (in years)
Sex		
Female	0	0
Male	+10	+5
Stroke severity (using the CNS)*		
Mild (CNS score ≥8)	0	0
Moderate (CNS score 5-7)	+40	+25
Severe (CNS score ≤4)	+65	+40
Coma (CNS score 0)	+105	+70
Stroke subtype		
Lacunar	0	0
Nonlacunar	+30	+15
Undetermined etiology	+35	+20
Risk factors		
Atrial fibrillation	+10	+5
Congestive cardiac failure	+10	+10
Previous myocardial infarction	NA	+5
Current smoker	NA	+5
Comorbid condition		
Cancer	+10	+15
Renal dialysis	+35	+40
Preadmission disability		
Independent	0	0
Dependent	+15	+20
Glucose level on admission		
<7.5 mmol/L (<135 mg/dL)	0	0
≥7.5 mmol/L (≥135 mg/dL)	+15	+10

Abbreviations: CNS, Canadian Neurological Scale; NA, not applicable.

A CNS score of ≥8 is equivalent to an NIHSS score of ≤8 (mild); a CNS score of 5-7 is equivalent to an NIHSS score of 9-13 (moderate); a CNS score of 1-4 is equivalent to an NIHSS score of 14-22 (severe); and a CNS score of 0 is equivalent to an NIHSS score of ≥23.[20]

*Patients in a coma should be assigned a score of 0.

Methods

The NINDS tPA Stroke Study is a multicenter, prospective, double-blind, placebo-controlled, randomized trial of IV tPA for acute ischemic stroke conducted from January 1991 through October 1994.[7] A noncontrast computed tomography (CT) scan of the brain was mandatory before enrollment in the study to rule out ICH. All CT scans were performed using third- or fourth-generation CT scanners, and all baseline CT scans were obtained with a 10-mm slice thickness. Further details on trial methodology are available elsewhere.[7,8] We used data from the NINDS tPA stroke trial parts I and II to determine the ability of the iScore to predict clinical outcomes and the risk of hemorrhagic complications in patients randomized to tPA or placebo. Details on the selection of variables for the iScore, data sources, and creation and conceptualization of the iScore are available elsewhere.[1,2,6] An online Web-based tool (www.sorcan.ca/iscore) and iPhone version are currently available. We estimated the individual iScore of each participant of the NINDS tPA Stroke Study. The only variable not captured was renal failure on dialysis.

Outcome Measures

The main outcome measures included ICH, symptomatic (sICH) and any type. Hemorrhagic transformation (ie, ICH) was defined the presence of any hemorrhagic transformation occurring within 36 hours after tPA treatment. A hemorrhage was considered symptomatic (ie, sICH) when a decline in neurologic status was evident.

Secondary outcomes included (1) favorable composite outcome, defined as a composite of a modified Rankin scale (mRS) score of 0 or 1, an NIHSS score ≤1, a Barthel Index ≥95, and a Glasgow Outcome Scale <1 at 3 months[9]; (2) favorable functional outcome, defined as an mRS score of 0-2 at 3 months and 12 months; (3) lack of neurologic improvement, defined as a <3-point difference between baseline and 24-hour NIHSS scores[5]; and (4) poor (catastrophic) outcome, defined as an mRS score of 4-6 at 3 months.

Statistical Analysis

The χ^2 test was used to compare categorical variables, and analysis of variance or the Kruskal-Wallis test was used to compare mean and median differences for continuous variables. The iScore was initially categorized into quartiles (quartile 1, iScore range 35-131; quartile 2, iScore range 132-166; quartile 3, iScore range 167-191; quartile 4, iScore range 192-262) to determine the presence of a gradient effect with the main outcomes. Following the findings in our previous study, and owing to the relatively small sample size in the NINDS tPA trials, the primary analysis was conducted to evaluate the associations between an iScore ≥200 and the outcomes of interest.[6] Secondary analyses were performed using logistic regression with adjustment for NIHSS tPA iScore to identify any iScore-by-treatment interaction. The number-needed-to-treat (NNT) and the number-needed-to-harm (NNH) were calculated as the inverse of the absolute risk difference accordingly, and 95% confidence intervals (CIs) for each are reported.[10] Functional outcomes after ICH were measured using the method proposed by Saver (1/absolute risk reduction × 0.058 - rate of increased ICH in recipients of tPA compared with recipients of placebo) to estimate clinically relevant NNH, which takes into account those patients destined to have catastrophic outcomes.[11]

Statistical analyses were performed using Stata version 9 (StataCorp, College Station, TX). All tests were 2-tailed, and a P value <.05 was considered significant. The St Michael's Hospital Institutional Review Board approved the study design. We described our findings in accordance with the CONSORT 2010 Statement.

Results

The iScore was calculated in all 624 patients enrolled in the NINDS tPA trials. The mean iScores were 161.3 ± 44.7 for the entire cohort, 159.4 ± 47.8 for the tPA group, and 163.2 ± 41.5 for the placebo group (P = .28). A total of 117 patients had an iScore ≥200, including 65 patients (20.8%) in the tPA group and 52 patients (16.7%) in the placebo group (P = .18). Higher iScore was associated with an escalating probability of hemorrhagic complications (P < .0001) and a lower probability of a favorable composite outcome at 3 months (P < .0001) (Fig 1).

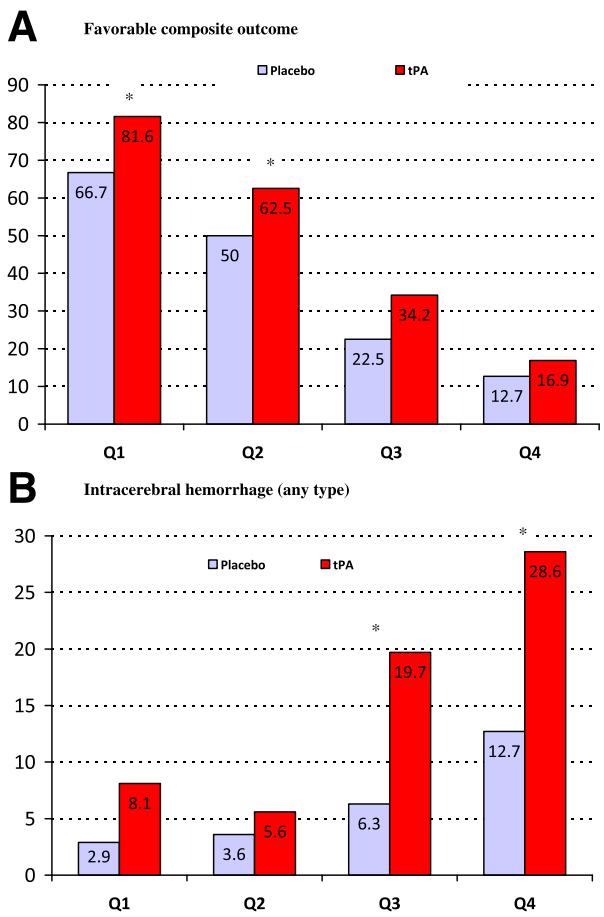

Figure 1. *Main outcomes by IScore quartile. (A) Favorable composite outcome. (B) ICH (any type). Favorable composite outcome is defined as an mRS score of 0 or 1, NIHSS ≤1, Barthel Index ≥95, or Glasgow Outcome Scale <1. Quartile 1: iScore range, 35-131; quartile 2: iScore range, 132-166; quartile 3: iScore range, 167-191; quartile 4: iScore range, 192-262. Note a gradient effect between the iScore and favorable outcome and ICH. *P < .05 for the comparison between tPA and placebo in each iScore quartile. Further details are provided in the text.*

The final mean infarct volume based on CT at 3 months was 49 ± 82 mL in patients with an iScore <200 and 134 ± 126 mL in those with an iScore ≥200 (P < .0001). Results by iScore quartile are shown in Figure 2.

Outcome Measures

ICH

Overall, there were 42 cases (8.3%) of ICH of any type in patients with an iScore <200 and 26 cases (22.2%) in those with an iScore ≥200 (P < .0001). Similarly, sICH was more common in patients with an iScore ≥200 (12 [10.3%] *v* 17 [3.4%]; P < .001).

For the primary analysis, an iScore ≥200 was associated with a higher rate of sICH in patients receiving tPA compared with those receiving placebo (15.4% *v* 3.9%; P = .041; NNH, 9). In patients with an iScore <200, sICH occurred in 2 patients (0.8%) receiving placebo and in 15 patients (6.1%) patients receiving tPA (P = .001; NNH, 19).

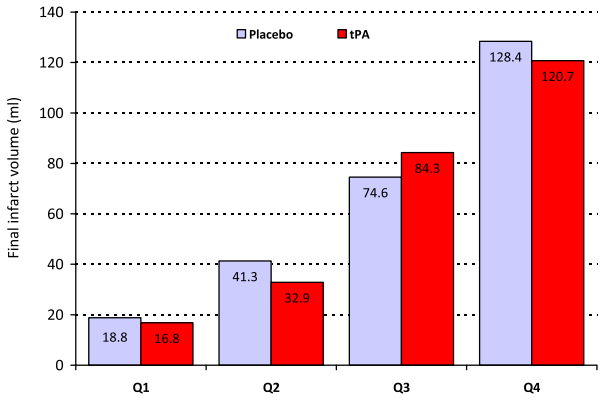

Figure 2. *Final infarct volume by iScore quartile. *P for trend <.001 comparing infarct volumes by iScore quartile among patients receiving tPA and those receiving placebo. There was no difference in infarct volume between tPA and placebo for any iScore quartile. Quartile 1: iScore range, 35-131; quartile 2: iScore range, 132-166; quartile 3: iScore range, 167-191; quartile 4: iScore range, 192-262.*

An iScore ≥200 was also associated with a higher rate of ICH of any type in the tPA group compared with the placebo group (30.8% *v* 11.5%; *P* = .014; NNH, 5) (Table 2). Mortality from hemorrhagic stroke at 3 months was significantly higher in patients with an iScore ≥200 (69.2% *v* 23.8%; *P* < .001; NNH, 2). This represents 13 more deaths (NNH, 13) for every 100 patients with ICH treated with tPA with an iScore ≥200, as estimated using clinically relevant NNH calculations.[11]

Similarly, poor functional outcome (mRS score 4-6) after ICH was more prevalent in patients with a higher iScore (88.5% of those with an iScore ≥200 *v* 71.4% of those with an iScore <200; NNH, 6) (Table 2). Using the method of Saver,[11] there would be 34 patients with poor functional outcome (NNH, 34) for every 100 patients with ICH with an iScore ≥200 treated with tPA.

Multivariate Analysis for ICH

In logistic regression analysis, after adjusting for tPA, an iScore ≥200 was associated with a 3-fold greater risk of sICH (odds ratio [OR], 3.08; 95% CI, 1.41-6.74; c-statistic, 0.745; correctly classified, 95.4%). There were no treatment effect interactions between iScore as a continuous variable (*P* for the interaction = .69) or iScore ≥200 (categorical) and tPA for sICH (*P* value for the interaction = .58; c-statistic, 0.745), likely owing to the small number of cases. In logistic regression analysis for ICH of any type, an iScore ≥200 was associated with a 3-fold greater risk of ICH (OR, 3.06; 95% CI, 1.77-5.27; c-statistic, 0.669; correctly classified, 89.1%). There was no treatment effect interaction between the iScore as continuous variable (*P* for the interaction = .51) or iScore ≥200 (categorical) and tPA (*P* for the interaction = .49; c-statistic, 0.669).

Similar findings were found for the interaction between iScore ≥200 and CT findings (edema or mass effect, or midline shift) (c-statistic, 0.725; 95% CI 0.653-0.789). OR (with 95% CI) estimations for each outcome by iScore group are provided in Table 2.

Secondary Outcomes

Patients with an iScore <200 had significantly better outcomes with tPA compared with placebo (favorable composite outcome at 3 months, 58.7% *v* 41.9%; *P* < .001; NNT, 6). However, in patients with an iScore ≥200,

Table 2. *Outcome analysis according to baseline iScore <200 and ≥200 by treatment assignment*

	iScore <200 (n = 507)			iScore ≥200 (n = 117)		
	tPA	Placebo	OR (95% CI)	tPA	Placebo	OR (95% CI)
Total patients, n (%)	247 (48.7)	260 (51.3)	—	65 (55.6)	52 (44.4)	—
Main outcome measures, n (%)						
ICH (any type)	28 (11.3)	14 (5.4)	2.24 (1.15-4.38)	20 (30.8)	6 (11.5)	3.41 (1.25-9.26)
sICH	15 (6.1)	2 (0.77)	8.34 (1.89-36.9)	10 (15.4)	2 (3.9)	4.54 (0.95-21.8)
Secondary outcomes, n (%)						
Favorable composite outcome at 3 months	145 (58.7)	109 (41.9)	1.97 (1.38-2.80)	10 (15.3)	7 (13.5)	1.16 (0.41-3.32)
Catastrophic outcome (mRS score 4-6)						
At 3 months	69 (27.9)	107 (41.2)	0.55 (0.38-0.80)	46 (70.7)	40 (76.9)	0.73 (0.31-1.68)
At 12 months	61 (25.9)	100 (40.2)	0.52 (0.35-0.76)	48 (77.4)	40 (78.4)	0.94 (0.39-2.31)
Good functional outcome (mRS score 0-2)	145 (58.7)	114 (43.9)	1.82 (1.28-2.59)	12 (18.5)	6 (11.5)	1.73 (0.60-4.99)
Discharge to home	129 (52.2)	97 (37.3)	1.84 (1.29-2.62)	11 (16.9)	5 (9.2)	1.91 (0.62-5.91)
Lack of improvement at 24 hours	124 (50.4)	166 (63.9)	0.58 (0.40-0.82)	40 (61.5)	24 (46.2)	1.87 (0.89-3.91)

Values in parentheses are column percentages, unless indicated otherwise. Favorable composite outcome is defined a defined as an mRS score of 0 or 1, NIHSS score ≤1, Barthel Index ≥95, or Glasgow Outcome Scale <1. Catastrophic functional outcome is defined as an mRS score of 4-6 at 3 months and 12 months. Lack of neurologic improvement is defined as a <3-point difference between baseline and 24-hour NIHSS score. Poor outcome is defined as an mRS score of 4-6 at 3 months. Data on favorable composite outcome, catastrophic functional outcome, discharge to home, and lack of improvement were available for all patients at 3 months. Data on catastrophic outcomes at 12 months were available for 598 patients.

tPA administration was not associated with significantly better outcomes (favorable composite outcome at 3 months, 15.4% *v* 13.4%; $P = .77$). Similar results were found for favorable composite outcome at 12 months (Table 2).

In the patients with an iScore <200, tPA administration was associated with a lower risk of poor functional outcome (mRS score 4-6) at 3 months compared with placebo (27.9% *v* 41.1%; $P < .002$; NNT, 8). In contrast, no significant reduction in the rate of death or major disability was associated with tPA administration in patients with an iScore ≥200 (70.8% with tPA vs 76.9% with placebo; $P = .45$) (Fig 3). Patients with an iScore ≥200 who received tPA were more likely to meet the criteria for lack of improvement (61.5% *v* 46.2%; $P = .14$).

Multivariate Analysis for Favorable and Poor Functional Outcomes

In logistic regression analysis with adjustment for tPA, an iScore ≥200 was associated with a greater risk of a poor functional outcome (mRS 4-6) at 3 months (OR, 5.57; 95% CI, 3.53-8.80; c-statistic, 0.667). An iScore ≥200 was associated with a lower favorable composite outcome after adjustment for tPA (OR, 0.16; 95% CI, 0.09-0.27; c-statistic, 0.667). There was no interaction between the iScore as either a continuous variable or a categorical variable and treatment effect for a functional outcome (*P* for the interaction for a favorable composite outcome = .58 for continuous and .35 for categorical; *P* for the interaction for an mRS score of 4-6 = .74 for continuous and .56 for categorical).

Discussion

The prediction of efficacy and risk of hemorrhagic complications after thrombolysis presents a challenge to clinicians. In the present study, we calculated the iScore for each participant in the NINDS tPA Stroke Study and evaluated the iScore's predictive ability in that randomized clinical trial. We found an iScore ≥200 was associated with a 3-fold greater risk of ICH (absolute ICH risk, 30.8% in the tPA group *v* 11.5% in the placebo group), a 5-fold greater risk of sICH (15.4% *v* 3.9%), and a nonsignificant increase in favorable composite outcome at 3 months or 12 months (Table 2). Moreover, the case fatality rate at 3 months due to ICH was significantly higher in patients with an iScore ≥200 (69.2% *v* 23.8%; $P < .001$; NNH, 2). Patients with an iScore ≥200 had a 2.7-fold greater mean final infarct volume (as determined by CT at 3 months) compared with patients with an iScore <200. No interaction was identified between iScore and treatment effect for ICH or a favorable composite outcome.

In a large cohort comprising 12,686 "real world" patients, our group compared clinical outcomes (death at 30 days, death or disability at discharge, and death or institutionalization at discharge) in patients receiving and not receiving tPA after adjusting for differences in baseline characteristics both using propensity score matching and logistic regression analysis.[6] We found that patients with an iScore ≥200 derived no apparent benefit from IV tPA and had a 3-fold greater risk of hemorrhagic complications compared with those with an iScore <200 (20% *v* 6%; $P < .001$). The results were consistent in the validation cohort (n = 4908). Previous studies also have demonstrated an influence of coexisting comorbidities on clinical outcomes and hemorrhagic complications after ischemic stroke.[12,13] The NINDS tPA Trials Group reported that only stroke severity as evaluated using the NIHSS (OR, 1.8; 95% CI, 1.2-2.9) and brain edema (defined as acute hypodensity) or mass effect detected on CT scan before treatment (OR, 7.8; 95% CI, 2.2-27.1) were associated with ICH.[8] The Hemorrhage after Thrombolysis (HAT) scale is a 5-point scale based on NIHSS score, extent of hypodensity on CT scan, serum glucose level at baseline, and history of diabetes that predicts the risk of hemorrhage after thrombolysis. The rate of any ICH in the NINDS tPA arm was 7% for 0 points, 13% for 1 point,

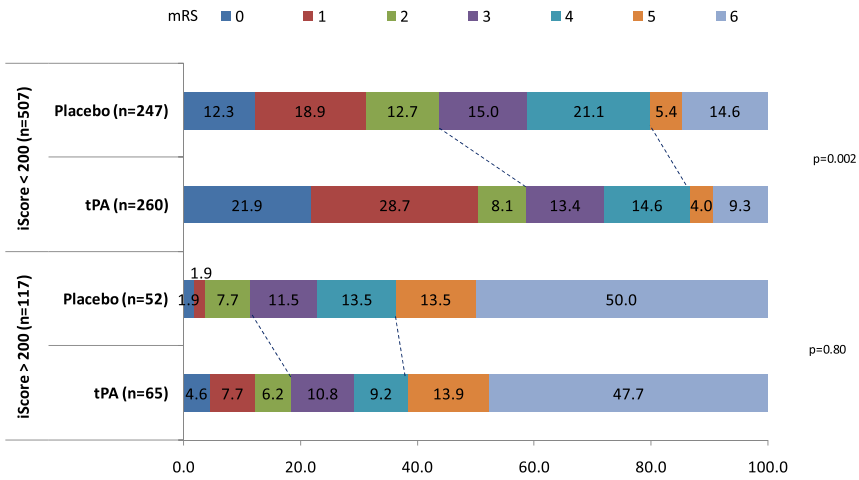

Figure 3. *Relationship between functional outcome at 3 months according to mRS score and baseline iScore by treatment assignment. This figure illustrates the disability at 3 months according to mRS score (0, no symptoms; 6, death) between tPA and placebo in patients stratified by iScore (<200 or ≥200). The dotted lines indicate the corresponding category (mRS score 0-2 or mRS score 5-6) between tPA and placebo in each strata. For patients with an iScore <200, tPA administration was associated with a significant likelihood of a favorable functional outcome (mRS score 0-2) at 3 months (OR, 1.82; 95% CI, 1.28-2.59). In contrast, those with an iScore ≥200 received no benefit from tPA administration (OR, 1.73; 95% CI, 0.60-4.99).*

20% for 2 points, 38% for 3 points, and 67% for 4 or more points (c-statistic, 0.70; 95% CI, 0.61-0.79).[14]

Other tools are available to estimate the clinical response to tPA and ICH.[3,14-17] The iScore is a single score that predicts both clinical response to tPA (favorable and poor outcomes at 24 hours, 3 month, and 1 year) and the risk of ICH and its associated outcomes. The iScore includes other relevant comorbid conditions (eg, atrial fibrillation, congestive heart failure, cancer) and preadmission independence in addition to the well-known predictors of outcome (eg, age, stroke severity) after stroke. The iScore performed similarly to the HAT score, with an associated increased risk of ICH of 31% for patients with an iScore ≥200.

As clinicians, our perception of the risks and benefits of tPA therapy without the use of validated tools might not be accurate. For example, in a previous survey, only 11% (95% CI, 0-22%) of emergency physicians and neurologists were able to correctly identify the benefit with tPA, and only 39% could estimate the risk of ICH.[18] Thus, clinical tools and online resources are needed to help clinicians provide information to stroke survivors and their families at the point of care.[19]

The present study confirms the consistency of our previous results[6] in a randomized trial, thus addressing the potential concerns regarding residual confounding reported in observational studies. Taken together, our results suggest that the iScore may help estimate the probability of a favorable outcome and the risk of hemorrhagic complications after IV tPA. These findings may be useful in identifying groups of patients less likely to benefit from IV tPA and at high risk for intracranial bleeding. Some clinicians may still elect to administer IV tPA in high-risk patients, given the unlikely possibility of spontaneous recovery. Others may consider alternative interventions (eg, endovascular clot removal) after consultation with and consent from patients and/or their families.

The present study has some limitations that merit mention. First, the lack of benefit from tPA in patients with an iScore ≥200 may be related to the relatively small sample size (type II error). A similar explanation may apply to the lack of interaction between the iScore and tPA for a favorable outcome, as observed in a previous larger sample size.[6] Second, because renal failure was not reported in the NINDS tPA trials, the final iScore might have been underestimated slightly. Third, the iScore does not include imaging predictors of tPA-related ICH (eg, infarct volume, leukoraiosis). Fourth, NINDS data were collected in the early 1990s, and most participants were treated early.

Despite these limitations, our study found that the iScore consistently estimates both the risk of hemorrhagic complications and clinical response to thrombolysis in observational studies and now in a large randomized clinical trial.[6] The iScore is a cross-validated tool that can assist clinicians in estimating the risk of death and disability in patients with ischemic stroke, as well as the potential benefits and risks of bleeding after tPA. Prospective studies are needed to examine the role of the iScore on treatment effect before any changes in clinical practice can be recommended.

References

1. Saposnik G, Kapral MK, Liu Y, et al. iScore: A risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation 2011;123:739-749.
2. Saposnik G, Kapral MK, Liu Y, et al. The iScore predicts functional outcomes early after hospitalization for an acute ischemic stroke. Stroke 2011;42:3421-3428.
3. Solberg OG, Dahl M, Mowinckel P, et al. Derivation and validation of a simple risk score for predicting 1-year mortality in stroke. J Neurol 2007;254:1376-1383.
4. German Stroke Study Collaboration. Predicting outcome after acute ischemic stroke: An external validation of prognostic models. Neurology 2004;62:581-585.
5. Saposnik G, Young B, Silver B, et al. Lack of improvement in patients with acute stroke after treatment with thrombolytic therapy: Predictors and association with outcome. JAMA 2004;292:1839-1844.
6. Saposnik G, Fang J, Kapral MK, et al. The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke. Stroke 2012;43:1315-1322.
7. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
8. NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28:2109-2118.
9. Hacke W, Bluhmki E, Steiner T, et al. Dichotomized efficacy end points and global end-point analysis applied to the ECASS intention-to-treat data set: Post hoc analysis of ECASS I. Stroke 1998;29:2073-2075.
10. Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309-1312.
11. Saver JL. Hemorrhage after thrombolytic therapy for stroke: The clinically relevant number needed to harm. Stroke 2007;38:2279-2283.
12. Blacker DJ, Phatouros CC. Beyond IV thrombolysis for acute ischaemic stroke. Intern Med J 2011;41:645.
13. Mitchell J, Lang E. Evidence-based emergency medicine. Update: Effect of thrombolysis in acute ischemic stroke. Ann Emerg Med 2011;57:e16-e17.
14. Lou M, Safdar A, Mehdiratta M, et al. The HAT score: A simple grading scale for predicting hemorrhage after thrombolysis. Neurology 2008;71:1417-1423.
15. Konig IR, Ziegler A, Bluhmki E, et al. Predicting long-term outcome after acute ischemic stroke: A simple index works in patients from controlled clinical trials. Stroke 2008;39:1821-1826.
16. Weimar C, Konig IR, Kraywinkel K, et al. Age and National Institutes of Health Stroke Scale score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: Development and external validation of prognostic models. Stroke 2004;35:158-162.
17. Kent DM, Selker HP, Ruthazer R, et al. The stroke-thrombolytic predictive instrument: A predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke 2006;37:2957-2962.

18. Merino JG, Silver B, Wong E, et al. Physician knowledge of the benefits, risks, and contraindications of tissue plasminogen activator for acute ischemic stroke. Stroke 2001; 32:2208-2209.
19. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: A systematic review. JAMA 2005;293:1223-1238.
20. Nilanont Y, Komoltri C, Saposnik G, et al. The Canadian Neurological Scale and the NIHSS: Development and validation of a simple conversion model. Cerebrovasc Dis 2010;30:120-126.