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

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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. © 2012 by National Stroke Association
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.\(^2\) 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 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.\(^7\) We used data from the NINDS tPA Stroke Study 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.

### 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 as 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 $\leq 1$, a Barthel Index $\geq 95$, and a Glasgow Outcome Scale $< 1$ at 3 months; (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; and (4) poor (catastrophic) outcome, defined as an mRS score of 4-6 at 3 months.

**Statistical Analysis**

The $\chi^2$ 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 $\geq 200$ and the outcomes of interest. 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. Functional outcomes after ICH were measured using the method proposed by Saver (1/absolute risk reduction - 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.

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 $\pm$ 44.7 for the entire cohort, 159.4 $\pm$ 47.8 for the tPA group, and 163.2 $\pm$ 41.5 for the placebo group ($P = .28$). A total of 117 patients had an iScore $\geq 200$, 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).
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% vs 11.5%; P = 0.014; NNH, 5) (Table 2). Mortality from hemorrhagic stroke at 3 months was significantly higher in patients with an iScore ≥200 (69.2% vs 23.8%; P < .001; NNH, 13). 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.

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 vs 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 and 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% vs 41.9%; P < .001; NNT, 6). However, in patients with an iScore ≥200,

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

<table>
<thead>
<tr>
<th></th>
<th>iScore &lt;200 (n = 507)</th>
<th>iScore ≥200 (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients, n (%)</strong></td>
<td>247 (48.7)</td>
<td>65 (55.6)</td>
</tr>
<tr>
<td><strong>Main outcome measures, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH (any type)</td>
<td>28 (11.3)</td>
<td>20 (30.8)</td>
</tr>
<tr>
<td>sICH</td>
<td>15 (6.1)</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td><strong>Secondary outcomes, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable composite outcome at 3 months</td>
<td>145 (58.7)</td>
<td>10 (15.3)</td>
</tr>
<tr>
<td>Catastrophic outcome (mRS score 4-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 months</td>
<td>69 (27.9)</td>
<td>48 (77.4)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>61 (25.9)</td>
<td>40 (78.4)</td>
</tr>
<tr>
<td>Good functional outcome (mRS score 0-2)</td>
<td>145 (58.7)</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Discharge to home</td>
<td>129 (52.2)</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>Lack of improvement at 24 hours</td>
<td>124 (50.4)</td>
<td>40 (61.5)</td>
</tr>
</tbody>
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Values in parentheses are column percentages, unless indicated otherwise. Favorable composite outcome is 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 score 4-6) at 3 months (OR, 5.57; 95% CI, 3.35-8.80; 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 .56 for categorical). For the interaction for an mRS score of 4-6 = .74 for continuous and .75 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. 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. The NINDS TPA Trials Group reported that only stroke severity as evaluated using the NIHSS (OR, 1.8; 95% CI, 1.2-2.5) 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. 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.
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

