Predicting Clinical Outcomes After Thrombolysis Using the iScore
Results From the Virtual International Stroke Trials Archive

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Background and Purpose—The ischemic stroke risk score (iScore) is a validated tool developed to estimate the risk of death and functional outcomes early after an acute ischemic stroke. Our goal was to determine the ability of the iScore to estimate clinical outcomes after intravenous thrombolysis tissue-type plasminogen activator (tPA) in the Virtual International Stroke Trials Archive (VISTA).

Methods—We applied the iScore (www.sorcan.ca/iscore) to patients with an acute ischemic stroke within the VISTA collaboration to examine the effect of tPA. We explored the association between the iScore (<200 and ≥200) and the primary outcome of favorable outcome at 3 months defined as a modified Rankin scale score of 0 to 2. Secondary outcomes included death at 3 months, catastrophic outcomes (modified Rankin scale, 4–6), and Barthel index >90 at 3 months.

Results—Among 7140 patients with an acute ischemic stroke, 2732 (38.5%) received tPA and 711 (10%) had an iScore ≥200. Overall, tPA treatment was associated with a significant improvement in the primary outcome among patients with an iScore <200 (38.9% non-tPA versus 47.5% tPA; P<0.001) but was not associated with a favorable outcome among patients with an iScore ≥200 (5.5% non-tPA versus 7.6% tPA; P=0.45). In the multivariable analysis after adjusting for age, baseline National Institutes of Health Stroke Scale, and onset-to-treatment time, there was a significant interaction between tPA administration and iScore; tPA administration was associated with 47% higher odds of a favorable outcome at 3 months among patients with an iScore <200 (odds ratio, 1.47; 95% confidence interval, 1.30–1.67), whereas the association between tPA and favorable outcome among those with an iScore ≥200 remained nonsignificant (odds ratio, 0.80; 95% confidence interval, 0.45–1.42). A similar pattern of benefit with tPA among patients with an iScore <200, but not ≥200, was observed for secondary outcomes including death.

Conclusions—The iScore is a useful and validated tool that helps clinicians estimate stroke outcomes. In stroke patients participating in VISTA, an iScore <200 was associated with better outcomes at 3 months after tPA. (Stroke. 2013;44:2755-2759.)

Key Words: iScore ■ outcomes ■ predicting score ■ prognosis

Several factors have been associated with better outcomes after intravenous thrombolysis (tissue-type plasminogen activator [tPA]) for an acute ischemic stroke.1,2 These include younger age, milder stroke, shorter door-to-needle time, normoglycemia, and absence of comorbidities.3,4 Current available risk prediction tools for acute stroke include some of these factors, but their accuracy in predicting death or disability after stroke is uncertain.5-7 The ischemic stroke risk score (iScore) is a validated score that can be used to estimate the risk of short- and long-term death and disability early after hospitalization for an acute ischemic stroke.8 The iScore (www.sorcan.ca/iscore) stratifies ischemic stroke patients into risk categories, from very low to very high risk, using clinical parameters and comorbid conditions.9,10 The presence of some concomitant comorbid conditions (eg, cardiac heart failure, atrial fibrillation),

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preadmission dependency, and dementia constitute a challenge when deciding about thrombolysis treatment. Patients and families wonder about the likelihood of a clinically meaningful recovery if tPA is given, especially in situations where in which the risk of a poor outcome or hemorrhagic complications is high. As a result, the prediction of response to intravenous thrombolysis may be useful for patients, their families, and clinicians in discussions related to the decision to give intravenous thrombolysis. A previous study from our group showed that the iScore predicts favorable outcome at discharge in >12,000 stroke patients from Canada.8,9 An iScore ≥200 was associated with no significant improvement after tPA and higher risk of intracerebral hemorrhages compared with propensity-matched controls.10,11 Our objective was to evaluate the ability of the iScore to predict clinical outcomes at 3 months in acute ischemic stroke patients treated with or without tPA in the Virtual International Stroke Trials Archive (VISTA).

Methods
We applied the iScore to participants with ischemic stroke in the VISTA database. VISTA (www.vista.gla.ac.uk/) is a collaborative registry that includes data from completed acute stroke/neuroprotective clinical trials and provides access to anonymized data for exploratory analyses. Further details of VISTA were published elsewhere.12–14 It is important to note that this database does not include trials of tPA therapy, per se, although tPA was commonly used as an adjunctive therapy. For the purpose of this analysis, relevant data were extracted from the VISTA database that met the following entry criteria: (1) minimum dataset of 100 patients; (2) documented entry criteria; (3) baseline assessment within 24 hours of stroke onset, including recording of neurological deficit by National Institutes of Health Stroke Scale (NIHSS); (4) confirmation of stroke diagnosis by cerebral imaging within 7 days; and (5) outcome assessed 3 months after stroke onset. This analysis is based on a total of 7140 patients participating in 4 neuroprotective trials who met the aforementioned inclusion criteria. Onset-to-treatment represents the elapsed time from stroke onset to receiving the studied intervention treatment (not tPA).

The iScore comprises 10 variables that were included in VISTA (Table I in the online-only Data Supplement). Details of the selection of variables for the iScore, data sources, and the creation and conceptualization of the iScore have been published elsewhere.4,8 Stroke subtype was categorized as lacunar versus nonlacunar. Similar to previous studies, renal failure was defined as a baseline creatinine ≥400 mg/L.8,9 Outcome Measures
The primary outcome was favorable outcome, defined as modified Rankin scale score (mRS) of 0 to 2 at 3 months. We also analyzed a composite favorable outcome defined as an mRS of 0 to 1 or an NIHSS ≤1 at 3 months. Secondary 3-month outcomes included catastrophic outcome (defined as an mRS of 4–6), death, Barthel index (BI) >90, and NIHSS 0 to 1.

Statistical Analysis
We compared the characteristics between patients with an iScore <200 and those with an iScore ≥200 using χ2 test for categorical variables and t test was used to compare mean differences for continuous variables. Mantel–Haenszel test was used in the analysis of stratified categorical data. The primary analysis was conducted to evaluate the association between tPA therapy and 3-month outcomes of interest according to different iScore strata. Because previous studies showed that an iScore ≥200 was associated with poor outcomes,11 we used the same binary cut-off point and tested other cut points in a sensitivity analysis. The independent associations between tPA therapy and outcomes were determined using multivariable logistic regression.

Adjustments for age, baseline NIHSS, iScore (<200 versus ≥200), and onset-to-treatment time for the non-tPA intervention agent were made because of differences in baseline characteristics between patients receiving and not receiving tPA (Table II in the online-only Data Supplement). To determine whether a differential effect of tPA on outcomes was present according to different levels of the iScore (<200 versus ≥200), we tested the significance of the iScore*tPA interaction term in the multivariable models. We conducted a sensitivity analysis to compare different cut-off points of the iScore (eg, 180, 200, and 220) expressed as the area under the curve. We also conducted a sensitivity analysis by excluding patients with an NIHSS ≥25.

Statistical analysis was performed using STATA version 9 (StataCorp LP; College Station, TX). Rocgold command was used to compare area under the curves for different iScore cut-off points. All tests were 2-tailed, and P values <0.05 were considered significant.

Results
Among 7140 patients with an acute ischemic stroke, 2732 (38.5%) received tPA, and 711 (10%) had an iScore ≥200. The median (interquartile range) iScore in the entire cohort was 157 (117, 181; for the tPA group: 162 [136, 183]; for the not-tPA: 154 [103, 179]). Patients with an iScore ≥200 were older and had more severe strokes and higher prevalence of vascular risk factors compared with an iScore <200 (Table 1). The distribution of the iScore is shown in the Figure in the online-only Data Supplement. Patients receiving tPA were younger (mean age in years, 68.1 versus 70.0; P<0.0001) and had a higher mean baseline NIHSS (14.2 versus 12.4; P<0.0001) and shorter mean onset-to-treatment (214 minutes versus 257 minutes; P<0.0001). Further details by the iScore strata are summarized in Table II in the online-only Data Supplement.

Primary Outcome Measures
Among participants with an iScore <200, favorable outcome at 3 months (mRS ≤2) was observed in 47.5% of tPA patients and 38.9% in the non-tPA (untreated) group (P<0.001; Figure 1). For patients with an iScore ≥200, favorable outcomes occurred only in the minority of patients, and there was no difference between tPA and non-tPA groups (7.6% versus 5.4%; P=0.45; Figure 1). Multivariable-adjusted analyses of the primary outcome are represented in Table 2. Because the analysis demonstrated a significant interaction effect (P<0.001) between tPA and the iScore on the primary outcome, we present all analyses separately for patients with an iScore <200 versus ≥200.

In the multivariable analysis after adjusting for age, baseline NIHSS, and onset-to-intervention treatment, tPA administration was associated with a 47% higher chance of a favorable outcome at 3 months among patients with an iScore <200 (odds ratio [OR], 1.47; 95% confidence interval [CI], 1.30–1.67). This effect was present according to different levels of the iScore (Table II in the online-only Data Supplement). To determine whether a differential effect of tPA on outcomes was present according to different levels of the iScore (<200 versus ≥200), we tested the significance of the iScore*tPA interaction term in the multivariable models. We conducted a sensitivity analysis to compare different cut-off points of the iScore (eg, 180, 200, and 220) expressed as the area under the curve. We also conducted a sensitivity analysis by excluding patients with an NIHSS ≥25.

Statistical analysis was performed using STATA version 9 (StataCorp LP; College Station, TX). Rocgold command was used to compare area under the curves for different iScore cut-off points. All tests were 2-tailed, and P values <0.05 were considered significant.

Secondary Functional Outcomes
Statistically significant interaction effects between the iScore and tPA were demonstrated for death at 3 months (P<0.001) and catastrophic outcome (death or disability) at 3 months (P<0.001). There was no significant interaction for either the BI (P=0.47) or the NIHSS (P=0.70) outcomes.
Among patients with an iScore <200, there was a significant improvement at 3 months for all secondary outcomes with tPA treatment. Contrarily, no significant improvement in outcomes after tPA therapy was detected among patients with an iScore ≥200, with the exception of catastrophic outcomes (Table 2 and Figure 2).

Sensitivity Analysis
The sensitivity analysis showed no change in the performance of other cut-off points (eg, iScore 180 or 220) for all the studied outcomes (Table III in the online-only Data Supplement). There was no significant difference between the areas under the curve that would justify a different cut-off point.

Because in some institutions, stroke patients with an NIHSS ≥25 may not receive tPA, a post hoc analysis was conducted excluding these cases. There was no difference in the proportion of patients with an NIHSS ≥25 between tPA and non-tPA patients (2.6% versus 2.5%; P=0.84). Moreover, there was no difference in an NIHSS ≥25 between tPA and non-tPA patients among those with an iScore ≥200 (22.8% versus 24.2%; P=0.65). After patients with an NIHSS ≥25 were excluded, there remained no significant association between

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**Table 1. Baseline Characteristics Among Participants in VISTA Cohort**

<table>
<thead>
<tr>
<th>Variables</th>
<th>iScore &lt;200, n=6429</th>
<th>iScore ≥200, n=711</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>68.2±12.5</td>
<td>78.2±9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age categories</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;65</td>
<td>2371 (36.9)</td>
<td>74 (10.4)</td>
<td></td>
</tr>
<tr>
<td>66 to 79</td>
<td>2895 (45.0)</td>
<td>262 (36.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1163 (18.1)</td>
<td>375 (52.7)</td>
<td></td>
</tr>
<tr>
<td>NIHSS on admission, mean±SD</td>
<td>12.1±4.9</td>
<td>21.4±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS ≤8</td>
<td>1872 (29.1)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS 9 to 15</td>
<td>2782 (43.3)</td>
<td>83 (11.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS ≥16</td>
<td>1775 (27.6)</td>
<td>628 (88.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, men</td>
<td>3453 (53.7)</td>
<td>408 (57.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure, mean±SD in mm Hg</td>
<td>155.3 (26.2)</td>
<td>155.7 (26.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Glucose on admission, mmol/dL±SD</td>
<td>7.46±3.0</td>
<td>8.0±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4605 (73.5)</td>
<td>546 (78.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1454 (23.2)</td>
<td>200 (28.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1433 (22.8)</td>
<td>407 (58.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>340 (6.6)</td>
<td>165 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>900 (14.5)</td>
<td>141 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1542 (24.4)</td>
<td>194 (27.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Renal failure</td>
<td>15 (0.3)</td>
<td>20 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>50 (0.8)</td>
<td>14 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>342 (5.3)</td>
<td>3 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Nonlacunar</td>
<td>6087 (94.7)</td>
<td>708 (99.6)</td>
<td></td>
</tr>
<tr>
<td>Stroke onset-to-treatment, mean±SD in min</td>
<td>241.1±62.9</td>
<td>236.9 (59.9)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values in parentheses are column percentages, unless otherwise indicated. Variable definitions as reported by the National Institute of Neurological Disorders and Stroke Recombinant Tissue-Type Plasminogen Activator Stroke trial. VISTA indicates Virtual International Stroke Trials Archive.

* t test was used to compare continuous variables (ie, age, National Institutes of Health Stroke Scale, systolic blood pressure, glucose, onset-to-treatment) and χ² for categorical variables.

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**Figure 1.** Adjusted favorable outcome (mRS 0–2) at 3 months by tissue-type plasminogen activator (tPA) treatment stratified by iScore group. Adjusted by age, National Institutes of Health Stroke Scale, and onset-to-treatment. Further details are explained in the Statistical Analysis section. There was no significant difference between tPA and non-tPA among patients with an iScore ≥200.
Table 2. Association Between tPA Therapy and Outcome Measures According to iScore Groups (<200 and ≥200)

<table>
<thead>
<tr>
<th>iScore &lt;200, n=6429</th>
<th>Multivariable Analysis*</th>
<th>iScore ≥200, n=711</th>
<th>Multivariable Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-tPA (%)</td>
<td>tPA (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>3941 (61.7)</td>
<td>2442 (38.3)</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable outcome (mRS 0–2)</td>
<td>1707 (44.7)</td>
<td>1110 (48.4)</td>
<td>1.47 (1.30–1.67)†</td>
</tr>
<tr>
<td>Composite favorable outcome</td>
<td>1438 (36.5)</td>
<td>895 (36.7)</td>
<td>1.38 (1.21–1.56)†</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 3 mo</td>
<td>547 (14.3)</td>
<td>275 (12.0)</td>
<td>0.70 (0.59–0.83)†</td>
</tr>
<tr>
<td>Catastrophic outcome (mRS 4–6) at 3 mo</td>
<td>1526 (40.0)</td>
<td>826 (36.1)</td>
<td>0.65 (0.57–0.74)†</td>
</tr>
<tr>
<td>Barthel index &gt;90 at 3 mo</td>
<td>1835 (56.1)</td>
<td>1210 (60.0)</td>
<td>1.52 (1.33–1.75)†</td>
</tr>
<tr>
<td>NIHSS 0 to 1 at 3 mo</td>
<td>1160 (35.9)</td>
<td>752 (38.0)</td>
<td>1.49 (1.30–1.70)†</td>
</tr>
</tbody>
</table>

Values in parentheses are column raw percentages, unless otherwise indicated. Composite favorable outcome defined as a mRS of 0 or 1 and NIHSS≤1 at 3 months. Catastrophic functional outcome defined as a mRS of 4 to 6 at 3 months. mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and rtPA, recombinant tissue-type plasminogen activator.

*Represents the OR (95% CI) for rtPA in the logistic regression analysis adjusted for age, baseline NIHSS, and onset-to-treatment.

†Statistically significant results.

tPA and favorable outcome (OR, 0.90; 95% CI, 0.48–1.71; P=0.76) among patients with an iScore ≥200.

Discussion

The prediction of clinical outcomes after thrombolysis is difficult. There are several risk scores (eg, Thrombolytic Predictive Instrument Acute Stroke Registry and Analysis of Lausanne [TPI ASTRAL]; Sugar, Early infarct signs, Dense cerebral artery sign, Age, and NIHSS [SEDAN]; Stroke Prognostication using Age and NIHSS [SPAN] 100) to predict clinical outcomes after stroke.15–17 Clinicians need practical and validated tools when discussing prognosis with stroke patients and their families.

In this study, we applied the iScore and analyzed a variety of clinical outcomes after thrombolysis in the VISTA data set. Overall, patients with an iScore ≥200 had a 9-fold higher risk of death and disability at 3 months and a lower chance of a favorable outcome. Furthermore, tPA administration was consistently associated with better outcomes (mRS, 0–2, death, Barthel index, >90, NIHSS 0–1 at 3 months) among stroke patients with an iScore <200, but no benefit was observed for those with an iScore ≥200 when compared with the non-tPA group. The benefit of tPA in decreasing catastrophic outcomes for patients with an iScore ≥200 was likely explained by a ceiling effect because a substantially higher number of patients achieved a bad outcome (86.2% non-tPA versus 75.2% tPA), and thus, increasing the probability of detecting significant differences. The lack of better outcomes with tPA among patients with an iScore ≥200 was irrespective of the baseline NIHSS. Finally, we found an interaction between tPA and the iScore, suggesting the iScore may predict clinical outcomes after tPA.

In a recent study, our group found that patients with an iScore >200 had no apparent benefit from intravenous tPA and a 3-fold higher risk of hemorrhagic complications (20% versus 6%; P<0.001).11 We also found an interaction between tPA and the iScore for favorable outcome at discharge. When the iScore was applied to the National Institute of Neurological Disorders and Stroke Tissue-Type Plasminogen Activator Stroke trial, an iScore >200 was associated with higher risk of ICH (30.8% tPA versus 11.5% placebo; P=0.014) and no significant benefit for tPA (for an mRS 0–2 at 3 months: 18.5 tPA versus 11.5 placebo, OR, 1.73; 95% CI, 0.60–4.99). In this study, participants having an iScore >200 had an even lower probability of a favorable outcome at 3 months, with no significant difference between patients receiving (9.9%) and not receiving (8.9%) tPA (OR, 0.80; 95% CI, 0.45–1.42). In addition, our study confirms that other cut-off points do not improve the performance of the iScore. More important, our results are consistent with previous findings and reveal that the prognostic value of the iScore for functional clinical outcomes is extended to 90 days.

Our study has some limitations that deserve comment. First, we cannot rule out a selection bias for tPA treatment considering the nonrandomized data even when derived from clinical trials.12,13 Second, we cannot rule out the possibility of...
a type II error related to smaller sample sizes for patients with an iScore ≥200 or residual confounding even after completing a multivariable analysis. This study may be useful to facilitate discussions about thrombolysis with stroke patients and their families. Previous studies showed clinicians are not accurate in predicting the risk of intracerebral hemorrhage or response to tPA.19 In a randomized study comparing clinician estimations (n=1661) and the iScore with actual stroke outcomes, only 17% of clinicians caring for stroke patients were able to accurately estimate actual death or disability compared with 80% to 90% accurate predictions by the iScore. These findings revealed the importance of using validated risk tools compared with single physician clinical experience.19

We showed that stroke patients with an iScore ≥200 had a 9-fold risk of death or disability at 3 months with no significant improvement with tPA. After adjustment, only 5% to 6% of those patients were independent at 3 months (Figure 1). Despite the limited effectiveness of tPA in patients with a high iScore, some clinicians and families may still want to proceed with intravenous tPA in the absence of contraindications or when other therapeutic alternatives are not available.

In summary, the iScore is a simple, validated risk score, applicable to most common acute clinical settings that can be used by emergency physicians, internists, and neurologists when counseling patients and families. The iScore differentially identifies the likelihood of a favorable outcome at 3 months after tPA.

Acknowledgments

We thank the Virtual International Stroke Trials Archive investigators for facilitating access to the data. We declare that we participated in the conception, design, analysis, interpretation of the results and drafting of the article, and made a critical revision of the article.

Disclosures

Dr Saposnik is supported by the Clinician-Scientist Award from the Heart and Stroke Foundation of Canada and the Canadian Institute for Health Research. P.M.W. Bath is the Stroke Association Professor of Stroke Medicine. The other authors have no conflicts to report.

References


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Supplemental Material
Univariate analysis for different outcome measures using the iScore as a continuous and categorical variable:

A higher iScore (continuous) was associated with a lower risk of a favorable outcome (mRS 0-2) at 3 months (OR 0.977; 95% CI 0.975-0.978; p<0.001). Similar trend was observed for an iScore ≥200 (categorical) compared to an iScore <200 (OR 0.120; 95% CI 0.092-0.157; p<0.001).

A higher iScore was associated with an increased risk of death and disability (OR 1.027; 95% CI 1.025-1.029), death (OR 1.024; 95% CI 1.022-1.026) and a lower probability of achieving a BI >90 (OR 0.977; 95% CI 0.976-0.979) at 3 months after tPA.

In the univariate analysis, an iScore ≥200 (categorical) was associated with nine fold higher risk of death and disability at 3 months (OR 9.41, 95% CI 7.00-12.6) and fivefold higher risk of death at 3 months (OR 5.18; 95% CI 4.37-6.15) compared to patients with iScore <200.
eTable I: Risk Scoring System in the iScore

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
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<td>Age, years</td>
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<tr>
<td>Sex</td>
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<td>Female</td>
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<td>Male</td>
<td>+ 10</td>
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<td>Stroke Severity</td>
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<td>Mild</td>
<td>0</td>
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<td>Moderate</td>
<td>+ 40</td>
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<td>Severe</td>
<td>+ 65</td>
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<tr>
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<td>+ 105</td>
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<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>0</td>
</tr>
<tr>
<td>Non Lacunar</td>
<td>+ 30</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>+ 35</td>
</tr>
<tr>
<td>Risk Factor</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>+ 10</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>+ 10</td>
</tr>
<tr>
<td>Comorbid Condition</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>+ 10</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>+ 35</td>
</tr>
<tr>
<td>Preadmission Disability</td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>0</td>
</tr>
<tr>
<td>Dependent</td>
<td>+ 15</td>
</tr>
<tr>
<td>Glucose on Admission</td>
<td></td>
</tr>
<tr>
<td>&lt; 7.5 mmol/L (&lt;135 mg/dL)</td>
<td>0</td>
</tr>
<tr>
<td>≥ 7.5 mmol/L (≥135 mg/dL)</td>
<td>+ 15</td>
</tr>
</tbody>
</table>
Table II – Differences in baseline characteristics for clinically relevant variables between patients receiving and not receiving tPA by iScore strata

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=7140)</th>
<th>iScore &lt;200 (n=6382)</th>
<th>iScore ≥200 (n=711)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-tPA</td>
<td>tPA</td>
<td>p-value</td>
</tr>
<tr>
<td>Age, mean (±SD)</td>
<td>70.0 (12.3)</td>
<td>68.1 (13.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS, mean (±SD)</td>
<td>12.4 (5.7)</td>
<td>14.2 (5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OTT, mean in min (±SD)</td>
<td>257 (63)</td>
<td>214 (52)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* t-test was used to compare patients receiving and not receiving tPA for continuous variables

OTT: onset to neuroprotective trial treatment

There were no clinically significant differences between tPA and non-tPA by iScore strata for other variables (e.g. risk factors)
eTable III- Area under the curve comparing different iScore cutoff points for the outcomes of interest

<table>
<thead>
<tr>
<th>SPAN cutoff</th>
<th>Favorable outcome</th>
<th>Catastrophic Outcomes</th>
<th>Death at 3 months</th>
<th>NIHSS 0-1 at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0.7983</td>
<td>0.8039</td>
<td>0.7586</td>
<td>0.7322</td>
</tr>
<tr>
<td>200</td>
<td>0.7981</td>
<td>0.8035</td>
<td>0.7576</td>
<td>0.7321</td>
</tr>
<tr>
<td>220</td>
<td>0.7980</td>
<td>0.8035</td>
<td>0.7574</td>
<td>0.7323</td>
</tr>
<tr>
<td>Continuous</td>
<td>0.7983</td>
<td>0.8043</td>
<td>0.7595</td>
<td>0.7323</td>
</tr>
</tbody>
</table>

Values represent the area under the curve (AUC) estimated from logistic regression analyses for the outcomes of interest adjusted by tPA, OTT, age and NIHSS for each iScore cutoff.

There was no significant difference when compare the established iScore cutoff of 200 with other cutoff points for any of the analyzed outcomes. Definition of favorable and catastrophic outcomes as described in Table 2 in the text.
**e-Figure** - Distribution of the iScore in the whole cohort (A) and stratified by tPA status (B)