The iScore Predicts Effectiveness of Thrombolytic Therapy for Acute Ischemic Stroke

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**Background and Purpose**—Tools to predict the clinical response after intravenous thrombolytic therapy (tPA) are scarce. The iScore is an existing validated tool to estimate outcomes after an acute ischemic stroke. The purpose of this study was to determine the ability of the iScore to predict clinical response and risk of hemorrhagic transformation after tPA.

**Methods**—We applied the iScore (www.sorcan.ca/iscore) to patients presenting with an acute ischemic stroke at 11 stroke centers in Ontario, Canada, between 2003 and 2009 identified from the Registry of the Canadian Stroke Network. A cohort of patients with stroke treated at 154 centers in Ontario was used for external validation. We compared outcomes between patients receiving and not receiving tPA after adjusting for differences in baseline characteristics using propensity-score matching. Patients were stratified into 3 a priori defined groups according to tPA benefit by the iScore.

**Results**—Among 12,686 patients with an acute ischemic stroke, 1,696 (13.4%) received intravenous thrombolysis. Higher iScores were associated with poor outcomes in both the tPA and non-tPA groups (P<0.001). Among those at low and medium risk based on their iScores, tPA use was associated with a benefit in the primary outcome (relative risk, 0.74 for those with low-risk iScores: 95% CI, 0.67–0.84; relative risk, 0.88 for those with medium risk iScores: 95% CI, 0.84–0.93). There was no difference in clinical outcomes between matched patients receiving and not receiving tPA in the highest iScore group (relative risk, 0.97; 95% CI, 0.94–1.01). Similar results were observed for discharge and length of stay. The incident risk of neurological deterioration and hemorrhagic transformation (any or symptomatic) with tPA increased with the iScore risk. Results were similar in the validation cohort for risk of poor outcome with tPA by iScore level.

**Conclusion**—The iScore may be used to predict clinical response and risk of hemorrhagic complications after tPA for an acute ischemic stroke. Patients with high iScores may not have a clinically meaningful benefit from intravenous tPA at the time of carrying a higher risk of hemorrhagic complications. (Stroke. 2012;43:00-00.)

**Key Words:** cerebral infarct ■ outcomes ■ prognosis ■ stroke care ■ thrombolysis

Stroke is a leading cause of adult disability that can be devastating for patients and their families. Approximately two thirds of stroke survivors continue to experience functional deficits that are associated with diminished quality of life.1,2 Intravenous thrombolysis has been shown to improve clinical outcomes after an acute ischemic stroke in randomized trials and observational studies.3,4

Some factors that have been associated with improved outcome after thrombolysis include: shorter door-to-needle time, younger age, normoglycemia, the absence of comorbidities, and milder stroke.5,6 In contrast, advanced age, National Institutes of Health Stroke Scale >20, hyperglycemia on admission, and congestive heart failure among other comorbid conditions are associated with lower clinical response to thrombolysis.7–9

The decision to administer intravenous thrombolysis may be challenging, especially in patients with a higher prevalence of comorbid conditions, preadmission dependency, and de-
mentia. Patients and families wonder about the likelihood of a good outcome if tissue plasminogen activator (tPA) is given, especially if the risk of developing hemorrhagic complications is high. Although a variety of risk prediction tools exist to estimate death or disability after stroke, it is not known whether any of these can be used to predict the likelihood of a good outcome after thrombolytic therapy.

The iScore is a recently developed and validated score that can be used to estimate the risk of short- and long-term mortality and clinical outcomes after an acute ischemic stroke.10,11 The iScore categorizes patients with ischemic stroke into risk categories, from very low to very high average risk, using clinical parameters and comorbid conditions.10 The prediction of response to intravenous thrombolysis may be useful for patients, their families, and clinicians in counseling or discussions related to the decision of giving intravenous thrombolysis. Our objectives were (1) to evaluate the ability of the iScore to predict clinical response after thrombolysis in patients admitted with an acute ischemic stroke; and (2) to determine whether a differential response to thrombolysis exists among low-, medium-, and high-risk groups predicted by the iScore.

Methods

Study Population

We used the Registry of the Canadian Stroke Network (RCSN) to identify patients admitted to 11 acute stroke centers in the province of Ontario, Canada. Since its inception, the RCSN is a clinical database of >40,000 patients seen in the emergency department or admitted to the hospital with an acute stroke or transient ischemic attack. Further details on the RCSN can be obtained from the RCSN Report at www.rcsn.org and published elsewhere.10,12 Information on poststroke all-cause mortality was obtained through linkages to the Ontario Registered Persons Database at the Institute for Clinical Evaluative Sciences. The Registered Persons Database is a population-based administrative database including basic demographic data and date of death, which provides complete follow-up for all residents in the province. For the validation study (to determine the consistency of the results), we used the RCSN Ontario Stroke Audit database. Data collection for the Ontario Stroke Audit occurs every 2 to 4 years through the abstraction of charts of a random sample of eligible patients seen in the emergency department or admitted to all types of hospitals with a diagnosis of stroke or transient ischemic attack. All hospitals (n=154) in the province with >10 stroke admissions per year are included and include teaching hospitals and community-based institutions from rural and urban areas throughout Ontario. In the present study, we used Ontario Stroke Audit data collected in 3 periods: 2002 to 2003, 2004 to 2005, and 2008 to 2009. This external validation cohort consisted of 4908 patients with ischemic stroke admitted at 154 Ontario Stroke Audit hospitals.

Eligibility Criteria

The cohort used in the present study included patients from Phase 3 of the RCSN that were ≥18 years of age with a primary diagnosis of acute ischemic stroke and having presented to any of the 11 participating institutions in Ontario between July 1, 2003, and June 30, 2008. Patients with missing baseline characteristics (Congress of Neurological Surgeons score, glucose on admission, unique health identifier; n=1005; 7.3%) were excluded (Figure). Patients with transient ischemic attack were not eligible for this study.

The iScore

For each patient, we calculated the iScore. The iScore is a recently developed and validated risk score that can be used to estimate the risk of death or disability after an acute ischemic stroke. The risk scoring system is represented in Table 1. Details of the selection of variables for the iScore, data sources, and the creation and conceptualization of the iScore have been published elsewhere.10,11 An online web-based tool (www.sorcan.ca/iscore) and iPhone version are currently available for practical use. Because our intention was to determine the ability of the iScore to predict a good clinical response after thrombolysis, patients were categorized a priori into 3 risk groups based on their probability of death or disability after stroke based on their iScore: low risk (iScore 139 with a >50% probability of a good outcome), moderate risk (iScore 1105 with a 50% probability of a good outcome), and high risk (iScore 135 with a <50% probability of a good outcome).

Table 1. iScore Risk Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>+ Age (in y)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>+10</td>
</tr>
<tr>
<td>Stroke severity*</td>
<td></td>
</tr>
<tr>
<td>Mild (CNS &gt;8)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate (CNS 5–7)</td>
<td>+40</td>
</tr>
<tr>
<td>Severe (CNS 1–4)</td>
<td>+65</td>
</tr>
<tr>
<td>Coma (CNS 0)</td>
<td>+105</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>0</td>
</tr>
<tr>
<td>Nonlacunar</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>CHF</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>

CHF indicates congestive heart failure; NIHSS, National Institutes of Health Stroke Scale.

* A Canadian Neurological scale (CNS) of ≥8=NIHSS score of ≤8 (mild), a CNS of 5–7=NIHSS score of 9–13 (moderate), CNS of 1–4=NIHSS score of 14–22 (severe), and a CNS of 0=a NIHSS score of >22.
medium risk (iScore 140–179 with a 10%–50% probability of a good outcome), and high risk (iScore ≥180 with a <10% probability of a good outcome).

Outcome Measures
Poor outcome, the primary outcome measure, was defined as death that occurred within 30 days of the stroke admission or severe disability at discharge according to on the modified Rankin Scale (mRS) score of 3 to 5. Secondary outcomes included: (1) disability at discharge (mRS 3–5); (2) death at 30 days; (3) length of hospital stay; and (4) intracerebral hemorrhage (any type or symptomatic) and neurological deterioration in the tPA cohort.

Statistical Analysis
Chi-square tests were used to compare categorical variables; analysis of variance or Kruskal-Wallis tests were used to compare mean and median differences for continuous variables. Due to systematic differences in baseline characteristics between patients who did and did not receive tPA, propensity-score matching methods were used to estimate the effectiveness of tPA within each stratum of stroke severity as defined using the iScore. Propensity-score matching is an analytic technique that allows one to eliminate or minimize systematic differences between treatment groups so that any observed differences in outcomes can be attributed to the exposure. Propensity-score matching was conducted separately within each of the 3 stratum of the iScore. The propensity score (PS) was estimated using a logistic regression model in which receipt of tPA was regressed on the following baseline covariates that were thought to be associated with the outcomes of interest: age, sex, stroke severity, stroke subtype (lacunar versus other), hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke or transient ischemic attack, renal failure on dialysis, level of consciousness on arrival, dysphasia, glucose on admission, independence, and arrival by ambulance. Prior research has shown that including prognostically important variables in the PS model is a good analytic strategy.13,14 tPA and non-tPA patients were matched on the logit of the PS with a matching ratio of 1:1.15

In the final PS-matched sample, we compared the main (all-cause mortality at 30 days or disability at discharge) and secondary (disability at discharge, death at 30 days) outcomes between those receiving and not receiving intravenous tPA using paired t tests for continuous variables and McNemar tests for the binary variables. We calculated the relative risk and the corresponding 95% CIs in the PS-matched cohort using the method proposed by Agresti and Min.16

Statistical analysis was performed using SAS statistical software Version 9.2.2 (SAS Institute Inc, Cary, NC). All tests were 2-tailed, and probability values <0.05 were considered significant. Approvals from the St Michael’s Hospital review board and the RCSN Publications Committee were obtained.

Results
Among 12,686 patients with ischemic stroke in the RCSN sample, 1696 (13.4%) received intravenous tPA. In this sample, patients receiving tPA had more severe strokes, defined as a Congress of Neurological Surgeons score <4 (37.9% versus 16.1%; standardized difference 0.56), were more likely to have presented with aphasia (51.0% versus 28.6%; standardized difference 0.49), to have had a nonlacunar stroke subtype (93.10% versus 81.5%; standardized difference 0.31), and were more likely to have arrived by ambulance (91% versus 67.3%; standardized difference 0.60) compared with those who did not receive tPA (Table 2). Overall, the mean time from symptoms onset to tPA was 160.5 (SD ±87) minutes, and 18.8% received thrombolysis after 3 hours.

After PS matching in the low-risk group (iScore ≤139), 589 patients who received tPA were matched with 589 patients who did not receive tPA. Similarly, for the medium-risk (iScore 140–179) and high-risk (risk score ≥180) groups, 682 and 419 patients who received tPA were matched with 682 and 419 patients not receiving tPA, respectively. We were not able to find a match pair in only 6 patients (1.0%).

After matching on the PS, systematic differences between tPA and non-tPA patients in all groups were substantially reduced with all standardized differences being <0.1 (Table 3).

Clinical Outcomes by Risk Score
Overall, the absolute reduction in death or disability (mRS ≥3) at discharge was 10.2% favoring tPA (low iScore 16.1%; medium iScore 9.7%; high iScore 3.1%). In the matched sample, higher iScores were associated with poor functional outcomes in both the tPA and non-tPA groups (P<0.001; Table 4). In both the low- and medium-risk iScore groups, thrombolysis use was associated with a lower risk of a poor outcome (relative risk [RR], 0.74 in the low-risk group; 95% CI, 0.67–0.84; RR, 0.88 in the medium-risk group; 95% CI, 0.84–0.93). In the high-risk iScore group, tPA showed no significant benefit (RR, 0.97; 95% CI, 0.94–1.10). Similar results were observed for disability at discharge and length of stay (Table 4).

Death at 30 days occurred in 5.1% of non-tPA and 4.9% of tPA patients with low-risk iScores, 14.5% of non-tPA and 17.7% of tPA patients with medium-risk iScores, and 38.2% of non-tPA and 36.3% of tPA patients with high-risk iScores. tPA administration was not associated with a significant reduction in death at 30 days either in the overall sample nor in the matched risk groups (for the low iScore RR, 0.97; 95% CI 0.59–1.60; for the medium iScore RR, 1.22; 95% CI, 0.96–1.56; and for the high iScore RR, 0.95, 95% CI, 0.79–1.14).

The Figure represents the RR for a favorable outcome at each level of the iScore as determined from the multivariable model fit in the original cohort (n=12,868). These results complement those from the PS-matched analyses to suggest the lack of benefit with tPA (and probability of being harmful) for patients with an iScore >200 (note the upper CI crossed the line of 1; probability value for the iScore by treatment interaction <0.001).

Hemorrhagic Complications and Neurological Deterioration
Hemorrhagic transformation of any type occurred in 12.4% (211 of 1696), and symptomatic hemorrhage occurred in 6.9% (117 of 1696) of patients receiving tPA (Table 5).
Patients receiving tPA in the high-risk iScore group had a higher incidence of intracerebral hemorrhage (any type and symptomatic hemorrhagic transformation) and neurological deterioration compared with lower risk iScore groups (Table 5; Supplemental Figure I; http://stroke.ahajournals.org).

Overall, 30-day mortality for patients with any hemorrhagic transformation after tPA was 38.4% (81 of 211), and a poor outcome was observed in the vast majority (92.9%) of these patients. Among those with hemorrhagic complications, outcomes were worse in the higher compared with the lower risk iScore groups (Table 5). The number needed to harm for death at 30 days or disability at discharge was 5 for any hemorrhagic complication and 17 for symptomatic hemorrhagic transformation.

**External Validation**

Similar to the observation in the original cohort, tPA administration was associated with lower risk of poor outcomes in the low and medium iScore groups (low iScore RR, 0.78; 95% CI, 0.63–0.98; medium iScore RR, 0.83; 95% CI, 0.71–0.97). A nonsignificant benefit was observed between matched patients receiving and not receiving tPA in the high iScore group (RR, 0.91; 95% CI, 0.82–1.04). Similar results were observed for disability at discharge. Further details and other outcomes are shown in the supplemental material.

**Discussion**

The prediction of a clinical response to a specific treatment or intervention is difficult. Particularly challenging is the prediction of a clinical response to thrombolysis considering the diverse interaction of coexisting comorbidities in patients with stroke and the potential risk of serious complications (ie, intracerebral hemorrhage).17,18 Physicians’ perceptions on tPA risk and benefit assessment may not be accurate. For example, in a survey including emergency physicians and
neurologists, only 11% (95% CI, 0%–22%) could correctly identify the magnitude of the benefit with tPA. Similarly, only 39% were able to estimate the risk of symptomatic and fatal intracerebral hemorrhage. As a result, misperceptions and misconceptions could affect clinical decision-making, especially in emergency situations. More important, decision support using clinical tools (eg, iScore) and electronic resources for diagnosis, screening, or prevention improve clinicians’ performance. In previous studies, we found the iScore to be a useful tool to predict death at 30 days and 1 year as well as functional clinical outcomes after ischemic stroke. We have also demonstrated that the iScore improves on the accuracy of other simple models (only including age and stroke severity), which may over- or underestimate the risk of poor functional outcomes.

In the present propensity-matched study, patients in the low (≤139) and medium (140–179) risk iScore categories who received tPA were significantly more likely than those who did not receive tPA to have a favorable outcome. The low and medium iScore group receiving tPA had a significant 26% and 12% reductions, respectively, in the risk of the combined outcome of death at 30 days or disability at discharge. In contrast, intravenous tPA resulted in a nonsignificant benefit among patients in the highest risk (≥180) iScore category (compared with those who did not receive tPA). Moreover, hemorrhagic complications after tPA increased with the iScore risk, being 3 times higher in the high iScore stratum (19.8%) compared with the lower risk category (6.4%). Results were consistent in the validation cohort despite a smaller sample size. The chance of achieving a

Table 3. Baseline Characteristics After Matching tPA and Non-tPA Patients by Propensity Score Stratified by iScore Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Risk (iScore ≤139)</th>
<th>Medium Risk (iScore 140–179)</th>
<th>High Risk (iScore ≥180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-tPA (n=589)</td>
<td>tPA (n=589)</td>
<td>Standardized Difference of Mean</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>64.7±15.6</td>
<td>64.1±15.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Age categories, y &lt;65</td>
<td>49.7</td>
<td>49.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>66–79</td>
<td>31.7</td>
<td>32.3</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;80</td>
<td>18.5</td>
<td>18.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex, women</td>
<td>45.8</td>
<td>44.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS score, mean SD</td>
<td>8.2±1.9</td>
<td>8.1±1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>CNS categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS &lt;4 (severe)</td>
<td>5.4</td>
<td>6.6</td>
<td>0.05</td>
</tr>
<tr>
<td>CNS 5–7 (moderate)</td>
<td>30.7</td>
<td>30.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CNS &gt;8 (mild)</td>
<td>63.8</td>
<td>62.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean glucose on admission, mmol/dL</td>
<td>7.16±3.3</td>
<td>7.14±3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>2</td>
<td>2.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Aphasia</td>
<td>38.4</td>
<td>39</td>
<td>0.01</td>
</tr>
<tr>
<td>Risk factors</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>57.7</td>
<td>54.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.9</td>
<td>14.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.2</td>
<td>7</td>
<td>0.08</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.4</td>
<td>3.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11.5</td>
<td>12.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30.2</td>
<td>30.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoker</td>
<td>25.5</td>
<td>24.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.2</td>
<td>3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>10.2</td>
<td>9.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Preadmission</td>
<td>96.9</td>
<td>95.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Independency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>88.3</td>
<td>86.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke subtype, lacunar</td>
<td>17.7</td>
<td>16.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values represent percentages unless indicated otherwise.
tPA indicates tissue plasminogen activator; CNS, Canadian Neurological Scale; LOC, decreased level of consciousness; TIA, transient ischemic attack.
favorable outcome with tPA sharply declined with higher iScore risk. Patients with iScore >200 had no apparent benefit after tPA with a potential harmful effect (Figure).

Together these findings suggest that the iScore can be used to predict the clinical response and major complications after tPA. These findings may be useful to clinicians in identifying groups of patients less likely to respond to tPA.

Previous studies have identified factors associated with good outcome and risk of hemorrhagic transformation after thrombolysis.3,5,21,22 In a pooled analysis of randomized trials including 2131 patients receiving tPA or placebo, the authors developed a model to predict good (mRS 0–1) and poor (mRS ≥5) outcome.23 Common variables associated with good outcome included the combination of age and National Institutes of Health Stroke Scale, hypertension and tPA, sex, and diabetes. Moreover, >60% of patients included in the study were treated between 3 and 6 hours after symptom onset. Despite this valuable information, no risk score has been validated in a large cohort including “real-world” patients to assist clinicians to determine the likely clinical response to thrombolysis. The iScore includes some of the well-established predictors (eg, age, stroke severity, hyperglycemia) and also adds other relevant concomitant conditions influencing stroke outcomes.10,11 Moreover, the observed absolute reductions in death or disability (mRS ≥3) in the matched cohort for tPA (10.2%) were similar to those reported in the National Institute of Neurological Disorders and Stroke (11.7%),24 European–Australian Acute Stroke Study (ECASS) III (6.8%),25 and Safe Implementation of Thrombolysis International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive (SITS/VISTA; 14.1%).26

The risk, benefits, and quality of life after tPA in selected high-risk groups has been under debate. In our study, the lack of benefit of tPA in the high-risk iScore group was in part driven by a 20% incident risk of intracerebral hemorrhage (any type and symptomatic), which was associated with a 48% mortality and 99% risk of death or major disability at discharge (Table 5). Although our functional outcome effectively integrates the benefits of tPA with any detrimental effect of hemorrhagic conversion, clinicians may have to balance options in the high iScore group for whom the chance of a good outcome is substantially lower than the risk of hemorrhagic complications. Many clinicians will still elect to administer intravenous iPA in this group given the poor outcomes in the absence of tPA (favorable outcome: 4.8% non-tPA versus 7.4% tPA group; RR, 2.8%; −0.8% to 6.2%) and the unlikely possibility of spontaneous recovery. Others may consider different therapeutic alternatives (eg, endovascular approach) after a discussion with the patient and/or their family. Regardless of the ultimate decision, the iScore facilitates useful information when counseling patients and their families.

Our study has several limitations and strengths. First, it is possible that some potentially relevant variables (eg, infarct size, imaging information) not included in the initial iScore

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**Table 4. Outcome Measures in the Matched Cohort by iScore Groups**

<table>
<thead>
<tr>
<th>iScore</th>
<th>30-Day Mortality or Disability at Discharge (%)</th>
<th>Disability at Discharge (mRS 3–5; %)</th>
<th>Mean Length of Stay, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITPA No ITPA RR (95% CI)</td>
<td>ITPA No ITPA RR (95% CI)</td>
<td>ITPA No ITPA RR (95% CI)</td>
</tr>
<tr>
<td>Low (&lt;iScore ≤139&gt;)</td>
<td>274 (46.7)</td>
<td>370 (62.8)</td>
<td>0.743 (0.670–0.824)</td>
</tr>
<tr>
<td>Medium (iScore 140–179)</td>
<td>517 (75.8)</td>
<td>585 (85.8)</td>
<td>0.884 (0.838–0.932)</td>
</tr>
<tr>
<td>High (iScore &gt;180)</td>
<td>388 (92.6)</td>
<td>399 (95.2)</td>
<td>0.972 (0.938–1.008)</td>
</tr>
</tbody>
</table>

Patients with stroke receiving intravenous thrombolysis (ITPA) were matched with patients with stroke not receiving thrombolytic therapy (no ITPA). Risk score range: low (<iScore ≤139), medium (iScore 140–179), high (iScore >180). Further details of outcomes definition is in the text. There was no improvement in any of the 3 clinical outcomes for patients with stroke receiving thrombolysis with the higher risk score.

mRS indicates modified Rankin Scale; RR, relative risk.
may be associated with variations in the response to thrombolysis with the potential of confounding by indication. Because the iScore was not created for this primary purpose, these factors were not included in the original iScore and are not available in our clinical database. Second, although several ethnic groups were included in the present study, the majority of patients were non-Hispanic whites. Third, we cannot rule out a Type II error. We would argue, however, the power to detect a difference may be less relevant in the light of only 2.6% (nonsignificant) benefit in the primary outcome between matched tPA and non-tPA patients in the high iScore group. Fourth, due to sparse data in some iScore groups, the regression models to generate the Figure may be unstable and should be viewed as hypothesis-generating. Moreover, our study does not rule out a potential clinically meaningful benefit using other therapeutic approaches (eg, endovascular revascularization, intra-arterial thrombolysis, hypothermia) in the high iScore group. Fifth, the determination of the stroke subtype early after hospitalization may be a limitation for nonstroke experts. Finally, although we used PS matching to minimize baseline differences, this is not a randomized study, and the results from this observational study should not substitute for expert clinical assessment when making decisions on the administration of thrombolysis.

Strengths of our study include a large sample size comprising "real-world" patients (with 19% receiving tPA beyond 3 hours), the use of a previously validated score with a nearly complete ascertainment of stroke severity and follow-up, good matching for all patients receiving tPA, and consistency of the results in 2 independent cohorts.

This study suggests that the iScore (www.sorcan.ca/iScore) can be used to estimate the response and risk of complications after thrombolytic therapy for ischemic stroke. These results may provide important information to clinicians when discussing therapeutic options and prognosis with patients and their families and support rational decision-making for thrombolysis administration. Prospective studies may help determine the best approach in the high iScore group. From the organizational and resource allocation perspective, the iScore may also facilitate discussions about thrombolytic therapy, especially in high-risk individuals who may require more careful monitoring and expend more resources.

### Table 5. Outcomes by iScore Groups Among Patients Receiving tPA Who Developed Hemorrhagic Complications

<table>
<thead>
<tr>
<th>iScore Group</th>
<th>No./No.</th>
<th>30-Day Mortality*</th>
<th>Death at 30 Days or Disability at Discharge†</th>
<th>No./No.</th>
<th>30-Day Mortality‡</th>
<th>Death at 30 Days or Disability at Discharge§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (iScore ≤139)</td>
<td>38/590 (6.4)</td>
<td>9 (23.7)</td>
<td>30 (78.9)</td>
<td>17/590 (2.9)</td>
<td>7 (41.2)</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td>Medium (iScore 140–179)</td>
<td>90/687 (13.1)</td>
<td>32 (35.6)</td>
<td>84 (93.3)</td>
<td>53/687 (7.7)</td>
<td>25 (47.2)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>High (iScore ≥180)</td>
<td>83/419 (19.8)</td>
<td>40 (48.2)</td>
<td>82 (98.8)</td>
<td>47/419 (11.2)</td>
<td>26 (55.3)</td>
<td>47 (100)</td>
</tr>
<tr>
<td>All</td>
<td>211/1696 (12.4)</td>
<td>81 (38.4)</td>
<td>196 (92.9)</td>
<td>117/1696 (6.9)</td>
<td>58 (49.6)</td>
<td>116 (99.1)</td>
</tr>
</tbody>
</table>

Further details of outcomes definition is in the text. No. represents the no. of patients receiving tPA who developed the outcome. No. represents the total no. of patients in the group. Values in parentheses are percentages unless indicated otherwise. 
P values for comparisons among iScore risk groups: *0.028. †<0.001. ¶0.54. §§0.05.

### Disclosures

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### References

The iScore Predicts Effectiveness of Thrombolytic Therapy for Acute Ischemic Stroke

Gustavo Saposnik, Jiming Fang, Moira K. Kapral, Jack V. Tu, Muhammad Mamdani, Peter Austin and S. Claiborne Johnston

on behalf of the Investigators of the Registry of the Canadian Stroke Network (RCSN) and the Stroke Outcomes Research Canada (SORCan) Working Group

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Supplemental File — The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke

The Registry of the Canadian Stroke Network

Legislation in Ontario enacted in 2004 established rules for the collection, use, and disclosure of personal health information to protect the privacy and confidentiality of individuals; the RCSN has the designation of a “prescribed registry”, thereby permitting the collection of patient data without consent for the purpose of facilitating the provision of stroke care in the province of Ontario. The RCSN regional center database collects data by chart abstraction performed during and after admission to hospital for the index event by trained neurology research nurses using custom software. Chart abstraction studies have shown good to excellent agreement within the RCSN database, with kappa scores of > 0.8 for key variables (such as age, sex, stroke type, and thrombolysis use).

Stroke severity:

We used the Canadian Neurological Stroke (CNS) Scale, which is analogous to the more widely used National Institute of Health (NIH) Stroke Scale for assessing stroke severity. A recent study validated the ability to use the CNS and NIH Stroke Scale interchangeably. As a result, the following conversion formula can be used: a CNS of 1-4 = a NIH score of 14-22 (severe), a CNS of 5-7 = a NIH score of 9-13 (moderate), a CNS of ≥ 8 = NIH score of ≤8 (mild), and a CNS of 0 = an NIH score of >22.1

The iScore:

The iScore has been shown to have good discrimination (c-statistics 0.85 for 30-day mortality, 0.84 for 1-year mortality, and 0.79 for death at 30-days or disability at discharge in the validation cohorts) and calibration.
Application of iScore (examples)

For a 70 year (+70) old man (+10) who was previously independent (+0), with history of atrial fibrillation (+10), presenting with a mild (+0) lacunar stroke (+0), and a glucose on admission <7.5mmol/L (+0), the iScore would be 90 and the estimated 30-day mortality would be ~1%. Similarly, the estimated risk of dead at 30 days or disability at discharge would be 22%.

For a 80 year (+80) old woman (+0), previously independent (+0), with history of congestive heart failure (+10) and renal failure on dialysis (+35), presenting with a moderate (+40) non-lacunar (+30) stroke, and a glucose on admission of 12.8 mmol/L (+15), her 30-day risk score would be 210 and the estimated mortality at 30 days would be 39%. Similarly, the estimated risk of dead at 30 days or disability at discharge would be 93%.

Statistical Analysis:

To determine whether the propensity score approach achieved balance in potential confounders, we compared the proportions of each covariate between the two treatment groups. Evidence of imbalance in potential confounders was identified by examining the reduction in absolute standardized differences, estimated as a percentage of the standard deviation. Differences between groups are divided by the pooled standard deviation of the two groups. Adequate balance was defined as a standardized difference less than 0.1.\(^2,3\)

As a sensitivity analysis to explore the effect to which the iScore modifies the effect of tPA on outcomes, we fit a Poisson regression model in which the occurrence of a favorable outcome was regressed on an indicator variable denoting tPA status, the iScore, and the interaction between these two variables. For each level of the iScore, the relative risk for a good outcome for tPA vs. no tPA was determined from the regression model. Results are presented graphically, as the relative risk [RR (95%CI)] of a good outcome [independent at discharge (mRS=0-2) and alive at 30-days].
External Validation

Among 4,908 eligible patients with an acute ischemic stroke in the OSA, 255 (5.2%) received tPA. Following 1:1 matching using the PS in strata defined by the iScore, 105 tPA patients were matched to 105 non-tPA patients for the low risk group (iScore \(\leq 139\)). Similarly, 88 (medium risk iScore 140-179) and 55 (high risk iScore \(\geq 180\)) tPA patients were matched with their non-tPA counterparts. There was a good matching for each group of the iScore (supplemental table).

No significant reduction in death at 30 days was observed between patients who did and did not receive tPA (low iScore: RR 0.71, 95%CI 0.25-2.04; medium iScore: RR 0.70, 95%CI 0.28-1.73; high iScore: RR 1.77, 95%CI 0.97-3.2). Length of stay was longer in patients not receiving tPA, although the differences didn’t reach significance (supplemental table).

Patients with higher iScores had a higher incident risk of hemorrhagic transformation (any type or symptomatic) with a rate and trend similar to that observed in the original cohort. For example, hemorrhagic transformation of any type was detected in 12.5% (33/255) of tPA patients (9.0% in the low iScore, 12.4% in the medium iScore, and 20% in the high iScore group). Symptomatic hemorrhagic transformation was observed in 6.3% (16/255) patients (4.5%, 2.2% and 16.4% in the low, medium and high iScore, respectively).
**Table 1: Baseline characteristics after matching stratified by iScore group in the validation cohort (OSA)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low risk (iScore ≤139)</th>
<th>Medium risk (iScore 140-179)</th>
<th>High risk (iScore ≥180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-tPA (n=105)</td>
<td>tPA (n=105)</td>
<td>non-tPA (n=88)</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>Variance</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Age, mean ± SD</strong></td>
<td>66.1 ± 16.7</td>
<td>64.9 ± 14.4</td>
<td>0.07 ± 0.72</td>
</tr>
<tr>
<td><strong>Age categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>49 (46.7%)</td>
<td>49 (46.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>66-79</td>
<td>30 (28.6%)</td>
<td>35 (33.3%)</td>
<td>0.1 ± 1.09</td>
</tr>
<tr>
<td>&gt;80</td>
<td>26 (24.8%)</td>
<td>21 (20.0%)</td>
<td>0.11 ± 0.86</td>
</tr>
<tr>
<td><strong>Sex, Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Score, mean ± SD</td>
<td>8.21 ± 1.72</td>
<td>8.27 ± 1.74</td>
<td>0.04 ± 1.02</td>
</tr>
<tr>
<td>CNS categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS &lt;4 (Severe)</td>
<td>2 (1.9%)</td>
<td>4 (3.8%)</td>
<td>0.11 ± 1.96</td>
</tr>
<tr>
<td>CNS 5-7 (Moderate)</td>
<td>35 (33.3%)</td>
<td>35 (33.3%)</td>
<td>&lt;0.01 ± 1</td>
</tr>
<tr>
<td>CNS &gt;8 (Mild)</td>
<td>68 (64.8%)</td>
<td>66 (62.9%)</td>
<td>0.04 ± 1.02</td>
</tr>
<tr>
<td>Mean Glucose on admission, mmol/L</td>
<td>6.79 ± 2.86</td>
<td>7.32 ± 2.97</td>
<td>0.18 ± 1.08</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>2 (1.9%)</td>
<td>2 (1.9%)</td>
<td>&lt;0.01 ± 1</td>
</tr>
<tr>
<td>Aphasia</td>
<td>30 (28.6%)</td>
<td>37 (35.2%)</td>
<td>0.14 ± 1.12</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (60.0%)</td>
<td>58 (55.2%)</td>
<td>0.1 ± 1.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25 (23.8%)</td>
<td>22 (21.0%)</td>
<td>0.07 ± 0.91</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>10 (9.5%)</td>
<td>7 (6.7%)</td>
<td>0.1 ± 0.72</td>
</tr>
<tr>
<td>Congestive Heart failure</td>
<td>5 (4.8%)</td>
<td>5 (4.8%)</td>
<td>&lt;0.01 ± 1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15 (14.3%)</td>
<td>13 (12.4%)</td>
<td>0.06 ± 0.89</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>34 (32.4%)</td>
<td>33 (31.4%)</td>
<td>0.02 ± 0.98</td>
</tr>
<tr>
<td>Smoker</td>
<td>18 (17.1%)</td>
<td>19 (18.1%)</td>
<td>0.02 ± 1.04</td>
</tr>
<tr>
<td>Dementia</td>
<td>6 (5.7%)</td>
<td>3 (2.9%)</td>
<td>0.14 ± 0.52</td>
</tr>
<tr>
<td>Renal Failure on Dialysis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal Failure on Dialysis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal Failure on Dialysis</td>
<td>11 (10.5%)</td>
<td>13 (12.4%)</td>
<td>0.06 ± 1.16</td>
</tr>
<tr>
<td>Previous Stroke/TIA</td>
<td>98 (93.3%)</td>
<td>98 (93.3%)</td>
<td>&lt;0.01 ± 1</td>
</tr>
<tr>
<td>Pre-admission Independency</td>
<td>87 (82.9%)</td>
<td>86 (81.9%)</td>
<td>0.02 ± 1.04</td>
</tr>
<tr>
<td>Arrival by Ambulance</td>
<td>29 (27.6%)</td>
<td>28 (26.7%)</td>
<td>0.02 ± 0.98</td>
</tr>
</tbody>
</table>

Values between brackets represent percentages, unless indicated otherwise. SD: standardized difference of the mean.
## eTable 2: Outcome measures in the validation cohort (OSA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>iScore group</th>
<th>Relative Risk</th>
<th>RR Lower CI</th>
<th>RR Upper CI</th>
<th>Risk Difference - McNemar Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 30 days or disability at discharge</td>
<td>Low risk</td>
<td>0.783</td>
<td>0.625</td>
<td>0.980</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Medium risk</td>
<td>0.829</td>
<td>0.708</td>
<td>0.971</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>0.907</td>
<td>0.820</td>
<td>1.004</td>
<td>0.125</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 30 days</td>
<td>Low risk</td>
<td>0.714</td>
<td>0.251</td>
<td>2.036</td>
<td>0.754</td>
</tr>
<tr>
<td></td>
<td>Medium risk</td>
<td>0.700</td>
<td>0.283</td>
<td>1.734</td>
<td>0.607</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>1.769</td>
<td>0.971</td>
<td>3.223</td>
<td>0.087</td>
</tr>
<tr>
<td>Disability (mRS 3-5)</td>
<td>Low risk</td>
<td>0.862</td>
<td>0.670</td>
<td>1.109</td>
<td>0.312</td>
</tr>
<tr>
<td></td>
<td>Medium risk</td>
<td>0.778</td>
<td>0.657</td>
<td>0.921</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>0.879</td>
<td>0.753</td>
<td>1.026</td>
<td>0.219</td>
</tr>
</tbody>
</table>
Supplemental File (online figures)- The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke

eFigure 1: Study Population

RCSN (2003 - 2008)
Ischemic strokes
n=13,700

Not eligible
< 18 years (n=9)

Eligible
n=13,691

Exclusions
Missing CNS (n=304)
Missing baseline glucose (n=701)

Final research sample
n=12,686
eFigure 2: Hemorrhagic complications and neurological deterioration in the tPA cohort

Legend:

Overall, patients with lower iScores had a lower risk of hemorrhagic complications with tPA. Patients in the lower iScore stratum (low and medium risk) had a lower incident risk of intracerebral hemorrhage (any type), symptomatic hemorrhagic transformation, and neurological deterioration compared to the highest iScore group (p<0.001).

* p-value for trend <0.0001
HT: hemorrhagic transformation
Note the graded effect between the iScore and the incident risk of neurological deterioration, hemorrhagic transformation (any type), and symptomatic hemorrhagic transformation.
eFigure 3: Outcome measures in the validation cohort (OSA)

**Figure 3A: Death at 30-days or disability at discharge in the validation cohort**

![Bar graph showing death rates in the validation cohort by risk group with p-values](image)

* p=0.044, ** p=0.029

**Figure 3B: Hemorrhagic transformation (HT) in the validation cohort**

![Bar graph showing HT rates in the validation cohort by risk group with p-values](image)

p-value for trend * p=0.05  ** p<0.001
Figure 3C: Length of stay (in days) in the validation cohort
References:


iScore는 급성 허혈뇌졸중의 혈전용해요법의 효과를 예측한다

The iScore Predicts Effectiveness of Thrombolytic Therapy for Acute Ischemic Stroke

Gustavo Saposnik, MD, MSc, FAHA; Jiming Fang, PhD; Moira K. Kapral, MD, MSc, FRCPC; Jack V. Tu, MD, PhD, FRCPC; Muhammad Mamdani, PharmD, MPH, MA; Peter Austin, PhD; S. Claiborne Johnston, MD, PhD, FAHA; on behalf of the Investigators of the Registry of the Canadian Stroke Network (RCSN) and the Stroke Outcomes Research Canada (SORCan) Working Group

(Stroke. 2012;43:1315-1322.)

Key Words: cerebral infarct ■ outcomes ■ prognosis ■ stroke care ■ thrombolysis

배경과 목적: 정맥내혈전용해(tPA) 이후 임상적 반응을 예측하는 도구는 적다. iScore는 급성 허혈뇌졸중 이후 결과를 예측하는 능력이 검증된 기존의 도구이다. 이 연구의 목적은 iScore가 tPA 이후 출혈변환의 위험과 임상적 반응을 예측하는 능력을 보는 것이다.


결과: 급성 허혈뇌졸중 환자 12,686명 중에서 1,696명(13.4%)이 tPA 치료를 받았다. 높은 iScore는 tPA군과 비tPA군에서 모두 불량한 결과와 관련이 있었다(P<0.001). iScore에 의하면 낮은 증상도 및 증동도의 위험도로 가진 환자는 임상결과에서 tPA가 도움이 되었다(낮은 위험의 iScore를 가진 환자의 RR, 0.74: 95% CI, 0.67-0.84: 증동도 위험의 iScore를 가진 환자의 RR, 0.88: 95% CI, 0.84-0.93). 높은 iScore를 가진 환자들은 tPA를 받은 환자와 그렇지 않은 환자들 간에 임상적 결과가 비슷했다 (RR, 0.97: 95% CI, 0.94-1.01). 퇴원 시의 장애와 재활기간의 경우에도 결과는 비슷했다. iScore 위험도가 증가할수록 tPA 사용 후 신경학적 악화와 출혈변환(모든 종류나 증상이) 발생할 위험은 증가했다. Validation 코호트에서도 iScore가 tPA에 의해 불량한 결과가 발생할 위험도에 미치는 영향은 비슷했다.

결론: iScore는 급성 허혈뇌졸중에서 tPA 이후 출혈변환이 발생한 위험이나 임상적 반응을 예측할 수 있을 것이다. 높은 iScore를 가진 환자는 출혈성 합병증의 위험이 높아서 정맥내tPA로 인한 임상적 이득이 없을 가능성이 있다.

노 | 졸중은 환자와 가족을 고통스럽게 만드는 성인에서의 장애의 주요한 원인이다. 뇌졸중 환자 중 2/3가 살 의 질 저하와 관련된 기능적 손실을 경험한다.12 정맥내혈전용해는 무작위 임상시험과 관찰연구에서 급성 허혈뇌졸중 이후

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임상적 결과를 모형시킨다.\textsuperscript{3,4}
혈전증후 결과를 양상시키는 요인은 내원 후 정주까지 결
린 짧은 시간, 성상 혈당, 동반이환 부재, 정미한 뇌졸중 등이 다.\textsuperscript{5,6} 반대로 고혈압, NIH 뇌졸중도 >20, 입원 시 고혈당, 음
혈성심부전은 혈전증후가 임상적으로 저조한 반응을 나타내는
것과 관리가 있다.\textsuperscript{7,8}
특히 동반이환, 기존의 장애, 치매가 있을 때 정맥내혈전용
해를 결정하는 것은 어렵다. 특히 출혈성 혈종증 수반한 가
능성이 높을 때 환자와 가족은 조직플라스마리노산원성체(tis-
sue plasminogen activator, tPA)를 정주할 때 결과가 좋은
가능성을 대해 긍정한다. 뇌졸중 이후 사망이나 장애가 발생
할 가능성은 예측하는 도구가 여러 가지 있으나 이 중 어느 것
이 혈전용요법 이후의 영향의 결과를 예측할 수 있는지에 대
해서는 아직 이해하지 못한다.

iScore는 급성 혈혈뇌졸중의 장단기 사망률과 임상적 결과
를 예측할 수 있다는 것을 최근에 출현한 간수체계이다.\textsuperscript{9,11}
iScore는 임상적 지표와 동반이환율 이용해서 대체 난은 위험
에 대우 높은 위험으로 혈혈뇌졸중 환자를 분류할 수 있다.\textsuperscript{10}
혈전증후에 대한 반응을 예측하는 것은 정맥내혈전용해를 할
것인지를 결정하기 위한 단단이나 논의를 하는 때에 있어서
환자, 가족, 의자에게 유용할 수 있다. 우리의 목표는 (1) iScore
가 급성 혈혈뇌졸중으로 입원하여 혈전용해를 한 후의 반응을
예측하는 능력을 평가하고, (2) iScore가 예측한 결과와 중위
협, 고위험 환자군에서 혈전용해가 다른 반응을 입으키는지 보
는 것이다.

방법

연구 계획

우리는 Registry of the Canadian Stroke Network (RCSN)을 이용하여 캐나다의 온타리오주에 있는 11개 급성뇌
졸증센터에 급성 혈혈뇌졸중으로 내원한 환자를 찾아냈다.
RCSN은 급성뇌졸중이나 TIA로 응급실 내원하거나 병원에
입원한 >40,000명의 환자의 임상적 자료들이다. RCSN에 대
한 자세한 사항은 www.rcsn.org의 RCSN Report나 다른 곳
에 게재된 자료에서 얻을 수 있다.\textsuperscript{12}\textsuperscript{13} Institute for Clinical
Evaluative Sciences의 Ontario Registered Persons Database를 이용해서 뇌졸중의 임상적 정보를 얻았다. Registered Persons Database는 인구기반의 행정자
료들로 인구학적 정보와 사용량에 대한 정보를 담고 있어서 주
내의 모든 주민에 대한 완벽한 추적조사가 가능하다. 결과가
일관성이 있는지 보기 위한 validation 연구를 위해서 RCSN
Ontario Stroke Audit 자료들을 이용했다. Ontario Stroke Audit을 위한 자료 수집은 2~4년 간격으로 하게 되는데 뇌졸
중 또는 TIA로 응급실에 내원하거나 병원에 입원한 적격한 환
자 중에서 무작위로 선택된 표본의 의무기록을 추출한다. 연간
>10명의 환자가 입원하는 주 안의 모든 병원(n=154)을 포함
하는데 수련병원과 온타리오의 도시와 농촌을 아우르는 지역
의료기관을 맡았다. 이 연구에서 우리는 세 개의 기간
Stroke Audit 자료를 사용했다. 이 external validation 코
호트는 154개의 Ontario Stroke Audit 병원에 입원한 4,908
명의 혈혈뇌졸중 환자로 이루어졌다.

적격성 기준

이 연구에서 사용한 코호트는 주 전단이 급성 혈혈뇌졸중이고
2003년 7월 1일부터 2008년 6월 30일 사이에 온타리오의 11개
의 참여의료기관 중 하나에 내원한 18세 이상인 RCSN 3기에
환자를 포함하고 있다. 초기 특성(Congress of Neurological
Surgeons 점수, 입원 시 혈당, 건강 정보)에 대한 기록이 없는
환자는 제외하였다(Figure). TIA 환자는 이 연구에 적격이 아니다.

\begin{table}
\centering
\caption{iScore Risk Scoring System\textsuperscript{7,8}}
\begin{tabular}{ll}
\hline
\textbf{Variable} & \textbf{Score} \\
\hline
Age, y & +Age (in y) \\
Sex & \\
Female & 0 \\
Male & +10 \\
Stroke severity* & \\
Mild (1NS >8) & 0 \\
Moderate (NS 5-7) & +40 \\
Severe (NS 1-4) & +65 \\
Coma (NS 0) & +105 \\
Stroke subtype & \\
Lacunar & 0 \\
Nonlacunar & +30 \\
Undetermined etiology & +35 \\
Risk factor & \\
Atrial fibrillation & +10 \\
CHF & +10 \\
Comorbid condition & \\
Cancer & +10 \\
Renal dialysis & +35 \\
Preadmission disability & \\
Independent & 0 \\
Dependent & +15 \\
Glucose on admission & \\
<7.5 mmol/L (<=135 mg/dL) & 0 \\
\geq 7.5 mmol/L (>=135 mg/dL) & +15 \\
\hline
\end{tabular}
\begin{flushright}
\textsuperscript{*A Canadian Neurological scale (NS) of \geq 8=NHSS score of \leq 8 (mild), a
NS of 5-7=NHSS score of 9-13 (moderate), NS of 1-4=NHSS score of
14-22 (severe), and a NS of 0= a NHSS score of 22-22.}
\end{flushright}
\end{table}
Table 2. Baseline Characteristics of Patients Receiving and Not Receiving Thrombolysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-IPA (n=10,990)</th>
<th>tPA (n=1,696)</th>
<th>Standardized Difference of Mean</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>72.15±13.78</td>
<td>71.55±13.87</td>
<td>0.04</td>
<td>0.093</td>
</tr>
<tr>
<td>Age categories, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>3097 (28.2)</td>
<td>486 (28.7)</td>
<td>0.01</td>
<td>0.686</td>
</tr>
<tr>
<td>66–79</td>
<td>4124 (37.5)</td>
<td>635 (37.4)</td>
<td>0</td>
<td>0.947</td>
</tr>
<tr>
<td>&gt;80</td>
<td>3769 (34.3)</td>
<td>575 (33.9)</td>
<td>0.01</td>
<td>0.752</td>
</tr>
<tr>
<td>Sex, women</td>
<td>5205 (47.4)</td>
<td>821 (48.4)</td>
<td>0.02</td>
<td>0.422</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS score, mean±SD*</td>
<td>8.32±3.05</td>
<td>5.83±2.51</td>
<td>0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS &lt;4 (severe)</td>
<td>1770 (16.1)</td>
<td>642 (37.9)</td>
<td>0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS 5–7 (moderate)</td>
<td>1828 (16.6)</td>
<td>651 (38.4)</td>
<td>0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS &gt;8 (mild)</td>
<td>7392 (67.3)</td>
<td>403 (23.3)</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean glucose on admission, mmol/L</td>
<td>7.70±3.45</td>
<td>7.56±2.84</td>
<td>0.04</td>
<td>0.112</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>1369 (12.5)</td>
<td>298 (17.6)</td>
<td>0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aphasia</td>
<td>3139 (28.6)</td>
<td>865 (51.0)</td>
<td>0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7518 (68.4)</td>
<td>1125 (66.3)</td>
<td>0.04</td>
<td>0.088</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2904 (26.4)</td>
<td>334 (19.7)</td>
<td>0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1868 (17.0)</td>
<td>316 (18.6)</td>
<td>0.04</td>
<td>0.099</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>979 (8.9)</td>
<td>173 (10.2)</td>
<td>0.04</td>
<td>0.085</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1665 (15.3)</td>
<td>260 (15.3)</td>
<td>0</td>
<td>0.998</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3832 (34.9)</td>
<td>605 (35.7)</td>
<td>0.02</td>
<td>0.518</td>
</tr>
<tr>
<td>Smoker</td>
<td>2164 (19.7)</td>
<td>305 (18.0)</td>
<td>0.04</td>
<td>0.086</td>
</tr>
<tr>
<td>Dementia</td>
<td>988 (8.9)</td>
<td>109 (6.4)</td>
<td>0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>102 (0.9)</td>
<td>9 (0.5)</td>
<td>0.04</td>
<td>0.102</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>2401 (21.8)</td>
<td>259 (15.3)</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preadmission independency</td>
<td>8512 (77.5)</td>
<td>1504 (88.7)</td>
<td>0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>6995 (63.6)</td>
<td>1544 (91.0)</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke subtype, lacunar</td>
<td>2031 (18.5)</td>
<td>117 (6.9)</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise. CNS indicates Canadian Neurological Scale; LOC, decreased level of consciousness; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

*A CNS score of ≥8=NIHSS score of ≥8 (mild); a CNS score of 5–7=NIHSS score of 9–13 (moderate); a CNS score of 1–4=NIHSS score of 14–22 (severe), and a CNS of 0=NIHSS score of >22.

**iScore**

각 환자에서 iScore를 계산하였으며, iScore는 급성 혈관뇌출혈 중 이외 사망이나 장애의 위험을 계산할 수 있도록 최근에 개발하고 임상적 의료도 전문가이기도 하다. 위험도 점수계수는 Table 1에서 나타나 있다. iScore에 사용하는 변수의 선정, 자료원, iScore의 개발과 개념화에 대한 상세정보는 다른 곳에 게재하였다.[10,11] 현실적인 사용을 위해 현재 온라인 웹사이트의 도구(www.sorcan.ca/iscore)와 아이폰 버전을 사용할 수 있다. 우리의 의도는 iScore가 환자에게 이로 인해 임상적 반응을 예측할 수 있는지를 보는 것이었기에 iScore를 이용해서 뇌졸중 이후의 사망이나 장애의 가능성을 근거하여 환자들을 선별적으로 정의한 3개의 위험도 집단으로 나누었다: 저위험(iScore ≤ 139이고 양호한 결과가 나올 >50%의 확률), 중위험(iScore 140~179이고 양호한 결과가 나올 10~50%의 확률), 고위험(iScore ≥180이고 양호한 결과가 나올 <10%의 확률).

결과적도

일차결과적으로 불량한 결과는 뇌졸중으로 입원한지 30일 이내에 사망하거나 퇴원 시 mRS 점수 3~5인 심한 장애가 있는 경우로 정의하였다. 이차 결과는 다음과 같다: (1) 퇴원 시 mRS 점수 3~5인 심한 장애; (2) 30일 이내 사망; (3) 재활기간: (4) tPA 코호트에서 뇌내출혈(모든 종류 또는 중간성)과 신경학적 악화.

통계 분석

범주형 변수는 카이제곱 검정으로 비교하고 연속형 변수의
### Table 3. Baseline Characteristics After Matching tPA and Non-tPA Patients by Propensity Score Stratified by iScore Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Risk (iScore ≤139)</th>
<th>Medium Risk (iScore 140–179)</th>
<th>High Risk (iScore ≥180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-tPA (n=589)</td>
<td>tPA (n=589)</td>
<td>Standardized Difference of Mean</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>64.7±15.6</td>
<td>64.1±15.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Age categories, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>49.7</td>
<td>49.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>66–79</td>
<td>31.7</td>
<td>32.3</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;80</td>
<td>18.5</td>
<td>18.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex, women</td>
<td>45.8</td>
<td>44.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS score, mean SD</td>
<td>8.2±1.9</td>
<td>8.1±1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>CNS categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS &lt;4 (severe)</td>
<td>5.4</td>
<td>6.6</td>
<td>0.05</td>
</tr>
<tr>
<td>CNS 5–7 (moderate)</td>
<td>30.7</td>
<td>30.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CNS &gt;8 (mild)</td>
<td>63.8</td>
<td>62.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean glucose on admission, mmol/dL</td>
<td>7.16±3.3</td>
<td>7.14±3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>2</td>
<td>2.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Aphasia</td>
<td>38.4</td>
<td>39</td>
<td>0.01</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.7</td>
<td>54.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.9</td>
<td>14.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.2</td>
<td>7</td>
<td>0.08</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.4</td>
<td>3.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11.5</td>
<td>12.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30.2</td>
<td>30.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoker</td>
<td>25.5</td>
<td>24.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.2</td>
<td>3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>10.2</td>
<td>8.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Predmission Independence</td>
<td>96.9</td>
<td>95.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>88.3</td>
<td>86.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke subtype, lacunar</td>
<td>17.7</td>
<td>16.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values represent percentages unless indicated otherwise.

tPA indicates tissue plasminogen activator; CNS, Canadian Neurological Scale; LOC, decreased level of consciousness; TIA, transient ischemic attack.

평가 및 잠상적 차이는 분석 방법이나 Kruskal–Wallis 검정으로 비교하였다. tPA를 받은 환자와 받지 않은 환자의 초기 특성의 체계적 차이 때문에 iScore를 이용해 정의한 뇌졸중 중증도의 각 측면에서 rPA의 효율을 예측하기 위해 propensity score (PS) 착석기를 이용했다. PS 착석기는 관찰한 결과의 차이가 일관적으로 일도의 것으로 생각할 수 있도록 치료군 간의 체계적 차이를 제거하거나 최소화하도록 하는 분석 기법이다. iScore의 3개 종의 각각에서 PS 착석기를 했다. 결과와 관련이 있다고 생각하는 다음의 초기 공변량(연령, 성별, 뇌졸중 중증도, 뇌졸중 야기, 고혈압, 당뇨, 고지질혈증, 심방세동, 뇌졸중이나 TIA의 과거력, 신경망사, 도착 시 의지수준, 언어 장애, 엽일 시 혈당, 장애, 구강사 표현)에 대해 보정한 로지스틱 회귀분석을 이용해 PS를 예측하였다. 과거의 연구들은 예후에 있어서 중요한 변수들을 PS모형에 넣어가지 좋은 분석 전략이라는 것을 확인 하였다. tPA 환자와 비tPA 환자는 1:1의 착석기 비율로 PS의 로짓의 0.2 SD의 caliper로 PS의 로짓에 대해 착석하였다. 

최종의 PS 착석기 표준에서 우리는 연속형 변수에는 t-검정을 이용하였으며 양변수에는 McNemar검정을 이용해 tPA를 받은 환자와 그렇지 않은 환자 간의 우등결과의 비율을 비교하였다. Agresti와 Min의 제안한 방법을 이용해...
Table 4. Outcome Measures in the Matched Cohort by iScore Groups

<table>
<thead>
<tr>
<th>iScore</th>
<th>30-Day Mortality or Disability at Discharge (%)</th>
<th>Disability at Discharge (mRS 3–5, %)</th>
<th>Mean Length of Stay, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPA No IPA RR (95% CI)</td>
<td>IPA No IPA RR (95% CI)</td>
<td>IPA No IPA RR (95% CI)</td>
</tr>
<tr>
<td>Low (iScore ≤139)</td>
<td>274 (46.7) 370 (62.8) 0.743 (0.670–0.824)</td>
<td>245 (43.8) 338 (60.5) 0.745 (0.671–0.827)</td>
<td>10.6 14.0 &lt;0.0001</td>
</tr>
<tr>
<td>Medium (iScore 140–179)</td>
<td>517 (75.8) 585 (85.8) 0.884 (0.838–0.932)</td>
<td>396 (70.6) 484 (83.0) 0.887 (0.841–0.936)</td>
<td>16.6 22.1 0.012</td>
</tr>
<tr>
<td>High (iScore ≥180)</td>
<td>382 (92.6) 389 (95.2) 0.972 (0.938–1.004)</td>
<td>233 (87.3) 239 (92.7) 0.967 (0.933–1.000)</td>
<td>18.8 24.8 0.004</td>
</tr>
</tbody>
</table>

 Patients with stroke receiving intravenous thrombolyis (IPA) were matched with patients with stroke not receiving thrombolytic therapy (no IPA). Risk score range: low (iScore 30–139), medium (iScore 140–179), high (180–284). Further details of outcomes definition is in the text. There was no improvement in any of the 3 clinical outcomes for patients with stroke receiving thrombolyis with the higher risk score.

iRS indicates modified Rankin Scale, RR, relative risk.

서 PS 폭기 코히트에서 RR 및 95% CI를 계산하였다.26

SAS 통계소프트웨어 9.2.2 버전(SAS Institute Inc, Cary, NC)을 이용해서 통계분석을 했다. 모든 검정은 양측검정이고
확률값 < 0.05를 의미 있게 보았다. St Michael’s Hospital
의 생명윤리위원회와 RCSN Publications Committee가 승인했다.

결과

RCSN 표본의 허혈뇌졸중 환자 12,686명 중에서 1,696명
(13.4%)의 환자에게 rPA정주를 했다. 이 표본에서 tPA정주를
한 환자들은 그렇지 않은 환자들과 비교하여 Congress of
Neurological Surgeons score < 4로 정의한 중증의 뇌졸중이
있었고(37.9% 대 16.1%; 표준화 차이 0.56), 실어증으로
발현하는 경우가 더 많았고(51.0% 대 28.6%; 표준화 차이
0.49), 비혈공격의중증상을 가지는 경우가 더 많았고(93.10%
대 81.5%; 표준화 차이 0.31), 구급차를 타고 온 경우가 더 많
았다(91% 대 67.3%; 표준화 차이 0.60) (Table 2). 전체적으
로 증상시작부터 tPA정주까지 걸린 평균 시간은 160.5분(SD
±87)이었고, 18.8%는 3시간 이내에 혈전용해를 받았다.

저위험군(iScore ≤139)에서 PS 폭기를 한 후, tPA를 정
주한 589명은 그렇지 않은 589명과 폭자었다. 중위험군
(iScore 140–179)과 고위험군(risk score ≥180)에서 tPA를
정주한 682명과 419명을 그렇지 않은 682명과 419명의 환자
와 각각 폭자었다. 우리는 6명(1.0%)에서만 폭을 지울 수
없었다.

PS 폭기를 한 후, 모든 집단에서 tPA 환자와 비tPA환자
간의 측정적 차이는 표준화 차이가 0.1 미만으로 상당히 감소
하였다(Table 3).

위험도 점수에 따른 임상적 결과

전체적으로 tPA 정주가 사망과 장애(mRS ≥3)를 10.2% 정
도로 절대 감소시켰다(いただいて iScore 16.1%; 중등도 iScore
9.7%; 높은 iScore 3.1%). 폭자된 표본에서 더 높은 iScore는
tPA군과 비tPA군에서 모두 브러.writer포한 기능적 결과를 낳았다(P
<0.001: Table 4). 저위험 및 중위험 iScore군에서 모두 혈
전용해가 불량한 예후가 발생할 위험이 더 났다(저위험군
RR, 0.74: 95% CI, 0.67–0.84; 중위험군 RR, 0.88: 95%
CI, 0.84~0.93). 고위험군iScore군에서 tPA는 의미 있는 이득
이 없었다(RR, 0.97: 95% CI, 0.94~1.01). 퇴원 시의 장애와
재원기간에 대해서도 비슷한 결과가 나왔다(Table 4).

30일 이내의 사망은 저위험iScore군의 경우 비tPA군의

Figure. Model estimating the probability of a favorable outcome (mRS 0–2) at discharge in tPA–
treated patients compared to non-tPA patients by the iScore. Dot lines indicate the 95% CIs of the
estimated outcome. The horizontal dashed line indicates the RR of 1 (no treatment effect). When
the upper CI crosses the line of 1, patients in the treatment group would have a lower probability of
a favorable outcome compared with those in the control group, so the treatment has no effect
and may be harmful. Adjusted for the same variables used for the propensity matching, including:
tPA, iScore, hypertension, diabetes, myocardial infarction/angina, hyperlipidemia, smoking, dementia,
previous stroke, arrival by ambulance, decreased level of consciousness, aphasia, and residence
before admission. Probability value for the iScore by treatment interaction <0.001. mRS indicates
modified Rankin Scale; tPA, tissue plasminogen activator; RR, relative risk.
Table 5. Outcomes by iScore Groups Among Patients Receiving tPA Who Developed Hemorrhagic Complications

<table>
<thead>
<tr>
<th>iScore Group</th>
<th>Hemorrhagic Transformation (Any Type)</th>
<th>Symptomatic Hemorrhagic Transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./No.</td>
<td>30-Day Mortality*</td>
</tr>
<tr>
<td>Low (iScore ≤139)</td>
<td>38/589 (6.4)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Medium (iScore 140–179)</td>
<td>90/687 (13.1)</td>
<td>32 (35.6)</td>
</tr>
<tr>
<td>High (iScore ≥180)</td>
<td>83/419 (19.8)</td>
<td>40 (48.2)</td>
</tr>
<tr>
<td>All</td>
<td>211/1692 (12.4)</td>
<td>81 (38.4)</td>
</tr>
</tbody>
</table>

Further details of outcomes definition is in the text. No. represents the no. of patients receiving tPA who developed the outcome. No. represents the total no. of patients in the group. Values in parentheses are percentages unless indicated otherwise.

*P values for comparisons among iScore risk groups: *P=0.028.

†<0.001.

‡0.54.

§0.05.

5.1% tPA 군의 4.9%에서, 중위험군의 14.5%, 고위험군의 17.7%에서, iScore가 발병한 경우 비tPA군의 38.2%, tPA군의 36.3%에서 발생했다. tPA 투여는 전체 표본집단이나 핑거는 혈압군에서 모두 30일 이내의 사망률을 감소시키지 못했다(노는 iScore의 RR, 0.97; 95%CI, 0.59~1.60). 중등도 iScore의 RR, 1.22; 95%CI, 0.96~1.56; 높은 iScore의 RR, 0.95, 95% CI, 0.79~1.14).

Figure는 최초의 희호트(n=12 868)에서 다변량모델작합으로 결정된 iScore의 각 수준에서 약간의 결과가 발생한 RR를 보여준다. 이 결과는 PS 적합지 분석의 결과를 보충하여 iScore >200인 환자에서 tPA가 이로운 효과가 있고 때로는 확률도 없다는 것을 시사한다(upper CI는 1의 선을 교차한다: iScore와 치료의 상호작용의 확률<0.001).

혈류이형 혈종과 신경학적 악화

tPA를 정주한 환자에서 모든 종류의 혈류이형은 12.4% (211/1692)에서, 중증성 혈으며 6.9% (117/1692)에서 발생했다(Table 5). 더 낮은 위험이Score군과 비교하여 고위험군 iScore군은 tPA정주를 함 경우 뇌내혈증(모든 종류 및 중증성 혈류이형) 발생률이 높고 신경학적 악화로 인해 생할 가능성이 더 높다(Table 5: Supplemental Figure I: http://stroke. ahajunctions.org).

전체적으로 tPA 정주 후 혈류이형이 발생한 환자의 30일 사망률은 38.4% (81 /211)이고 평균한 결과가 대부분(92.9%)의 환자에서 나타났다. 혈류이형 발생은 경우 더 낮은 위험이Score군보다 더 높은 위험의 iScore군에서 결과가 더 나졌다(Table 5). 30일 사망률이나 위험 시 장애에 있어서 해를 수지에 필요한 치료수는 혈류이형 발생의 경우 5이고 중증성 혈류이형의 경우 17이었다.

External Validation

최초의 희호트에서 관찰한 결과와 비슷하게 저위험 및 중위험군에서 tPA정주는 블러닝 결과를 낮을 가능성이 낮았다(노는 iScore RR, 0.78; 95% CI, 0.63~0.98: 중등도 iScore RR, 0.83; 95% CI, 0.71~0.97), 높은 iScore군에서 tPA를 정주한 환자는 그렇지 않은 환자와 비교하여 발생적으 로 의미 있는 이득이 있었다(RR, 0.91; 95% CI, 0.82~1.04). 편관 시의 장애에 대해서도 비슷한 결과를 나타내었다. 세부자료로 다른 결과는 supplemental material에 나와 있다.

고찰

특정 치료나 증상에 대한 임상적 반응을 예측하는 것은 어렵다. 뇌종증 환자에서 동반진단들의 다양한 상호작용과 심각한 혈류증에 뇌내혈증의 위험성이 있는 것을 고려할 때 혈류증의 위험부여는 많은 임상적 반응을 예측하는 것은 특히 어렵다.11,12 의사는 tPA의 위험과 이에 대해 인식하고 평가하는 것은 중요하지 않을 수 없다. 예를 들면, 응급의학과 의사와 신경과 의사를 대상으로 한 설문조사에서 거의 11% (95% CI, 0~22%)가 tPA의 위험의 정도를 정확하게 인식할 수 있었다.14 비슷하게 보직 39%만이 중증성 및 치명적 뇌내혈증의 위험을 예측할 수 있었다.14 결과적으로 오인 및 오해는 응급상황에서 더 더욱 임상적인 의사결정에 영향을 줄 수 있다. 더 중요한 것은 진단, 선별검사, 예방을 위한 임상적 도구에, iScore나 전자자원을 이용한 의사결정지원이 의사의 업무수행을 향상시킬 수 있다.15 과거의 연구에서 우리는 iScore가 혈류증증증 증후기의 가능성을 판단하는 30일 및 1년 사망률을 예측하는 유용한 도구임을 발견했다.16,19 또한 우리는 iScore가 블러닝 가능성 결과의 위험을 과소평가하거나 과대평가하는 다른 간단한 모형(유형 영역, 뇌종증 중증도의 인식)의 정확도를 간호 시켰음을 증명하였다.19

이 FS 핫키지 연구에서 저위험(≤139) 및 중위험(140~179)의 iScore 범주에 해당하는 환자들은 tPA를 정주할 경우 하지 않았을 때보다 약한 결과를 나타났다. 저위험
및 증후군 iScore군은 tPA를 정주할 경우 30일 사망하거나 퇴원 시 장애가 있을 위험이 각각 26%, 12% 감소하였다. 반대로 tPA정주는 가장 높은 위험 ≥180 iScore 폭주에서 통계적으
로 의미 없는 이득을 나타냈다. 결국 tPA의 출혈성 합병증 은 iScore 위험과 비례하였는데 높은 iScore(10.8%)는 낮은 위험 폭주(6.4%)에 비해하여 출혈성 합병증이 3배 높았다. 표본수가 적지 않은 validation 코호트에서도 결과는 비슷했다.
tPA정주로 양호한 결과를 달성한 가능성은 iScore 위험이 증가함수록 급격히 감소왔다. iScore >200의 환자들은 tPA가 영
확한 이득을 없고 잠재적인 해양 있었다(Figure).

이런 소견은 iScore가 tPA정주 이후 임상적 반응과 주요한 합병증을 예측할 수 있다는 것을 시사한다. 이런 소견은 의사
들이 tPA에 반응하지 않을 환자를 과다히는 데 있어서 도움이 될 수 있을 것이다.

과거의 연구들은 헌혈수혈이 이후의 양호한 결과나 출혈환
의 위험과 관련 있는 인자를 찾았다.23,24,25 tPA 또는 위약을 투
여한 2,131명의 환자를 무작위배정한 임상시험을 모아서 분석
하여 저자는 양호한 결과(mRS<1)와 불량한 결과(mRS≥5)
를 예측하는 모형을 만들었다.25 양호한 예후와 관련 있는 공통
적인 변수는 연령, NIH 뇌졸중척도, 고혈압, tPA, 성별, 당뇨
였다. 또한 이 연구에 포함된 환자의 ≥60%는 증상 발생 3~6
시간 사이에 치료 받았다. 이런 극단한 현상에도 불구하고 의사
가 헌혈수혈에 대한 임상적 반응을 예측하는데 도움이 했던 위험도 점
수가 실제 환자의 환자를 대상으로 하는 대규모 코호트에서 증
명된 바가 없다. iScore는 잘 알려진 예측지수(예, 연령, 뇌졸중
증증도, 고혈당) 중 일부만을 포함하고 뇌졸중 예후에 영향을 줄
수 있는 다른 동반현상을 추가했다.23,24 또한, 핫핑키 코호트에서
관찰한 사망률이나 장애(mRS≥3)의 감소의 절대값(10.2%)은
National Institute of Neurological Disorders and Stroke
(NINDS),21 European–Australian Acute Stroke Study
(ECASS) III (6.8%),22 Safe Implementation of Thrombolysis
International Stroke Thrombolysis Registry and Virtual
International Stroke Trials Archive (SITS/VISTA: 14.1%)26
등에서 발표한 것과 흡사한다.

고위험군에서 tPA의 위험, 이득, 살의 점에 미치는 영향은
논란의 대상이다. 우리 연구에서 고위험군에서 tPA가
이득 없는 것은 뇌졸중이 20%에서 발생하는 것에 의해서
일부분 설명이 가능하며 뇌졸중은 48%의 사망률 및 99%의
사망 또는 퇴원 시의 주요 장애와 관련이 있다(Table 5). 우리
의 기능적 결과가 효과적으로 tPA의 이익과 출혈환의 유해
함을 종합하기는 하지만 의사는 출혈환의 가능성이 양호한
경과의 가능성이 높은 iScore군에서 어떤 선택을 할 것인지
말을 해야해야 한다. 상담의 의사들이 이 정책에 tPA를
정주하지 않을 경우 높은 결과(양호한 결과: 4.8% 비tPA군
대 7.4% tPA군; RR, 2.8%; -0.8% to 6.2%)를 보일 것이며
자발적인 헌혈의 가능성이 희박하다는 사실 때문에 계속 tPA
를 정주할 것이다. 다른 의사는 환자 및 가족과 상의한 후 다
른 치료(예, 혈관내 접근)를 고려할 수 있다. 헌혈 선택과 상관
없이 iScore는 환자 및 가족과 상의할 때 유용한 정보를 제공
할 것이다.

우리의 연구는 몇 가지 약점과 강점이 있다. 첫째로, 초기의
iScore에 포함하지 않은 관련성이 있을 법한 변수들(예, 뇌경
색 크기, 영상 정보)이 적용증에 따른 교환의 가능성을 위해
혈전해제의 반응에 영향을 줄 수 있다. iScore는 이런 목적으로
만들 것이 아니기 때문에 초기의 iScore에는 이런 변수들이 들
어가지 않았고 우리의 임상자료들에도 이런 내용은 없다. 둘째
로, 몇 인종이 내재의 연구에 참여하기는 했으나 환자의 대다
수는 라틴 아메리카계가 아닌 백인이었다. 셋째로 우리는 2종 오
류를 배제할 수 없다. 그러나 우리는 낮은 iScore군의 핫핑키, 
tPA환자와 비tPA환자간의 일차결과에 2.6%의 통계적으로
의미 없는 이득을 고려할 때 차이를 감지할 수 있는 power의
문제는 아니라고 본다. 넷째로 어떤 iScore군은 자료가 거의
없어서 Figure를 만든 화폐모형이 불안정할 수 있고 가설형성
의 관점에서 봤다. 또한 우리 연구는 높은 iScore군에서
다른 치료방법(예, 혈관내혈관계개통, 동맥내혈전해제, 저체온)
을 사용하는 것이 임상적으로 의미 있는 이득을 가져올 가능성을
배제할 수 없다. 다섯째로, 입원 후에 뇌졸중의 악화를 빠르게 결
정하는 것이 뇌졸중 비판문제에서 제약이 될 수도 있다. 마지막
으로 초기의 핫핑키를 최소화하기 위해서 PS 핫핑키를 하였으나
이것은 무작위임상시험이 아니므로 이 관찰연구의 결과는 헌
혈수혈을 할지 결정할 때 전문가의 임상적 판단을 대체할 수
없다.

우리 연구의 강점은 현실세계의 환자(19%가 3시간을 초과하
여 tPA정주를 포함하는 대규모의 표본수와 감증된 신속 체계
의 사용, 뇌졸중 증증도와 주요소자가 거의 완벽한 확신, tPA
를 정주할 환자의 흔적을 핫핑키, 두 개의 병자 코호트에서의
결과의 일관성이 있다.

이 연구는 iScore (www.sorcan.ca/iscore)가 헌혈뇌졸중
의 혈전용해요법 이후 헌혈환의 위험과 반응을 예측할 수 있음
을 보여준다. 이 결과는 환자와 가족에게 치료의 선택권과 예
후에 대해 상담할 때 중요한 정보를 의사에게 제공하여 헌혈용
해에 대한 합리적 의사결정을 도와줄 수 있다. 높은 iScore군
에 대해 가장 좋은 치료적 접점을 결정하는 것을 전문적 연구가
도와 줄 것이다. 조직화 및 자원배분의 관점에서 볼 때 사례 같
은 감지 및 더 많은 자원을 요구하는 고위험 환자에서의 혈전용
해요법에 대한 논의를 촉진시키게 줄 것이다.
References


