Predicting Clinical Outcomes and Response to Thrombolysis in Acute Stroke Patients With Diabetes

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ON BEHALF OF THE INVESTIGATORS OF THE REGISTRY OF THE CANADIAN STROKE NETWORK (RCSN) AND THE STROKE OUTCOMES RESEARCH CANADA (SORCan) WORKING GROUP

OBJECTIVE—Few tools are available to evaluate clinical outcomes and response to thrombolysis (tPA) in stroke patients with diabetes. We explored how the iScore (www.sorcan.ca/iscore), a validated risk score, predicts clinical outcomes in stroke patients with and without diabetes.

RESEARCH DESIGN AND METHODS—We applied the iScore to stroke patients presenting to stroke centers participating in the Registry of the Canadian Stroke Network. Main outcomes included favorable outcome, defined as a modified Rankin scale (mRS) 0–2 at discharge, and intracerebral hemorrhage (ICH) after tPA.

RESULTS—Among 12,686 patients with an acute ischemic stroke, 3,228 (25.5%) had diabetes. Among patients receiving tPA (n = 1,689), those with diabetes had a lower rate of a favorable outcome compared with their counterparts (24.3 vs. 31.1%; RR 0.90 [95% CI 0.82–0.98]). The risk of ICH was not significantly different in patients with or without diabetes (for any type 12.6 vs. 12.5%, RR 1.01 [0.72–1.40]; for symptomatic ICH 7.5 vs. 6.8%, RR 1.11 [0.70–1.72]). The regression analysis revealed a decline in the probability of a favorable outcome after tPA with increments in the iScore (P value for iScore × tPA interaction <0.001). There was no difference in the response to tPA predicted by the iScore between stroke patients with and without diabetes (P value = 0.07).

CONCLUSIONS—Stroke patients with diabetes have poorer outcomes compared with patients without diabetes, which is not explained by ICH. The iScore similarly predicts response to tPA between stroke patients with and without diabetes.

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Stroke is a leading cause of neurologic disability and death worldwide with a negative physical and psychosocial impact on patients and their families (1–3). More than two-thirds of stroke patients will remain with radically reduced quality of life (4,5). Diabetes is a cardinal risk factor for stroke, affecting 347 million individuals worldwide (6). The prevalence of diabetes has dramatically risen over the last three decades, especially in younger adults. With elevated rates of obesity, further increases in the incidence of diabetes are expected (7,8).

Some studies suggest that diabetes is associated with higher death and disability in stroke patients (9,10).

The iScore (www.sorcan.ca/iscore) is a newly established and validated scoring system that can be used to foresee the risk of death and disability after an acute ischemic stroke. The iScore classifies patients with ischemic stroke into risk categories from very low to very high average risk, using clinical parameters and comorbidity conditions (11,12). In previous work, our group showed that iScore could be used to approximate the risk of intracerebral hemorrhage and clinical responses after thrombolysis (tPA) (13). However, limited information is available on patients with diabetes. In most large clinical trials, the number of patients with diabetes was too limited to study an interaction with tPA (14,15).

The objectives in this study were as follows: 1) to assess clinical outcomes in patients with and without diabetes using the iScore and 2) to outline the ability of the iScore to predict clinical responses and hemorrhagic complications after tPA in stroke patients with and without diabetes.

RESEARCH DESIGN AND METHODS—The Registry of the Canadian Stroke Network (RCSN) was used to identify patients admitted with acute stroke to stroke centers across the province of Ontario, Canada. Eligibility criteria included age ≥18 years, a primary diagnosis of acute ischemic stroke, and admission to any of the 11 participating institutions between 1 July 2003 and 30 June 2008. Any patient with missing baseline characteristics (Canadian Neurological Scale score, glucose on admission, and unique health identifier) (n = 1,005 [7.3%]) was excluded. Also, patients with transient ischemic attack (TIA) were not eligible for this study. TIA was defined as a stroke with transient symptoms <24 h with no evidence of acute infarction on computed tomography or magnetic resonance imaging. Further details on the RCSN can be obtained from the RCSN Report at www.rcsn.org and have previously
iScore predicts outcomes in stroke patients with diabetes

been published (11,16). 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 that provides complete follow-up for all residents in the province.

Diabetes is one of the variables systematically collected in the RCSN, identified from documented history and medical notes, including any of the following: adult-onset diabetes, diet-controlled diabetes, type 1 or type 2 diabetes, insulin-dependent diabetes, and non–insulin-dependent diabetes.

The iScore is a risk score that estimates functional outcomes in patients with an ischemic stroke early after hospitalization using clinical parameters and comorbid conditions, which include age, sex, stroke severity, stroke subtype, smoking status, preadmission dependency, the presence or absence of atrial fibrillation, heart failure, previous myocardial infarction, cancer, renal failure on dialysis, and hyperglycemia on admission (11,12). The risk scoring system is represented in Supplementary Table 1.

We calculated the iScore for each eligible participant in the RSCN. Details of the selection of variables for the iScore, data sources, and the creation and conceptualization of the iScore have previously been published (11). An online Web-based tool (www.sorcan.ca/iscore) and an iPhone version are currently available free of charge.

Outcome measures
The primary outcomes included favorable outcome (modified Rankin scale [mRS] 0–2) at discharge and intracerebral

| Characteristic | All | Yes | No | P |
|---------------|-----|-----|----|---|
| n             | 12,686 | 3,238 | 9,448 | |
| Age (years), mean ± SD | 71.98 ± 13.79 | 71.71 ± 11.46 | 72.07 ± 14.50 | 0.193 |
| Stroke severity | | | | |
| ≤59 | 2,331 (18.4) | 500 (15.4) | 1,831 (19.4) | |
| 60–69 | 2,279 (18.0) | 716 (22.1) | 1,563 (16.5) | |
| 70–79 | 3,732 (29.4) | 1,124 (34.7) | 2,608 (27.6) | |
| ≥80 | 4,344 (34.2) | 898 (27.7) | 3,446 (36.5) | <0.001 |
| Female sex | 6,026 (47.5) | 1,380 (42.6) | 4,646 (49.2) | <0.001 |
| Stroke subtype | | | | |
| Lacunar | 2,148 (16.9) | 643 (19.9) | 1,505 (15.9) | |
| Nonlacunar | 6,021 (47.5) | 1,387 (42.8) | 4,634 (49.0) | |
| Undetermined etiology | 4,517 (35.6) | 1,208 (37.3) | 3,309 (35.0) | <0.001 |
| Risk factors | | | | |
| Atrial fibrillation | 2,185 (17.2) | 550 (17.0) | 1,635 (17.3) | 0.678 |
| CAD | 3,042 (24.0) | 1,048 (32.4) | 1,994 (21.1) | <0.001 |
| CHF | 1,152 (9.1) | 390 (12.0) | 762 (8.1) | <0.001 |
| Hyperlipidemia | 4,437 (35.0) | 1,633 (50.4) | 2,804 (29.7) | <0.001 |
| Hypertension | 8,643 (68.1) | 2,711 (83.7) | 5,932 (62.8) | <0.001 |
| Previous MI | 1,945 (15.3) | 698 (21.6) | 1,247 (13.2) | <0.001 |
| Current smoker | 2,469 (19.5) | 577 (17.8) | 1,892 (20.0) | 0.006 |
| Comorbid conditions | | | | |
| Cancer | 1,244 (9.8) | 311 (9.6) | 933 (9.9) | 0.655 |
| Dementia | 1,097 (8.6) | 311 (9.6) | 786 (8.3) | 0.025 |
| Renal dialysis | 111 (0.9) | 49 (1.5) | 62 (0.7) | <0.001 |
| Preadmission disability: dependent | 2,670 (21.0) | 805 (24.9) | 1,865 (19.7) | <0.001 |
| Glucose on admission ≥7.5 mmol/L | 4,494 (35.4) | 2,255 (69.6) | 2,239 (23.7) | <0.001 |
| tPA administered | 1,696 (13.4) | 334 (10.3) | 1,362 (14.4) | <0.001 |
| iScore at 30 days | | | | |
| Mean ± SD | 135.43 ± 41.90 | 140.61 ± 41.75 | 133.65 ± 41.81 | <0.001 |
| Median (quartile 1–3) | 129 (106–162) | 133 (112–169) | 127 (104–159) | <0.001 |
| iScore at 1 year | | | | |
| Mean ± SD | 114.03 ± 31.54 | 118.28 ± 31.13 | 112.57 ± 31.56 | <0.001 |
| Median (quartile 1–3) | 110 (92–134) | 114 (96–139) | 108 (90–132) | <0.001 |

Data are n (%) unless otherwise indicated. CAD, coronary artery disease; CHF, congestive heart failure; MI, myocardial infarction.
hemorrhage (ICH) after tPA administration. Symptomatic intracranial hemorrhage was defined as worsening of neurologic status of the patient in the first 36 h after receiving tPA and evidence of intracranial hemorrhage documented by neuroimaging.

Secondary outcomes were analyzed in the entire cohort, including the following: 1) death within 30 days or death at discharge (mRS 3–5), 2) death at 30 days, 3) death at 1 year, 4) discharge to home or same place of residence prior to stroke, and 5) discharge to a long-term care facility after stroke.

**Statistical analysis**

χ² tests were used to study categorical variables; ANOVA or Kruskal-Wallis tests were used to compare mean and median differences for continuous variables. Based on the results of a prior study on the response to tPA, an iScore cutoff of 200 was used to compare favorable outcome (mRS 0–2) at discharge with risk of ICH (13). We used tertiles of the iScore to ascertain a gradient effect for the studied outcomes in the whole cohort.

Poisson regression models were used to estimate the response to tPA (expressed as relative risk [RR] [95% CI]) among patients with and without diabetes adjusting for age, sex, stroke severity, stroke subtype (lacunar vs. other), hypertension, hyperlipidemia, atrial fibrillation, coronary artery disease, heart failure, previous stroke or TIA, renal failure on dialysis, level of consciousness on arrival, dysphasia, glucose on admission, independence, time from symptom onset to hospital arrival, and arrival by ambulance.

Statistical analysis was completed using SAS statistical software (version 9.2.2; SAS Institute, Cary, NC). All tests were two-tailed, and P 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 registry, 3,238 (25.5%) had diabetes. Compared with patients with no diabetes, diabetic patients were more likely male and had more comorbid conditions including hypertension, hyperlipidemia, and coronary artery disease. There was no significant difference in stroke severity between patients with and without diabetes. Differences in baseline characteristics are summarized in Table 1. The mean iScore was 7 points higher among diabetic patients compared with that in their counterparts (mean iScore 140.61 [diabetes] vs. 133.65 [no diabetes]; P < 0.001). In addition, similar differences were observed in the scoring system to estimate 1-year mortality (Table 1). Differences <10 points are not considered clinically meaningful, as they have limited influence on the final outcomes. The range of iScore in the whole population was 30–300.

**Clinical outcomes after thromolytic therapy**

Intravenous tPA was administered to 1,689 (13.3%) patients (n = 1,356 non-diabetic and n = 333 diabetic). Compared with nondiabetic patients, a lower proportion of patients with diabetes received tPA (10.3 vs. 14.4, respectively; P < 0.001). Patients with diabetes had a lower likelihood of a favorable outcome (24.3 vs. 31.1%; RR 0.90 [95% CI 0.82–0.98]) at discharge after tPA compared with nondiabetic patients. Other outcomes stratified by the iScore are summarized in Table 2.

Figure 1 represents the adjusted probability of a favorable outcome comparing tPA with no tPA at each level of the iScore stratified by diabetes status, as determined from the multivariable model fit in the original cohort (n = 12,686). Figure 1A reveals a similar slope in the probability of a favorable outcome (response to tPA) by the iScore between patients with and without diabetes (P = 0.07).

There was a treatment effect (tPA) interaction with the iScore for the whole cohort (P < 0.0001) (Fig. 1). There was no significant treatment interaction with the iScore (P > 0.05) by diabetes, likely due to the smaller sample size. Together, these results suggest that the iScore similarly predicts a clinical response to tPA among patients with and without diabetes.

**ICH after tPA**

The risk of intracranial hemorrhage (any type or symptomatic) was not different in patients with and without diabetes. Intracranial hemorrhage of any type occurred in 12.6% of patients with diabetes and 12.5% of patients without diabetes (RR 1.01 [95% CI 0.72–1.4]). Symptomatic hemorrhage was observed in 7.5% of diabetic patients vs. 6.8% of nondiabetic patients (1.11 [0.70–1.72]) (Table 2).

**Clinical outcomes in the whole cohort stratified by diabetes**

Overall, the risks of death or disability at discharge (RR 1.09 [95% CI 1.05–1.12])
and death at 1 year (1.18 [1.1–1.27]) were higher in the diabetic group. However, there was no significant difference in mortality at 30 days between patients with and patients without diabetes. There was no meaningful difference between patients with and patients without diabetes in rate of patients discharged home after an acute ischemic stroke and rate of mortality or discharge to a long-term facility (Table 3). Furthermore, there were no major differences in the outcomes of interest between patients with and without diabetes in the stratified analysis by the iScore (Table 3). Supplementary Fig. 1 represents functional outcomes according to the mRS at discharge among patients receiving and patients not receiving tPA stratified by diabetes.

**CONCLUSIONS**—Diabetes is a growing worldwide concern. A recent study showed a twofold increase in number of adults with diabetes over the past three decades (6). Compared with nondiabetic patients, those with diabetes face more than twice the risk of ischemic stroke with less favorable outcome (9,10).

In the current work, we evaluated clinical outcomes and response to tPA among patients with and without diabetes. We showed higher death and disability at discharge and long-term mortality in patients with diabetes. There were no major differences in outcomes between patients with and without diabetes by iScore strata, suggesting similar estimations for patients with expected favorable or poor outcomes. The probability of a favorable outcome after tPA declined with increments in the iScore for both stroke patients with and stroke patients without diabetes. More importantly, there was no difference in the response to tPA between these groups (Fig. 1A). Finally, diabetes was not associated with higher risk of hemorrhagic complications after tPA.

Although diabetes is not a contraindication for tPA, patients with diabetes are being undertreated with tPA (17). This could be explained by the concern of higher risk of ICH and poor functional outcome in stroke patients with hyperglycemia on admission or known diabetes (10,18,19). Nevertheless, our findings revealed no differences in the risk of ICH after tPA.

There are several tools available for predicting clinical outcomes after ischemic stroke. The majority of these scoring systems do not include diabetes (20–23). In the Stroke-Thrombolytic Predictive
Instrument, diabetes is listed among the variables affecting good outcome. However, in predicting catastrophic outcome, baseline serum glucose remained in the model overcoming the impact of diabetes (24). Other larger studies showed worse outcomes among stroke patients with diabetes after age stratification (19).

Hyperglycemia on admission is a competing factor (and commonly overcomes the effect of diabetes) when outcomes are compared between patients with and patients without diabetes. Different studies also showed that hyperglycemia is associated with poorer outcomes after tPA in acute stroke (25–28). However, the role of diabetes in predicting outcomes after tPA administration is less clear. In a recent study of 109 patients who received tPA, the authors showed that insulin resistance was associated with worse long-term outcome after acute stroke (29). In a larger study of 2,594 thrombolysed patients, Bateman et al. (30) reported a nonsignificant association between diabetes and in-hospital mortality after acute stroke. Similar to our results, the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) showed that patients with diabetes had higher odds for mortality and poor functional outcome at 3 months, while the rate of symptomatic ICH was not significantly different between patients with and without diabetes (27).

The clinical response after tPA has not been widely studied in patients with diabetes. In a recent study, patients with higher admission glucose or diabetes had poorer outcomes after intra-arterial tPA, whereas the rate of symptomatic ICH in patients with and without diabetes was similar (28). Most large clinical trials had a small number of patients with diabetes for examination of an interaction with tPA (14,15). In the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial, diabetes was associated with a lower chance of a global favorable outcome (odds ratio 0.57 [95% CI 1.02–1.12]) than their control counterparts. Our observational study showed results consistent with those of the NINDS and ECASS III trials. Patients with diabetes had higher rates of death or disability (mRS >3) at discharge after tPA compared with nondiabetic patients (75.7 vs. 68.9%; RR 1.10 [95% CI 1.02–1.18]).

Our study has some limitations and strengths. Firstly, we were not able to evaluate imaging variables (e.g., infarct size, recanalization) known to affect clinical outcomes. Nevertheless, our goal was to assess a differential influence of diabetes on clinical outcomes when applying a clinical score. In addition, a

Table 3—Outcome measures in the entire cohort (n = 12,686) stratified by diabetes and by iScore tertiles

| iScore | Diabetes | RR (95% CI) | P  |
|--------|----------|-------------|----|
|        | Yes | No |       |
| 30-day mortality |  |  |  |
| 1st tertile (n = 4,222) | 14 (1.6) | 45 (1.3) | 1.17 (0.65–2.13) | 0.60 |
| 2nd tertile (n = 4,117) | 55 (4.8) | 162 (5.5) | 0.88 (0.65–1.19) | 0.40 |
| 3rd tertile (n = 4,252) | 355 (30.0) | 928 (30.2) | 0.99 (0.89–1.10) | 0.87 |
| Total | 424 (13.2) | 1,135 (12.1) | 1.09 (0.98–1.21) | 0.10 |
| 1-year mortality |  |  |  |
| 1st tertile (n = 4,222) | 49 (5.5) | 160 (4.8) | 1.22 (0.88–1.68) | 0.24 |
| 2nd tertile (n = 4,117) | 176 (15.4) | 450 (15.1) | 1.04 (0.88–1.22) | 0.68 |
| 3rd tertile (n = 4,252) | 599 (50.6) | 1,425 (46.4) | 1.05 (0.98–1.12) | 0.13 |
| Total | 824 (25.6) | 2,035 (21.7) | 1.18 (1.10–1.27) | <0.001 |
| 30-day mortality or disability at discharge |  |  |  |
| 1st tertile (n = 4,222) | 328 (37.1) | 1,099 (32.9) | 1.12 (1.02–1.24) | 0.02 |
| 2nd tertile (n = 4,117) | 619 (54.0) | 1,533 (51.6) | 1.05 (0.98–1.12) | 0.16 |
| 3rd tertile (n = 4,252) | 1,025 (86.6) | 2,660 (86.7) | 1.00 (0.97–1.03) | 0.91 |
| Total | 1,972 (60.9) | 5,292 (56.0) | 1.09 (1.05–1.12) | <0.001 |
| Discharged home (or same place of residence) |  |  |  |
| 1st tertile (n = 4,222) | 549 (62.9) | 2,241 (67.1) | 0.93 (0.88–0.98) | 0.01 |
| 2nd tertile (n = 4,117) | 565 (49.3) | 1,415 (47.6) | 0.98 (0.92–1.05) | 0.60 |
| 3rd tertile (n = 4,252) | 194 (16.4) | 499 (16.3) | 1.01 (0.87–1.18) | 0.86 |
| Total | 1,308 (40.4) | 4,155 (42.0) | 0.97 (0.93–1.01) | 0.13 |
| Death at 30 days or institutionalization at discharge |  |  |  |
| 1st tertile (n = 4,222) | 29 (3.3) | 109 (3.3) | 0.95 (0.62–1.45) | 0.81 |
| 2nd tertile (n = 4,117) | 137 (12.0) | 363 (12.2) | 1.07 (0.89–1.29) | 0.44 |
| 3rd tertile (n = 4,252) | 546 (46.1) | 1,358 (44.3) | 1.04 (0.97–1.11) | 0.30 |
| Total | 712 (22.0) | 1,830 (19.4) | 1.04 (0.97–1.12) | 0.21 |

Data are n (%) unless otherwise indicated.
type II error may play a role in subgroup analysis as a result of smaller sample sizes. Consequently, we cannot rule out the possibility of residual confounding despite the adjustment in the regression models.

Strengths of our study encompass a large sample size of “real-world” patients and a substantial number of patients with and without diabetes receiving tPA. Further, we used a previously validated score with a near complete verification of stroke severity and follow-up.

Our study suggests that the iScore is a powerful tool for estimating clinical outcomes that could be reliably applied to both patients with and patients without diabetes. Despite the fact that patients with diabetes have a slightly higher risk of death and disability at discharge and long-term mortality, there is no significant difference in rate of ICH compared with that in patients without diabetes. These results provide useful information to clinicians for evaluating patients with diabetes in an acute stroke setting and discussing outcomes with patients and their families.

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D.N. wrote the manuscript; researched data; participated in the conception, design, analysis, and interpretation of the results; drafted the manuscript; and made a critical revision of the manuscript. R.R. researched data; participated in the conception, design, analysis, and interpretation of the results; drafted the manuscript; and made a critical revision of the manuscript. J.P. contributed to discussion; researched data; participated in the conception, design, analysis, and interpretation of the results; drafted the manuscript; and made a critical revision of the manuscript. L.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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