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

DAVAR NIKNESHAN, MD[1]
ROULA RAPTIS, MSC[2]
JITPHAPA PONGMORAGOT, MD[1]
LIMEI ZHOU, PHD[3]
S. CLAIBORNE JOHNSTON, MD, PHD, FAHA[4]
GUSTAVO SAPOSNIK, MD, MSC, FAHA, FRCPC[1,5,6]
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.

Diabetes Care 36:2041–2047, 2013

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 comorbid 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

From the [1]Stroke Outcomes Research Centre, Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada; the [2]Applied Health Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada; the [3]Institute for Clinical Evaluative Sciences, Toronto, Canada; the [4]Clinical and Translational Science Institute and Department of Neurology, University of California, San Francisco, San Francisco, California; the [5]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada; and the [6]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada.
Corresponding author: Gustavo Saposnik, saposnikg@smh.ca.
Received 13 October 2012 and accepted 19 December 2012.
DOI: 10.2337/dc12-2095
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-2095/-/DC1.
S.C.J. and G.S. contributed equally to qualify as senior authors of this study.
© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

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

Table 1—*Characteristics of the ischemic stroke cohort stratified by diagnosis of diabetes*

Characteristic	All	Diabetes: Yes	Diabetes: 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
Age (years)				
≤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 severity				
0	354 (2.8)	81 (2.5)	273 (2.9)	
≤4	1,564 (12.3)	396 (12.2)	1,168 (12.4)	
5–7	2,495 (19.7)	635 (19.6)	1,860 (19.7)	
≥8	8,273 (65.2)	2,126 (65.7)	6,147 (65.1)	0.688
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 disability 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

χ^2 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 thrombolytic therapy

Intravenous tPA was administered to 1,689 (13.3%) patients (*n* = 1,356 nondiabetic 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 1*A* 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])

Table 2—*Clinical outcomes after tPA stratified by the iScore among stroke patients with and without diabetes*

	30-day mortality and disability at discharge				Hemorrhagic transformation (any type)				Symptomatic hemorrhagic transformation			
	Diabetes				Diabetes				Diabetes			
iScore	Yes	No	RR (95% CI)	*P*	Yes	No	RR (95% CI)	*P*	Yes	No	RR (95% CI)	*P*
<200 (*n* = 1,516)	199 (72.4)	825 (66.5)	1.09 (1.00–1.18)	0.05	27 (9.8)	140 (11.3)	0.88 (0.59–1.29)	0.048	15 (5.5)	76 (6.1)	0.89 (0.52–1.53)	0.67
≥200 (*n* = 173)	53 (91.4)	109 (94.8)	0.96 (0.87–1.05)	0.43	15 (25.9)	29 (25.2)	1.03 (0.60–1.76)	0.93	10 (17.2)	16 (13.9)	1.24 (0.60–2.56)	0.56
Total	252 (75.7)	934 (68.9)	1.10 (1.02–1.18)	0.01	42 (12.6)	169 (12.5)	1.01 (0.72–1.40)	0.93	25 (7.5)	92 (6.8)	1.11 (0.70–1.72)	0.64

Data are *n* (%) unless otherwise indicated.

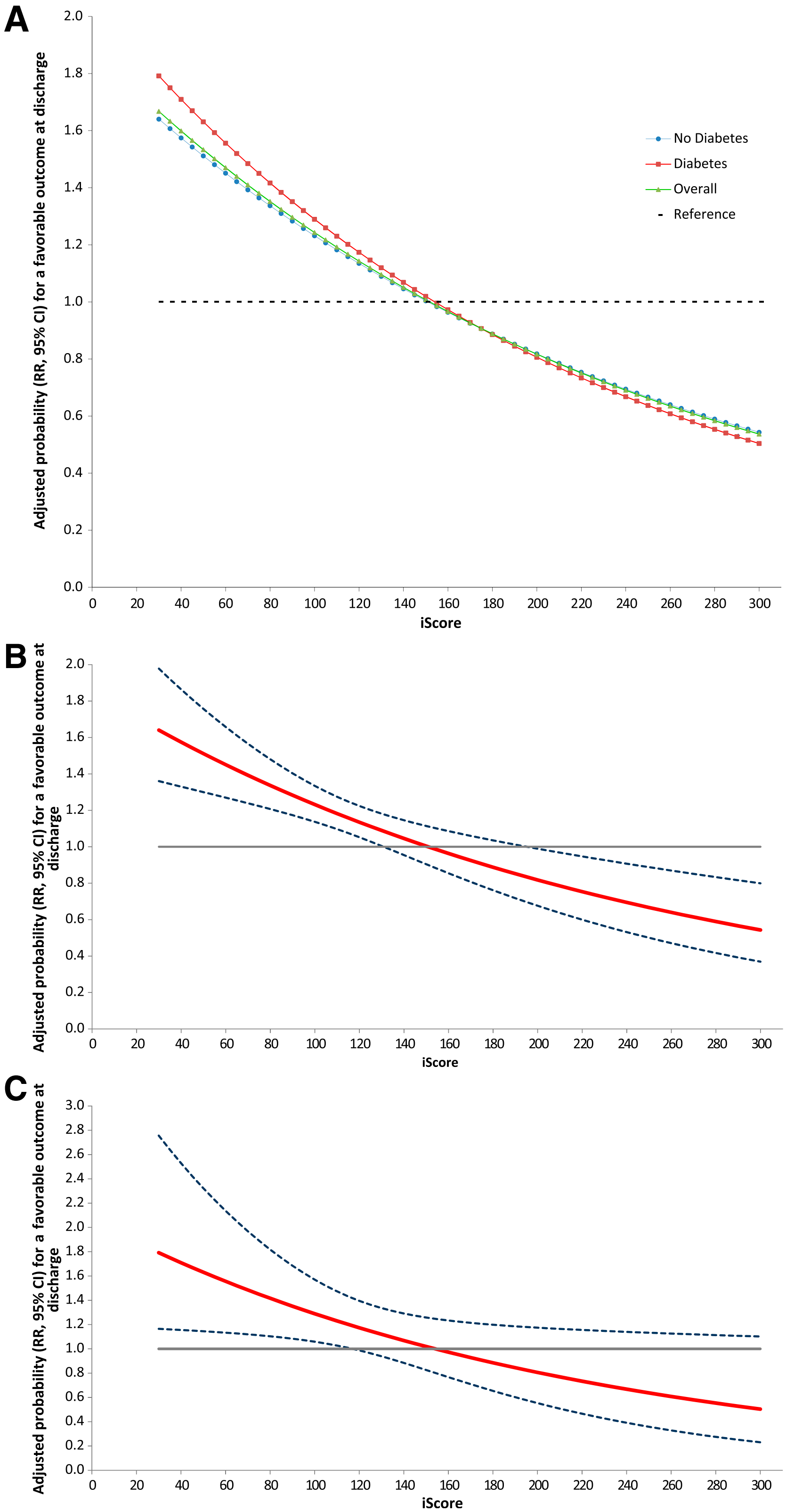

Figure 1—*Adjusted probability of a favorable outcome in tPA-treated patients compared with non-tPA patients by the iScore.* A: *Probability of a favorable outcome in the whole population and in patients with and patients without diabetes. The probability of favorable outcome and the 95% CI are represented for patients without diabetes* (B) *and for patients with diabetes* (C). *Note that there was no difference in the response to tPA (slope of the curves) between patients with and without diabetes* (P = *0.07*). *(A high-quality color representation of this figure is available in the online issue.)*

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. 1*A*). 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

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

iScore	Diabetes Yes	Diabetes No	RR (95% CI)	*P*
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.

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 thrombolyzed 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 0.39–0.84]) with borderline treatment interaction (14). Further, in the European Cooperative Acute Stroke Study III (ECASS III), there were 62 patients with diabetes receiving tPA and 67 in the placebo group. There was a trend for less favorable outcome at 90 days among patients with diabetes (15). Mishra et al. (31) compared outcomes after tPA in patients with diabetes (*n* = 5,354) in the SITS-ISTR cohort versus diabetic patients from the VISTA database who did not receive tPA. Patients with diabetes who received tPA had higher rates of hypertension, history of prior stroke, atrial fibrillation, and heart failure. After adjustment, stroke patients with diabetes receiving tPA had better outcomes (1.45 [1.30–1.62]) 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 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.

Acknowledgments—G.S. is supported by Distinguished Clinician-Scientist Award from the Heart and Stroke Foundation of Canada.

The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

No potential conflicts of interest relevant to this article were reported.

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. researched data; provided statistical expertise; participated in the conception, design, analysis, and interpretation of the results; drafted the manuscript; and made a critical revision of the manuscript. S.C.J. reviewed and edited the manuscript; participated in the conception, design, analysis, and interpretation of the results; drafted the manuscript; and made a critical revision of the manuscript. G.S. reviewed and edited the manuscript; contributed to discussion; 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.

The authors thank the investigators of the RCSN, Dr. M. Kapral, and Dr. F. Silver for providing access to the data.

References

1. Roth EJ, Heinemann AW, Lovell LL, Harvey RL, McGuire JR, Diaz S. Impairment and disability: their relation during stroke rehabilitation. Arch Phys Med Rehabil 1998;79:329–335
2. Forsberg-Wärleby G, Möller A, Blomstrand C. Spouses of first-ever stroke patients: psychological well-being in the first phase after stroke. Stroke 2001;32:1646–1651
3. Duncan PW, Zorowitz R, Bates B, et al. Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. Stroke 2005;36:e100–e143
4. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors' quality of life during subacute recovery. Stroke 2005; 36:1480–1484
5. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009 8;8:741–754
6. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011;378:31–40
7. Ford ES, Mokdad AH. Epidemiology of obesity in the Western Hemisphere. J Clin Endocrinol Metab 2008;93(Suppl 1.):S1–S8
8. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549–1555
9. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012 3;11:261–271
10. Megherbi SE, Milan C, Minier D, et al.; European BIOMED Study of Stroke Care Group. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke 2003;34:688–694
11. Saposnik G, Kapral MK, Liu Y, et al.; Investigators of the Registry of the Canadian Health Network: Stroke Outcomes Research Canada (SORCan) Working Group. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation 2011;123:739–749
12. Saposnik G, Raptis S, Kapral MK, et al.; Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcome Research Canada Working Group. The iScore predicts poor functional outcomes early after hospitalization for an acute ischemic stroke. Stroke 2011;42:3421–3428
13. Saposnik G, Fang J, Kapral MK, et al.; Investigators of the Registry of the Canadian Stroke Network (RCSN); Stroke Outcomes Research Canada (SORCan) Working Group. The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke. Stroke 2012;43: 1315–1322
14. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. Stroke 1997;28:2119–2125
15. Bluhmki E, Chamorro Á, Dávalos A, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. Lancet Neurol 2009;8:1095–1102
16. Kapral MK, Silver FL, Richards JA, et al. Registry of the Canadian Stroke Network. Progress Report 2001–2005. Toronto, ICES, 2005
17. Reeves MJ, Vaidya RS, Fonarow GC, et al.; Get With The Guidelines Steering Committee and Hospitals. Quality of care and outcomes in patients with diabetes hospitalized with ischemic stroke: findings from Get With the Guidelines-Stroke. Stroke 2010;41:e409–e417
18. Demchuk AM, Morgenstern LB, Krieger DW, et al. Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. Stroke 1999;30:34–39
19. Knoflach M, Matosevic B, Rücker M, et al.; Austrian Stroke Unit Registry Collaborators. Functional recovery after ischemic stroke—a matter of age: data from the Austrian Stroke Unit Registry. Neurology 2012;78:279–285
20. König IR, Ziegler A, Bluhmki E, et al.; Virtual International Stroke Trials Archive (VISTA) Investigators. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke 2008;39: 1821–1826
21. Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC; German Stroke Study Collaboration. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke 2004; 35:158–162
22. Strbian D, Meretoja A, Ahlhelm FJ, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology 2012;78:427–432

23. Solberg OG, Dahl M, Mowinckel P, Stavem K. Derivation and validation of a simple risk score for predicting 1-year mortality in stroke. J Neurol 2007;254: 1376–1383
24. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke 2006;37:2957–2962
25. Alvarez-Sabín J, Molina CA, Ribó M, et al. Impact of admission hyperglycemia on stroke outcome after thrombolysis: risk stratification in relation to time to reperfusion. Stroke 2004;35:2493–2498
26. Ribo M, Molina C, Montaner J, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke 2005;36:1705–1709
27. Ahmed N, Dávalos A, Eriksson N, et al.; SITS Investigators. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). Arch Neurol 2010;67:1123–1130
28. Arnold M, Mattle S, Galimanis A, et al. Impact of admission glucose and diabetes on recanalization and outcome after intra-arterial thrombolysis for ischaemic stroke. Int J Stroke. 13 September 2012 [Epub ahead of print]
29. Calleja AI, García-Bermejo P, Cortijo E, et al. Insulin resistance is associated with a poor response to intravenous thrombolysis in acute ischemic stroke. Diabetes Care 2011;34:2413–2417
30. Bateman BT, Schumacher HC, Boden-Albala B, et al. Factors associated with in-hospital mortality after administration of thrombolysis in acute ischemic stroke patients: an analysis of the nationwide inpatient sample 1999 to 2002. Stroke 2006;37:440–446
31. Mishra NK, Ahmed N, Davalos A, et al.; SITS and VISTA collaborators. Thrombolysis outcomes in acute ischemic stroke patients with prior stroke and diabetes mellitus. Neurology 2011;77:1866–1872