

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
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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 \times 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.

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).

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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

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 RSCN, 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		P
		Yes	No	
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 value <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 to 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 value <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 value = 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

iScore	30-day mortality and disability at discharge			Hemorrhagic transformation (any type)			Symptomatic hemorrhagic transformation					
	Diabetes		RR (95% CI)	Diabetes		RR (95% CI)	Diabetes		RR (95% CI)			
	Yes	No		Yes	No		Yes	No				
<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 = 1,73)	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.

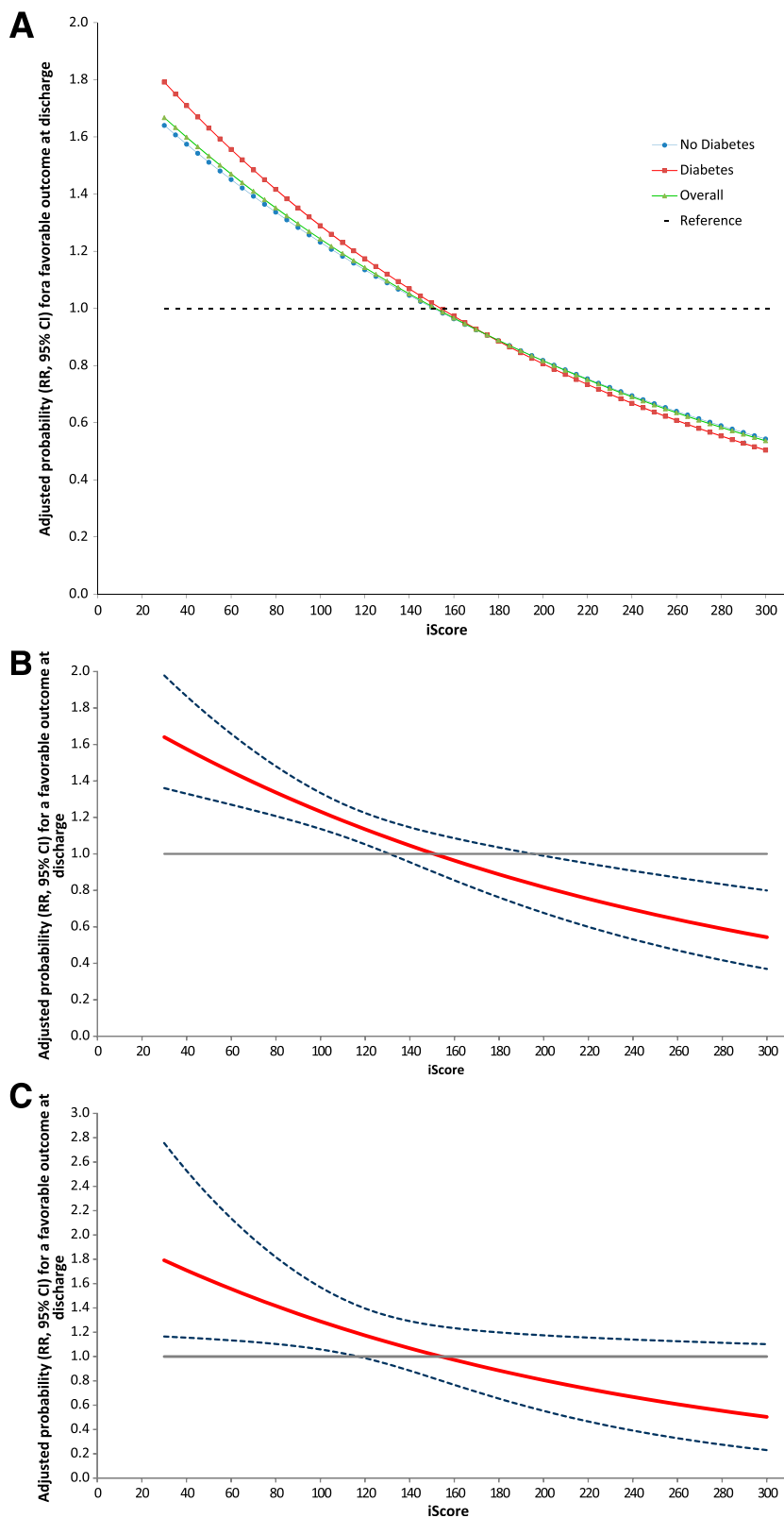


Figure 1—Adjusted probability of a favorable outcome in tPA-treated patients compared with non-tPA patients by the iScore. A: Probability of a favorable outcome in the whole population and in patients with and patients without diabetes. The probability of favorable outcome and the 95% CI are represented 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. 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

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.

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 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.

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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. 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.

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