# Association of Acute and Chronic Hyperglycemia With Acute Ischemic Stroke Outcomes Post‐ Thrombolysis: Findings From Get With The Guidelines‐Stroke

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# Association of Acute and Chronic Hyperglycemia With Acute Ischemic Stroke Outcomes Post-Thrombolysis: Findings From Get With The Guidelines-Stroke

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***Background***—Hyperglycemia has been associated with adverse outcomes in patients with acute ischemic stroke (AIS) and may influence outcomes after tissue plasminogen activator (tPA). We sought to analyze the association of acute and chronic hyperglycemia on clinical outcomes in tPA-treated patients.

***Methods and Results***—We identified 58 265 AIS patients from 1408 sites who received tPA from 2009 to 2013 in Get With The Guidelines-Stroke. Acute hyperglycemia at admission was defined as a plasma glucose level >140 mg/dL. Chronic hyperglycemia was defined by plasma glycosylated hemoglobin (HbA1c) >6.5%. Post–tPA outcomes were analyzed using logistic regression. Blood glucose >140 mg/dL and HbA1c >6.5 were associated with worse clinical outcomes (symptomatic intracranial hemorrhage [sICH], life-threatening hemorrhage, and in-hospital mortality and length of stay) in diabetic and nondiabetic patients. Among patients with documented history of diabetes, increasing admission glucose up to 200 mg/dL was associated with increased adjusted odds ratio (aOR) of in-hospital mortality (aOR, 1.07) and sICH (aOR, 1.05) per 10 mg/dL increase in blood glucose. Increasing HbA1C to 8% was associated with increased odds of in-hospital mortality (aOR, 1.19) and sICH (aOR, 1.16) per 1% increase in HbA1c. Similar findings were observed in patients without a documented history of diabetes. There was no further increase in poor outcomes above the blood glucose level of 200 mg/dL or HbA1c >8.

***Conclusion***—Acute and chronic hyperglycemia are both associated with increased mortality and worse clinical outcomes in AIS patients treated with tPA. Controlled trials are needed to determine whether acute correction of hyperglycemia can improve outcomes after thrombolysis. (*J Am Heart Assoc*. 2015;4:e002193 doi: 10.1161/JAHA.115.002193)

**Key Words:** acute stroke • hyperglycemia • tissue plasminogen activator

S troke outcomes are worse in patients with diabetes.[1,2] This is likely due to hyperglycemia, which is considered a poor prognostic factor in stroke patients.[3,4] Increased admission glucose levels in acute stroke have also been associated with longer in-hospital stay, increased cost, and mortality.[5] Hyperglycemia before reperfusion potentially decreases the beneficial effect of tissue-type plasminogen activator (tPA)[6] given that hyperglycemia may act as an inhibitor of fibrinolysis.[7]

Some studies have reported an increased risk of symptomatic intracranial hemorrhage (sICH) after tPA treatment in patients with diabetes or hyperglycemia,[8–10] and admission glucose has been used in prognostic models to identify patients at risk of sICH after tPA.[11] Even though studies did not find overall reduced benefit of tPA in diabetic patients,[12] decreased rates of tPA administrations are observed in diabetic patients.[13] Guidelines recommend against tPA use in the 3- to 4.5-hour window in patients with prior stroke plus diabetes based on insufficient evidence for its effectiveness, as patients with both prior stroke and diabetes were excluded from the European Cooperative Acute Stroke Study 3 trial.[14] In this study, we sought to evaluate the relationship between admission hyperglycemia and the chronic hyperglycemic state on clinical outcomes in acute ischemic stroke patients with and without a recognized history of diabetes who were treated with tPA.

## Methods

We identified 87 975 AIS patients from 1586 sites that received intravenous tPA from 2009 to 2013 using the Get With The Guidelines Stroke (GWTG-Stroke) database. Details of the GWTG-Stroke program, including the methods of data collection and data definitions used, have been described previously.[15–18] All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board (IRB) approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Quintiles (Cambridge, MA) served as the registry coordinating center for the American Heart Association/American Stroke Association Get With The Guidelines programs. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center, and IRB approval was granted to analyze aggregate deidentified data for research purposes. We excluded 3843 patients because of missing documentation on the National Institutes of Health Stroke Scale (NIHSS), and 11 223 patients discharged or transferred to another acute care facility left against medical advice or discharge destination not documented. Of the remaining 72 909 patients, admission glucose was not documented for 14 644 patients. The final cohort consisted of 58 265 AIS patients treated with tPA. Because abnormal glucose metabolism might exert its effects by several different mechanisms, either through chronic injury resulting from diabetes or acute injury through hyperglycemia, we classified patients based on either laboratory findings or clinical history. Random plasma glucose measured at admission identified subjects with or without acute hyperglycemia. Chronic hyperglycemia was manifest as either a known previous diagnosis of diabetes mellitus (DM) in some patients, whereas others presented with occult diabetes diagnosed during the index stroke admission by elevated levels of glycosylated hemoglobin (HbA1c). The two types of hyperglycemia were defined using the latest American Diabetes Association criteria: Acute hyperglycemia at admission was defined as a random plasma glucose level >140 mg/dL, and chronic hyperglycemia was defined as a plasma level of HbA1c >6.5%.[19]

## Statistical Analysis

Contingency tables were generated to explore the relationship between important covariates, including demographics, clinical variables, medical history, and hospital-level characteristics, by presence of acute hyperglycemia in AIS patients treated with tPA. Primary outcomes of interest were complications of tPA thrombolytic therapy (symptomatic hemorrhage [sICH] and life-threatening systemic hemorrhage) and all-cause in-hospital mortality. Other outcomes of interest were length of stay and ambulatory status at discharge. Chi-square for categorical variables or Wilcoxon test for continuous data were used as tests for statistical associations.

Outcomes among stroke patients receiving tPA were compared between acute hyperglycemic and nonhyperglycemic patients using logistic regression with generalized estimating equations to account for within-site clustering. Each outcome was modeled using a tiered approach. First, the unadjusted odds ratios were calculated. Next, patient characteristics were added to the model (age, gender, race [white vs other], medical history of atrial fib/flutter, previous stroke/transient ischemic attack [TIA], coronary artery disease [CAD]/previous myocardial infarction [MI], carotid stenosis, DM, peripheral vascular disease [PVD], hypertension, dyslipidemia, smoking, and NIHSS). Finally, hospital characteristics (region, academic/teaching hospital, number of beds, rural location, TJC primary stroke center status, annual ischemic stroke volume, and annual tPA volume) were added to the model. Blood glucose and HbA1c were not included in the multivariable models. Single imputations were used to reduce missingness in the models. Blood glucose and HbA1c as continuous variables were modeled with linear splines to analyze relationships with outcomes of in-hospital mortality and sICH. A knot point of 200 mg/dL provided the best fit. There was no evidence of further association above blood glucose 200 mg/dL. Next, blood glucose was modeled from 40 to 200 mg/dL with a linear spline. HbA1c was modeled from 0% to 20%.

Analyses were also performed in 2 important subgroups: (1) patients with chronic hyperglycemia as determined solely by HbA1c values and (2) patients with a documented history of DM and available hyperglycemia laboratory values. For each outcome, interaction between patients with documented history of diabetes versus no diabetes in relation to acute hyperglycemia or HbA1c were analyzed, where an interaction test *P*<0.05 would suggest evidence of a significant interaction between diabetic and nondiabetic patients in relation to acute hyperglycemia or HbA1c and outcomes.

Laboratory data on admission were not recorded in a large number of subjects for plasma glucose (n=14 644; 20.1%) and HbA1c (n=26 760; 36.7%). In order to determine whether this missingness was nonrandom, we compared patients characteristics between those with versus without a recorded admission glucose and those with versus without a recorded HbA1c (Tables S1 and S2).

## Results

There were 72 909 patients available for analysis overall. Over the entire cohort, median age was 72 years (interquartile
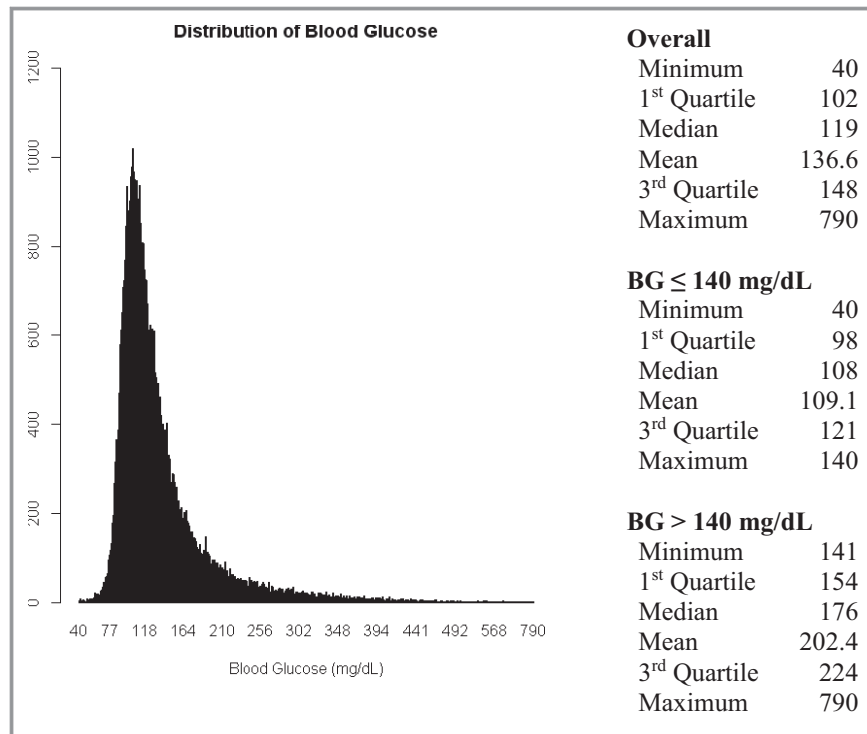
**Figure 1.** Distribution of admission blood glucose (BG) values.

range [IQR], 59 to 82), 50.3% were female, and median NIHSS was 10 (6 to 17). Admission glucose was available for 58 265 and HbA1c for 31 505 patients. Median blood glucose level was 119 mg/dL (IQR, 102 to 148), and median HbA1c was 5.9% (IQR, 5.5 to 6.6). The distribution of recorded blood glucose and HbA1c values are shown in Figures 1 and 2,



**Figure 2.** Distribution of glycosylated hemoglobin (HbA1c) values.

**Table 1.** Baseline Patient Characteristics of Acute Stroke Patients With vs Without Acute Hyperglycemia

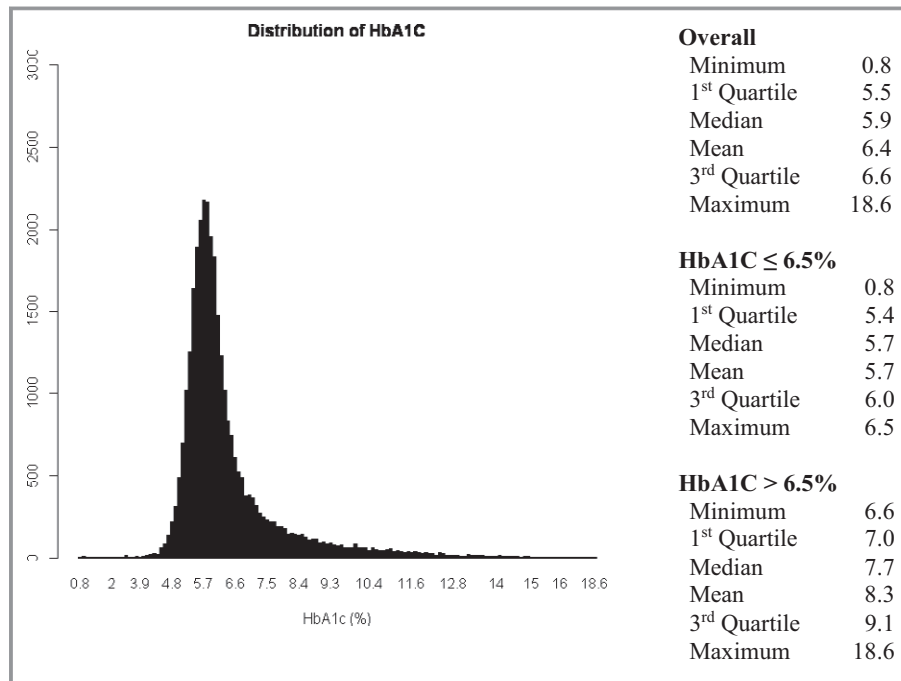| Variable | Level | Overall (N=58 265) | | Acute Hyperglycemia (BG >140 mg/dL) (N=17 203) | | No Acute Hyperglycemia (BG ≤140 mg/dL) (N=41 062) | | P Value |
|---|---|---|---|---|---|---|---|---|
| Age | Median | 58 265 | 72.0 | 17 203 | 72.0 | 41 062 | 71.0 | 0.0001 |
| | 25th | | 59.0 | | 61.0 | | 59.0 | |
| | 75th | | 82.0 | | 81.0 | | 82.0 | |
| Sex | Female | 29 306 | 50.30 | 8465 | 49.2 | 20 841 | 50.8 | 0.0006 |
| Onset to treatment time (minutes) | Median | 55 869 | 141.0 | 16 463 | 145.0 | 39 406 | 140.0 | <0.0001 |
| | 25th | | 110.0 | | 112.0 | | 109.0 | |
| | 75th | | 175.0 | | 175.0 | | 174.0 | |
| Medical history | | | | | | | | |
| CAD/previous MI | | 14 588 | 25.1 | 4999 | 29.1 | 9589 | 23.4 | <0.0001 |
| Carotid stenosis | | 1548 | 2.7 | 528 | 3.1 | 1020 | 2.5 | <0.0001 |
| Diabetes mellitus | | 15 232 | 26.2 | 9363 | 54.5 | 5869 | 14.3 | <0.0001 |
| PVD | | 2058 | 3.5 | 736 | 4.3 | 1322 | 3.2 | <0.0001 |
| Hypertension | | 42 660 | 73.3 | 13 763 | 80.1 | 28 897 | 70.4 | <0.0001 |
| Smoker | | 10 605 | 18.2 | 2614 | 15.2 | 7991 | 19.5 | <0.0001 |
| Dyslipidemia | | 23 907 | 41.1 | 7720 | 44.9 | 16 187 | 39.4 | <0.0001 |
| Heart failure | | 5330 | 9.2 | 1905 | 11.1 | 3425 | 8.4 | <0.0001 |
| NIHSS Score | Median | 58 265 | 10.0 | 17 203 | 11.0 | 41 062 | 10.0 | <0.0001 |
| | 25th | | 6.0 | | 6.0 | | 6.0 | |
| | 75th | | 17.0 | | 18.0 | | 17.0 | |
| HbA1C, % | Median | 31 505 | 5.9 | 10 626 | 6.8 | 20 879 | 5.8 | <0.0001 |
| | 25th | | 5.5 | | 6.0 | | 5.4 | |
| | 75th | | 6.6 | | 8.3 | | 6.1 | |
| Complications of thrombolytic therapy | | | | | | | | |
| Symptomatic ICH | | 2717 | 4.7 | 1067 | 6.2 | 1650 | 4.0 | <0.0001 |
| Serious/life-threatening hemorrhage | | 594 | 1.0 | 279 | 1.6 | 315 | 0.8 | <0.0001 |
| Other complication | | 1968 | 3.4 | 717 | 4.2 | 1251 | 3.1 | <0.0001 |
| Other outcomes | | | | | | | | |
| In-hospital mortality | | 4572 | 7.9 | 1937 | 11.3 | 2635 | 6.4 | <0.0001 |
| LOS >4 days | | 29 026 | 51.4 | 9435 | 56.5 | 19 591 | 49.3 | <0.0001 |
| Unable to ambulate at discharge | | 15 112 | 29.0 | 5616 | 36.5 | 9496 | 25.9 | <0.0001 |
| Hospital characteristics | | | | | | | | |
| Academic/teaching hospital | | 36 909 | 63.7 | 10 953 | 64.0 | 25 956 | 63.6 | 0.36 |
| Region | West | 11 517 | 19.8 | 3306 | 19.2 | 8211 | 20.0 | 0.0002 |
| | South | 20 743 | 35.6 | 6128 | 35.6 | 14 615 | 35.6 | |
| | Midwest | 11 300 | 19.4 | 3237 | 18.8 | 8063 | 19.6 | |
| | Northeast | 14 705 | 25.2 | 4532 | 26.3 | 10 173 | 24.8 | |

BG indicates blood glucose; CAD, coronary artery disease; HbA1c, glycosylated hemoglobin; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease.

respectively. A previous history of diabetes was documented in 15 232 patients; of these with history of diabetes, 9363 had blood glucose >140 mg/dL at admission and 6346 had HbA1c >6.5.

## Acute Hyperglycemia on Admission

Characteristics of AIS patients treated with intravenous tPA according to admission blood glucose level are presented in

**Table 2.** Multivariable Model of the Association Between Acute Hyperglycemia* and Clinical Outcomes

| Outcome | Unadjusted Model | | | Adjusted Model (Patient Characteristics) | | | Fully Adjusted Model (Patient and Hospital Characteristics) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value | OR | 95% CI | P Value |
| Complications of thrombolytic therapy | | | | | | | | | |
| Symptomatic ICH | 1.57 | (1.45, 1.69) | <0.0001 | 1.40 | (1.29, 1.53) | <0.0001 | 1.41 | (1.29, 1.53) | <0.0001 |
| Serious/life-threatening hemorrhage | 2.13 | (1.82, 2.49) | <0.0001 | 1.90 | (1.61, 2.25) | <0.0001 | 2.13 | (1.82, 2.49) | <0.0001 |
| Other complication | 1.38 | (1.26, 1.52) | <0.0001 | 1.24 | (1.12, 1.38) | <0.0001 | 1.25 | (1.12, 1.39) | <0.0001 |
| Other outcomes | | | | | | | | | |
| In-hospital mortality | 1.87 | (1.76, 1.98) | <0.0001 | 1.69 | (1.58, 1.82) | <0.0001 | 1.68 | (1.57, 1.80) | <0.0001 |
| LOS >4 | 1.31 | (1.27, 1.36) | <0.0001 | 1.17 | (1.12, 1.22) | <0.0001 | 1.17 | (1.12, 1.22) | <0.0001 |
| Unable to ambulate at discharge | 1.65 | (1.58, 1.72) | <0.0001 | 1.52 | (1.45, 1.59) | <0.0001 | 1.51 | (1.44, 1.59) | <0.0001 |

Variables used for patient characteristics: age, gender, race (white vs other), medical history of atrial fib/flutter, previous stroke/TIA, CAD/previous MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, presentation during off hours, NIHSS, and systolic blood pressure. For hospital characteristics: region, academic/teaching hospital, number of beds, rural location, TJC primary stroke center status, annual ischemic stroke volume, and annual tPA volume. BG indicates blood glucose; CAD, coronary artery disease; CI, confidence interval; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack; TJC, the joint commission; tPA, tissue plasminogen activator.
*Acute hyperglycemia defined as BG >140 mg/dL.

Table 1. When compared to patients with no acute hyperglycemia, those with acute hyperglycemia (n=17 203) were older in age, more frequently males, and had higher median stroke severity as measured by NIHSS. They had longer median onset to treatment time and had more frequently documented medical history of CAD, DM, PVD, hypertension, carotid stenosis, dyslipidemia, and heart failure and were more likely to be smokers. There were higher rates of sICH (6.2% vs 4.0%; *P*<0.0001), life-threatening hemorrhage (1.6% vs 0.8%; *P*<0.0001), and in-hospital mortality (11.3% vs 6.4%; *P*<0.0001) in patients with acute hyperglycemia when compared to no hyperglycemia (Table 1). Almost one third of patients with hyperglycemia that survived in hospital were unable to ambulate independently at discharge.

In multivariable analyses, fully adjusting for patient and hospital characteristics, blood glucose >140 mg/dL was independently associated with sICH (adjusted odds ratio [aOR], 1.41; 95% confidence interval [CI], 1.29 to 1.53), life-threatening hemorrhage (aOR, 2.13; 95% CI, 1.82 to 2.49), in-patient mortality (aOR, 1.68; 95% CI, 1.57 to 1.8), length of stay >4 days (aOR, 1.17; 95% CI, 1.12 to 1.22), and inability to ambulate at discharge (aOR, 1.51; 95% CI, 1.44 to 1.59) (Table 2).

## Chronic Hyperglycemia by HbA1c

HbA1C was documented in 31 505 AIS patients treated with tPA. When compared to patients with HbA1c ≤6.5%, patients with elevated HbA1c were younger in age, more frequently male, and had a longer median onset to tPA treatment time. They had more-frequent documented history of CAD, DM,

hypertension, PVD, dyslipidemia, and heart failure (Table 3). Patients with elevated HbA1c had higher rates of post-tPA complications, in-patient mortality, and increased length of stay and were less likely to ambulate at discharge. After adjustment for patient and hospital characteristics, patients with HbA1c of >6.5%, compared to those with ≤6.5%, was independently associated with sICH (aOR, 1.25; 95% CI, 1.07 to 1.46), life-threatening hemorrhage (aOR, 1.34; 95% CI, 1.05 to 1.72), in-patient mortality (OR, 1.36; 95% CI, 1.21 to 1.53), length of stay >4 days (aOR, 1.21; 95% CI, 1.13 to 1.3), and inability to ambulate at discharge (aOR, 1.29; 95% CI, 1.19 to 1.39; Table 4).

To determine whether the nature of the association with hyperglycemia was linear or nonlinear, we also analyzed the relationship of admission blood glucose and HbA1c as continuous variables with the outcomes of in-hospital mortality and sICH. This analysis was performed separately in those with and without a documented history of diabetes. Because admission blood glucose among patients with documented history of diabetes increased from 40 to 200 mg/dL, it was associated with an increased odds of in-hospital mortality (OR, 1.07; 95% CI, 1.05 to 1.09; Figure 3A) and sICH (OR, 1.05; 95% CI, 1.03 to 1.07; Figure 3B) for every 10 mg/dL increase in blood glucose. Further increases in admission blood glucose above 200 mg/dL were not associated with further increases in rates of in-patient mortality or sICH. Similar findings were observed in patients without a documented history of diabetes. Because HbA1c among diabetics increased from 6.5% to 8%, it was associated with an increased odds of in-hospital mortality (OR, 1.19; 95% CI, 1.11 to 1.28; Figure 4A) and sICH (OR, 1.16; 95% CI, 1.06 to 1.26;

**Table 3.** Baseline Patient Characteristics of Acute Stroke Patients With vs Without Chronic Hyperglycemia as Measured by HbA1C Levels

| Variable | Level | Overall (N=31 505) | | HbA1C >6.5% (N=8060) | | HbA1C ≤6.5% (N=23 445) | | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Patient characteristics | | | | | | | | |
| Age | Median | 31 505 | 70.0 | 8060 | 68.0 | 23 445 | 71.0 | <0.0001 |
| | 25th | | 58.0 | | 58.0 | | 58.0 | |
| | 75th | | 81.0 | | 78.0 | | 82.0 | |
| | Mean | | 68.9 | | 67.7 | | 69.3 | |
| Gender | Female | 15 344 | 48.7 | 3689 | 45.8 | 11 655 | 49.7 | <0.0001 |
| Onset to treatment time (minutes) | Median | 30 222 | 141.0 | 7710 | 145.0 | 22 512 | 140.0 | <0.0001 |
| | 25th | | 110.0 | | 114.0 | | 108.0 | |
| | 75th | | 175.0 | | 177.0 | | 174.0 | |
| Medical history | | | | | | | | |
| Atrial fibrillation/flutter | | 6329 | 20.1 | 1407 | 17.5 | 4922 | 21.0 | <0.0001 |
| Previous stroke/TIA | | 7632 | 24.2 | 2128 | 26.4 | 5504 | 23.5 | <0.0001 |
| CAD/previous MI | | 7954 | 25.3 | 2588 | 32.1 | 5366 | 22.9 | <0.0001 |
| Carotid stenosis | | 829 | 2.6 | 244 | 3.0 | 585 | 2.5 | 0.01 |
| Diabetes mellitus | | 9954 | 31.6 | 6346 | 78.8 | 3608 | 15.4 | <0.0001 |
| PVD | | 1102 | 3.5 | 376 | 4.7 | 726 | 3.1 | <0.0001 |
| Hypertension | | 23 450 | 74.5 | 6701 | 83.2 | 16 749 | 71.5 | <0.0001 |
| Smoker | | 6103 | 19.4 | 1377 | 17.1 | 4726 | 20.2 | <0.0001 |
| Dyslipidemia | | 13 034 | 41.4 | 3961 | 49.8 | 9073 | 38.7 | <0.0001 |
| Heart failure | | 2913 | 9.3 | 911 | 11.3 | 2002 | 8.5 | <0.0001 |
| NIHSS Score | Median | 31 505 | 10.0 | 8060 | 10.0 | 23 445 | 10.0 | <0.0001 |
| | 25th | | 6.0 | | 6.0 | | 6.0 | |
| | 75th | | 17.0 | | 16.0 | | 17.0 | |
| | Mean | | 11.7 | | 11.4 | | 11.8 | |
| Blood glucose, mg/dL | Median | 31 505 | 122.0 | 8060 | 183.0 | 23 445 | 114.0 | <0.0001 |
| | 25th | | 104.0 | | 140.0 | | 100.0 | |
| | 75th | | 156.0 | | 250.0 | | 134.00 | |
| Complications of thrombolytic therapy | | | | | | | | |
| Symptomatic ICH | | 1379 | 4.4 | 405 | 5.1 | 974 | 4.2 | 0.001 |
| Serious/life-threatening hemorrhage | | 271 | 0.9 | 85 | 1.1 | 186 | 0.8 | 0.02 |
| Other complication | | 1011 | 3.2 | 291 | 3.6 | 720 | 3.1 | 0.02 |
| Other outcomes | | | | | | | | |
| In-hospital mortality | | 2145 | 6.8 | 639 | 7.9 | 1506 | 6.4 | <0.0001 |
| LOS >4 days | | 16 071 | 52.8 | 4438 | 57.2 | 11 633 | 51.3 | <0.0001 |
| Unable to ambulate at discharge | | 8064 | 27.5 | 2265 | 30.3 | 5799 | 26.5 | <0.0001 |
| Hospital characteristics | | | | | | | | |
| Academic/Teaching Hospital | | 21 144 | 67.4 | 5301 | 66.1 | 15 843 | 67.9 | 0.003 |
| Region | West | 6336 | 20.1 | 1530 | 18.9 | 4806 | 20.5 | 0.02 |
| | South | 11 360 | 36.1 | 2958 | 36.7 | 8402 | 35.8 | |
| | Midwest | 6186 | 19.6 | 1566 | 19.4 | 4620 | 19.7 | |
| | Northeast | 7623 | 24.2 | 2006 | 24.9 | 5617 | 23.9 | |

CAD indicates coronary artery disease; HbA1c, glycosylated hemoglobin; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; TIA, transient ischemic attack.

**Table 4.** Multivariable Model of the Association Between Chronic Hyperglycemia* and Clinical Outcomes

| Outcome | Unadjusted Model | | | Adjusted Model (Patient Characteristics Only) | | | Adjusted Model (Patient and Hospital Characteristics) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value | OR | 95% CI | P Value |
| Complications of thrombolytic therapy | | | | | | | | | |
| Symptomatic ICH | 1.22 | (1.08, 1.38) | 0.002 | 1.24 | (1.06, 1.45) | 0.01 | 1.25 | (1.07, 1.46) | 0.01 |
| Serious/life-threatening hemorrhage | 1.34 | (1.05, 1.72) | 0.02 | 1.37 | (0.99, 1.89) | 0.07 | 1.34 | (1.05, 1.72) | 0.02 |
| Other complication | 1.18 | (1.04, 1.35) | 0.01 | 1.05 | (0.89, 1.24) | 0.57 | 1.06 | (0.89, 1.25) | 0.52 |
| Other outcomes | | | | | | | | | |
| In-hospital mortality | 1.28 | (1.17, 1.40) | <0.0001 | 1.37 | (1.21, 1.54) | <0.0001 | 1.36 | (1.21, 1.53) | <0.0001 |
| LOS >4 | 1.26 | (1.20 1.3) | <0.0001 | 1.21 | (1.13, 1.30) | <0.0001 | 1.21 | (1.13, 1.30) | <0.0001 |
| Unable to ambulate at discharge | 1.22 | (1.16, 1.3) | <0.0001 | 1.30 | (1.20, 1.40) | <0.0001 | 1.29 | (1.19, 1.39) | <0.0001 |

Variables used for patient characteristics: age, gender, race (white vs other), medical history of atrial fib/flutter, previous stroke/TIA, CAD/previous MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, presentation during off hours, NIHSS, and systolic blood pressure. For hospital characteristics: region, academic/teaching hospital, number of beds, rural location, TJC primary stroke center status, annual ischemic stroke volume, and annual tPA volume. CAD indicates coronary artery disease; CI, confidence interval; HbA1c, glycosylated hemoglobin; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack; TJC, the joint commission; tPA, tissue plasminogen activator.
*Chronic hyperglycemia defined as HbA1C >6.5%.

Figure 4B) per 1% increase in HbA1c. Further increases in HbA1c above 8% were not associated with further increases in rates of in-patient mortality or sICH.

## Patients With a Documented History of DM

We performed additional exploratory analyses comparing the influence of acute hyperglycemia on clinical outcomes after thrombolysis in patients with a known history of DM. Patients with a history of diabetes who presented with acute hyperglycemia (blood glucose, >140 mg/dL) had worse outcomes when compared to those who presented without acute hyperglycemia (Table 5). In multivariable analysis, hyperglycemia in patients with a history of diabetes was independently associated with sICH (aOR, 1.39; 95% CI, 1.20 to 1.61), life-threatening hemorrhage (aOR, 1.68; 95% CI, 1.26 to 2.23), in-patient mortality (OR, 1.54; 95% CI, 1.35 to 1.75), length of stay >4 days (aOR, 1.17; 95% CI, 1.10 to 1.25), and inability to ambulate at discharge (aOR, 1.52; 95% CI, 1.40 to 1.66). Finally, we compared clinical outcomes post-tPA in patients with acute hyperglycemia or elevated HbA1c and who were with versus without a known history of diabetes. Patients with acute hyperglycemia or elevated HbA1c had an increased
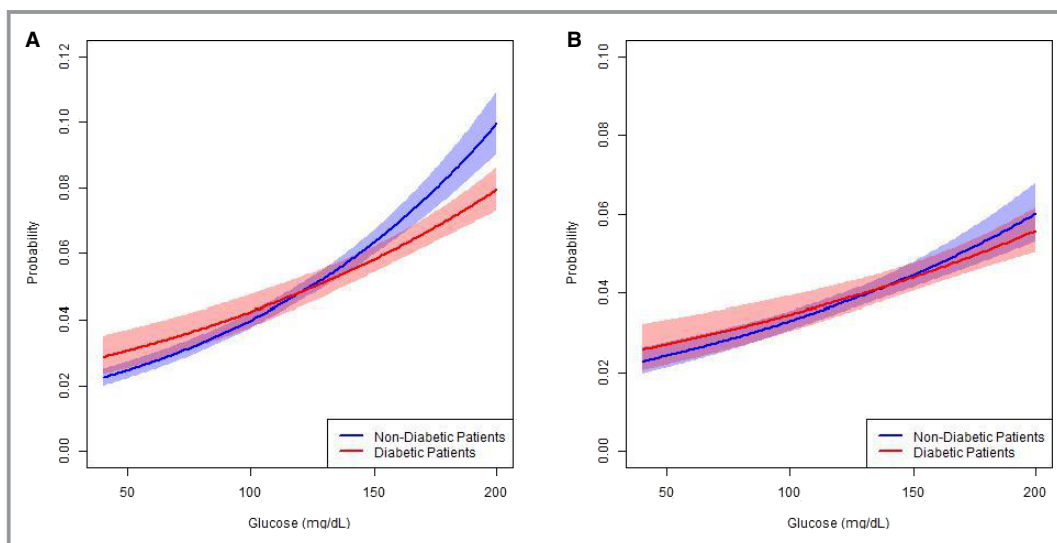


**Figure 3.** A, Predicted probability of in-hospital mortality (adjusted) with 95% confidence intervals; B, predicted probability of symptomatic intracranial hemorrhage (adjusted) with 95% confidence intervals.
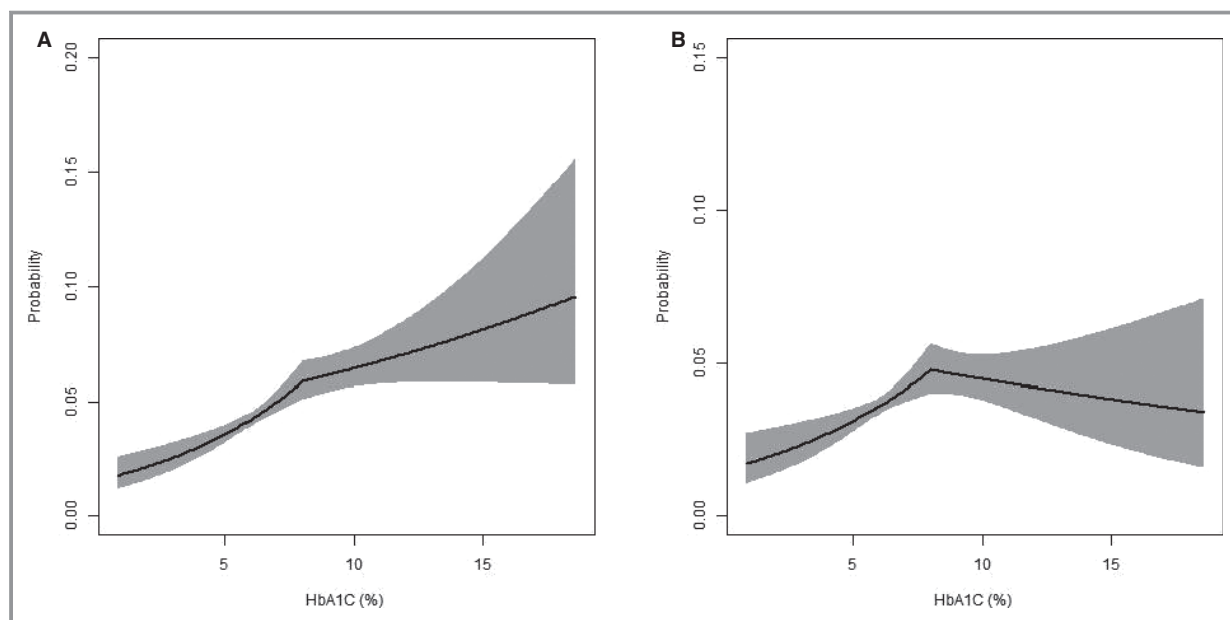
**Figure 4.** A, Predicted probability of in-hospital mortality (adjusted) with 95% confidence intervals; B, predicted probability of symptomatic intracranial hemorrhage (adjusted) with 95% confidence intervals. HbA1c indicates glycosylated hemoglobin.

odds of poor outcomes regardless of a history of known diabetes (Tables 6 and 7, respectively).

## Discussion

In this study, we sought to evaluate the association of disorders of glucose metabolism with outcomes of AIS patients treated with intravenous tPA. We characterized patients as having a disorder of glucose metabolism by admission hyperglycemia, a known diagnosis of diabetes, or by use of glycosylated hemoglobin levels. Hyperglycemia, acute or chronic, was associated with increased mortality and worse clinical outcomes in AIS patients treated with tPA. This held true regardless of a previous known diagnosis of diabetes. The relationship was nonlinear, with a plateau observed at glucose levels above 200 mg/dL and HbA1C levels above 8.0%.

Acute hyperglycemia on admission testing is frequently observed in acute stroke. In patients treated with tPA within 3 hours of stroke onset, acute hyperglycemia has been associated with poor outcomes.[12] These observations may be owing, in part, to the possibility of decreased thrombolytic effectiveness of alteplase in the setting of hyperglycemia. A previous study observed that acute, but not chronic, hyperglycemia was associated with lower rates of tPA-induced recanalization.[20] That study was small and the mean reported HbA1c was 6.3±0.8%. Our study is consistent with, and builds upon, previous studies showing that acute hyperglycemia is associated with fewer favorable outcomes in tPA-

treated patients. However, it is also likely that chronic hyperglycemia may be exerting a role in poor outcomes. Our data also demonstrate that patients with chronic hyperglycemia (as defined by HbA1c >6.5%) also experienced worse outcomes compared to those with HbA1c levels ≤6.5%. Subset analyses also suggest that the actual values of plasma glucose and HbA1c during admission are more important than a previous documented diagnosis of diabetes per se. These data should raise concern about the risks of poor outcome after thrombolysis for patients with disorders of glucose metabolism, a condition with increasing incidence and prevalence in the United States.[21] It is possible that this risk could be mitigated by better chronic and acute glycemic control. However, because of the nonrandomized design of our study, we were unable to determine whether this increased sICH risk was associated with fewer benefits from tPA. Previous subgroup analyses of tPA randomized, controlled trials show that the effect of tPA is the same in diabetic versus nondiabetic patients.[22] This supports the recommendations of others that thrombolysis can be safely given to diabetic patients.[23]

The exact threshold at which elevated blood glucose levels are associated with elevated risk has not been well established. Previous studies suggested that a blood glucose level of 160 mg/dL or more may be a cutoff for poor outcomes.[20,24] One study reported a linear relation between admission glucose and an increase in the odds of sICH (OR 1.75 per 100 mg/dL increase in admission glucose).[5] Admission blood glucose levels were identified as a risk factor for sICH after intravenous tPA in several risk models for

**Table 5.** Baseline Patient Characteristics of Acute Stroke Patients and a Documented History of Diabetes (n=15 232) With vs Without Acute Hyperglycemia

| Variable | Level | Overall (N=15 232) | | Acute Hyperglycemia (BG >140 mg/dL) (N=9363) | | No Hyperglycemia (N=5869) | | P Value |
|---|---|---|---|---|---|---|---|---|
| Patient characteristics | | | | | | | | |
| Age | Median | 15 232 | 71.0 | 9363 | 70.0 | 5869 | 72.0 | <0.0001 |
| | 25th | | 61.0 | | 60.0 | | 62.0 | |
| | 75th | | 80.0 | | 79.0 | | 81.0 | |
| Gender | Female | 7585 | 49.8 | 4505 | 48.1 | 3080 | 52.5 | <0.0001 |
| Onset to treatment time (minutes) | Median | 14 580 | 145.0 | 8956 | 146.0 | 5624 | 144.0 | 0.002 |
| | 25th | | 113.0 | | 115.0 | | 112.0 | |
| | 75th | | 176.0 | | 176.5 | | 175.0 | |
| | Mean | | 156.2 | | 157.9 | | 153.3 | |
| | STD | | 134.2 | | 155.6 | | 90.1 | |
| Medical history | | | | | | | | |
| Atrial fibrillation/flutter | | 3120 | 20.5 | 1848 | 19.7 | 1272 | 21.7 | 0.004 |
| Previous stroke/TIA | | 4540 | 29.8 | 2655 | 28.4 | 1885 | 32.1 | <0.0001 |
| CAD/previous MI | | 5220 | 34.3 | 3224 | 34.4 | 1996 | 34.0 | 0.59 |
| Carotid stenosis | | 506 | 3.3 | 321 | 3.4 | 185 | 3.2 | 0.36 |
| PVD | | 815 | 5.4 | 496 | 5.3 | 319 | 5.4 | 0.71 |
| Hypertension | | 13 223 | 86.8 | 8117 | 86.7 | 5106 | 87.0 | 0.59 |
| Smoker | | 2247 | 14.8 | 1356 | 14.5 | 891 | 15.2 | 0.25 |
| Dyslipidemia | | 8093 | 53.1 | 4883 | 52.15 | 3210 | 54.7 | 0.002 |
| Heart failure | | 1936 | 12.7 | 1185 | 12.7 | 751 | 12.8 | 0.80 |
| NIHSS Score | Median | 15 232 | 10.0 | 9363 | 10.0 | 5869 | 10.0 | 0.003 |
| | 25th | | 6.0 | | 6.0 | | 6.0 | |
| | 75th | | 17.0 | | 17.0 | | 17.0 | |
| HbA1C, % | Median | 9954 | 7.0 | 6244 | 7.6 | 3710 | 6.3 | <0.0001 |
| | 25th | | 6.2 | | 6.7 | | 5.9 | |
| | 75th | | 8.3 | | 9.1 | | 6.9 | |
| Complications of thrombolytic therapy | | | | | | | | |
| Symptomatic ICH | | 826 | 5.5 | 570 | 6.1 | 256 | 4.4 | <0.0001 |
| Serious/life-threatening hemorrhage | | 188 | 1.2 | 137 | 1.5 | 51 | 0.9 | 0.001 |
| Other complication | | 595 | 3.9 | 395 | 4.2 | 200 | 3.4 | 0.01 |
| In-hospital mortality | | 1349 | 8.9 | 951 | 10.2 | 398 | 6.8 | <0.0001 |
| LOS >4 days | | 8168 | 55.3 | 5169 | 56.9 | 2999 | 52.7 | <0.0001 |
| Unable to ambulate at discharge | | 4402 | 32.5 | 2952 | 35.3 | 1450 | 27.9 | <0.0001 |

BG indicates blood glucose; CAD, coronary artery disease; HbA1c, glycosylated hemoglobin; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; TIA, transient ischemic attack.

sICH post-tPA.[11,25–28] Although blood glucose is one of the potential modifiable factor in these risk scores, further studies are required to evaluate whether treatment of hyperglycemia reduces risk of sICH post-tPA. Furthermore, these studies were designed to identify patients at increased risk of sICH and do not conclude benefit or harm of tPA in patients with higher predicted risk. Our study supports the previous observations that worsening of acute or chronic plasma glucose control is associated with increasing mortality, but that the effects are nonlinear and plateau above modest levels

**Table 6.** Multivariable Model of the Association Between Acute Hyperglycemia and Clinical Outcomes for Patients With vs Without a Documented History of Diabetes

| Outcome | Unadjusted Model | | | Adjusted Model (Patient Characteristics Only) | | | Fully Adjusted Model (Patient and Hospital Characteristics) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Complications of thrombolytic therapy | | | | | | | | | |
| Symptomatic ICH | | | 0.13* | | | 1.0* | | | 0.9* |
|   Diabetic patients | 1.41 | (1.23, 1.63) | <0.0001 | 1.40 | (1.22, 1.62) | <0.0001 | 1.40 | (1.21, 1.62) | <0.0001 |
|   Nondiabetic patients | 1.63 | (1.46, 1.81) | <0.0001 | 1.41 | (1.26, 1.56) | <0.0001 | 1.41 | (1.27, 1.57) | <0.0001 |
| Serious/life-threatening hemorrhage | | | 0.06* | | | 0.29* | | | 0.27* |
|   Diabetic patients | 1.69 | (1.28, 2.25) | 0.0003 | 1.66 | (1.25, 2.21) | 0.0006 | 1.64 | (1.23, 2.20) | 0.0007 |
|   Nondiabetic patients | 2.43 | (1.98, 2.97) | <0.0001 | 2.01 | (1.64, 2.46) | <0.0001 | 2.02 | (1.64, 2.47) | <0.0001 |
| Other outcomes | | | | | | | | | |
| In-hospital mortality | | | <0.0001* | | | 0.21* | | | 0.16* |
|   Diabetic patients | 1.56 | (1.37, 1.76) | <0.0001 | 1.58 | (1.39, 1.80) | <0.0001 | 1.55 | (1.37, 1.76) | <0.0001 |
|   Nondiabetic patients | 2.13 | (1.96, 2.31) | <0.0001 | 1.75 | (1.61, 1.91) | <0.0001 | 1.74 | (1.60, 1.89) | <0.0001 |
| LOS >4 | | | 0.005* | | | 1.0* | | | 0.9* |
|   Diabetic patients | 1.17 | (1.10, 1.25) | <0.0001 | 1.17 | (1.09, 1.25) | <0.0001 | 1.16 | (1.09, 1.24) | <0.0001 |
|   Nondiabetic patients | 1.31 | (1.25, 1.37) | <0.0001 | 1.17 | (1.11, 1.23) | <0.0001 | 1.17 | (1.11, 1.23) | <0.0001 |
| Unable to ambulate at discharge | | | <0.0001* | | | 0.61* | | | 0.73* |
|   Diabetic patients | 1.41 | (1.31, 1.53) | <0.0001 | 1.55 | (1.42, 1.69) | <0.0001 | 1.53 | (1.41, 1.67) | <0.0001 |
|   Nondiabetic patients | 1.78 | (1.68, 1.89) | <0.0001 | 1.51 | (1.41, 1.61) | <0.0001 | 1.50 | (1.41, 1.60) | <0.0001 |

Variables used for patient characteristics: age, gender, race (white vs other), medical history of atrial fib/flutter, previous stroke/TIA, CAD/previous MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, presentation during off hours, NIHSS, and systolic blood pressure. For hospital characteristics: region, academic/teaching hospital, number of beds, rural location, TJC primary stroke center status, annual ischemic stroke volume, and annual tPA volume. CAD indicates coronary artery disease; CI, confidence interval; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack; TJC, the joint commission; tPA, tissue plasminogen activator.
*Interaction *P* value: differences in outcomes between patients with documented history of diabetes vs no diabetes.

of hyperglycemia. Whereas early studies suggested that there may be a role of tight glucose control for reducing MI and coronary heart disease events, randomized, clinical trials have failed to demonstrate measurable benefits for strict acute or chronic glycemic control, and some have suggested increased harm.[29] The potential benefit of strict glucose control with aggressive insulin titration in acute stroke is unclear,[30] and this hypothesis is currently being tested in a large, randomized, clinical trial.[31] To avoid the risk of adverse effects related to hypoglycemia, guidelines recommend to maintain blood glucose in a range of 140 to 180 mg/dL.[32] Whereas our retrospective study suggests that better blood glucose regulation measured at admission is associated with better short-term clinical outcomes, we did not test or measure any interventions that were given in response to these glucose measurements, and thus these findings require prospective, randomized, clinical trials to evaluate the potential benefits and potential risks of any treatment in this patient population.

The study has important limitations owing to its observational nature and retrospective design. Residual measured and unmeasured confounding may account for some of these findings. Acute and chronic hyperglycemic may be a marker, rather than a mediator, for these adverse outcomes and no cause-and-effect relationships should be inferred. Some patients with hyperglycemia on admission, but without diagnosed diabetes, may have had preexisting undiagnosed diabetes. There were missing data for admission glucose and HbA1c, which may have introduced bias into these findings. When compared to patients with missing admission blood glucose, patients with documented admission glucose were similar except for clinically insignificant history of hypertension (73% vs 72%; *P*<0.001) and being smokers (18% vs 17%; *P*=0.002). When compared to patients with HbA1c not recorded, patients with HbA1c recorded were younger in age (70 vs 73 years; *P*<0.0001), had more-frequent documented history of DM (31.6% vs 19.7%; *P*<0.0001), hypertension (74.5% vs 71.9; *P*<0.0001), and were more likely to be smokers (19.4% vs 16.8%; *P*<0.0001). Data on postdischarge outcomes were not available. In addition, data were not available regarding any treatment of hyperglycemia.

**Table 7.** Multivariable Model of the Association Between Chronic Hyperglycemia and Clinical Outcomes for Patients With vs Without a Documented History of Diabetes

| Outcome | Unadjusted Model | | | Adjusted Model (Patient Characteristics Only) | | | Adjusted Model (Patient and Hospital Characteristics) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value | OR | 95% CI | P Value |
| Complications of thrombolytic therapy | | | | | | | | | |
| Symptomatic ICH | | | 0.45* | | | 0.87* | | | 0.89* |
| Diabetic patients | 1.14 | (0.93, 1.39) | 0.20 | 1.26 | (1.20, 1.55) | 0.03 | 1.26 | (1.02, 1.55) | 0.03 |
| Nondiabetic patients | 1.27 | (1.02, 1.58) | 0.03 | 1.23 | (0.98, 1.53) | 0.07 | 1.24 | (0.99, 1.54) | 0.06 |
| Serious/life-threatening hemorrhage | | | 0.06* | | | 0.15* | | | 0.14* |
| Diabetic patients | 1.04 | (0.69, 1.56) | 0.87 | 1.11 | (0.74, 1.67) | 0.60 | 1.10 | (0.74, 1.65) | 0.63 |
| Nondiabetic patients | 1.84 | (1.20, 2.83) | 0.005 | 1.73 | (1.13, 2.64) | 0.01 | 1.73 | (1.13, 2.63) | 0.01 |
| Other outcomes | | | | | | | | | |
| In-hospital mortality | | | 0.02* | | | 0.45* | | | 0.35* |
| Diabetic patients | 1.11 | (0.94, 1.30) | 0.21 | 1.31 | (1.10, 1.55) | 0.002 | 1.29 | (1.09, 1.53) | 0.003 |
| Nondiabetic patients | 1.11 | (1.24, 1.75) | <0.0001 | 1.45 | (1.21, 1.74) | <0.0001 | 1.46 | (1.22, 1.74) | <0.0001 |
| LOS >4 | | | <0.0001* | | | 0.02* | | | 0.02* |
| Diabetic patients | 1.05 | (0.96, 1.14) | 0.31 | 1.13 | (1.03, 1.24) | 0.09 | 1.13 | (1.03, 1.24) | 0.01 |
| Nondiabetic patients | 1.39 | (1.25, 1.55) | <0.0001 | 1.35 | (1.21, 1.51) | <0.0001 | 1.35 | (1.21, 1.51) | <0.0001 |
| Unable to ambulate at discharge | | | <0.0001* | | | 0.14* | | | 0.12* |
| Diabetic patients | 0.97 | (0.89, 1.06) | 0.57 | 1.23 | (1.12, 1.37) | <0.0001 | 1.22 | (1.11, 1.35) | <0.0001 |
| Nondiabetic patients | 1.36 | (1.21, 1.53) | <0.0001 | 1.40 | (1.23, 1.60) | <0.0001 | 1.40 | (1.23, 1.59) | <0.0001 |

Variables used for patient characteristics: age, gender, race (white vs other), medical history of atrial fib/flutter, previous stroke/TIA, CAD/previous MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, presentation during off hours, NIHSS, and systolic blood pressure. For hospital characteristics: region, academic/teaching hospital, number of beds, rural location, TJC primary stroke center status, annual ischemic stroke volume, and annual tPA volume. CAD indicates coronary artery disease; CI, confidence interval; ICH, intracranial hemorrhage; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack; TJC, the joint commission; tPA, tissue plasminogen activator.

*Interaction P value: differences in outcomes between patients with documented history of diabetes vs no diabetes.

In summary, hyperglycemia, whether acute or chronic, is associated with worse clinical outcomes in AIS patients treated with tPA regardless of a previous known diagnosis of diabetes. Admission glucose and HbA1c may help identify patients at increased risk of adverse outcomes, including sICH. Improving glycemic control in the population by primary prevention may help in better outcomes, but needs further evaluation in a prospective, randomized trial.

## Disclosures

Dr Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Get With The Guidelines Steering Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Associate Editor; Section Editor, Pharmacology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), WebMD (CME steering committees); Other: Clinical

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