Association of Baseline Hyperglycemia With Outcomes of Patients With and Without Diabetes With Acute Ischemic Stroke Treated With Intravenous Thrombolysis: A Propensity Score–Matched Analysis From the SITS-ISTR Registry

Georgios Tsivgoulis,[1,2] Aristeidis H. Katsanos,[1,3] Dimitris Mavridis,[4,5] Vaia Lambadiari,[6] Christine Roffe,[7] Mary Joan Macleod,[8] Petr Sevcik,[9] Manuel Cappellari,[10] Miroslava Nevšímalová,[11] Danilo Toni,[12] and Niaz Ahmed[13,14]

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Available data from observational studies on the association of admission hyperglycemia (aHG) with outcomes of patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT) are contradictory, especially when stratified by diabetes mellitus (DM) history. We assessed the association of aHG (≥144 mg/dL) with outcomes stratified by DM history using propensity score–matched (PSM) data from the SITS-ISTR. The primary safety outcome was symptomatic intracranial hemorrhage (SICH); 3-month functional independence (FI) (modified Rankin Scale [mRS] scores 0–2) represented the primary efficacy outcome. Patients with and without aHG did not differ in baseline characteristics both in the non-DM (*n* = 12,318) and DM (*n* = 6,572) PSM subgroups. In the non-DM group, patients with aHG had lower 3-month FI rates (53.3% vs. 57.9%, *P* < 0.001), higher 3-month mortality rates (19.2% vs. 16.0%, *P* < 0.001), and similar symptomatic intracerebral hemorrhage (SICH) rates (1.7% vs. 1.8%, *P* = 0.563) compared with patients without aHG. Similarly, in the DM group, patients with aHG had lower rates of 3-month favorable functional outcome (mRS scores 0–1, 34.1% vs. 39.3%, *P* < 0.001) and FI (48.2% vs. 52.5%, *P* < 0.001), higher 3-month mortality rates (23.7% vs. 19.9%, *P* < 0.001), and similar SICH rates (2.2% vs. 2.7%, *P* = 0.224) compared with patients without aHG. In conclusion, aHG was associated with unfavorable 3-month clinical outcomes in patients with and without DM and AIS treated with IVT.

More than one-third of patients with acute ischemic stroke (AIS) present with increased plasma glucose on hospital admission (1,2). Hyperglycemia (HG) after AIS has been acknowledged as an independent predictor of poor outcome for >20 years (3), and more recently, several observational studies suggested that increased plasma glucose on presentation is also an independent predictor

[1]Second Department of Neurology, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[2]Department of Neurology, University of Tennessee Health Science Center, Memphis, TN
[3]Department of Neurology, St. Josef-Hospital, Ruhr University, Bochum, Germany
[4]Department of Primary Education, University of Ioannina, Ioannina, Greece
[5]Faculté de Médecine, Université Paris Descartes, Paris, France
[6]Research Unit and Diabetes Center, Second Department of Internal Medicine, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece
[7]University Hospital of North Midlands, Stoke-on-Trent, U.K., and Keele University, Keele, U.K.
[8]Division of Applied Medicine, University of Aberdeen, Foresterhill, U.K.
[9]Department of Neurology, Faculty of Medicine in Pilsen, Charles University in Prague, Pilsen, Czech Republic
[10]Stroke Unit, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy
[11]Department of Neurology, Hospital Ceske Budejovice, Statutory City, Czech Republic
[12]Neurovascular Unit, Policlinico Umberto I, Department of Human Neurosciences, University of Rome, "La Sapienza," Rome, Italy
[13]Department of Neurology, Karolinska University Hospital Solna, Stockholm, Sweden
[14]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Corresponding author: Georgios Tsivgoulis, tsivgoulisgiorg@yahoo.gr

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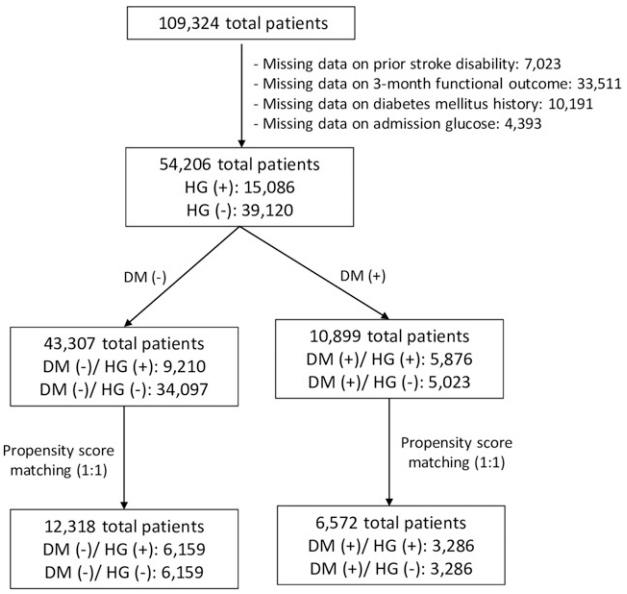

Figure 1—Flowchart presenting the selection of eligible and PSM patients.

for symptomatic intracerebral hemorrhage (SICH) and unfavorable clinical outcomes in patients with AIS treated with intravenous thrombolysis (IVT) (4–7). Interestingly, this association of HG with poor clinical outcomes has also been reported in patients with successful recanalization following IVT (8).

However, when stratified by the history of diabetes mellitus (DM), data from observational studies on the association of HG with IVT outcomes yield contradictory findings. In the Canadian Alteplase for Stroke Effectiveness Study (CASES), admission HG (aHG) (>144 mg/dL) was independently associated with poor outcomes following IVT administration in patients with and without DM (9), while in the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR), aHG was associated with a higher risk of SICH and mortality in patients without a history of DM but not in patients with DM (10). In view of these discrepant findings, we sought to assess the association of HG with early outcomes of patients with AIS treated with IVT, stratified by history of DM, using propensity score–matched (PSM) data from the SITS-ISTR.

RESEARCH DESIGN AND METHODS

We analyzed prospectively collected data from the SITS-ISTR from participating centers that treat patients with AIS with IVT using the IVT register platform, as previously described (11). We included all IVT-treated patients with AIS registered in the SITS-ISTR standard data set between January 2010 and December 2017 if they had available data regarding their *1*) history of DM, *2*) baseline plasma glucose values, *3*) disability before stroke onset (modified Rankin Scale [mRS] scores >1), and *4*) 3-month functional outcome assessment using the mRS score. Patients who have had endovascular treatment, alone or following administration of tissue plasminogen activator (tPA), were excluded from the present analysis. We also excluded patients enrolled in the SITS-ISTR before January 2010 because the data of these patients have been included in previous studies investigating the association of aHG with outcomes in patients with AIS treated with IVT (10).

The primary safety outcome was the difference in SICH rates according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition (local or remote parenchymal hemorrhage type 2 on 22- to 36-h post-IVT imaging scans combined with a National Institutes of Health Stroke Scale [NIHSS] score increase ≥4 points or leading to death within 24 h) (12), while the primary efficacy outcome was the difference in functional independence (FI) rates at 3 months (defined as mRS scores 0–2) between patients with and without aHG. Secondary outcome events of interest included *1*) mortality rates at 3 months, *2*) favorable functional outcome (FFO) rates at 3 months (defined as mRS scores of 0 or 1), *3*) SICH rates according to the European Cooperative Acute Stroke Study (ECASS) II definition (any intracranial bleed with ≥4 points worsening on the NIHSS score) (13), *4*) rates of any parenchymal hemorrhage (PH), and *5*) the distribution of the 3-month mRS scores (functional improvement) between patients with and without aHG. All outcomes were evaluated separately for patients with and without DM, and all analyses were performed in both the unmatched and the PSM populations.

Statistical Analyses

After dichotomization according to the history of DM and the presence of aHG (≥144 mg/dL) before tPA bolus (14), patients in the active group (presence of aHG) were matched to those in the control group (absence of aHG) using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between the two groups. The PSM was performed separately for patients with and without DM. In the PSM algorithm, we included all baseline characteristics except for the history of DM and aHG. The corresponding propensity score of the aHG variable was then calculated for each patient, and a nearest neighbor matching algorithm was then used to match patients with aHG to patients in the control group (patients without aHG) on a 1:1 ratio (with no replacement) within 0.2 * SD of the logit of the propensity score. The process of PSM has been described in detail in similar analyses of the SITS-ISTR (15). To determine whether PSM achieved balance in all potential confounders, we compared all baseline characteristics of patients with aHG to their PSM counterparts.

Statistical comparisons were performed between the aforementioned PSM groups using the χ^2 test (or the Fisher exact test) and the unpaired *t* test (or Mann-Whitney

U test), where appropriate. The distributions of the mRS scores at 3 months between the PSM groups were compared using the Cochran-Mantel-Haenszel test. The associations of aHG and DM history with the outcomes of interest were also evaluated using univariable and multivariable binary logistic or ordinal logistic regression models. In univariable models of all baseline characteristics, a threshold of $P < 0.1$ was used to identify candidate variables for inclusion in the multivariable regression models that tested the statistical significance hypothesis at a significance level of 0.05. All statistical analyses were performed with RStudio: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) (16), with the use of the MatchIt package (matching software for causal inference) for matching patients across the two groups (17), and with Stata 13 (StataCorp, College Station, TX).

RESULTS

Of a total of 109,324 consecutive patients with AIS treated with IVT between 1 January 2010 and 30 December 2017, we identified 54,206 eligible patients (Fig. 1). In the unmatched cohort, patients without DM with aHG were older ($P < 0.001$) and more likely to be female ($P < 0.001$) with greater neurological severity on admission ($P < 0.001$); a higher prevalence of hypertension ($P < 0.001$), hyperlipidemia ($P = 0.012$), atrial fibrillation ($P < 0.001$), and congestive heart failure ($P < 0.001$); a lower prevalence of current smoking ($P < 0.001$) and previous stroke ($P < 0.001$); higher rates of disability before the index event ($P = 0.006$); higher systolic blood pressure on admission; and longer onset-to-treatment times ($P < 0.001$) compared with patients without DM without aHG. Patients without DM with aHG had lower rates of 3-month FFO (39.3% vs. 46.9%, $P < 0.001$) and FI (51.9% vs. 61.3%, $P < 0.001$), higher rates of any PH (5.6% vs. 4.5%, $P < 0.001$) and SICH according to the ECASS II definition (5.5% vs. 3.8%, $P < 0.001$), higher 3-month mortality rates (21.2% vs. 14.2%, $P < 0.001$), and higher mRS scores at 3 months (median [interquartile range (IQR)] 2 [1–5] vs. 2 [0–4], $P < 0.001$) compared with patients without DM without aHG. No difference in the SITS-MOST SICH rates was detected between the two groups (1.9% vs. 1.6%, $P = 0.083$) (Supplementary Table 1).

Table 1—Baseline characteristics and outcomes of matched groups

	No DM history (*n* = 12,318)			DM history (*n* = 6,572)		
Variable	HG+ (*n* = 6,159)	HG− (*n* = 6,159)	*P* value	HG+ (*n* = 3,286)	HG− (*n* = 3,286)	*P* value
Age, mean ± SD, years	71.5 ± 13.0	71.3 ± 13.2	0.396	72.4 ± 10.3	72.9 ± 10.3	0.097
Male sex, %	51.8	52.6	0.387	57.0	56.9	0.980
Admission NIHSS, median (IQR)	11 (6–17)	11 (6–17)	0.937	10 (6–16)	10 (6–16)	0.193
Hypertension, %	67.9	68.5	0.486	85.0	85.5	0.531
Hyperlipidemia, %	26.5	26.4	0.935	48.3	50.0	0.175
Current smoking, %	14.8	15.3	0.421	13.0	13.1	0.826
Atrial fibrillation, %	21.4	21.7	0.661	22.3	22.0	0.744
Congestive heart failure, %	8.3	8.3	0.974	13.2	13.4	0.856
History of previous stroke, %	9.9	9.6	0.585	15.7	15.9	0.787
Prestroke disability (mRS >1), %	12.3	11.8	0.423	17.4	18.2	0.439
Statin pretreatment, %	24.8	24.8	0.983	47.0	46.8	0.863
Antiplatelet pretreatment, %	34.6	34.4	0.865	52.9	53.1	0.902
Anticoagulant pretreatment, %	3.8	4.0	0.578	5.2	4.8	0.461
Admission SBP baseline, mean ± SD, mmHg	153.2 ± 24.3	152.8 ± 23.7	0.364	157.2 ± 24.2	156.3 ± 24.1	0.115
Admission DBP, mean ± SD, mmHg	83.0 ± 14.9	83.1 ± 14.8	0.853	82.9 ± 14.8	82.4 ± 14.5	0.212
Admission plasma glucose, mean ± SD, mg/dL	180.5 ± 40.4	107.9 ± 17.3	<0.001	211.7 ± 62.1	111.9 ± 19.5	<0.001
Onset-to-treatment time, mean ± SD, min	163.7 ± 65.0	163.3 ± 65.8	0.750	165.6 ± 64.1	166.1 ± 64.8	0.735
SICH, %, SITS-MOST definition	1.7	1.8	0.563	2.2	2.7	0.224
SICH, %, ECASS II definition	5.0	4.6	0.307	6.9	5.8	0.084
Any PH, %	5.1	4.6	0.176	6.4	6.1	0.551
FFO, %	40.6	44.2	<0.001	34.1	39.3	<0.001
FI, %	53.3	57.9	<0.001	48.2	52.5	<0.001
Mortality at 3 months, %	19.2	16.0	<0.001	23.7	19.9	<0.001
3-month mRS, median (IQR)	2 (1–4)	2 (1–4)	<0.001	3 (1–5)	2 (1–5)	<0.001

DBP, diastolic blood pressure; PH, parenchymal hemorrhage; SBP, systolic blood pressure.

In the unmatched cohort of patients with DM, those with aHG were younger ($P < 0.001$) with a lower prevalence of hyperlipidemia ($P < 0.001$) and higher systolic and diastolic blood pressure on admission ($P < 0.001$) compared with patients with DM without aHG (Supplementary Table 1). Patients with DM with aHG had lower rates of 3-month FFO (32.7% vs. 37.7%, $P < 0.001$) and FI (46.3% vs. 50.6%, $P < 0.001$), higher rates of any PH (7.5% vs. 6.1%, $P = 0.008$) and SICH according to the ECASS II definition (7.3% vs. 6.2%, $P = 0.039$), higher 3-month mortality rates (26.0% vs. 21.5%, $P < 0.001$), and higher mRS scores at 3 months (median [IQR] 3 [1–6] vs. 2 [1–5], $P < 0.001$). There was no difference in the SITS-MOST SICH rates (2.8% vs. 2.3%, $P = 0.130$) between the two groups (patients with DM with and without aHG).

PSM in patients without DM resulted in two groups of 6,159 patients each (Fig. 1), balanced for all baseline characteristics (Table 1). Distributions of propensity scores before and after matching are presented in Supplementary Fig. 1. Patients without DM with aHG (68% treated within 3 h from symptom onset) had lower rates of 3-month FFO (40.6% vs. 44.2%, $P < 0.001$), lower rates of 3-month FI (53.3% vs. 57.9%, $P < 0.001$), and higher rates of 3-month mortality (19.2% vs. 16.0%, $P < 0.001$) compared with patients without DM without aHG (Fig. 2*A*). We detected no difference in the rates of any PH

Figure 2—Distribution of mRS scores at 3 months between patients without DM (*A*) and patients with DM (*B*) with AIS with and without HG before the administration of IVT.

(5.1% vs. 4.6%, P = 0.176) and SICH between the two groups according to SITS-MOST (1.7% vs. 1.8%, P = 0.563) and ECASS II (5.0% vs. 4.6%, P = 0.307) definitions.

Likewise, PSM in patients with DM resulted in two groups of 3,286 patients each (Fig. 1), balanced for all baseline characteristics (Table 2). Distributions of propensity scores before and after matching are presented in Supplementary Fig. 2. Patients with DM with aHG (65% treated within 3 h from symptom onset) had lower rates of 3-month FFO (34.1% vs. 39.3%, $P < 0.001$), lower rates of 3-month FI (48.2% vs. 52.5%, $P < 0.001$), and higher rates of 3-month mortality (23.7% vs. 19.9%, $P < 0.001$) compared with patients with DM without aHG (Fig. 2*B*). There was no difference in the rates of any PH (6.4% vs. 6.1%, P = 0.551) and SICH according to SITS-MOST (2.2% vs. 2.7%, P = 0.224) and ECASS II (6.9% vs. 5.8%, P = 0.084) definitions between the two groups.

Both history of DM and aHG were independently ($P < 0.05$) associated with a lower likelihood of 3-month FFO and 3-month FI, higher risk of 3-month mortality, and worse 3-month functional outcomes (shift analysis) on multivariable logistic regression analyses of the unmatched cohort after adjustment for potential confounders (Table 2 and Supplementary Tables 2–6). The risk of SICH was associated with a history of DM (odds ratio [OR] 1.41 [95% CI 1.16–1.72], P = 0.001) but not with aHG (1.10 [0.92–1.32], P = 0.292) in unmatched patients with AIS treated with IVT (Table 2 and Supplementary Table 2). There was no interaction ($P > 0.1$) of the history of DM on the association of aHG with SICH according to the SITS-MOST definition, 3-month FI, 3-month mortality, and 3-month functional improvement in the unmatched cohort of patients with AIS treated with IVT (Supplementary Fig. 3). We detected a significant interaction (P = 0.032) of the history of DM on the association of aHG with 3-month FFO (Supplementary Fig. 3). More specifically, aHG had a more pronounced adverse impact on FFO in patients with DM (0.72 [0.65–0.82]) than in patients without DM (0.84 [0.79–0.90]).

Finally, increasing admission plasma glucose levels were linearly associated with a lower odds of 3-month FI (unadjusted analyses) (Fig. 3*A*) and of 3-month FFO (unadjusted analyses) (Supplementary Fig. 4) in patients with and without DM. We also documented a linear relationship of increasing admission plasma glucose levels with a higher likelihood of 3-month mortality in patients with and without DM (Fig. 3*B*). The associations of admission plasma glucose levels with outcomes of interest on multivariable logistic regression analyses of the unmatched cohort after adjustment for potential confounders are presented in Supplementary Table 7. Increasing admission plasma glucose levels were associated with higher adjusted odds of 3-month mortality, while they were negatively related to the likelihood of 3-month FFO, FI, and functional improvement. No independent association of admission plasma glucose with SICH according to the SITS-MOST definition was found.

DISCUSSION

Our study showed that aHG is associated with unfavorable clinical outcomes, including 3-month FFO, FI, and functional improvement, in patients with and without DM with AIS. These associations were documented both in the unmatched cohort after adjustment for potential confounders and in the PSM cohorts of patients with and without DM with AIS. We documented no relationship of aHG with the risk of SICH in either patients with or patients without DM with AIS.

Our results are in agreement with the findings of CASES (9), confirming HG as an independent risk factor for unfavorable outcomes in patients with AIS receiving IVT treatment, although they are not in accordance with the findings of the previous SITS report (10), suggesting potential disparities in the association of aHG with early functional outcomes according to the history of DM. However, it should be noted that the difference in findings may be attributable to differences in sample sizes (16,049 patients with AIS in the previous study [10] vs. 54,206 in the current report) and the statistical analysis plan (PSM vs. multivariable analyses adjusting for confounders). Despite the strong association of HG in AIS outcomes, also evident in cases of large vessel occlusion treated with mechanical thrombectomy (18,19), there is currently no evidence of improved outcomes in AIS with HG and tight glycemic control in the acute phase in patients treated conservatively (20,21) or with IVT (22). Moreover, the

Table 2—Overview of the adjusted analyses on the association of aHG and DM history with outcomes of interest in the unmatched cohort

	aHG		DM	
Outcome	OR/cOR (95% CI)	*P* value	OR/cOR (95% CI)	*P* value
SICH (SITS-MOST)	1.10 (0.92–1.32)	0.292	1.41 (1.16–1.72)	0.001
3-month FFO	0.82 (0.77–0.86)	<0.001	0.73 (0.68–0.78)	<0.001
3-month FI	0.79 (0.74–0.83)	<0.001	0.71 (0.66–0.75)	<0.001
3-month mortality	1.36 (1.27–1.46)	<0.001	1.52 (1.41–1.64)	<0.001
3-month functional improvement	0.82 (0.79–0.85)	<0.001	0.71 (0.68–0.75)	<0.001

cOR, common odds ratio.

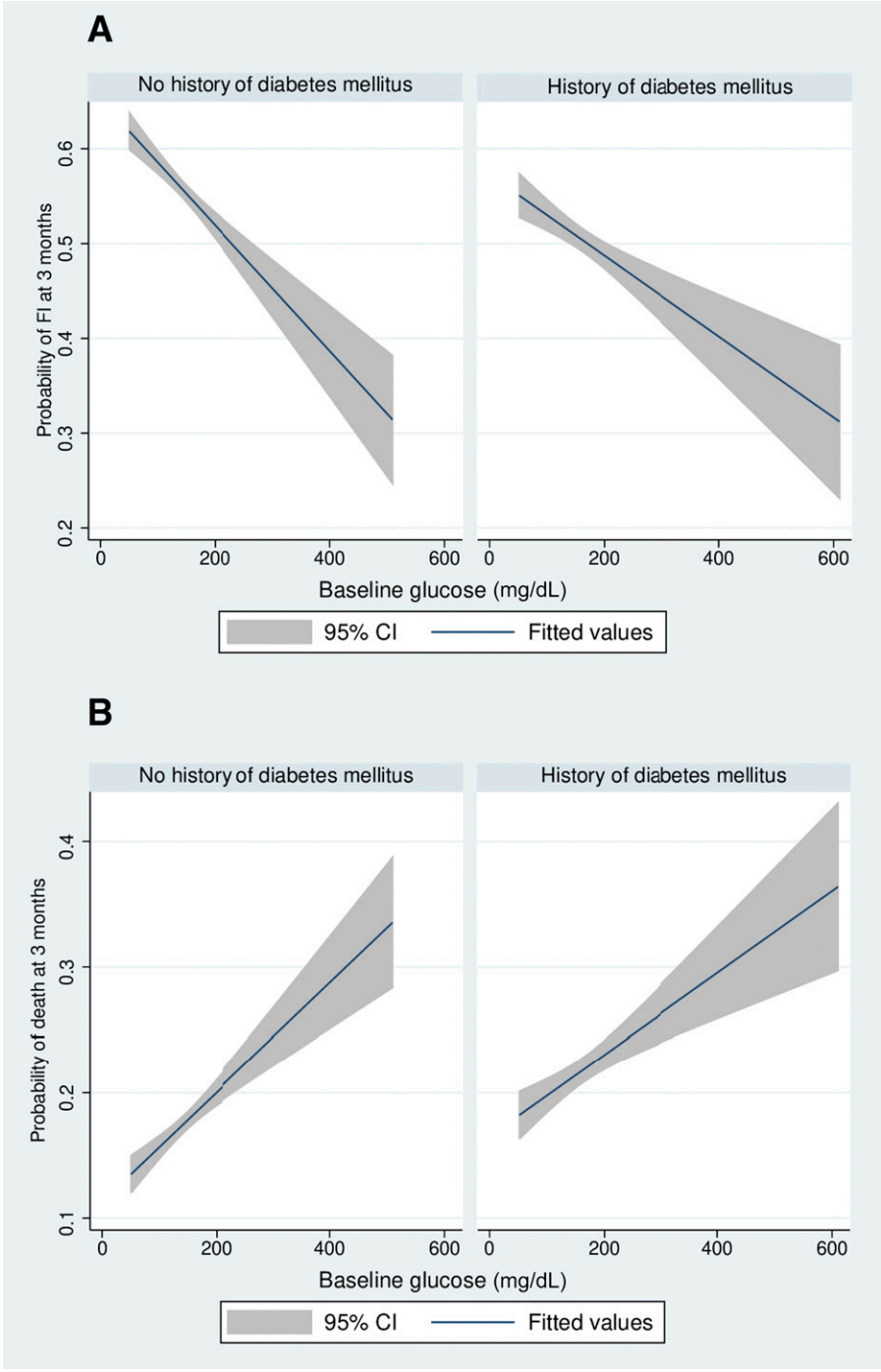

Figure 3—Modeled probability of FI (*A*) and mortality (*B*) at 3 months following IVT treatment by admission blood glucose (unadjusted analyses).

recently presented results from a multicenter, phase III randomized controlled clinical trial (Stroke Hyperglycemia Insulin Network Effort [SHINE]) suggested that intensive glucose control (between 80 and 130 mg/dL) with intravenous insulin administration in AIS not only fails to improve functional outcomes but also is, on the contrary, associated with a substantially higher risk for hypoglycemia (23). In accordance with the aforementioned findings, both guidelines from the European Stroke Organization and from the American Heart Association/American Stroke Association recommend against the tight treatment of HG in AIS and suggest moderate glycemic control in the range of 140–180 mg/dL (24,25). In the latest guideline of the American Diabetes Association for in-hospital management for critically ill patients, it is advised that intravenous or subcutaneous insulin should be used to

manage persistent HG starting at a cutoff point of 180 mg/dL (10.0 mmol/L). The recommended target glucose range for the majority of critically ill patients should be 140–180 mg/dL (7.8–10.0 mmol/L) (26).

HG during the acute phase of stroke may indicate patients with abnormal glucose metabolism who are known to have an increased risk for adverse cardiovascular outcomes (27). HG is also known to enhance glucose and energy delivery to the ischemic tissue at the cost of exacerbation of cell injury through multiple mechanisms, including lactic acidosis and oxidative stress (28). Experimental models suggest that HG following ischemia results in blood-brain barrier dysfunction through an increase in oxidative stress and matrix metalloproteinase-9 activity (29). Postischemic HG has also been associated with exacerbation of ischemic neuronal damage mediated by transporter signaling (30,31) in both normal animals and animals with metabolic syndrome (32) and with ineffective collateral circulation as a result of impaired cerebrovascular reactivity (33). Interestingly, in a small cohort, increased blood glucose was associated with greater acute-subacute lactate production and reduced salvage of brain tissue only in patients with AIS with perfusion-diffusion mismatch and not in patients with AIS without evidence of viable penumbra on neuroimaging (34).

Baseline plasma glucose before IVT administration has been incorporated in the available prediction scores for post-IVT SICH, namely the SITS SICH score (12), the Hemorrhage After Thrombolysis (HAT) score (35), the SEDAN (blood Sugar [glucose] on admission, Early infarct signs and [hyper] Dense cerebral artery sign on admission computed tomography [CT] head scan, Age, and NIHSS) score (36), and the STARTING (systolic blood pressure, age, onset-to-treatment time for thrombolysis, NIHSS score, glucose, aspirin alone, aspirin plus clopidogrel, anticoagulant with international normalized ratio $\leq$1.7, current infarction sign, hyperdense artery sign)-SICH score (37). However, in a retrospective cohort study of 1,112 consecutive IVT-treated patients with AIS, not only baseline plasma glucose but also glycated hemoglobin (HbA_{1c}) were highlighted as important predictors of SICH risk following IVT administration, suggesting that the association between increased plasma glucose and SICH risk may be a consequence of long-term vascular injury attributed to DM rather than the sole result of acute HG (38).

Compared with previous reports, our study included significantly higher numbers of patients with and without DM, incorporating also patients with AIS >80 years of age and with IVT administration beyond 3 h. Additionally, we are the first to our knowledge to provide PSM analyses on the association of baseline plasma glucose with outcomes separately for patients with and without DM. Despite these strengths, some limitations of the current report also need to be acknowledged. First, selection and reporting biases cannot be excluded in this retrospective analysis of prospectively collected data from a multinational registry with self-reported safety and effectiveness outcomes and no central adjudication of imaging and clinical outcomes. It should also be noted that the history of DM was recorded according to the relevant information provided in the registry, while HbA_{1c} values were not available. Therefore, the possibility that some patients with either undiagnosed DM or with unrecorded (in the charts) history of DM being falsely allocated to the group of patients without DM cannot be excluded. Second, although the PSM groups were balanced for all available baseline characteristics, potential imbalances in unmeasured confounders cannot be excluded. More specifically, in patients with DM, we were not able to assess potential drug class effects of antidiabetic medications on stroke outcomes following IVT (39–41). Additionally, information on antidiabetic treatment duration, adherence, and long-term control of DM was not available. Likewise, information on the causes of death was unavailable, and thus, the relative risk of SICH-related mortality between the two groups cannot be assessed. However, it should be noted that cerebral edema represents a substantial cause of 3-month mortality in the SITS-ISTR, ranging from 18 to 65% according to cerebral edema type (42). Third, it should be noted that the cutoff value of 144 mg/dL (8 mmol/L) in admission glucose for the definition of HG was used for comparability with other studies (3,8,9,14). Thus, the optimal threshold for the definition of clinically relevant HG in patients with AIS eligible for IVT treatment remains unknown. Finally, missing 3-month follow-up in one-third of the total number of patients and unavailable outcomes of interest in nearly one-half of the whole patient population included in the present registry (Fig. 1) may have introduced additional bias on the reported associations.

In conclusion, our findings indicate that aHG is associated with unfavorable clinical outcomes in patients with and without DM treated with tPA for AIS in adjusted and PSM analyses. We found no significant increase in the risk of SICH in patients with HG and AIS treated with IVT. Future randomized controlled clinical trials on the potential utility of moderate glycemic control in the population of patients with AIS treated with IVT who present with HG before tPA bolus appear to be warranted.

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Data and Resource Availability. The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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