Stroke

CLINICAL TRIAL

Intensive Versus Standard Treatment of Hyperglycemia in Acute Ischemic Stroke Patient: A Randomized Clinical Trial Subgroups Analysis

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BACKGROUND: Benefit from blood glucose (BG) control during acute ischemic stroke may depend on glycemic parameters. We evaluated for associations between the SHINE (Stroke Hyperglycemia Insulin Network Effort) randomized treatment group and the SHINE predefined 90-day functional outcome, within-patient subgroups defined by various glycemic parameters.

METHODS: The SHINE Trial randomized 1151 patients within 12 hours with acute ischemic stroke and hyperglycemia to standard (target BG 80–179 mg/dL) or intensive (target BG 80–130 mg/dL) BG control for 72 hours. We predefined 6 glycemic parameters: acute BG level, absence versus presence of diagnosed and undiagnosed diabetes, hemoglobin A1c, glycemic gap (acute BG–average daily hemoglobin A1c based BG), stress hyperglycemia ratio (acute BG/average daily hemoglobin A1c based BG), and BG variability (SD). Favorable functional outcome was defined by the SHINE Trial and based on the modified Rankin Scale score at 90 days, adjusted for stroke severity. We computed relative risks adjusted for baseline stroke severity and thrombolysis use.

RESULTS: Likelihood for favorable outcome was lowest among patients with undiagnosed diabetes compared to patients with true nondiabetes (adjusted relative risk, 0.42 [99% CI, 0.19–0.94]). We did not find any relationship between the favorable outcome rate and baseline BG or any of the glycemic parameters. No differences between SHINE treatment groups were identified among any of these patient subgroups.

CONCLUSIONS: In this exploratory subgroup analysis, intensive versus standard insulin treatment of hyperglycemia in acute ischemic stroke patient subgroups, did not influence the 90-day functional outcomes, nor did we identify associations between these glycemic parameters and 90-day functional outcomes.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: diabetes ■ glucose ■ hemoglobin ■ insulin ■ ischemic stroke

Hyperglycemia during acute ischemic stroke has been associated with worse functional outcomes and hemorrhagic complications in the setting of thrombolysis.[1,2] Whether hyperglycemia during acute ischemic stroke worsens functional outcomes or is merely a biomarker of stress or insulin resistance is unclear. Two randomized efficacy trials studied intensive hyperglycemia treatment during acute ischemic stroke.[3,4] The first GIST-UK (United Kingdom Glucose Insulin in Stroke Trial) enrolled 933 patients, primarily without diabetes.[3]

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Nonstandard Abbreviations and Acronyms

GIST-UK	United Kingdom Glucose Insulin in Stroke Trial
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
SHR	stress hyperglycemia ratio

Intensive treatment consisted of intravenous insulin for 24 hours. During protocol treatment, the difference between the mean blood glucose (BG) concentrations in the 2 treatment groups was only 10 mg/dL. Functional outcomes at 90 days were not significantly different between the 2 treatment groups.

The second trial, SHINE (Stroke Hyperglycemia Insulin Network Effort), enrolled 1151 patients, primarily with diabetes.[4] Intensive treatment consisted of intravenous insulin for up to 72 hours. During protocol treatment, the difference between the mean BG concentrations in the 2 treatment groups was 61 mg/dL. Functional outcomes at 90 days were not significantly different between the 2 treatment groups.

Although intensive insulin treatments during acute ischemic stroke with hyperglycemia did not improve functional outcomes in the 2 efficacy trials, there may be subgroups of acute stroke patients who might benefit from such intervention. Different glycemic measures may indicate different relationships between BG levels and acute ischemic brain injury.[2,5,6] For example, clinically important differences in the effects of acute hyperglycemia may exist between patients with or without diabetes,[7] those with greatest variations in BG levels during the acute stroke, or those with the highest levels of chronic hyperglycemia.[8–14] In this analysis, we evaluated for associations between the SHINE randomized treatment group and the SHINE predefined 90-day functional outcome, within-patient subgroups defined by various glycemic parameters.

METHODS

Study Population and Data Collection

The data used to prepare this manuscript is available through the SHINE public use dataset in the National Institutes of Health (NIH) Data Repository (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets). The design and primary outcome results of SHINE have been reported.[4,15] Briefly, SHINE randomized 1:1 1151 patients with acute ischemic stroke and admission hyperglycemia (BG >110 mg/dL [6.1 mmol/L] if diabetes history was present or ≥150 mg/dL [8.3 mmol/L] if no diabetes history), within 12 hours from symptom onset to standard or intensive insulin treatment for up to 72 hours (Figure S1). Standard treatment consisted of subcutaneous regular insulin 4 times daily as needed according to a sliding-scale protocol. Intensive treatment consisted of intravenous insulin and subcutaneous rapid-acting meal insulin, and long-acting basal insulin. The BG targets were 80 to 180 mg/dL in the standard treatment group and 80 to 130 mg/dL in the intensive group. BG was usually monitored every 3 hours in the standard treatment group and every 1 hour in the intensive group. A computerized program calculated intravenous insulin doses and effectively and safely achieved the desired glucose target.

SHINE data collection included patient demographics, medical history, medication history, and glycated hemoglobin A1c (HbA1c) during hospitalization. Baseline stroke severity was defined according to the National Institutes of Health Stroke Scale (NIHSS) as mild (3–7), moderate (8–14), or severe (15–22). The primary favorable outcome was assessed in a double-blind fashion and defined as a 90-day modified Rankin Scale (mRS) score of 0, if the baseline NIHSS score was 3 to 7; an mRS score 0 to 1, if the baseline NIHSS was 8 to 14; and an mRS score 0 to 2, if the baseline NIHSS was 15 to 22. We used the same definition of favorable functional outcome in this analysis. SHINE was approved at each participating institution and all patients gave a valid informed consent.

Patient Subgroups

Based on previously reported glycemic parameters, we defined multiple subgroups for secondary analysis of efficacy of the SHINE trial intervention (Table). The patient subgroups included those without diabetes (true nondiabetic—no history of diabetes and HbA1c ≤6.5%), with history of diabetes, and those with undiagnosed diabetes (no history of diabetes and HbA1c >6.5%).

In addition, we examined the following continuous measurements: baseline (point of care) BG, glycemic gap, stress hyperglycemia ratio (SHR), and BG variability during SHINE protocol treatment. We used the glycemic gap definition of baseline BG concentration−expected average daily BG concentration. The expected average BG concentration was based on the HbA1c with the formula (28.7×HbA1c)−46.7.[16] We used the SHR definition of baseline BG concentration/HbA1c.[17] We used BG variability defined in each patient as the SD of all their BG measurements during the SHINE protocol treatment.

Statistical Analysis

Favorable functional outcomes by subgroup are reported as a proportion and compared between the 2 treatment groups using a relative risk and 2-sided 99% CI. Generalized linear models with a log link function were used to compare favorable outcomes between patient subgroups and between treatment groups within each patient subgroup. Relative risks are reported as unadjusted and adjusted by the primary prognostic variables used in the SHINE trial, baseline stroke severity according to the NIHSS, and thrombolysis use (yes/no). Linearity assumption for continuous variables was examined, and piecewise linear variables were created when indicated to account for nonlinear relationships between continuous covariates and outcomes. Any patients with missing data were excluded from the analysis. All analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). As prespecified in the SHINE statistical analysis plan for all exploratory subgroup analyses, a 2-sided significance level was 0.01.

Table. SHINE Defined Favorable Functional Outcome by Patient Subgroup and Continuous Variables

Patient subgroup	Favorable outcome, n/N (%)	Unadjusted relative risk (99% CI)	Adjusted* relative risk (99% CI)
Diabetes status†			
True nondiabetes (HbA1c ≤6.5% and no History)	37/126 (29.4)	Reference group	Reference group
Diagnosed diabetes (history of diabetes)	194/892 (21.7)	0.74 (0.50–1.10)	0.71 (0.49–1.04)
Undiagnosed diabetes (HbA1c >6.5% and no history)	11/81 (13.6)	0.46 (0.21–1.03)	0.42 (0.19–0.94)
HbA1c category‡			
HbA1c ≤6.5%	76/295 (25.8)	Reference group	Reference group
HbA1c >6.5-9.0%	97/452 (21.5)	0.83 (0.59–1.18)	0.80 (0.57–1.12)
HbA1c >9.0%	67/329(20.4)	0.79 (0.54–1.15)	0.78 (0.54–1.14)
Continuous variables			
With 1 unit increase in			
Baseline blood glucose ≤238 mg/dL		0.998 (0.994–1.002)	0.998 (0.994–1.002)
Baseline blood glucose >238 mg/dL		1.001 (0.997–1.005)	1.001 (0.997–1.005)
Glycemic gap ≤43.8		1.002 (0.998–1.006)	1.002 (0.998–1.006)
Glycemic gap >43.8		0.999 (0.994–1.004)	0.999 (0.994–1.004)
Stress hypoglycemia ratio ≤1.38		1.066 (0.565–2.011)	1.177 (0.624–2.221)
Stress hypoglycemia ratio >1.38		1.125 (0.642–1.972)	1.065 (0.574–1.975)
Blood glucose variability		0.996 (0.987–1.006)	0.996 (0.987–1.006)

HbA1c indicates hemoglobin A1c; NIHSS, National Institutes of Health Stroke Scale; and SHINE, Stroke Hyperglycemia Insulin Network Effort.

*The adjusted relative risks were adjusted for baseline stroke severity (NIHSS score of 3–7 [mild]; 8–14 [moderate]; 15–22 [severe]), thrombolysis use (yes/no), and treatment group.

†11 patients had missing comprehensive diabetes history data.

‡34 patients had missing HbA1c data.

RESULTS

Between April 2012 and August 2018, 1151 patients (mean age, 66 years [SD, 13.1 years]; 529 [46%] women, 920 [80%] with history of diabetes) were randomized. The primary outcome was not significantly different between the 2 treatment groups.[4]

Twenty-three percent of the patients had lacunar stroke, and 50% had mild stroke (NIHSS of 3–7) with an overall median NIHSS of 7. Reperfusion therapy was used in 68% of patients (63% received standard intravenous tissue-type plasminogen activator, 3% intraarterial therapies, and 13% mechanical thrombectomy). The median baseline glucose concentration was 188 mg/dL (interquartile range, 153–250) in the intensive treatment group and 187 mg/dL (interquartile range, 155–248) in the standard treatment group.

The Table shows the risks of favorable outcomes by diabetes patient subgroup. Likelihood for favorable outcome is lowest among patients with undiagnosed diabetes compared to patients with true nondiabetes (adjusted relative risk, 0.42 [99% CI, 0.19–0.94]). The Table also shows there is no relationship between the favorable outcome rate and baseline BG or any of the glycemic parameters.

Figure 1 shows the SHINE treatment effects within-patient subgroups. The 99% CIs for all comparisons include the relative risk value of 1.00. No differences between SHINE treatment groups were identified among any of these patient subgroups at the nominal 0.01 level.

Nonlinear relationships between 3 continuous variables and favorable outcomes resulted in split continuous variables based on changes in slopes at the following points: baseline BG 238 mg/dL, glycemic gap 43.8 mg/dL, and stress hypoglycemia ratio 1.38 (Figure S2).

Figure 2 shows adjusted relative risks and 99% CIs for favorable outcomes at specific values for the 4 continuous variables analyzed. No differences between SHINE treatment groups were identified in any of these patient subgroups at the nominal 0.01 level.

DISCUSSION

In this secondary analysis of data from a randomized clinical acute stroke treatment trial, we evaluated the relationship between treatment and 90-day functional outcome in patient subgroups defined by glycemic parameters previously associated with functional outcome after stroke. Undiagnosed diabetes has been associated with worse functional outcomes after stroke.[7,18] Our findings agree with this observation (Table). However, there is no clear SHINE treatment effect in this relatively small subgroup of patients with undiagnosed diabetes (Figure 1).

Several studies found glycemic variability and SHR to be independent risk factors of death in heterogeneous populations of critically ill patients.[19,20] However, in acute stroke, the roles of these factors are not well defined.

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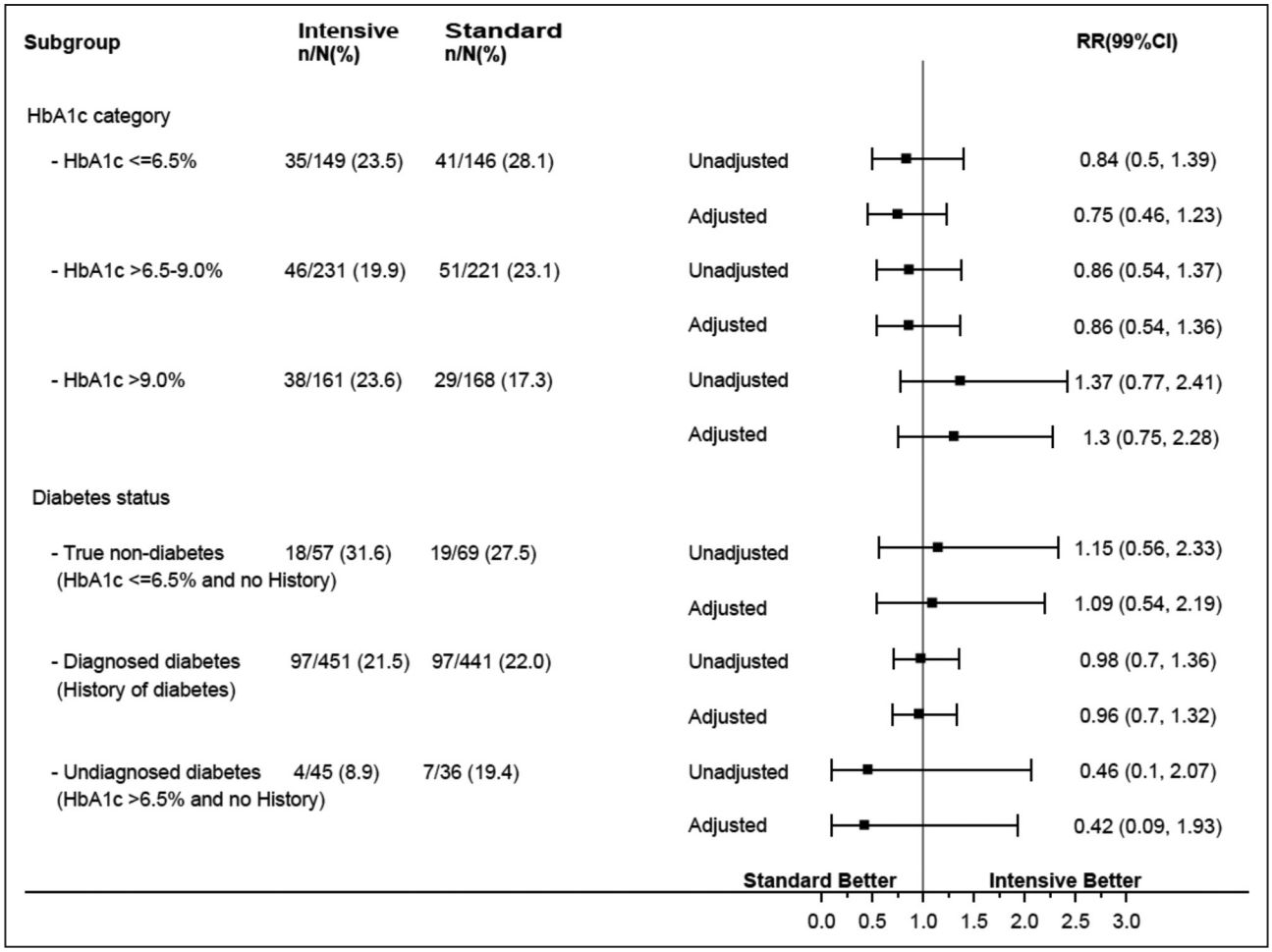

Figure 1. Adjusted relative risks (RR) with 99% CIs for favorable functional outcomes by SHINE (Stroke Hyperglycemia Insulin Network Effort) treatment group within diabetes status and hemoglobin A1c (HbA1c) subgroups.

Several studies showed an association with worse neurological outcome,[8–14] which differs from our findings. This discrepancy might be due to differences in study design. The majority of prior studies were retrospective with variable definitions of SHR, lesser standardization of BG measurements, and without adjustment for the impact of stroke severity on functional outcome.[8]

In one study of 666 patients with acute ischemic stroke undergoing intravenous thrombolysis, a higher SHR was independently associated with worse functional outcome adjusted for stroke severity. Two other studies found an association between higher SHR and worse clinical outcome in acute stroke patient treated with mechanical thrombectomy.[14,21] However, Tziomalos et al[22] reviewed 790 patients with acute ischemic stroke and found that the SHR was not associated with functional outcome after controlling for stroke severity, similar to our findings.

In a prospective registry of 1504 consecutive patients with diabetes and acute ischemic stroke[23] higher BG concentrations were associated with worse functional outcomes. Patients in that study had relatively mild strokes, with average NIHSS from 2 to 4. In meta-analysis, admission hyperglycemia has also been associated with worse functional outcomes in stroke patients treated with mechanical thrombectomy.[24] Thrombectomy retained its benefit during hyperglycemia, and the BG concentration was not associated with recanalization. However, in the SHINE trial, baseline BG concentration was not associated with functional outcome (Table), and there is no SHINE treatment effect along the range of baseline BG concentrations (Figure 2).

Poor glycemic control prestroke, as indicated by elevated serum HbA1c, has been associated with worse functional outcomes after ischemic stroke.[25] In this study, an association between elevated HbA1c and reduced likelihood of favorable outcome was not detected (Table). Possibly, the SHINE trial patient selection criteria requiring prestroke functional independence created a selection bias that influenced our findings. In addition, there is no SHINE treatment effect within any of the HbA1c categories (Figure 1).

Greater BG fluctuations (variability) and admission glycemic gap during acute ischemic stroke have been associated with worse functional outcomes.[6,23,26,27] In this study, an association between favorable outcome,

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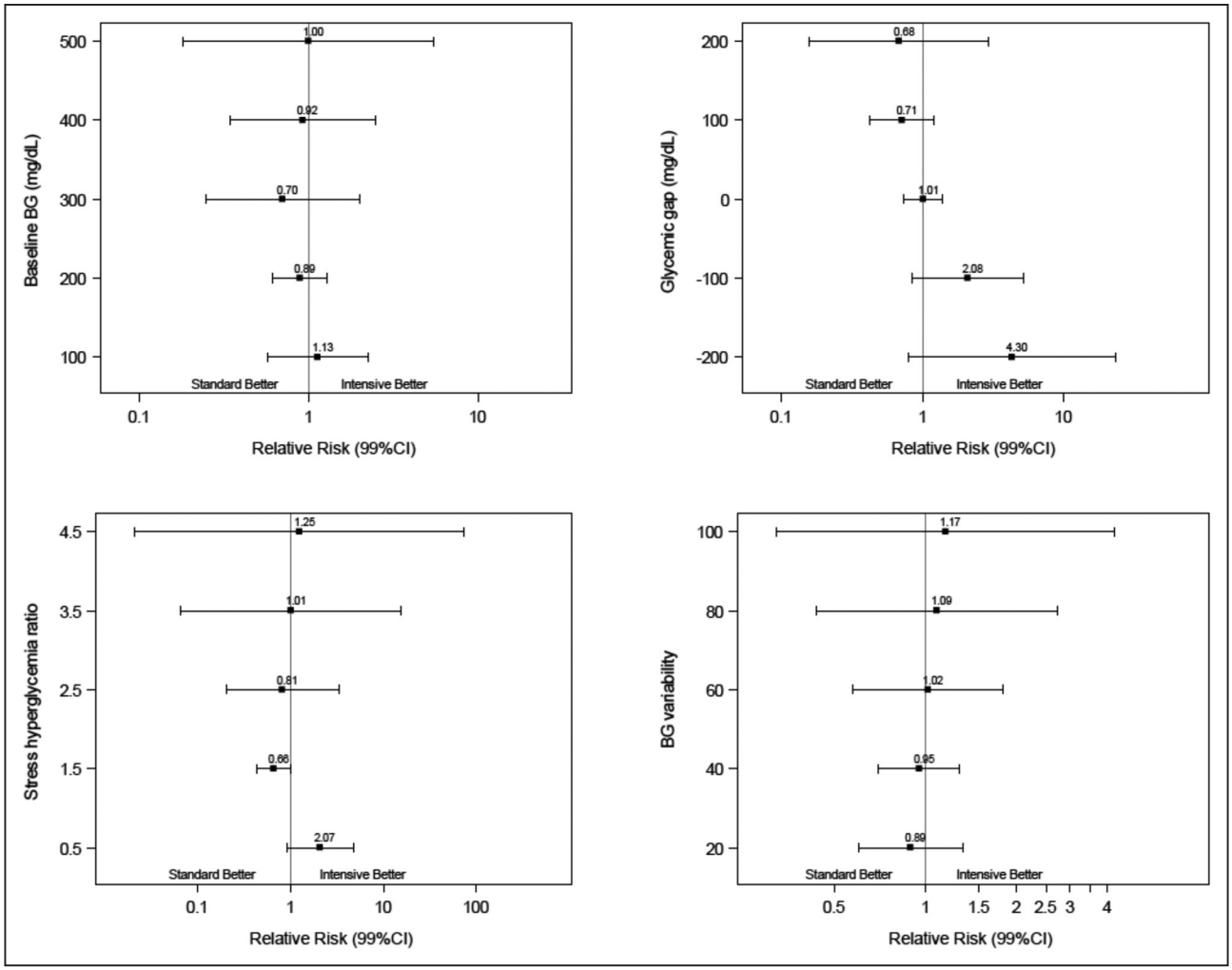

Figure 2. Adjusted relative risks with 99% CIs for favorable functional outcomes by SHINE (Stroke Hyperglycemia Insulin Network Effort) treatment group at specific values for baseline blood glucose (BG), glycemic gap, stress hyperglycemia ratio, and BG variability.

glycemic variability, and glycemic gap was not detected (Table). In addition, there was no SHINE treatment effect along the range of BG variabilities or admission glycemic gap (Figure 2).

A limitation of our findings is that this study was a post hoc analysis from the SHINE trial and as such was not powered to detect clinically important differences between treatment groups. In addition, the 0.01 threshold for statistical significance does not constitute an accurate correction for increased type I error. Nonetheless, our exploratory findings could help inform future studies.

CONCLUSIONS

In this exploratory subgroup analysis based on 6 glycemic parameters, intensive versus standard insulin treatment of hyperglycemia in patients with acute ischemic stroke, did not influence the 90-day functional outcome, nor did we identify associations between these parameters and the 90-day functional outcome.

ARTICLE INFORMATION

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Supplemental Material

Figure S1–S2

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