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Collateral status, hyperglycemia, and functional outcome after acute ischemic stroke

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Abstract

Background: Mixed data exist regarding the association between hyperglycemia and functional outcome after acute ischemic stroke when accounting for the impact of leptomeningeal collateral flow. We sought to determine whether collateral status modifies the association between treatment group and functional outcome in a subset of patients with large vessel occlusion enrolled in the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial.

Methods: In this post-hoc analysis, we analyzed patients enrolled into the SHINE trial with anterior circulation large vessel occlusion who underwent imaging with CT angiography prior to glucose control treatment group assignment. The primary analysis assessed the degree to which collateral status modified the effect between treatment group and functional outcome as defined by the 90-day modified Rankin Scale score. Logistic regression was used to model the data, with adjustments made for thrombectomy status, age, post-perfusion thrombolysis in cerebral infarction (TICI) score, tissue plasminogen activator (tPA) use, and baseline National Institutes of Health Stroke Scale (NIHSS) score. Five SHINE trial centers contributed data for this analysis. Statistical significance was defined as a p -value < 0.05 .

Results: Among the 1151 patients in the SHINE trial, 57 with angiographic data were included in this sub-analysis, of whom 19 had poor collaterals and 38 had good collaterals. While collateral status had no effect ($p = 0.855$) on the association between glucose control treatment group and functional outcome, patients with good collaterals were more likely to have a favorable functional outcome ($p = 0.001$, OR 5.02; 95% CI 1.37–16.0).

Conclusions: In a post-hoc analysis using a subset of patients with angiographic data enrolled in the SHINE trial, collateral status did not modify the association between glucose control treatment group and functional outcome. However, consistent with prior studies, there was a significant association between good collateral status and favorable outcome in patients with large vessel occlusion stroke.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier is NCT01369069. Registration date is June 8, 2011.

Keywords: Intracranial collaterals, Hyperglycemia, Diabetes, Angiography, Ischemic stroke, Outcome

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Background

Acute or progressive steno-occlusive disease of the intracranial arterial network can trigger the induction of blood flow to the affected vascular territory via leptomeningeal collaterals. Enhanced collateral flow results



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in lumen enlargement of the supplying vasculature and subsequent dependence of affected parenchyma on collateral flow [1]. In patients and animal models with type two diabetes mellitus (T2DM), collateral perfusion is more susceptible to hemodynamic compromise relative to individuals without known T2DM [2, 3]. Mechanistically, this has been attributed to the negative effect of hyperglycemia on smooth muscle tone, conferring hypercoagulability and promoting collateral rarefaction, which collectively result in enhanced resistance within and downstream of the collateral network.

In the setting of acute ischemic stroke, the association between hyperglycemia and poor functional outcomes has been shown to be influenced by collateral status [4]. Several large retrospective analyses of patients with large vessel occlusions, including patients enrolled into the SWIFT, SWIFT PRIME, and STAR studies, found that the association between hyperglycemia (glucose level >140 mg/dL) and poor functional outcome was diminished in those with poor collaterals [5–7]. However, older studies suggest that final infarct volume independent of collateral status in patients with hyperglycemia [8, 9].

The recently completed Stroke Hyperglycemia Insulin Network Effort (SHINE) trial demonstrated no significant difference in functional outcomes in hyperglycemic patients with acute ischemic stroke that received intensive compared to standard glucose control [10]. However, the SHINE study did not account for collateral status as a potential treatment effect modifier in either the primary or secondary endpoints. In the present study, we hypothesize that collateral status modifies the treatment effect of glucose control on functional outcome in hyperglycemic patients with large vessel occlusion acute ischemic stroke enrolled in the SHINE trial. Specifically, we hypothesized that intensive glycemic control will lead to improved functional outcomes relative to standard therapy in patients with good collaterals but not in patients with poor collaterals.

Methods

Patient selection

This post-hoc study was approved by the local institutional review board and ethics committee at each participating center. Sites which enrolled the highest number of large vessel occlusion patients were approached for inclusion into this analysis. Five of those sites agreed to participate and were included in the analysis. All enrolled patients provided written informed consent for the original trial.

Eligibility criteria for enrollment of hyperglycemic stroke patients in the SHINE trial is available from the primary results manuscript [7]. This study included additional imaging data that was completed as part of

standard care but not originally collected for the SHINE trial. To create a standardized cohort for analysis, this sub-study only included patients with large vessel occlusions of the intracranial internal carotid artery or proximal middle cerebral artery on computed tomography angiography (CTA). The primary outcome was the degree of functional independence as assessed by the modified Rankin Scale (mRS) at 3 months.

Collateral assessment

Assessment of collateral grade was performed using pre-treatment single phase CTA. Collateral status was evaluated by two neuroradiologists (MW and DJ), each with 7 years or more of post-training neuroradiology experience. The evaluators were blinded to patient treatment groups and outcomes. Any disagreements after initial independent evaluation were resolved by discussion and consensus. Collaterals were stratified into good (2–3) or poor (0–1) categories based upon the grading system by Tan et al. [11].

Statistical methods

The statistical analysis plan and primary outcome for this sub-study were determined prior to analysis. Categorical data were compared using χ^2 tests. To test the hypothesis that collateral status is an effect modifier between treatment groups, a multivariable logistic regression model was applied to the primary outcome. Adjustments to the model included the following predetermined variables: SHINE intervention group (categorical), collateral grade (categorical), thrombectomy status (categorical), age (continuous), post-perfusion thrombolysis in cerebral infarction (TICI) score (categorical), tissue plasminogen activator (tPA) use (categorical), and the National Institutes of Health Stroke Scale (NIHSS) score (categorical). Effect modification was determined by assessing the interaction between SHINE intervention group and collateral status. Statistical significance was defined as a p -value < 0.05.

Results

Study population baseline characteristics

Of the 1151 patients enrolled into the SHINE trial, 58 with angiographic data eligible for analysis. One patient was excluded because angiographic data could not be linked with the public SHINE database. Of the remaining 57 patients, 38 had good collaterals and 19 had poor collaterals (Table 1). Overall, the proportion of patients that underwent thrombectomy was similar between the good collateral group (66%) and the poor collateral group (58%). While 63% of patients in the poor collateral group received tPA, less than half (48%) of patients with good collaterals received tPA.

Table 1 Patient characteristics

Characteristics	Category	Poor Collaterals	Good Collaterals	Total	P-Value
		(n = 19) N (%)	(n = 38) N (%)		
Treatment Group	Intensive	7 (37%)	24 (63%)	31 (54%)	0.060
	Standard	12 (63%)	14 (37%)	26 (46%)	
Sex	Male	11 (58%)	16 (42%)	27 (47%)	0.260
	Female	8 (42%)	22 (58%)	30 (53%)	
Race	Asian	2 (11%)	2 (5%)	4 (7%)	0.599
	Black	5 (26%)	7 (18%)	12 (21%)	
	Pacific Islander	0 (0%)	1 (3%)	1 (2%)	
	White	10 (53%)	26 (68%)	36 (63%)	
	Unknown	2 (11%)	2 (5%)	4 (7%)	
Ethnicity	Hispanic or Latino	3 (16%)	4 (11%)	7 (12%)	0.516
	Not Hispanic or Latino	15 (79%)	34 (89%)	49 (86%)	
	Unknown	1 (5%)	0 (0%)	1 (2%)	
TPA	No	7 (37%)	20 (52%)	27 (47%)	0.260
	Yes	12 (63%)	18 (48%)	30 (53%)	
Prior Stroke	No	17 (89%)	32 (84%)	49 (86%)	0.590
	Yes	2 (11%)	6 (16%)	8 (14%)	
Diabetes	No	4 (21%)	13 (34%)	17 (30%)	0.306
	Yes	15 (79%)	25 (66%)	40 (70%)	
Atrial Fibrillation	No	4 (31%)	9 (43%)	13 (38%)	0.481
	Yes	9 (69%)	21 (57%)	21 (62%)	
Hypertension	No	2 (11%)	6 (16%)	8 (14%)	0.590
	Yes	17 (89%)	32 (84%)	49 (86%)	
Hyperlipidemia	No	7 (37%)	14 (37%)	21 (37%)	1.00
	Yes	12 (63%)	24 (63%)	36 (63%)	
Thrombectomy	No	8 (42%)	13 (34%)	21 (37%)	0.560
	Yes	11 (58%)	25 (66%)	36 (63%)	
TICI score	Poor (0 – 2A)	0 (0%)	3 (12%)	3 (8%)	0.230
	Good (2B – 3)	11 (100%)	22 (88%)	33 (92%)	

TICI Thrombolysis in cerebral infarction

Effect of collateral status

The association between collateral status and functional outcome is presented in Fig. 1. Patients with good collaterals were more likely to have a favorable functional outcome ($p=0.001$, OR 5.02; 95% CI 1.37–16.0), as defined by a mRS score of 0–2, when adjusted for age, sex, NIHSS, thrombectomy status, and TICI score. More detailed data, stratified across ordinal values in the mRS, can be seen in Supplemental Table 1. Collateral status did not modify the association between insulin treatment group and functional outcome (unadjusted p -value = 0.378; adjusted p -value = 0.855).

Discussion

Our post-hoc analysis of the SHINE data reveals that the quality of collateralization did not significantly modify the association between functional outcomes and

treatment with intensive compared to standard glucose control in patients with hyperglycemic acute ischemic stroke. However, the analysis confirmed that collateral status was directly associated with functional outcomes in patients with anterior circulation large vessel occlusion stroke, a finding consistent with previously published data [5].

Hyperglycemia is a common condition in patients presenting with acute ischemic stroke, with an incidence as high as 67% in this population [12, 13]. While several large retrospective analyses have demonstrated a negative association between high glucose levels and functional outcome [14, 15], the treatment of hyperglycemic stroke patients with intensive glucose control was not shown to improve functional outcomes in the SHINE trial [10]. In the present *post-hoc* study of the SHINE trial, we stratified patients by collateral status with the hypothesis that

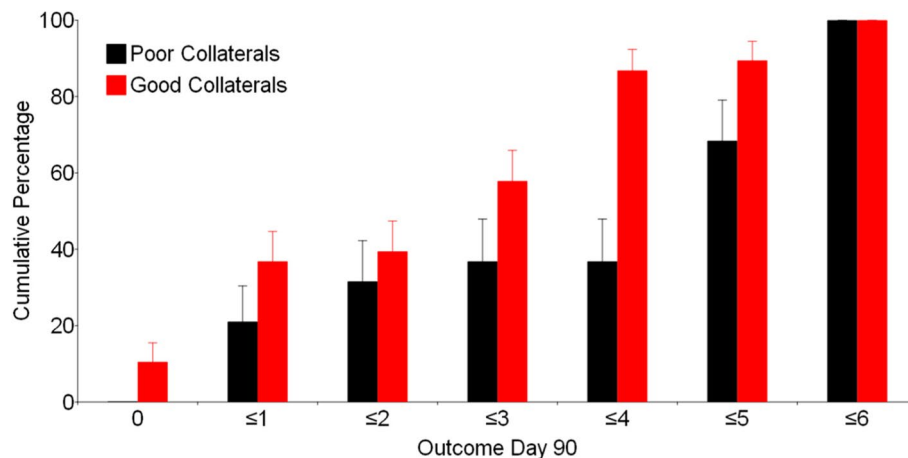


Fig. 1 Association between collateral grade and 90-day mRS. mRS = modified Rankin Scale

intensive glucose control would improve outcomes in patients with good collaterals. However, in our patient population, no association with collateral status was seen (p -value = 0.378, unadjusted). One major difference between our study and similar studies [5–7], which identified collateral status as a statistically significant effect modifier between glucose levels and functional outcome, was sample size.

It is important to note that diabetes was not considered as an independent variable in the present study as the vast majority (80%) of patients enrolled in the SHINE trial were found to have this condition. Furthermore, while the relationship between diabetes and leptomeningeal collateralization has been extensively explored [3, 16, 17], modifiable conditions in the acute setting, such as hyperglycemia, are poorly explored. From a pathophysiologic perspective, collaterals provide an alternative conduit to ischemic tissue, and a may provide a route through which glucose can potentiate direct neurotoxic effects in already compromised brain parenchyma, potentially amplifying the effects of reperfusion injury [7].

While collateral status ultimately did not modify the association between glucose control and functional outcomes in our sub-analysis, we did identify a skewed patient profile within the included SHINE population. Although the difference was not statistically significant (p = 0.06), it is notable that a higher percentage (63%) of patients in the intense glucose control arm of the trial were classified as having good collateral flow compared to those in the standard arm (37%). This finding raises possibility that baseline differences in collateralization between treatment arms may have impacted other outcome metrics in the initial analysis. In addition, while statistical significance was not achieved (p = 0.25), patients with poor collaterals received tPA at a higher rate (63%) compared to those with good collaterals (48%), suggesting

that additional factors such as hemodynamic instability or medical comorbidities may have decreased thrombectomy candidacy and/or affected collateralization status.

The sub-analysis was limited by the relatively small number of patients that had angiographic data for inclusion. While we could not include all patients with angiographic data in the SHINE trial due to resource and technical limitations, we were able to select patients from the centers with the highest enrollment numbers. In addition, other cardiovascular risk factors such as hypertension, hyperlipidemia, and smoking history may have influenced the baseline level of collateralization after stroke and responsiveness to aggressive glucose management. However, due to limited power as a result of a smaller study size, we were unable to include these additional covariates. Given this limited power, it was decided a priori that only the primary endpoint of the SHINE trial would be considered when assessing the effect of collateral status. Additional exploratory analyses in future studies may help to identify the association of collateral status with secondary SHINE endpoints, including 90-day NIHSS score, 90-day Barthel Index score, and 90-day Stroke Specific Quality of Life Score. There is also the possibility of selection bias given that collateral status was not considered during patient randomization, and decisions to pursue thrombectomy were at the discretion of each site.

Conclusions

In conclusion, we found that baseline collateral status did not modify the association between glucose control treatment group and functional outcome in patients with large vessel occlusion stroke. However, we did find a positive association between good collaterals and favorable outcome in this cohort, consistent with previously published research.

Abbreviations

SHINE: Stroke Hyperglycemia Insulin Network Effort; TICI: Thrombolysis In Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; T2DM: Type Two Diabetes Mellitus; mRS: Modified Rankin Scale; tPA: Tissue Plasminogen Activator.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12883-022-02943-4>.

Additional file 1.

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None.

Authors' contributions

Substantial contributions to conception and design: DFA, AMS, KCJ. Acquisition, analysis, and interpretation of data: RU, DFA, KK, MC, MW, DJ, VS, KH, DG, YH, YA, LS, AV, AW, KW, SG, HH, AB, VP. Drafting a significant portion of the manuscript or figures: DFA, KK, JF. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the Center for Health Humanities and Ethics committee at the University of Virginia, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol for the original SHINE trial was approved by the institutional review board at each participating site, and all patients were enrolled after providing written informed consent.

Consent for publication

Not applicable.

Competing interests

AMS discloses research support from the American Heart Association, Difusion Pharmaceuticals, Inc. and Abbvie, Inc. He also performs paid expert consultation in medical legal review of stroke related cases.

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