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Black Patients with Ischemic Stroke and Hyperglycemia Have Worse Outcome Than Whites If Given Intensive Glucose Control

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Abstract

Background—Hyperglycemia is common after acute ischemic stroke and is associated with worse outcome, but intensive glucose control has not improved outcome. There is also a racial disparity in outcome after stroke, with Black patients more likely to have functional impairment than whites. We aimed to evaluate if there were racial differences in outcomes in acute ischemic stroke patients treated with intensive glucose control.

Methods—We performed a post-hoc analysis of the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial to determine if Black patients had worse functional outcome than whites and if standard versus intensive glucose control modified that association. We included non-Hispanic white and Black patients. The primary outcome was excellent functional outcome (90-day modified Rankin Score of 0-1). To account for patient clustering by study site, we fit mixed-effects logistic regression models to our outcome and tested the interaction of treatment and race.

Results—We included 895 patients, of which 304 (34%) were Black and 591 (66%) were white. The rate of excellent outcome was 31.6% in Black patients versus 41.0% in white patients (p=0.006). After adjusting for potential confounders, the odds ratio for excellent outcome in Black patients was 0.54 (95% CI 0.38-0.77). The interaction term between treatment and race was significant (p=0.067). In the intensive treatment arm, Black patients had a predicted probability of excellent outcome of 26.4% (20.1-32.8) versus 42.7% (37.6-47.9) for white patients (p<0.001), while in the standard treatment arm the difference was not significant.

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Statement of Ethics: Because the dataset was deidentified, ethical review board approval or informed consent was not required.

Conclusions—Black patients with acute ischemic stroke and hyperglycemia had worse functional outcome at 90 days than white patients, particularly if given intensive glucose control. These findings are from a post-hoc analysis and may be confounded, thus warrant additional study.

Keywords

acute ischemic stroke; hyperglycemia; health disparities; race

Introduction

Hyperglycemia is common in patients with acute ischemic stroke, affecting up to 40%, and is associated with worse outcome,[1] but intensive glucose control in the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial did not improve functional outcome.[2] There is also a racial disparity in outcome after stroke, with Black patients more likely to have functional impairment than whites.[3] Because prior analyses of the SHINE trial did not investigate the impact of hyperglycemia and its treatment by race, we conducted a post-hoc analysis of SHINE to determine if Black patients had worse functional outcome than whites and if standard versus intensive glucose control modified that association.

Materials and Methods

This is a post-hoc analysis of the SHINE trial (clinicaltrials.gov identifier NCT01369096) using a deidentified publicly available dataset.[4] Because the dataset was deidentified, ethical review board approval at the University of Utah or informed consent was not required. The SHINE protocol and manual of operations are available as an appendix to the original publication.[2] We included self-or proxy-reported non-Hispanic white and Black patients who had a documented 90-day modified Rankin Score (mRS). The primary outcome was 90-day excellent outcome (mRS of 0-1). The secondary outcome was 6-week excellent outcome (mRS 0-1). As an exploratory outcome we evaluated the 90-day Stroke-Specific Quality of Life (SS-QOL) as an interval score that represented the mean of the 12 domains.[5]

All models were *a priori* adjusted for age, sex, hypertension, prior stroke, treatment arm, baseline NIH Stroke Scale (NIHSS), intravenous alteplase (tPA), endovascular thrombectomy (EVT), baseline glucose and Hgb A1c. To account for patient clustering by study site, we fit mixed-effects logistic regression models with study site as the clustering variable, which accounts for study site differences, such as the proportion of white or Black patients enrolled. We also report odds ratios for our primary outcome after stratification by race.

To investigate the impact of intensive glucose management by patient race, we included the interaction term of treatment (intensive vs standard glucose control) and race in our multivariable model. An interaction term with a p value of <0.1 was considered significant. After multivariable logistic regression, we used marginal effects to derive predicted probability of our outcomes with the treatment*race interaction. To further investigate this interaction, we stratified the cohort by baseline Hgb A1c ≤ 7 vs >7, the American College of Physicians stratification for optimal diabetes control.[6] The SS-QOL was tested with linear

regression utilizing identical adjustment as the main model described in the prior paragraph. All analysis was performed in Stata 16.1 (StataCorp, College Station, TX).

Results

Of the 1,151 patients enrolled in SHINE, we included 895 and excluded 33 patients for missing 90-day outcome, 172 Hispanic patients, and 51 patients with “other” race. Amongst the 895 patients, 304 (34%) were Black and 591 (66%) were white. Black patients were significantly younger, more likely to be female, have hypertension, a higher baseline glucose and Hgb A1c, and to have a hypoglycemia adverse event, but did not have a significant difference in tPA administration, EVT, or body mass index (Table 1). The rate of excellent outcome was 31.6% in Black patients versus 41.0% in white patients (p=0.006).

After adjusting for potential confounders, the odds ratio in Black patients, compared to white, for excellent outcome at 90 days was 0.54 (95% CI 0.38-0.77) and at 6 weeks was 0.70 (95% CI 0.49-1.01). The SS-QOL was insignificantly lower in Black compared to white patients (coefficient −0.09, 95% CI −0.23-0.06). After stratification by race, the odds ratio for excellent outcome with intensive treatment in white patients was 1.04 (95% CI 0.70-1.54), while in Black patients it was 0.57 (95% CI 0.32-1.02).

The interaction term between treatment and race was significant for excellent outcome at 90 days (p=0.067) and at 6 weeks (p=0.013), as well as for SS-QOL (p=0.004). The predicted probabilities of outcomes by race and treatment are seen in Table 2. Although Black patients, compared to white, had a lower probability of excellent outcome at 90 days in the standard treatment arm, it was not significant (p=0.227). However, in the intensive treatment arm, Black patients had a predicted probability of excellent outcome of 26.4% (20.1-32.8) versus 42.7% (37.6-47.9) for white patients (p<0.001). When comparing the effect of treatment by race in the same model, Black patients had a significant 10.2% lower odds of excellent outcome with intensive compared to standard treatment (p=0.039), while white patients did not have a significant difference by treatment arm (p=0.809).

After stratification by baseline Hgb A1c, the interaction between treatment*race retained significance only in patients with baseline Hgb A1c ≤7 (p=0.026), while in patients with baseline Hgb A1c >7 the interaction was not significant (p=0.734). The probability of excellent functional outcome at 90 days in the subgroup of patients with baseline Hgb A1c ≤7 (n=336) is shown in Figure 1.

Discussion

We found that Black patients with acute ischemic stroke and hyperglycemia had worse functional outcome at 90 days than white patients, particularly with intensive glucose control. This association was strongest in patients with good pre-stroke glucose control evidenced by a Hgb A1c ≤7. While the association between intensive glucose control and lower odds of excellent outcome in the subgroup of Black patients was not significant (OR 0.57, 95% CI 0.32-1.02), the direction and size of effect was similar, and potentially lacked significance from the smaller subgroup sample size. When comparing the effect of intensive glucose control in the full cohort with marginal effects after the multivariable

logistic regression with the interaction term of race#treatment, we found a race differential in the response to treatment and that Black patients given intensive glucose control had a significant 10.2% lower odds of excellent outcome compared to standard glucose control.

These results have not been previously reported in the SHINE trial. Although the main results of the SHINE trial were consistent with more risk than benefit for intensive glucose control [2], these data show that the risk was particularly important in Black patients. Possible explanations include racial disparities in post-stroke care,[7,8] which we cannot account for in the current dataset. An alternate explanation is that intensive treatment resulted in an excess of adverse events in Black patients. Although we did find that Black, as compared to white, patients had a higher rate of at least one hypoglycemic event (35.2% vs. 25.6%, p=0.003), adjusting for this imbalance did not change our results (data not shown) and the overall rate of Serious Adverse Events and recurrent strokes was not different in Black versus white patients. Additionally, these findings may be related to systemic bias and or social determinants of health that were not captured in the SHINE trial and likely impacted outcome. These findings may also be due to confounding or chance, although the disparity in post-stroke outcomes for Black verses white stroke patients is consistent with prior research.[3,9] Ultimately, we are not able to explain why Black patients show an association between lower odds of excellent outcome and intensive glucose control, and this warrants further study.

Limitations of our study include that it is a post-hoc subgroup analysis of a clinical trial that was not designed to answer this hypothesis. We recognize that race is a social construct that was being captured as if it were a biological construct. We also did not have data on social determinants of health that may have impacted the reported associations. It is known that social determinants of health can impact post-stroke recovery and may have confounded our analysis.[10]

Conclusion

Consistent with prior research in other studies, Black patients in the SHINE trial had worse post-stroke outcome than white patients, particularly when given intensive glucose control. The reasons for this race differential in response to treatment are not apparent, and warrant additional research to better understand disparities in post-stroke outcome.

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Conflicts of Interest:

Dr. de Havenon has investigator-initiated funding from AMAG and Regeneron pharmaceuticals. Dr. Johnston has investigator-initiated funding from Rivanna Medical, LLC, is on DSMBs for Biogen and is a consultant to Diffusion Pharmaceuticals, Neurotrauma Science LLC, and the FDA.

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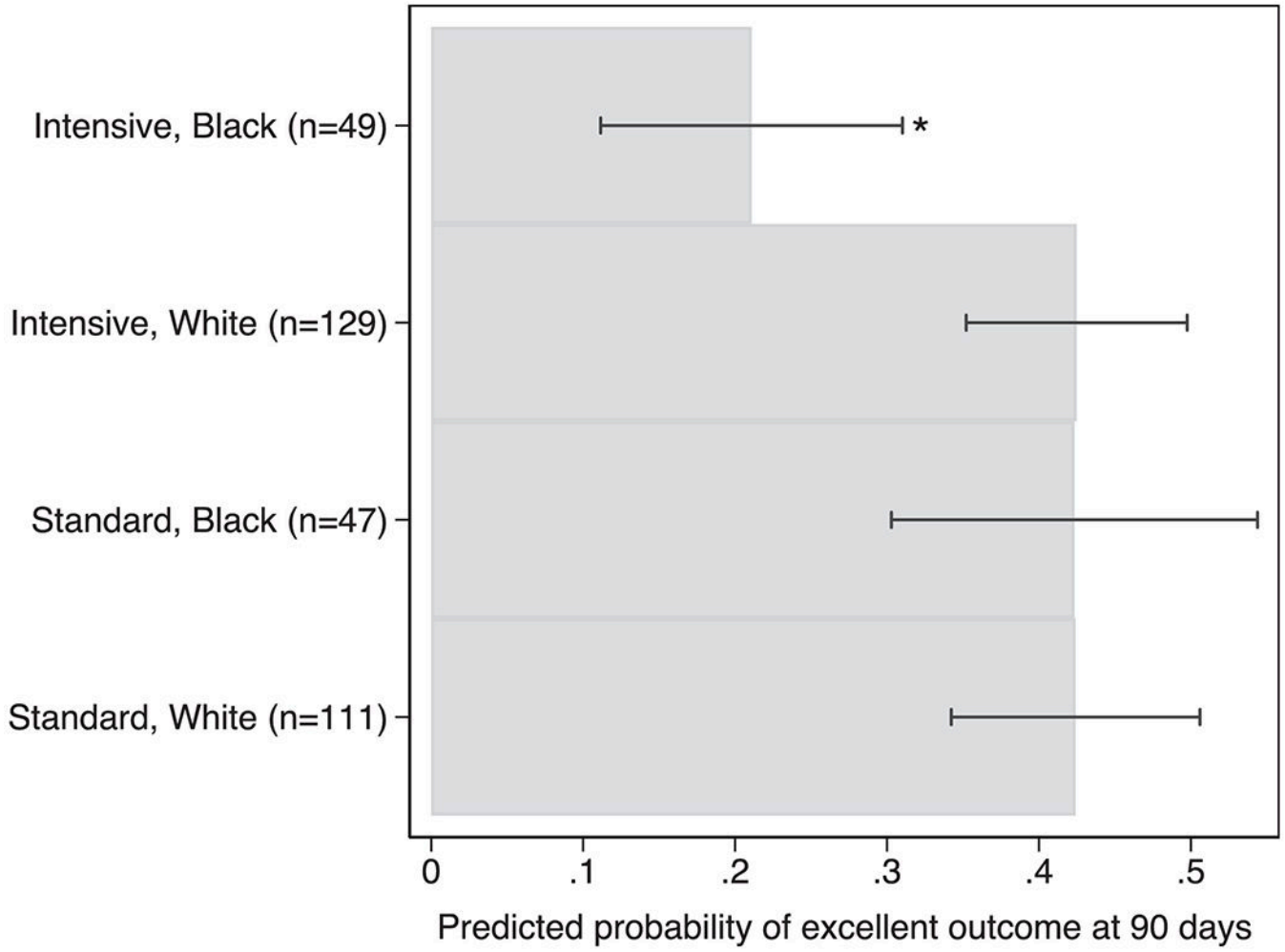

Figure 1.

Predicated probability of excellent functional outcome at 90 days in the subgroup of patients with baseline Hgb A1c ≤7 (n=336).

*p<0.001 for difference between Black vs. White intensive treatment arm, adjusted for age, sex, hypertension, prior stroke, treatment arm, baseline NIHSS, intravenous alteplase, EVT, baseline glucose, and Hgb A1c.

Table 1.

Baseline demographics and outcome of the cohort, and stratified by race.

Variable	Full cohort (n=895)	White patients (n=591)	Black patients (n=304)	p value*
Age	65.8±13.1	68.3±12.8	61.1±12.4	<0.001
Female sex	408 (45.6%)	254 (43.0%)	154 (50.7%)	0.029
Hypertension** (n=893)	790 (88.5%)	511 (86.8%)	279 (91.8%)	0.026
Hyperlipidemia** (n=883)	521 (59.0%)	368 (63.1%)	153 (51.0%)	0.001
Diabetes** (n=890)	714 (80.2%)	461 (78.7%)	253 (83.2%)	0.106
Prior stroke** (n=887)	146 (16.5%)	90 (15.3%)	56 (18.8%)	0.183
Body mass index (n=876)	31.7±7.4	31.5±7.0	32.2±8.1	0.161
Baseline glucose (mg/dL) (n=887)	207.3±73.5	202.2±70.5	217.1±78.1	0.004
Hemoglobin A1c (n=865)	8.2±2.3	7.9±2.1	8.7±2.5	<0.001
Baseline NIH Stroke Scale	8, 5-12	8, 5-13	8, 4-12	0.709
Intravenous Alteplase	554 (61.9%)	360 (60.9%)	194 (63.8%)	0.397
Endovascular thrombectomy	115 (12.9%)	80 (13.5%)	35 (11.5%)	0.392
SHINE intensive treatment arm	458 (51.2%)	291 (49.2%)	167 (54.9%)	0.106
Serious Adverse Event	318 (35.5%)	214 (36.2%)	104 (34.2%)	0.554
Recurrent stroke	27 (3.0%)	16 (2.7%)	11 (3.6%)	0.450
Modified Rankin Scale at 90 days	2, 1-4	2, 1-4	3, 1-4	0.122
Excellent outcome at 6 weeks (n=889)	289 (32.5%)	203 (34.6%)	86 (28.4%)	0.059
Stroke Specific Quality of Life (n=727)	3.7±0.9	3.7±0.9	3.6±0.9	0.204
Excellent outcome at 90d	338 (37.8%)	242 (41.0%)	96 (31.6%)	0.006
Standard tx arm	171 (39.1%)	122 (40.7%)	49 (35.8%)	0.888
Intensive tx arm	167 (36.5%)	120 (41.2%)	47 (28.1%)	0.155

* Binary variables presented as n (%); ordinal variables as median, IQR; interval variables as mean±standard deviation. P values for difference between white and Black subgroups, calculated with the chi-squared test for binary variables, the Wilcoxon rank sum test for ordinal variables, and Student's t-test for interval variables.

** Hypertension, hyperlipidemia, diabetes, and prior stroke are patient or caregiver reported past medical history.

Table 2.

Predicted probability of outcomes by race and treatment.

	Predicted probability or value*	95% Confidence interval	P value for difference by race
Excellent outcome at 90 days			
White patients, standard treatment (n=285)	41.9%	36.8-46.9	0.257
Black patients, standard treatment (n=131)	36.6%	29.2-44.0	
White patients, intensive treatment (n=277)	42.7%	37.6-47.9	<0.001
Black patients, intensive treatment (n=154)	*26.4%*	*20.1-32.8*	
Excellent outcome at 6 weeks			
White patients, standard treatment (n=285)	32.3%	27.1-37.4	0.666
Black patients, standard treatment (n=131)	34.9%	27.6-42.2	
White patients, intensive treatment (n=277)	38.4%	33.3-43.6	0.001
Black patients, intensive treatment (n=154)	25.3%	18.9-31.8	
Stroke Specific Quality of Life at 90 days			
White patients, standard treatment (n=285)	3.67	3.57-3.78	0.227
Black patients, standard treatment (n=131)	3.80	3.63-3.96	
White patients, intensive treatment (n=277)	3.73	3.62-3.84	0.005
Black patients, intensive treatment (n=154)	*3.45*	*3.30-3.61*	

*Adjusted for age, sex, hypertension, prior stroke, treatment arm, baseline NIHSS, intravenous alteplase, EVT, baseline glucose, and Hgb A1c. n=847.