Glucose modifies the effect of endovascular thrombectomy in patients with acute stroke: a pooled-data meta-analysis

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Abstract

Background and Purpose: Hyperglycemia is a negative prognostic factor following acute ischemic stroke but is not known whether glucose is associated with the effects of endovascular thrombectomy in patients with large vessel stroke. In a pooled-data meta-analysis, we analyzed whether serum glucose is a treatment modifier of the efficacy of endovascular thrombectomy in acute stroke.

Methods: Seven randomized trials compared endovascular thrombectomy with standard care between 2010 and 2017 (HERMES Collaboration). 1764 patients with large vessel stroke were allocated to endovascular thrombectomy (n=871) or standard care (n=893). Measurements included blood glucose on admission and functional outcome [modified Rankin Scale (mRS) range: 0-6; lower scores indicating less disability] at 3 months. The primary analysis evaluated whether glucose modified the effect of EVT over standard care on functional outcome, using ordinal logistic regression to test the interaction between treatment and glucose level.

Results: Median (IQR) serum glucose on admission was 120 (104-140) mg/dl [6.6mmol/l (5.7-7.7) mmol/l]. Endovascular thrombectomy (EVT) was better than standard care in the overall pooled-data analysis [common odds ratio (acOR), 2.00 (95% CI 1.69–2.38); however, lower glucose levels were associated with greater effects of EVT over standard care. The interaction was nonlinear such that significant interactions were found in subgroups of patients split at glucose < or > 90mg/dl (5.0mmol/l) [(p=0.019 for interaction, acOR 3.81 (95% CI 1.73–8.41) for patients < 90 mg/dl vs 1.83 (95% CI 1.53–2.19) for patients > 90 mg/dl], and glucose < or > 100mg/dl (5.5mmol/l) [(p=0.004 for interaction, acOR 3.17 (95% CI 2.04–4.93) vs acOR 1.72 (95% CI 1.42–2.08)], but not between subgroups above these levels of glucose.

Conclusions: Endovascular thrombectomy improved stroke outcomes compared to standard treatment regardless of glucose levels but the treatment effects were larger at lower glucose levels, with significant interaction effects persisting up to 90 to 100mg/dl (5.0-5.5mmol/l). Whether tight control of glucose improves the efficacy of endovascular thrombectomy following large vessel stroke warrants appropriate testing.

Introduction

Glucose is essential for normal brain function but may also exacerbate ischemic brain injury through mechanisms occurring within the brain vasculature, microglia, neural cells, and infiltrating leukocytes.[1] Observational studies have shown that hyperglycemia is associated with poor stroke outcomes,[2] whether the patients are treated with intravenous thrombolysis or not. [3-5] Hyperglycemia has also been associated with less favorable outcomes in stroke patients treated with endovascular thrombectomy in observational studies, [6-8] and in one randomized controlled trial (RCT) that compared the Merci and the Solitaire FR device. [9] However, a *post hoc* analysis of the MR CLEAN trial found no evidence for effect modification of intra-arterial treatment by glucose > 140mg/dl (7.8mmol/l). [10] Hyperglycemia is frequent in the acute phase of ischemic stroke, [11] but its definition varies widely across stroke studies, with cutoffs ranging from 109.8mg/dl (6.1mmol/l) to >180mg/dl (9.9mmol/l) random glucose levels.[12] Hyperglycemia promotes tissue acidosis and the production of reactive oxygen and nitrogen species (ROS) that increase infarct size, brain swelling, hemorrhagic transformation, blood–brain barrier disruption and results in more severe neurological deficits under experimental ischemic conditions. [13-14] Patients treated with endovascular thrombectomy have the highest rate of recanalization of the occluded vessel, and arguably have a greater exposure to redox mediated mechanisms which are activated by the re-oxygenation of the ischemic brain and also fueled by the levels of glucose.[15] It is uncertain whether in patients with large vessel stroke treated with endovascular thrombectomy, glucose could be not only a negative prognostic factor, but also a treatment modifier of the efficacy of the procedure. Clarification of this important question is the main objective of the current analysis for it could provide evidence for or against strategies to maximize the benefits of endovascular thrombectomy by

optimization of glucose management in this population. To this end, we sought for modification of the effect of endovascular thrombectomy by glucose level in the randomized phase 3 trials in which stent retrievers were used for acute treatment of ischemic stroke.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The highly effective reperfusion using multiple endovascular devices (HERMES) collaboration [15] pooled individual patient data from all randomized phase 3 trials in which stent retrievers or other second-generation devices were used in the majority of endovascular interventions for treatment of acute ischemic stroke, and for which a peer-reviewed, complete primary results manuscript was published by May 31, 2017. Comparative design features of the contributing trials have been described,[15-16] and included MR CLEAN, [17] ESCAPE, [18] EXTEND-IA, [19] SWIFT PRIME, [20] REVASCAT, [21] PISTE, [22] and THRACE[23] trials. The HERMES executive committee (comprising representatives of each trial) confirmed that all eligible trials were included and contributed their trial data. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. The current analysis was prospectively designed by one of the authors (AC), but not registered. We followed the PRISMA Guidelines (See supplementary material).

In the HERMES trials, glucose was collected as part of the pre-randomization screening blood work and patients with whole blood or plasma glucose levels between 48mg/dl (2.7mmol/l) and 400mg/dl (22.2mmol/l) fulfilled the entry criteria of the pooled trials. The reported management of glucose in the early phase of AIS was not identical amongst the different studies, as two trials (ESCAPE and MR CLEAN) referred to

national standards and guidelines for glucose management, one trial (REVASCAT) recommended a target blood glucose level of less than 160mg/dl (8.9mmol/l) while advising against the correction of baseline glucose laboratory values to meet the inclusion criteria of the study, and four trials (EXTEND-IA, SWIFT PRIME, PISTE, THRACE) provided no specific recommendations for glucose management.

The primary outcome was defined as the degree of disability at 3 months, assessed across 6 levels of the modified Rankin Scale (mRS), with ranks 5 and 6 combined into a single worst outcome rank (primary outcome). Secondary outcomes included (1) functional independence at 3 months, defined as mRS scores of 0 through 2; (2) excellent outcome at 3 months, defined as mRS score of 0 through 1; (3) early neurological recovery at 24 hours, defined as a reduction in National Institutes of Health Stroke Scale (NIHSS) score from baseline of at least 8 points or reaching mRS of 0–1; and (4) complete reperfusion, defined as a modified treatment in cerebral infarction (mTICI) score 2b or 3 at the end of endovascular thrombectomy. Safety outcomes evaluated were 90-day mortality, and symptomatic intracranial hemorrhage (sICH) within 36 hours. sICH was classified according to the actual definitions used in each trial while ICH was defined as parenchymal hematoma type 2 (PH-2). [24]

Data were provided by the authors of all the trials meeting eligibility criteria and collected by independent statisticians. SB coordinated the creation of the unified database. We used a one-stage approach, defined as the use of individual patient data with analysis including covariates and random study effects to appropriately incorporate any between-study differences. [25]

To account for between-study variance in relationships among predictors and outcomes, the statistical models incorporated random effects for study and study-by-treatment interaction (in those models assessing both treatment groups). Analyses were based on

all randomized patients based on their original group of randomization, after excluding missing values for admission glucose and 90-mRS, and the relationship of glucose with clinical and radiological outcomes was evaluated principally through logistic regression models.

A detailed description of the analytic approach is provided in the statistical analysis plan (Appendix). The primary analysis evaluated whether glucose modified the effect of treatment on mRS at 90 days, when adjusted for pre-specified covariates using ordinal logistic regression adjusted for age, sex, NIHSS score at admission, prior use of IV alteplase, occlusion location (ICA/M1/M2), time from stroke onset to randomization, and history of diabetes. Treatment assignment was included as a variable with two levels: endovascular thrombectomy and standard care. Baseline and procedural characteristics were compared between treatment groups and between glucose subgroups using t-tests for continuous variables, Fisher's exact test for binomial outcomes and Pearson's chi-square for multinomial outcomes The interaction between glucose and treatment assignment on the primary outcome assessed glucose using subgroups defined by 10 mg/dl increments from 80 to 180mg/dl (4.9-9.9mmol/l); all subgroup results for the various cutoffs evaluated were then presented. Category-specific effects were reported (in text and using figures) and the presence of significant interactions were noted. For this purpose, p-values are presented; adjustment for multiplicity of testing was applied in assessing the optimal cutoff for distinguishing treatment by glucose interaction. Secondary outcomes and safety outcomes were also adjusted for the same baseline prognostic factors. Statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cary, NC, USA), and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria). All p-values presented are two-sided, with values less than 0.05 defining statistical significance.

Results

After pooling and screening data from all 7 trials in the HERMES collaboration, glucose was not available in 60 (3.4%) of 1764 patients, with 30 patients lacking glucose data in the endovascular group, and 30 patients lacking glucose data in the standard care group **(Appendix Figure I)**.

Across the entire study population, the median glucose on admission was 120mg/dl (6.6mmol/l) (IQR 104-140mg/dl) (5.7-7.7mmol/l), and the distribution of glucose levels in the whole study group was well balanced between the two treatment arms (**Appendix Figure II)**. Results were consistent across the analysis methods and showed higher glucose levels to be significantly associated with worse outcomes including reduced excellent outcome (mRS 0-1), functional independence (mRS 0-2), and early neurological recovery, and increased all-cause mortality, and symptomatic hemorrhagic complications (**Table 1**). In contrast, blood glucose concentration was not associated with the occurrence of successful reperfusion at the end of endovascular thrombectomy. In the entire population, endovascular thrombectomy improved the primary outcome compared with standard care [acOR 2.00 (95% CI 1.69–2.38)]. Notwithstanding, the treatment effect on the primary outcome was found to be nonlinearly dependent on the levels of glucose (**Figure 1)**, and significant treatment interactions were found for subgroup cutoffs of 90mg/dl (5.0mmol/l), 6% of the study sample, and 100mg/dl (5.5mmol/l), 17% of the study sample, but not for the subgroups of patients with glucose cutoffs above this level **(Appendix Table I**). After Bonferroni correction, for the primary outcome only the difference in treatment effect between glucose <100 mg/dL and glucose ≥ 100 mg/dL remained significant. For the glucose cutoff of 90mg/dl (5.0mmol/l) **(Figure 2A)**, there were significant interactions for the rates of functional independence (mRS 0 to 2), and mortality; for the glucose cutoff of 100mg/dl

(5.5mmol/l) **(Figure 2B)**, there were significant interactions for functional independence, early neurological recovery, and mortality. The interaction effect between treatment assignment and glucose level was also highly significant when comparing patients with glucose <100mg/dL (5.5mmol/l) with those >100mg/dl (5.5mmol/l) (p=0.004) after Bonferroni adjustment for multiple comparisons against a threshold of 0.05/10 = 0.005; for the glucose cutoff of 110mg/dl (6.6mmol/l), there were significant interactions for functional independence **(Appendix Table II)**. The magnitude of these associations were clinically meaningful: for every 100 patients with glucose <100mg/dl (5.5mmol/l) treated with endovascular thrombectomy, 45 will have a less disabled outcome than with best medical management, and 32 more will achieve functional independence (mRS 0–2) as a result of treatment; for every 100 patients with glucose >100mg/dl (5.5mmol/l) treated with endovascular thrombectomy, 23 will have a less disabled outcome than with best medical management, and 14 more will achieve functional independence (mRS 0–2) as a result of treatment

The rates of excellent outcome and sICH showed no significant interactions with the treatment effect at any glucose cutoff.

Patients with glucose levels <100mg/dl (5.5mmol/l) were younger, had a lower rate of diabetes, were more likely to have a history of tobacco use and had shorter time from stroke onset to randomization than patients without this range, but did not differ in baseline clinical stroke severity (according to NIHSS), occlusion location, affected hemisphere, or rates of hypertension, hyperlipidemia, and tPA use (**Appendix Table III**).

The number needed to treat for benefit to improve outcome by one mRS category at 3 months was 2.2 in patients with glucose <100 mg/dl (5.5mmol/l) versus 4.4 in patients with glucose ≥100mg/dl (5.5mmol/l).

Discussion

This meta-analysis of individual patient data from seven randomized trials provides post hoc evidence that endovascular thrombectomy improved the primary outcome (mRS at 3 months) more effectively than standard care in patients with large vessel ischemic stroke regardless of glucose levels at stroke onset. The analysis also identified that the patients with glucose ranging between 90 and 100mg/dl (5.0-5.5mmol/l) at stroke onset (17% of the study sample) had the largest treatment effect in favor of the intervention. Consistently, in subgroups with lower glucose levels the larger benefits also extended to predefined secondary outcomes including functional independence (dichotomized mRS 0-2), early neurological recovery at 24 hours, and all-cause mortality, while there were no significant differences in the rate of symptomatic or asymptomatic hemorrhagic complications.

The differences in efficacy between the randomly assigned treatments were significantly lower at glucose levels above 100mg/dl (5.5mmol/l).The study included a large cohort of diabetic and non-diabetic patients and the findings were consistent with those of prior studies that did not include patients treated with endovascular thrombectomy[1, 9, 26-27] showing that higher glucose levels were associated with worse functional outcomes at 3 months, and were also associated with increased all-cause mortality, and greater risks of symptomatic hemorrhagic complications. Hyperglycemia was deemed to impair the efficacy of intravenous thrombolysis in previous studies, [5] while we found similar rates of successful reperfusion following endovascular thrombectomy regardless of glucose levels, arguing that the worse outcomes found in patients with higher glucose levels were not the consequence of impaired brain reperfusion following the endovascular procedure.

The key question is whether lower glucose is a simply a marker for patients who have a better prognosis, or if acutely lowering glucose could improve prognosis. The benefits of lowering glucose concentration in patients with acute ischemic stroke remain to be demonstrated, but all the reported previous attempts have been unsuccessful.[28-29] In the GIST-UK trial, 24-hour glucose potassium insulin (GKI) infusion targeted to maintain glucose at 72-126mg/dl (4–7mmol/l) did not improve outcome in patients with admission glucose concentration between 108-306mg/dl (5.9–16.9mmol/l). [28] However, this study was compromised by under-recruitment, late treatment initiation, and marginal reduction of blood glucose [10mg/dl (0.5mmol/l)] compared with control. [28] In the SELESTIAL trial, [29] GKI infusion targeted to maintain blood glucose between 72–126mg/dl (4 –7mmol/l), did lower blood glucose from 6 to 12 hours after GKI initiation and attenuated an increase in brain lactate, but the therapy did not affect cerebral infarct growth, and hypoglycemia [<72mg/dl (4.0mmol/l)] occurred in 76% of GKI-treated subjects although it was predominantly asymptomatic. [29] The mean glucose levels obtained in these trials ranged between 105-112mg/dl (5.8-6.2mmol/l), and there was a very low risk of symptomatic hypoglycemia. The SHINE trial (#NCT01369069) is currently determining the safety and efficacy of attaining a glucose range of 80–179mg/dl (4.4-9.9mmol/l) versus 80–130mg/dl (4.4-7.2mmol/l) for up to 72 h, starting within 12 h of stroke symptom onset, and the TEXAIS trial (NCT03287076), is comparing exenatide to standard of care in patients with acute ischemic stroke commencing treatment within 9 hours of symptom onset, although in this trial there is not a target glucose level. However, in none of the ongoing trials it is anticipated the inclusion of a sufficient number of patients that will receive endovascular thrombectomy to detect a treatment effect in that subgroup. Altogether, it appears that moderate lowering of glucose levels in patients with acute ischemic stroke not treated

with endovascular thrombectomy prevents lactic acidosis, but this effect seems not to translate into clinical benefits. Indeed, extracellular lactate accumulation is not a crucial determinant of brain injury in experimental hyperglycemia, [30]for prevention of tissue acidosis does not avoid brain tissue damage under hyperglycemic conditions.[31] Endovascular thrombectomy achieves a high rate of successful reperfusion, facilitating the reentry of oxygen into the ischemic brain to a much larger extent than any other therapeutic options. Because oxygen boosts the formation of free radicals in parallel with the availability of glucose, [2-3] it is possible that patients receiving endovascular thrombectomy are more vulnerable to the redox mediated effects of glucose. Classical experimental studies of focal cerebral ischemia support the significance of reperfusion in contributing to the detrimental effect of hyperglycemia.[32]

The results of this post hoc pooled-data meta-analysis need to be interpreted with caution and cannot be used to change clinical recommendations. These data do provide clinical justification for the study of tight glucose management in patients receiving endovascular thrombectomy. Testing a glucose target of 90-100mg/dl (5.0-5.5mmol/l) seems justified, despite the risk that this approach might increase the occurrence of hypoglycemia, which has been predominantly asymptomatic in previous trials.[28-29] Therapeutic alternatives without the risk of hypoglycemia could also be considered for further clinical testing, including the administration of the antioxidant uric acid. In the URICOICTUS trial, [33] in addition to the antioxidant uric acid or placebo, all the patients received intravenous thrombolysis within 4.5 hours of stroke onset, and some also received rescue endovascular thrombectomy. [34] In this trial, uric acid therapy reduced infarct growth and improved the functional outcome at 3 months more effectively than placebo even in hyperglycemic patients, [35]supporting the idea that the toxicity of hyperglycemia can be minimized by enhancing antioxidant exposure. Indeed,

inactivation of the glucose-dependent nicotinamide adenine dinucleotide phosphate oxidase enzyme blocks neuronal ROS production and negates the deleterious effects of hyperglycemia. [36]

Some limitations of this pooled data analysis include the lack of information on the longitudinal course of glucose at follow up, the undocumented use of lowering glucose drugs, or whether glucose concentration was measured in venous or capillary samples. Three of the trials analyzed patients that were treated following widely accepted guidelines recommending the administration of insulin in patients with glucose concentrations >140mg/dl (7.8mmol/l) to 185mg/dl (10.3mmol/l), although four trials provided no specific treatment recommendations. Low glucose at stroke onset could be associated with good prognostic variables not measured in this study, such as lower body mass index, better collaterals, or less need for general anesthesia. Given the exploratory analyses testing the effect modification of pretreatment glucose, concerns about type 1 error with multiple testing might arise, but the p-value for interaction with glucose 100 mg/dl cut-off values remained significant after Bonferroni correction. Further, the pooled patients were treated at many centers in multiple countries on 4 continents, suggesting wide applicability.

In conclusion, in this individual patient data meta-analysis of 7 randomized clinical trials of patients with large-vessel ischemic stroke, the effect of endovascular thrombectomy on functional outcome at 3 months compared to standard treatment was severely diminished with increasing glucose levels.

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Figure legends

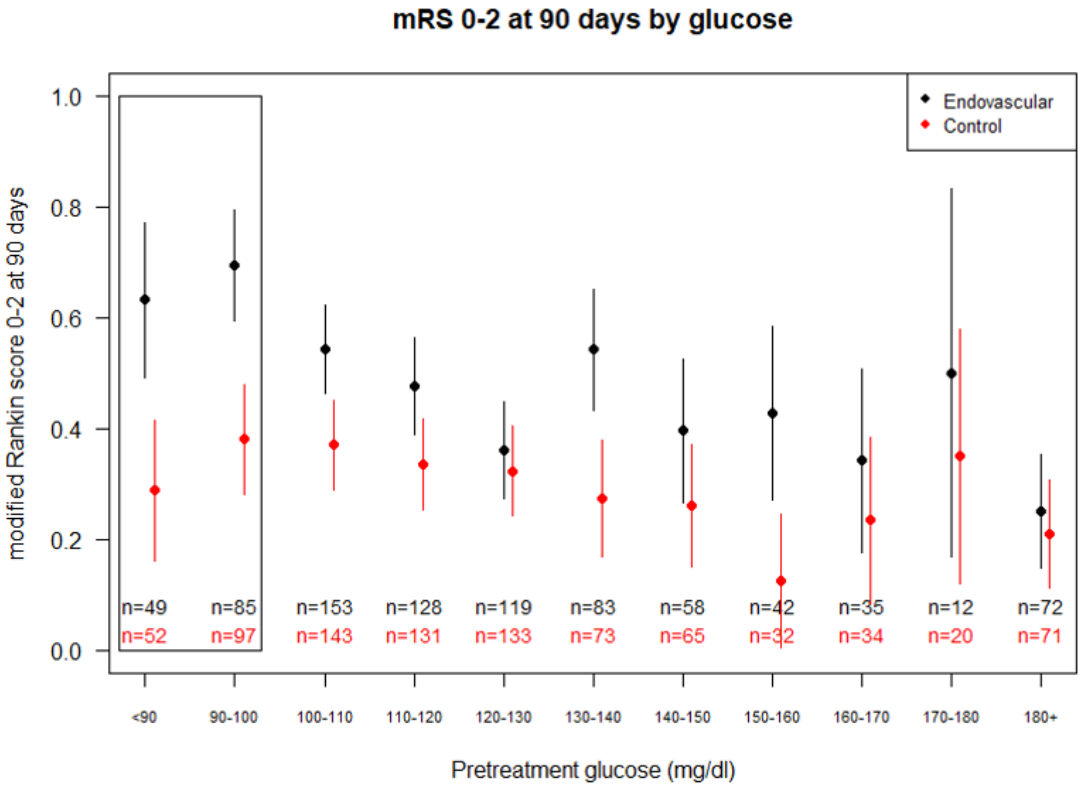

Figure 1: Modification of pretreatment glucose on treatment effect of endovascular thrombectomy over standard care on the rate of functional independence (modified Rankin Scale 0 to 2).

Fig 2A

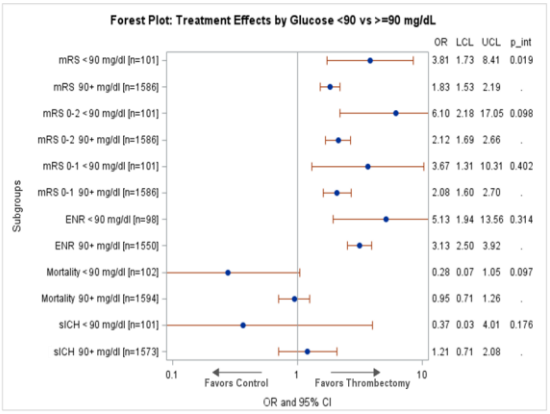

Fig 2B

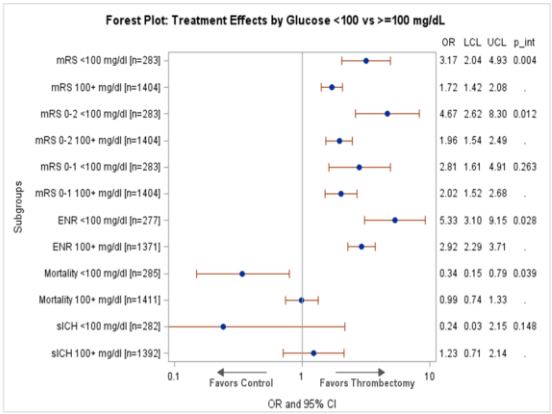

Figure 2: Forest plots of odds ratios for the model of main treatment effects of endovascular thrombectomy or standard care according to admission glucose concentration < or ≥ 90mg/dl (5.0mmol/l) **(Fig 2A)** and 100mg/dl (5.5mmol/l) **(Fig 2B)** in the HERMES population.

ENR=early neurological recovery; mRS=modified Rankin Scale; sICH=symptomatic intracerebral hemorrhage.

Table 1: Associations between continuous glucose levels and outcomes

	n	Glucose, mg/dl Mean±SD [Median] (IQR)	P value	Unadjusted OR (95% CI) [a]	P value	Adjusted OR (95% CI) [b]	P value
Excellent outcome mRS 0-1 mrS 2-6	 383 1304	120.2 +/- 33.5 [113.4] (100·0,130.0) 134.8 +/- 74.6 [121.8] (106.2,145.0)	<0.001	0.92 (0.88, 0.95)	<0.0001	0.93 (0.89, 0.96)	<0.0001
Good outcome mRS 0-2 mrS 3-6	 662 1025	123.7 +/- 54.8 [114.5] (101.8,133.2) 136.5 +/- 74.6 [123.0] (107·3,147.0)	<0.001	0.92 (0.90, 0.95)	<0.0001	0.93 (0.90, 0.96)	<0.0001
Death Yes No	 271 1425	147.1 +/- 111.3 [129.1] (107.3,157.0) 128.4 +/- 55.1 [118.2] (104.4,138.2)	<0.0001	1.07 (1.04, 1.10)	<0.0001	1.06 (1.03, 1.09)	<0.0001
ENR Yes No	 602 1046	123.1 +/- 34.6 [115.2] (102.6,134.0) 134.5 +/- 63.6 [121.8] (106.0,145.5)	<0.0001	0.92 (0.88, 0.96)	<0.001	0.93 (0.89, 0.97)	0.002
sICH Yes No	 62 1612	172.9 +/- 213.4 [127.5] (110.9,161.0) 129.6 +/- 54.3 [119.0] (104.4,140.0)	<0.0001	1.07 (1.03, 1.12)	0.001	1.06 (1.02, 1.11)	0.006
mTICI score 2b/3 0-2[a]	 535 179	129.5 +/- 55.5 [119.0] (105.0,140.0) 140.1 +/- 127.2 [121.8] (107.3,143.0)	0.124	0.97 (0.93, 1.01)	0.175	0.97 (0.93, 1.02)	0.242

CI=confidence interval; ENR=early neurological recovery; sICH=symptomatic intracerebral hemorrhage; mRS=modified Rankin Scale; OR, odds ratio; mTICI=modified Thrombolysis In Cerebral Infarction.

[a]Odds ratio for experiencing the first listed outcome; the incremental unit of glucose is 10 mg/dL

[b] Adjusted for age, gender, NIHSS, occlusion location, tPA administration , history of diabetes, and time from onset to randomization