Glucose Modifies the Effect of Endovascular Thrombectomy in Patients With Acute Stroke A Pooled-Data Meta-Analysis

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A Pooled-Data Meta-Analysis

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Background and Purpose—Hyperglycemia is a negative prognostic factor after acute ischemic stroke but is not known whether glucose is associated with the effects of endovascular thrombectomy (EVT) 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 EVT in acute stroke.

Methods—Seven randomized trials compared EVT with standard care between 2010 and 2017 (HERMES Collaboration [highly effective reperfusion using multiple endovascular devices]). One thousand seven hundred and sixty-four patients with large-vessel stroke were allocated to EVT (n=871) or standard care (n=893). Measurements included blood glucose on admission and functional outcome (modified Rankin Scale 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.

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Results—Median (interquartile range) serum glucose on admission was 120 (104–140) mg/dL (6.6 mmol/L [5.7–7.7] mmol/L). EVT was better than standard care in the overall pooled-data analysis adjusted 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 >90 mg/dL (5.0 mmol/L; *P*=0.019 for interaction; acOR, 3.81; 95% CI, 1.73–8.41 for patients < 90 mg/dL versus 1.83; 95% CI, 1.53–2.19 for patients >90 mg/dL), and glucose < or >100 mg/dL (5.5 mmol/L; *P*=0.004 for interaction; acOR, 3.17; 95% CI, 2.04–4.93 versus acOR, 1.72; 95% CI, 1.42–2.08) but not between subgroups above these levels of glucose.

Conclusions—EVT improved stroke outcomes compared with 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 100 mg/dL (5.0–5.5 mmol/L). Whether tight control of glucose improves the efficacy of EVT after large-vessel stroke warrants appropriate testing. **(*Stroke*. 2019;50:690-696. DOI: 10.1161/STROKEAHA.118.023769.)**

Key Words: blood glucose ■ hyperglycemia ■ meta-analysis ■ patients ■ thrombectomy

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 patients with stroke treated with endovascular thrombectomy (EVT) in observational studies[6–8] and in 1 randomized controlled trial that compared the Merci and the Solitaire FR device.[9] However, a post hoc analysis of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) found no evidence for effect modification of intraarterial treatment by glucose >140 mg/dL (7.8 mmol/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 109.8 mg/dL (6.1 mmol/L) to >180 mg/dL (9.9 mmol/L) random glucose levels.[12] Hyperglycemia promotes tissue acidosis and the production of reactive oxygen and nitrogen species 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 EVT 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 reoxygenation 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 EVT, 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 EVT by optimization of glucose management in this population. To this end, we sought for modification of the effect of EVT 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 on reasonable request. The HERMES collaboration (highly effective reperfusion using multiple endovascular devices)[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 article was published by May 31, 2017. Comparative design features of the contributing trials have been described[15,16] and included MR CLEAN,[17] ESCAPE (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times),[18] EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial),[19] SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment),[20] REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset),[21] PISTE (Pragmatic Ischaemic Thrombectomy Evaluation),[22] and THRACE (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke)[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 (Dr Chamorro), but not registered. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (See the online-only Data Supplement).

In the HERMES trials, glucose was collected as part of the prerandomization screening blood work, and patients with whole blood or plasma glucose levels between 48 mg/dL (2.7 mmol/L) and 400 mg/dL (22.2 mmol/L) fulfilled the entry criteria of the pooled trials. The reported management of glucose in the early phase of acute ischemic stroke was not identical among the different studies, as 2 trials (ESCAPE and MR CLEAN) referred to national standards and guidelines for glucose management, 1 trial (REVASCAT) recommended a target blood glucose level of >160 mg/dL (8.9 mmol/L) while advising against the correction of baseline glucose laboratory values to meet the inclusion criteria of the study, and 4 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 score from baseline of at least 8 points or reaching mRS of 0 to 1; and (4) complete reperfusion, defined as a modified treatment in cerebral infarction score 2b or 3 at the end of EVT. Safety outcomes evaluated were 90-day mortality and symptomatic intracranial hemorrhage within 36 hours. Symptomatic intracranial hemorrhage was classified according to the

actual definitions used in each trial, whereas intracranial hemorrhage was defined as parenchymal hematoma type 2.[24]

Data were provided by the authors of all the trials meeting eligibility criteria and collected by independent statisticians. Dr Brown coordinated the creation of the unified database. We used a 1-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 in the online-only Data Supplement). The primary analysis evaluated whether glucose modified the effect of treatment on mRS at 90 days, when adjusted for prespecified covariates using ordinal logistic regression adjusted for age, sex, National Institutes of Health Stroke Scale score at admission, prior use of intravenous alteplase, occlusion location (internal carotid artery/M1/M2), time from stroke onset to randomization, and history of diabetes mellitus. Treatment assignment was included as a variable with 2 levels: EVT and standard care. Baseline and procedural characteristics were compared between treatment groups and between glucose subgroups using *t* tests for continuous variables, Fisher exact test for binomial outcomes, and Pearson χ^2 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 180 mg/dL (4.9–9.9 mmol/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) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values presented are 2-sided, with values <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 in the online-only Data Supplement).

Across the entire study population, the median glucose on admission was 120 mg/dL (6.6 mmol/L; interquartile range 104–140 mg/dL; 5.7–7.7 mmol/L), and the distribution of glucose levels in the whole study group was well balanced between the 2 treatment arms (Appendix Figure II in the online-only Data Supplement). 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). In contrast, blood glucose concentration was not associated with the occurrence of successful reperfusion at the end of EVT.

In the entire population, EVT improved the primary outcome compared with standard care (adjusted common odds ratio 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 90 mg/dL (5.0 mmol/L), 6% of the study sample and 100 mg/dL (5.5 mmol/L), 17% of the study sample, but not for the subgroups of patients with glucose cutoffs above this level (Appendix Table I in the online-only Data Supplement). 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 90 mg/dL (5.0 mmol/L; Figure 2A), there were significant interactions for the rates of functional independence (mRS 0–2) and mortality; for the glucose cutoff of 100 mg/dL (5.5 mmol/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 <100 mg/dL (5.5 mmol/L) with those >100 mg/dL (5.5 mmol/L; *P*=0.004) after Bonferroni adjustment for multiple comparisons against a threshold of 0.05/10=0.005; for the glucose cutoff of 110 mg/dL (6.6 mmol/L), there were significant interactions for functional independence (Appendix Table II in the online-only Data Supplement). The magnitude of these associations were clinically meaningful: for every 100 patients with glucose <100 mg/dL (5.5 mmol/L) treated with EVT, 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 >100 mg/dL (5.5 mmol/L) treated with EVT, 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 symptomatic intracranial hemorrhage showed no significant interactions with the treatment effect at any glucose cutoff.

Patients with glucose levels <100 mg/dL (5.5 mmol/L) were younger, had a lower rate of diabetes mellitus, 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 National Institutes of Health Stroke Scale), occlusion location, affected hemisphere, or rates of hypertension, hyperlipidemia, and tPA (tissue-type plasminogen activator) use (Appendix Table III in the online-only Data Supplement).

The number needed to treat for benefit to improve outcome by 1 mRS category at 3 months was 2.2 in patients with glucose <100 mg/dL (5.5 mmol/L) versus 4.4 in patients with glucose ≥100 mg/dL (5.5 mmol/L).

Discussion

This meta-analysis of individual patient data from 7 randomized trials provides post hoc evidence that EVT improved the primary outcome (mRS at 3 months) more effectively than

Table. Associations Between Continuous Glucose Levels and Outcomes

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

ENR indicates early neurological recovery; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarctions; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; sICH, symptomatic intracranial hemorrhage; and tPA, tissue-type plasminogen activator.

*OR for experiencing the first listed outcome; the incremental unit of glucose is 10 mg/dL.

†Adjusted for age, sex, NIHSS, occlusion location, tPA administration, history of diabetes mellitus, and time from onset to randomization.

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 100 mg/dL (5.0–5.5 mmol/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, whereas 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 100 mg/dL (5.5 mmol/L).The study included a large cohort of patients with and without diabetes mellitus, and the findings were consistent with those of prior studies that did not include patients treated with EVT[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] whereas we found similar rates of successful reperfusion after EVT regardless of glucose levels, arguing that the worse outcomes found in patients with higher glucose levels were not the consequence of impaired brain reperfusion after 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

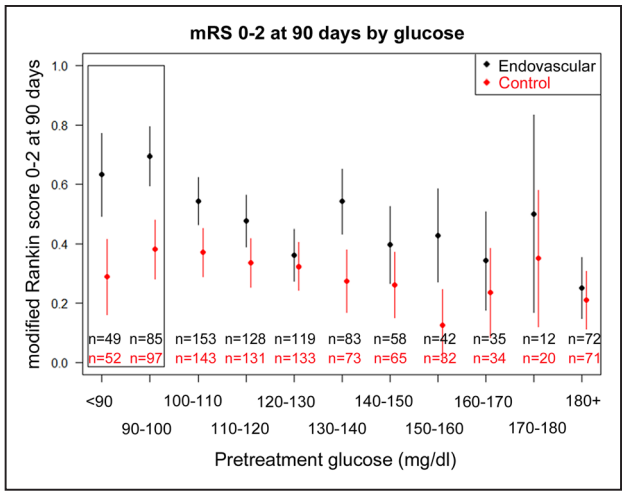

Figure 1. Modification of pretreatment glucose on treatment effect of endovascular thrombectomy over standard care on the rate of functional independence (modified Rankin Scale [mRS] 0–2).

stroke remain to be demonstrated, but all the reported previous attempts have been unsuccessful.[28,29] In the GIST-UK trial (UK Glucose Insulin in Stroke Trial), 24-hour glucose potassium insulin infusion targeted to maintain glucose at 72 to 126 mg/dL (4–7 mmol/L) did not improve outcome in patients with admission glucose concentration between 108-306 mg/dL (5.9–16.9 mmol/L).[28] However, this study was compromised by under-recruitment, late treatment initiation, and marginal reduction of blood glucose (10 mg/dL [0.5 mmol/L]) compared with control.[28] In the SELESTIAL trial (Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic Acidosis),[29] glucose potassium insulin infusion targeted to maintain blood glucose between 72 and 126 mg/dL (4–7 mmol/L), did lower blood glucose from 6 to 12 hours after glucose potassium insulin initiation, and attenuated an increase in brain lactate, but the therapy did not affect cerebral infarct growth, and hypoglycemia (<72 mg/dL [4.0 mmol/L]) occurred in 76% of glucose potassium insulin–treated subjects, although it was predominantly asymptomatic.[29] The mean glucose levels obtained in these trials ranged between 105 and 112 mg/dL (5.8–6.2 mmol/L), and there was a low risk of symptomatic hypoglycemia. The SHINE trial (Stroke Hyperglycemia Insulin Network Effort Trial; https://www.clinicaltrials.gov. Unique identifier: NCT01369069) is currently determining the safety and efficacy of attaining a glucose range of 80 to 179 mg/dL (4.4–9.9 mmol/L) versus 80 to 130 mg/dL (4.4–7.2 mmol/L) for up to 72 hours, starting within 12 hours of stroke symptom onset, and the TEXAIS trial (Trial of Exenatide Versus Standard Care in Acute Ischemic Stroke; https://www.clinicaltrials.gov. Unique identifier: 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 EVT to detect a treatment effect in that subgroup. Altogether, it seems that moderate lowering of glucose levels in patients with acute ischemic stroke not treated with EVT 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 EVT 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

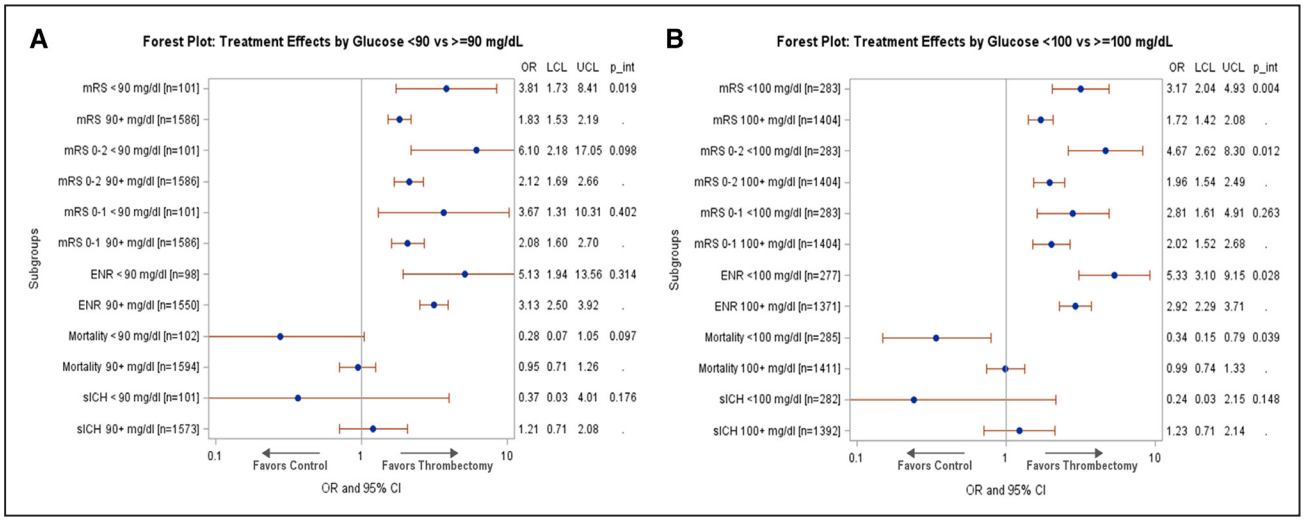

Figure 2. Forest plots of odds ratios for the model of main treatment effects of endovascular thrombectomy or standard care according to admission glucose concentration < or ≥90 mg/dL (5.0 mmol/L; A) and 100 mg/dL (5.5 mmol/L; B) in the HERMES (highly effective reperfusion using multiple endovascular devices) population. ENR indicates early neurological recovery; LCL, lower confidence limits; mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracranial hemorrhage; and UCL, upper confidence limits.

clinical justification for the study of tight glucose management in patients receiving EVT. Testing a glucose target of 90 to 100 mg/dL (5.0–5.5 mmol/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 EVT.[34] In this trial, uric acid therapy reduced infarct growth and improved the functional outcome at 3 months more effectively than placebo even in patients with hyperglycemia,[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 reactive oxygen and nitrogen species 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 >140 mg/dL (7.8 mmol/L) to 185 mg/dL (10.3 mmol/L), although 4 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 cutoff values remained significant after Bonferroni correction. Furthermore, 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 EVT on functional outcome at 3 months compared with standard treatment was severely diminished with increasing glucose levels.

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References

1. Martini SR, Kent TA. Hyperglycemia in acute ischemic stroke: a vascular perspective. *J Cereb Blood Flow Metab*. 2007;27:435–451. doi: 10.1038/sj.jcbfm.9600355
2. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, et al; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59:669–674. doi: 10.1212/WNL.59.5.669
3. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke*. 2005;36:1705–1709. doi: 10.1161/01.STR.0000173161.05453.90.9f
4. Desilles JP, Meseguer E, Labreuche J, Lapergue B, Sirimarco G, Gonzalez-Valcarcel J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. *Stroke* 2013; 44:1915–1923.
5. Costalat V, Lobotesis K, Machi P, Mourand I, Maldonado I, Heroum C, et al. Prognostic factors related to clinical outcome following thrombectomy in ischemic stroke (RECOST study). 50 patients prospective study. *Eur J Radiol*. 2012;81:4075–4082. doi: 10.1016/j.ejrad.2012.07.012

6. Ozdemir O, Giray S, Arlier Z, Baş DF, Inanc Y, Colak E. Predictors of a good outcome after endovascular stroke treatment with stent retrievers. *ScientificWorldJournal*. 2015;2015:403726. doi: 10.1155/2015/403726
7. Arnold M, Mattle S, Galimanis A, Kappeler L, Fischer U, Jung S, et al. Impact of admission glucose and diabetes on recanalization and outcome after intra-arterial thrombolysis for ischaemic stroke. *Int J Stroke*. 2014;9:985–991. doi: 10.1111/j.1747-4949.2012.00879.x
8. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Katsanos AH, Magoufis G, et al. Admission hyperglycemia and outcomes in large vessel occlusion strokes treated with mechanical thrombectomy. *J Neurointerv Surg*. 2018;10:112–117. doi: 10.1136/neurintsurg-2017-012993
9. Kim JT, Jahan R, Saver JL; SWIFT Investigators. Impact of glucose on outcomes in patients treated with mechanical thrombectomy: a post hoc analysis of the solitaire flow restoration with the intention for thrombectomy study. *Stroke*. 2016;47:120–127. doi: 10.1161/STROKEAHA.115.010753
10. Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos YBWEM, Beumer D, et al; MR CLEAN Investigators. Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke. *Stroke*. 2017;48:1299–1305. doi: 10.1161/STROKEAHA.116.016071
11. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
12. Robbins NM, Swanson RA. Opposing effects of glucose on stroke and reperfusion injury: acidosis, oxidative stress, and energy metabolism. *Stroke*. 2014;45:1881–1886. doi: 10.1161/STROKEAHA.114.004889
13. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology*. 1982;32:1239–1246.
14. Suh SW, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, et al. Glucose and NADPH oxidase drive neuronal superoxide formation in stroke. *Ann Neurol*. 2008;64:654–663. doi: 10.1002/ana.21511
15. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
16. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
17. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
18. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
19. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
20. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
21. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
22. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, et al; PISTE Investigators. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38–44. doi: 10.1136/jnnp-2016-314117
23. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al; THRACE Investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
24. Berger C, Fiorelli M, Steiner T, Schäbitz WR, Bozzao L, Bluhmki E, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke*. 2001;32:1330–1335.
25. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, United Kingdom: The Cochrane Collaboration; 2011.
26. Muir KW, McCormick M, Baird T, Ali M. Prevalence, predictors and prognosis of post-stroke hyperglycaemia in acute stroke trials: individual patient data pooled analysis from the Virtual International Stroke Trials Archive (VISTA). *Cerebrovasc Dis Extra*. 2011;1:17–27. doi: 10.1159/000324319
27. Ahmed N, Dávalos A, Eriksson N, Ford GA, Glahn J, Hennerici M, et al; SITS Investigators. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). *Arch Neurol*. 2010;67:1123–1130. doi: 10.1001/archneurol.2010.210
28. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406. doi: 10.1016/S1474-4422(07)70080-7
29. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol*. 2010;67:570–578. doi: 10.1002/ana.21983
30. Park WS, Chang YS, Lee M. Effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after acute transient global hypoxia-ischemia in the newborn piglet. *Brain Res*. 2001;901:102–108.
31. Tsuruta R, Fujita M, Ono T, Koda Y, Koga Y, Yamamoto T, et al. Hyperglycemia enhances excessive superoxide anion radical generation, oxidative stress, early inflammation, and endothelial injury in forebrain ischemia/reperfusion rats. *Brain Res*. 2010;1309:155–163. doi: 10.1016/j.brainres.2009.10.065
32. Yip PK, He YY, Hsu CY, Garg N, Marangos P, Hogan EL. Effect of plasma glucose on infarct size in focal cerebral ischemia-reperfusion. *Neurology*. 1991;41:899–905.
33. Chamorro A, Amaro S, Castellanos M, Segura T, Arenillas J, Martí-Fábregas J, et al; URICO-ICTUS Investigators. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet Neurol*. 2014;13:453–460. doi: 10.1016/S1474-4422(14)70054-7
34. Chamorro Á, Amaro S, Castellanos M, Gomis M, Urra X, Blasco J, et al; URICO-ICTUS Investigators. Uric acid therapy improves the outcomes of stroke patients treated with intravenous tissue plasminogen activator and mechanical thrombectomy. *Int J Stroke*. 2017;12:377–382. doi: 10.1177/1747493016684354
35. Amaro S, Llull L, Renú A, Laredo C, Perez B, Vila E, et al. Uric acid improves glucose-driven oxidative stress in human ischemic stroke. *Ann Neurol*. 2015;77:775–783. doi: 10.1002/ana.24378
36. Ling PR, Smith RJ, Bistrian BR. Hyperglycemia enhances the cytokine production and oxidative responses to a low but not high dose of endotoxin in rats. *Crit Care Med*. 2005;33:1084–1089.