Stroke

CLINICAL TRIALS

Management of Poststroke Hyperglycemia: Results of the TEXAIS Randomized Clinical Trial

Christopher F. Bladin, MD; Ngai Wah Cheung, PhD; Helen M. Dewey, PhD; Leonid Churilov, PhD; Sandy Middleton, PhD; Vincent Thijs, MD; Elif Ekinci, PhD; Christopher R. Levi, MD; Richard Lindley, MD; Geoffrey A. Donnan, MD; Mark W. Parsons, PhD; Atte Meretoja, PhD; Marjaana Tiainen, PhD; Philip M.C. Choi, MB ChB; Dennis Cordato, PhD; Helen Brown, MB BCh; Bruce C.V. Campbell, PhD; Stephen M. Davis, MD; Geoffrey Cloud, MD; Rohan Grimley, MD; Matthew Lee-Archer, MD; Darshan Ghia, MD; Lauren Sanders, PhD; Romesh Markus, MD; Claire Muller, MBBS; Patrick Salvaris, MD; Teddy Wu, PhD; John Fink, MD; on behalf of the TEXAIS Investigators*

BACKGROUND: Hyperglycemia in acute ischemic stroke reduces the efficacy of stroke thrombolysis and thrombectomy, with worse clinical outcomes. Insulin-based therapies are difficult to implement and may cause hypoglycemia. We investigated whether exenatide, a GLP-1 (glucagon-like peptide-1) receptor agonist, would improve stroke outcomes, and control poststroke hyperglycemia with minimal hypoglycemia.

METHODS: The TEXAIS trial (Treatment With Exenatide in Acute Ischemic Stroke) was an international, multicenter, phase 2 prospective randomized clinical trial (PROBE [Prospective Randomized Open Blinded End-Point] design) enrolling adult patients with acute ischemic stroke ≤9 hours of stroke onset to receive exenatide (5 µg BID subcutaneous injection) or standard care for 5 days, or until hospital discharge (whichever sooner). The primary outcome (intention to treat) was the proportion of patients with ≥8-point improvement in National Institutes of Health Stroke Scale score (or National Institutes of Health Stroke Scale scores 0–1) at 7 days poststroke. Safety outcomes included death, episodes of hyperglycemia, hypoglycemia, and adverse event.

RESULTS: From April 2016 to June 2021, 350 patients were randomized (exenatide, n=177, standard care, n=173). Median age, 71 years (interquartile range, 62–79), median National Institutes of Health Stroke Scale score, 4 (interquartile range, 2–8). Planned recruitment (n=528) was stopped early due to COVID-19 disruptions and funding constraints. The primary outcome was achieved in 97 of 171 (56.7%) in the standard care group versus 104 of 170 (61.2%) in the exenatide group (adjusted odds ratio, 1.22 [95% CI, 0.79–1.88]; *P*=0.38). No differences in secondary outcomes were observed. The per-patient mean daily frequency of hyperglycemia was significantly less in the exenatide group across all quartiles. No episodes of hypoglycemia were recorded over the treatment period. Adverse events of mild nausea and vomiting occurred in 6 (3.5%) exenatide patients versus 0 (0%) standard care with no withdrawal.

CONCLUSIONS: Treatment with exenatide did not reduce neurological impairment at 7 days in patients with acute ischemic stroke. Exenatide did significantly reduce the frequency of hyperglycemic events, without hypoglycemia, and was safe to use. Larger acute stroke trials using GLP-1 agonists such as exenatide should be considered.

REGISTRATION: URL: www.australianclinicaltrials.gov.au; Unique identifier: ACTRN12617000409370. URL: https://www.clinicaltrials.gov; Unique identifier: NCT03287076.

This article is part of the Null Hypothesis Collection, a collaborative effort between CBMRT, AHA Journals, and Wolters Kluwer. For more information, visit https://www.ahajournals.org/null-hypothesis.

Correspondence to: Christopher F. Bladin, MD, Department of Neurosciences, Eastern Health, 5 Arnold St, Box Hill, Victoria 3128, Australia. Email chris.bladin@unimelb.edu.au

*A list of all TEXAIS Investigators is given in the Supplemental Material.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.123.044568.

For Sources of Funding and Disclosures, see page 2970.

Stroke is available at www.ahajournals.org/journal/str

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

Key Words: exenatide ■ hyperglycemia ■ ischemic stroke ■ stroke ■ thrombectomy

Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
cFPG	capillary finger prick glucose
GIST-UK	Glucose Insulin in Stroke trial
GLP-1	glucagon-like peptide-1
IQR	interquartile range
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PSH	poststroke hyperglycemia
SHINE	Stroke Hyperglycemia Insulin Network Effort
TEXAIS	Treatment With Exenatide in Acute Ischemic Stroke
tPA	tissue-type plasminogen activator

Acute elevations in blood glucose are associated with adverse outcomes in many conditions, including myocardial infarction, critical illness, traumatic brain injury, and stroke. Hyperglycemia promotes cellular acidosis and oxidative stress, endothelial dysfunction, and a procoagulation/proinflammatory state.[2] Many of these effects are exacerbated by fluctuating raised glucose levels, rather than chronic hyperglycemia per se.[2]

Poststroke hyperglycemia (PSH) is reported in ≈30% to 40% of patients at admission, more in those with diabetes.[3–6] The timing of PSH is also variable—up to 30% of patients with normal blood glucose on admission may go on to develop PSH within 48 hours (or later) of stroke onset. PSH can lead to accelerated brain infarction (penumbra-into-infarction conversion) and is an independent risk factor for reduced tPA (tissue-type plasminogen activator) recanalization, with reduced plasma fibrinolytic activity, decreased reperfusion via collateral vessels, and increased risk of intracerebral hemorrhage after tPA thrombolysis.[1,2,7–9]

In patients with acute stroke, insulin-based trials to achieve tight control of glucose levels have not translated to any clinical benefits. The INSULINFARCT study reported intensive (intravenous) insulin therapy to be more effective than subcutaneous insulin therapy in controlling glucose levels but with hypoglycemia in 5.7% of patients, no difference in clinical outcomes, and some worse magnetic resonance imaging outcomes.[10] The multicenter GIST-UK trial (Glucose Insulin in Stroke) reported no significant benefits for mortality at 90 days or for secondary outcomes, with 16% requiring rescue intravenous dextrose for hypoglycemia.[11] More recently, the (SHINE) Stroke Hyperglycemia Insulin Network Effort trial enrolled 1151 patients with hyperglycemia and acute ischemic stroke within 12 hours from stroke onset, comparing intensive insulin (continuous intravenous-target blood glucose 4.4–7.2 mmol/L) versus standard insulin (subcutaneous sliding scale-target blood glucose 4.4–9.9 mmol/L) for up to 72 hours.[6] Type 2 diabetes was present in 80% of patients. Trial enrollment in SHINE was ceased early following a prespecified futility analysis.[6] Glucose control was tighter in the intensive group (mean, 6 versus 9 mmol/L) but with no significant difference in the primary outcome (modified Rankin Scale [mRS] score at 90 days), or for secondary outcomes, between the 2 groups. In 11.2% of patients in the intensive treatment group, and 3.2% in the standard treatment group, treatment was stopped early due to hypoglycemia or other adverse events.[6] These trials showed that treatment with insulin leads to hypoglycemia, may not improve outcomes, and necessitate alternative therapies to lower glucose in these high-risk patients.

An alternative to insulin-based therapies is glucagon-like peptide-1 (GLP-1) receptor agonists that stimulate the release of insulin and suppress glucagon release.[12,13] Importantly, the actions of GLP-1R agonists are highly glucose dependent—as blood glucose levels decrease, the GLP-1 activity subsides, significantly reducing the likelihood of hypoglycemia.[14,15] GLP-1 receptors are present throughout the body, including the brain. Exenatide is a rapid-onset (median 2.1 hours) GLP-1 receptor agonist, administered as a subcutaneous injection, which is lipophilic, readily crosses the blood-brain barrier, and limits glucose transport into the cerebral gray matter.[12,13] Animal studies indicate that exenatide attenuates oxidative-induced cellular apoptosis, promotes antiapoptotic proteins, and reduces brain infarct volume.[16] Importantly, this effect is independent of insulin and hence independent of glucose levels.[17] Exenatide is, therefore, potentially protective against the major mechanisms of cellular injury following stroke, both directly (anti-inflammatory/apoptosis) and indirectly (antihyperglycemia). The rapid onset of action of exenatide is favorable to target the time-critical ischemic penumbra.[14,15]

The aim of the TEXAIS randomized clinical trial (Treatment With Exenatide in Acute Ischemic Stroke) was to determine if the early use of exenatide can improve neurological outcomes by reducing the occurrence of hyperglycemia (without causing hypoglycemia) in acute ischemic stroke.

METHODS

Study Design

TEXAIS was a phase 2, international, prospective, randomized, open label, and blinded end point (PROBE [Prospective Randomized Open Blinded End-Point]) trial comparing exenatide to standard of care. The trial was undertaken at 12 hospitals across Australia, New Zealand, and Finland (Supplemental Material). The trial rationale, design, and methods have been published.[18] The trial protocol was approved by the Human Research Ethics Committee at each participating site. The trial statistical analysis plan appears in the Supplemental Material. Data will be available upon reasonable request and subject to approval by the institutional ethics committee.

Participants

All participants were enrolled after providing written informed consent. Eligible participants were ≥18 years of age, presenting with a diagnosis of acute ischemic stroke (based on clinical examination and neuroimaging), within 9 hours of stroke onset, with a blood glucose level ≥4 mmol/L (72.07 mg/dL), and a prestroke mRS score of ≤2. Wake-up patients with ischemic stroke were included with stroke onset time taken as mid-point between going to bed and waking up. There were no restrictions based on the National Institutes of Health Stroke Scale (NIHSS) score, prior stroke, glucose level at presentation to the emergency department, or diabetes status. Participants were ineligible if they had known allergy/hypersensitivity to exenatide, or they were on other GLP-1 agonists, had a history of active pancreatitis, or had impaired renal function (creatinine clearance <30 mL/min). A full list of eligibility criteria appears in the Statistical Analysis Plan (Supplemental Material).

Randomization

Eligible patients were randomized using a centralized computer-generated assignment procedure allowing for concealment of the random allocation sequence to receive either exenatide (plus standard) or standard stroke care alone in a ratio of 1:1. Randomization was stratified by the presence or absence of reperfusion therapy and baseline stroke severity according to NIHSS strata: mild, 0 to 6; moderate, 7 to 14; and severe, 15 to 42.

Procedures

Patients randomized into the treatment arm received exenatide 5 µg subcutaneously twice daily with the initial dose given within 9 hours of stroke symptom onset. Exenatide treatment was given for 5 days or until hospital discharge (whichever came first). Antiemetic therapy (metoclopramide 10 mg intravenous TID or ondansetron 4–8 mg orally or intravenous BID) was commenced with the first dose of exenatide and continued for 48 hours and then given only as needed. In patients receiving reperfusion therapy, for example, tPA or mechanical thrombectomy, exenatide was given as soon as possible following treatment. Patients with diabetes already on oral agents (other than GLP-1 agonists) or insulin could continue these medications in addition to exenatide. Patients randomized to standard care received stroke unit care as per local hospital protocols.

Hypoglycemia was capillary finger prick glucose (cFPG) defined as <4 mmol/L (<72.07 mg/dL), hyperglycemia as >7 mmol/L (>126.13 mg/dL), and abnormal HbA1c (glycated hemoglobin) as ≥6.5%. Admission glucose was measured as soon as possible after stroke onset in both groups by cFPG performed in the ambulance and emergency department. cFPG tests were taken from all participants up to 4× daily until day 7 or discharge, whichever was earlier. For patient with diabetes, hyperglycemia or hypoglycemia, any additional investigations and treatment were recommended as per guidelines.[19,20] In addition to cFPG testing, whenever possible, a continuous glucose monitoring device was inserted (Medtronic iPro2 Professional Continuous Glucose Monitor) with a continuous glucose monitoring data recorded for the first 5 days after admission (or until discharge, if sooner) in both patient groups. Clinical care was guided by the cFPG level—the continuous glucose monitoring data were for research purposes only.

Outcomes

The primary efficacy outcome was the proportion of patients with major neurological improvement at 7 days poststroke or at the time of discharge from acute care, whichever was earliest.[21] Major neurological improvement is defined as ≥8-point improvement in NIHSS or achieving NIHSS scores 0 to 1.[21] Outcome assessment was made at 7 days (or time of hospital discharge), and at follow-up at 90 days, by outcome assessors certified in NIHSS and mRS and blinded to treatment allocation. Secondary outcomes included the proportion of patients with mRS scores 0 to 2 at 90 days, NIHSS score at 90 days, and the difference in NIHSS score between baseline and 90 days poststroke.

The key safety outcomes were proportion of participants with death due to any cause at 90 days, and the proportion of participants with serious adverse events other than death at 90 days. Glucose safety outcomes focused on the treatment period (5 days or until hospital discharge or death, whichever is earlier):

- Mean daily within-patient frequency of hyperglycemia (cFPG BSL>7.0; >126.13 mg/dL)
- Mean daily within-patient frequency of hypoglycemia (cFPG BSL<4.0; <72.07 mg/dL)
- Mean daily within-patient frequency of severe hypoglycemia (cFPG BSL<3.0; <54.05 mg/dL)

Statistical Analysis

Sample size estimation was based on previous stroke trials and pooled outcome data indicating that maintenance of normoglycemia in the first 48 hours was independently associated with improved outcomes.[5] We hypothesized that achieving normoglycemia increases the proportion of major neurological improvement from 35% in the control group to 48% in the treatment group with an absolute improvement of 13%, which was considered a clinically relevant treatment effect.[5] Recruiting 528 patients would yield 80% power to observe the hypothesized treatment effect at 2-sided level of α=0.05

The trial design included a preplanned blinded adaptive sample size reestimation procedure to be conducted at the interim analysis based on the primary outcome of 320 recruited patients as per the promising zone methodology of Mehta and Pocock.[22] The conditional power was to be evaluated to allow for an increase in sample size to a predetermined upper limit

 Stroke. 2023;54:2962–2971. DOI: 10.1161/STROKEAHA.123.044568

of 650 patients. However, following disruptions to recruitment due to COVID-19, and funding constraints, the TEXAIS Executive Management Committee made a unanimous decision to finish recruitment in July 2021 with the final sample size of 350 patients and no adaptive sample size reestimation was performed.

The statistical analysis plan prespecifying all the analyses was formulated and finalized before the study data lock. The analyses were conducted using Stata ICv16 (StataCorp, College Station, TX) and R Statistical Software (v4. 1.2; R Core Team 2021). The trial is reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines. Primary and all secondary efficacy and safety outcomes analyses were conducted on a modified intention-to-treat and per-protocol basis. The modified intention-to-treat data set included all participants randomized into the study irrespective of adherence to interventions, excluding patients who withdrew consent before the primary outcome collection point. The per-protocol data set included all randomized participants who started treatment, did not have eligibility criteria violation, had a final diagnosis of ischemic stroke, received sufficient dose of the interventional drug, and had a 7-day primary outcome recorded. Receiving a sufficient dose of trial drug was defined as receiving at least 75% of the prescribed dose of exenatide up to either 5 days or discharge from acute care, or withdrawal of care/death, whichever occurred earlier.

The prespecified primary analysis compared with the proportion of patients with major neurological improvement between the 2 treatment groups using binary logistic regression adjusted for baseline NIHSS (as a continuous variable) and the presence or absence of reperfusion therapy as covariates. The treatment effect is presented as adjusted odds ratio (aOR) with respective 95% CI.

Relevant safety outcomes are presented as within-patient mean daily frequencies and described at the group level as median (50th), 25th, and 75th percentiles. Logistic regression was used for binary outcomes and quantile regression for continuous outcomes. Appropriate covariate adjustments were made for primary, secondary, and safety outcomes (Statistical Analysis Plan; Supplemental Material). Treatment effects are presented as aOR with 95% CI between-group differences in median (50th), 25th, and 75th percentiles with 95% CI.

Differences in end points between the 2 arms of the study were tested independently at the 2-tailed 0.05 level of significance with estimates of treatment effects presented with respective 95% CIs. No formal adjustments were undertaken to constrain the overall type I error associated with the secondary and exploratory analyses. Their purpose is to supplement evidence from the primary analysis to characterize the treatment effect more fully. Results from the secondary and exploratory analyses are interpreted in this context.

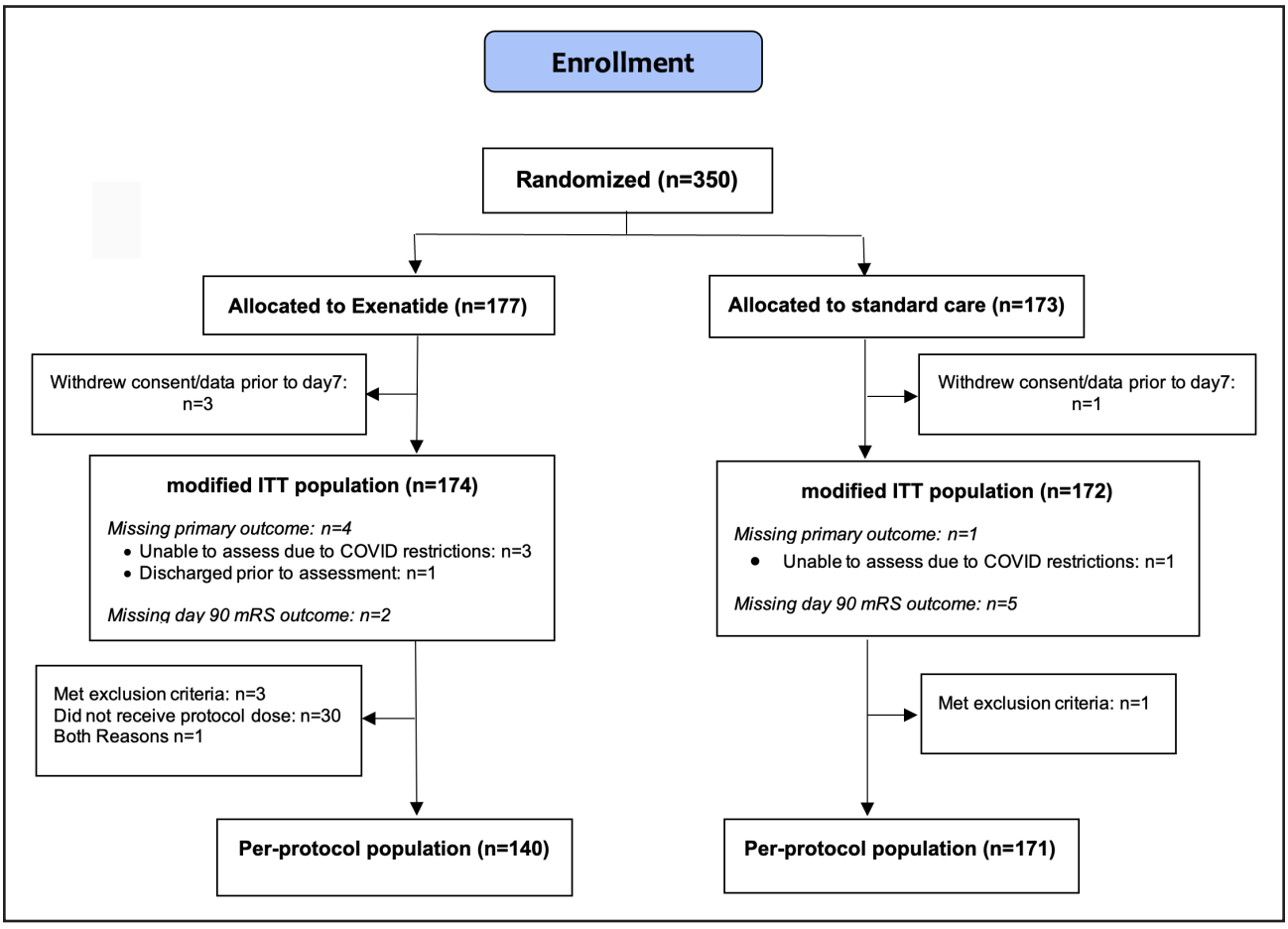

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) chart: enrollment, randomization, and follow-up.
ITT indicates intention to treat; and mRS, modified Rankin scale.

Table 1. Baseline Patient Characteristics

	Standard care (n=172)	Exenatide (n=174)
Patient age, y median (IQR)	71 (63–78)	72 (61–80)
Sex (male), n (%)	117 (68.0%)	124 (71.3%)
Ischemic stroke, n (%)	172 (100%)	174 (100%)
Cortical	77 (45.03%)	76 (43.43%)
Subcortical, n (%)	39 (22.81%)	42 (24%)
Both (cortical/subcortical)	39 (22.81%	36 (20.57%)
Brainstem or cerebellum, n (%)	16 (9.3%)	21 (12%)
Not identified, n (%)	1 (0.6%)	2 (1.2%)
Stroke etiology (TOAST criteria)		
Large artery, n (%)	40 (23.3%)	32 (18.4%)
Cardioembolism, n (%)	51 (29.6%)	57 (32.8%)
Small vessel occlusion, n (%)	37 (21.5%)	36 (20.7%)
Other/undetermined, n (%)	52 (30.2%)	39 (22.4%)
Use of reperfusion therapies (tPA, MT)		
No reperfusion therapy, n (%)	73 (42.4%)	76 (43.7%)
Any kind of reperfusion therapy, n (%)	99 (57.6%)	98 (56.3%)
Medical history		
Hypertension, n (%)	108/171 (63.2%)	99/174 (56.9%)
Type 1 diabetes, n (%)	1/172 (0.6%)	3/174 (1.7%)
Type 2 diabetes, n (%)	43/172 (25.0%)	38/174 (21.8%)
Hyperlipidemia, n (%)	79/171 (46.2%)	80/173 (46.2%)
IHD, n (%)	15/172 (8.7%)	19/174 (10.9%)
Atrial fibrillation, n (%)	45/172 (26.2%)	44/174 (25.3%)
Previous stroke, n (%)	28/172 (16.3%)	22/174 (12.7%)
Large vessel atherosclerosis, n (%)	3/172 (1.7%)	0/174 (0%)
Blood glucose level on admission (mmol/L), median (IQR), mg/dL	6.60 (5.70–8.20), 118.8 (102.6–147.6)*	6.70 (5.60–8.95), 120.6 (100.8–161.1)*
HbA1c% level on admission	5.63 (5.35–6.36)	5.54 (5.26–6.13)
Baseline NIHSS, median (IQR)	4 (2–8)	4 (2–9)
Stroke category		
NIHSS mild scores 0–6, n (%)	117 (68.0%)	118 (67.8%)
NIHSS moderate scores 7–14, n (%)	38 (22.1%)	38 (21.8%)
NIHSS severe scores 15–42, n (%)	17 (9.9%)	18 (10.3%)

HbA1c indicates glycated hemoglobin; IHD, ischemic heart disease; IQR, interquartile range; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10 172 in Acute Stroke Treatment; and tPA, tissue-type plasminogen activator.

*mg/dl.

The independent Data Safety Monitoring Safety Board regularly reviewed unblinded data after each 100 participants completed their 7-day assessment. A recommendation of early termination due to safety reasons was to be considered by the board if the corresponding Haybittle-Peto boundary (Z=3) at a given interim analysis was to be crossed. No formal interim analyses for efficacy or futility were planned. The board was notified about the decision by TEXAIS Executive Management Committee to terminate the trial in July 2021.

RESULTS

Between April 2016 and June 2021, 350 patients were randomized (median age, 71 years [IQR, 62–79]; median NIHSS score 4 [IQR, 2–8]). This represented 66% of the planned initial recruitment of 528 patients. Patient follow-up was completed in October 2021. Four patients withdrew consent and data before day 7 resulting in 346 patients in the modified intention-to-treat analysis. Five patients missed to record the primary outcome (7 days) largely because of COVID restrictions. Further exclusions (largely because of incomplete exenatide dosing) resulted in 311 patients in the per-protocol analysis (CONSORT chart; Figure 1).

The treatment groups were well balanced for baseline demographics and clinical characteristics, glucose level, diabetes status, HbA1c, stroke severity, and treatment with reperfusion therapies (Table 1). Overall, 25% of patients had a history of diabetes (4 type 1 and 81 type 2), 22% had lacunar strokes, and 68% of patients had mild stroke (NIHSS scores, 0–6). Reperfusion therapies were given in 57% of patients (tPA and mechanical thrombectomy). On admission, the baseline median glucose level was 6.70 mmol/L (120.72 mg/dL; IQR, 5.70–8.50), and 42% of patients were documented with hyperglycemia (>7 mmol/L; >126.13 mg/dL).

The median time from stroke onset to the first dose of exenatide was 405 minutes (IQR, 249.0–514.7) and from randomization to treatment initiation 32 minutes (IQR, 14.7–63.0; Table S1).

The primary efficacy outcome in the modified intention-to-treat population of ≥8-point improvement in NIHSS score (or achieving NIHSS score 0–1) at 7 days poststroke (or time of discharge, whichever earliest) was achieved in 97 of 171 patients (56.7%) in the Standard treatment group and in 104 of 170 patients (61.2%) in the exenatide treatment group (aOR, 1.22 [95% CI 0.79–1.88]; *P*=0.38; Table 2). The per-protocol analysis yielded similar results (Table S2). Prespecified subgroup analyses of the primary outcome did not demonstrate a material effect of NIHSS severity, diabetes status, or reperfusion therapy on the primary outcome (Figure 2).

For the secondary efficacy outcomes, no significant differences between treatment groups were identified (Table 2). No significant difference between treatment groups in the distribution of mRS scores at 90 days was observed (Figure 3).

Safety and Adverse Events

There were no episodes of symptomatic hypoglycemia or hyperglycemia (serious adverse events) in either group that required intervention or stopping treatment.

 Stroke. 2023;54:2962–2971. DOI: 10.1161/STROKEAHA.123.044568

Table 2. Modified Intention to Treat: Efficacy and Safety Outcomes and Adverse Events

	Standard care (n=171)	Exenatide (n=140)	Effect size (95% CI)	*P* value
Primary efficacy outcome				
≥8-point improvement in NIHSS stroke score (or NIHSS scores 0–1) at 7 d poststroke or time of discharge from acute care whichever earliest, n (%)	97 (56.7%)	104 (61.2%)	1.22 (0.79–1.88)*	0.38
Secondary efficacy outcomes				
Participants with mRS scores 0–2 at 90 d, n (%)	127 (74.7%)	125 (74.0%)	0.96 (0.56–1.66)†	0.89
NIHSS score at 90 d, median (IQR)	1 (0–2)	0 (0–2)	50th: −0.14 (−0.39 to 0.10)‡	0.26
			25th: –	…
			75th: 0.05 (−0.71 to 0.80)‡	0.90
Difference in NIHSS score between baseline and 90 d, median (IQR)	3 (1–5)	3 (1–5)	50th: 0.14 (−0.10 to 0.39)§	0.26
			25th: −0.05 (−0.83 to 0.73)§	0.91
			75th: 0 (0–0)§	0.99
Safety (and adverse events)				
Participants with death: any cause at 90 d, n (%)	8 (4.7%)	10 (5.8%)	1.21 (0.43–3.38)†	0.71
Participants with SAEs other than death at 90 d, n (%)	21 (12.2%)	16 (9.2%)	0.99 (0.93–1.06)†	0.78
Within-participant mean daily frequency of hyperglycemia episodes (cFPG>7.0) [126.0]¶ over treatment period# median (IQR) [min–max]	0.90 (0.33–2.00) [0.00–5.60]	0.60 (0.20–1.60) [0.00–6]	50th: −0.20 (−0.40 to 0)‖	0.050
			25th: −0.20 (−0.36 to −0.04)‖	0.02
			75th: 0.40 (−0.65 to −0.15)‖	0.002
Within-participant mean daily frequency of hypoglycemia episodes (cFPG<4.0) [72.0]¶ over treatment period,# median (IQR) [min–max]	0 (0–0) [0–0.75]	0 (0, 0) [0–1]	50th: NA‖	…
			25th: NA‖	…
			75th: NA‖	…
Within-participant mean daily frequency of hypoglycemia episodes (cFPG<3.0) [54.0]¶ over treatment period,# median (IQR) [min–max]	0 (0, 0) [0–0]	0 (0, 0) [0–0.20]	50th: NE‖	NE
			25th: NE‖	NE
			75th: NE‖	NE
Participants with at least 1 episode of symptomatic hyperglycemia over treatment period, n (%)	0 (0%)	0 (0%)	NE	NE
Participants with at least 1 episode of nausea and vomiting over treatment period, n (%)	0 (0%)	6 (3.5%)	0.034 (0.01–0.06)**	0.03**
Participants with at least 1 AE over treatment period, n (%)	45 (26.2%)	63 (36.2%)	1.60 (1.01–2.54)††1.62 (1.01–2.58)†	0.05, 0.04

Treatment period: 5 d or until discharge/death if earlier. AE indicates adverse event; aOR, adjusted odds ratio; cFPG, capillary finger prick glucose; IQR, interquartile range; max, maximum; min, minimum; mRS, modified Rankin scale; NA, not applicable; NE, not examinable; NIHSS, National Institutes of Health Stroke Scale; and SAE, serious adverse event.

*aOR for baseline NIHSS and reperfusion therapy.

† aOR for baseline NIHSS, age, and reperfusion therapy.

‡Difference in key quantiles adjusted for baseline NIHSS.

§Difference in key quantiles adjusted for baseline NIHSS and reperfusion therapy.

‖Difference in key quantiles adjusted for diabetes.

¶Blood glucose values given in mmol/L (mg/dL).

#The within-participant mean daily frequencies over treatment period are summarized at the group level as median (50th), 25th, and 75th percentiles, followed by min and max.

**Risk difference, Fishers exact *P* value.

††Odds ratio.

Seven patients (4 standard care groups and 3 exenatide groups) had reported adverse events of hyperglycemia treated with subcutaneous insulin (6/7 were diabetic). Deaths occurred in 10 patients (5.8%) in the exenatide treatment group and in 8 patients (4.7%) in the standard care treatment group (aOR, 1.21 [95% CI, 0.56–1.66]; *P*=0.71). One or more episodes of nausea/vomiting during the treatment period only occurred in the exenatide group (6 patients [3.5%]), but these were mild and short-lived (aOR, 0.034 [95% CI, 0.01–0.06]; *P*=0.03; Table 2).

There were no episodes of hypoglycemia (cFPG<4.0 mmol/L; <72.07 mg/dL) or severe hypoglycemia (cFPG <3.0 mmol/L; <54.05 mg/dL) in either treatment group (Table 2). The mean daily frequency of episodes of hyperglycemia (cFPG>7.0 mmol/L; >126.13 mg/dL) for each individual patient over the treatment period was significantly less in those receiving exenatide compared with the standard care group. This is expressed as a group median: 0.60 (IQR, 0.20–1.60) versus 0.90 (IQR, 0.33–2.00; Table 2).

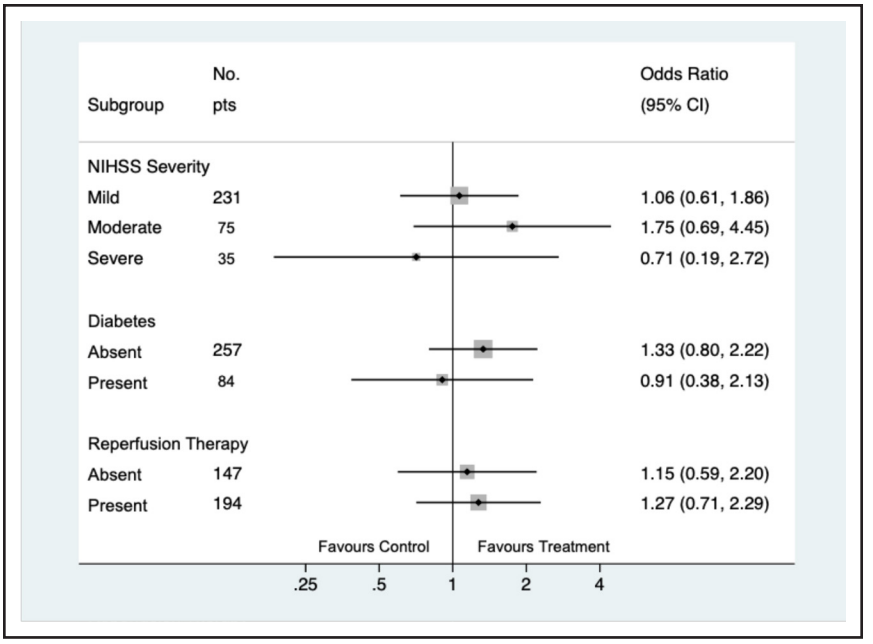

Figure 2. Primary efficacy outcome: prespecified subgroup analyses (forest plot).
P values for interaction: National Institutes of Health Stroke Scale (NIHSS) severity, *P*=0.19; diabetes, *P*=0.14; and reperfusion therapy, *P*=0.81.

The cFPG levels over the 5 days of treatment were consistently lower in the exenatide group for each 24-hour time period (Figure 4; Table 3). Data from patients' continuous glucose monitors similarly indicated significantly lower within-participant glucose levels in the exenatide group over the first 24, 48, and 72 hours (Table S3).

DISCUSSION

TEXAIS is the first phase 2 multicenter randomized clinical trial investigating the use of the GLP-1 receptor agonist exenatide, administered within 9 hours of stroke onset, in patients with acute ischemic stroke, regardless of the presence or absence of diabetes, or admission blood glucose level (cFPG). No significant differences were observed between the exenatide and standard care groups in the primary efficacy end point of early neurological improvement, mortality, or secondary efficacy end points of functional recovery at 90 days. The presence of diabetes, or admission glucose level, did not affect the primary outcome.

Importantly, the safety profile of exenatide was highly favorable with no episodes of hypoglycemia. No dextrose rescue therapy was required, despite being used in a diverse patient population in which a significant proportion were normoglycemic. The use of exenatide resulted in consistently lower daily glucose readings, and significantly fewer recorded episodes of hyperglycemia across all IQRs. Some patients (3.5%) treated with exenatide experienced nausea (and occasional vomiting), a well-described side effect of GLP-1 agonists. However, these events were mild, short-lived, and easily treated.

The detection, timing, and subsequent treatment of PSH are highly variable. In TEXAIS, the time window of 9 hours was focused on early treatment, while the ischemic

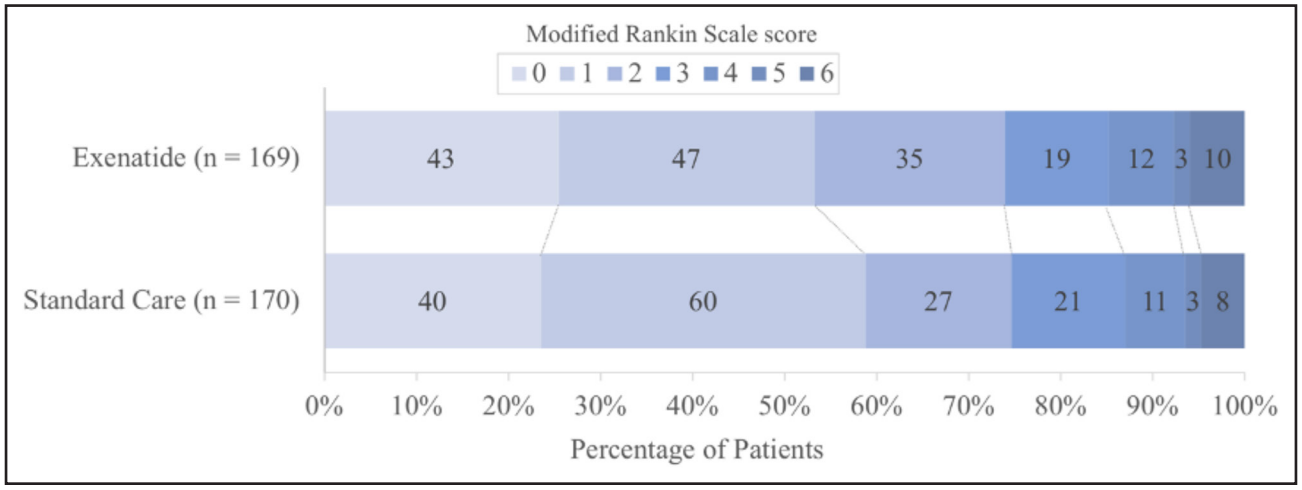

Figure 3. Bar chart showing proportion of patients in each modified Rankin Scale score by treatment arm (90 d).

 Stroke. 2023;54:2962–2971. DOI: 10.1161/STROKEAHA.123.044568

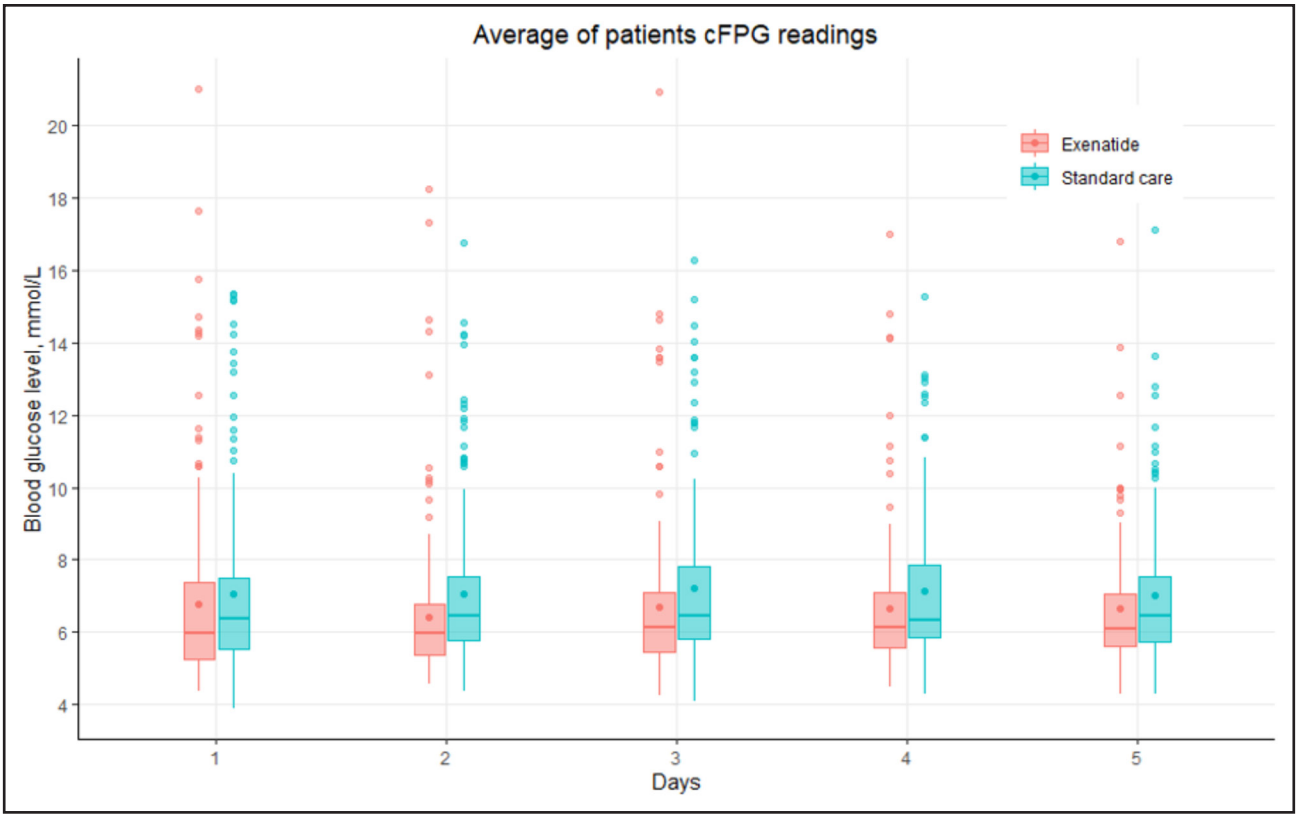

Figure 4. Blood glucose levels (capillary finger prick glucose [cFPG]) per 24 h during the treatment period (and associated Table 3).

The box plots represent daily cFPG data for each treatment group. The box shows the interquartile range, with the bottom and top indicating the 25th and 75th percentiles. The line inside the box indicates the median. The dots inside the box indicate the means.

penumbra is susceptible to the impact of hyperglycemia.[23] The median time from stroke onset to first dose was 6.7 hours, indicating that treatment was initiated early enough to achieve this. Studies using continuous glucose monitoring have identified 2 phases of PSH: an early phase within the first 8 hours and a later phase at about 66 hours poststroke.[4] Studies have demonstrated that persistent hyperglycemia on serial glucose monitoring is an independent predictor of stroke infarct expansion as measured by magnetic resonance imaging and is associated with increased short- and long-term mortality and worse functional outcome.[24,25] Interestingly, for both ischemic and hemorrhagic stroke, the serial profile of glycemic status (ie, the dynamic change over time) was a more robust indicator of stroke evolution and clinical outcome than an isolated measure of glucose on admission to hospital.[25,26]

Table 3. Blood Glucose Levels (cFPG) per 24 Hours During the Treatment Period

	Standard care (n=172)	Exenatide (n=174)
Within-participant mean cFPG on day 1, median (IQR)	6.37 (5.55–7.5); 114.7 (99.9–135.0)*	5.99 (5.25–7.37); 107.8 (94.5–132.7)*
Within-participant mean cFPG on day 2, median (IQR)	6.45 (5.78–7.55); 116.1 (104.0–135.9)*	5.95 (5.38–6.78); 107.1 (96.8–122.0)*
Within-participant mean cFPG on day 3, median (IQR)	6.44 (5.82–7.84); 115.9 (104.8–141.1)*	6.12 (5.47–7.08); 110.2 (98.5–127.4)*
Within-participant mean cFPG on day 4, median (IQR)	6.35 (5.85–7.87); 114.3 (105.3–141.7)*	6.13 (5.57–7.13); 110.3 (100.3–128.3)*
Within-participant mean cFPG on day 5, median (IQR)	6.45 (5.71–7.53); 116.1 (102.8–135.5)*	6.09 (5.60–7.07); 109.6 (100.8–127.3)*

Blood glucose values given in mmol/L. cFPG indicates capillary finger prick glucose; and IQR, interquartile range.

*Blood glucose values given in mg/dL.

The impact of PSH (and its treatment) on stroke outcomes requires more research. Studies of routine clinical stroke care have noted that glucose levels are at times not well recorded, and even when higher levels of PSH are detected (eg, glucose ≥11 mmol/l [198 mg/dL]), it may be insufficiently managed.[27] The difficulties of implementing insulin-based therapy for PSH may well underpin this. A simple-to-use, rapid-onset GLP-1 agonist, such as exenatide may, therefore, be a safe and effective alternative. Long-acting GLP-1 agonists have now become common place in the treatment of diabetes, with fewer vascular events (including stroke) in high-risk

patients on long-term follow-up.[28,29] However, for some GLP-1 agonists, the glucose-lowering effects can take several days to eventuate, which would be less beneficial in the early treatment of acute PSH.

The TEXAIS trial has several limitations. First, the sample size was constrained due to the significant impact of COVID-19 on the timelines and conduct of the study. A decision was made to not to proceed with the planned sample size reestimation and conclude the study, possibly leading to a type II error.

Second, while there were no differences in NIHSS strata between the 2 groups, approximately two-thirds of patients had mild stroke (NIHSS scores 0–6) with overall median NIHSS score of 4. The favorable natural history in this patient population may have limited the ability to demonstrate any potential benefit from exenatide in achieving the primary end point (≥8-point improvement in NIHSS [or 0–1] at 7 days). Nevertheless, the primary outcome stratified by stroke severity did not support a differential treatment effect.

Third, reperfusion rates were higher than expected (>50% of patients) but were evenly matched across the 2 groups. TEXAIS did not record brain infarct size or vessel recanalization status (after tPA and mechanical thrombectomy), all factors which could potentially impact changes in NIHSS in the 2 treatment groups. However, reperfusion therapy had no differential effect on primary outcome (Figure 2).

Fourth, TEXAIS was a pragmatic study, and while all sites were encouraged to follow standard stroke treatment guidelines, 60% of the patients were recruited by the top 3 sites, and local hospital practices may possibly have impacted generalizability of the results.

In conclusion, treatment with exenatide in routine patients with acute ischemic stroke significantly reduced the frequency of hyperglycemic events and was safe to use but did not result in a significant reduction in neurological impairment at 7 days. The favorable profile of exenatide (and possibly other GLP-1 agonists) warrants further investigation in larger clinical trials.

ARTICLE INFORMATION

Received May 13, 2023; final revision received September 19, 2023; accepted October 6, 2023.

Affiliations

Department of Neurosciences, Eastern Health and Eastern Health Clinical School, Department of Neurology, Monash University, Clayton, Victoria, Australia (C.F.B., H.M.D., P.M.C.C.). Department of Medicine (L.C.), The Florey Institute of Neuroscience and Mental Health (C.F.B., V.T., B.C.V.C.), Australian Centre for Accelerating Diabetes Innovations (L.C., E.E.), Department of Medicine and Neurology, Melbourne Brain Centre, Royal Melbourne Hospital (G.A.D., B.C.V.C., S.M.D), University of Melbourne, Parkville, Australia. Faculty of Medicine and Health, Westmead Hospital (N.W.C.) Faculty of Medicine and Health, Sydney Medical School (R.L.), University of Sydney, New South Wales, Australia. Nursing Research Institute, St Vincent's Health Network Sydney, St Vincent's Hospital Melbourne and School of Nursing, Midwifery and Paramedicine, Australian Catholic University, Sydney, Australia (S.M.). Austin Health, Australia (L.C., E.E.). Department of Neurology, Priority Research Centre for Brain and Mental Health Research, John Hunter Hospital, University of Newcastle, Newcastle, Australia (C.R.L.). George Institute for Global Health, Sydney, Australia (R.L.). Department of Neurology, Ingham Institute for Applied Medical Research, Liverpool Hospital, University of New South Wales, Sydney, Australia (M.W.P., D.C.). Department of Neurology, Helsinki University Hospital, Finland (A.M., M.T.). Princess Alexandra Hospital, Brisbane, Queensland, Australia (H.B.). Department of Neurology, Fiona Stanley Hospital, Perth, Western Australia, Australia (D.G.). Department of Medicine, St John of God Midland Public and Private Hospitals, Perth, Western Australia (P.S.). Department of Neurology, Launceston General Hospital, Tasmania, Australia (M.L.-A.). Department of Neurology, Christchurch Hospital, New Zealand (T.W., J.F.). Department of Neurosciences, St Vincent's Hospital, Melbourne, Australia (L.S.). Department of Neurology, St Vincent's Hospital, Sydney, Australia (R.M.). School of Medicine and Dentistry, Griffith University, Birtinya, Queensland, Australia (R.G.). Department of Neurology, Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Australia (C.M.).

Acknowledgments

The authors thank Fiona Ellery (Neuroscience Trials Australia) for trial management. Dr Bladin is the principal investigator. Dr Bladin is the TEXAIS (Treatment With Exenatide in Acute Ischemic Stroke) lead investigator and principal author. Dr Churilov is the TEXAIS principal statistician and directly accessed and verified the underlying data reported in this article and takes responsibility for its integrity and the data analysis.

Sources of Funding

The TEXAIS (Treatment With Exenatide in Acute Ischemic Stroke) was supported by research grant 1126070 from the National Health and Medical Research Council of Australia. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Material support from Medtronic in the use of Medtronic iPro2 Professional Continuous Glucose Monitors.

Disclosures

The authors declare no competing interests for the TEXAIS trial (Treatment With Exenatide in Acute Ischemic Stroke). Dr Grimley declares travel support from Boehringer Ingleheim. Dr Meretoja declares research funding support from Monash University. Dr Davis declares research funding support from Medtronic, Amgen, CSL Behring, AstraZeneca, and Boehringer Ingelheim. Dr Ekinci is a consultant in Eli Lilly, Australia and reports research funding support from Eli Lilly, Australia, Amgen, Boehringer Ingelheim, and Bayer. Dr Thijs is a consultant in Bayer, Boehringer Ingelheim, Medtronic, and Novo Nordisk. Dr Lee-Archer declares research funding support from Clifford Craig Foundation. The other authors report no conflicts.

Supplemental Material

Statistical Analysis Plan
TEXAIS Participating Sites
TEXAIS Trial Committees
List of Nonauthor Contributors
Tables S1–S3
Reference 30

REFERENCES

1. Kawai N, Keep RF, Betz AL, Nagao S. Hyperglycemia induces progressive changes in the cerebral microvasculature and blood-brain barrier transport during focal cerebral ischemia. *Acta Neurochir Suppl*. 1998;71:219–221. doi: 10.1007/978-3-7091-6475-4_63
2. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol*. 2010;6:145–155. doi: 10.1038/nrneurol.2009.231
3. 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. doi: 10.1161/hs1001.096194
4. Allport L, Baird T, Butcher K, MacGregor L, Prosser J, Colman P, Davis S. Frequency and temporal profile of poststroke hyperglycemia using continuous glucose monitoring. *Diabetes Care*. 2006;29:1839–1844. doi: 10.2337/dc06-0204
5. 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

6. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, Fansler A, Van de Bruinhorst K, Janis S, Durkalski-Mauldin VL; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA*. 2019;322:326–335. doi: 10.1001/jama.2019.9346
7. Pandolfi A, Giaccari A, Cilli C, Alberta MM, Morviducci L, De Filippis EA, Buongiorno A, Pellegrini G, Capani F, Consoli A. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta Diabetol*. 2001;38:71–76. doi: 10.1007/s005920170016
8. Venables GS, Miller SA, Gibson G, Hardy JA, Strong AJ. The effects of hyperglycaemia on changes during reperfusion following focal cerebral ischaemia in the cat. *J Neurol Neurosurg Psychiatry*. 1985;48:663–669. doi: 10.1136/jnnp.48.7.663
9. Ribo M, Molina CA, Delgado P, Rubiera M, Delgado-Mederos R, Rovira A, Munuera J, Alvarez-Sabin J. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622. doi: 10.1038/sj.jcbfm.9600460
10. Rosso C, Corvol JC, Pires C, Crozier S, Attal Y, Jacqueminet S, Deltour S, Multlu G, Leger A, Meresse I, et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized INSULINFARCT trial. *Stroke*. 2012;43:2343–2349. doi: 10.1161/STROKEAHA.112.657122
11. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; 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
12. Salameh TS, Rhea EM, Talbot K, Banks WA. Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochem Pharmacol*. 2020;180:114187. doi: 10.1016/j.bcp.2020.114187
13. Gejl M, Egefjord L, Lerche S, Vang K, Bibby BM, Holst JJ, Mengel A, Moller N, Rungby J, Brock B, et al. Glucagon-like peptide-1 decreases intracerebral glucose content by activating hexokinase and changing glucose clearance during hyperglycemia. *J Cereb Blood Flow Metab*. 2012;32:2146–2152. doi: 10.1038/jcbfm.2012.118
14. Smilowitz NR, Donnino R, Schwartzbard A. Glucagon-like peptide-1 receptor agonists for diabetes mellitus: a role in cardiovascular disease. *Circulation*. 2014;129:2305–2312. doi: 10.1161/CIRCULATIONAHA.113.006985
15. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705. doi: 10.1016/S0140-6736(06)69705-5
16. Kimura R, Okouchi M, Fujioka H, Ichiyanagi A, Ryuge F, Mizuno T, Imaeda K, Okayama N, Kamiya Y, Asai K, et al. Glucagon-like peptide-1 (GLP-1) protects against methylglyoxal-induced PC12 cell apoptosis through the PI3K/Akt/mTOR/GCLc/redox signaling pathway. *Neuroscience*. 2009;162:1212–1219. doi: 10.1016/j.neuroscience.2009.05.025
17. Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Powers K, Shen H, Egan JM, Sambamurti K, et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci USA*. 2009;106:1285–1290. doi: 10.1073/pnas.0806720106
18. Muller C, Cheung NW, Dewey H, Churilov L, Middleton S, Thijs V, Ekinci EI, Levi C, Lindley R, Donnan G, et al. Treatment with exenatide in acute ischemic stroke trial protocol: a prospective, randomized, open label, blinded end-point study of exenatide vs standard care in post stroke hyperglycemia. *Int J Stroke*. 2018;13:857–862. doi: 10.1177/1747493018784436
19. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, et al; QASC Trialists Group. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*. 2011;378:1699–1706. doi: 10.1016/S0140-6736(11)61485-2
20. Stroke Foundation. Australian clinical guidelines for stroke management. In: Stroke Foundation; 2022.
21. Kerr DM, Fulton RL, Lees KR, Collaborators V. Seven-day NIHSS is a sensitive outcome measure for exploratory clinical trials in acute stroke: evidence from the virtual international stroke trials archive. *Stroke*. 2012;43:1401–1403. doi: 10.1161/STROKEAHA.111.644484
22. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med*. 2011;30:3267–3284. doi: 10.1002/sim.4102
23. Garg R, Chaudhuri A, Munschauer F, Dandona P. Hyperglycemia, insulin, and acute ischemic stroke: a mechanistic justification for a trial of insulin infusion therapy. *Stroke*. 2006;37:267–273. doi: 10.1161/01.STR.0000195175.29487.30
24. Mi D, Wang P, Yang B, Pu Y, Yang Z, Liu L. Correlation of hyperglycemia with mortality after acute ischemic stroke. *Ther Adv Neurol Disord*. 2018;11:1756285617731686. doi: 10.1177/1756285617731686
25. Baird T, Parsons M, Phanh T, Butcher K, Desmond P, Tress B, Colman P, Chambers B, Davis S. Persistent post stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214. doi: 10.1161/01.STR.0000085087.41330.FF
26. Wu TY, Putaala J, Sharma G, Strbian D, Tatlisumak T, Davis SM, Meretoja A. Persistent hyperglycemia is associated with increased mortality after intracerebral hemorrhage. *J Am Heart Assoc*. 2017;6:e005760. doi: 10.1161/JAHA.117.005760
27. Drury P, Levi C, D'Este C, McElduff P, McInnes E, Hardy J, Dale S, Cheung NW, Grimshaw JM, Quinn C, et al. Quality in acute stroke care (QASC): process evaluation of an intervention to improve the management of fever, hyperglycemia, and swallowing dysfunction following acute stroke. *Int J Stroke*. 2014;9:766–776. doi: 10.1111/ijs.12202
28. Gerstein HC, Hart R, Colhoun HM, Diaz R, Lakshmanan M, Botros FT, Probstfield J, Riddle MC, Ryden L, Atisso CM, et al. The effect of dulaglutide on stroke: an exploratory analysis of the REWIND trial. *Lancet Diabetes Endocrinol*. 2020;8:106–114. doi: 10.1016/S2213-8587(19)30423-1
29. Strain WD, Frenkel O, James MA, Leiter LA, Rasmussen S, Rothwell PM, Sejersten Ripa M, Truelsen TC, Husain M. Effects of semaglutide on stroke subtypes in type 2 diabetes: post hoc analysis of the randomized SUSTAIN 6 and PIONEER 6. *Stroke*. 2022;53:2749–2757. doi: 10.1161/STROKEAHA.121.037775
30. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ*. 2011;342:d40. doi: 10.1136/bmj.d40