Stroke

ORIGINAL CONTRIBUTION

GLP-1 Receptor Agonists as Treatment of Nondiabetic Ischemic Stroke—A Systematic Review and Meta-Analysis

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BACKGROUND: Reperfusion therapies for ischemic stroke are a cornerstone of acute treatment, though only available for a subset of patients due to a narrow time window. Other supplementary treatment is warranted, as only half of the patients reach functional independence. GLP-1 RA (glucagon-like peptide-1 receptor agonists) are associated with decreased cardiovascular disease, mainly driven by reduced stroke risk, and have gained interest as therapeutic agents for stroke recovery in experimental stroke models. This review aims to evaluate the current data on the effect and safety of GLP-1 RA in nondiabetic patients with ischemic stroke and in animal models of cerebral ischemia. We will describe its potential neuroprotective mechanisms.

METHODS: On June 20, 2024, keyword-based literature searches were conducted in PubMed and Embase and repeated on March 6, 2025. Records evaluating GLP-1-based therapies in animals and patients with ischemic stroke who did not have diabetes were included.

RESULTS: In total, 35 studies, 31 preclinical and 4 clinical, applying 9 different GLP-1 therapies were reviewed. GLP-1 RA improved functional outcome and induced a marked infarct volume reduction compared with vehicle (placebo) in preclinical animal stroke models. The proposed mechanisms include reduced oxidative stress, hypoxia-triggered cell death, and inflammatory response following acute ischemic stroke. Despite these neuroprotective effects observed in stroke models, evidence for improved clinical outcomes in humans remains limited. Recent randomized trials have not shown a significant effect on stroke incidence or neurological recovery in patients without diabetes who are treated with GLP-1 RA. GLP-1 RA appears safe and well-tolerated in both acute and chronic settings.

CONCLUSIONS: GLP-1 RA improves functional outcome and reduces infarct volume in preclinical animal stroke models without diabetes. Translating these promising preclinical findings into clinical benefits remains a key challenge and a critical opportunity for future research.

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

Key Words: cardiovascular disease ■ cell death ■ incidence ■ ischemic stroke ■ neuroprotection

Rationale

Stroke is a leading cause of mortality and long-term disability worldwide. Acute ischemic stroke (AIS) contributes to ≈65% of all strokes[1] and is caused by a reduction of blood flow to the brain parenchyma, leading to decreased oxygenation, cell death, and infarct development.[2,3] The evolution of the irreversibly damaged infarct

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
CAMARADES	Collaborative Approach to Meta-analysis and Review of Animal Data in Experimental Studies
eNOS	endothelial nitric oxide synthase
GFAP	glial fibrillary acidic protein
GLP-1 R	glucagon-like peptide 1 receptor
GLP-1 RA	glucagon-like peptide 1 receptor agonist
Iba-1	ionized calcium-binding adaptor molecule 1
IL	interleukin
iNOS	inducible nitric oxide synthase
MCAO	middle cerebral artery occlusion
MMP	matrix metalloproteinase
MPO	myeloperoxidase
NF-κB	nuclear factor kappa B
PARP	poly ADP-ribose polymerase
SOD	superoxide dismutase
SPAN	Stroke Preclinical Assessment Network
STAIR	Stroke Therapy Academic Industry Roundtable
TGF-β	transforming growth factor-β
TLR	toll-like receptor
TNF	tumor necrosis factor
tPA	tissue-type plasminogen activator
TUNEL	terminal-deoxynucleotidyl transferase-mediated nick end labeling
VEGF	vascular endothelial growth factor
vWF	von Willebrand Factor

core following AIS is mostly determined by the degree of ischemia and the time between symptom onset and revascularization.[4,5]

To date, the only approved acute pharmacological treatment is thrombolysis with tPA (tissue-type plasminogen activator), aimed at dissolving the thromboembolism and preserving the impaired, yet salvageable ischemic penumbra.[6] However, globally <10% of patients with AIS receive tPA, and 2% receive endovascular thrombectomy in the case of large vessel occlusion stroke.[7] Despite the effectiveness of reperfusion therapies, only half of the treated patients reach functional independence.[8–10] Furthermore, despite successful restoration of blood flow, the infarct continues to grow due to reperfusion injuries.[11]

To improve the recovery for patients with AIS, it is of clinical importance to develop novel adjunctive agents. Treatment strategies targeting the ischemic, excitotoxic, and inflammatory cascade have the potential to prolong neuronal survival, alleviate infarct growth, reduce reperfusion injuries, protect the blood-brain barrier (BBB), and improve functional outcome, especially for tPA and endovascular thrombectomy ineligible patients.[12,13]

GLP-1 RAs (glucagon-like peptide-1 receptor agonists) are glucose-lowering anti-diabetic drugs used to treat type 2 diabetes by augmenting insulin secretion and inhibiting glucagon secretion from the pancreas in a blood glucose concentration-dependent manner with low risk of hypoglycemia.[14] Due to the weight-lowering ability, it is also used in the management of overweight and obesity.[15–17] Recent studies reveal a significantly lower risk of major adverse cardiovascular events, including stroke, with acceptable clinical safety data.[18–21]

The GLP-1 R is widely distributed in the brain.[22,23] Although the ability of the GLP-1 RAs to cross the BBB remains uncertain and may differ between compounds,[24,25] growing evidence from experimental stroke studies indicates that GLP-1 R activation can exert direct neuroprotective effects by activating antiapoptotic pathways and suppressing the harmful effects of free radicals and neuroinflammation.[26] Although the exact mechanisms by which GLP-1 R activation attenuates brain injury after AIS are not completely understood, they are likely mediated through multiple pathways.

Objectives

The aim of the review is to synthesize and examine current evidence regarding GLP-1 receptor agonists in the treatment of patients with ischemic stroke and preclinical stroke models without diabetes, with particular focus on their mechanisms of action, impacts on infarct volume, and neurological recovery. A secondary objective is to evaluate the feasibility and safety of clinical implementation in acute stroke care.

METHODS

Our study adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines. The data analyzed during the current study are available on reasonable request.

Study Protocol

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[27]

Information Sources

Studies were identified by searching PubMed and Embase databases. The initial search took place on June 20, 2024, and was repeated for an update on March 6, 2025.

Literature Search Strategy

Table 1 contains the search terms and the Boolean algorithm. To include the latest articles, the search included both controlled vocabulary (MeSH) and free-text terms, which were coupled by the Boolean operator "OR" in each PICOS (population, intervention, comparison, outcomes, and study design) category. Subsequently, the PICOS were coupled with each other by the Boolean operator "AND." Articles were retrieved for inclusion assessment by searching the reference list of relevant papers.

Eligibility Criteria

Included records comprised randomized and nonrandomized controlled trials, observational studies (case-control studies, cohort studies, and case series), and preclinical interventional in vivo animal studies (study design). These studies contained humans without diabetes who underwent a sudden onset of disabling deficits due to an AIS or animal models of ischemic stroke (population). Records were considered eligible if the patients/subjects were treated (pre, per, poststroke) with GLP-1 RA (intervention). Studies assessing neuroprotective efficacy by infarct volume reduction, improvement in neurological function or mortality, and improvement in stroke incidence or composite cardiovascular outcomes (outcome) compared with control/vehicle/placebo/sham group (comparator) were included.

Excluded records were reviews, meta-analyses, case reports, conference abstracts, letters, practice guidelines, book chapters, and unpublished studies. Studies not investigating ischemic stroke, concerning diabetes, and not applying GLP-1-based therapies as intervention were excluded. Articles focusing on hemorrhagic transformation secondary to an AIS were included, but articles only concerning hemorrhagic stroke were excluded. No restriction on animal species or stroke models was applied, and the search was limited to articles published in English with no restrictions on publication period.

Selection Process and Data Collection Process

Records were imported to Covidence systematic review software, and duplicates were removed.[28] One review author (M.K.M.) performed a title and abstract screening of each article according to predefined eligibility criteria as described above. Remaining studies were assessed in full-text eligibility screen performed independently in an unblinded standardized manner by 2 review authors (M.K.M. and R.A.B.). Any conflicts were settled by the assessment of a third author (C.Z.S. or K.R.D.).

Data Items

When available the following information was extracted and registered: first author, year of publication, country, animal species, number of animals in control and intervention (GLP-1 RA) group, strain, sex, body weight, stroke model and duration of ischemia, anesthetic protocol before ischemia, intervention (GLP-1 RA), dose and route of administration, control group, timing of administration (pre-, per-, or poststroke), GLP-1 RA mechanism of action, infarct volume, neurological outcome/deficit, stroke risk, and adverse events. Data extraction was performed by M.K.M. To ensure accuracy of data extraction, R.A.B. cross-checked the rat studies, K.R.D. the mouse studies, and C.Z.S. the clinical studies.

For preclinical studies, mean or median values with SD, SEM, or interquartile range were extracted for infarct volume and neurological outcomes in both intervention and vehicle groups. If the values were only represented graphically, the software WebPlotDigitizer (version 4.8) was used to estimate from graphs.[29] Any disagreement of individual judgements was resolved by consensus.

Table 1. Overview of the PubMed and Embase Search According to the PICOS Framework

PICOS-approach	Boolean operators used	MeSH-terms	Inclusion criteria	Exclusion criteria
Population	Stroke* OR Cerebrovascular accident* OR Apoplexy OR Brain vascular accident OR Brain vascular event	Stroke	Acute and chronic ischemic stroke in clinical and preclinical (in vivo) studies	Only other disorders (eg, hemorrhagic stroke, myocardial infarction), diabetes
Intervention	Glucagon-like Peptide-1 receptor agonists OR rGLP-1 protein OR Glucagon-like Peptide 1 receptor OR GLP-1 Receptor OR Semaglutide OR Dulaglutide OR Liraglutide OR Exendin-4 OR Exenatide OR Lixisenatide OR Albiglutide	Glucagon-like Peptide Receptors OR Glucagon-Like Peptide-1 Receptor Agonists OR Liraglutide OR Exenatide	GLP-1 receptor agonists	Drugs not related to GLP-1 as the only treatment.
Comparator	None used	None used	Control (usual ischemic stroke care), vehicle, sham, additional medications	No baseline and follow-up
Outcome	None used	None used	Changes in infarct volume and clinical symptoms. GLP-1 molecular pathways. Stroke incidence.	No baseline and follow-up
Study designs	None used	None used	Randomized and nonrandomized controlled trials, case control studies, cohort studies, case series, experimental studies	Case reports, conference abstracts, practice guidelines, unpublished studies, non-peer-reviewed journals, book chapters

GLP-1 indicates glucagon-like peptide 1; and PICOS, population, intervention, comparison, outcomes, and study design.

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Statistical Analysis for Preclinical Studies

The software Stata, version 18 (StataCorp LLC), was used to perform the meta-analysis. For infarct volume, the mean difference in percentage change between the intervention and control groups was calculated along with the corresponding SE. Functional outcome was assessed using various neurological scoring systems across the included studies; therefore, standardized mean differences were computed when different scales were used. Heterogeneity among studies was assessed using the I^2 statistic, and the random effect models using restricted maximum likelihood estimation were performed with a 95% CI. Studies were categorized into subgroups based on the specific GLP-1RAs used.

Risk of Bias Assessment

The risk of bias in each preclinical study was appraised using the modified CAMARADES (Collaborative Approach to Meta-analysis and Review of Animal Data in Experimental Studies) quality checklist, which includes the following 10 items: (1) peer-reviewed publication; (2) control temperature during procedure; (3) random allocation to treatment or control; (4) blinded conduct of ischemia; (5) blinded assessment of outcomes; (6) use of anesthetic without marked significant intrinsic neuroprotective activity; (7) animal with comorbidities (aged, or hypertensive); (8) sample size calculation; (9) statement of compliance with animal welfare regulations; and (10) statement of potential conflict of interests.[30]

Ethical Statement

This review does not contain studies performed by any of the authors.

RESULTS

Study Selection

The comprehensive PubMed and Embase searches revealed a total of 3316 entries, where 1416 remained after duplicates were removed. One thousand three hundred fourteen were rejected based on title and abstract alone, and 102 were read in full-text screening, and of these, 67 were excluded, mostly due to wrong study design (n=36) and wrong patient population (n=19). All excluded full-text studies, including the reason for exclusion, are presented in Table S1. Ultimately, a total of 35 studies, including 4 clinical and 31 preclinical, were enrolled. The selection process is presented in Figure 1.

Study Characteristics

Preclinical Studies

This review contains 31 studies investigating the efficacy of GLP-1 RA in experimental stroke models. The main characteristics are presented in Table 2.[31–61]

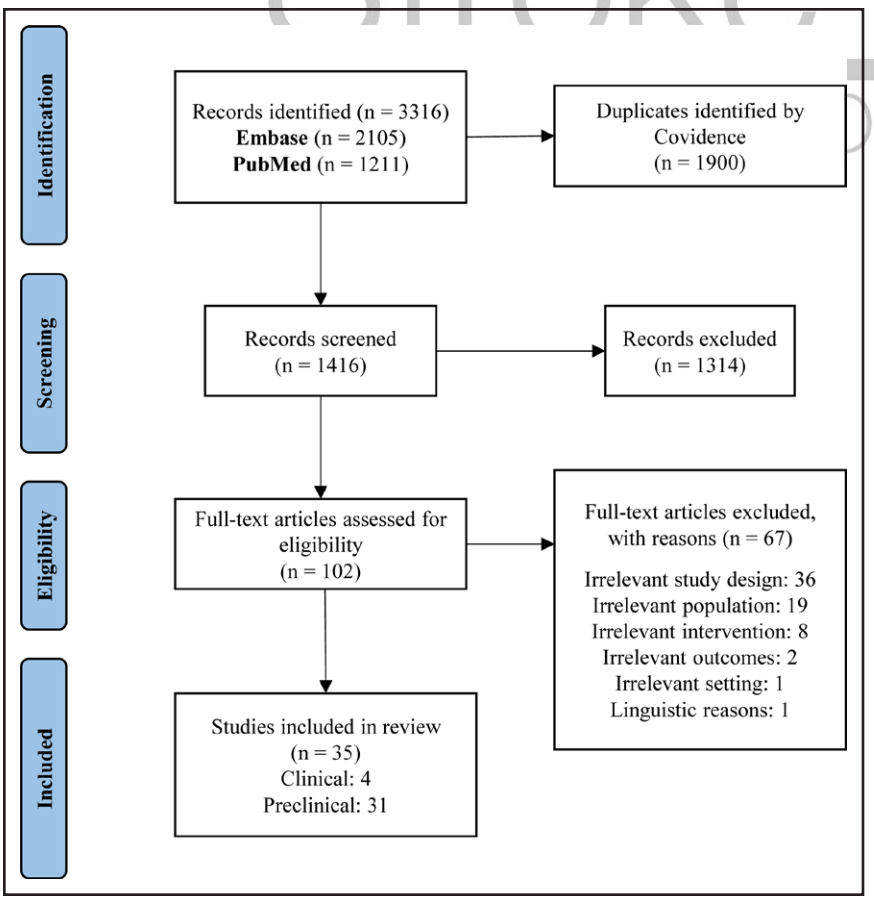

Figure 1. PRISMA flow chart of the article selection process.

Table 2. Study Characteristics (Preclinical)*

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
GLP-1 RA administered prestroke									
Zhang et al,[31] 2015	C57BL/6 mice, male, 18–22 g (n=40)	Right tMCAO (90 min). 1% pentobarbital sodium	Pro-GLP-1 i.p. 0.3 nmol/kg, 1 nmol/kg or 3 nmol/kg	Sham vehicle. GLP-1R knockdown	Once daily for 7 d	None	↓ Apoptosis (↓Bax, ↑ Bcl-2, ↓caspase-3) mediated by cAMP/PKA and PI3K/Akt pathway. No change in glucose or insulin. No neuroprotection in GLP-1 R knockdown mice (shRNA administration). Measured 24 h post MCAO	$TTC\ staining_{24h}$,‡ S: 0. V: 38.22±6.6%. $I_{(0.3)}$: 25±4.89%, ↓ 34.59%, *P*<0.01. $I_{(1)}$: 19.06±6.8%, ↓ 50.13%, *P*<0.01. $I_{(3)}$: 12.07±4.89%, ↓ 68.42%±13.91, *P*<0.01	mBS_{24h},‡ S: 0, V: 3.24±0.56. $I_{(0.3)}$: 2.43±0.47, ↓25%, *P*<0.01. $I_{(1)}$: 1.51±0.61, ↓53.47, *P*<0.01. $I_{(3)}$: 1.21±0.4, ↓ 62.5%, *P*<0.01
Zhang et al,[32] 2016, China	C57BL/6 mice, male, 18–22 g, (n=84)	Right tMCAO (90 min). 1% pentobarbital sodium (10 mg/kg i.p.)	Ex-4 i.n. or i.p: 0.5 or 5.0 µg/kg	Sham vehicle. Exendin-4 i.p. GLP-1R knockdown	Once daily for 7 d	None	Exendin-4 concentration in the ischemic penumbra: i.n>i.p. ↓ Cell death (↓caspase-3) mediated by ↑PI3K/AKT and ↑cAMP/PKA pathways in hippocampus and olfactory bulb. No change in glucose or insulin. No neuroprotection in GLP-1 R knockdown mice (shRNA administration). Measured 24 h post MCAO	$TTC\ staining_{24h}$,‡ S: 0%, $V_{(i.p)}$: 28.52±5.57%. $I_{(0.5, i.p)}$: 25.04±4.87%, ↓12.2%, *P*>0.05. $I_{(5, i.p)}$: 16.35±4.52%, ↓42.67%±7.92, *P*<0.01. $V_{(i.n)}$: 27.36±5.68%. $I_{(0.5, i.n)}$: 17.04±4.87%, ↓37.71%, *P*<0.01. $I_{(5, i.n)}$: 9.04±4.17%, ↓66.96%±6.82, *P*<0.01	Bederson's $score_{24h}$,§ S: 0. $V_{(i.p)}$: 3.25±0.43. $I_{(0.5, i.p)}$: 2.75±0.43, ↓15.38%, *P*>0.05. $I_{(5, i.p)}$: 1.75±0.43, ↓46.15%, *P*<0.01. $V_{(i.n)}$: 3.125±0.33. $I_{(0.5, i.n)}$: 1.625±0.48, ↓48%, *P*<0.01. $I_{(5, i.n)}$: 1.125±0,33, ↓64%, *P*<0.01
Briyal et al,[33] 2014, United States	Sprague-Dawley rats, male, 350 g (n=30)	Right pMCAO Ketamine/xylazine (100/10 mg/kg, i.p.)	Liraglutide s.c. 50 µg/kg	Vehicle sham	Once daily for 2 wk	None	↓ Oxidative stress (↓MDA, ↑GSH, ↑SOD). ↓ Apoptosis (↑Bcl-2, ↓Bax). Measured 24 h post MCAO	TTC_{24h}, S: 0 mm^3. V: 169±5 mm^3. I: 57±5 mm^3, ↓ 66.27%±3.12, *P*<0.05	Longa $scale_{24h}$, S: 0. V: 3.5±0.18. I: 1.75±0.16, ↓ 50%, *P*<0.001
Huang et al,[34] 2020, China	C57BL/6 mice, 8–10 wk old, weight, sex and n=N/A	Right tMCAO (60 min). 1% pentobarbital sodium	GLP-1 (9–36) i.p. 250, 500, and 1000 ng/g/d	Vehicle sham. GLP-1 R knockout mice	Once daily for 1 wk	None	↓Astrogliose (↓GFAP pos cells). ↓Cell death (↓TUNEL) 72 h post MCAO. ↓Inflammation (↓TNF, ↓IL-1β, ↓IL-6). Effects still observed in GLP-1 R knockout mice indicating GLP-1(9–36) activates IGF-1 receptor and the PI3K/AKT pathway.	TTC_{24h},‡ V: 42.98±7.99%. $I_{(250)}$: 37.13±8.38%, ↓13.61%, *P*<0.01. $I_{(500)}$: 28.16±5.85%, ↓34.48%, *P*<0.01. $I_{(1000)}$: 21.14±6.04%, ↓50.81%±16.77, *P*<0.01	$mNSS_{24h}$,‡,§ S: 0, V: 15.375±1.22. $I_{(250)}$: 14.125±1.54, ↓8.13%. $I_{(500)}$: 10.25±1.56, ↓33.33%. $I_{(1000)}$: 7.625±1.11, ↓50.41%, *P*<0.05 in all groups

(*Continued*)

Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
Murasheva et al,[35] 2024, Russia	Wistar rats, male, 220–250 g, (n=50)	tMCAO (30 min). Zoletil + Xylazine i.m.	Dulaglutide (DULA) s.c. 0.12 mg/kg	Vehicle (0.9% NaCl). MET 200 mg/kg. SGLT2i (EMPA: 2 mg/kg or CANA: 25 mg/kg	1 wk: DULA: every 72 h (3 injections in total). MET or SGLT2i: once daily	None	Neuroprotective and neurotropic properties. ↓NfL, None of the drugs significantly influenced NSE or S100BB. Vehicle: ischemic stroke is characterized by ↑NfL, ↑NSE, and ↑S100BB. Measured 48 h post MCAO. Anesthesia caused hyperglycemia which was diminished in the MET-, SGLT2i, and mostly in the DULA group. No hypoglycemia observed.	TTC staining$_{48h}$,‡ V: 16.63% (13.4–20.73). I: 3.03% (2.74–4.01), ↓80.73%±3.05, P<0.05. MET: 12.71 (6.75–23.37), ↓23.53%, P<0.05. CANA$_{(SGLT2i)}$: 8.31 (3.72–8.31), ↓50%, P<0.05. EMPA$_{(SGLT2i)}$: 5.77 (4.11–6.36), ↓65.29%, P<0.05. No significant difference between GLP-1 and SGLT2i	Garcia score$_{48h}$,‡ V: 11.99 (10.97–13.96). I: 14.98 (13.49–15.97), ↓24.94%, P<0.05. MET: 10.5 (6.46–12.5). MET and SGLT2i did not decrease deficit
Zhang et al,[36] 2016, China	C57BL/6 mice, male, adult, 18–22g (n=48)	Right tMCAO (60 min). 1% pentobarbital sodium	DMB p.o. 5 µmol/kg. Ex-4, 10 nmol/kg i.p.	Vehicle sham	30 min	None	↓ Apoptosis (↓Bax, ↑Bcl-2, ↓TUNEL). ↓ DNA damage (↓TUNEL). ↑cAMP-PKA-CREB pathway. No change in plasma insulin or glucose. Measured 24 h+7 d post MCAO	TTC staining$_{24h}$ ‡,‖ S: 0%, V: 33.33±6.67%, I$_{(DMB)}$: 17±5%, ↓49%±7.4, P<0.01. I$_{(Ex-4)}$: 15±3%, ↓55%±5.2, P<0.01. I$_{(DMB+Ex-4)}$: 11.33±3.67%, ↓66%±5.28, P<0.01	Bederson's score$_{24h}$,‖,§ V: 3.25±0.43. I$_{(DMB)}$: 1.75±0.66, ↓46.16%, P<0.01. I$_{(Ex-4)}$: 1.875±0.6, ↓42.31%, P<0.01. I$_{(DMB+Ex-4)}$: 1.375±0.48, ↓ 57.69%, P<0.01
Gad et al,[37] 2020 Egypt	Wistar rats 230–250 g, sex unknown (n=75)	Bilateral tCCAO (60 min). Chloral hydrate, 360 mg/kg	Lixisenatide i.p. 0.7 or 7 nmol/kg	Vehicle sham	Once daily for 2 wk	None	Lixisenatide: In dose-dependent manner: ↓ Neuronal damage (↑intact hippocampus CA1 neurons). ↓ Oxidative stress (↓MDA, ↑GSH, ↑SOD). ↓ Apoptosis (↓Bax, ↑ Bcl-2, ↓caspase-3). ↓Inflammation (↓neutrophil infiltration (↓MPO), ↓TLR2/4, ↓NF-kB, ↓IL-1β, ↓TNF, ↓P38, ↑ERK1/2). Measured 1 h post CCAO	Not examined	Not examined
Kim et al,[38] 2017, South Korea	Sprague-Dawley rats, male, 8 wk old, 280–300 g (n=N/A)	tMCAO (60 min). 2.0% isoflurane in 30% O_2 and 70% N_2O	Ex-4 i.c.v, 1 nmol	Vehicle, sham. Ex-9-39 (GLP-1R antagonist), i.c.v.	30 min before tMCAO	None	Ex-4: ↓Oxidative stress. ↑GLP-1 R expression. ↑cAMP (measure of GLP-1 R activation). ↓Inflammation (↓COX-2 and ↓PGE_2 through ↓JNK-↑IBI/JIPI pathway). Infarct size was also reduced significantly by GLP-1R antagonist Ex-9-39	TTC$_{0h}$‡ S: 0%, V: 31.07±1%. I: 6.78±0.71%, ↓78.18%±2.39, P<0.001. Ex-9-39: 13.38±2.06%, ↓56.93%, P<0.001. I vs Ex-9-39: ↓49.34%, P<0.01	↓ Deficits (no data presented)

(*Continued*)

Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
Briyal et al,[39] 2012, United States	Sprague-Dawley rats, male, 300–350 g (n=30)	Right pMCAO Ketamine/Xylazine (100/10 mg/kg, i.p.)	Ex-4 i.p. 0.5 µg/kg	Vehicle sham	Twice daily for 1 wk	None	↓ Oxidative stress (↓MDA, ↑GSH, ↑SOD). Measured 24 h post MCAO.	TTC_{24h} S: 0 mm^3. V: 176.6±10.4 mm^3. I: 128.3±6.1 mm^3, ↓ 27.35%±5.5, *P*<0.001	$Longa\ scale_{24h}$ S: 0. V: 4±0.3. I: 2.8±0.2, ↓ 30%, *P*<0.01
Zhang et al,[40] 2021, China	C57BL/6 mice, male, 8–10 wk old, 18–22 g, (n=N/A)	pMCAO conducted 0, 2, 4, 6, 8, or 10 d after Ex-4 cessation. 1% pentobarbital sodium	Ex-4 i.p. 5.0 µg/kg/d	Sham vehicle. GLP-1R knockdown	Once daily for 7 d	None	Extended ischemic tolerance (↑IGF-1R expression → ↑PI3K/AKT/mTOR/HIF-1α pathway → ↑GLUT-1, -3, VEGF, EPO). ↓Apoptosis (↓TUNEL, ↓caspase-3). No change in glucose or insulin. No neuroprotection in GLP-1 R knockdown mice (shRNA administration). Measured 24 h post MCAO	TTC staining,‡ S: 0% V: 28.1±4.92%. $I_{(MCAO\ 0\ d\ post\ GLP\text{-}1)}$: 12.03±5%, ↓57.19%±6.83, *P*<0.01. $I_{(MCAO\ 6\ d\ post\ GLP\text{-}1)}$: 14.97±6.15%, ↓46.72%, *P*<0.01. No infarct reduction in GLP-1 R knockdown mice.	Longa scale,§ S: 0. V: 3.25±0.43. $I_{(MCAO\ 0\ d\ post\ GLP\text{-}1)}$: 1.125±0.6, ↓65.38%, *P*<0.01. $I_{(MCAO\ 6\ d\ post\ GLP\text{-}1)}$: 1.25±0.43, ↓61.54%, *P*<0.01
GLP-1 RA administered prestroke and poststroke									
Darsalia et al,[41] 2016, Sweden	C57BL/6 (wild type) mice, 10–14 wk old. Weight=N/A (n=11)	Left tMCAO (30 min). 3% isoflurane	Chronic Ex-4 i.p. 0.1 µg/kg	Vehicle. GLP-1 R knockout mice, male, adult (10–14 wk old) weight=N/A (n=19)	4 wk	3 wk	Ex-4 mediated neuroprotection in wild type mice treated with Ex-4 chronic for 4 w before and 3 w after MCAO but not in GLP-1 R knockout mice. Measured 3w post MCAO.	NeuN immunostaining‖ $V_{(wild\ type)}$: 100±32%. $I_{(wild\ type)}$: 63.45±19.86%, ↓36.55%±12.15, *P*<0.05. $V_{(GLP\text{-}1\ R\ knockout)}$: 100±27%. $I_{(GLP\text{-}1\ R\ knockout)}$: 90.21±20.14%, ↓9.79%±10.89, *P*>0.05	Not examined
Yang et al,[42] 2022, China	C57BL/6 mice, male, adult (3 mo old) 23–29 g (n=N/A)	Right distal pMCAO. Avertin (400 mg/kg, Sigma–Aldrich)	Liraglutide s.c. 246.7 µg/kg/d	Sham vehicle	Once daily for 3 d	Once daily for 3 d	↑Cerebral blood flow (↑angiogenesis). ↓Inflammation, ↓Pyroptosis (mRNA+protein: ↓NLRP3 inflammasome, ↓Caspase1, ↓IL-1β, ↓gasdermin D). No change in blood glucose or body weight. Measured 1 d post MCAO	$TTC\ staining_{72h}$,‡ V: 13.7±3.36%. I: 8.36±1.81%, ↓38.98%±8.15, *P*<0.01	$mNSS_{24h}$,‡ V: 9±1.04, I: 7.69±1.16, ↓*14.54%*, *P*<0.05. $mNSS^{day3}$,‡ V: 7.18±1.33. I: 5.71±1.23. ↓20.4%, *P*<0.05
Lee et al,[43] 2011, South Korea	Mongolian Gerbils, male, mo 65–75 g (n=72)	Bilateral tCCAO (5 min). 2.5% isoflurane in 33% O_2 and 67% N_2O	Ex-4 i.p.0.3, 1, or 3 µg/kg	Vehicle sham	120 min	60 min	Ex-4: In a dose-dependent manner: ↓ Neuronal damage. ↓ Inflammation (↓microglial activation [↓Iba-1]). ↑ GLP-1 R expression and immunoreactivity in the CA1 hippocampal region measured 10 d post MCAO	$NeuN\ immunostaining_{day4}$ S: 78.1±2. V: 7.5±0.8. $I_{(0.3)}$: 9.1±0.75, 21.33%, *P*>0.05. $I_{(1)}$: 33±4.1 340%, *P*<0.05. $I_{(3)}$: 59.8±3.39, 697.33%±96.31, *P*<0.05	Spontaneous motor activity $_{24\ h}$ S: 127.7±8.6 m. V:336.4±14.3 m. $I_{(0.3)}$: 318.2±15.6 m, ↓5.42%, *P*>0.05. $I_{(1)}$: 242.8±13.4 m, ↓27.82%, *P*<0.05. $I_{(3)}$:186.1±12.9 m, ↓44.68%, *P*<0.05

(*Continued*)

Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
GLP-1 administered poststroke									
Han et al,[44] 2016, China	Sprague-Dawley Rats, male, weight unknown, (n=78)	Right tMCAO (60 min) 10% chloral hydrate (350 mg/kg, i.p.)	GLP-1/GIP i.p. 25 nmol/kg	Vehicle sham. GLP-1 25 nmol/kg i.p	None	60 min	GLP-1/GIP dual-RA is more neuroprotective than GLP-1 RA: ↓ Apoptosis (↓Bax, ↑ Bcl-2, ↓TUNEL). ↓ Inflammation (↓iNOS). Measured on day 1, 3, and 7 post MCAO	TTC_{24h},‖ S: 0 ; V: 28.3±4%; $I_{(GLP-1)}$: 17±4%. ↓39.93%±16.49. $I_{(GLP-1/GIP)}$: 12±6.3%. ↓57.6%±23.05. $I_{(GLP-1/GIP)}$ vs $I_{(GLP-1)}$: ↓ *29.41%*. *P*<0.05 in all groups	$Longa\ scale_{24h}$,‖ S: 0; V: 2.83±0.4; $I_{(GLP-1)}$: 2.17±0.41, ↓8.82%. $I_{(GLP-1/GIP)}$: 2±0.63, ↓15.97%. $I_{(GLP-1/GIP)}$ vs $I_{(GLP-1)}$: ↓*7.83%*. *P*<0.05 in all groups
Kuroki et al,[45] 2016, Japan	C57BL/6 mice, male, adult (10 wk old), 20–25 g (n=N/A)	Left tMCAO (60 min). 4% isoflurane, maintained at 1–1.5 % in 30% O_2 and 70% N_2O	Ex-4 i.p.1 µg	Vehicle (normal p-glucose). TIH: b-glucose > 300 mg/dL	50% dextrose (0.6 mL/kg) i.p 15 min prestroke	60 min	↓Oxidative stress. ↓Inflammation (↓neutrophil infiltration, ↓microglial activation (↓Iba-1), ↓TNF). BBB-protection (↓MMP-9 activation, ↓IgG leakage). Measured 24 h and 7 d post MCAO. TIH increased infarct volume, HT, inflammation, oxidative stress, and BBB disruption.	$Cresyl\ violet\ staining_{24h}$,‡,‖ V: 26.91±1.42 mm^3; TIH: 36.46±1.46 mm^3, ↑*35.48%*, *P*<0.001. $I_{(+TIH)}$: 23.75±1 mm^3 vs *V:* ↓11.74%, *P*>0.05 vs *TIH:* ↓*34.86%*±3.79, *P*<0.001. Day 7‡ V: 20.63±1.25 mm^3. TIH: 29.58±1.42 mm^3, ↑43.43%, *P*<0.001. $I_{(+TIH)}$: 21.25±0.83 mm^3 vs V: ↑3.03%, *P*>0.05 vs TIH: ↓28.17%, *P*<0.001	$NSS_{24\ h}$,‡,‖ V: 4.41±0.53. TIH: 8.58±0.78. ↑94.44%, *P*<0.001. $I_{(+TIH)}$: 4.41±0.93 vs V: *0%*, *P*>0.05 vs. TIH: ↓48.57%, *P*<0.001. NSS_{Day7},‡ V: 0.83±0.59, TIH: 4.18±1.3, *P*<0.01. $I_{(+TIH)}$: 1.42±1.17 vs V: 0%, *P*>0.05 vs TIH: ↓48.57%, *P*<0.01
Liu et al,[46] 2022, China	Sprague-Dawley rats, male, adult, 250–280 g (n=20)	Left tMCAO (240 min) 4% pentobarbital sodium (50 mg/kg)	Ex-4 i.v.100 µg/kg +rtPA (actilyse 10 mg/kg)	Vehicle vehicle+rtPA	None	0 min after rtPA injection	↑ BBB integrity (↑ Wnt/β-catenin signaling pathway → ↓Inflammation (↓neutrophil infiltration (↓MPO), ↓ROS, ↓ MMP-9 activation → ↓BBB tight-junction degradation →↓rtPA-induced HT)	$TTC\ staining_{24h}$,‡,‖ V: 43.51±2.73%. $V_{(+rtPA)}$: 49.97±1.4%, ↑14.86% compared with V. $I_{(+rtPA)}$: 46.66±1.57%, ↓6.62%±1.83 compared with V(+rtPA), *P*<0.05. ↓rtPA-induced infarct volume and brain edema	$Longa\ scale_{24h}$,‡,‖ V: 2.49±0.95. $V_{(+rtPA)}$: 3.49±0.9, ↑40.28% compared with V. $I_{(+rtPA)}$: 2.71±0.99, ↓22.28% compared with V(+rtPA), *P*<0.05
Yang et al,[47] 2019, China	Sprague-Dawley Rats, male, adult (3 mo) 250–300 g (n=48)	Left pMCAO. Halothane (4% for induction, 1% for maintenance) in 30% O_2 and 70% N_2O	Semaglutide i.p. 10 nmol/kg	Vehicle sham	None	120 min, then every 2. day for 1, 7, 14, or 21 d	↓ Apoptosis (↑c-raf, ↑ERK2, ↓Bax, ↑Bcl-2, ↓caspase-3). ↓ Inflammation (↓microglial activation (↓Iba-1), ↓p38 MAPK – MKK - c-Jun - NF-κB p65 pathway). ↓Neuronal loss in CA1, CA3, and dentate gyrus hippocampal region. ↑Neurogenesis, ↑Growth factor (ERK1, IRS-1). Measured day 1–21 post MCAO. No significant change in blood glucose	NeuN immunostaining,‖ ↓Lesion size at day 1 to day 21 (increased NeuN density/section representing decreased neuronal loss). Day 1 *P*<0.01. Others *P*<0.001	Significantly ↓neurological deficit (travel velocity, beam walking test, screen test, hanging wire test, grip strength test). Total distance $traveled_{day\ 21}$,‡,‖ S: 76.76±5.08 m; V: 53.63±5.95 m; I: 67.65±4.38 m 26.14%, *P*<0.05

(*Continued*)

Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
Zhang et al,[48] 2022, China	ICR mice, male, adult, 25–30 g (n=97)	tMCAO (90 min) 1.5%–2% isoflurane in 30% O_2 and 70% N_2O	Semaglutide i.p. 30 nmol/kg	Sham vehicle	None	2 h, then every 5. d	↓Inflammation (↓IL-1α, ↓TNF, ↓C1q mRNA, ↓M1 microglial polarization, and ↓ CD16/32$^+$ expression). →↓ C3d$^+$/GFAP$^+$ A1 Astrocyte. ↑S100A10$^+$ A2 Astrocyte conversion. →↓ BBB disruption/permeability (↓gap formation distance of tight junction proteins ZO-1, claudin-5, occluding) ↓IgG leakage. Measured 3 d post MCAO	Cresyl violet staining$_{72}$ h‡,‖ S: 0%. V: 63.8±8.9%. I: 44.79±12.58%. ↓29.8%±22.02, *P*<0.05. Atrophy volume$_{day2.8}$ S: 0%, V: 35.69±4.6%, I: 8.98±2.19%, *↓74.85%, P*<0.05	mNSS$_{72}$ h‡,‖ V: 6.7±0.34, I: 4.85+0.41, ↓27.61%, *P*<0.05. mNSS$_{day\ 28}$,‡ V: 5.54±0.62. I: 3.42+0.38. ↓38.27%, *P*<0.05
Chen et al,[49] 2016, China	C57BL/6 mice, male, 18-25g (n=N/A)	Right tMCAO (45 min). Ketamine/xylazine (65/6 mg/kg, i.p.)	Ex-4 t.v. 10 mg/kg	Vehicle (warfarin 2 mg/kg)	None	0 min	↓ Oxidative stress (↓HHE, ↓8-OHdG). ↓Inflammation (↓microglial activation (↓Iba-1), ↓IKK-β, ↓NF-kB, ↓TNF, ↓IL-1β), ↓Neutrophil infiltration (↓MPO). ↑ BBB integrity (PI3K/AKT-GSK-3β pathway). ↓ warfarin associated HT. Measured 72 h post MCAO	TTC$_{72\ h}$.‡,‖ V: 47±3.07 mm^3. I: 28.2±1.81 mm^3, ↓40%, *P*<0.05. V$_{(+warfarin)}$: 48.25±2.71mm^3. I$_{(+warfarin)}$: 39.94±2.53 mm^3, ↓17.23%, *P*<0.05	Neuroscore$_{72\ h}$.‡,‖ V: 3; I: 1; ↓66.67%, *P*<0.05. V$_{(+warfarin)}$: 3. I$_{(+warfarin)}$: 2, ↓33.33%, *P*<0.005
Chen et al,[50] 2018, China	CD-1 mice, male, adult 25–30 g (n=N/A)	First CCA ligation and then right distal pMCAO. Avertin (2.4 mg/10 g)	Liraglutide i.p. 100 µg/kg or 200 µg/kg	Vehicle sham	None	24 h, then once daily for 2 wk	↑ Angiogenesis (↑ VEGF), ↑Microvessel density (CD31), ↑Endothelial cell proliferation (BrdU$^+$ CD31$^+$). No change in blood glucose. CD31 was measured 14 d+28 d post MCAO. BrdU 14 d and VEGF 7+14 d post MCAO	TTC$_{Day\ 7}$.‡,‖ V: 11.61+0.42%. I$_{(200)}$: 8.32+0.19%. ↓ 28.34%±3.07, *P*<0.01. I$_{(100)}$: not examined due to no significant neurological improvement	Rotarod.‡,‖ Day 0–1: no change. Day 7: V: 22.68±1.3 s. I$_{(100)}$: 25±2.66 s, *↓10.24%, P*>0.05. I$_{(200)}$: 35.96±2.2 s, ↓58.54%, *P*<0.05
Darsalia et al,[51] 2014, Sweden	C57BL/6 mice, male, 2 mo old, weight unknown (n=128)	tMCAO (30 min). 3% isoflurane and maintained at 1.5%	Ex-4 i.p.5 or 50 µg/kg then 0.2 µg/kg/d i.p.	Vehicle	None	90,180,270 min, then once daily for 1 wk	↓Neuronal damage (in striatum not in cortex–opposite in aged mice), no protection when Ex-4 started 270 min poststroke. ↑ M2 microglial subtype (↑CD206 mRNA). No significant reduction in proinflammatory cytokine mRNA levels. Measured 7 d post MCAO for most studies. Inflammation measured 3 d post MCAO	NeuN immunostaining$_{Day}$.‡ V: 7.34±0.53 mm^3. I$_{(5)\ 3\ h}$: 8.88±1.11 mm^3, *P*>0.05. I$_{(50)\ 3\ h}$: 7.43±0.72 mm^3, ↑1.23%±12.23, *P*>0.05	Not examined

(*Continued*)

Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
Dong et al,[52] 2017, China	Sprague-Dawley rats, male, 240–270 g (n=N/A)	Right tMCAO (90 min). 1.5% pentobarbital sodium (50 mg/kg), i.p.	Liraglutide s.c. 50, 100, or 200 μg/kg	Vehicle sham	None	24 h, then once daily for 4 wk	Liraglutide: In dose-dependent manner: ↑ glucose metabolism (↑ 18F-FDG-PET accumulation in infarction measured day 1 and week 1–4). ↑ Neurovascular remodeling (↑ NeuN (neurons), ↑GFAP (glial), ↑vWF (endothelial cells) in the cerebral ischemic area at 4 wk). ↑ GLP-1R expression. Measured 4w post MCAO	NeuN immunostaining $_{week4}$.‡,‖ S: 95.41±15.8. V: 49.17±5.85. $I_{(50)}$: 60.88±6.44; 23.82%, *P*>0.05. $I_{(100)}$: 73.76±9.37; 50.01%, *P*<0.05. $I_{(200)}$: 81.95±10.54; 66.67%±11.92, *P*<0.01	$mNSS_{week1}$.‡,‖ S: 0.35±0.05. V: 11.3±1.4. $I_{(50)}$: 10.2±1.3; ↓9.73%, *P*>0.05. $I_{(100)}$: 9.3±1.6; ↓ 17.7%, *P*<0.05. $I_{(200)}$: 8.8±1.5; ↓ 24.78%, *P*<0.01. $mNSS_{week4}$.‡,‖ S: 0. V:8.9±1. $I_{(50)}$: 7.4±0.9; ↓16.85%, *P*<0.01. $I_{(100)}$: 5.4±1; ↓39.33%, *P*<0.01. $I_{(200)}$: 6.0±0.8; ↓32.58%, *P*<0.01
Mi et al,[53] 2024, China	Sprague-Dawley rats, male, adults, 280-300g (n=126)	Right tMCAO (120 min). 5% chloral hydrate (5 mL/kg), i.p.	Semaglutide 10 nmol/kg, i.p.	Vehicle sham	None	Every second day	↓Inflammation: Microglia phenotype: ↑M2 (↑CD206) and ↓M1 (↓CD68) polarization. ↓P65 (inhibition of NF-κB signaling cascade), ↓TNF, ↑TGF-β. Measured day 1, 3, and 7 post MCAO. No change in blood glucose	TTC $staining_{24h}$.‡; S: 0 (no infarction). V: 19.5+1.53%. I: 17.56+0.85%; ↓9.95%±1.28, *P*<0.01. TTC $staining_{Day\ 7}$.‡; V: 14.24+0.61%. I: 10.94+0.91%; ↓23.18%, *P*<0.001	$mNSS_{24\ h}$.‡; S: 0 (no deficit). V: 13.9+0.94. I: 9.01+1.84; ↓35.18%, *P*<0.001. $mNSS_{day\ 7}$.‡; V: 10.22+0.54. I: 6.05+1.36; ↓40.8%, *P*<0.001
Teramoto et al,[54] 2011, Japan	C57BL/6mice, male, adult (8 wk old), 20–25 g (n=81)	Left tMCAO (60 min). Pentobarbital 50 mg/kg, i.p.	Ex-4 t.v. 0.1, 1, 10, or 50 μL/100 μL	Vehicle	None	0,60,180 min	↓ Oxidative stress (↓8-OHdG, ↓HHE). ↓ Inflammation (↓ microglial activation), ↓iNOS. ↓Cell death (↓TUNEL). ↑ Intracellular cAMP, ↑pCREB. Measured 24 h, 72 h, 7 d post MCAO	Cresyl violet $staining_{24h}$.‡; V: 31.57±1.23 mm^3. $I_{(0.1)}$: 31.32±1.06 mm^3, no change. $I_{(1)}$: 28.46±3.84 mm^3; ↓9.84%, *P*>0.05. $I_{(10)}$:17.34±0.82 mm^3; ↓39.01%, *P*<0.001. $I_{(50)}$: 17.09±0.57 mm^3; ↓45.85%±2.78, *P*<0.001. Ex-4 injection 0 h post reperfusion showed the best effect.	mBS‡; V_{24h}: 2.2±0.64. $I_{(10)\ 24\ h}$: 1±0.4; ↓ 54.55%, *P*<0.05. V_{72h}: 2±0.8. $I_{(10)\ 72\ h}$: 0.81±0.65; ↓59.39%, *P*<0.05. V_{day7}: 1.6±0.47. $I_{(10)\ day7}$: 0.61±4.49; ↓62.2%, *P*<0.05

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Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
Abdel-latif et al,[55] 2018, Egypt	Wistar rats male, adult (13–14 wk old). 200–250 g (n=96)	Bilateral tCCAO (30 min). Ketamine/xylazine (50/10 mg/kg, i.p.)	Lixisenatide i.p. 1 and 10 nmole/kg	Vehiclesham. Ex9-39 (antagonist)	None	1, 24 h	↓Oxidative stress (↓MDA, ↑GSH, ↓NO, ↓catalase). ↓ Inflammation (↓TNF). ↓ Cell death (↓caspase-3). ↑CBF through vasodilation (↑eNOS) and ↑angiogenesis (↑VEGF). Effects not inhibited by GLP-1 R antagonist. Measured 1 h after last drug administration (24 h poststroke)	TTC_{24h}‡; S: 1.16±0.16%. V: 8.76±0.78%. $I_{(1)}$: 1.94±0.31%; *↓77.85%±4.05, P<0.05.* $I_{(10)}$: 3.57%±0.31%; ↓59.25%, *P<0.05.* $I_{(Ex9-39)}$: 5.57±0.47%; ↓36.42%, *P<0.05*	Garcia $score_{24h}$‡; S: 16.66±0.34. V: 6.66±0.41. $I_{(1)}$: 14.64±0.61; ↓119.68%, *P<0.05.* $I_{(10)}$: 9.77±0.54; ↓46.65%, *P<0.05.* $I_{(Ex9-39)}$: 11.19±0.68; ↓67.95%, *P<0.05*
Basalay et al,[56] 2019, United Kingdom	Sprague-Dawley rats, male, 220–250 g (n=105)	Right tMCAO (90,120, or 180 min). 2% isoflurane	Liraglutide single bolus i.v. 350, 700, 1050 µg/kg. Liraglutide s.c: 1050 µg/kg. Semaglutide s.c: 12 µg/kg	Vehicle	None	0 or 5 min before reperfusion onset	Liraglutide: dose-dependent infarct reduction. Liraglutid and semaglutide: similar neuroprotective abilities. More animals treated with semaglutide survived 72 h and no large intracerebral hemorrhages were observed. GLP-1R antagonist Ex(9–39) abolished the neuroprotective effects of semaglutide	TTC_{24h}‡; MCAO 90 min: V: 40% (34.8–46). $I_{(350)}$: 35.57% (24.4–42.6). ↓11.21%, *P>0.05.* $I_{(700)}$: 10.55% (7–23). ↓73.66%, *P<0.05.* $I_{(1050)}$: 3.95% (2.4–5.8). ↓89.94%±2.88, *P<0.001.* MCAO 120 or 180 min: no significant infarct reduction	$Neuroscore_{24h}$‡; V: 10.04 (9.48–12.54). $I_{(350)}$: 10.04 (8.02–10.79). ↓0%, *P>0.05.* $I_{(700)}$: 6.51 (4.01–7.74). ↓35.2%, *P<0.05.* $I_{(1050)}$: 1.98 (1.23–3.73). ↓80.2%, *P<0.001*
Li et al[57] 2021, China	C57BL/6J mice, male, 7–8 wk old, weight unknown, (n=24)	tMCAO (120 min) 3% pentobarbital sodium (80 mg/kg), i.p.	Liraglutide 6 µg/kg/4 h. Route of administration unknown	Vehicle	None	0 min, then every 4 h	Proteomics with differentially expressed proteins: ↓Neuronal cell death. ↓Oxidative stress. ↑Cell growth. ↓Inflammation. Measured 48 h post MCAO	$TTC\ staining_{48h}$ ↓infarct volume after cerebral ischemia-reperfusion injury (data not presented) *P<0.05*	Not examined
Sato et al,[58] 2013, Japan	Wistar rats, male, adult, 200–250 g(n=44)	Right tMCAO (90 min). 1% halothane in 69% N_2O and 30% O_2	Liraglutide i.p. 700 µg/kg	Vehicle	None	60 min	↓Oxidative stress (↓d-ROMs). ↑Angiogenesis (↑ VEGF in cortex, not in striatum) 24 h post MCAO. No significant glucose reduction 8 h post MCAO.	$TTC\ staining_{24h}$, V: 18.7±0.8%. I: 15.4±1.3%. ↓17.65%±7.79, *P<0.05*	mBS_{24h} V: 1.7±0.18, I: 1.1±0.14. ↓35.29%, *P<0.05*
Zhu et al,[59] 2016, China	Sprague-Dawley. Rats, male, 300–350 g (n=84)	Right pMCAO. Chloral hydrate (0.3 mg/kg), i.p.	Liraglutide s.c. 100 µg/kg	Vehicle sham	None	60 min, then once daily for 1, 3 and 7 d	↓Apoptosis, ↓DNA damage (↓ROS, ↓JNK, ↓p38, ↓caspase-3, -8, -9, ↓PARP, ↑Bcl-2, ↓Bax, ↓TUNEL) mediated by PI3K/AKT, ERK, and MAPK pathways). ↓Stress related hyperglycemia without causing hypoglycemia measured during and 1, 3, and 7 d post MCAO	$TTC\ staining_{72h.}$ V: 25±1.2%. I: 19.5±0.6%. ↓22%±4.45, *P<0.01.* ↓Infarct areas in brain slice 2, 3, and 4 compared with vehicle	String test $_{day7}$‡. S: 4.85 (4.58–5). V: 2.7 (1.75–2.92). I: 3 (2.75–3.33). *↓11.11%, P<0.05*

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Table 2. Continued

Author, year, country, refs.	Species, sex, body weight, number (n)	Stroke model (duration of ischemia) anesthetic	Intervention (GLP-1 RA), dosage, route of administration	Control	Timing of administration		Mechanism of action	Infarct volume compared with control group (S=sham, V=vehicle, I=intervention)	Neurological deficit† (S=Sham, V=vehicle, I=intervention)
					Prestroke	Poststroke			
He et al,[60] 2020, China	C57BL/6 mice, female, age, weight, and n=N/A	Right pMCAO. Avertin (0.4 g/kg, i.p.)	Liraglutide s.c. 246.7 µg/kg per day	Vehicle sham	None	Once daily for 1 wk	↑Axonal sprouting in both ipsi- and contralesional cortical neurons (BDA stain) assayed 14 d post MCAO (7 d post BDA injection). ↑ Mitochondrial activity (↑ICDH, α-KGDH, and SDH activity), 14 d post MCAO. ↑ATP production. ↓Oxidative stress (↑NeuN)	Not examined	↓Day 7, 14, and 28 (P<0.01). Rota-Rod testday28,‡ S: 174.3±15 s; V: 76.5±6 s; I: 107±7 s; ↓39.87%
Tu et al,[61] 2023, China	Sprague-Dawley rats, male, 250–300 g (n=180)	Right pMCAO 2% isoflurane	Liraglutide s.c. 50, 100, or 300 µg/kg. Single dose or for 3 d	Sham vehicle GLP-1R or Nrf2 knockdown	None	0 min	↑GLP-1R expression (↑Nrf2. ↓Cell death (↓caspase-1). ↓Oxidative stress. ↓Iba-1 expression. ↓Inflammation (↓microglia activation (↓NLRP3 inflammasome) → ↑M2, ↓M1 polarization). Effects abrogated in GLP-1R knockdown rats or Nrf2 knockdown. Measured 24 h and 72 h post MCAO.	TTC staining$_{24\,h}$‡ S: 0%; V: 41±3.5%; I(50): 31.89±4.86%. ↓22.22%, P<0.01 I(100): 16.22±2.97%. ↓60.44%, P<0.01 I(300): 9.73±2.43%. ↓76.27%±6.26, P<0.01	Longa scale‡ S: 0; V: 2.64±0.54; $I_{(50)}$: 2.49±0.55. ↓5.89%, P>0.05 $I_{(100)}$: 1.82±0.41. *↓31.01%, P<0.05* $I_{(300)}$: 1.47±0.58. *↓44.41%, P<0.01*

Data extracted from included articles. 18F-FDG-PET indicates 18F-fluorodeoxyglucose positron emission tomography imaging; 8-OHdG, 8-dehydroxy-2'-deoxyguanosine;cAMP, cyclic adenosine mono phosphate; CCAO, common carotid artery occlusion; COX-2, cyclooxygenase-2; DMB, 6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline; d-ROM, derivatives of reactive oxygen metabolites; Ex-4, exendin-4; GFAP, glial fibrillary acidic protein; GIP, glucose dependent insulinotropic polypeptide; GLP-1RA, glucagon-Like peptide-1 receptor agonist; GSH, glutathione; HHE=4-hydroxyhexenal; HIF-1α, hypoxia-inducible factor 1; HT, hemorrhagic transformation; i.c.v, intracerebroventricular; i.n., intranasal; i.p., intraperitoneal; IB1, islet-brain 1; ICDH, isocitrate dehydrogenase; iNOS, inducible nitric oxide synthase; JNK, C-Jun NH2 terminal kinase; MAPK, mitogen-activated protein kinase pathway; mBS, modified Bederson's score; MCAO, middle cerebral artery occlusion; MDA, malondialdehyde; mNSS, modified neurological severity score; MPO, myeloperoxidase; NeuN, neuronal nuclear antigen; NfL, neurofilament light chain; NLRP3, NOD-like receptor protein 3; NSE, neuron-specific enolase; p.o., per oral; PARP, poly ADP-ribose polymerase; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; rtPA, recombinant tissue-type plasminogen activator; s.c., subcutaneous; SDH, succinate dehydrogenase; SOD, superoxide dismutase; t.v., transvenous; t/p MCAO, transient/permanent MCAO; TGF-β, transforming growth factor beta; TIH, transient induced hyperglycemia; TLR, toll-like receptors; TNF, tumor necrosis factor; TTC, 2,3,5-triphenyltetrazolium chloride; TUNEL, terminal-deoxynucleotidyl transferase-mediated nick end labelling; VEGF, vascular endothelial growth factor; vWF, von Willebrand Factor; and α-KGDH, α-ketoglutarate dehydrogenase.

*Plus–minus values are means ±SD unless otherwise indicated.

†Functional outcomes were reported using Bederson's score, modified Bederson's score (mBS),[62] modified neurological severity score (mNSS),[63] Garcia score,[64] Longa scale,[65] RotaRod,[66] spontaneous motor activity,[67] and string test.[68] In contrast to other scoring methods, where higher neuroscores indicate greater disability, higher Garcia scores and RotaRod test results indicate better neurobehavior.

‡Values approximated using WebPlotDigitizer.

§Mean and SD values calculated from graphs.

‖Outcome assessed in a blinded manner.

The studies were performed between 2011 and 2024, and most studies took place in China (n=17). All studies were conducted on rodents, with the vast majority being performed on adult, healthy, male C57BL/6 mice (n=13), Sprague-Dawley rats (n=11), or Wistar rats (n=4), with body weights ranging from 18 to 350 g.

Nearly all studies (n=28) used the endovascular filament middle cerebral artery occlusion model (MCAO), while 3 studies performed a common carotid artery occlusion, of which 2 studies induced global (bilateral) ischemia.[43,55] Twenty-two studies induced transient cerebral ischemia lasting between 5 and 240 minutes, and 9 studies performed a persisting focal cerebral ischemia. The anesthetics used were pentobarbital (n=9), isoflurane (n=8), chloral hydrate (n=4), ketamine/xylazine (n=4), avertin (n=3), halothane (n=2), and zoletil/xylazine (n=1). The techniques used to measure the infarct volumes were 2,3,5-triphenyltetrazolium chloride staining (n=21),[69] cresyl violet staining (n=3),[70] and 5 studies used NeuN immunostaining as a proxy for neuronal loss. 2 studies did not examine infarct volumes.

In total, 9 different GLP-1 based therapies, including exenatide (n=12), liraglutide (n=10), semaglutide (n=4), lixisenatide (n=2), dulaglutide (n=1), GLP-1(9–36; n=1), GLP-1/GIP dual agonist (n=1), pro-GLP-1 (n=1), and DMB (GLP-1 R agonist and allosteric modulator of the GLP-1 R; n=1) were administered with varying dose, route (subcutaneous, oral, intranasal, intraperitoneal, intravenous, or intracerebroventricular administration), duration, and timing of administration (prestroke [n=10], poststroke [n=18], or both pre- and poststroke [n=3]). Control groups included sham, vehicle, GLP-1 R antagonist (exendin 9-39), GLP-1 R knockout/knockdown species, or additional medication (rtPA,[46] warfarin,[49] metformin, canagliflozin, empagliflozin[35]).

Primary Outcomes

Infarct Size

Twenty-nine studies examined the impact of GLP-1 RA on infarct size following nondiabetic animal models of ischemic stroke injury. Time of evaluation varied across studies (from right after reperfusion to week 3) after MCAO.

A consistent finding across the majority of studies was a significant reduction in infarct size following GLP-1-based treatment prestroke,[31–36,38–40] poststroke,[44–50,52–59,61] or both pre- and poststroke.[41–43] Moreover, a dose-response relationship was observed between GLP-1 RA administration and infarct size reduction, indicating that higher doses of GLP-1 RA may lead to more pronounced neuroprotective effects.[31,32,34,54,56,61] The reductions in infarct size following GLP-1 RA (pooled effect size; 46.3% [95% CI, 36.9–55.7]) varied substantially across studies and are visualized in Figure 2.

Two studies found no significant reduction in infarct size in the acute setting after administration of exenatide.[41,51] However, stroke volume was reduced when exenatide was chronically administered 4 weeks prestroke and 3 weeks poststroke (36.6% [95% CI, 12.7–60.4]).[41]

Additional investigations revealed that the infarct-reducing effect of GLP-1 RA could be attenuated or abolished when the treatment was administered in combination with a GLP-1 RA antagonist (Ex-9-39)[56] or in GLP-1 R knockout/knockdown species,[31,32,40,41,61] indicating GLP-1 R-dependent pathways. In contrast, a study found a significant reduction in infarct size in animals treated with GLP-1 RA, even when they were also given the GLP-1 RA antagonist (Ex-9-39), with a 56.9% reduction compared with vehicles, suggesting potential alternative mechanisms of action.[38]

Functional Outcome

Twenty-seven studies evaluated the impact of GLP-1 RA on functional outcome following nondiabetic animal models of ischemic stroke. Neurological function was examined at a variation of times (from 1 hour to 4 weeks) after MCAO using different scoring systems across studies.

In all cases, average neurological deficit scores were significantly reduced in the intervention group compared with the vehicle group, and a dose-response relationship was found, with a trend towards higher doses being associated with fewer neurological deficits.[31,32,34,43,50,52,54,56,61] The effect on functional outcome was already observed 24 hours poststroke and persisted for 28 days in some cases.[48,52,60] Ten studies showed an improved neurological function after exenatide treatment,[32,38–40,43,45,46,49,54,61] 8 after liraglutide treatment,[33,42,50,52,56,58–60] 3 after semaglutide treatment,[47,48,53] 1 after lixisenatide treatment,[55] 1 after dulaglutide treatment,[35] 1 after GLP-1/GIP dual agonist treatment,[44] 1 after pro-GLP-1 treatment,[31] 1 after DMB treatment,[36] and 1 after GLP-1(9–36) treatment[34] compared with vehicle. The neurological improvements following GLP-1 RA (standardized mean difference, −2.4 [95% CI, −3.0 to −1.9]) are visualized in Figure 3.

Secondary Outcomes

Mechanism of Action

The proposed mechanism of action is presented in Figure 4.

Eleven of the included studies investigated the effects of GLP-1-based therapies on blood-glucose levels in animals without diabetes. All studies reported no significant change in blood glucose levels, and 4 found no alterations in insulin concentrations, indicating that the observed neuroprotective effects were independent of systemic glycemic modulation, and that the risk of hypoglycemia is low.[31,32,35,36,40,42,47,50,53,58,59]

Oxidative Stress

Fourteen studies reported the effects of GLP-1-based therapies on markers of oxidative stress in ischemic stroke models. Compared with vehicles, the GLP-1-treated animals showed decreased levels of malondialdehyde,[33,37,39,55] increased glutathione,[33,37,39,55] and improved activity of SOD (superoxide dismutase).[33,37,39] Additionally, 2 studies demonstrated a reduction in reactive oxygen species,[46,59] 2 studies investigating exenatide reported lower levels of 4-hydroxy-2-hexenal and 8-hydroxy-2'-deoxyguanosine.[49,54] One study evaluating liraglutide showed a decrease in derivatives of reactive oxygen metabolites,[58] and 1 study found that lixisenatide improved catalase activity and reduced NO compared with vehicle groups.[55] These findings suggest associations between GLP-1-based therapies and reduced oxidative stress markers, but do not establish direct mechanistic evidence.

Cell Death

Fifteen studies investigated the effects of GLP-1-based therapies on dysregulated cell death following ischemic stroke. In GLP-1-treated animals, increased expression of the antiapoptotic protein Bcl-2 and reduced expression of the proapoptotic protein Bax were observed compared

ORIGINAL CONTRIBUTION

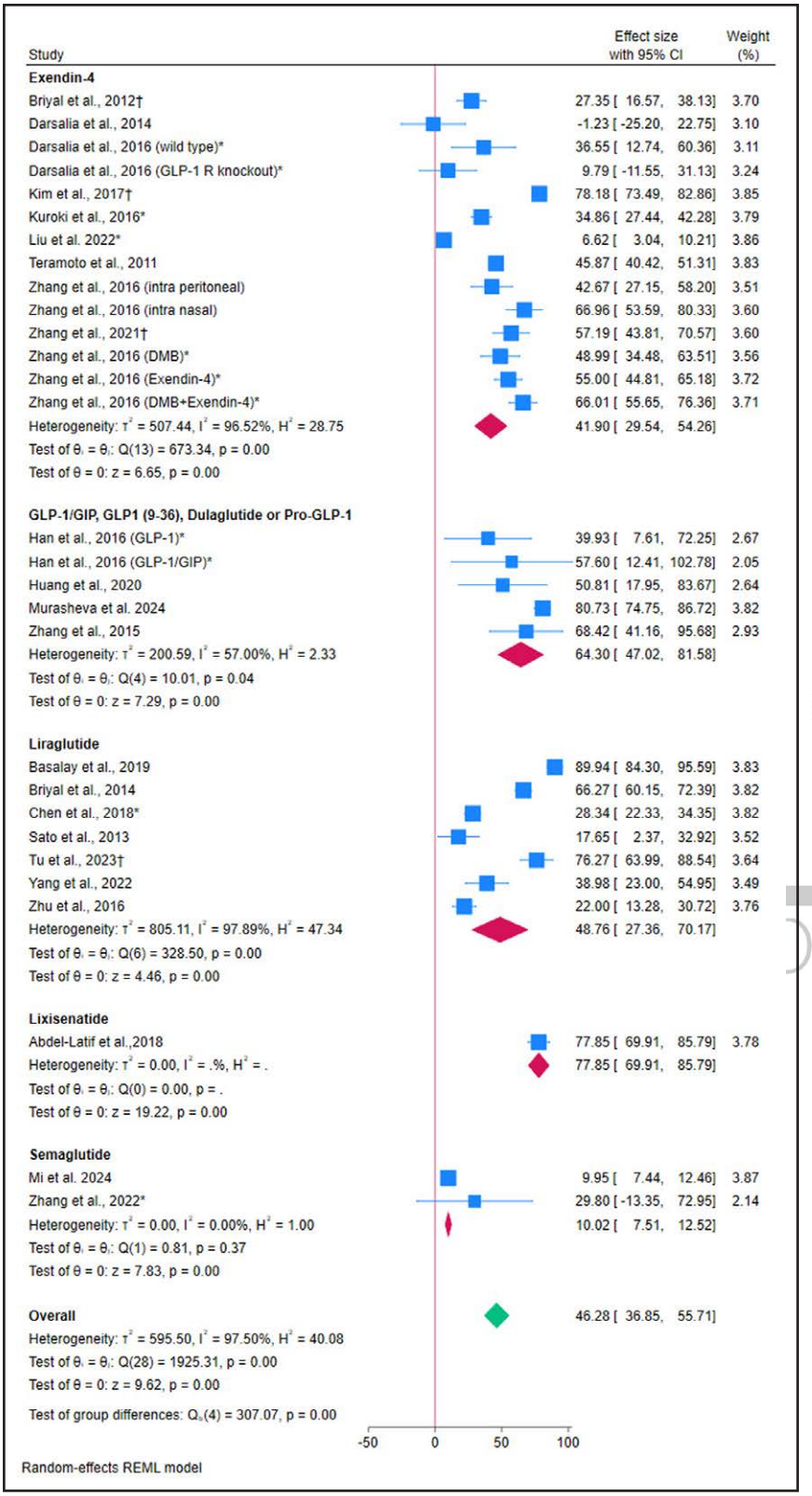

Figure 2. Forest plot on mean percent infarct volume reduction in preclinical studies.
Effect sizes represent the mean percent reduction with corresponding standard errors. A random-effects model using restricted maximum likelihood (REML) estimation was applied. The pooled effect size is shown with a 95% CI. *Outcome assessed in a blinded manner. †High risk of bias according to CAMARADES (Collaborative Approach to Meta-analysis and Review of Animal Data in Experimental Studies) checklist. GLP-1 R indicates glucagon-like peptide 1 receptor.

with vehicle.[31,33,36,37,44,47,59] Seven studies showed down-regulation of caspase-3 protein,[31,32,37,40,47,55,59] 2 studies reported that liraglutide reduced caspase-1 activity,[42,61] and 1 study demonstrated a reduction in PARP (poly ADP-ribose polymerase).[59] In 6 studies, GLP-1 treatment was associated with a reduced number of terminal-deoxynucleotidyl transferase-mediated nick end labeling (TUNEL)-positive cells compared with

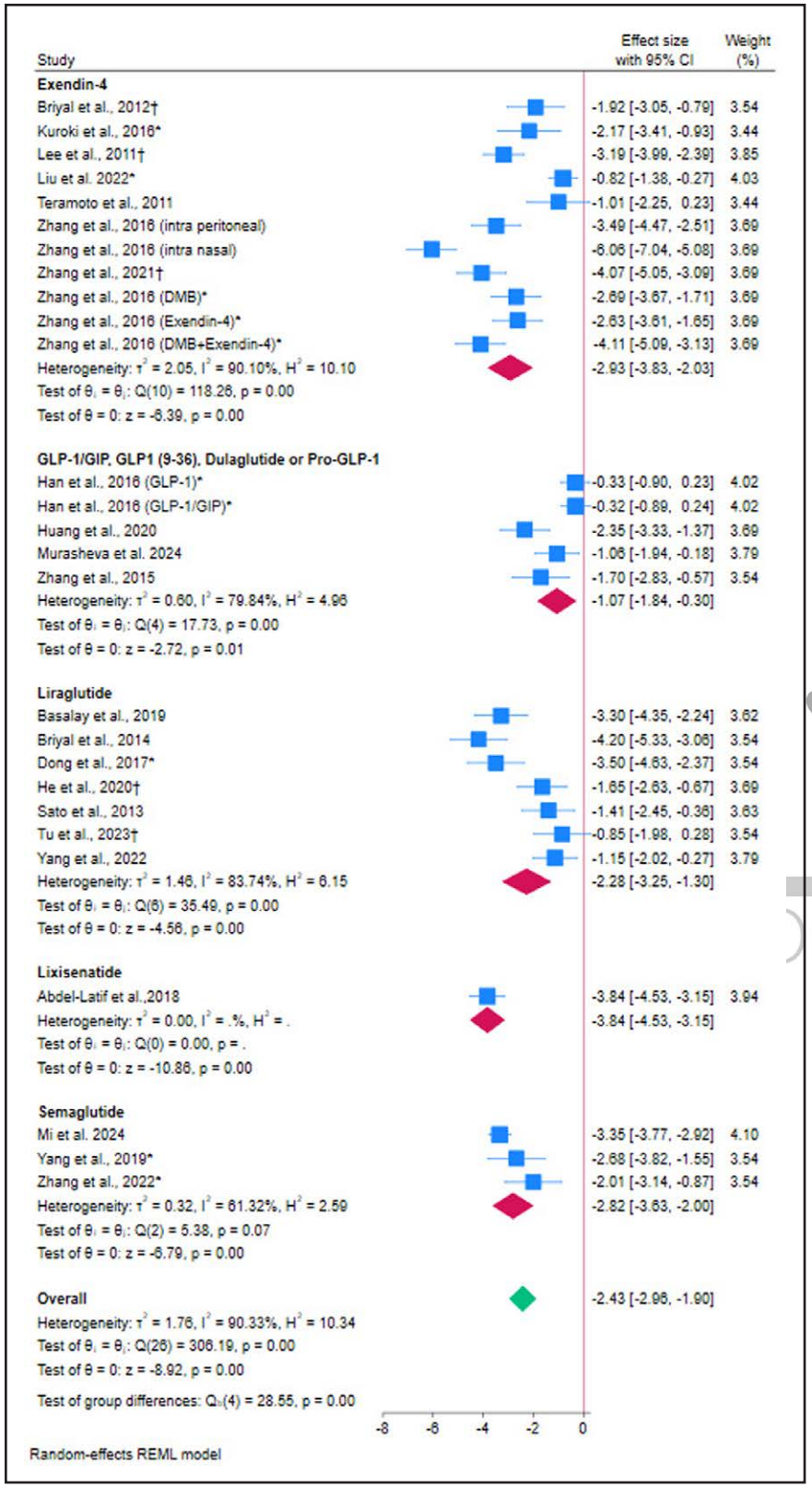

Figure 3. Forest plot on standardized mean change in neurological outcome score in preclinical studies. Effect sizes represent the mean change in standardized neurological outcome with corresponding standard errors. A random-effects model using restricted maximum likelihood (REML) estimation was applied. The pooled effect size is shown with a 95% CI. *Outcome assessed in a blinded manner. †High risk of bias according to CAMARADES (Collaborative Approach to Meta-analysis and Review of Animal Data in Experimental Studies) checklist. GLP-1 R indicates glucagon-like peptide 1 receptor.

vehicle.[34,36,40,44,54,59] Although these observations suggest associations between GLP-1 treatment and changes in markers related to different modes of cell death, it should be emphasized that these markers are not specific and cannot accurately distinguish between different cell death pathways: caspase-1 activation is linked to pyroptosis, PARP activity to parthanatos, and TUNEL positivity can occur in both apoptotic and necrotic cells.[71–73]

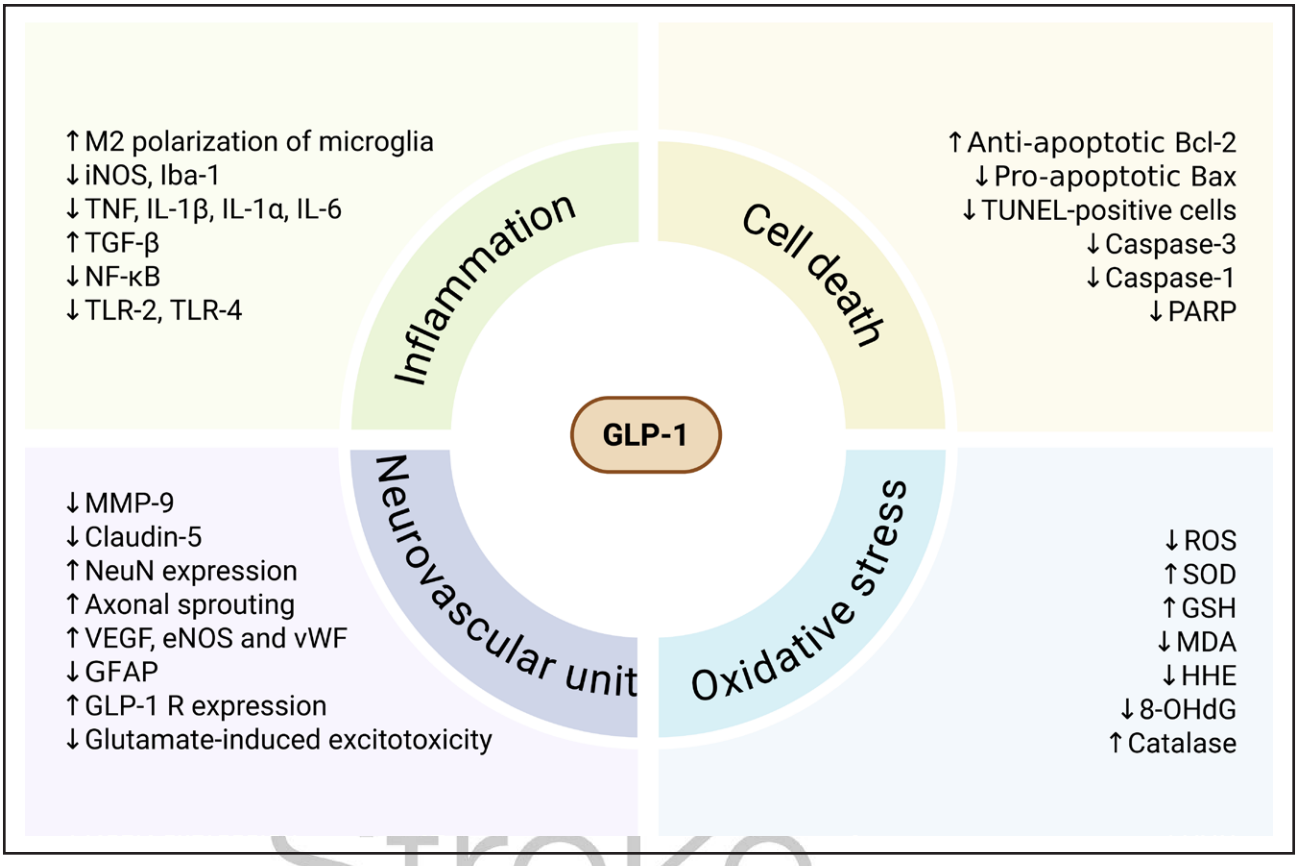

Figure 4. Proposed Mechanisms of Action for GLP-1 RA (glucagon-like peptide 1 receptor agonist).
Ligand binding (eg, semaglutide, liraglutide, exenatide) to the G-protein-coupled GLP-1 receptor triggers several downstream signaling cascades, including cAMP/PKA/CREB and PI3K/Akt pathways involved in neuroprotection. Created in BioRender.com. 8-OHdG indicates 8-hydroxy-2'-deoxyguanosine; eNOS, endothelial nitric oxide synthase; GFAP, glial fibrillary acidic protein; GSH, glutathione; HHE, 4-hydroxy-2-hexenal; IL, interleukin; iNOS, Inducible nitric oxide synthase; MDA, malondialdehyde; NF-κB, nuclear factor kappa B; PARP, poly ADP-ribose polymerase; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF tumor necrosis factor; VEGF, vascular endothelial growth factor; and vWF, von Willebrand factor.

Inflammation

Sixteen studies evaluated the anti-inflammatory effects of GLP-1-based therapies in ischemic stroke models. GLP-1 modulates the microglial polarization by downregulating the proinflammatory M1 phenotype while promoting the anti-inflammatory M2 phenotype.[43,45,48,49,51,53,54,61] iNOS (inducible nitric oxide synthase), a marker of the proinflammatory M1 phenotype, was suppressed by GLP-1/GIP[44] and exenatide,[54] and Iba-1 (ionized calcium binding adaptor molecule 1) was attenuated by exenatide[43,45,49] and semaglutide.[47] The GLP-1 treated animals showed increased production of the anti-inflammatory cytokines, including TGF-β (transforming growth factor-beta),[53] and reduced amounts of proinflammatory cytokines, including TNF (tumor necrosis factor),[34,37,45,48,49,53,55] IL-1β (interleukin-1β),[34,37,42,49] IL-1α (interleukin-1α),[48] and IL-6 (interleukin-6),[34] compared with vehicle. Four studies reported reduced neutrophil infiltration in brain tissue,[45] measured by an attenuation of MPO (myeloperoxidase).[37,46,49] Exenatide, lixisenatide, and semaglutide diminished the mRNA expression of inflammatory mediators, such as NF-κB (nuclear factor kappa B),[37,47,49,53] and semaglutide also mitigated the expression of TLR-2 (toll-like receptor 2) and TLR-4 (toll-like receptor 4).[37] Collectively, these findings indicate associations between GLP-1-based therapies and inflammatory markers, but do not prove causality.

BBB and Endothelial Function

Markers of BBB integrity preservation were observed in 4 studies.[45,46,48,49] Specifically, 2 studies reported that exenatide decreased expression of MMP-9 (matrix metalloproteinase-9) when administered after tMCAO,[45,46] while 1 study demonstrated that semaglutide reduced the levels of claudin-5.[48] Additionally, 1 study reported increased NeuN expression,[52] and 1 study described enhanced axonal sprouting compared with vehicle, which could suggest neuronal plasticity and regenerative potential.[60] GLP-1 receptor activation was shown to increase expression of VEGF (vascular endothelial growth factor),[42,50,55,58] suggesting promotion of angiogenesis, and possibly enhance endothelial function by upregulating eNOS (endothelial nitric oxide synthase)[55] and vWF (von

Willebrand factor)[52] compared with vehicle. One study showed that the VEGF level of liraglutide-treated rats was significantly increased in the cortex, but not in the striatum, compared with that of control rats.[58]

Three studies examining liraglutide, GLP-1 (9–39), and semaglutide in tMCAO stroke models showed decreased expression of GFAP (glial fibrillary acidic protein), indicating reduced astrocyte activation and gliosis.[34,48,52] Four studies reported increased expression of the GLP-1 Rs in the brain, suggesting that treatment may sensitize neural tissue to GLP-1 signaling and potentially amplify neuroprotective responses.[38,43,52,61]

Risk of Bias in Studies

The CAMARADES scores varied from 3 to 7 across the included studies, and the median score was 5, indicating moderate methodological rigor. The study quality scores are presented in Table S2.

Among the assessed domains, peer-reviewed publication (100%), random allocation to treatment or control (61.3%), reporting of potential conflicts of interest (83.9%), and a statement of compliance with animal welfare regulations (96.8%) were the most consistently reported. In contrast, key indicators of methodological robustness, such as blinded conduct of ischemia (19.4%), sample size calculation (3.2%), and use of animals with comorbidities (6.5%), were infrequently described. Only 33.3% of the studies reported blinded outcome assessment, raising concerns about potential detection bias.

Regarding confounding factors, 67.7% of the studies mentioned adequately reported control of body temperature during procedures using heating pads, and 61.3% used anesthetics without known neuroprotective effects.

Clinical Studies

Four clinical studies met the predefined inclusion criteria for this review. Three randomized controlled trials and 1 retrospective cohort study were included. The main characteristics are presented in Table 3.[74–77]

The SELECT trial, a large, randomized, double-blind, placebo-controlled study including over 17 000 overweight or obese patients with established cardiovascular disease but without diabetes, demonstrated a significant 20% reduction in the composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients receiving 2.4 mg semaglutide weekly for a mean duration (+SD) of 33.3±14.4 months (hazard ratio, 0.8 [95% CI, 0.72–0.9]; $P<0.001$).[76] These benefits were accompanied by a considerable decline in body weight, waist circumference, blood pressure, and inflammation, with a 37.8% reduction in C-reactive protein. However, semaglutide did not significantly reduce the risk of nonfatal stroke (hazard ratio, 0.93 [95% CI, 0.74–1.15]). No significant difference in the rate of serious adverse events between the semaglutide and placebo groups, and no increased risk of hypoglycemia was observed.

A large retrospective cohort study examined over 24 000 propensity-matched individuals with obesity but without diabetes over 5 years.[75] GLP-1 RA treatment was associated with a 47% lower risk of stroke. In subgroup analyses, semaglutide was associated with a 50% reduction in stroke risk, whereas liraglutide reduced stroke risk by 44%. In contrast, dulaglutide showed no significant stroke reduction compared with control. Additionally, GLP-1 RA treatment was associated with a significantly lower risk of all-cause mortality (hazard ratio, 0.23 [95% CI, 0.15–0.34]). GLP-1 RAs were generally well tolerated with no increased risk of hypoglycemia.

In the TEXAIS trial, an international, multicenter, phase 2 prospective randomized open-label blinded end point (PROBE) study, 346 patients with AIS were randomized to receive exenatide 5 µg twice daily for up to 5 days, initiated within 9 hours of symptom onset, or control.[74] Primary outcome was defined as ≥8-point improvement in National Institutes of Health Stroke Scale score, or National Institutes of Health Stroke Scale score of 0 to 1 at day 7. Neurological outcome did not differ significantly from standard care (61.2% versus 56.7%; $P=0.38$). However, exenatide significantly reduced the frequency of poststroke hyperglycemia without causing hypoglycemia, suggesting a favorable safety profile and glucose-stabilizing effect, even among patients with normoglycemia.

A Swedish open-label RCT was the first to assess the feasibility and safety of GLP-1 therapy in the prehospital management of AIS.[77] Single-dose subcutaneous exenatide 10 µg was administered to patients with moderate hyperglycemia (8–15 mmol/L) and suspected AIS. Only 19 of the intended 42 patients were enrolled over 5 years, and the study was terminated early due to low recruitment rates. Though underpowered with only 8 patients receiving exenatide, the study suggests that early GLP-1 RA administration was safe, well-tolerated, and did not cause hypoglycemia.

DISCUSSION

This review examined the potential of GLP-1 RAs as a therapeutic strategy for AIS in nondiabetic individuals, synthesizing evidence from 31 preclinical and 4 clinical studies.

We found that GLP-1 RAs reduced infarct size and improved neurological function compared with vehicle (placebo) in animal models.

Although the exact mechanisms by which GLP-1 RAs mitigate ischemic injury are not fully understood, the pleiotropic mechanisms seem to extend beyond glycemic regulation, with beneficial effects observed in nondiabetic animal models. The findings of this review indicate that GLP-1RAs exert promising direct neuroprotective properties by targeting multiple components of the ischemic

Table 3. Study Characteristics (Clinical)

Author, year, country, refs., study design	Sample size (n), sex (m, f), mean age	GLP-1 RA, dose, route of administration, duration	Control	Timing of initial dose post-stroke	Reperfusion therapy	Outcome	Adverse events
Bladin et al,[74] 2023, TEXAIS, Australia, International, multicenter, PROBE, phase 2 trial	(n=346, f=105) Age: 71 Median NIHSS: 4	Exenatide (n=174) 5 µg, s.c. BID. duration: 5 d DM (n=41)	Standard AIS care (n=172) DM (n=44)	Patients with AIS <9 h from onset. Median time: 6.8 h	Exenatide group n=98 Control group n=99	$NIHSS_{(day\ 7)}$ improvement ≥8-point (or NIHSS 0–1) Exenatide: 61.2%. Control: 56.7%. aOR. 1.22 (95% CI, 0.79–1.88); *P*=0.38 OR for favorable outcome mRS score of 0–2 at 90 d: 0.96 (0.56–1.66), *P*=0.89	$Death_{(day\ 90)}$: exenatide n=10 Control n=8 aOR: 1.21 (95% CI, 0.56–1.66); *P*=0.71 One episode of nausea/vomiting: aOR, 0.034 [95% CI, 0.01–0.06]; *P*=0.03 Hypoglycemia (<4 mmol/l; n=0)
Huang et al,[75] 2024, China, Propensity matched observational retrospective cohort study using the TriNetX research network	(n=24 246, f=19 545) Age: GLP-1 RA: 42.9±13 y Control: 41.6±15.3 y	Semaglutide 162±42.8 d Liraglutide 174±26.2 d Dulaglutide 112.1±59.3 d (n=12 123, f=80%)	Standard care (n=12 123, f=81%)	Inclusion: non-diabetic patients with obesity	NA	All-cause mortality: 5-year HR: 0.23 (95% CI, 0.15–0.34); *P*<0.001 Stroke risk: all GLP-1 RA: HR, 0.53 (95% CI, 0.40–0.69) Semaglutide: HR, 0.5 (95% CI, 0.37–0.66) Liraglutide: HR, 0.56 (95% CI, 0.38–0.84) Dulaglutide: no significant stroke reduction	No statistically significant risk of thyroid cancer, pancreatitis, pancreatic cancer, or hypoglycemia was observed.
Lincoff et al,[76] 2023, USA, SELECT, Multicenter, double-blind, RCT in 41 countries	(n=17 604, f=4872, 28%) Age: 61.6±8.9	Semaglutide 2.4 mg s.c. Once weekly(n=8803) Mean duration 33.3±14.4 mo History of stroke: n=1578 (17.9%)	Placebo (n=8801) History of stroke: (n=1556, 17.7%)	Inclusion: preexisting CVD, BMI >27, no DM Follow-up: 39.8±9.4 mo	NA	Cardiovascular composite end point: HR, 0.8 (95% CI, 0.72–0.90); *P*<0.001 Nonfatal stroke: semaglutide: n=154 (1.17%) Placebo: n=165 (1.9%) HR, 0.93 (95% CI, 0.74–1.15) Body weight: ↓8.51% (95% CI, 8.27–8.75) No data on events in patients were included based on the stroke inclusion criteria	Discontinuation due to AE: semaglutide: 1461 (16.6%) Control: 718 (8.2%) *P*<0.001 No data on events in patients were included based on the stroke inclusion criteria
Larsson et al,[77] 2019, Sweden, Open label RCT	(n=19, f=9) Age: Control: 80 (63–89) exenatide: 71 (54–82) 4 stroke mimics 2 ICH	Exenatide (n=8) 10 µg s.c., single dose NIHSS score: 4.5	Standard care (n=11) NIHSS: 1	Prehospital (in ambulance)	1 (in control group)	No difference in p-glucose at 4 h (7.6±1.6 vs 7.0±1.9; *P*=0.56) No hypoglycemia observed Study prematurely stopped due to slow inclusion.	No major adverse events Mild nausea/vomiting (1 in the exenatide group)

Data extracted from included articles. AIS indicates acute ischemic stroke; aOR, adjusted odds ratio; BID, bis in die (twice daily); BMI, body mass index; CVD, cardiovascular disease; DM, diabetes; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PROBE, prospective randomized open label blinded end point.

cascades triggered after stroke that contribute to infarct consolidation and poor functional outcome.

The most consistently reported mechanisms preclinically are attenuation of oxidative stress, dysregulated cell death, and inflammation following AIS. In addition, GLP-1 increases the cerebral blood flow through arteriolar vasodilation, promotes angiogenesis via upregulation of VEGF, and protects the BBB integrity.

In several of the included studies, reduced infarct size was accompanied by a reduction in oxidative stress, cell death markers, or inflammatory mediators, but these observations are largely associative and do not establish causality. Direct evidence for the putative mechanisms, such as experiments using pathway-specific knockdown, overexpression, or pharmacological inhibition, is still limited, and the specific contribution of individual pathways should be interpreted with caution.

The BBB is essential for preserving central nervous system homeostasis by restricting the entry of harmful substances while allowing vital nutrients to pass.[78] Whether all GLP-1 RAs can penetrate the BBB is still under debate.[79] Small but pharmacologically relevant

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amounts have been suggested to access the brain via saturable transport mechanisms,[80] but direct evidence for central penetration, particularly of larger molecules like semaglutide, is absent. Given its molecular size and structure, passive diffusion across an intact BBB appears unlikely. However, under pathological conditions such as stroke or small vessel disease, where the BBB integrity may be compromised, large GLP-1 RAs could potentially penetrate and gain access to brain regions. Semaglutide has been reported to reach areas such as the brainstem, septal nucleus, and hypothalamus through interactions with ventricular and circumventricular regions that exhibit increased permeability.[25] Further studies are required to determine whether GLP-1 RAs can access the brain under physiological conditions.

The effects on reduced infarct size and improved functional outcome are likely mediated through activation of the GLP-1 R, which is widely expressed in the central nervous system and brain vasculature.[81] When activated, the GLP-1 R modulates several downstream signaling pathways, including cAMP/PKA and PI3K/Akt, both essential for neurosurvival, although evidence also indicates the involvement of GLP-1 R-independent pathways.[38]

GLP-1 RAs are suggested to exert anti-thrombotic and vascular protective effects through enhanced NO bioavailability, mediated by cAMP/PKA-dependent activation of eNOS, leading to reduced platelet aggregation and thrombosis formation.[82] GLP-1 RAs have been shown in animal models to reduce inflammation, improve endothelial and left ventricular function, and enhance plaque stability.[83] In humans, it is associated with modulation of cardiovascular biomarkers, such as blood pressure, lipid levels, and C-reactive protein.[76,84]

In a systematic review and meta-analysis including 10 randomized controlled trials constituted by overweight individuals mainly affected by type 2 diabetes, semaglutide significantly decreased the occurrence of incident atrial fibrillation by 42% compared with control.[85] The modulation of platelet reactivity, endothelial function, and systemic inflammation points to a prophylactic therapeutic potential of GLP-1 RAs, especially for individuals at high risk of suffering from a stroke. In addition, GLP-1 RAs upregulate the expression of BDNF (brain-derived neurotrophic factor) that has a pivotal function in post-stroke recovery by promoting neuroplasticity, neuronal survival, regeneration, and neurogenesis.[86,87]

Recent findings indicate that GLP-1 RAs activate neurons expressing BDNF in the medial nucleus of the solitary tract. These neurons are essential for the anorectic and metabolic effects of GLP-1 RAs and contribute to increased fatty acid oxidation.[88]

Despite consistent preclinical evidence of neuroprotection, clinical translation of neuroprotective strategies, including GLP-1 RAs, has remained limited, reflecting a longstanding challenge in stroke research. Over the past decades, numerous neuroprotective interventions aimed at preventing brain injury after AIS have failed to demonstrate efficacy in clinical trials. This translational gap is partly due to limitations in animal models, which often rely on small cohorts of young, healthy, genetically similar male rodents where stroke is induced during the daytime in these nocturnal animals. Although the vast majority of the included preclinical studies investigated focal cerebral ischemia, 2 studies examined global ischemia, which involves distinct mechanisms of neuronal death and brain injury. The diversity may contribute to variability in the observed effects and limit the comparability of results across studies. In many preclinical studies, GLP-1 RA was administered immediately or shortly after stroke induction. This timing is not clinically relevant, as significant delays in AIS treatment initiation are common. Overall, such models poorly represent the heterogeneity of human stroke populations.[89,90]

Critical confounders in stroke models are hypothermia and certain anesthetics, as they exert neuroprotective effects by reducing cerebral metabolic demand and attenuating inflammatory responses.[91–93] We acknowledge concerns about publication bias as an inherent problem, in that studies with interesting or statistically significant findings are more likely to be published. All factors that will artificially overestimate the efficacy of GLP-1. This highlights the need for methodological rigor and heterogeneity in future preclinical trials, as reported by the STAIR (Stroke Therapy Academic Industry Roundtable)[94] guidelines and the SPAN (Stroke Preclinical Assessment Network) trial.[95]

Although GLP-1 RAs have shown robust reductions in infarct size and improvements in functional outcome in preclinical models, clinical trials targeting patients with AIS are scarce, and there is currently no evidence for improved clinical outcomes in patients with AIS without diabetes.

However, GLP-1 RAs continue to show acceptable safety profiles in clinical trials with low risk of hypoglycemia, and the most common adverse events are gastrointestinal complications, including nausea, vomiting, diarrhea, and constipation. GLP-1 RAs have the potential to be administered ultra-early in a prehospital setting based on clinical suspicion. If future trials confirm a negligible impact on platelets and coagulation in the acute phase, this could pave the way for prehospital use, enabling treatment and neuroprotection to begin even before neuroimaging distinguishes between ischemic and hemorrhagic stroke.

Limitations

Some limitations must be considered when interpreting the results. First, this review was not preregistered. Otherwise, it follows the PRISMA guidelines in applying

clearly defined eligibility criteria and provides a thorough description of the methodology to maintain rigor.

The studies are dominated by the absence of sufficient quantitative data for infarct volume and neurological deficit score. For the majority of the studies, the outcomes were presented graphically, and we used the software WebPlotDigitizer to estimate the values from graphs.

The authors across the studies used different techniques to measure infarct volumes and different neurological scoring systems, complicating direct comparisons. To estimate treatment effects, we calculated percentage reductions between the control and intervention groups. However, neuroscores evaluating functional outcome in stroke models are not inherently linear and are not designed for proportional interpretations, meaning that identical absolute differences in scores may not reflect proportional changes in neurological function. Despite this, we believe this approach provides a simplified approximation of the treatment effect for clinicians who are not used to interpreting animal neuroscores. To facilitate comparisons across studies using different outcome measures, we calculated the standardized mean difference for the meta-analysis.

Another important limitation concerns the terminology used to describe the mode of cell death in the included studies. The pathophysiology behind stroke is very complex, and a variety of methods have been applied to visualize different aspects of postischemic cell death. However, these techniques have limitations, and the term apoptosis is often used incorrectly, confounding the interpretation of the results.[71] According to the Nomenclature Committee on Cell Death, we emphasize that the findings reported as apoptosis in the primary studies may more accurately reflect cell death more broadly.[96] A more precise and descriptive nomenclature based on the actual markers investigated (eg, TUNEL-positive cells, caspases, and PARP) would improve comparability and reproducibility. The use of at least 2 independent markers or techniques is recommended to reliably identify a specific mode of cell death.[71]

CONCLUSIONS

GLP-1 RAs improve neurological deficits and reduce infarct volume in preclinical animal stroke models without diabetes. Evidence from clinical studies is limited and not useful to establish the neuroprotective efficacy in humans. Larger randomized controlled trials are required before conclusions can be drawn to determine the exact efficacy.

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Supplemental Material

Table S1–S2

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