GLP-1RA and SGLT-2I in Stroke

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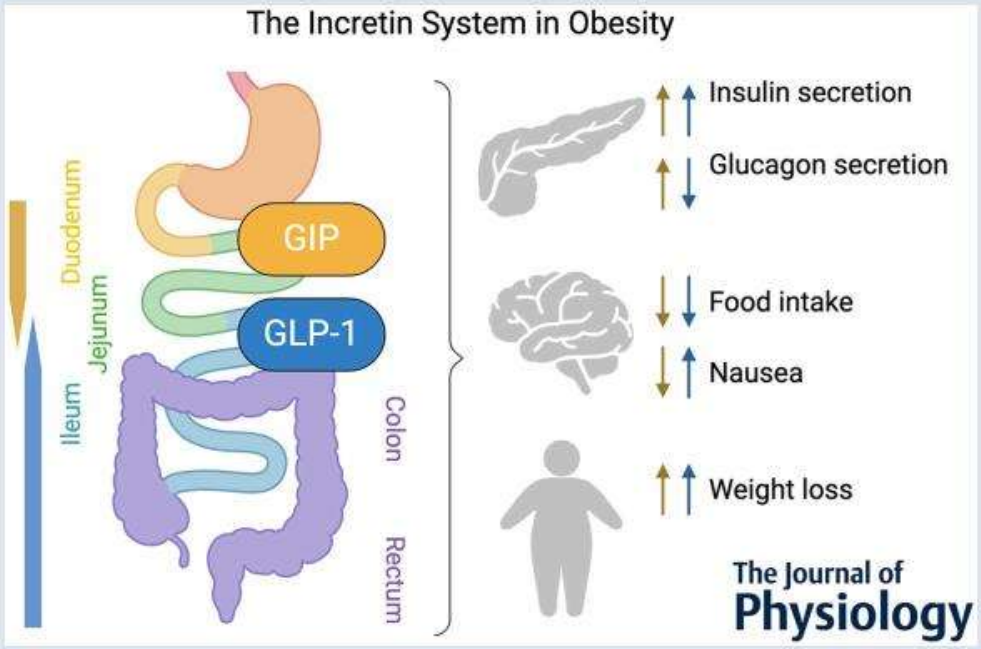
Disclosure

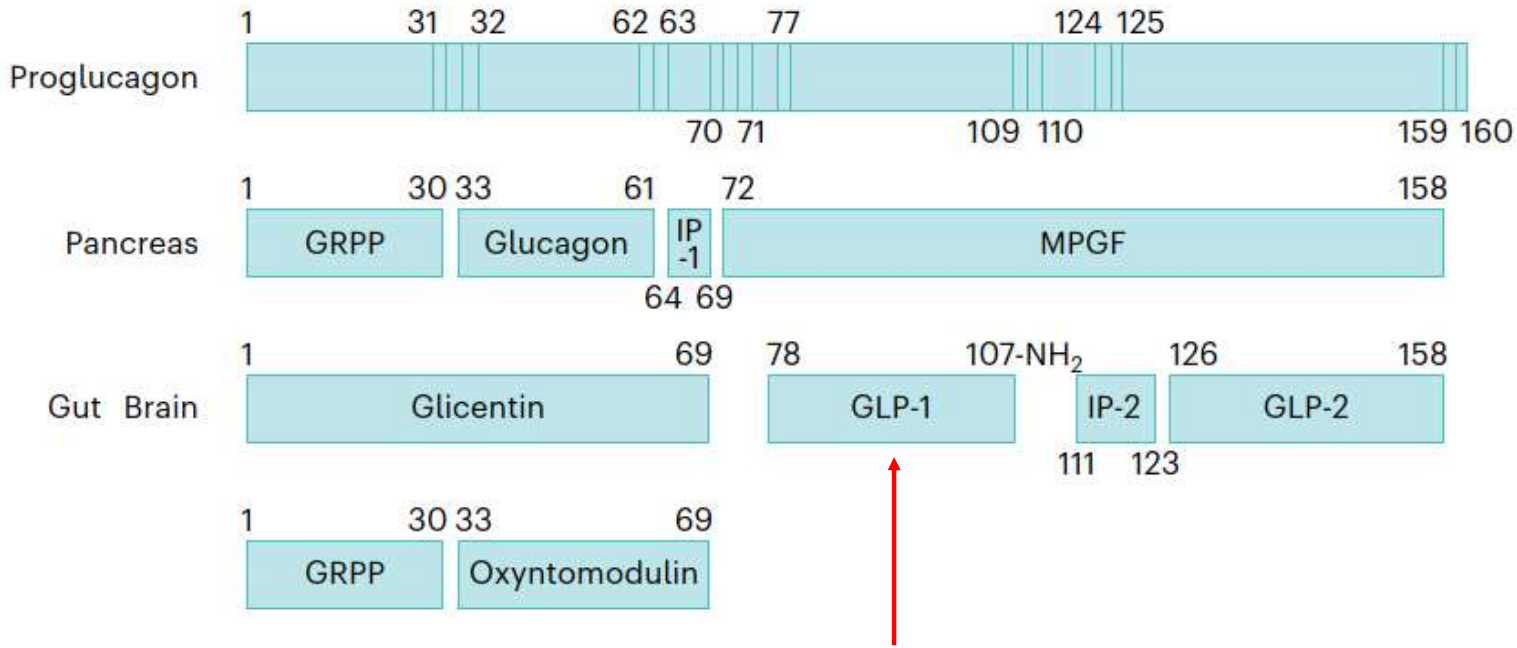
- I have no Disclosure
- I have consulted ChatGPT

Incretin Hormones



Abstract figure legend The incretin system in obesity. The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) (yellow) and glucagon-like peptide-1 (GLP-1) (blue) are produced by the proximal and distal small intestinal epithelium, where they are released postprandially into the bloodstream to modulate a myriad of physiological and metabolic functions. GIP is mostly produced by K-cells in the duodenum and jejunum, whereas GLP-1 is produced by L-cells mostly in the ileum and large intestine. These incretin hormones act on the pancreas causing an increase in insulin secretion. GIP increases glucagon production, whereas GLP-1 decreases it. These hormones have been shown to reduce food intake, causing weight loss. Central GLP-1 increases nausea, whereas GIP has been shown to decrease nausea by acting on GIP receptors in the brainstem.

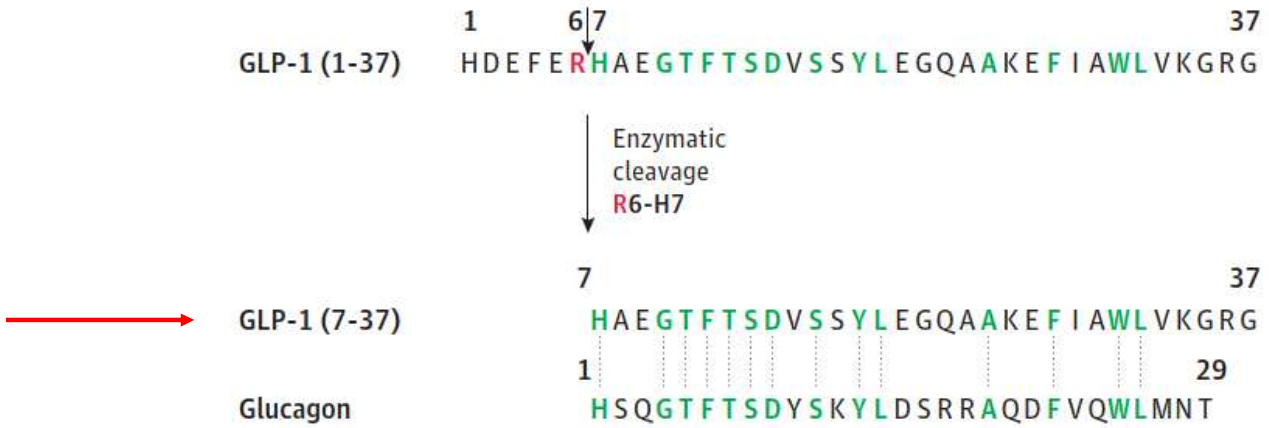
Glucagon-Like Peptide-1 (GLP-1)



Nature Metabolism | Volume 6 | October 2024 | 1866–1885

History of GLP-1 Receptor Agonist (GLP-1RA)

Figure. The Biologically Active Sequence of Glucagon-Like Peptide 1 (GLP-1 [7-37])



Enzymatic cleavage at the arginine amino acid at position 6 in GLP-1 (1-37) sequence would release the biologically active GLP-1 (7-37) with high homology to amino acids in glucagon that are important for glucagon biological activity.

History of GLP-1RA

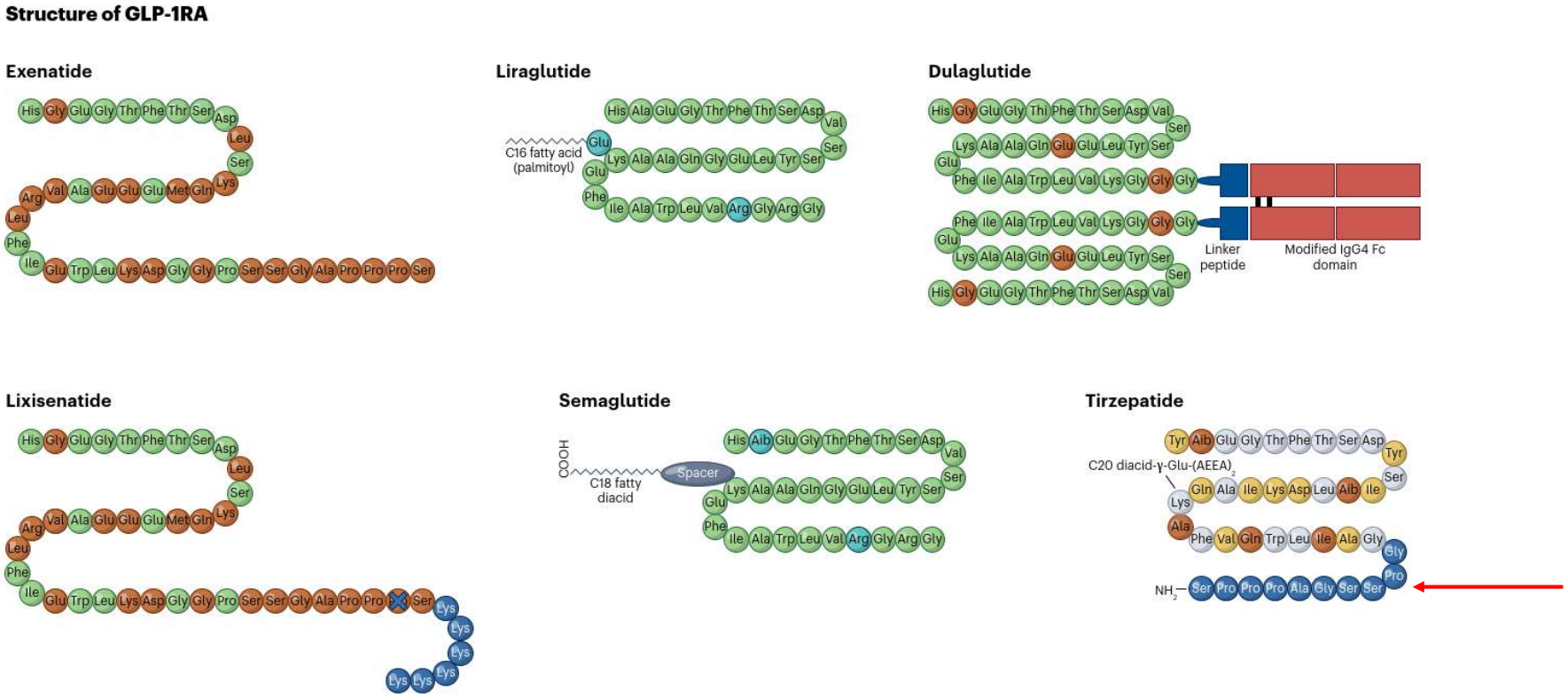


Fig. 2 | Structures of the currently approved GLP-1RAs. For the first five agonists, green circles indicate amino acids identical to those of GLP-1. For exenatide and lixisenatide, amino acids in red circles are specific for exendin 4. The blue residues of lixisenatide are specific for that peptide. Blue circles in liraglutide and semaglutide and red circles in dulaglutide indicate substitutions. Grey residues in light blue are from GLP-1, yellow residues are from GIP, red residues are substitutions, and the dark blue residues are identical to the C-terminal tail of exenatide (based on publicly available company information).

GLP-1RA Withdrawal or Discontinued in USA

Drug	Brand(s)	Approval Date	Modification	Half-life	Dosing
Exenatide IR	Byetta	2005 (US)	Exendin-4 analog	2.4 h	SC BID
Exenatide ER	Bydureon	2011 (US)	Microsphere extended release	2 wks	SC weekly
Lixisenatide	Adlyxin	2013 (EU), 2016 (US)	Exendin-4 extension	3 h	SC QD
Albiglutide	Tanzeum	2014 (US)	Dimer fused to albumin	5 days	SC weekly

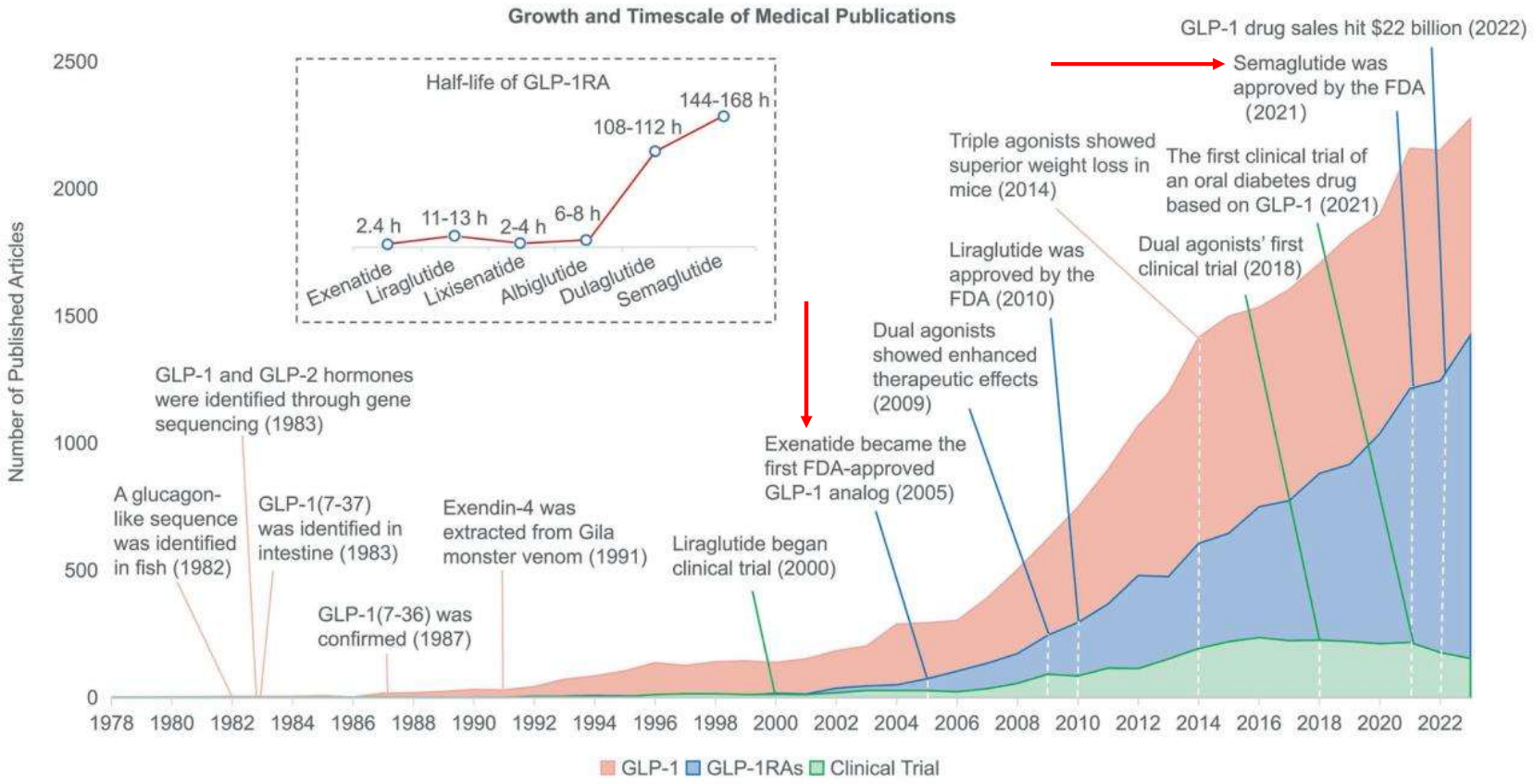
GLP-1RA Currently Available

Drug	Brand(s)	Approval Date	T2D Dose	Obesity Dose	Half-life
Liraglutide	Victoza / Saxenda	2010 / 2014	1.2-1.8 mg daily (Victoza)	3.0 mg daily (Saxenda)	~13 h
Dulaglutide	Trulicity	2014 (US)	0.75-1.5 mg weekly (Trulicity)	Not approved	~5 days
Semaglutide (inj)	Ozempic / Wegovy	2017 / 2021	0.25-2.0 mg weekly (Ozempic)	2.4 mg weekly (Wegovy)	~7 days
Semaglutide (oral)	Rybelsus	2019 (US)	7-14 mg daily (Rybelsus)	Not approved	~7 days
Tirzepatide	Mounjaro / Zepbound	2022/2023 (US)	2.5-15 mg weekly (Mounjaro)	5-15 mg weekly (Zepbound)	~5 days

Benefit of GLP-1RA

- **DM**
- **Obesity**
  - Semaglutide can lose up to 15% of body weight
  - Tirzepatide can lose more than 20% of body weight

Growth and Timescale of GLP-1 and GLP-1RAs



Signal Transduction and Targeted Therapy (2024)9:234

LASKER FOUNDATION

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GLP-1-based therapy for obesity

2024 Lasker~DeBakey Clinical Medical Research Award

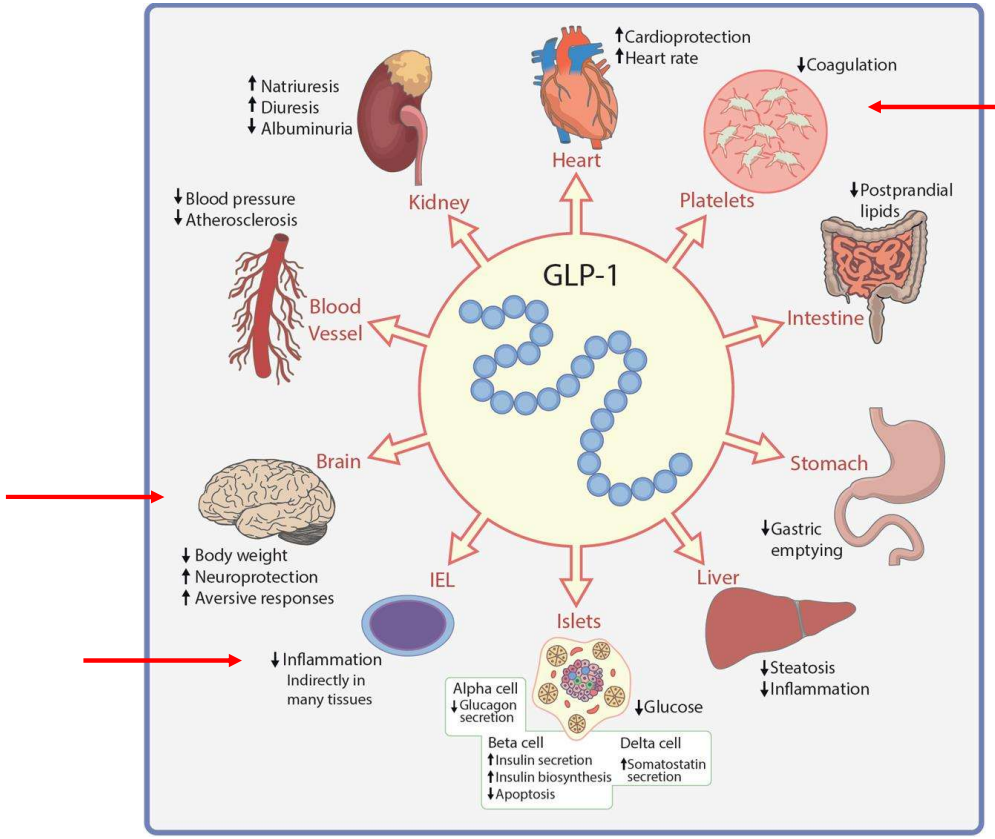
Joel Habener
Massachusetts General Hospital

Lotte Bjerre Knudsen
Novo Nordisk

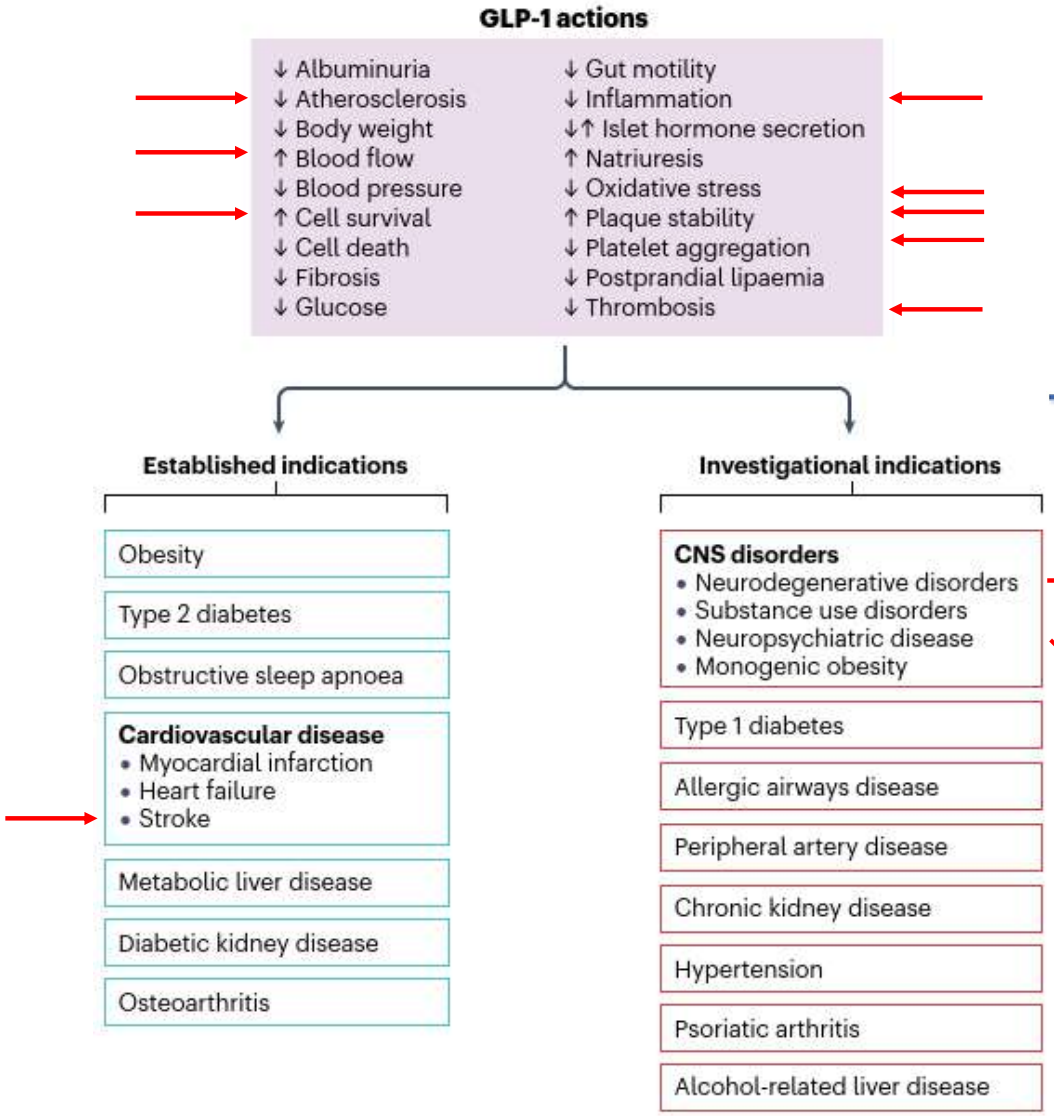
Svetlana Mojsov
The Rockefeller University

Benefit of GLP-1RA: More than DM and Obesity

- **The metabolic Actions of GLP-1RA in Different Organs and Cell Types**



Diabetologia (2023) 66:1765–1779



➢ **Neurological disorders**

- IIH (Idiopathic Intracranial Hypertension)
- Cognitive disorder and Neurodegeneration

➢ **Psychiatric disorders**

- Mood and anxiety disorders
- Eating disorders
- Suicidal ideation

Nature Reviews Drug Discovery | Volume 24 | August 2025 | 631–650

GLP-1RA in Stroke and Cerebrovascular Disease

- **Cardiovascular Disease**
- **Cerebrovascular Disease**
- **Neuroprotection**

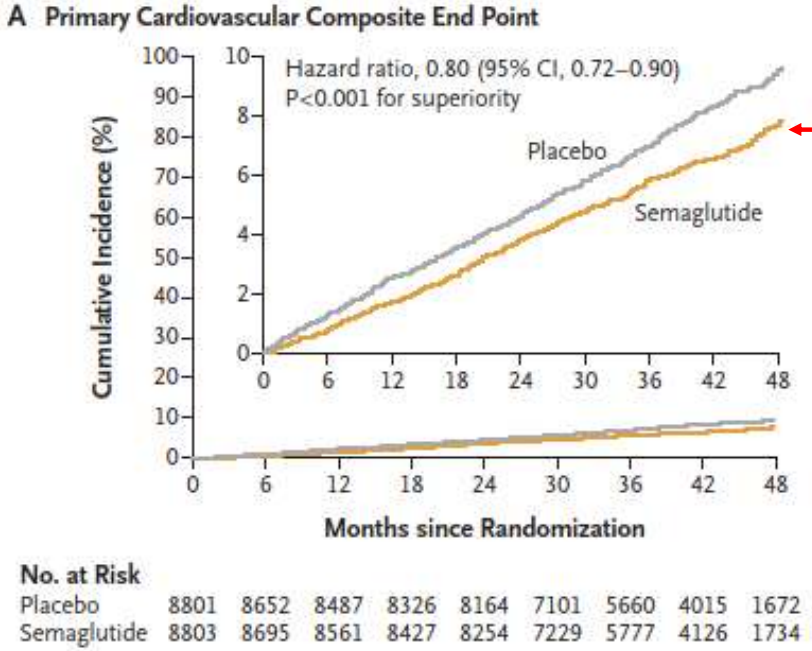
MACE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*



Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial

John Deanfield, A Michael Lincoff, Steven E Kahn, Scott S Emerson, Ildiko Lingvay, Benjamin M Scirica, Jorge Plutzky, Robert F Kushner, Helen M Colhoun, G Kees Hovingh, Signe Stensen, Peter E Weeke, Ole Kleist Jeppesen, Rafael Bravo, Chau-Chung Wu, Issei Komuro, Ferruccio Santini, Jøran Hjelmesæth, Miguel Urina-Triana, Silvio Buscemi, Donna H Ryan

Interpretation The cardioprotective effects of semaglutide were independent of baseline adiposity and weight loss and had only a small association with waist circumference, suggesting some mechanisms for benefit beyond adiposity reduction.

N Engl J Med 2023;389:2221-32.

Lancet 2025; 406: 2257-68

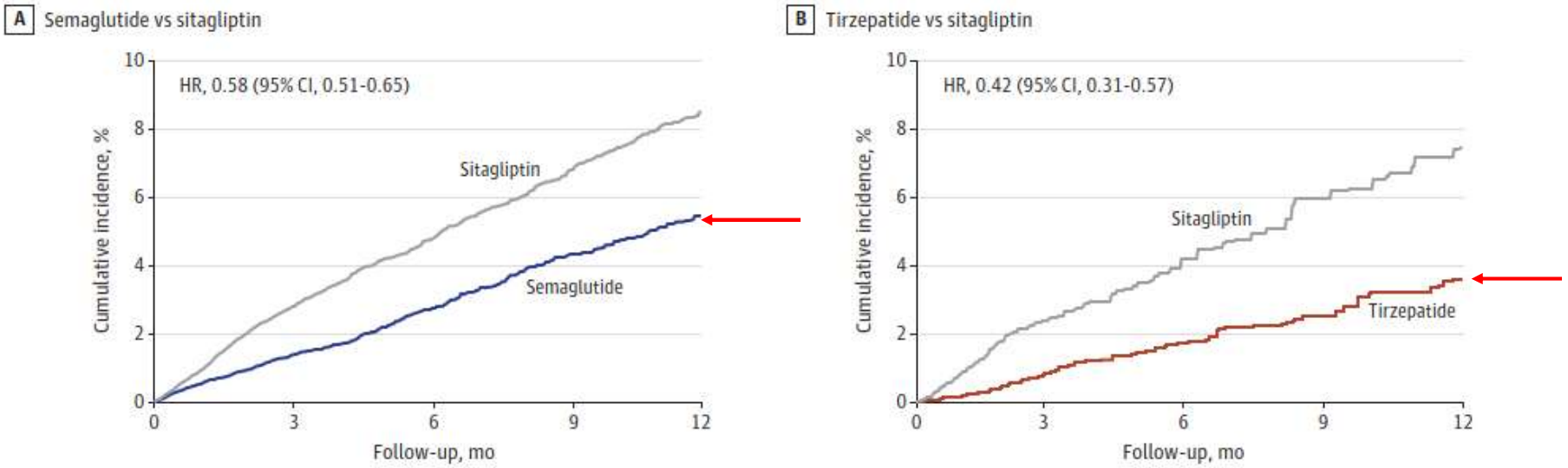
HFpEF

JAMA | Original Investigation

Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction

Nils Krüger, MD; Sebastian Schneeweiss, MD, ScD; Kenshiro Fuse, MD, MPH; Sofiya Matseyko; Sushama Kattinakere Sreedhara, MBBS; Georg Hahn, PhD; Heribert Schunkert, MD; Shirley V. Wang, PhD

- Semaglutide and Tirzepatide: > 40% risk reduction for hospitalization for heart failure or all-cause mortality compared with a placebo proxy



JAMA. 2025;334(14):1255-1266. doi:10.1001/jama.2025.14092

GLP-1RAs: Decrease Stroke Risk

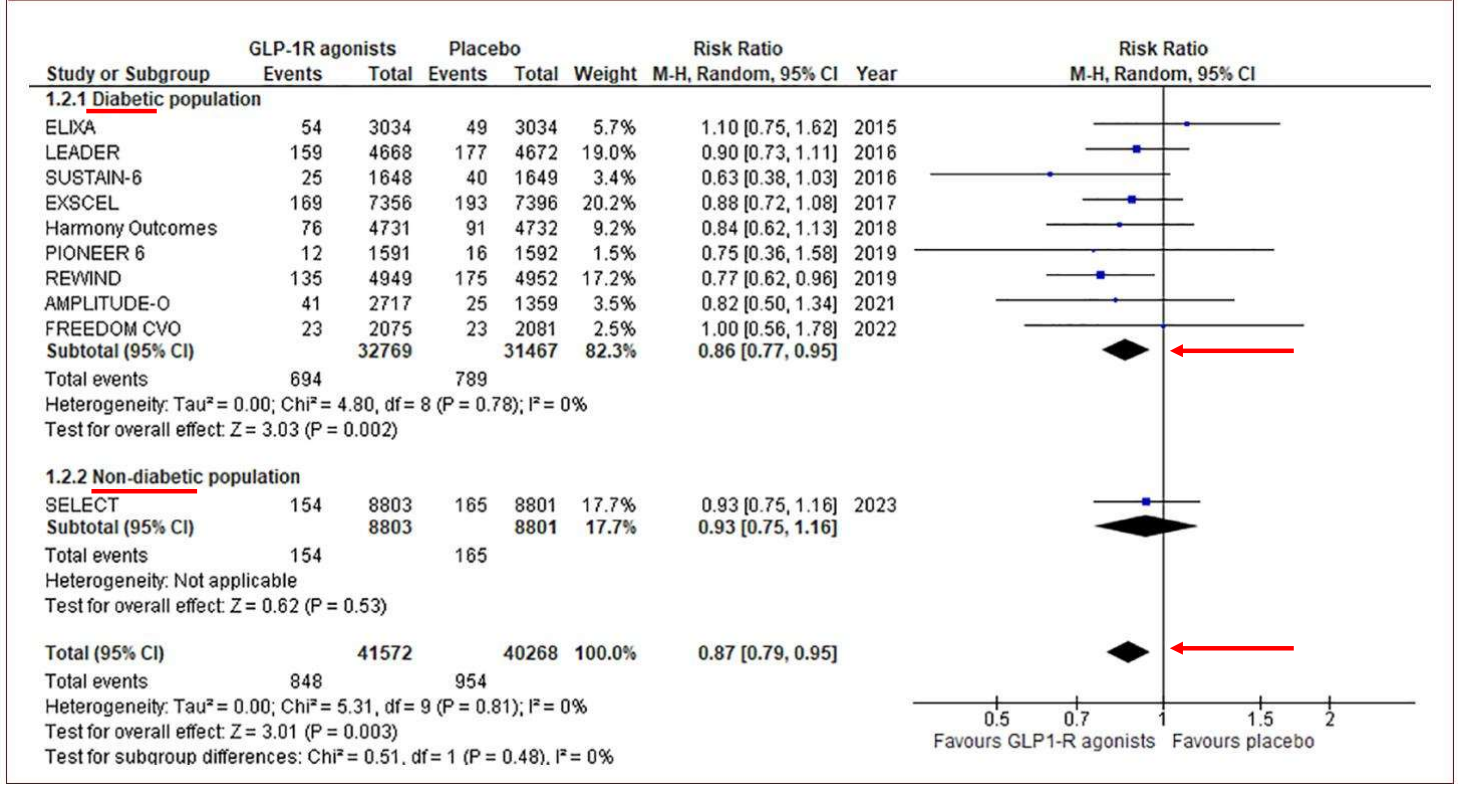
Glucagon-like peptide-1 receptor agonists and stroke: A systematic review and meta-analysis of cardiovascular outcome trials

International Journal of Stroke
2024, Vol. 19(8) 876–887

DOI: 10.1177/17474930241253988
journals.sagepub.com/home/wso
Sage

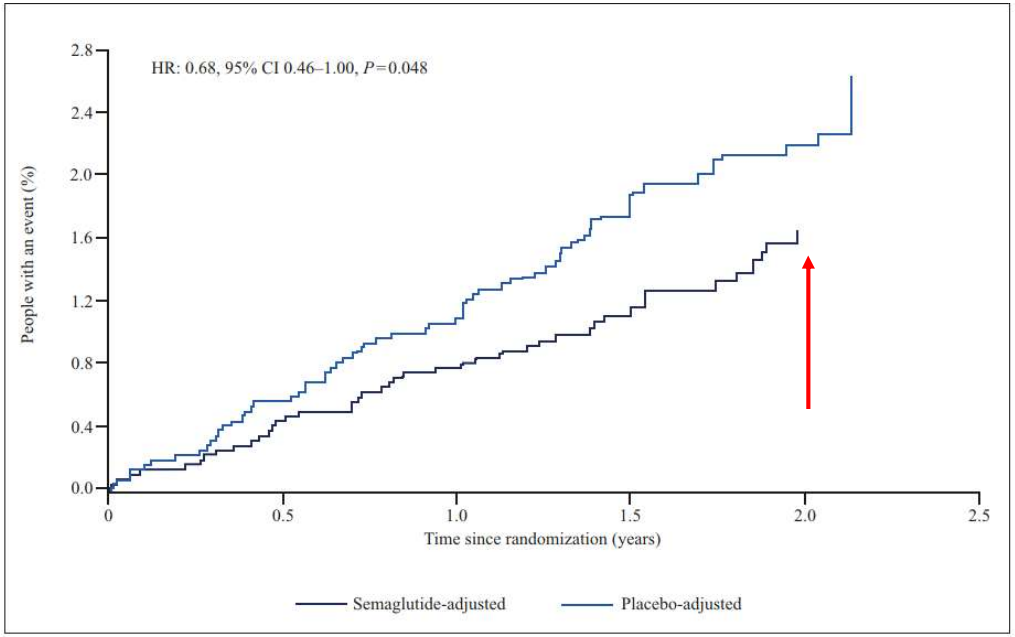
- 11 randomized CVOTs, 82,140 participants (34.6% women) with and without DM
- A 16% RR reduction in stroke risk compared to placebo

Figure 4. Forest plots of RRs of non-fatal stroke in diabetic and non-diabetic participants treated with GLP-1R agonists versus placebo.

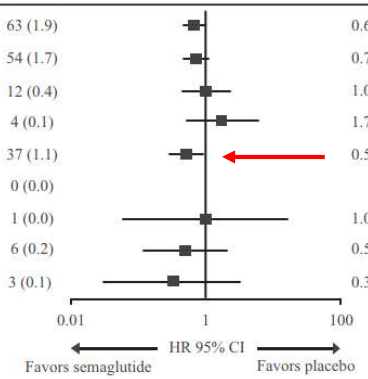


Effects of Semaglutide on Stroke Subtypes in Type 2 Diabetes: Post Hoc Analysis of the Randomized SUSTAIN 6 and PIONEER 6

W. David Strain, MD; Ofir Frenkel, MD; Martin A. James, FRCP; Lawrence A. Leiter, MD; Søren Rasmussen, PhD; Peter M. Rothwell, FMedSci; Maria Sejersten Ripa, DMSc; Thomas C. Truelsen, TC, DMSc; Mansoor Husain, MD



	n (%) Semaglutide (N=3239)	Placebo (N=3241)	HR (95% CI)	*P*-value
Any stroke	43 (1.3)	63 (1.9)	0.68 (0.46–1.00)	0.048
Ischemic stroke*	39 (1.2)	54 (1.7)	0.72 (0.47–1.08)	0.11
Large artery disease	12 (0.4)	12 (0.4)	1.00 (0.45–2.22)	0.99
Cardioembolic	7 (0.2)	4 (0.1)	1.74 (0.51–5.95)	0.38
Small vessel occlusion	19 (0.6)	37 (1.1)	0.51 (0.29–0.89)	0.017
Other determined aetiology	0 (0.0)	0 (0.0)	N/A	N/A
TOAST etiology undetermined†	1 (0.0)	1 (0.0)	1.00 (0.06–15.9)	1.00
Hemorrhagic stroke	3 (0.1)	6 (0.2)	0.50 (0.12–1.99)	0.32
Stroke subtype unknown	1 (0.0)	3 (0.1)	0.33 (0.03–3.20)	0.34



Stroke. 2022;53:2749–2757. DOI: 10.1161/STROKEAHA.121.037775

Original Investigation | Diabetes and Endocrinology

Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity

Huan-Tang Lin, MD, PhD; Yung-Fong Tsai, MD, PhD; Pei-Lun Liao, MSc; James Cheng-Chung Wei, MD, PhD

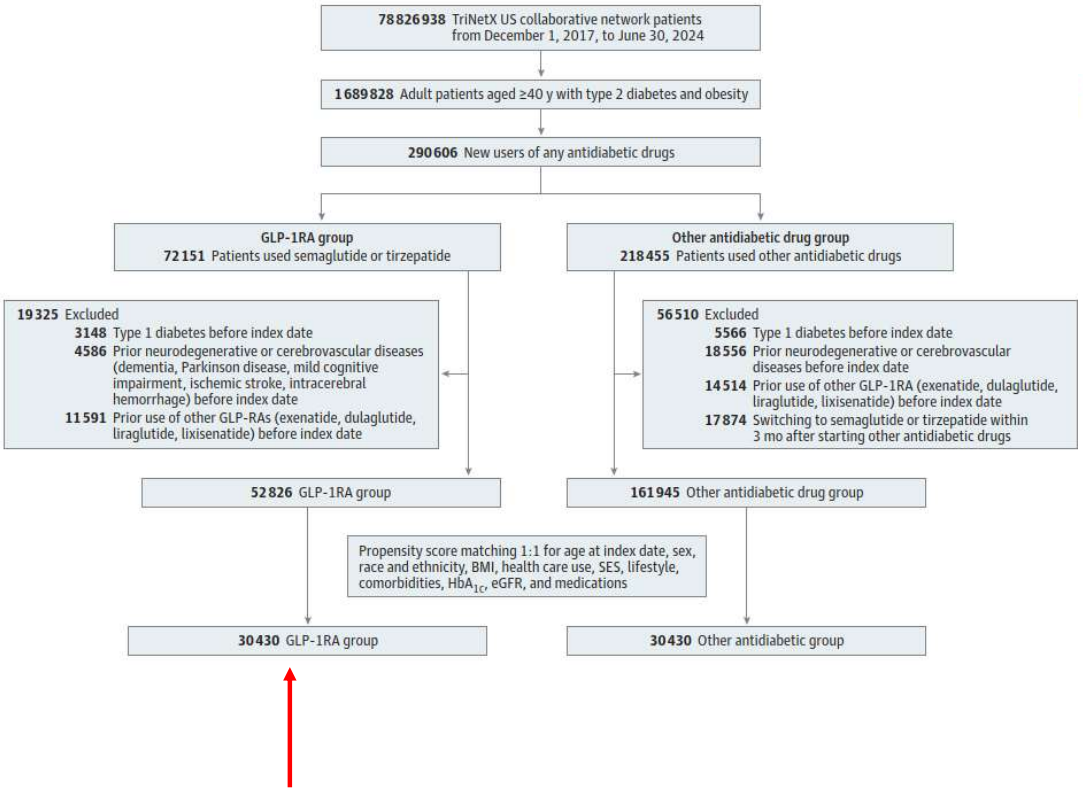
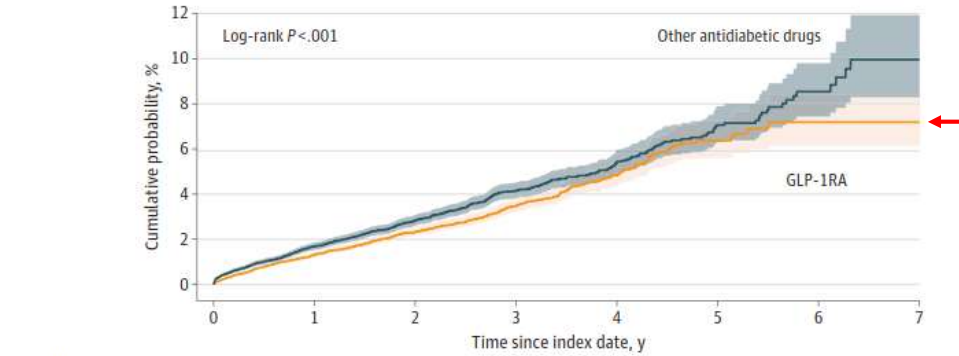


Figure 2. Cumulative Probability of Neurodegenerative and Cerebrovascular Diseases in Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA) vs Other Antidiabetic Drug Users



No. at risk

GLP-1RA	30430	29968	29694	29519	29445	29408	29395	29395
Other antidiabetic drugs	30430	29900	29642	29479	29403	29359	29338	29332

JAMA Network Open. 2025;8(7):e2521016. doi:10.1001/jamanetworkopen.2025.21016

BRIEF REPORT

Glucagon-Like Peptide-1 Receptor Agonists and Risk of Nontraumatic Intracerebral Hemorrhage in Patients With Type 2 Diabetes

Marco Pasi, MD, PhD; Arnaud Bretonnière, MD, PhD; Lisa Lochon, MD; Arnaud Dosda, MD; Arnaud Bisson, MD, PhD; Grégoire Boulouis, MD, PhD; Pierre Henri Ducluzeau, MD, PhD; Laurent Fauchier, MD, PhD

Table 2. Clinical Outcomes During Follow-Up in the Matched Population

	Diabetes, GLP-1RAs (n=255 460)		Diabetes, no GLP-1RAs (n=255 460)			
	No. of events	Yearly rate, %	No. of events	Yearly rate, %	Hazard ratio (95% CI)	*P* value
Nontraumatic intracerebral hemorrhage, all location	958	0.16	1382	0.21	0.743 (0.684–0.807)	<0.0001
Subcortical nontraumatic intracerebral hemorrhage	173	0.03	238	0.04	0.775 (0.637–0.943)	0.01
Cortical nontraumatic intracerebral hemorrhage	195	0.03	303	0.04	0.686 (0.573–0.822)	<0.0001
Brainstem nontraumatic intracerebral hemorrhage	38	0.01	71	0.01	0.577 (0.389–0.856)	0.01
Cerebellar nontraumatic intracerebral hemorrhage	63	0.01	101	0.02	0.667 (0.486–0.914)	0.01
Intraventricular nontraumatic intracerebral hemorrhage	180	0.03	253	0.04	0.762 (0.629–0.922)	0.01
Death	9443	1.57	19 350	2.77	0.525 (0.512–0.538)	<0.0001
Ischemic stroke	6263	1.08	7715	1.20	0.871 (0.843–0.901)	<0.0001

Stroke. 2025;56:2761–2766. DOI: 10.1161/STROKEAHA.125.050972

Liraglutide in Acute Minor Ischemic Stroke or High-Risk Transient Ischemic Attack With Type 2 Diabetes
The LAMP Randomized Clinical Trial

Huili Zhu, MD; Bin Yang, MD; Longyan Lu, MMed; Yufeng Li, MD; Rubo Sui, MD; Kewei Liu, MD; Suling Tan, MD; Lihua Wang, MD; Jianmin Qiu, MD; Jianbin Zhong, MD; Tongguo Wei, MD; Yuzhang Bei, MD; Jianmin Huang, MD; Suping Zhang, MD; Yan Ji, MD; Wenjun Wu, MD; Youjia Li, MD; Ying Huang, MD; Yangkun Chen, MD; Xiaoyun Huang, MD; Guoyong Zeng, MD; Yusheng Zhang, MD; Lian Huang, MD; Hao Li, PhD; Xiangbing Wang, MD; Yongjun Wang, MD; Anding Xu, MD; for the LAMP Investigators

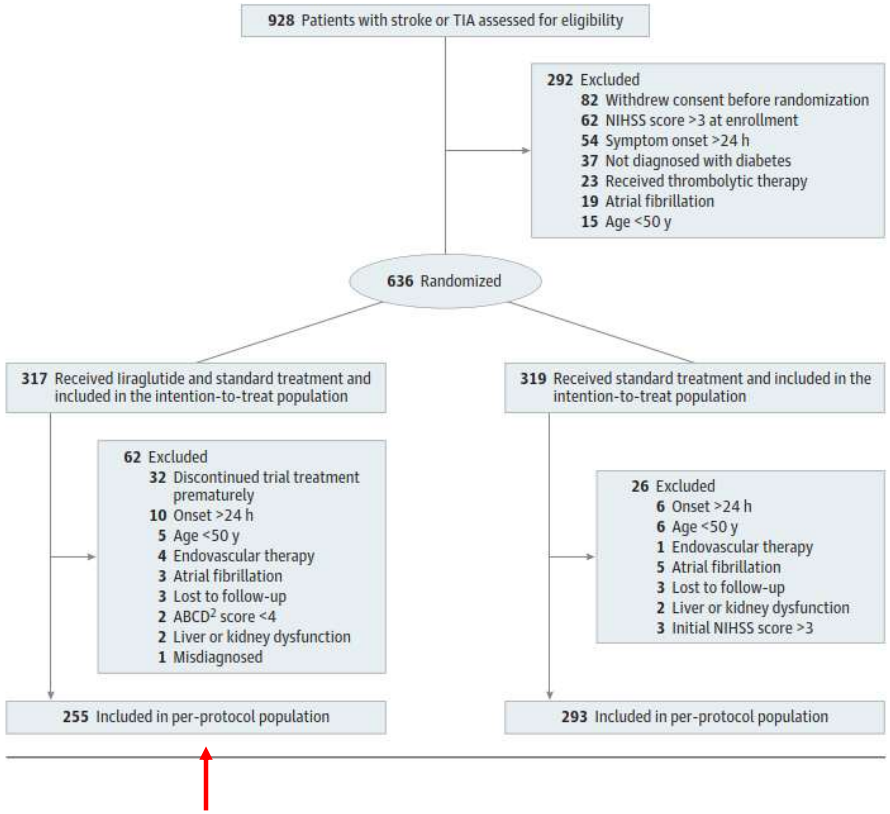
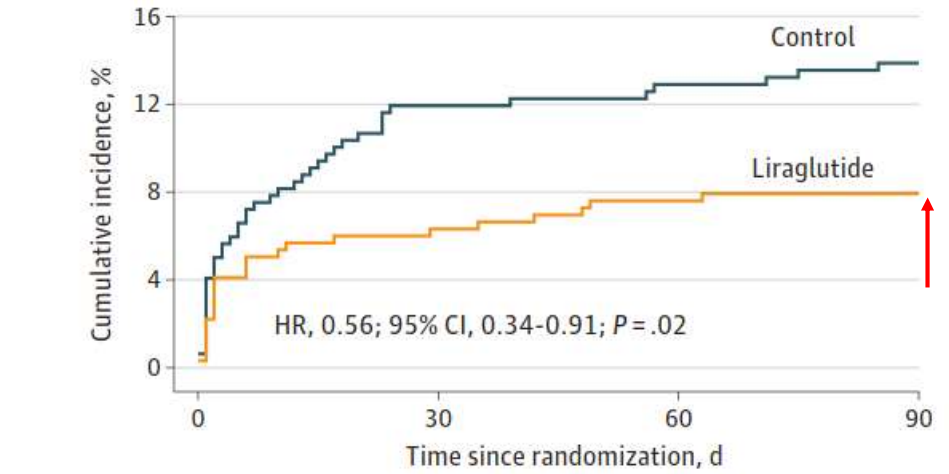


Figure 2. Cumulative Incidence of Stroke



No. at risk				
Control	319	277	269	116
Liraglutide	317	295	288	132

JAMA Intern Med. doi:10.1001/jamainternmed.2025.5684

Neuroprotection

Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial

Tali Cukierman-Yaffe, Hertzel C Gerstein*, Helen M Colhoun, Rafael Diaz, Luis-Emilio García-Pérez, Mark Lakshmanan, Angelyn Bethel, Denis Xavier, Jeffrey Probstfield, Matthew C Riddle, Lars Rydén, Charles Messan Atisso, Stephanie Hall, Purnima Rao-Melacini, Jan Basile, William C Cushman, Edward Franek, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev*

	Dulaglutide (n=4456)	Placebo (n=4372)
Age, years	65·5 (61·6–70·2)	65·5 (61·4–70·0)
Sex		
Female	2081 (47%)	2027 (46%)
Male	2375 (53%)	2345 (54%)
White ethnic origin	3421 (77%)	3321 (76%)
Education for ≤12 years	2717 (61%)	2633 (60%)
Current tobacco use	616 (14%)	625 (14%)
Cardiovascular disease*	1373 (31%)	1351 (31%)
Previous stroke or TIA	388 (9%)	393 (9%)
Hypertension	4150 (93%)	4066 (93%)
Atrial fibrillation	293 (7%)	268 (6%)
Heart failure	374 (8%)	381 (9%)
Diabetes duration, years	10·3 (7·1)	10·4 (7·1)
Diabetic retinopathy	406 (9%)	395 (9%)
Albuminuria†	1491 (34%)	1501 (34%)
Body-mass index, kg/m²	32·4 (5·7)	32·4 (5·7)
Systolic blood pressure, mm Hg	136·9 (16·5)	137·2 (17·0)
Diastolic blood pressure, mm Hg	78·4 (9·8)	78·6 (9·9)
HbA_{1c}, %	7·3 (1·1)	7·3 (1·0)
HbA_{1c}, mmol/mol	56·0 (12·0)	56·0 (10·9)
eGFR, mL/min per 1·73 m²	77·7 (22·5)	77·1 (22·6)
LDL cholesterol, mmol/L	2·6 (1·0)	2·5 (1·0)
MoCA score	25·0 (22·0–28·0)	25·0 (22·0–28·0)
DSST score	37·0 (25·0–49·0)	37·0 (25·0–49·0)

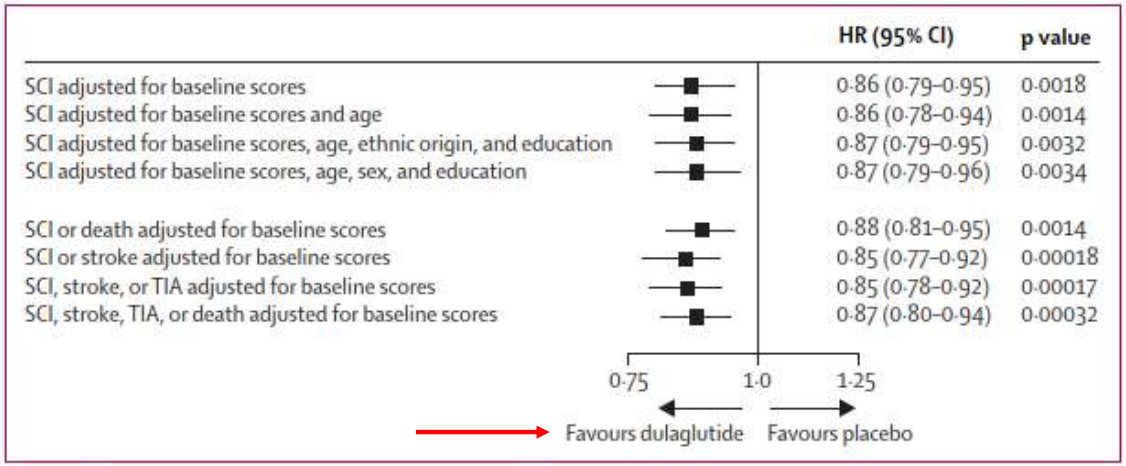


Figure 1: Risk of SCI, adjusted for baseline standardised MoCA and DSST scores

- Median follow-up of 5·4 (IQR 5·1–5·9) years
- After adjustment baseline scores, the hazard of substantive cognitive impairment was reduced by 14% (HR 0·86, 95% CI 0·79–0·95; p=0·0018).

Lancet Neurol 2020; 19: 582–90

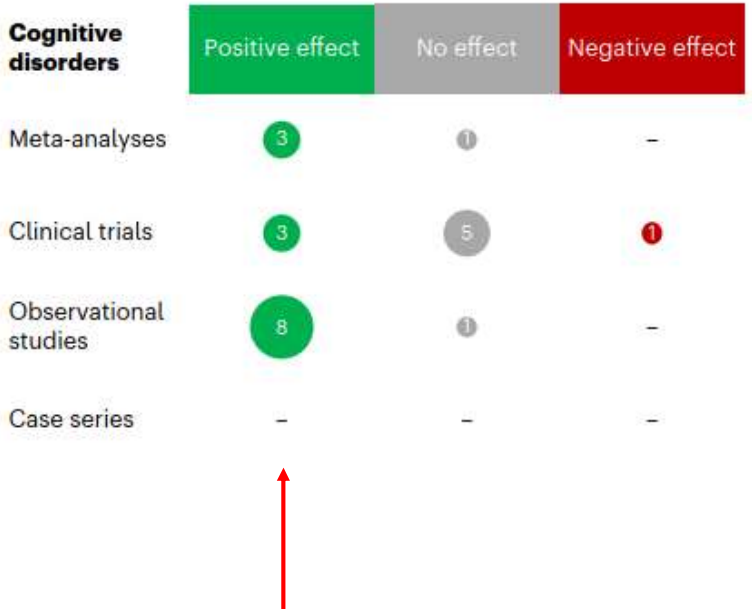
nature mental health

An analysis on the role of glucagon-like peptide-1 receptor agonists in cognitive and mental health disorders

Table 1 | Clinical studies of GLP-1RAs for cognitive disorders (meta-analysis)

Study ID	Design	Population	Intervention/exposure	Comparison	Follow-up	Outcomes	Major findings	
Luan 2022[38]	Meta-analysis of 5 studies (5 RCTs)	7,732 adults T2DM	Dulaglutide, exenatide, liraglutide	Pre-treatment baseline	3 months–5 years	MMSE, MoCA	SMD=0.33 95% CI=−0.03, 0.69 (*P*=0.017)	=
Nørgaard 2022[39]	Pooled analysis of 3 RCTs	15,820 adults T2DM	Liraglutide, semaglutide	Placebo	1.3–3.8 years	Risk of any dementia	HR=0.47 95% CI=0.25, 0.86	+
Tang 2023[40]	Meta-analysis of 4 studies (1 pooled analysis of 3 RCTs, 3 observational studies)	210,521 adults T2DM	Any GLP-1RAs	Non-users of GLP-1RAs	3.6–7.4 years	Risk of any dementia	RR=0.72 95% CI=0.54, 0.97 (*P*=0.000)	+
Tian 2023[41]	Network meta-analysis of 27 studies (4 for GLP-1RAs: 1 RCT, 3 case-control studies)	149,560 adults T2DM	Dulaglutide, exenatide, liraglutide	Non-users of GLP-1RAs	4–7.2 years	Risk of any dementia	OR=0.34 95% CI=0.14, 0.85 (*P*=0.021)	+

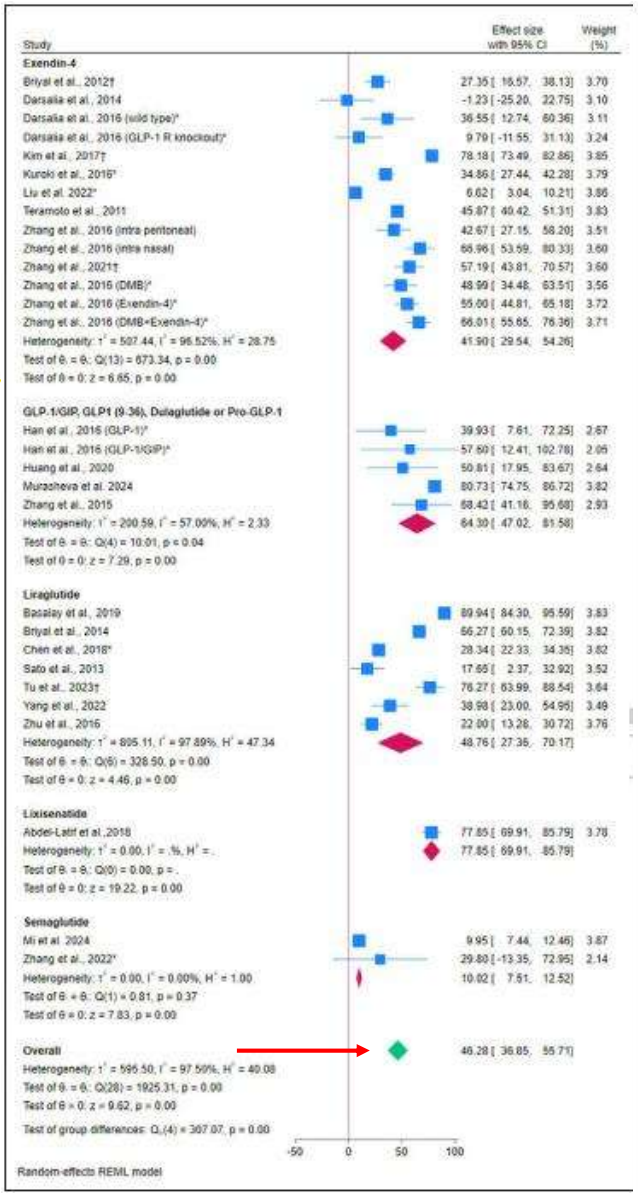
Plus and equals symbols indicate positive effect and no effect, respectively. Values are mean ± s.d. unless otherwise specified. Study ID reports the first author and year only. CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk; SMD, standardized mean difference.

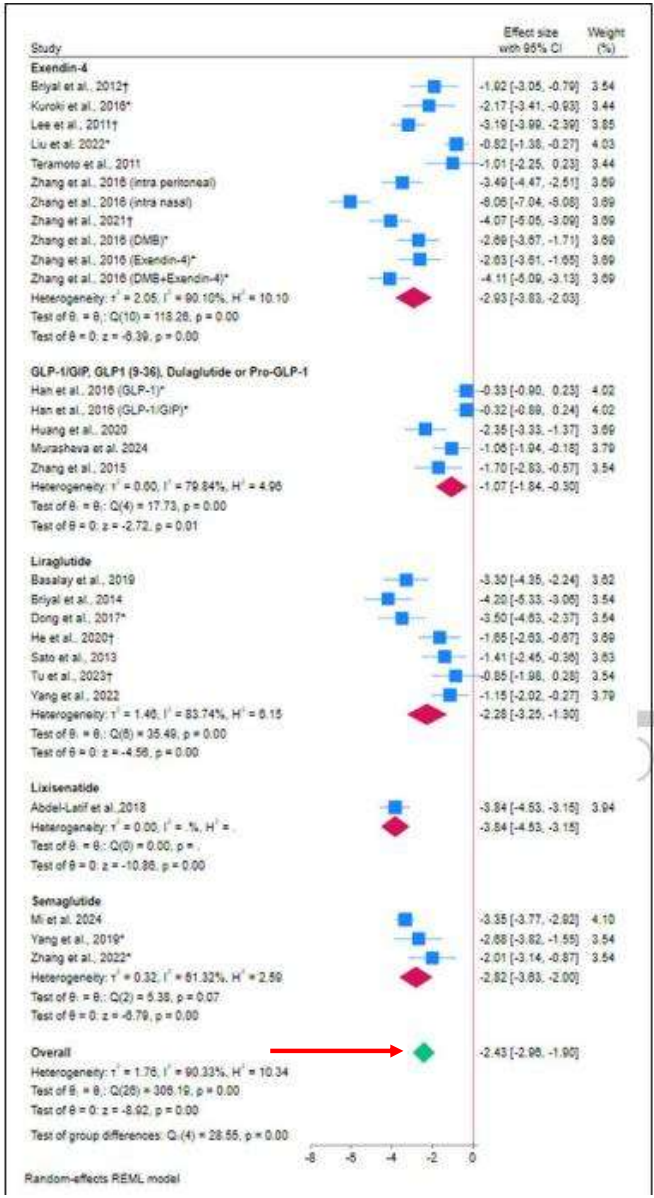


ORIGINAL CONTRIBUTION

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

Michael K. Michaelsen, MD; Kim Ryun Drasbek, MSc, PhD; Jan Brink Valentin, MSc; Mads Svart, MD, PhD; Julie B. Larsen, MD, PhD; Christina Kruuse, MD, PhD; Claus Ziegler Simonsen, MD, PhD; Rolf Ankerlund Blauenfeldt, MD, PhD





Stroke. 2026;57:00–00. DOI: 10.1161/STROKEAHA.125.053075

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)
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)

Ongoing Clinical Trials in Stroke

- **Completed**
  - GLP-1RA in Acute Large Vessel Occlusion Stroke Treated by Reperfusion Therapies (GALLOP) (Semaglutide)
- **Active**
  - GLP-1RA in Acute Large Vessel Occlusion Stroke After Endovascular Treatment (GALLOP2) (Semaglutide)
  - Efficacy of Semaglutide in Improving Neurological Outcomes After Endovascular Thrombectomy for AIS: A Randomized Double-Blind Controlled Trial (STARS)
  - Acute Subcutaneous Semaglutide in AIS (ASSET)

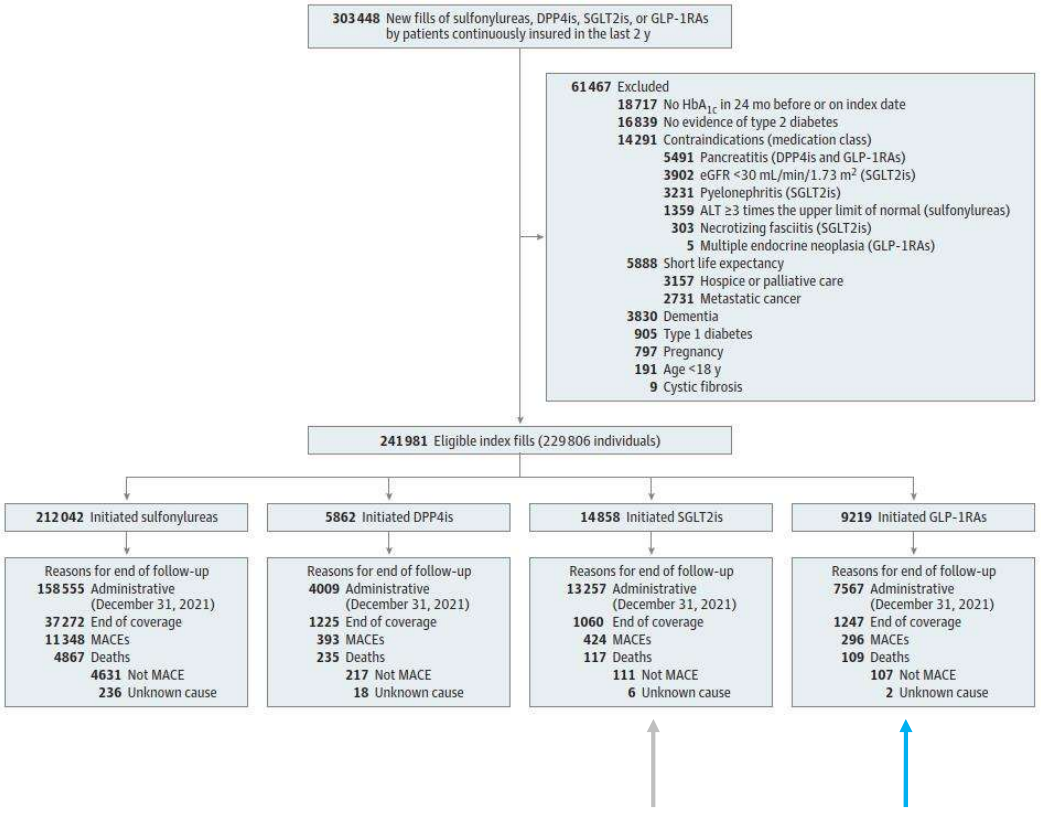
GLP-1RA vs SGLT2I for stroke

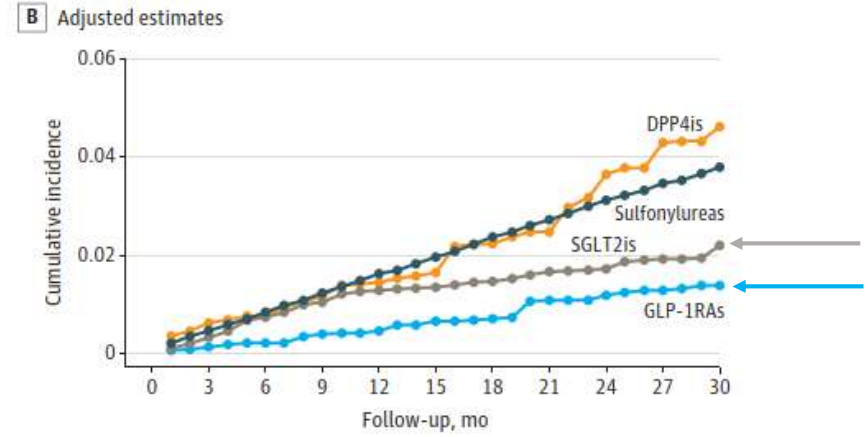
Approved SGLT2I – Comparison Table

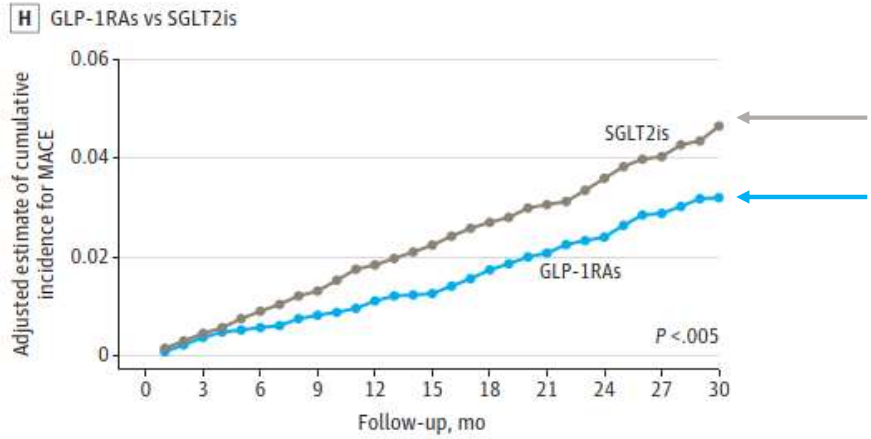
Drug	Brand Name(s)	Approval Year	Selectivity	Primary Indications	Dosing	Key Benefits	Notable Side Effects
Canagliflozin	Invokana	2013	SGLT2 >> SGLT1	T2D, CKD, ↓ CV events	100–300 mg QD	↓ A1c, ↓ CKD progression, ↓ CV events	Genital infections, rare amputation risk
Dapagliflozin	Farxiga	2014	SGLT2 >> SGLT1	T2D, HF, CKD	5–10 mg QD	↓ HF hospitalization, ↓ CKD progression	UTI, volume depletion
Empagliflozin	Jardiance	2014	SGLT2 >> SGLT1	T2D, ↓ CV death, HF	10–25 mg QD	↓ CV mortality, ↓ HF hospitalization	Genital infections, dehydration
Ertugliflozin	Steglatro	2017	SGLT2 >> SGLT1	T2D	5–15 mg QD	↓ A1c, modest weight loss	Genital infections, dehydration

Original Investigation | Diabetes and Endocrinology

Glucose-Lowering Medication Classes and Cardiovascular Outcomes in Patients With Type 2 Diabetes







JAMA Network Open. 2025;8(10):e2536100. doi:10.1001/jamanetworkopen.2025.36100

GLP-1 RAs vs SGLT2I: Side-by-Side Comparison

Feature	GLP-1 Receptor Agonists	SGLT2 Inhibitors
Drug Type	Biologic peptide (mostly injectable)	Small molecule (oral tablets)
Primary Target	GLP-1 receptor (pancreas, brain, gut)	SGLT2 transporter (kidneys)
Mechanism	↑ Insulin, ↓ glucagon, ↓ appetite	↓ Renal glucose reabsorption → ↑ glucosuria
A1c Reduction	~1–1.5+%	~0.5–1%
Weight Loss	Significant (up to 15%)	Modest (2–3 kg)
CV Benefit	↓ MACE, ↓ CV mortality	↓ HF hospitalization, ↓ CV death
Renal Benefit	Moderate (indirect)	Strong: ↓ CKD progression
Side Effects	Nausea, diarrhea, gallbladder issues	Genital infections, dehydration
Route	Injection (weekly/daily), 1 oral option	Oral once daily
Uses beyond diabetes	Obesity, possibly neuroprotection	CKD, Heart failure

Side Effects of GLP-1RA

Side Effects: GI Adverse Events

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

Outcomes	GLP-1 agonists, HR (95% CI)[a]		Bupropion-naltrexone
	Crude	Adjusted[b]	
Primary analysis			
Biliary disease	1.48 (0.88-2.47)	1.50 (0.89-2.53)	1 [Reference]
Pancreatitis	10.33 (1.44-74.40)	9.09 (1.25-66.00)	1 [Reference]
Bowel obstruction	5.16 (1.27-21.00)	4.22 (1.02-17.40)	1 [Reference]
Gastroparesis	3.31 (1.04-10.50)	3.67 (1.15-11.90)	1 [Reference]

Safety outcomes						
sICH[f]	2	0.6	1	0.3	0.48 (0.04-5.27)	.50
Hypoglycemia[g]	25	7.8	24	7.6	0.93 (0.53-1.62)	.80
Gastrointestinal disorders[h]	13	4.1	60	18.9	4.81 (2.64-8.78)	<.001
Pneumonia	2	0.6	2	0.6	0.97 (0.14-6.90)	>.99
Acute pancreatitis	0	0	0	0	NA	NA
Death[i]	4	1.3	1	0.3	0.24 (0.03-2.10)	.10

Side Effects:
Optic Nerve and Visual Pathway Disorders

- NAION (Nonarteritic Anterior Ischemic Optic Neuropathy)
  - HR: Zero to double
  - 0.04% in the semaglutide or tirzepatide group and 0.02% in the matched group (HR 1.76)
- Macular Degeneration
- Diabetic Retinopathy
- Lower risk of uveitis

JAMA Ophthalmology September 2025 Volume 143, Number 9
JAMA Network Open. 2025;8(8):e2526327. doi:10.1001/jamanetworkopen.2025.26327
JAMA Ophthalmol. 2025;143(4):304-314. doi:10.1001/jamaophthalmol.2024.6555

Side Effects: Cost

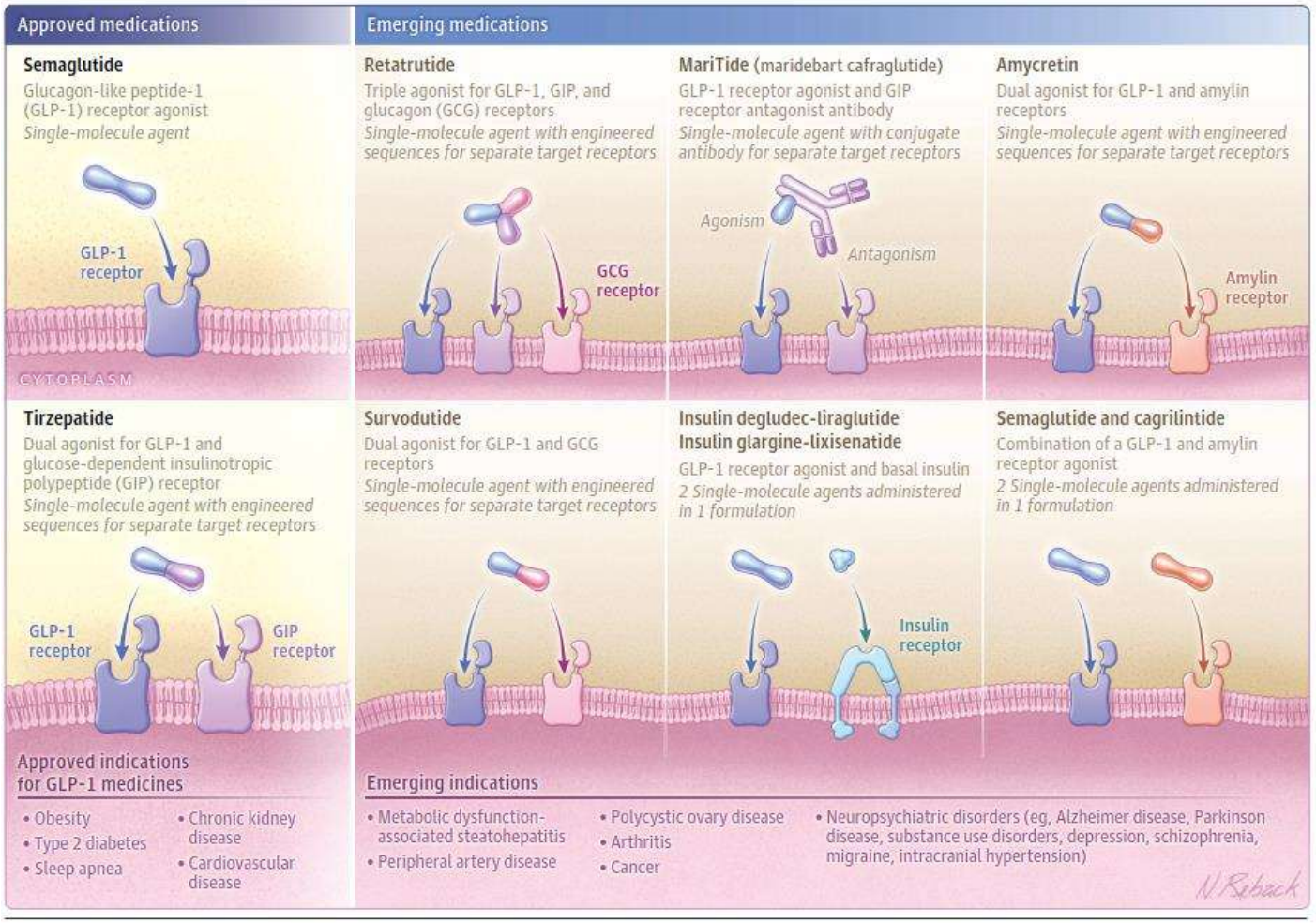
Dosing, Efficacy and Pricing

	Dosing	Bioavailability	Weight Loss (%, Highest Dose)	Approximate Monthly AWP
Liraglutide (Saxenda®) **SC**	0.6-3 mg QD	55%	8.0%[1]	$1349
Semaglutide (Wegovy®) **SC**	0.25-2.4 mg QW	89%	14.9%[2]	$1349
Tirzepatide (Zepbound®) **SC**	2.5-15 mg QW	80%	20.9%[3]	$1086

1. Pi-Sunyer X, et al. N Engl J Med. 2015;373:11–22.
2. Wilding JPH, et al. N Engl J Med. 2021;384:989–1002.
3. Jastreboff AM, et al. N Engl J Med. 2022;387:205–216.
4. Jastreboff AM, et al. N Engl J Med. 2023;389:514-526.
5. Knop FK, et al. Lancet. 2023;402:705-719.
6. Wharton S, et al. N Engl J Med. 2025.

New Molecules in GLP-1 Based Therapy in Future

Figure. New Molecules and Emerging Indications for GLP-1 Medicines



JAMA Published online September 15, 2025

N Engl J Med 2025;392:2001-12.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

D.K. McGuire,[1,2] N. Marx,[3] S.L. Mulvagh,[4] J.E. Deanfield,[5] S.E. Inzucchi,[6] R. Pop-Busui,[7] J.F.E. Mann,[8,9] S.S. Emerson,[10] N.R. Poulter,[11] M.D.M. Engelmann,[12] M.S. Ripa,[12] G.K. Hovingh,[12] K. Brown-Frandsen,[12] S.C. Bain,[13] M.A. Cavender,[14] M. Gislum,[12] J.-P. David,[12] and J.B. Buse,[14] for the SOUL Study Group*

N Engl J Med 2025;393:1077-87.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

Sean Wharton, M.D.,[1-4] Ildiko Lingvay, M.D.,[5,6] Pawel Bogdanski, M.D.,[7] Ruben Duque do Vale, M.D.,[8] Stephan Jacob, M.D.,[9] Tobias Karlsson, M.D.,[8] Chaithra Shaji, M.Sc.,[10] Domenica Rubino, M.D.,[11] and W. Timothy Garvey, M.D.,[12] for the OASIS 4 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

Sean Wharton, M.D.,[1-3] Louis J. Aronne, M.D.,[4] Adam Stefanski, M.D., Ph.D.,[5] Nasreen F. Alfaris, M.D., M.P.H.,[6] Andreea Ciudin, M.D., Ph.D.,[7-11] Koutaro Yokote, M.D., Ph.D.,[12] Bruno Halpern, M.D., Ph.D.,[13] Alpana P. Shukla, M.D.,[4] Chunmei Zhou, M.S.,[5] Lisa Macpherson, M.S.P.H.,[5] Sheryl E. Allen, M.D.,[5] Nadia N. Ahmad, M.D., M.P.H.,[5] and Suzanne R. Klise, B.S.,[5] for the ATTAIN-1 Trial Investigators*

DOI: 10.1056/NEJMoa2511774

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

J. Rosenstock,[1] S. Hsia,[2] L. Nevarez Ruiz,[3] S. Eyde,[4] D. Cox,[4] W.-S. Wu,[4] R. Liu,[4] J. Li,[4] L. Fernández Landó,[4] M. Denning,[4] L. Ludwig,[4] and Y. Chen,[4] for the ACHIEVE-1 Trial Investigators*

N Engl J Med 2025;393:1065-76.

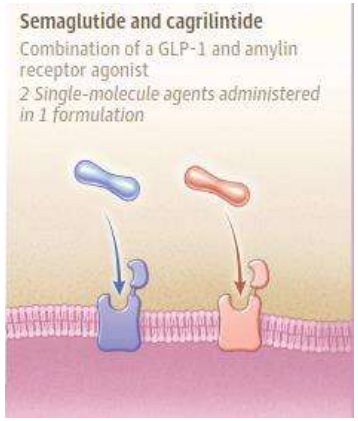
DOI: 10.1056/NEJMoa2502081

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity

W.T. Garvey,[1] M. Blüher,[2,3] C.K. Osorto Contreras,[4] M.J. Davies,[5,6] E. Winning Lehmann,[4] K.H. Pietiläinen,[7,8] D. Rubino,[9] P. Sbraccia,[10] T. Wadden,[11] N. Zeuthen,[4] and J.P.H. Wilding,[12] for the REDEFINE 1 Study Group*

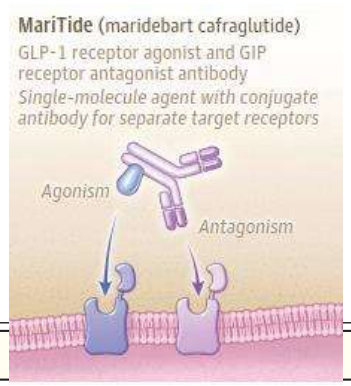


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

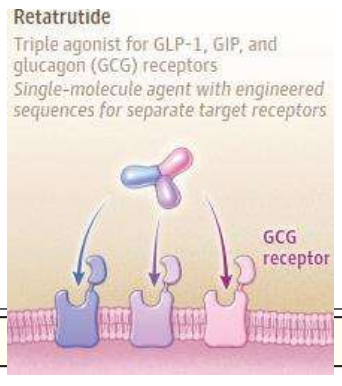
Melanie J. Davies, M.D.,[1,2] Harpreet S. Bajaj, M.D.,[3] Christa Broholm, Ph.D.,[4] Astrid Eliasen, M.D., Ph.D.,[4] W. Timothy Garvey, M.D.,[5] Carel W. le Roux, F.R.C.P.,[6] Ildiko Lingvay, M.D.,[7,8] Christian Bøge Lyndgaard, Ph.D.,[4] Julio Rosenstock, M.D.,[9] and Sue D. Pedersen, M.D.,[10] for the REDEFINE 2 Study Group*



Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity — A Phase 2 Trial

A.M. Jastreboff,[1-3] D.H. Ryan,[4] H.E. Bays,[5] P.R. Ebeling,[6] M.G. Mackowski,[7] N. Philipose,[7] L. Ross,[7] Y. Liu,[7] C.E Burns,[7] S.A. Abbasi,[7] and N. Pannacciulli,[7] for the MariTide Phase 2 Obesity Trial Investigators*

DOI: 10.1056/NEJMoa2504214



Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

DOI: 10.1056/NEJMoa2504214

Indications for GLP-1 Based Therapy in Future

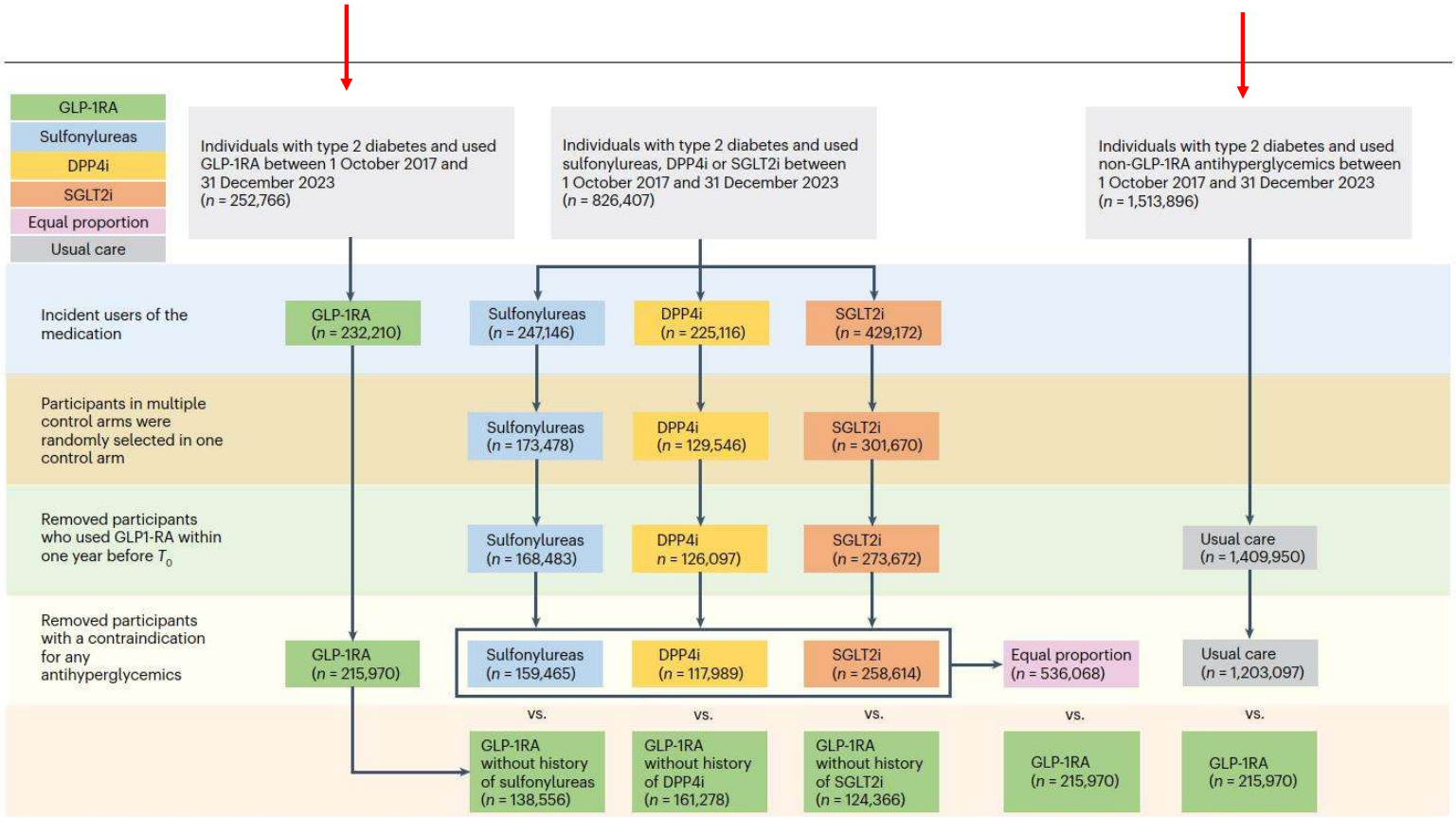
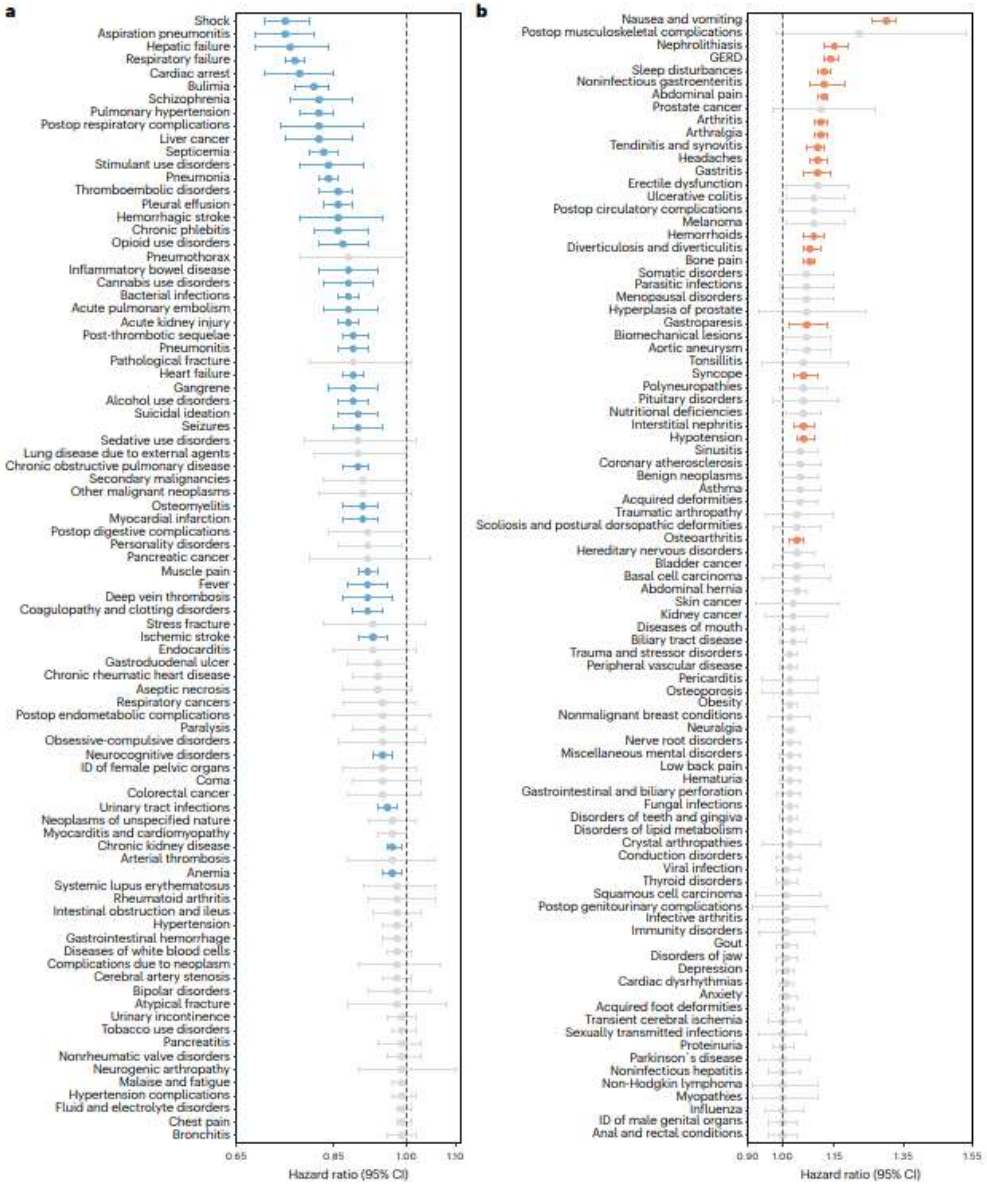


Fig. 1 | Cohort construction flow chart. The equal-proportion control group was composed of an equal proportion of incident users of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors. The usual care control group represents individuals who continued the use of non-GLP-1RA antihyperglycemics. GLP-1RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase 4 inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitors.

Unlocking the broad health benefits and risks of GLP-1 receptor agonist drugs

This study systematically analyzed 175 health outcomes in 2 million people using glucagon-like peptide-1 receptor agonists (GLP-1RAs) or other antihyperglycemics. GLP-1RAs reduce risks of neurocognitive, substance use, cardiovascular and respiratory disorders, but increase risks of gastrointestinal issues, hypotension and pancreatitis. The study provides important insights for clinical practice and future research.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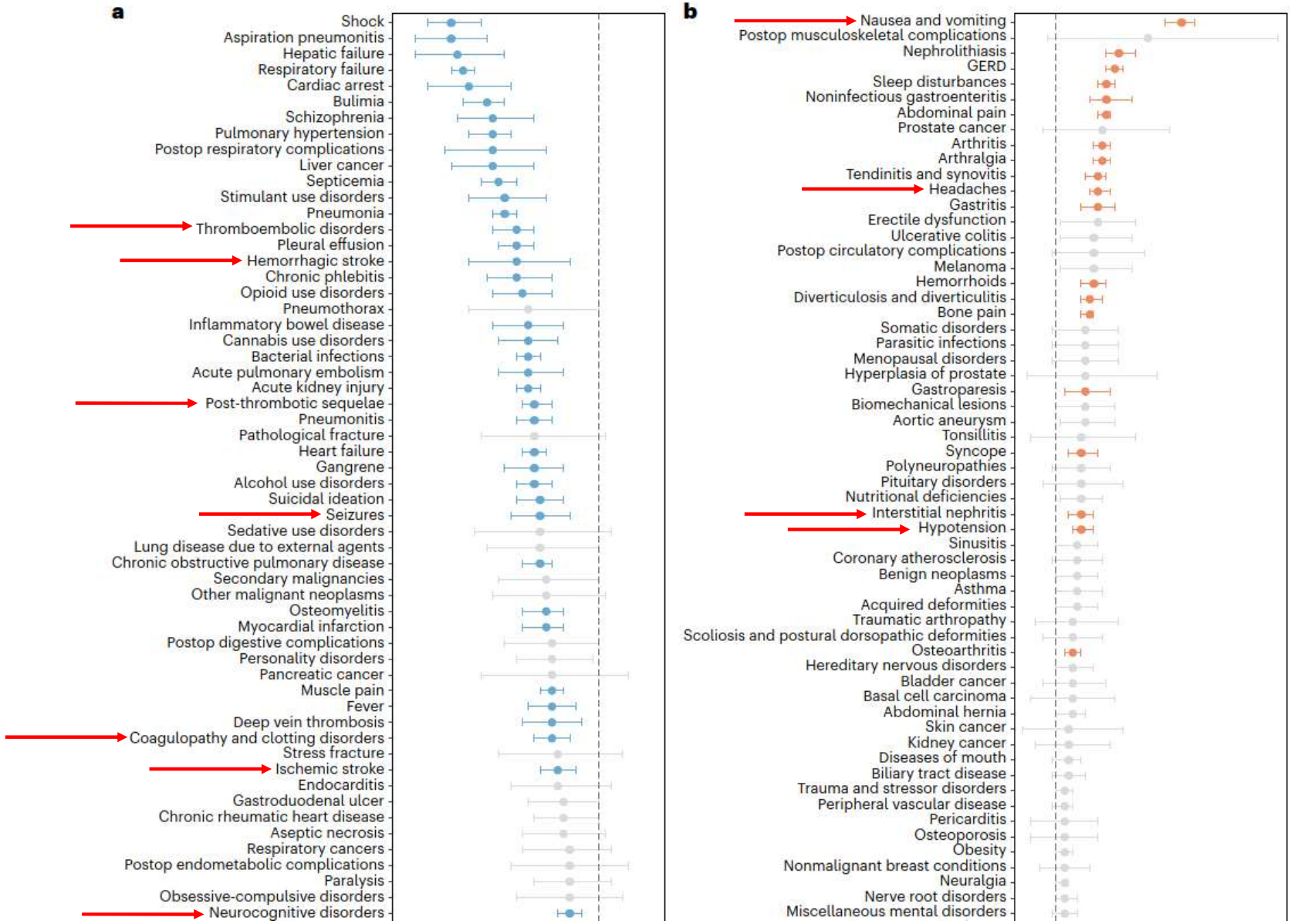
Shock
Aspiration pneumonitis
Hepatic failure
Respiratory failure
Cardiac arrest
Bulimia
Schizophrenia
Pulmonary hypertension
Postop respiratory complications
Liver cancer
Septicemia
Stimulant use disorders
Pneumonia
Thromboembolic disorders
Pleural effusion
Hemorrhagic stroke
Chronic phlebitis
Opioid use disorders
Pneumothorax
Inflammatory bowel disease
Cannabis use disorders
Bacterial infections
Acute pulmonary embolism
Acute kidney injury
Post-thrombotic sequelae
Pneumonitis
Pathological fracture
Heart failure
Gangrene
Alcohol use disorders
Suicidal ideation
Seizures
Sedative use disorders
Lung disease due to external agents
Chronic obstructive pulmonary disease
Secondary malignancies
Other malignant neoplasms
Osteomyelitis
Myocardial infarction
Postop digestive complications
Personality disorders
Pancreatic cancer
Muscle pain
Fever
Deep vein thrombosis
Coagulopathy and clotting disorders
Stress fracture
Ischemic stroke
Endocarditis
Gastroduodenal ulcer
Chronic rheumatic heart disease
Aseptic necrosis
Respiratory cancers
Postop endometabolic complications
Paralysis
Obsessive-compulsive disorders
Neurocognitive disorders
ID of female pelvic organs
Coma
Colorectal cancer
Urinary tract infections
Neoplasms of unspecified nature
Myocarditis and cardiomyopathy
Chronic kidney disease
Arterial thrombosis
Anemia
Systemic lupus erythematosus
Rheumatoid arthritis
Intestinal obstruction and ileus
Hypertension
Gastrointestinal hemorrhage
Diseases of white blood cells
Complications due to neoplasm
Cerebral artery stenosis
Bipolar disorders
Atypical fracture
Urinary incontinence
Tobacco use disorders
Pancreatitis
Nonrheumatic valve disorders
Neurogenic arthropathy
Malaise and fatigue
Hypertension complications
Fluid and electrolyte disorders
Chest pain
Bronchitis
0.65
0.85
1.00
1.30
Hazard ratio (95% CI)
b
Nausea and vomiting
Postop musculoskeletal complications
Nephrolithiasis
GERD
Sleep disturbances
Noninfectious gastroenteritis
Abdominal pain
Prostate cancer
Arthritis
Arthralgia
Tendinitis and synovitis
Headaches
Gastritis
Erectile dysfunction
Ulcerative colitis
Postop circulatory complications
Melanoma
Hemorrhoids
Diverticulosis and diverticulitis
Bone pain
Somatic disorders
Parasitic infections
Menopausal disorders
Hyperplasia of prostate
Gastroparesis
Biomechanical lesions
Aortic aneurysm
Tonsillitis
Syncope
Polyneuropathies
Pituitary disorders
Nutritional deficiencies
Interstitial nephritis
Hypotension
Sinusitis
Coronary atherosclerosis
Benign neoplasms
Asthma
Acquired deformities
Traumatic arthropathy
Scoliosis and postural dorsopathic deformities
Osteoarthritis
Hereditary nervous disorders
Bladder cancer
Basal cell carcinoma
Abdominal hernia
Skin cancer
Kidney cancer
Diseases of mouth
Biliary tract disease
Trauma and stressor disorders
Peripheral vascular disease
Pericarditis
Osteoporosis
Obesity
Nonmalignant breast conditions
Neuralgia
Nerve root disorders
Miscellaneous mental disorders
Low back pain
Hematuria
Gastrointestinal and biliary perforation
Fungal infections
Disorders of teeth and gingiva
Disorders of lipid metabolism
Crystal arthropathies
Conduction disorders
Viral infection
Thyroid disorders
Squamous cell carcinoma
Postop genitourinary complications
Infective arthritis
Immunity disorders
Gout
Disorders of jaw
Depression
Cardiac dysrhythmias
Anxiety
Acquired foot deformities
Transient cerebral ischemia
Sexually transmitted infections
Proteinuria
Parkinson's disease
Noninfectious hepatitis
Non-Hodgkin lymphoma
Myopathies
Influenza
ID of male genital organs
Anal and rectal conditions
0.90
1.00
1.15
1.35
1.55
Hazard ratio (95% CI)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Shock
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Other malignant neoplasms
Osteomyelitis
Myocardial infarction
Postop digestive complications
Personality disorders
Pancreatic cancer
Muscle pain
Fever
Deep vein thrombosis
Coagulopathy and clotting disorders
Stress fracture
Ischemic stroke
Endocarditis
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Headaches
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Erectile dysfunction
Ulcerative colitis
Postop circulatory complications
Melanoma
Hemorrhoids
Diverticulosis and diverticulitis
Bone pain
Somatic disorders
Parasitic infections
Menopausal disorders
Hyperplasia of prostate
Gastroparesis
Biomechanical lesions
Aortic aneurysm
Tonsillitis
Syncope
Polyneuropathies
Pituitary disorders
Nutritional deficiencies
Interstitial nephritis
Hypotension
Sinusitis
Coronary atherosclerosis
Benign neoplasms
Asthma
Acquired deformities
Traumatic arthropathy
Scoliosis and postural dorsopathic deformities
Osteoarthritis
Hereditary nervous disorders
Bladder cancer
Basal cell carcinoma
Abdominal hernia
Skin cancer
Kidney cancer
Diseases of mouth
Biliary tract disease
Trauma and stressor disorders
Peripheral vascular disease
Pericarditis
Osteoporosis
Obesity
Nonmalignant breast conditions
Neuralgia
Nerve root disorders
Miscellaneous mental disorders

Late Breaking News: Oceanic-Stroke

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

OCEANIC STROKE

Date: 23 November 2025

OCEANIC-STROKE

Dear OCEANIC-STROKE Investigators,

The topline results of the OCEANIC-STROKE trial have been released by Bayer.

A press release has been distributed to media outlets at 5 pm CET and is available here: *Bayer's Asundexian Met Primary Efficacy and Safety Endpoints in Landmark Phase III OCEANIC-STROKE Study in Secondary Stroke Prevention*.

We are pleased to inform you that OCEANIC-STROKE met its primary efficacy & safety endpoint. Asundexian, 50 mg once daily, in combination with antiplatelet therapy, significantly reduced the risk of ischemic stroke compared to placebo plus antiplatelet therapy in patients after a non-cardioembolic ischemic stroke or high-risk transient ischemic attack without increasing significantly ISTH major bleeding.

Medscape

Anti-Obesity Medications Set to Explode Entering 2026

Julie Peck

October 22, 2025

With the supply of GLP-1 medications finally stabilizing as their use skyrocketed 600% among Americans from 2018 to 2024, the pharmaceutical landscape for anti-obesity medications is now poised to undergo another monumental shift.

Thank you!

UT Southwestern
Medical Center