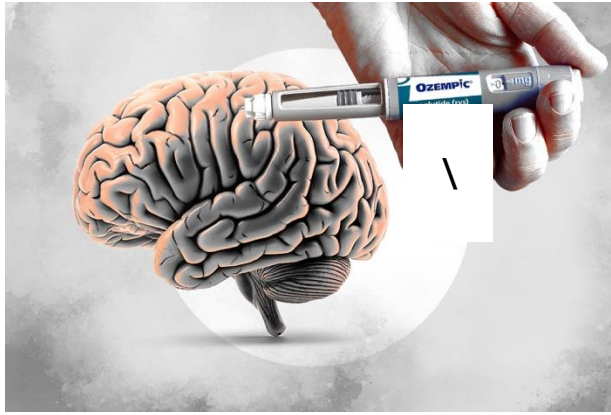


GLP-1 Therapy and the Brain

Arthi Thirumalai

Associate Professor, UW School of Medicine

Section Head of Endocrinology at Harborview Medical Center

November 14th, 2025

UW Project Echo Dementia

Disclosures

- Research funding from Fractyl Health
- Consultant Novo Nordisk Inc.

Learning Objectives

- Review the impact of metabolic health on the brain
- Understand the impact of weight loss and glycemic improvement on the brain
- Overview of the pharmacology of GLP-1 therapy
- Understand the effects of GLP-1 on the brain
- Review the clinical evidence behind GLP-1 therapy use and cognitive outcomes
- Review evidence behind GLP-1 therapy and substance use disorders
- Review sub-group analyses of GLP-1 therapy and stroke risk
- Review data on GLP-1 therapy use and movement disorders

Clinical Case

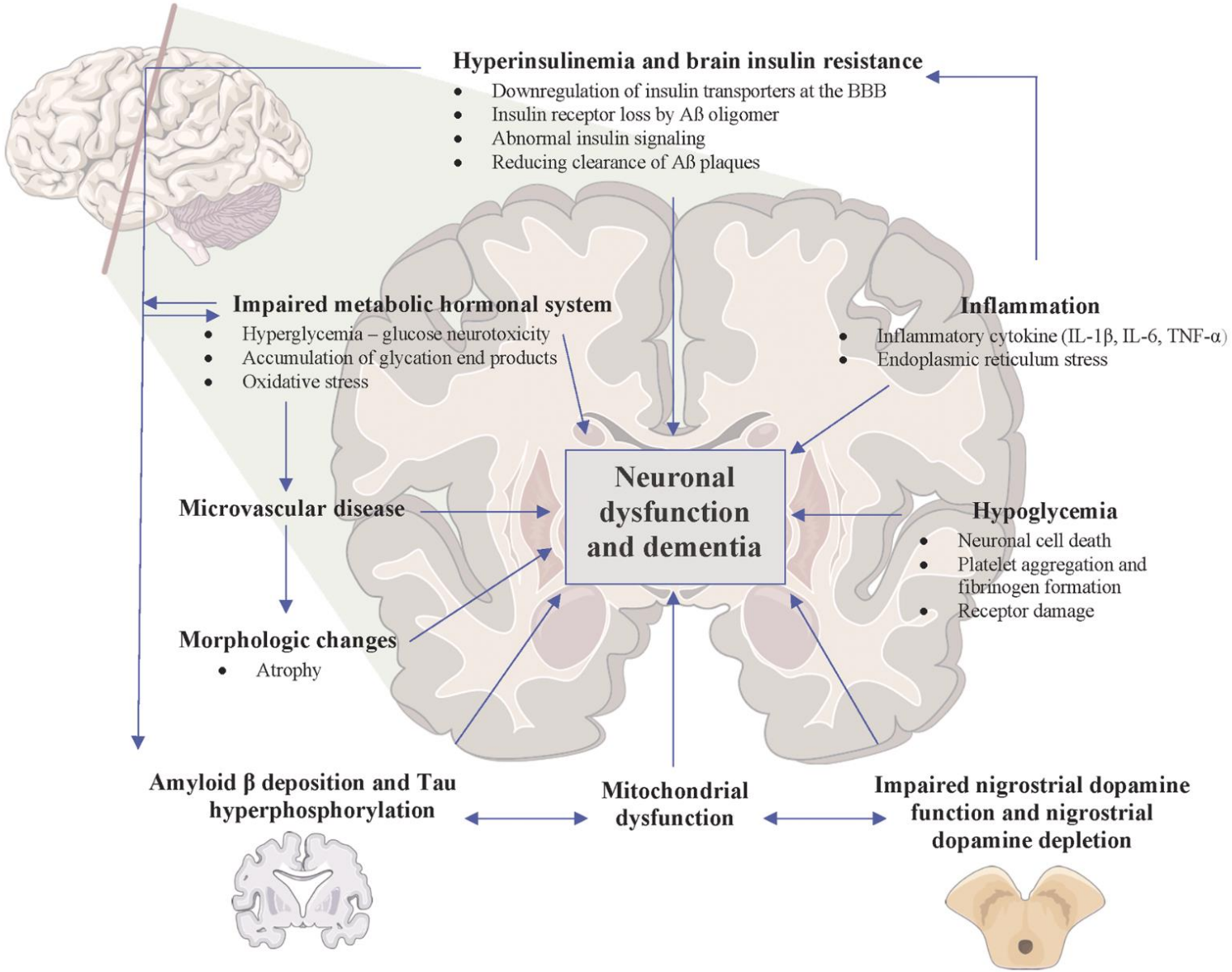
- 57/F with type 1 diabetes of 44 years' duration. Currently using an insulin pump for management. No known DM complications
- PMH: Hyperlipidemia
- Current Meds: Insulin pump, atorvastatin, multivitamin
- Exam: P 60, BP 115/73, BMI 22.9 kg/m^2
- Labs: HbA1C 6.4%, LDL-C 50 mg/dL, TSH 1.687 mIU/mL
- She asked if she should take Ozempic to protect against dementia?

Metabolic Disorders and the Brain

- CDC reports that 38 million Americans have diabetes (11.6%)
- Over 100 million Americans live with obesity (40.3%)
- CDC reports that 11.3% of Americans have Alzheimer's or mild cognitive impairment
- A meta-analysis of 15 trials showed that diabetes increases the the risk of all forms of dementia by 1.7X (95% CI 1.5-1.8)
- Cohort study of 5 million patients showed that central obesity (measured by waist circumference) increased the risk of cognitive impairment or dementia 1.1X (95% CI 1.05-1.15)
  - HR was 1.13 (95% CI .108-1.19) in age>65 yrs

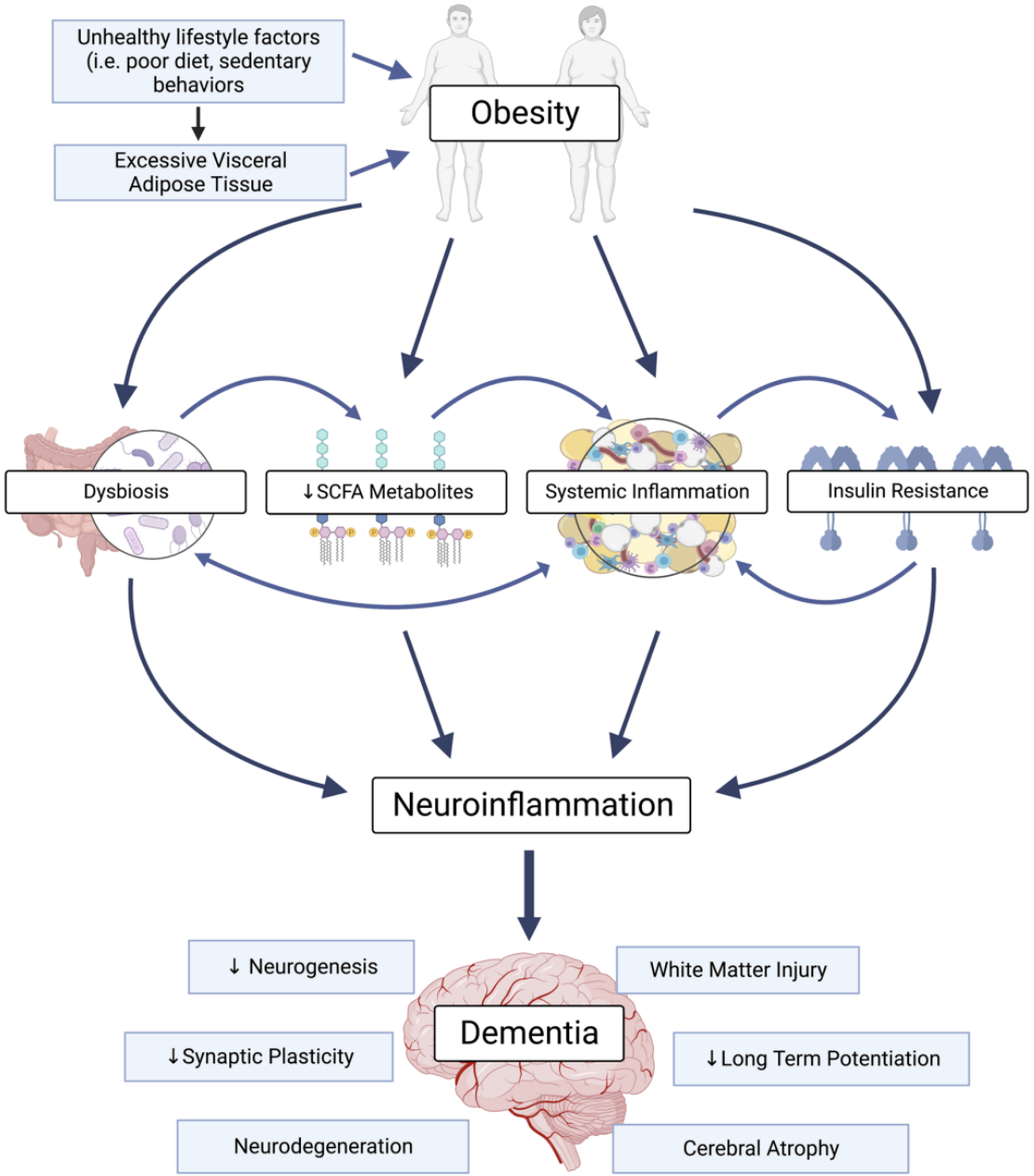
Curr Diab Rep 2014;14:487.
Neurosci Biobehav Rev. 2021 Nov:130:301-313.

Diabetes and Dementia – Pathophysiology



Diabetes Metab. 2023 Sep;49(5):101470.

Obesity and Dementia – Pathophysiology



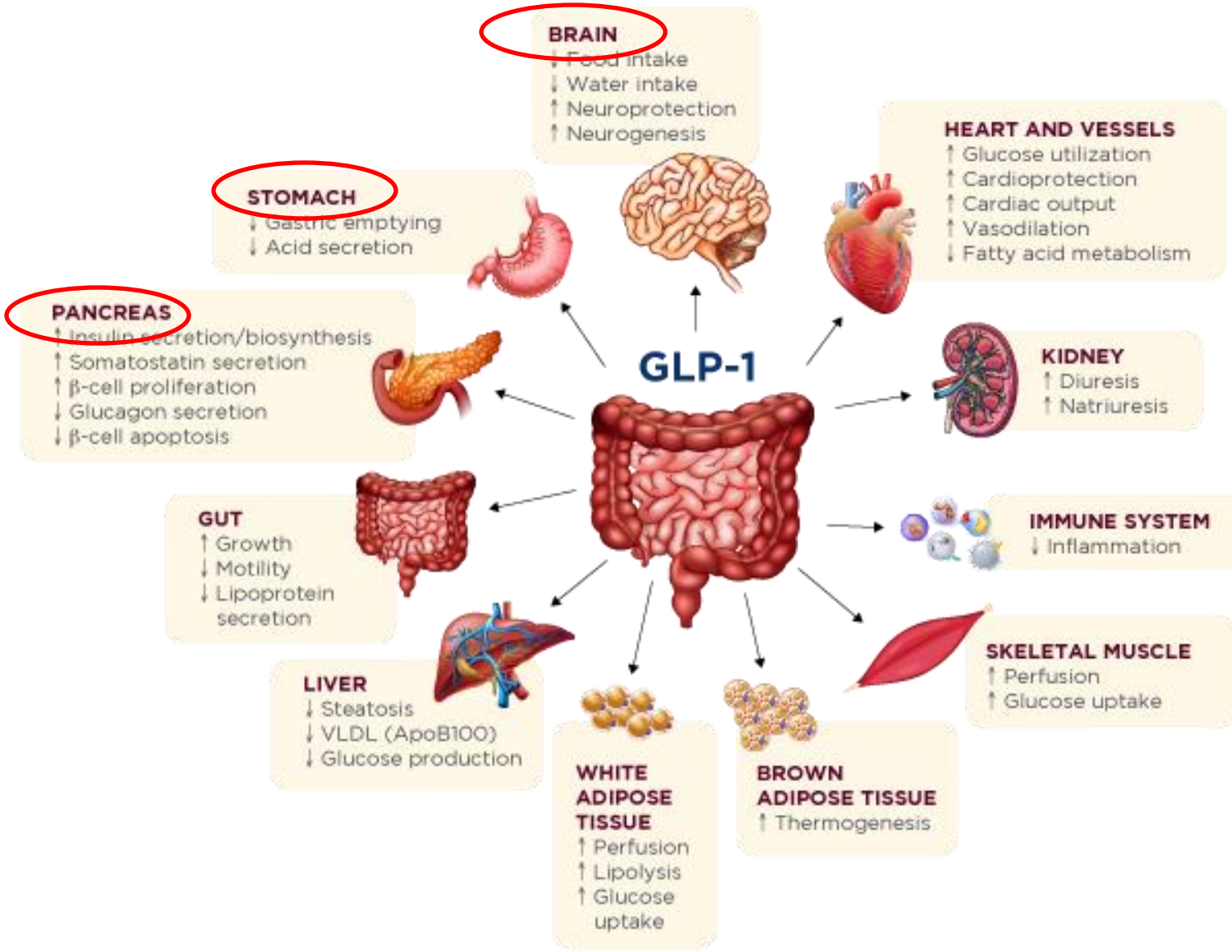
NeuroMolecular Medicine (2023) 25:451–456.

Impact of Improved Metabolic Health on the Brain

- Studies of various glucose-lowering agents show that treated patients have lower risk of cognitive decline than those untreated
- Patients with higher HbA1C and plasma glucose are associated with lower brain volume and cognitive function than those with lower values
- One meta-analysis showed that weight loss was associated with an increased risk of all dementia (in normal and overweight patients)
- Another cohort study showed that weight loss in normal weight patients resulted in increased dementia risk, but not in those with obesity

Alzheimers Res Ther. 2024 Dec 23;16(1):272.
Diabetes Res Clin Pract. 2025 Aug:226:112366.
Curr Alzheimer Res. 2021;18(2):125-135.
Alzheimer's Dement. 2023;19:5471–5481.

Actions of GLP-1



Decrease in plasma glucose

Weight reduction

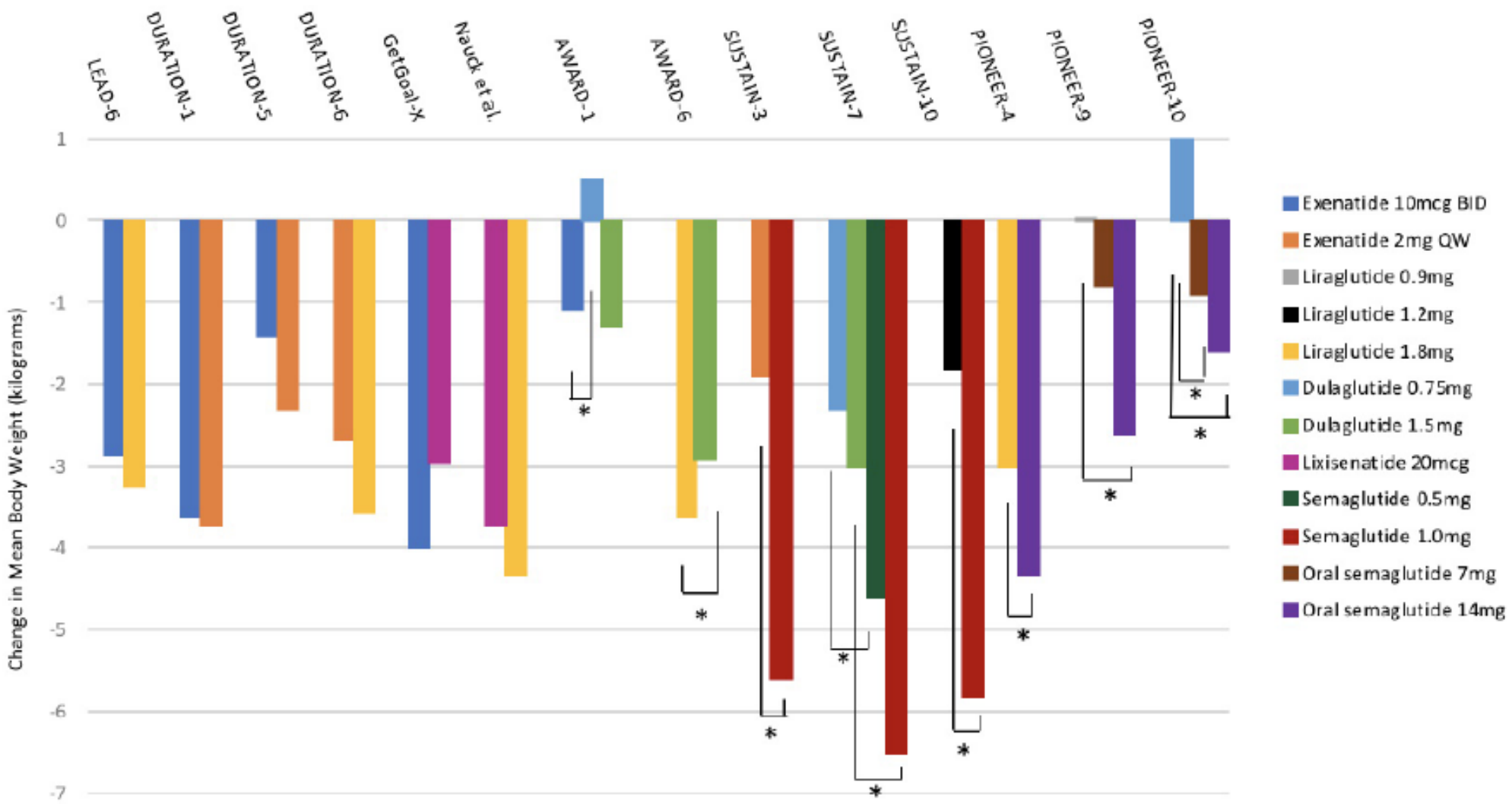
Non-glycemic benefits

Adapted from Nat Rev Nephrol 13, 605–628 (2017).

Current GLP-1Ra/Dual Agonists

Chemical Name	Trade Name	Available Doses	Dosing Frequency	Route of Administration	Pharma Co.
Exenatide	Byetta	5 mcg, 10 mcg	Twice Daily	SQ	AstraZeneca
Exenatide ER	Bydureon, Bydureon BCise	2 mcg	Once weekly	SQ	AstraZeneca
Lixisenatide*	Adlyxin*/Soliqua	10 mcg, 20 mcg	Once daily	SQ	Sanofi
Liraglutide	Victoza/Saxenda/Generic	0.6 mg, 1.2 mg, 1.8 mg, 3.0 mg	Once daily	SQ	Novo Nordisk
Dulaglutide	Trulicity	0.75 mg, 1.5 mg, 3 mg, 4.5 mg	Once weekly	SQ	Eli Lilly
Semaglutide	Ozempic/Wegovy	0.25 mg, 0.5 mg, 1 mg, (1.7 mg W), 2 mg, 2.4 mg W)	Once weekly	SQ	Novo Nordisk
Semaglutide	Rybelsus	3 mg, 7 mg, 14 mg	Once daily	PO	Novo Nordisk
Tirzepatide#	Mounjaro/Zepbound	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Once weekly	SQ	Eli Lilly

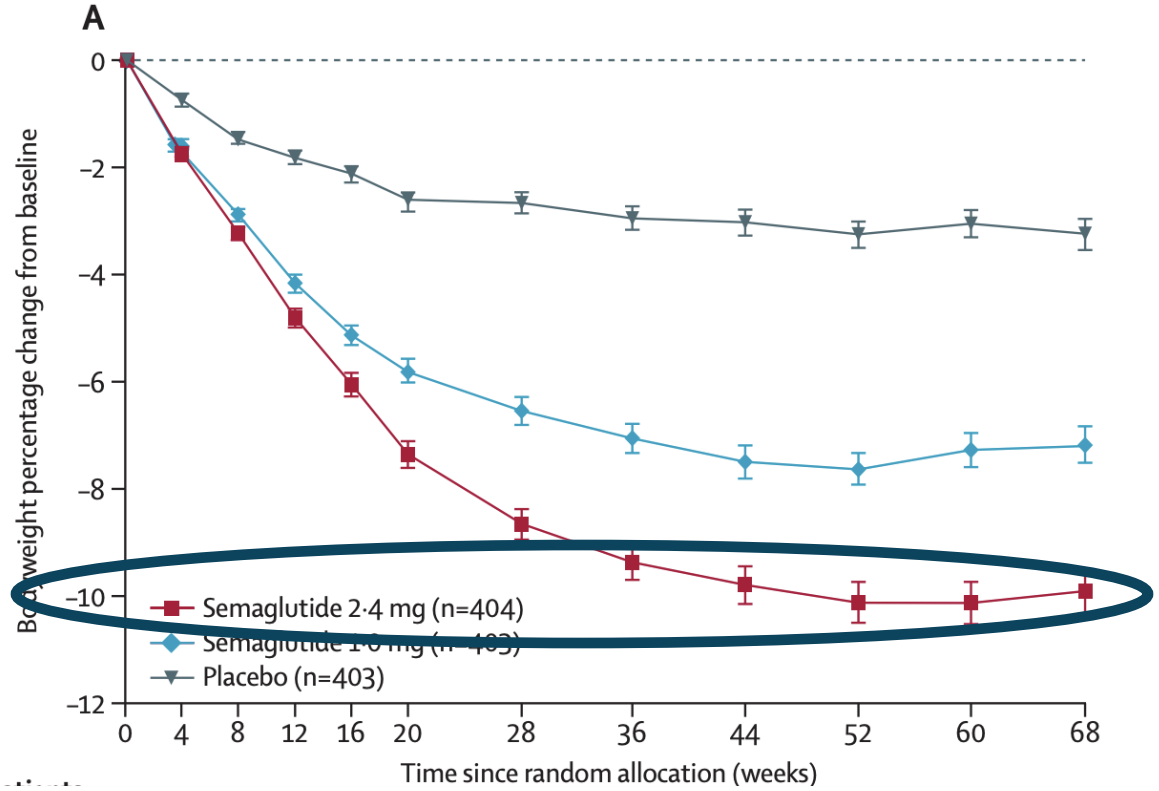
Weight Loss Benefits



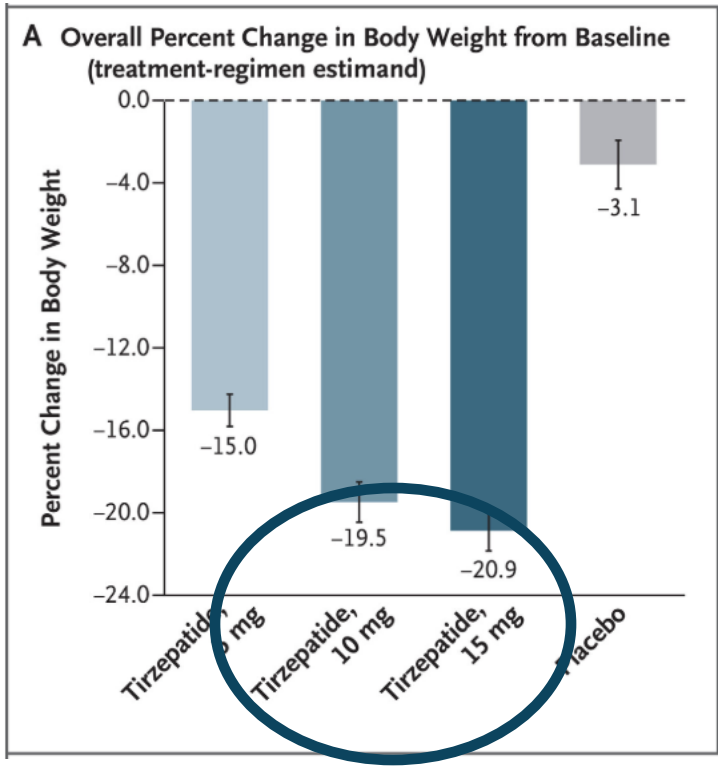
Semaglutide >> Liraglutide > Dulaglutide > Exenatide QW= Exenatide BID = Lixisenatide

Ther Adv Endocrinol Metab 2021, Vol. 12: 1–15.

More Potent Agents

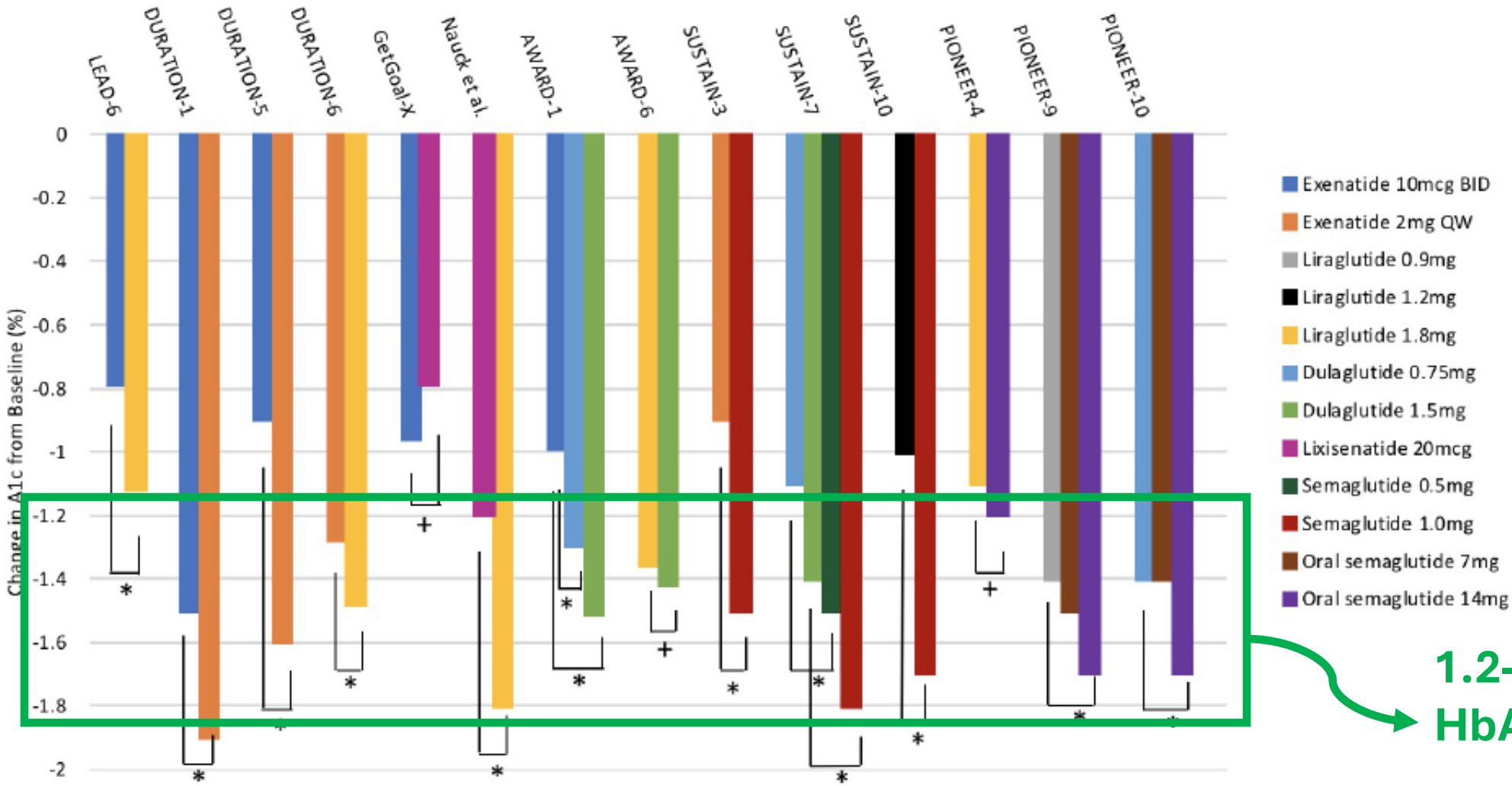


Davies et al. Lancet 2021; 397: 971–84



Jastreboff et al. N Engl J Med 2022;387:205-216.

Glycemic Efficacy



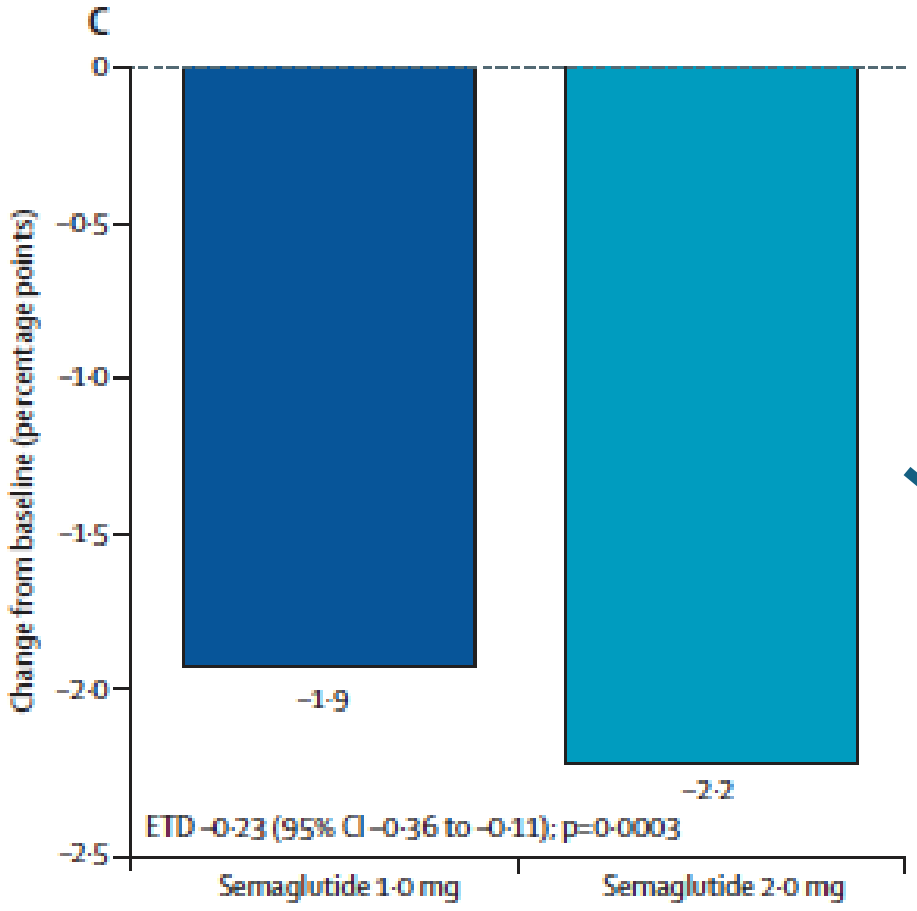
1.2-1.8 % ↓ in HbA1c

Semaglutide > Liraglutide=Dulaglutide > Exenatide QW> Lixisenatide=Exenatide BID

Ther Adv Endocrinol Metab 2021, Vol. 12: 1–15.

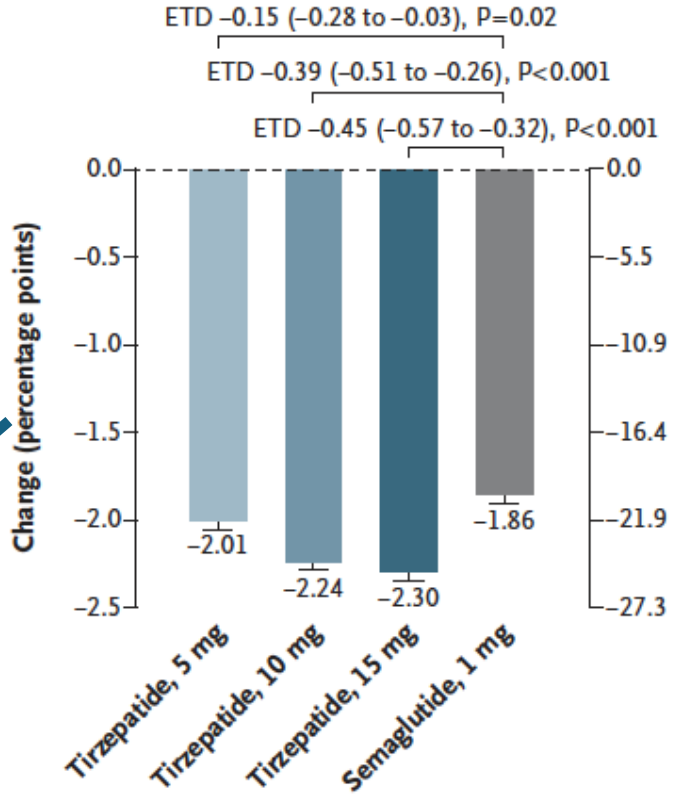
Results: More Potent Agents

Semaglutide 2 mg



Lancet Diabetes Endocrinol. 2021 Sep;9(9):563-574.

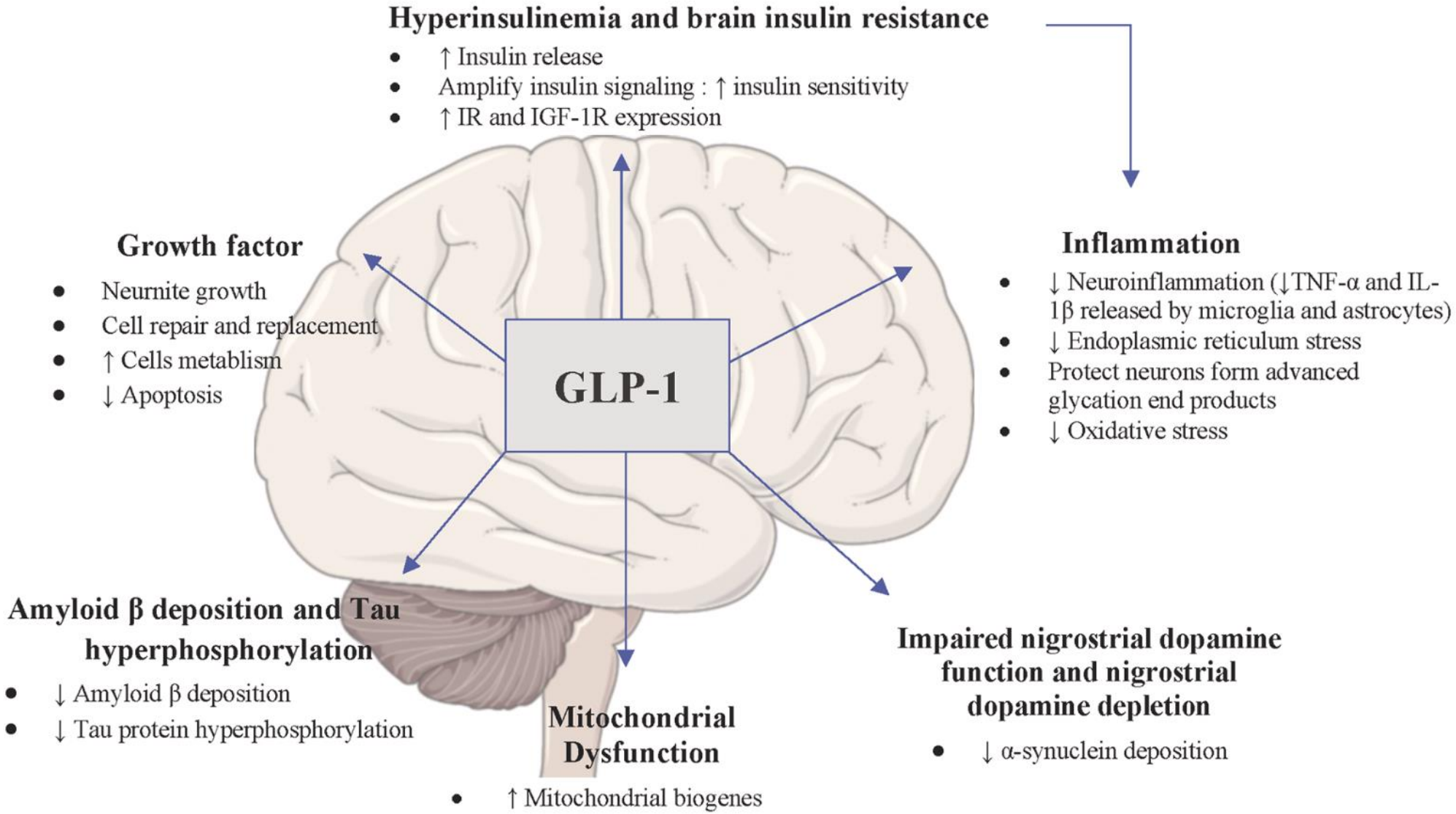
Tirzepatide



N Engl J Med 2021;385:503-15.

2.2% ↓ in HbA1c

Effects of GLP-1 on Cognition

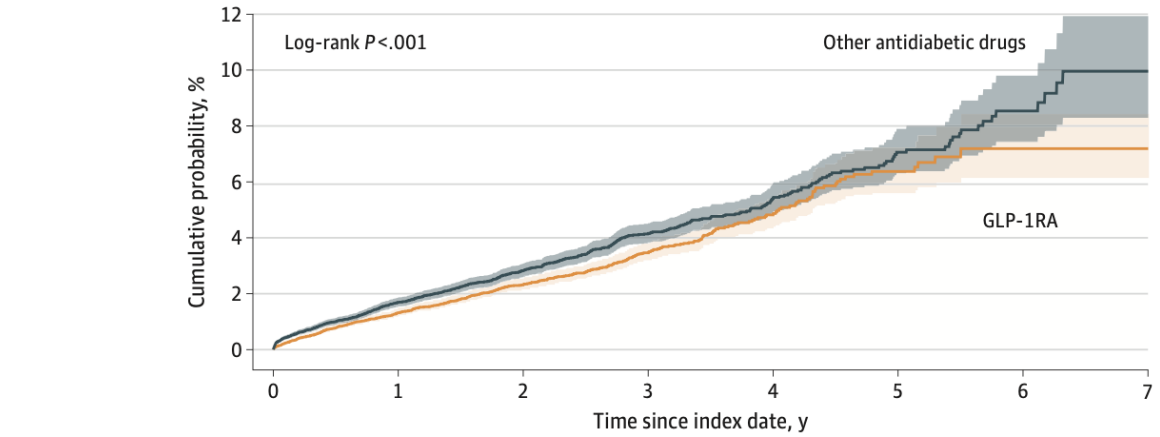


Diabetes Metab. 2023 Sep;49(5):101470.

GLP-1 vs Other Glucose-lowering Agents

- Retrospective cohort study using electronic database (TriNetX US)
- N~60,000; 7-year follow-up
- Age >40, type 2 DM, starting on semaglutide or tirzepatide (GLP-1RA) or other DM meds (other)
- Primary outcome: incidence of neurodegenerative diseases (dementia, Parkinson disease, and mild cognitive impairment) and cerebrovascular (stroke and intracerebral hemorrhage) diseases
- Secondary outcome: all-cause mortality
- Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% CIs.

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

Lower risk of:

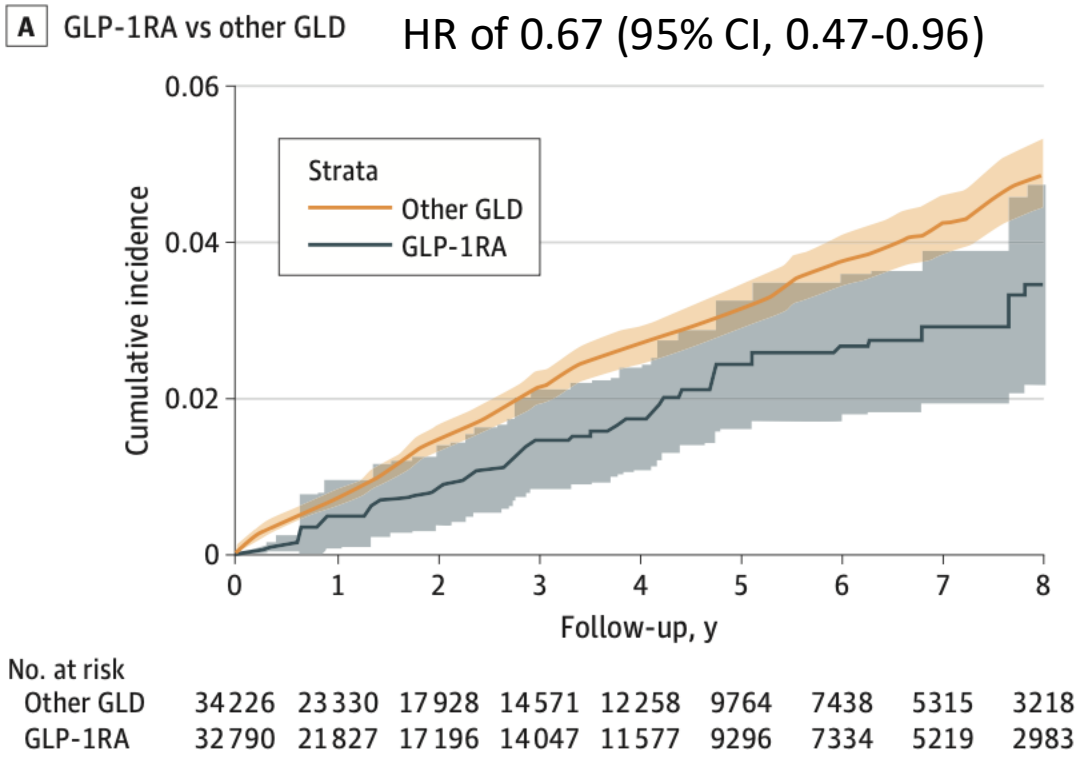
- Dementia (HR, 0.63; 95% CI, 0.50-0.81)
- Stroke (HR, 0.81; 95% CI, 0.70-0.93)
- All-cause mortality (HR, 0.70; 95% CI, 0.63-0.78)

No difference in the risk of Parkinson disease or intracerebral hemorrhage

JAMA Network Open. 2025;8(7):e2521016.

GLP-1 vs Other Agents for Alzheimer's

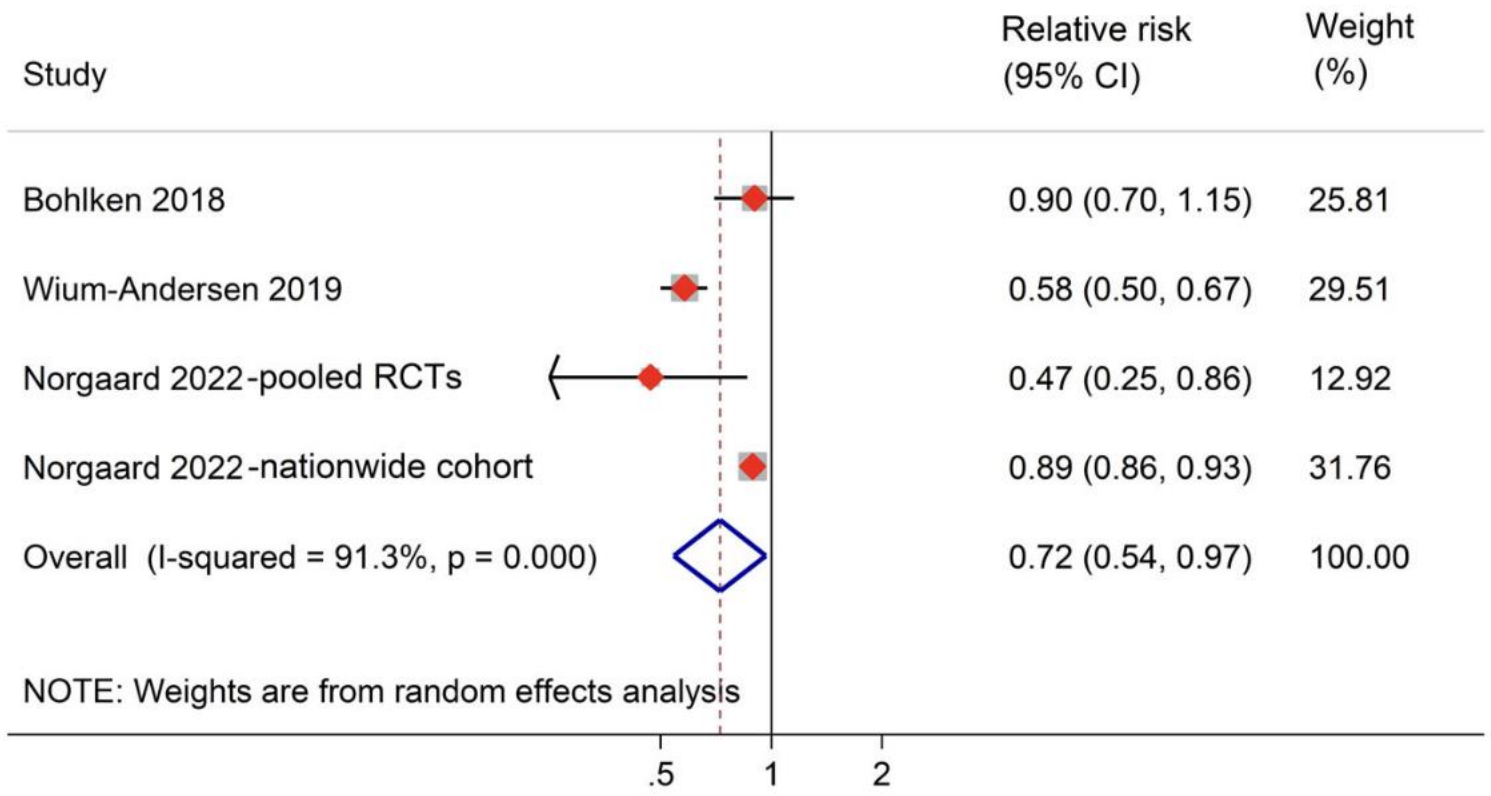
- Target trial emulation study using EHR
- N~34,000; 9-year follow-up
- Age >50, type 2 DM, starting GLP-1RA vs other glucose lowering agents
- Primary outcome: Alzheimer's disease or related dementias (clinical diagnosis code)
- Cox proportional hazard regression models with inverse probability of treatment weighting (IPTW) to adjust for potential confounders.



JAMA Neurol. 2025;82(5):439-449.

GLP-1 and All-cause Dementia

- Meta-analysis of 5 studies with GLP-1Ra use
- Lower overall risk of all-cause dementia with GLP-1Ra use



J Am Geriatr Soc. 2023 Jul;71(7):2096-2106.

Dulaglutide and Cognitive Impairment

- Secondary Analysis from REWIND trial (CVOT in type 2DM patients)
- Cognitive function assessed with MOCA and DSST
- N~5000 1:1 dulaglutide or placebo
- F/u 5.4 years
- Primary outcome: first occurrence of a score ≥ 1.5 SD below baseline score

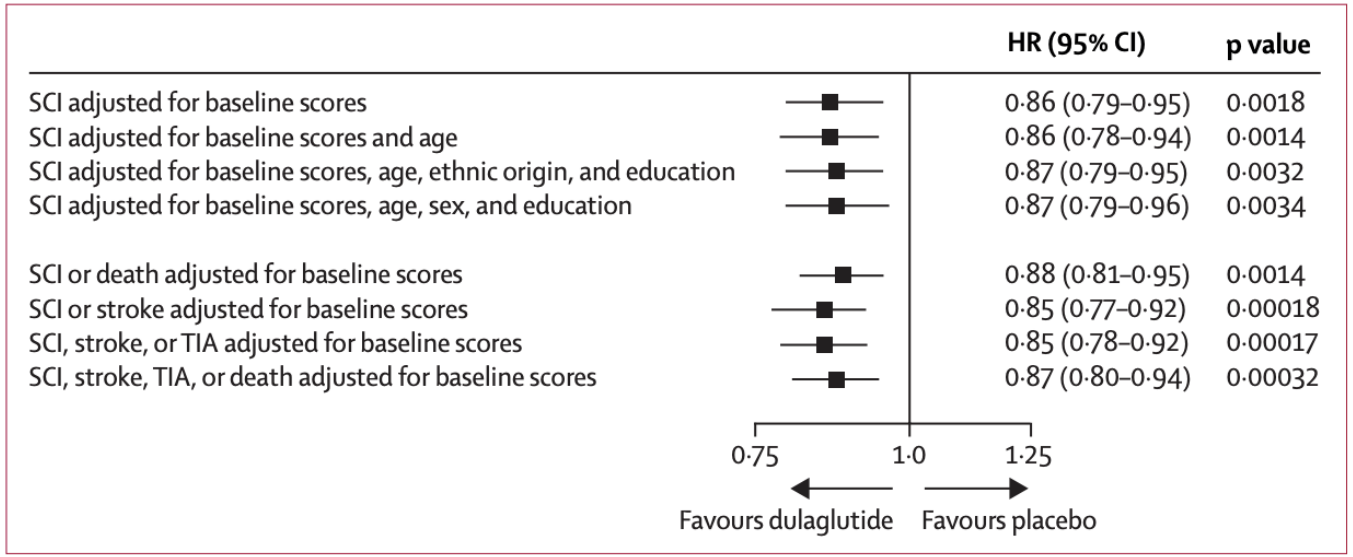
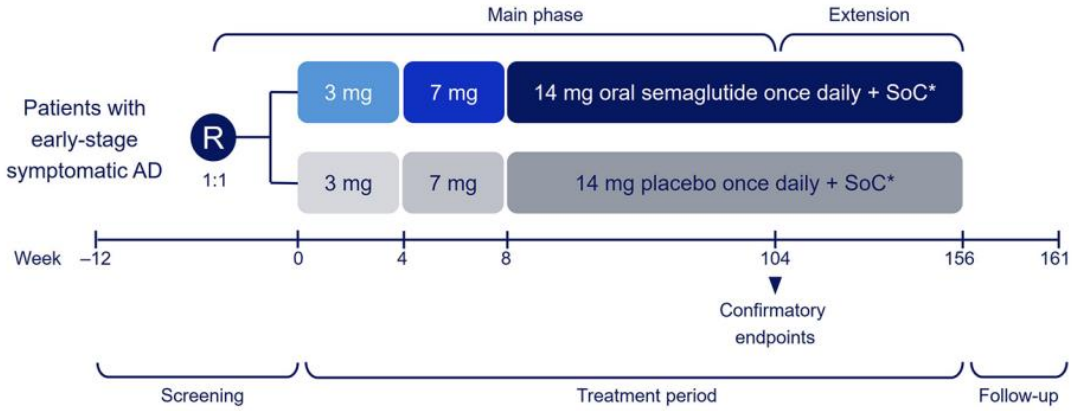


Figure 1: **Risk of SCI, adjusted for baseline standardised MoCA and DSST scores**

Lancet Neurol 2020; 19: 582–90.

Clinical Trials of Semaglutide

- EVOKE and EVOKE+ are ongoing phase 3 RCTs
- Testing efficacy, safety and tolerability of once daily PO Semaglutide vs placebo in early-stage symptomatic Alzheimer's disease
- Age 55-85 years with mild cognitive impairment or dementia with confirmed amyloid abnormalities (PET or CSF)
- **Primary outcome:** difference on change from baseline to week 104 in the Clinical Dementia Rating – Sum of Boxes score
- **Secondary outcomes:** Analyses of plasma biomarkers and a CSF sub-study (planned n=210) will explore semaglutide effects on AD biomarkers and neuroinflammation

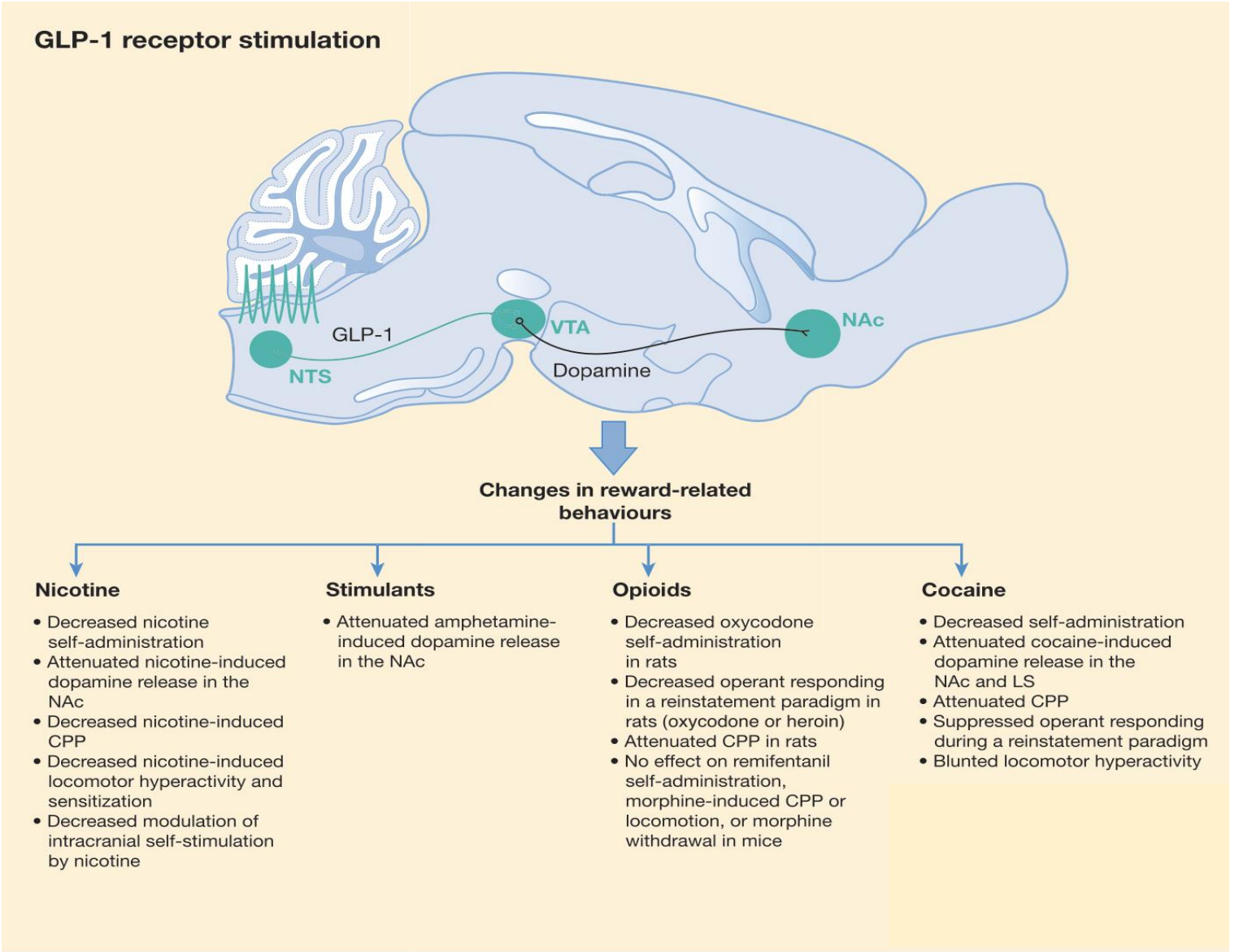


Trial enrollment completed 5/2021 to 9/2023. Main rx period completed 9/2025. Extension period will end 10/2026.

Alzheimers Res Ther. 2025 Jan 8;17(1):14.

GLP-1 and Substance Use Disorder

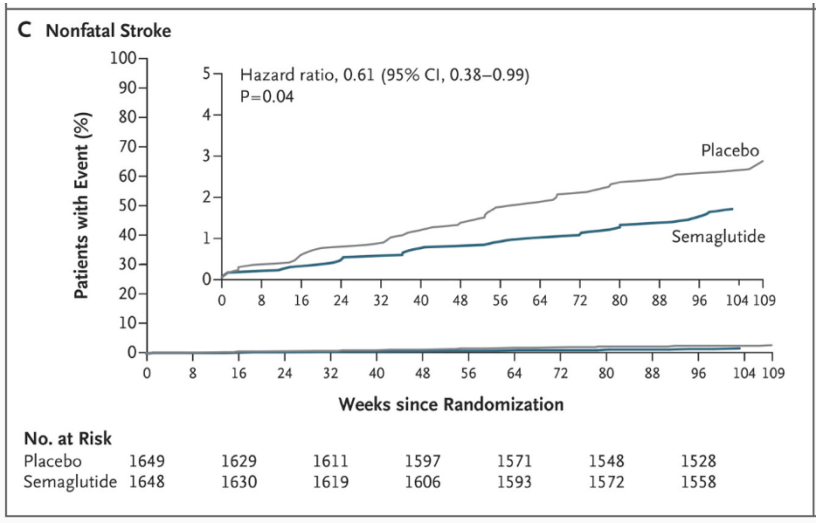
GLP-1R	Outcome
GLP-1R agonists	Reduced desire to consume alcohol, interest in alcohol, and alcohol consumption in patients treated for obesity or diabetes type 2
	Lowered alcohol-related events posted online in patients treated for obesity or diabetes type 2
Exenatide (Ex4)	Decreased alcohol intake in overweight alcohol use disorder (AUD) patients
Liraglutide	Lowered self-reported alcohol intake in patients with type 2 diabetes
Dulaglutide	Decreased alcohol intake in smoking AUD patients
Semaglutide	Lowered binge drinking, Alcohol Use Disorders Identification Test (AUDIT) scores, and self-reported alcohol intake in overweight individuals with high alcohol intake
	Reduced the AUDIT scores in overweight patients with AUD co-morbidity
	Reduced alcohol-related posts in social media among overweight individuals and those with type 2 diabetes
	Reduction in stimulatory and sedative effects



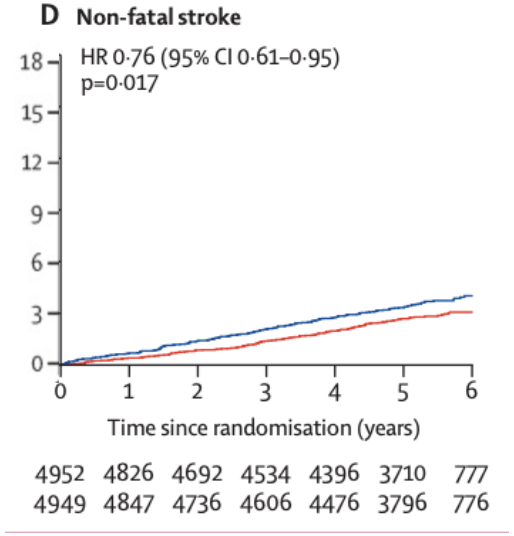
Endocrinology, Volume 166, Issue 4, April 2025, bqaf028.

Br J Pharmacol. 2022;179:625–641.

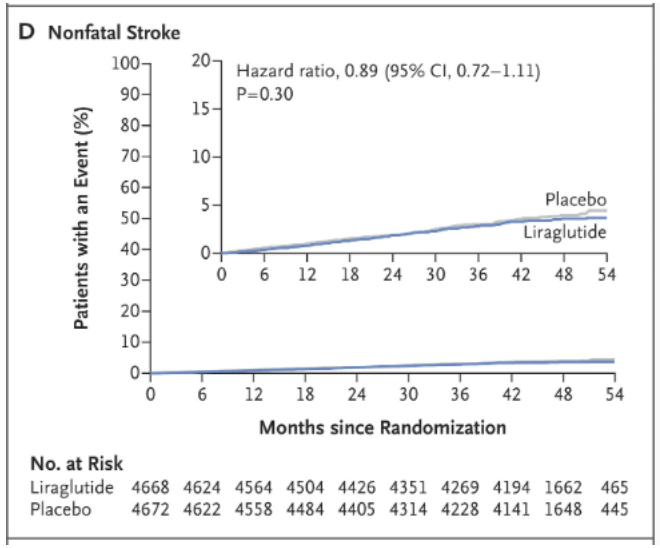
GLP-1Ra Therapy and Stroke Risk Reduction – Diabetes Patients



Semaglutide in DM: SUSTAIN-6 Trial
N Engl J Med 2016;375:1834-1844.



Dulaglutide in DM: REWIND Trial
Lancet 2019; 394: 121–30.



Liraglutide in DM: LEADER Trial
N Engl J Med 2016;375:311-322.

SURPASS-CVOT Trial of Tirzepatide in DM patient announced the risk of cardiovascular death, heart attack, or stroke was 8% lower for tirzepatide versus dulaglutide (hazard ratio [HR], 0.92; 95.3% CI, 0.83 to 1.01). Sub-group data not yet published

GLP-1Ra Therapy and Stroke Risk Reduction – Obese Patients

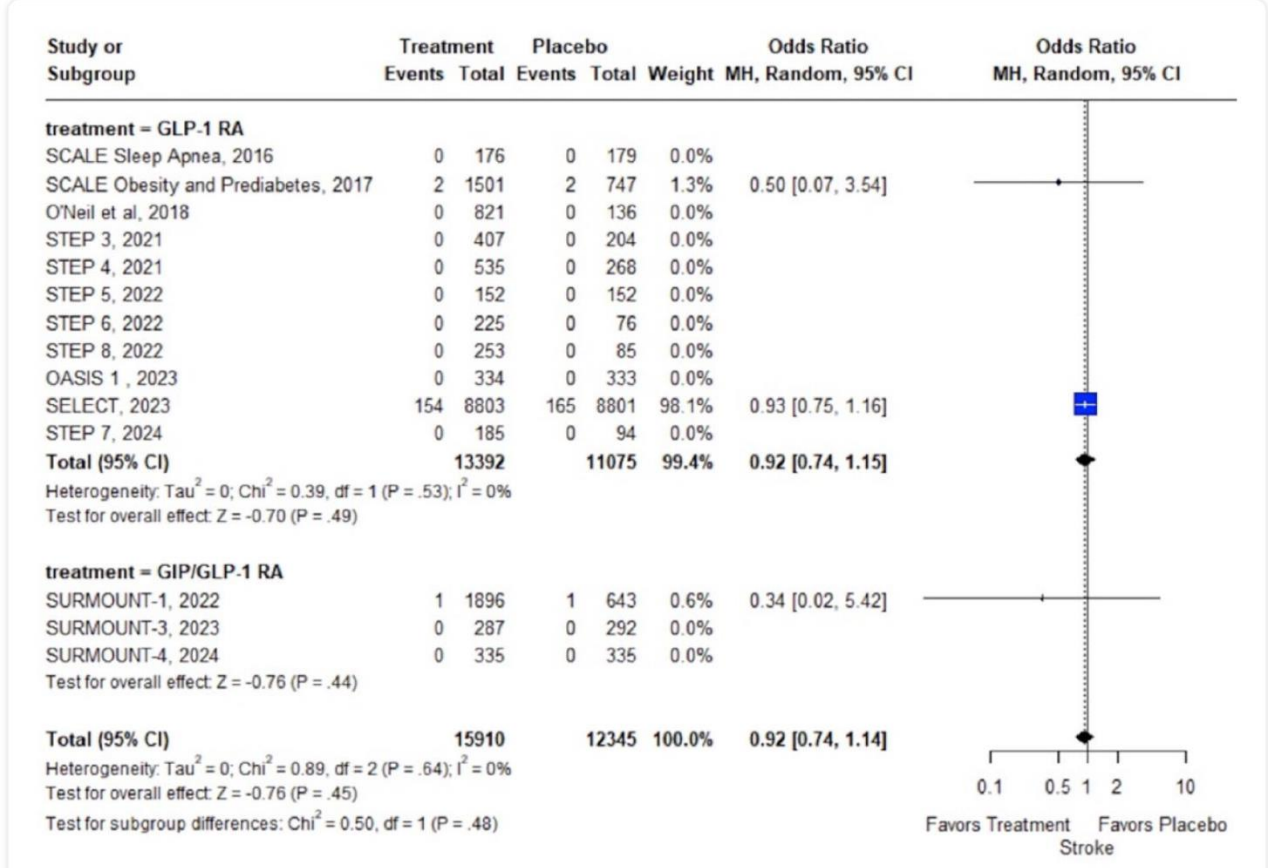


Figure 4. Forest plot comparing the risk of stroke in overweight or obese adults without diabetes treated with GLP-1 or GIP/GLP-1 RAs versus placebo.

Therapeutic Advances in Neurological Disorders. 2024;17.

GLP-1Ra and Stroke Risk (Meta-analysis)

TABLE 1 Absolute Event Rates and Risk Reduction

	Event Count GLP-1 RA	Patients GLP-1 RA	Absolute Risk, % GLP-1 RA	Event Count Control	Patients Control	Absolute Risk, % Control	RD (95% CI)	Trials Contributing to the Analysis, n
All-cause death	3,234	47,873	6.8	3,608	46,537	7.8	−0.008 (−0.011 to −0.005)	18
CV death	1,895	48,656	3.9	2,184	49,851	4.4	−0.006 (−0.008 to −0.003)	19
MACE	4,596	47,552	9.7	5,300	48,748	10.9	−0.015 (−0.018 to −0.011)	15
SAE	17,910	48,806	36.7	19,826	50,017	39.6	−0.035 (−0.051 to −0.018)	18
HF hospitalizations	1,067	34,603	3.1	1,257	37,151	3.4	−0.006 (−0.010 to −0.001)	14
Nonfatal MI	2,043	47,786	4.3	2,374	49,001	4.8	−0.006 (−0.009 to −0.003)	13
Nonfatal stroke	1,054	47,396	2.2	1,164	48,608	2.4	−0.002 (−0.004 to 0.000)	12

JACC. 2025;86:1805–1819.

GLP-1Ra and Parkinson's Disease

- Diabetes is a risk factor for Parkinson's disease
- Treatment of diabetes with GLP-1Ra has been shown to reduce the risk of incident Parkinson's by over 50%
- Animal models suggest GLP-1Ra are protective against Parkinson's
- In participants with early Parkinson's disease, lixisenatide therapy resulted in less progression of motor disability than placebo at 12 months in a phase 2 trial
- Two prior trials (23- and 48-months' duration) of exenatide have also shown similar results

Mov Disord 2023;38:162-177. *Brain* 2020;143:3067-3076.
Nat Med 2018;24:931-938. *N Engl J Med* 2024;390:1176-1185.
J Clin Invest 2013;123:2730-2736. *Lancet* 2017;390:1664-1675.

Conclusions

- Diabetes and obesity are risk factors for cognitive decline
- Treatment of diabetes has shown reduction in risk of the development of dementia and cognitive impairment
- GLP-1Ra have many proposed mechanisms by which they may lower the risk of dementia, including Alzheimer's disease
- Large RCT of semaglutide for treatment of Alzheimer's is currently underway
- Preclinical and early (not RCT) clinical studies suggests potential for benefit from GLP-1Ra therapy in substance use disorder
- Sub-group analyses of impact of GLP-1Ra therapy on stroke risk reduction is variable
- There may be preventive and therapeutic benefit from GLP-1Ra therapy in Parkinson's disease

THANK YOU

Questions?

arthidoc@uw.edu

TEACHING PEER EVALUATION:

Arthi Thirumalai, MBBS