

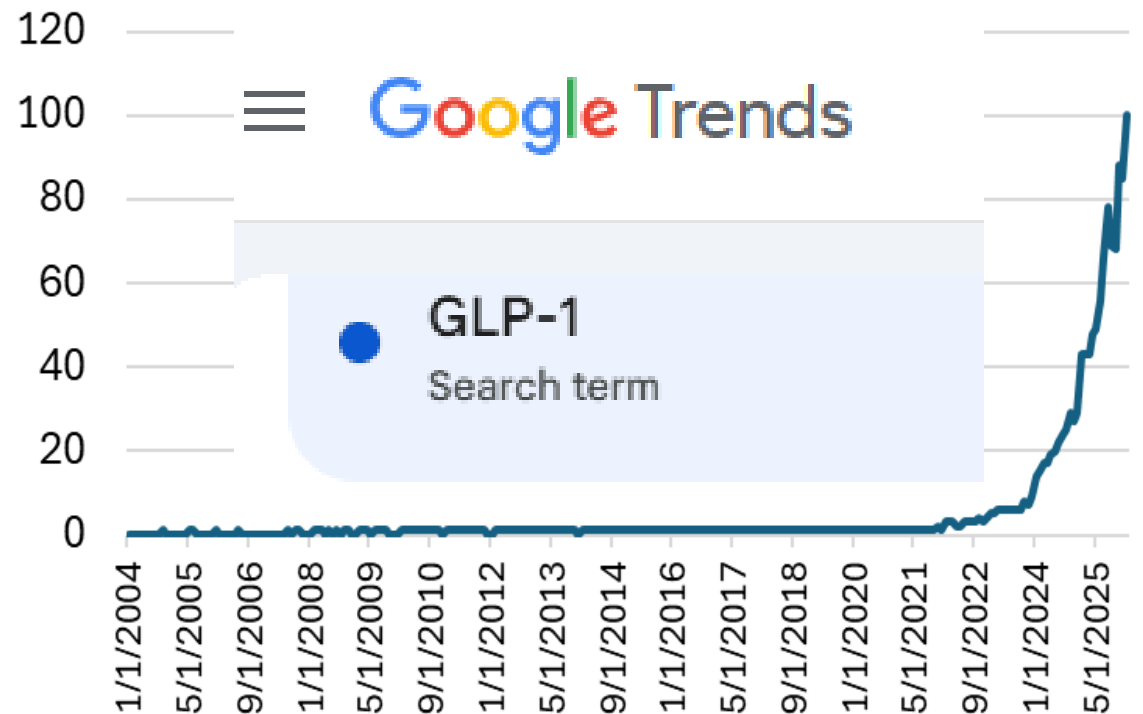
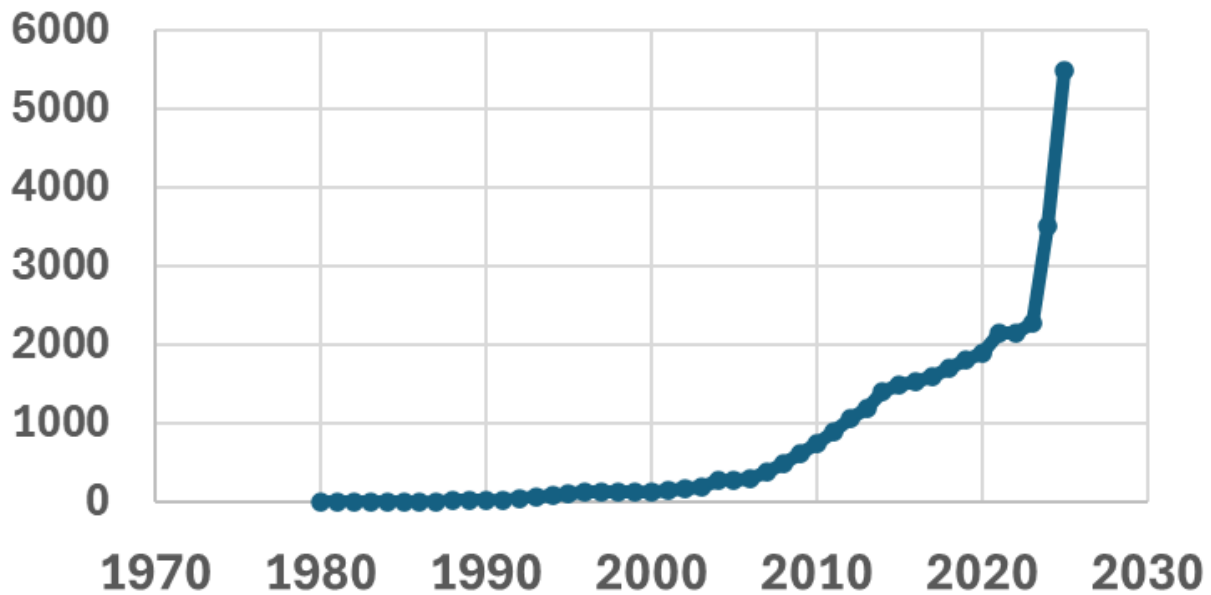


GLP-1 Receptor Agonists: Are They a Cure for Everything?

Todd T. Brown, MD, PhD
Professor of Medicine and Epidemiology
Division of Endocrinology, Diabetes, & Metabolism
Johns Hopkins University
Baltimore, Maryland, USA

The medications that have taken the world by storm

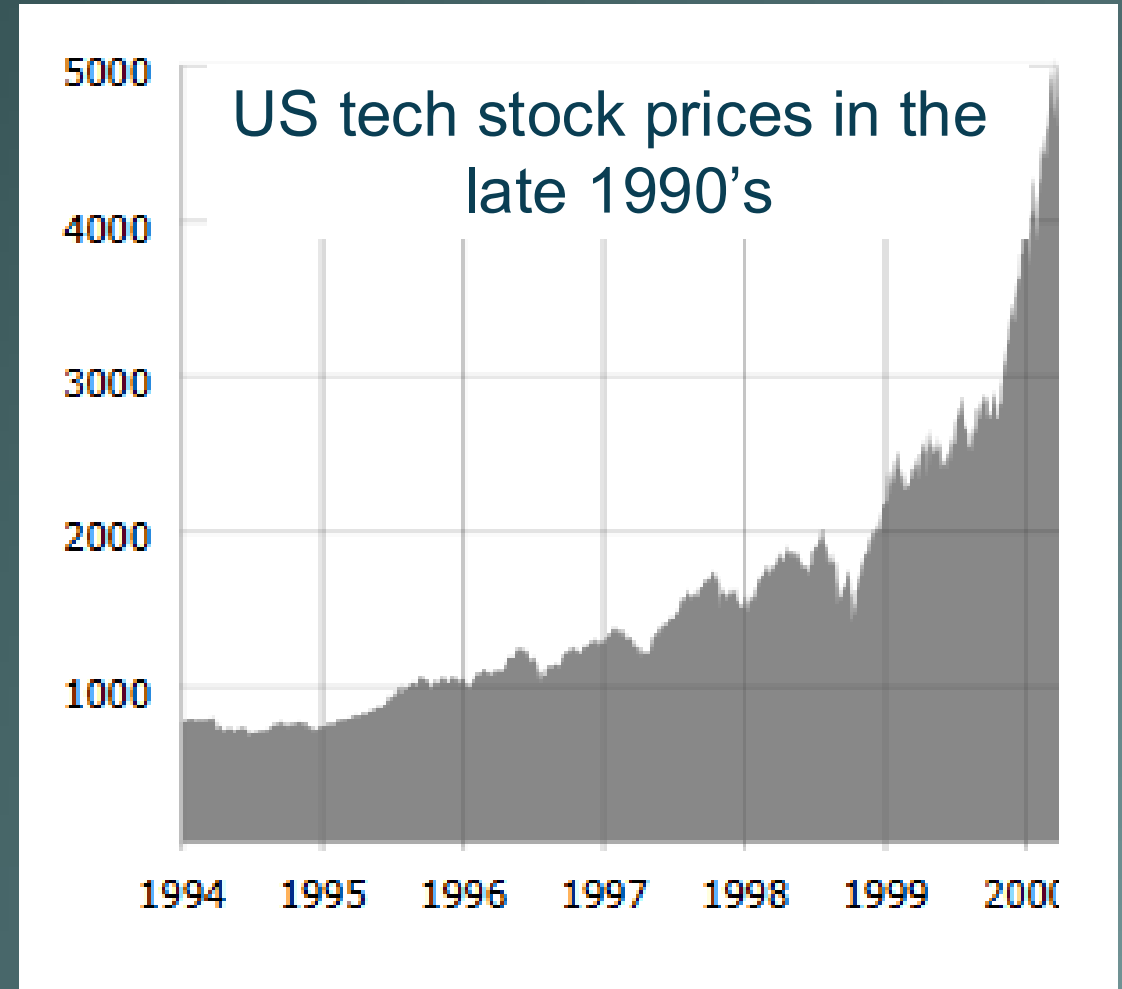
PubMed Articles "GLP-1"



1999 Dot Com Bubble: NASDAQ Composite Index

US Federal Reserve Board Chairman,
Alan Greenspan, 1996:

“Irrational Exuberance”





GLP-1 Receptor Agonists: Are They a Cure for Everything?

Is our exuberance rational or irrational?

Todd T. Brown, MD, PhD
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Outline

- What are incretins and how do they work?
- What are the effects in people with diabetes or obesity?
- What about other indications, such as substance use disorders?
- What are the special considerations across the life course?
- What are the issues with access?
- What are the key questions for people with HIV (PWH)?

What are Incretins?

Incretin Milestones

- **1964:** Incretin effect first demonstrated
- **1983:** Identification of glucagon-like peptides expressed in gut

Pro-glucagon



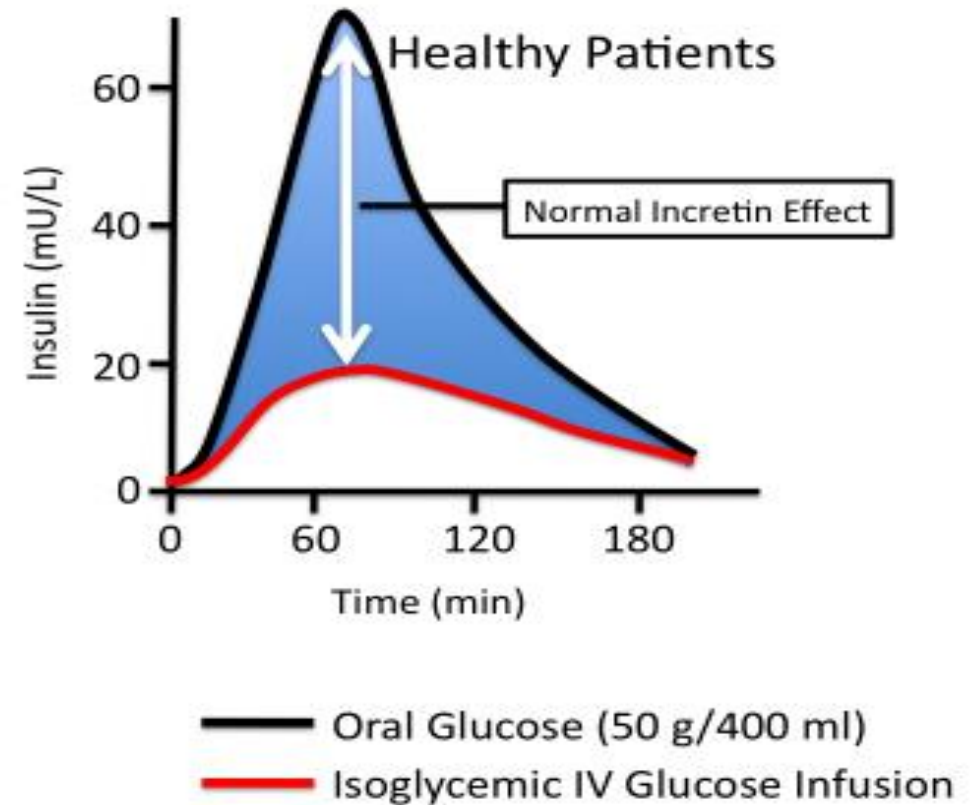
GLP-1

GLP-2

- Works locally
- Regulates gut epithelial function
- Decreases gut permeability

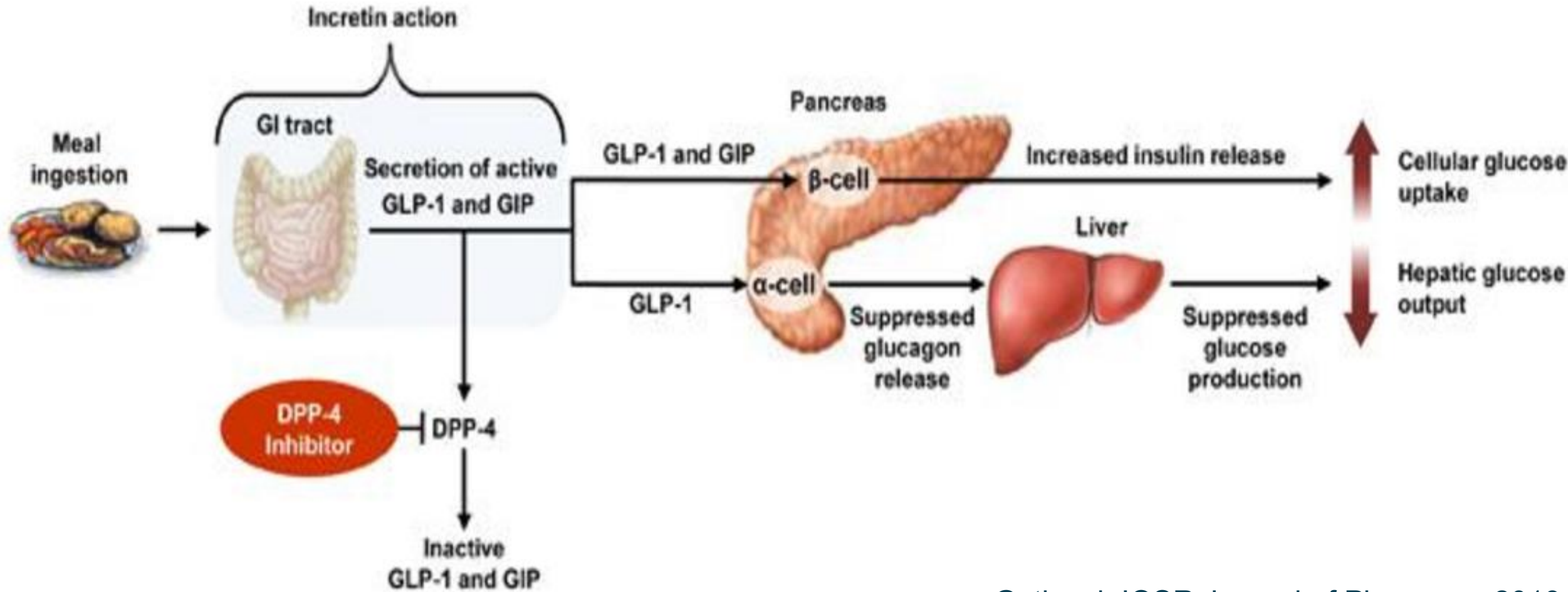
- **1987:** GLP-1 has marked effects on insulin secretion and inhibits glucagon secretion.

The “Incretin Effect”

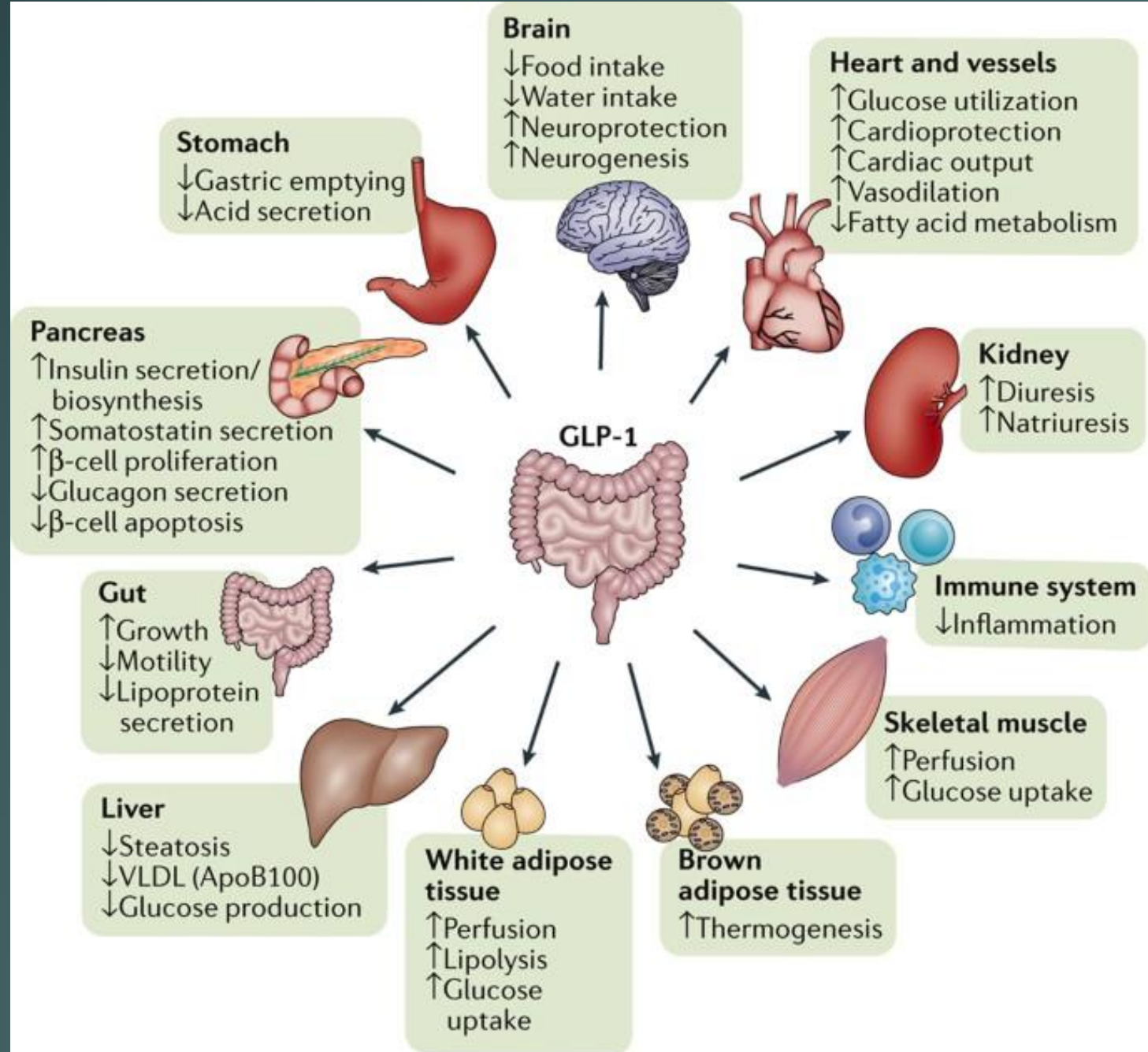


Nauck, Diabetologia, 1986

Incretins: Mechanisms of Action



Multiple Sites of Action of GLP-1 RA



Muskiet, NatureReviewsNephrology, 2017

GLP1 RAs in Diabetes: Effects on Glucose and Weight

Drug	Duration	Glucose Effect	Weight Effect
Exenatide	24 weeks	-0.9%	-2.9 kg
Liraglutide	52 weeks	-1.1 %	-2.5 kg
Lixisenatide	24 weeks	-0.72%	-2.7 kg
Dulaglutide	36 weeks	-1.8%	-4.6 kg
Semaglutide	40 weeks	-2.1%	-6.4 kg
Tirzepatide	40 weeks	-2.3%	-11.2 kg

Glucose and weight data from FDA Package Inserts at highest approved dose

GLP1 RAs in Diabetes: Effects on CV Outcomes

Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12% (1.5 mg)
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26% (1 mg)
Tirzepatide	40 weeks	-2.3%	-11.2 kg	Equivalent to Dulaglutide

Glucose and weight data from FDA Package Inserts at highest approved dose

GLP1 RA for Obesity

Drug	Duration	Max Dose	Weight Effect
Liraglutide	72 w	3.0 mg	-8.4 kg/-8%
Semaglutide	68 w	2.4 mg	-18.4 kg/-16%
Tirzepatide	72 w	15 mg	-22 kg/-18.4%

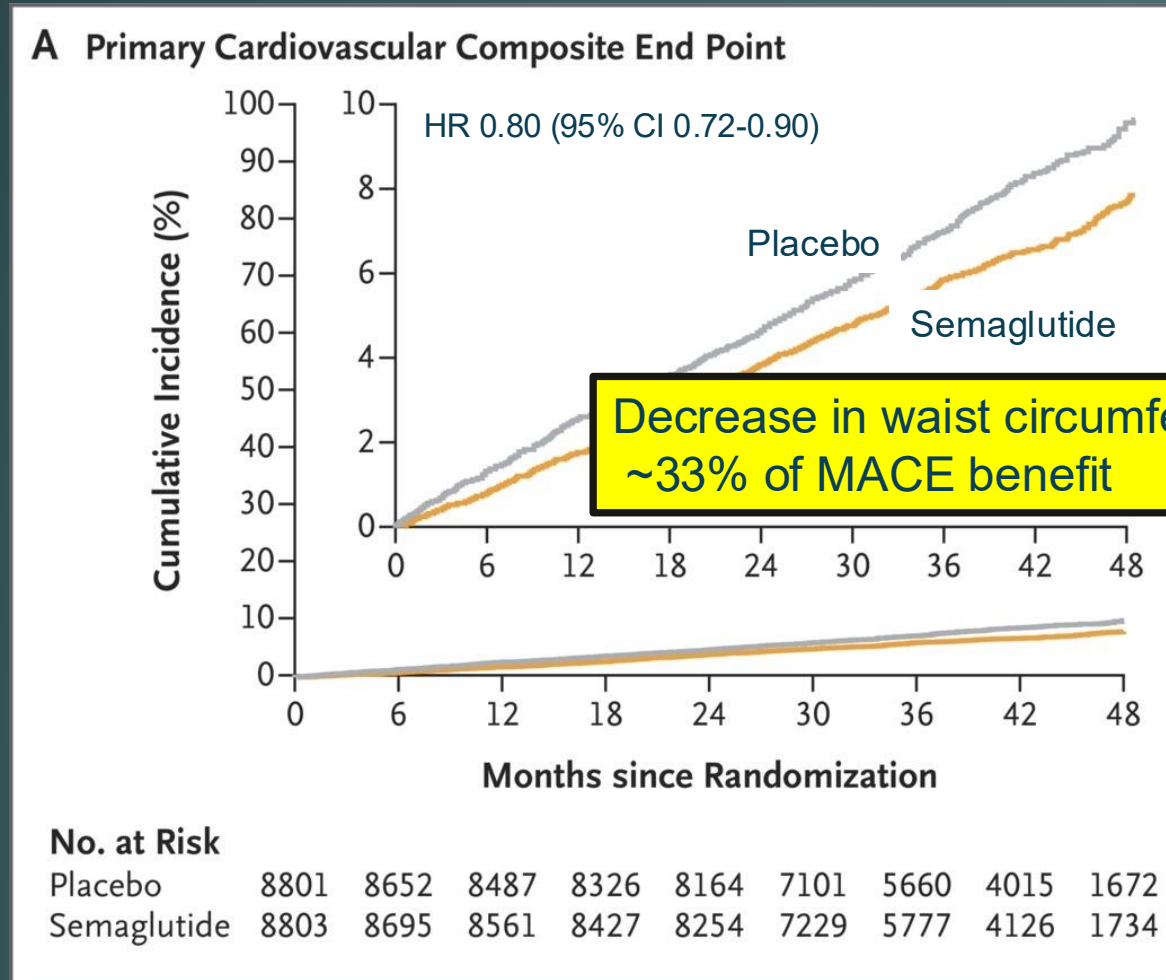
GLP1RA for Obesity-related Conditions

Condition	Efficacy	FDA approval	Comments
CVD	↓ 20% MACE (SELECT)	Semaglutide	Secondary Prevention
Heart Failure	↑ 13% Clin Summary Score ↓ 40% HF Events		Preserved Ejection Fraction
MASH	↓ 29% Steatohepatitis Resolution ↓ 14% Fibrosis	Semaglutide	
Sleep Apnea	↓ 64% sleep apnea events (apnea-hypopnea index)	Tirzepatide	
Chronic Kidney Disease	↓ 20% albuminuria ↓ 22% in composite kidney endpoint (FLOW)		FDA approved for diabetic kidney disease (semaglutide)
Knee Osteoarthritis	↓ 21% WOMAC Pain Score		

MACE: Major Adverse Cardiovascular Event; MASH: Metabolic-Dysfunction Associated Steatohepatitis

Are CVD benefits of GLP-1 RAs mediated by weight loss? : SELECT Trial

Primary Cardiovascular Endpoint

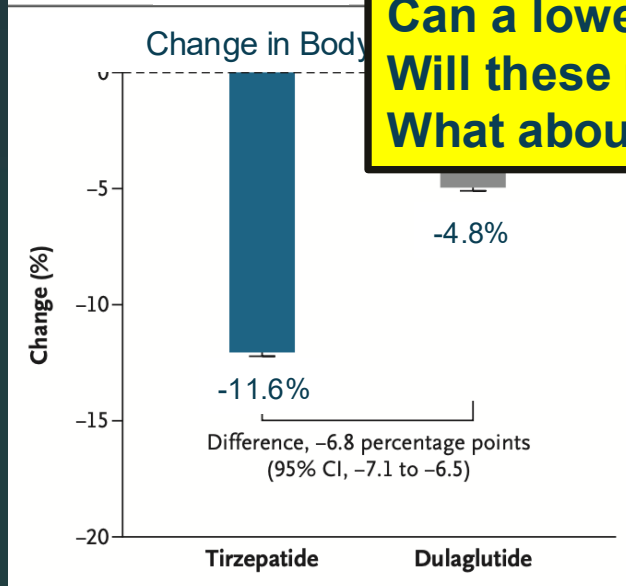
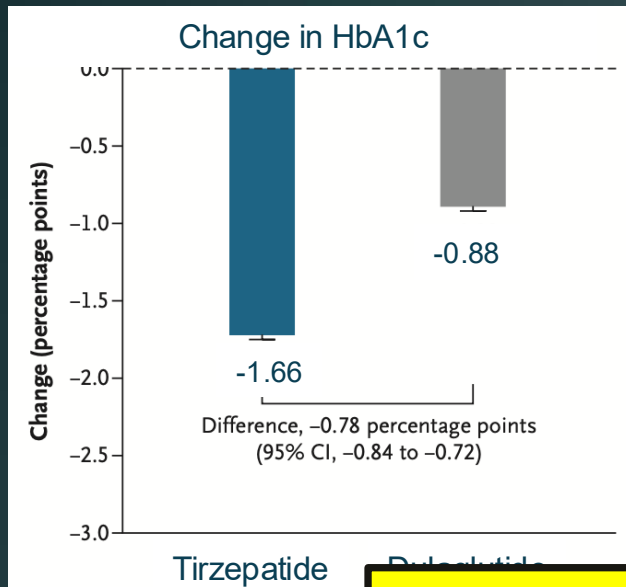


MACE: CVD death,
non-fatal MI, non-fatal stroke

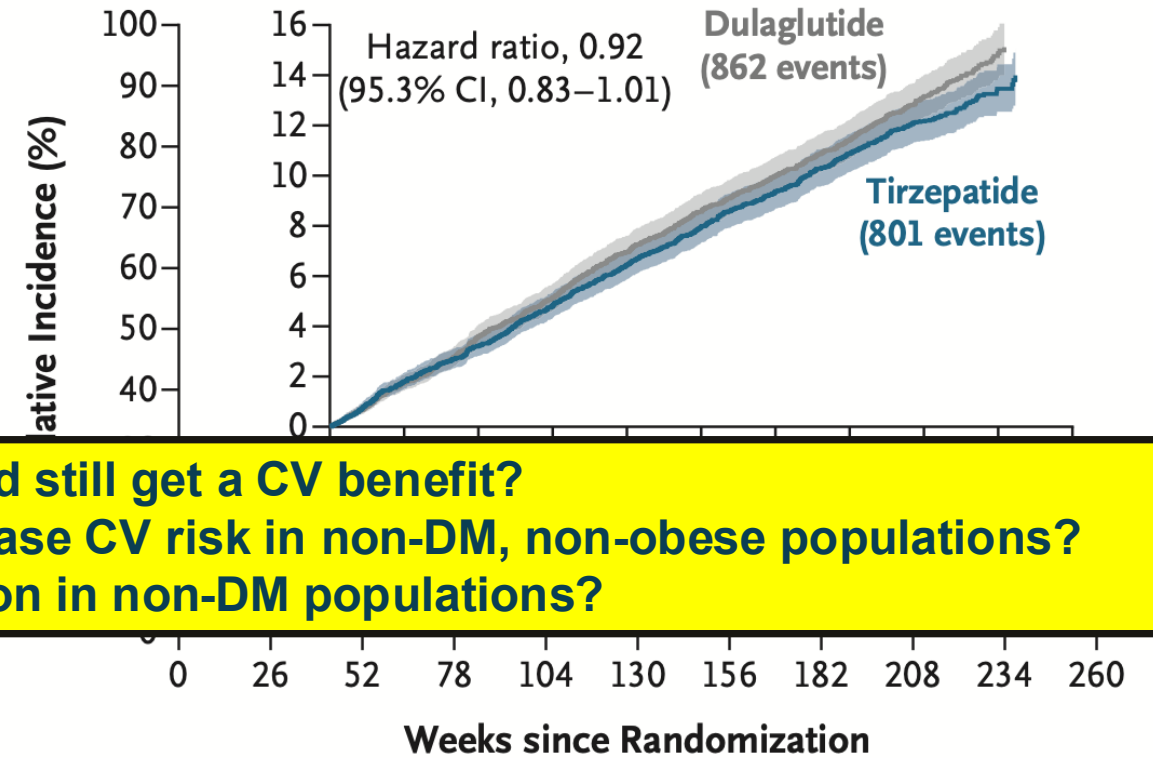
Deanfield, Lancet 2025

Lincoff, NEJM, 2023

Tirzepatide vs Dulaglutide on CV Outcomes in DM: SURPASS-CVOT



A Composite of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke

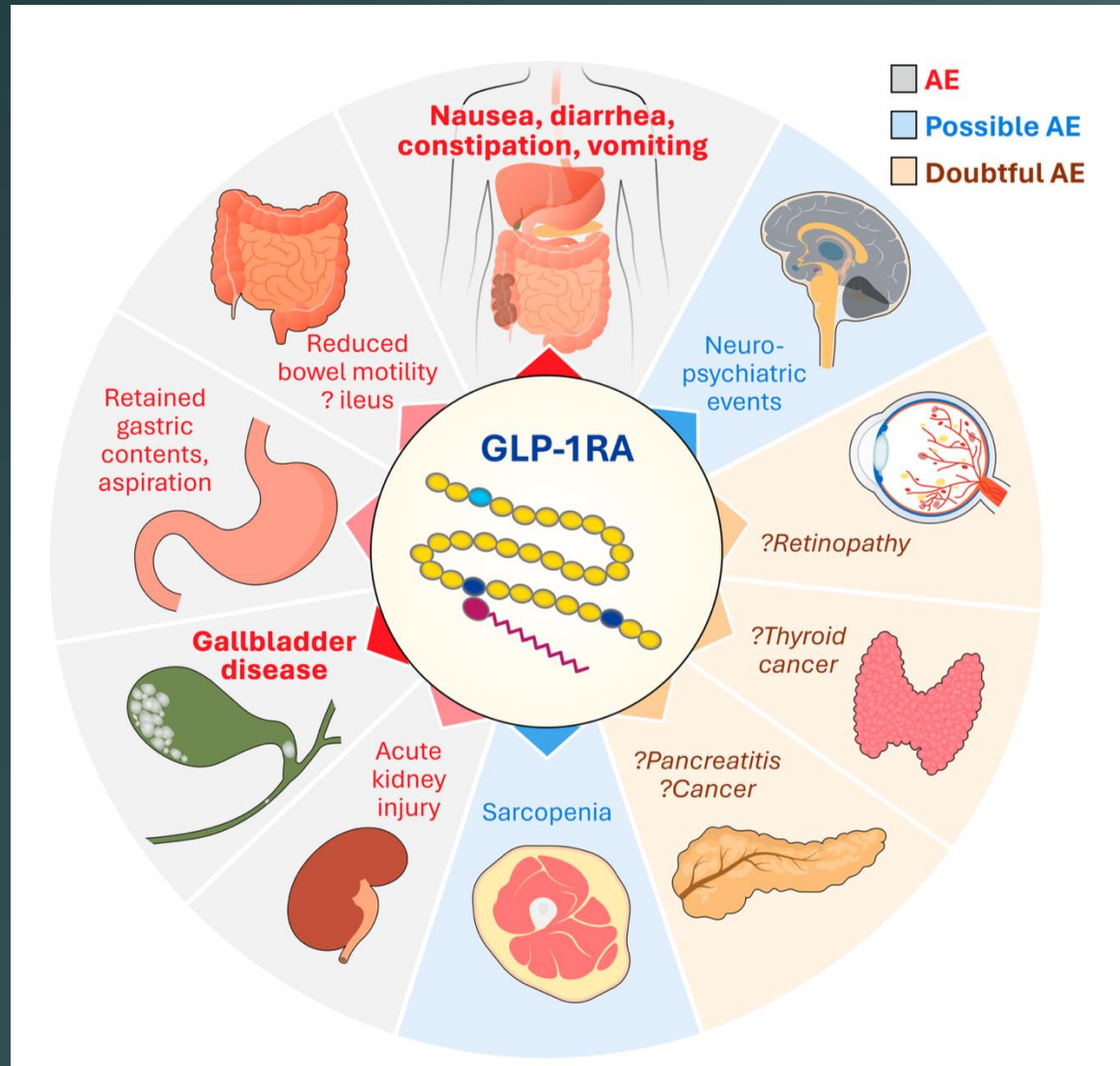


**Can a lower dose be used and still get a CV benefit?
 Will these medications decrease CV risk in non-DM, non-obese populations?
 What about primary prevention in non-DM populations?**

No. at Risk

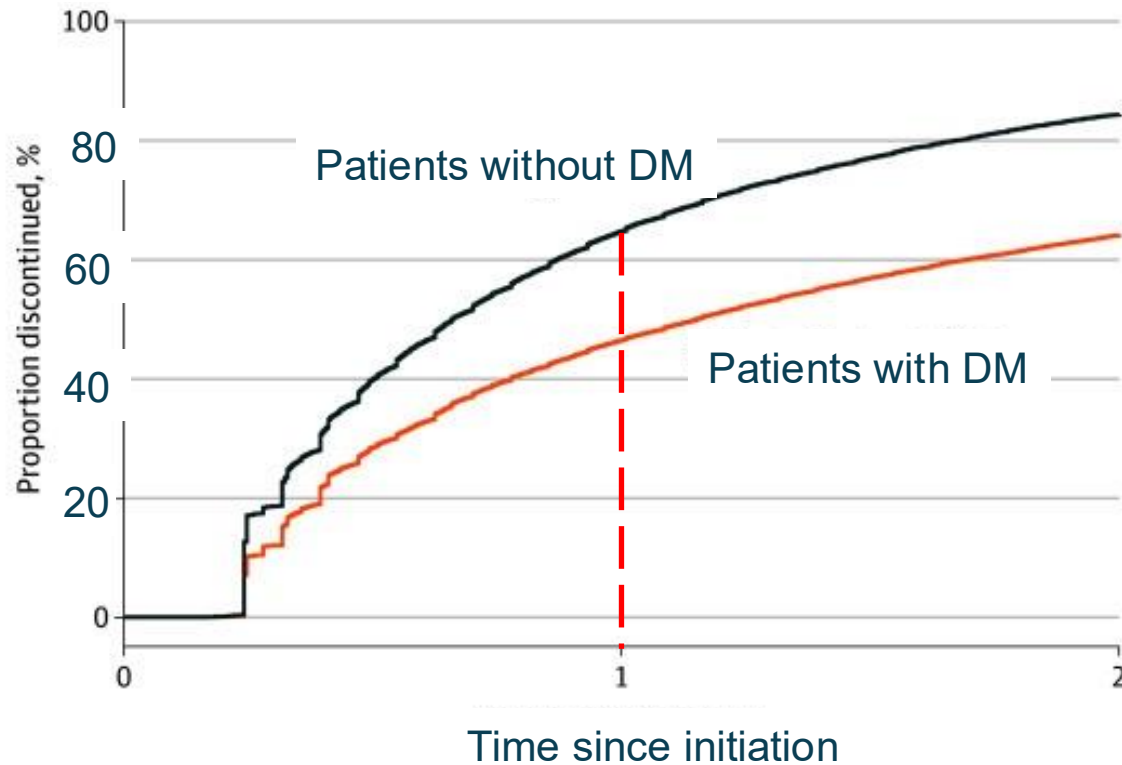
Dulaglutide	6579	6421	6267	6125	5954	5822	5618	5249	3226	777	0
Tirzepatide	6586	6433	6309	6167	6029	5907	5703	5307	3305	803	0

Adverse Effects of GLP1 RAs



GLP1 RA Discontinuation Rates

Time to discontinuation of GLP-1 RA



1 Year D/C Rates

DM: 46%

Non-DM: 65%

No. at risk	0	1	2
Patients with type 2 diabetes	76524	36709	10774
Patients without type 2 diabetes	48950	15696	2750

Factors Associated with D/C

- Age \geq 65 years
- Black race
- Low Income
- Less weight loss
- GI adverse effects

Weight Regain after GLP1 RA Discontinuation

Comparison

Intervention

Pharmacological interventions currently or previously licensed for weight loss

6322

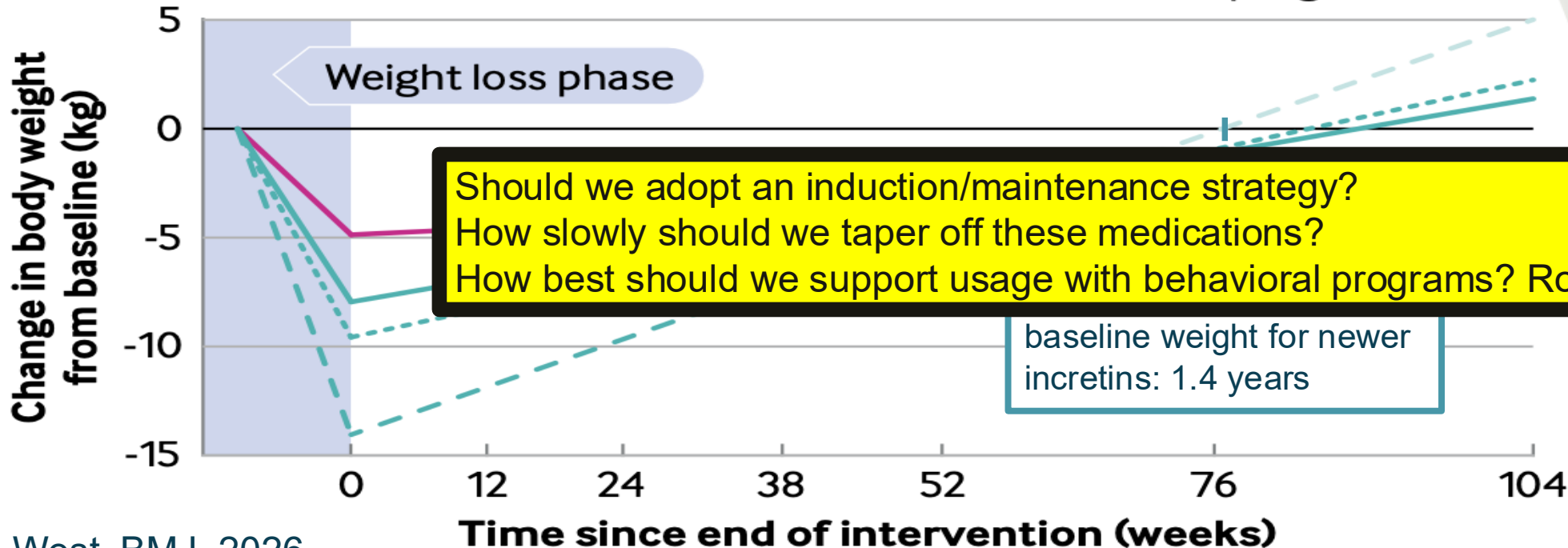
Control

Non-pharmacological weight loss interventions or placebos

3019

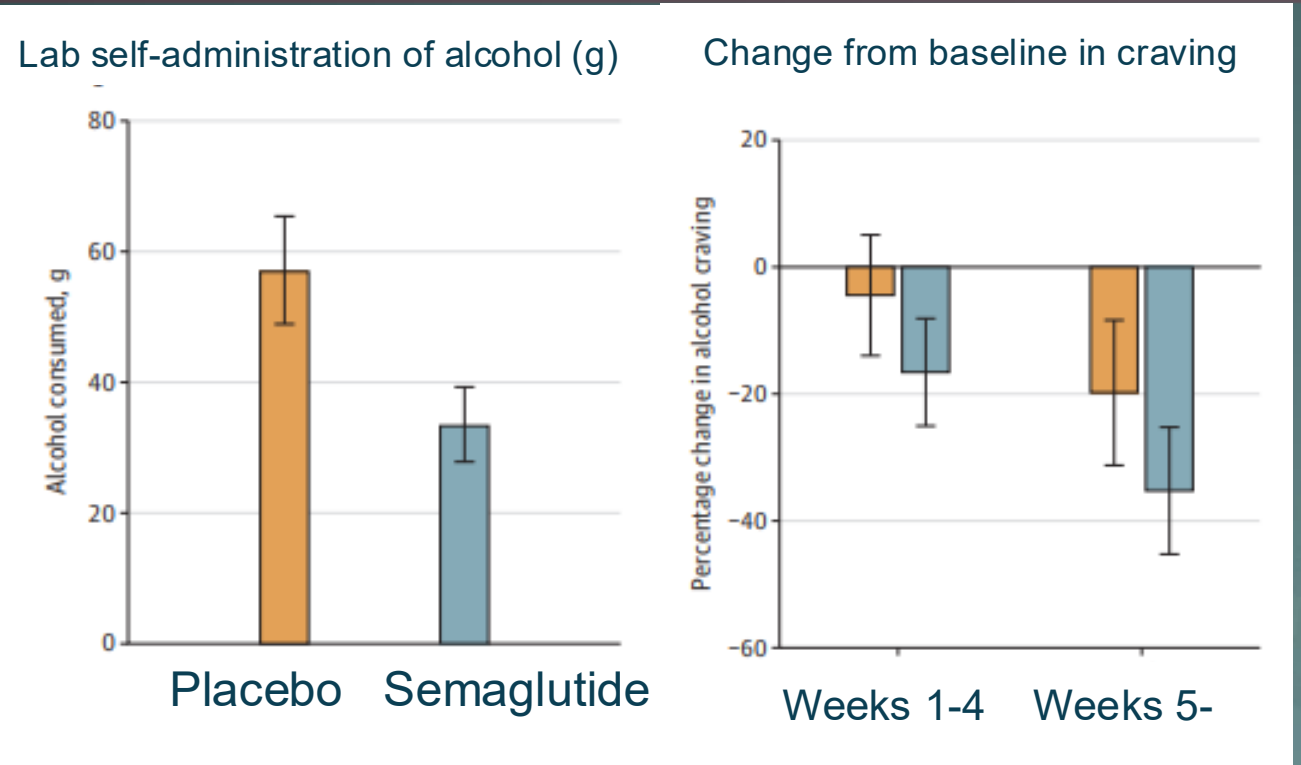
Outcomes

- All medication
- All incretin mimetics
- Newer incretin mimetics
- Behavioural programmes



GLP1 RA in the Treatment of Substance Use Disorders

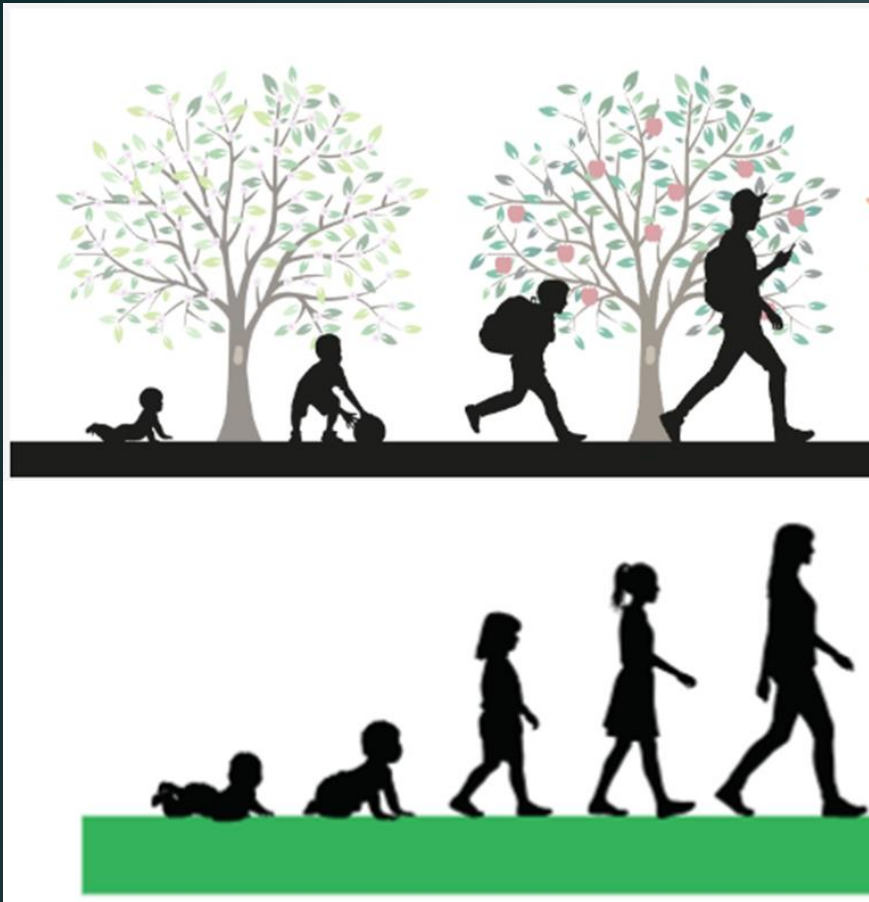
- GLP-1 receptors found in brain reward areas
- Robust pre-clinical data in animal models of:
 - Alcohol
 - Opioids
 - Nicotine
 - Psychostimulant addictions
- Randomized phase 2 clinical trial evidence emerging
- > 20 RCTs ongoing including three in PWH
 - Cocaine use disorder
 - Alcohol use disorder



Weekly Semaglutide in Adults with Alcohol Use Disorder

- 9 week randomized, controlled trial in 48 people with AUD
- Weekly Semaglutide: 0.25 mg x 4w; 0.5 mg x4w
- Lab alcohol self- administration, craving
- Significant decrease in cigarettes/day

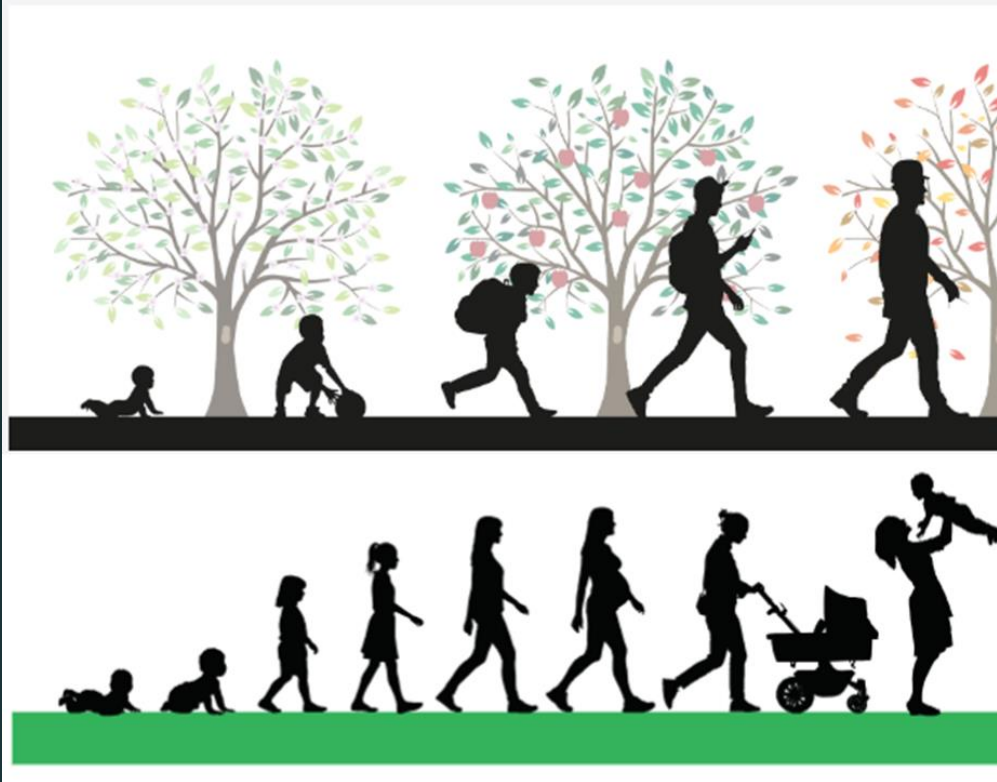
GLP1 RA: Considerations across the life course



GLP1 RAs in Children and Adolescents

- US FDA approved
 - DM: ≥ 10 years
 - exenatide, liraglutide, dulaglutide, tirzepatide
 - Second line after metformin
 - Obesity: ≥ 12 years
 - liraglutide, semaglutide
- Similar efficacy/adverse effects to adults
- Long term risks and benefits unclear

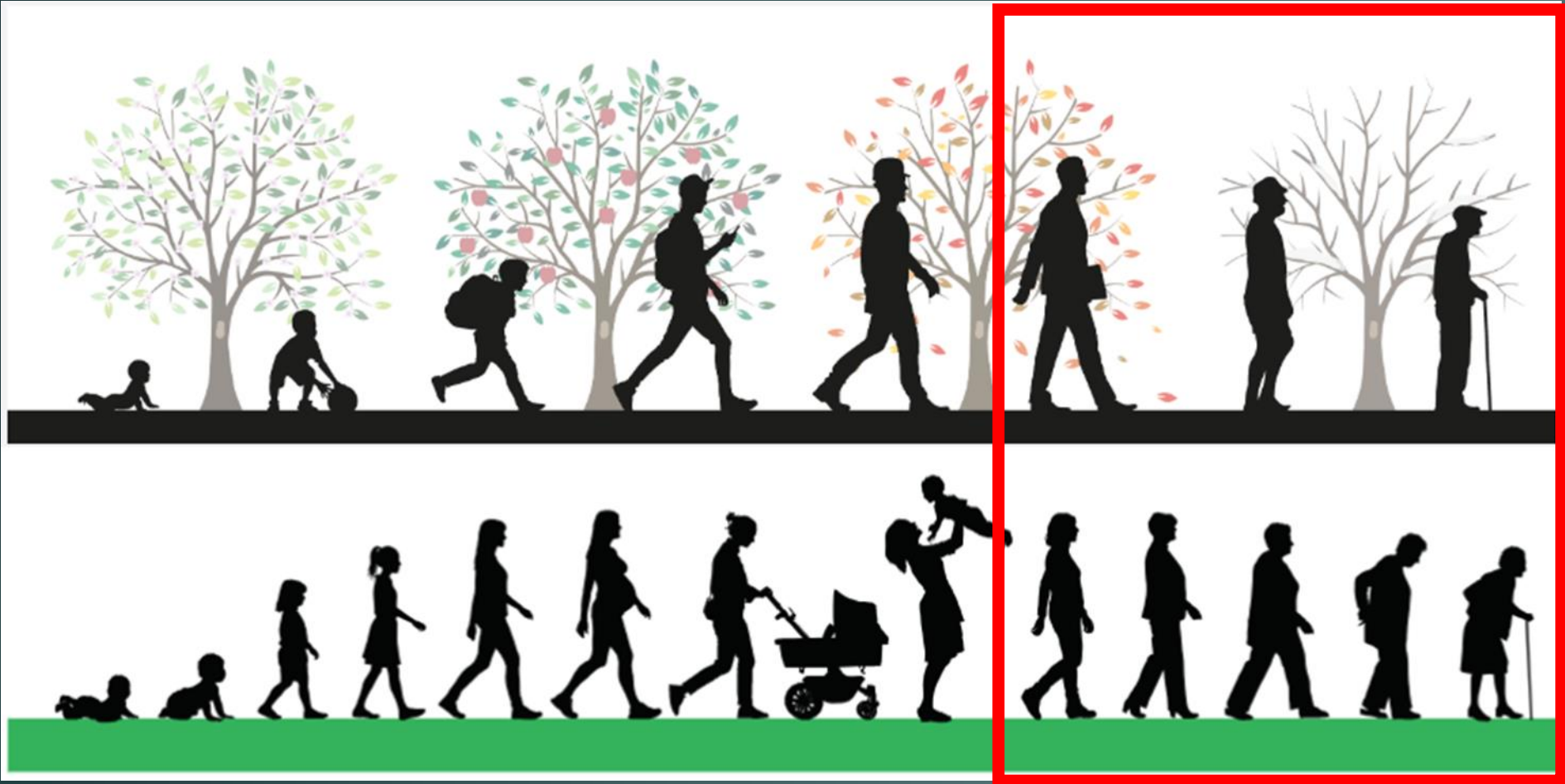
GLP1 RA: Considerations across the life course



GLP1 RAs in Reproductive Health

- Obesity associated with reproductive dysfunction in both men and women
- Unclear if GLP-1 RAs improve fertility in men and women, especially in PCOS.
- GLP-1 RA safety during pregnancy uncertain; use not recommended
- Clinicians can consider switching to short-acting GLP-1 RA 2 months before planned pregnancy

GLP1 RA: Considerations across the life course



FDA Package Insert; Section 8.5: Geriatric Use

Population	Drug	Trial	> 65 years	>75 years
Diabetes	Dulaglutide	Glycemic Control	19%	2%
		CVOT	53%	10%
	Semaglutide	Glycemic Control	24%	3%
		CVOT	48%	10%
	Tirzepatide	Glycemic Control	19%	2%
Obesity	Semaglutide	Weight Reduction	9%	1%
		CVOT (SELECT)	30%	8%
		MASH	26%	2%
	Tirzepatide	Weight Reduction	9%	0.5%
		OSA	Not reported	

GLP1 RA in Older Adults: Possible Effects on Aging

Can GLP-1 Medications Help You Live Longer?
Is Starting to Reveal



THE ROLE OF GLP-1 IN
AGING AND LONGEVITY

Editorial

<https://doi.org/10.1038/s41587-025-02932-1>

Are GLP-1s the first longevity drugs?

nature biotechnology

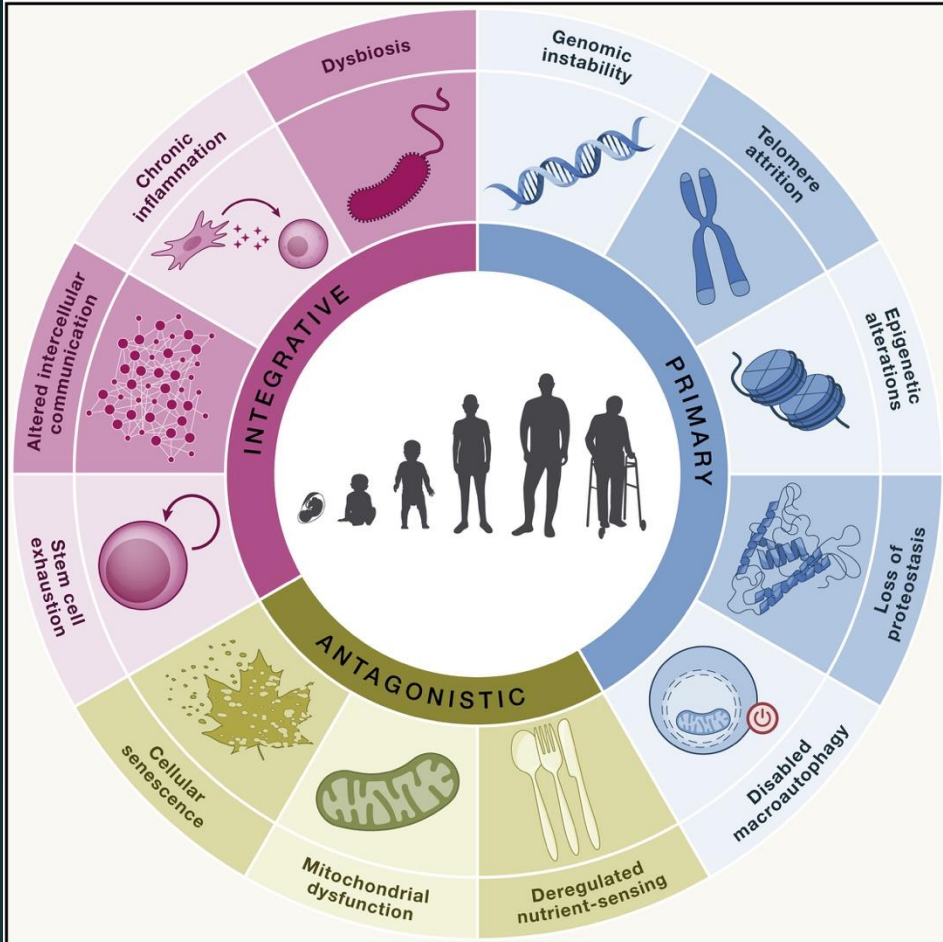
Volume 43 | November 2025 | 1741-1742 | 1741

The Role of GLP-1 in Aging and Longevity:
Why More Seniors Should Consider It

RETATRUTIDE IS A
LONGEVITY WEAPON
(THE TRIPLE-AGONIST PEPTIDE THAT TARGETS
THE 3 BIOLOGICAL FAILURES BEHIND AGING
AND CHRONIC DISEASE)

GLP1 RA in Older Adults: Possible Effects on Aging

Hallmarks of Aging



Geroscience hypothesis: cellular mechanisms of biologic aging drive chronic diseases

- Mitochondrial dysfunction
- Cellular senescence
- Telomere attrition
- Gut dysbiosis
- Epigenetic alterations (Corley, CROI 2025)
- Chronic inflammation

GLP-1 RA decrease markers of systemic inflammation in people with and without HIV

The Journal of Clinical Investigation

REVIEW SERIES: CLINICAL INNOVATION AND
SCIENTIFIC PROGRESS IN GLP-1 MEDICINE
Series Editor: Daniel J. Drucker

Antiinflammatory actions of glucagon-like peptide-1-based therapies beyond metabolic benefits

Chi Kin Wong¹ and Daniel J. Drucker^{1,2}

¹Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada. ²Department of Medicine, University of Toronto, Ontario, Canada.

- In clinical studies, GLP-1 RAs decrease markers of systemic inflammation (eg, CRP) by 40-60 %
 - ↓ weight and glucose account for 20-60% of reduction
- Mechanisms vary:
 - Direct effect on T cells, NKT cells
 - Effects on CNS control of peripheral inflammation
 - Specific tissues (eg endotheli

Open Forum Infectious Diseases

Infectious Diseases Society of America

MAJOR ARTICLE

HIV Medicine Association

OXFORD

The Effects of Semaglutide on Inflammation and Immune Activation in HIV-associated Lipohypertrophy

Nicholas T. Funderburg,^{1,2} Allison Ross Eckard,^{2,3} Qian Wu,³ Abdus Sattar,^{3,4} Kate Ailstock,¹ Morgan Cummings,¹ Danielle Labbato,⁴ and Grace A. McComsey^{2,4}

¹Division of Medical Laboratory Sciences, School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, Ohio, USA, ²Departments of Pediatrics and Medicine, Medical University of South Carolina, Charleston, South Carolina, USA, ³School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA, and ⁴Departments of Pediatrics and Medicine, University Hospitals of Cleveland, Cleveland, Ohio, USA

- RCT in 108 people with HIV-associated lipohypertrophy
- Semaglutide vs placebo for 32 weeks, max dose 1 mg
- ↓19% body fat, ↓31% VAT (Eckard, Lancet Diabetes, 2025)
- ↓48% CRP, ↓10% sCD163, ↓17% IL-6
- Effect independent of changes in adiposity

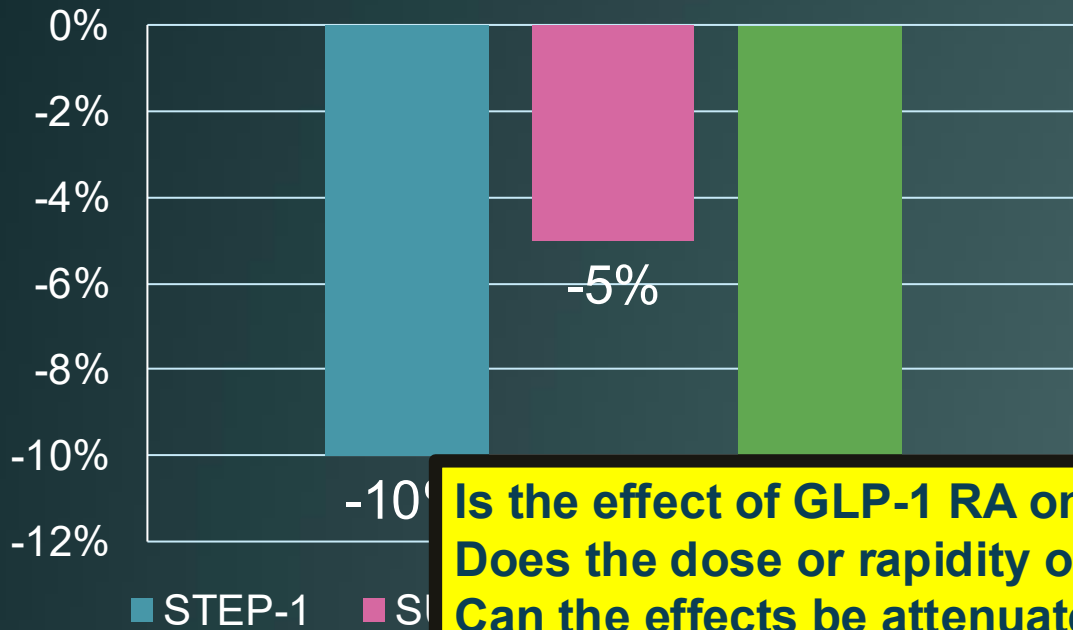
group withdrew prematurely. Thirty-two weeks of semaglutide treatment reduced baseline levels of C-reactive protein, interleukin-6, and soluble CD163 (all $P < .02$) and trended to reduce levels of sCD14 ($P = .08$). Circulating monocyte proportions and T-cell phenotypes were not altered by semaglutide.

Conclusions. In this randomized controlled trial of semaglutide in PWH, we report significant decreases in markers of

Abstract 115: Liraglutide effects on gut T-cell and epithelial remodeling in PWH

GLP1 RA in Older Adults: Loss of Lean Mass

Change in Lean Mass in GLP-1 RA Clinical Trials



**Is the effect of GLP-1 RA on muscle mass clinically relevant in certain populations?
Does the dose or rapidity of weight loss matter for muscle mass?
Can the effects be attenuated with protein intake and/or resistance training?**

- General population:
annual decrease in lean mass over 50 years ~1-2%

Rossi, Acta Diabetologia, 2025

Clinical Infectious Diseases
MAJOR ARTICLE

IDSIA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Effects of Semaglutide on Muscle Structure and Function in the SLIM LIVER Study

Grace L. Ditzenberger,^{1,6} Jordan E. Lake,^{2,6} Douglas W. Kitch,³ Amy Kantor,³ Raja Muthupillai,^{4,6} Carlee Moser,^{3,6} Pablo F. Belaunzaran-Zamudio,⁵ Todd T. Brown,⁶ Kathleen Corey,⁷ Alan L. Landay,⁸ Anchalee Avihingsanon,⁹ Fred R. Sattler,¹⁰ and Kristine M. Erlandson^{1,6}

↓9.3% psoas muscle volume

¹Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; ²Department of Internal Medicine, UTHealth, Houston, Texas, USA; ³Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA; ⁴School of Engineering Medicine, Texas A&M University, Houston, Texas, USA; ⁵National Institute of Allergy and Infectious Diseases (Contractor), Rockville, Maryland, USA; ⁶Department of Medicine, Brigham Young University, Salt Lake City, Utah, USA; ⁷Department of Medicine, Brigham Young University, Salt Lake City, Utah, USA; ⁸Harvard Medical School, Boston, Massachusetts, USA; ⁹Department of Medicine, Brigham Young University, Salt Lake City, Utah, USA; ¹⁰Thai Red Cross AIDS Research Centre, Bangkok, Thailand

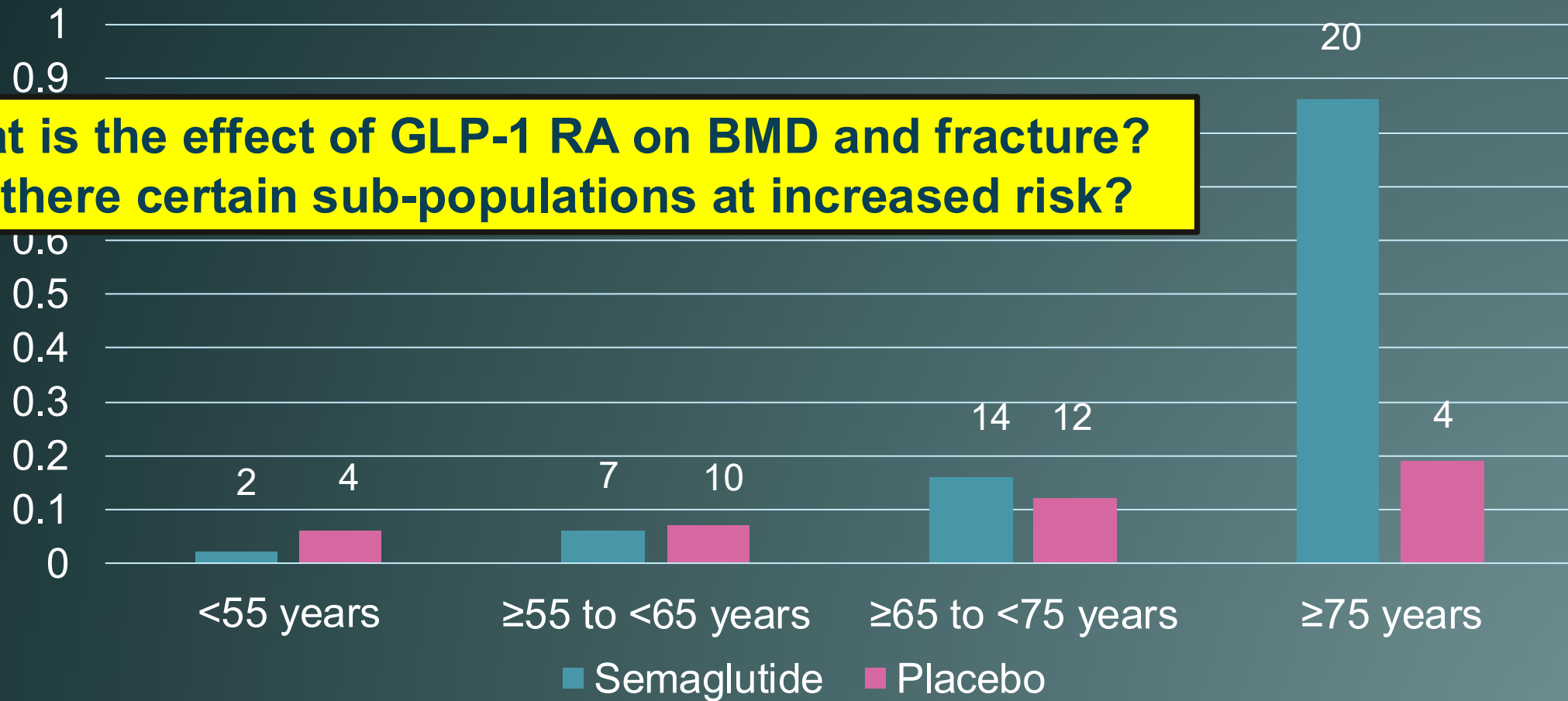
Results: Change in physical function

CROI 2024

Parameter	Baseline	Week 24	Change, Baseline to Week 24 (estimate, 95% CI)	P-value
5x Chair Rise (seconds)	12.5 (3.6)	11.9 (3.3)	-0.66 (-1.4, 0.07)	0.077
Presence of slow gait speed (<1 meters/second)	No: 16 (51%) Yes: 31 (63%)	No: 26 (54%) Yes: 22 (46%)	RR: 0.73 (0.55, 0.97)	0.029

Rate of Hip/Pelvis Fractures per 100 Person-years in SELECT by Age

**What is the effect of GLP-1 RA on BMD and fracture?
Are there certain sub-populations at increased risk?**



Kushner, Obesity, 2025, calculated from Table S5;
numbers above columns represent absolute number of events

GLP1 RA in Older Adults: Possible Effects on Cognition

JAMA Neurology | Original Investigation

Cardioprotective Glucose-Lowering Agents and Dementia Risk A Systematic Review and Meta-Analysis

Allie Seminer, MSc; Alfredi Mulihano; Clare O'Brien, MD; Finn Krewer, PhD; Maria Costello, PhD; Conor Judge, PhD; Martin O'Donnell, PhD; Catriona Reddin, MD

← Editorial page 437

+ Supplemental content

IMPORTANCE Although diabetes is a risk factor for dementia, the effect of glucose-lowering therapy for prevention of incident dementia is uncertain.

OBJECTIVE To determine whether cardioprotective glucose-lowering therapy (sodium-glucose cotransporter-2 inhibitors [SGLT2is], glucagon-like peptide-1 receptor agonists [GLP-1RAs], metformin, and pioglitazone), compared with controls, was associated with a reduction in risk of dementia or cognitive impairment, and among primary dementia subtypes.

- **GLP-1 RAs (n=10 studies) associated with 45% reduction in incident dementia vs placebo**

therapy with controls that reported dementia or change in cognitive scores. Cardioprotective glucose-lowering therapies were defined as drug classes recommended by guidelines for reduction of cardiovascular events, based on evidence from phase III randomized clinical trials. Inclusion criteria were assessed independently and inconsistencies were resolved by consensus.

DATA EXTRACTION AND SYNTHESIS Data were screened and extracted independently by 2 authors adhering to the PRISMA guidelines in August 2024. Random-effects meta-analysis models were used to estimate a pooled treatment effect.

MAIN OUTCOMES AND MEASURES The primary outcome measure was dementia or cognitive impairment. The secondary outcomes were primary dementia subtypes, including vascular and Alzheimer dementia, and change in cognitive scores.

company
announcement

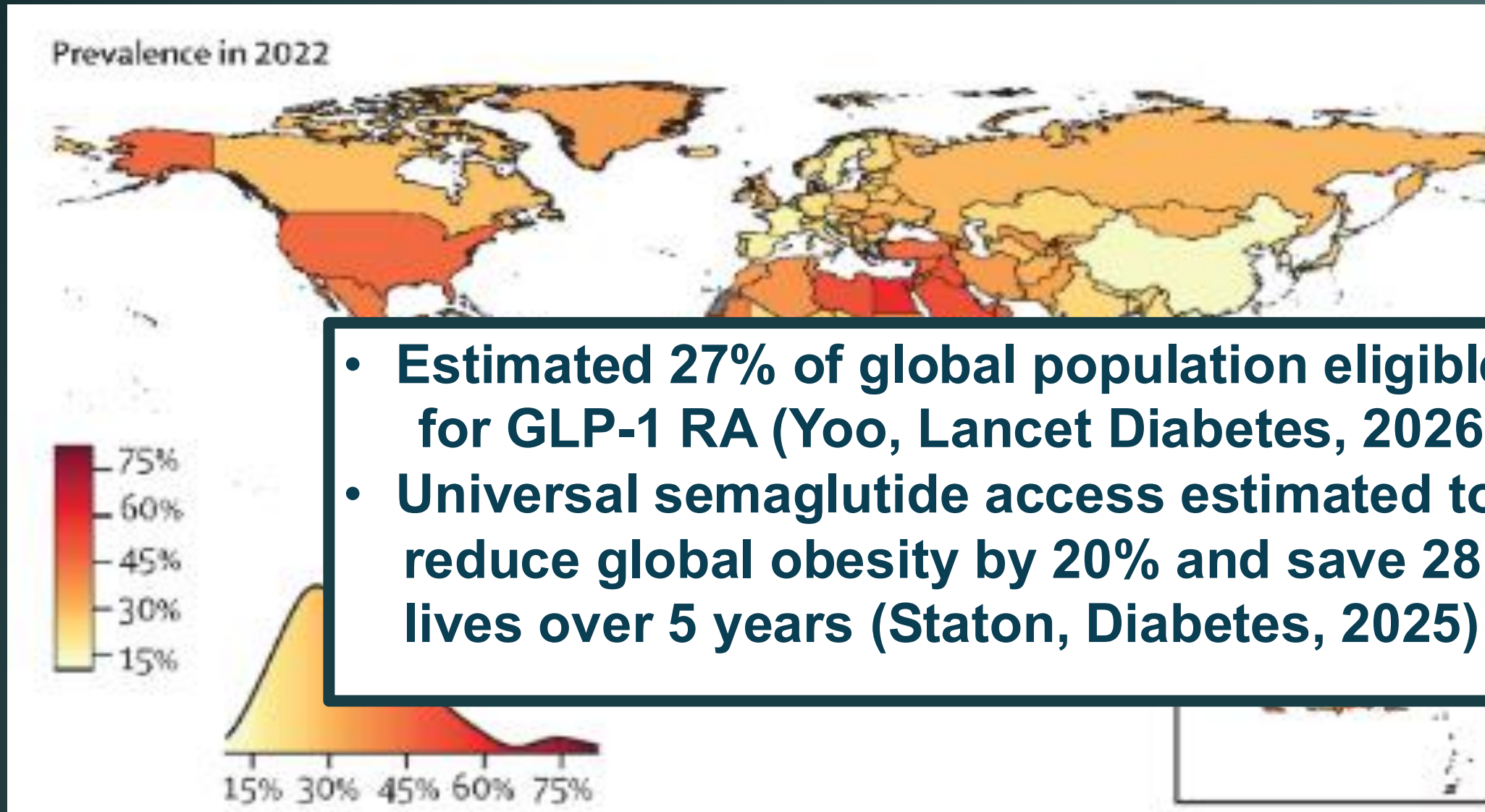


Evoke phase 3 trials did not demonstrate a statistically significant reduction in Alzheimer's disease progression

Bagsværd, Denmark, 24 November 2025 – Novo Nordisk today announced the top-line results from the 2-year primary analysis of evoke and evoke+ phase 3 trials in early-stage symptomatic Alzheimer's disease. The two trials were randomised, double-blinded, enrolled a total of 3808

Was disease too advanced?
Was brain penetration adequate?

Obesity Prevalence Around the World



World Health Organization Guideline on the Use and Indications of Glucagon-Like Peptide-1 Therapies for the Treatment of Obesity in Adults

Francesca Celletti, MD, PhD; Jeremy Farrar, MD, PhD; Luz De Regil, PhD

- “GLP-1 therapies may be used as a long-term treatment for obesity”
- Current GLP-1 production could cover 100 M people, 10% of those with obesity
- “An integrated global obesity ecosystem” is needed



Access: Achilles' Heel of GLP-1 RAs

Rapidly changing landscape may decrease cost, increase production and improve access

- New oral formulations: Oral semaglutide, Orforglipron (small molecule)
- Patent Expirations: Semaglutide: 2026 in India, China, Brazil, Canada, Turkey; 2032 in US
- Development of multi-agonists
 - GLP-1 RA/(GIP RA) + Amylin, Glucagon, IGF-1, GDF-15, FGF-21, Activin, NPY
- > 60 GLP-1 based compounds in development for multiple indications

GLP1 RA & HIV: What are the key questions?

- Are the risks and benefits any different in PWH compared to PWOH?
- Can GLP-1 RA attenuate inflammation and immune activation in PWH? What dose? What are the mechanisms?
- What is the impact on common comorbid conditions in PWH? (eg CVD,)
- What is the long term impact of GLP-1 RA in PWH?

Abstract 447: Effect of semaglutide on depressive symptoms in CNICS

Abstract 601: Effect of semaglutide on liver fibrosis scores in CNICS

Abstract 695: Use and weight effects of GLP-1 RAs in the DC Cohort

Abstract 696 & 697: Tirzepatide use and efficacy

Abstract 698: Semaglutide effects on cigarette smoking in CNICS

Abstract 699: RCT of semaglutide on subclinical CVD

Is our exuberance for GLP-1 RAs rational or irrational?

- This class of medications has transformed the treatment of multiple diseases
- We are only at the beginning of this transformation.
- Data should guide GLP-1 RA use, not enthusiasm
- Global access will be a major challenge that requires careful management.

Acknowledgements

SLIM LIVER:

- Kristine Erlandson
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- Grace Kulik

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- Lorenzo Leggio, NIDA
- Peter Hunt
- Paddy Mallon

MWCCS Metabolic WG

Grace McComsey & Nick Funderburg