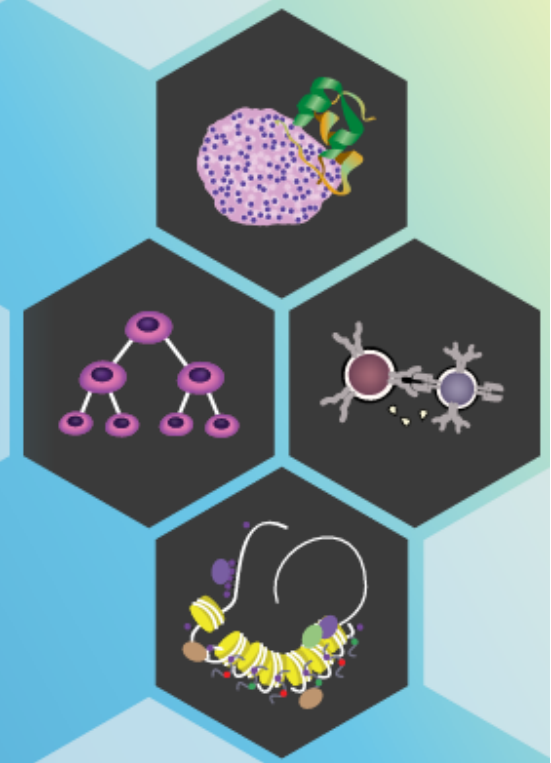
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

The Evolving Story of Incretins – Magic Bullet or Hot Air?



David D'Alessio, MD

Professor, Duke Department of Medicine

Director, Duke Division of Endocrinology

Duke University Medical Center

Disclosures

- Consultant for Altimmune, Arrowhead Pharmaceuticals, Eli Lilly and Company, MBX Biosciences, Structure Therapeutics, and Sun Pharma.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Overview

1. History of the incretin effect, incretins and incretin-based drugs
2. Development of GLP-1RA for treating diabetes
3. The use of GLP-1RA for weight loss
4. GLP-1RA and prevention of clinical ASCVD
5. Development of MRA
6. The future- promise and limitations

The Origin of Endocrinology… was in the gut

THE MECHANISM OF PANCREATIC SECRETION.

By W. M. [illegible] BAYLISS AND ERNEST H. STARLING.

Incretin- humoral factors from the duodenum (intestine) that stimulate internal secretions of the pancreas (eg. insulin)

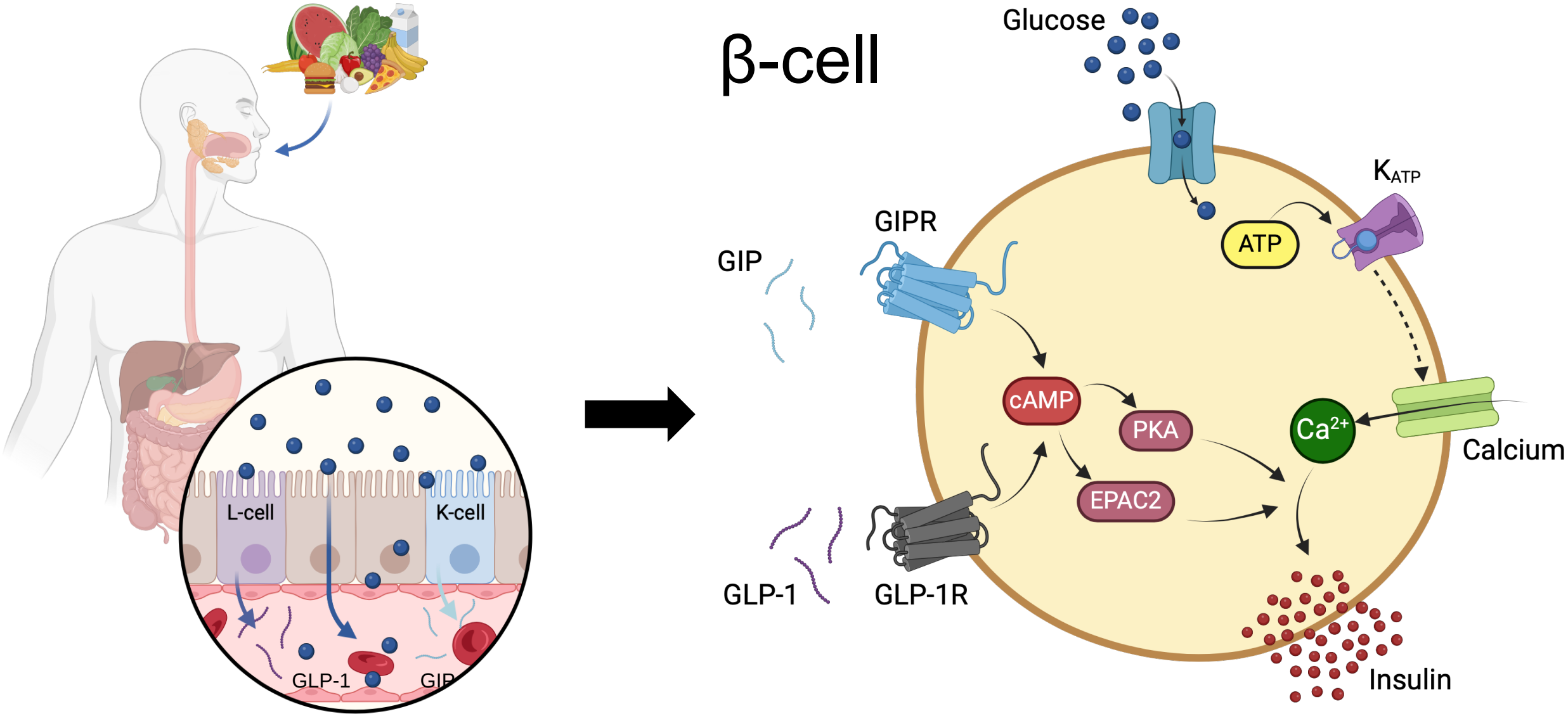
pool.

STUDIES ON THE PHYSIOLOGY OF SECRETIN

III. Further Studies on the Effects of Secretin on the Blood Sugar

JEAN LA BARRE and EUGENE U. STILL

The incretin axis



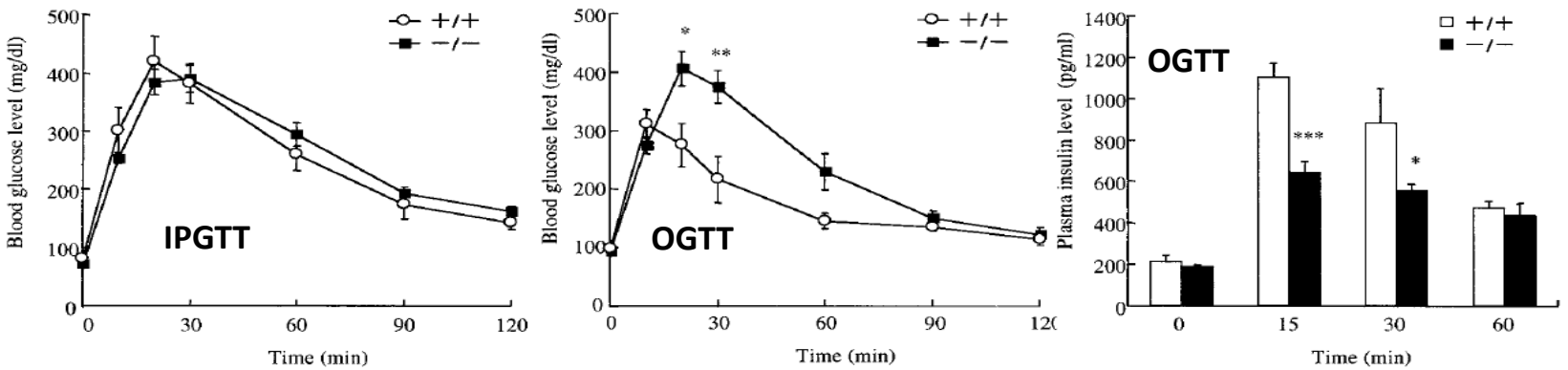
What qualifies as an Incretin?

The Creutzfeldt criteria

1. **Gut hormone secreted after meals (esp CHO)** ✓
2. **Stimulates insulin in glucose-dependent manner** ✓
3. **Acts at physiologic concentrations** ✓

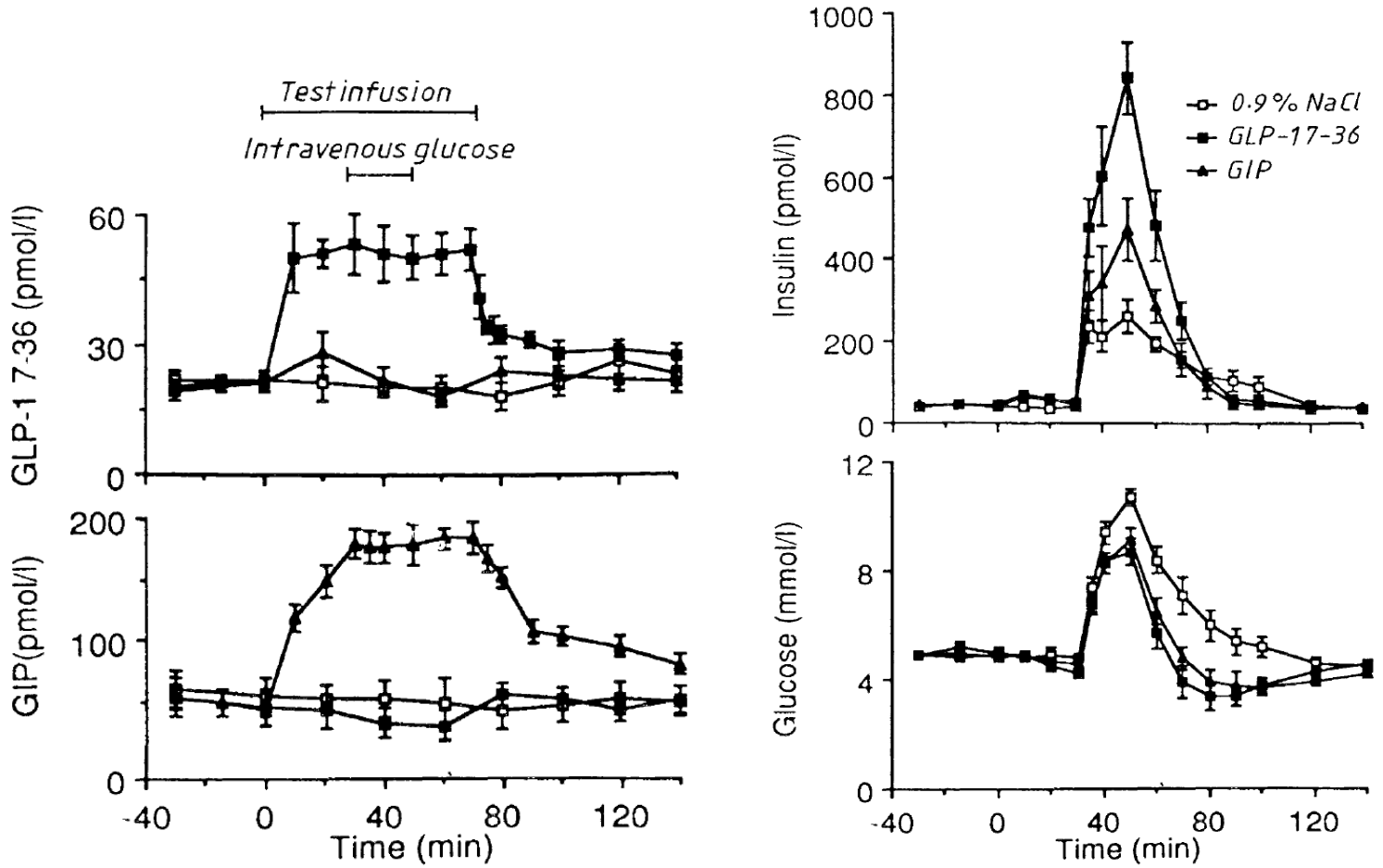
W Creutzfeldt, Diabetologia 1979

A Loss-of-Function Model



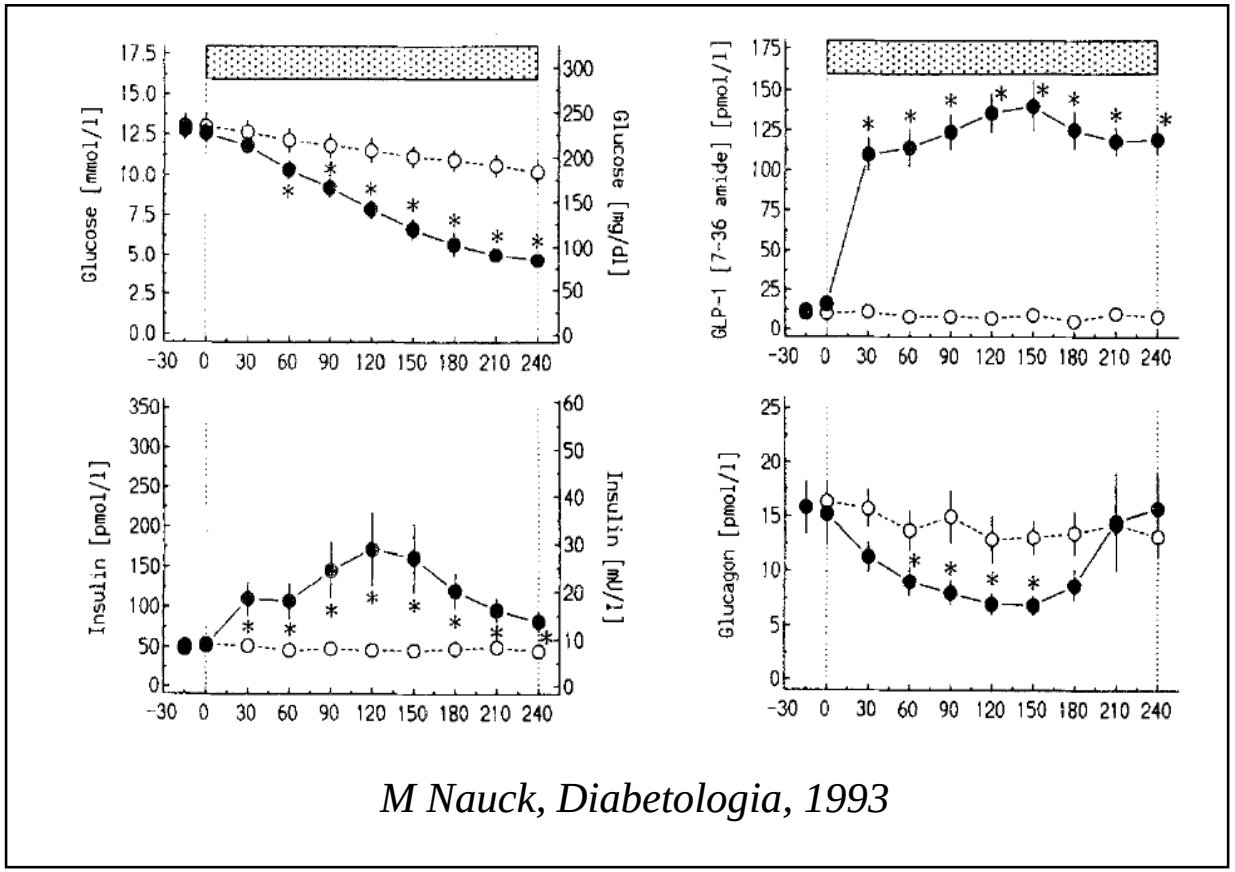
K Miyawaki PNAS, 2000

Insulinotropic effects of GLP-1 and GIP in healthy humans

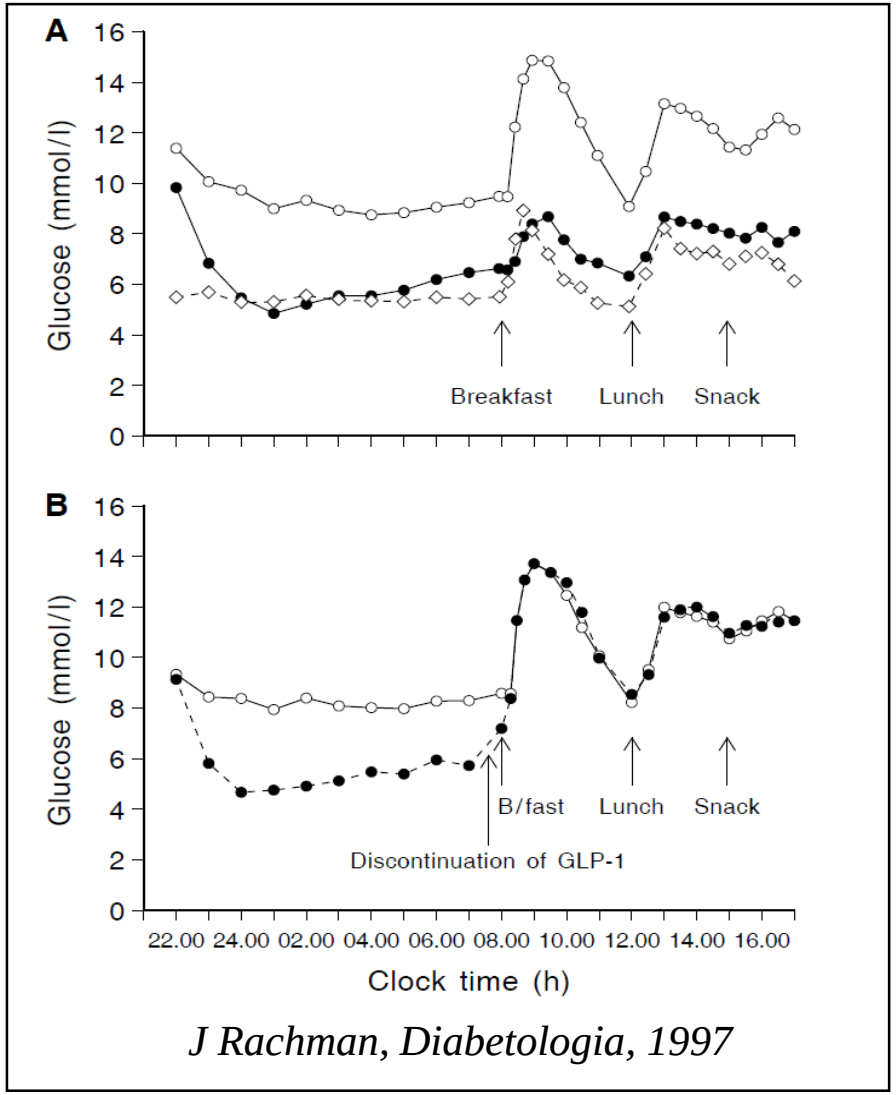


B Kreymann, Lancet, 1987

GLP-1 stimulates insulin release and normalizes fasting glucose in patients with T2DM… but the effect is short-lived



M Nauck, Diabetologia, 1993



J Rachman, Diabetologia, 1997

The Development of GLP-1RA to treat Diabetes

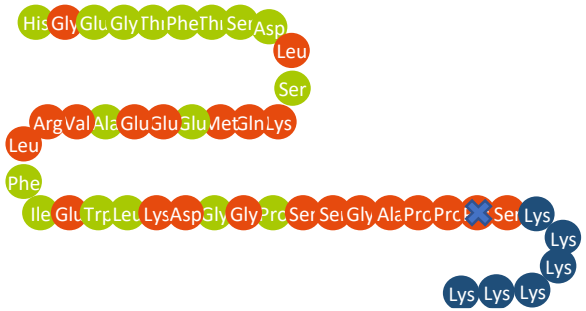
Challenges and goals:

- Peptides- minimal oral availability
- Protection from inactivation by DPP4
- Acceptable pharmacokinetics
- Side effects and mitigation of these

The different flavors of GLP-1 RA

Exendin-based GLP-1RAs

Lixisenatide *(4.86 kDa, ~50% homology)*



Exenatide ER *(4.19 kDa, 53% homology)*

Once weekly

Human GLP-1 analogues

Small

Liraglutide *(3.75 kDa, 97% homology)*

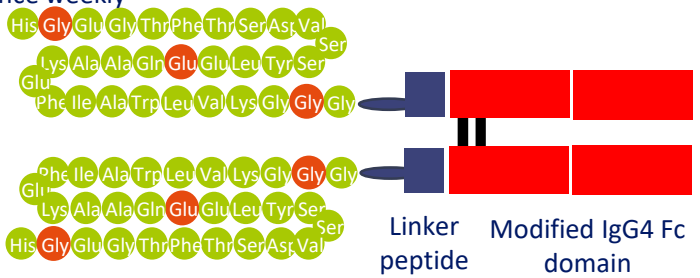
Semaglutide *(4.11 kDa, 94% homology)*

Once weekly

Large

Dulaglutide *(~63 kDa, 90% homology)*

Once weekly



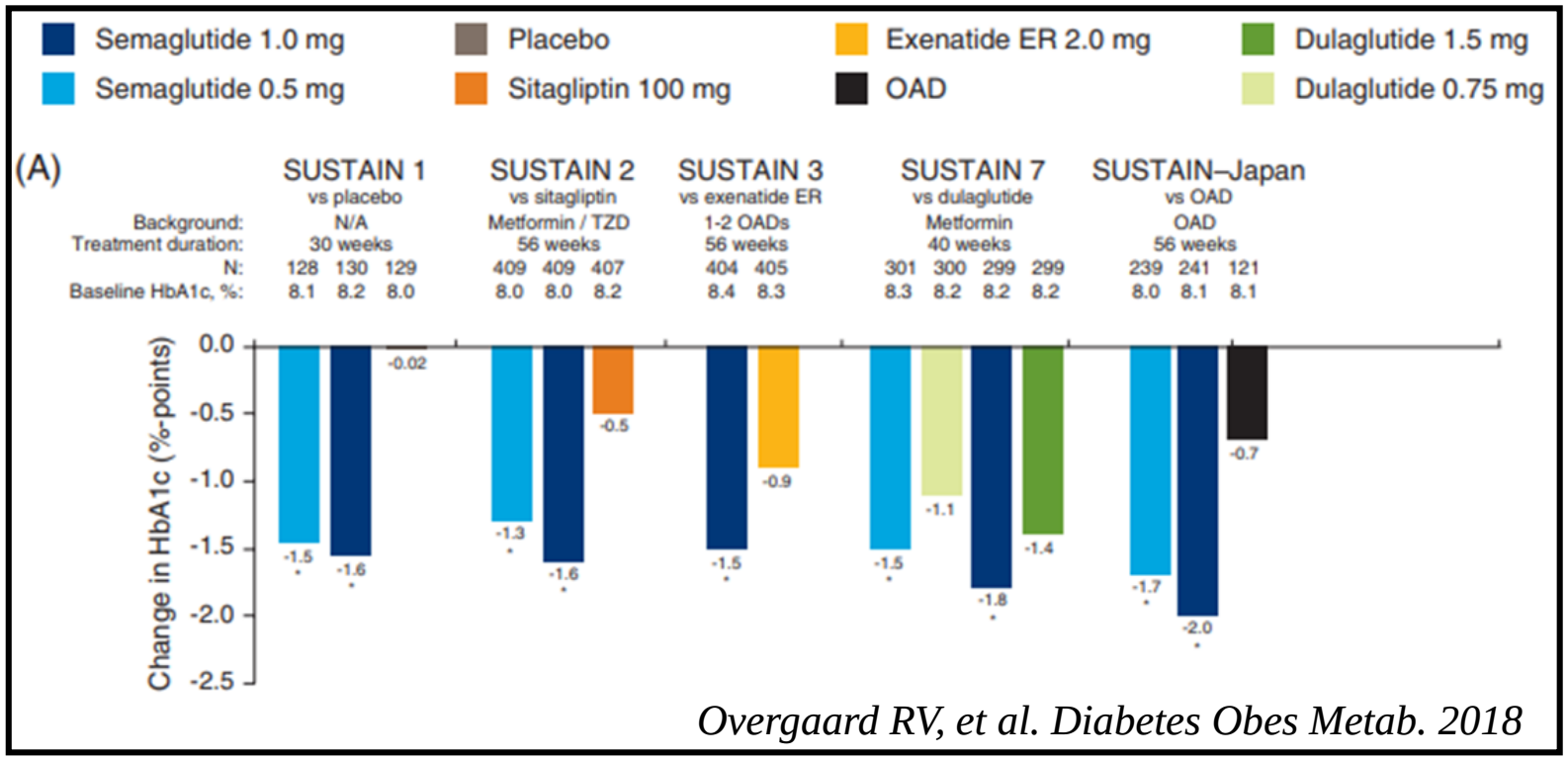
Lund A et al. Eur J Intern Med, 25: 407-414, 2014

Pharmacologic effects of GLP-1r agonists in T2DM
The first decade

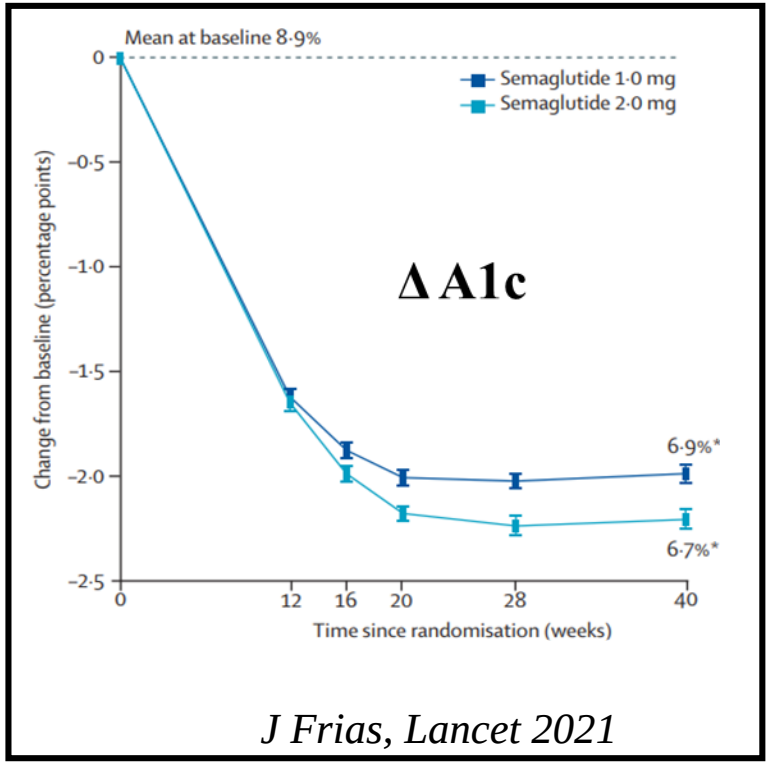
1. Stimulation of glucose-stimulated insulin secretion
2. Suppression of glucagon
3. Delayed gastric emptying
4. Reduced food intake and weight loss

Reduction of A1c ~ 1%
2-4 kg of body weight loss

Semaglutide comparative efficacy
The second decade



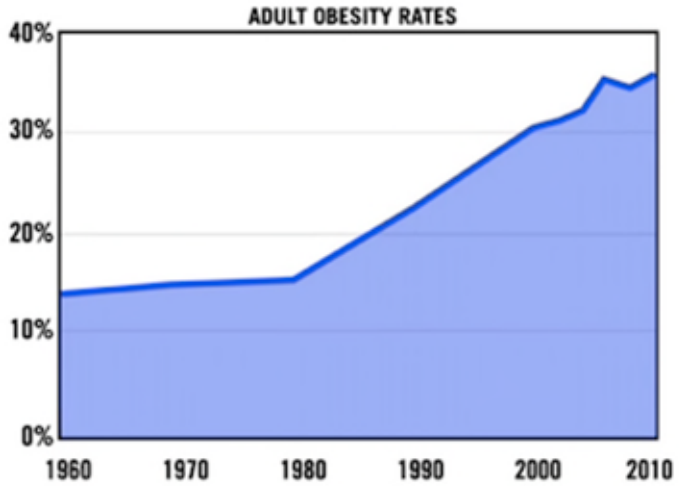
Overgaard RV, et al. Diabetes Obes Metab. 2018

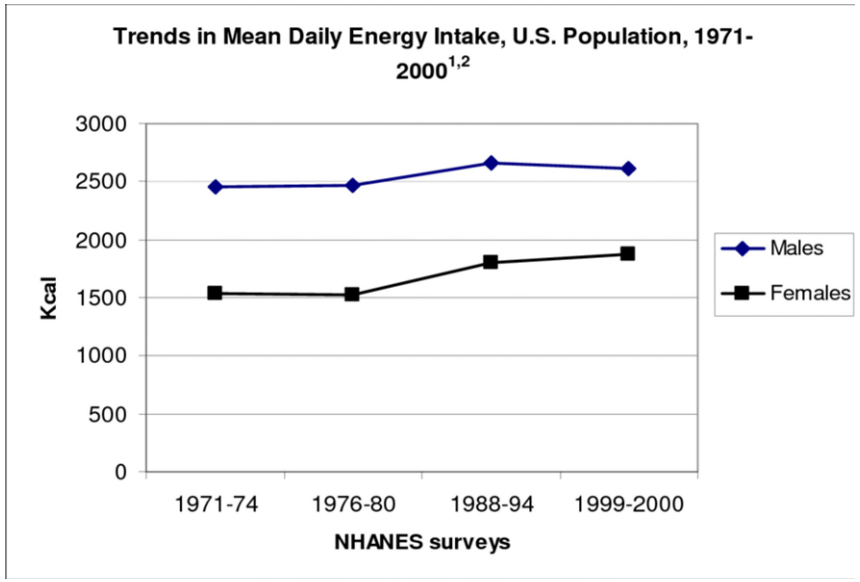


J Frias, Lancet 2021

The use of GLP-1RA for weight loss

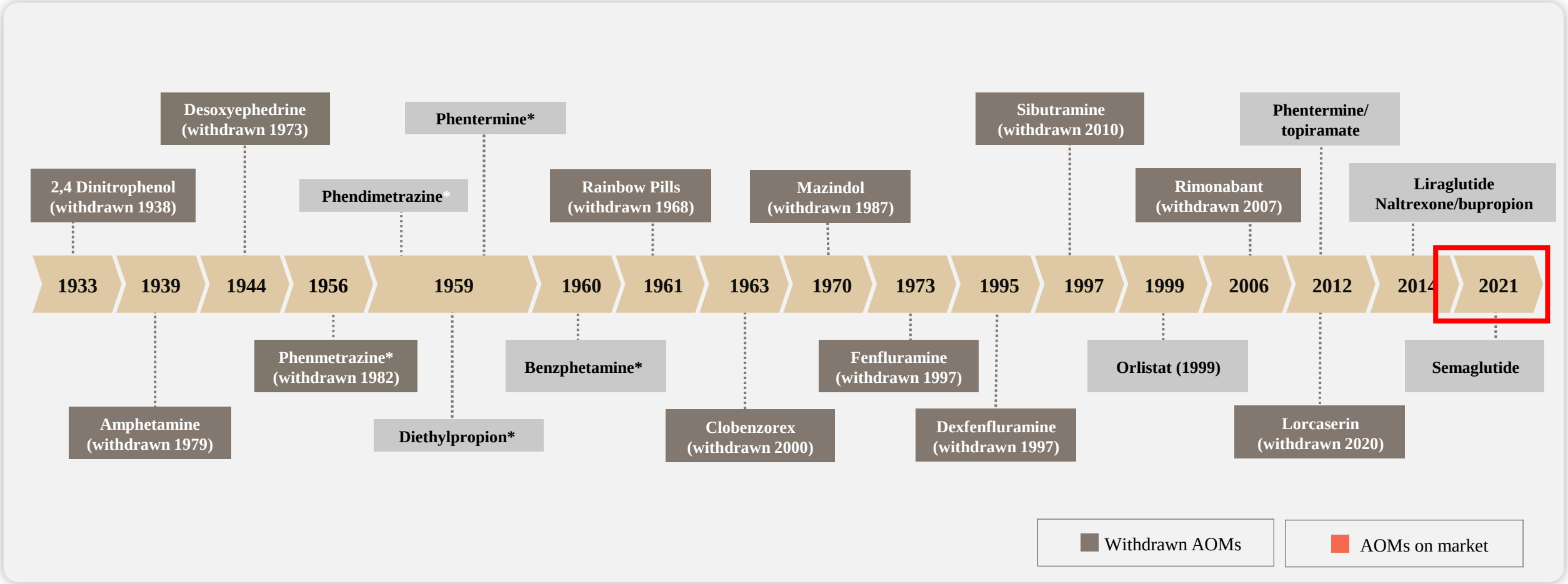
Rates of obesity have increased steadily since ~ 1980





Chronology of Anti-Obesity Pharmacotherapies

Based on First Approval



*Approved for short term use in the United States.

AOMs = Antiobesity medications

1. Pilitsi E, et al. *Metabolism*. 2019;92:170-192.
2. Müller TD, et al. *Nat Rev Drug Discov*. 2021;1-23.
3. Onakpoya IJ, et al. *BMC Med*. 2016;14:191.

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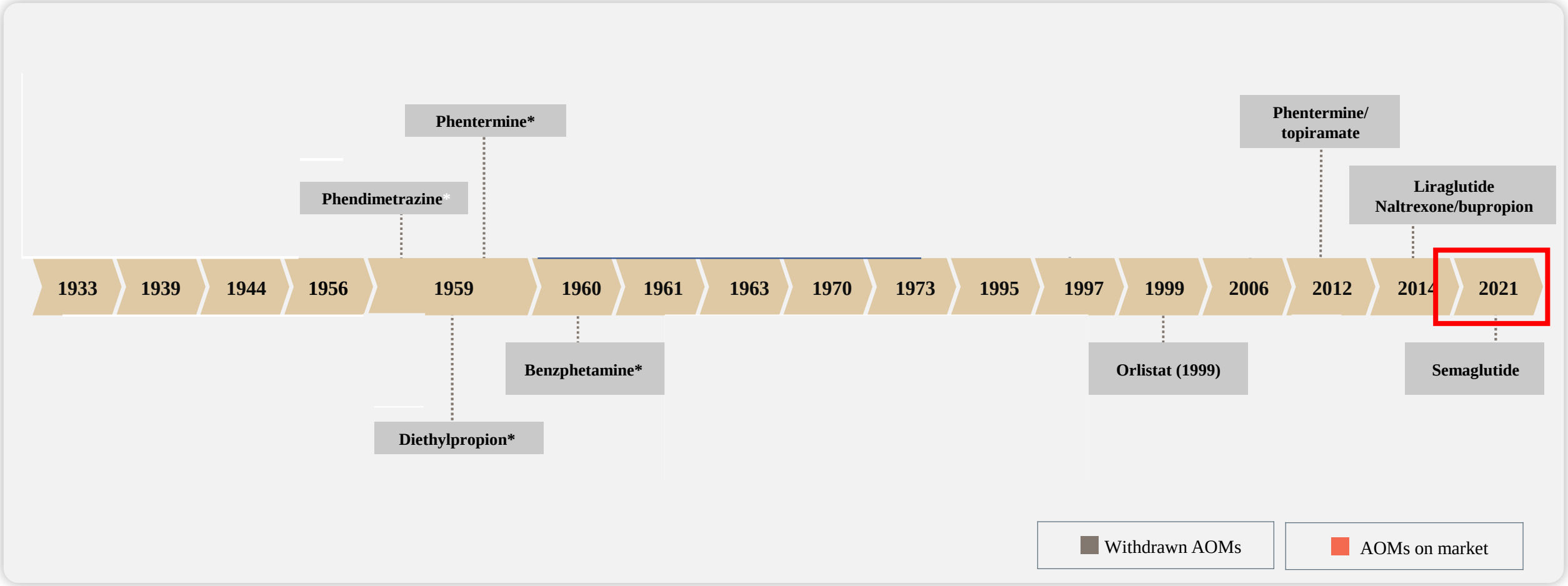

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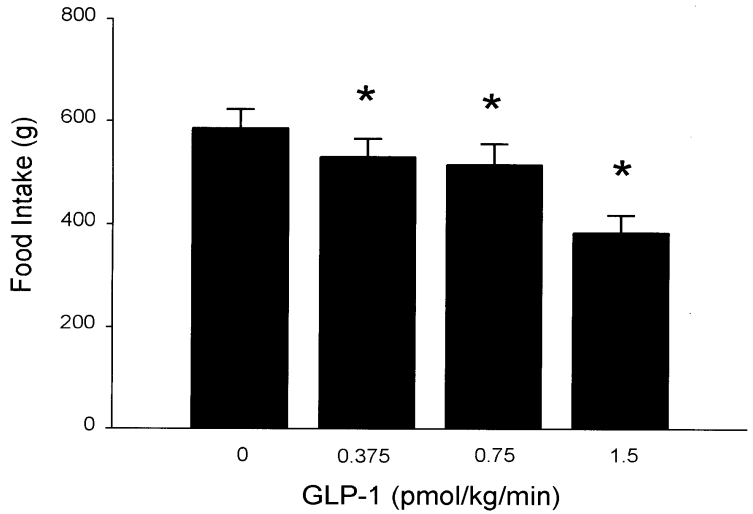
Food Intake in Healthy and Diabetic Men Given IV GLP-1



Gutzwiler et al, Gut, 1999

Table 1. *Effect of GLP-1 on eating behavior in 12 patients with diabetes mellitus type 2 compared with saline (control)*

Parameter	Saline	GLP-1
Food quantity, g	377 ± 45	268 ± 31*
Calorie intake, kcal	944 ± 99	694 ± 79*
Fluid intake, ml	441 ± 56	360 ± 60†

Data are means ± SE. Dose of glucagon-like peptide-1 (GLP-1) was 1.5 pmol·kg^{-1}·min^{-1}. *$P = 0.034$; †$P = 0.011$.

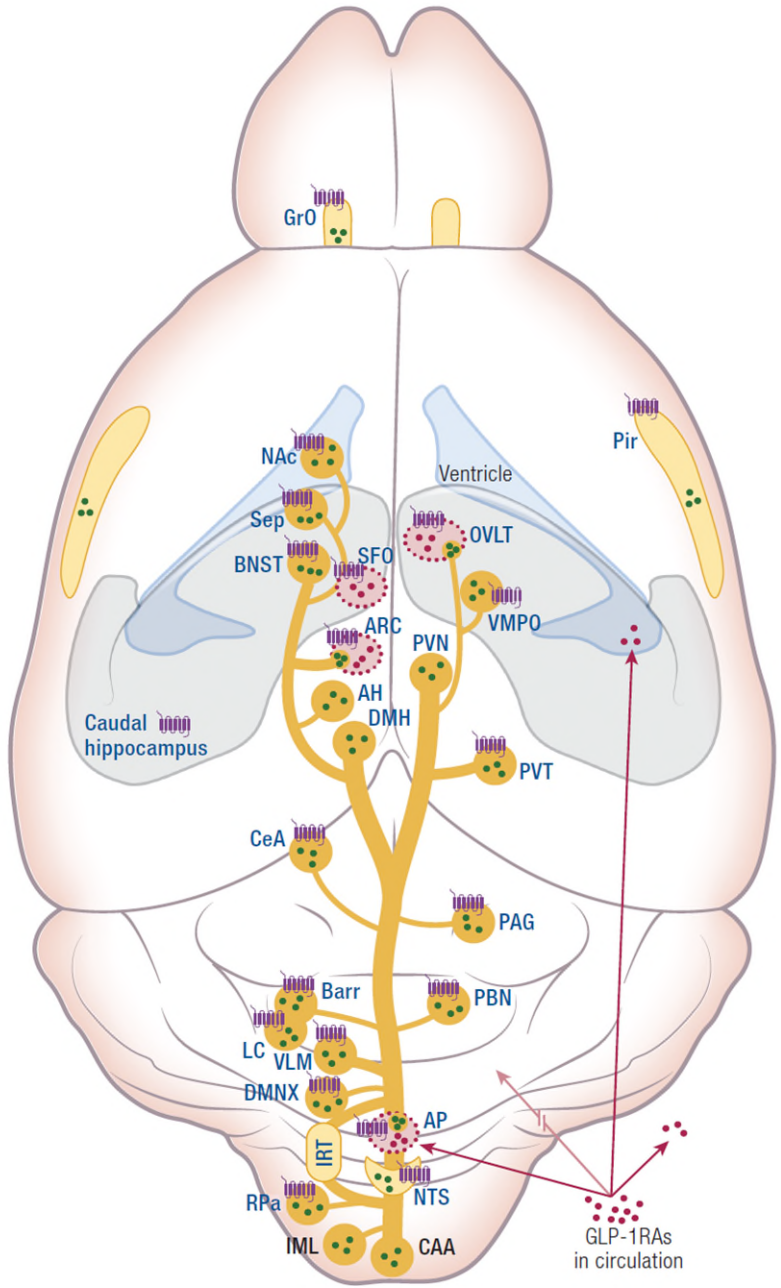
Gutzwiler et al, AJP, 1999

GLP-1RA actions

↓Food intake
↑Aversive response
↓Gut motility
↓Neuroinflammation
↑Neuroprotection

PPG neuron actions

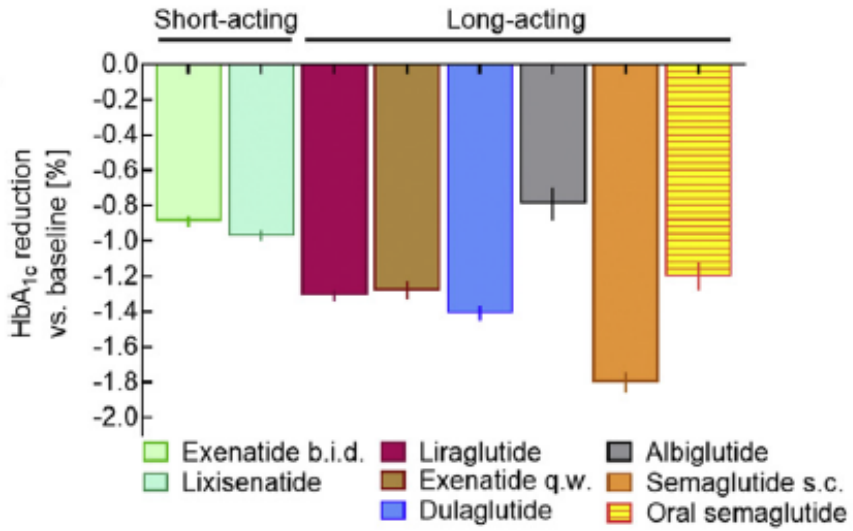
↓Food intake
↑Heart rate



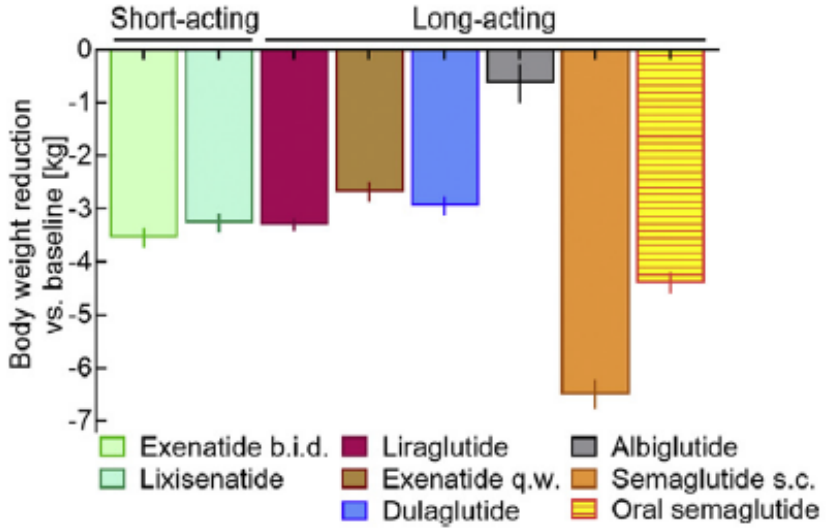
Leaky blood-brain barrier
PPG+ cell bodies
PPG+ axon
GLP-1R
Brain GLP-1
GLP-1RA

Comparisons (cross-trial) of GLP-1RA

A1c



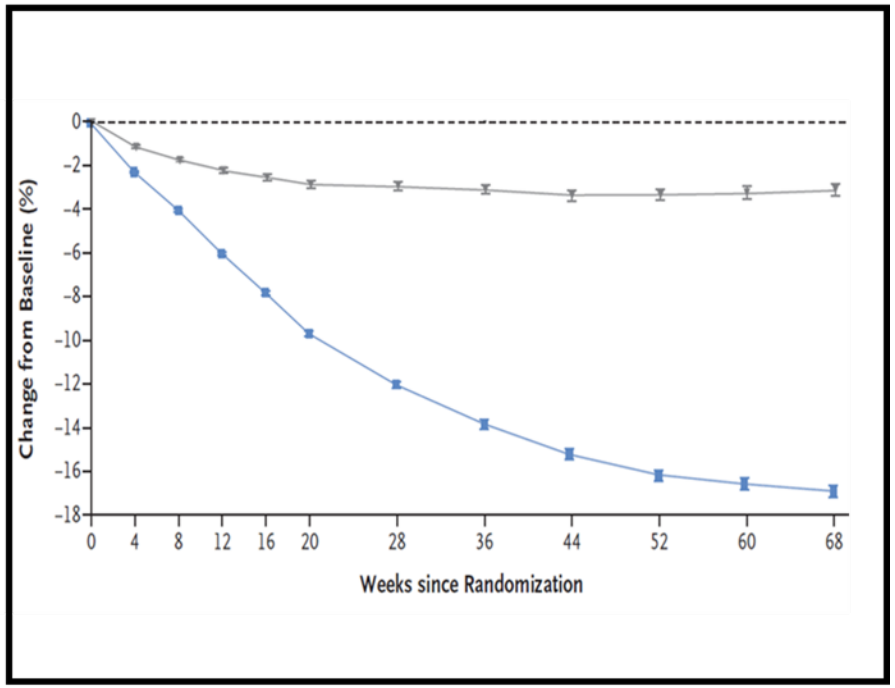
Body Weight



M Nauck and J Meier, Mol Metab 2020

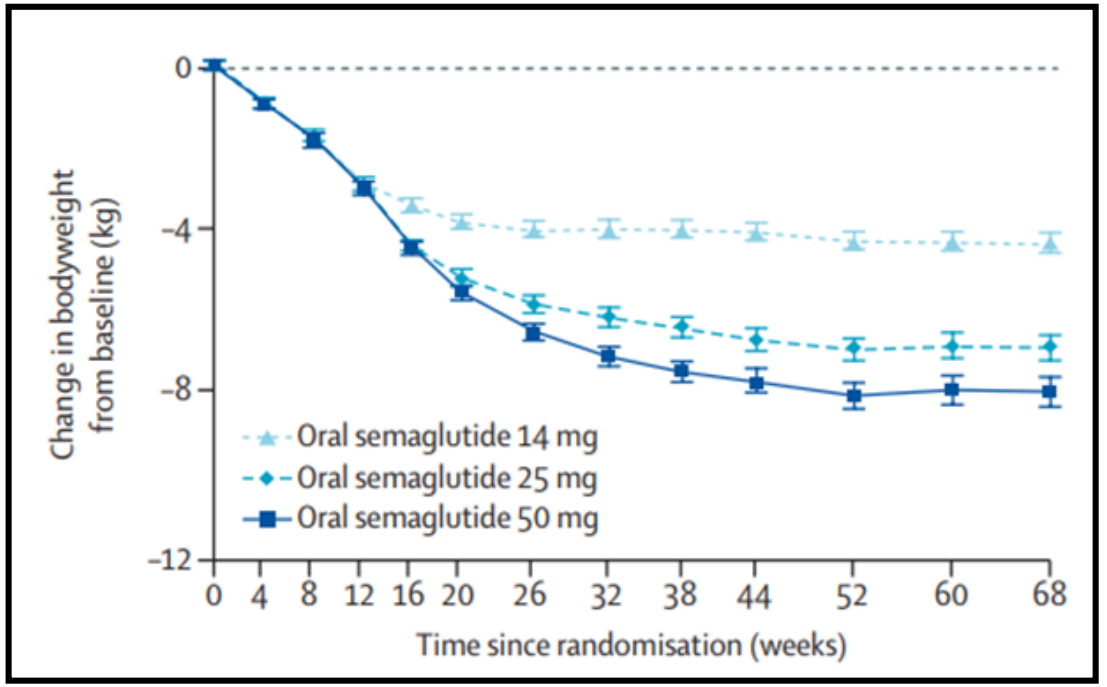
Unprecedented potency of semaglutide for weight loss in nondiabetic subjects

Injectable Semaglutide



J Wilding, NEJM 2021

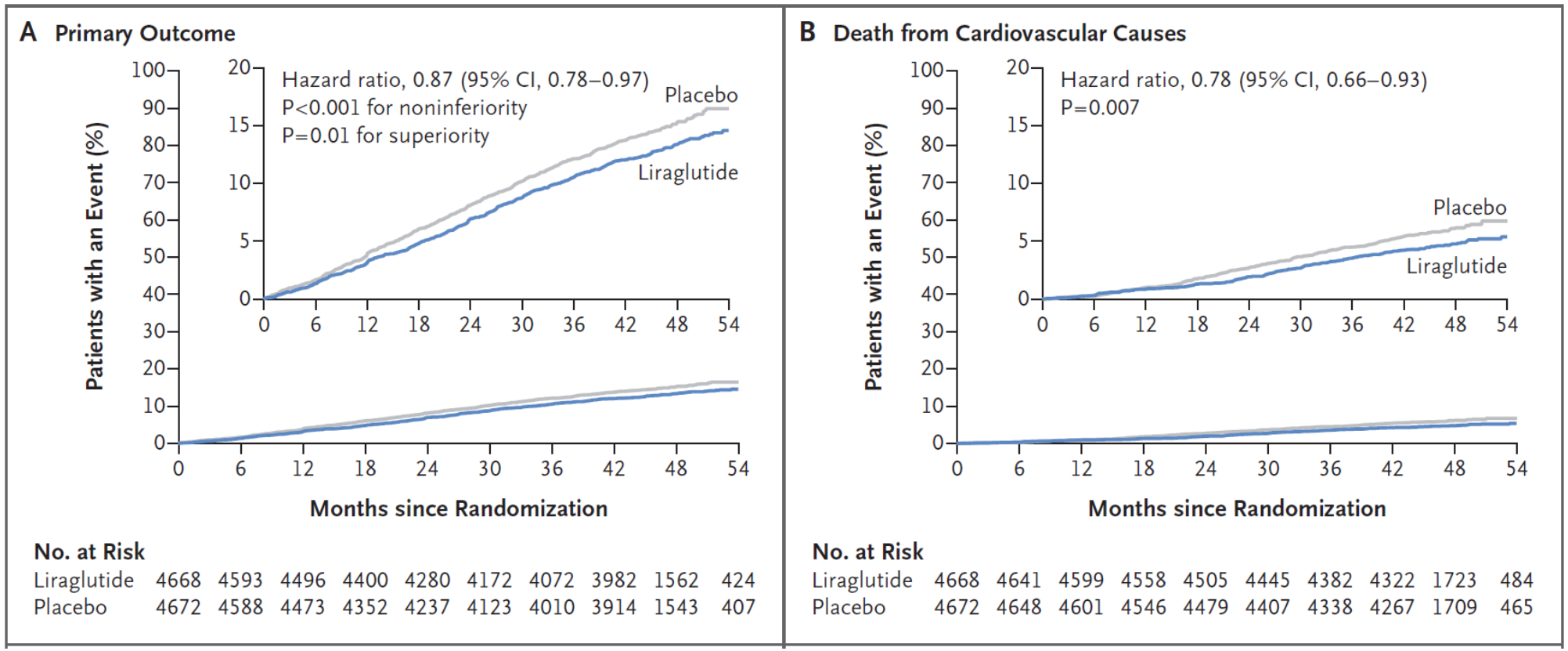
Oral Semaglutide



V Aroda, Lancet 2023

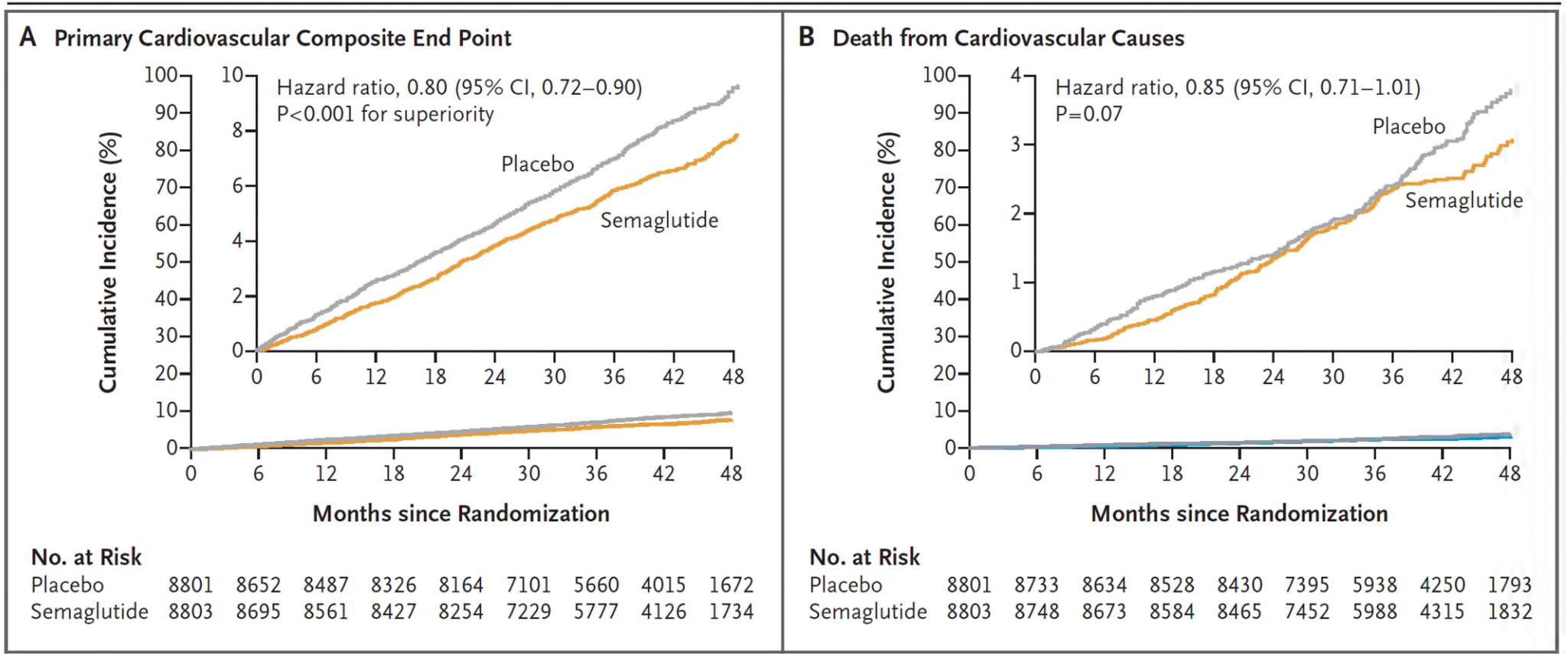
GLP-1RA and prevention of clinical ASCVD

The LEADER trial demonstrates significance of Liraglutide in the prevention of MACE



S Marso, NEJM 2016

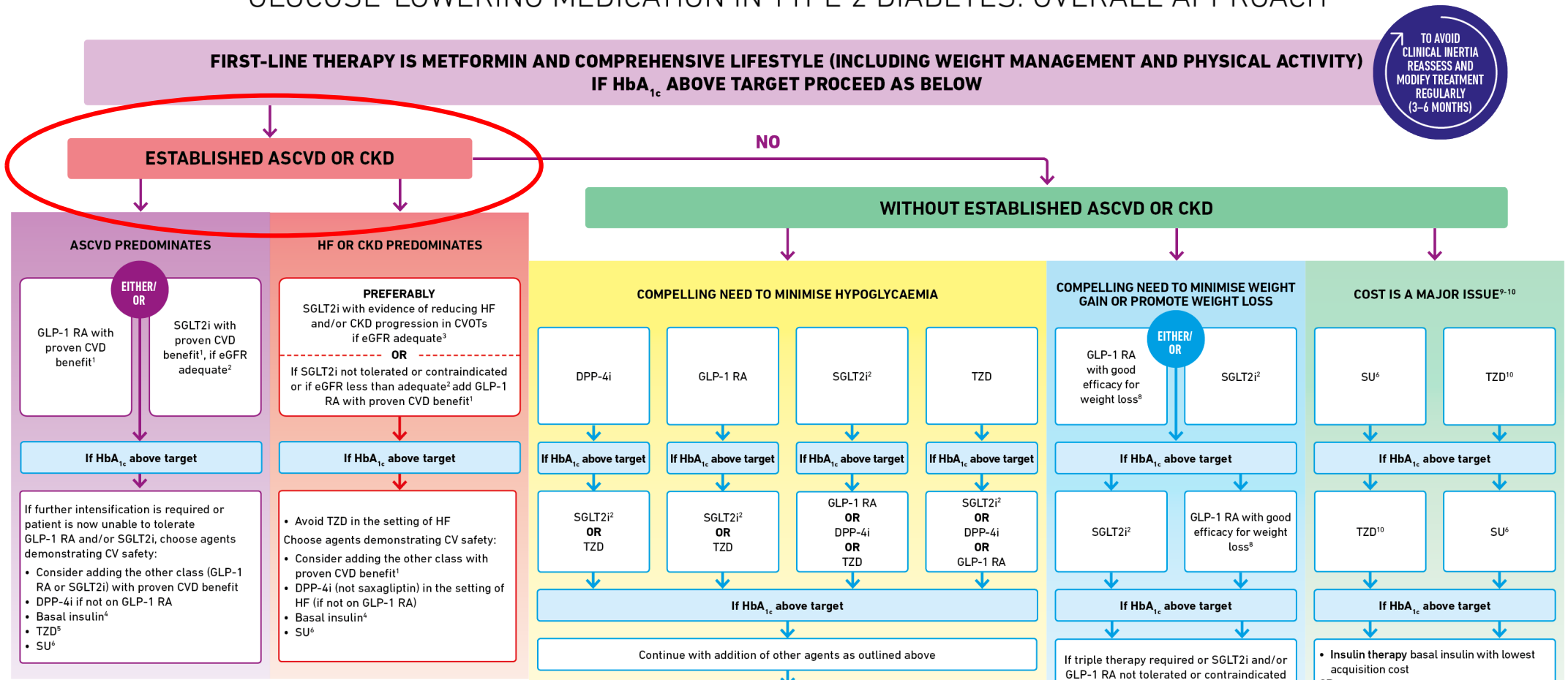
Semaglutide reduces MACE in overweight/obese subjects without diabetes



AM Lincoff, NEJM 2023

Figure 2

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



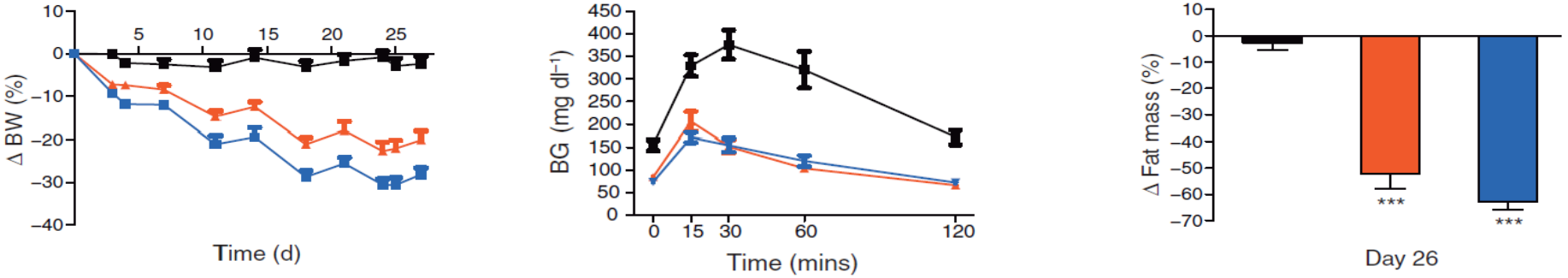
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

The Development of Multi-receptor agonists (MRA)

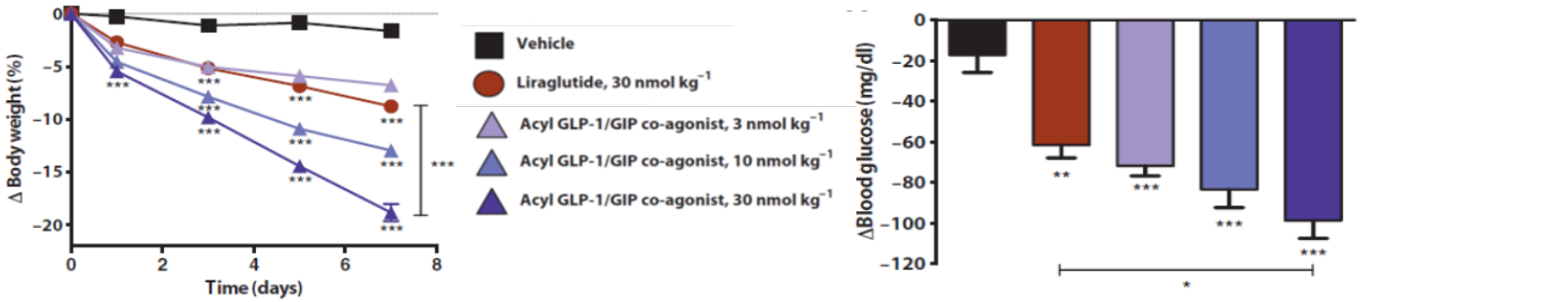
How to make a multi-receptor agonist

GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
GIP	YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNIT
Gcg	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT
MRA	HXQGTFTSDKSKYLDERAAQDFVQWLLDGGPSSGAPPPS-NH_2

Iterative Chemical Refinement

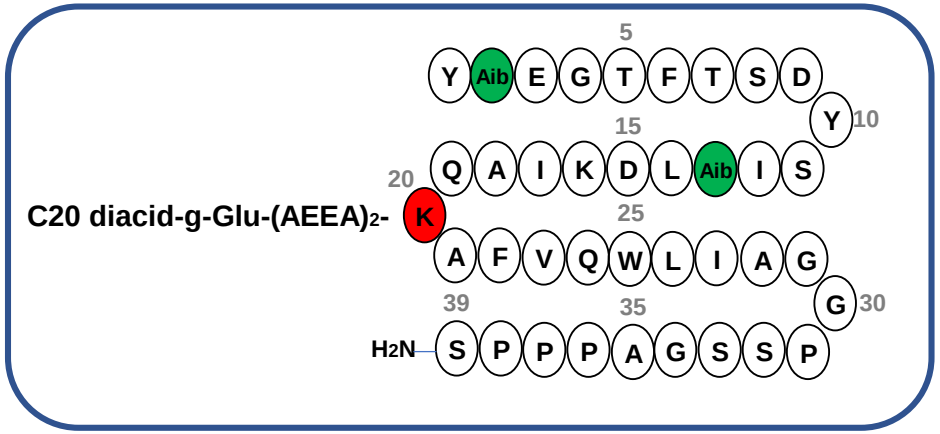


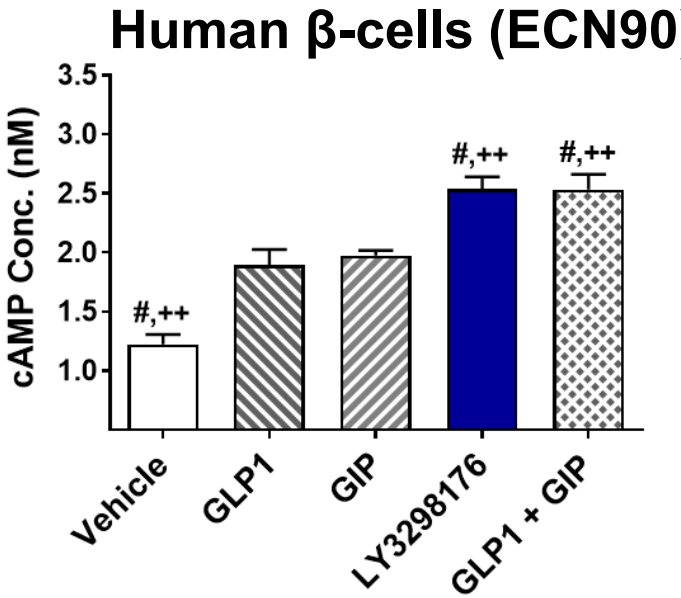
J Day, Nat Chem Biol, 2009

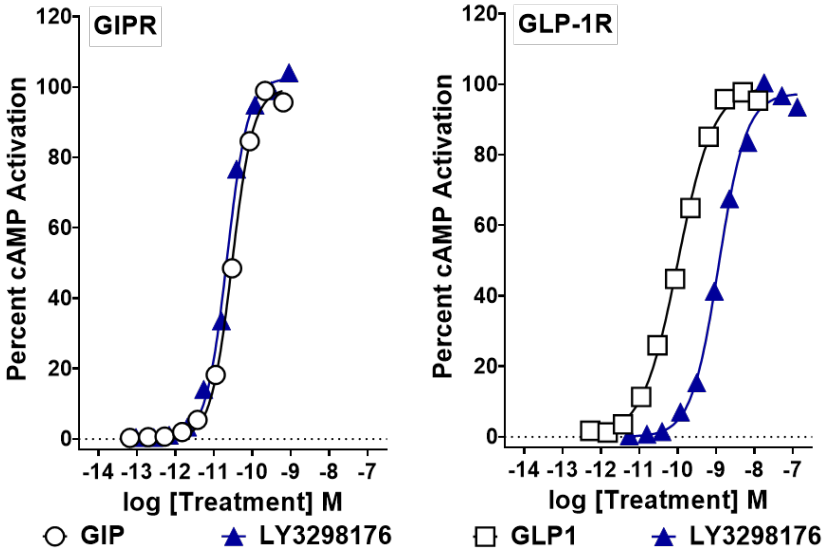


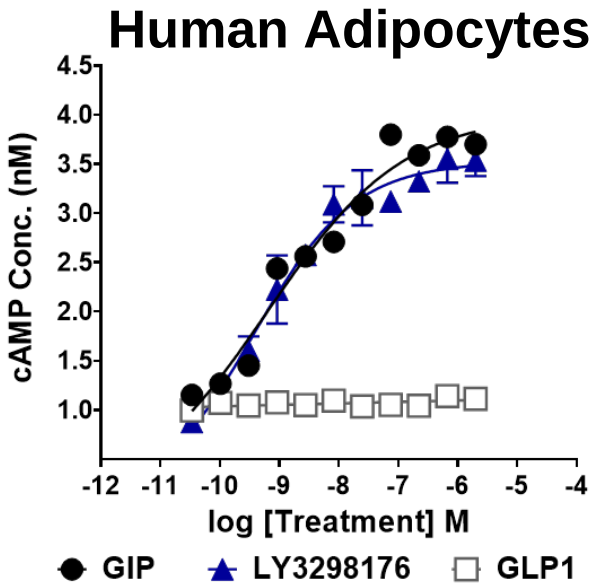
B Finan, Sci Trans Med, 2013

LY3298176: a Novel dual GIP and GLP-1 receptor agonist





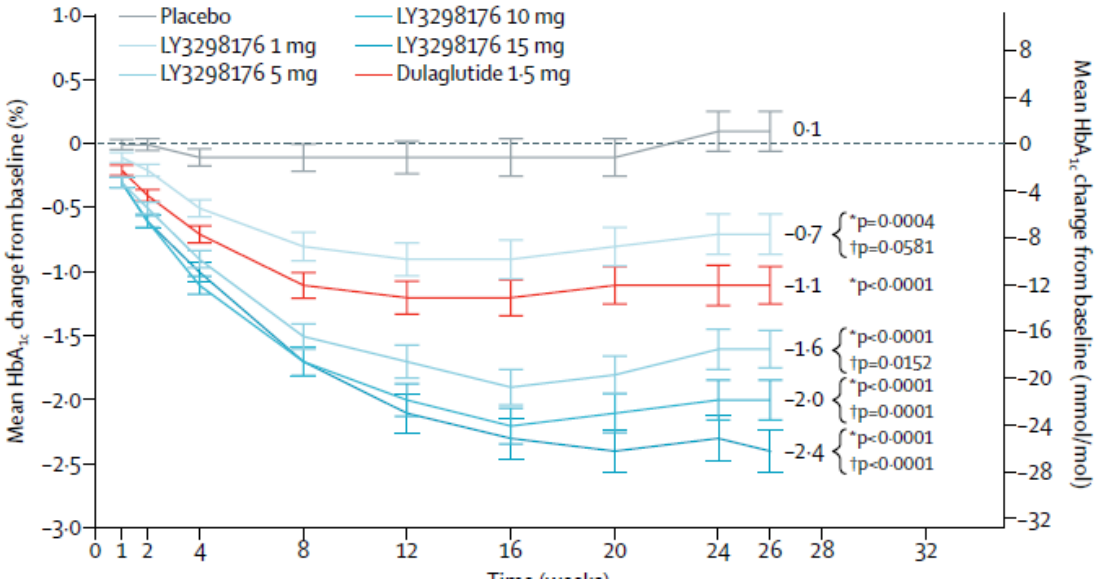




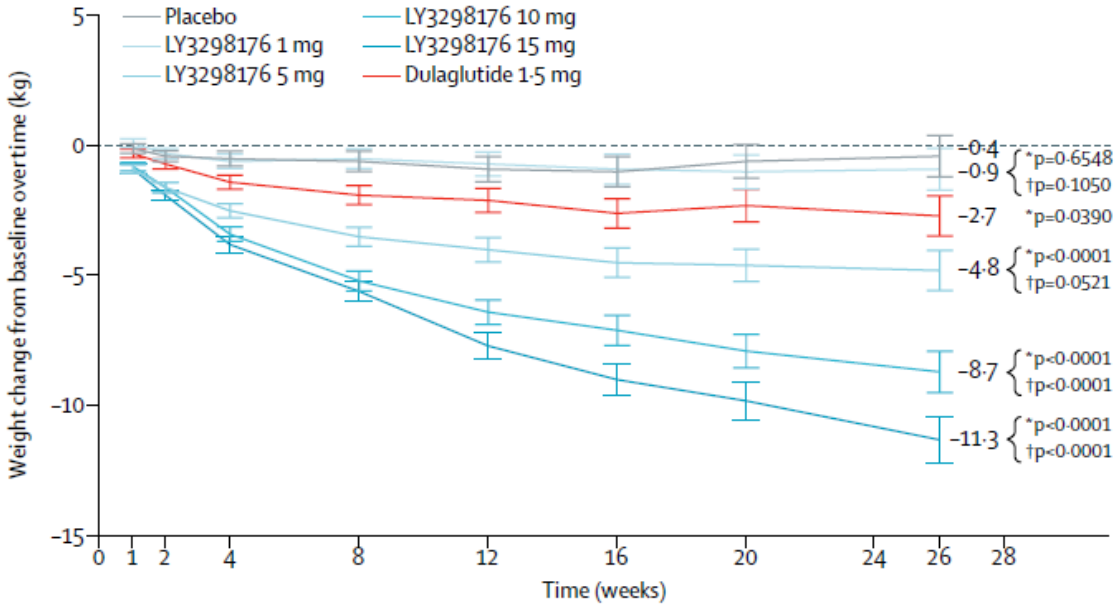
Coskun T et al. Mol Metab. 2018

Effect of Tirzepatide on A1c and body weight in persons with T2DM

A1c

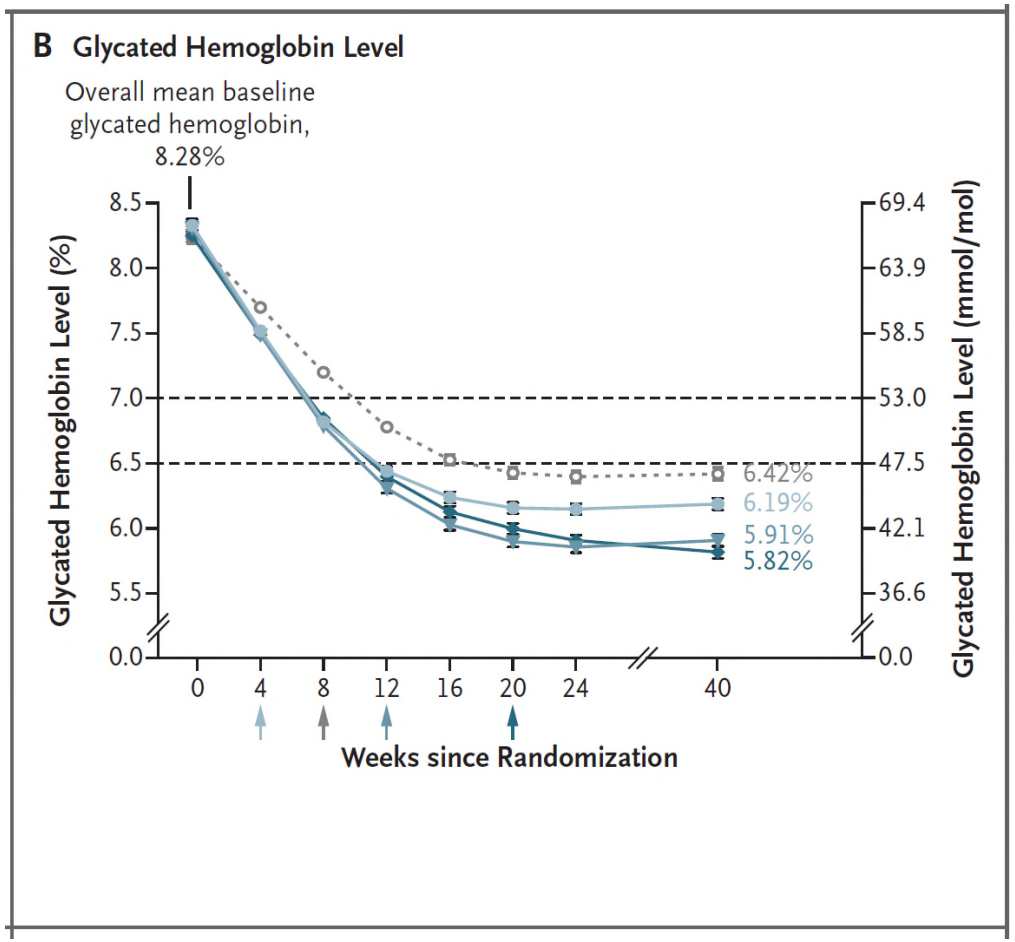


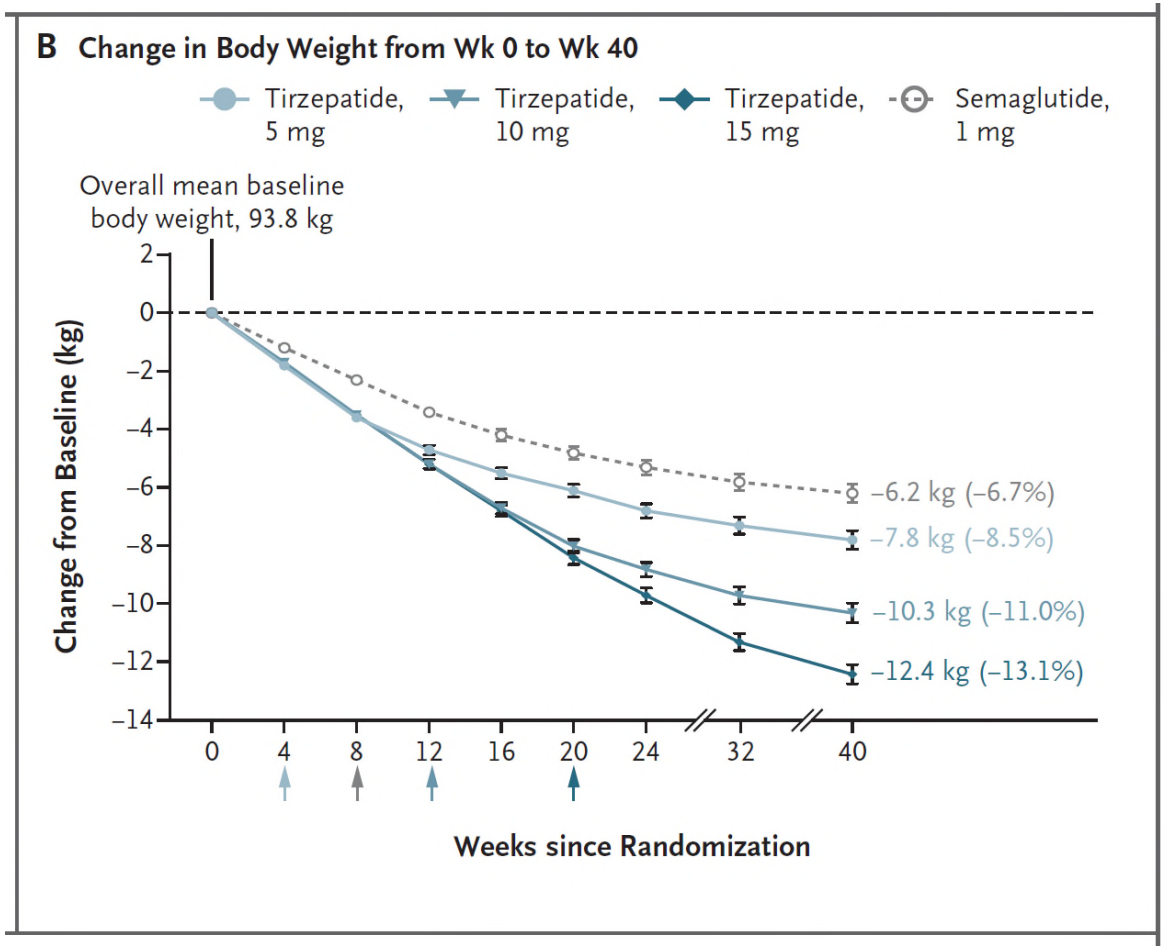
Body Weight



J Frias, Lancet 2018

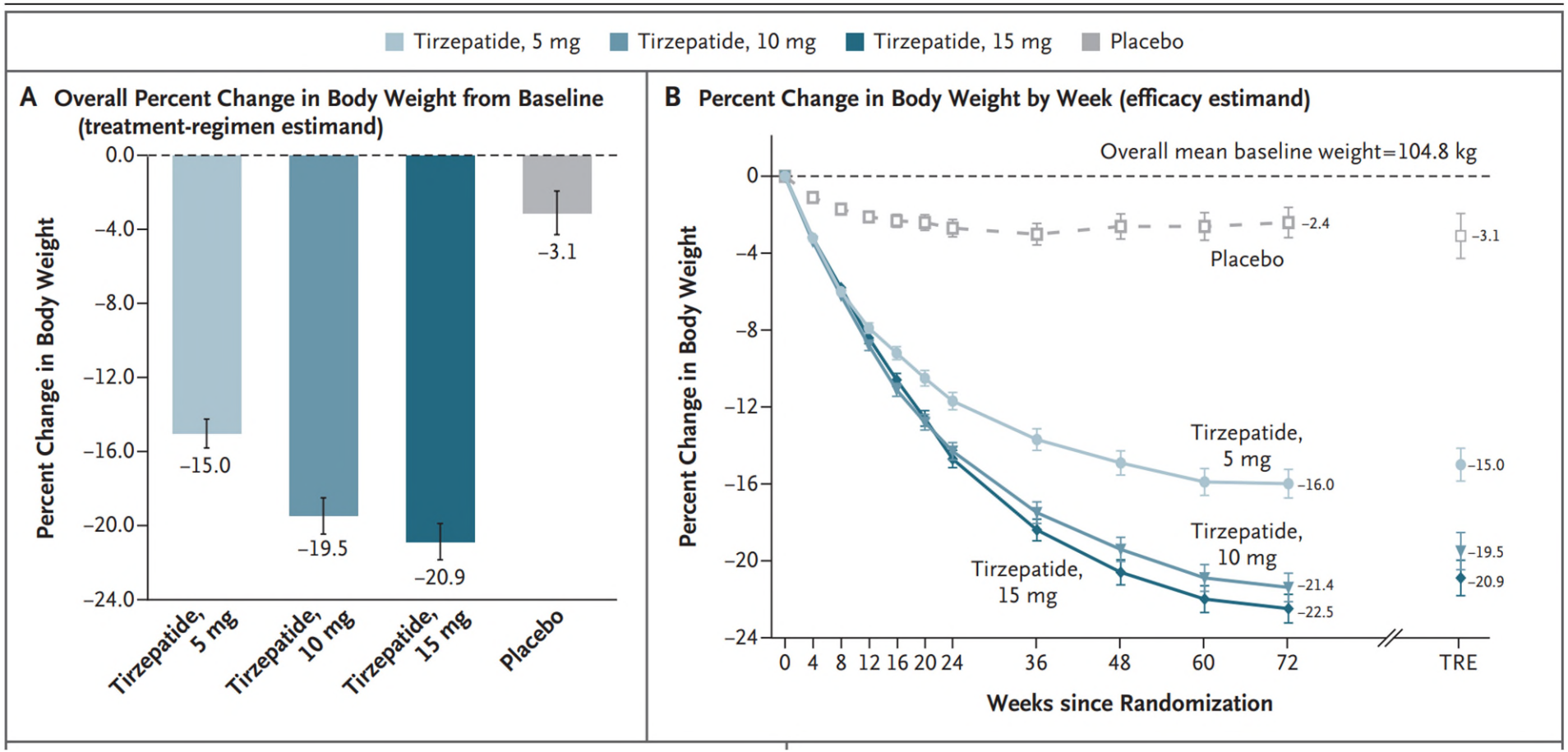
TZP and Semaglutide effects on A1c and Body Weight





J Frias, NEJM 2021

Tirzepatide reduces body weight in overweight/obese subject without diabetes



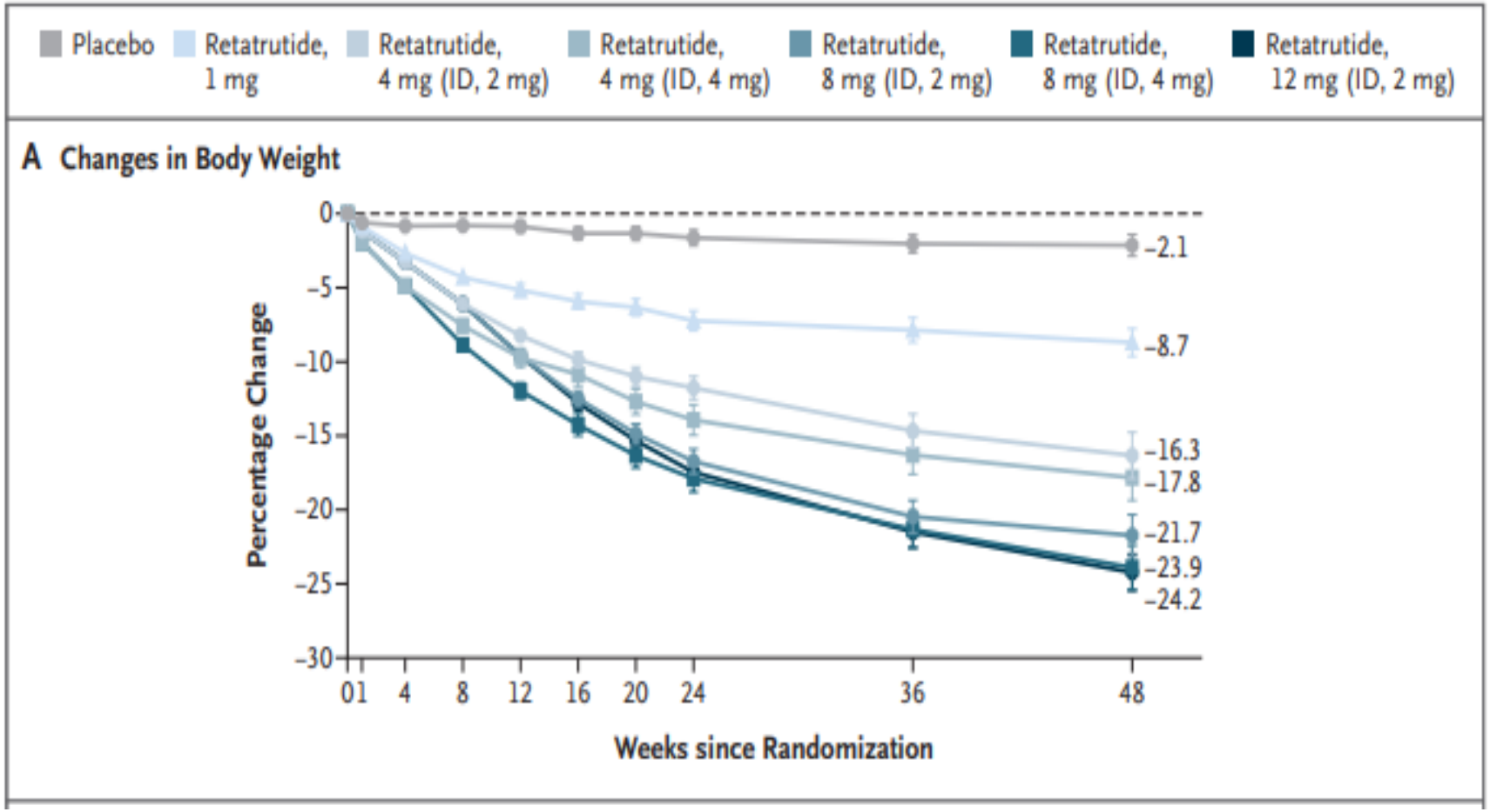
A Jastreboff, NEJM 2022

How do MRA work?

1. **Simple additivity: $cAMP_1$ + $cAMP_2$ + $cAMP_3$**
2. **Complementary down stream signaling**
3. **Heterodimerization and unique signaling**
4. **Distinct actions at the GLP-1R**
5. **Distinct actions in separate tissues**

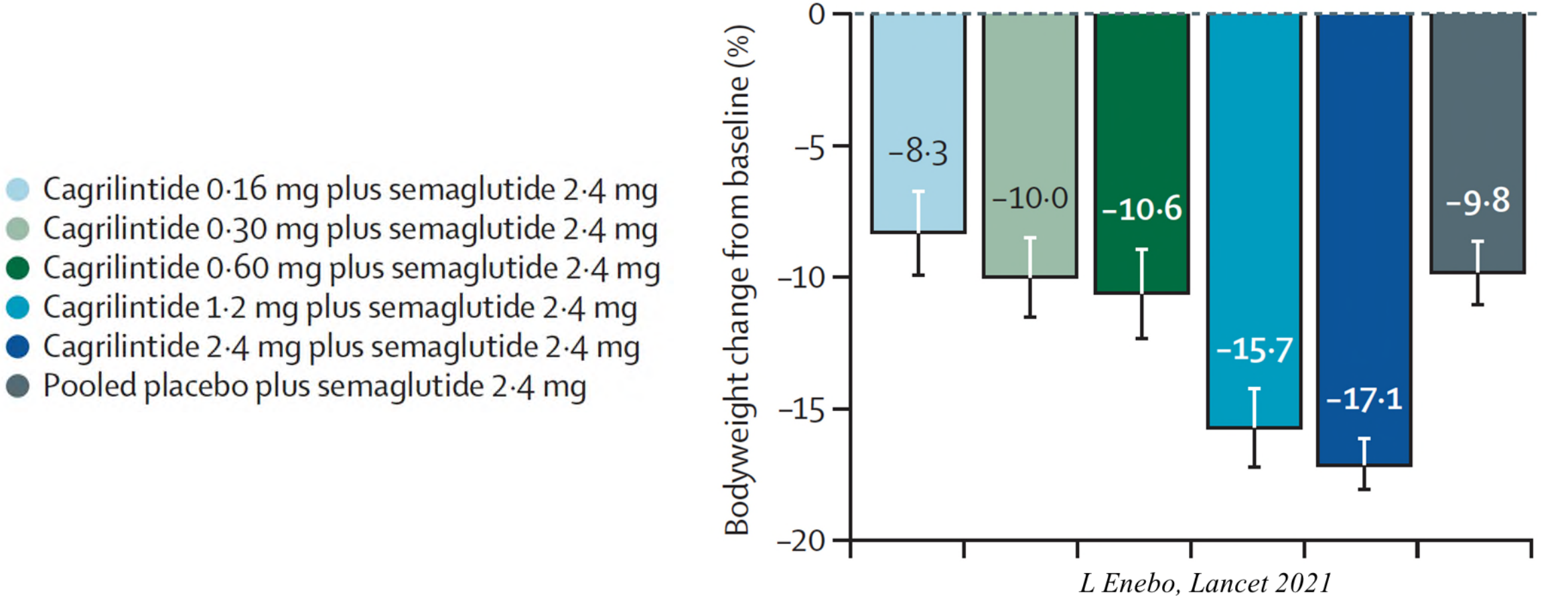
Where is this all headed?

GLP-1R/GIPR/GCGR triple agonist for weight loss in nondiabetic subjects

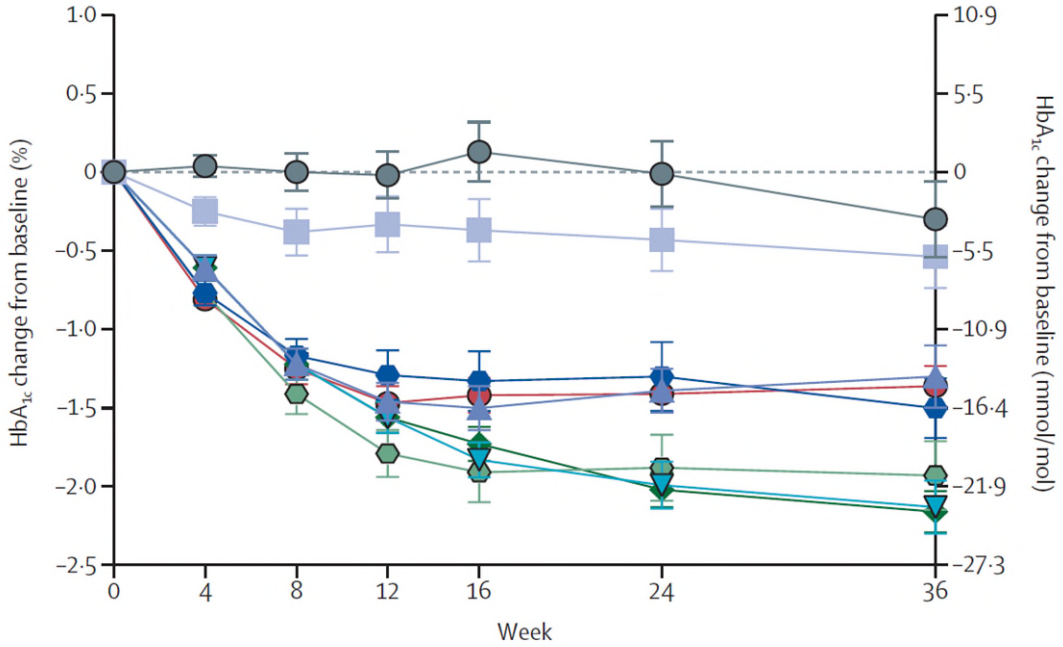


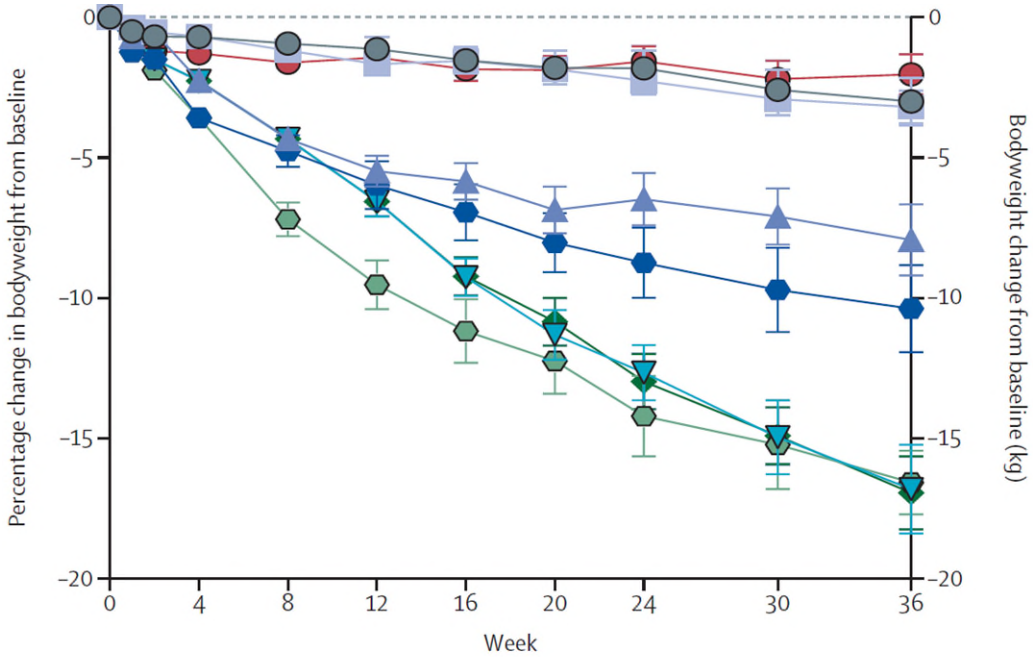
A Jastreboff, NEJM 2023

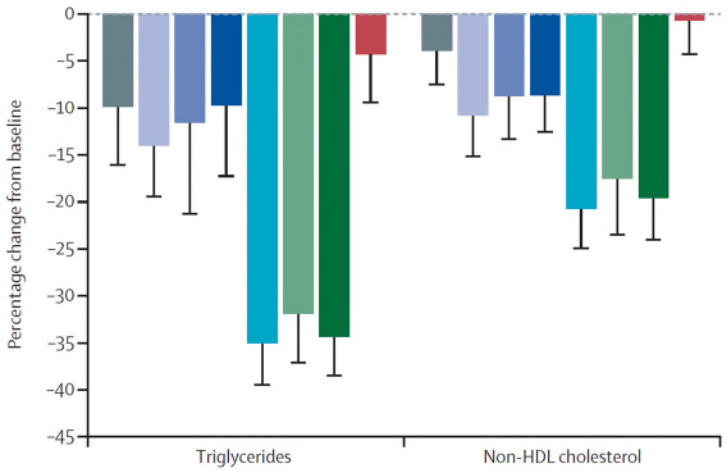
Addition of semaglutide to amylin analogue Cagrilintide shows additive effects on weight loss

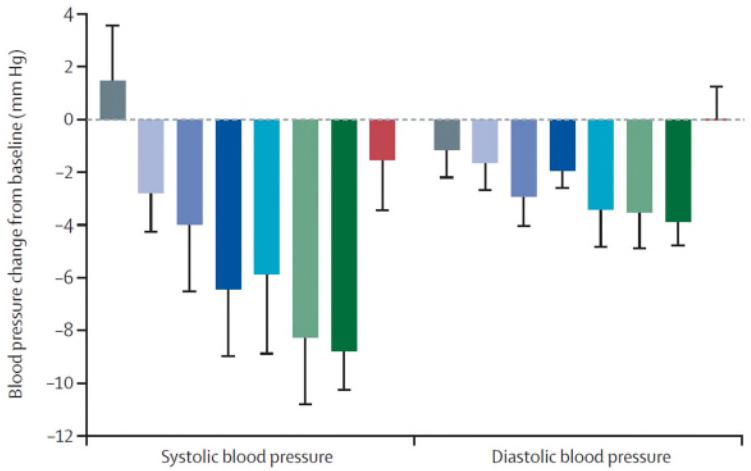


Effects of retatrutide on clinical parameters in T2DM



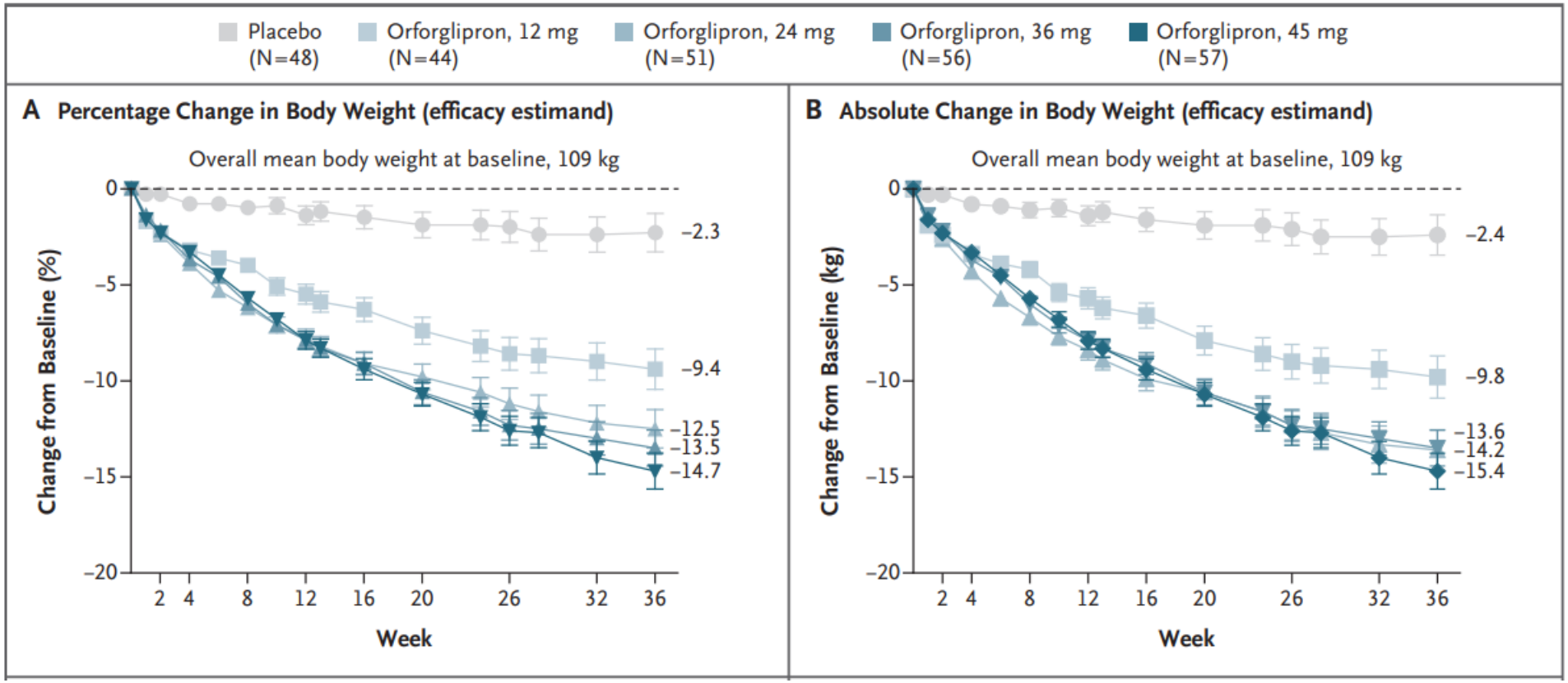






J Rosenstock, Lancet 2023

The future: Can small molecule agents replicate the effects of incretin-based injectables



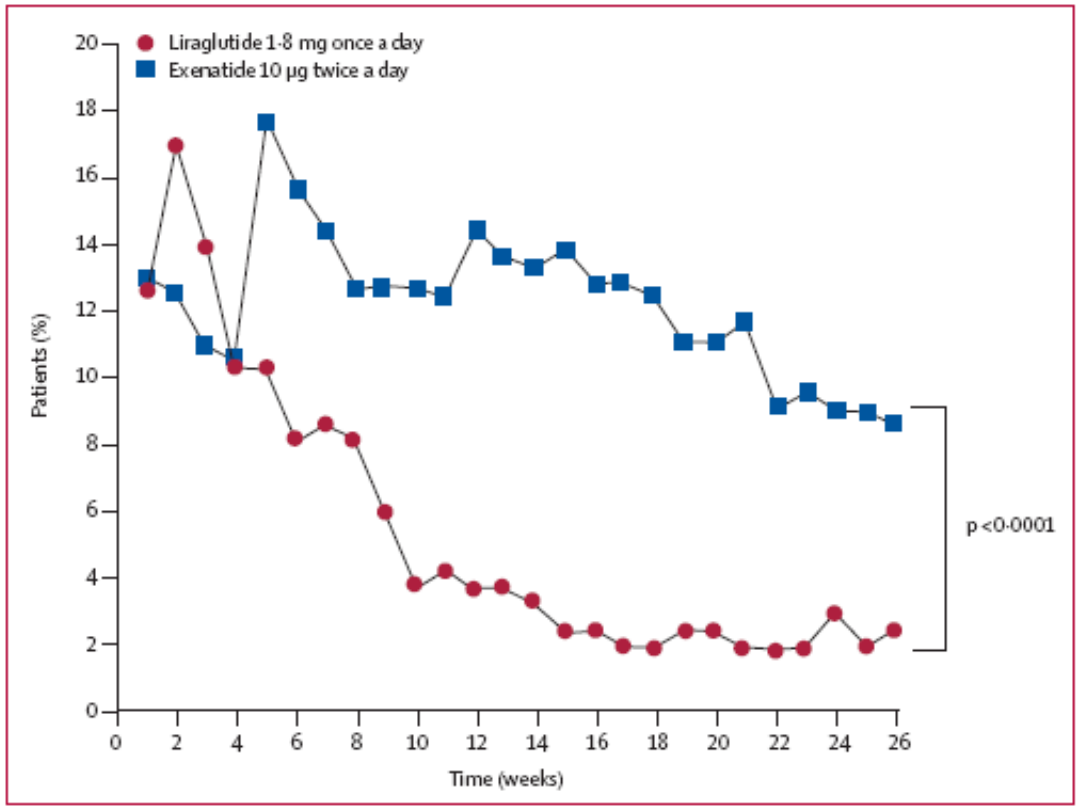
S Wharton et al, NEJM 2023

What does the future hold?

- More and stronger injectable MRA/GLP-1RA
- Small molecule agents that are orally available but work through the incretin system
- Deeper understanding of the relevant biology
    - fewer side effects and a wider therapeutic window
    - personalized or targeted therapy

Are there any downsides to these miracle drugs?

GI side effects of GLP-1RA abate over time



J Buse, Lancet, 2009

TABLE. Annual Event Rates for Treatment-Emergent Adverse Events With a 10% or Greater Incidence During the Controlled and Open-Ended Extension Phases in the Intent-to-Treat Population[a]

	Controlled phase (weeks 0-30)		
Adverse event	Exenatide twice daily (n=145)[b]	Exenatide once weekly (n=148)	Open-ended extension phase (weeks 30-260) of exenatide once weekly (n=258)
Nausea	92.0	84.6	8.0
Vomiting	47.3	36.1	7.1
Upper respiratory tract infection	35.8	16.2	17.4
Diarrhea	34.5	37.3	10.3
Urinary tract infection	14.1	22.4	7.8
Sinusitis	12.8	8.7	10.5
Nasopharyngitis	11.5	18.7	16.3
Gastroenteritis, viral	11.5	16.2	3.4
Headache	10.2	26.1	3.6
Back pain	7.7	8.7	6.2
Arthralgia	7.7	12.4	7.1
Bronchitis	7.7	5.0	4.8
Hypertension	5.1	6.2	4.5
Pain in extremity	2.6	2.5	5.0
Cough	2.6	6.2	3.2
Musculoskeletal pain	0	2.5	4.2

GLP-1 receptor agonists are the most expensive diabetes medications on the market today

GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$882
	• Exenatide	10 μg pen	$752
	• Dulaglutide	4.5/0.5 mL pen	$957
	• Semaglutide	1 mg pen	$973
		14 mg (tablet)	$927
	• Liraglutide	18 mg/3 mL pen	$1,161
	• Lixisenatide	300 μg/3 mL pen	$774

ADA Standards of Care, Chapt 9, Diabetes Care, Jan 2020

The Downsides

- GI toxicity
- Potential for rare but serious side effects
- Low rates of drug persistence
- Absence of long term outcome studies
- Incomplete understanding of mechanisms
- Expensive to produce, ship and store
- EXPENSIVE.

Summary

- The incretin effect is now nearly 100 years old and remains important physiology
- Understanding incretin biology has opened the door to an important new class of therapeutics
- The GLP-1R system has turned out to be a great drug target
- Incretin-based drugs are still a dynamic area of development with potential for an even greater impact on metabolic disease
- For GLP-1RA/MRA to bend the curves of diabetes and obesity will require greater availability and expanded access to the people who need them.