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# A primer on contemporary pharmacotherapy for obesity and T2D

## IFSO Congress, September 2024


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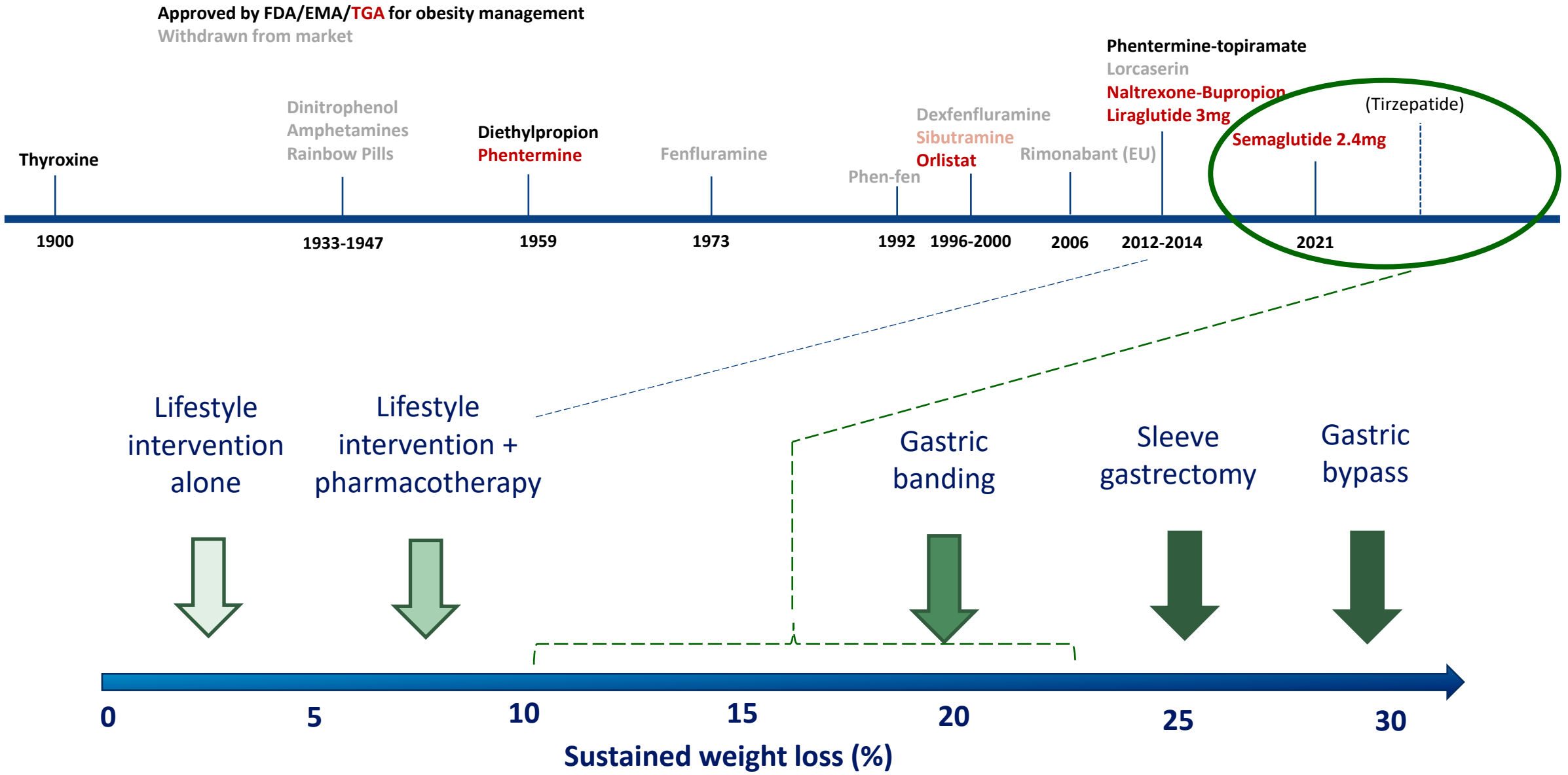
A partnership between:

MONASH University | AlfredHealth

Alfred Alliance in Diabetes

# Disclosures

- Co-authorship of manuscripts with medical writer provided by Novo Nordisk, Eli Lilly


Approved by FDA/EMA/TGA for obesity management
Withdrawn from market
Thyroxine
1900
Dinitrophenol
Amphetamines
Rainbow Pills
1933-1947
Diethylpropion
Phentermine
1959
Fenfluramine
1973
Phen-fen
1992
Dexfenfluramine
Sibutramine
Orlistat
1996-2000
Rimonabant (EU)
2006
Phentermine-topiramate
Lorcaserin
Naltrexone-Bupropion
Liraglutide 3mg
2012-2014
Semaglutide 2.4mg
2021
(Tirzepatide)
Lifestyle intervention alone
Lifestyle intervention + pharmacotherapy
Gastric banding
Sleeve gastrectomy
Gastric bypass
0
5
10
15
20
25
30
Sustained weight loss (%)

# New wonder drug hailed a game changer in the fight to tackle obesity

FT Magazine Drugs research + Add to myFT

## A new 'miracle' weight-loss drug really works – raising huge questions

BBC Sign in Home News Sport Reel Worklife

NEWS

**A 'game-changer' weight-loss drug was approved in 2021. Demand was so high that there were shortages within months.**

## Obesity: Appetite drug could mark 'new era' in tackling condition

The New York Times

## *Patients Taking Experimental Obesity Drug Lost More Than 50 Pounds, Maker Claims*

## Are Semaglutide and Tirzepatide Weight Loss Miracle Cures? Why the Choice is Yours

← Tweet

Elon Musk
@elonmusk

Replying to @Teslarati and @ResidentSponge

In the meantime, semaglutide (aka Ozempic/Rybelsus) appears to be effective in appetite control with minor side effects

11:35 pm · 24 Apr 2022 · Twitter for iPhone

## 'Gamechanging' weight loss drug to be made available on NHS

# USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

**HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)**

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

**Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)***

**+ASCVD†**

Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularisation procedure). Variably included: conditions such as transient ischaemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

**+Indicators of high risk**

While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)

**+ASCVD/Indicators of High Risk**

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If $HbA_{1c}$ above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

**+HF**

Current or prior symptoms of HF with documented HFrEF or HFpEF

**+HF**

SGLT2i§ with proven HF benefit in this population

**+CKD**

eGFR < 60 ml/min per 1.73 $m^2$ OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)). These measurements may vary over time; thus, a repeat measure is required to document CKD.

**+CKD (on maximally tolerated dose of ACEi/ARB)**

**PREFERABLY**

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 $m^2$; once initiated should be continued until dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If $HbA_{1c}$ above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

**If additional cardiorenal risk reduction or glycaemic lowering needed**

**Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals**

**Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:**

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals

Efficacy for glucose lowering

**Very High:**
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

**High:**
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

**Intermediate:**
DPP-4i

**Achievement and Maintenance of Weight Management Goals:**

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/physical activity

Intensive evidence-based structured weight management programme

Consider medication for weight loss

Consider metabolic surgery

**When choosing glucose-lowering therapies:**

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

**Very High:**
Semaglutide, Tirzepatide

**High:**
Dulaglutide, Liraglutide

**Intermediate:**
GLP-1RA (not listed above), SGLT2i

**Neutral:**
DPP-4i, Metformin

**If $HbA_{1c}$ above target**

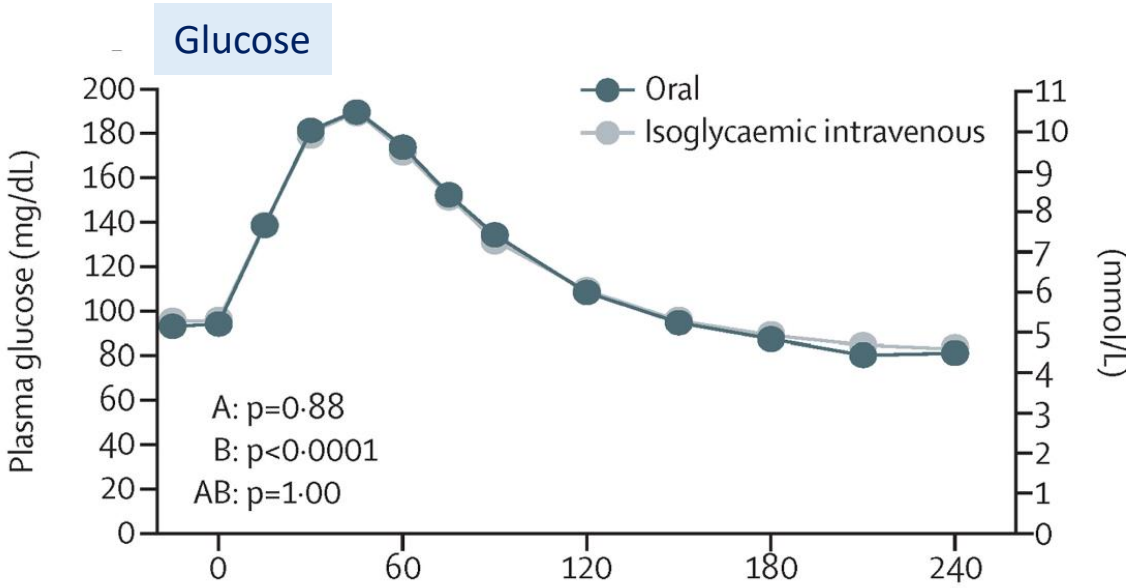
Identify barriers to goals:

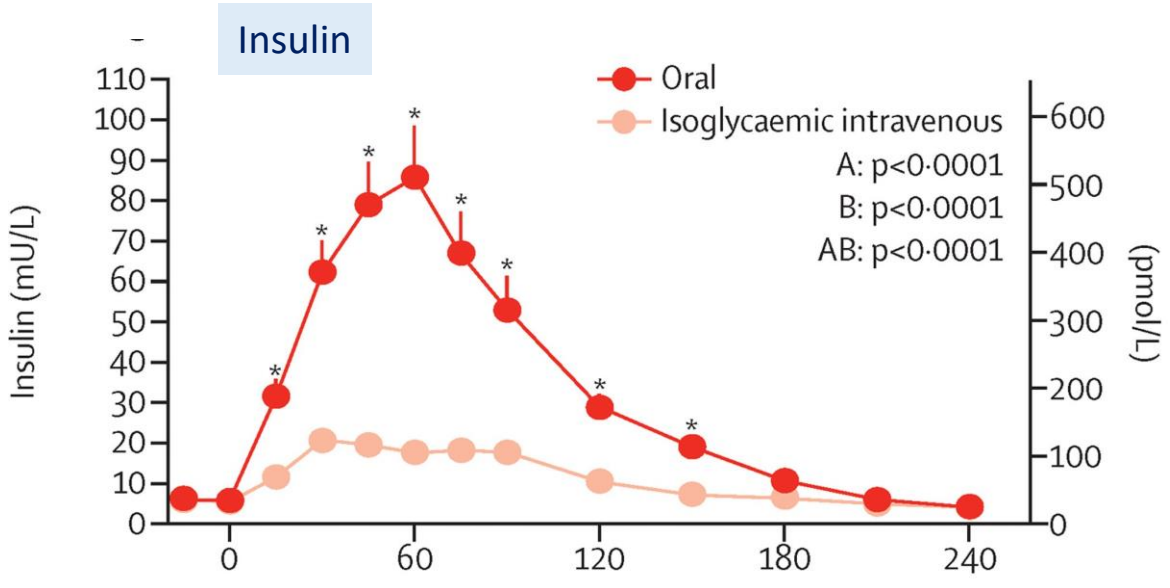
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

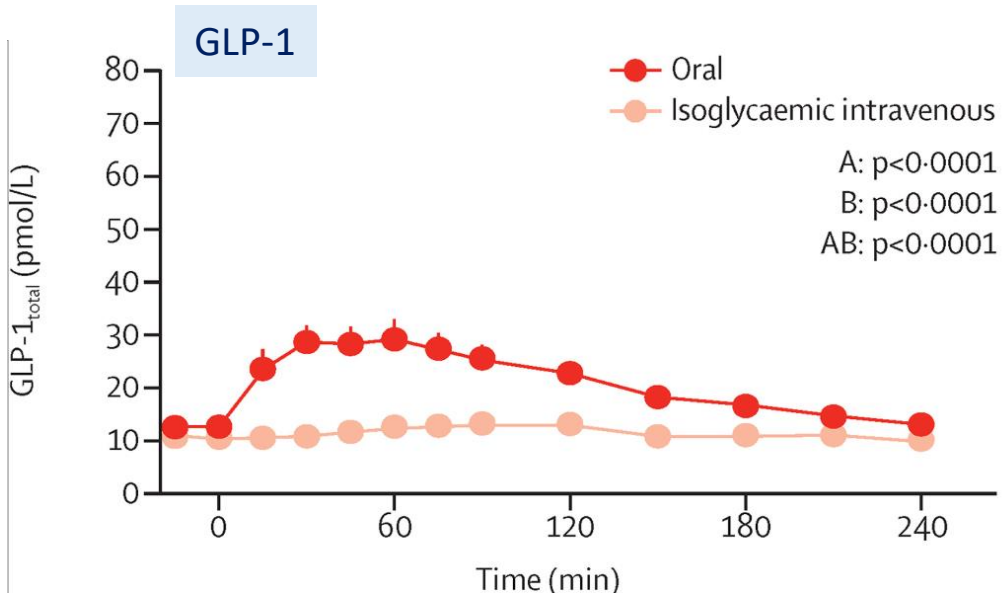
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

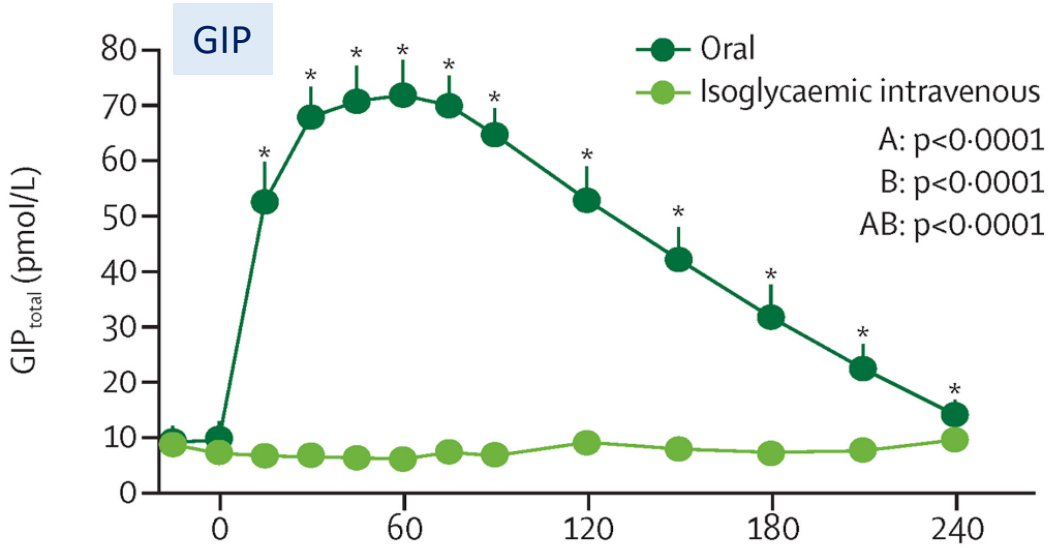
Davies *Diab Care* 2022

# Incretin effect



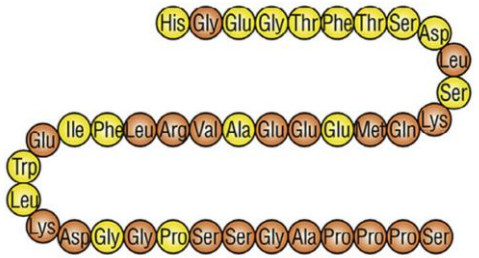




Nauck *Lancet DE* 2016

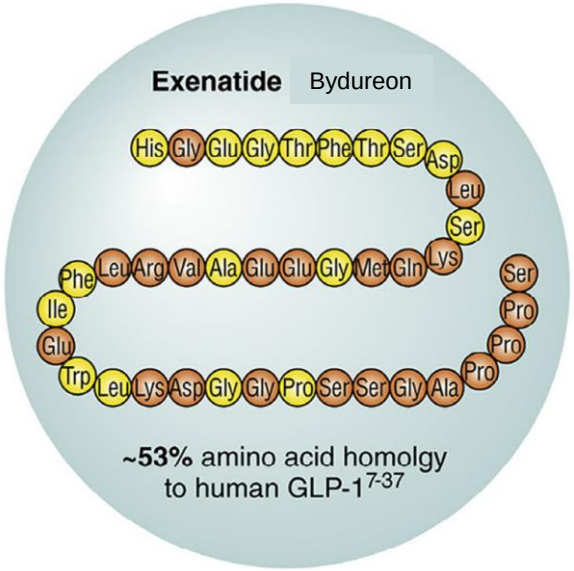
**Exenatide** Byetta




**53%** amino acid homolgy to human GLP-1$^{7-37}$

twice daily

**Exenatide** Bydureon



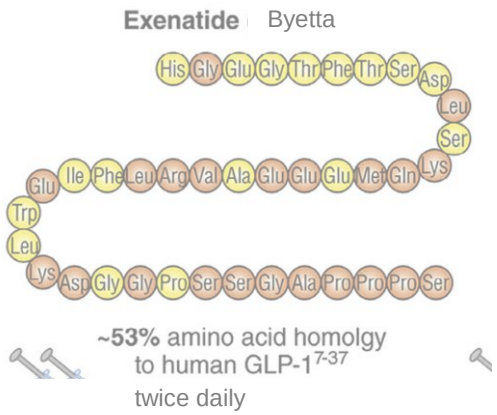

**~53%** amino acid homolgy to human GLP-1$^{7-37}$

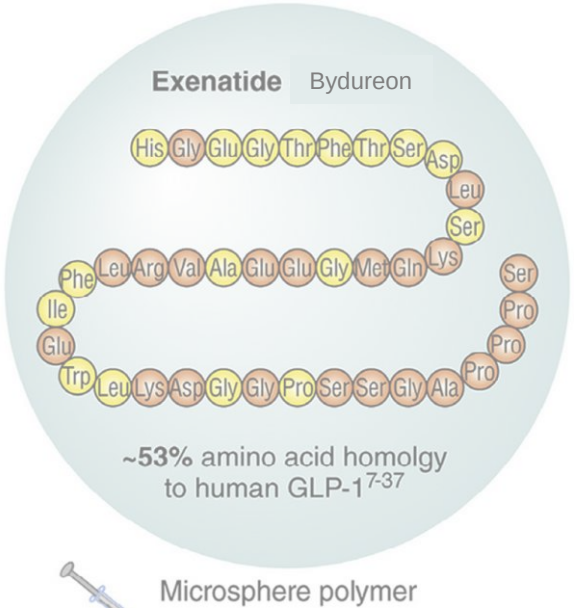
Microsphere polymer

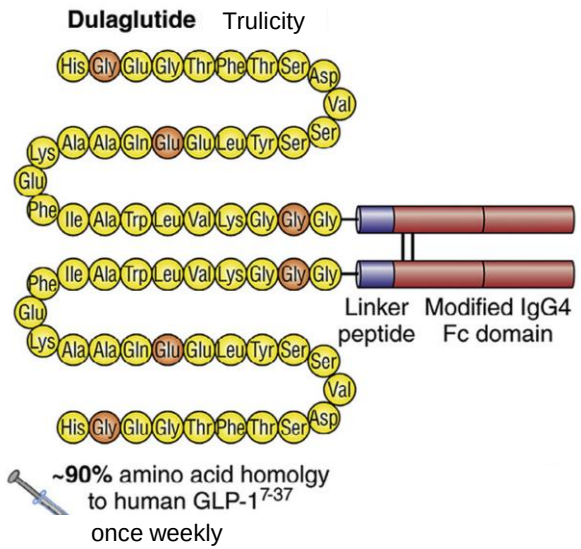
once weekly

Lovshin *Can J Diab* 2017

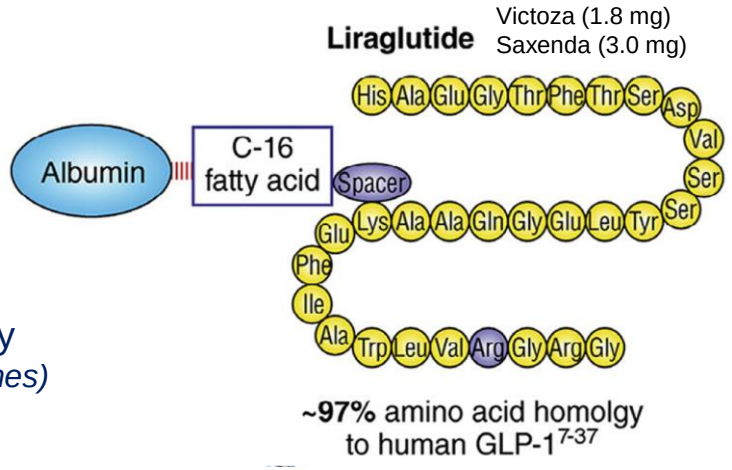
TGA approval:
type 2 diabetes

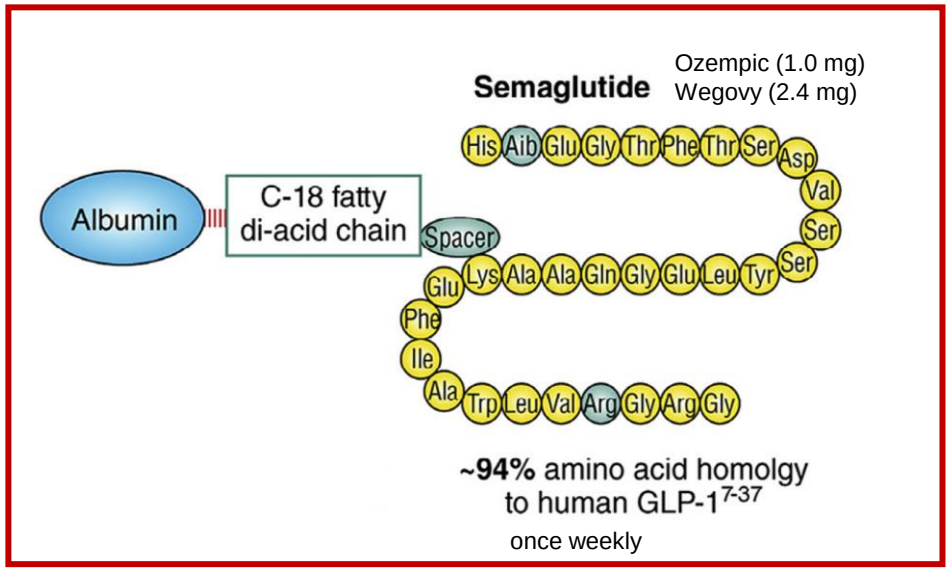


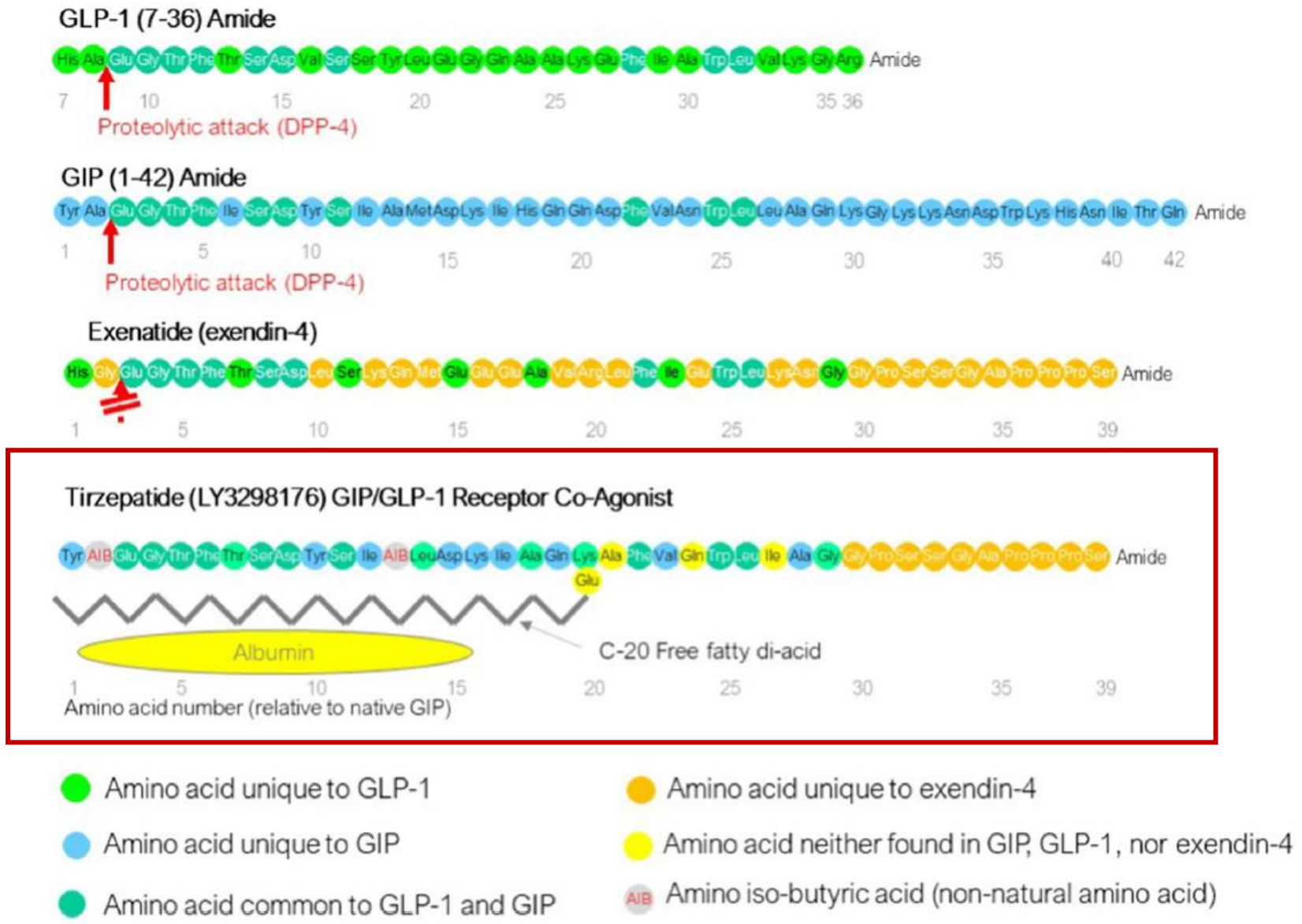

TGA approval:
type 2 diabetes and obesity
*(different doses and brand names)*



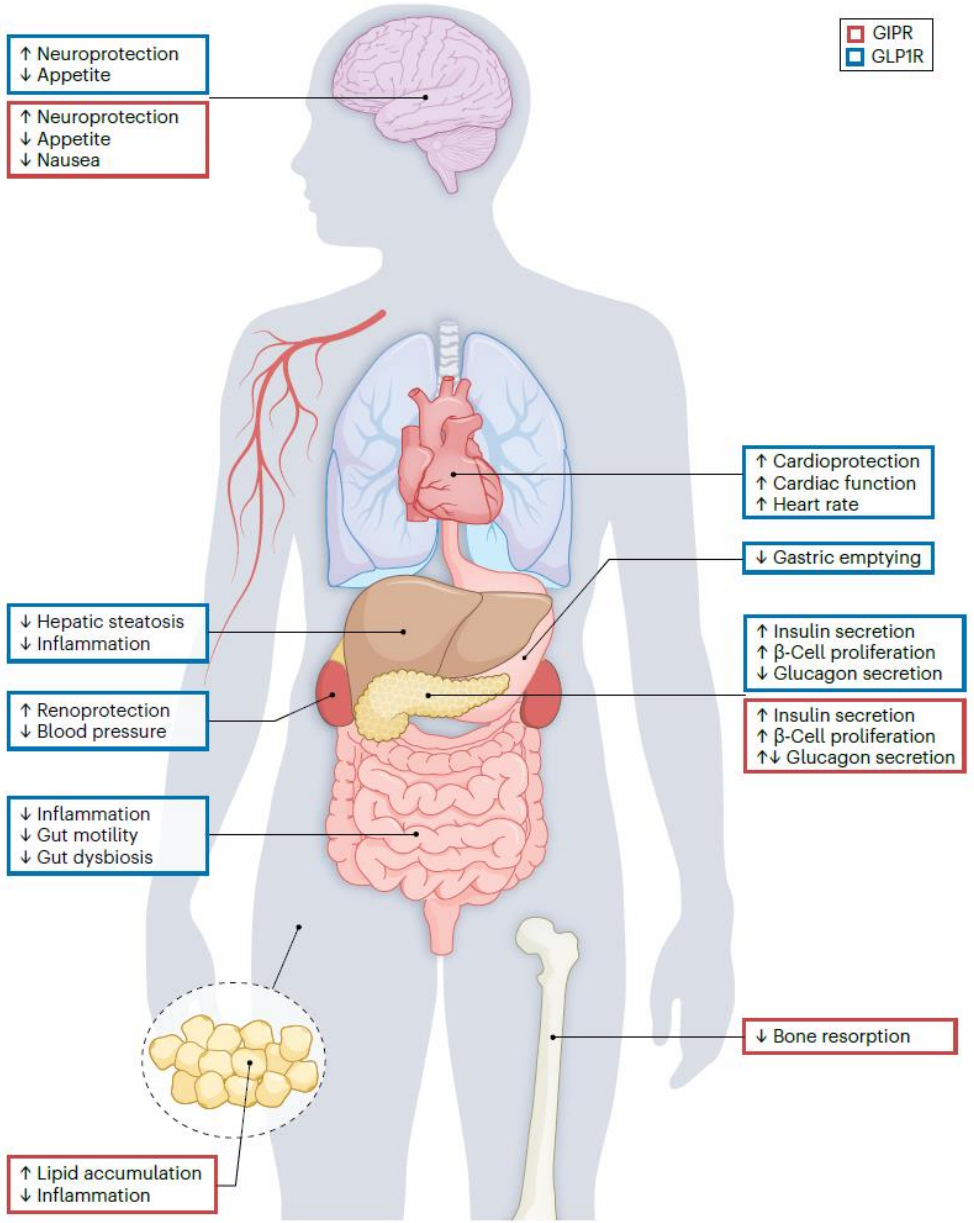

Lovshin *Can J Diab* 2017

# Tirzepatide



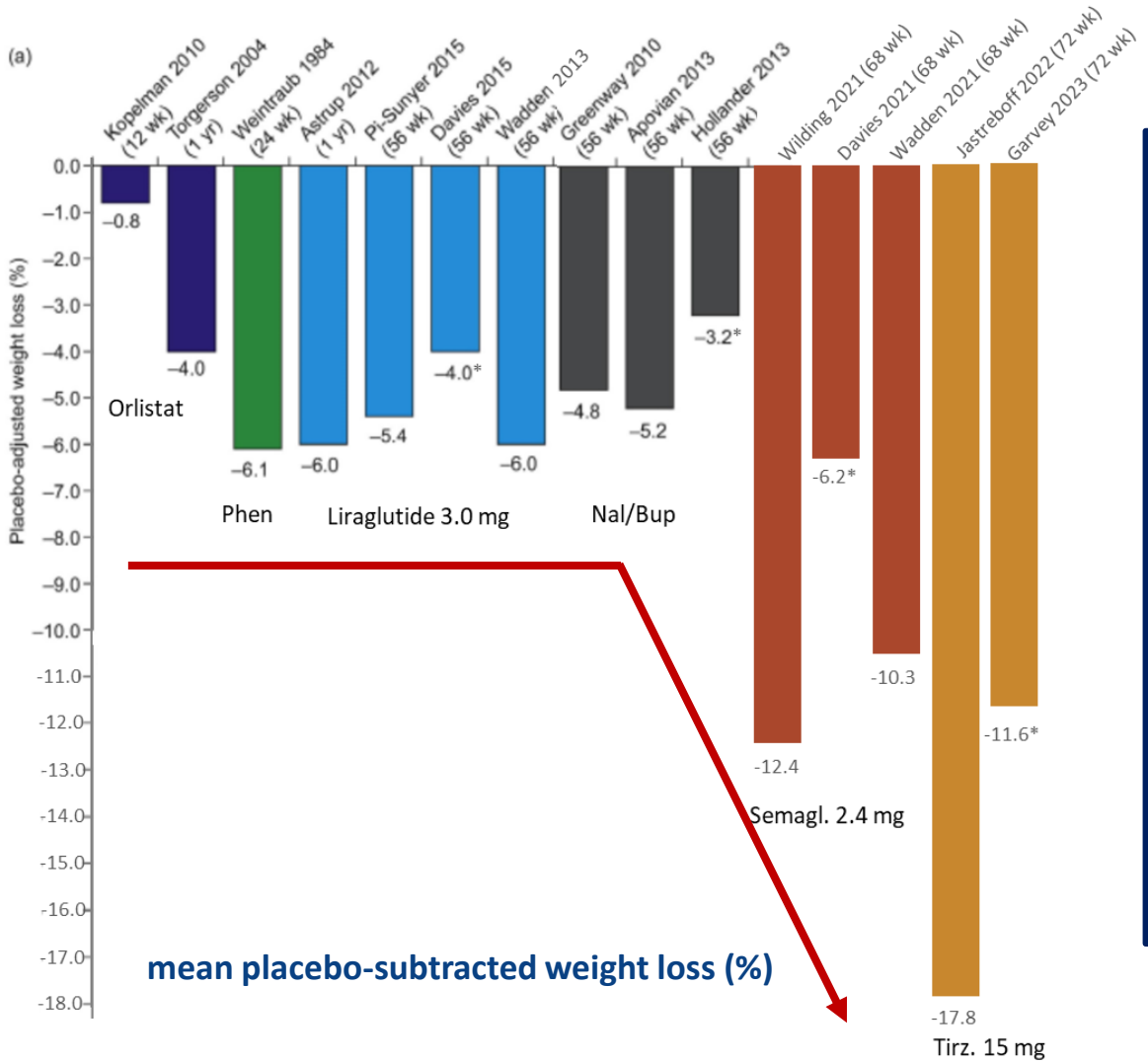

Nauck *Cardiovasc Diabetol* 2022

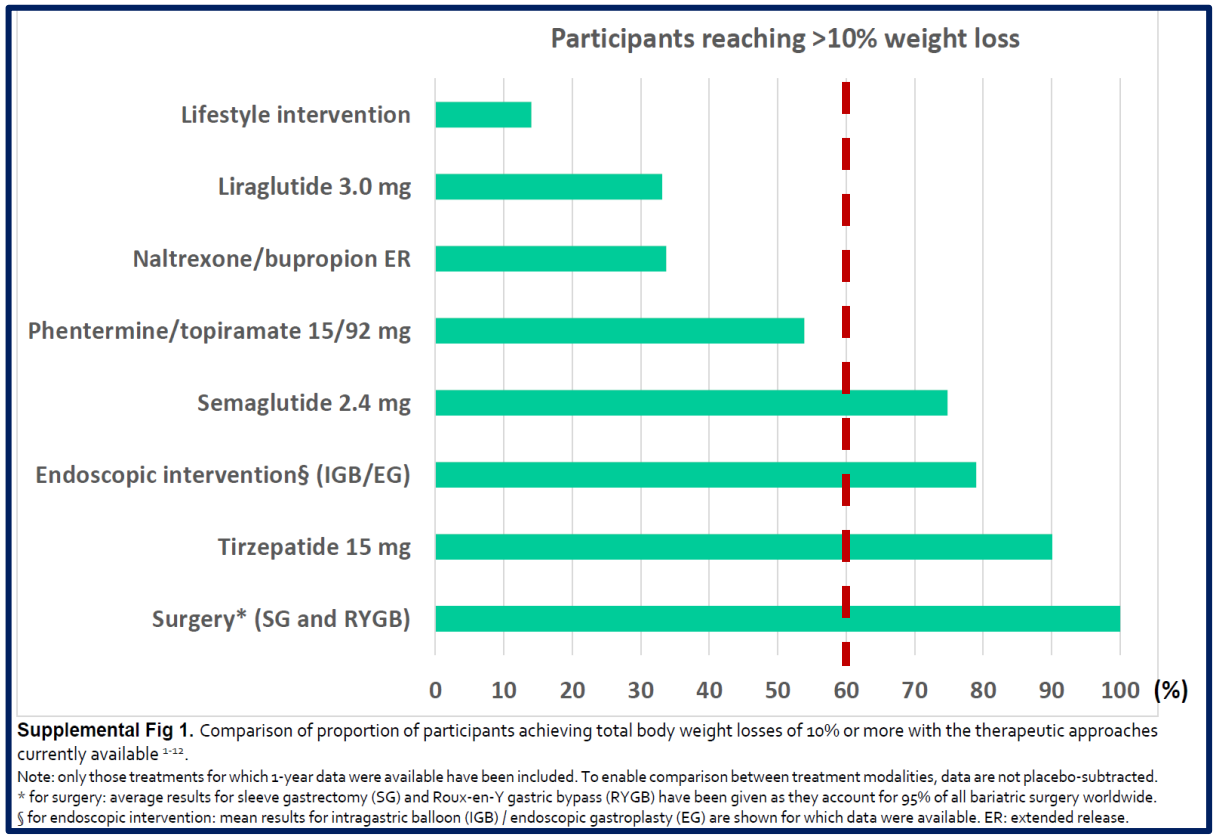
# GLP-1 and GIP have numerous biological actions




Hammoud *Nat Rev Endocrinol* 2022

# Efficacy: weight loss



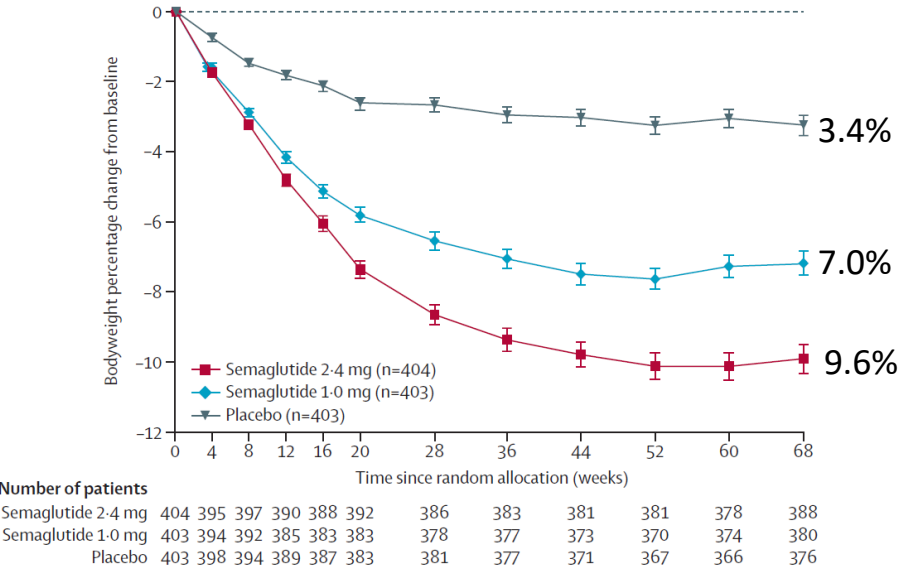

**Supplemental Fig 1.** Comparison of proportion of participants achieving total body weight losses of 10% or more with the therapeutic approaches currently available [1-12].
Note: only those treatments for which 1-year data were available have been included. To enable comparison between treatment modalities, data are not placebo-subtracted.
* for surgery: average results for sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) have been given as they account for 95% of all bariatric surgery worldwide.
§ for endoscopic intervention: mean results for intragastric balloon (IGB) / endoscopic gastroplasty (EG) are shown for which data were available. ER: extended release.

Perdomo, Cohen, Sumithran…*Lancet* 2023

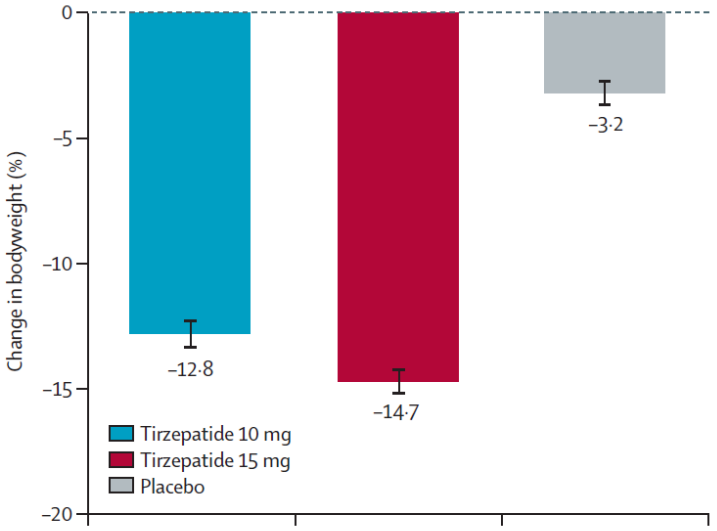
modified from Hocking *Obes Res Clin Pract* 2017

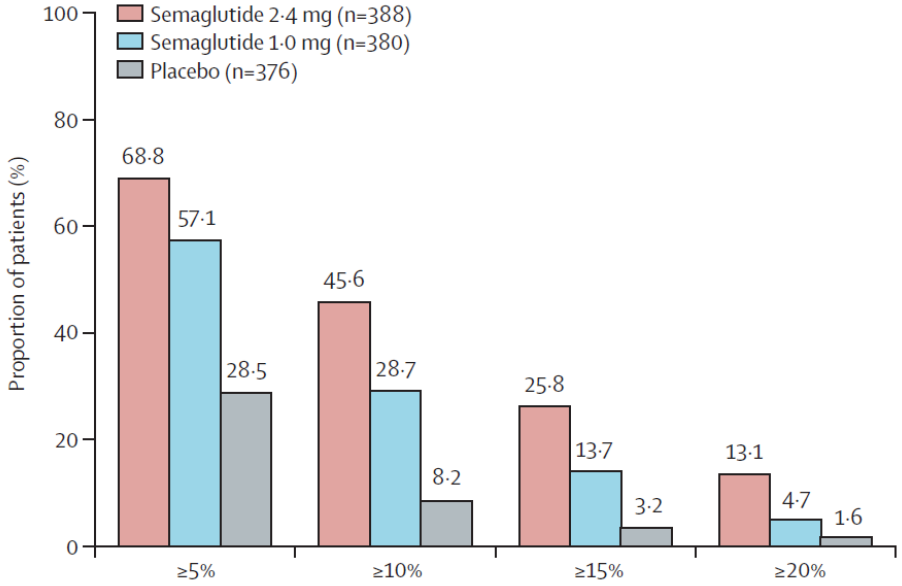
## semaglutide 1 mg vs 2.4 mg vs placebo

+ behavioural intervention

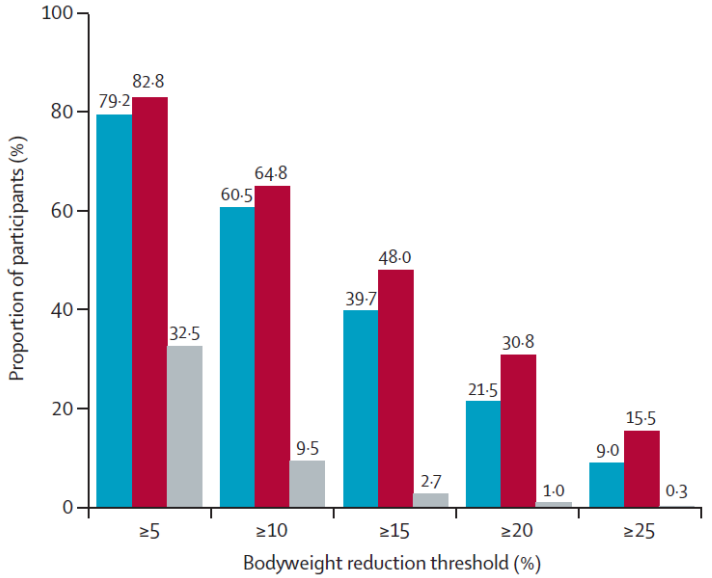



## tirzepatide 10 mg vs 15 mg vs placebo



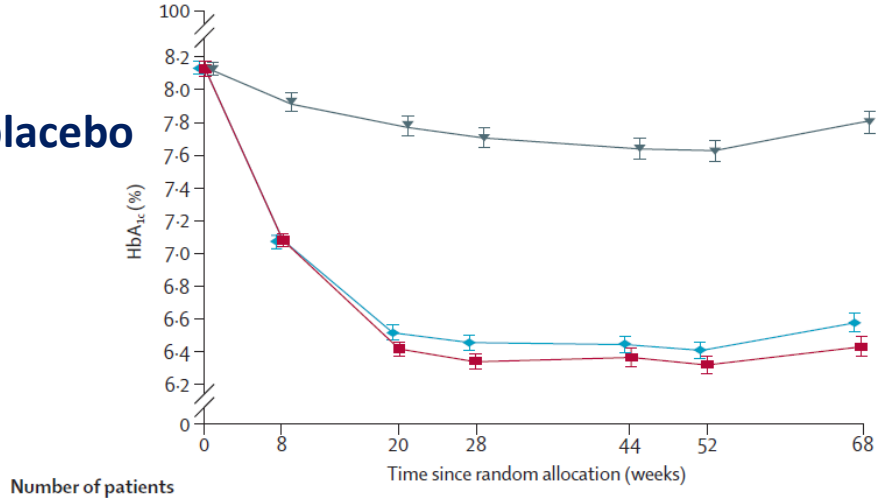

Davies *Lancet* 2021

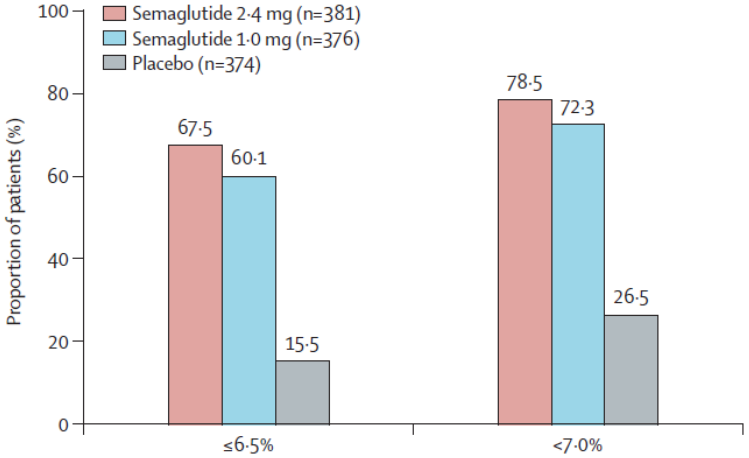



Garvey *Lancet* 2023

# Glycaemic control

**semaglutide 1 mg vs 2.4 mg vs placebo**

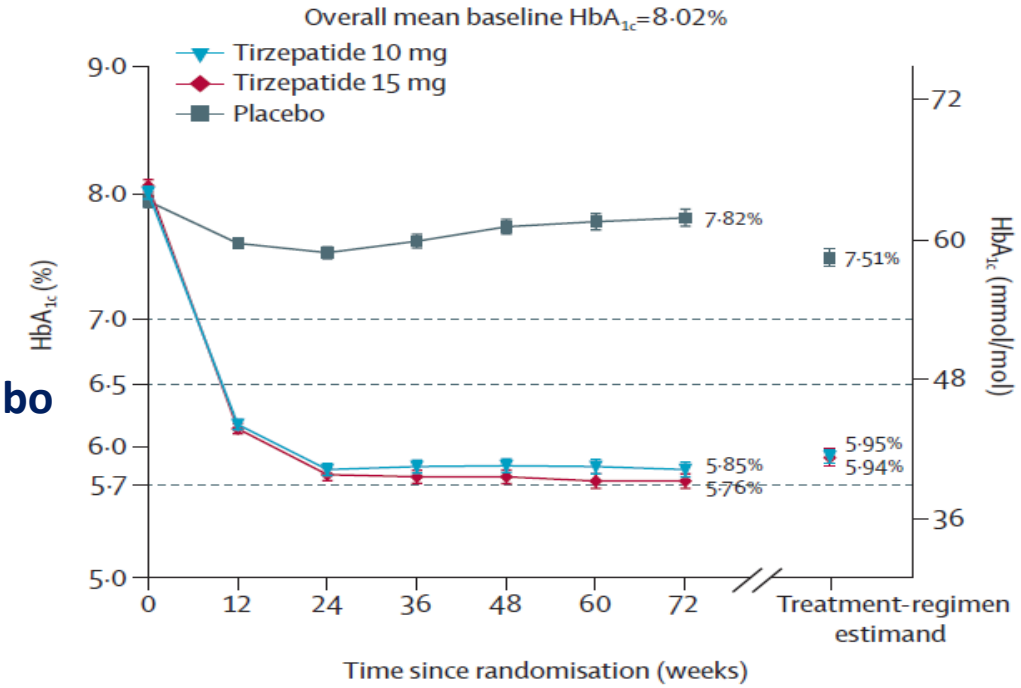


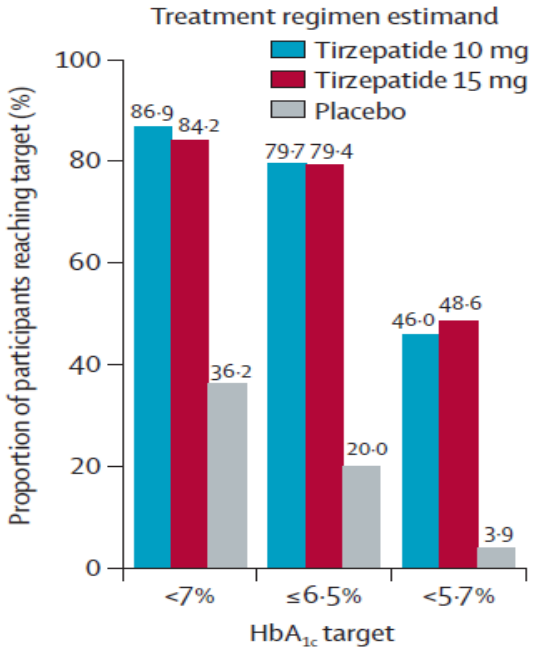




Davies *Lancet* 2021

Treatment of obesity in people with T2D (with behavioural intervention)

**tirzepatide 10 mg vs 15 mg vs placebo**




Garvey *Lancet* 2023

# Additional health benefits

| semaglutide 2.4 mg vs placebo | | tirzepatide pooled vs placebo |
|---|---|---|
| **-13.5 cm** with semaglutide 2.4 mg vs -4.1 cm placebo, p<0.001 | Waist circumference | **-18.5 cm** with tirzepatide 15 mg vs -4.0 cm placebo, p<0.001 |
| **-6.2 mmHg** with semaglutide 2.4 mg vs -1.1 mmHg placebo, p<0.001 | Systolic BP | **-7.2 mmHg** with with pooled tirzepatide vs -1.0 mmHg placebo, p<0.001 |
| **-2.8 mmHg** with semaglutide 2.4 mg vs -0.4 mmHg placebo, p=NA* | Diastolic BP | **-4.8 mmHg** with pooled tirzepatide vs -0.8 mmHg placebo, p=NA* |
| **+2.2** with semaglutide 2.4 mg vs +0.4 placebo, p<0.001 | SF-36 physical function score | **+3.6** with pooled tirzepatide vs +0.4 placebo, p<0.001 |

*Not part of the statistical testing hierarchy; p-value not available (NA).
All values are estimated for the treatment policy estimand.
**$HbA_{1c}$:** glycated haemoglobin **SF-36:** Short-Form 36-item Health Survey.

Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated *Data are for the pooled tirzepatide 10 mg and 15 mg groups

Wilding *N Eng J Med* 2021
Jastreboff *N Engl J Med* 2022

# Additional health benefits

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

Lilly INVESTORS

Stock Info | Webcasts & Presentations | Financials | Individual Investors

Tirzepatide reduced sleep apnea severity by up to nearly two-thirds in adults with obstructive sleep apnea (OSA) and obesity

April 17, 2024

*Tirzepatide achieved a mean apnea-hypopnea index reduction of up to 63% (about 30 fewer events per hour), meeting all primary and key secondary endpoints in two phase 3 clinical trials*

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## 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*

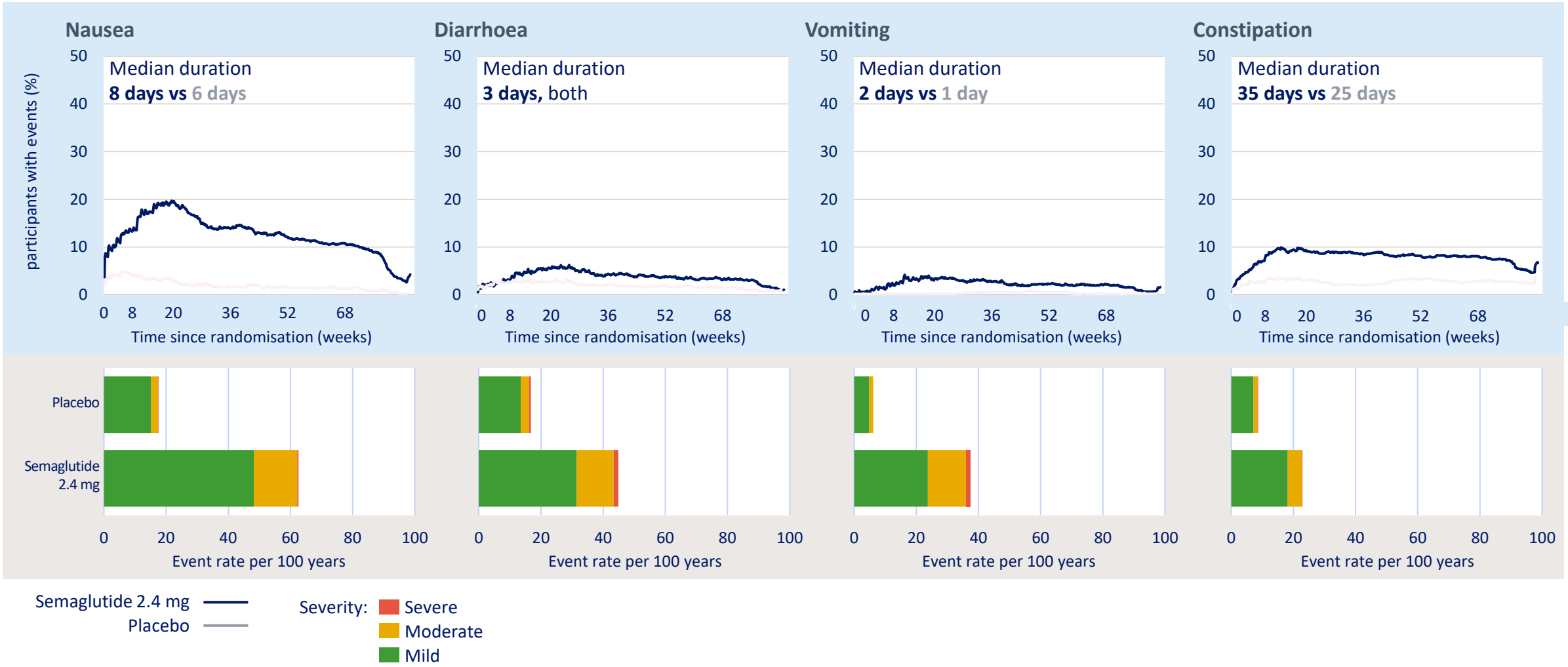
ORIGINAL ARTICLE

## Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

**Authors**: Mikhail N. Kosiborod, M.D., Mark C. Petrie, M.D., Barry A. Borlaug, M.D., Javed Butler, M.D., Melanie J. Davies, M.D., G. Kees Hovingh, M.D., Dalane W. Kitzman, M.D., +25, for the STEP-HFpEF DM Trial Committees and Investigators* Author Info & Affiliations

**Published March 28, 2024** | **N Engl J Med 2024;390:1394-1407** | **DOI: 10.1056/NEJMoa2313917** | **VOL. 390 NO. 15**

# Semaglutide 2.4 mg: GI events



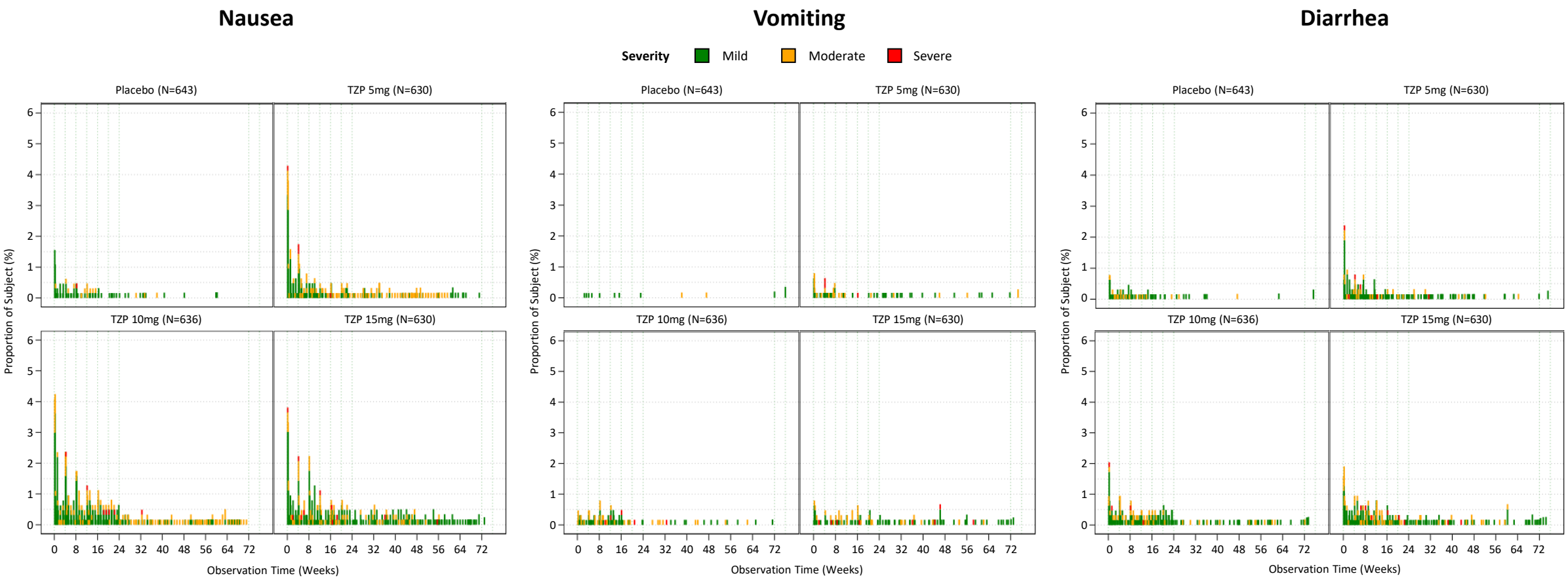

Data are for the on-treatment observation period.

**GI:** gastrointestinal.

slide courtesy of A/Prof Samantha Hocking

Wilding *N Eng J Med.* 2021

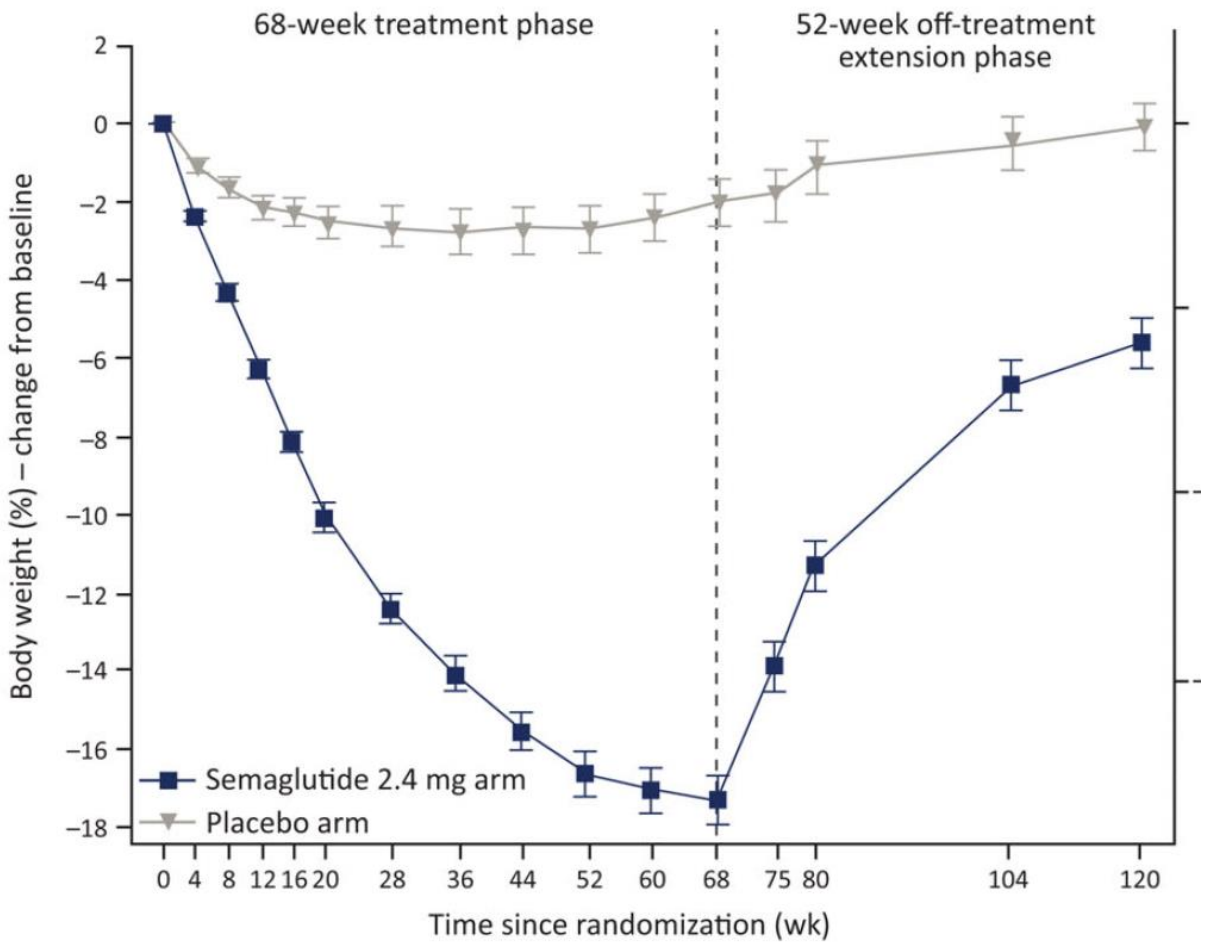
# Tirzepatide: GI events




Note: Percentages are based on number of participants at risk at specific observation time

Jastreboff *N Engl J Med* 2022

# Reversal of weight loss and health improvements  if treatment is ceased




Wilding *Diab Obes Metab* 2022

# Key points

1. new generation incretin-based treatments represent a substantial advance in treatment of obesity and T2D
2. numerous health benefits in addition to weight and glycaemia
3. inter-individual variability in treatment response – no single treatment modality works well in all people
4. gastrointestinal adverse effects are common
5. chronic disease management requires a long-term approach