EPIC DIABETES CONFERENCE

MAY 3, 2025 CU ANSCHUTZ MEDICAL CAMPUS

EMPOWERING PATIENTS FOR INDIVIDUALIZED CARE

Barbara Davis Center for Diabetes • Children's Diabetes Foundation •

SESSION 3
ADULT SESSION

INSULIN RESISTANCE AND WEIGHT MANAGEMENT

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NO CONFLICTS OF INTEREST

Global Overweight and Obesity Metrics 2020-2035*

	2020	2025	2030	2035
Number of overweight or obese* (BMI>=25 kg/m^2)	2.6 billion	3.0 billion	3.5 billion	4.0 billion
As proportion of global population	38%	42%	46%	51%
Global economic impact	$2 trillion	$2.5 trillion	$3 trillion	$4 trillion

* Overweight and obese definitions are based on western criteria

>67% of patients with T1D are overweight or have obesity[1]
~90% of patients with T2D are overweight or have obesity[2]

1. Foster NC et al. Diabetes Technology and Therapeutics, 21:66-72, 2019. PMID: 30657336
2. Centers for Disease Control and Prevention, National diabetes statistics report: 2022 https://www.cdc.gov/diabetes/data/statistics-report/risks-complications.html (accessed May, 2023)

World Obesity Atlas 2023

Global Diabetes Burden: 589 M Patients With Diabetes Worldwide*

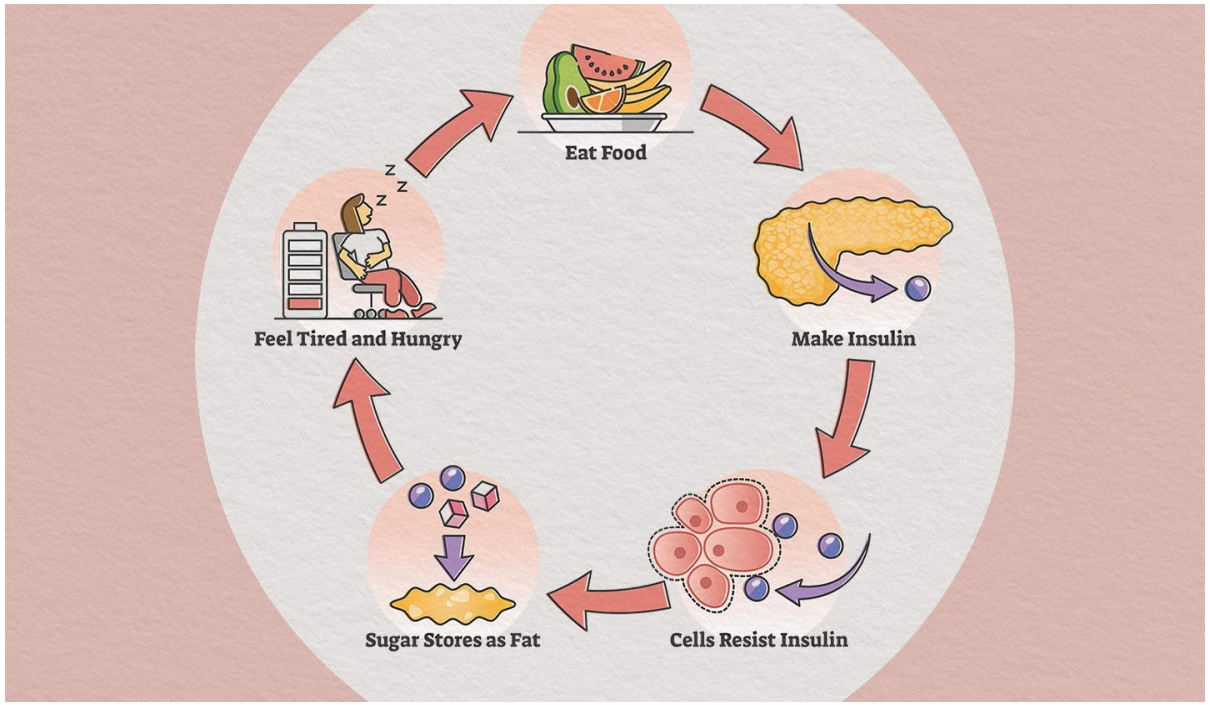
(predicted to be 853 M by 2050) *IDF Atlas 2025, 11th Ed

- 30 million patients with T1D; 1.5 to 3.0 million in the US[1]
- ≈ 4% increase/Yr for both T1D and T2D[2,3]
- Obesity Increase significantly (CDC) [4,5,8]
- 10%-20% of patients misdiagnosed with T2D (antibody positive)[6,7]
- Estimated 252 million adults living with diabetes are unaware they have the condition

1. Garg SK, et al. *N Engl J Med*. 2017;377:2337-2348.
2. Dabelea D, et al. *JAMA*. 2014;311:1778-1786.
3. Mayer-Davis EJ, et al. *N Eng J Med*. 2017;376:1419-1429.
4. Menke A, et al. *Epidemiology*. 2013;24:773-773
4. Greenbaum C, Diabetes Care 2015; 38:476-81.
5. *Lancet*. 2022.
6. World Health Organization. Diabetes. http://www.who.int/mediacentre/factsheets/fs312/en/.
7. Lipska K, et al. *Diabetes Care*. 2016;40:468-475.
8.World Obesity Atlas 2023; https://data.worldobesity.org/publications/?cat=19

WHAT IS INSULIN RESISTANCE?

- Insulin helps move glucose from your blood into your cells to be used for energy.
- Insulin resistance (reduced insulin sensitivity) happens when cells in your muscles, fat, and liver can't use glucose properly for energy or for storage and glucose builds up in your blood.
- When cells don't respond properly to insulin, the pancreas needs to produce more insulin to keep blood sugar levels in a normal range.
- Overtime, hyperglycemia leads to prediabetes and Type 2 Diabetes
- People with Type 1 Diabetes can become resistant to the insulin they take from injections or pump



CAUSES OF INSULIN RESISTANCE

- Genetics
- Excess body weight/obesity (especially around the belly)
- Physical inactivity
- Food choices – highly processed foods, high carbohydrate or high saturated fat diet
- Medications – steroids
- Hormones – cortisol (Cushing's syndrome, poor sleep, stress), hypothyroidism, growth hormone, estrogen (menopause, oral contraceptives), testosterone

>67% of patients with T1D are overweight or obese[1]

Treatment with Intensive Insulin Treatment

Treatment of hypoglycemia and defensive eating to avoid hypoglycemia

Genetic susceptibility

Environment – increase in energy dense food especially in “food deserts”

Reduced physical activity (fear of hypoglycemia?)

Psychological – depression/burnout/disordered eating behavior

1. Foster NC et al. Diabetes Technology and Therapeutics, 21:66-72, 2019
2. International Journal of Obesity (2024) 48:289-301

TREATMENT OF INSULIN RESISTANCE

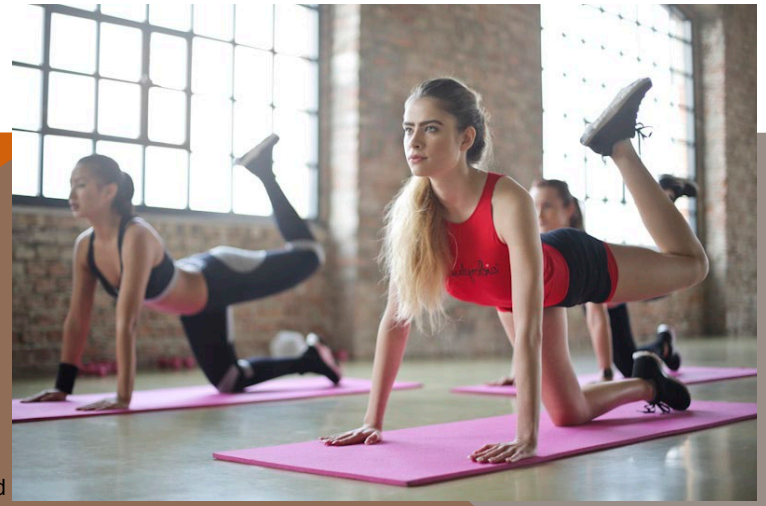
- Weight loss
- Diet

  - Lower carb, reduced simple sugars and trans fat (found mostly in processed foods)

  - Increase complex carbohydrates, fiber, and lean protein
- Increased physical activity

  - 20-30 minutes per day of strength and cardio
- Improved sleep and reduced stress

  - Aim for 7-9 hours of sleep, yoga, meditation
- Medications



NON-MEDICATION OPTIONS FOR WEIGHT LOSS

Low Calorie Diet

Low Carb or Keto diet

Mediterranean diet

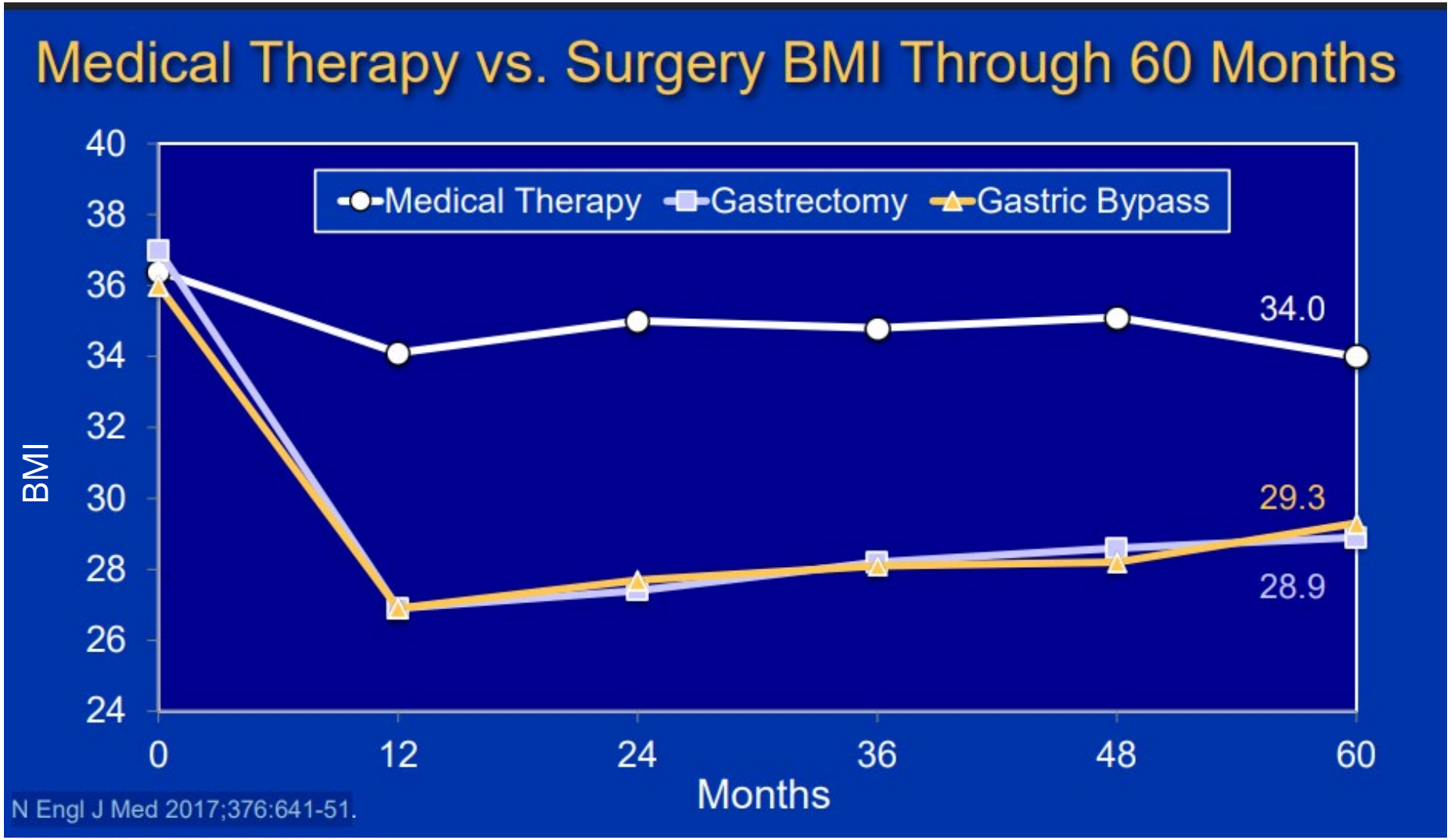
Intermittent fasting

Exercise – usually minimal weight loss

Many diets can work for some people but are difficult to sustain long term

Lifestyle modification should be part of any weight loss regimen with or without medications

SURGICAL INTERVENTION FOR WEIGHT LOSS



Stampede Study 2017

The Sad History of Conventional Drugs to Treat Obesity

- Amphetamines - high abuse potential, hypertension
- Fenfluramine - fatal pulmonary hypertension (withdrawn)
- Fenfluramine/phentermine - valvular heart disease (withdrawn)
- Sibutramine – hypertension, arrhythmias, sudden death, increased CV morbidity/mortality (withdrawn)
- Orlistat – Anal leakage, deficiency in fat soluble vitamins
- Rimonabant – Suicide and other psychiatric effects (withdrawn)
- Lorcaserin – Malignancy (withdrawn)
- Bupropion-naltrexone (No CV benefit)

Non-Insulin Treatment Options for T1D-for OW and OB

Pramlintide (Symlin): FDA approved for T1D and T2D, not used in clinical practice (GI side effects and severe hypoglycemia)

Metformin: Minimal weight loss or A1c improvement

DPP-IV inhibitors (Januvia, Onglyza): No effect on A1c or weight loss

Daily GLP-1 Analogs (Victoza): Minimal weight loss & effect on A1c, >DKA & severe hypoglycemia

SGLT 1 & 2 Inhibitors (Invokana, Farxiga, Jardiance): A1c improvement, minimal weight loss, risk of DKA

Newer GLP-1 Analogs (Semaglutide, Tirzepatide): Significant weight loss with improvement in A1c

CURRENT GLP-1 MEDICATIONS TO TREAT OBESITY

Once weekly injections

Semaglutide

- Ozempic – approved for treatment of Type 2 Diabetes
- Wegovy - approved for weight loss (BMI >30 or BMI >27 with at least one weight related condition such as diabetes, high BP, or high cholesterol)

Tirzepatide

- Mounjaro – approved for treatment of Type 2 Diabetes
- Zepbound – approved for weight loss (BMI >30 or BMI >27 with at least one weight related condition such as diabetes, high BP, or high cholesterol)

"Off label" for Type 1 diabetes

Prevention of T2D in people living with obesity by semaglutide

STUDY DESIGN

Multicenter, double-blind, randomized controlled trial

≥45 years of age
BMI ≥27 kg/m²
Preexisting cardiovascular disease (CVD) but without diabetes

Once-weekly subcutaneous **semaglutide** 2.4 mg
N = 8,803

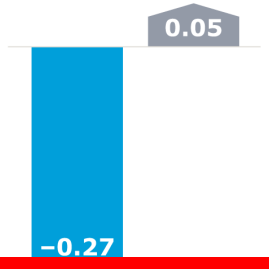
Once-weekly subcutaneous **placebo**
N = 8,801

Mean ± SD follow-up:
176±40 weeks

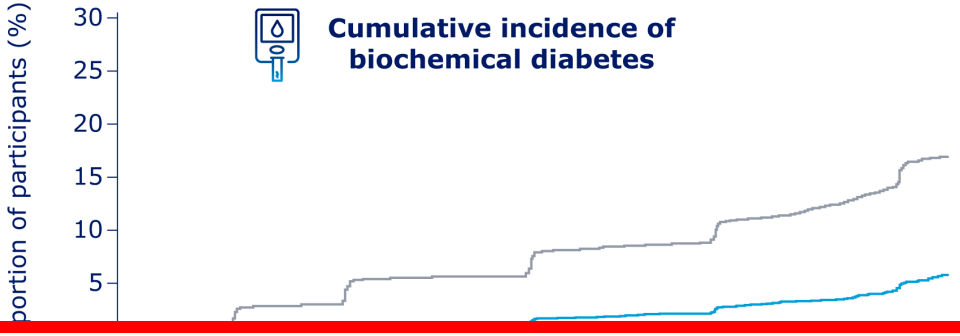
Mean ± SD intervention exposure:
152±56 weeks

RESULTS

HbA_{1c} % change at week 156



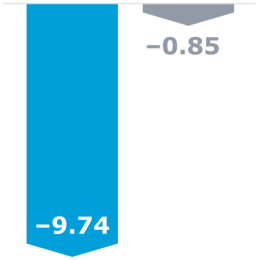
Cumulative incidence of biochemical diabetes



At week 156, a greater proportion treated with semaglutide were normoglycemic (69.5% vs. 35.8%; P < 0.0001) and a smaller proportion had diabetes by week 156 (1.5% vs. 6.9%; P < 0.0001).

Semaglutide 2.4 mg	8,800	8,713	8,609	8,494	8,340	7,312	5,853	4,210	1,767
Placebo	8,797	8,487	8,248	8,050	7,805	6,792	5,353	3,789	1,577

% body weight loss at week 65



Mean difference:
−8.9% (p<0.0001)

Semaglutide was associated with:

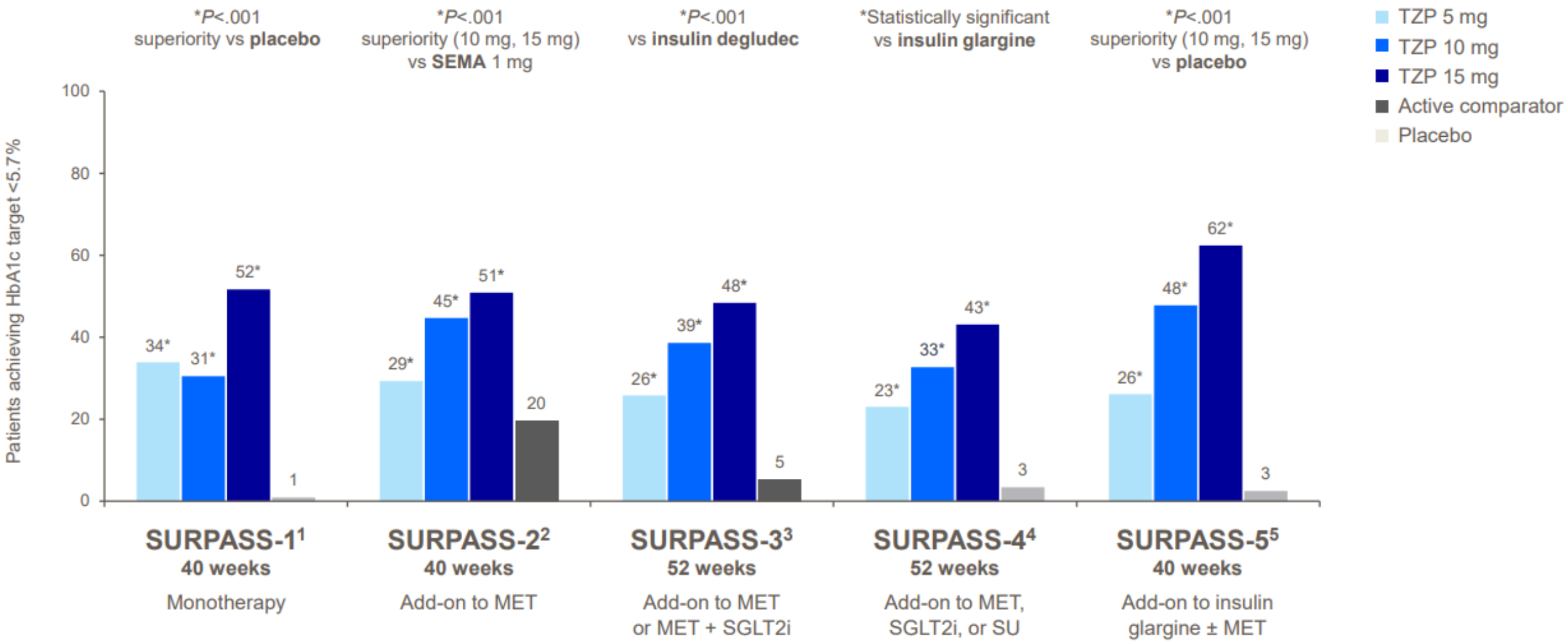
73%
reduction in relative risk of developing biochemical diabetes

18.5
Number needed to treat to prevent one case of biochemical diabetes

CONCLUSION: For people with preexisting CVD and overweight or obesity but without diabetes, long-term treatment with semaglutide reduces progression to biochemical diabetes (HbA_{1c} >6.5%)

Kahn SE et al Diabetes Care 2024

Tirzepatide: reversal of T2D (SURPASS)



- Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
- HbA1c = glycated haemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

GLP-1RA and SGLT 2-is in People With Type 1 Diabetes

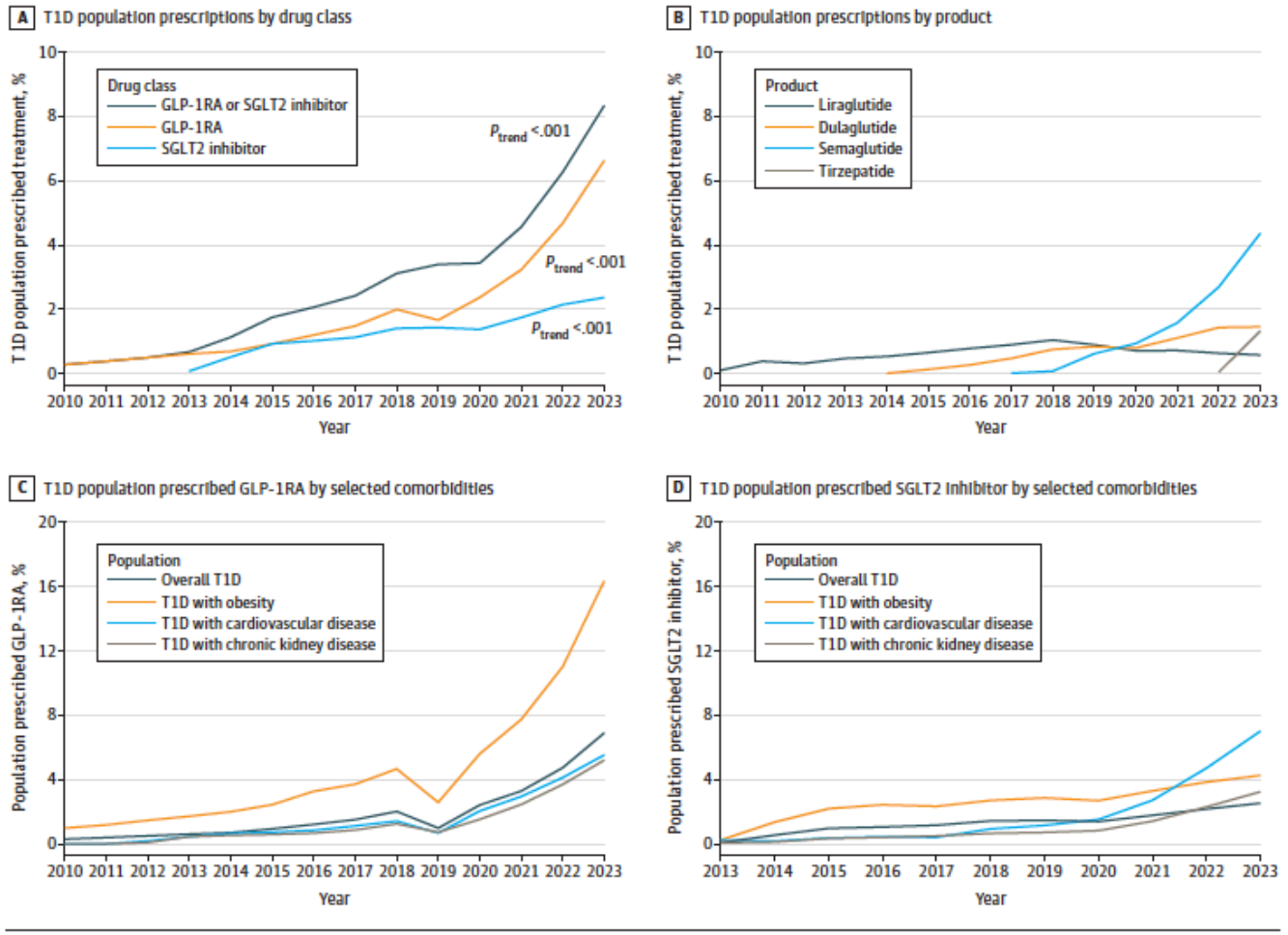
EPIC Cosmos Integrated data of ~257 Million US population - Had ~1M people with T1D

The % of the T1D patients prescribed GLP-1RAs increased from 0.3% in 2010 to 6.6% by 2023 and SGLT 2is prescribing rose from 0.1%to 2.4%. Overall, the % of T1D patients prescribed either GLP-1RAs or SGLT 2is increased from 0.7%to 8.3%

Table. Demographic and Clinical Characteristics of the Type 1 Diabetes (T1D) Population Newly Prescribed Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) or Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in Epic Cosmos, 2023

	Overall T1D population, No. (%)[a] (n = 405 019)	T1D population newly prescribed GLP-1RAs, No. (%)[a] (n = 18 725)	*P* value[b]	T1D population newly prescribed SGLT2 inhibitors, No. (%)[a] (n = 7210)	*P* value[c]
Age, mean (SD), y	41.5 (20.6)	47.1 (15.6)	<.001	56.8 (15.1)	<.001
Sex					
Female	200 416 (49.5)	11 834 (63.2)	<.001	3223 (44.7)	<.001
Male	204 603 (50.5)	6891 (36.8)	<.001	3987 (55.3)	<.001
Race and ethnicity[d]					
Hispanic	30 263 (7.5)	1590 (8.5)	<.01	656 (9.1)	<.001
Non-Hispanic Black	53 339 (13.2)	2753 (14.7)		1232 (17.1)	
Non-Hispanic White	283 631 (70.0)	12 608 (67.3)		4558 (63.2)	
Other[e]	37 786 (9.3)	1774 (9.5)		764 (10.6)	
SVI[f]					
1st quartile	125 556 (31.0)	6011 (32.1)	.03	1896 (26.3)	<.001
2nd quartile	96 314 (23.8)	4457 (23.8)		1687 (23.4)	
3rd quartile	95 584 (23.6)	4363 (23.3)		1781 (24.7)	
4th quartile	85 054 (21.3)	3914 (20.9)		1853 (25.7)	
HbA_{1c}, mean (SD), %	8.09 (1.9)	7.97 (1.7)	<.01	8.4 (2.0)	<.001
BMI, mean (SD)	27.5 (7.0)	35.0 (7.51)	<.001	31.0 (7.5)	<.001
LDL, mean (SD), mg/dL	97.9 (37.6)	101.4 (39.7)	<.001	93.2 (46.9)	<.001
SBP, mean (SD), mm Hg	126.1 (17.6)	128.4 (15.6)	<.001	129.5 (17.9)	<.001
Comorbidity					
Myocardial infarction	6845 (1.7)	295 (1.6)	.25	587 (8.1)	<.001
Stroke	5556 (1.4)	213 (1.1)	.01	277 (3.8)	
Heart failure	11 228 (2.8)	487 (2.6)	.17	1193 (16.6)	
Ischemic heart disease	18 384 (4.5)	844 (4.5)	.85	1323 (18.3)	
Chronic kidney disease	64 575 (15.9)	2412 (12.9)	<.001	1937 (26.9)	
Obesity	108 347 (26.8)	12 997 (69.4)	<.001	3292 (45.7)	
Retinopathy	13 114 (3.2)	548 (2.9)	.02	474 (6.6)	
Neuropathy	27 315 (6.7)	1093 (5.8)	<.001	1085 (15.1)	
Nephropathy	21 762 (5.4)	857 (4.6)	<.001	1071 (14.9)	

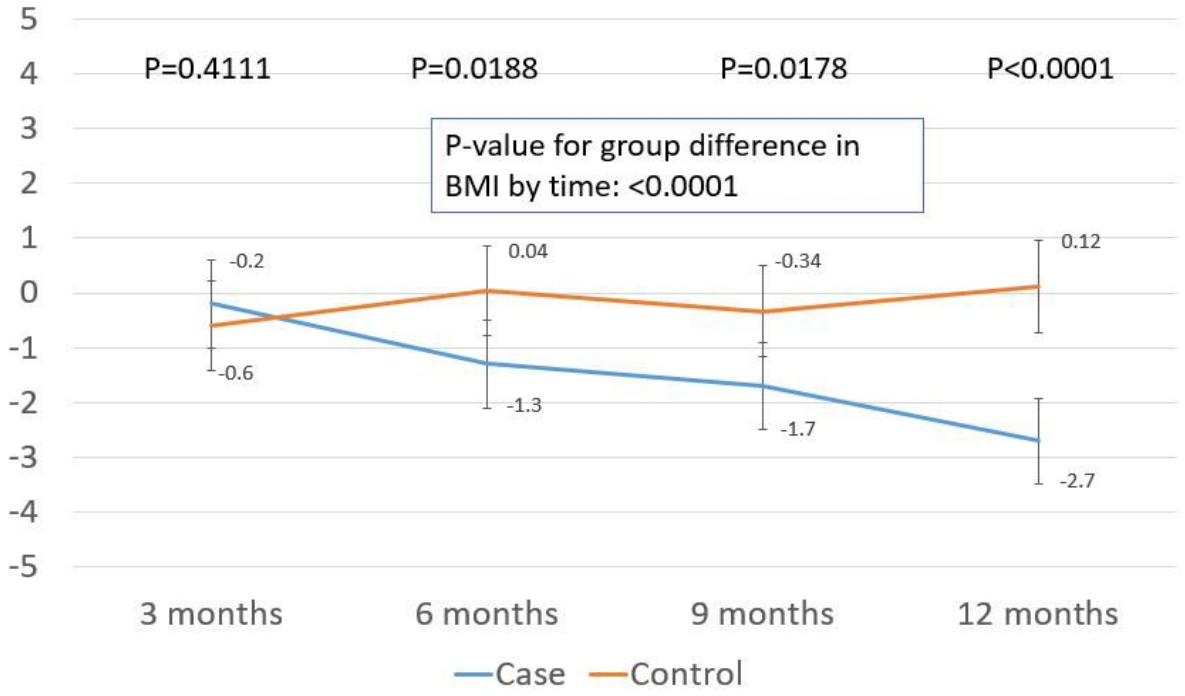
Figure. Trends in Drugs Prescribed Among People With Type 1 Diabetes (T1D), 2010-2023



Piaopiao Li et al. doi:10.1001/JAMA.2024.18581

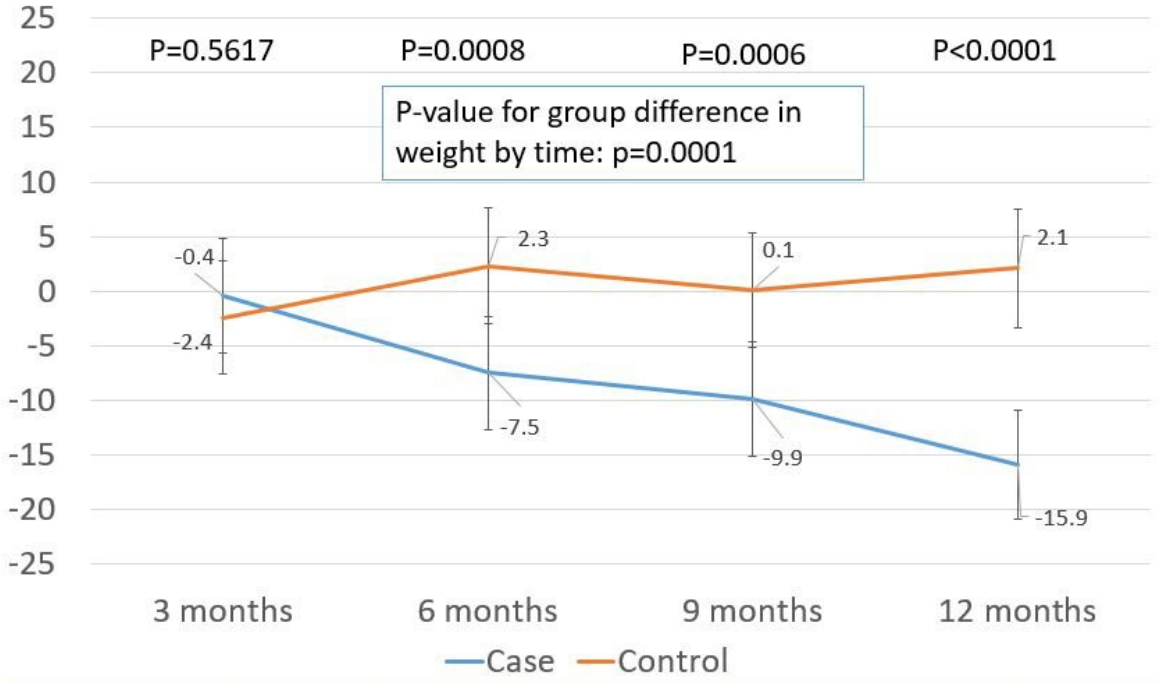
Semaglutide on Weight Loss in Patients with Type 1 Diabetes

Figure 1 A: Change in BMI after starting semaglutide

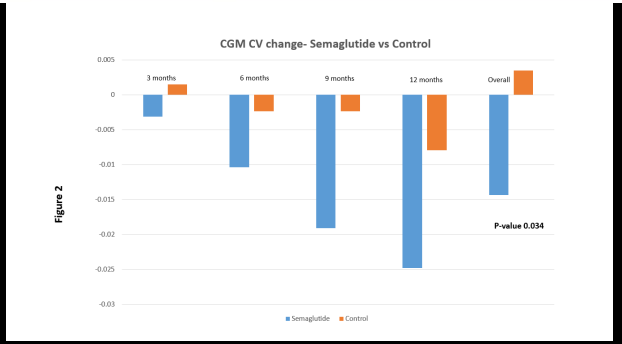


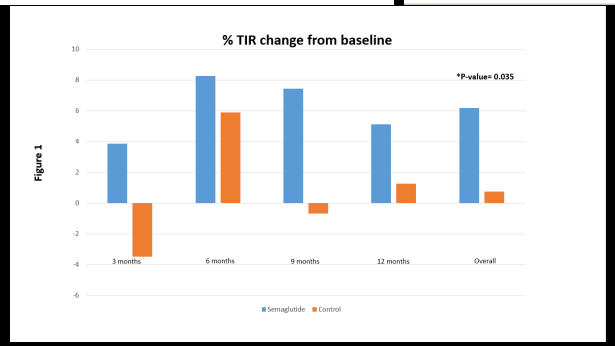
Group	Baseline	3 months	6 months	9 months	12 months
Case	33.0 ± 0.81	32.2 ± 0.84	31.4 ± 0.85	30.9 ± 0.85	29.8 ± 0.87
Control	32.2 ± 0.81	31.8 ± 0.85	32.7 ± 0.86	32.4 ± 0.85	32.5 ± 0.88

Figure 1B: Weight loss (pounds) after starting semaglutide



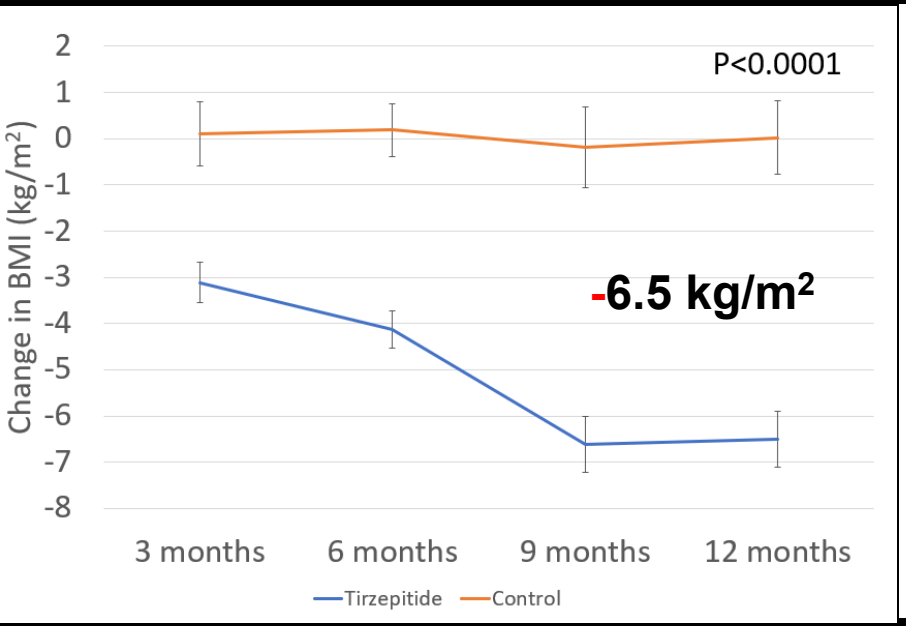
Weight in pounds and weight loss percentage over time	Group	Baseline	3 months	6 months	9 months	12 months
	Case	217 ± 5.5	211 ± 5.6 (-0.2%)	206 ± 5.7 (-3.4%)	203 ± 5.7 (-4.7%)	196 ± 5.8 (-7.6%)
	Control	212 ± 5.5	209 ± 5.7 (-1.2%)	216 ± 5.7 (+0.8%)	214 ± 5.7 (+0.01%)	215 ± 5.8(+1.1%)

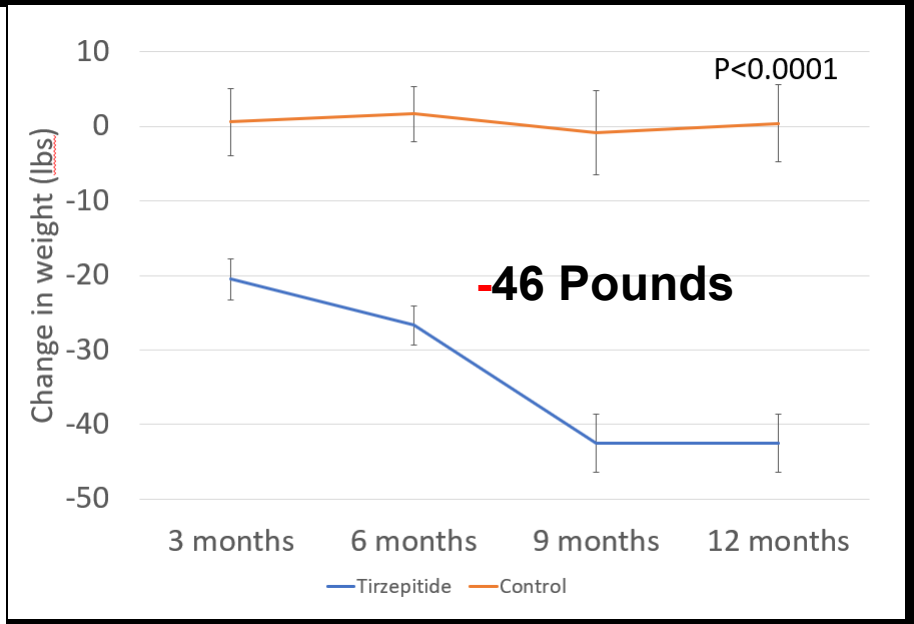


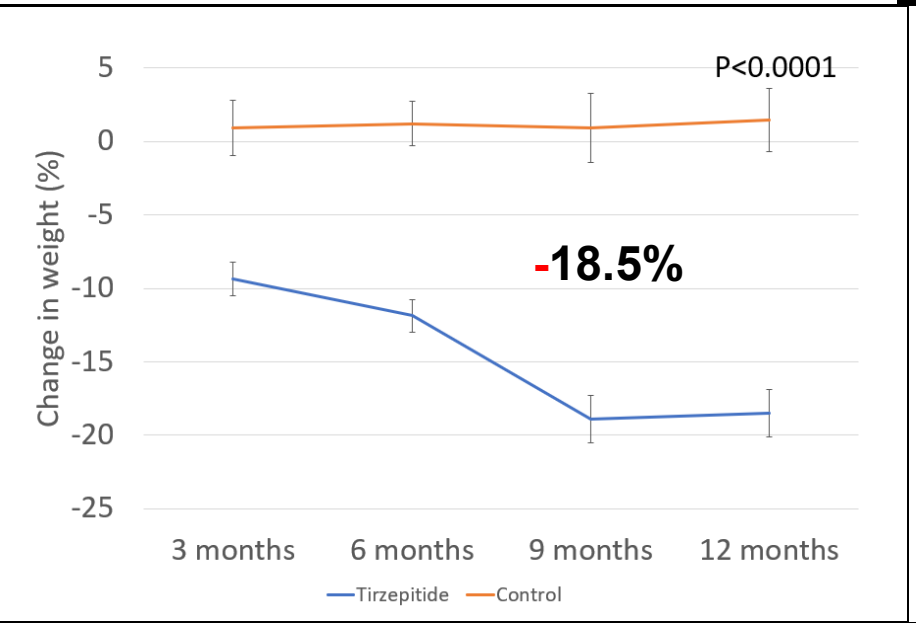


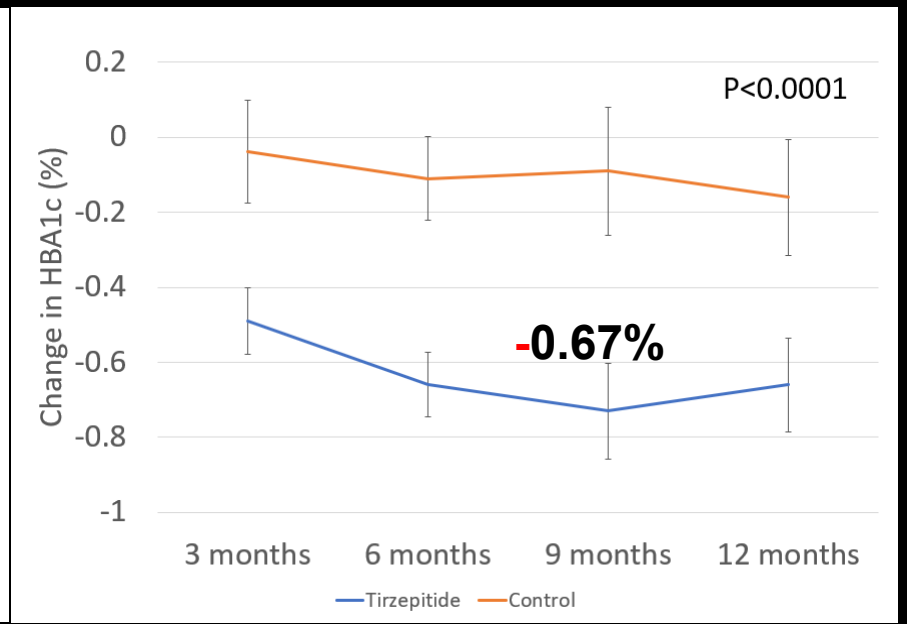
Garg SK et al: Diabetes Technol Ther: 2024,26:184-189

Tirzepatide in T1D: Change in BMI, Weight and HbA1c over 1-Year by Rx group









Tirzepatide treated group

- Weight decreased by >46 pounds (18.5%)
- Change in BMI at 1 year by -6.5 kg/m²
- HbA1c Improved by 0.67%
- ↑ TIR, ↓ TAR, ↓ SD and CV

Garg SK et al: Diabetes Technol Ther: 2024;26:367-374

Cardiovascular and Renal Biomarkers in Overweight and Obese Adults with Type 1 Diabetes Rx with Tirzepatide for 21 months

Figure 2A Change in Weight (lbs) by Treatment Group

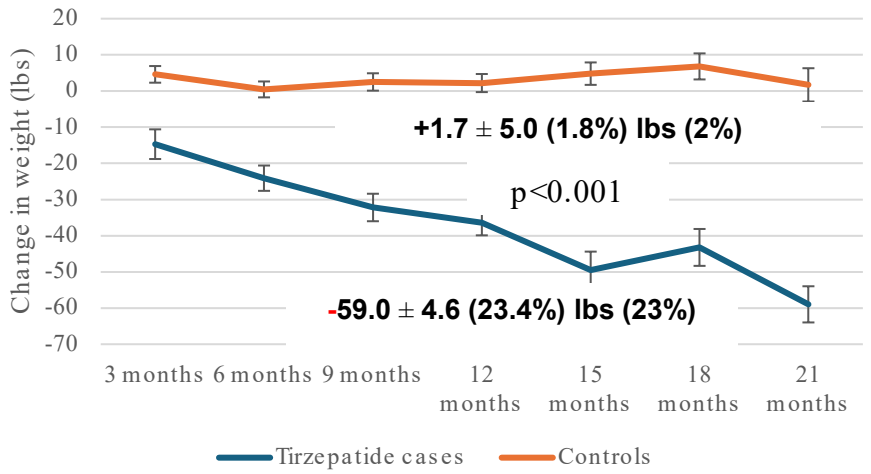
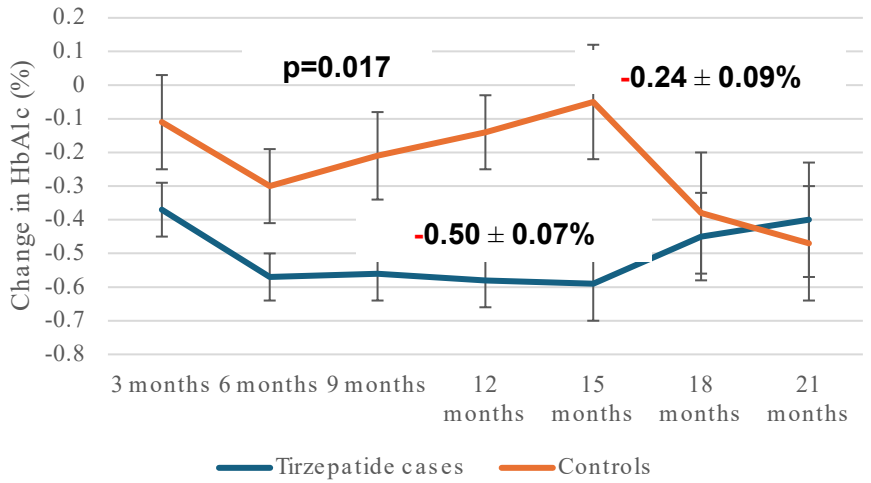


Figure Change in HbA1c by Treatment Group



Change in cardiovascular and renal biomarkers† for tirzepatide users compared to controls

	Controls (n=38)	Cases (n=84)	P-value
Adjusted for age, sex, time point			
Δ Total Cholesterol (mg/dL)	**-2.4 ± 7.2**	**-20.9 ± 5.3****	0.049
Δ LDL Cholesterol (mg/dL)	**-1.4 ± 6.5**	**-18.3 ± 4.8***	0.047
Δ HDL Cholesterol (mg/dL)	-1.1 ± 2.0	1.8 ± 1.5	0.27
Δ Triglycerides (mg/dL)	**5.2 ± 7.5**	**-23.8 ± 5.5****	0.004
Δ SBP (mm Hg)	**-0.3 ± 2.3**	**-5.8 ± 1.7****	0.054
Δ DBP (mm Hg)	-1.3 ± 5.3	-1.8 ± 4.2	0.94
Δ eGFR (mL/min/1.73 m²)	**-5.6 ± 2.5***	**1.4 ± 1.8**	0.03
Adjusted for age, sex, time point, HbA1c and BMI at each time point			
Δ Total Cholesterol (mg/dL)	**-2.3 ± 8.0**	**-21.4 ± 5.7***	0.07
Δ LDL Cholesterol (mg/dL)	**-2.6 ± 7.1**	**-17.9 ± 5.1***	0.10
Δ HDL Cholesterol (mg/dL)	-0.6 ± 2.1	1.1 ± 1.5	0.54
Δ Triglycerides (mg/dL)	**12.9 ± 88.0**	**-26.0 ± 5.6****	0.0009
Δ SBP (mm Hg)	-1.7 ± 2.4	-5.3 ± 1.7*	0.23
Δ DBP (mm Hg)	-3.0 ± 5.7	-0.3 ± 4.3	0.71
Δ eGFR (mL/min/1.73 m²)	**-6.4 ± 2.7***	**2.3 ± 1.9**	0.02

†Change (Δ) in markers is shown as LS mean and SE changes *<0.05 for change from baseline; **<0.001 for change from baseline.

Garg SK et al. Diabetes Technol and Ther 2025, 27; ------

Challenge #1: Obtaining the medication

GLP1 are off label for use in Type 1 diabetes

Often not covered by insurance companies for patients with T1D

Almost always require time consuming prior authorization showing patient has T2D and may require documentation of diagnosis and "step therapy" of drugs not typically used in treatment of T1D such as Metformin, Liraglutide, or Dulaglutide

Providers may need to document in the patients chart:

- "Double Diabetes": features of Type 2 DM such as insulin resistance and obesity
- May need to start with other medications first
- Some insurance companies require documentation of A1c ≥ 6.5% (does not need to be recent)

Even if the prior authorization is approved can often be >$100/month

- Can use manufacturers coupons/saving card
- Mail order of 90 day supply sometimes cheaper

Challenge #2: Managing Expectations

Have conversations with patient about weight loss goals

- No more than 2 lbs/week
- Patients should still be eating normal foods

Discuss before starting medications:

- Long term side effects of medications are unknown
- It is unknown if patients can stop or reduce medications and maintain weight loss
- Insurance may not always cover especially if patient changes insurance policies
- Insurance plans may change coverage
- Medications are hard to find and certain doses may not be available
- Close follow up with HCP is essential

Challenge #3: Managing Side Effects

GI side effects are common (nausea, vomiting, belching, gas, diarrhea, constipation)

Ozempic: can start with a smaller dose than recommended and slowly increase (# of pen clicks)

Other medications such as Mounjaro, Zepbound and Wegovy are set doses, start with lowest dose and increased as tolerated.

- May stay at lower dose for longer than 1 month
- Eating small frequent meals may help reduce side effects
- Medications for nausea, diarrhea, or constipation may be necessary

Hypoglycemia

- Reduce insulin doses by 20% initially and titrate as necessary, use CGM
- Frequent insulin dose adjustments and follow up with provider
- Have glucagon available

Ketones/DKA

- Advise patients not to reduce insulin too much
- Lack of insulin and decreased carbohydrate, fluid intake can increase risk for DKA
- Advise patients to monitor ketones and prescribe blood ketone meter (CKM coming soon)

Challenge #4: Medication Dose Adjustments

At Initiation of GLP1

- Decrease insulin dose by 20% for the first few days
- Titrate up as necessary

- At each dose increase of GLP1, insulin doses may need to be adjusted
- Basal insulin may need to be adjusted if patients are not eating much carbohydrate
- Decrease total insulin dose and patient loses weight

- AID systems:
  - Patient may need to use Temp Targets or Exercise mode when transitioning to higher doses
  - Check and adjust manual mode basal settings to match automated basal delivery as patient lose weight
  - Adjust Targets, Carb Ratios, Active Insulin Time if needed

Challenge #5: Nutrition and Exercise Concerns

Medications causes decreased appetite and patients may not be eating much at all

Advice for Patients:

Small nutrient dense meals and snacks (high protein, high fiber, complex carbohydrates)

- ideas: low fat cheeses or cottage cheese, whole gain crackers/breads/tortillas, lean meats such as chicken, turkey, ham, fruits, hard boiled eggs, nuts, hummus, high protein shakes, raw veggies, Greek yogurt, oatmeal, avocado

Plan meals and meal times (set reminders)

Drink plenty of Water

Consider a vitamin/mineral supplement

Weight bearing exercises 3 times per week to prevent muscle loss

Challenge #6: Ongoing Management

Use of GLP1 in patients with Type 1 Diabetes require frequent monitoring and follow up

- Initially every 1-2 weeks virtually
- Every 3 months ongoing
- Close follow up of TSH, lipids, blood pressure and adjust medications as necessary
- Eye exam
- Consider GI consult? When? Who?

- For elective surgeries, stop medication 1-2 weeks prior to surgery
- For emergency procedures, inform surgeon patients are taking GLP1 medications

Challenge #8:Weight Maintenance

Once desired weight goal is achieved, consider reducing or discontinuing GLP treatment

Patients must continue diet and lifestyle modification

HCP must discuss the possibility that patient may regain weight

- In large study in patient with T2D and/or Obesity, only 17% of patients were able to keep the weight off after discontinuing GLP treatment.

A low dose of GLP may be necessary to maintain weight though there are no randomized control trials or guidelines for overweight or obese patients with T1D and the use of GLP treatment.

Two Randomized Control Trials using Tirzepatide (Mounjaro) in T1D to start at the BDC in May/June 2025

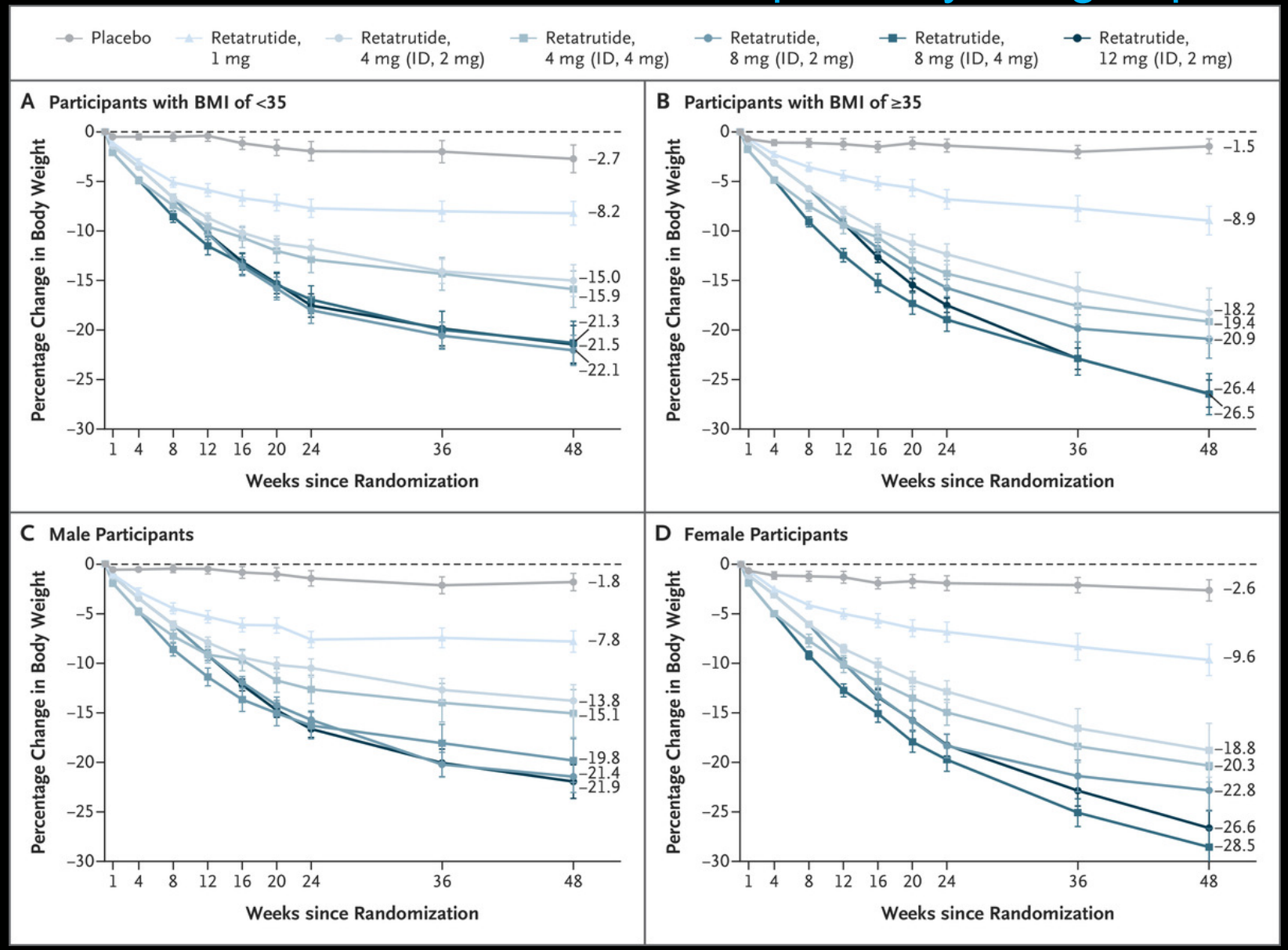
A1c >7%, BMI >25

FUTURE MEDICATIONS - ONGOING STUDIES IN T2DM

Retatrutide – Triple Hormone-receptor Agonist, weekly subcutaneous injection

Orforglipron – Daily oral GLP-1

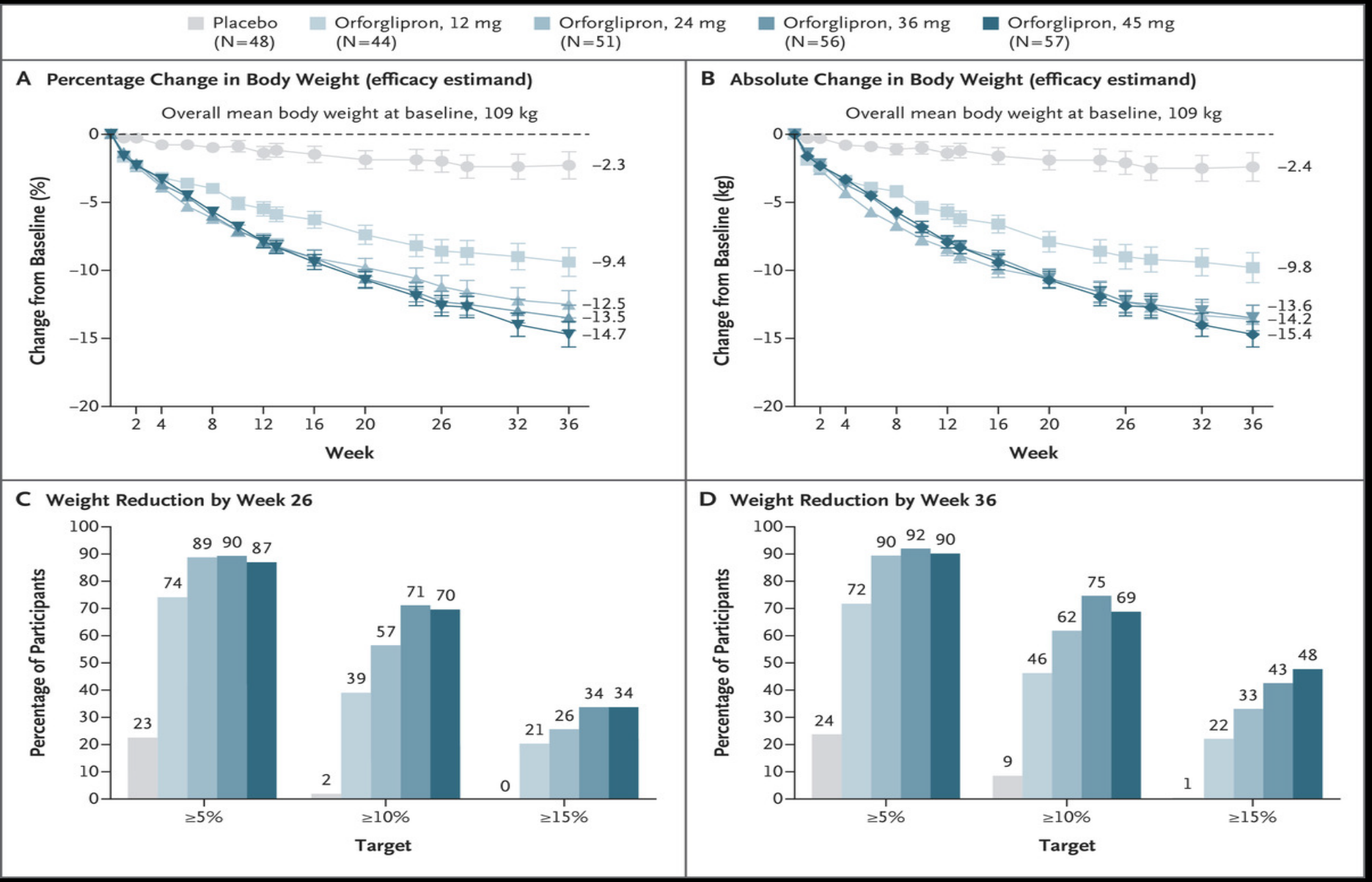
Changes in Body Weight with Retatrutide as Compared with Placebo in Prespecified Exploratory Subgroups.



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

AM Jastreboff et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2301972

Change in Body Weight with Daily Oral Orforglipron versus Placebo.



First Oral non-peptide GLP
Low activation of the β-arrestin pathway,

S Wharton et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2302392

CONCLUSIONS

Overweight and Obesity are a global epidemic expected to reach 4 billion people by 2035

Overweight and Obesity are common in patients with T1D and T2D

Overweight and Obesity contribute to insulin resistance in T1D and T2D

Weight loss is difficult with lifestyle modification alone but is still important (alone or in combinations with meds)

Newer medications such as GLP-1 have shown to be effective in lowering A1c and reducing weight in patients with T1D and T2D

GLP-1 medications present many challenges (cost, insurance coverage, side effects, nutrient deficiencies)

It is unknown if patients can stop GLP-1 medications and maintain weight loss

New medications are being studied for both weight loss and glucose control in T2D

Thank You