CARDIOMETABOLIC BENEFIT BEYOND GLYCEMIC CONTROL FOR T2D: DUAL AGONISM DUEL

WELCOME

Dr. Juan Pablo Frias

POLLING RESULTS

Dr. Juan Pablo Frias

Meet Mr. Murray

Background

- 52-year-old black male
- Oil rig technician for over 25 years
- Diagnosed with T2D 10 years ago
- Has always struggled to achieve good glycemic control and has had progressive increase in body weight over the past 15 years
- Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself

Social History/Lifestyle

- Married and has 4 grown children that have left the house; non-smoker and rare ETOH
- "No time for healthy eating or exercise due to demands at work…. Often away from home and healthy diet is difficult"
- Excellent health insurance through employer

Not an actual patient or profile; "Mr. Murray" will be used throughout the presentation.

Mr. Murray's clinical history

Medical History

- T2D, obesity, hypertension, dyslipidemia, sleep apnea, NAFLD, and OA of knees (no known ASCVD)

Physical Exam and Labs

- BP 132/75 mmHg
- Weight 115 kg, BMI 36 kg/m^2
- Normal retinal and thyroid exam
- A1c 8.6% (6 months ago 8.4%)
- Lipids: TC 182 mg/dL, LDL-C 108 mg/dL, TG 181 mg/dL, HDL-C 38 mg/dL
- Mildly elevated AST and ALT
- eGFR: 92 mL/min/1.73 m^2
- UACR: <30 mg/g

Current Medications T2D

metformin 1000 mg BID, glimepiride 4 mg QD, sitagliptin 100 mg QD

Other Meds/Treatments

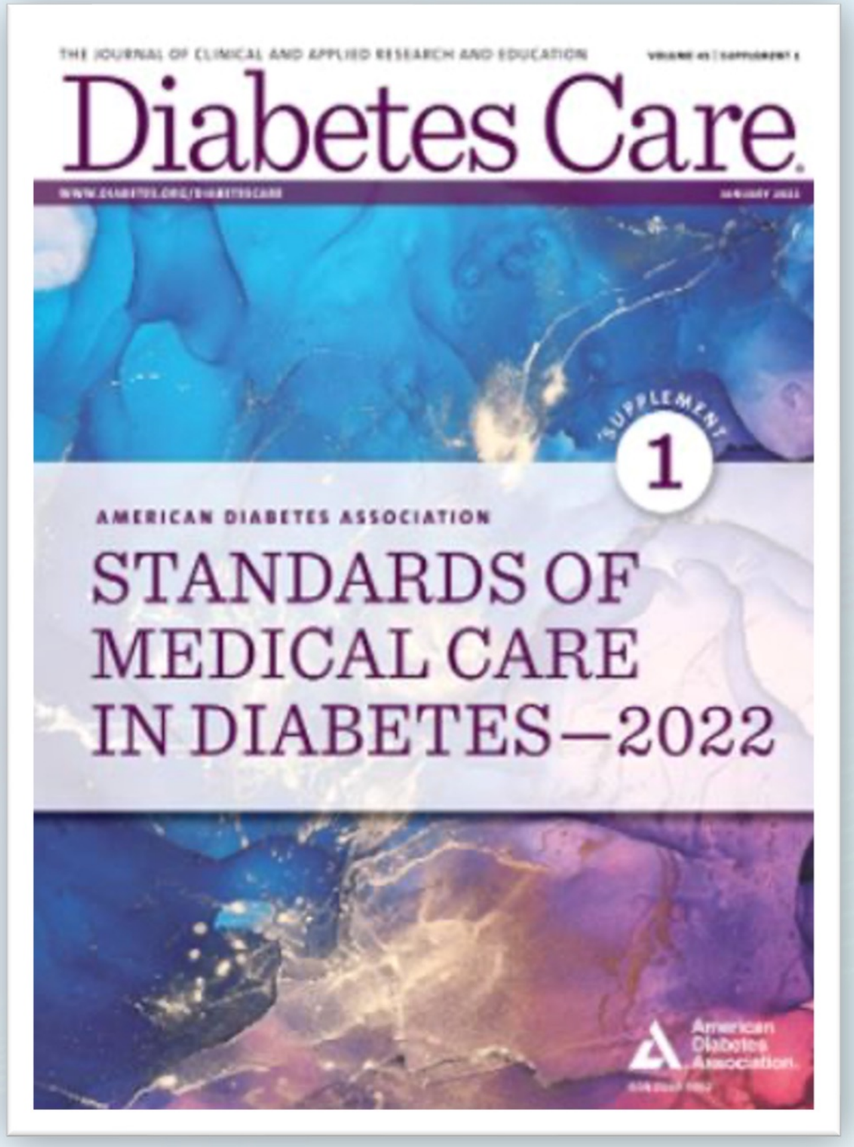
losartan 100 mg QD, amlodipine 5 mg QD, chlorthalidone 50 mg QD, atorvastatin 10 mg QD, nightly CPAP

UNMET NEEDS IN T2D

Dr. Donna Ryan

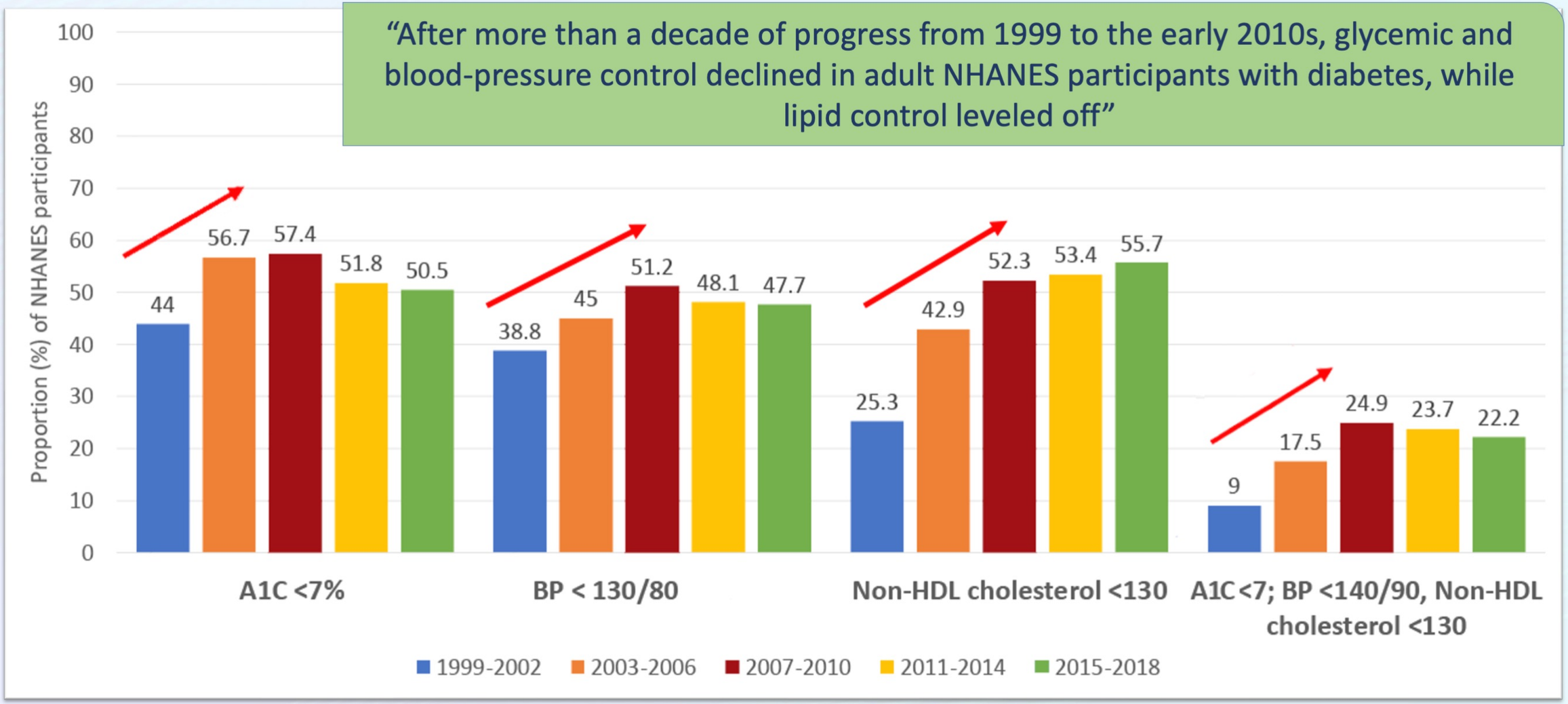
Goals of diabetes care

- Improve cardiometabolic health
- Prevent complications
- Improve health-related quality of life



Where do we stand in optimal diabetes care?

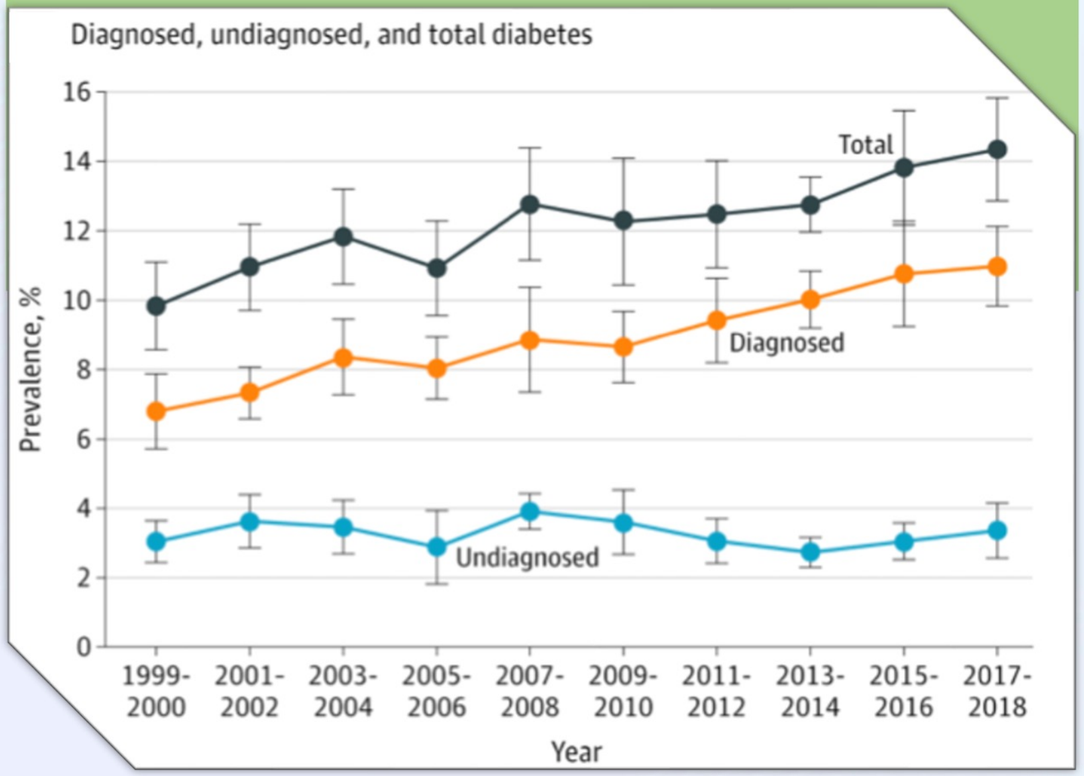
"After more than a decade of progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adult NHANES participants with diabetes, while lipid control leveled off"



Fang M, et al. ***N Engl J Med***. 2021;384:2219-2228.

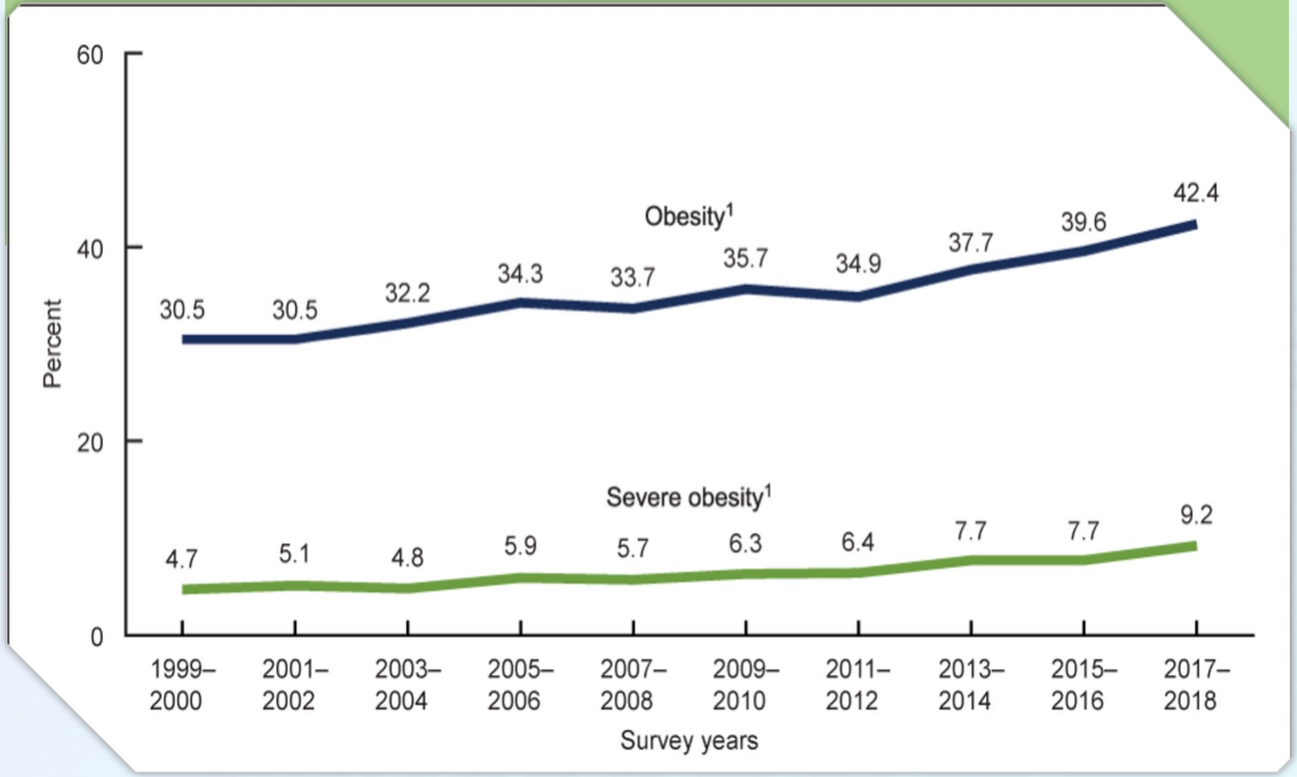
Twin epidemics of T2D and obesity

T2D: 9.8% →→→→14.3%



Wang L, et al. **JAMA**. 2021;326:704–716.

Obesity (BMI > 30): 30.5% →→→→42.4%



https://www.cdc.gov/nchs/products/databriefs/db360.htm#fig4

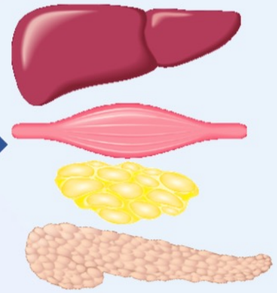
The obesity and diabetes syndemic

Physical environment
- Food
- Physical activity
- Safety
- Alcohol

- Sleep disorders
- Inability to be active
- Stigma and impaired mental health

Social environment
- Disadvantage
- Sociocultural barriers
- Income inequality

Obesity



Promotes 2 core defects
- Insulin resistance
- B-cell decompensation

T2D

- Medication-induced weight gain
- Neuropathy and decreased activity
- Hypoglycemia and stimulation of food intake
- Stigma and impaired mental health

Moderate weight loss has benefits—greater weight loss is associated with greater benefits

- Measures of glycemia[1]
- Triglycerides and HDL cholesterol[1]
- Systolic and diastolic blood pressure[1]
- Progression from prediabetes to diabetes[1]
- Hepatic steatosis (measured by MRS)[2]
- Measures of feeling and function
  - Symptoms of urinary stress incontinence[1]
  - Measures of sexual function[3]
  - Quality of life measures (IWQOL)[4]
- NASH activity score (measured by biopsy)[1]
- Apnea-hypopnea index[1]
- Reduction in CV events, mortality, remission of T2D[5,6]

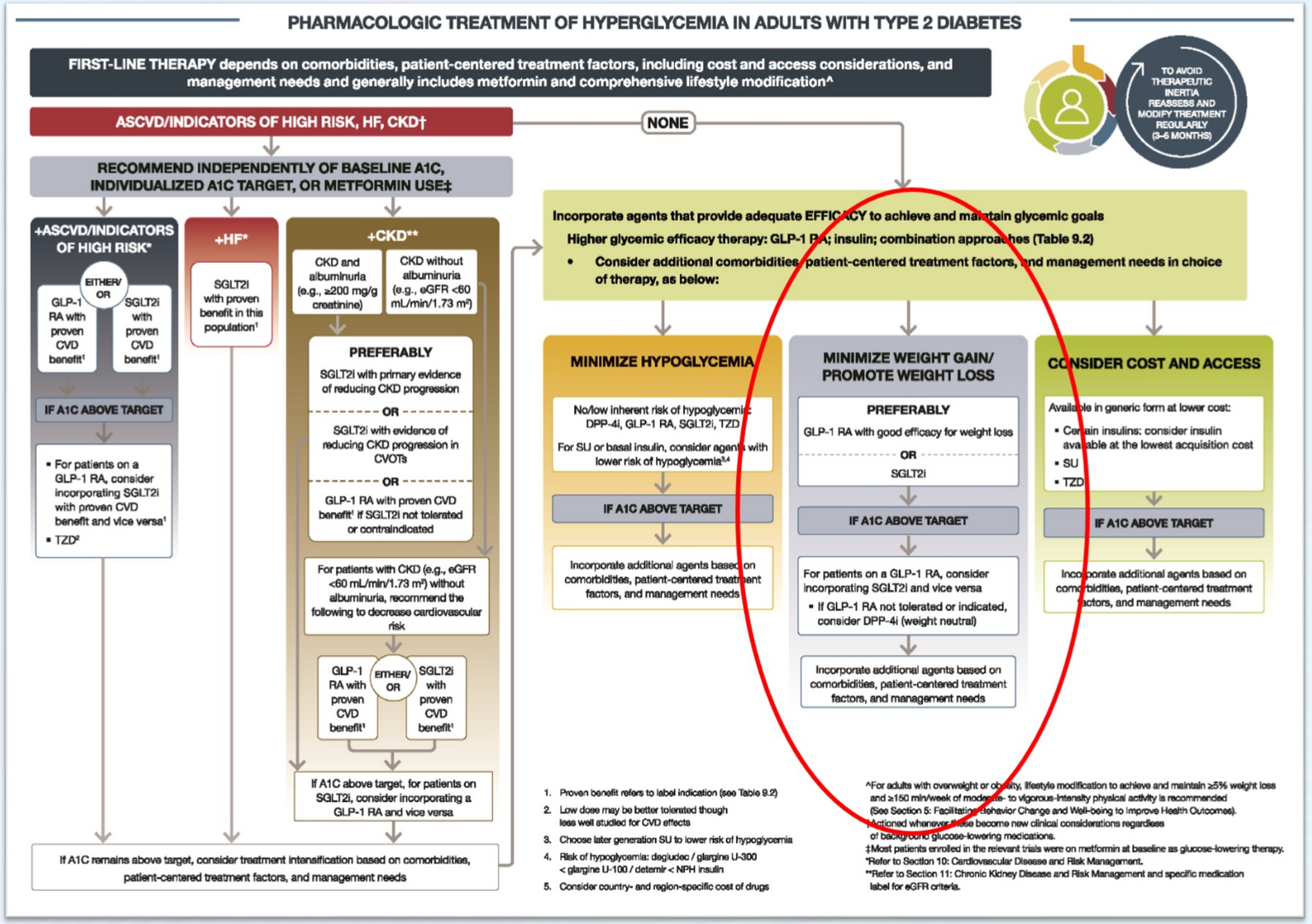
1. Cefalu WT, et al. ***Diabetes Care***. 2015;38:1567-1582; 2. Lazo M, et al. ***Diabetes Care***. 2010;33:2156-2163. 3. Wing R, et al. ***Diabetes Care***. 2013;36:2937-2944; 4. Kolotkin RL, et al. ***Obes Res***. 2001;9:564-571. 5. Sjostrom L, et al. ***JAMA***. 2012;307:56-65; 6. Sjostrom L, et al. ***JAMA***. 2014;311:2297-2304.

Emergence of new classes of T2D therapeutics

- GLP-1 RAs (2005)
  - Favorable weight loss profiles (liraglutide and semaglutide)
  - CV risk reduction (liraglutide, dulaglutide, semaglutide)
- SGLT2 inhibitors (2015)
  - Favorable weight loss and blood pressure profile
  - CV risk reduction, nephropathy reduction
- Dual GIP/GLP-1R agonist (2022)
  - Novel, once-weekly GIP and GLP-1 dual receptor agonist – new class
  - Enhanced glycemic control and weight loss benefits

1. Wing RR. Look AHEAD Research Group. ***Obesity*** (Silver Spring). 2021;29:1246-1258.
2. Schauer PR, et al for the STAMPEDE Investigators. ***N Engl J Med***. 2017;376:641-651.
3. Thomas MK, et al. ***J Clin Endocrinol Metab***. 2021;106(2):388-396

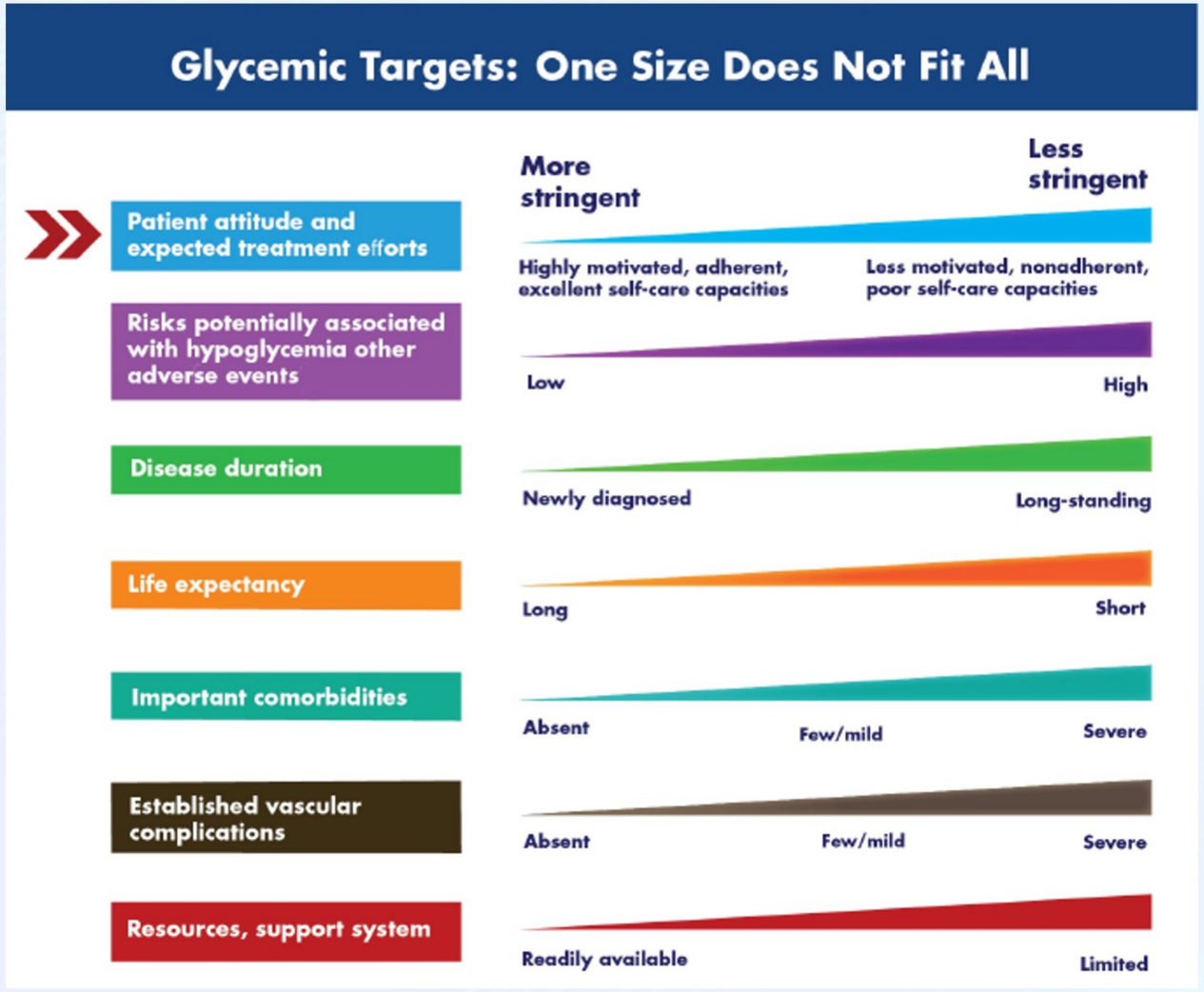
Treatment for T2D to minimize weight gain/promote weight loss



American Diabetes Association®

Used with permission from: Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. ***Clin Diabetes***. 2022;40:10-38. doi:10.2337/cd22-as01

Meeting the challenge of weight-centric diabetes management



- Be selective in choosing patients for intensive efforts in weight management, just as in the ADA approach to individualizing glycemic targets
- Prescribe wisely; choose medications with favorable weight profiles whenever possible
- Remember to use motivational interviewing and shared decision-making techniques

Inzucchi S, et al, ***Diabetes Care.*** 2012;35:1364-1379.

How to talk to your patients about weight management

Individualizing and achieving glycemic targets with shared decision making optimizes T2D outcomes

Patient communication is key to weight management success

Patients prefer the terms "excess body weight," "BMI," "above ideal body weight," and "maintaining a healthy weight"

They dislike the terms "excess fat," "obese," and "obesity"

Seek the patient's permission to discuss weight

- "As we get your glucose under control, do you have additional goals concerning your weight?"
- "What kind of help from me would you like regarding your weight?"

https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/weight-management/talking-adult-patients-tips-primary-care-clinicians

Mr. Murray

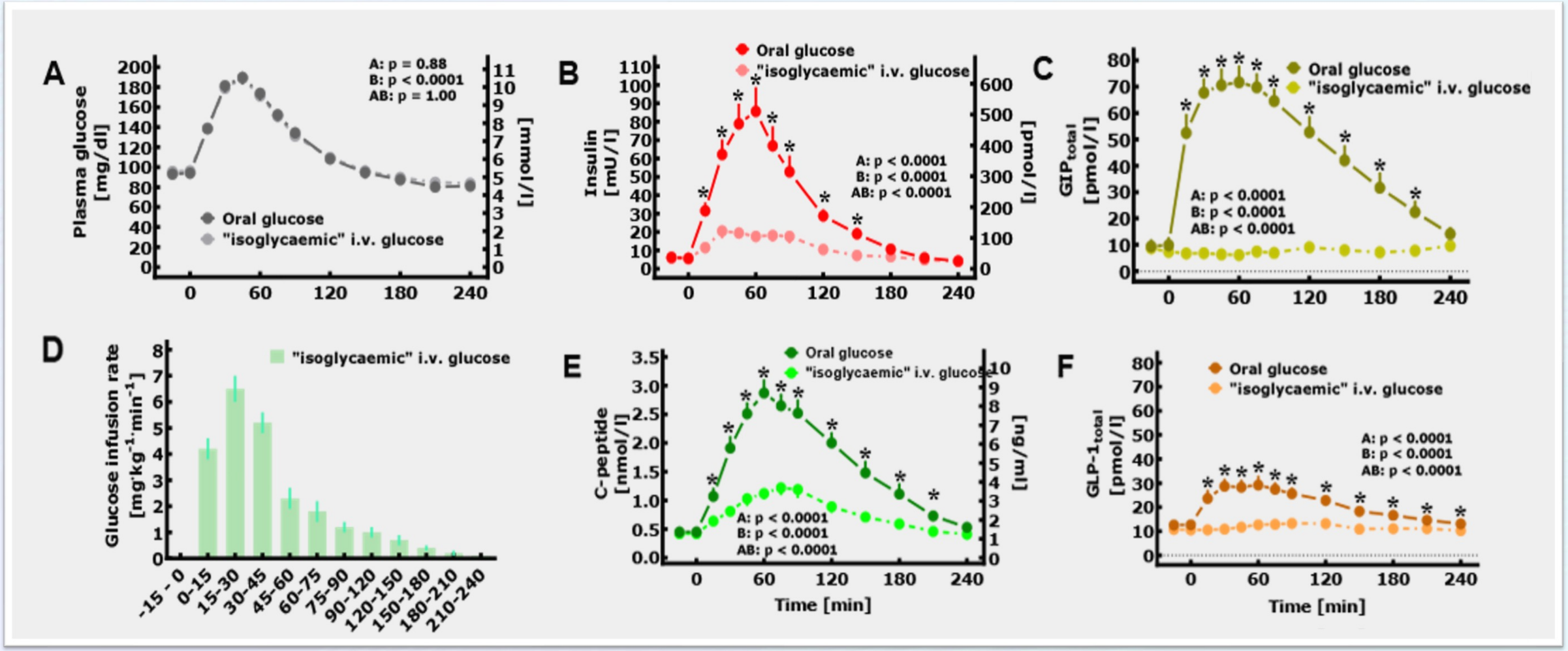
Mr. Murray	• 52-year-old black man • Oil rig technician for over 25 years • Diagnosed with T2D 10 years ago • Has struggled to achieve glycemic control and has had progressive increase in body weight over the past 15 years • Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself
Medical History	• T2D, obesity, hypertension, dyslipidemia, sleep apnea, NAFLD, and OA of knees (no known ASCVD)
Social History/ Lifestyle	• Married and has 4 grown children that have left the house; non-smoker and rare ETOH • "No time for healthy eating or exercise due to demands at work…. Often away from home and healthy diet is difficult" • Excellent health insurance through employer
Physical Exam & Labs	• BP 132/75 mmHg • Weight 115 kg, BMI 36 kg/m^2 • Normal retinal and thyroid exam • A1c 8.6% (6 months ago 8.4%) • Lipids: TC 182 mg/dL, LDL-C 108 mg/dL, TG 181 mg/dL, HDL-C 38 mg/dL • eGFR: 92 mL/min/1.73 m^2 • UACR: <30 mg/g
Current Medications	• T2D - metformin 1000 mg BID, glimepiride 4 mg QD, sitagliptin 100 mg QD
Other Meds/ Treatments	• Losartan 100 mg QD, amlodipine 5 mg QD, chlorthalidone 50 mg QD, atorvastatin 10 mg QD, nightly CPAP

DELINEATING THE INCRETIN EFFECT AND THE ROLES OF GLP-1 AND GIP

POTENTIAL BENEFITS OF AGONISM OF MULTIPLE RECEPTORS: MECHANISM OF ACTION OF UNIMOLECULAR DUAL AGONISTS

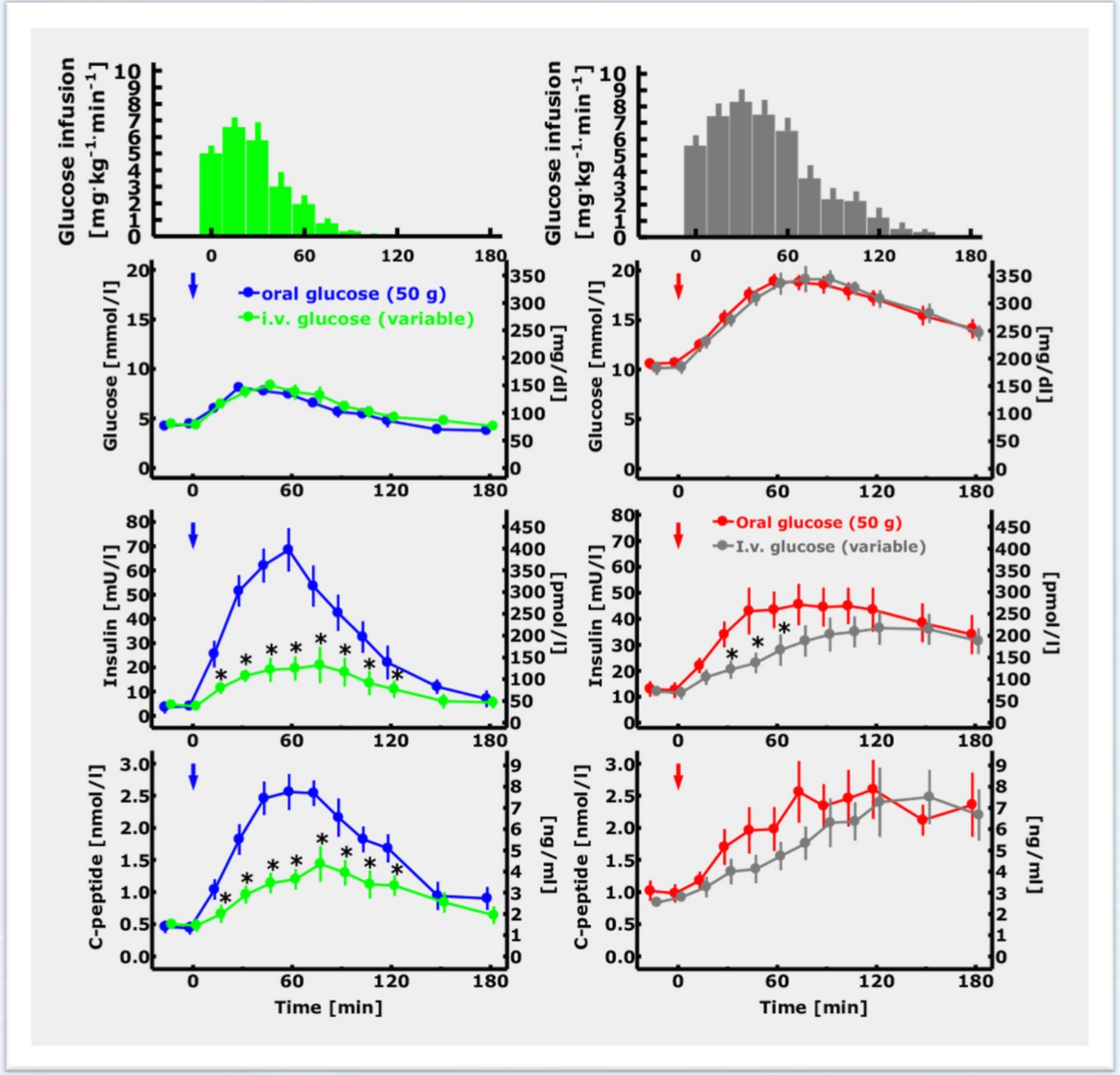
Dr. Michael Nauck

The incretin effect in healthy subjects



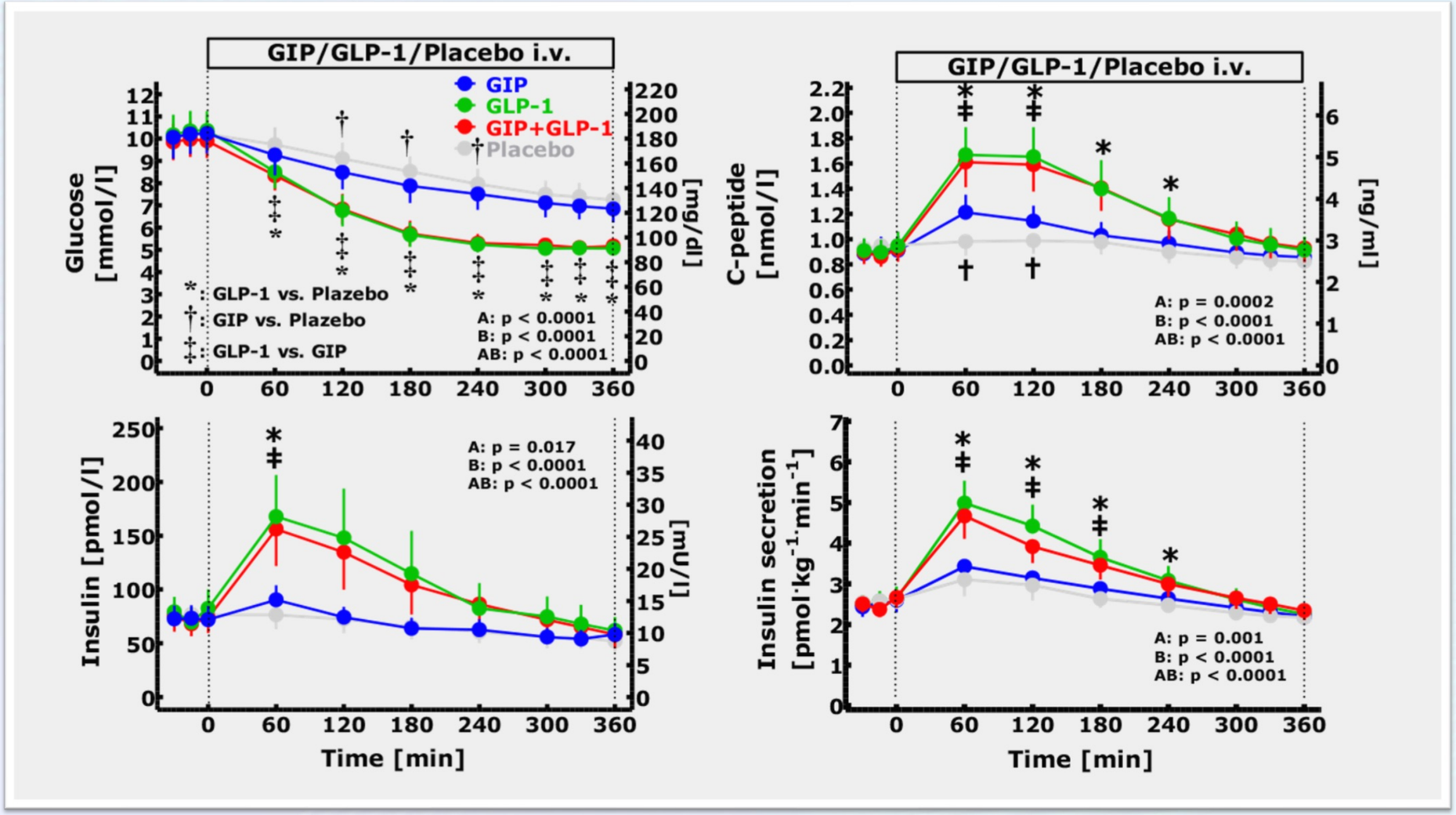
Used with permission from: Nauck MA, Meier JJ. ***Lancet Diabetes Endocrinol***. 2016;4:525-536.

The incretin effect in type 2 diabetes



Nauck MA, et al. ***Diabetologia***.1986;29:46-52.

GIP and GLP-1 administered as single agents or in combination in T2D patients



GLP-1 stimulates insulin secretion and reduces plasma glucose, but GIP has no effect

Mentis N, et al. ***Diabetes***. 2011;60:1270-1276.

The traditional view

A reduced incretin effect in T2D indicates an inability of GIP to stimulate insulin secretion

Is GIP the obesity hormone?

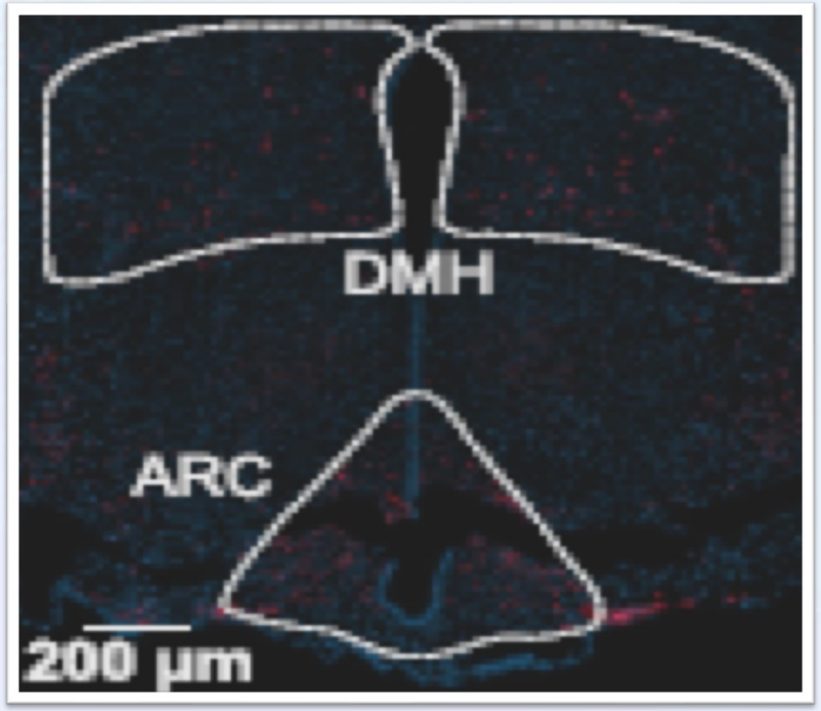
The traditional view

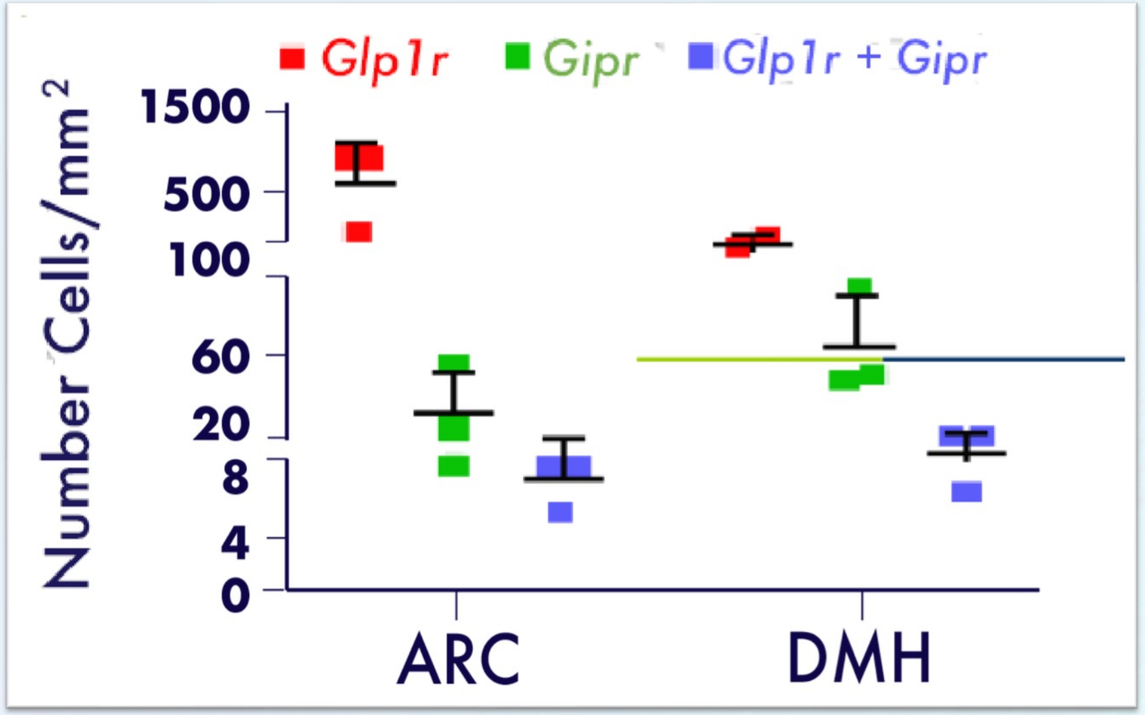
GIP receptor stimulation promotes obesity

Recent findings on GIP receptor agonism and body weight in animal studies

GIP receptor stimulation leads to reduced food intake and weight loss

GIP add GLP-1 receptor expression in hypothalamic neurons (eg, arcuate nucleus)

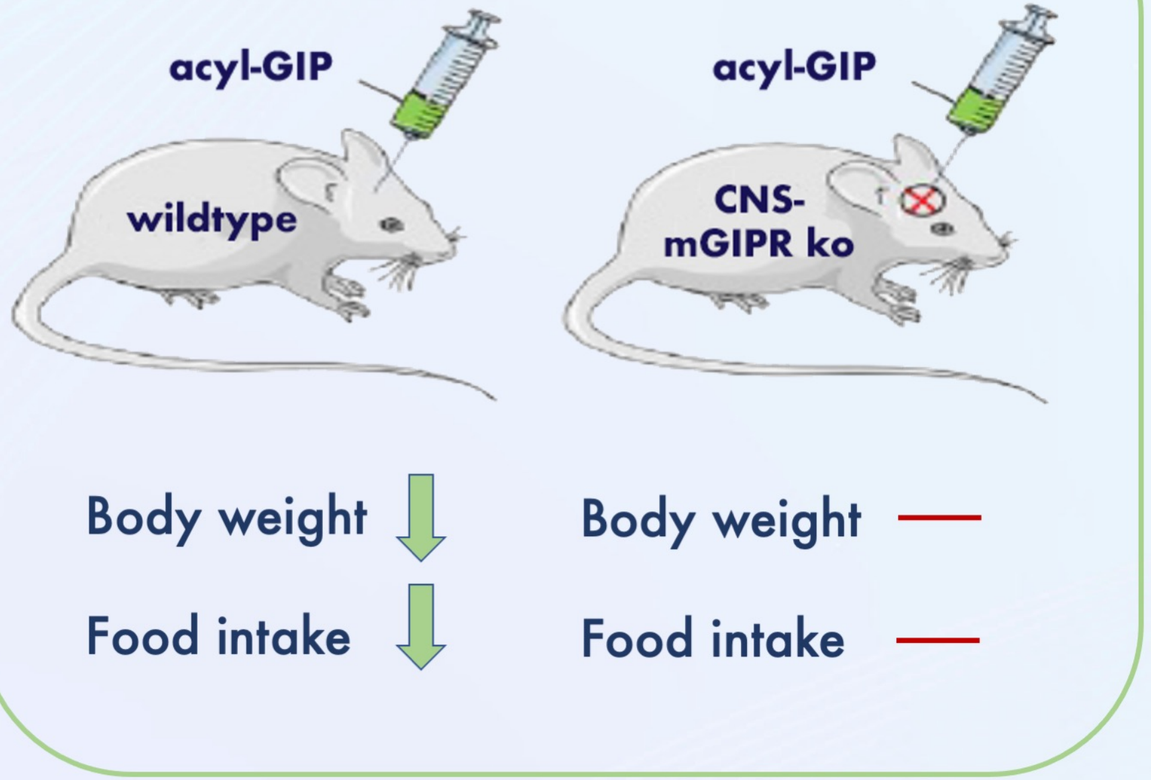


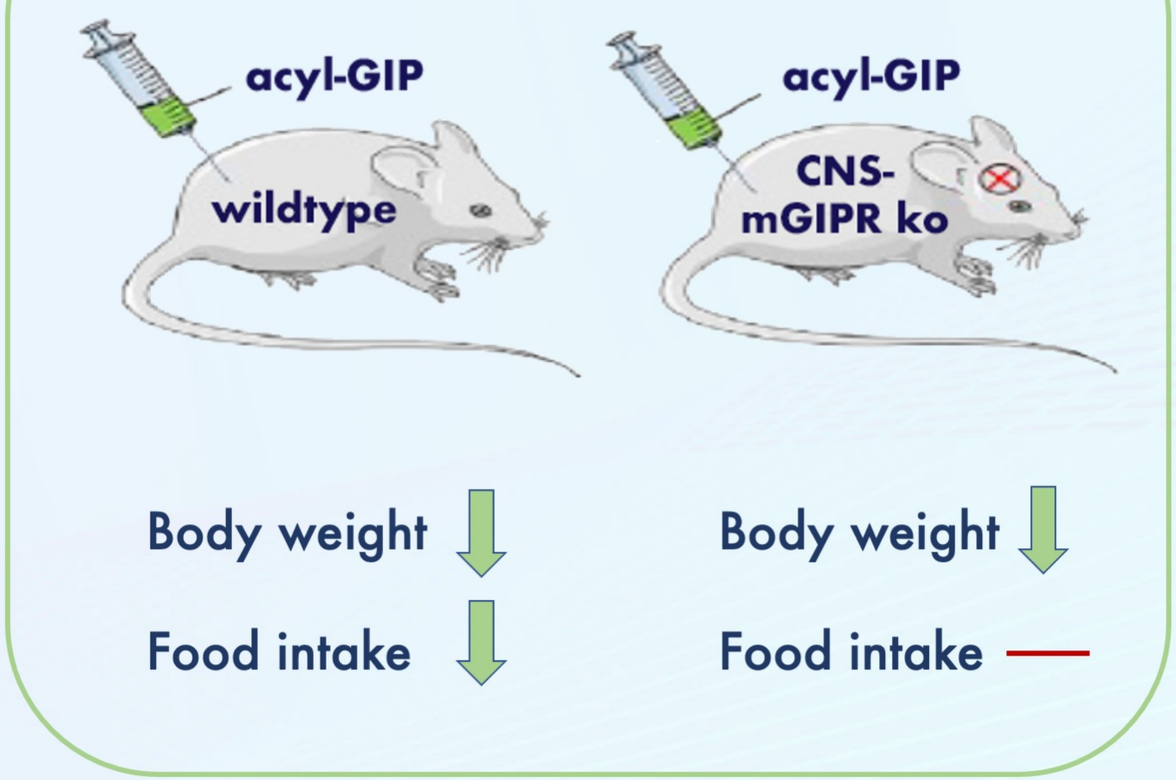


Adriaenssens AE, et al. ***Cell Metab***. 2019;30:987-996**.**

ARC, arcuate; DMH, dorsomedial hypothalamic; Gip, glucose-dependent insulinotropic polypeptide; Gipr, GIP receptor; Glp1r, glucagon-like peptide-1 receptor

GIP reduces food intake and body weight by interacting with CNS-GIPR

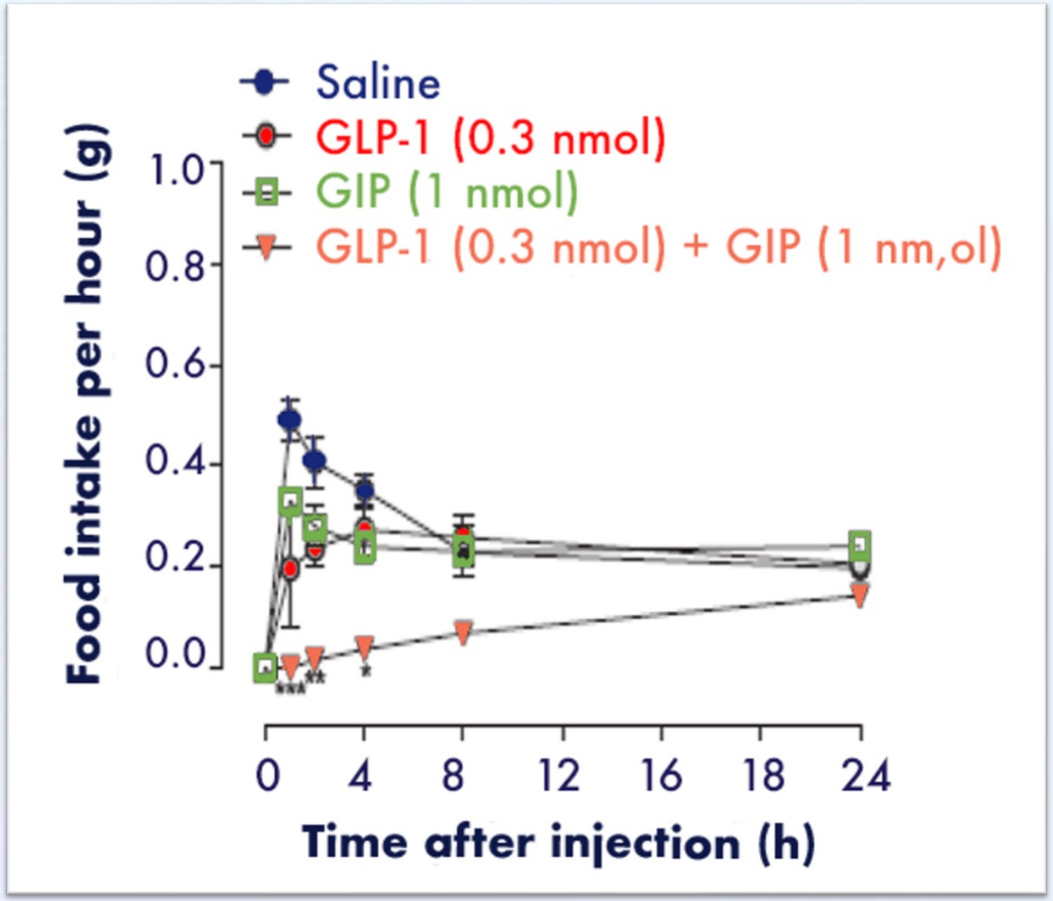


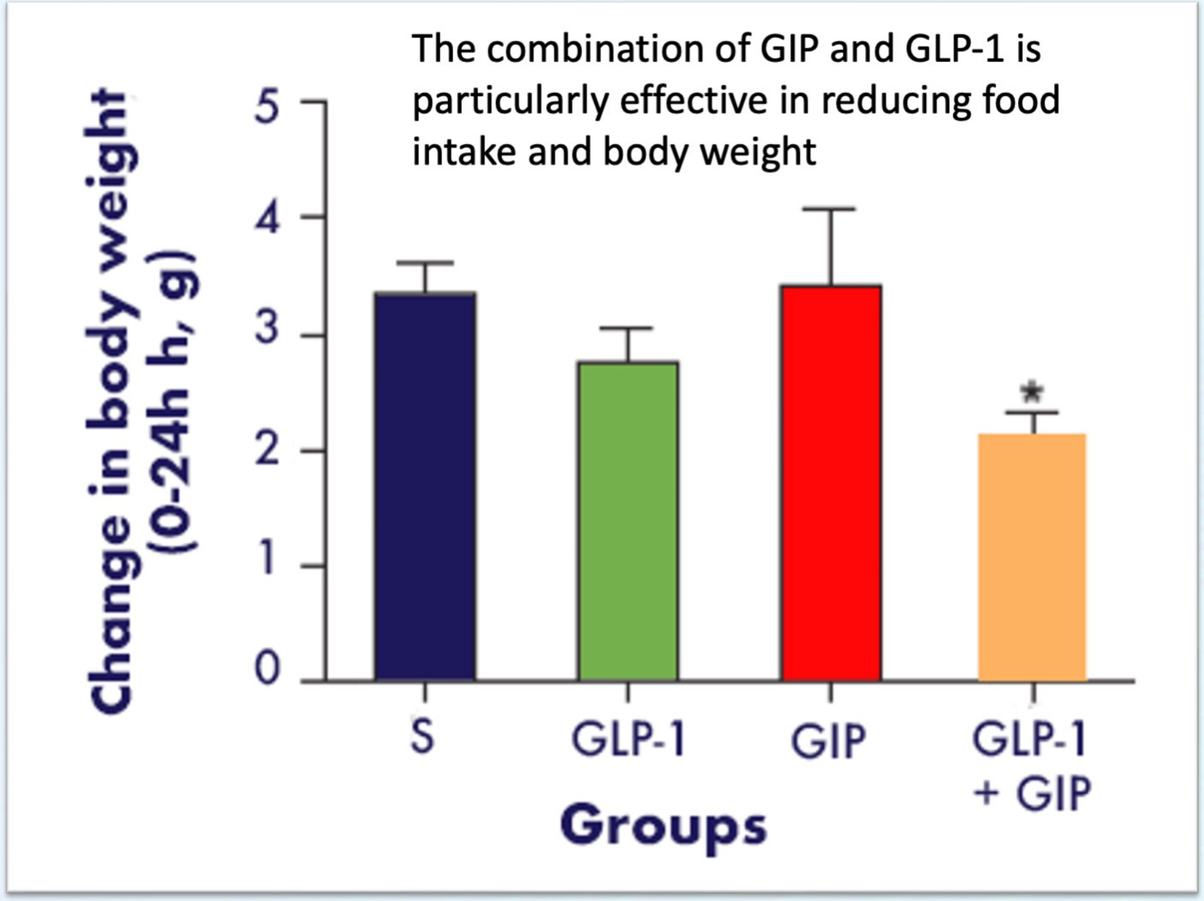


Adapted from Zhang Q, et al. ***Cell Metab***. 2021;33:833-844.

Acyl, acylated (free fatty acid residue attached); mGIPR ko, mouse GIP receptor knockout

GIP, GLP-1, and their combination reduce food intake and body weight in mice

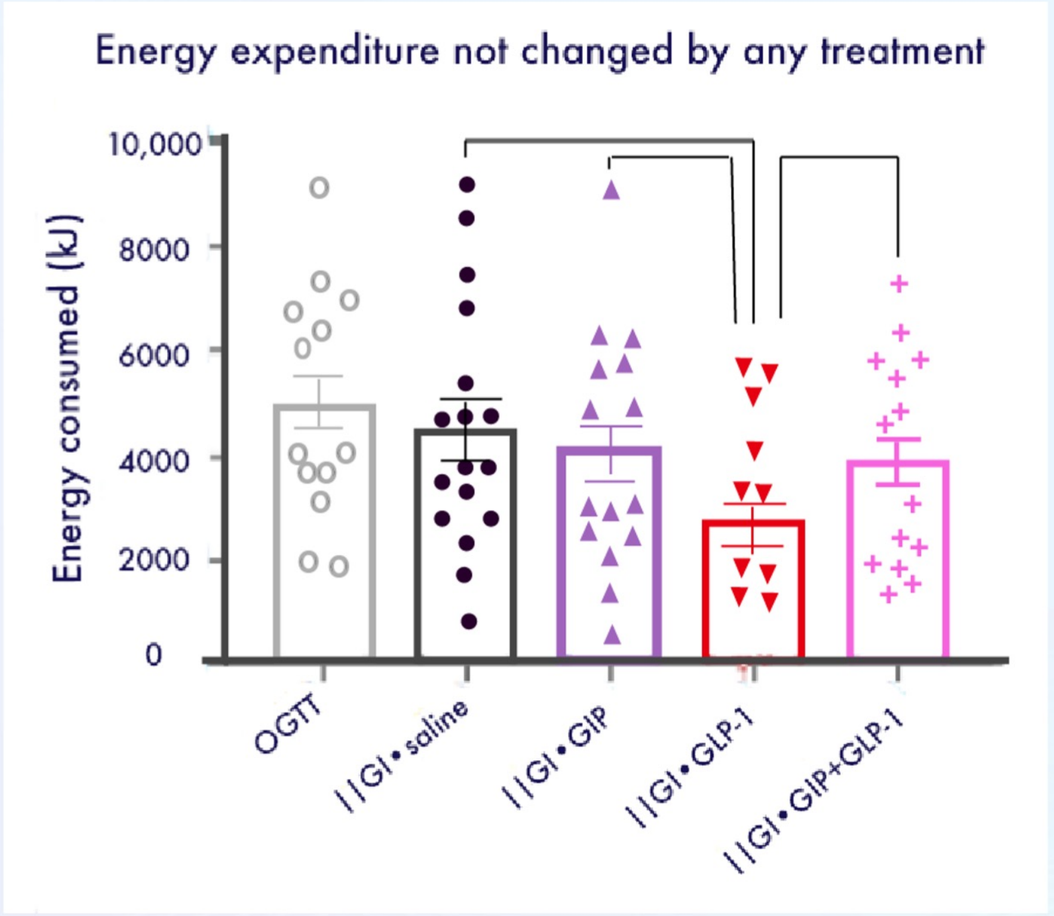




Intracerebroventricular injection

NamKoong C, et al. ***Biochem Biophys Res Comm.*** 2017;490:247-252.

Effects of exogenous GIP, GLP-1, and their combination on food intake in human subjects



Intravenous injection

The reduction in energy intake with GLP-1 is confirmed. GIP alone was without effect. The combination with GLP-1 showed a reduced effect.

Bergman NC, et al. ***Diabetologia***. 2019;62:665-675.

Bariatric surgery creates a novel pancreatic-intestinal hormonal milieu

Gut/Pancreas Peptide Hormone	Secretion After Gastric Bypass	Effect on appetite	Body Weight Energy Expenditure	Effects on Plasma Glucose
GLP-1	↑ ↑ ↑	↓	≈	↓ ↓
Glucagon	↑	↓	↑	↑ ↑
GIP	↑ / ≈	(↓/↑)	≈	(↓/↑)
PYY	↑ ↑ ↑	↓ ↓	≈	↓

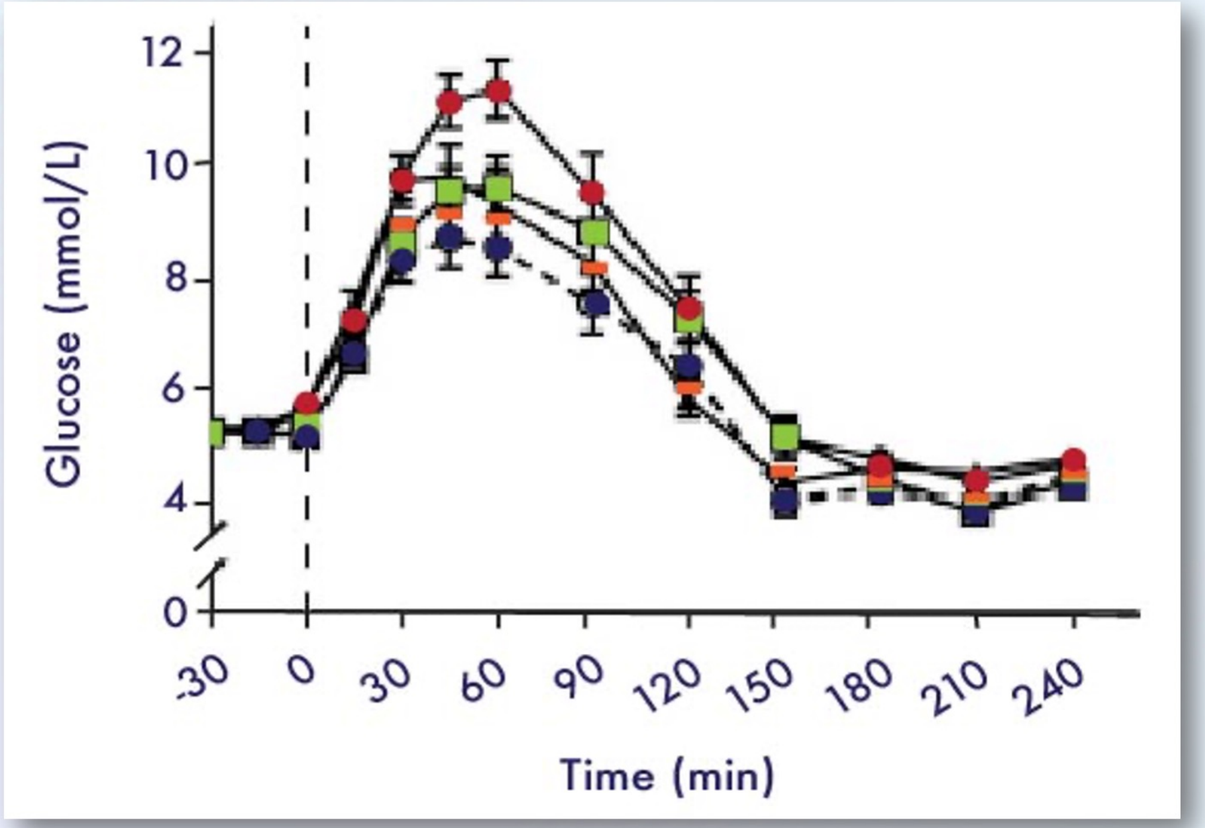
Modified from: Nauck MA, et al. ***Lancet Diabetes Endocrinol***. 2021;9:525-544.

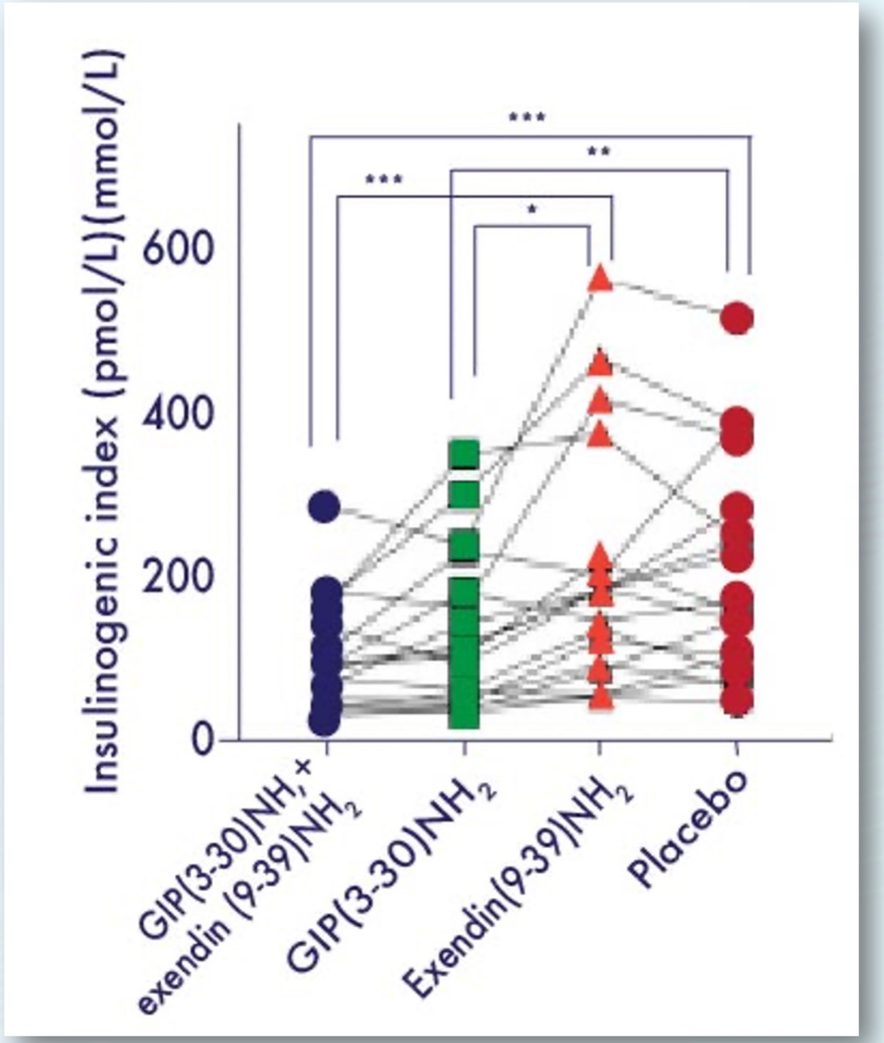
PYY, peptide YY

Bariatric surgery creates a gut hormonal milieu associated with weight loss and T2D remission

GIP and GLP-1 (plus additional hormones) together may participate in these effects

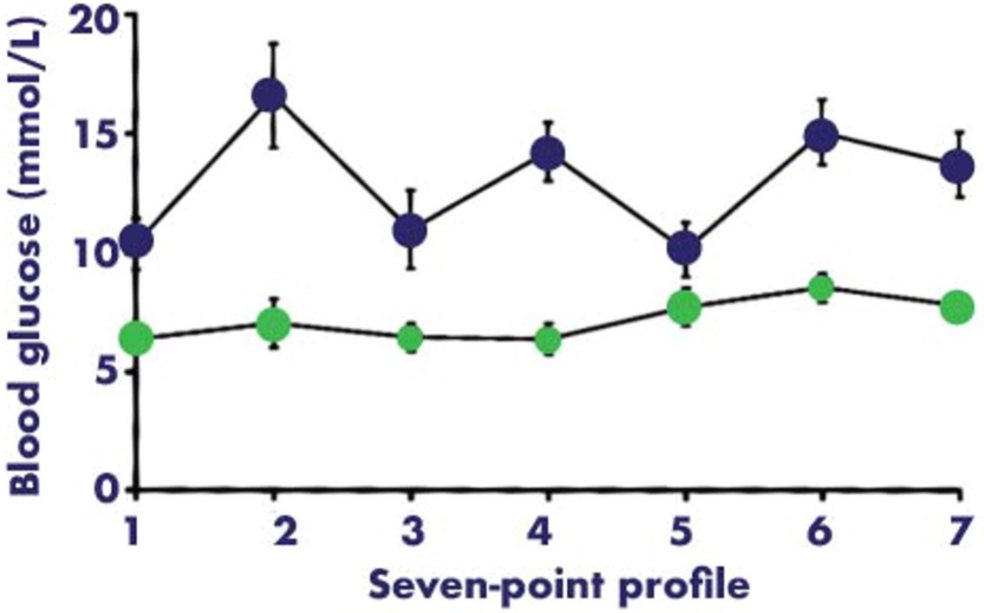
The influence of GIP and GLP-1 on postprandial glucose tested by use of specific receptor antagonists in human subjects



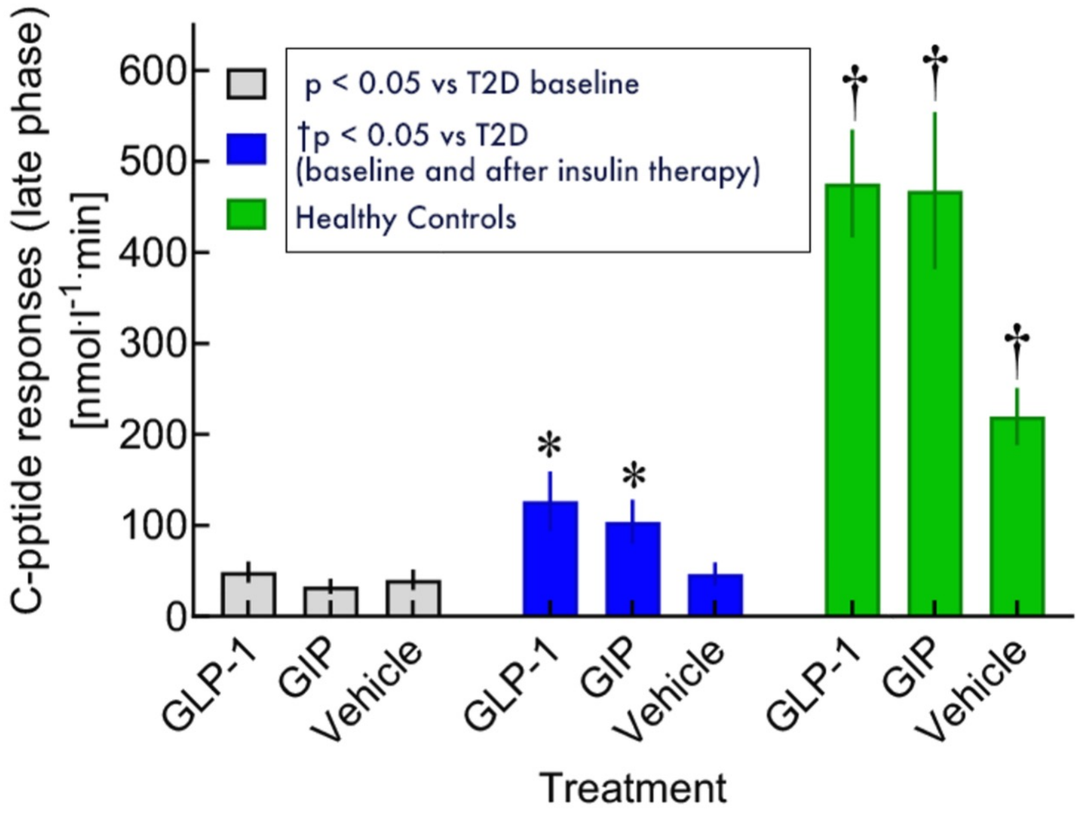


Gasbjerg LS, et al. ***Diabetes***. 2019;68:906-917.

Glucose control (intensified regimen) improved insulin and ß-cell response to GLP-1 and GIP in patients with T2D

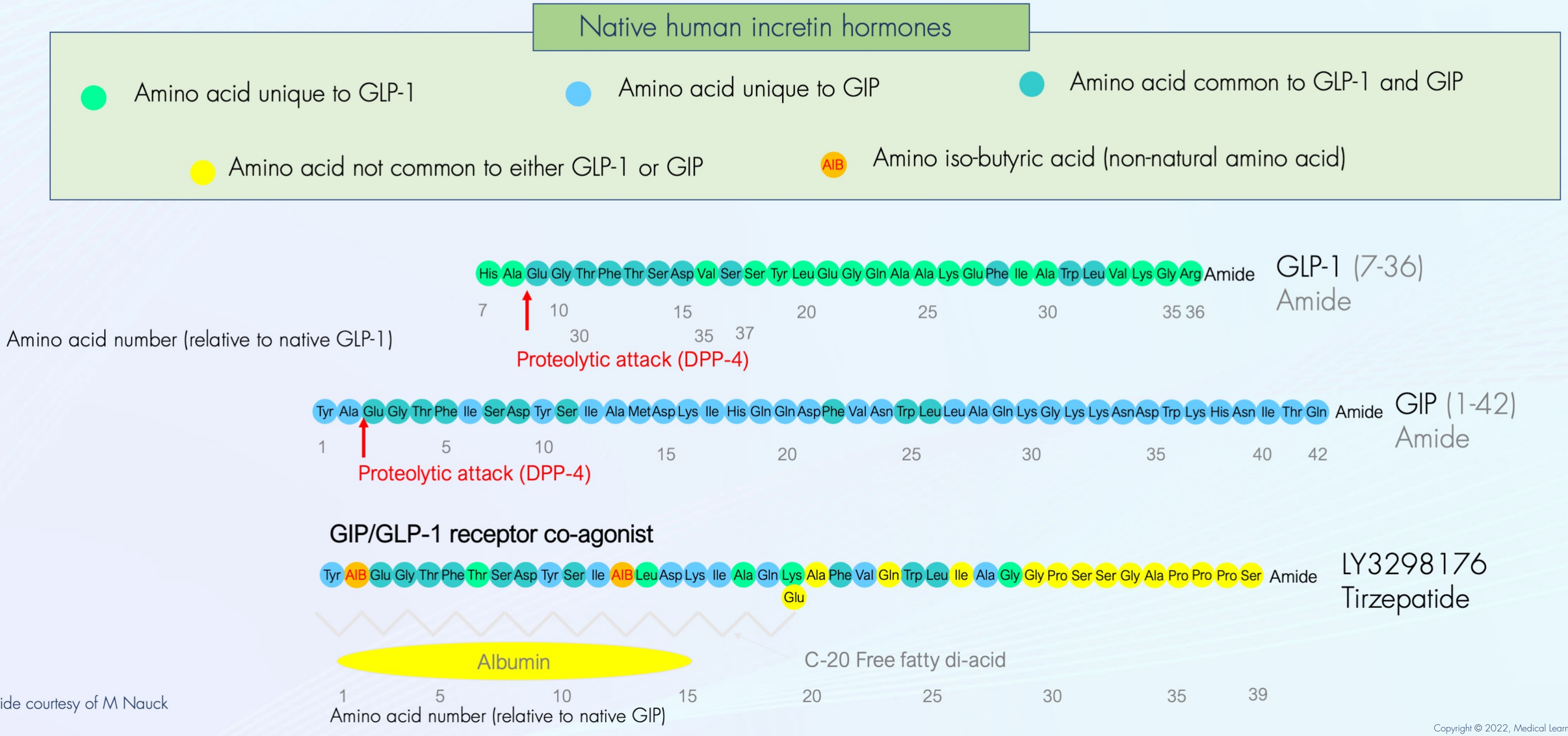


Mean blood glucose before (navy circles) and during (green circles) 4 weeks of insulin treatment. The patients measured blood glucose seven times per day three times per week. Data are mean± SEM



Adapted from Højberg P, et al. ***Diabetologia***. 2009;52:199-207.

Tirzepatide: a single molecule stimulating GIP and GLP-1 receptors



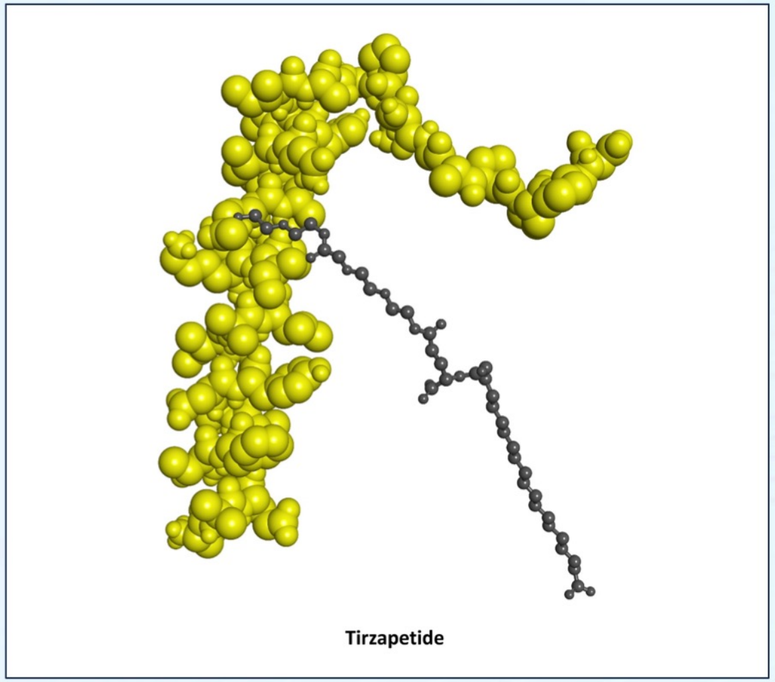
Slide courtesy of M Nauck

CLINICAL IMPLICATIONS OF DUAL AGONIST EFFICACY DATA: GLUCOSE

Dr. Juan Pablo Frias

Advanced engineering: dual GIP/GLP-1 receptor agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, engineered to bind to both GIP and GLP-1 receptors
- 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Mean half-life of ~5 days (116.7 h), enabling once-weekly dosing
- Plasma concentrations in people with renal and hepatic impairment do not differ from healthy people



Tirzapetide

Single agent possessing activity at 2 pharmacologic targets

Coskun T, et al. ***Mol Metab.*** 2018;18:3-14. Urva S, et al. ***Diabetes***. 2020 (Suppl. 1); abstract 971-P.

GIP, glucose-dependent insulinotropic polypeptide; GLP-1 Ras, glucagon-like peptide-1 receptor agonists

The SURPASS program: clinical trials across the spectrum of T2D

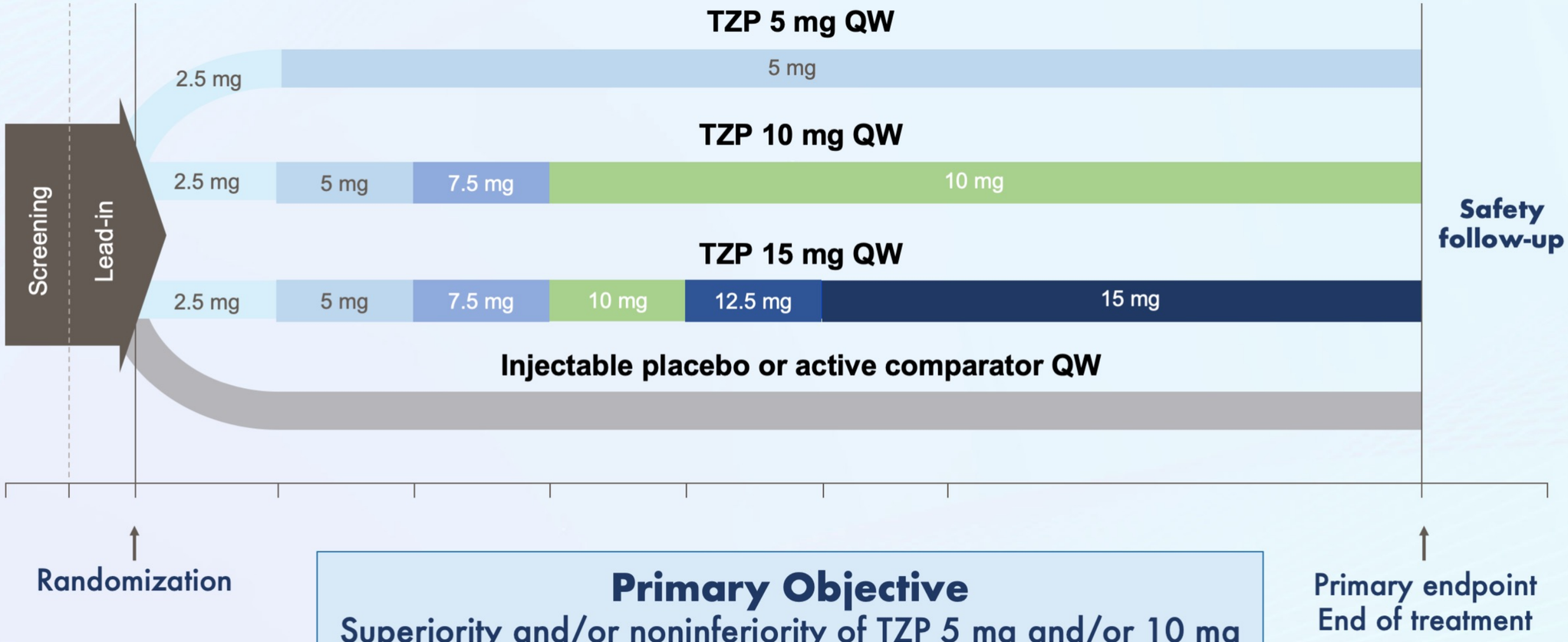
Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
SURPASS-1 vs placebo[1] Drug-naïve or washout from any OAM	**SURPASS-2** vs semaglutide[2] Add-on to metformin	**SURPASS-3** vs insulin degludec[3] Add-on to metformin with or without SGLT-2i	**SURPASS-4** vs insulin glargine[4] Add-on to ≥ 1 and ≤ 3 OAMs (metformin, SGLT-2i, or SU)	**SURPASS-5** vs placebo[5] Both with insulin glargine with or without metformin **SURPASS-6** vs insulin lispro (TID)[6] Both with insulin glargine with or without metformin (ongoing)

SURPASS-CVOT vs dulaglutide[7] (ongoing)

1. Rosenstock J, et al. ***Lancet***. 2021;398:143-155. 2. Frías JP, et al. ***N Engl J Med***. 2021;385:503-515. 3. Ludvik B, et al. ***Lancet***. 2021;398:583-598.
4. Del Prato S, et al. ***Lancet***. 2021;398:1811-1824. 5. Dahl D, et al. ***JAMA***. 2022;327:534-545. 6. SURPASS-6. Available at: https://clinicaltrials.gov/ct2/show/NCT04537923. Accessed April 2021. 7. SURPASS-CVOT. Available at: https://clinicaltrials.gov/ct2/show/NCT04255433. Accessed April 2021.

OAM = oral antihyperglycemic medication; SU = sulfonylurea; TID = three times daily

SURPASS trial design: tirzepatide 5, 10, and 15 mg versus active comparator or placebo

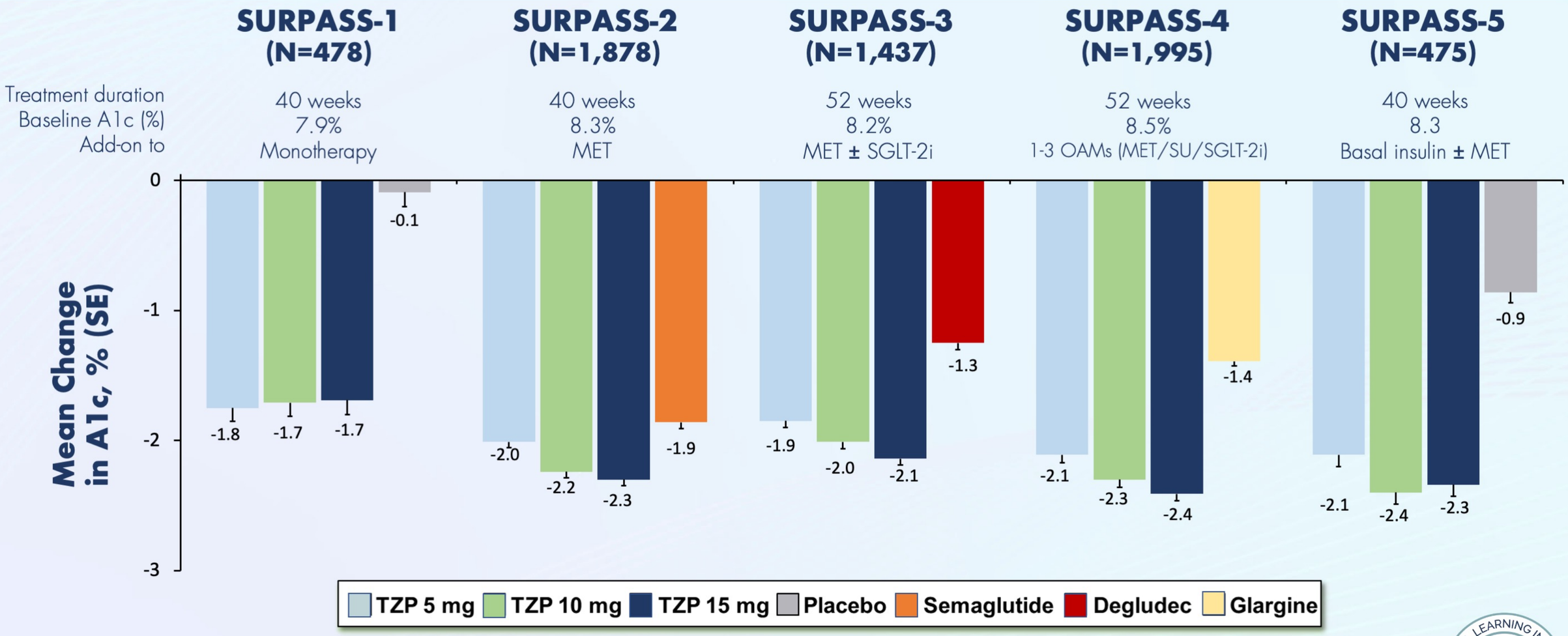


Primary Objective

Superiority and/or noninferiority of TZP 5 mg and/or 10 mg and/or 15 mg vs placebo or active comparator in mean change in A1c from baseline at 40 or 52 weeks.

1. Rosenstock J et al. ***Lancet***. 2021;398:143-155. 2. Frías JP et al. ***N Engl J Med***. 2021;385:503-515. 3. Ludvik B et al. ***Lancet***. 2021;398:583-598.
4. Del Prato S et al. ***Lancet***. 2021;398:1811-1824. 5. Dahl D et al. ***JAMA***. 2022;327:534-545.

Tirzepatide at all doses significantly reduced A1c versus placebo or active comparators



Treatment-regimen estimand.

1. Rosenstock J et al. ***Lancet***. 2021;398:143-155. 2. Frías JP et al. ***N Engl J Med***. 2021;385:503-515. 3. Ludvik B et al. ***Lancet***. 2021;398:583-598.
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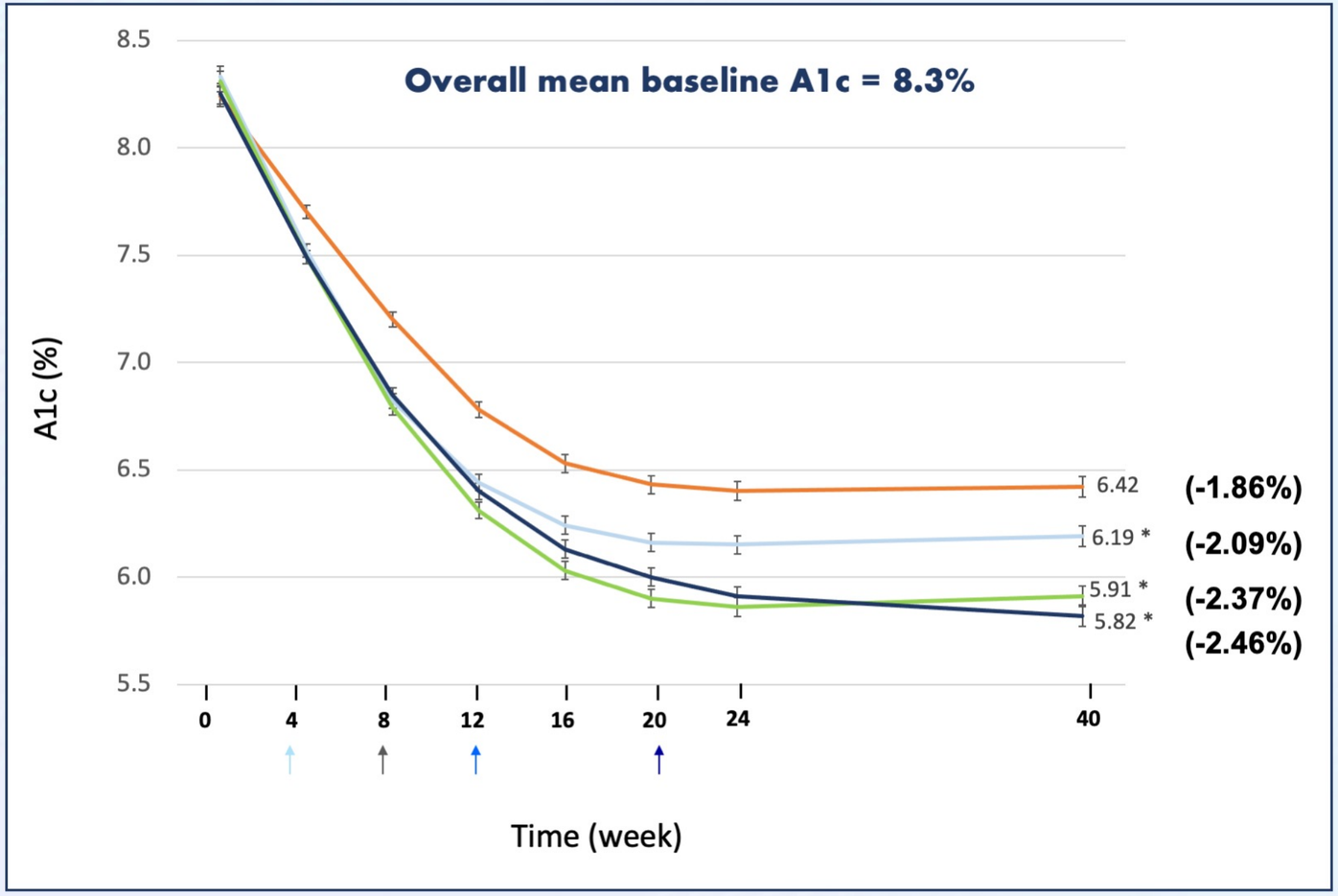
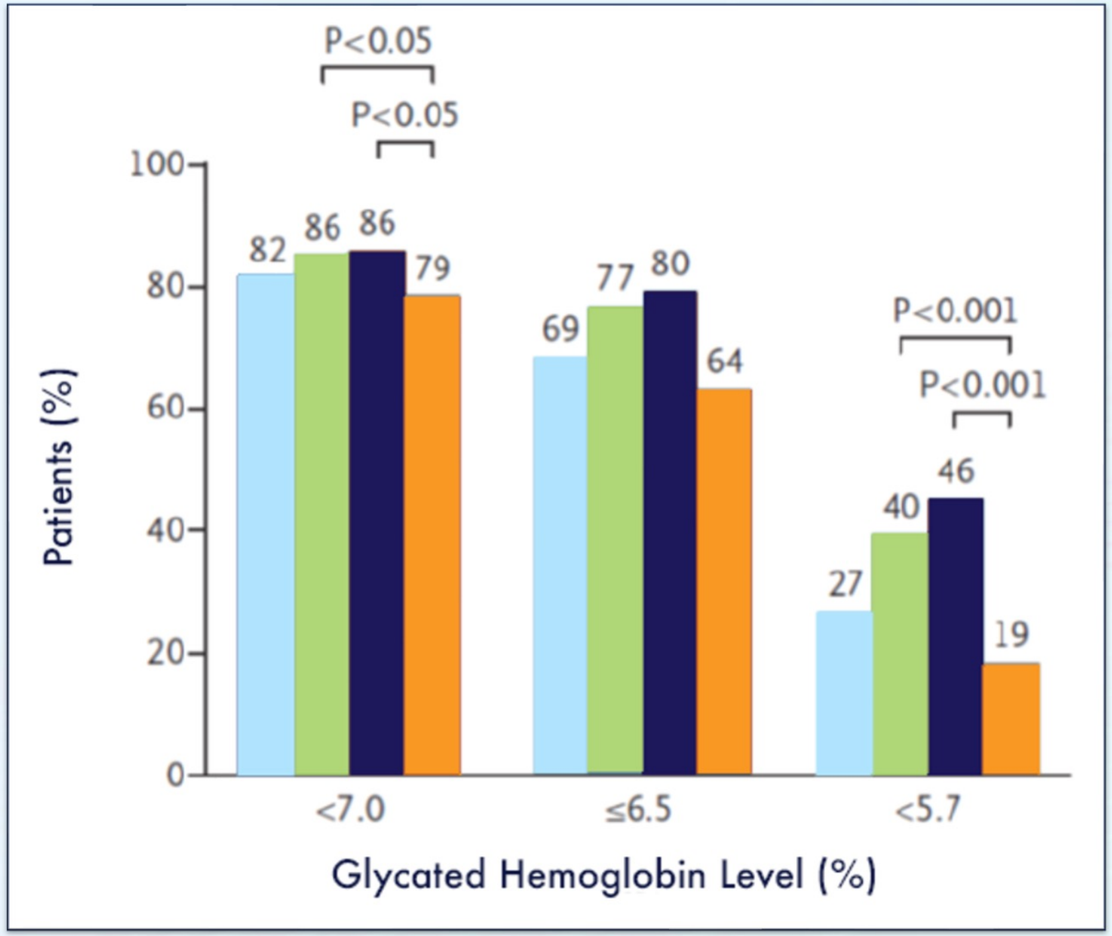
Tirzepatide significantly reduced A1c and more patients achieved A1c targets compared with semaglutide 1 mg



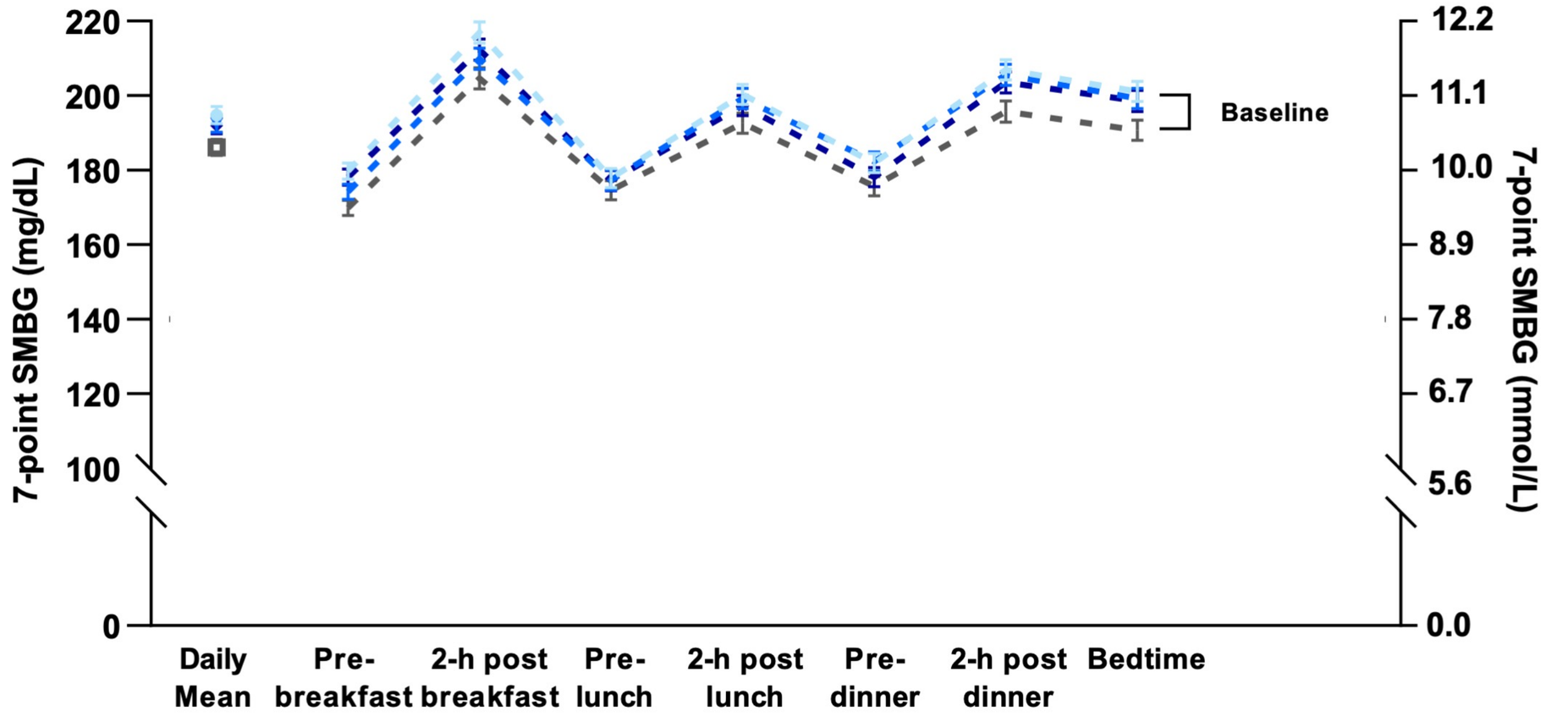


Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg | Semaglutide 1 mg

Data are LSM (SE); mITT (efficacy analysis set) ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. *p<0.001 vs. semaglutide 1 mg

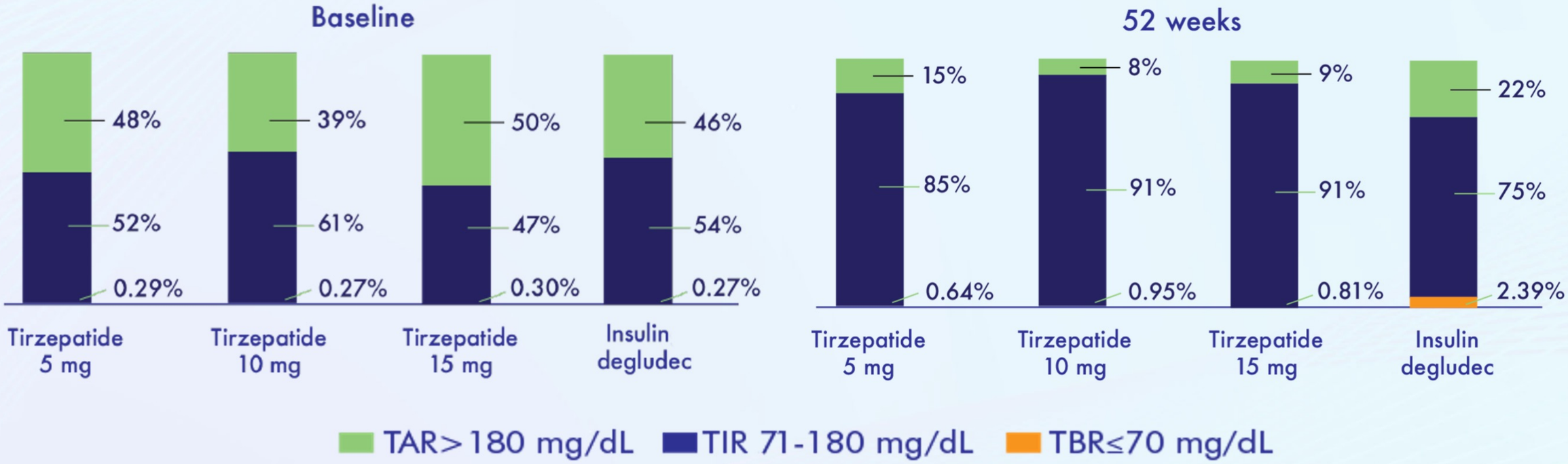
Frías JP, et al. ***N Engl J Med***. 2021;385:503-515

Tirzepatide improved self-monitored pre- and postprandial glucose compared with semaglutide 1 mg



Frías JP, et al. ***N Engl J Med***. 2021;385:503-515

Tirzepatide improved time in range versus insulin degludec after 52 weeks of treatment



All tirzepatide doses (5, 10, and 15 mg) had greater time in range (70-180 mg/dL) and less time below range (<70 mg/dL) compared with insulin degludec at week 52

Battelino T, et al. ***Lancet Diabetes Endocrinol***. 2022;10:407-417.

Mr. Murray

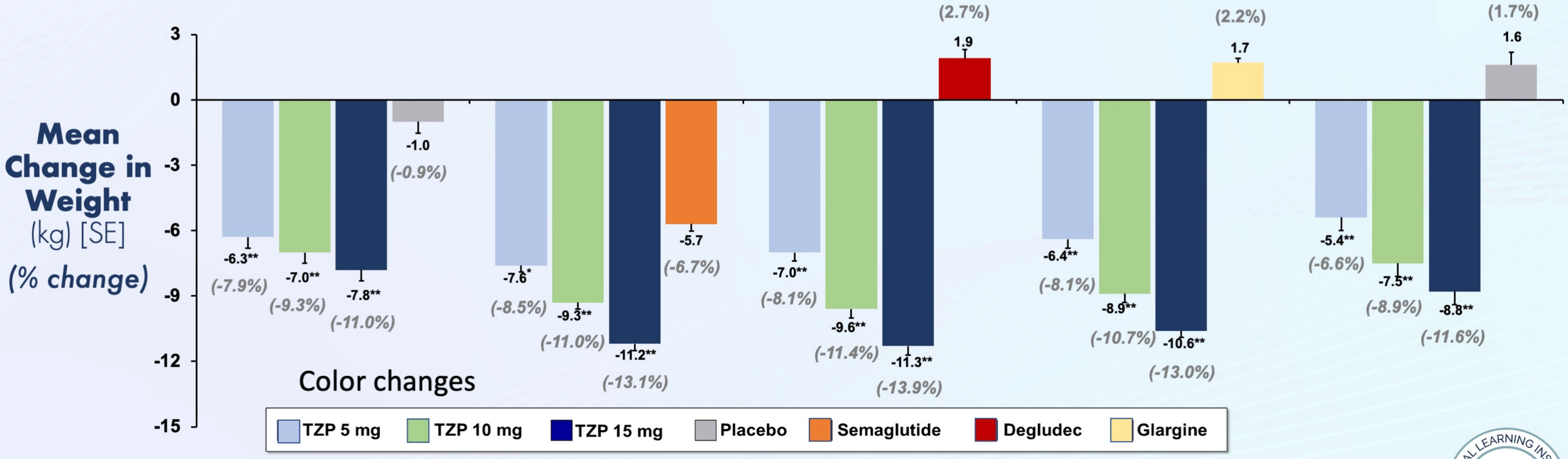
Mr. Murray	• 52-year-old black man • Oil rig technician for over 25 years • Diagnosed with T2D 10 years ago • Has struggled to achieve glycemic control and has had progressive increase in body weight over the past 15 years • Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself
Medical History	• T2D, obesity, hypertension, dyslipidemia, sleep apnea, NAFLD, and OA of knees (no known ASCVD)
Social History/ Lifestyle	• Married and has 4 grown children that have left the house; non-smoker and rare ETOH • "No time for healthy eating or exercise due to demands at work…. Often away from home and healthy diet is difficult" • Excellent health insurance through employer
Physical Exam & Labs	• BP 132/75 mmHg • Weight 115 kg, BMI 36 kg/m^2 • Normal retinal and thyroid exam • A1c 8.6% (6 months ago 8.4%) • Lipids: TC 182 mg/dL, LDL-C 108 mg/dL, TG 181 mg/dL, HDL-C 38 mg/dL • eGFR: 92 mL/min/1.73 m^2 • UACR: <30 mg/g
Current Medications	• T2D - metformin 1000 mg BID, glimepiride 4 mg QD, sitagliptin 100 mg QD
Other Meds/ Treatments	• Losartan 100 mg QD, amlodipine 5 mg QD, chlorthalidone 50 mg QD, atorvastatin 10 mg QD, nightly CPAP

CLINICAL IMPLICATIONS OF DUAL AGONIST EFFICACY DATA: WEIGHT AND LIPIDS

Dr. Donna Ryan

Tirzepatide decreased weight (kg and %) more than comparators in SURPASS trials

	SURPASS-1[1] (N=478)	SURPASS-2[2] (N=1,878)	SURPASS-3[3] (N=1,437)	SURPASS-4[4] (N=1,995)	SURPASS-5[5] (N=475)
Treatment Duration	40 weeks	40 weeks	52 weeks	52 weeks	40 weeks
Baseline weight (kg)	85.9	93.7	94.3	90.3	95.2
Add-on to	Monotherapy	MET	MET ± SGLT-2i	1-3 OAMs (MET/SU/SGLT-2i)	Basal insulin ± MET



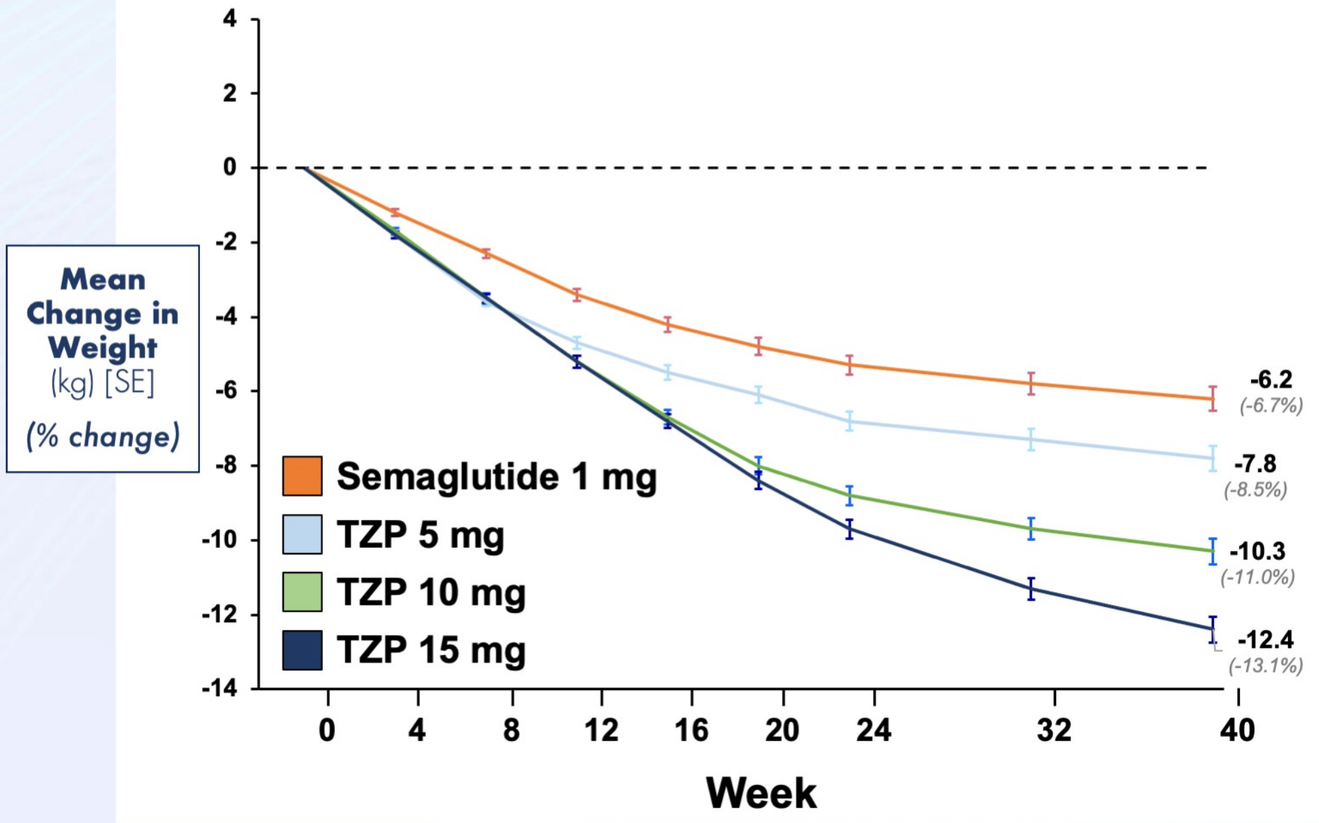
1. Rosenstock J, et al. ***Lancet***. 2021;398:143-155. 2. Frías JP, et al. ***N Engl J Med***. 2021;385:503-515.
3. Ludvik B, et al. ***Lancet***. 2021;398:583-598. 4. Del Prato S, et al. ***Lancet***. 2021;398:1811-1824.
5. Dahl D, et al. ***JAMA***. 2022;327:534-545.

Treatment-regimen estimand
Superiority vs placebo or active comparator: *p < 0.05; **p < 0.001

Tirzepatide sustained the trajectory of weight change (kg and %) over 40 and 52 w better than comparators (SURPASS 2 and 3)

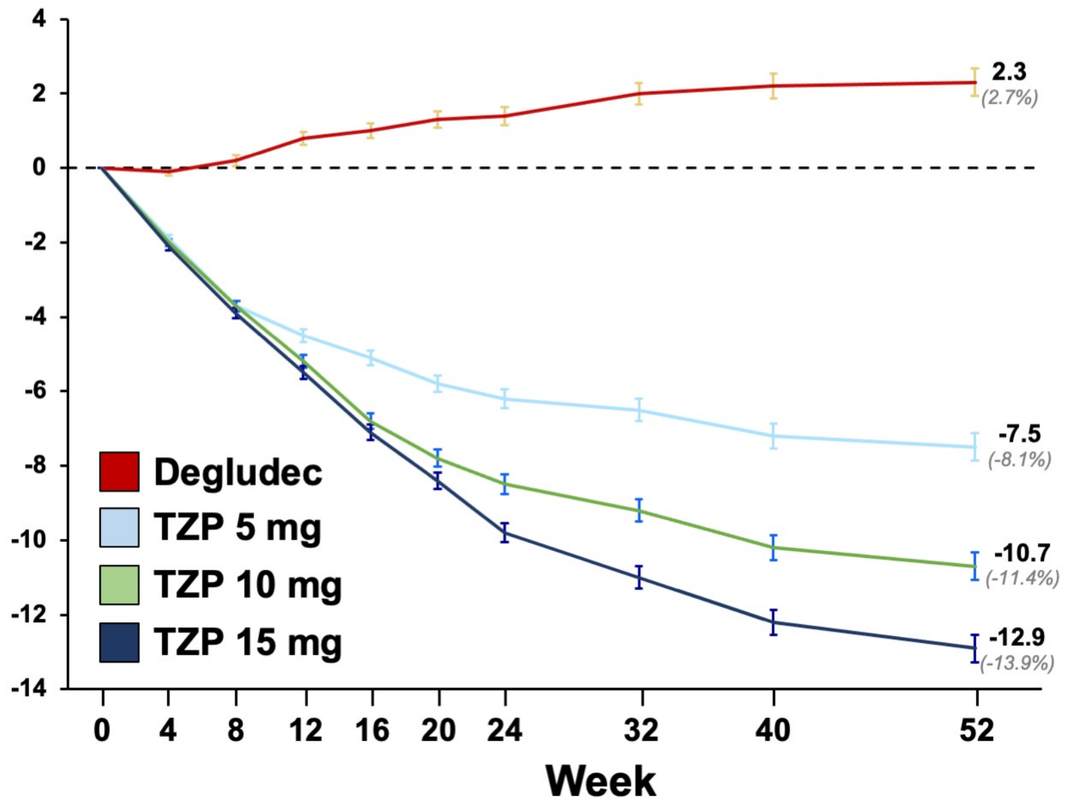
SURPASS-2[1]

Overall mean baseline weight = 93.8 kg



SURPASS-3[2]

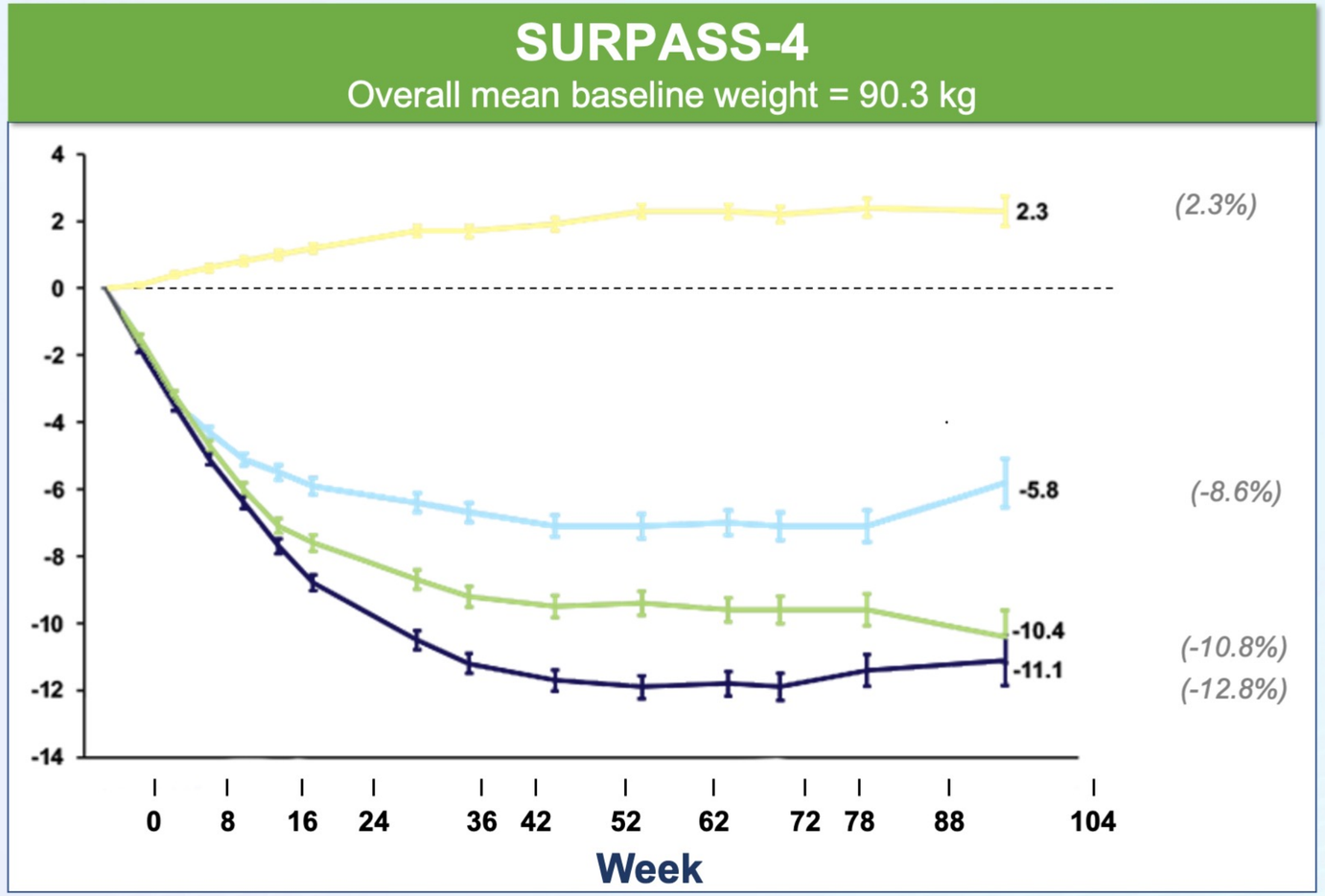
Overall mean baseline weight = 94.5 kg



Efficacy estimand

1. Frias JP, et al. ***N Engl J Med***. 2021; 385:503-515.
2. Ludvik B, et al. ***Lancet***. 2021;398:583-598.

All doses of tirzepatide resulted in greater mean weight change (kg and %) over 2 years (SURPASS 4)



Number of patients

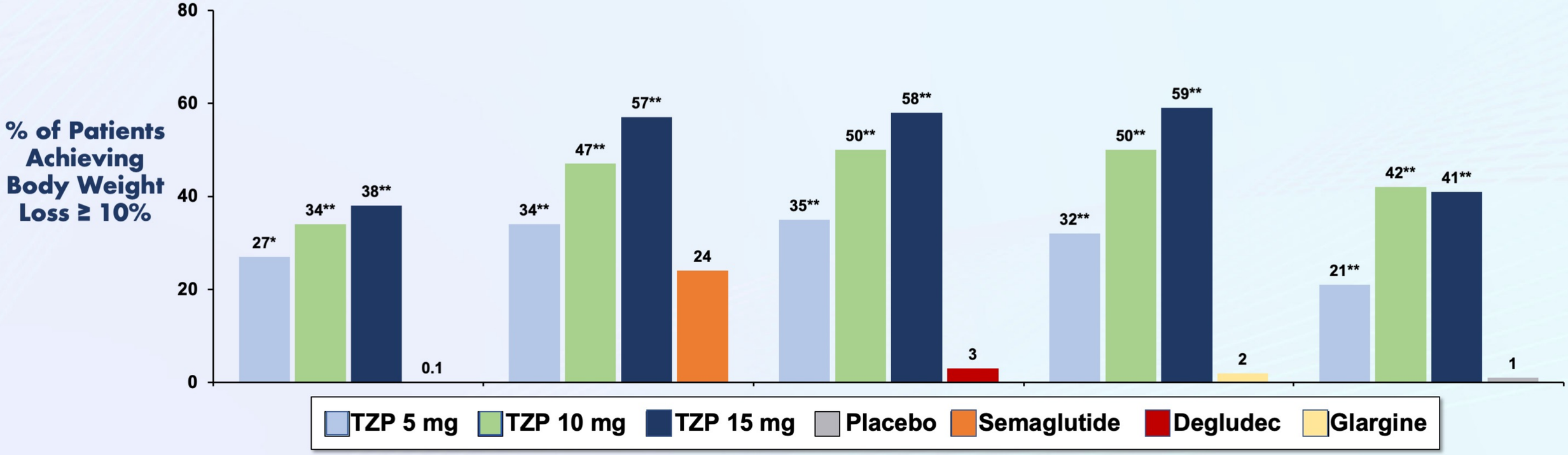
Insulin glargine	978	880	891	600	97
TZP 5 mg	326	283	285	196	38
TZP 10 mg	321	289	288	193	32
TZP 15 mg	334	291	291	194	35

Efficacy estimand

Del Prato S, et al. ***Lancet***. 2021;398:1811-1824.

More participants achieved 10% weight loss with all disease of tirzepatide vs comparators

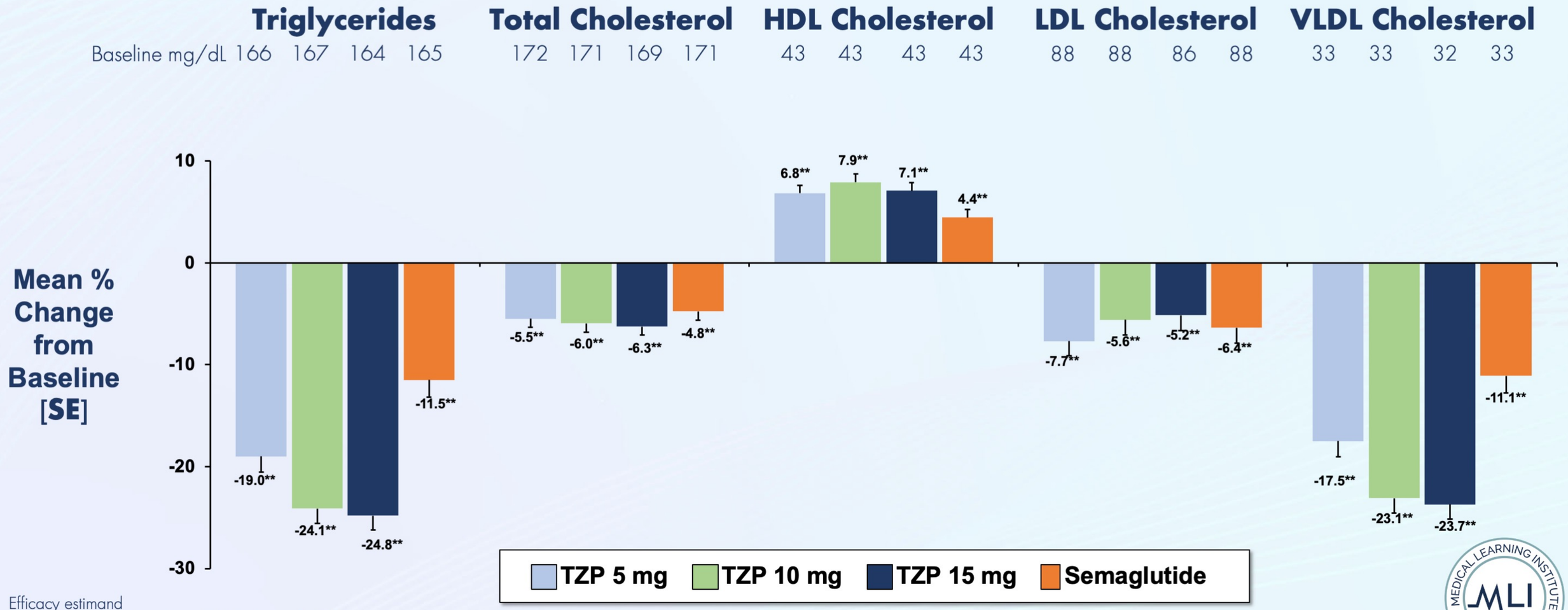
	SURPASS-1[1] (N=478)	SURPASS-2[2] (N=1,878)	SURPASS-3[3] (N=1,437)	SURPASS-4[4] (N=1,995)	SURPASS-5[5] (N=475)
Treatment Duration Add-on to	40 weeks Monotherapy	40 weeks MET	52 weeks MET ± SGLT-2i	52 weeks 1-3 OAMs (MET/SU/SGLT-2i)	40 weeks Basal insulin ± MET



1. Rosenstock J, et al. ***Lancet***. 2021;398:143-155. 2. Frías JP, et al. ***N Engl J Med***. 2021;385:503-515.
3. Ludvik B, et al. ***Lancet.*** 2021;398:583-598. 4. Del Prato S, et al. ***Lancet.*** 2021;398:1811-1824.
5. Dahl D, et al. ***JAMA***. 2022;327:534-545.

Treatment-regimen estimand
Superiority vs placebo or active comparator: *p < 0.05; **p < 0.001

All doses of tirzepatide generally improved lipid profiles better than semaglutide at 40 weeks (SURPASS-2)



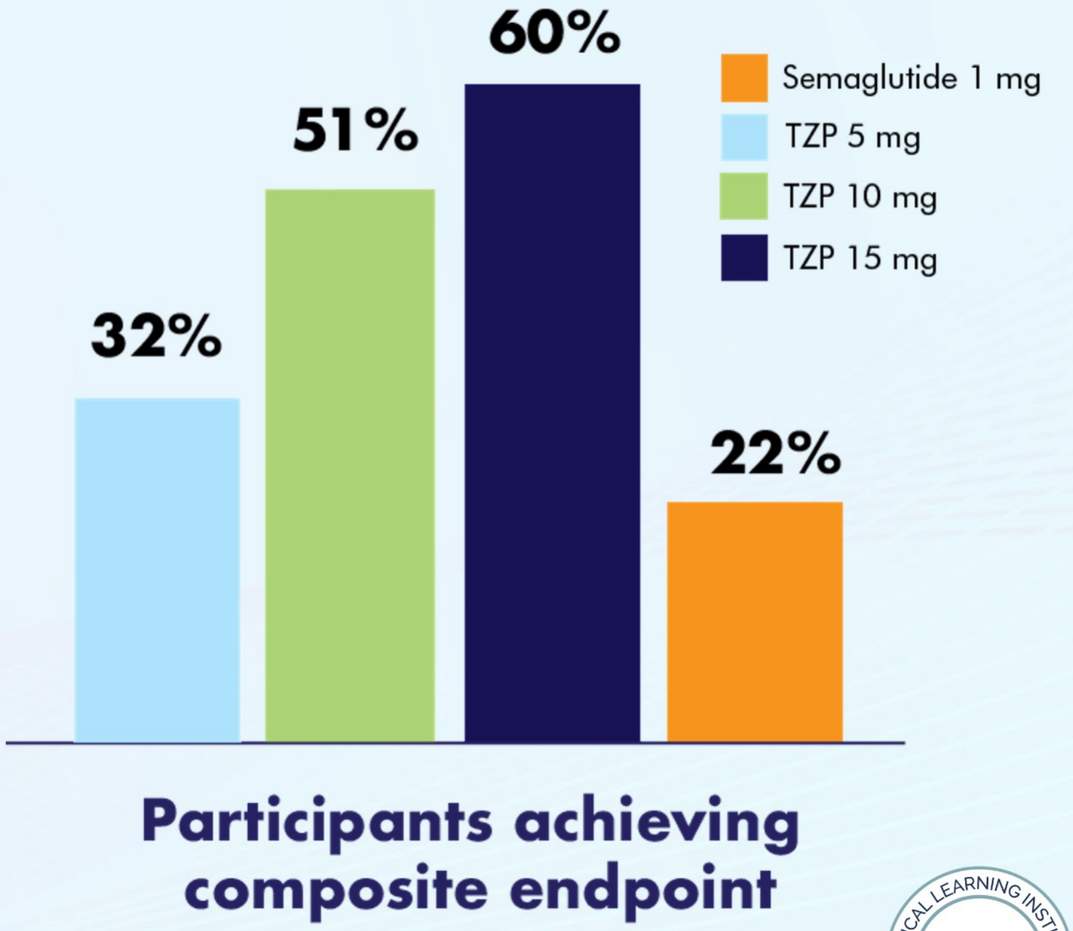
Efficacy estimand
Change from Baseline: *p < 0.05; **p < 0.001

Frias JP, et al. ***N Engl J Med***. 2021; 385:503-515.

Up to 60% of participants on tirzepatide achieved composite endpoint compared to 22% on once-weekly semaglutide 1 mg (SURPASS-2)

Prespecified composite endpoint

- A1c ≤6.5%, and
- Weight loss ≥10%, and
- No Level 2 (<54 mg/dL [3.0 mmol]) or Level 3 (severe) hypoglycemia



Frías JP, et al. ***N Engl J Med***. 2021;385:503-515

Mr. Murray

Mr. Murray	• 52-year-old black man • Oil rig technician for over 25 years • Diagnosed with T2D 10 years ago • Has struggled to achieve glycemic control and has had progressive increase in body weight over the past 15 years • Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself
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Back to Mr. Murray

- You discuss all options with the patient. You agree to target 15% weight loss and better glycemic control.
- He attends a group discussion of bariatric surgery but says, "I want to try something less aggressive, first."
- He also agrees to follow your lead on changing his medications and adding medications to promote weight loss.

CLINICAL IMPLICATIONS OF DUAL AGONIST DATA: SAFETY, TOLERABILITY, AND CV EFFECTS

Dr. Juan Pablo Frias

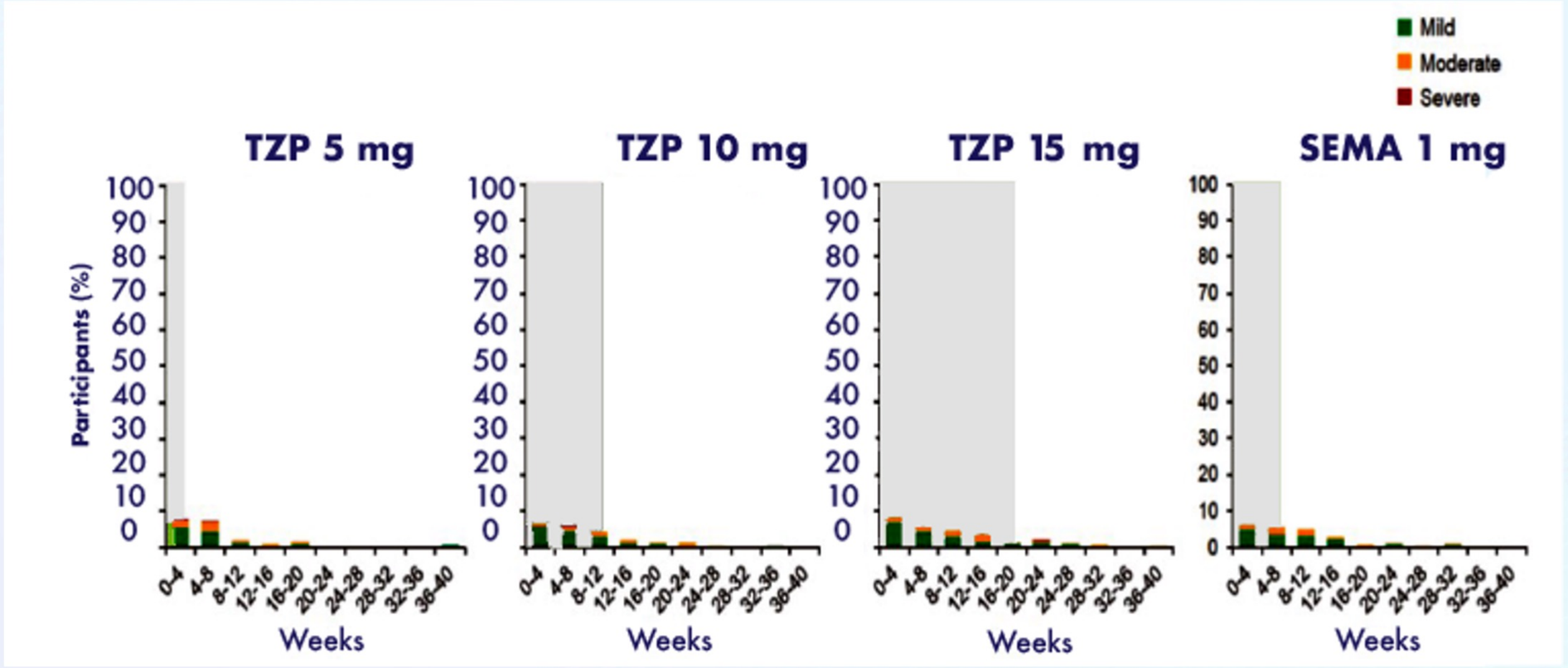
Tirzepatide safety and tolerability

- Side effect profile similar to that of selective GLP-1 receptor agonists
- Most common adverse events were gastrointestinal in nature and occurred primarily during dose escalation period

Preferred Term, %	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=470)	Sema 1 mg (N=469)
Any GI TEAE	40.0	46.1	44.9	41.2
Nausea	17.4	19.2	22.1	17.9
Diarrhea	13.2	16.4	13.8	11.5
Vomiting	5.7	8.5	9.8	8.3
Dyspepsia	7.2	6.2	9.1	6.6
Constipation	6.8	4.5	4.5	5.8
Abdominal pain	3.0	4.5	5.1	5.1

Frías JP, et al. ***N Engl J Med***. 2021;385:503-515.

Incidence of nausea over time through 40 weeks (SURPASS-2)



Most cases of nausea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

Frías JP, et al. ***N Engl J Med***. 2021;385:503-515.

Low incidence of hypoglycemia in SURPASS trials

SURPASS-1 (40 weeks) *Monotherapy*		TZP 5 mg (N=121)	TZP 10 mg (N=119)	TZP 15 mg (N=120)	Placebo (N=115)
	Hypoglycemia*	0	0	0	0.9
	Severe hypoglycemia	0	0	0	0
SURPASS-2 (40 weeks) *Metformin*		TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=470)	Semaglutide (N=469)
	Hypoglycemia*	0.9	0.2	1.7	0.4
	Severe hypoglycemia	0.21	0	0.21	0
SURPASS-3 (52 weeks) *Metformin ± SGLT-2i*		TZP 5 mg (N=356)	TZP 10 mg (N=360)	TZP 15 mg (N=359)	Degludec (N=358)
	Hypoglycemia*	1.4	1.1	2.2	7.3
	Severe hypoglycemia	0	0	0.28	0
SURPASS-4 (52 weeks) *± Metformin ± SU ± SGLT-2i*		TZP 5 mg (N=329)	TZP 10 mg (N=328)	TZP 15 mg (N=338)	Glargine (N=1,000)
	Hypoglycemia*	8.8	6.1	8.0	19.1
	Severe hypoglycemia	0.30	0	0.89	1.10
SURPASS-5 (40 weeks) *Basal insulin ± Metformin*		TZP 5 mg (N=116)	TZP 10 mg (N=119)	TZP 15 mg (N=120)	Placebo (N=120)
	Hypoglycemia*	15.5	19.3	14.2	12.5
	Severe hypoglycemia	0	1.68	0.83	0

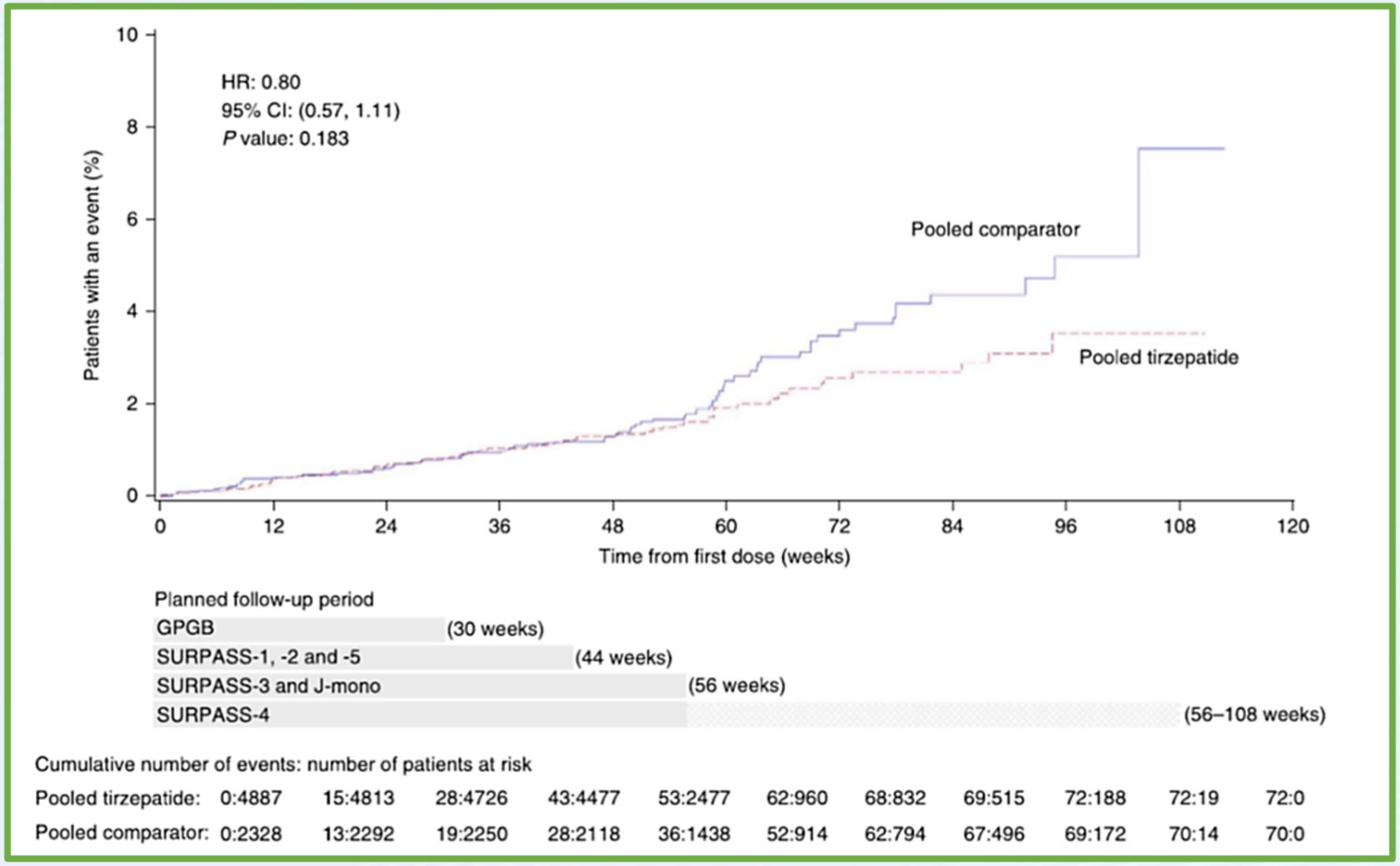
1. Rosenstock J, et al. Lancet. 2021;398:143-155. 2. Frías JP, et al. N Engl J Med. 2021;385:503-515. 3. Ludvik B, et al. Lancet. 2021;398:583-598. 4. Del Prato S, et al. Lancet. 2021;398:1811-1824. 5. Dahl D, et al. JAMA. 2022;327:534-545.

Other adverse events of special interest

Parameters	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Pancreatitis[3]	0	2 (TZP 10 mg) 2 (TZP 15 mg) 3 (SEMA 1 mg)	0	3 (TZP 5mg) 2 (TZP 10 mg) 1 (TZP 15 mg) 1 (Insulin Glargine)	0
Cholelithiasis	1 (TZP 5 mg)	4 (TZP 5 mg) 4 (TZP 10 mg) 4 (TZP 15mg) 2 (SEMA 1 mg)	2 (TZP 5mg) 1 (TZP 10 mg) 1 (TZP 15 mg)	3 (TZP 5mg) 1 (TZP 10 mg) 1 (TZP 15 mg) 4 (Insulin Glargine)	1 (TZP 5 mg)
Medullary Thyroid Carcinoma	0	0	0	0	N/A*
Diabetic Retinopathy	0	2 (TZP 10 mg)	2 (TZP 5 mg) 1 (TZP 15 mg)	2 (TZP 5mg) 1 (TZP 10 mg) 1 (TZP 15 mg) 1 (Insulin Glargine)	N/A*

1. Rosenstock J, et al. Lancet. 2021;398:143-155. 2. Frías JP, et al. N Engl J Med. 2021;385:503-515. 3. Ludvik B, et al. Lancet. 2021;398:583-598.
4. Del Prato S, et al. Lancet. 2021;398:1811-1824. 5. Dahl D, et al. JAMA. 2022;327:534-545.

Pooled tirzepatide vs pooled comparator effect on time to first MACE-4[1]



SURPASS-CVOT is estimated to complete in 2024[2]

MACE-4, CV death, MI, stroke, and hospitalized unstable angina. ***P*** values were based on the Wald chi-square test.

1. Sattar N, et al. ***Nat Med***. 2022;28:591–598. 2. https://clinicaltrials.gov/ct2/show/record/NCT04255433.

Mr. Murray

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Reflection: What do you consider the most important goal(s) and action(s) for the management of Mr. Murray?

1. Better glycemic and lipid control. We need to add a thiazolidinedione and intensify lipid-lowering therapy.
2. Better glycemic, lipid, and weight control. We need to stop the glimepiride and add tirzepatide. Intensify lipid-lowering therapy and consider adding a SGLT2i.
3. Better glycemic, lipid, and weight control. We need to intensify lipid-lowering therapy and refer for bariatric surgery.
4. Better glycemic, lipid, and weight control. We need to stop the glimepiride and add a GLP-1 RA with a good CV risk and weight loss profile and consider adding an SGLT2i.

Tirzepatide: key prescribing information and instructions for use

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D

- Single-dose prefilled pen
- 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL

- The recommended starting dosage is 2.5 mg SC once weekly
- After 4 weeks, increase to 5 mg SC once weekly
- If additional glycemic control is needed, increase the dosage in 2.5-mg increments after at least 4 weeks on the current dose
- The maximum dosage is 15 mg SC once weekly
- Administer once weekly at any time of day, with or without meals
- Inject SC in the abdomen, thigh, or upper arm; rotate injection sites with each dose

Tirzepatide prescribing information. https://pi.lilly.com/us/mounjaro-uspi.pdf?s=pi
Instructions for use. https://pi.lilly.com/us/mounjaro-us-ifu.pdf?s=ug0

Tirzepatide: key prescribing information and instructions for use

Contraindications

- Personal or family history of MTC or patients with MEN2
- Known serious hypersensitivity to tirzepatide or any of the excipients

Limitations of Use

- Has not been studied in patients with a history of pancreatitis
- Is not indicated for use in patients with type 1 diabetes

Warnings and Precautions

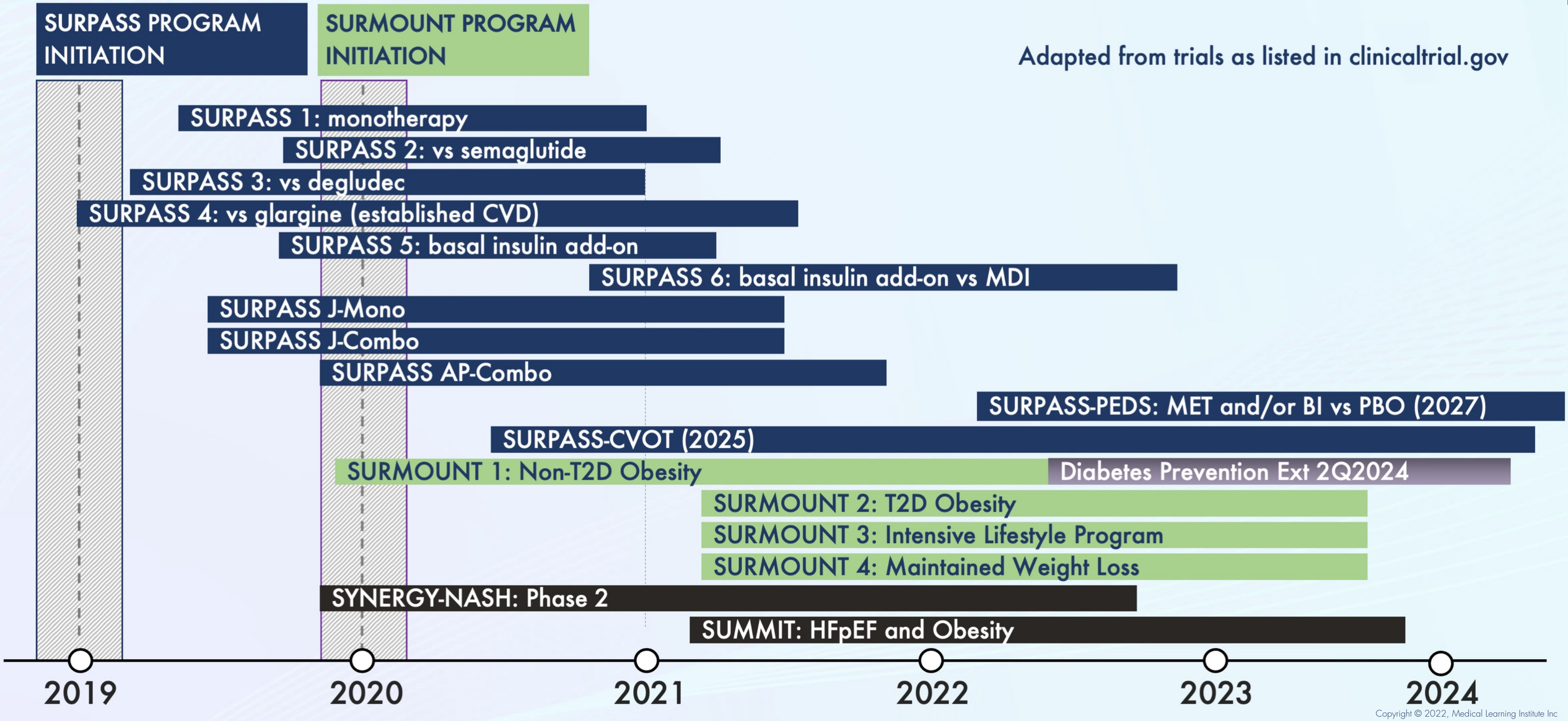
- Pancreatitis
- Hypoglycemia with concomitant use of insulin secretagogues or insulin
- Hypersensitivity reactions
- Acute kidney injury
- Severe gastrointestinal disease
- Diabetic retinopathy complications in patient with a history of diabetic retinopathy
- Acute gallbladder disease

Tirzepatide prescribing information. https://pi.lilly.com/us/mounjaro-uspi.pdf?s=pi
Instructions for use. https://pi.lilly.com/us/mounjaro-us-ifu.pdf?s=ug0

PREVIEWS OF COMING ATTRACTIONS: DUAL AND TRIPLE AGONISTS IN DEVELOPMENT

Dr. Juan Pablo Frias

Tirzepatide development program includes weight loss, NASH, and HF trials



Peptide-based multi-agonists: a new paradigm in metabolic pharmacology

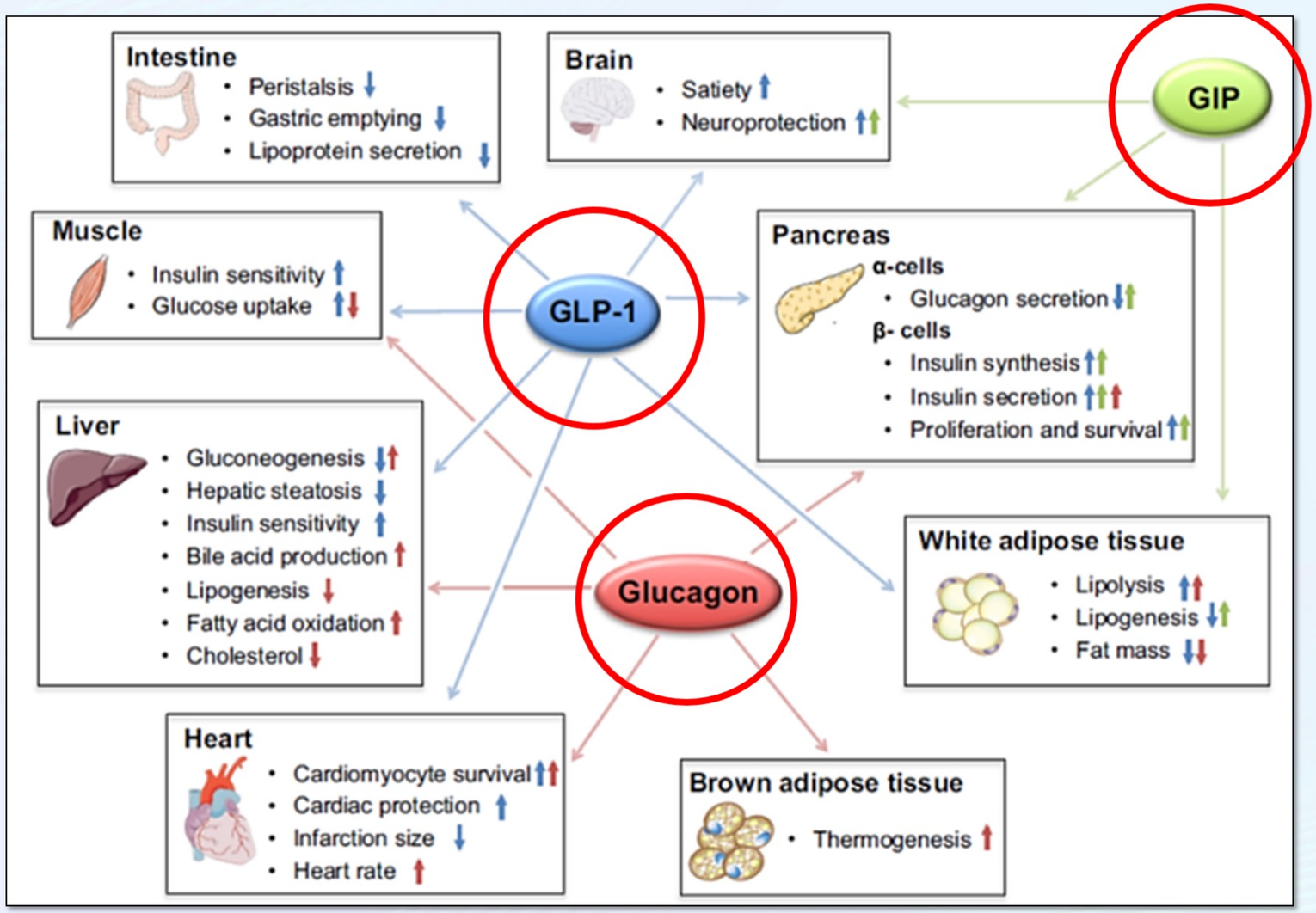


Figure from Brandt SJ, et al. ***J Intern Med***. 2018;284:581-602.

- Cotadutide (MEDI0382)[1]
- Pemvidutide (ALT-801)[2]

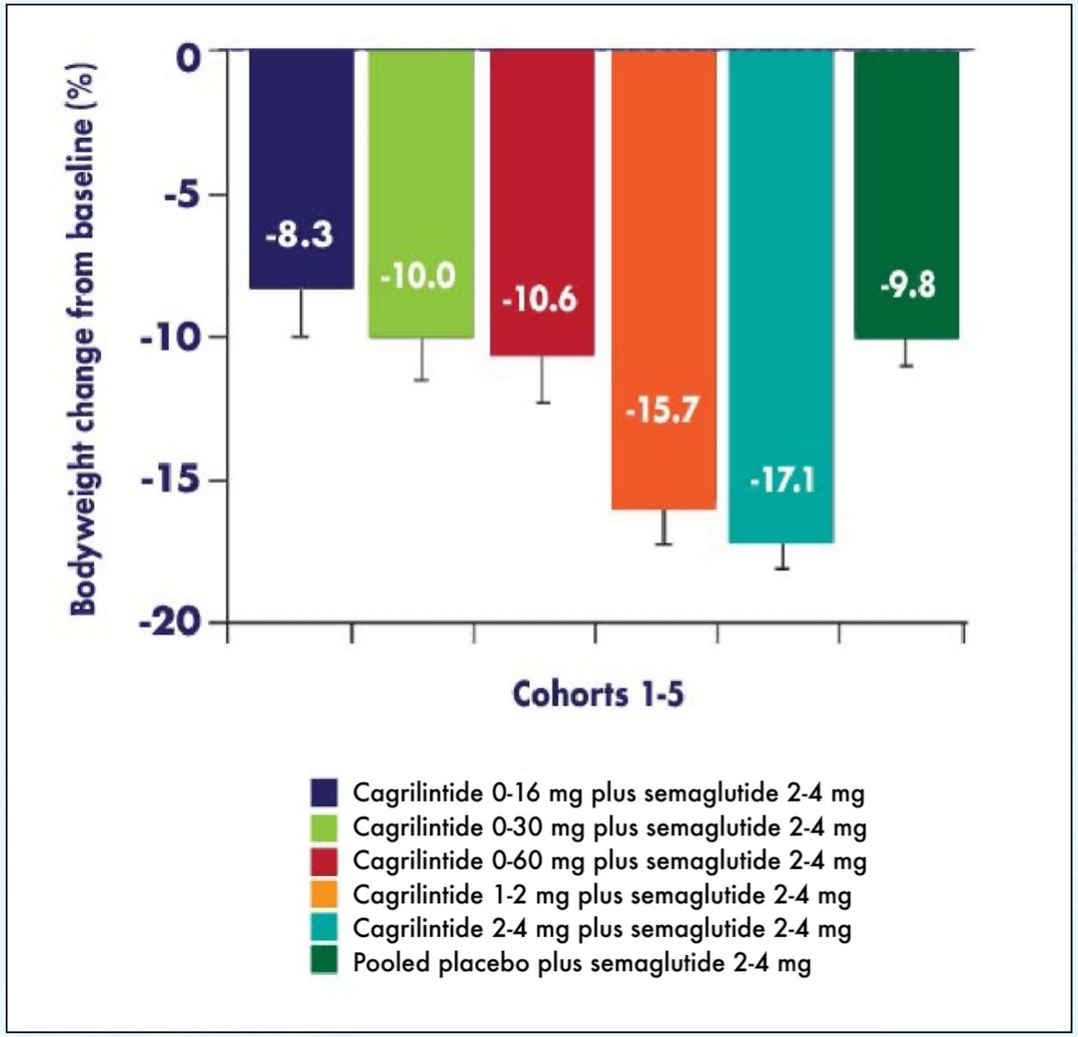
- Tirzepatide
- CT-868[3] and CT-388[4]
- OW semaglutide + OW NNC0480-0389[5]

- HM15211[6]
- LY3437943[7]

1. Robertson D, et al. ***Diabetes.*** 2020;69(Supplement_1):951-P.
2. https://adisinsight.springer.com/drugs/800037378
3. https://clinicaltrials.gov/ct2/show/NCT05110846
4. https://clinicaltrials.gov/ct2/show/NCT04838405
5. https://trialbulletin.com/lib/trials/term=Co-formulation+NNC0480+0389+Semaglutide+A+10+1+mg+ml
6. https://clinicaltrials.gov/ct2/show/NCT04505436
7. https://clinicaltrials.gov/ct2/show/NCT04881760

Long-acting amylin analog + long-acting GLP-1 RA for the management of obesity and T2D

- Phase 1b, randomized, placebo-controlled, multiple-ascending dose study
- Otherwise healthy volunteers with overweight or obesity (BMI 27.0 – 39.9 kg/m^2)
- Cagrilintide plus semaglutide vs placebo plus semaglutide
- 20-week treatment period



Used with permission from: Enebo LB, et al. ***Lancet***. 2021;397:1736-1748.

TAKE HOME MESSAGES

Dr. Juan Pablo Frias
Dr. Donna Ryan
Dr. Michael Nauck