PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI

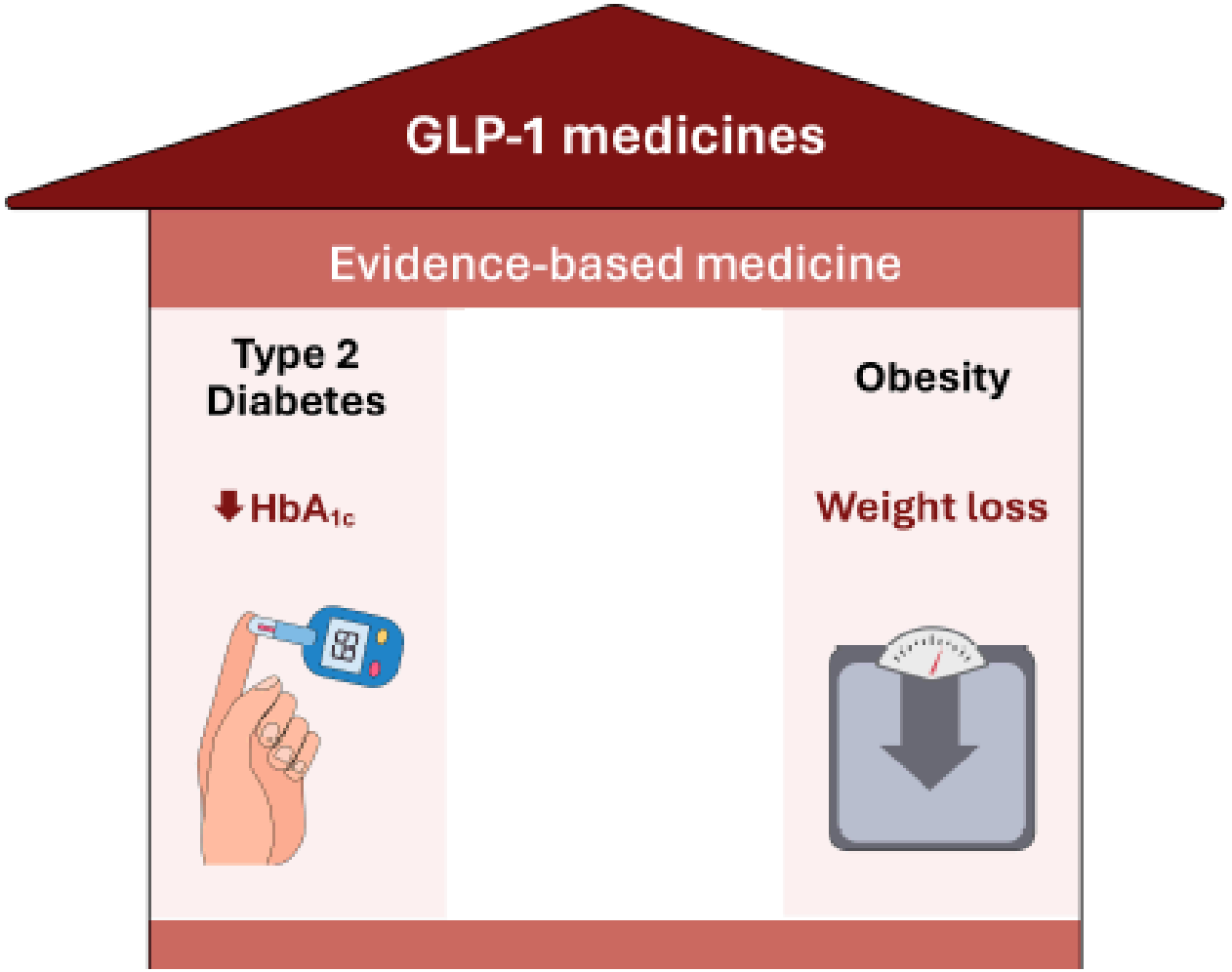
Stefano Del Prato – Interdisciplinary Research Center "Health Science", Sant'Anna School of Advanced Studies, Pisa, Italy

Presenter Disclosures

Research support -	AstraZeneca, Boehringer Ingelheim
Advisory board -	Abbott, Altimmune, Amarin Corporation, Applied Therapeutics, AstraZeneca, Eli Lilly & Co., Eva Pharma, Jiangsu Hengrui Pharmaceutical Co., Menarini International, Merck Sharpe & Dohme, Novo Nordisk, Sanofi, Sun Pharma
Speaking Engagements -	Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Laboratori Guidotti, Menarini International, Merck Sharpe & Dohme, Novartis Pharmaceutical Co., Novo Nordisk, Sanofi
Institutional roles -	Past-President EASD/EFSD President European Diabetes Forum

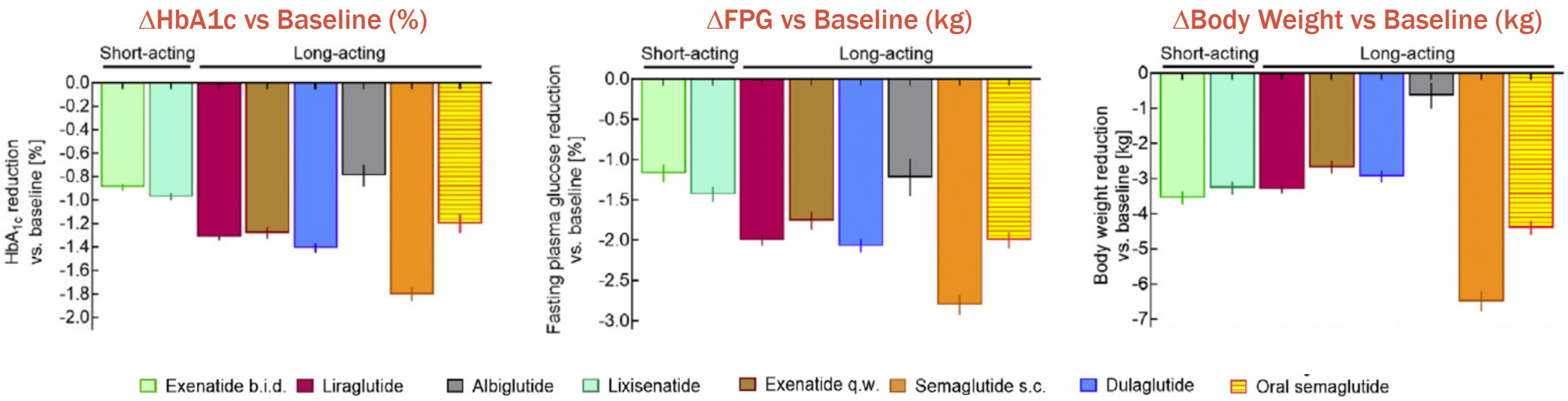
PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



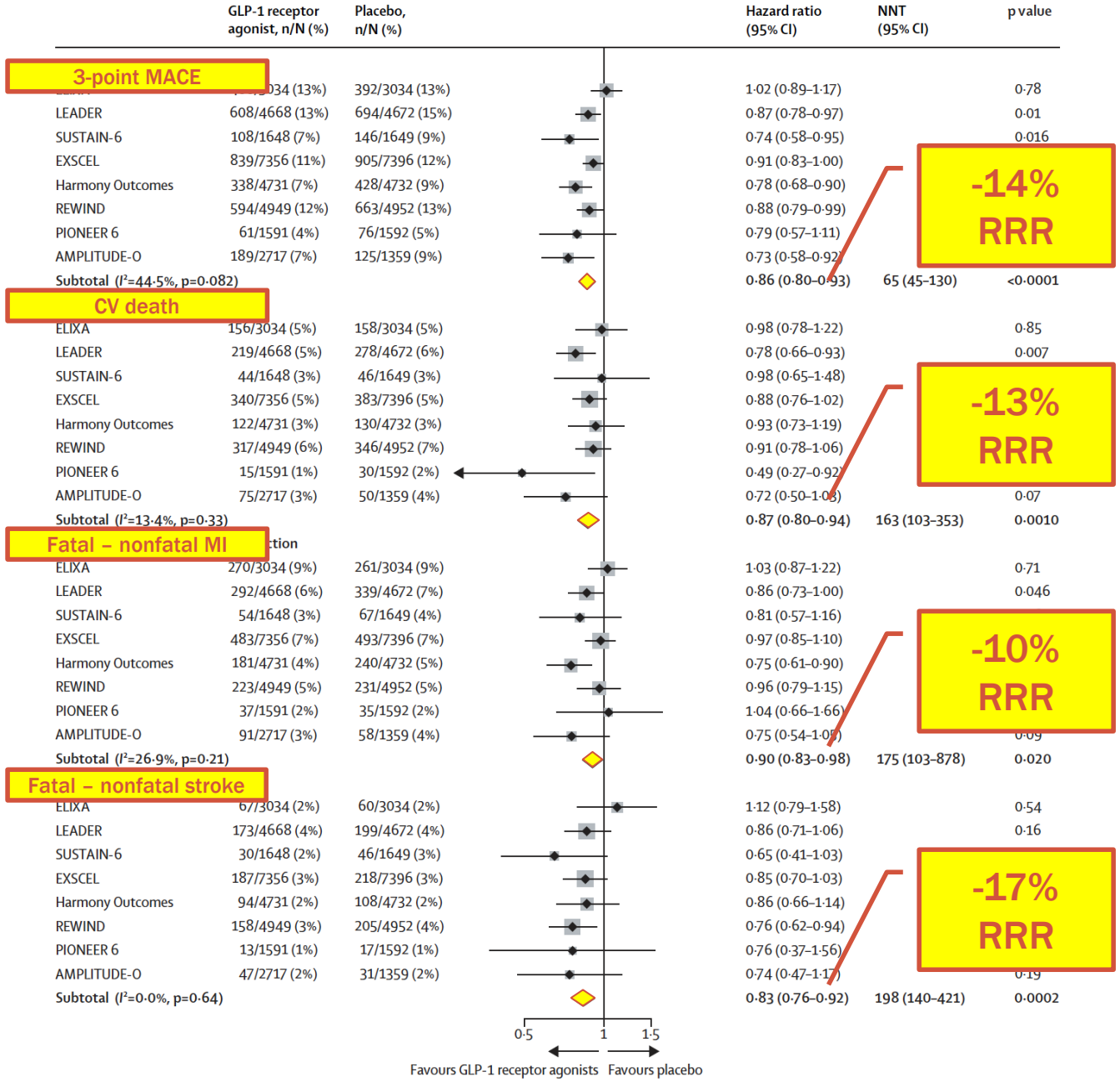
Drucker DJ *Diabetes Care* 2024 https://doi.org/10.2337/dci24-0003

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



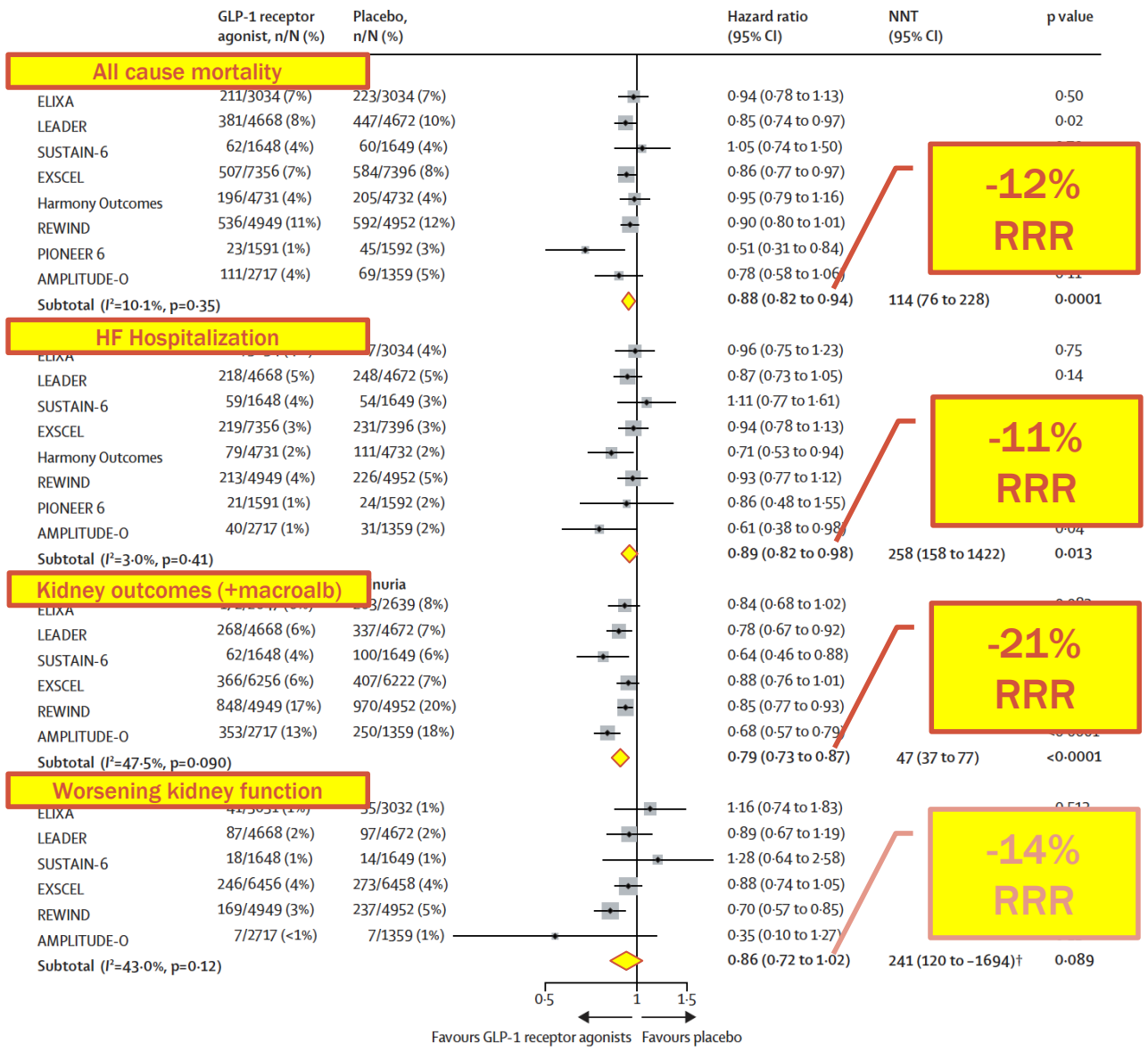
Nauck MA et al *Mol Metab.* 2021;46:101102

Risk of MACE and Each of Its Components with GLP-1 Receptor Agonists in T2DM Patients



Sattar N et al ***Lancet Diabetes Endocrinol*** 2021; 9:653-662

Risk of MACE and Each of Its Components with GLP-1 Receptor Agonists in T2DM Patients



Sattar N et al ***Lancet Diabetes Endocrinol*** 2021; 9:653-662

ADA-EASD 2022 Consensus on Treatment of T2DM

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

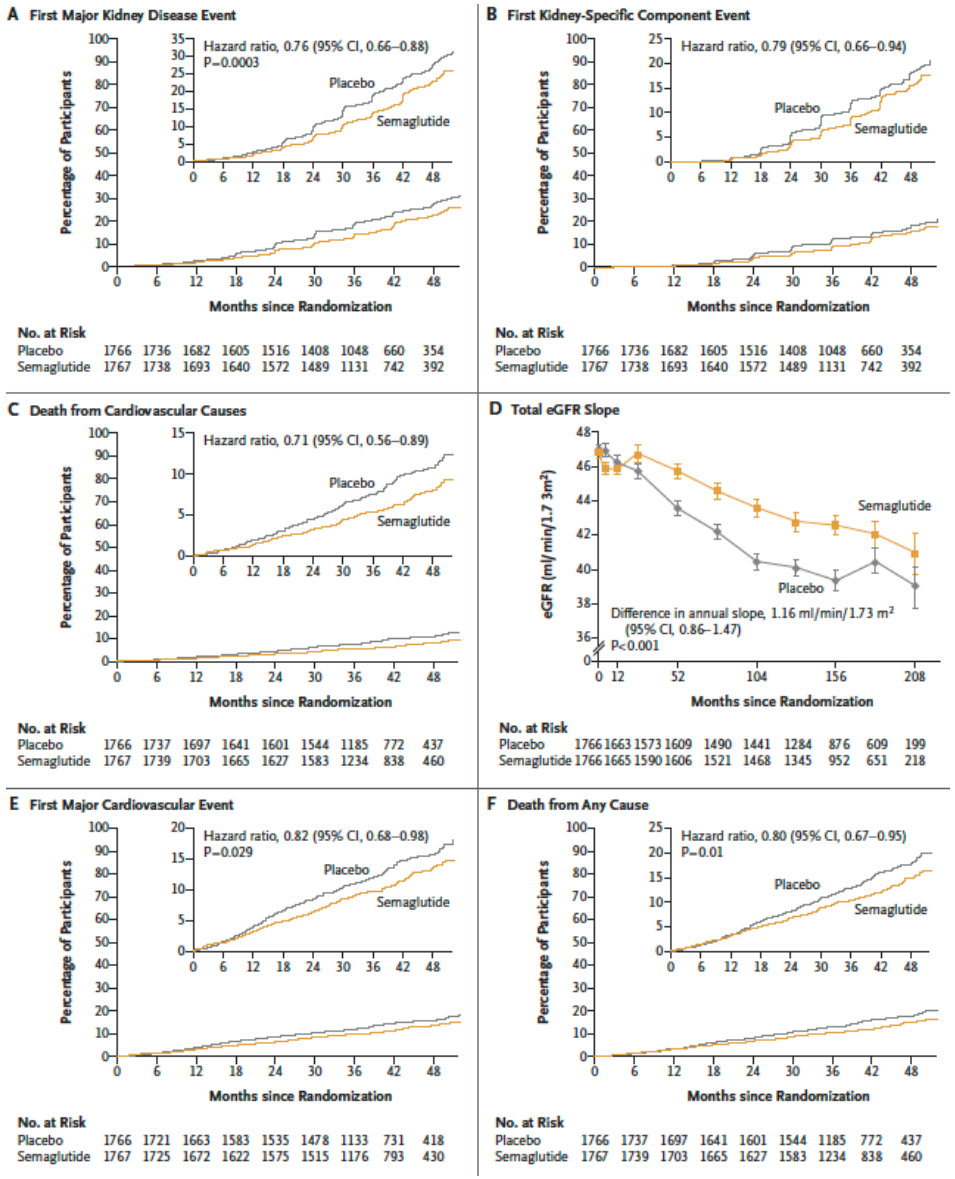
Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB
Diabetes Care 2022; 45:2753-2786 - *Diabetologia* 2022; 65:1925-1966

Dulaglutide and Kidney Function–Related Outcomes in Type 2 Diabetes: A REWIND Post Hoc Analysis

Compared with placebo, DU was associated with a **25% reduced hazard** of the composite kidney function–related outcome (HR 0.75 [95% CI: 0.62, 0.92])

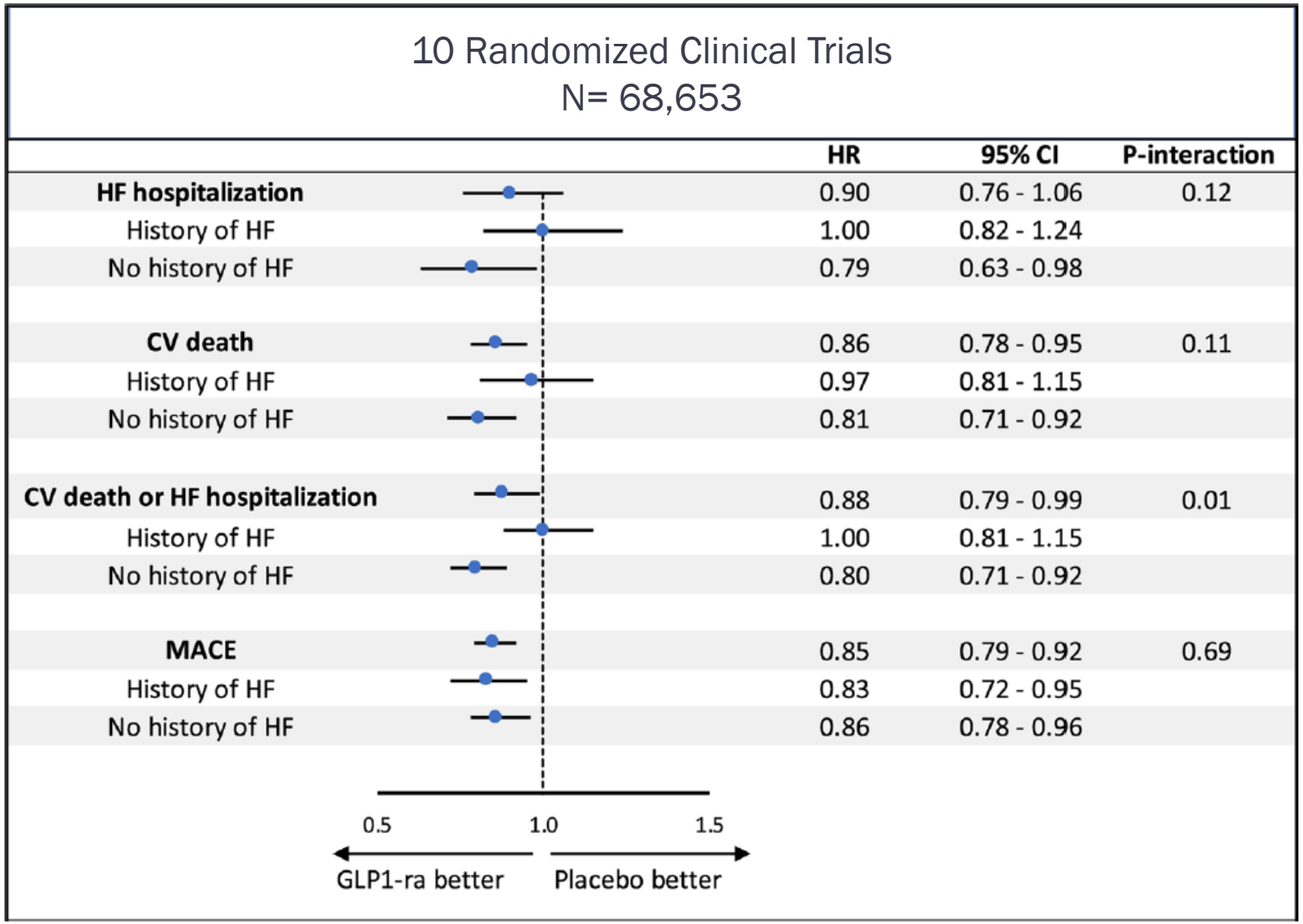
Botros FT et al *Diabetes Care* 2023;46:1524–1530

Effects of Semaglutide on Chronic Kidney Disease in T2DM Patients



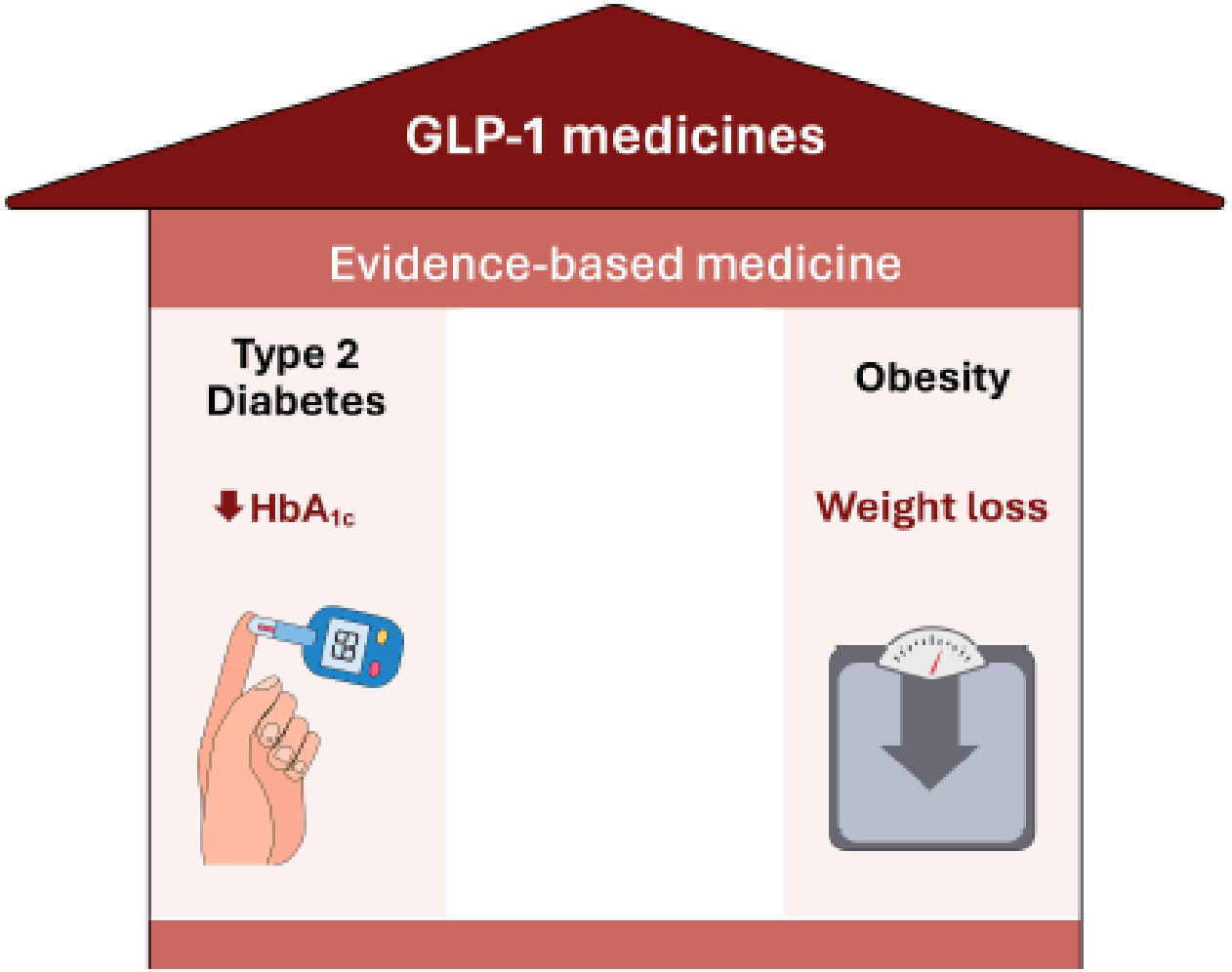
Perkovic V et al *N Engl J Med.* 2024 May 24. Online ahead of print

GLP1-RAs and CV Outcomes in Patients With and Without HF



Villaschi A et al *Clin Res Cardiol* 2024;113:898–909

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



Drucker DJ *Diabetes Care* 2024 https://doi.org/10.2337/dci24-0003

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI

Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI

New, Oral, Small-molecule, GLP-1 Receptor Agonists

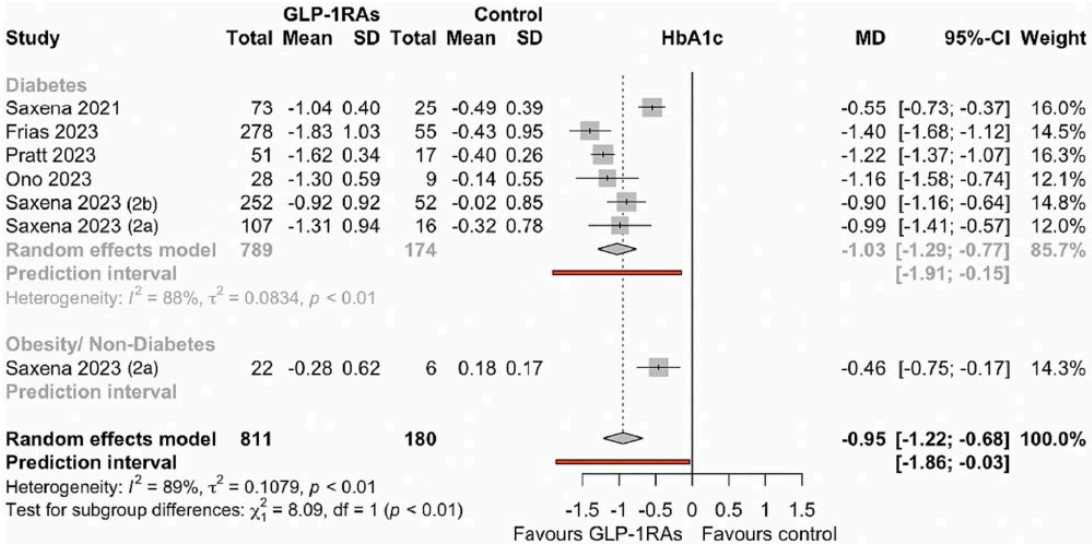
Orforglipron
Danuglipron

Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

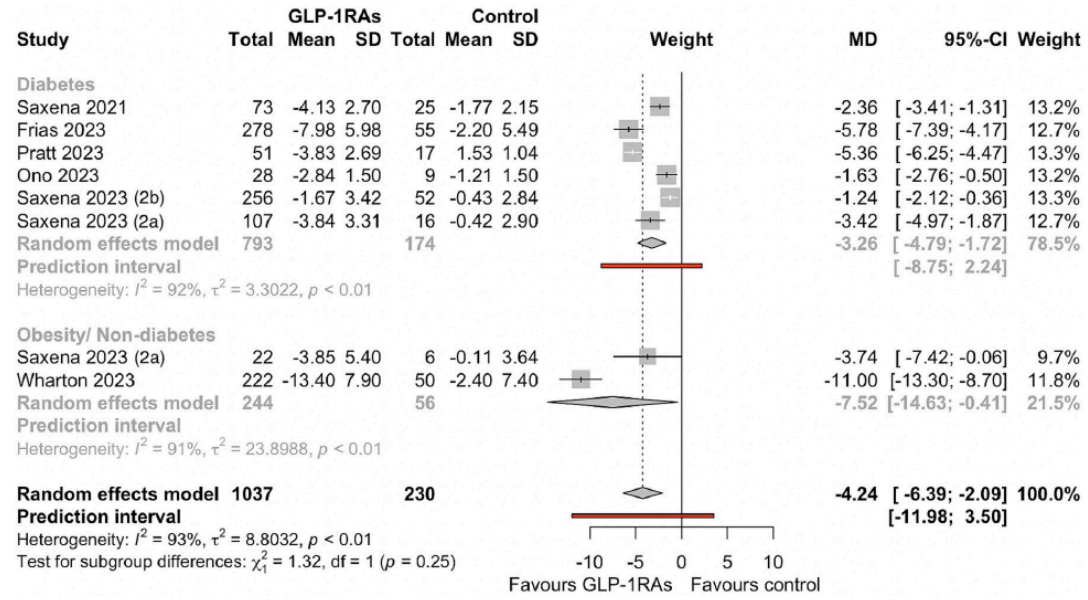
Efficacy of New, Oral, Small-molecule, GLP-1 RAs, Orforglipron and Danuglipron for T2DM and Obesity Treatment

Karakasis P et al *Metabolism* 2023;149:155710

Glycated Hemoglobin



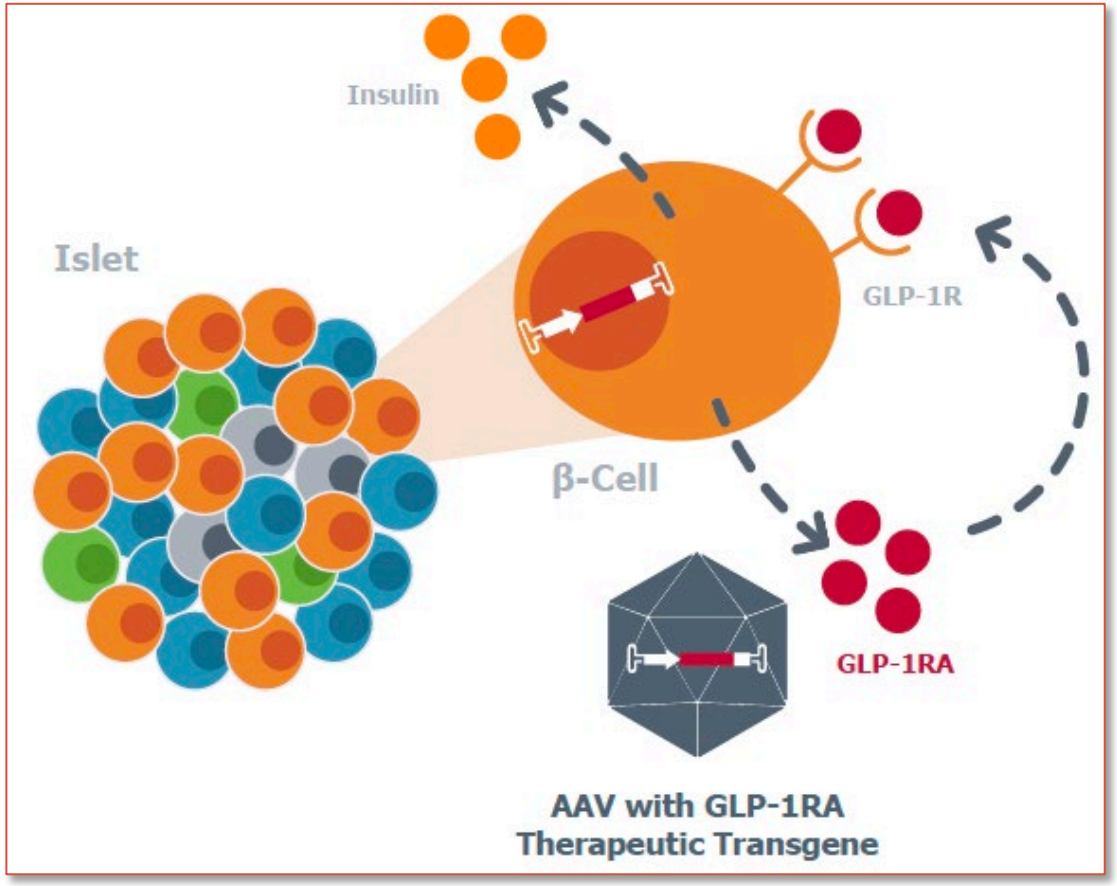
Body Weight



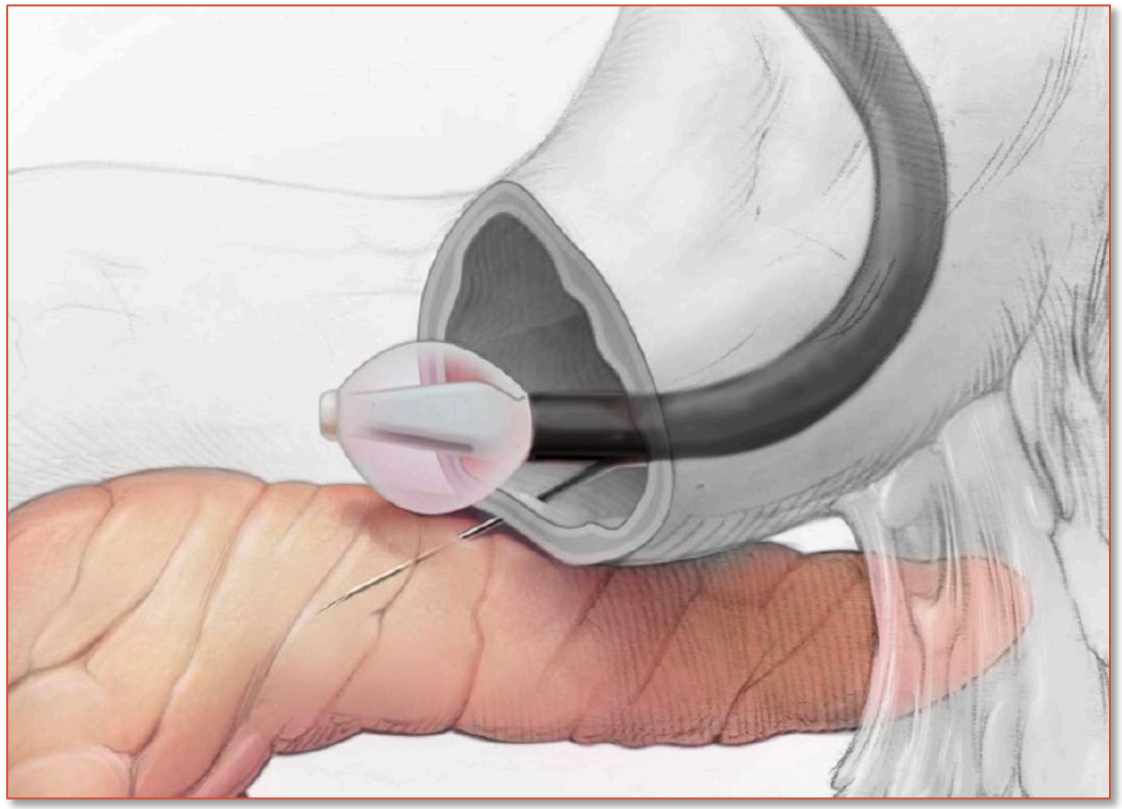
Pancreatic Gene Therapy (PGTx) to Modify Islet Function

Potential for durable improvement in metabolic health

GLP-1RA PGTx, driven by the insulin promoter, may offer differentiated benefit via durable local production of GLP-1RA



Pancreas is readily accessible via endoscopic ultrasound, and local delivery enables PGTx feasibility and safety

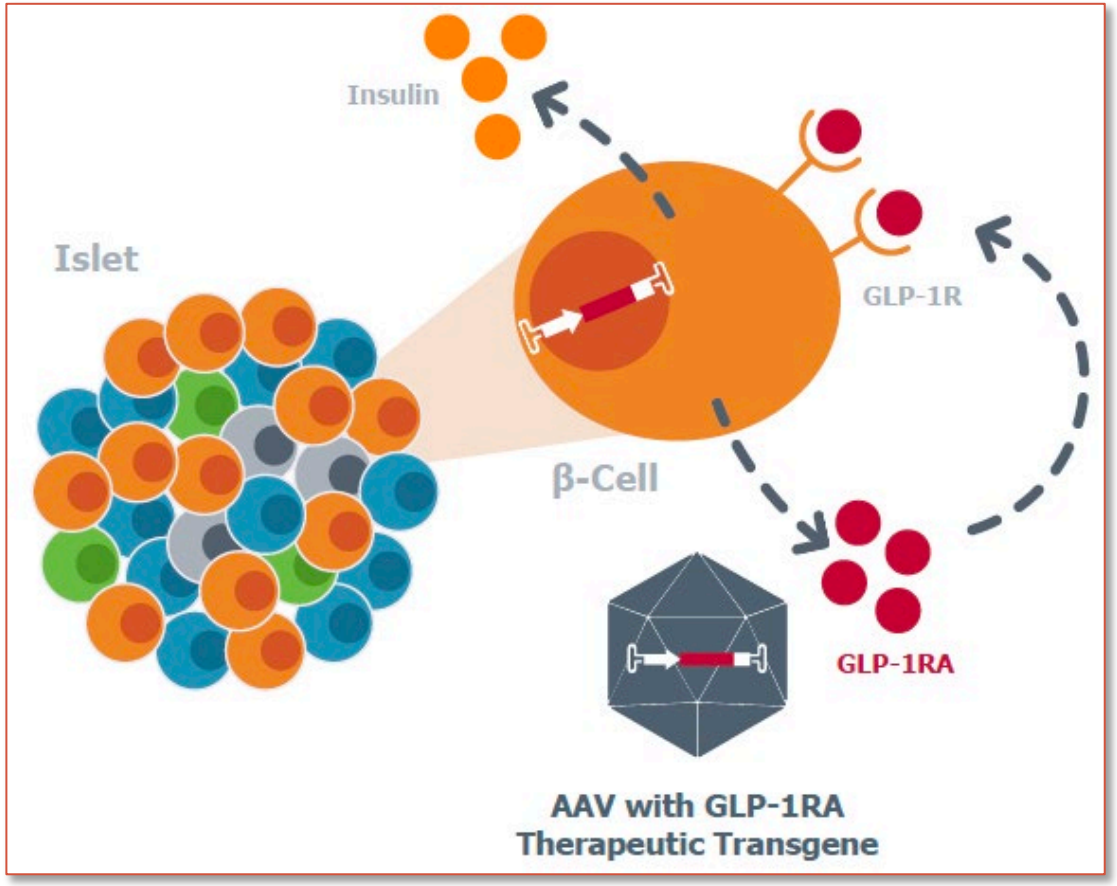


Rajagopalan H et al Disease Digestive Week 2024. Washington DC 19-21 May 2024

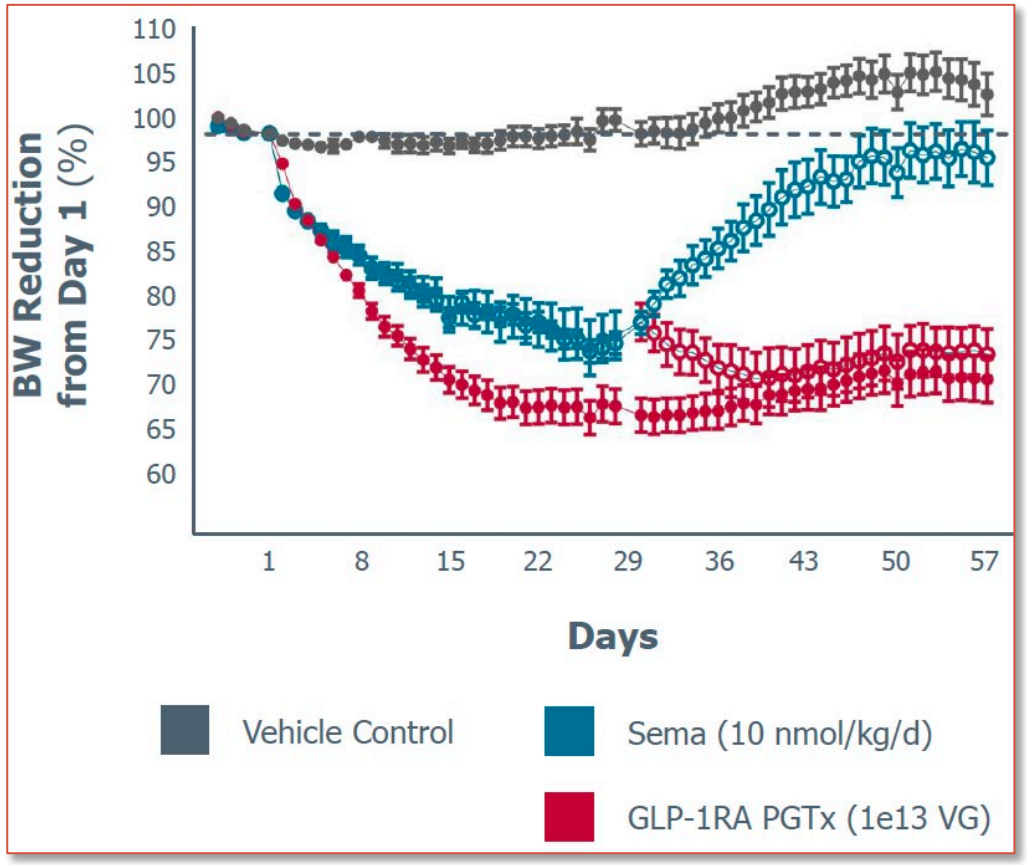
Pancreatic Gene Therapy (PGTx) to Modify Islet Function

Potential for durable improvement in metabolic health

GLP-1RA PGTx, driven by the insulin promoter, may offer differentiated benefit via durable local production of GLP-1RA



Change in BW Over Time in DIO murine model



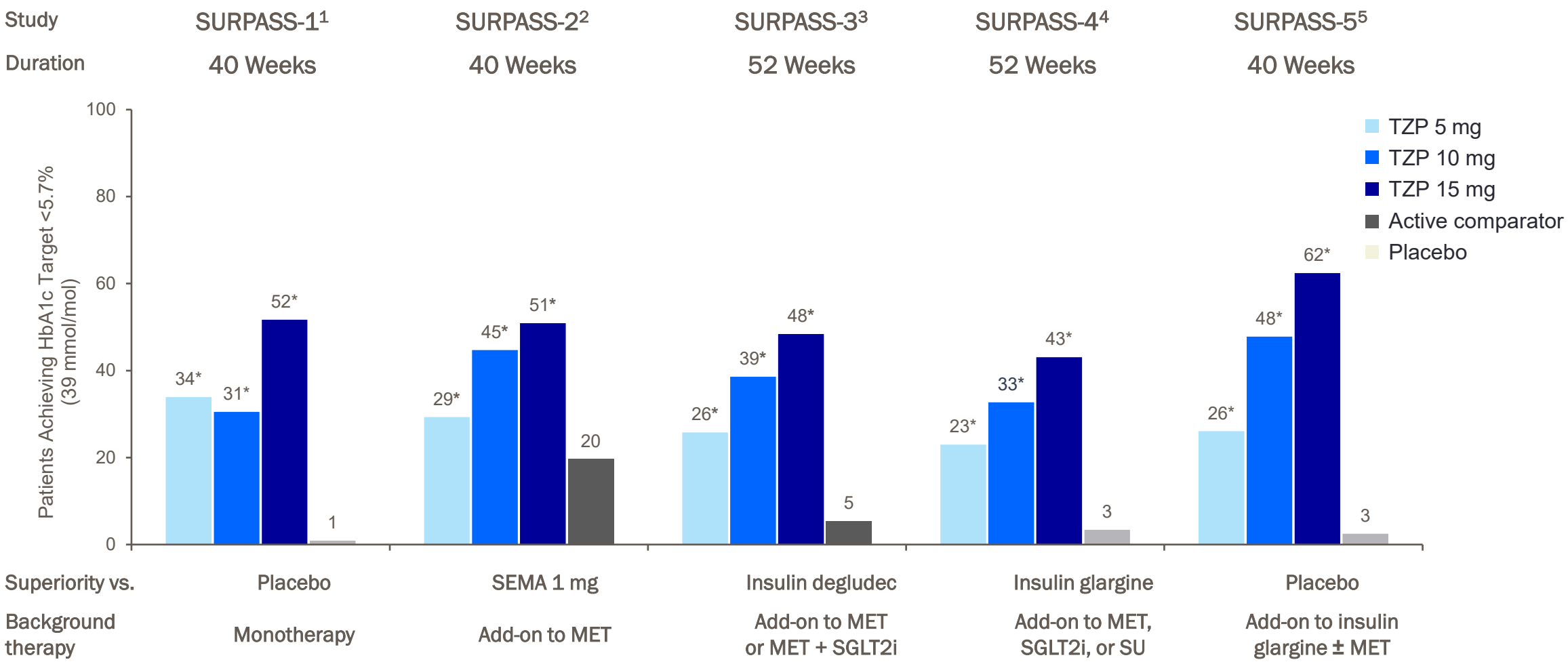
Rajagopalan H et al Disease Digestive Week 2024. Washington DC 19-21 May 2024

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI

Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

Proportion of Patients Achieving HbA1c <5.7%

Efficacy Estimand



*p<0.001 vs. placebo or active comparator.

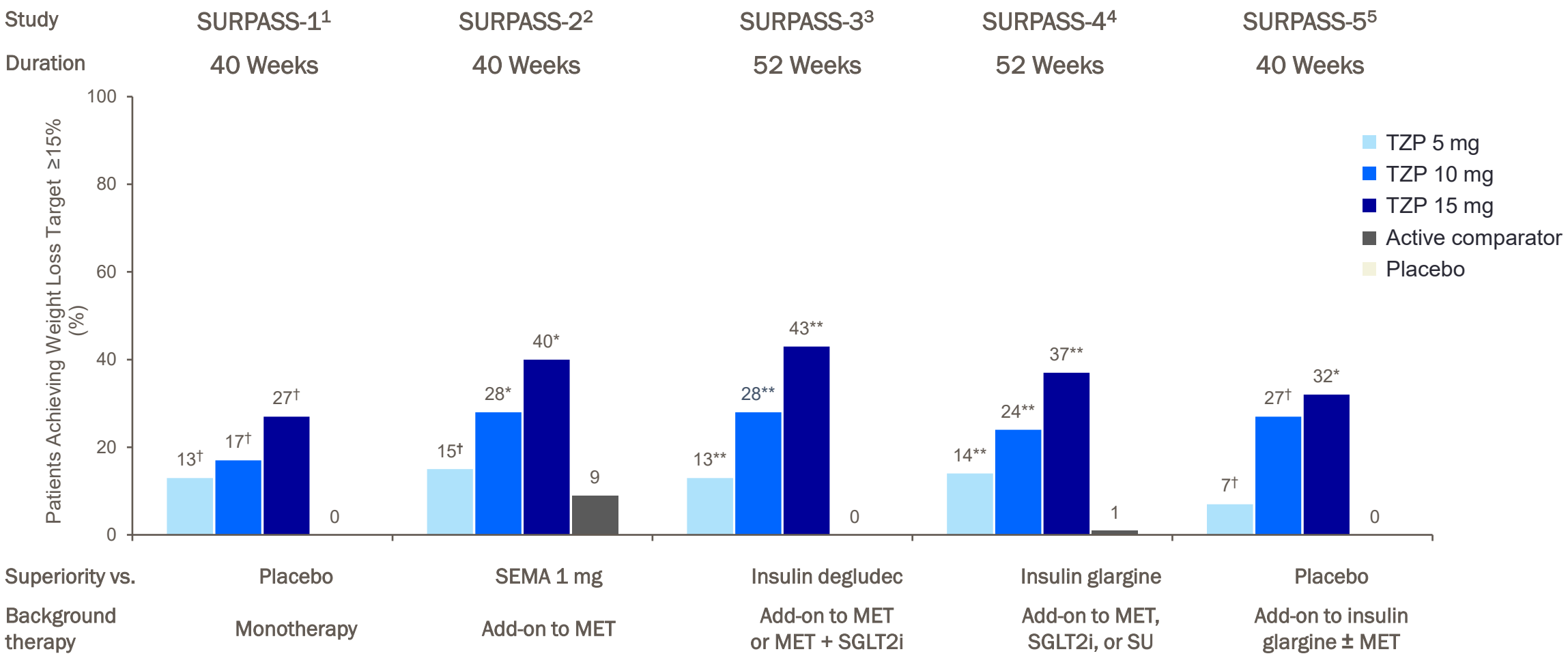
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

HbA1c = glycated hemoglobin; MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545.

Proportion of Patients Achieving Body Weight Loss Target ≥15%

Efficacy Estimand



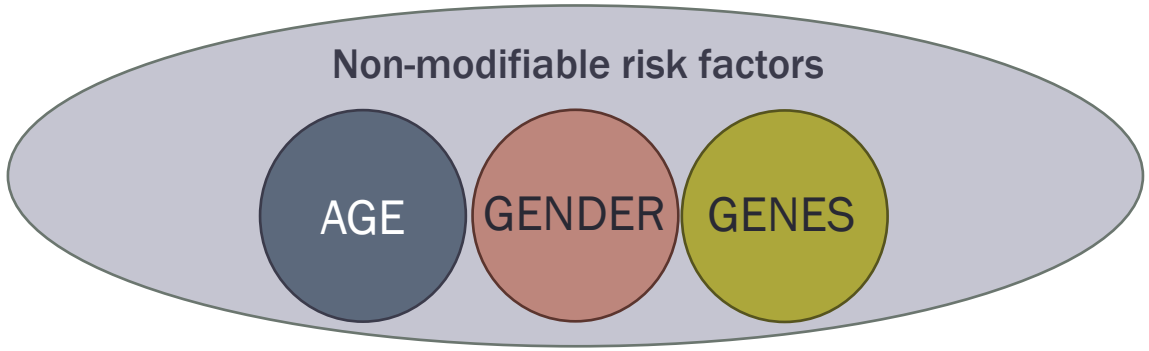
†p<.05, *p<.001, **p<.0001 vs. placebo or active comparator.

Note: mITT population (efficacy analysis set). Proportion of participants achieving weight loss ≤5%, ≤10% and ≤15% was obtained by dividing the number of participants reaching respective goals at Week 40 for SURPASS-1,2, and 5 and Week 52 for SURPASS 3,4 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at study end period was predicted from MMRM analysis.

MET = metformin; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545.

Tirzepatide - A Wide Spectrum Metabolic Effect



Modifiable risk factors

HbA1c <5.7% @TZP 15mg **43-62%**[1-5]	**BW Loss >15%** @TZP 15mg **27-43%**[1-5]	 Sedentary Lifestyle	**LIPIDS** @TZP 5-15mg **Triglycerides -16; -23%**[4] **Non-HDL Chol -10; -12%**[4]	**SBP** @TZP 5-15mg **-5-9 mmHg**[4]	**Inflammatory Biomarkers**[6] @TZP 5-15mg **hsCRP -36%** **YKL-40 -31%** **ICAM-1 –11%** **Leptin – 34%**	 Smoking	**LFC** @TZP 10-15mg **-8.1%**	**>40% eGFR decline 13% RRR**[8] **New-onset macroalbuminuria 59% RRR**[8]

Adapted from Ferrannini G et al. **Diabetes Care** 2020;43:2001–9.

SURPASS - CVOT

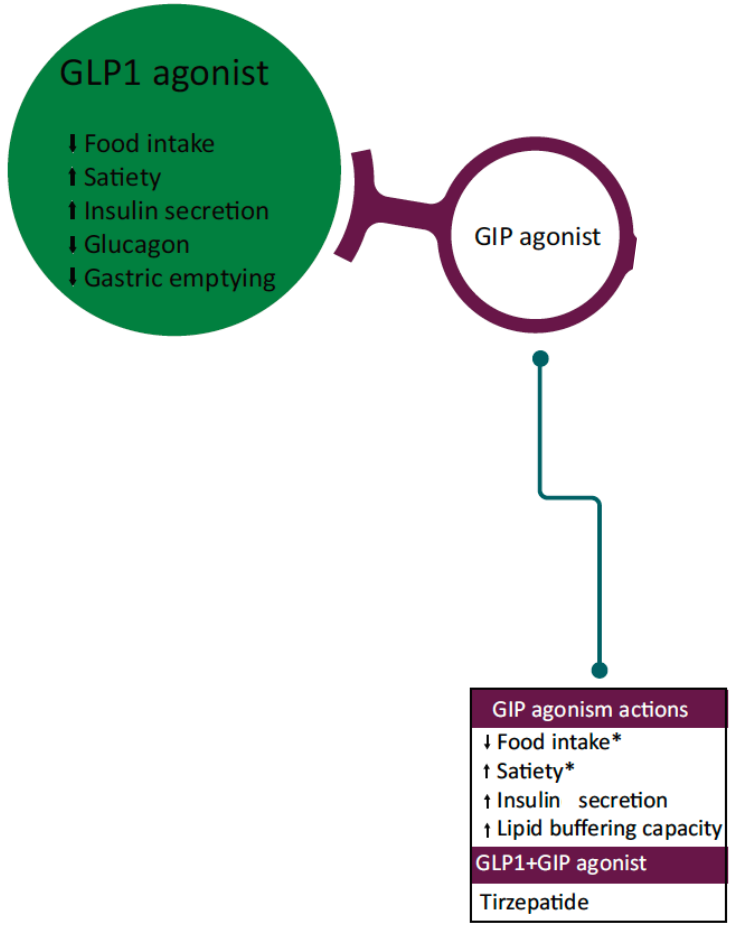
Comparison of tirzepatide and dulag
major adverse cardiovascular events
participants with type 2 diabetes an
atherosclerotic cardiovascular diseas
SURPASS-CVOT design and baseline characteristics

Stephen J. Nicholls, MBBS, PhD[a], Deepak L Bhatt, MD[b], John B Buse, MD[c], St
Steven E Kahn, MBChB[e], A Michael Lincoff, MD[f], Darren K McGuire, MD, MP
Steven E Nissen, MD[f], Naveed Sattar, MD[i], Bernard Zinman, MD[j], Sophia Zou
Amy Bartee, DNP[m], Debra Miller, RN[m], Hiroshi Nishiyama, PhD[m], Imre Pavo
Govinda Weerakkody, PhD[m], Russell J Wiese, PhD[m], and David D'Alessio, MI
investigators *Melbourne, Australia; New York, NY; Chapel Hill, NC; Pisa, Ita*
Dallas, TX; Bochum, Germany; United Kingdom; ON, Canada; Melbourne, Au
Indianapolis, IN; Durham, NC

	SURPASS-CVOT (*N* = 13,299)
Age, years	64.1 ± 8.8
Sex, female	3849 (28.9)
Geography	
North America	1955 (14.7)
South America	3833 (28.8)
Europe	6149 (46.2)
Asia-Pacific	1,362 (10.2)
Weight, kg	92.5 ± 18.8
BMI, kg/m^2	32.6 ± 5.5
History	
Coronary artery disease	8,649 (65.0)
Myocardial infarction	6,288 (47.3)
Coronary revascularization procedure	7,630 (57.4)
Stroke	2,541 (19.1)
Peripheral artery disease	3,369 (25.3)
Hypertension	11,986 (90.1)
Dyslipidemia	1,1406 (85.8)
Current tobacco use	1,978 (14.9)
Diabetes duration, years	14.7 ± 8.8
Systolic blood pressure, mm Hg	135.0 ± 15.7
Diastolic blood pressure, mm Hg	77.7 ± 9.7
HbA1c, %	8.4 ± 0.9
eGFR (CKD-EPI), mL/Min/1.73 m^2	76.5 ± 21.3
<60 mL/Min/1.73 m^2	3,029 (22.8)
UACR, mg/g	22.0 (9.0, 83.0)
Microalbuminuria	4,179 (32.0)
Macroalbuminuria	1,503 (11.5)

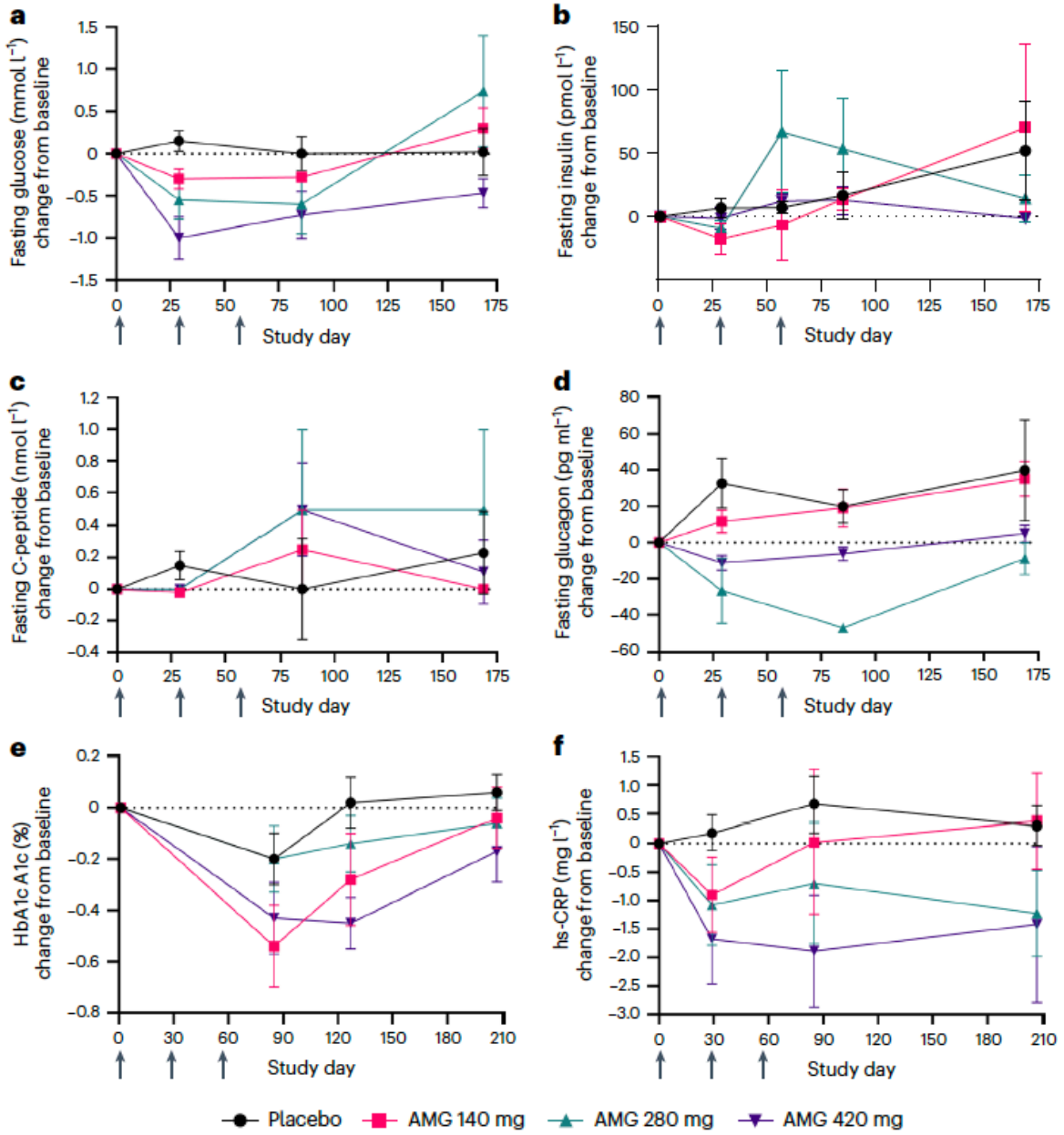
Nicholls SJ et al. *Am Heart J.* 2024;267:1-11.

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



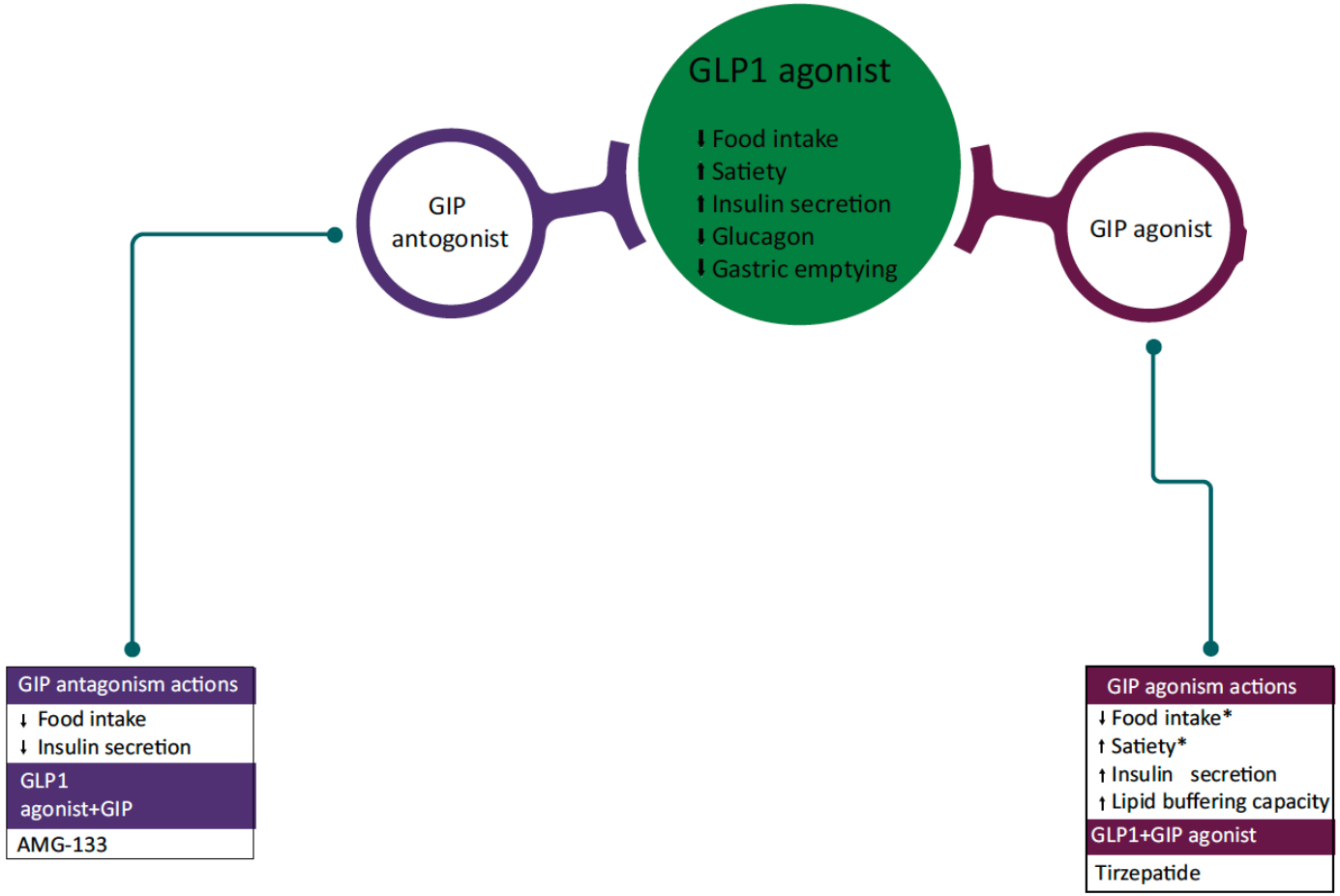
Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

Changes in Body Weight Parameters in Humans with Multiple Ascending Doses of AMG 133.



Véniant MM et al *Nat Metab.* 2024;6:290-303

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

A trial to learn how safe AZD9550 is in people with type 2 diabetes who are overweight or obese - CONTEMPO

Study identifier:
D8460C00002

ClinicalTrials.gov identifier:
NCT06151964

EudraCT identifier:
N/A

CTIS identifier:
2023-504215-32-00

Recruiting

Overview | *Arms and interventions* | *Contacts*

Official Title

A Phase I/II, Randomised, Single-blind, Placebo-controlled, Multiple-ascending-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AZD9550 in Overweight and Obese Participants with Type 2 Diabetes Mellitus

Mazdutide Reduced Blood Glucose and Body Weight in Chinese T2DM Patients

Objectives:

Mazdutide is a once-weekly glucagon-like peptide 1 and glucagon receptor dual agonist under development for the treatment of obesity and type 2 diabetes.

This randomized, double-blind, placebo-controlled, active-referenced phase 2 study evaluated the efficacy and safety of mazdutide in Chinese patients with type 2 diabetes.

Study Design:

Type 2 diabetes inadequately controlled with diet and exercise alone or stable metformin (HbA_{1c} of 7.0%–10.5% [53–91 mmol/mol])

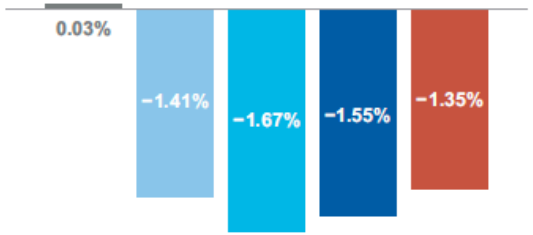
- Mazdutide 3 mg (*n* = 51)
- Mazdutide 4.5 mg (*n* = 49)
- Mazdutide 6 mg (*n* = 49)
- Dulaglutide 1.5 mg (*n* = 50)
- Placebo (*n* = 51)

Two-week lead-in, 20-week treatment, and 4-week follow-up

Results:

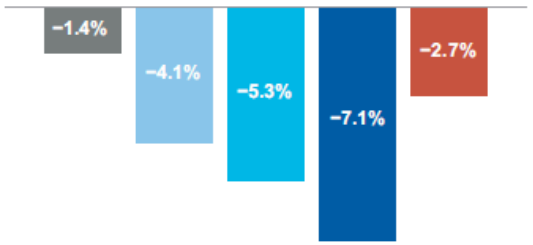
Primary outcome: percent change from baseline to week 20 in HbA_{1c}

Overall mean baseline HbA_{1c} 8.06%

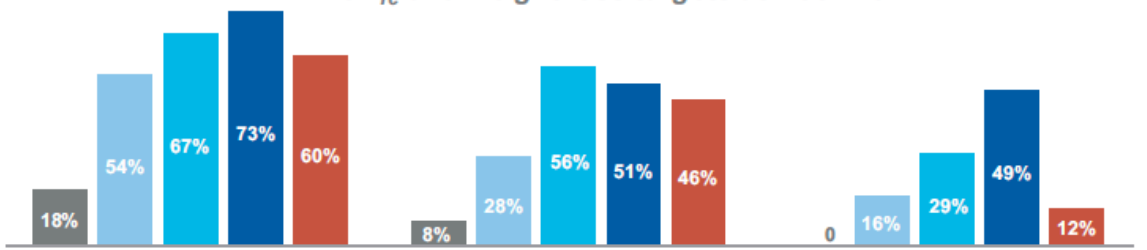


Secondary outcome: percent change from baseline to week 20 in body weight

Overall mean baseline body weight 75.2 kg



Secondary outcomes: proportions of participants achieving HbA_{1c} and weight loss targets at week 20

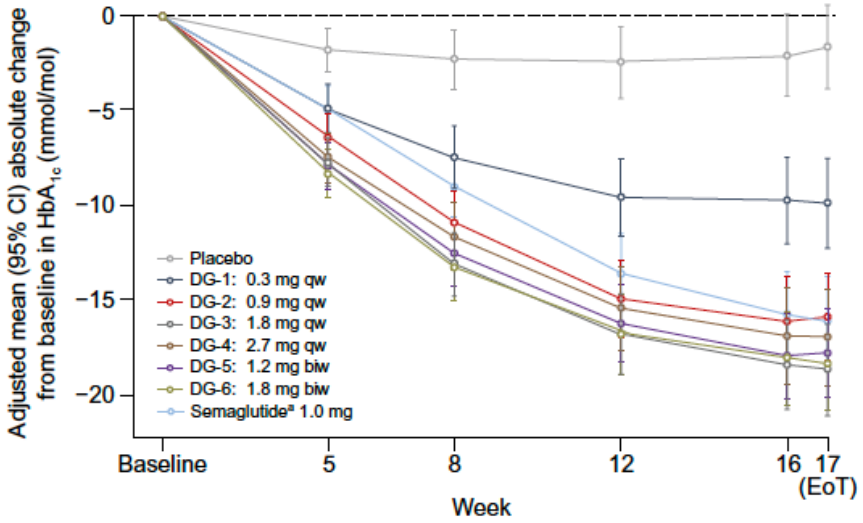


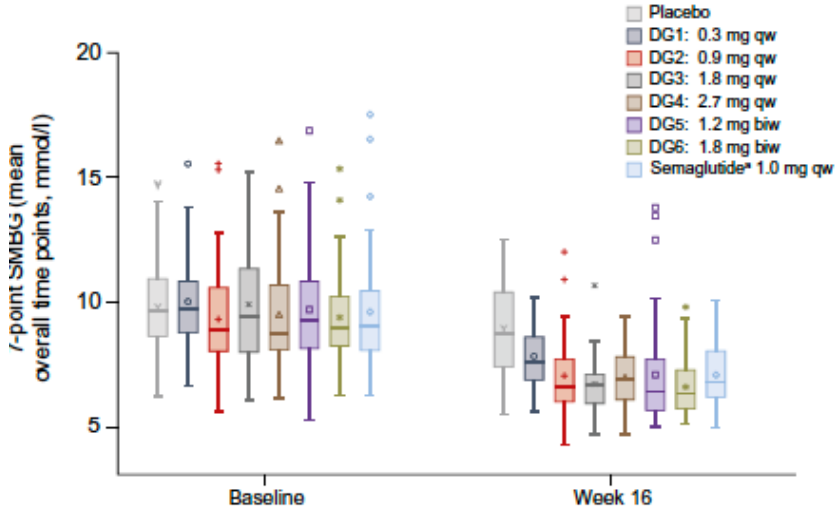
Conclusions:

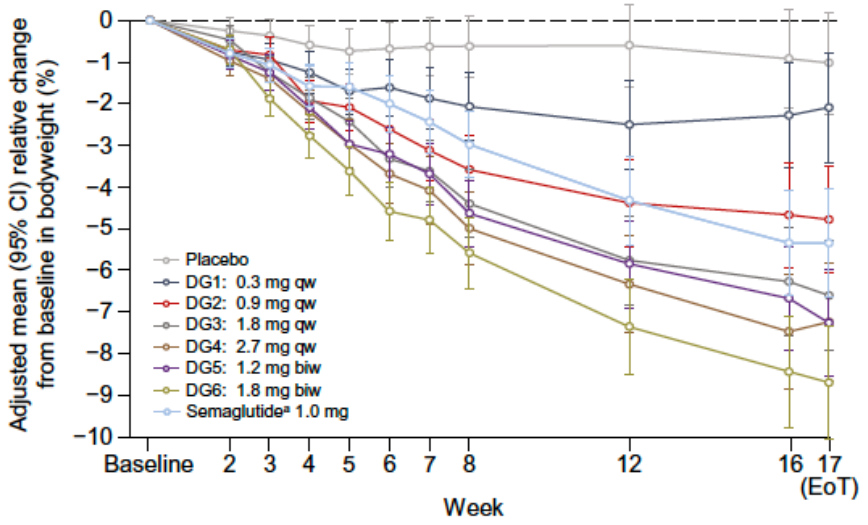
In Chinese patients with type 2 diabetes, mazdutide dosed up to 6 mg was generally safe and demonstrated clinically meaningful HbA_{1c} and body weight reduction.

Zhang B et al *Diabetes Care* 2024;47:160–168

Effects on HbA1c and Body Weight Reduction of Survodutide, a Dual Glucagon/GLP-1 Receptor Agonist, vs. Placebo and Semaglutide in T2DM Patients







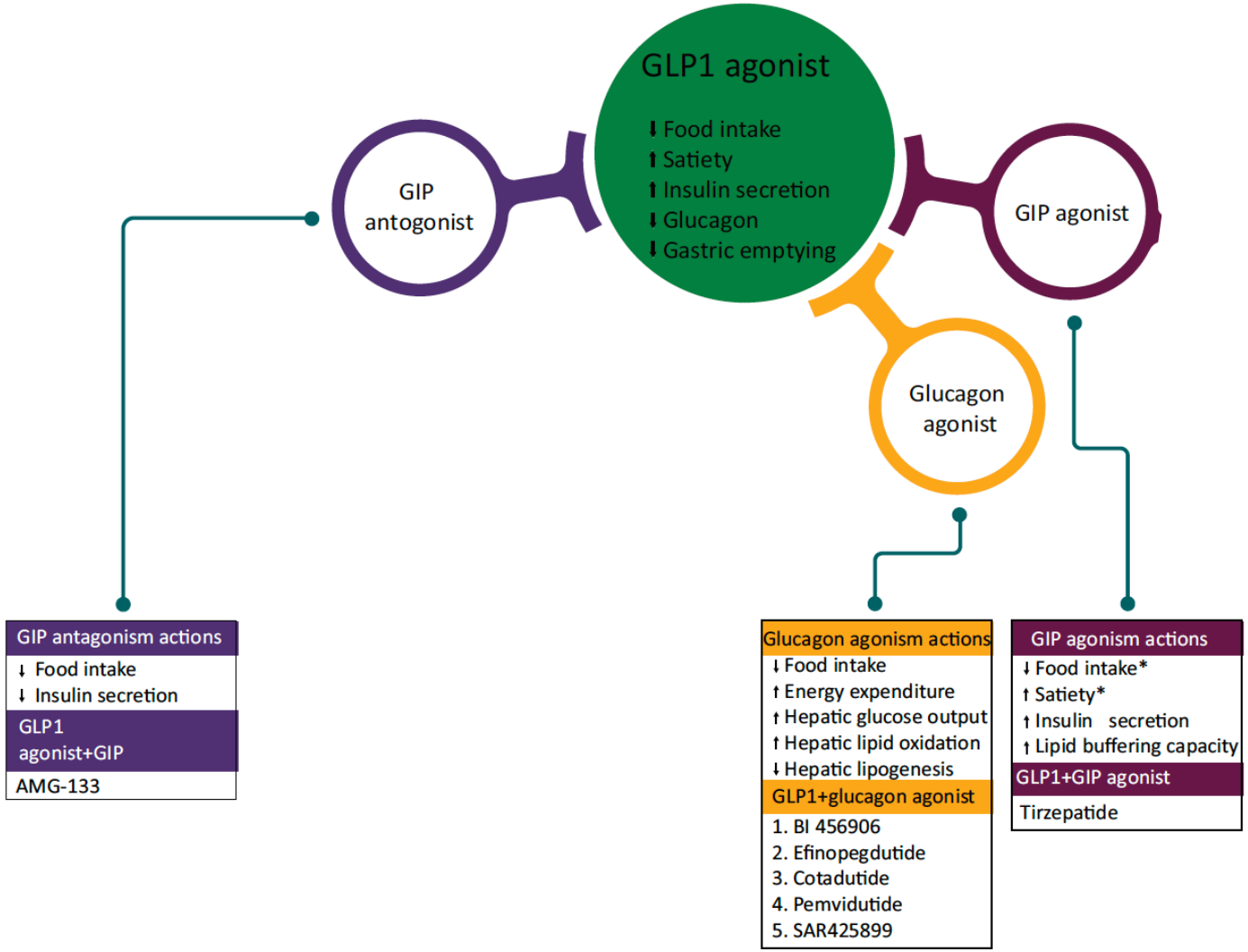
Bluher M et al *Diabetologia* 2023;67:470–482

Safety of Survodutide, a Dual Glucagon/GLP-1-RA, vs. Placebo and Semaglutide in T2DM Patients

AE	DG1: Survodutide 0.3 mg qw (*n*=50)	DG2: Survodutide 0.9 mg qw (*n*=50)	DG3: Survodutide 1.8 mg qw (*n*=52)	DG4: Survodutide 2.7 mg qw (*n*=50)	DG5: Survodutide 1.2 mg biw (*n*=51)	DG6: Survodutide 1.8 mg biw (*n*=49)	Semaglutide 1.0 mg qw (*n*=50)	Placebo (*n*=59)	Total survodutide (*n*=302)
Any TEAE	33 (66.0)	38 (76.0)	42 (80.8)	41 (82.0)	39 (76.5)	42 (85.7)	26 (52.0)	31 (52.5)	235 (77.8)
Investigator-defined, drug-related AEs[a]	25 (50.0)	26 (52.0)	33 (63.5)	29 (58.0)	28 (54.9)	36 (73.5)	19 (38.0)	13 (22.0)	177 (58.6)
Nausea	10 (20.0)	13 (26.0)	24 (46.2)	20 (40.0)	14 (27.5)	22 (44.9)	6 (12.0)	5 (8.5)	103 (34.1)
Vomiting	6 (12.0)	7 (14.0)	12 (23.1)	13 (26.0)	6 (11.8)	10 (20.4)	2 (4.0)	1 (1.7)	54 (17.9)
Diarrhoea	11 (22.0)	5 (10.0)	8 (15.4)	7 (14.0)	8 (15.7)	9 (18.4)	4 (8.0)	5 (8.5)	48 (15.9)
Dyspepsia	4 (8.0)	3 (6.0)	3 (5.8)	4 (8.0)	3 (5.9)	6 (12.2)	1 (2.0)	0	23 (7.6)
Decreased appetite	6 (12.0)	7 (14.0)	5 (9.6)	9 (18.0)	8 (15.7)	15 (30.6)	3 (6.0)	2 (3.4)	50 (16.6)
Headache	2 (4.0)	5 (10.0)	3 (5.8)	0	3 (5.9)	2 (4.1)	0	1 (1.7)	15 (5.0)
Severe AEs[b]	3 (6.0)	1 (2.0)	4 (7.7)	3 (6.0)	2 (3.9)	3 (6.1)	0	4 (6.8)	16 (5.3)
Nausea	1 (2.0)	0	1 (1.9)	0	0	1 (2.0)	0	0	3 (1.0)
Vomiting	2 (4.0)	0	0	0	2 (3.9)	0	0	0	4 (1.3)
Dizziness	0	0	0	0	0	2 (4.1)	0	0	2 (0.7)
Serious AEs	1 (2.0)	4 (8.0)	3 (5.8)	2 (4.0)	1 (2.0)	0	0	3 (5.1)	11 (3.6)
Drug-related serious AEs	1 (2.0)	1 (2.0)	1 (1.9)	1 (2.0)	0	0	0	0	4 (1.3)
AEs leading to treatment discontinu-ation	5 (10.0)	5 (10.0)	11 (21.2)	15 (30.0)	4 (7.8)	8 (16.3)	2 (4.0)	3 (5.1)	48 (15.9)

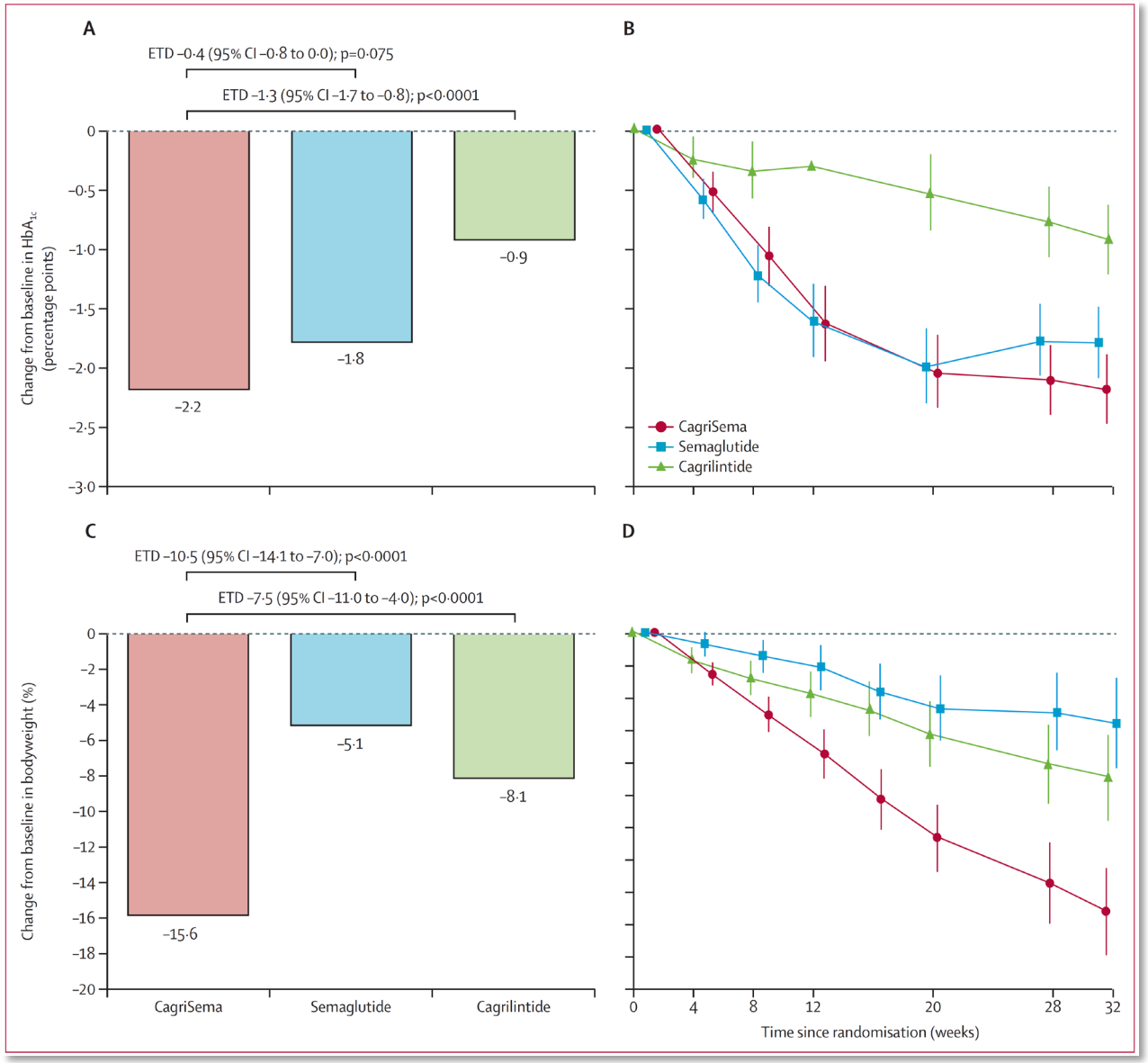
Bluher M et al *Diabetologia* 2023;67:470–482

Dual Agonists – Building on Top of GLP1RAs



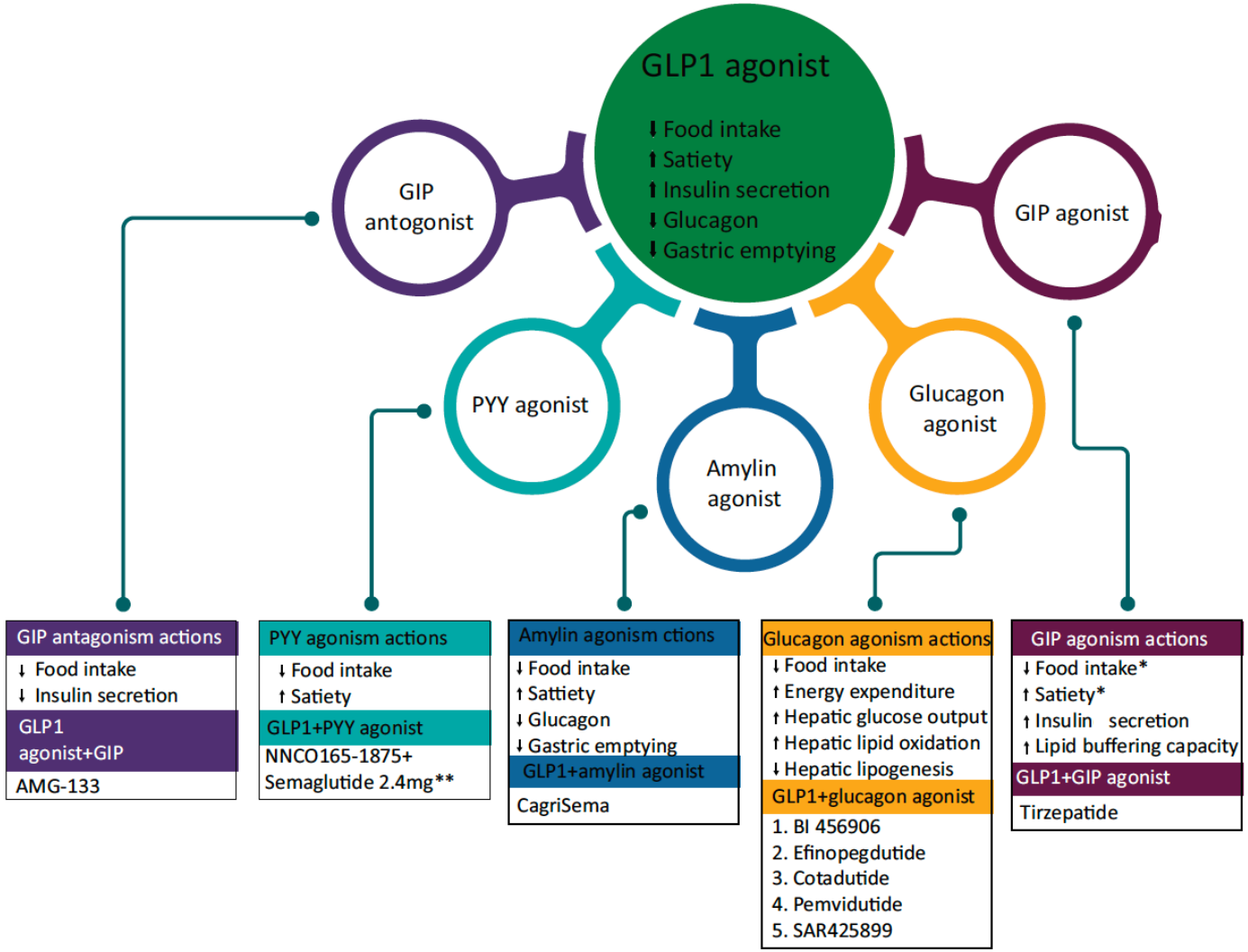
Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

Efficacy of Co-administered QW Cagrilintide 2·4 mg with QW Semaglutide 2·4 mg in T2DM



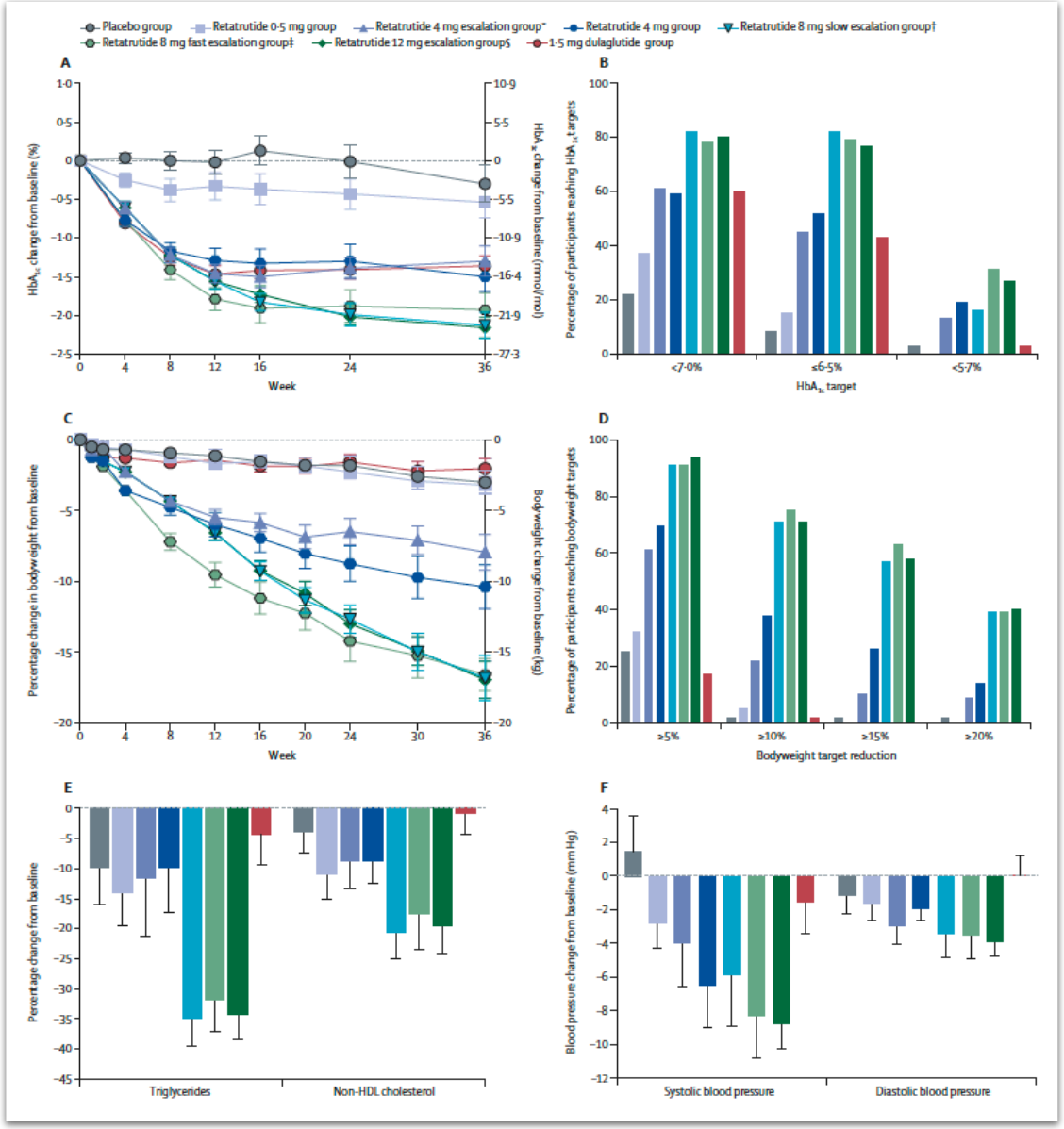
Frias JP, et al *Lancet*.2023;402: 720-730

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI



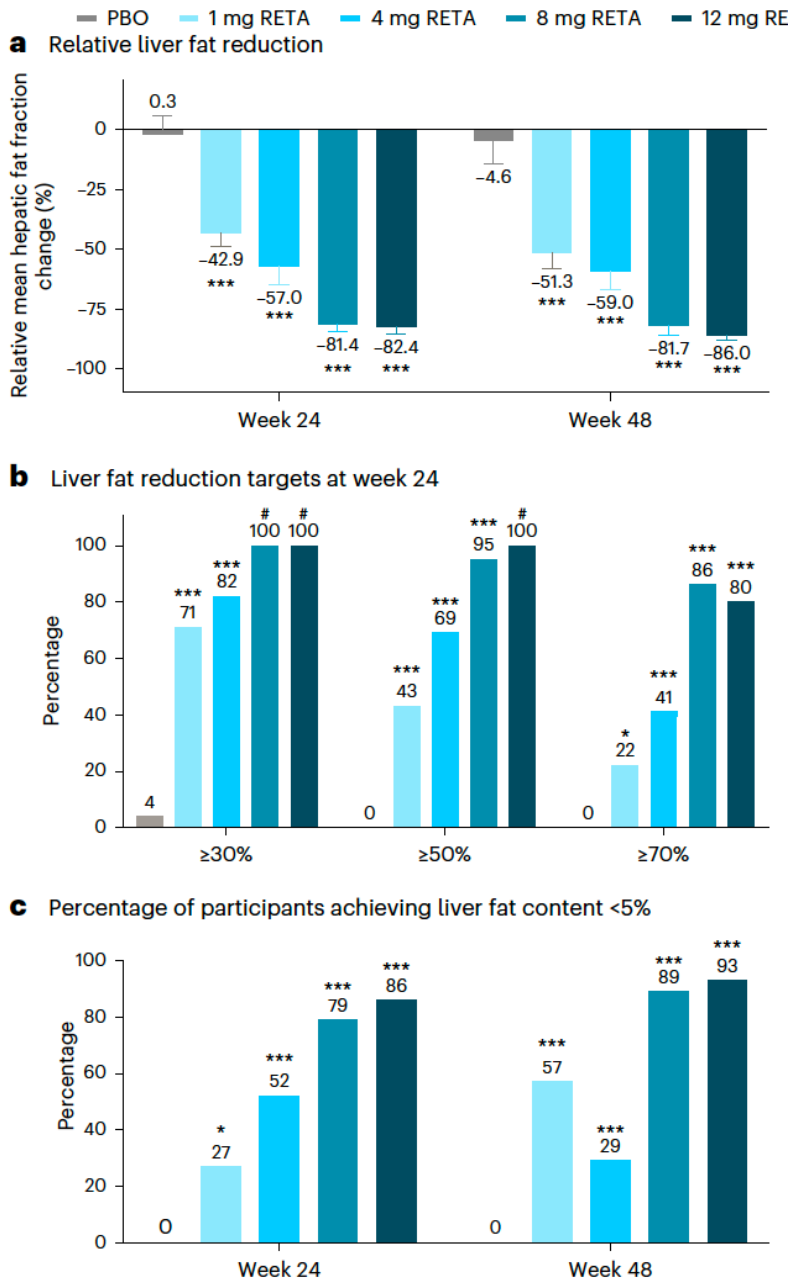
Melson E et al *Clinical Medicine* 2023 Vol 23, No 4: 337–46

Efficacy of Retatrutide (GIP,/GLP-1/Glucagon Receptor Agonist) in T2DM People: a Randomised, Double-blind, Placebo and Active-controlled, Parallel-group, Phase 2 Trial



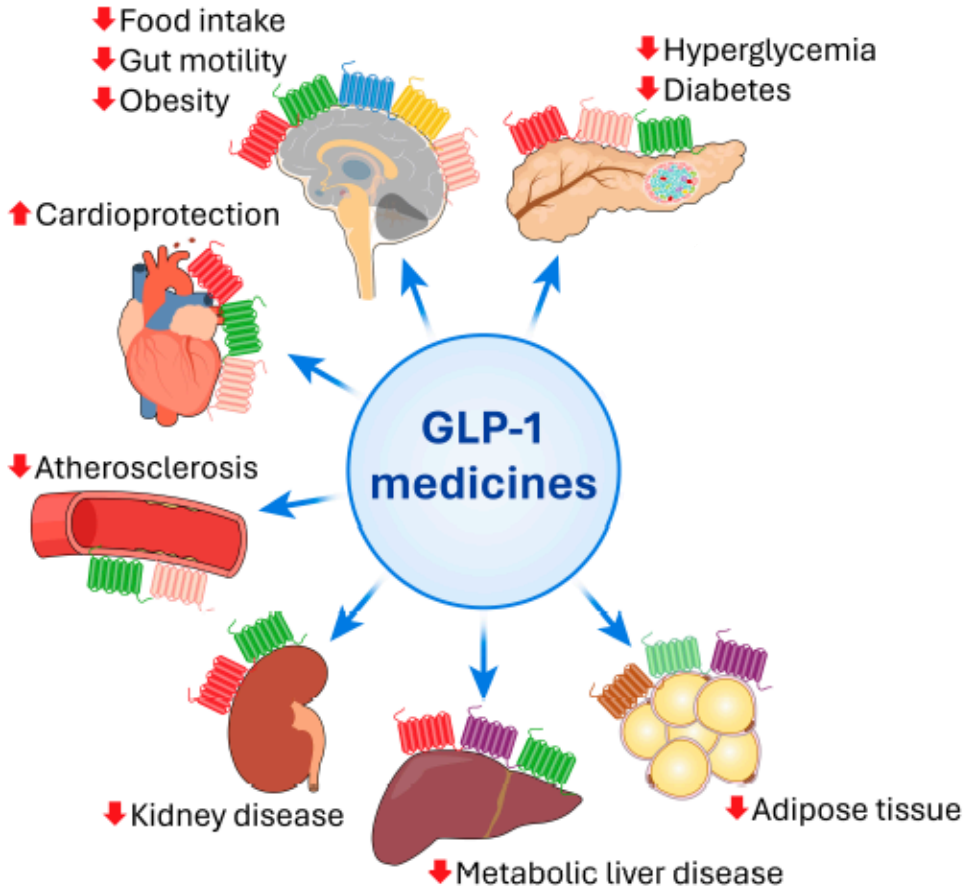
Rosenstock J., et al. *Lancet*. 2023; 402:529-544

Triple Hormone Receptor Agonist Retatrutide for Metabolic Dysfunction-associated Steatotic Liver Disease



Sanyal AJ et al *Nat Med*. 2024 Jun 10. Online ahead of print.

The future of GLP-1 Medicines Encompasses a Multiagonist Approach



Drucker DJ *Diabetes Care* 2024
https://doi.org/10.2337/dci24-0003

PRESENTE E FUTURO DELLA TERAPIA CON ORMONI INCRETINICI