# Effect of incretin based drugs on body weight and cardiovascular end points

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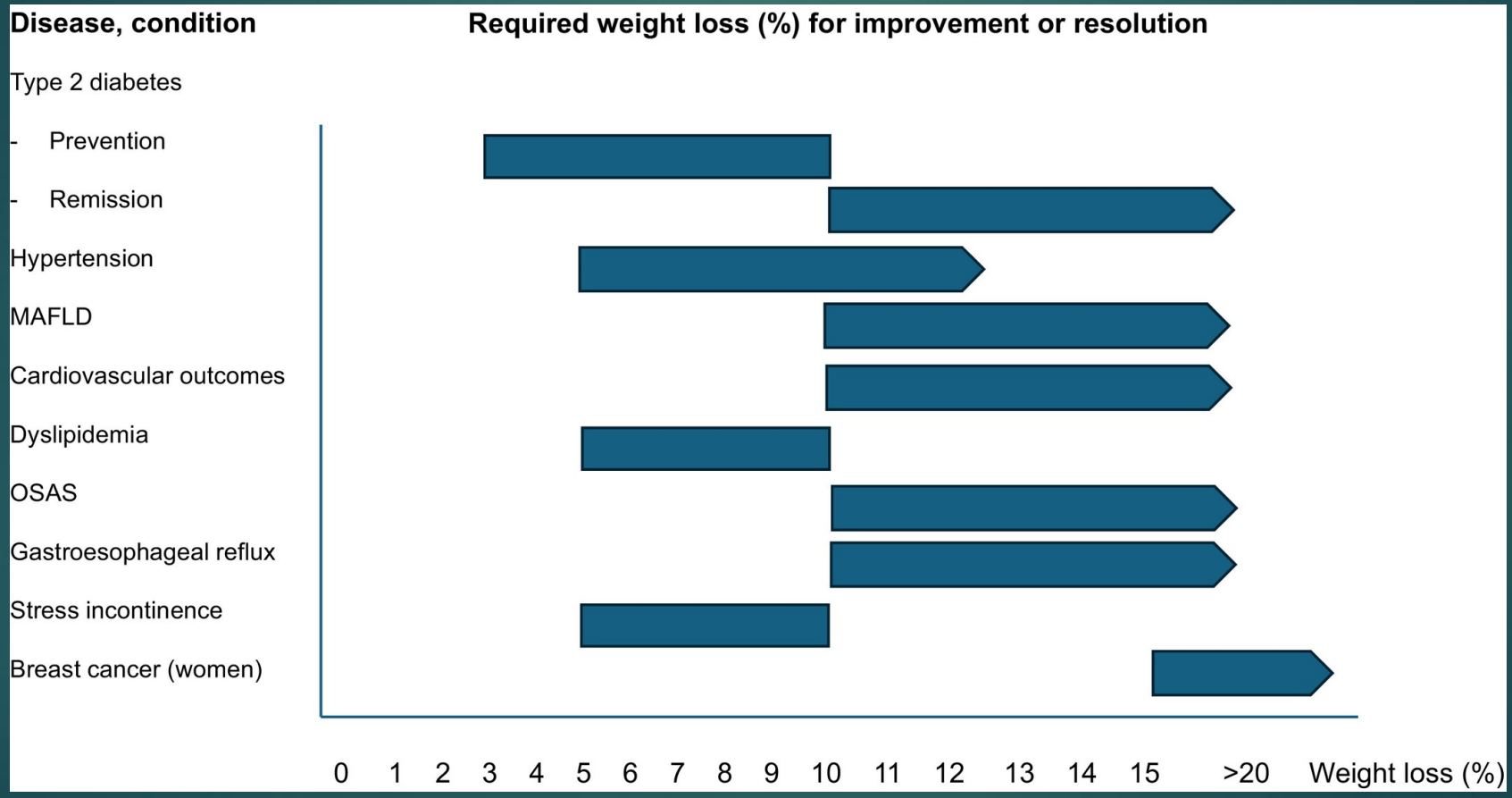
# Agenda

- Introduction
- Effect of incretin based drugs on body weight
  - Liraglutide in obesity treatment
  - Semaglutide in obesity treatment
  - Oral Semaglutide in obesity treatment
  - Tirzepatide in obesity treatment
  - Retatrutide in obesity treatment
  - Comparison of the incretin based drugs
- Effect of incretin based drugs on cardiovascular disease
  - Effect on cardiovascular risk factors
  - Effect on cardiovascular events
  - Effect on heart failure
- Take home message

# a number of obesity complications can be improved, prevented even with moderate weight loss



## Glucagon-like Peptide-1 Receptor Agonism

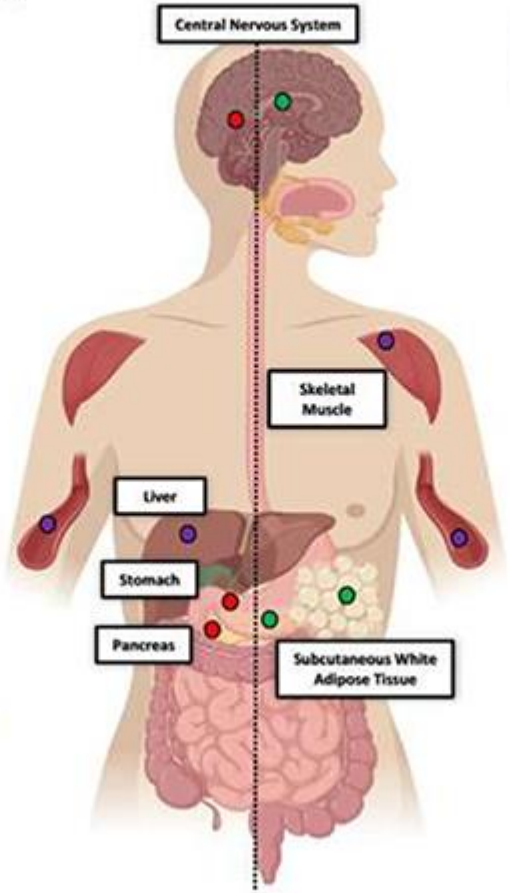
### Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

### Pancreas
- ↑ Insulin
- ↓ Glucagon

### Stomach
- ↓ Gastric Emptying

### Systemic
- ↓ Hyperglycemia

### Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation




Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

## Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

### Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

### Pancreas
- ↑ Insulin
- ↑ Glucagon

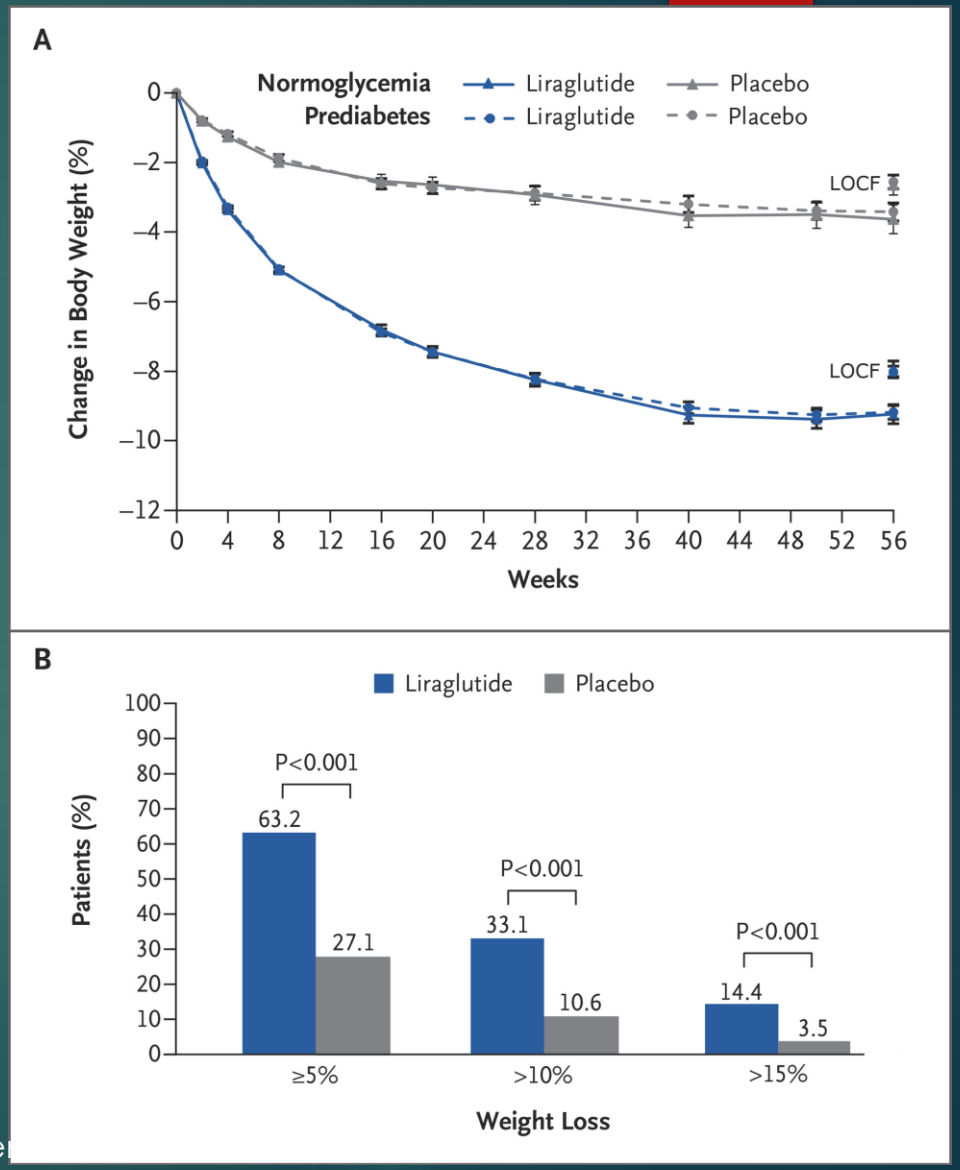
### Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

### Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

### Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

# SCALE (Satiety and Clinical Adiposity Liraglutide Evidence)

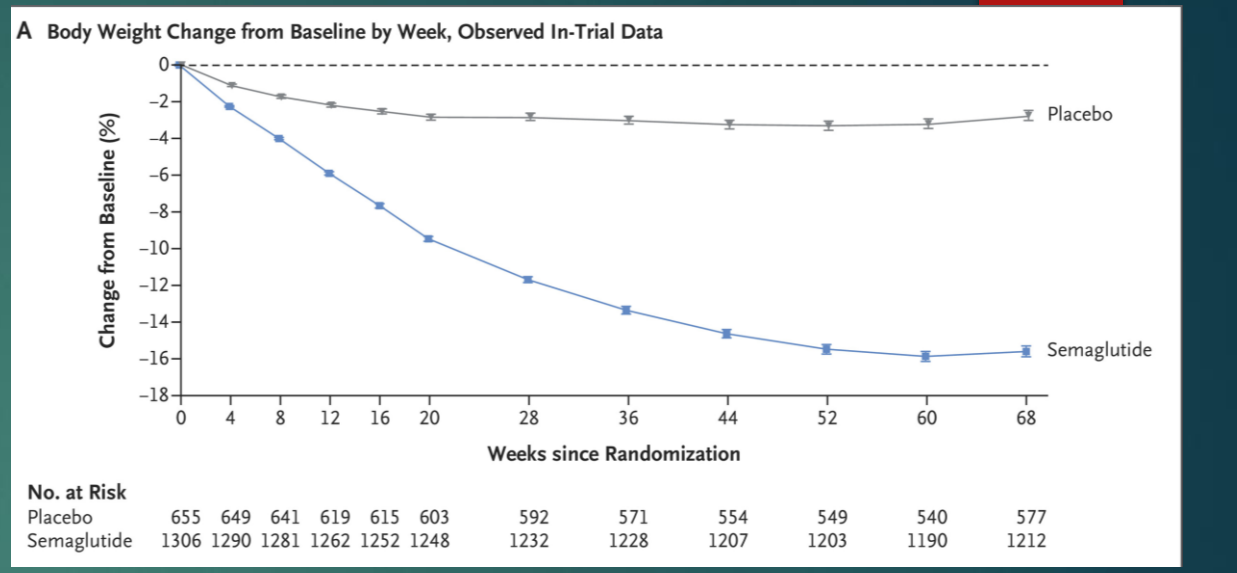
- 3731 patients without diabetes
- BMI of at least 30 or a BMI of at least 27+ dyslipidemia or hypertension.
- liraglutide group had lost a mean of 8.4±7.3 kg
- placebo group had lost a mean of 2.8±6.5 kg

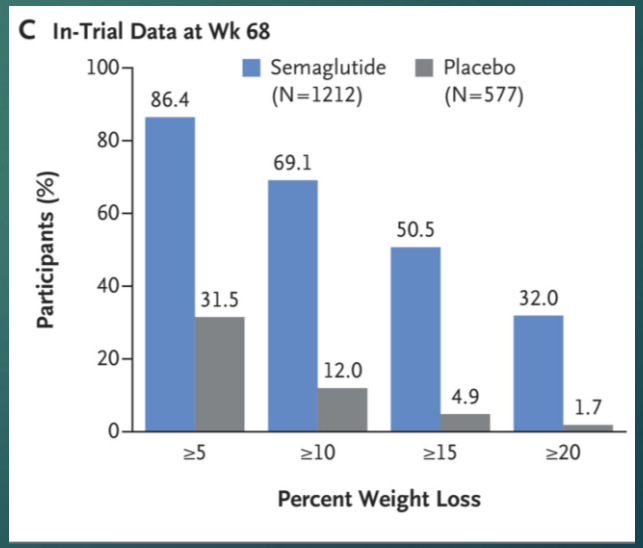



Pi-Sunyer Xet al.A randomized, controlled trial of 3.0 mg of liraglutide in weight manageme
New England Journal of Medicine. 2015

# STEP (Semaglutide Treatment Effect in People with obesity)

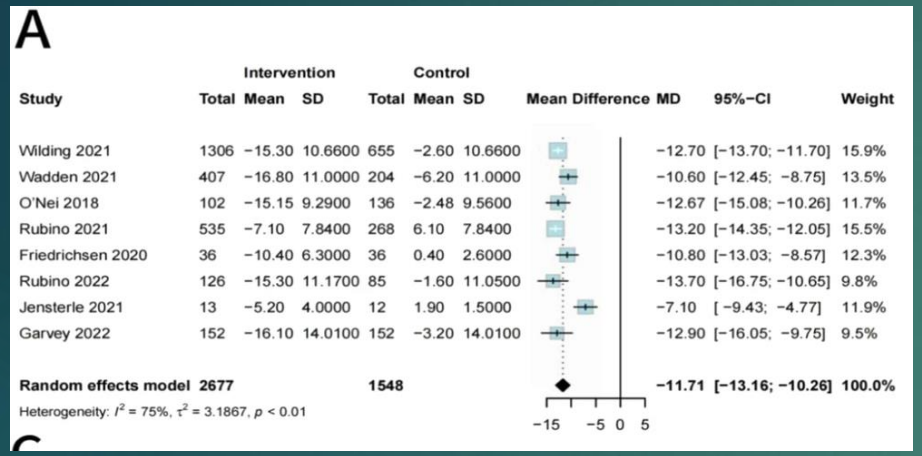
- 1961 adults without diabetes
- BMI: 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition
- The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group

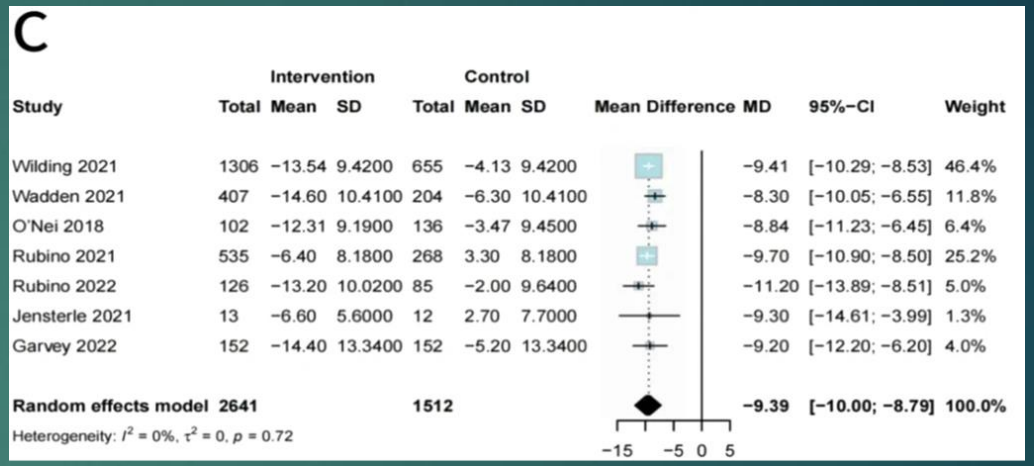


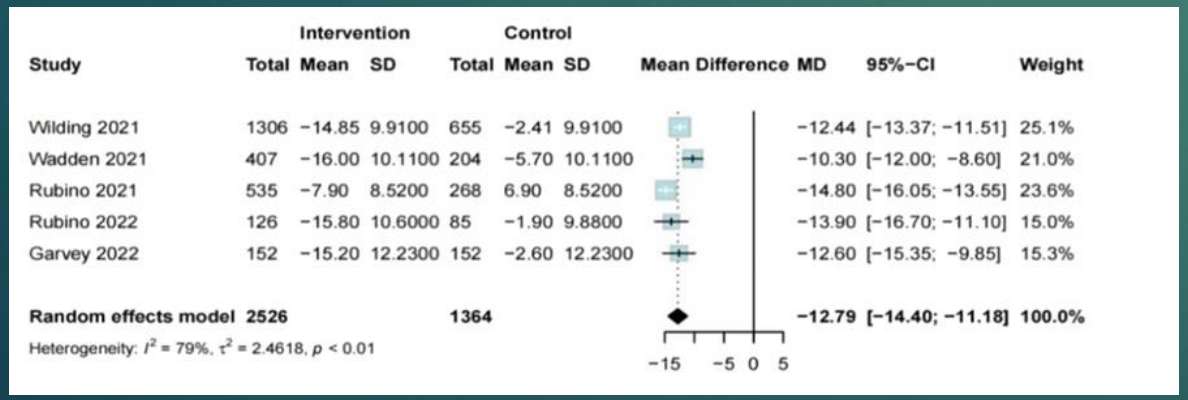



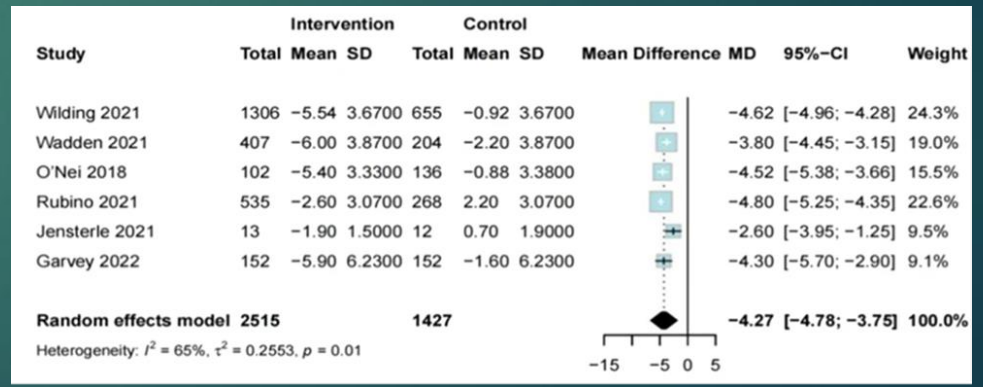

Wilding JP, et al. Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine. 2021.

# Semaglutide led to a weight reduction of 11.71 kg and 12.79% reduction in weight percentage, 9.39 cm in waist circumference and 4.27 kg/m^2 reduction in BMI compared to a placebo



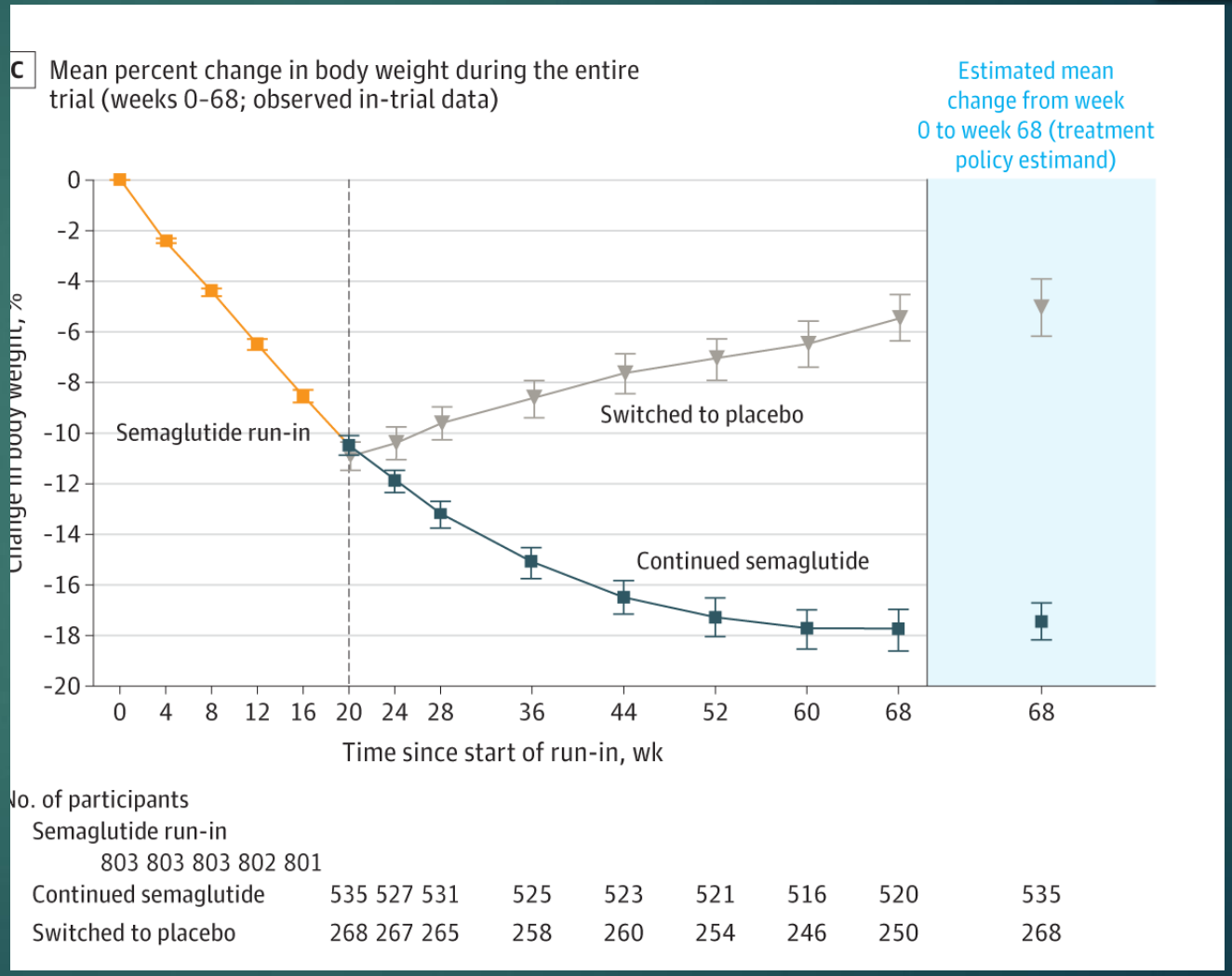




Hu X, et al. Effect of semaglutide with obesity or overweight individuals without diabetes: an Umbrella review of systematic reviews. Endocrine. 2025

# maintenance of body weight loss

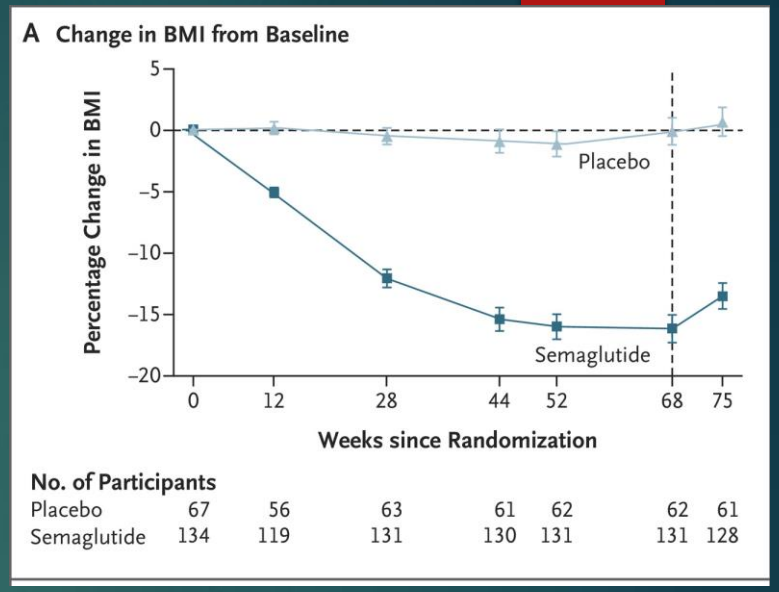
- 803 participants completed the 20-week run-in period ,with a mean weight loss of 10.6%
- With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs +6.9% with the switch to placebo

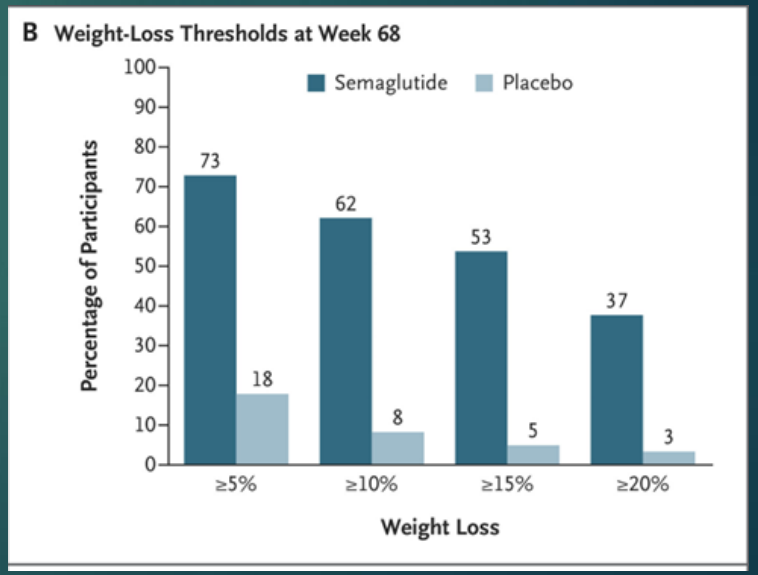



Rubino D,et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. Jama. 2021

# Semaglutide in Adolescents with Obesity

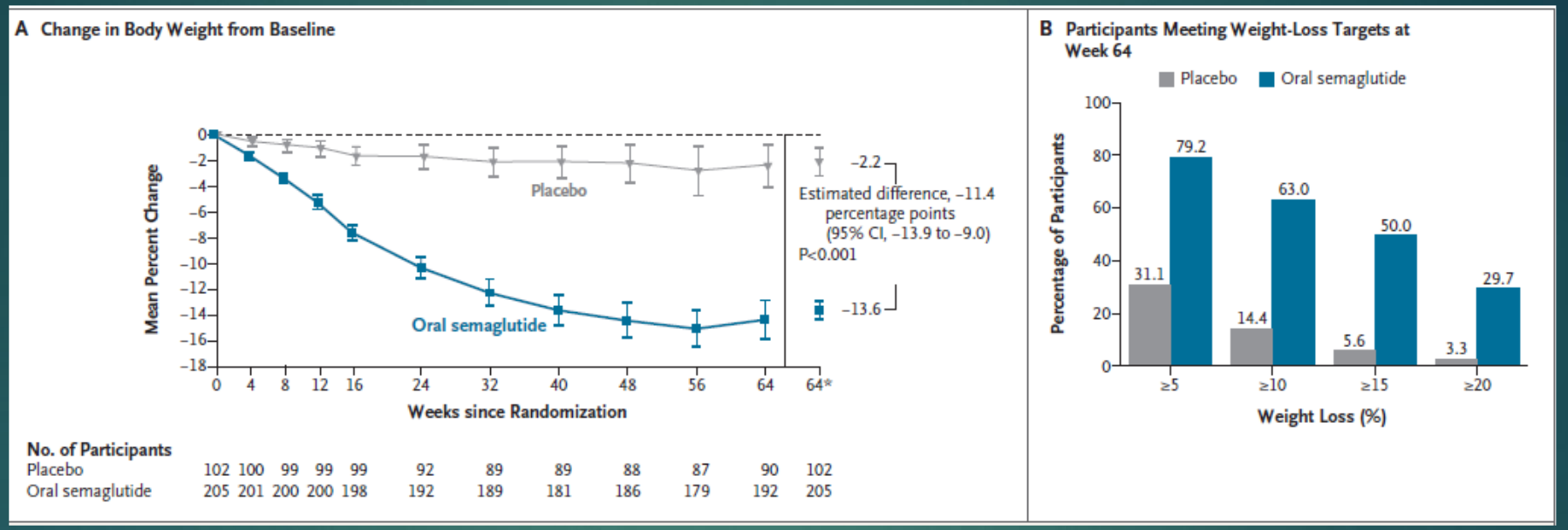
- 201 adolescents (12 to <18 years of age) with obesity or overweight and at least one weight-related coexisting condition.
- semaglutide (at a dose of 2.4 mg) or placebo for 68 weeks
- The mean change in BMI from baseline to week 68 was −16.1% with semaglutide and 0.6% with placebo




Weghuber D et al.Once-weekly semaglutide in adolescents with obesity. New England Journal of Medicine. 2022

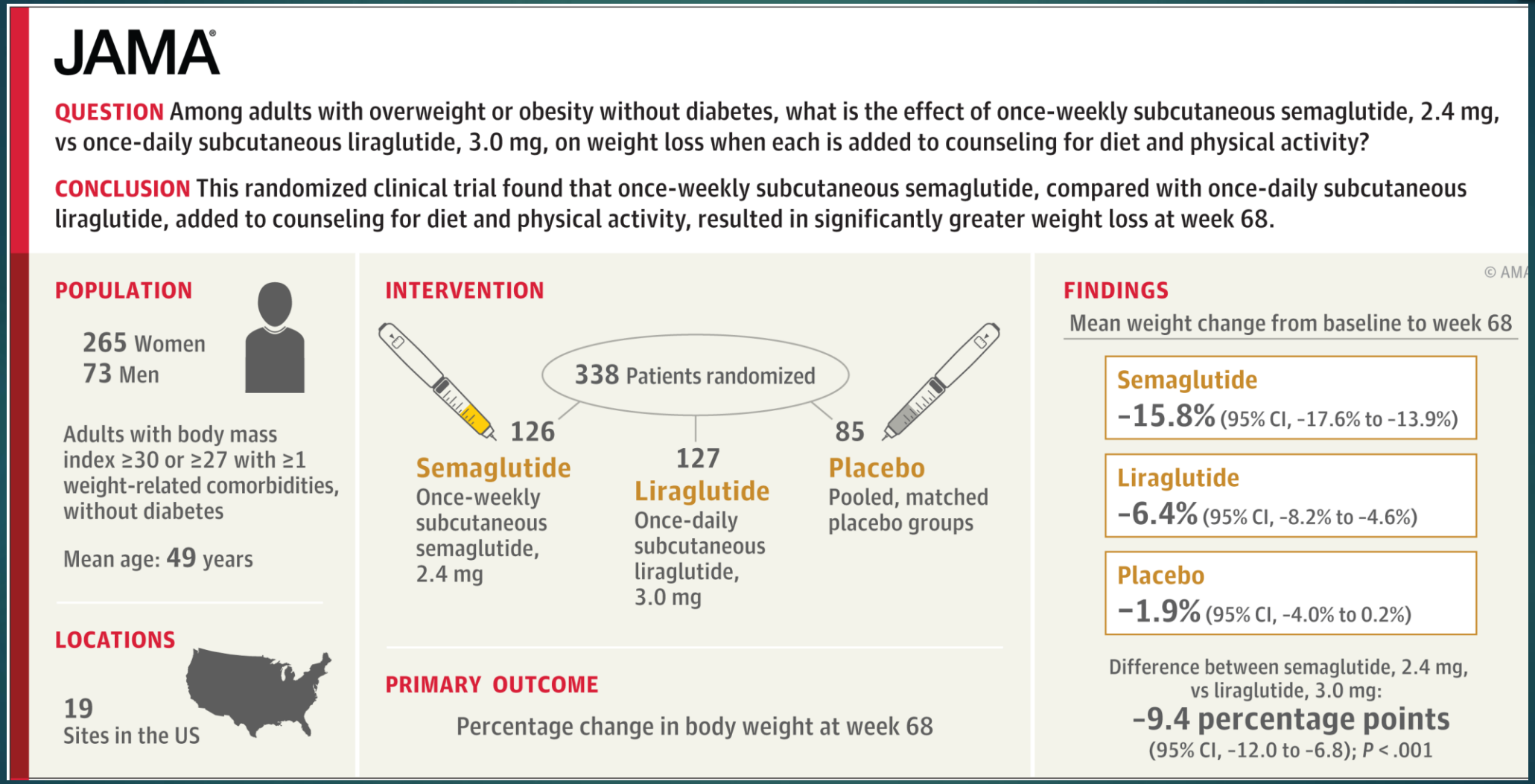
# Oral Semaglutide  in Adults with Overweight or Obesity




A total of 205 participants without diabetes with BMI of30 or more or27+one obesity relate complication were randomly assigned to receive oral semaglutide, and 102 to receive placebo

Wharton S,et al.Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. New England Journal of Medicine. 2025

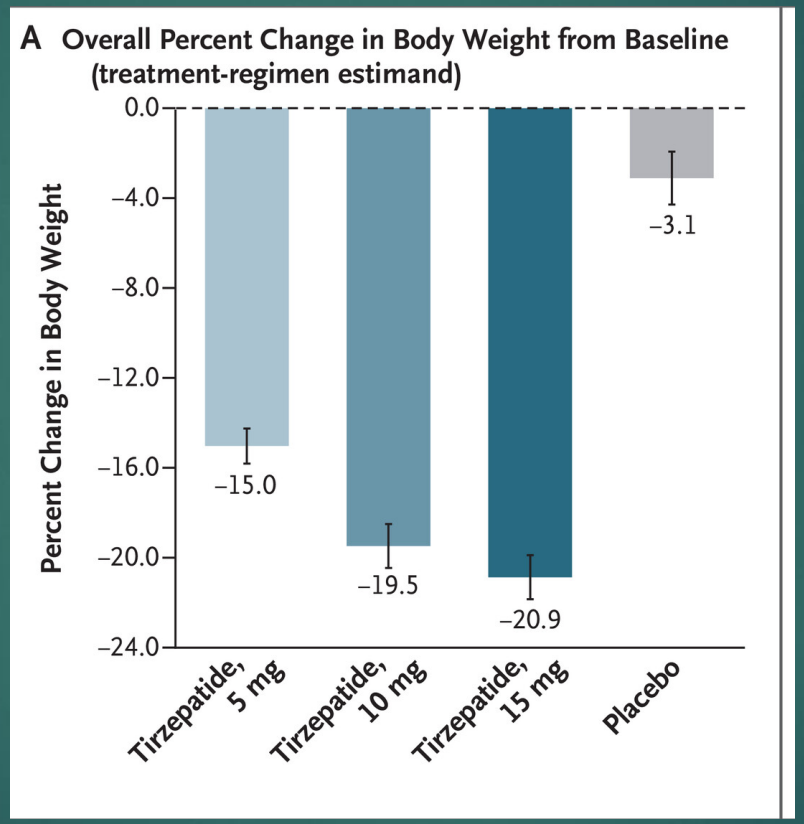
# Weekly Subcutaneous Semaglutide vs Daily Liraglutide

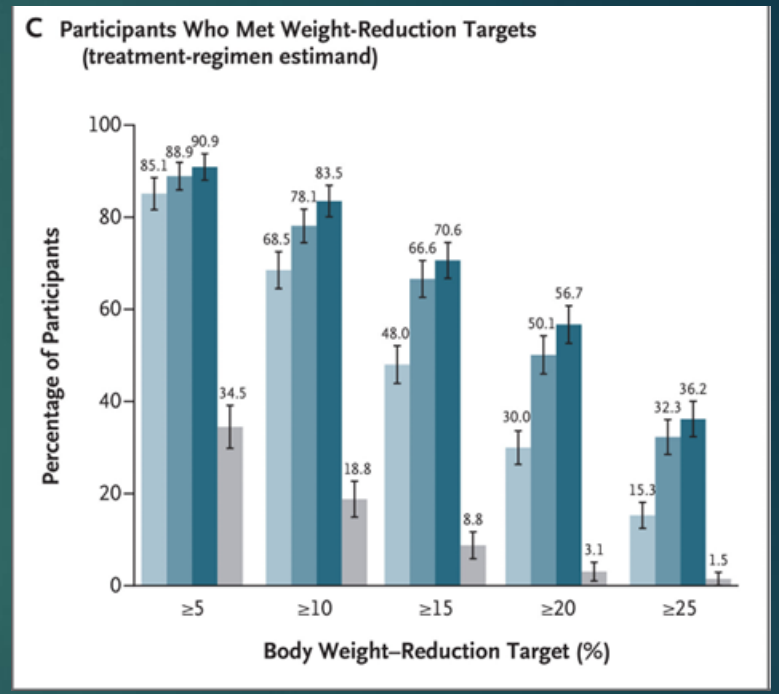



Rubino DM, et al Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. Jama. 2022

# Tirzepatide once weekly for the treatment of obesity(SURMOUNT-1)

2539 adults with a BMI of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period

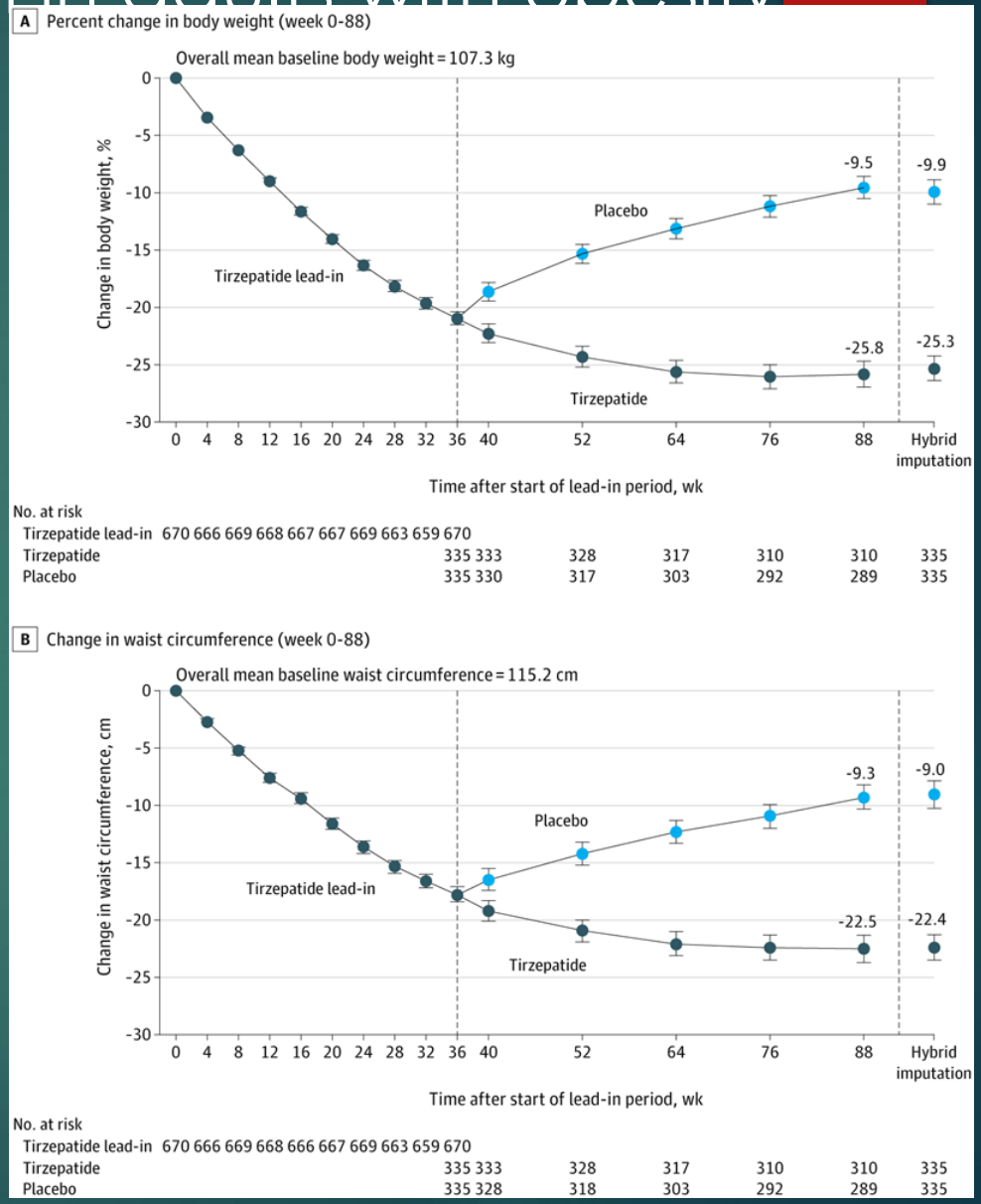



Jastreboff AM, et al.Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine. 2022

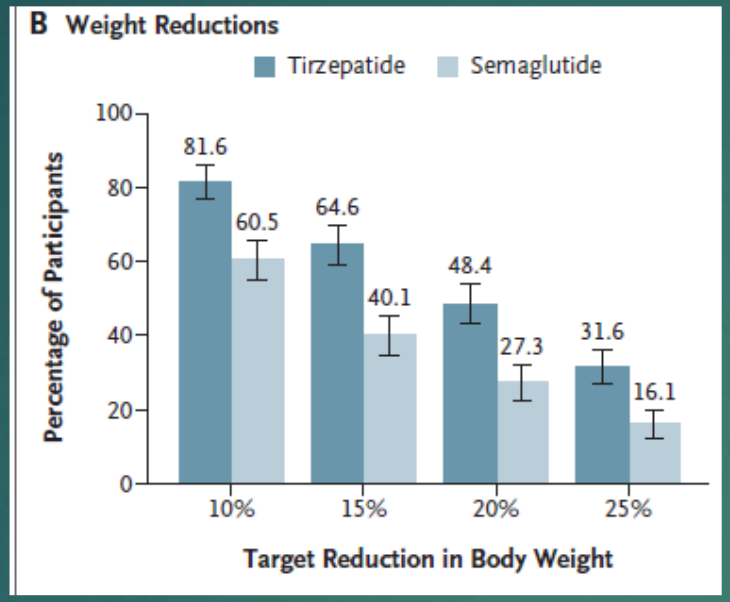
# maintenance of weight reduction in adults with obesity

After 36 weeks tirzepatide (10 or 15 mg), adults (n = 670) experienced a mean weight reduction of 20.9%. From randomization (at week 36), those switched to placebo experienced a 14% weight regain and those continuing tirzepatide experienced an additional 5.5% weight reduction



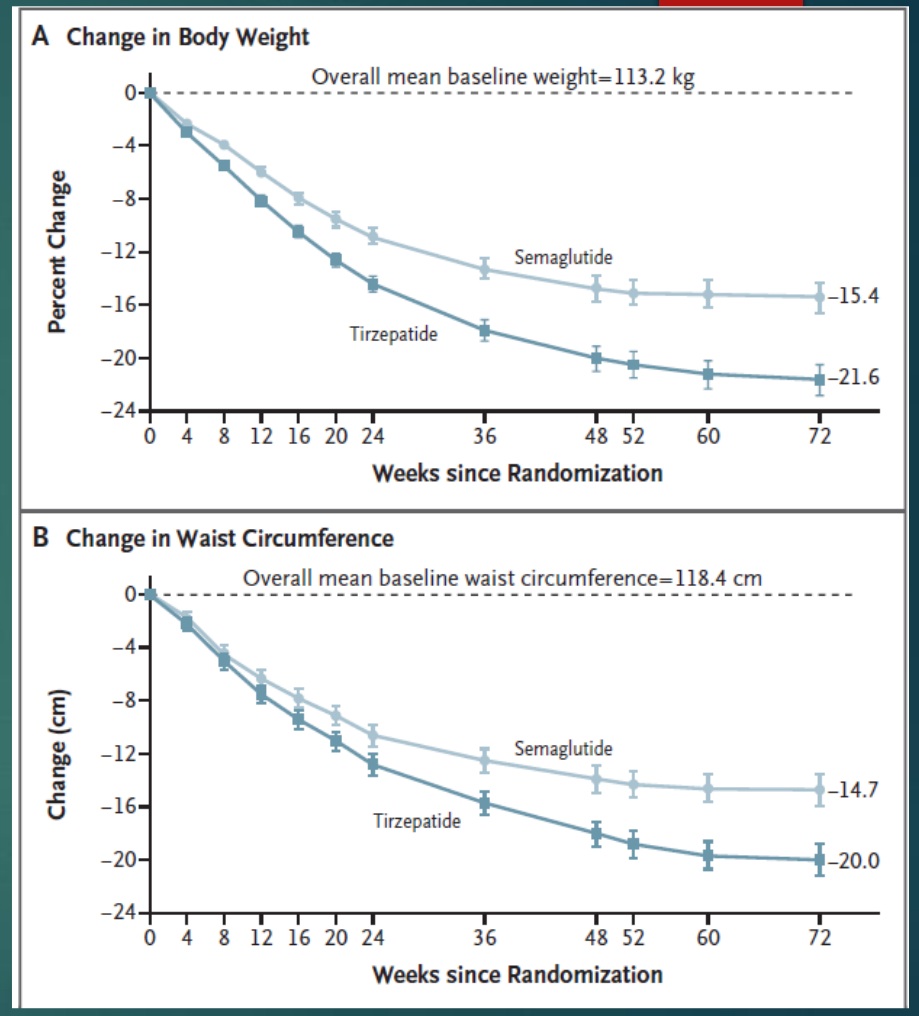

Aronne LJ, al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. Jama. 2024

# Tirzepatide Compared with Semaglutide




751adult participants with obesity but without type 2 diabetes

maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) for 72 weeks.

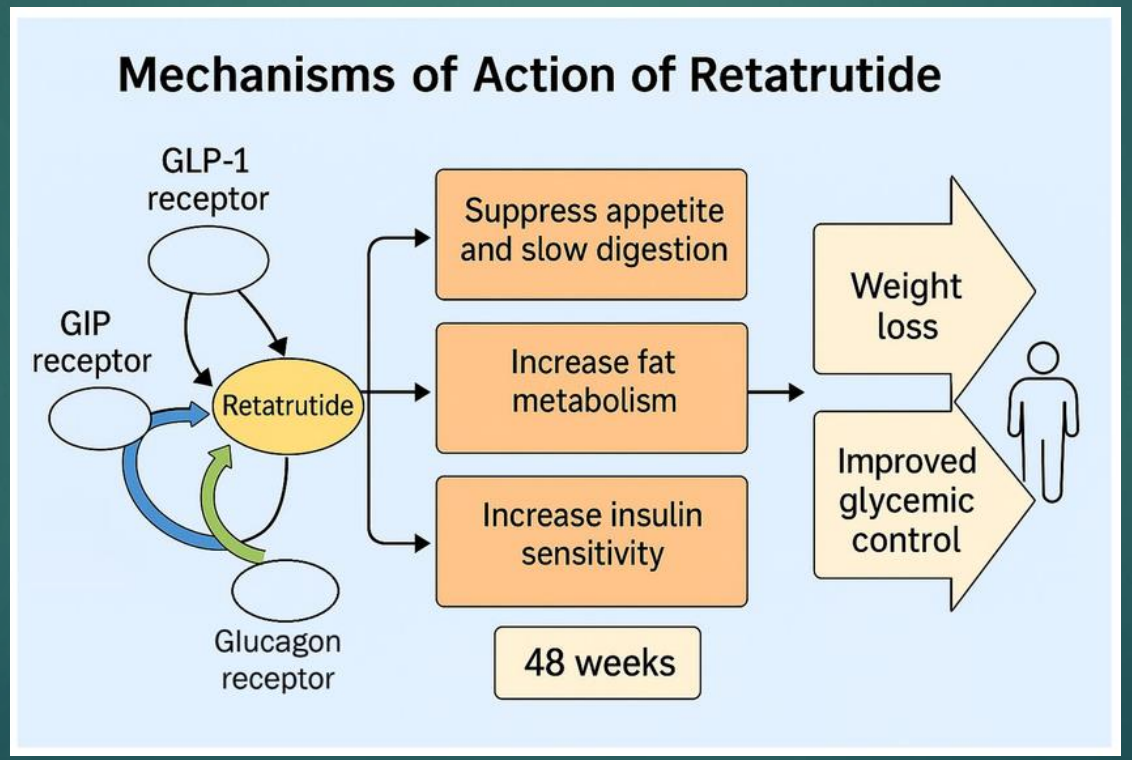



Aronne LJ et al. Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med. 2025

The NEW ENGLAND JOURNAL of MEDICINE

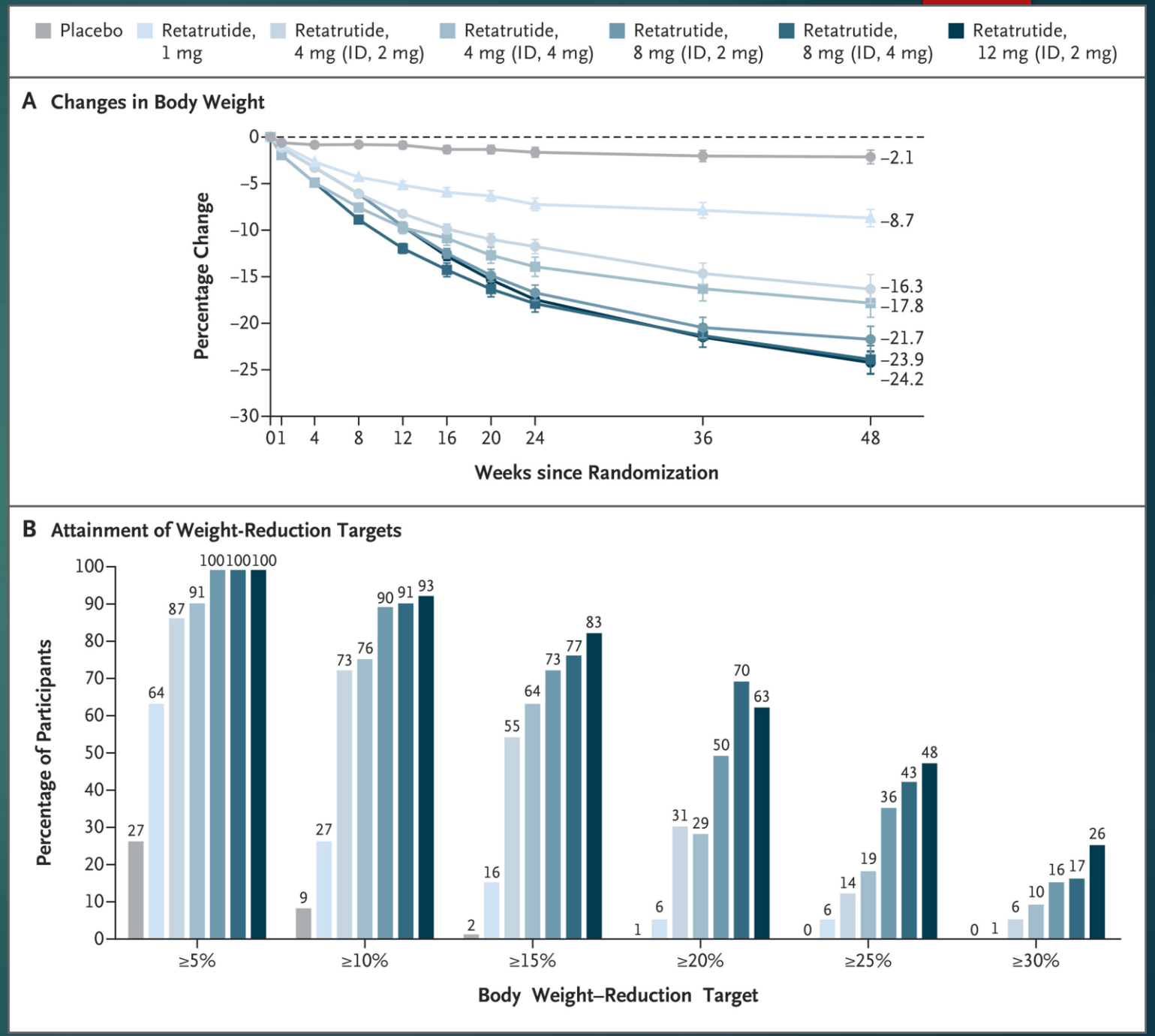
ORIGINAL ARTICLE

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




Jastreboff AM, et al.Triple–hormone-receptor agonist retatrutide for obesity—a phase 2 trial. New England Journal of Medicine. 2023

We enrolled 338 adults, to receive subcutaneous retatrutide (1 mg, 4 mg ,8mg, 12 mg or placebo once weekly for 48 weeks.



the SCALE trials, the proportion of patients losing

- >5%:46.3–63.2%
- >10%:22.8–33.1%
- > 15% :11.0–18.1%
- > 20% 6.0%,

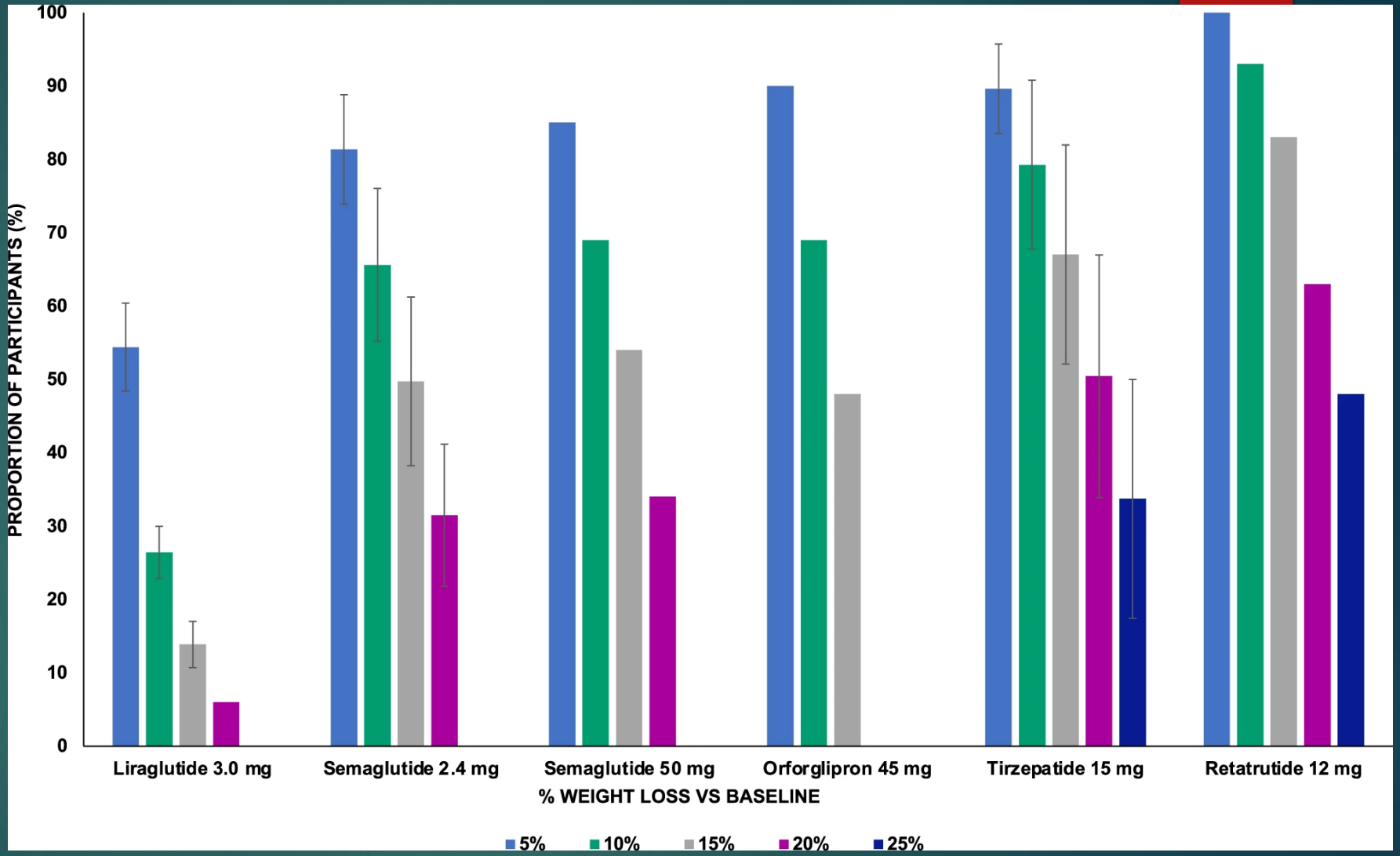
Across the STEP trials,

- >5%:68.8–88.7%
- >10%:45.6–75.3%
- >15% :25.8–63.7%
- >20% :13.1–39.6%,

the SURMOUNT trials,

- >5%: 79.2–97.3%,
- >10%: 60.5–92.1%
- >15% :39.7–84.1%
- >20% 21.5–69.5%,

respectively




Caruso I, et al. Incretin-based therapies for the treatment of obesity-related diseases. npj Metabolic Health and Disease. 2024

tirzepatide 15 mg had the highest probability of being ranked first in terms of percentage weight loss, followed
by tirzepatide 10 mg, and then weekly semaglutide 2.4 mg Weekly

**(A) Mean actual (kg) and percentage (%) weight reduction**

| | | | | | |
|---|---|---|---|---|---|
| **Tirzepatide 15 mg (Weekly)** | -1.40 (-5.45, 2.58) | **-5.13 (-9.82, -0.68)** | **-6.67 (-12.1, -1.24)** | **-13.02 (-17.44, -8.57)** | **-17.79 (-21.77, -13.76)** |
| -1.20 (-5.2, 2.77) | **Tirzepatide 10 mg (Weekly)** | -3.72 (-8.44, 0.76) | -5.27 (-10.7, 0.16) | **-11.63 (-16.05, -7.19)** | **-16.39 (-20.35, -12.39)** |
| **-9.23 (-13.76, -5.05)** | **-8.04 (-12.47, -3.80)** | **Semaglutide 2.4 mg (Weekly)** | -1.54 (-5.67, 2.86) | **-7.91 (-10.48, -5.01)** | **-12.66 (-14.81, -10.26)** |
| **-9.73 (-14.57, -4.97)** | **-8.53 (-13.29, -3.70)** | -0.53 (-3.45, 2.81) | **Semaglutide 0.4 mg (Daily)** | **-6.35 (-10.08, -2.58)** | **-11.12 (-14.81, -7.36)** |
| **-16.81 (-21.13, -12.62)** | **-15.62 (-19.85, -11.4)** | **-7.60 (-9.53, -5.34)** | **-7.07 (-9.79, -4.42)** | **Liraglutide 3 mg (Daily)** | **-4.77 (-6.73, -2.81)** |
| **-22.00 (-26.02, -18.03)** | **-20.81 (-24.76, -16.8)** | **-12.79 (-14.39, -10.81)** | **-12.27 (-14.94, -9.56)** | **-5.20 (-6.64, -3.67)** | **Placebo** |

Alkhezi OS,et al Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. Obesity reviews. 2023

Tirzepatide 10 and 15 mg, along with weekly semaglutide 2.4 mg and daily semaglutide 0.4 mg, all yielded comparable results to each other and significantly better results in comparison with the liraglutide regimen at the 5%, 10%, cutoff

**(A) Patients with weight reduction of ≥ 5% and ≥ 10%**

| | | | | | |
|---|---|---|---|---|---|
| **Tirzepatide 15 mg (Weekly)** | 1.27 (0.39 – 4.04) | 1.59 (0.41 – 6.04) | 1.43 (0.28 – 7.28) | **4.87 (1.33 – 17.81)** | **19.29 (6.13 – 61.44)** |
| 1.42 (0.44 – 4.57) | **Tirzepatide 10 mg (Weekly)** | 1.26 (0.33 – 4.67) | 1.13 (0.22 – 5.74) | **3.84 (1.08 – 13.87)** | **15.22 (4.91 – 48.42)** |
| 1.59 (0.41 – 6.14) | 1.11 (0.29 – 4.27) | **Semaglutide 2.4 mg (Weekly)** | 0.90 (0.25 – 3.41) | **3.05 (1.40 – 6.98)** | **12.08 (6.38 – 24.15)** |
| 1.63 (0.31 – 8.24) | 1.15 (0.22 – 5.78) | 1.03 (0.28 – 3.71) | **Semaglutide 0.4 mg (Daily)** | **3.39 (1.07 – 10.75)** | **13.48 (4.25 – 42.93)** |
| **6.78 (1.88 – 25.70)** | **4.77 (1.33 – 18.07)** | **4.28 (1.95 – 10.00)** | **4.17 (1.40 – 13.21)** | **Liraglutide 3 mg (Daily)** | **3.96 (2.23 – 7.06)** |
| **21.94 (6.79 – 70.82)** | **15.46 (4.82 – 50.19)** | **13.85 (7.06 – 27.52)** | **13.47 (4.34 – 43.06)** | **3.23 (1.73 – 5.73)** | **Placebo** |

Alkhezi OS,et al Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. Obesity reviews. 2023

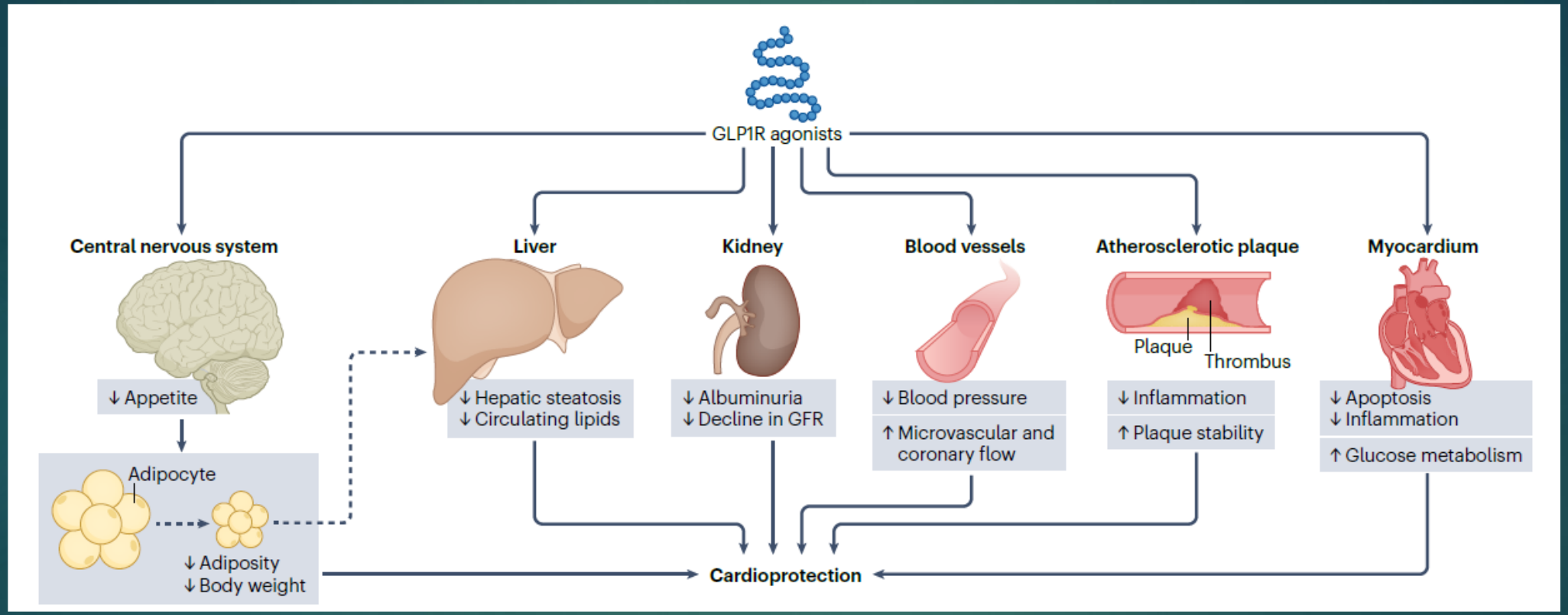
for the ≥15% and 20% comparisons, all GLP-1 RAs were better than placebo except for liraglutide 3 mg.

**(B) Patients with weight reduction of ≥ 15% and ≥ 20%**

| | | | | | |
|---|---|---|---|---|---|
| **Tirzepatide 15 mg (Weekly)** | 1.20 (0.21 – 6.84) | 1.55 (0.21 – 11.57) | 2.00 (0.18 – 22.4) | **8.83 (1.22 – 69.32)** | **24.95 (4.46 – 146.15)** |
| 1.29 (0.20 – 7.93) | **Tirzepatide 10 mg (Weekly)** | 1.29 (0.18 – 9.72) | 1.66 (0.16 – 18.56) | **7.36 (1.04 – 57.71)** | **20.79 (3.79 – 121.86)** |
| 1.97 (0.21 – 16.42) | 1.53 (0.17 – 12.93) | **Semaglutide 2.4 mg (Weekly)** | 1.28 (0.20 – 8.42) | **5.69 (1.65 – 20.92)** | **16.07 (6.09 – 43.79)** |
| 2.17 (0.14 – 28.36) | 1.67 (0.11 – 22.94) | 1.09 (0.13 – 8.78) | **Semaglutide 0.4 mg (Daily)** | 4.45 (0.87 – 23.37) | **12.52 (2.39 – 66.03)** |
| **20.49 (1.81 – 204.99)** | **15.85 (1.37 – 163.24)** | **10.35 (2.23 – 49.92)** | **9.48 (1.45 – 64.85)** | **Liraglutide 3 mg (Daily)** | 2.82 (0.99 – 7.64) |
| **41.91 (6.36 – 256.38)** | **32.48 (4.72 – 203.03)** | **21.08 (7.2 – 66.24)** | **19.33 (2.99 – 142.68)** | 2.05 (0.48 – 9.21) | **Placebo** |

Alkhezi OS,et al Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. Obesity reviews. 2023

# cardiovascular benefits and mechanisms of action




Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nature reviews cardiology. 2023

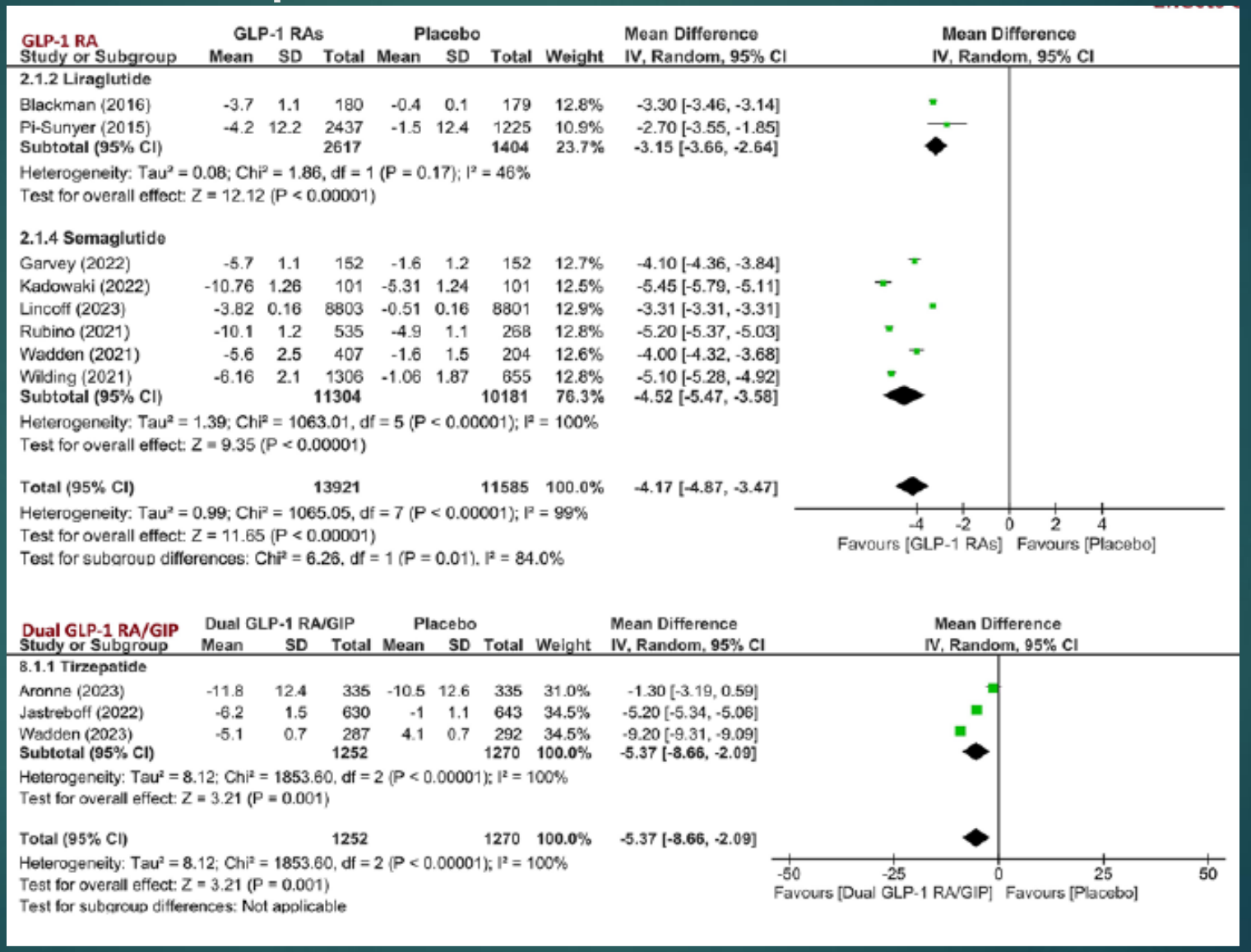
American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-024-00695-9

SYSTEMATIC REVIEW

# Role of Incretin Mimetics in Cardiovascular Outcomes and Other Classical Cardiovascular Risk Factors beyond Obesity and Diabetes Mellitus in Nondiabetic Adults with Obesity: a Meta-analysis of Randomized Controlled Trials

- comprised 11 qualified RCTs. liraglutide (two trials) and semaglutide (six trials) tirzepatide (three trials)
- Mean of treatment duration : 61.3 weeks (range 28–104 weeks).
- mean age of the participants was 48.2 years,
- 37.9% of patients were male
- Previous hypertension:43.8%, dyslipidemia: 39.3%, ,and preexisting cardiovascular disease 13.4%
- receiving antihypertensive drugs (25.8%) and lipid lowering medications (27.9%).

# Systolic blood pressure



| GLP-1 RA<br>Study or Subgroup | GLP-1 RAs<br>Mean | SD | Total | Placebo<br>Mean | SD | Total | Weight | Mean Difference<br>IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.1.2 Liraglutide** | | | | | | | | |
| Blackman (2016) | -3.7 | 1.1 | 180 | -0.4 | 0.1 | 179 | 12.8% | -3.30 [-3.46, -3.14] |
| Pi-Sunyer (2015) | -4.2 | 12.2 | 2437 | -1.5 | 12.4 | 1225 | 10.9% | -2.70 [-3.55, -1.85] |
| **Subtotal (95% CI)** | | | **2617** | | | **1404** | **23.7%** | **-3.15 [-3.66, -2.64]** |
| Heterogeneity: Tau² = 0.08; Chi² = 1.86, df = 1 (P = 0.17); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 12.12 (P < 0.00001) | | | | | | | | |
| **2.1.4 Semaglutide** | | | | | | | | |
| Garvey (2022) | -5.7 | 1.1 | 152 | -1.6 | 1.2 | 152 | 12.7% | -4.10 [-4.36, -3.84] |
| Kadowaki (2022) | -10.76 | 1.26 | 101 | -5.31 | 1.24 | 101 | 12.5% | -5.45 [-5.79, -5.11] |
| Lincoff (2023) | -3.82 | 0.16 | 8803 | -0.51 | 0.16 | 8801 | 12.9% | -3.31 [-3.31, -3.31] |
| Rubino (2021) | -10.1 | 1.2 | 535 | -4.9 | 1.1 | 268 | 12.8% | -5.20 [-5.37, -5.03] |
| Wadden (2021) | -5.6 | 2.5 | 407 | -1.6 | 1.5 | 204 | 12.6% | -4.00 [-4.32, -3.68] |
| Wilding (2021) | -6.16 | 2.1 | 1306 | -1.06 | 1.87 | 655 | 12.8% | -5.10 [-5.28, -4.92] |
| **Subtotal (95% CI)** | | | **11304** | | | **10181** | **76.3%** | **-4.52 [-5.47, -3.58]** |
| Heterogeneity: Tau² = 1.39; Chi² = 1063.01, df = 5 (P < 0.00001); I² = 100% | | | | | | | | |
| Test for overall effect: Z = 9.35 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **13921** | | | **11585** | **100.0%** | **-4.17 [-4.87, -3.47]** |
| Heterogeneity: Tau² = 0.99; Chi² = 1065.05, df = 7 (P < 0.00001); I² = 99% | | | | | | | | |
| Test for overall effect: Z = 11.65 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 6.26, df = 1 (P = 0.01), I² = 84.0% | | | | | | | | |

Mean Difference
IV, Random, 95% CI

-4 -2 0 2 4
Favours [GLP-1 RAs] Favours [Placebo]

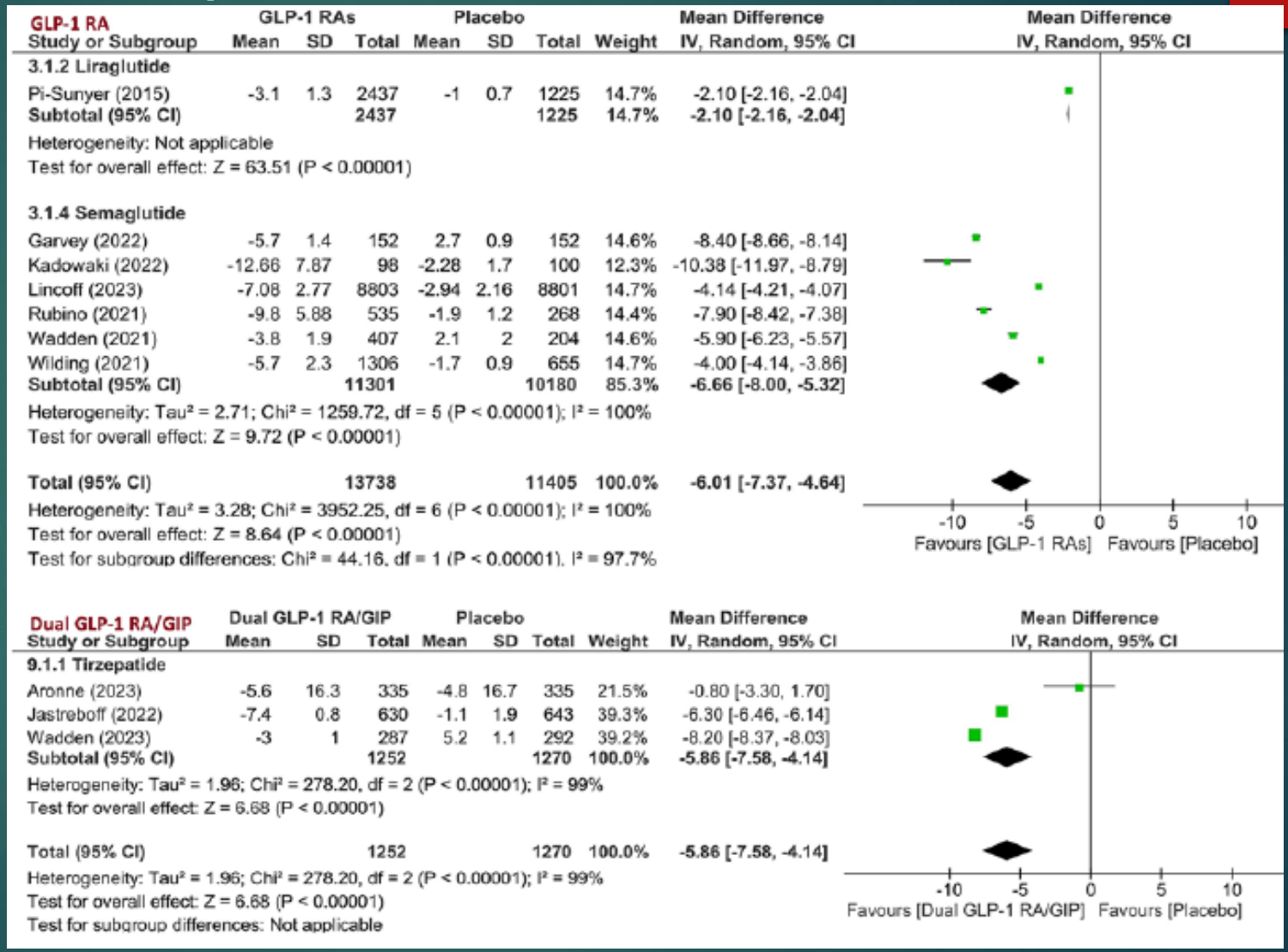
| Dual GLP-1 RA/GIP<br>Study or Subgroup | Dual GLP-1 RA/GIP<br>Mean | SD | Total | Placebo<br>Mean | SD | Total | Weight | Mean Difference<br>IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **8.1.1 Tirzepatide** | | | | | | | | |
| Aronne (2023) | -11.8 | 12.4 | 335 | -10.5 | 12.6 | 335 | 31.0% | -1.30 [-3.19, 0.59] |
| Jastreboff (2022) | -6.2 | 1.5 | 630 | -1 | 1.1 | 643 | 34.5% | -5.20 [-5.34, -5.06] |
| Wadden (2023) | -5.1 | 0.7 | 287 | 4.1 | 0.7 | 292 | 34.5% | -9.20 [-9.31, -9.09] |
| **Subtotal (95% CI)** | | | **1252** | | | **1270** | **100.0%** | **-5.37 [-8.66, -2.09]** |
| Heterogeneity: Tau² = 8.12; Chi² = 1853.60, df = 2 (P < 0.00001); I² = 100% | | | | | | | | |
| Test for overall effect: Z = 3.21 (P = 0.001) | | | | | | | | |
| **Total (95% CI)** | | | **1252** | | | **1270** | **100.0%** | **-5.37 [-8.66, -2.09]** |
| Heterogeneity: Tau² = 8.12; Chi² = 1853.60, df = 2 (P < 0.00001); I² = 100% | | | | | | | | |
| Test for overall effect: Z = 3.21 (P = 0.001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |

Mean Difference
IV, Random, 95% CI

-50 -25 0 25 50
Favours [Dual GLP-1 RA/GIP] Favours [Placebo]

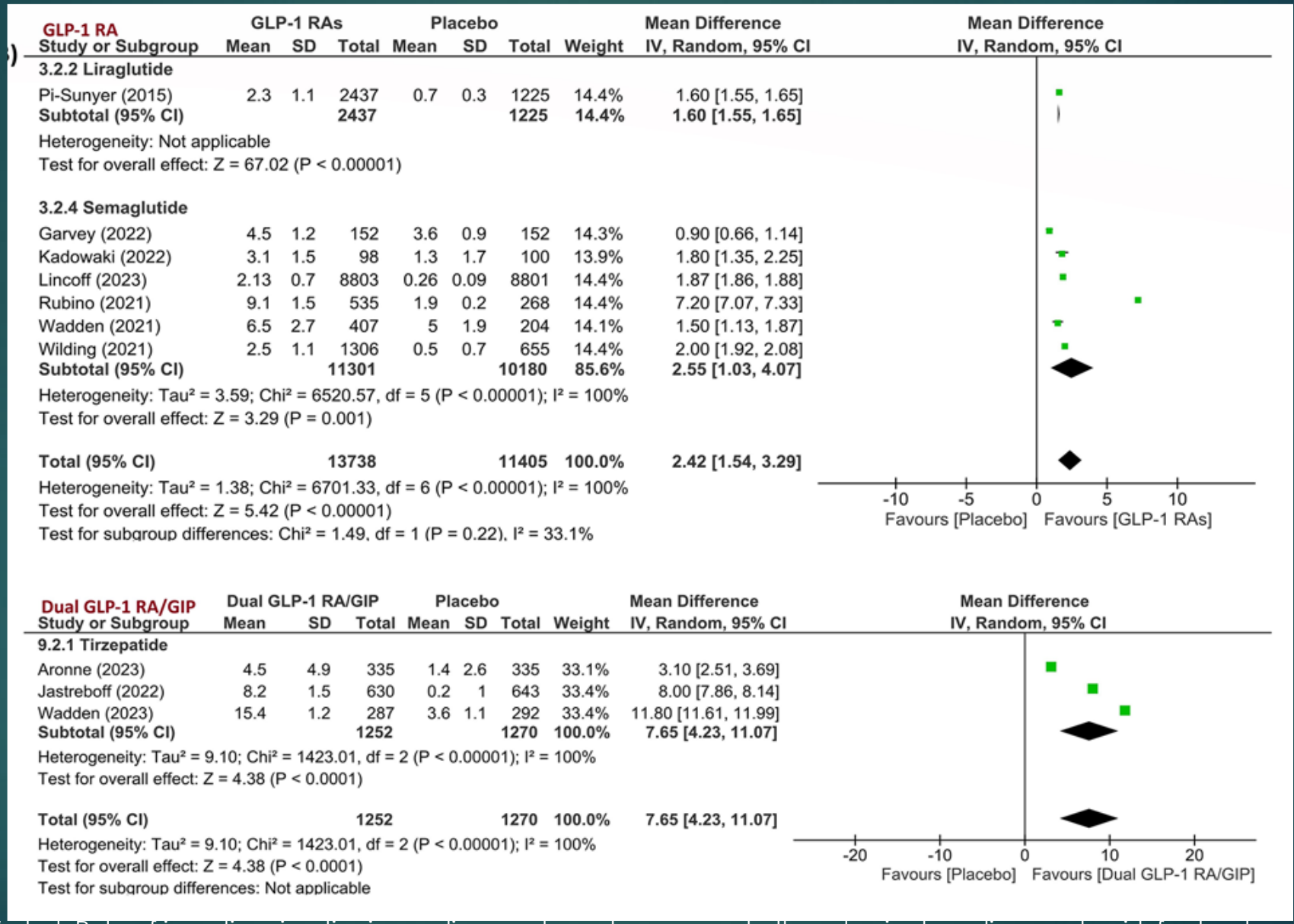
Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2025

# Diastolic blood pressure



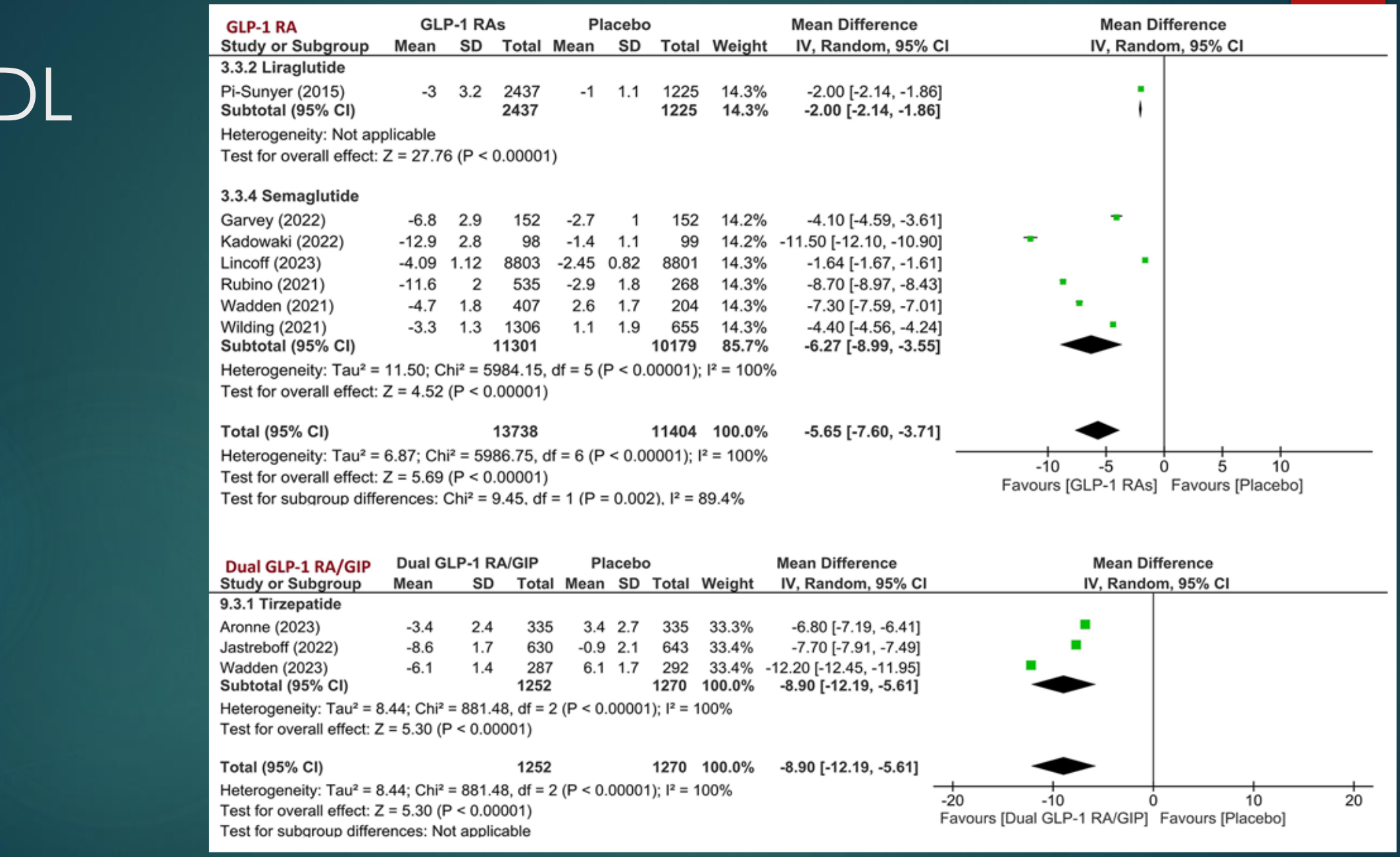

Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2025

# HDL



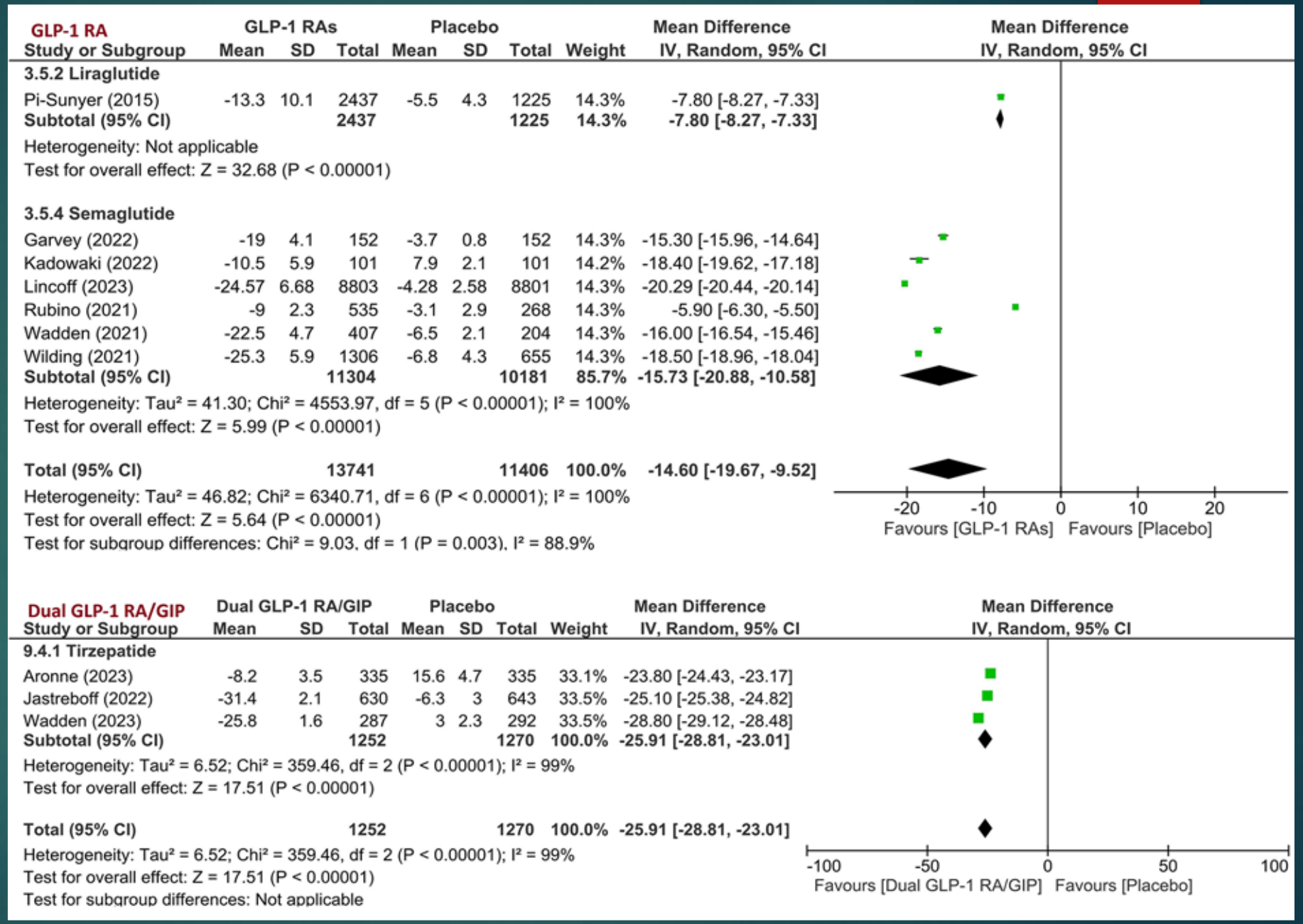

Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2025

# LDL



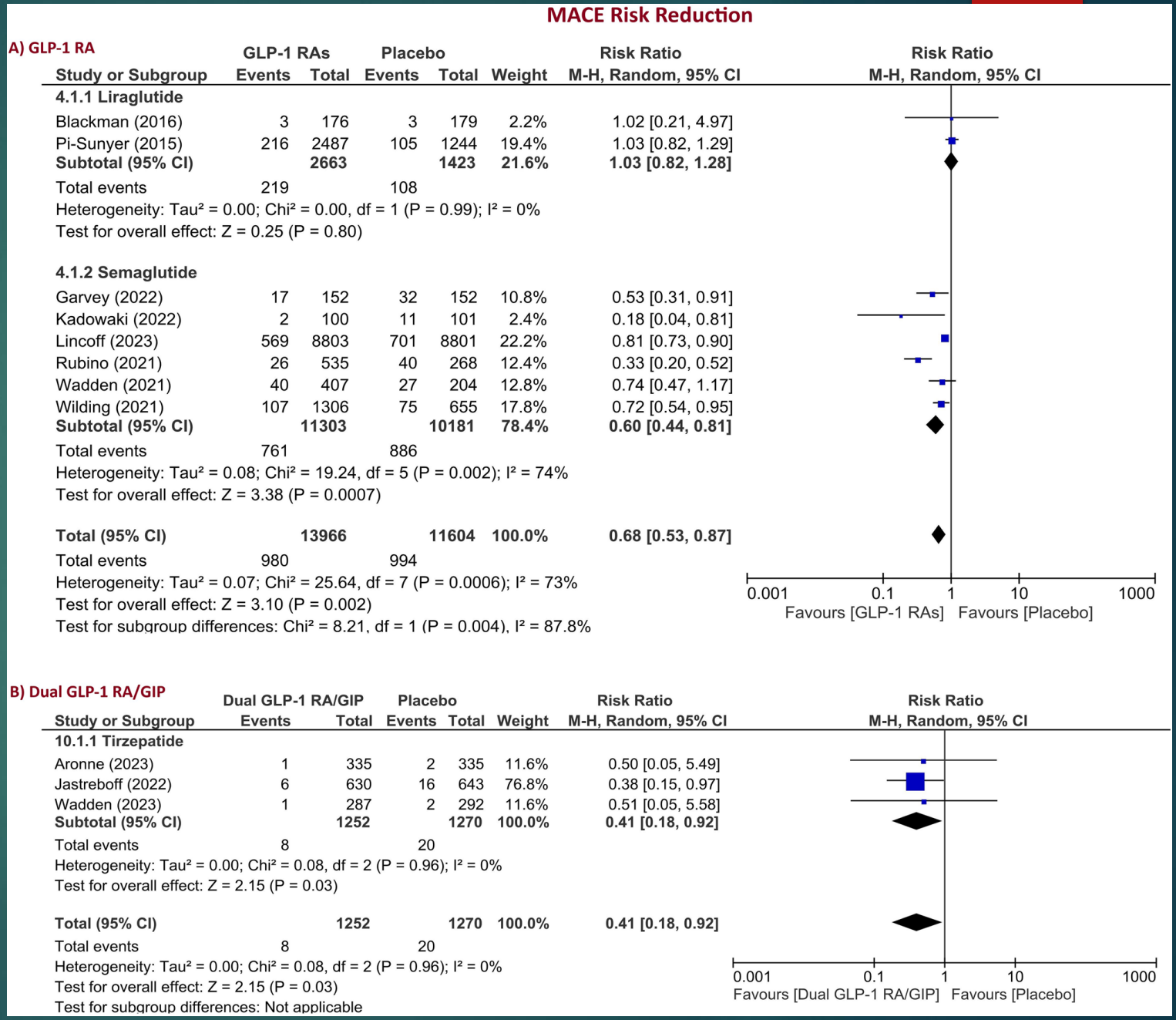

Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2025

# triglyceride




Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2025

MACE :a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death




Kamarullah W,et al. Role of incretin mimetics in cardiovascular outcomes and other classical cardiovascular risk factors beyond obesity and diabetes mellitus in nondiabetic adults with obesity: A meta-analysis of randomized controlled trials. American Journal of

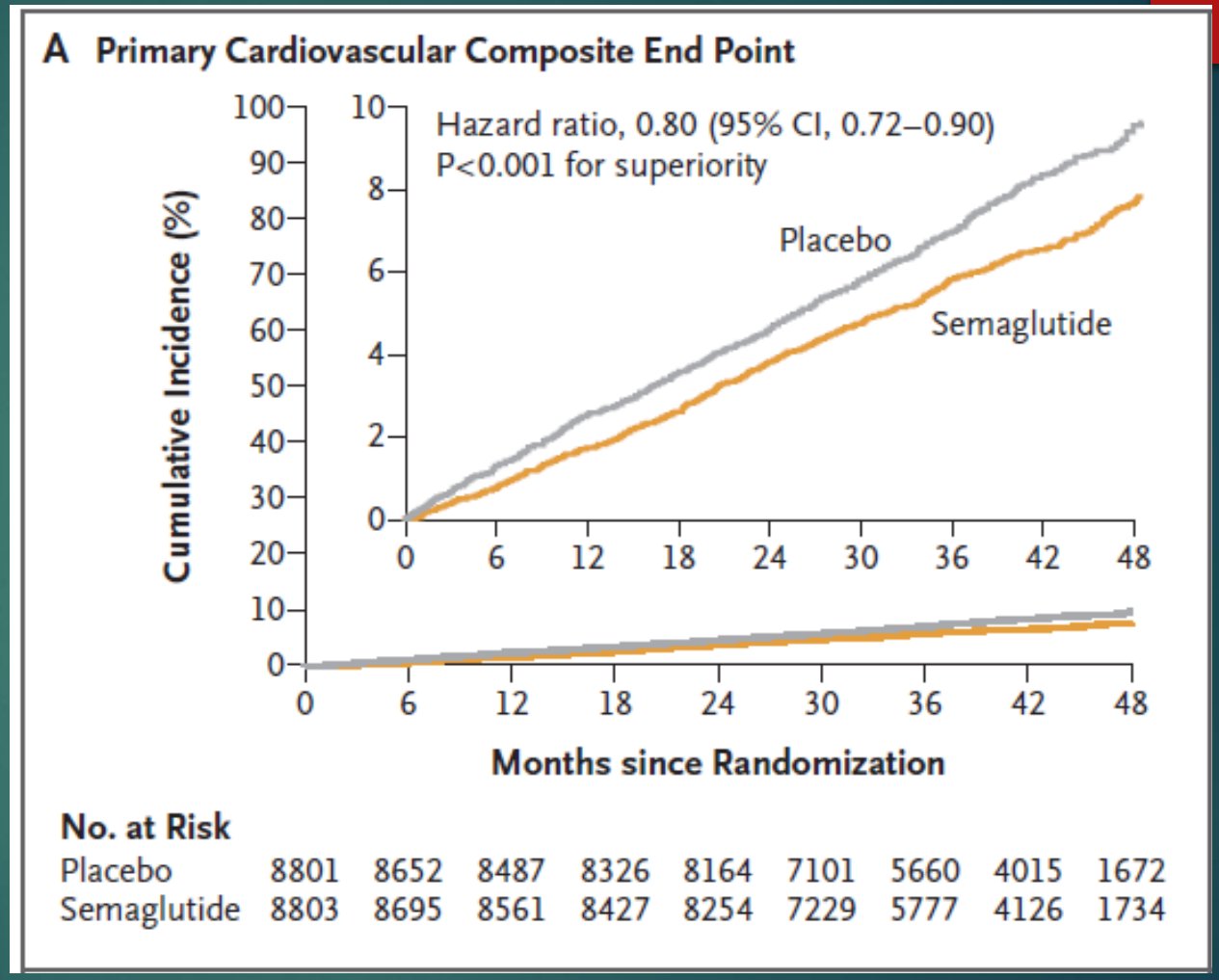
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

# Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

- 17,604 patients patients 45 years of age or older with preexisting cardiovascular disease and a body-mass index of 27 or greater but no history of diabetes
- 8803 were assigned to receive semaglutide and 8801 to receive placebo
- The mean duration of exposure to semaglutide or placebo was 34.2+-13.7months, and the mean duration of follow-up was39.8 months

primary cardiovascular end-point event(a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in (6.5%) in the semaglutide group and (8.0%) in the placebo group




Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I. Semaglutide and cardiovascular outcomes in obesity without diabetes. New England Journal of Medicine. 2023 Dec 14;389(24):2221-32.

ESC European Society of Cardiology

European Heart Journal Open (2025) **5**, oeaf117
https://doi.org/10.1093/ehjopen/oeaf117

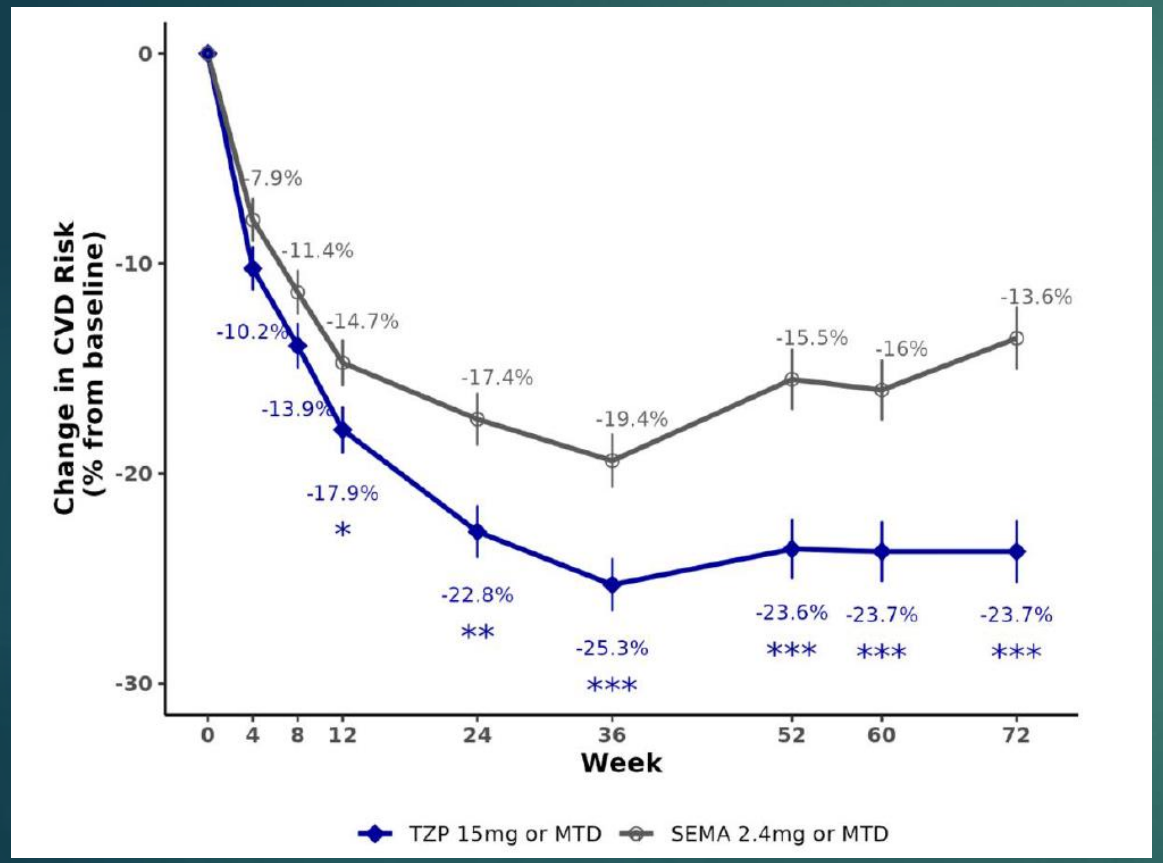
**ORIGINAL ARTICLE**
*Special populations*

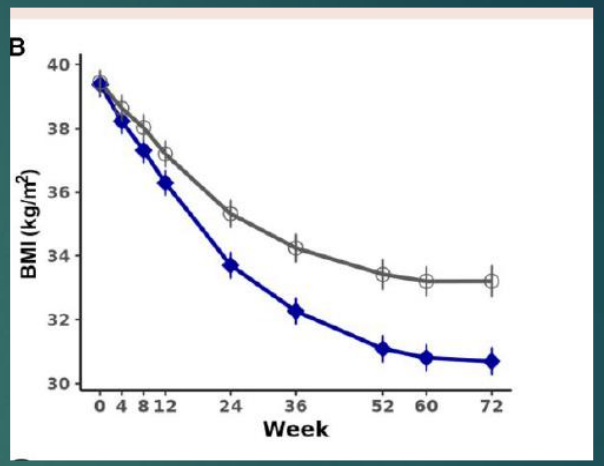
# Tirzepatide compared with semaglutide and 10-year cardiovascular disease risk reduction in obesity: *post-hoc* analysis of the SURMOUNT-5 trial

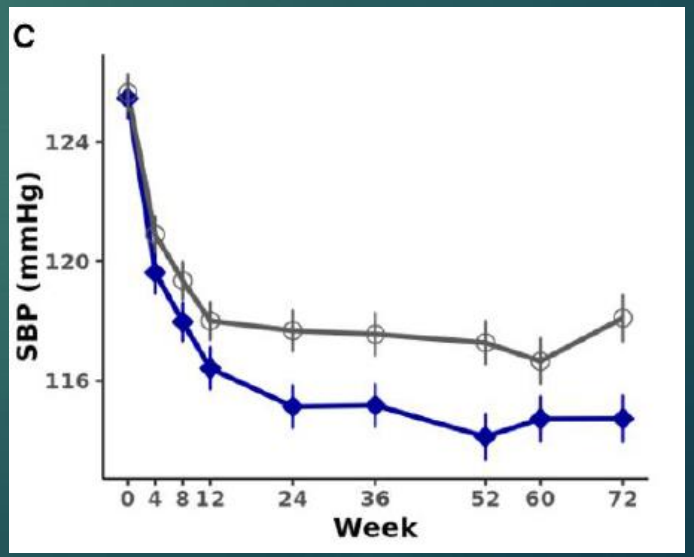
**Mamas A. Mamas[1], Harold Bays[2], Runjia Li[3], Navneet Upadhyay[3], Tanya Irani[3], Cagri Senyucel[3], Julia P. Dunn[3], and Hong Liu-Seifert[3,*]**

- participants with obesity and without Type-2 diabetes without prior CVD
- predicted CVD risk reduction following weight loss in persons with obesity for primary prevention between tirzepatide and semaglutide
- Predicted 10-year CVD risks were compared between treatments at baseline and up to 72 weeks post-treatment

tirzepatide was associated with a 23.72% relative reduction from baseline in 10-year CVD risk compared with a 13.56% relative reduction from baseline in semaglutide (P < 0.001)..




Mamas MA,et al. Tirzepatide compared with semaglutide and 10-year cardiovascular disease risk reduction in obesity: post-hoc analysis of the SURMOUNT-5 trial. European Heart Journal Open. 2025

American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-024-00647-3

SYSTEMATIC REVIEW

# Cardiovascular Benefits of GLP-1 Receptor Agonists in Patients Living with Obesity or Overweight: A Meta-analysis of Randomized Controlled Trials

- 13 RCTs :obese or overweight patients without diabetes
- comprising 30,512 patients, 17,629 (57.8%) recieved GLP-1 RA, 12,883 (42.2%) received placebo
- Six studies used liraglutide, seven used semaglutide, and one used tirzepatide.
- follow-up period :20 to159 weeks.
- The mean age :31 to 61.6 years
- 16,213 patients (53.1%) were men.
- Mean BMI ranged:31.9 to 40.1 kg/m2

GLP-1 RA significantly reduced the occurrence of myocardial infarction (RR0.72; 95% CI 0.61, 0.85; $p < 0.001$; $I2 = 0\%$).

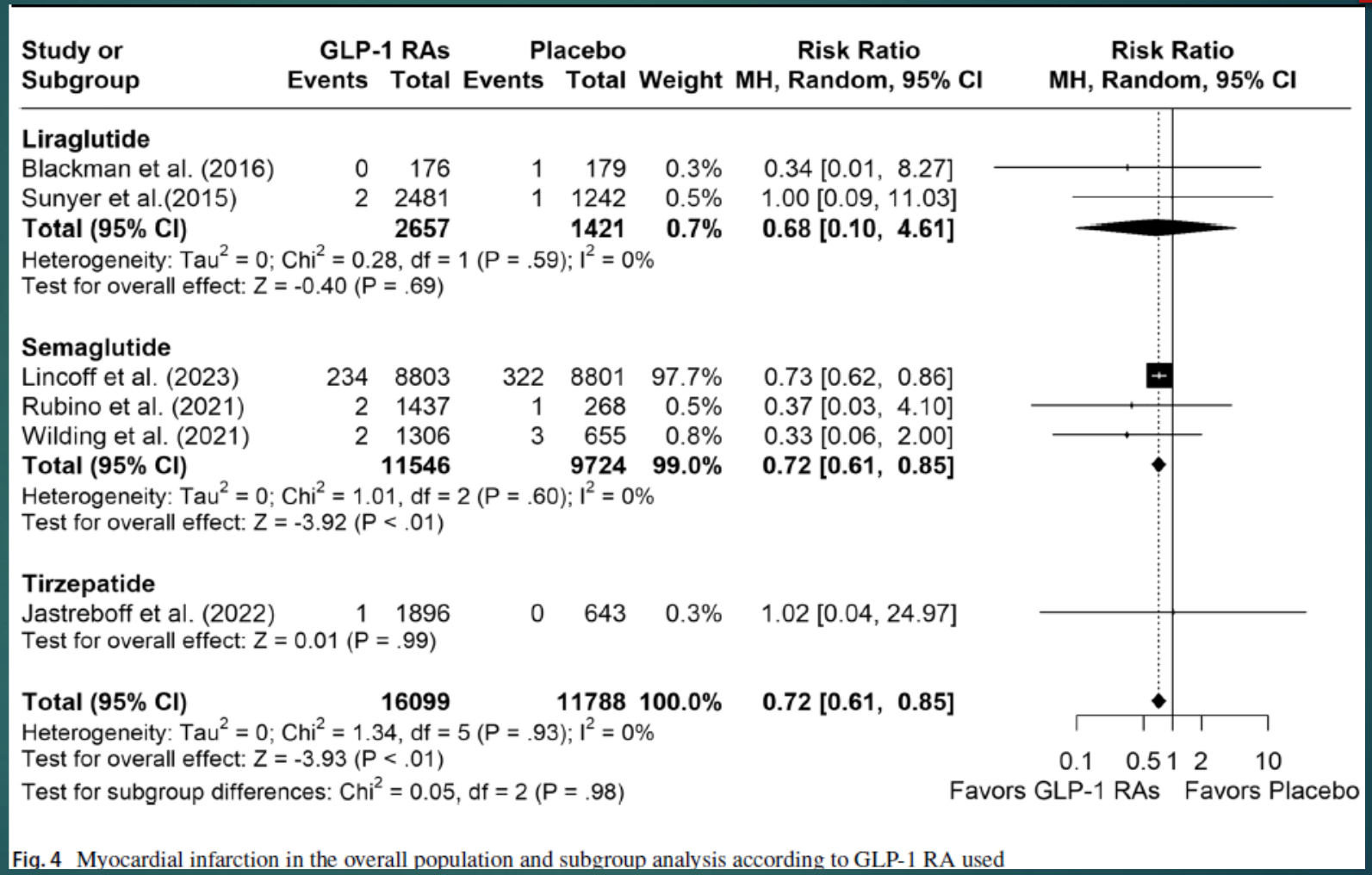



Fig. 4 Myocardial infarction in the overall population and subgroup analysis according to GLP-1 RA used

de Oliveira Almeida G, et al. Cardiovascular benefits of GLP-1 receptor agonists in patients living with obesity or overweight: a meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs. 2024

# there was no significant difference between groups in UA, stroke, AF, and deep vein thrombosis.

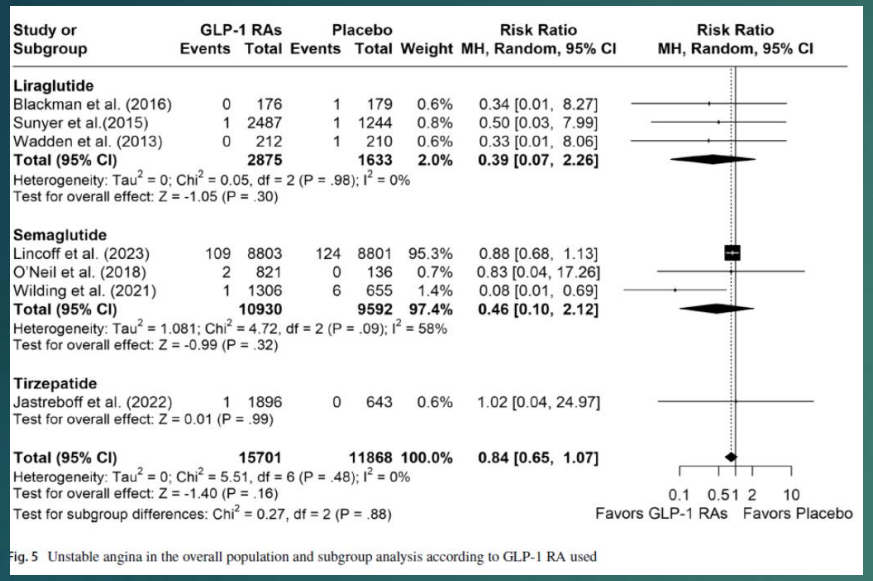
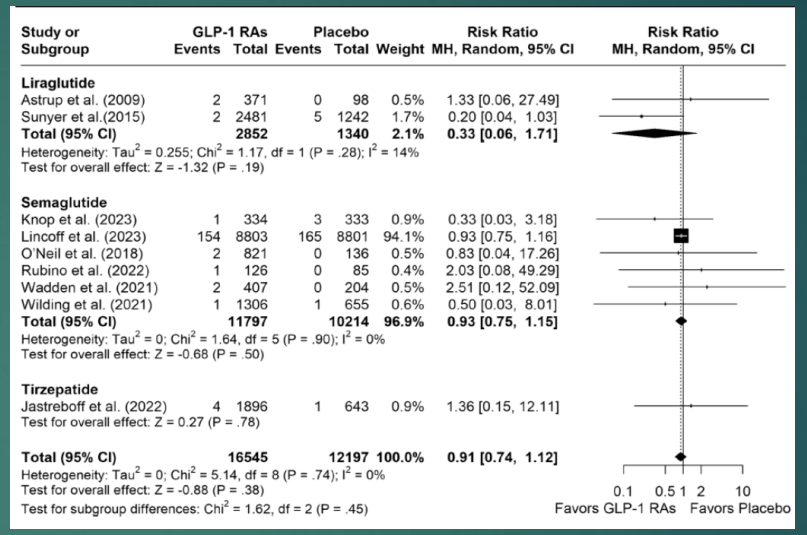



Fig. 5 Unstable angina in the overall population and subgroup analysis according to GLP-1 RA used



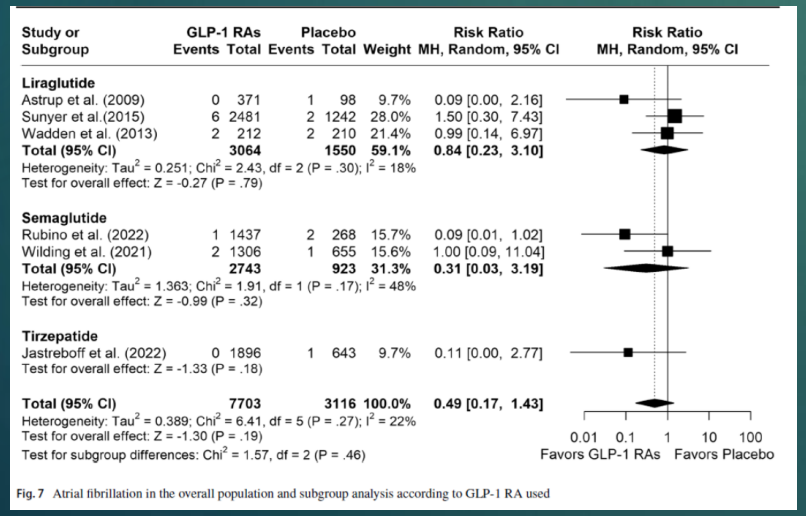




Fig. 7 Atrial fibrillation in the overall population and subgroup analysis according to GLP-1 RA used

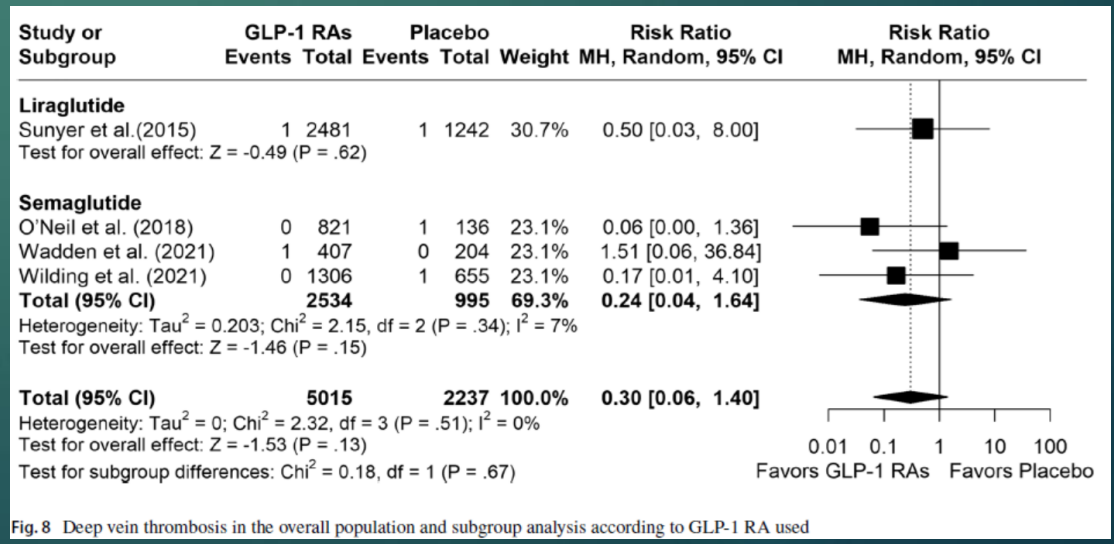
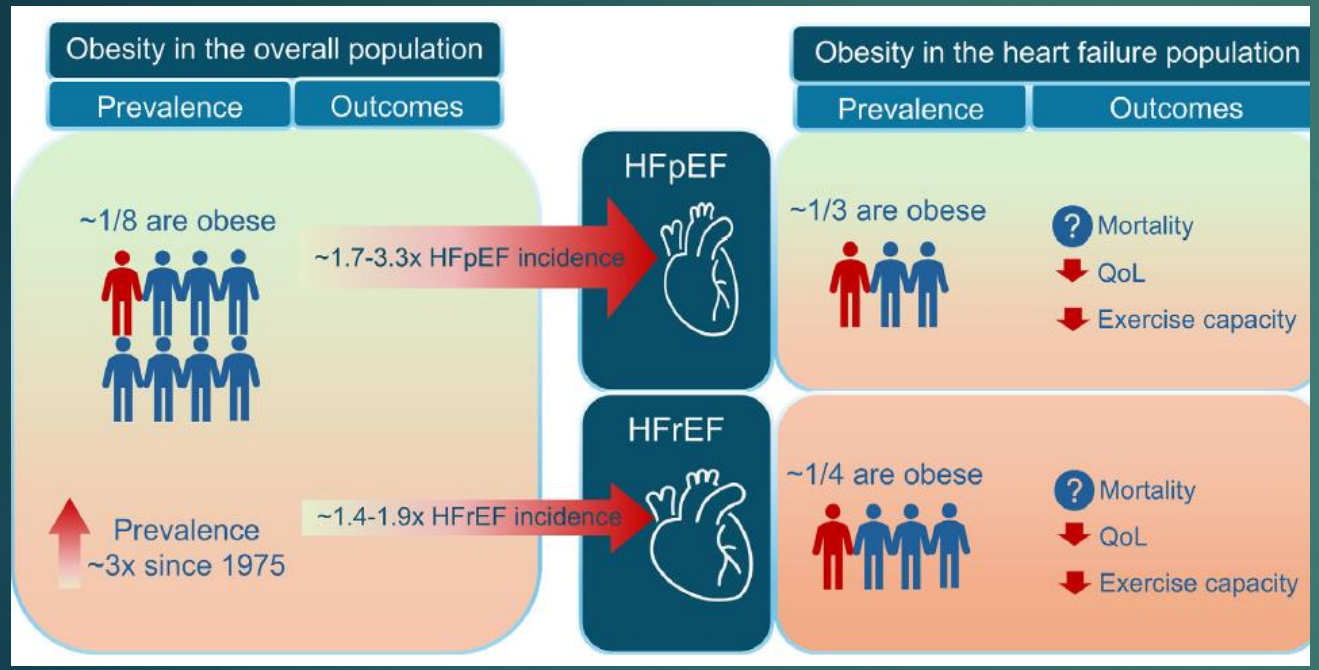



Fig. 8 Deep vein thrombosis in the overall population and subgroup analysis according to GLP-1 RA used

# Obesity and heart failure



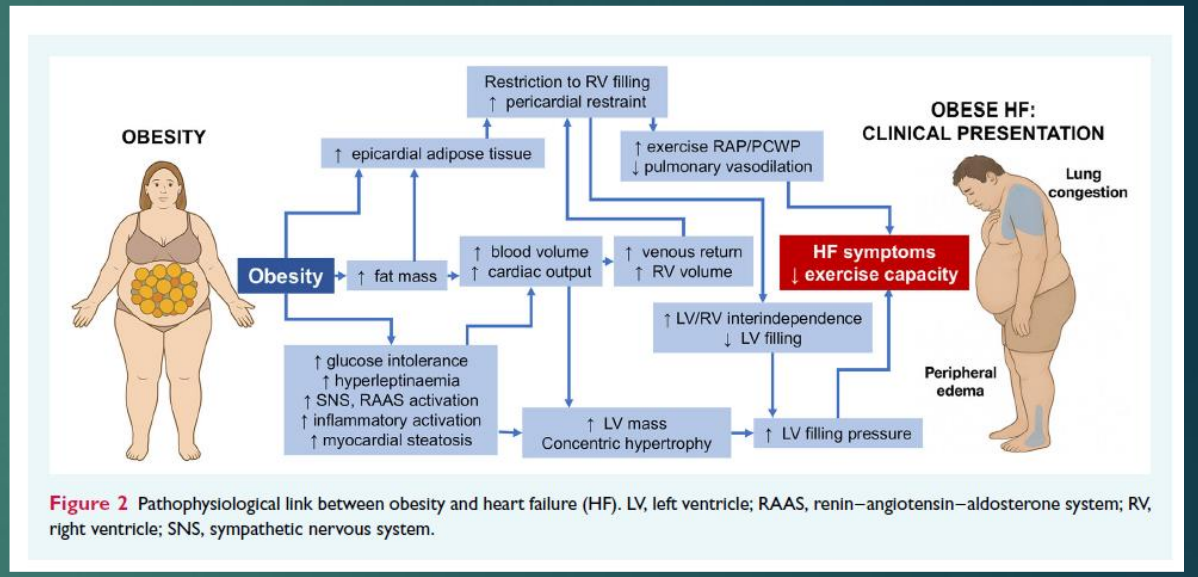
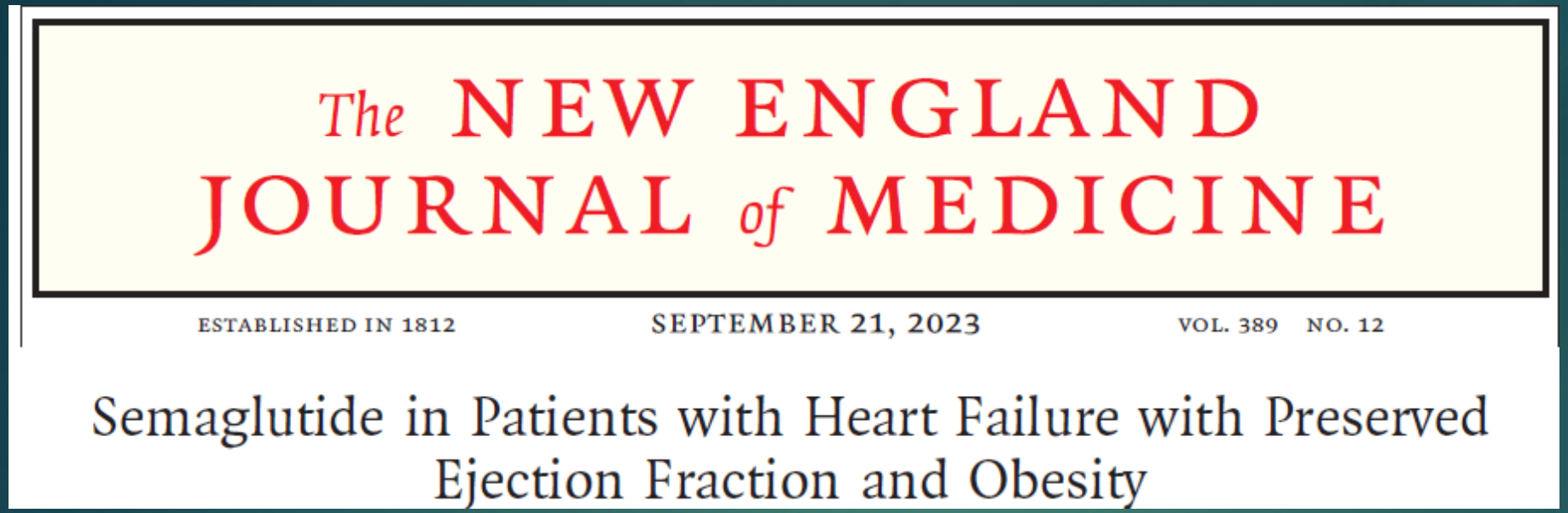
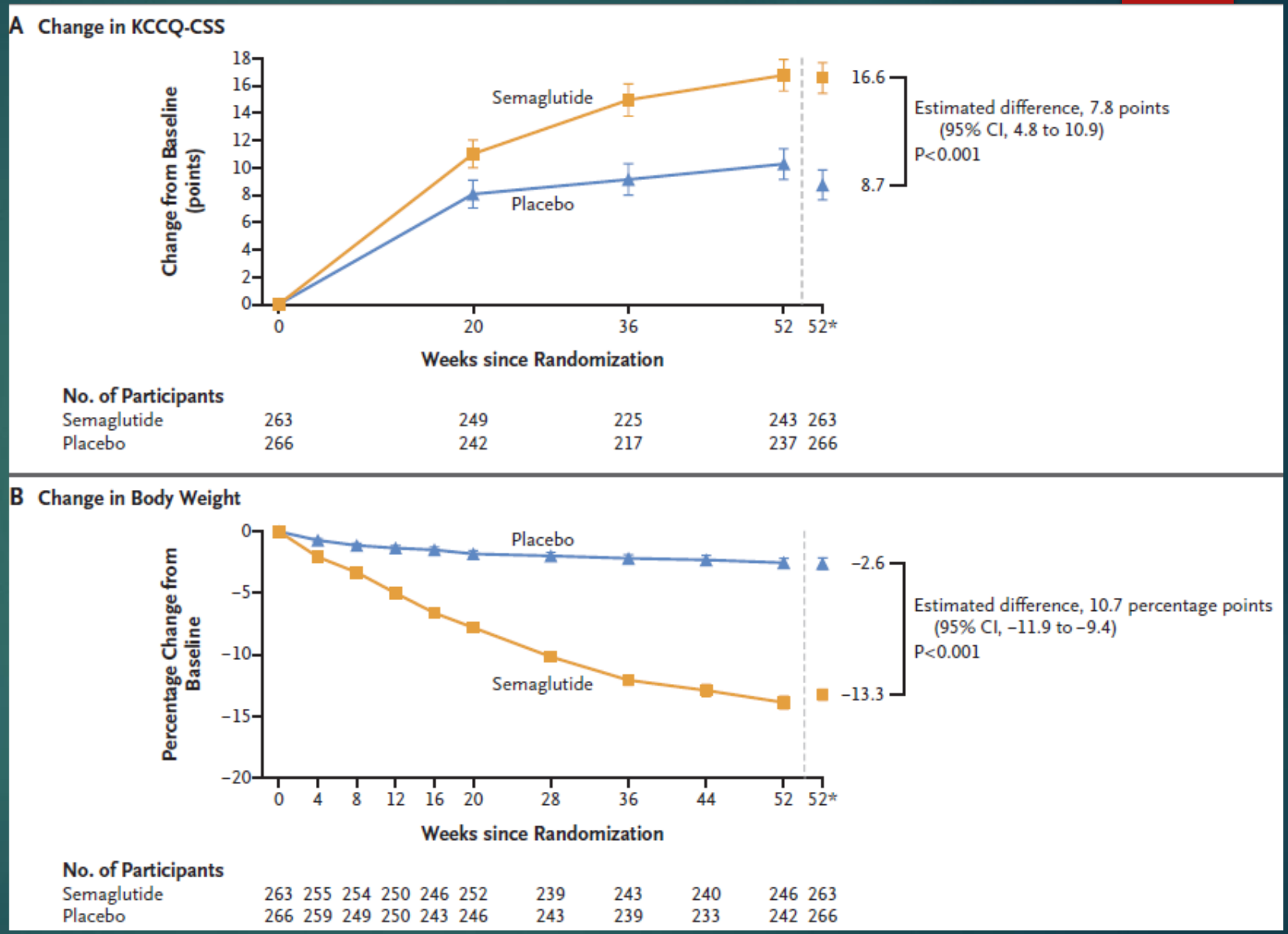




**Figure 2** Pathophysiological link between obesity and heart failure (HF). LV, left ventricle; RAAS, renin–angiotensin–aldosterone system; RV, right ventricle; SNS, sympathetic nervous system.

Heart failure and obesity: Translational approaches and therapeutic perspectives. A scientific statement of the Heart Failure Association of the ESC

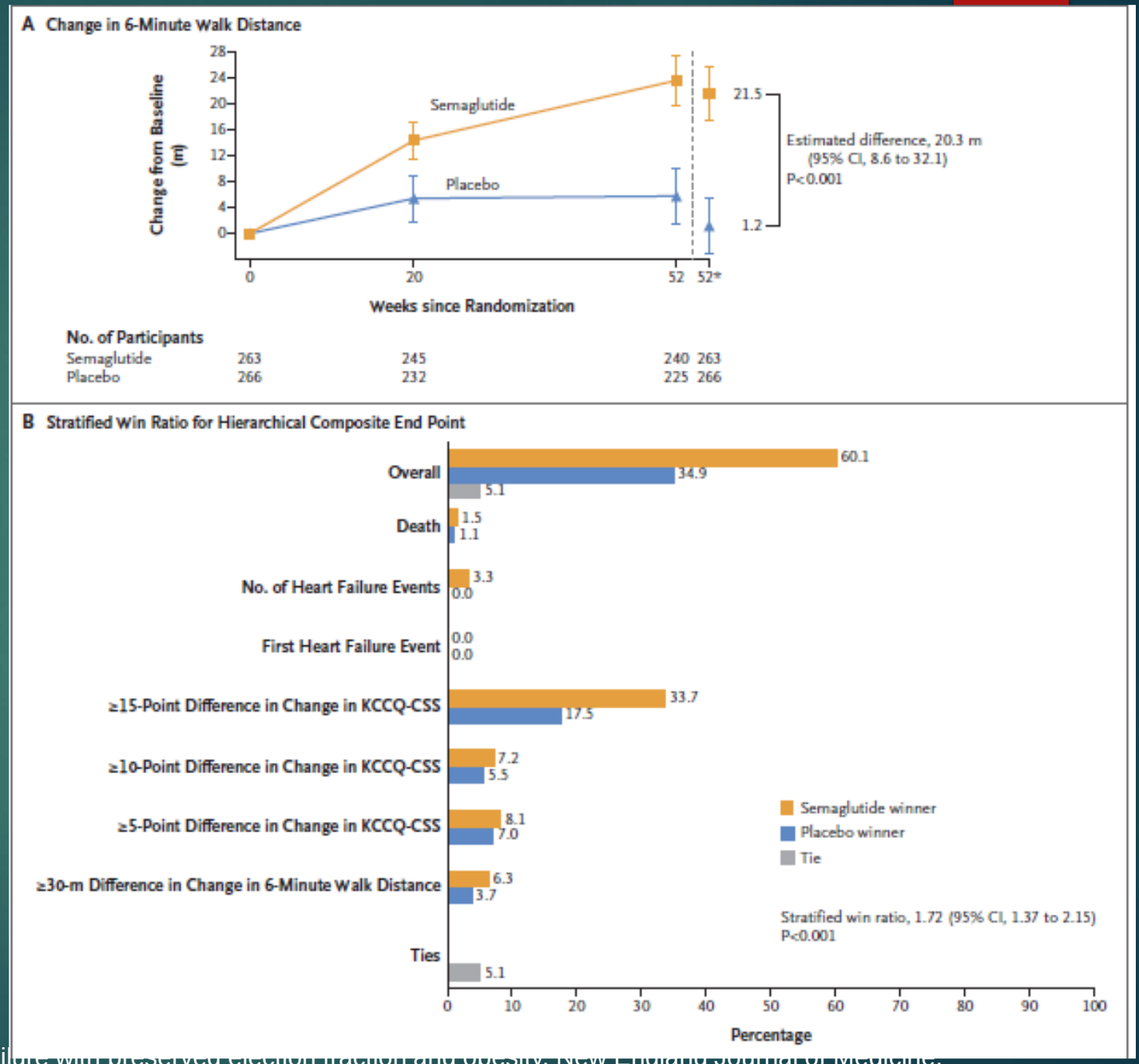



- 529 patients who had heart failure with preserved ejection fraction and a BMI of 30 or higher
- receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks
- primary end points : the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score(KCCQ-CSS)
- secondary end points : the change in the 6-minute walk distance



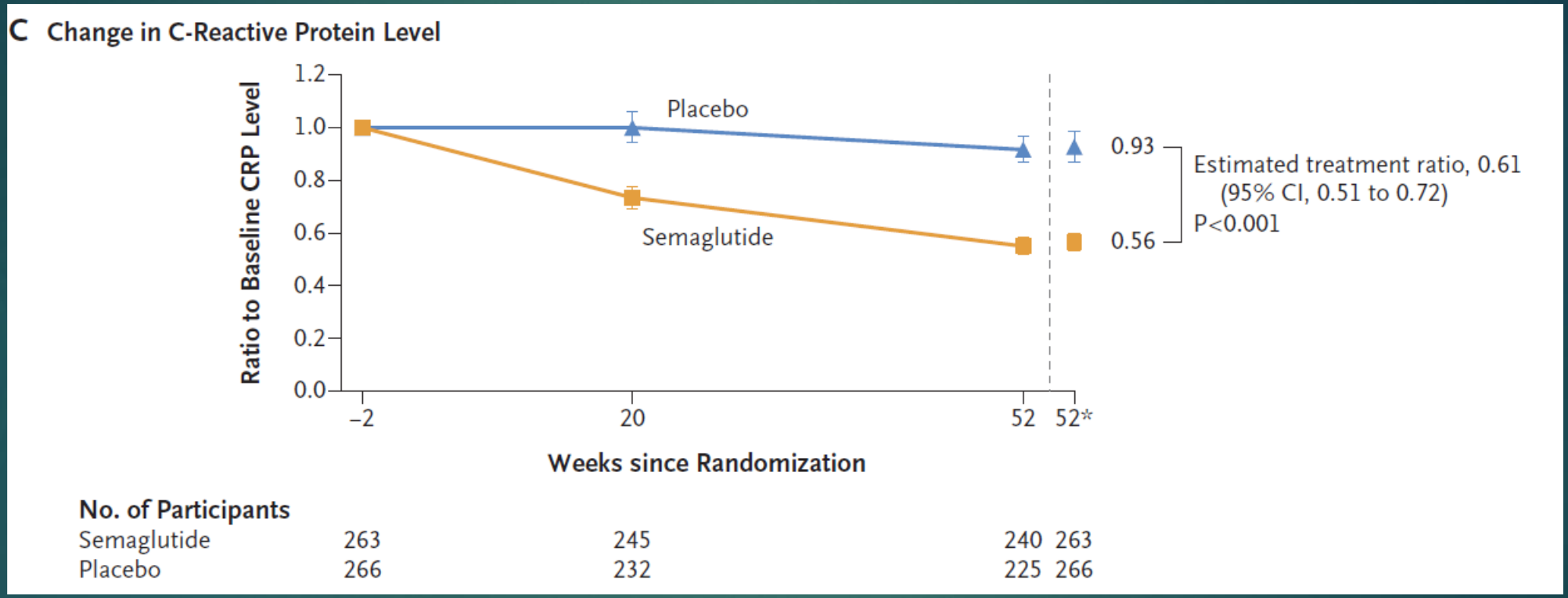

Kosiborod MN,et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. New England Journal of Medicine. 2023

In the analysis of the hierarchical composite end point, semaglutide produced more wins than placebo (win ratio,1.72; 95% CI, 1.37 to 2.15; P<0.001).




Kosiborod MN,et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. New England Journal of Medicine. 2023

The mean percentage change in the CRP level was –43.5% with semaglutide and –7.3% with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001).



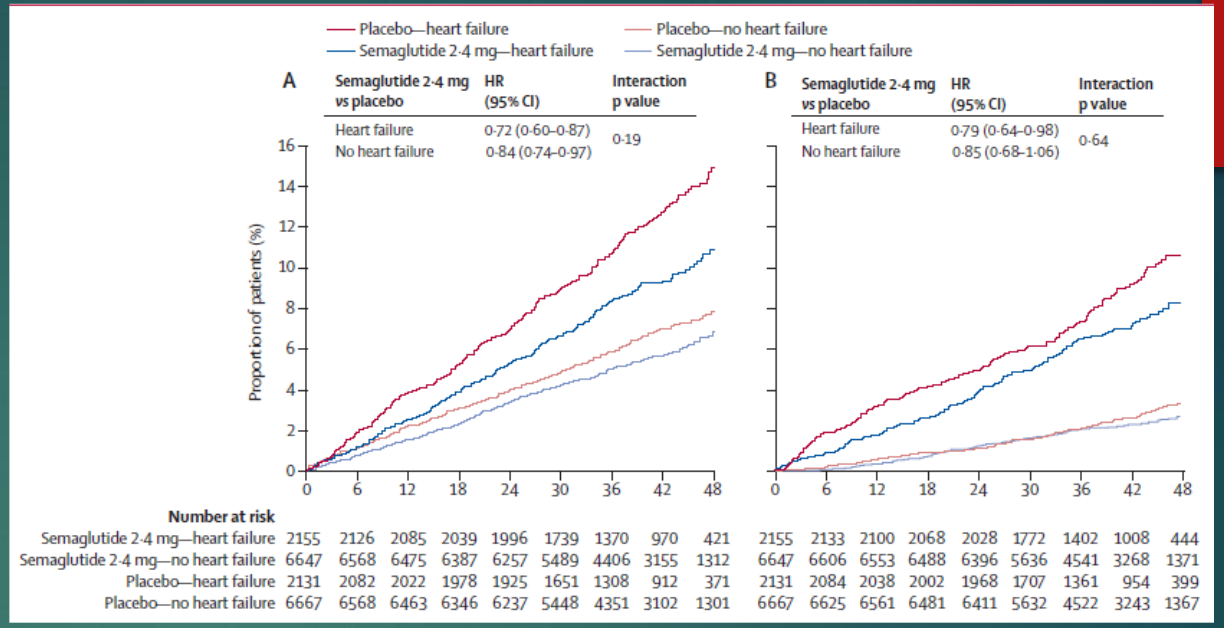
# Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

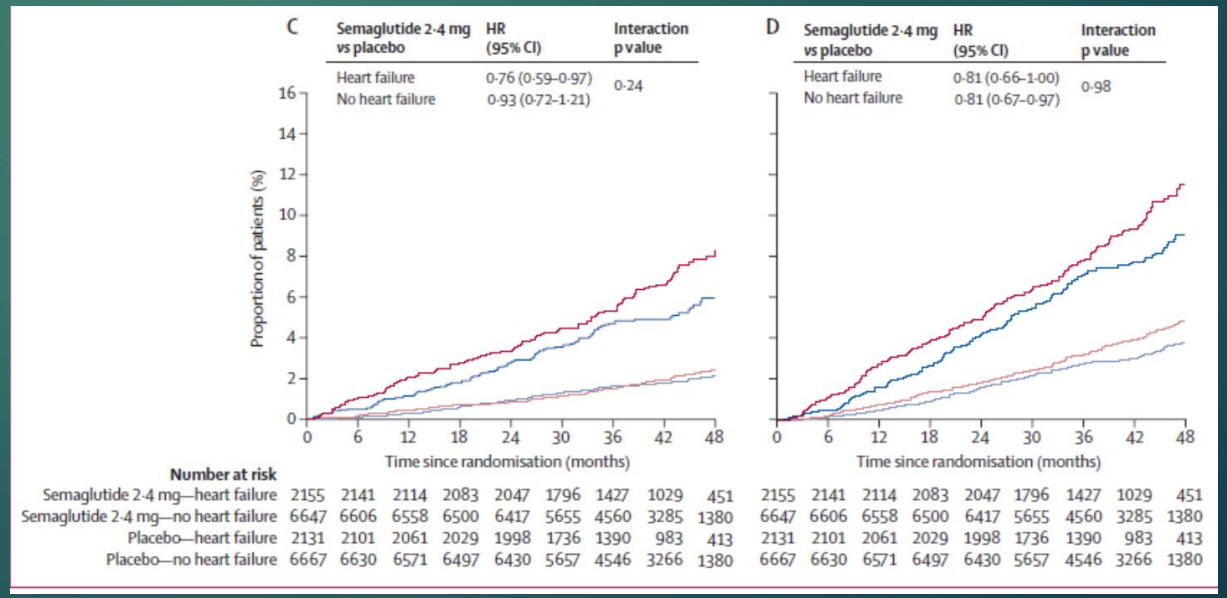
*John Deanfield, Subodh Verma, Benjamin M Scirica, Steven E Kahn, Scott S Emerson, Donna Ryan, Ildiko Lingvay, Helen M Colhoun, Jorge Plutzky, Mikhail N Kosiborod, G Kees Hovingh, Søren Hardt-Lindberg, Ofir Frenkel, Peter E Weeke, Søren Rasmussen, Assen Goudev, Chim C Lang, Miguel Urina-Triana, Mikko Pietilä, A Michael Lincoff, for the SELECT Trial Investigators*

4286 (24·3%) of 17 604 patients had a history of heart failure at enrolment: 2273 (53·0%) had heart failure with preserved ejection fraction, 1347 (31·4%) had heart failure with reduced ejection fraction, and 666 (15·5%) had unclassified heart failure

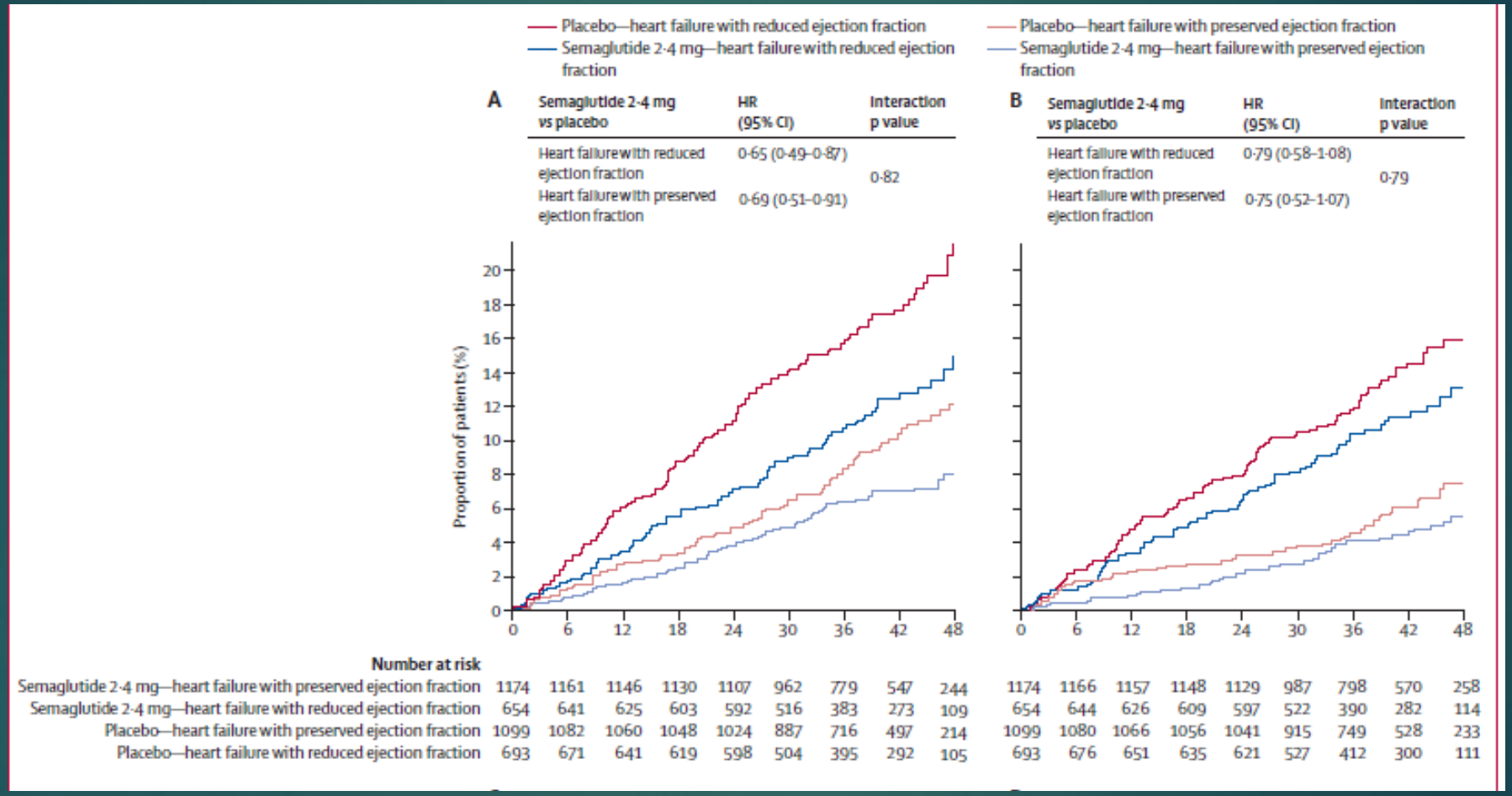
OUTCOME:MACE (defined as a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); a heart failure composite (consisting of cardiovascular death or hospitalisation or urgent hospital visit for heart failure);

Cumulative incidence curves comparing the risk of major adverse cardiovascular events (A), heart failure composite (B) cardiovascular death (C), and all-cause death (D)



- semaglutide resulted in improved outcomes in both HFrEFand HFpEF patients with HFrEF had higher absolute event rates

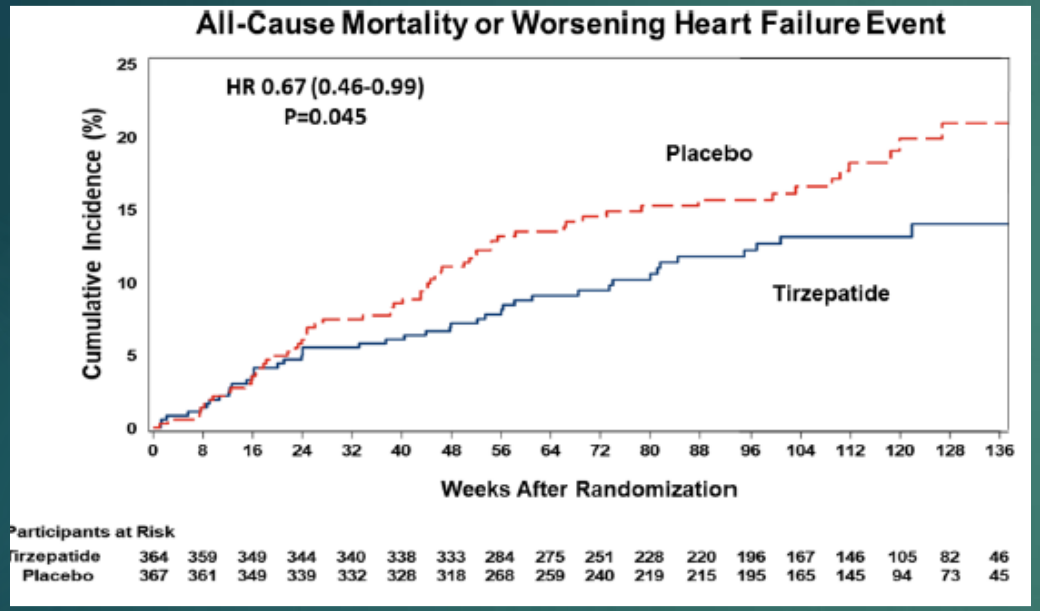


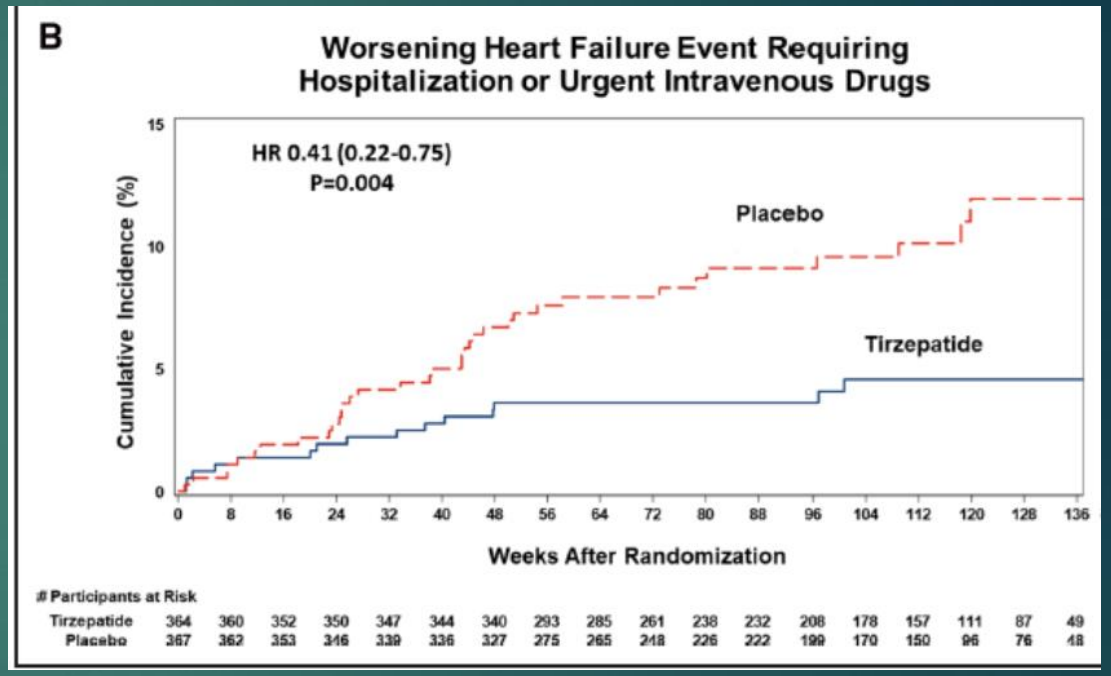

risk of major adverse cardiovascular events (A), heart failure composite (B),


- 731 patients with class II to IV heart failure, ejection fraction ≥50%, and BM≥30 kg/m2
- tirzepatide (titrated up to 15 mg SC weekly; n=364) or placebo (n=367)
- Patients were 65.2±10.7 years of age; 53.8% (n=393) were female; body mass index was 38.2±6.7 kg/m2
- 53% (n=388) had a worsening heart failure event in the previous 12 months.

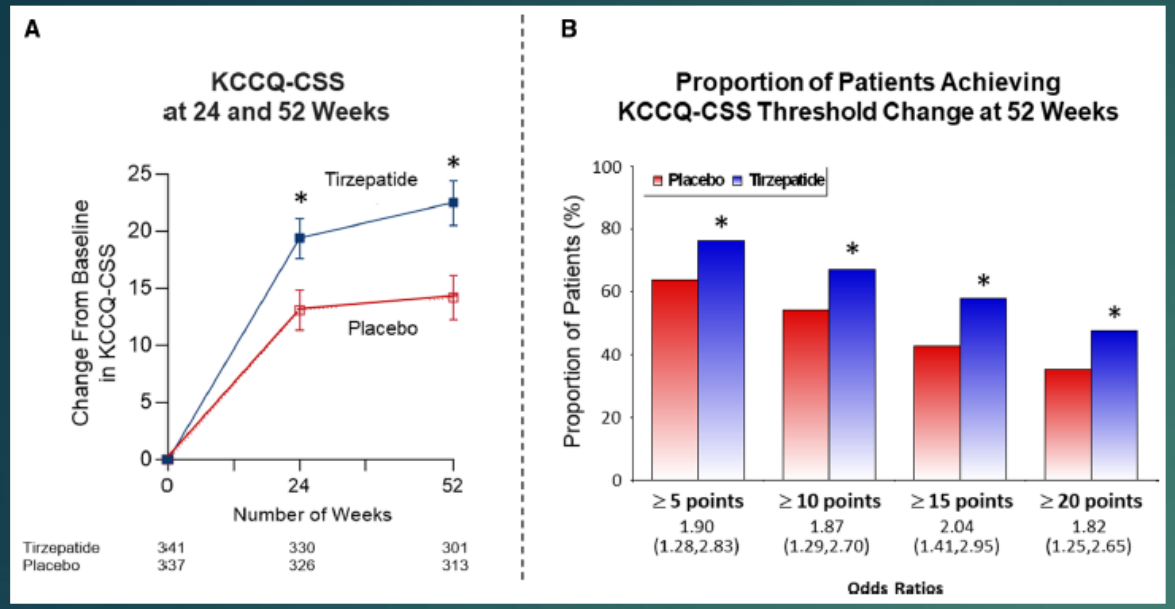
Zile MR, et al. Effects of tirzepatide on the clinical trajectory of patients with heart failure, preserved ejection fraction, and obesity. Circulation. 2025.

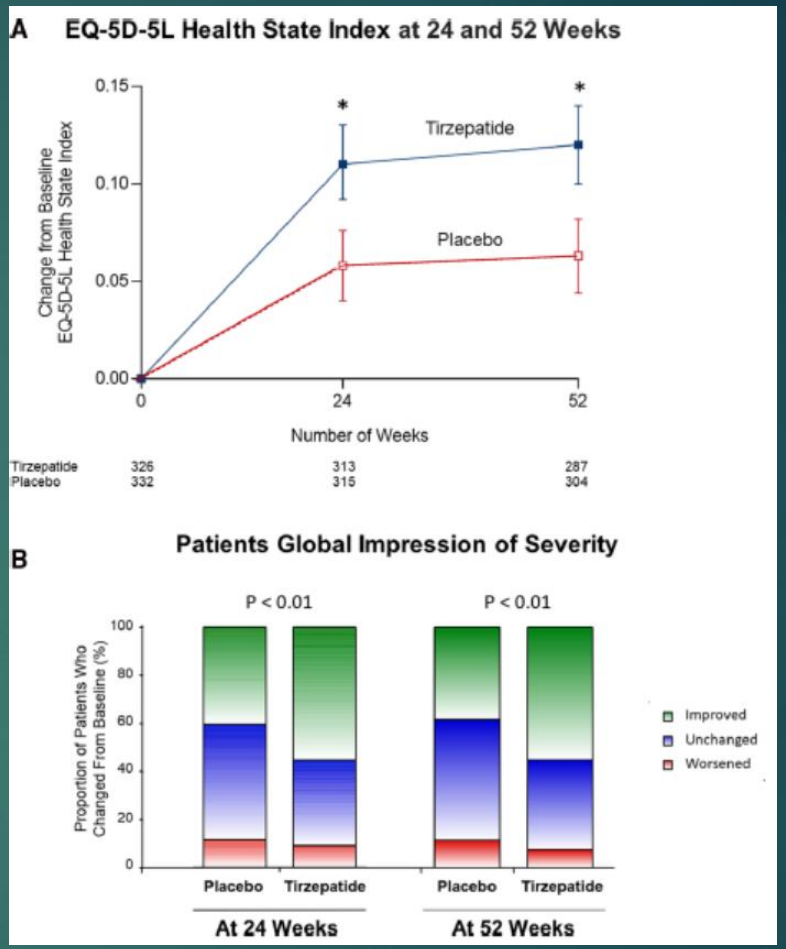
# Tirzepatide produced a comprehensive, meaningful improvement in heart failure across multiple complementary domains

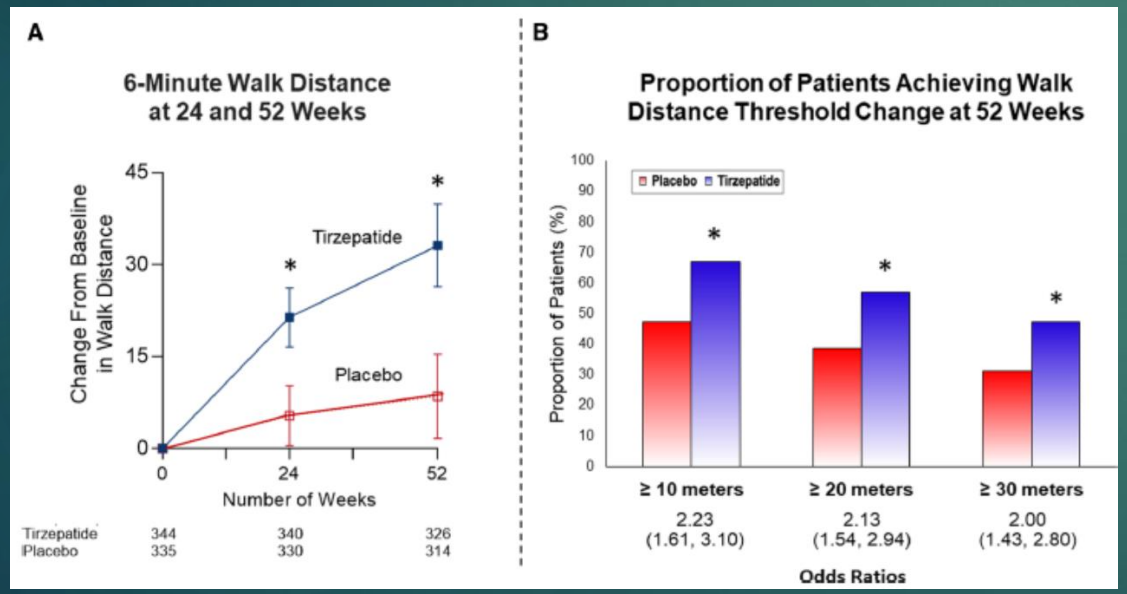



Zile MR, et al. Effects of tirzepatide on the clinical trajectory of patients with heart failure, preserved ejection fraction, and obesity. Circulation. 2025.

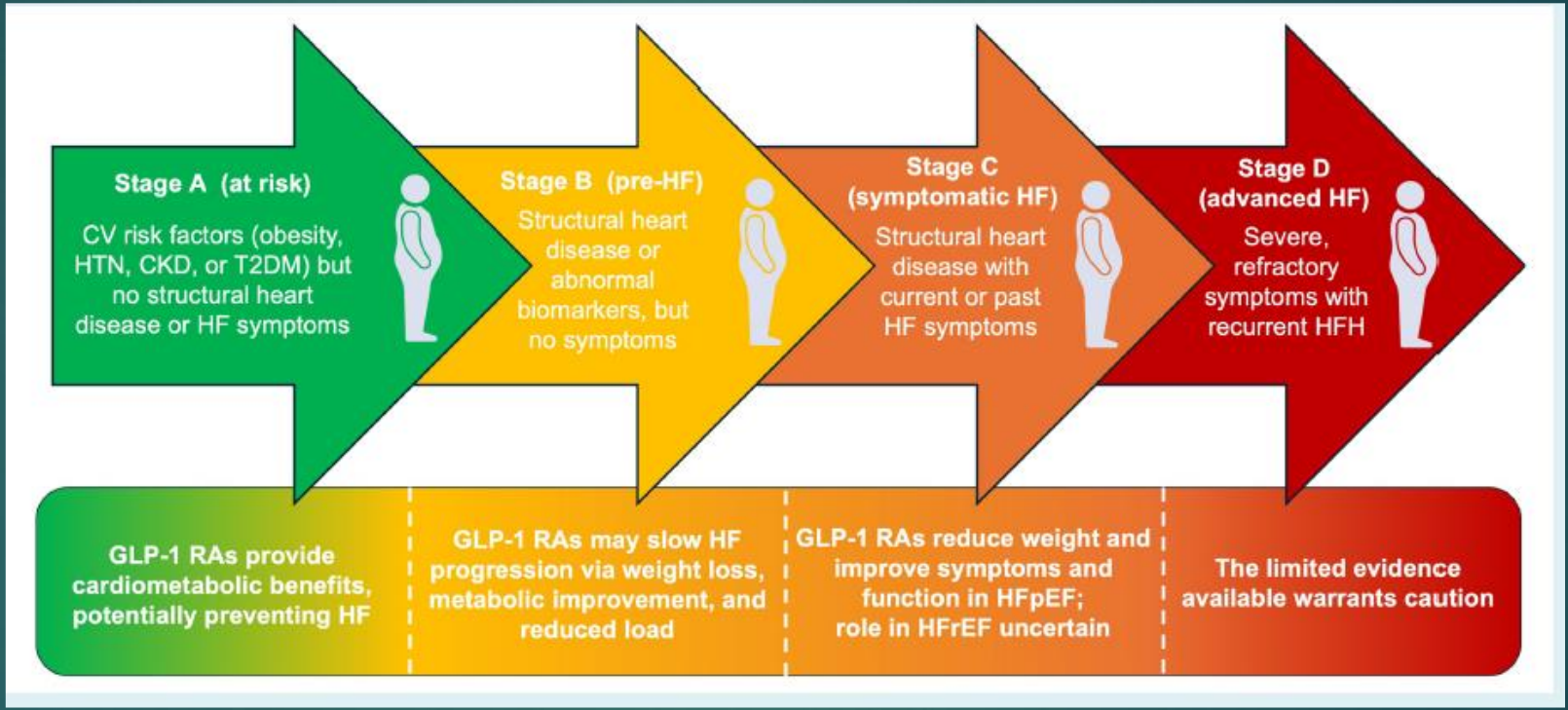



Zile MR, et al. Effects of tirzepatide on the clinical trajectory of patients with heart failure, preserved ejection fraction, and obesity. Circulation. 2025.

# Role of glucagon-like peptide-1 receptor agonists across the Universal Definition of Heart Failure stages.




Monzo L, et al .Pharmacological treatment for patients with obesity and heart failure: Focus on glucagon-like peptide-1 receptor agonists. European Journal of Heart Failure expert consensus document. European Journal of Heart Failure. 2025 Nov 27.

# Take home message

- Incretin-based AOM are the most efficacious weight loss AOM
- Tirzepatide 10 and 15 mg, along with weekly semaglutide 2.4 mg and daily liraglutide have potential body weight lowering effect comparing with placebo
- Tirzepatide 10 and 15 mg, along with weekly semaglutide 2.4 mg and , all yielded comparable results to each other and significantly better results than placebo and liraglutide in reducing body weight more than 5%
- incretin mimetics have beneficial effect on improving several classical cardiovascular risk factors, with tirzepatide sustaining the most profound impact, followed by semaglutide and liraglutide

# Take home message

- Incretin mimetics have shown promise in reducing MACE risk
- Incretin based drugs showed meaningful reductions in body weight alongside improvements in health status and exercise capacity in patients with HFPEF
- Tirzepatide and semaglutide showed fewer HF events or lower cardiovascular mortality in current  limited evidence
- efficacy and safety of incretin based drugs in HF with reduced ejection fraction is uncertain


Thank you