PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

CONGRESSO
ROMA, 25 - 27 Giugno 2026

# Il ruolo del dual-agonist incretinico nel paziente obeso con HFpEF

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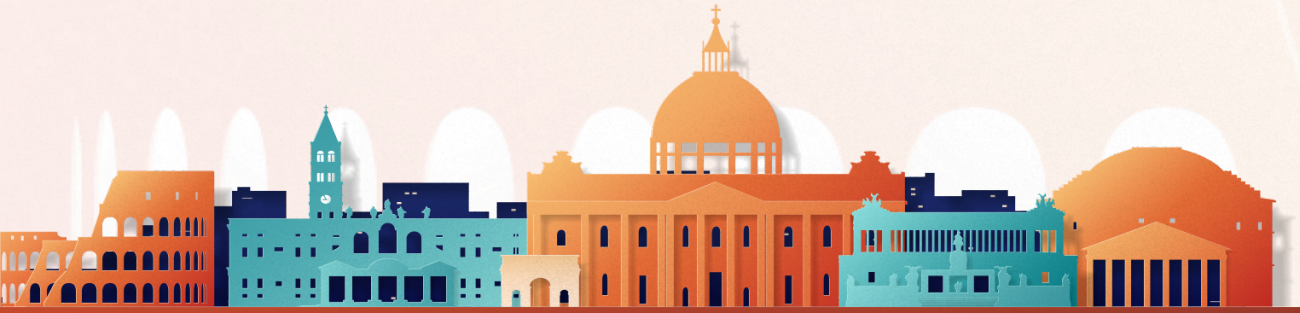


Nessun conflitto di interesse da dichiarare per questa relazione

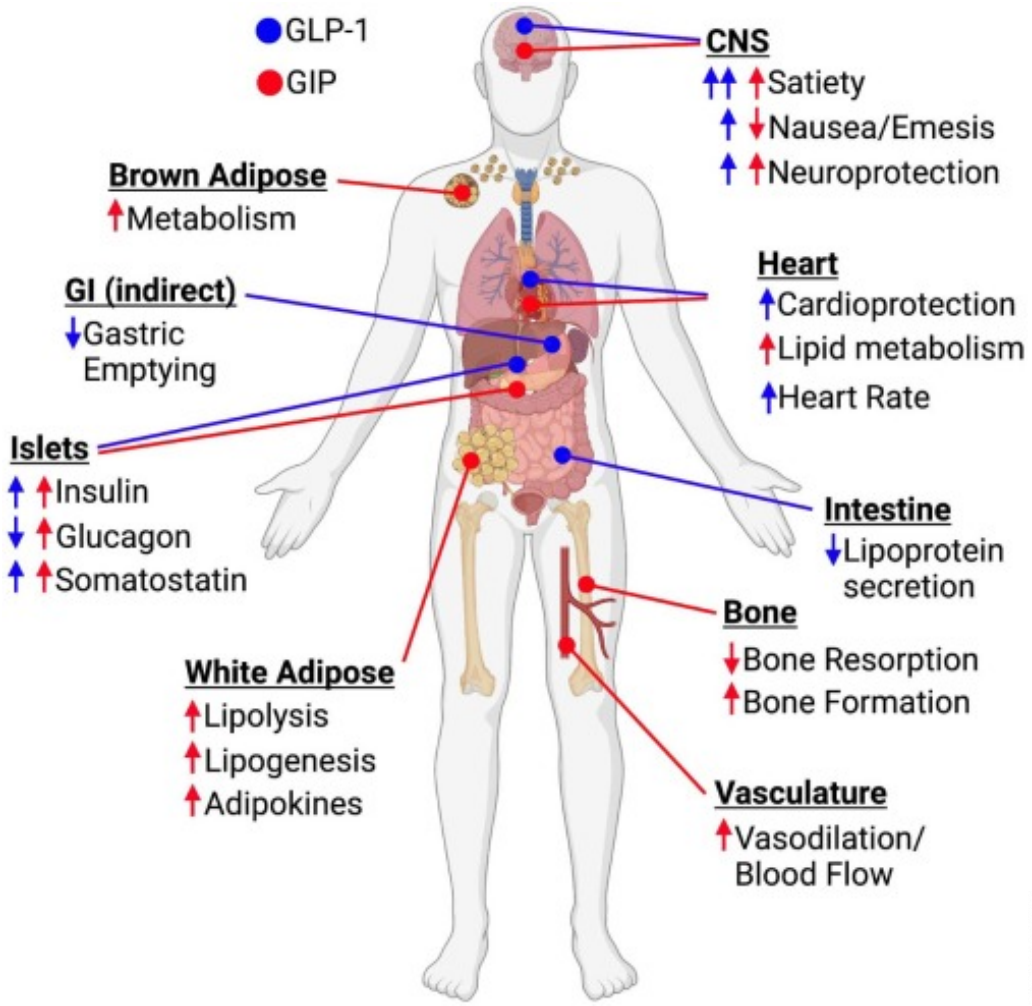
# The incretin system

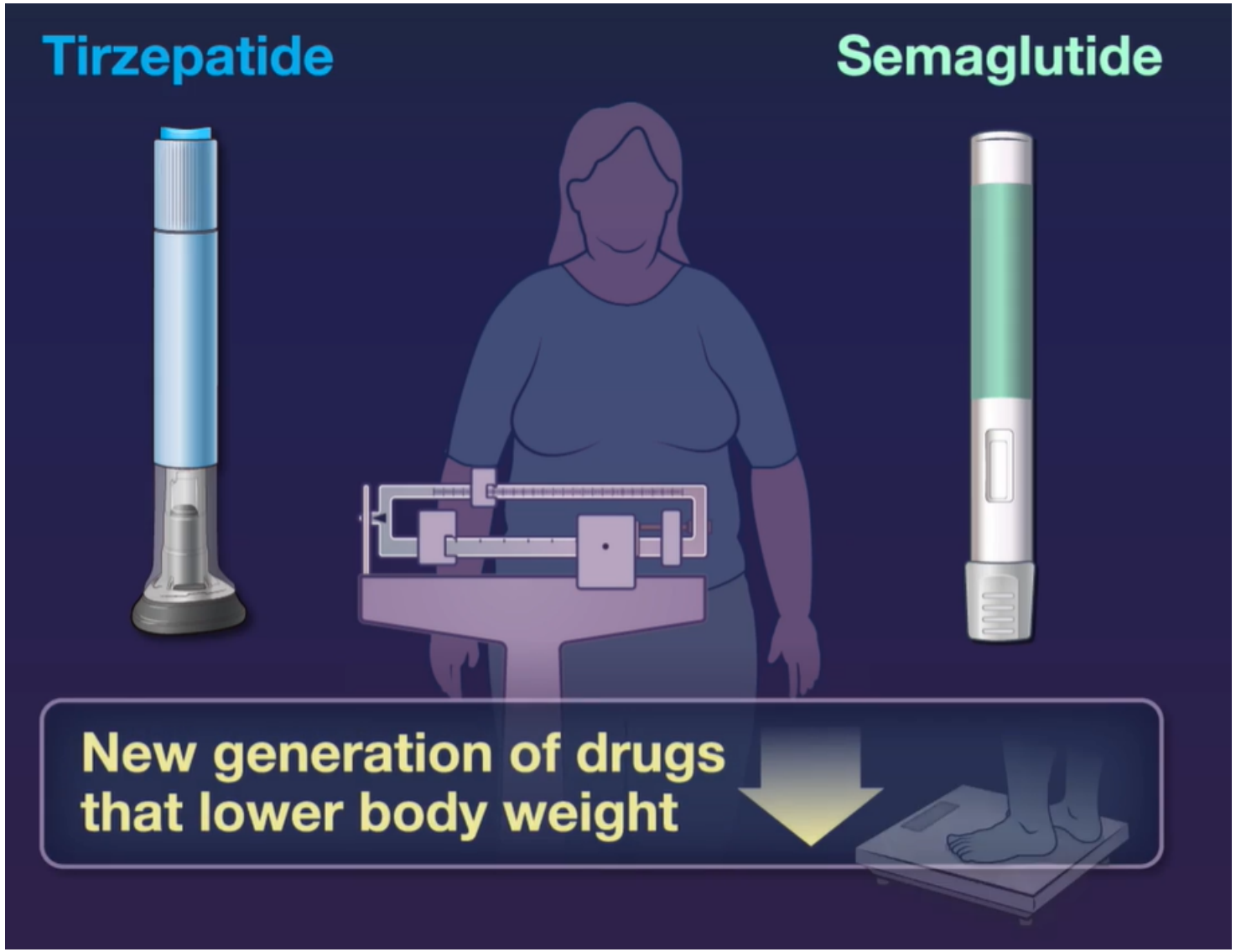
**essential metabolic axis that regulates postprandial metabolism**

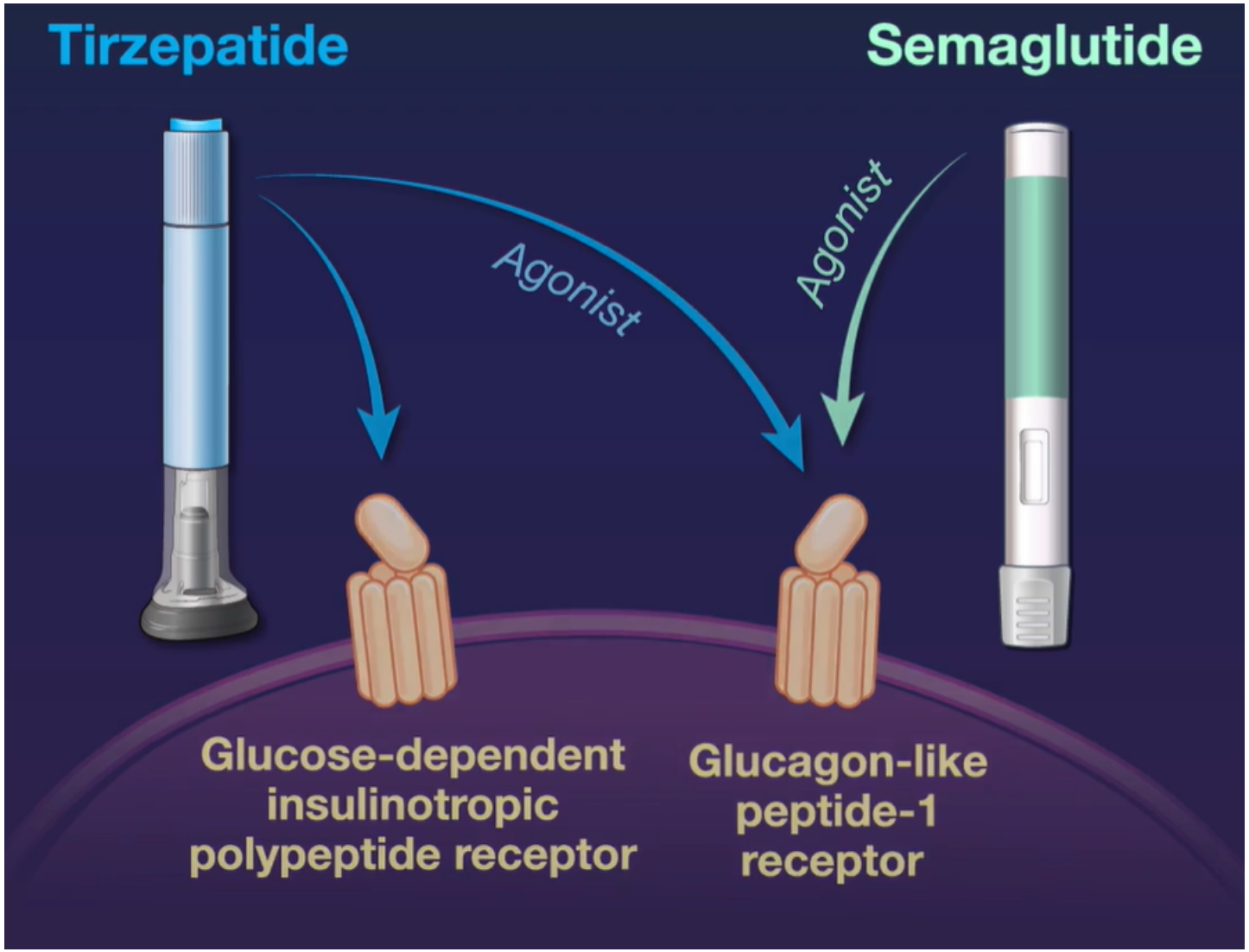
*Two incretin peptides that enable this effect :*

- *glucose-dependent insulinotropic polypeptide (GIP)*
- *glucagon-like peptide 1 (GLP-1)*

which have **GIPR and GLP-1R receptors on islet β cells as well as in other tissues**.

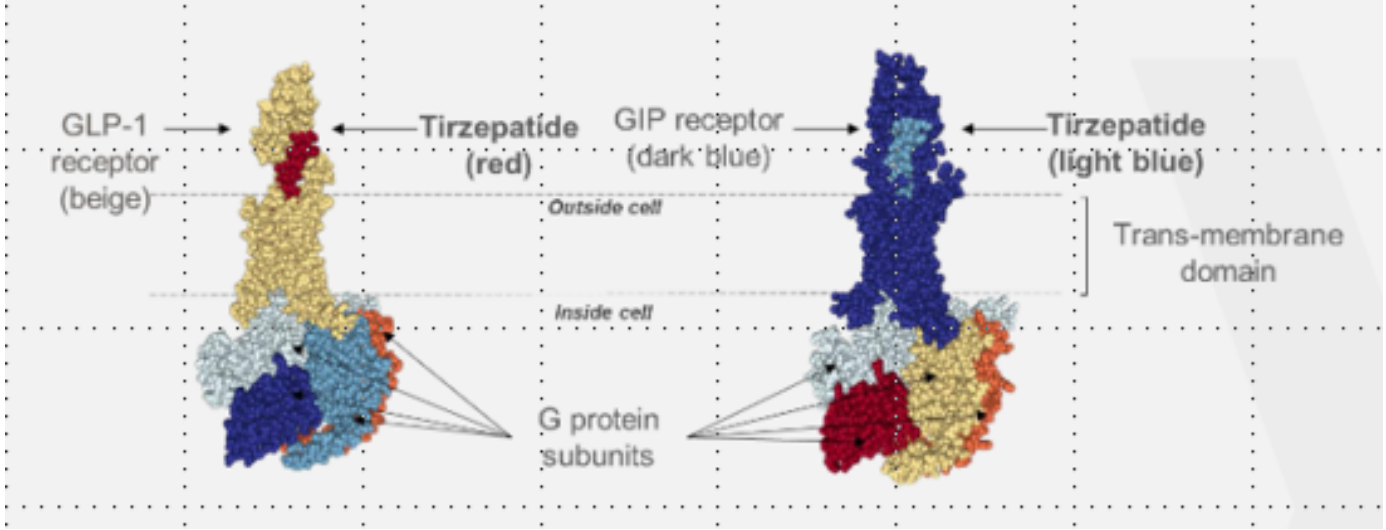



Tirzepatide
Semaglutide
New generation of drugs
that lower body weight


Tirzepatide
Semaglutide
Agonist
Agonist
Glucose-dependent insulinotropic polypeptide receptor
Glucagon-like peptide-1 receptor

# Tirzepatide: Unimolecular coagonist

**Single molecule possessing activity at 2 pharmacologic targets**



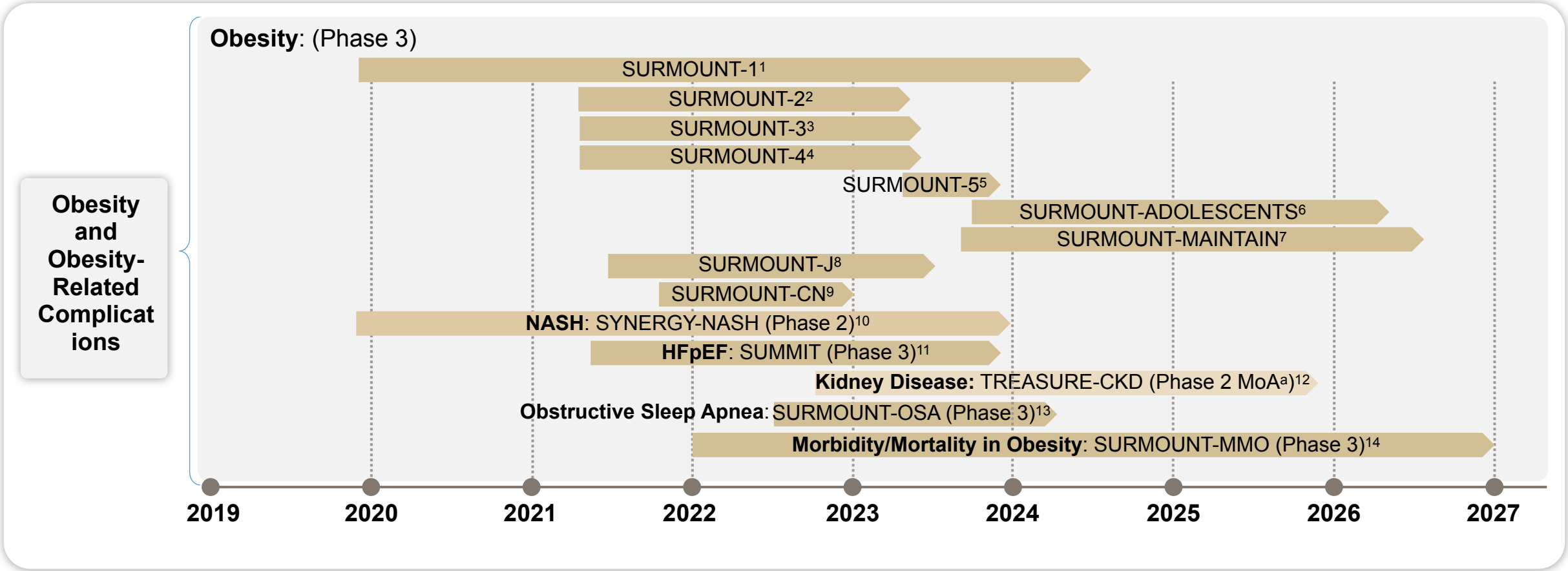

## Pharmacokinetics

- Mean half-life of ~5 days (116.7 hours), enabling **once-weekly dosing**[1]
- Plasma concentrations in people with **renal and hepatic impairment do not differ** versus healthy people[2]

Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2

# Tirzepatide Clinical Development Program

For Obesity and Obesity-Related Complications




[a]Not an outcomes study.

CKD=Chronic Kidney Disease; HFpEF=Heart Failure With Preserved Ejection Fraction; MMO=Morbidity/Mortality in Obesity; MoA=Mechanism of Action; NASH=Non-Alcoholic Steatohepatitis; OSA=Obstructive Sleep Apnea.

1. https://clinicaltrials.gov/ct2/show/NCT04184622 (Accessed November 12, 2023). 2. https://clinicaltrials.gov/ct2/show/NCT04657003 (Accessed November 12, 2023). 3. https://clinicaltrials.gov/ct2/show/NCT04657016 (Accessed November 12, 2023). 4. https://clinicaltrials.gov/ct2/show/NCT04660643 (Accessed November 12, 2023). 5. https://classic.clinicaltrials.gov/ct2/show/NCT05822830 (Accessed November 12, 2023). 6. https://classic.clinicaltrials.gov/ct2/show/NCT06047548 (Accessed November 12, 2023). 7. https://classic.clinicaltrials.gov/ct2/show/NCT06075667 (Accessed November 12, 2023). 8. https://www.clinicaltrials.gov/ct2/show/NCT04844918 (Accessed November 12, 2023). 9. https://www.clinicaltrials.gov/ct2/show/NCT05024032 (Accessed November 12, 2023). 10. https://clinicaltrials.gov/ct2/show/NCT04166773 (Accessed November 12, 2023). 11. https://clinicaltrials.gov/ct2/show/NCT04847557 (Accessed November 12, 2023). 12. https://clinicaltrials.gov/ct2/show/NCT05536804 (Accessed November 12, 2023). 13. https://clinicaltrials.gov/ct2/show/NCT05412004 (Accessed November 12, 2023). 14. https://clinicaltrials.gov/ct2/show/NCT05556512 (Accessed November 12, 2023).

# SURMOUNT Clinical Trial Program

## Overview (1 of 2)

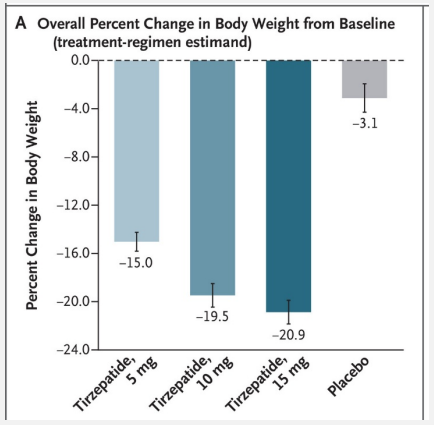
### Phase 3 SURMOUNT Program

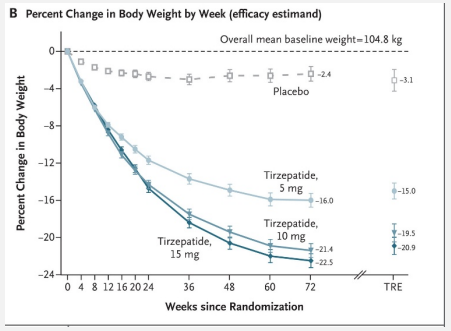
| | SURMOUNT-1: Weight Management[1] | SURMOUNT-2: Weight Management in T2D[2] | SURMOUNT-3: Weight Management After Intensive Lifestyle Intervention[3] | SURMOUNT-4: Maintenance of Weight Loss[4] | SURMOUNT-5: Weight Management in Participants With Weight-Related Comorbidities[5] |
|---|---|---|---|---|---|
| Primary completion date: | April 2022 | April 2023 | May 2023 | May 2023 | November 2024 |
| Number of study participants: | 2539 | 938 | 806 | 783 | 700 |
| Treatment duration: | 72 weeks → Prediabetes Extension to 176 Weeks | 72 weeks | 72 weeks | 88 weeks (36 weeks open-label treatment followed by 52 weeks double-blind treatment) | 72 weeks |
| Intervention/treatment: | TZP 5, 10, 15 mg QW; PBO QW | TZP 10, 15 mg QW; PBO QW | TZP MTD (10 or 15 mg) QW; PBO QW | TZP MTD (10 or 15 mg) QW; PBO QW | TZP QW; SEMA QW |

# SURMOUNT Clinical Trial Program

## SURMOUNT-1: Weight Management[1]

In adults with **obesity**, tirzepatide 5 mg, 10 mg, or 15 mg provided substantial and sustained **reductions in body weight.**

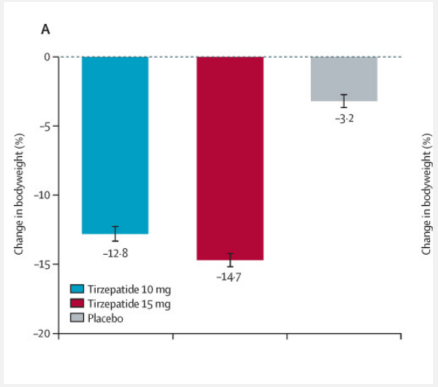


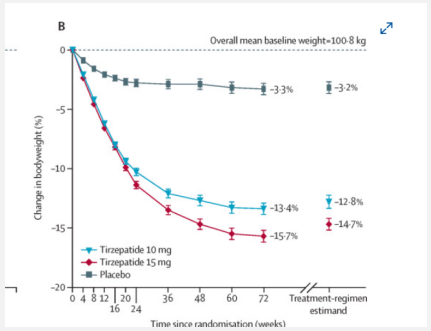




NE*JM*. 2022;387(3):205-216

## SURMOUNT-2: Weight Management in T2D[2]

In adults with **obesity + T2DM** tirzepatide 10 mg and 15 mg provided **reduction in body weight**, with a safety profile.

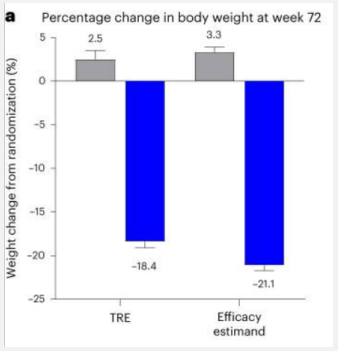


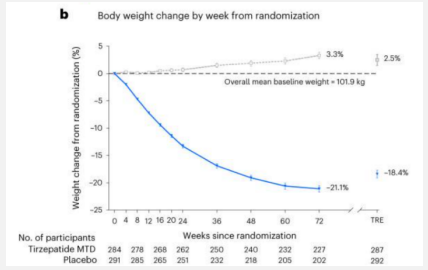




*Lancet*. 2023;402(10402):613-626

## SURMOUNT-3: Weight Management After Intensive Lifestyle Intervention[3]

Tirzepatide(10 or 15 mg) provided substantial **additional reduction in body weight** in participants who had achieved ≥5.0% weight reduction **with intensive lifestyle intervention**

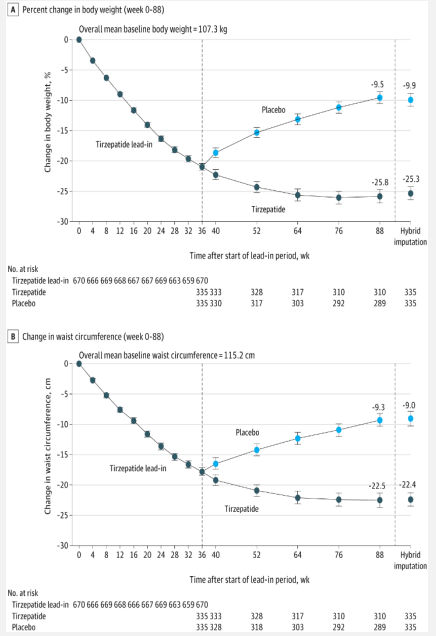



*Nat Med*. 2023;29:2909-2918

## SURMOUNT-4: Maintenance of Weight Loss[4]

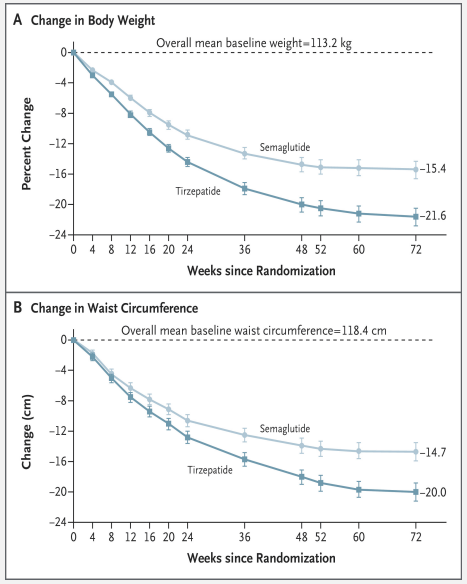
In participants with **obesity or overweight**, withdrawing tirzepatide led to substantial regain of lost weight, whereas **continued treatment maintained and augmented initial weight reduction**.




*JAMA*. 2024;331(1)38-48

## SURMOUNT-5: Weight Management in Participants With Weight-Related Comorbidities[5]

In adults with **obesity but without T2DM**, tirzepatide was **superior to** treatment with **semaglutide** in **reduction in weight and waist circumference**

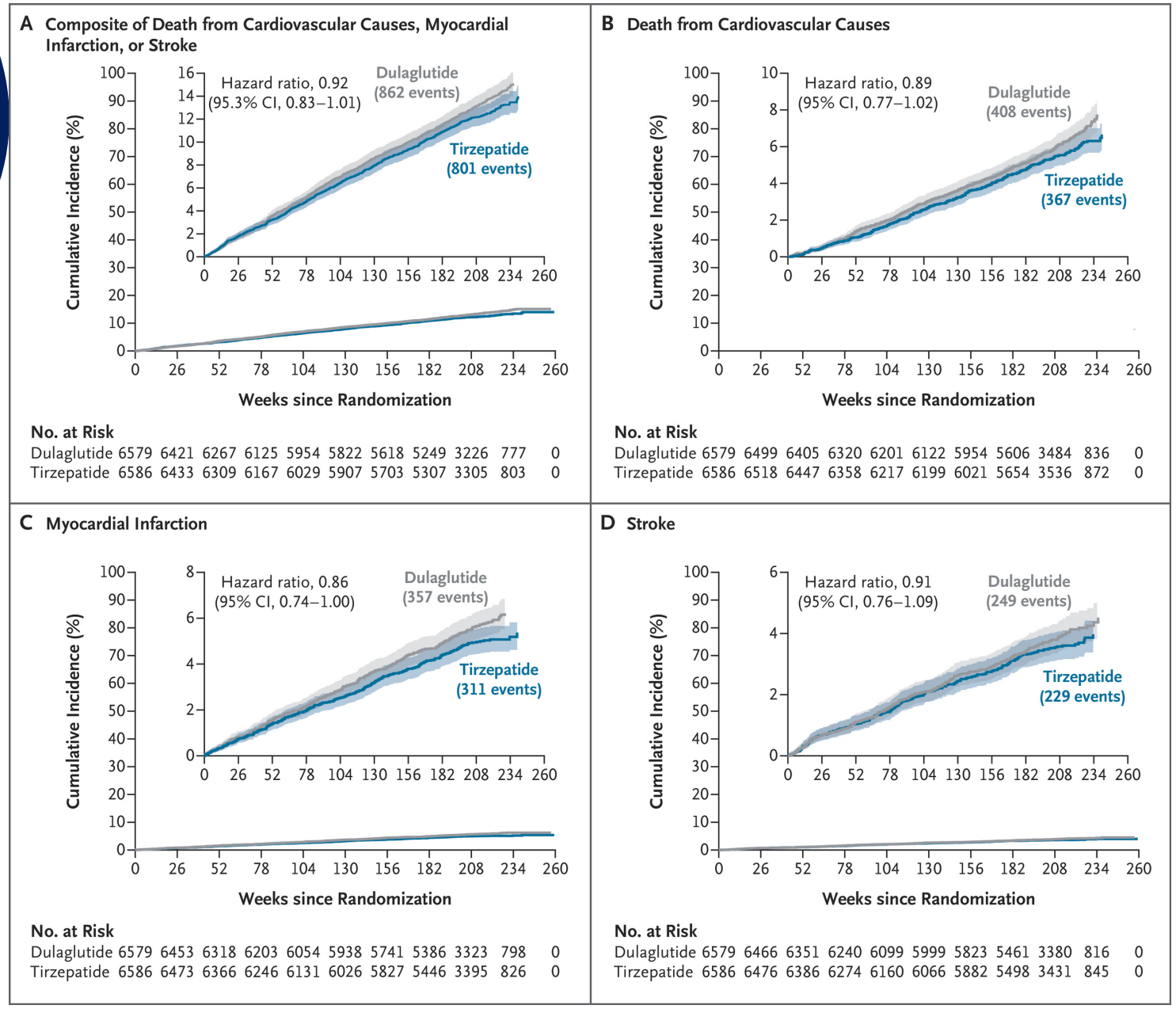



NEJM 2025;393:26-36

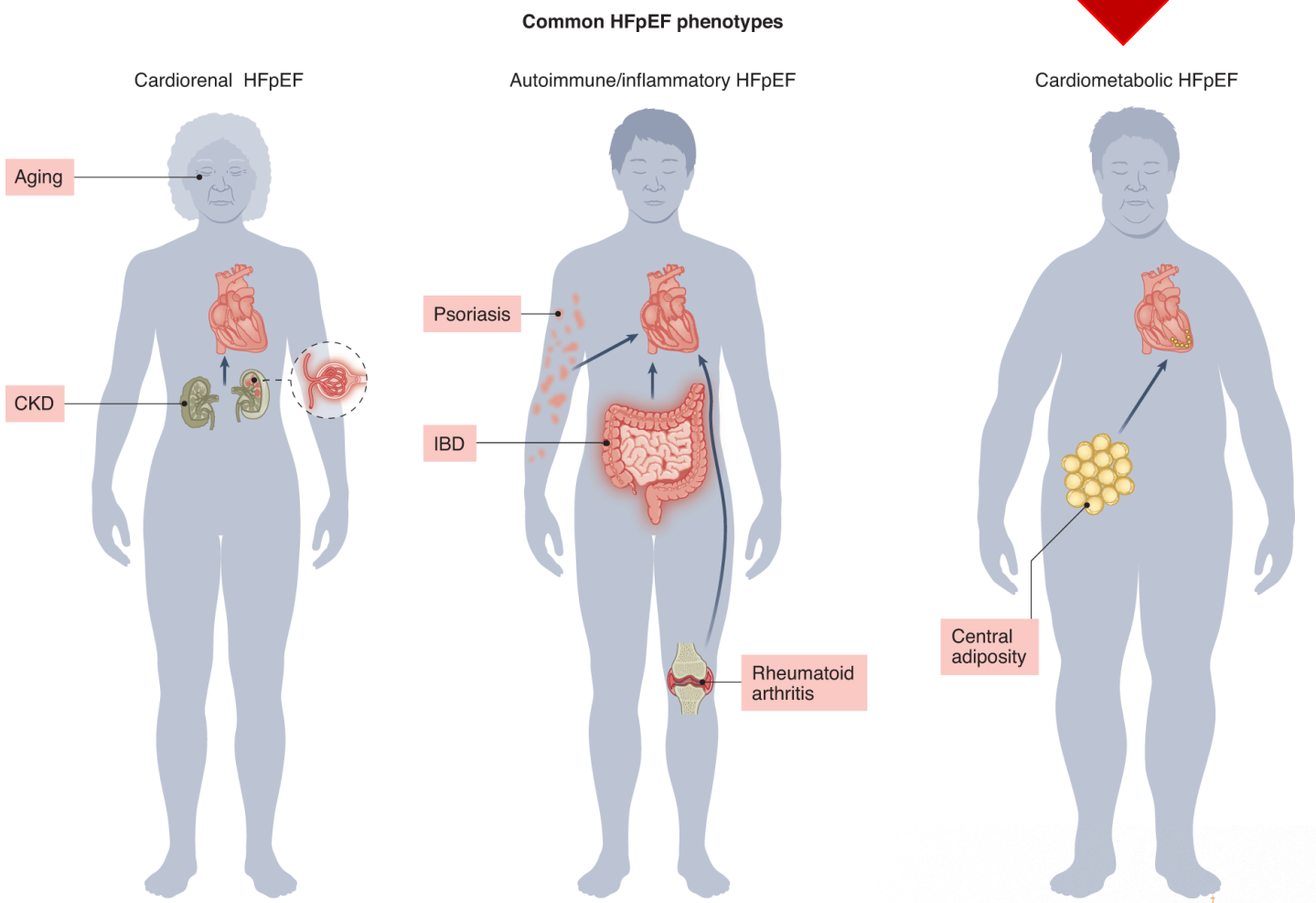
# SURPASS-CVOT

SURPASS-CVOT on CV effects of TZP in >13,000 participants with T2D and established CVD (65% CAD, 19% prior stroke, 25% PAD).
30% of the participants were already on an SGLT2 inhibitor at baseline

The SURPASS-CVOT trial compared tirzepatide with dulaglutide, demonstrating noninferiority for major adverse cardiovascular events (MACE; HR 0.92; 95.3% CI 0.83–1.01; p = 0.086) and suggesting a potential 28% MACE risk reduction versus an imputed placebo. Greater improvements in glycemia (0.8% greater HbA1c reduction) and weight (7% greater weight loss)



# *HFpEF e i suoi fenotipi*



# CENTRAL ILLUSTRATION: Clinical Phenogroups in HFpEF

**P1**

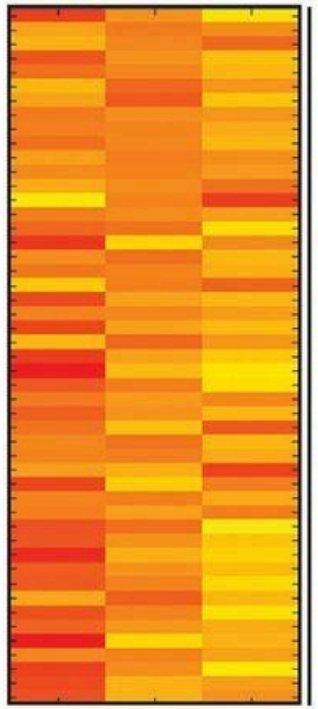
- Normal LV geometry
- Low arterial stiffness
- Low natriuretic peptides
- Markers of COPD (not genuine HFpEF?)
- Low event rate
- Preferentially enrolled in Russia/Georgia

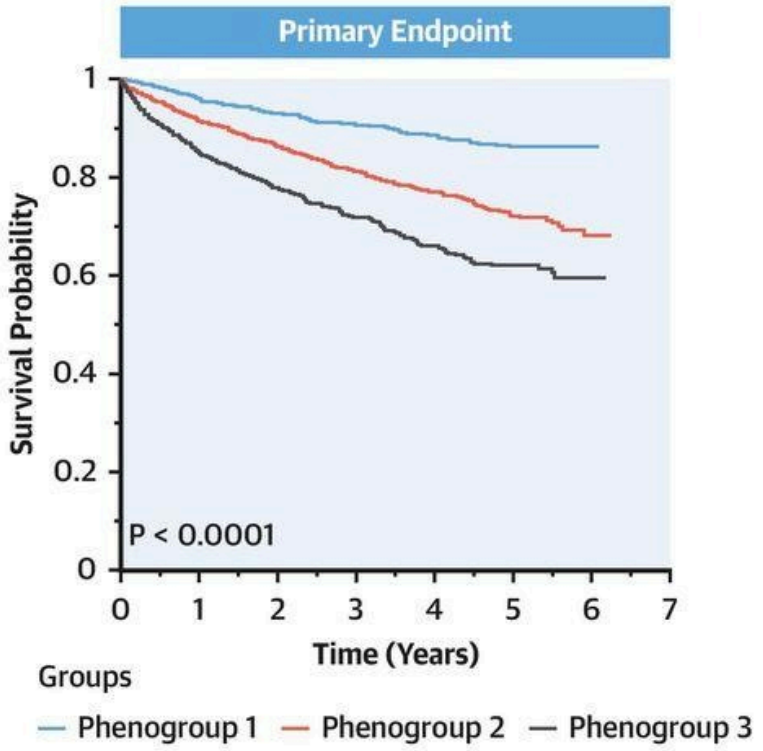
**P2**

- Concentric remodeling
- Very stiff arteries
- LA enlargement and AF
- High natriuretic peptides
- Innate immunity activation
- High risk of primary endpoint

**P3**

- Obesity/Diabetes
- Inflammation (TNF-α)
- Abnormal metabolism, liver and renal injury/dysfunction
- High renin
- Highest risk of primary endpoint
- Preferential response to spironolactone



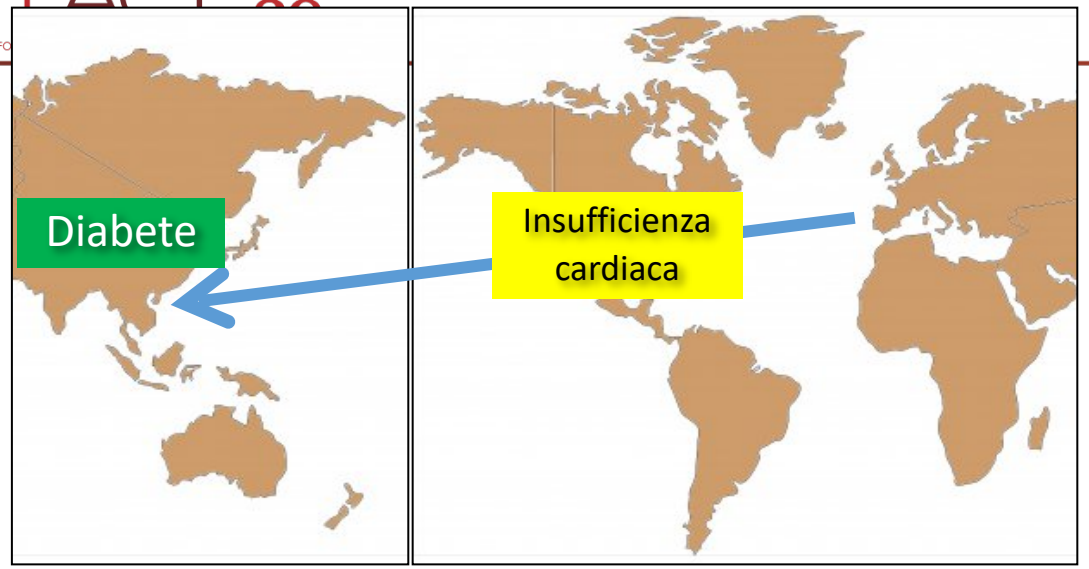

Cohen, J.B. et al. J Am Coll Cardiol HF. 2020;8(3):172-84.


# A *new* serendipity story

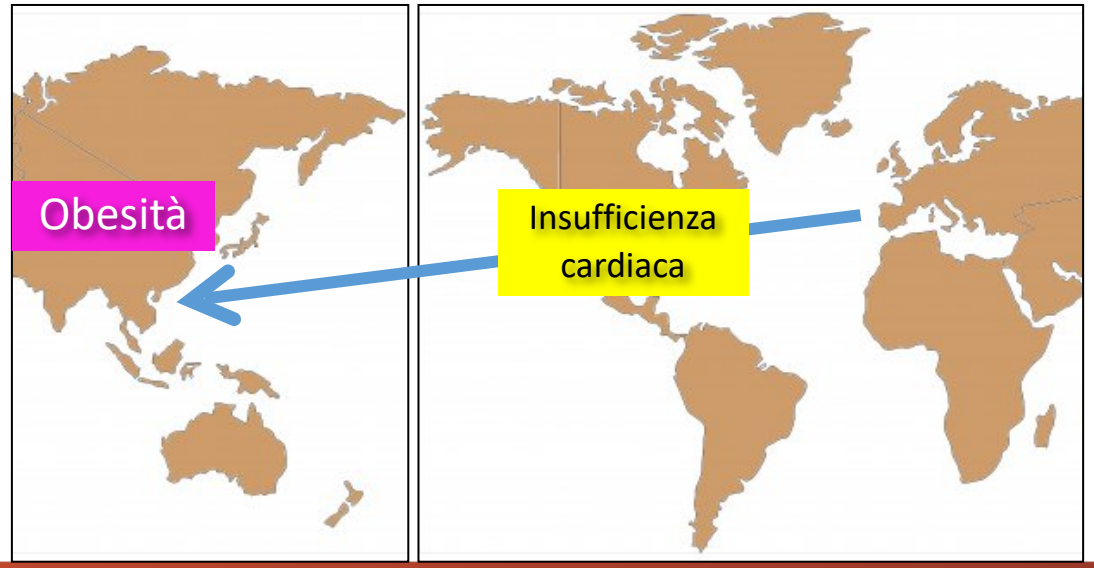
Serendipità

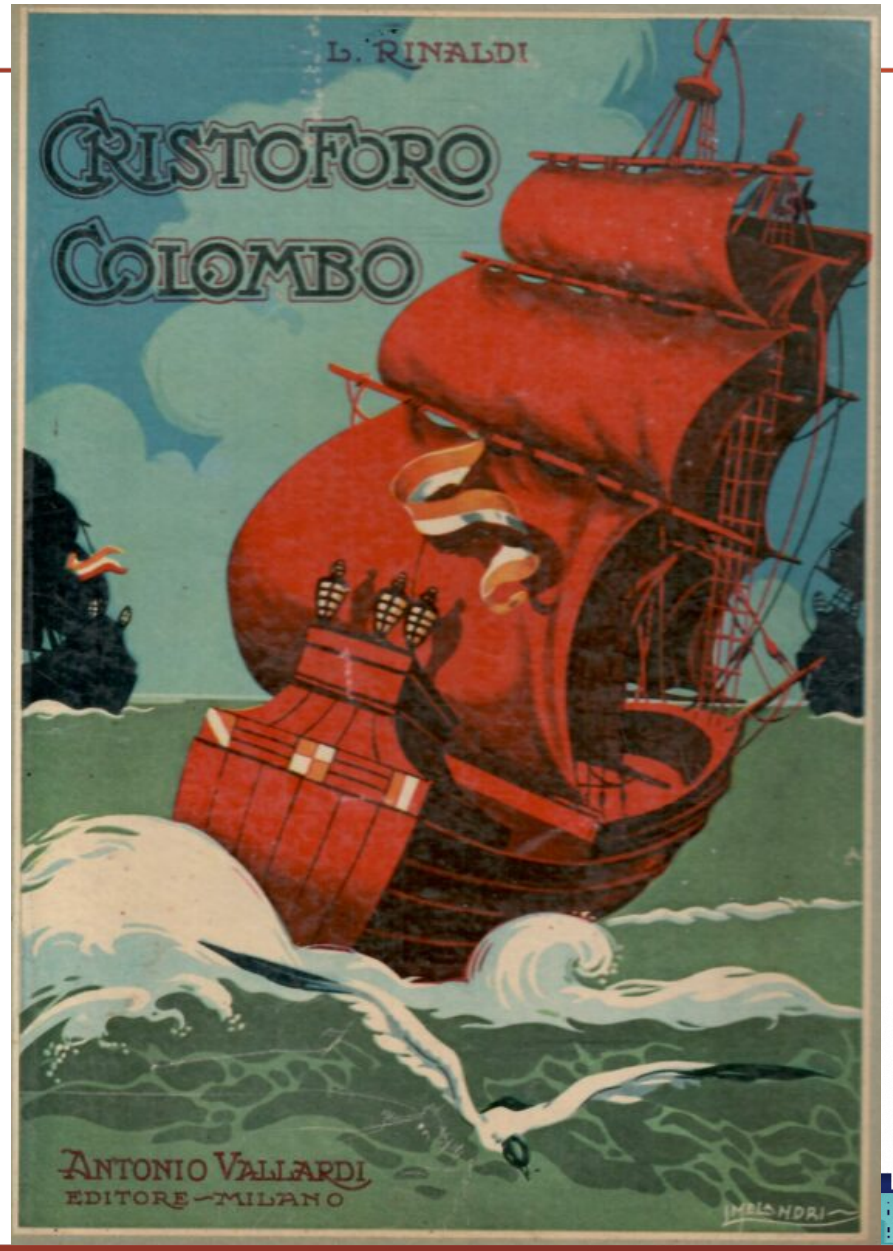
Trovare una cosa non cercata mentre se ne stava cercando un'altra.

## GLIFLOZINE




## INCRETINE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2025 VOL. 392 NO. 5

# Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*

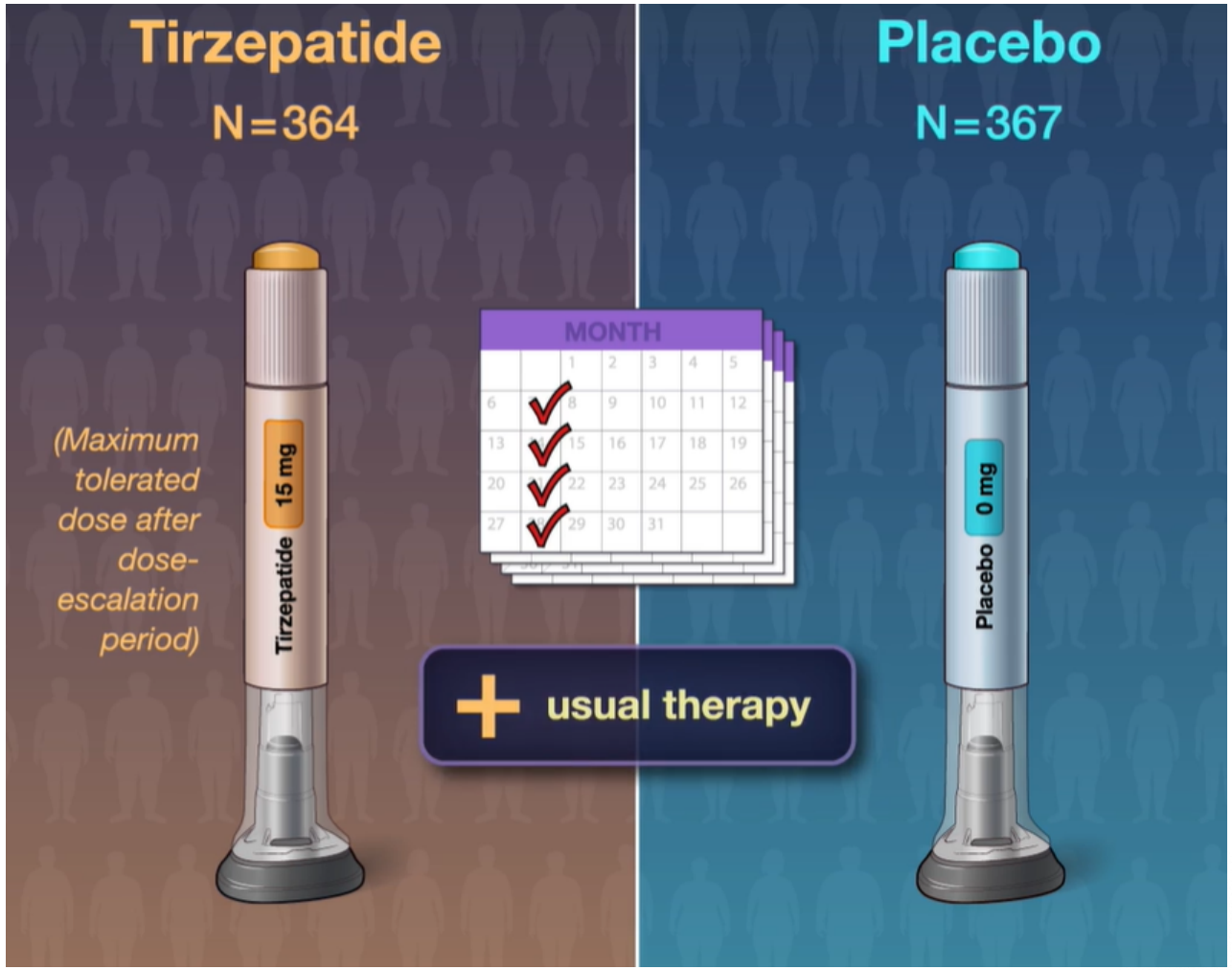
# SUMMIT Trial

## SUMMIT Trial

- International
- Double-blind
- Randomized
- Placebo-controlled

## SUMMIT Trial

- 731 Adults
- Chronic heart failure
  *(NYHA class II–IV heart failure)*
- Preserved ejection fraction
  *(LVEF of ≥50%)*
- Obesity
  *(BMI of ≥30)*




Packer M, et al. N Engl J Med 2025;392:427-37

# SUMMIT Trial: Rationale

Weight-loss interventions like gastric bypass surgery and **GLP-1 agonists** reduce systemic inflammation, decrease epicardial adipose volume, lower the risk of HF and **improve symptoms in patients with HFpEF.**[1]

**Tirzepatide,** a long-acting GIP and GLP-1 RA, results in up to 22.5% weight loss in people with obesity. However, its effects in patients with HFpEF and obesity have not been evaluated.[2]

The **SUMMIT trial** investigated the **effect of tirzepatide on CV death, worsening HF events, health status and functional capacity in people with HFpEF and obesity**.[1]

- CV=Cardiovascular; GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1 RA=Glucagon-Like Peptide-1 Receptor Agonist; HF=Heart Failure; HFpEF=Heart Failure with Preserved Ejection Fraction.
- 1. Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print). 2. Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

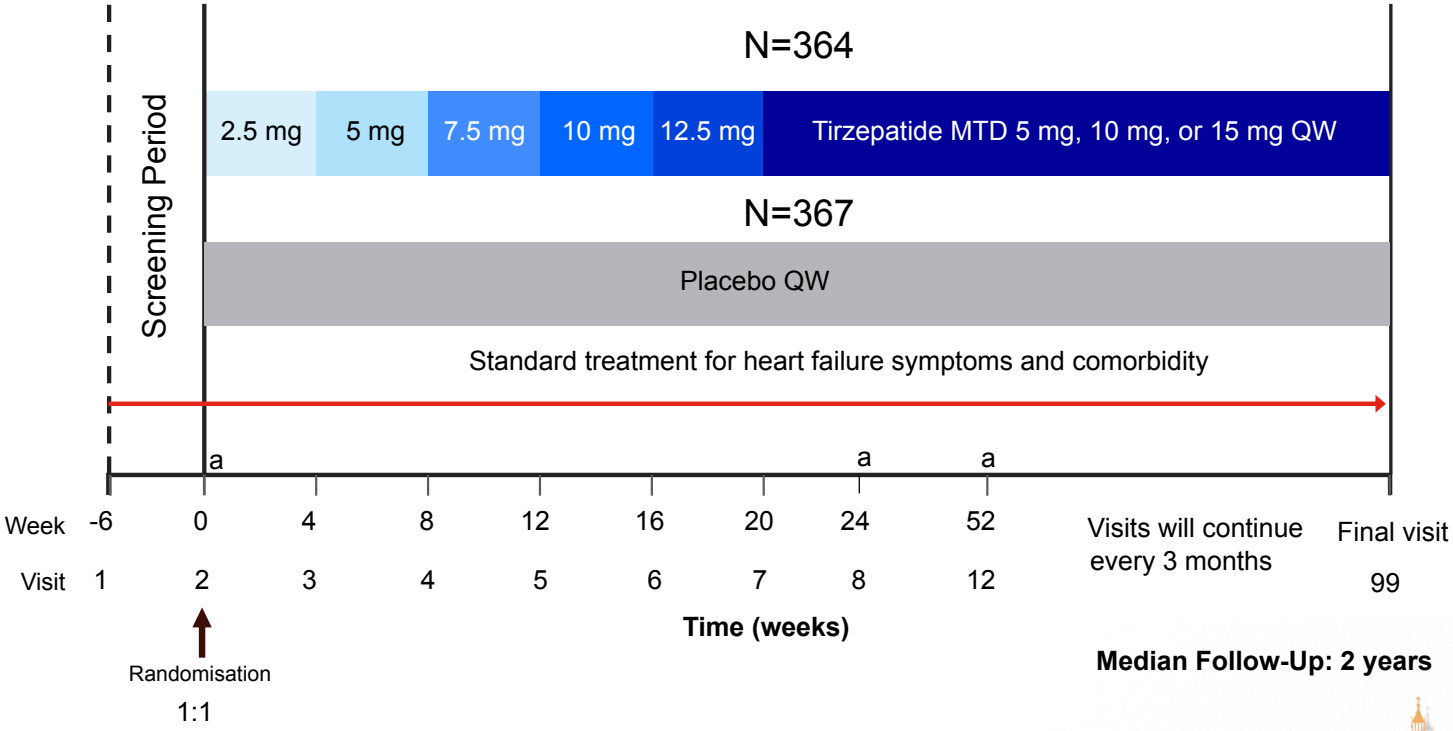
# SUMMIT Trial Design

**SUMMIT is a randomised, multicenter, international, placebo-controlled, double-blind, parallel-arm Phase 3 study. The study was designed to evaluate the efficacy and safety of once-weekly tirzepatide in participants with HFpEF and obesity.**

**Participants Enrolled:** 731

**Participating Countries**

United States, Argentina, Brazil, China, India, Israel, Mexico, Russia, and Taiwan

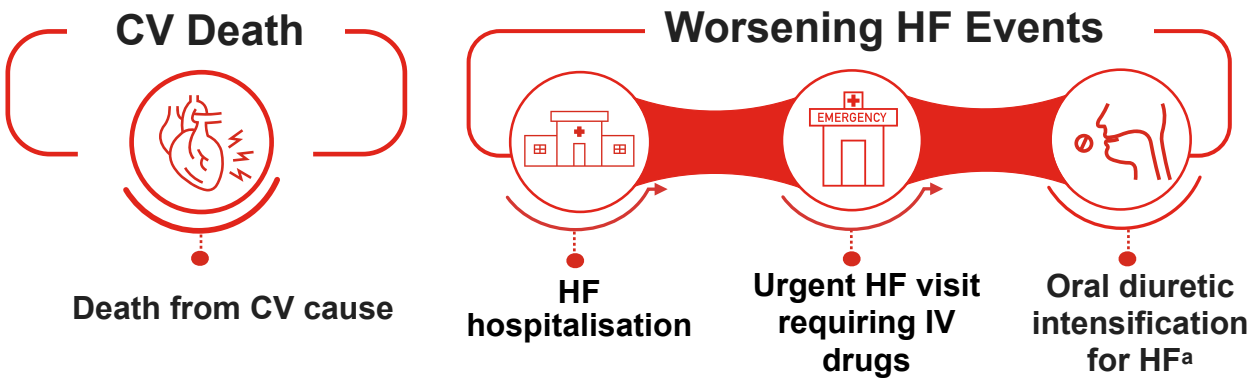



Packer M, et al. N Engl J Med 2025;392:427-37

# SUMMIT Trial Endpoints

## Dual Primary Endpoints

**Time-to-first occurrence of the composite endpoint of CV death or worsening HF events**




**Change in KCCQ-CSS** from Baseline to Week 52

## Key Secondary Endpoints

- Change from baseline to Week 52 in **6MWD**
- Percent change from baseline to Week 52 in **body weight**
- Change from baseline to Week 52 in **hs-CRP**

- [a]Diuretic intensification in the absence of worsening heart failure was not designated as an event.
- Packer M, et al. N Engl J Med 2025;392:427-37

# SUMMIT: Key Inclusion and Exclusion Criteria

## Key Inclusion Criteria

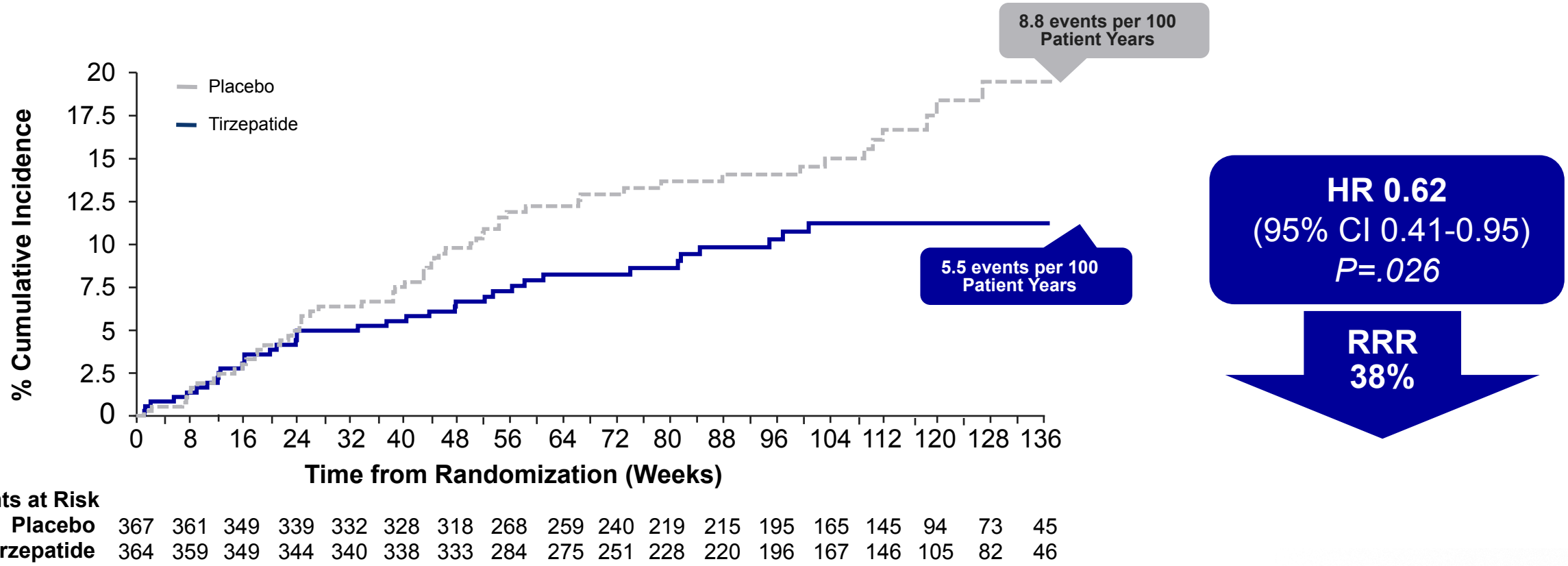
- Age ≥40 years and BMI ≥30 kg/m²
- Chronic HF NYHA class II-IV, LVEF ≥50%, on stable guideline-directed medical therapy
- At least one of the following as documented evidence of heart failure
  - Structural heart disease (LA enlargement)
  - Elevated NT-proBNP (defined as >200 pg/mL for participants without AF or >600 pg/mL for participants with AF)
  - Elevated LV filling pressure
- eGFR <70 mL/min/1.73 m² at screening, or HF decompensation within 12 months of screening
- 6MWD ≥100 m to ≤425 m
- KCCQ CSS ≤80

## Key Exclusion Criteria

- Acute decompensated HF within 4 weeks
- MI, stroke, or major CV surgery/intervention within 90 days
- Hypertrophic cardiomyopathy, cardiac amyloidosis, and valvular diseases requiring surgery
- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm
- LVEF <40% within 2 years
- eGFR <15 mL/min/1.73 m² or requiring dialysis
- Severe lung diseases (COPD, PAH, and CTEPH)
- T1D or uncontrolled T2D HbA1c >9.5%


- Packer M, et al. N Engl J Med 2025;392:427-37

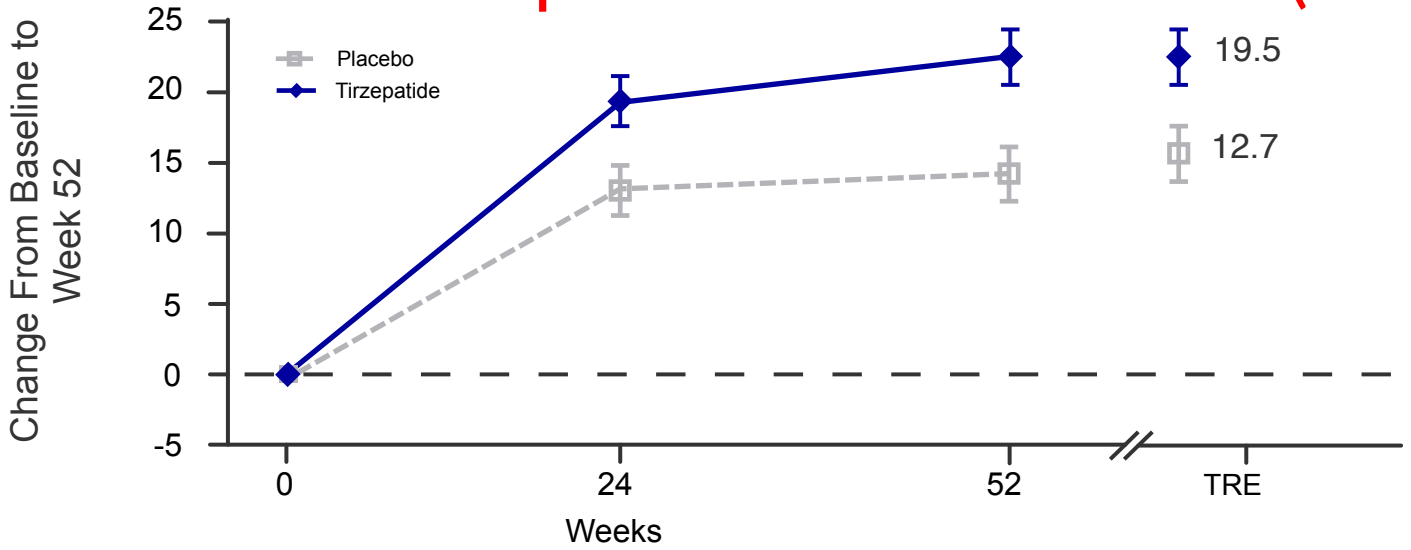
# Primary Endpoint: Time to First Event for CV Death or Worsening HF Event[a]




- Packer M, et al. N Engl J Med 2025;392:427-37

# SUMMIT Co-Primary Endpoint:

## Effect of Tirzepatide on Health Status (KCCQ-CSS)




No. of Participants

| | | | |
|---|---|---|---|
| Placebo | 337 | 326 | 313 |
| Tirzepatide | 341 | 330 | 301 |

**Treatment Regimen Estimand**

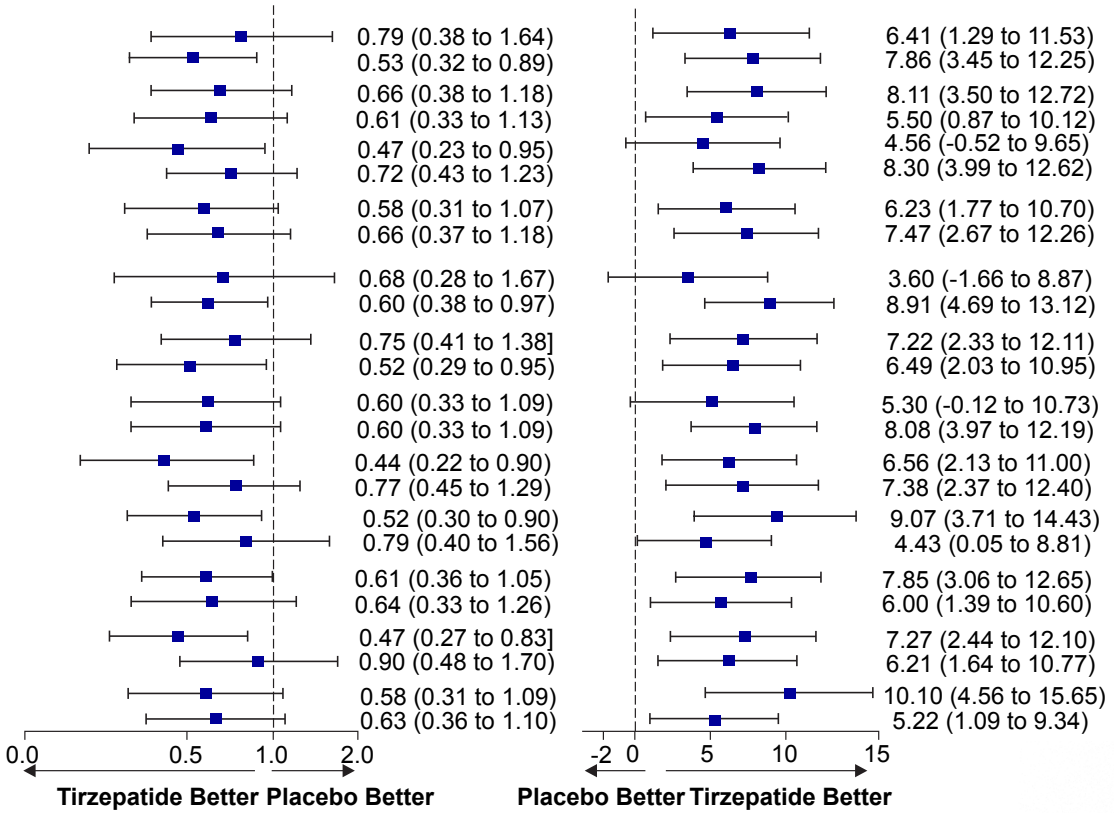
**ETD 6.9**
(95% CI 3.3-10.6)[a]
*P<.001*

Treatment with tirzepatide significantly improved heart failure symptoms and physical limitations.

- [a]Hodges-Lehmann estimate of location shift and corresponding CI.
- Tirzepatide vs. placebo: ***P<0.001.
- Packer M, et al. N Engl J Med 2025;392:427-37

# The Effects of Tirzepatide on Primary Outcomes Were Consistent Across Pre-specified Subgroups

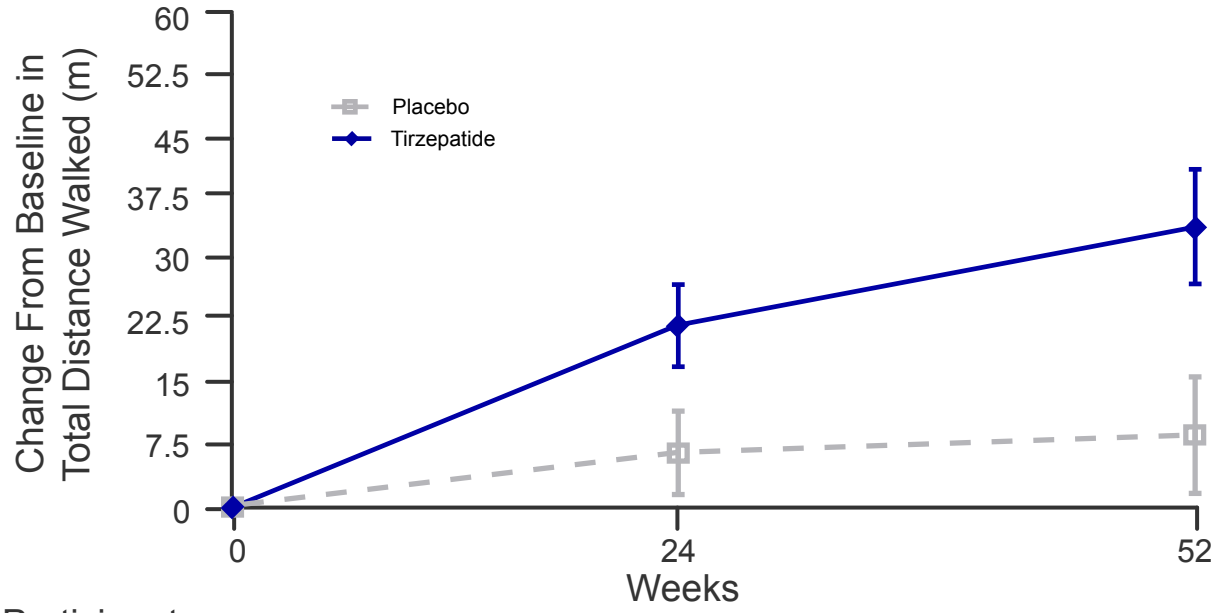
| Subgroup | | Placebo (no. of patients with event/ no. of patients at risk) | Tirzepatide (no. of patients with event/ no. of patients at risk) | Hazard Ratio for Death from Cardiovascular Causes or a Worsening Heart-Failure Event (95% CI) | KCCQ-CSS Treatment Difference (95% CI) |
|---|---|---|---|---|---|
| Age | <65 yr | 17/166 | 13/158 | 0.79 (0.38 to 1.64) | 6.41 (1.29 to 11.53) |
| | ≥65 yr | 39/201 | 23/206 | 0.53 (0.32 to 0.89) | 7.86 (3.45 to 12.25) |
| Sex | Female | 29/193 | 20/200 | 0.66 (0.38 to 1.18) | 8.11 (3.50 to 12.72) |
| | Male | 27/174 | 16/164 | 0.61 (0.33 to 1.13) | 5.50 (0.87 to 10.12) |
| Body-mass index | <35 | 23/148 | 12/147 | 0.47 (0.23 to 0.95) | 4.56 (-0.52 to 9.65) |
| | ≥35 | 33/219 | 24/217 | 0.72 (0.43 to 1.23) | 8.30 (3.99 to 12.62) |
| History of type 2 diabetes | Yes | 28/178 | 16/174 | 0.58 (0.31 to 1.07) | 6.23 (1.77 to 10.70) |
| | No | 28/189 | 20/190 | 0.66 (0.37 to 1.18) | 7.47 (2.67 to 12.26) |
| HFpEF ABA score | <0.8 | 12/140 | 8/133 | 0.68 (0.28 to 1.67) | 3.60 (-1.66 to 8.87) |
| | ≥0.8 | 44/ 227 | 28/231 | 0.60 (0.38 to 0.97) | 8.91 (4.69 to 13.12) |
| Recent heart-failure decompensation | Yes | 24/172 | 19/171 | 0.75 (0.41 to 1.38] | 7.22 (2.33 to 12.11) |
| | No | 32/195 | 17/193 | 0.52 (0.29 to 0.95) | 6.49 (2.03 to 10.95) |
| Ejection fraction | <60% | 28/144 | 18/141 | 0.60 (0.33 to 1.09) | 5.30 (-0.12 to 10.73) |
| | ≥60% | 28/223 | 18/223 | 0.60 (0.33 to 1.09) | 8.08 (3.97 to 12.19) |
| NT-proBNP | <200 pg/mL | 24/197 | 11/186 | 0.44 (0.22 to 0.90) | 6.56 (2.13 to 11.00) |
| | ≥200 pg/mL | 32/170 | 25/178 | 0.77 (0.45 to 1.29) | 7.38 (2.37 to 12.40) |
| KCCQ-CSS | <Median | 39/192 | 20/173 | 0.52 (0.30 to 0.90) | 9.07 (3.71 to 14.43) |
| | ≥Median | 17/174 | 16/191 | 0.79 (0.40 to 1.56) | 4.43 (0.05 to 8.81) |
| Estimated GFR | <60 | 34/168 | 22/167 | 0.61 (0.36 to 1.05) | 7.85 (3.06 to 12.65) |
| | ≥60 | 22/199 | 14/197 | 0.64 (0.33 to 1.26) | 6.00 (1.39 to 10.60) |
| Systolic blood pressure | <130 mm Hg | 36/189 | 18/185 | 0.47 (0.27 to 0.83] | 7.27 (2.44 to 12.10) |
| | ≥130 mm Hg | 20/178 | 18/179 | 0.90 (0.48 to 1.70) | 6.21 (1.64 to 10.77) |
| Use of mineralocorticoid receptor antagonist | Yes | 24/125 | 16/131 | 0.58 (0.31 to 1.09) | 10.10 (4.56 to 15.65) |
| | No | 32/242 | 20/233 | 0.63 (0.36 to 1.10) | 5.22 (1.09 to 9.34) |




- [a]Worsening HF event was defined as heart failure symptoms requiring hospitalisation, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.
- BMI=Body Mass Index; BP=Blood Pressure; CI=Confidence Interval; CV=Cardiovascular; eGFR=Estimated Glomerular Filtration Rate; HF=Heart Failure; HFpEF=Heart Failure With Preserved Ejection Fraction; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; MRA=Mineralocorticoid Receptor Antagonist; NT-proBNP=N-terminal Prohormone of Brain Natriuretic Peptide; T2D=Type 2 Diabetes.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

# Change From Baseline to Week 52 in 6 MWD

- Key Secondary Endpoint




No. of Participants

| | | | |
|---|---|---|---|
| Placebo | 335 | 330 | 314 |
| Tirzepatide | 344 | 340 | 326 |

**Treatment Regimen Estimand**

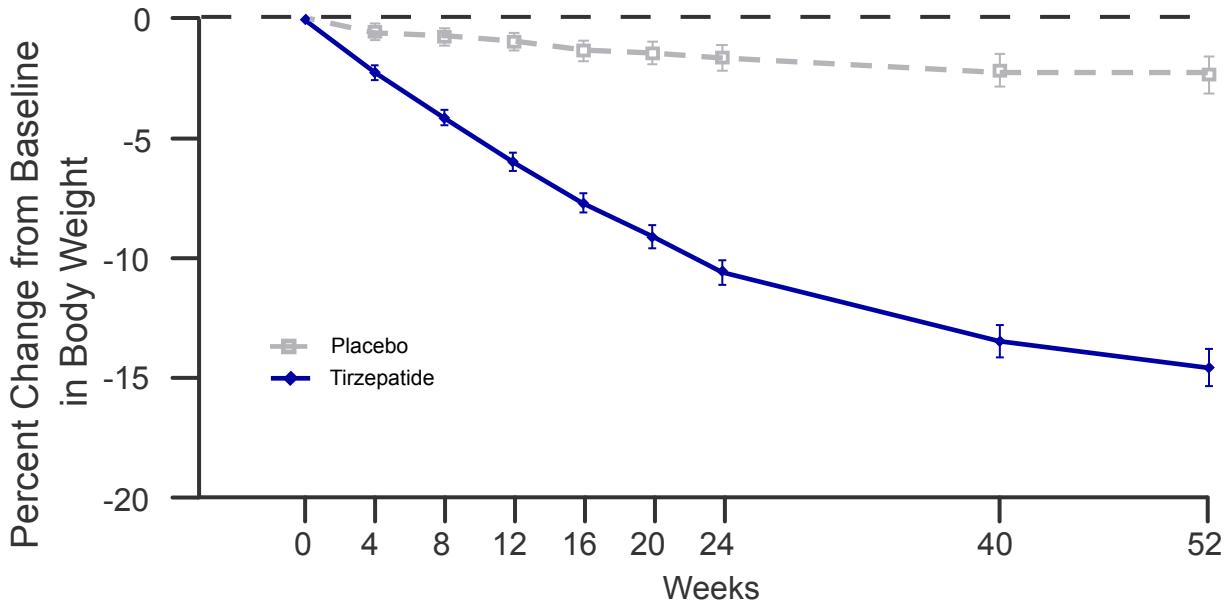
**ETD 18.3**
(95% CI 9.9-26.7)[a]
*P<.001*

A significant improvement in 6MWD was observed in patients on tirzepatide compared to placebo

- [a]Hodges-Lehmann estimate of location shift and corresponding CI.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand; 6MWD=6-Minute Walk Distance.
- Packer M, et al. *NEJM*. 2025

# Change From Baseline to Week 52 in Body Weight

- Key Secondary Endpoint




No. of Participants

| | | | |
|---|---|---|---|
| Placebo | 363 | 339 | 333 |
| Tirzepatide | 364 | 341 | 331 |

**Treatment Regimen Estimand**

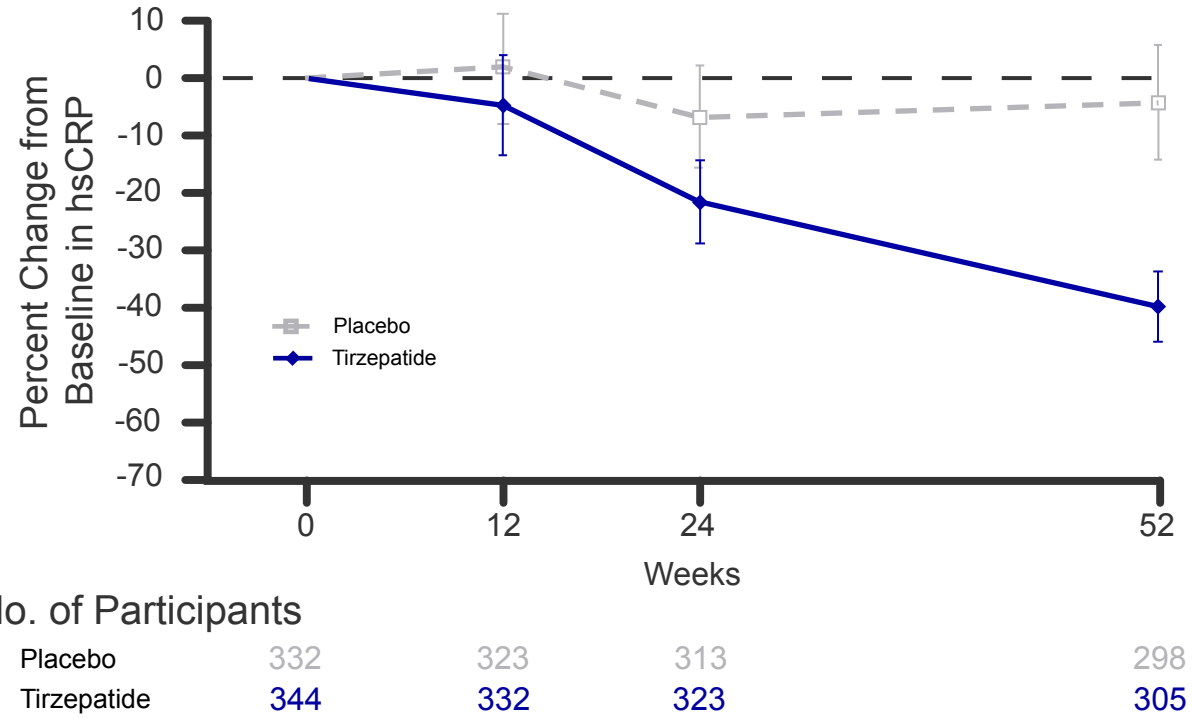
**ETD -11.6**
(95% CI -12.9 to -10.4)
*P<.001*

A greater reduction in body weight was observed in patients on tirzepatide compared to placebo.

- Tirzepatide vs. placebo: ***P<0.001.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.
- Packer M, et al. *NEJM*. 2025

# Change From Baseline to Week 52 in hsCRP

- Key Secondary Endpoint




No. of Participants

| | | | | |
|---|---|---|---|---|
| Placebo | 332 | 323 | 313 | 298 |
| Tirzepatide | 344 | 332 | 323 | 305 |

**Treatment Regimen Estimand**

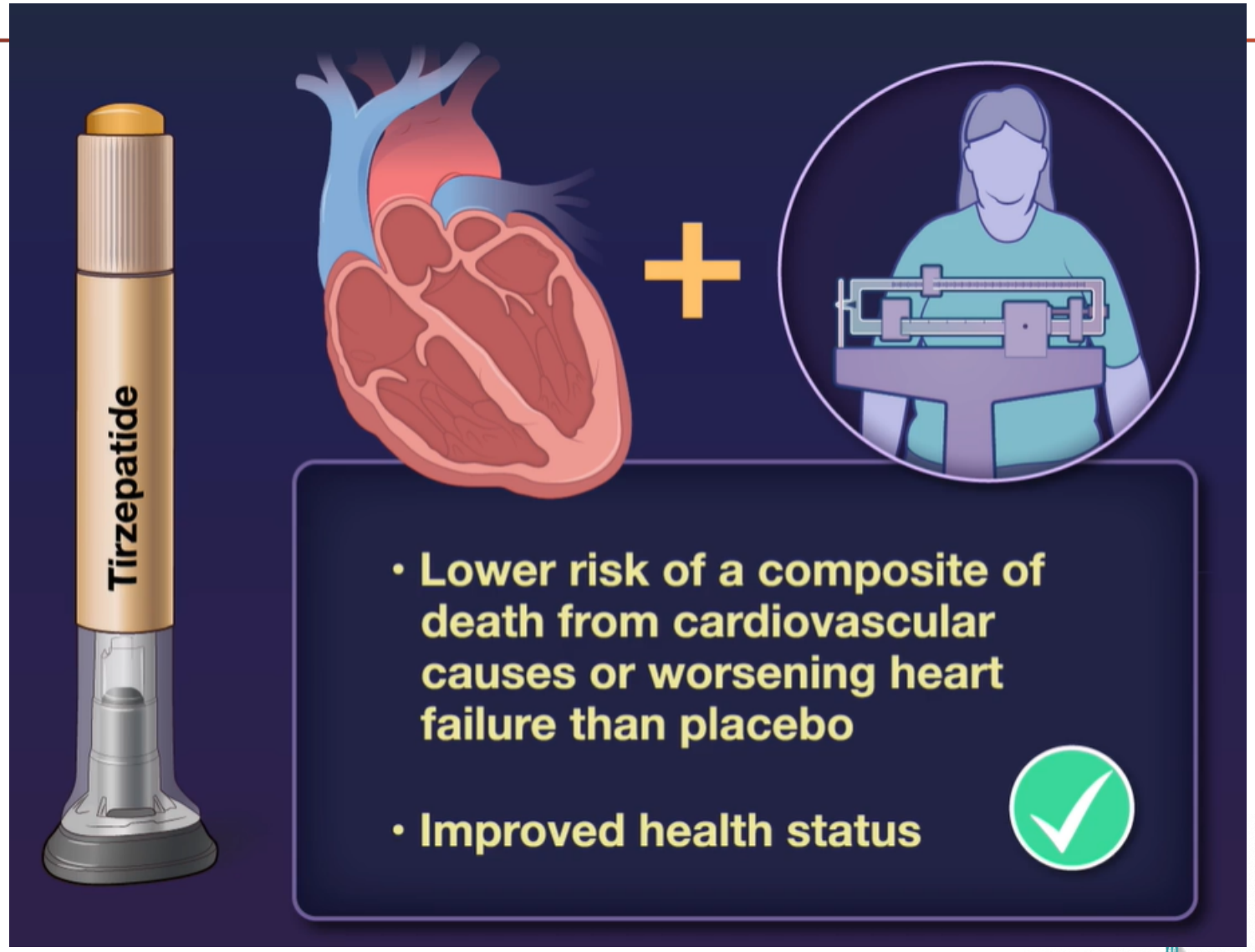
**ETD -34.9**
(95% CI -45.6 to -22.2)[a]
*P<.001*

A greater reduction in hsCRP was observed in patients on tirzepatide compared to placebo.

- [a]Data were log-transformed before analysis.
- Tirzepatide vs. placebo: ***P<0.001.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; hsCRP=High Sensitivity C-reactive Protein; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.
- Packer M, et al. *NEJM*. 2025

# SUMMIT trial

- **Chronic heart failure**
  *(NYHA class II–IV heart failure)*
- **Preserved ejection fraction**
  *(LVEF of ≥50%)*
- **Obesity**
  *(BMI of ≥30)*




Packer M et al . N Engl J Med 2025;392:427-437

# Influence of Type 2 Diabetes on the Effects of Tirzepatide in Patients With Heart Failure and a Preserved Ejection Fraction With Obesity

## A Prespecified Stratification-Based Analysis

Milton Packer, MD,[a,b] Michael R. Zile, MD,[c] Christopher M. Kramer, MD,[d] Joseph M. DiMaria, BA,[d] Seth J. Baum, MD,[e] Sheldon E. Litwin, MD,[c] Masahiro Murakami, MD,[f] Chunmei Zhou, MS,[f] Yang Ou, PhD,[f] Lisette Koeneman, MD,[f] Barry A. Borlaug, MD,[g,h] the SUMMIT Trial Study Group

Patients with HFpEF, obesity, and T2DM responded favorably to tirzepatide, reflected by a **reduced risk of adverse HF outcomes and improved health status, quality of life, and functional capacity**, as well as a **decrease in LV mass and paracardiac fat**, to a degree that was similar to that in patients without diabetes.

**FIGURE 1** Placebo-Corrected Effect of Tirzepatide in Patients With and Without Diabetes

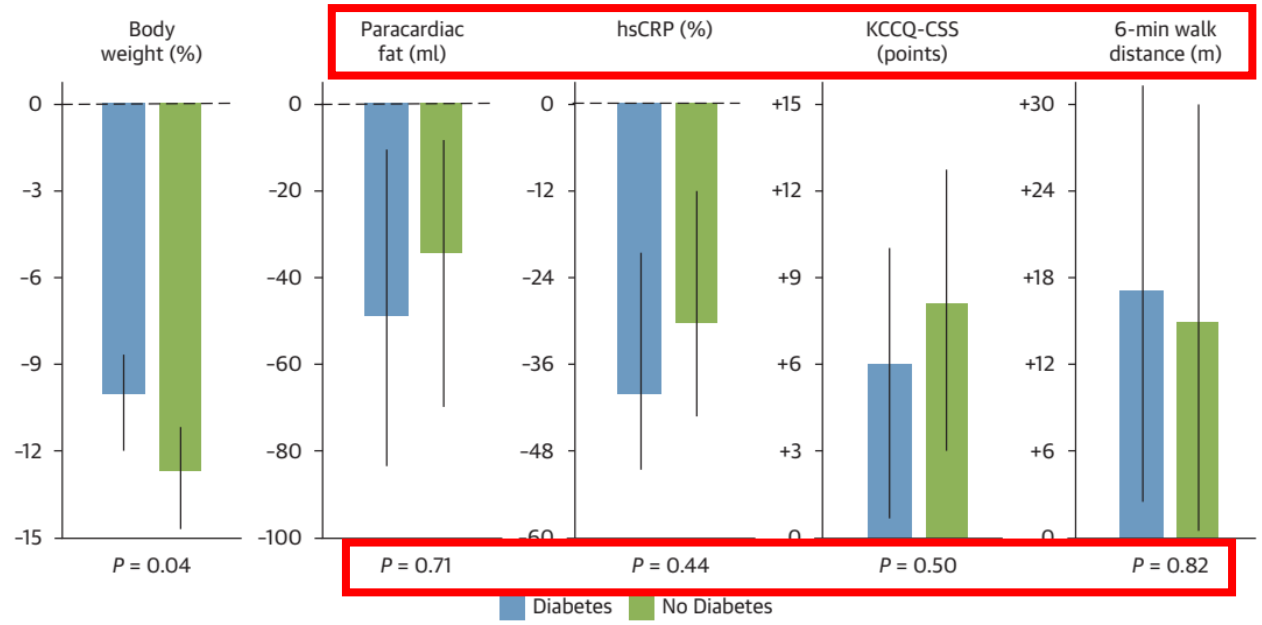
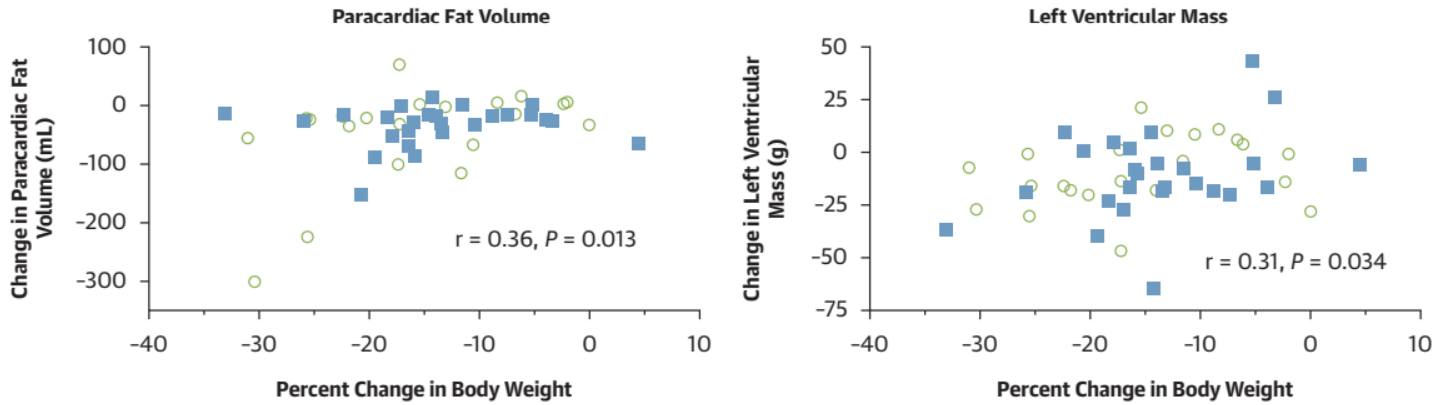



**FIGURE 2** Correlation Analyses of Weight Loss and Changes in Paracardial Fat and Left Ventricular Mass After 52 Weeks of Double-Blind Treatment




Shaded rectangles and open ovals show effect in patients with diabetes and without diabetes, respectively

doi:10.1002/ejhf.70012

# Cardiovascular outcomes with tirzepatide in heart failure with preserved ejection fraction associated with obesity

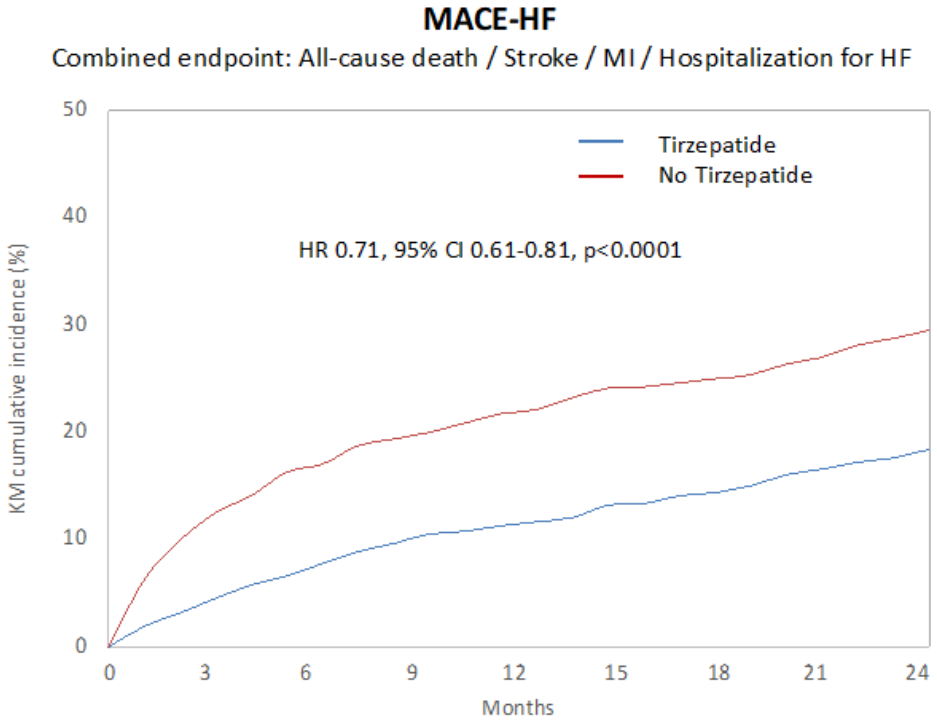
The largest **real-world evaluation of tirzepatide** in **HFpEF** with **obesity** from electronic health records in 18 countries

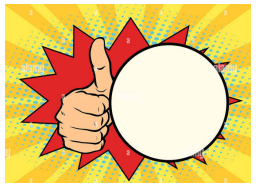
Higher prevalence of diabetes mellitus (approximately 80%) compared to the SUMMIT (approximately 50%)

**Table 2 Clinical outcomes at follow-up**

| | Number of events, yearly rate (%) | | Hazard ratio (95% CI) | p-value |
|---|---|---|---|---|
| | Tirzepatide ($n=825$) | No tirzepatide ($n=825$) | | |
| MACE-HF | 352 (13.62) | 511 (17.22) | 0.71 (0.61–0.81) | <0.0001 |
| All-cause death | 38 (2.94) | 127 (5.23) | 0.55 (0.38–0.80) | 0.001 |
| Ischaemic stroke | 27 (1.60) | 40 (1.84) | 1.23 (0.74–2.04) | 0.43 |
| Acute MI | 28 (5.22) | 50 (3.13) | 1.07 (0.66–1.73) | 0.79 |
| Incident AF | 18 (2.02) | 66 (5.50) | 0.47 (0.28–0.80) | 0.01 |
| VT/VF/cardiac arrest | 62 (4.77) | 112 (4.76) | 0.88 (0.64–1.21) | 0.43 |
| Hospitalization for HF | 303 (11.09) | 427 (13.79) | 0.68 (0.59–0.79) | <0.0001 |
| Hospitalization for any cause | 269 (13.09) | 476 (16.66) | 0.65 (0.56–0.76) | <0.0001 |
| Hospitalization/visit for CV reason | 372 (12.47) | 479 (15.05) | 0.71 (0.62–0.81) | <0.0001 |

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.



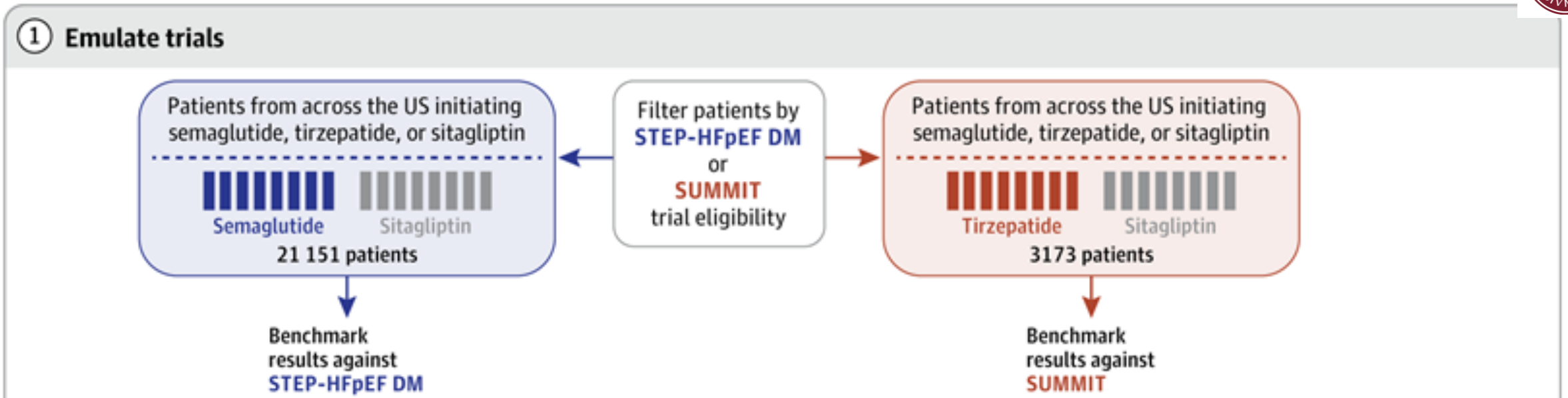
A real-world evidence that **tirzepatide is associated with a reduced risk of CV events in patients with HFpEF and obesity**.

**Supplemental Figure 2.** Cumulative incidence of the combined endpoint according to tirzepatide use in patients with obesity and HFpEF



EJHF 2025 https://doi.org/10.1002/ejhf.70012

# Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction




**STEP-HFpEF DM trial eligibility**

**Inclusion:** Age ≥18 y, HFpEF, BMI ≥30, type 2 diabetes, elevated heart failure (HF) biomarker or recent HF hospitalization, and stable diabetes therapy

**Exclusion:** Recent cardiovascular event, uncontrolled blood pressure, severe lung or kidney disease, severe anemia, insulin pump use, GLP-1 RA use, type 1 diabetes, severe hypoglycemia, unstable retinopathy, pancreatitis, psychiatric or substance disorder, suicidality, amyloidosis, hypertrophic cardiomyopathy, valvular or congenital heart disease, cancer, medullary thyroid cancer/multiple endocrine neoplasia type 2, bariatric surgery, or pregnancy

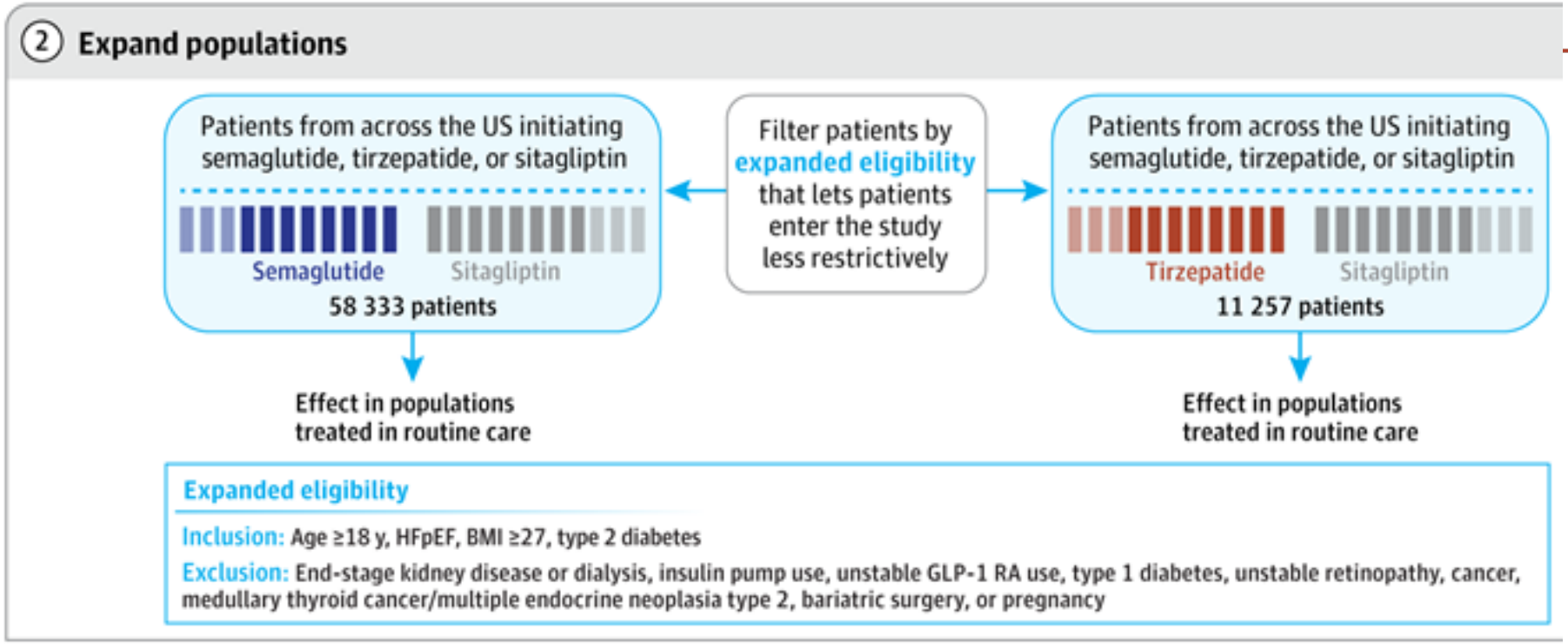
**SUMMIT trial eligibility**

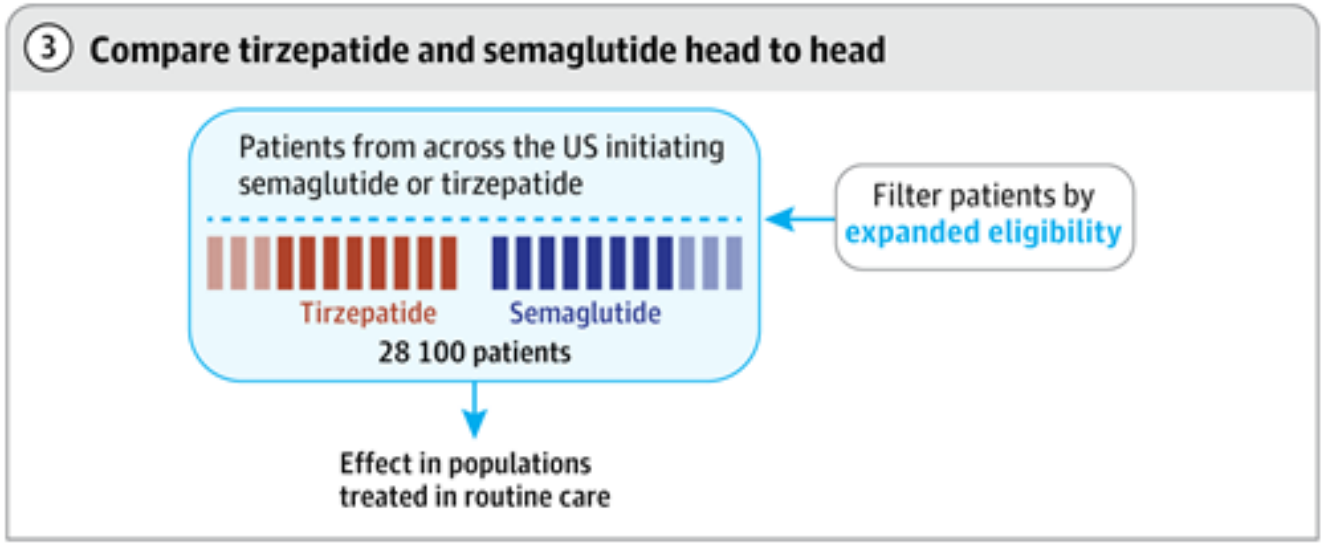
**Inclusion:** Age ≥40 y, HFpEF, BMI ≥27,[a] type 2 diabetes,[b] structural heart disease, eGFR <70 or recent HF hospitalization, and stable HF medication

**Exclusion:** Recent cardiovascular event, uncontrolled blood pressure, severe lung, kidney, or liver disease, anemia, atrial arrhythmia, device therapy, untreated thyroid disease, insulin pump use, GLP-1 RA use, type 1 diabetes, uncontrolled type 2 diabetes, severe hypoglycemia, unstable retinopathy, pancreatitis, gastrointestinal disorders, weight-altering medication, psychiatric or substance disorder, mobility limits, muscular dystrophy, amyloidosis, hypertrophic cardiomyopathy, valvular disease, cancer, medullary thyroid cancer/multiple endocrine neoplasia type 2, bariatric surgery, or pregnancy

Nils Krüger et al JAMA 2025. doi:10.1001/jama.2025.14092

# Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction



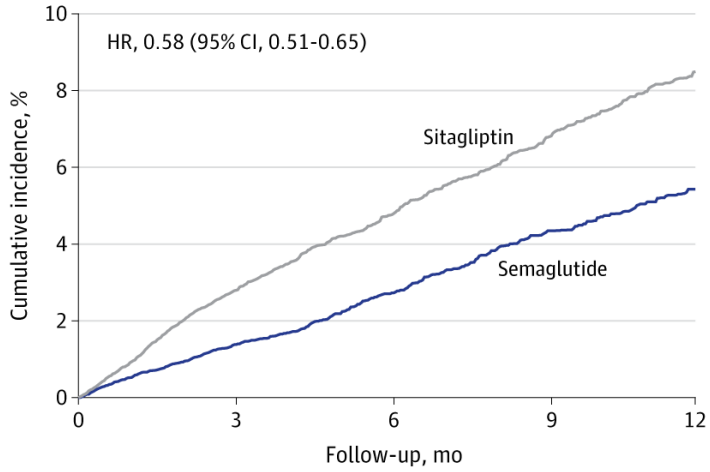




**The comparator, sitagliptin, served as a placebo proxy**

Nils Krüger et al JAMA 2025. doi:10.1001/jama.2025.14092

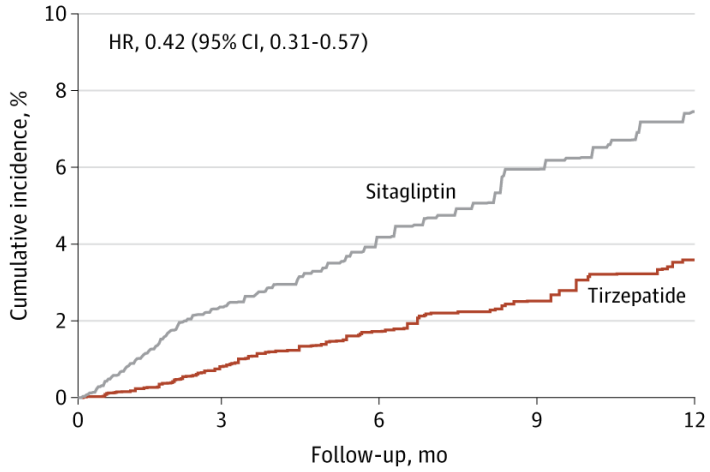
# Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction

**A** Semaglutide vs sitagliptin



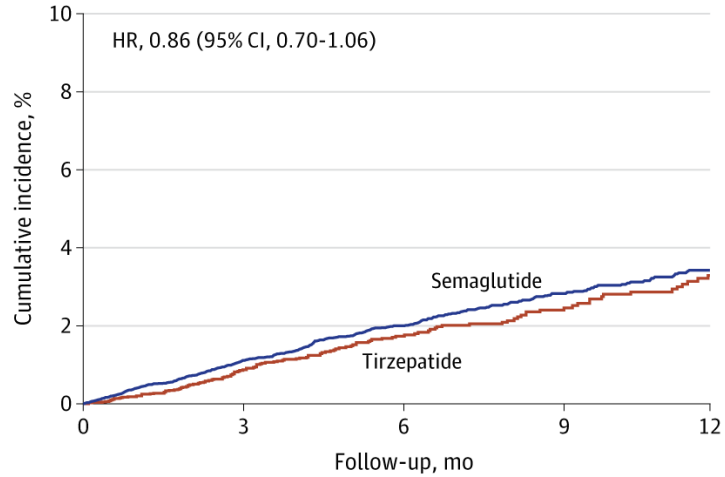

| No. at risk | | | | | |
|---|---|---|---|---|---|
| Semaglutide | 7640 | 5257 | 2865 | 1873 | 1284 |
| Death | 0 | 27 | 45 | 60 | 70 |
| HHF | 0 | 73 | 107 | 129 | 138 |
| Sitagliptin | 7640 | 5497 | 3234 | 2087 | 1352 |
| Death | 0 | 57 | 92 | 112 | 126 |
| HHF | 0 | 139 | 194 | 229 | 249 |

**B** Tirzepatide vs sitagliptin




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Tirzepatide | 1647 | 1092 | 635 | 403 | 265 |
| Death | 0 | 6 | 9 | 11 | 12 |
| HHF | 0 | 8 | 12 | 14 | 16 |
| Sitagliptin | 1647 | 1116 | 588 | 328 | 198 |
| Death | 0 | 12 | 21 | 23 | 25 |
| HHF | 0 | 25 | 31 | 37 | 39 |

**C** Tirzepatide vs semaglutide




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Tirzepatide | 5746 | 3851 | 2261 | 1402 | 874 |
| Death | 0 | 16 | 28 | 33 | 37 |
| HHF | 0 | 25 | 41 | 48 | 54 |
| Semaglutide | 5746 | 3938 | 1965 | 1064 | 649 |
| Death | 0 | 16 | 28 | 35 | 36 |
| HHF | 0 | 38 | 54 | 60 | 63 |


In patients with cardiometabolic HFpEF, **semaglutide and tirzepatide showed more than 40% risk reduction for the composite of hospitalization for heart failure or all-cause mortality** compared with a placebo proxy.

No differences Tirze VS Sema in HFpEF

Nils Krüger et al JAMA 2025. doi:10.1001/jama.2025.14092

# Key home message

•**Oltre il Controllo Glicemico:** I recettori per GIP e GLP-1 non sono espressi solo a livello pancreatico, ma sono diffusi in molteplici tessuti extra-pancreatici, inclusi il sistema cardiovascolare e il sistema nervoso centrale.

Dagli studi clinici **SURPASS** (sul diabete di tipo 2) e **SURMOUNT** (sull'obesità), si dimostra una efficace perdita di peso e vs dulaglutide una **non-inferiorità** rispetto all'endpoint composito MACE.

•Tirzepatide ha **ridotto significativamente il rischio di eventi di insufficienza cardiaca o morte cardiovascolare** nei pazienti **con HFpEF correlata all'obesità (SUMMIT), con e senza diabete,** migliorando anche **capacità di esercizio e qualità della vita**, riducendo la massa ventricolare e il grasso paracardiaco. Inoltre, **migliora lo stato infiammatorio** cruciale dal punto di vista fisiopatologico in questo fenotipo di pazienti HFpEF.

•Dati di **real world** su **HFpEF con fenotipo obeso** confermano efficacia Tirzepatide nel **ridurre profilo di rischio CV** (MACE, All cause death, HHF, AF)