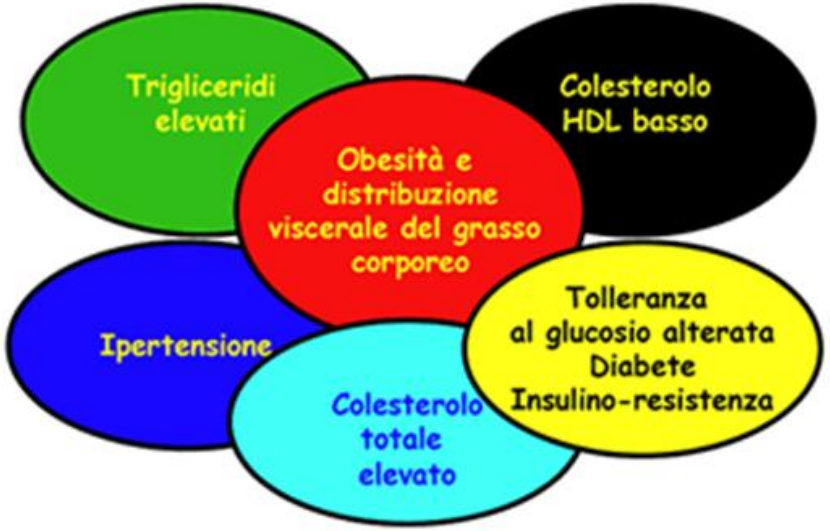
BIELLA CUORE
12-13 SETTEMBRE 2025

Utilizzo dei GLP1 – RA: indicazioni ed effetti

QUALI PROSPETTIVE PER IL PAZIENTE CARDIOMETABOLICO

Monica Andriani
Cardiologia
Città della Salute e della Scienza
Torino



SINDROME CARDIOMETABOLICA

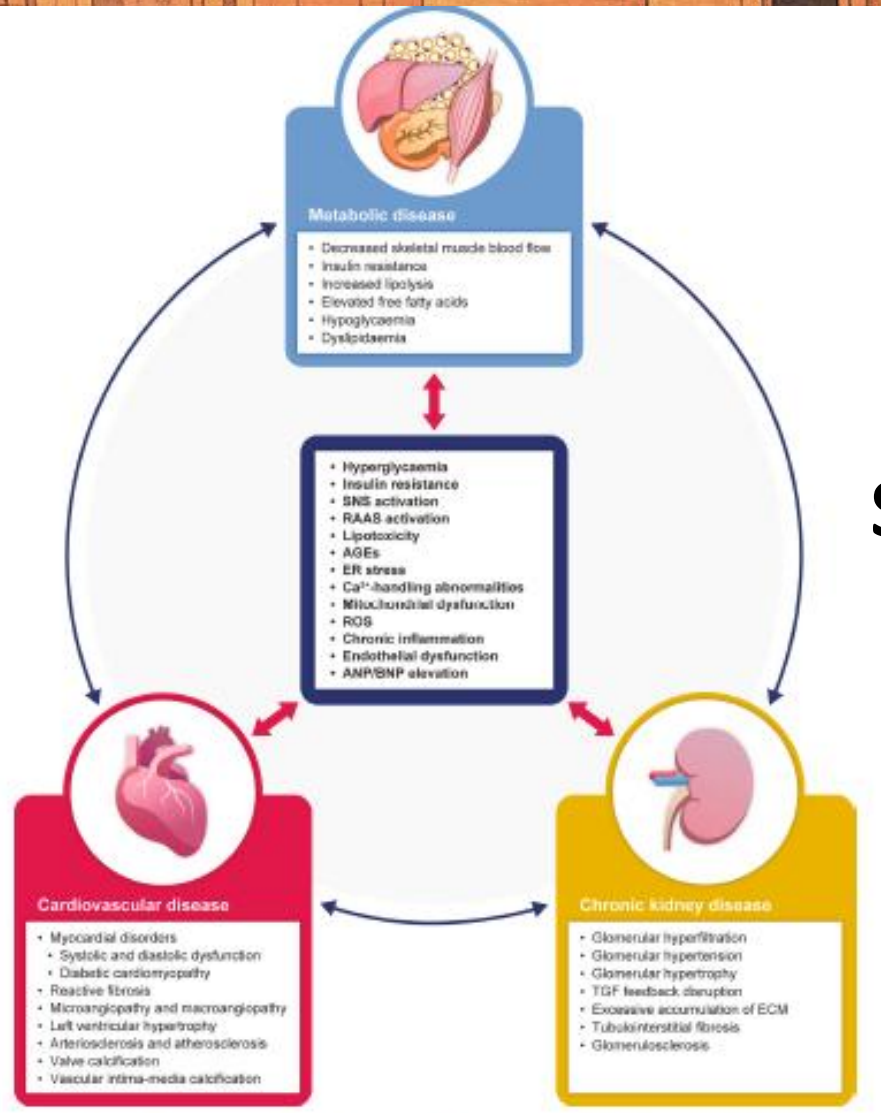
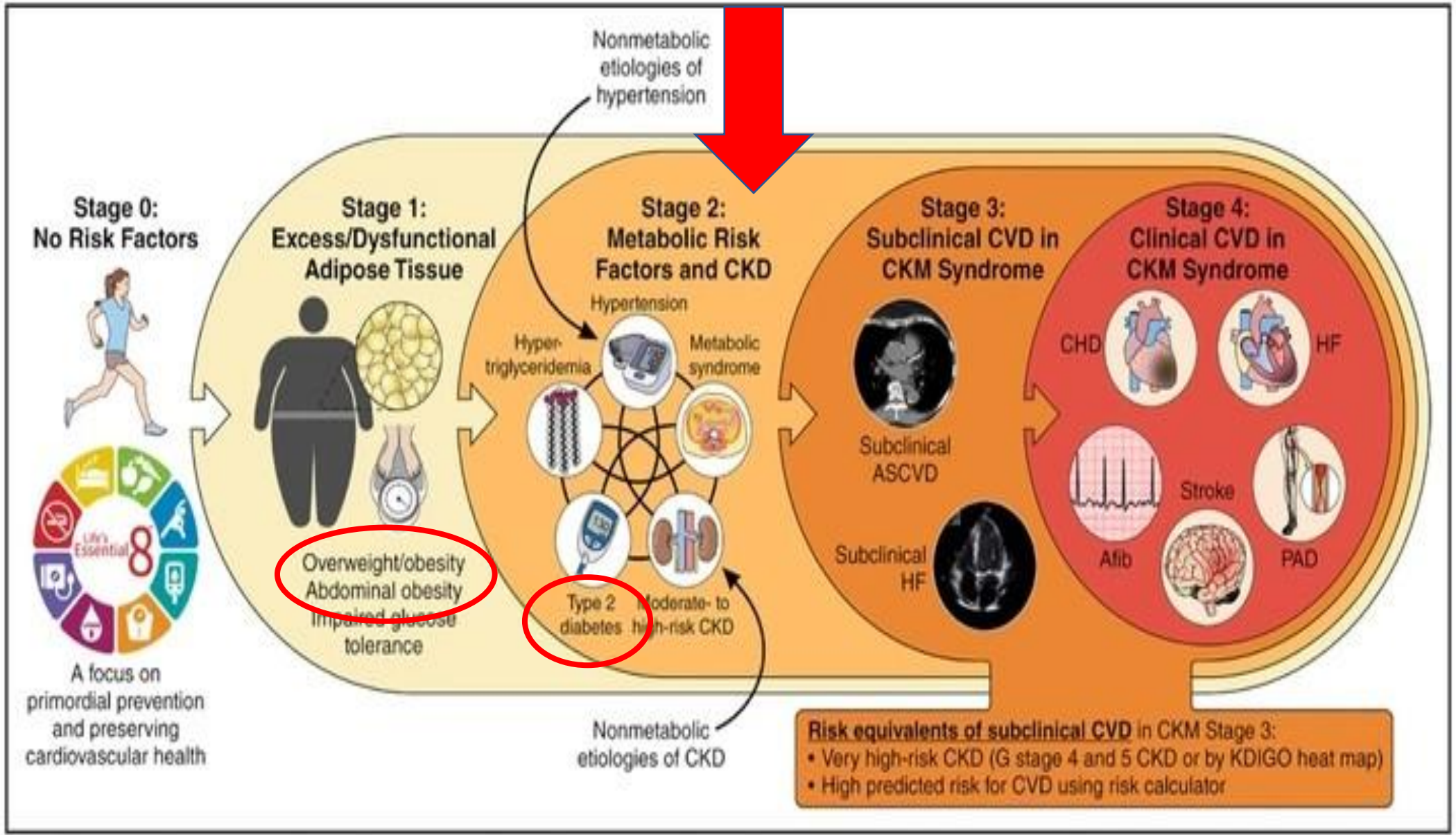


FIGURE 2 Molecular and pathophysiological interplay between cardiovascular disease, chronic kidney disease and metabolic disease. AGEs, advanced glycated end-products; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; ECM, extracellular matrix; ER, endoplasmic reticulum; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF, tubuloglomerular feedback

SINDROME CARDIO-NEFROMETABOLICA


Nonmetabolic etiologies of hypertension
Stage 0: No Risk Factors
Stage 1: Excess/Dysfunctional Adipose Tissue
Stage 2: Metabolic Risk Factors and CKD
Stage 3: Subclinical CVD in CKM Syndrome
Stage 4: Clinical CVD in CKM Syndrome
Hypertension
Hyper-triglyceridemia
Metabolic syndrome
Type 2 diabetes
Moderate- to high-risk CKD
Overweight/obesity
Abdominal obesity
Impaired glucose tolerance
Subclinical ASCVD
Subclinical HF
CHD
HF
Stroke
Afib
PAD
Life's Essential 8
A focus on primordial prevention and preserving cardiovascular health
Nonmetabolic etiologies of CKD
Risk equivalents of subclinical CVD in CKM Stage 3:
• Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)
• High predicted risk for CVD using risk calculator

DIABETES WORLDWIDE IN 2024

589 M adulti con diabete nel mondo

↓

853 M nel 2050

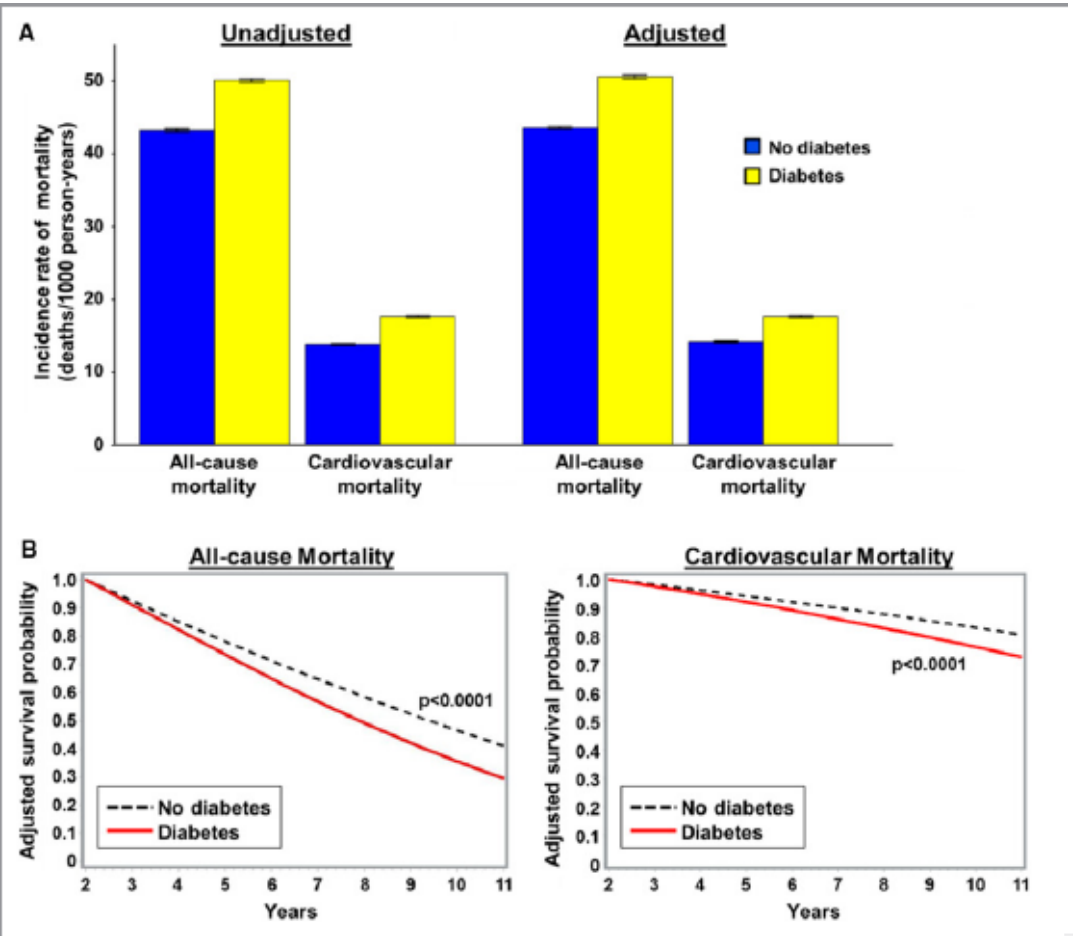
4 su 10 non diagnosticati

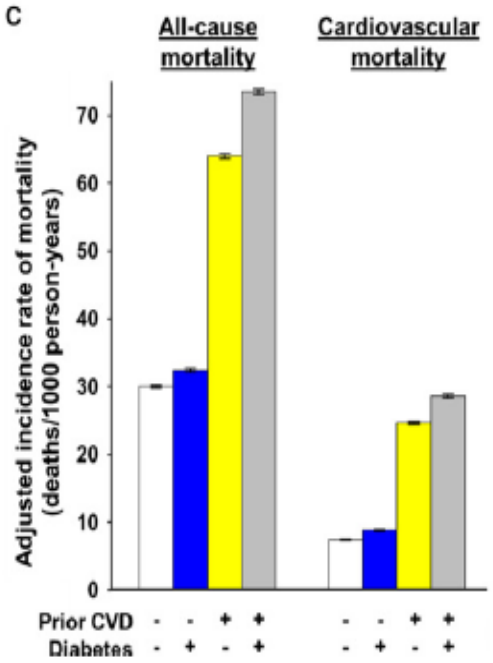
3.4 M morti
per diabete

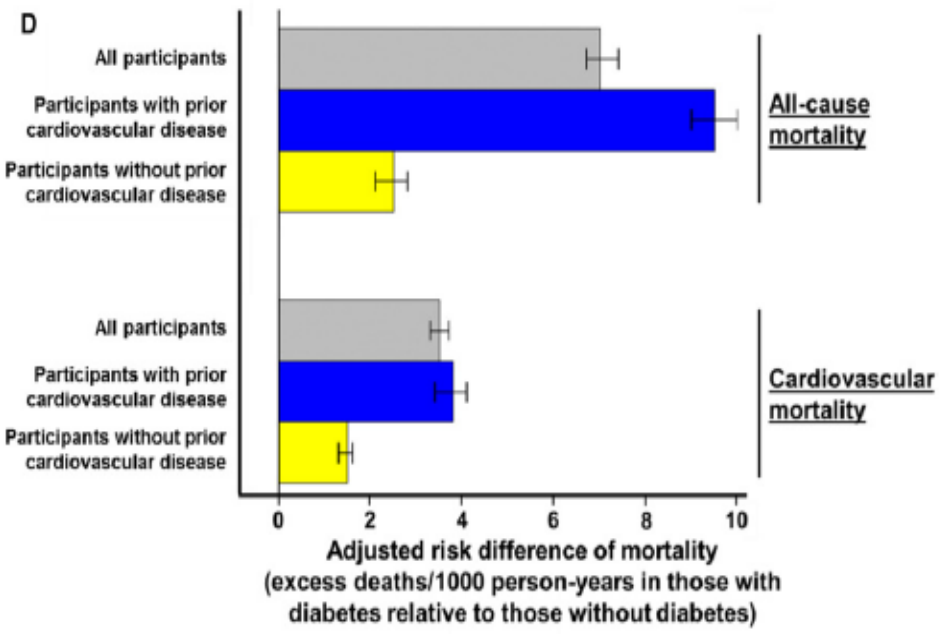
Spesa sanitaria
1 trilione di dollari pari a 11.9% della spesa sanitaria globale

International Diabetes Federation (IDF)

DIABETES MORTALITY







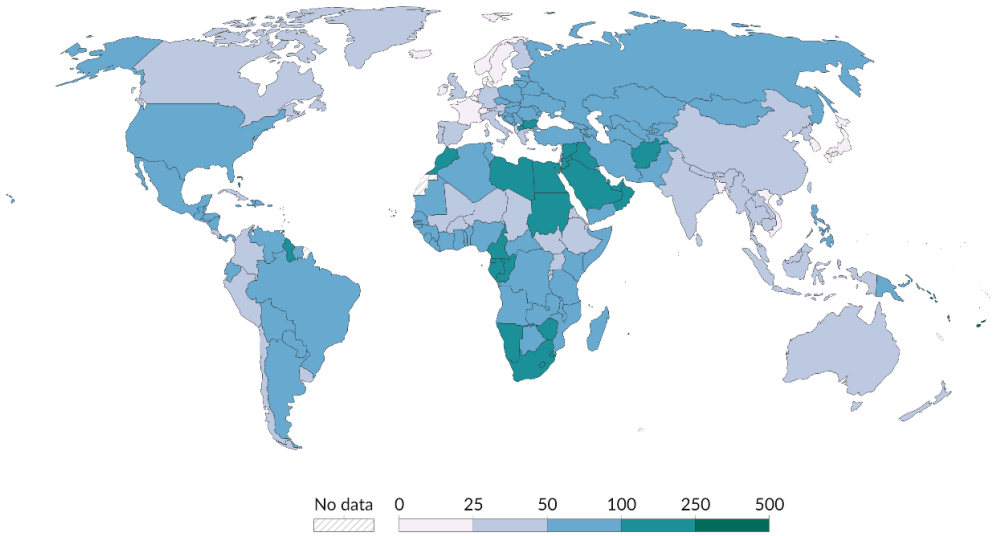
S. Raghavan Heart Assoc. 2019

OBESITA'

Death rate from obesity, 2021

Our World in Data

Estimated annual number of deaths attributed to obesity[1] per 100,000 people.



Data source: IHME, Global Burden of Disease (2024) OurWorldinData.org/obesity | CC BY

Note: To allow for comparisons between countries and over time, this metric is age-standardized[2]. Obesity is defined as having a body-mass index (BMI) ≥ 30. BMI is a person's weight (in kilograms) divided by their height (in meters) squared.

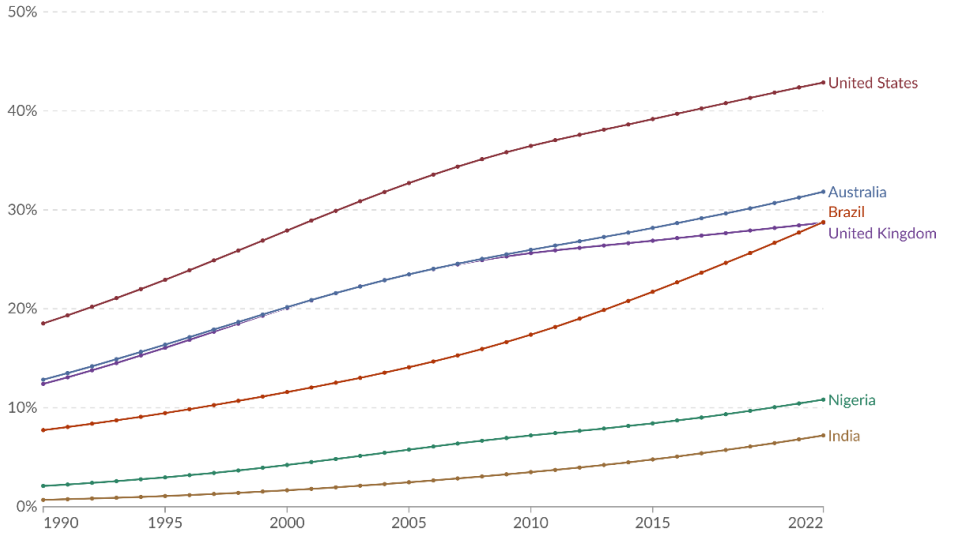
1. Obesity Obesity is defined as having a body-mass index (BMI) above 30.
A person's BMI is calculated as their weight (in kilograms) divided by their height (in meters) squared. For example, someone measuring 1.60 meters and weighing 64 kilograms has a BMI of 64 / 1.6^2 = 25.
Obesity increases the mortality risk of many conditions, including cardiovascular disease, gastrointestinal disorders, type 2 diabetes, joint and muscular disorders, respiratory problems, and psychological issues.

2. Age standardization Age standardization is an adjustment that makes it possible to compare populations with different age structures, by standardizing them to a common reference population.
Read more: How does age standardization make health metrics comparable?

Obesity in adults, 1990 to 2022

Our World in Data

Estimated prevalence of obesity[1], based on general population surveys and statistical modeling. Obesity is a risk factor[2] for chronic complications, including cardiovascular disease, and premature death.



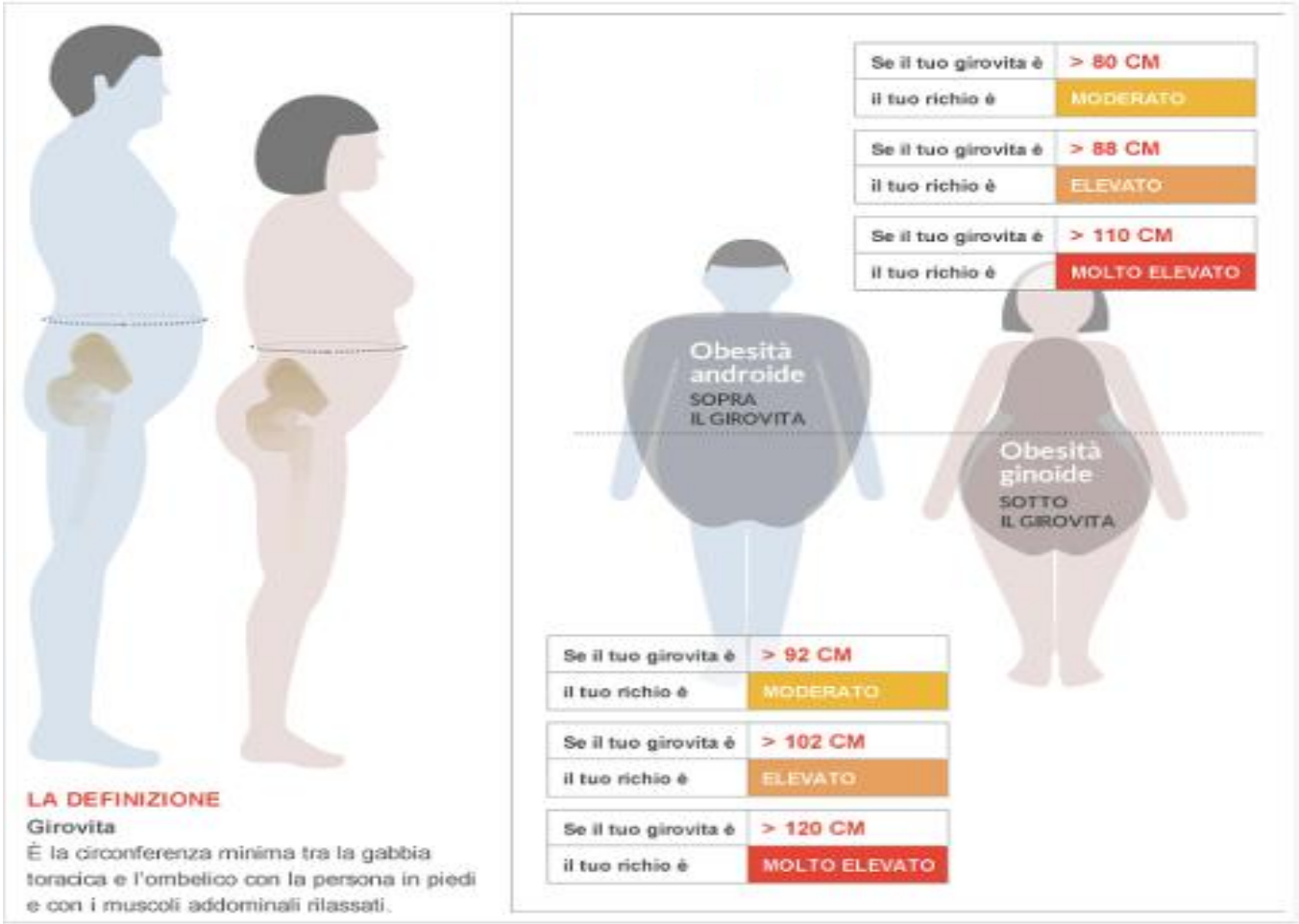
Data source: World Health Organization - Global Health Observatory (2025) OurWorldinData.org/obesity | CC BY

1. Obesity Obesity is defined as having a body-mass index (BMI) above 30.
A person's BMI is calculated as their weight (in kilograms) divided by their height (in meters) squared. For example, someone measuring 1.60 meters and weighing 64 kilograms has a BMI of 64 / 1.6^2 = 25.
Obesity increases the mortality risk of many conditions, including cardiovascular disease, gastrointestinal disorders, type 2 diabetes, joint and muscular disorders, respiratory problems, and psychological issues.

2. Risk factor A risk factor is a condition or behavior that increases the likelihood of developing a given disease or injury, or an outcome such as death.
The impact of a risk factor is estimated in different ways. For example, a common approach is to estimate the number of deaths that would occur if the risk factor was absent.
Risk factors are not mutually exclusive: people can be exposed to multiple risk factors, which contribute to their disease or death. Because of this, the number of deaths caused by each risk factor is typically estimated separately.
Read more: How do researchers estimate the death toll caused by each risk factor, whether it's smoking, obesity or air pollution?
Read more: Why isn't it possible to sum up the death toll from different risk factors?

Obesity
When did obesity increase? How do rates vary across the world? What is the health impact?
By: Hannah Ritchie and Max Roser

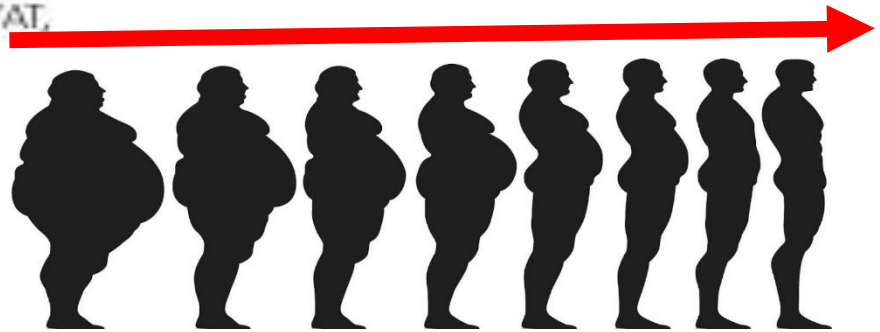
Classificazione	BMI (kg/m^2)
Sottopeso	< 18.5
Normopeso	18.5 - 24.9
Sovrappeso	≥ 25.0
pre-obeso	25.0 - 29.9
obeso classe I	30.0 - 34.9
obeso classe II	35.0 - 39.9
obeso classe III	≥ 40.0

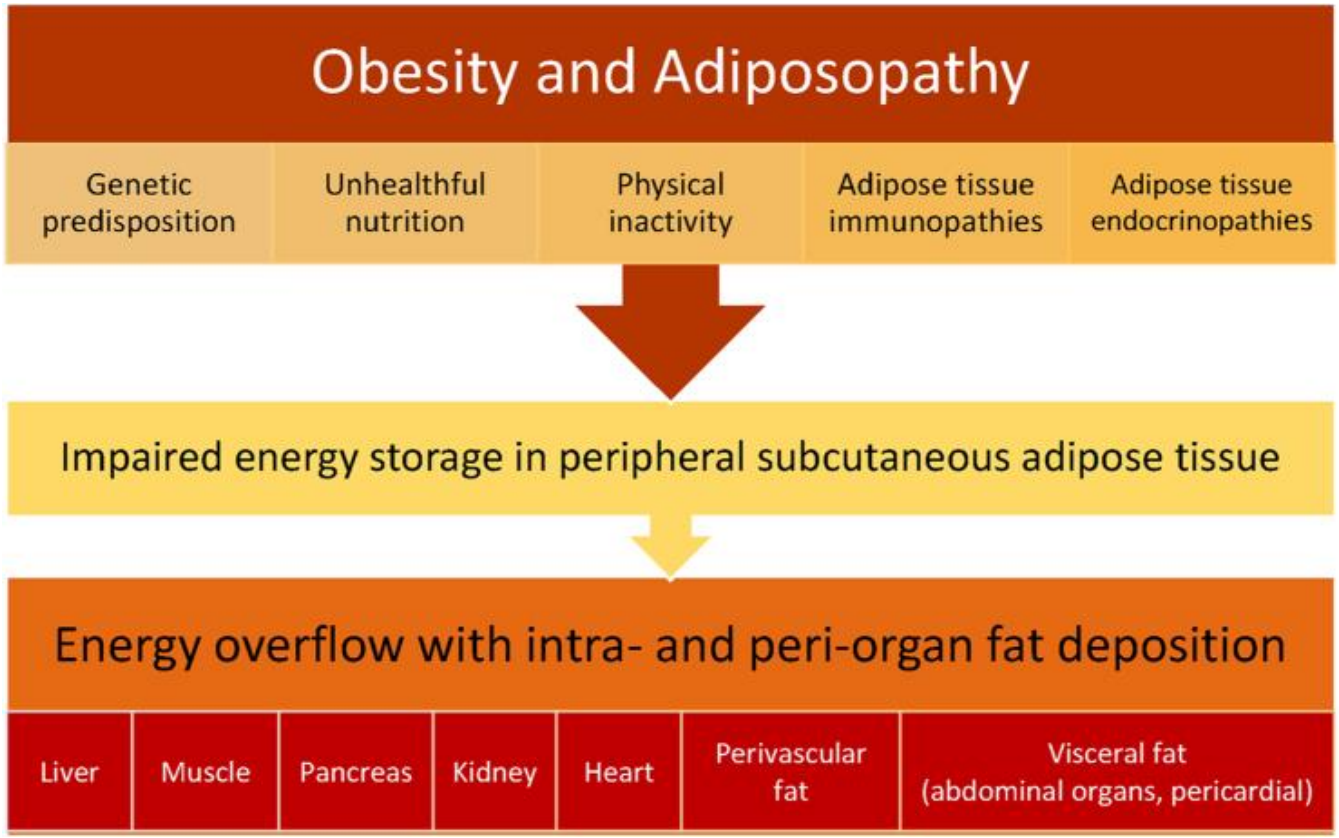




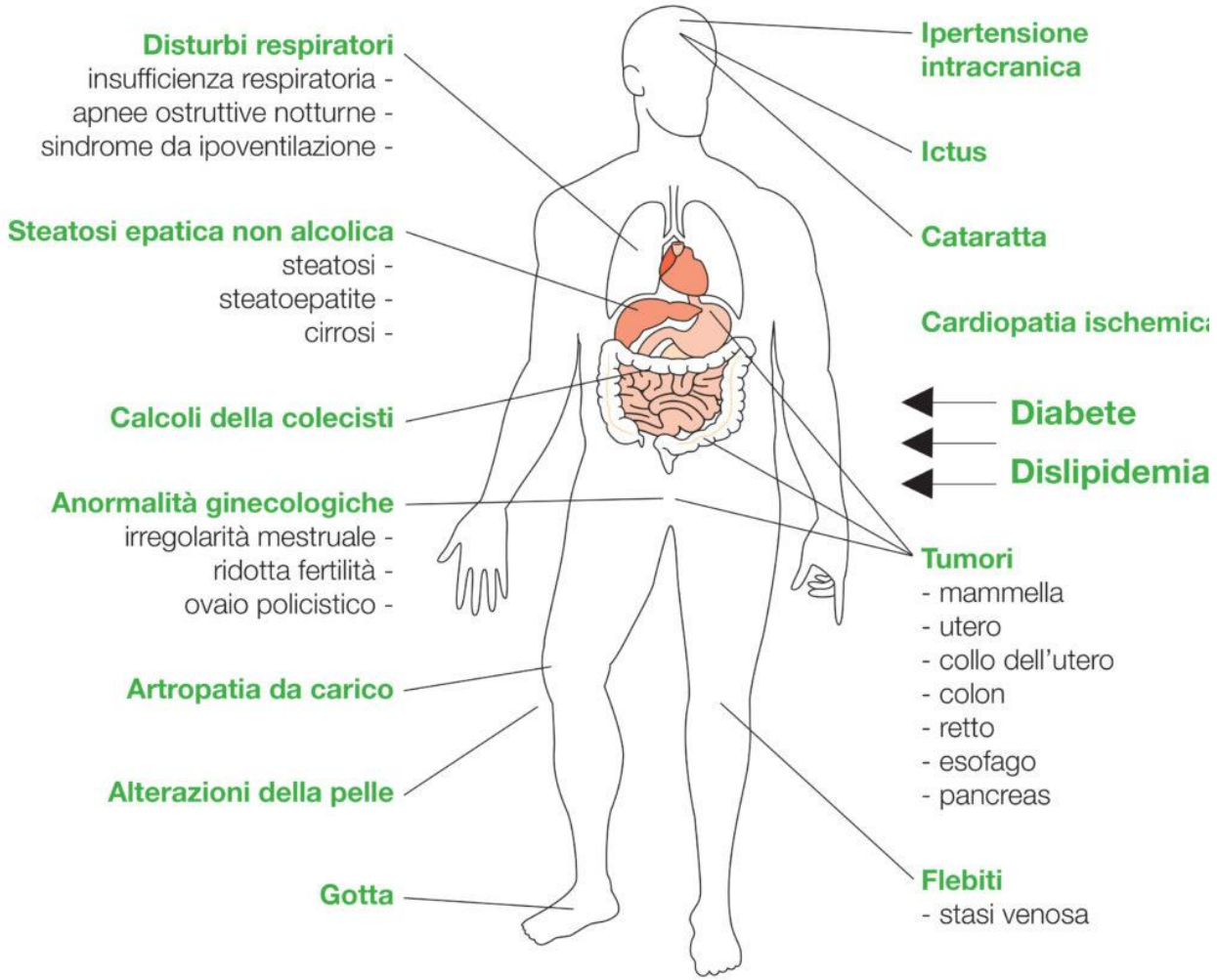

	Obeso metabolicamente sano	Normopeso metabolicamente obeso	Obeso normopeso	Obeso sarcopenico
BMI (kg/m²)	>30	15.5-25	15.5-25	>30
VAT/FM	VAT basso	VAT alto	Massa grassa>30%	VAT alto
Massa magra	Alto	Normale	Normale	Basso
CRF	Alto	Basso	-	Basso
Anomalie metaboliche	Assente	Presente	Assente	Presente

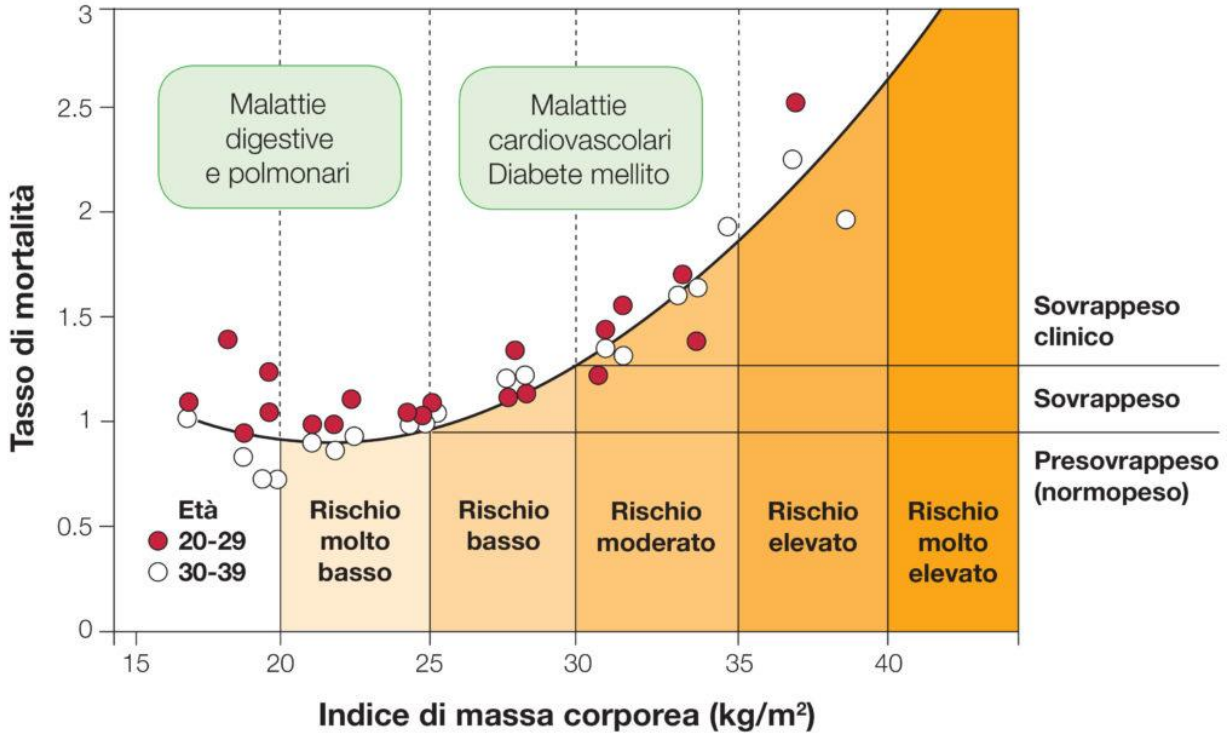
Figura 6. Caratteristiche di diversi fenotipi di obesità.
BMI, indice di massa corporea; CRF, fitness cardiorespiratoria; FM, massa grassa; VAT, tessuto adiposo viscerale.
Modificata da Vecchiè et al.[14]

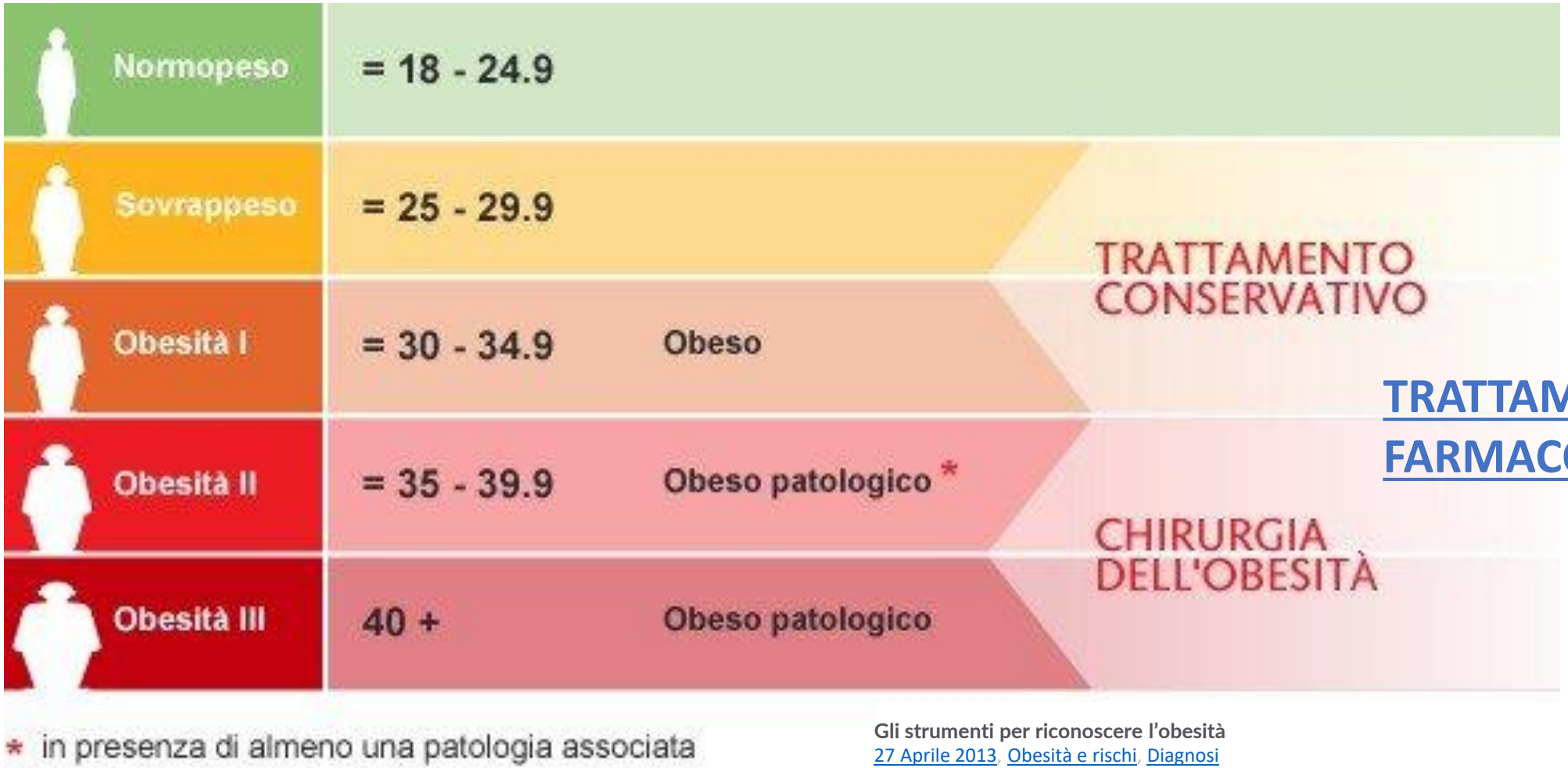




Obesity, diabetes mellitus, and cardiometabolic risk: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023
Harold Edward Bays et al.


Disturbi respiratori
insufficienza respiratoria -
apnee ostruttive notturne -
sindrome da ipoventilazione -
Steatosi epatica non alcolica
steatosi -
steatoepatite -
cirrosi -
Calcoli della colecisti
Anormalità ginecologiche
irregolarità mestruale -
ridotta fertilità -
ovaio policistico -
Artropatia da carico
Alterazioni della pelle
Gotta
Ipertensione intracranica
Ictus
Cataratta
Cardiopatia ischemica
Diabete
Dislipidemia
Tumori
- mammella
- utero
- collo dell'utero
- colon
- retto
- esofago
- pancreas
Flebiti
- stasi venosa

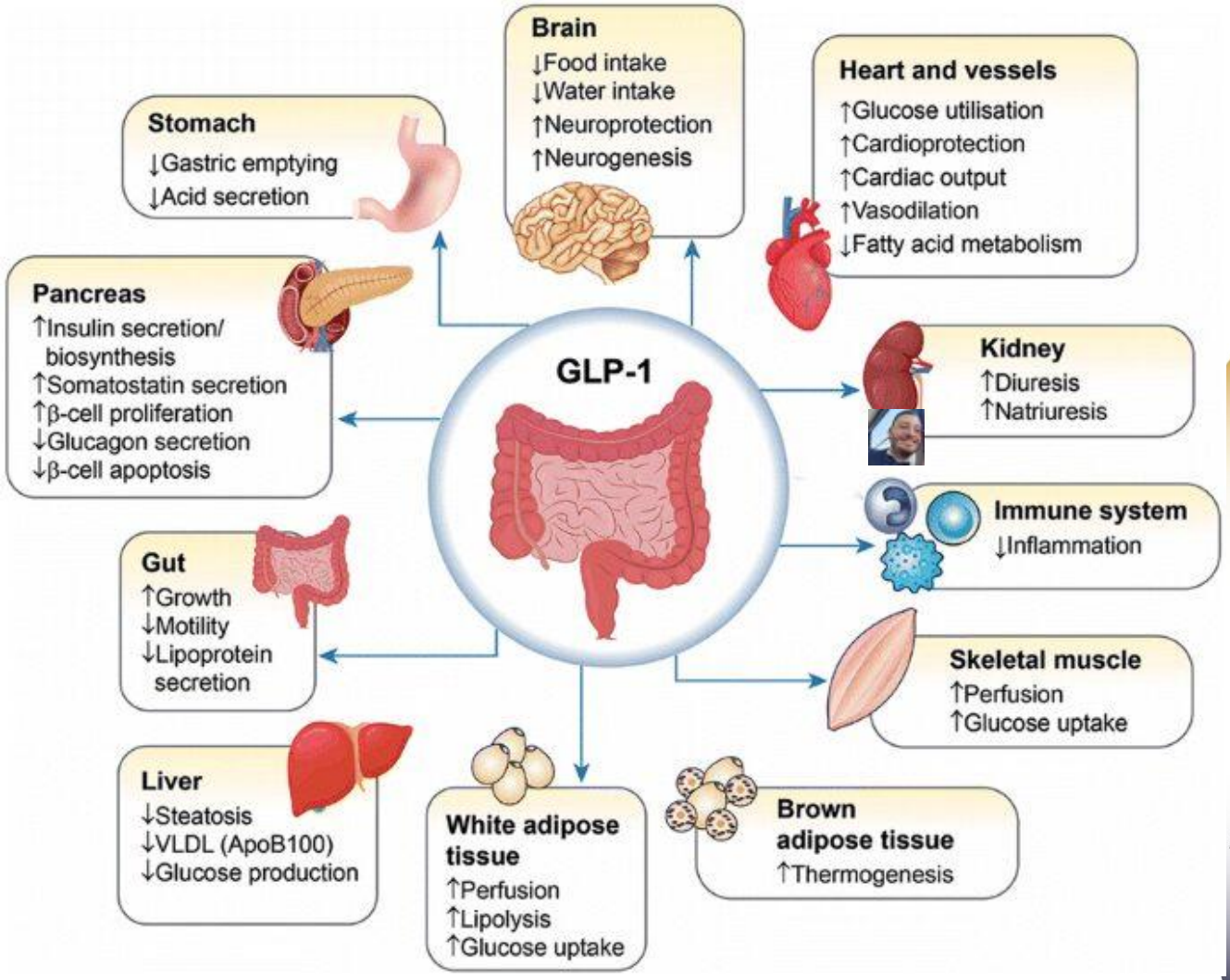

Tasso di mortalità
Indice di massa corporea (kg/m²)
Malattie digestive e polmonari
Malattie cardiovascolari Diabete mellito
Età
20-29
30-39
Rischio molto basso
Rischio basso
Rischio moderato
Rischio elevato
Rischio molto elevato
Sovrappeso clinico
Sovrappeso
Presovrappeso (normopeso)



TRATTAMENTO FARMACOLOGICO

Gli strumenti per riconoscere l'obesità
27 Aprile 2013, Obesità e rischi, Diagnosi

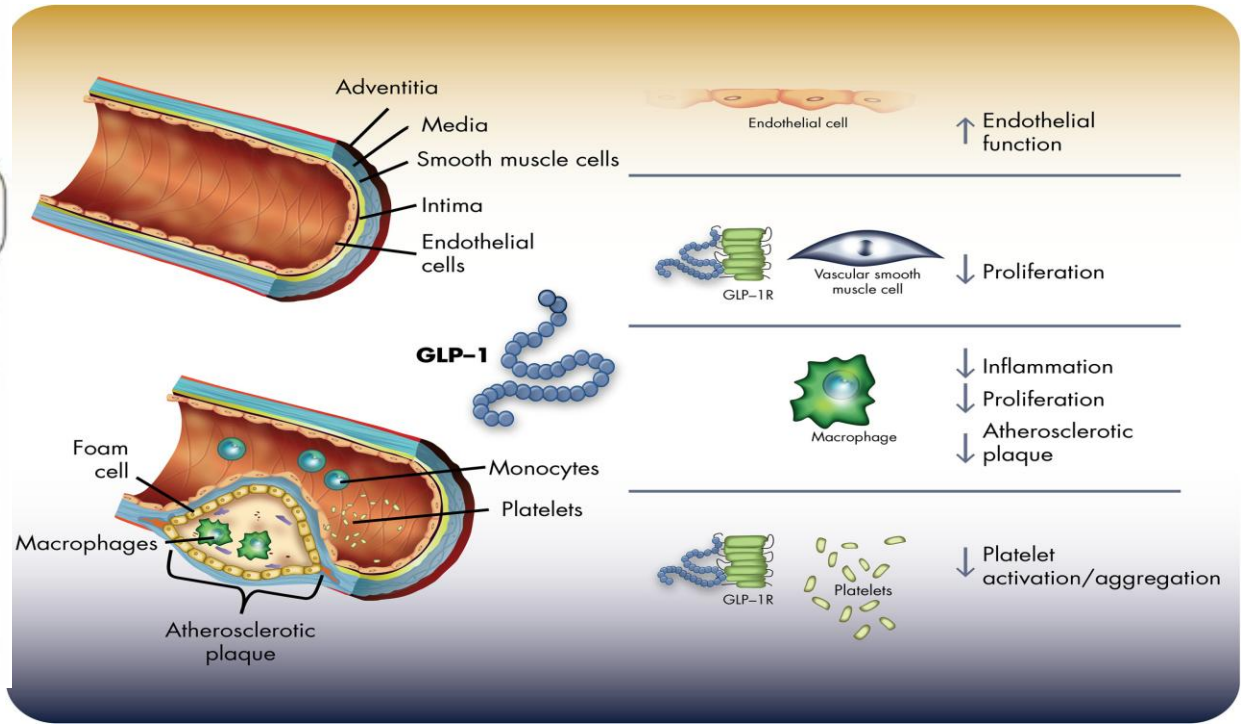
Indice di Massa Corporea (IMC), un indice per conoscersi meglio, l'indicatore più accreditato a livello scientifico per definire la presenza di obesità e graduarne il livello.



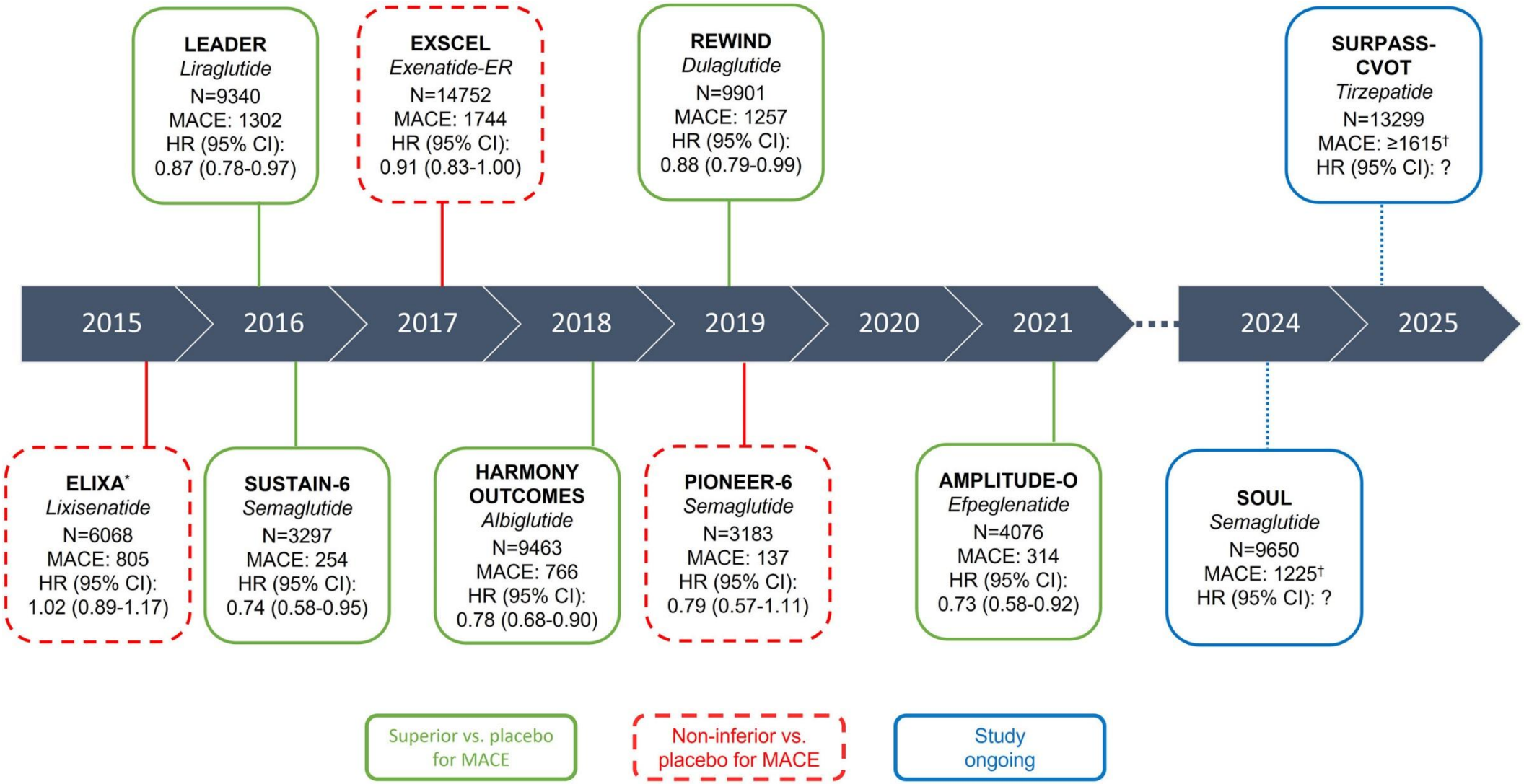
Agonisti del GLP-1: descrizione, principi attivi e indicazioni terapeutiche

By Francesco Centorrino

GLP1-RA
Disease Modifiers



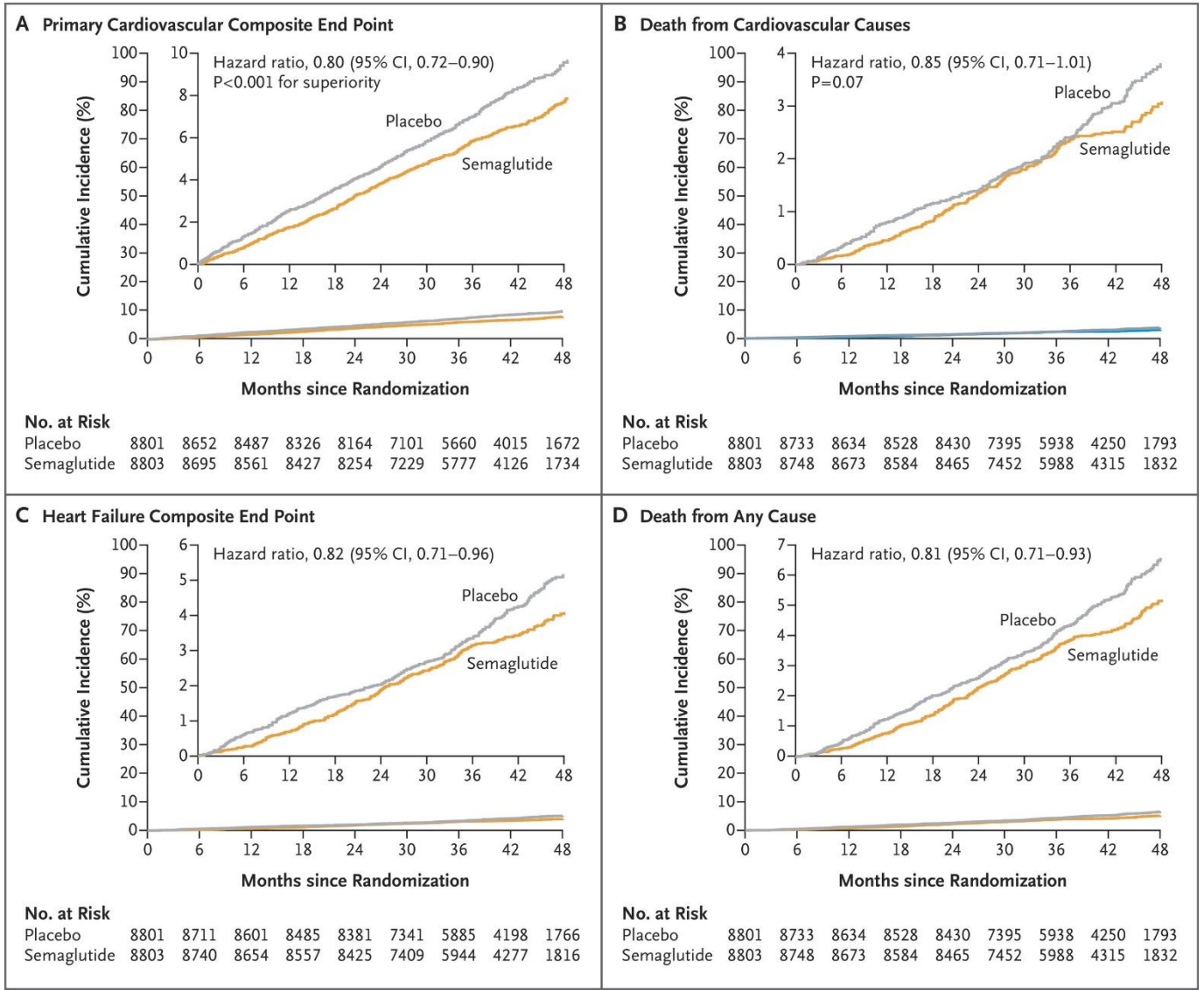
Pujadas et al. End Rev 2016


LEADER
Liraglutide
N=9340
MACE: 1302
HR (95% CI):
0.87 (0.78-0.97)
EXSCEL
Exenatide-ER
N=14752
MACE: 1744
HR (95% CI):
0.91 (0.83-1.00)
REWIND
Dulaglutide
N=9901
MACE: 1257
HR (95% CI):
0.88 (0.79-0.99)
SURPASS-CVOT
Tirzepatide
N=13299
MACE: ≥1615†
HR (95% CI): ?
2015
2016
2017
2018
2019
2020
2021
2024
2025
ELIXA*
Lixisenatide
N=6068
MACE: 805
HR (95% CI):
1.02 (0.89-1.17)
SUSTAIN-6
Semaglutide
N=3297
MACE: 254
HR (95% CI):
0.74 (0.58-0.95)
HARMONY OUTCOMES
Albiglutide
N=9463
MACE: 766
HR (95% CI):
0.78 (0.68-0.90)
PIONEER-6
Semaglutide
N=3183
MACE: 137
HR (95% CI):
0.79 (0.57-1.11)
AMPLITUDE-O
Efpeglenatide
N=4076
MACE: 314
HR (95% CI):
0.73 (0.58-0.92)
SOUL
Semaglutide
N=9650
MACE: 1225†
HR (95% CI): ?
Superior vs. placebo for MACE
Non-inferior vs. placebo for MACE
Study ongoing

Semaglutide and CardiovascularOutcomes in Obesity without Diabetes

SELECT TRIAL

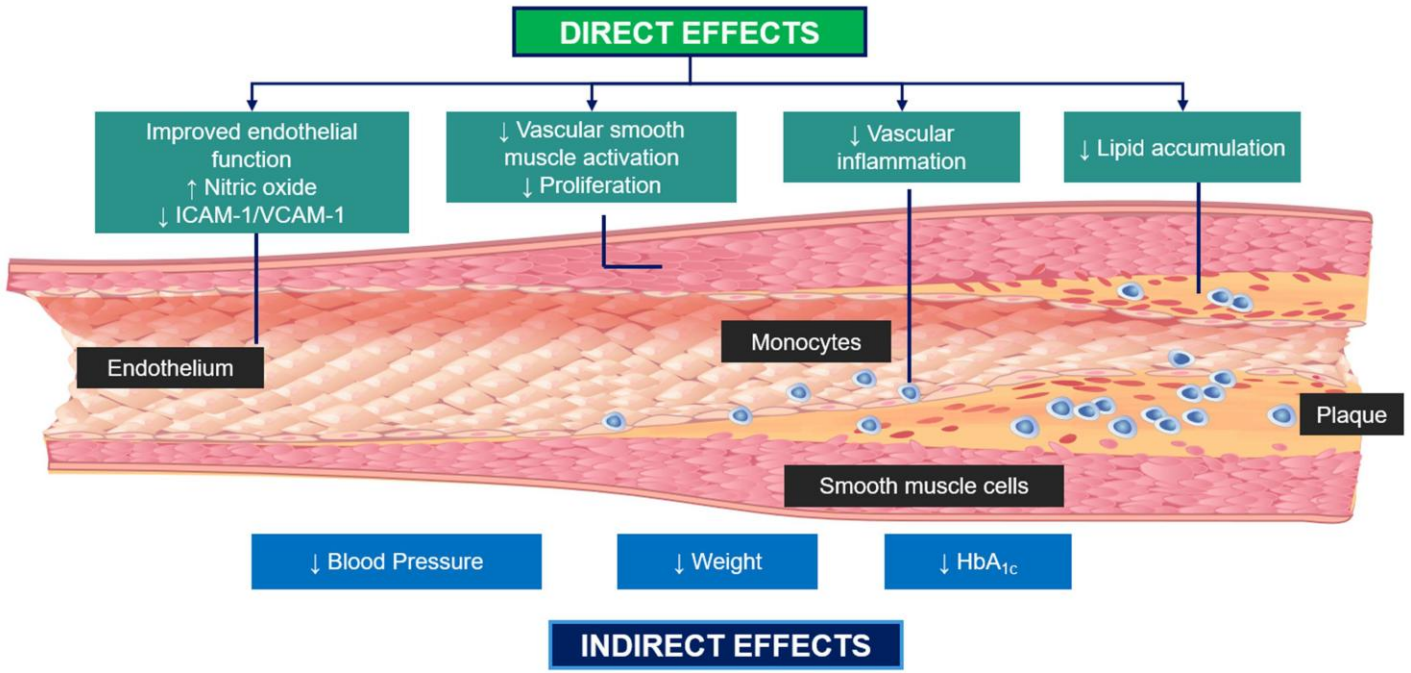
- 17604 pz obesi, con precedente evento CV, non diabetici
- Randomizzati a Semaglutide 2.4 mg OW vs placebo
- Età media 61 aa
- BMI >30



Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes
A.Michael Lincoff, M.D.
N Engl J Med 2023;389

Sottoanalisi

- **Risultati indipendenti da effetti indiretti su PA, assetto lipidico, hsPCR, HbA1c**
- **Risultati precoci, ancor prima delle riduzione del peso corporeo**



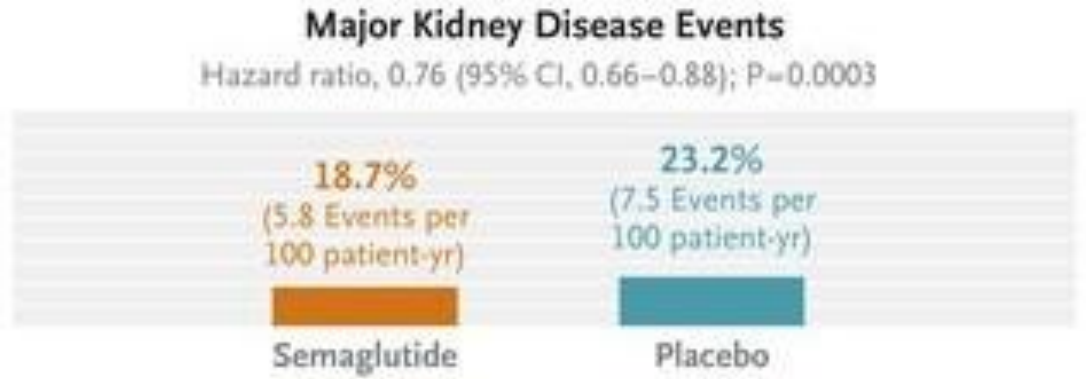
Sharma A and Verma S. Can J Diabetes 2020;44:93

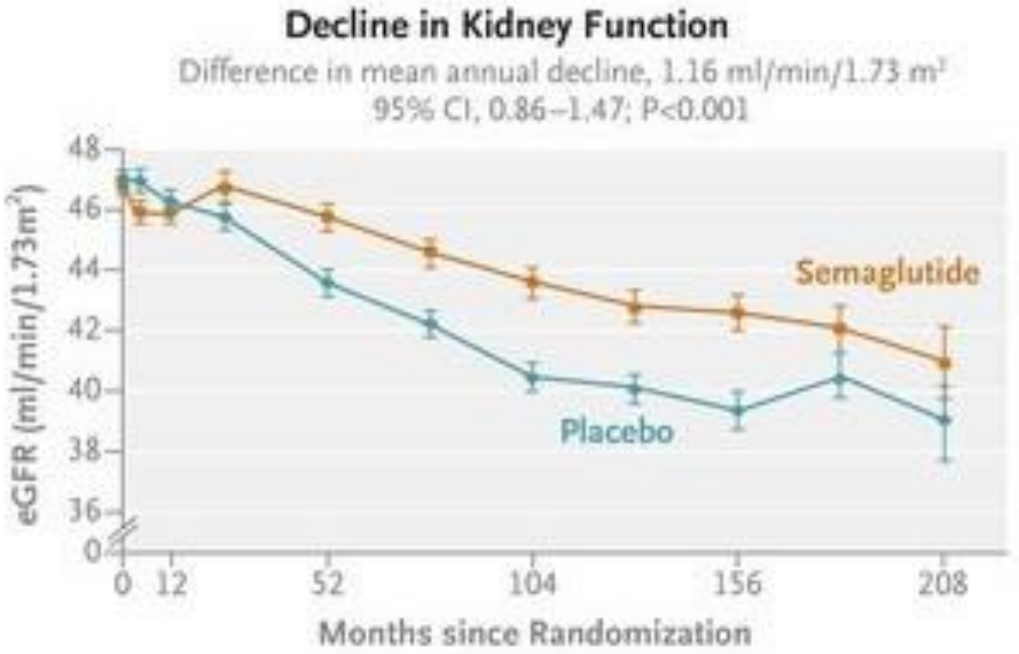
Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

FLOW TRIAL

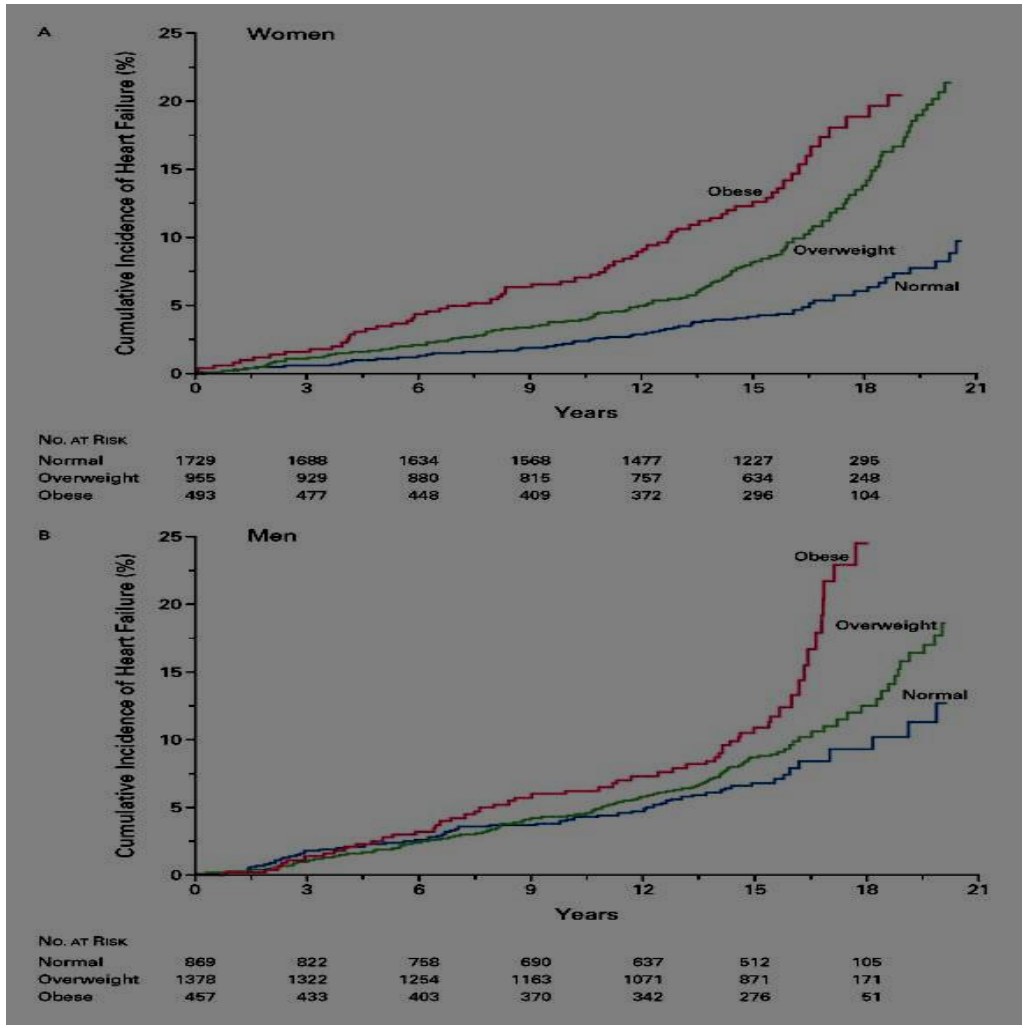
- **3533 pazienti obesi, diabetici con CKD (22% storia di malattia CV, 19% HF)**
- **Randomizzati a semaglutide 1 mg OW vs palcebo**
- **Età media 66,6 anni**
- **eGFR media 47,0 ml/min/per 1,73**

Secondo il calcolatore del rischio del Chronic Kidney Disease: Improving Global Outcomes (CKD: Improving Global Outcomes) il 68% dei pazienti arruolati presentava un rischio molto alto di progressione della malattia renale, di insufficienza renale, di eventi cardiovascolari o di morte.



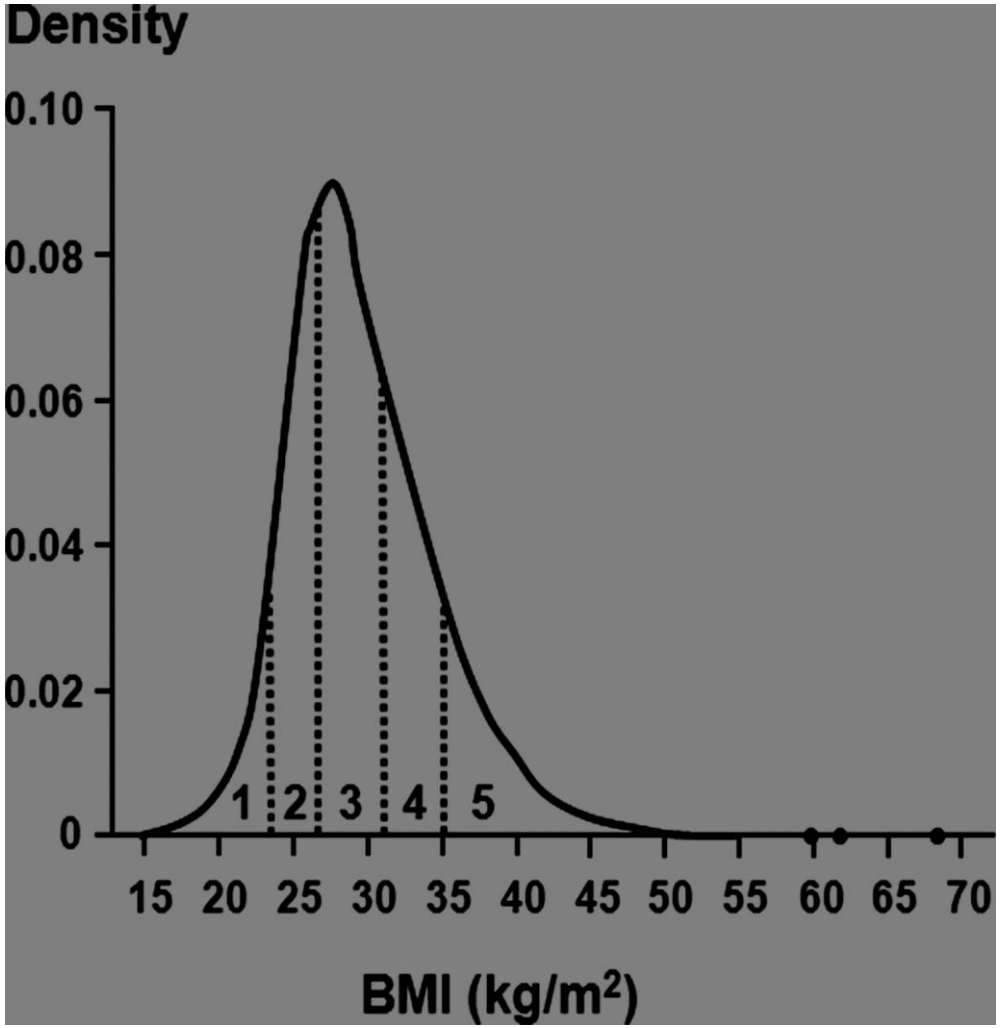


N Engl J Med 2024;391:109-121, Vlado Perkovic, M.B., B.S., Ph.D

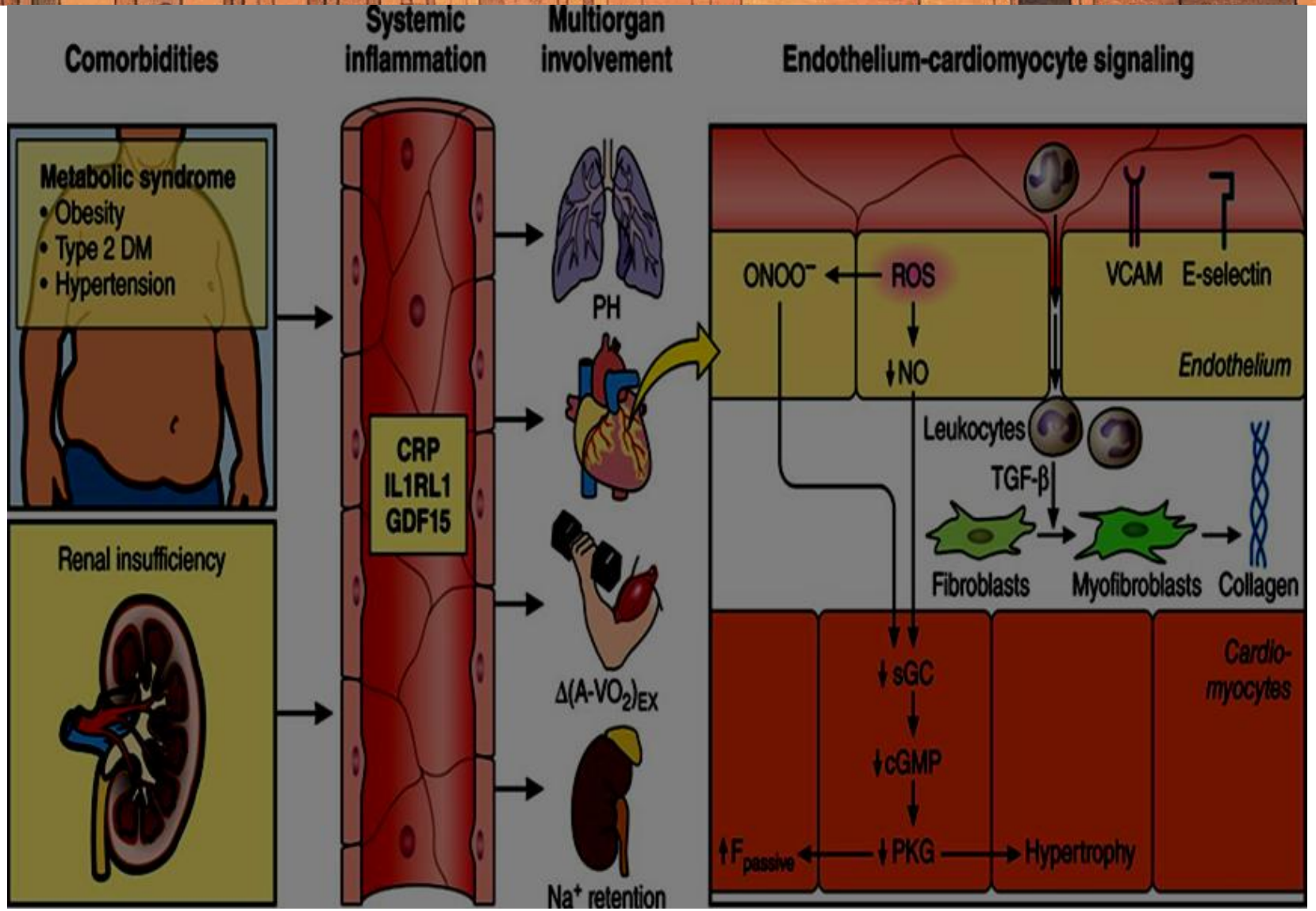


Obesity and the Risk of Heart Failure
N Engl J Med 2002;347, Satish Kenchaiah, M.D.

HEART FAILURE



Body Mass Index and Adverse CardiovascularOutcomes in Heart Failure Patients with Preserved Ejection Fraction: Results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) Trial
Markus Haass et al. Circulation: Heart Failure, vo, 4, number3, 2011



Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction
Sanjiv J. Shah Circulation vol n 134

STEP HFpEF

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Kosiborod MN et al. DOI: 10.1056/NEJMoa2306963

CLINICAL PROBLEM

Patients with heart failure with preserved ejection fraction often have obesity, a condition that is associated with a greater burden of heart failure–related symptoms, worse functional capacity, and more impaired quality of life. Whether therapies that target obesity in such patients can alleviate symptoms and physical limitations is unknown.

CLINICAL TRIAL

Design: A multinational, double-blind, randomized, placebo-controlled trial evaluated whether treatment with semaglutide — a glucagon-like peptide 1 receptor agonist approved for long-term weight management — would reduce heart failure–related symptoms and improve physical function, in addition to inducing weight loss, in adults with heart failure with preserved ejection fraction and obesity.

Intervention: 529 patients with a body-mass index of ≥30 were assigned to receive subcutaneous semaglutide (2.4 mg) or placebo once weekly for 52 weeks. The dual primary end points were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), which quantifies heart failure–related symptoms and physical function, and the change in body weight from baseline to week 52.

RESULTS

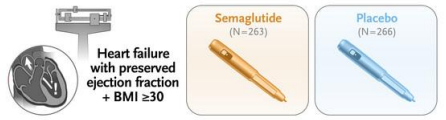
Efficacy: The mean change in KCCQ-CSS and the mean percentage change in body weight were significantly greater with semaglutide than with placebo.

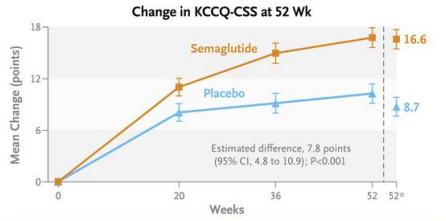
Safety: Serious adverse events occurred less often with semaglutide than with placebo, primarily because fewer cardiac disorders occurred in the semaglutide group. Adverse events leading to treatment discontinuation were more common with semaglutide.

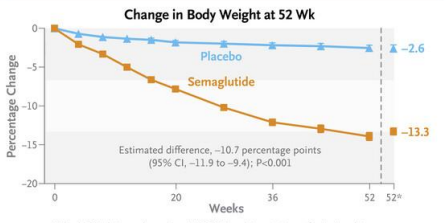
LIMITATIONS AND REMAINING QUESTIONS

- The number of non-White trial participants was low.
- The trial was not sufficiently powered to evaluate the effects of semaglutide on clinical events, such as hospitalization for heart failure.
- Whether the observed effects of semaglutide would last beyond 1 year is unknown.

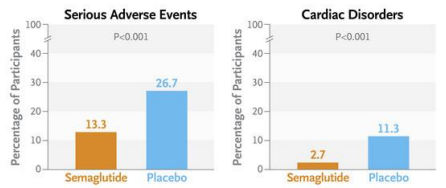
Links: Full Article | NEJM Quick Take | Editorial







Week 52 data are based on ANCOVA and imputation of missing data.



CONCLUSIONS

In adults with heart failure with preserved ejection fraction and obesity, once-weekly treatment with semaglutide was associated with greater reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo over 52 weeks.

STEP HFpEF DM

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Kosiborod MN et al. DOI: 10.1056/NEJMoa2313917

CLINICAL PROBLEM

In patients with heart failure with preserved ejection fraction and obesity, but without type 2 diabetes, semaglutide treatment has led to larger reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo. However, the efficacy of the glucagon-like peptide-1 receptor agonist in patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes is unknown.

CLINICAL TRIAL

Design: A multinational, double-blind, randomized, controlled trial assessed the efficacy and safety of semaglutide in adults with heart failure with preserved ejection fraction, a body-mass index ≥30, and type 2 diabetes.

Intervention: 616 participants were randomly assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo for 52 weeks. The first primary end point was the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), which ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. The second primary end point was the change in body weight.

RESULTS

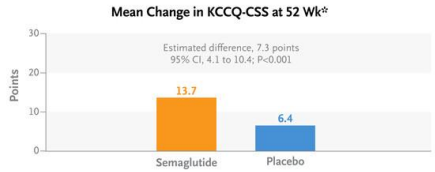
Efficacy: Treatment with semaglutide was associated with a significantly greater improvement in the KCCQ-CSS and with greater weight loss at week 52 than placebo.

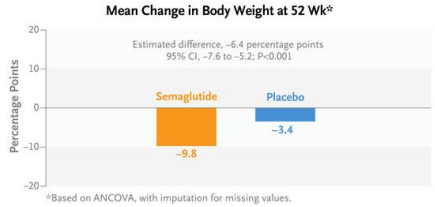
Safety: The placebo group had a higher incidence of serious adverse events than the semaglutide group.

LIMITATIONS AND REMAINING QUESTIONS

- Non-White participants were underrepresented in the trial, thus limiting generalizability.
- The trial was not designed to evaluate clinical events such as hospitalizations and urgent visits for heart failure.
- The trajectory of the effects of semaglutide suggested persistent improvements over time as compared with placebo, but the durability of these effects beyond 1 year is unknown.

Links: Full Article | NEJM Quick Take





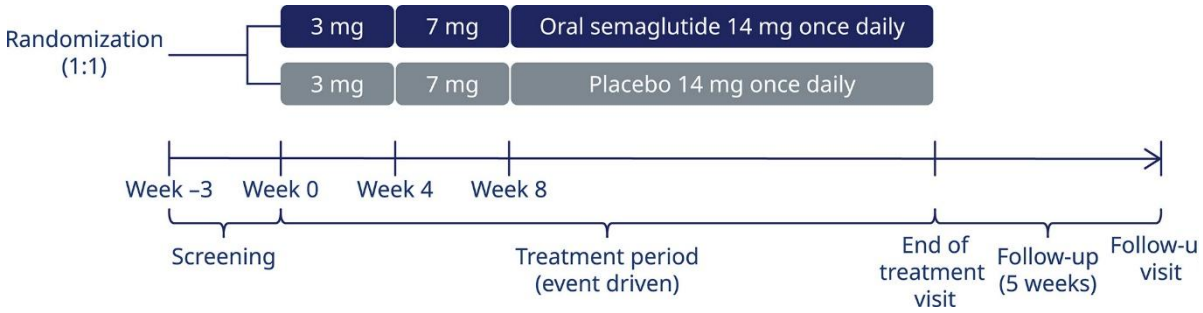
*Based on ANCOVA, with imputation for missing values.

CONCLUSIONS

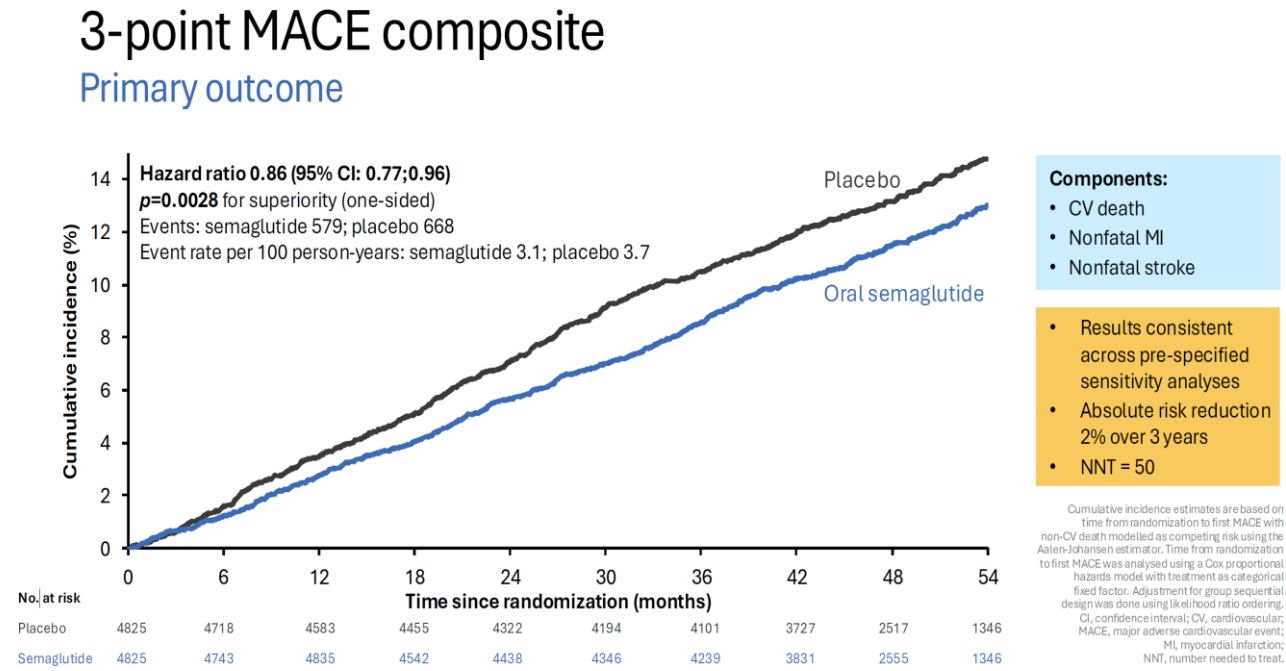
In patients with type 2 diabetes and heart failure with preserved ejection fraction, once-weekly semaglutide led to fewer heart failure–related symptoms and physical limitations and greater weight loss than placebo at 1 year.

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

SOUL trial

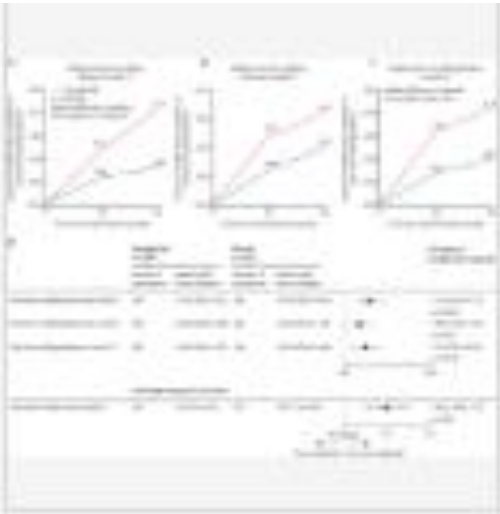


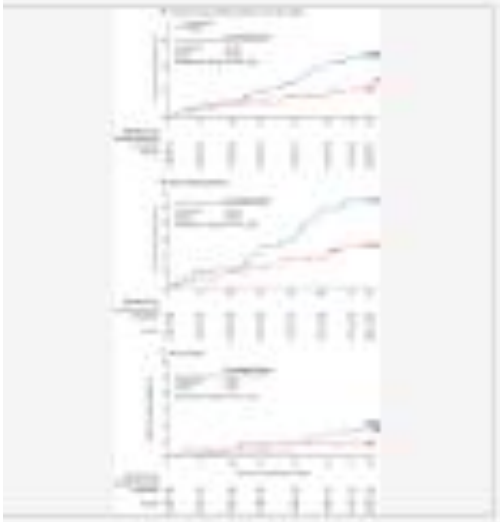
- **9650 pz diabetici**
- **Randomizzati a Semaglutide orale vs placebo**
- **Età media 66 aa**
- **60% CVD; 27% CVD+CKD**



Engl J Med 2025;392:2001-2012 Darren K. McGuire

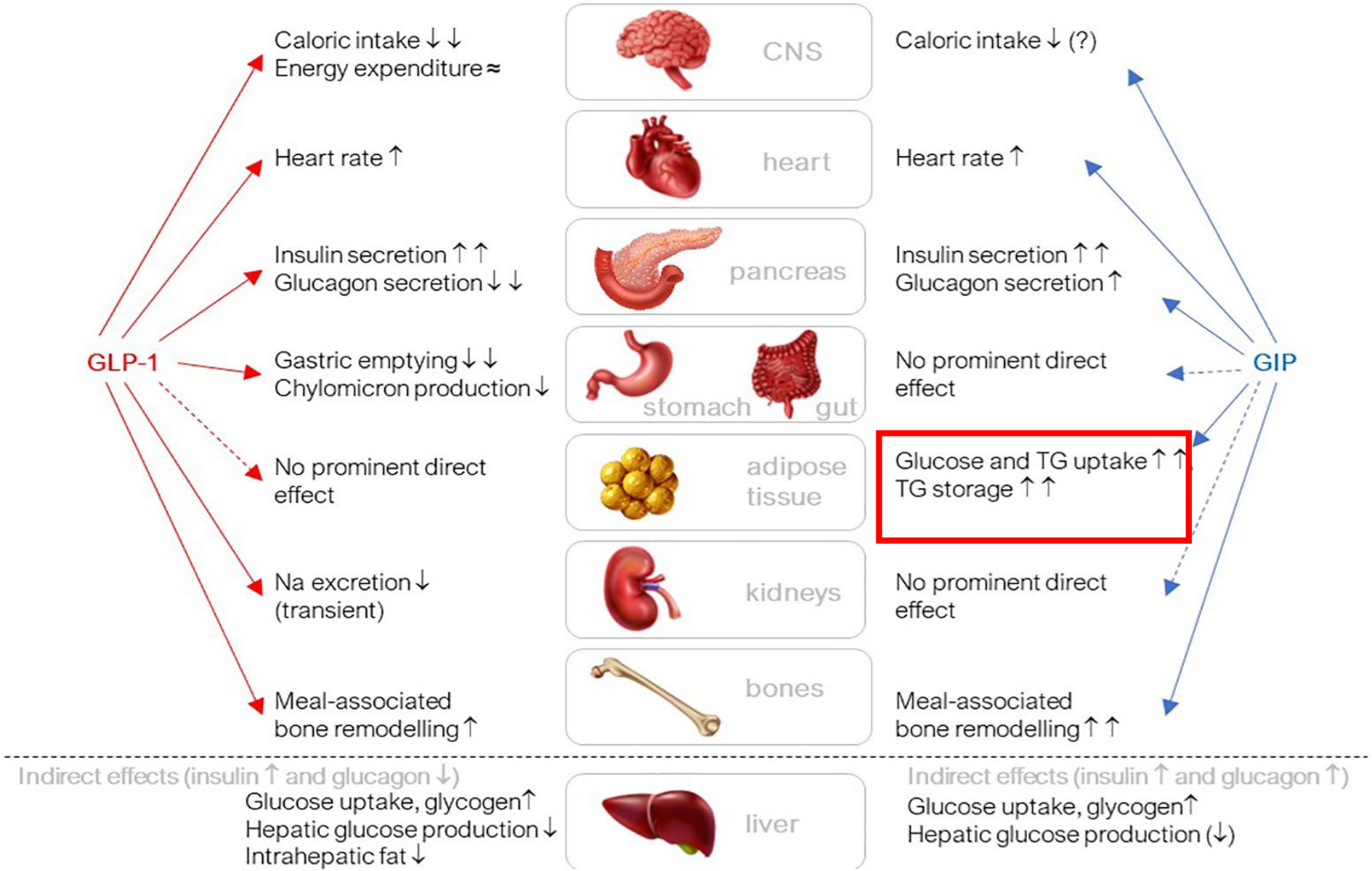
Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial





M.P. Bonaca Lancet, vol 405; May 03, 2025

TIRZEPATIDE
DUAL
RECEPTOR
AGONIST



Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

SURMOUNT-5

- 750 pz obesi (BMI medio 39) non diabetici, almeno una comorbidità: ipertensione, dislipidemia, apnea ostruttiva del sonno o disturbi cardiovascolari
- Tirzepatide (10 mg or 15 mg) vs Semaglutide (1.7 mg or 2.4 mg) OW per 72 settimane
- End point primario: variazione di peso fino a 72 settimane
- End points secondary riduzione ponderale del 10%, 15%, 20%, and 25% e riduzione della circonferenza vita

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide vs. Semaglutide for the Treatment of Obesity

A Research Summary based on Aronne LJ et al. | 10.1056/NEJMoa2416394 | Published on May 11, 2025

WHY WAS THE TRIAL DONE?

Tirzepatide and semaglutide are part of a new generation of highly effective medications for the management of obesity. Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, and semaglutide is a long-acting GLP-1 receptor agonist. How the two drugs compare with each other in adults with obesity but without type 2 diabetes is unknown.

HOW WAS THE TRIAL CONDUCTED?

Adults without diabetes who had a body-mass index (BMI) of 30 or higher, or a BMI of 27 or higher and at least one prespecified obesity-related complication, and who reported at least one unsuccessful dietary effort for weight reduction were assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in body weight from baseline to week 72.

TRIAL DESIGN

- Phase 3b
- Open-label
- Randomized
- Controlled
- Location: 32 sites in the United States and Puerto Rico

RESULTS

At week 72, participants in the tirzepatide group had lost significantly more weight than those in the semaglutide group. In both groups, the most common adverse events were gastrointestinal; these events were usually mild to moderate in severity and occurred most often during dose escalation.

LIMITATIONS AND REMAINING QUESTIONS

- The trial was not blinded.
- Although the effect of semaglutide on cardiovascular outcomes has been reported, the effect of tirzepatide on such outcomes is unknown. An ongoing trial may provide data on the use of tirzepatide for both primary and secondary prevention of cardiovascular disease.

CONCLUSIONS

In adults with obesity but without diabetes, weekly treatment with tirzepatide led to significantly greater weight loss than weekly treatment with semaglutide over 72 weeks.

NEJM QUICK TAKE | EDITORIAL

Participants

- 750 adults
- Mean age, 45 years
- Women: 65%; Men: 35%
- Mean BMI, 39.4

GIP receptor + GLP-1 receptor

Tirzepatide N=374 | Semaglutide N=376

Change in Body Weight

Estimated difference, −6.5 percentage points; 95% CI, −8.1 to −4.9; P<0.001

Least-Squares Mean Change (%): −20.2 (Tirzepatide), −13.7 (Semaglutide)

Change in Waist Circumference

Estimated difference, −5.4 cm; 95% CI, −7.1 to −3.6; P<0.001

Least-Squares Mean Change (cm): −18.4 (Tirzepatide), −13.0 (Semaglutide)

Louis J. Aronne, M.D **N Engl J Med 2025;393:26-36**

Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics

SURPASS-CVOT is an event-driven, randomized, doubleblind

- active comparator: tirzepatide OW, up to 15 mg, on MACE, vs dulaglutide 1.5 mg OW
- T2D on standard of care with established ASCVD
- 13,299 people
- mean age 64.1 years,
- BMI 32.6 kg/m^2.
- 65.0% CVD
- 25.3% PAD

Outcome:

- Time to first occurrence of any major adverse cardiovascular event (MACE), defined as CV death, myocardial infarction, or stroke.
- The primary analysis is non-inferiority
- To determine whether tirzepatide produces a greater CV benefit than dulaglutide (superiority analysis)

Conclusion

SURPASS-CVOT will provide definitive evidence as to the CV safety and efficacy of tirzepatide as compared with dulaglutide, a GLP-1 receptor agonist with established CV benefit.

S.J.Nicholls.. AHJ, vol 267, January 2024

GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review

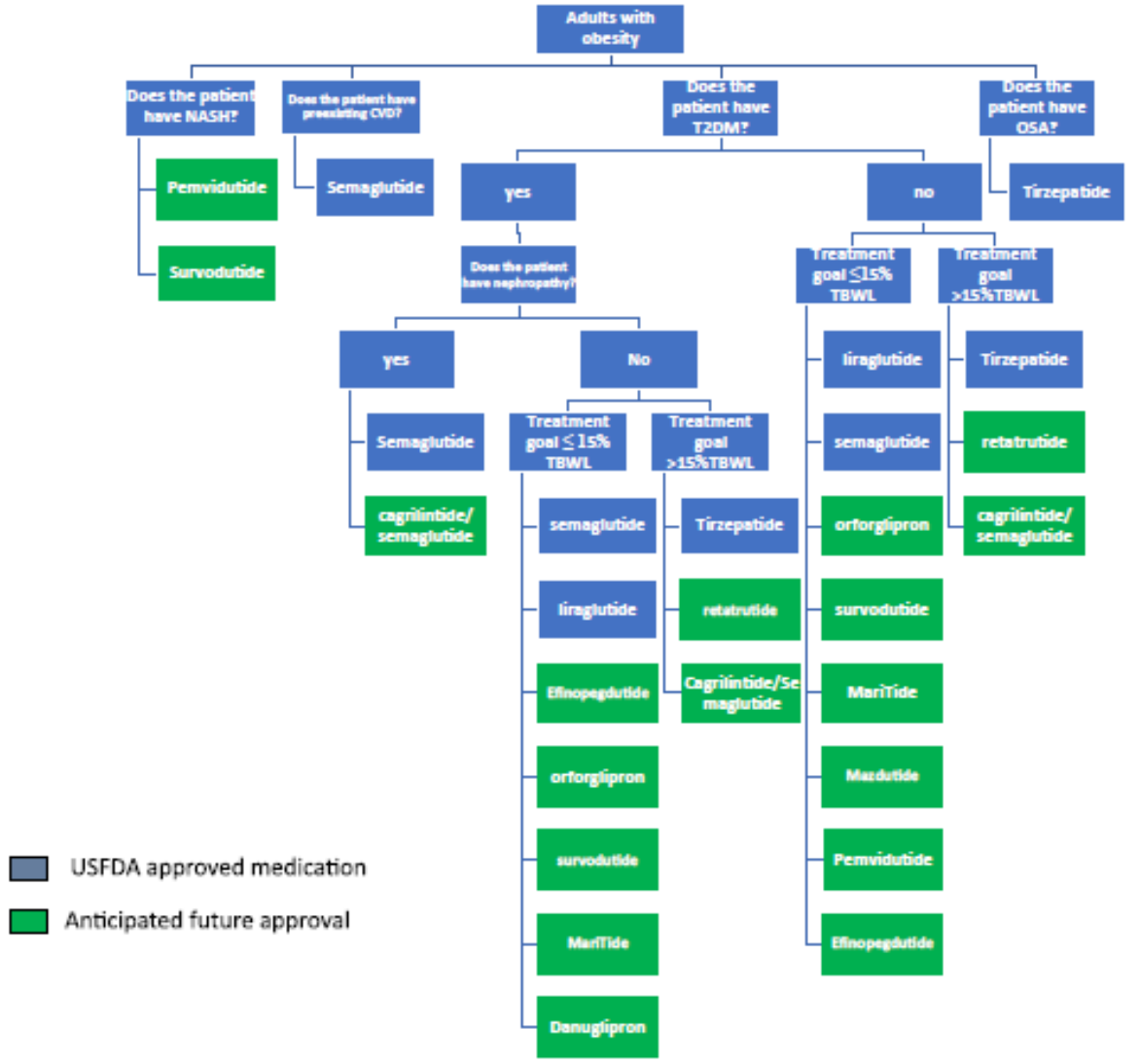
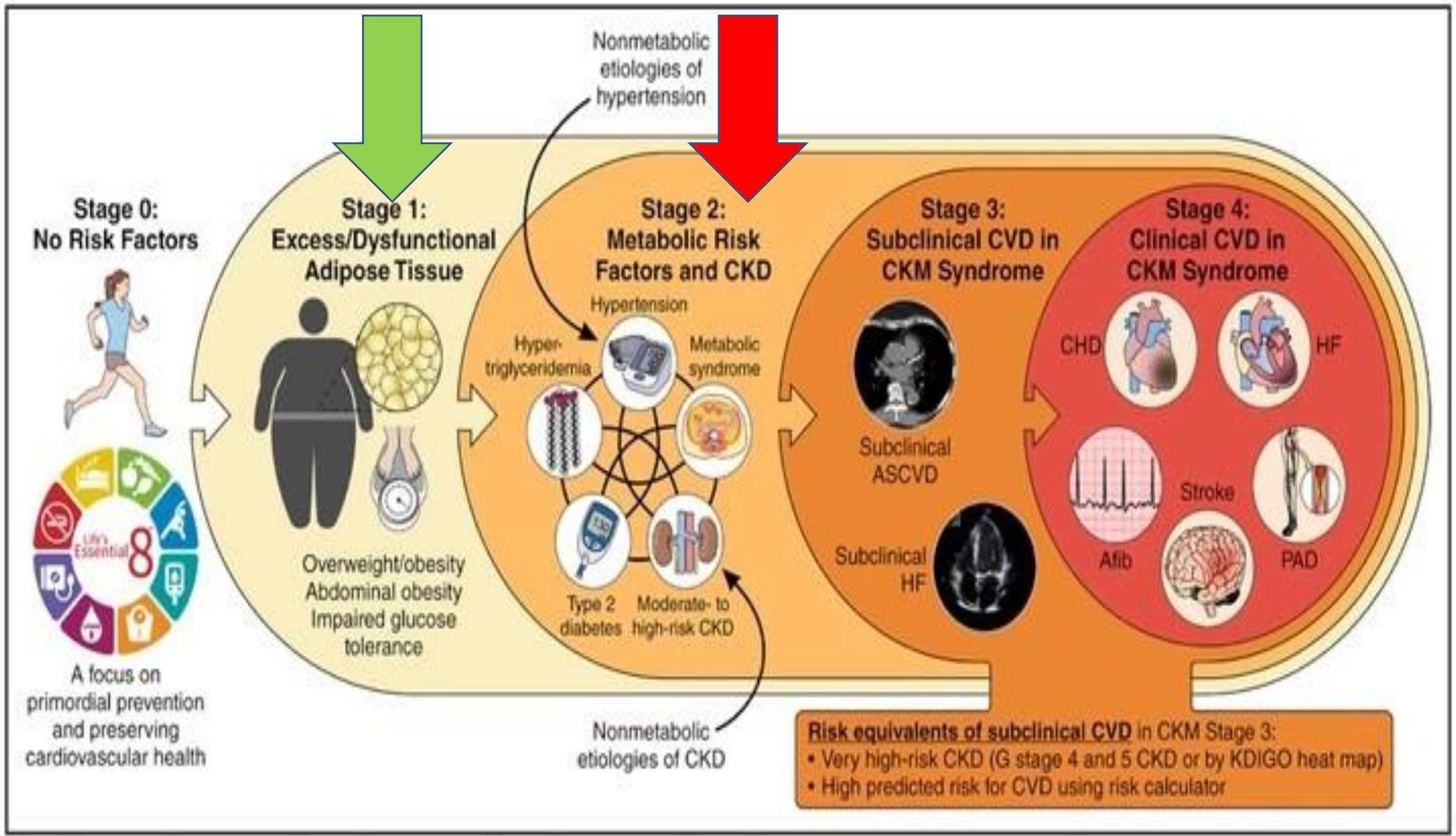


Fig. 4: Suggested treatment algorithm for the choice of GLP1-RA, dual, and triple agonists in the treatment of obesity.

Nasreen Alfaris
www.thelancet.com Vol 75 September, 2024


Nonmetabolic etiologies of hypertension
Stage 0: No Risk Factors
Stage 1: Excess/Dysfunctional Adipose Tissue
Stage 2: Metabolic Risk Factors and CKD
Stage 3: Subclinical CVD in CKM Syndrome
Stage 4: Clinical CVD in CKM Syndrome
Life's Essential 8
A focus on primordial prevention and preserving cardiovascular health
Overweight/obesity
Abdominal obesity
Impaired glucose tolerance
Hypertension
Hyper-triglyceridemia
Metabolic syndrome
Type 2 diabetes
Moderate- to high-risk CKD
Nonmetabolic etiologies of CKD
Subclinical ASCVD
Subclinical HF
CHD
HF
Stroke
Afib
PAD
Risk equivalents of subclinical CVD in CKM Stage 3:
• Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)
• High predicted risk for CVD using risk calculator

Ma le rose hanno le spine

Navigating Sarcopenia Risks in GLP-1RA Therapy for Advanced Heart Failure

Advanced HF and Sarcopenia

- Involuntary weight loss and muscle wasting in advanced heart failure (HF) = cardiac cachexia
- GLP-1RAs further exacerbate this risk

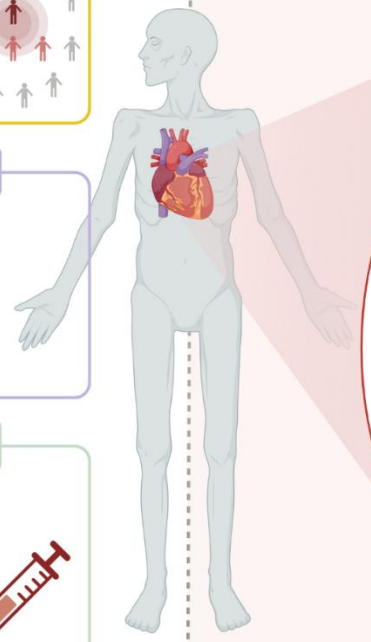
Pathophysiology

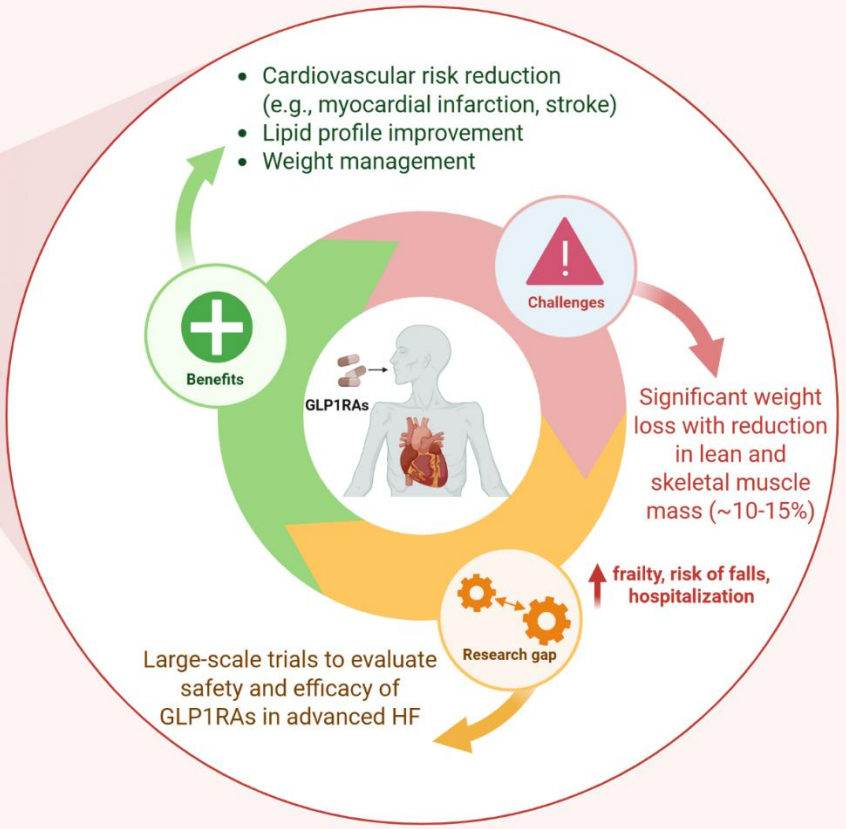
- Neurohormonal changes (e.g., SNS overactivation)
- Inflammatory cytokines driving catabolism
- Gastrointestinal dysfunction and malabsorption

Management

- **Nutritional support:** high-protein, high-calorie diets, PUFAs, L-alanyl-L-glutamine
- **Structured exercise program**: aerobic and resistance training, cardiac rehabilitation programs
- **Pharmacologic intervention:** Beta-blockers, ACE inhibitors, testosterone, ghrelin agonists, myostatin inhibitors, GLP1RAs

Abbreviations: ACE=Angiotensin-Converting Enzyme, GLP1RAs=Glucagon-like peptide-1 receptor agonists, HF=Heart failure, PUFAs=Polyunsaturated fatty acids, SNS=Sympathetic nervous system





- The observed weight reduction in clinical practice overall tends to be lower than in randomized controlled trials
- Real-world studies demonstrate high discontinuation rates of GLP-1RAs (20%–50%) within the first year, and the use of much lower doses than those evaluated in clinical trials
- No clear increase in risks of severe events like pancreatitis or pancreatic cancer, thyroid disorders, or depression and self-harm
- Studies of the effects of stopping GLP-1RA treatment

Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies

Reimar W. Thomsen Diabetes Obes Metab. 2025;27(Suppl. 2):66–88