Congresso congiunto
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" Happy Birthday: "
Forever young
Innovazione farmacologica e tecnologica:
Il futuro della Diabetologia

Centro Congressi
The Place TORINO
11-12 ottobre
2024

# I "disease modyfing drugs": SGLT2i, GLP1-RA, GIP, ns-MRA

**Enrico Gabellieri**
**AOU Alessandria**
**SC Endocrinologia e Malattie Metaboliche**

DICHIARAZIONE CONFLITTO D’INTERESSE

In ottemperanza alla normativa ECM ed al principio di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, dichiaro i miei conflitti d’interesse degli ultimi due anni, quali partecipazione ad advisory board, relazioni, protocolli clinici di ricerca:

Novo Nordisk
Sanofi
AstraZeneca
Guidotti

# RECENTE PASSATO: 2014

# R.S. Visita febbraio 2014
# DM 2

Uomo 63 aa
Lavoro di ufficio
Sposato, 2 figli che non vivono vicino a lui
DM2 noto da 9 anni

Ipertensione arteriosa
Obesità di 3° grado
Dislipidemia
IRC stadio G3a
RDNP
OSAS in C pap
NYHA classe 2
NAFLD

Ex fumatore
Modico consumo di vino ai pasti
Stile di vita sedentario
Colecistectomia per calcolosi
Pregressi ricoveri per Obesità (non propenso a chirurgia bariatrica)

## Terapia

- [Metformina 1000 mg 1 cp x 2 (2005-2011), Metformina 1000 mg 1 cp x 2 e Gliclazide 60 mg 1/2 cp (2011-2013)]
- Sitagliptin/Metformina 50/1000 mg 1 cp x 2/die dal 2013
- Ramipril 5mg 1 cp
- Bisoprololo 2.5 mg 1 cp
- Furosemide 25 mg 1 cp
- Atorvastatina 20 mg 1 cp

6 cp /die

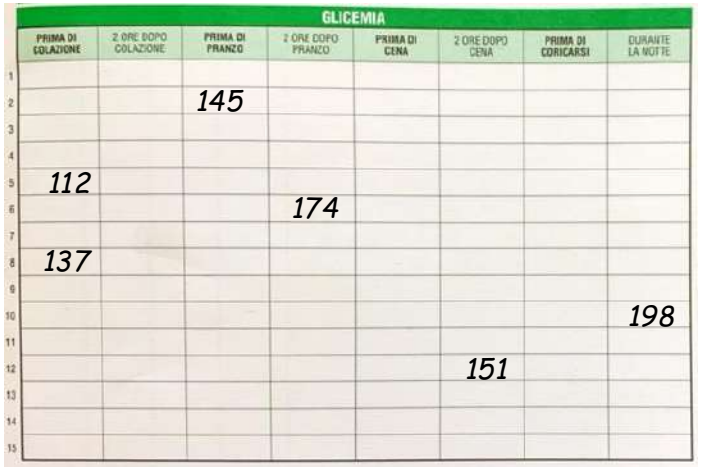
## Esami Laboratorio

| | | |
|---|---|---|
| FPG | 134 mg/dl | |
| HbA1c | 6,4% | |
| CT | 154 mg/dl | |
| HDL | 42 mg/dl | |
| TG | 76 mg/dl | |
| LDL-C | 97 mg/dl | |
| Creatinina | 1,3 mg/dl | |
| eGFR | 59 ml/min | |
| ACR | 88 mg/g | |
| TSH | 1,7 uUI/ml | |
| AST UI/l | | 57 |
| ALT UI/l | | 54 |
| GammaGT | 52 UI/l | |

## Visita

PA 135/80 mmHg, FC 76 bpm
Peso 122 kg, h170 cm, BMI 42,2 kg/mq
*Cuore*: toni validi ritmici
*Polmoni*: MV lievemente ridotto alle basi
*Addome*: globoso per adipe, NDP
*Neuro*: ridotta sensibilità arti inferioiri
Piedi: callosità a livello delle testa metatarsali

## Diario glicemico *(acquista strisce reattive)*




## Studio complicanze

ECG RS
Ecocardio: FE 48%
FOO: RDNP laser trattata
TSA: stenosi 20% bilat

*DM2, diabete mellito tipo 2, FPG, glicemia a digiuno, CT, colesterolo totale, FOO, esame del fondo oculare, TSA, tronchi sovaortici. PA, pressione arteriosa. FC frequenza cardiaca, BMI, indice di massa corporea, NDP nulla di patologico. RD, retinopatia diabetica.*

Nel 2014 raccomandato il calo ponderale e proseguita la terapia in atto

# RECENTE PASSATO: 2014


**Tabella 13. Terapia farmacologica**

| |
|---|
| **1. Iniziare una terapia farmacologica orale** quando gli interventi sullo stile di vita non sono più in grado di mantenere il controllo della glicemia ai valori desiderati (in genere $HbA_{1c}$ 53 mmol/mol o <7%). Mantenere e rinforzare sempre l'orientamento del paziente verso un corretto stile di vita. Valutare l'eventuale inizio o aumento della dose del farmaco orale ogni 2-6 mesi, con il fine di raggiungere e mantenere nel tempo valori di $HbA_{1c}$ 53 mmol/mol o <7%. |
| **2. Iniziare con la metformina (prima scelta)** partendo con basse dosi da incrementare nel tempo al fine di evitare intolleranza gastrointestinale. Ove tollerata e non controindicata, raggiungere sempre la dose di almeno 2 g/die, indipendentemente dagli obiettivi glicemici raggiunti. Controllare periodicamente la funzione renale (eGFR con CKD-EPI). Utilizzare particolare cautela per filtrato glomerulare <60 ml/min/1,73m$^2$ e sospendere per filtrato glomerulare <30 ml/min/1,73m$^2$ o in pazienti a rischio di insufficienza renale acuta; in caso di controindicazioni o di intolleranza, passare direttamente al paragrafo successivo. |
| **3. Aggiungere** (o, in caso di intolleranza/controindicazione alla metformina, sostituire con) un secondo farmaco (acarbosio/sulfonilurea/repaglinide/glitazone/gliptina/agonista recettore GLP1/gliflozina/insulina) quando: a) la metformina da sola non riesce a mantenere il buon controllo della glicemia; b) non è tollerata o è controindicata; c) si ritiene che il valore di emoglobina glicata prima di iniziare il farmaco sia troppo elevato per raggiungere, con la sola metformina, il target terapeutico. Scegliere fra le diverse opzioni terapeutiche sulla base del profilo di rischio e beneficio, anche in funzione delle eventuali comorbilità, riportate in figura. Se la terapia può indurre ipoglicemia, prescrivere l'uso di presìdi per l'automonitoraggio. Quando la compliance può essere un problema, prediligere farmaci in monosomministrazione. |
| **4. Usare la triplice terapia** quando le associazioni precedentemente prescritte non sono in grado di mantenere il controllo dell'emoglobina glicata prescelta; non esistono studi di confronto che mostrino la superiorità di uno schema rispetto a un altro. |
| **5. In ogni passaggio valutare** la possibilità di un inizio precoce della terapia insulinica. |

**Tabella 14. Terapia non insulinica nel diabete tipo 2 con insufficienza renale cronica**

| Stadio IRC | LIEVE | MODERATA | GRAVE | DIALISI |
|---|---|---|---|---|
| eGFR | eGFR >60 | 60 >eGFR >30 | 30 >eGFR >15 | eGFR <15 |
| Exenatide | da titolare | cautela | NO | NO |
| Liraglutide | da titolare | NO | NO | NO |
| Lixisenatide | da titolare | cautela | NO | NO |

**Gli inibitori di SGLT2 o gliflozine** (dapaglifozin attualmente in classe C, canagliflozin, empagliflozin non ancora disponibili in Italia) sono una classe di recente sviluppo di farmaci che bloccano tale riassorbimento, lasciando che circa il 40% del glucosio filtrato venga eliminato con le urine

**GLP1 RA**
Questa classe di farmaci è generalmente non indicata nei pazienti con insufficienza renale (vedi **Tabella 14**).

PRESENTE: 2024

Se lo stesso paziente R.S. fosse valutato nel 2024 le decisioni terapeutiche **dovrebbero** essere diverse

**Adeguato controllo glicemico ma…. rischio cardio-vascolare molto alto, scompenso cardiaco, obesità grave, IRC con microalbuminuria, OSAS, NAFLD**

The joint statement focuses on a holistic, person-centered approach to the management of T2D and considers cardiorenal protection as well as glycemic, body weight, and CV risk management as components of care. In principle, **the choice of glucose-lowering agents should be guided by the individual profile and the presence of comorbidities such as obesity, CVD, HF, CKD, and non-alcoholic fatty liver disease (NAFLD).**

# Cosa è cambiato nel trattamento del DM2 dal 2014 al 2024?

## 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2024*

*Diabetes Care 2024;47(Suppl. 1):S52–S76 | https://doi.org/10.2337/dc24-S004*

**Table 4.2—Assessment and treatment plan**

Assessing risk of diabetes complications
- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (see Section 6, "Glycemic Goals and Hypoglycemia")
- Assessment for retinopathy
- Assessment for neuropathy
- Assessment for NAFLD/NASH

Goal setting
- Set A1C/blood glucose/time in range
- If hypertension is present, establish blood pressure goal
- Weight management and physical activity goals
- Diabetes self-management goals

Therapeutic treatment plans
- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and kidney disease risk factors
- Weight management with pharmacotherapy or metabolic surgery, as appropriate
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education, behavioral health, and medical specialists

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

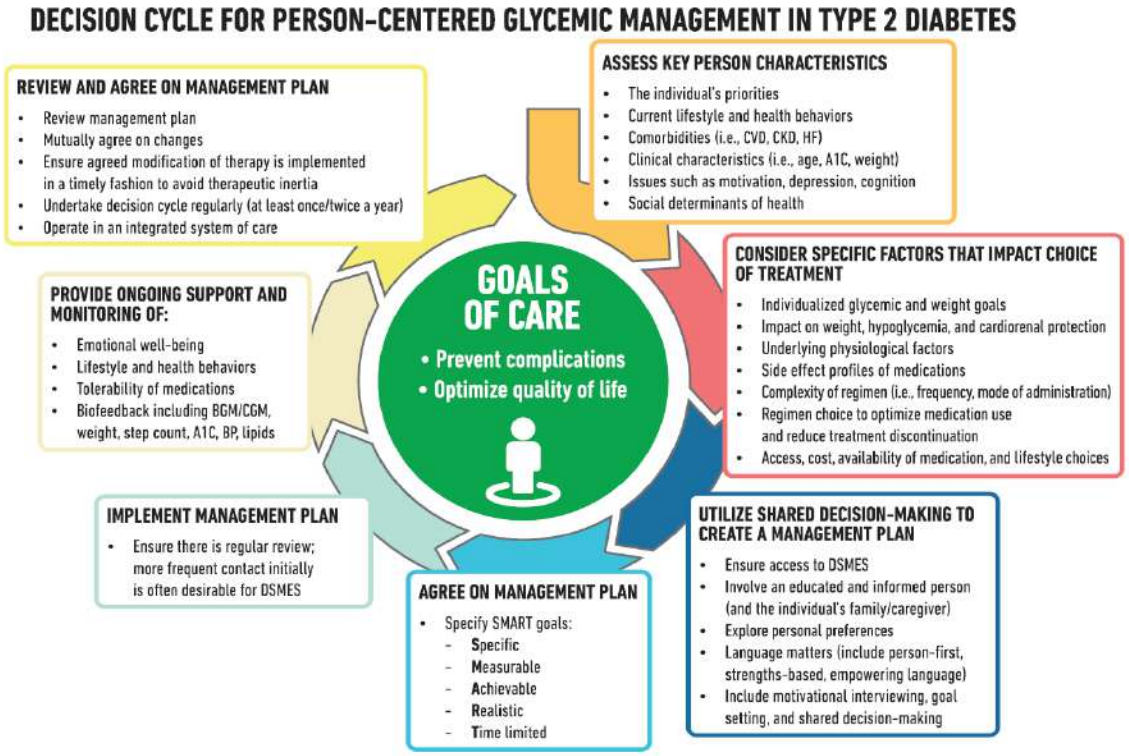



**Figure 4.1**—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (294). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

Il cambiamento relativo alla scelta terapeutica è legato all'evidenza che alcuni farmaci sono efficaci nel ridurre/modificare diverse condizioni cliniche e i rischi correlati indipendentemente dal controllo glicemico

- ✓ I risultati dei trials e dati di real-world hanno evidenziato come determinate terapie farmacologiche riducano i MACE, progressione IRC, ospedalizzazione per scompenso cardiaco, favoriscano il calo ponderale, migliorino MAFLD. Tenendo conto che una parte di questi studi ha riguardato pazienti non affetti da DM

- ✓ Abbiamo oggi a disposizione terapie che hanno un ruolo nella **gestione terapeutica di condizioni cliniche gravate da importante bisogno terapeutico (Obesità, MASLD, OSAS, ACVD, HF, IRC)**, farmaci che sono in grado di migliorare la sopravvivenza e QOL

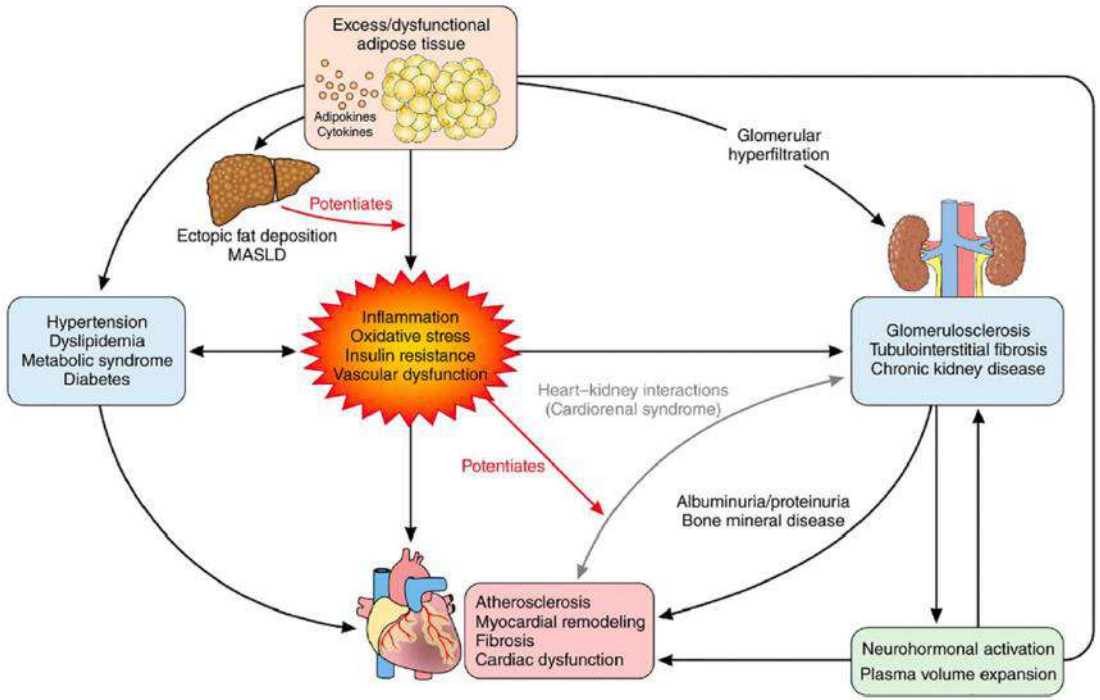
# Adeguato controllo glicemico non è più sufficiente come obiettivo della terapia del paziente diabetico tipo 2

- Evolution in the management of T2D.
- T2D is no longer a glucose-centric disease with A1c goal attainment as the primary target. We must also identify patients at risk of CVD, heart failure, and CKD, and initiate therapies with proven benefits, irrespective of whether a patient's A1c is <7 % or at their individualized target.
- **CKM Syndrome** with its pathophysiological consequences reflecting **multidirectional relationships** among metabolic risk factors, CKD, and the cardiovascular system

Circulation

AHA SCIENTIFIC STATEMENT

A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association



# Rivoluzione dell'approccio al trattamento del DM2: risultati di CVOT di SGLT2-i e dei GLP1- RA

- ✓ The advent of two new classes of anti-hyperglycemic agents, the sodium-glucose cotransporter-2 inhibitors **(SGLT2-i)** and the glucagon-like peptide-1 receptor agonists **(GLP-1 RA)**, and **their respective large cardiovascular outcome trials**, has led to a **paradigm shift in how conceptualize T2D treatment**.

- ✓ Given the potentially groundbreaking findings of their respective trials, the use of SGLT-2i and GLP-1RA therapy has **revolutionized the treatment approach for T2D**. While previous guidelines emphasized glycemic control and A 1c targets to prevent adverse outcomes, SGLT-2i and GLP-1RA therapies are now considered as options for treatment, independent of A1c levels, and are instead indicated based on the presence of established ASCVD or notable risk factors for arteriosclerotic vascular disease (ASVD), as well as heart failure and/or CKD

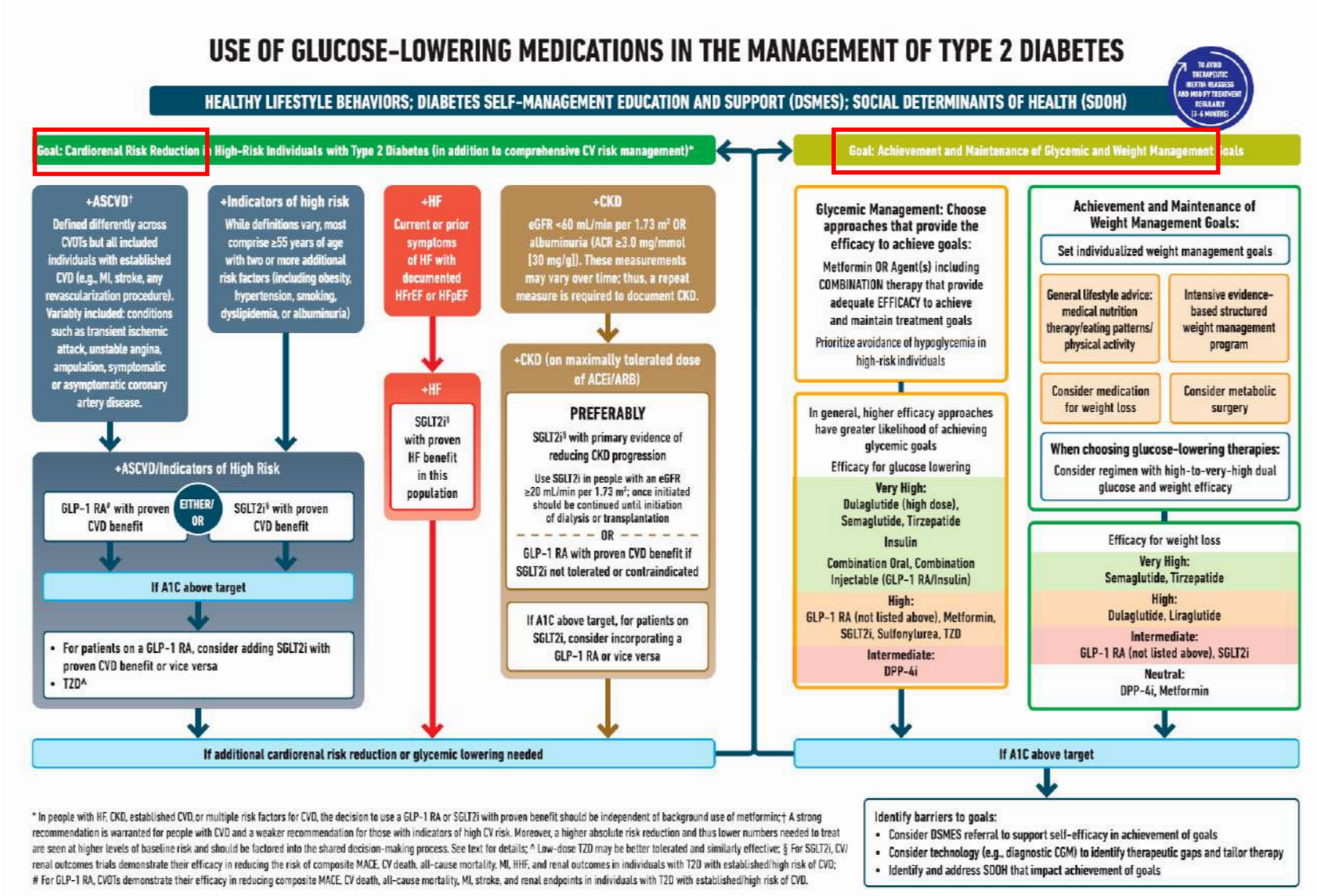
# SGLT2-i e GLP1-RA nel DM2

GLP-1 agonist

SGLT2 inhibitor

SGLT-2i and GLP-1RA therapies are now considered as options for treatment, **independent of A1c levels**, and are instead indicated based on the presence of established ASCVD or notable risk factors for arteriosclerotic vascular disease (ASVD), as well as heartfailure and/or CKD

# Linee guida trattamento DM2: ADA 2024




9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*

American Diabetes Association Professional Practice Committee*

Diabetes Care 2024;47(Suppl. 1):S158–S178 | https://doi.org/10.2337/dc24-S009

# SGLT2-i e GLP1 RA

**Table 1:** SGLT-2i CVOTs.

| SGLT-2i CVOTs | Primary outcome definition | Primary outcome hazard ratio | 95 % CI | p-Value |
|---|---|---|---|---|
| EMPA-REG (empagliflozin) | Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | 0.86 | 0.74–0.99 | 0.04 for superiority |
| CANVAS/ CANVAS-R (canagliflozin) | | 0.86 | 0.75–0.97 | 0.02 for superiority |
| [a]DECLARE TIMI (dapagliflozin) | | 0.93 | 0.84–1.03 | 0.17 for superiority |
| VERTIS (ertugliflozin) | | 0.97 | 0.85–1.11 | >0.001 for noninferiority |

Overall, it was clearly demonstrated that the use of SGLT-2i had a positive impact on cardiovascular risk. Importantly, these beneficial effects were independent of the effect of SGLT-2i on glycemiccontrol and $A_{1c}$ levels

**Table 2:** SGLT-2i CHF trials.

| SGLT-2i CHF trials[a] | Primary outcome | Primary outcome hazard ratio | 95 % CI | p-Value |
|---|---|---|---|---|
| EMPEROR reduced (empagliflozin) | Composite of cardiovascular death or hospitalization for worsening heart failure | 0.75 | 0.65–0.86 | <0.001 |
| EMPEROR preserved (empagliflozin) | | 0.79 | 0.69–0.90 | <0.001 |
| Dapa-HF (dapagliflozin) | | 0.74 | 0.65–0.85 | <0.001 |
| DELIVER (dapagliflozin) | | 0.82 | 0.73–0.92 | <0.001 |

**Table 3:** SGLT-2i CKD trials.

| SGLT-2i CKD trials | Primary outcome | Primary outcome hazard ratio | 95 % CI | p-Value |
|---|---|---|---|---|
| CREDENCE (canagliflozin)[a] | End-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/ 1.73 $m^2$), a doubling of serum creatinine, or death from renal or cardiovascular causes | 0.7 | 0.59–0.82 | 0.00001 |
| Dapa-CKD (dapagliflozin) | Sustained decline in eGFR of at least 50 %, end-stage kidney disease, or death from renal or cardiovascular causes | 0.61 | 0.51–0.72 | <0.001 |
| EMPA-KIDNEY (empagliflozin) | Progression of kidney disease (end-stage kidney disease, a sustained eGFR of <10 mL/ min/1.73 $m^2$), a sustained decrease in eGFR of ≥40 % from baseline, or death from renal or cardiovascular causes | 0.72 | 0.64–0.82 | <0.001 |

Overall, both empagliflozin and dapagliflozin were shown to have beneficial effects on both death and hospitalizations secondary to CHF. Infact, the use of SGLT-2i is now standard therapy in the treatment of CHF irrespective of a history for T2D

Results from these studies demonstrated significant reduction in the progression to ESKD and mortality related to CKD or CVD. Although these studies did have varying definitions of their primary outcomes, these trials succeeded as a whole to demonstrate the efficacy of SGLT-2i therapy against worsening renal outcomes in patients with T2D.

**Table 4:** GLP-1RA CVOTs.

| GLP-1RA CVOTs | Primary outcome | Primary outcome hazard ratio | 95 % CI | p-Value |
|---|---|---|---|---|
| SUSTAIN (subcutaneous semaglutide) | Death from cardiovascular causes, myocardial infarction, or nonfatal stroke | 0.74 | 0.58–0.95 | <0.001 for superiority |
| LEADER (liraglutide) | | 0.87 | 0.78–0.97 | 0.007 for superiority |
| EXSCEL (exenatide) | | 0.91 | 0.83–1.00 | 0.06 for superiority; <0.001 for noninferiority |
| HARMONY (albiglutide) | | 0.78 | 0.68–0.90 | 0.0006 for superiority |
| REWIND (dulaglutide) | | 0.88 | 0.79–0.99 | 0.026 for superiority |
| PIONEER-6 (oral semaglutide) | | 0.79 | 0.57–1.11 | <0.001 for noninferiority |
| ELIXA (lixisenatide) | Identical as above, but with the addition of the hospitalization for unstable angina | 1.02 | 0.89–1.17 | 0.81 for superiority; <0.001 for noninferiority |

A meta-analysis of these trials conducted in 2019 sought to consolidate these findings and provide a clearer picture of the effect of GLP-1RA on the occurrence of CVD.

the FLOW study (effect of semaglutide vs. placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease)

# SGLT2i e HF

**Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113] | I | A |
| A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120] | I | A |
| An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122] | I | A |
| Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109] | I | A |
| Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105] | I | B |

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

**Supplementary Table 6** **Practical guidance on the use of the sodium-glucose co-transporter 2 inhibitors dapagliflozin and empagliflozin in patients with heart failure with reduced ejection fraction[a]**

| |
|---|
| **WHY?** |
| To improve QOL, reduce the risk of HF hospitalization, and increase survival. |
| **IN WHOM AND WHEN?** |
| **Indications:** |
| 1. Patients with HFrEF (regardless of concomitant diabetes mellitus). |
| **Contraindications:** |
| 1. Known allergic reaction/other adverse reaction (drug-specific). |
| 2. Pregnancy/risk of pregnancy and breastfeeding period. |
| 3. eGFR <20 mL/min/1.73 $m^2$.* |
| 4. Symptoms of hypotension or a SBP <95 mmHg. |
| **DAPA-CKD (dapagliflozin) enrolled patients with an eGFR >25 mL/min/1.73 $m^2$* |

## 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

**Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)**

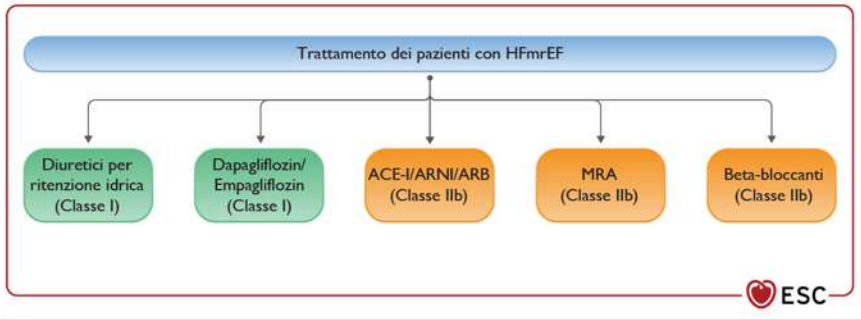



**Figura 1.** Trattamento dei pazienti con scompenso cardiaco e frazione di eiezione lievemente ridotta.
ACE-I, inibitore dell'enzima di conversione dell'angiotensina; ARB, antagonista recettoriale dell'angiotensina; ARNI, inibitore del recettore dell'angiotensina e della neprilisina; HFmrEF, scompenso cardiaco con frazione di eiezione lievemente ridotta; MRA, antagonista del recettore dei mineralcorticoidi.

## Focused update 2023 delle linee guida ESC 2021 per la diagnosi e il trattamento dello scompenso cardiaco acuto e cronico

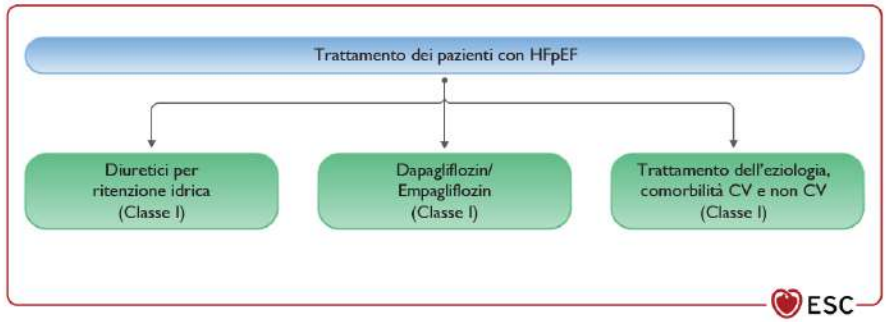



**Figura 2.** Trattamento dei pazienti con scompenso cardiaco e frazione di eiezione preservata.
CV, cardiovascolare; HFpEF, scompenso cardiaco con frazione di eiezione preservata.

**Tabella 4 delle raccomandazioni – Raccomandazioni per la prevenzione dello scompenso cardiaco nei pazienti con diabete mellito di tipo 2 e malattia renale cronica**

| Raccomandazioni | Classe[a] | Livello[b] |
|---|---|---|
| Nei pazienti con T2DM e CKD[c] è raccomandato il trattamento con inibitori di SGLT2 per ridurre il rischio di ospedalizzazione per HF e di morte CV[35]. | I | A |
| Nei pazienti con T2DM e CKD[c] è raccomandato il trattamento con finerenone per ridurre il rischio di ospedalizzazione per HF[10,11,34,40]. | I | A |

CKD, malattia renale cronica; CV, cardiovascolare; eGFR, velocità di filtrazione glomerulare stimata; HF, scompenso cardiaco; SGLT2, co-trasportatore sodio-glucosio di tipo 2; T2DM, diabete mellito di tipo 2.
[a]Classe della raccomandazione.
[b]Livello di evidenza.
[c]La CKD è stata così definita: eGFR 25-75 ml/min/1.73 $m^2$ e rapporto albumina/creatinina urinaria ≥200-5000 mg/g nello studio DAPA-CKD[5]; eGFR 20-45 ml/min/1.73 $m^2$ o eGFR 45-90 ml/min/1.73 $m^2$ con rapporto albumina/creatinina urinaria ≥200 mg/g nello studio EMPA-KIDNEY[7]; eGFR 25-60 ml/min/1.73 $m^2$ e rapporto albumina/creatinina urinaria 30-300 mg/g e retinopatia diabetica, o eGFR 25-75 ml/min/1.73 $m^2$ e rapporto albumina/creatinina urinaria 300-5000 mg/g nello studio FIDELIO-DKD[10]; eGFR 25-90 ml/min/1.73 $m^2$ e rapporto albumina/creatinina urinaria 30-<300 mg/g o eGFR >60 ml/min/1.73 $m^2$ e rapporto albumina/creatinina urinaria 300-5000 mg/g nello studio FIGARO-DKD[11].

# SGLT2i e IRC

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

SGLT2i

The recommendation is consistent with but expands on Recommendation 1.3.1 from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease to include people with causes of CKD not related to diabetes.

**KDIGO: Prognosis of CKD by GFR and albuminuria categories**

| GFR categories (ml/min/1.73 m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |
| | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60–89 | | | |
| | G3a | Mildly to moderately decreased | 45–59 | | | |
| | G3b | Moderately to severely decreased | 30–44 | | | |
| | G4 | Severely decreased | 15–29 | | | |
| | G5 | Kidney failure | <15 | | | |

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

**Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 $m^2$ with an SGLT2i *(1A)*.**

Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 $m^2$, unless it is not tolerated or KRT is initiated.

Practice Point 3.7.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

**Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:**
- **eGFR ≥20 ml/min per 1.73 $m^2$ with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

**Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 $m^2$ with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.**

# GLP1- RA e IRC

### 3.9 Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

The Work Group highlights a key recommendation and practice point from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.[23]

**Recommendation 3.9.1: In adults with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.**

Practice Point 3.9.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

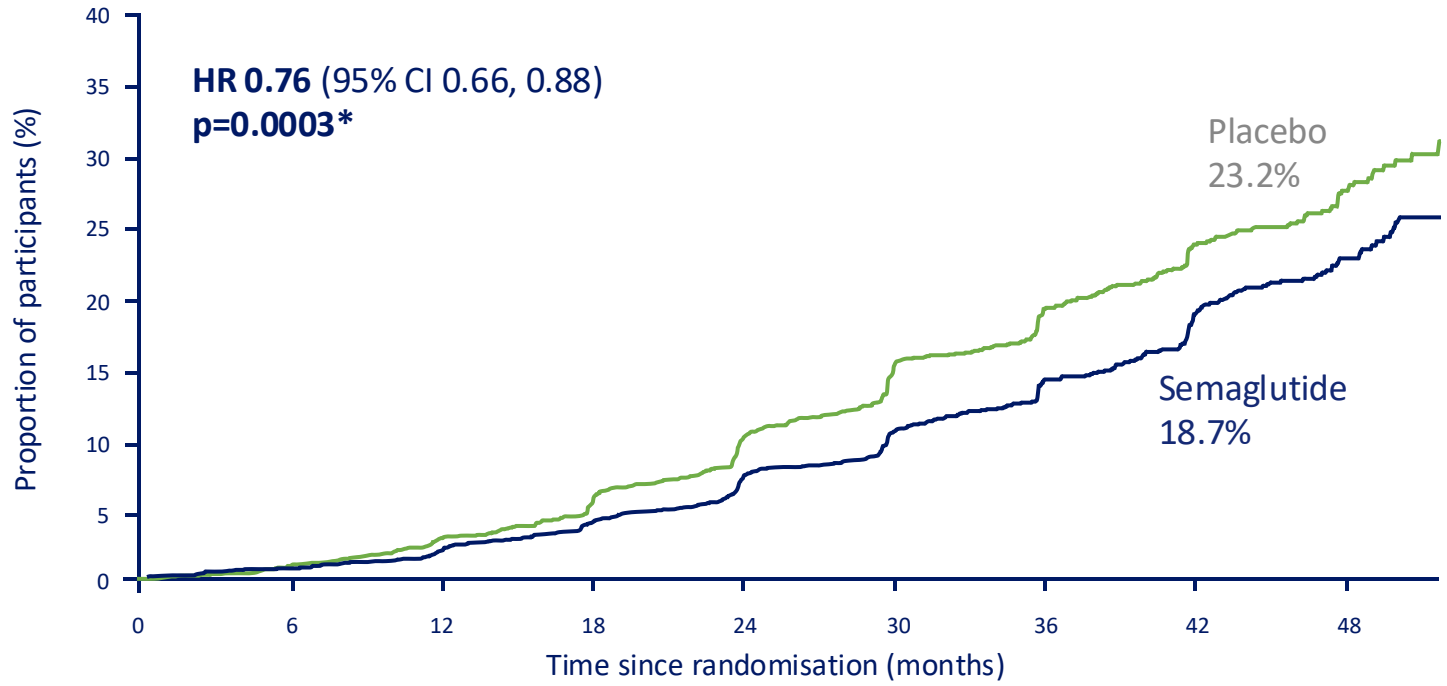
**Primary kidney endpoint**

# OW semaglutide s.c. 1.0 mg showed a 24% risk reduction of a composite outcome, incl. kidney disease progression, CV and kidney death in people with CKD and T2D

Time to first occurrence of a composite endpoint consisting of:

- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Onset of persistent eGFR <15 mL/min/1.73 $m^2$
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death

## First composite kidney event: Primary outcome




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Semaglutide | 1,767 | 1,738 | 1,693 | 1,640 | 1,572 | 1,489 | 1,131 | 742 | 392 |
| Placebo | 1,766 | 1,736 | 1,682 | 1,605 | 1,516 | 1,408 | 1,048 | 660 | 354 |

- Full analysis set. Data from the in-trial period. * Superiority if p value <0.0322
Numbers shown in the lower panels represent the number of participants at risk. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

# SGLT2-i e GLP1 RA

REVIEW Open Access

Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM)

Pierre Gourdy[1,2*], Patrice Darmon[3], François Dievart[4], Jean-Michel Halimi[5,6] and Bruno Guerci[7]

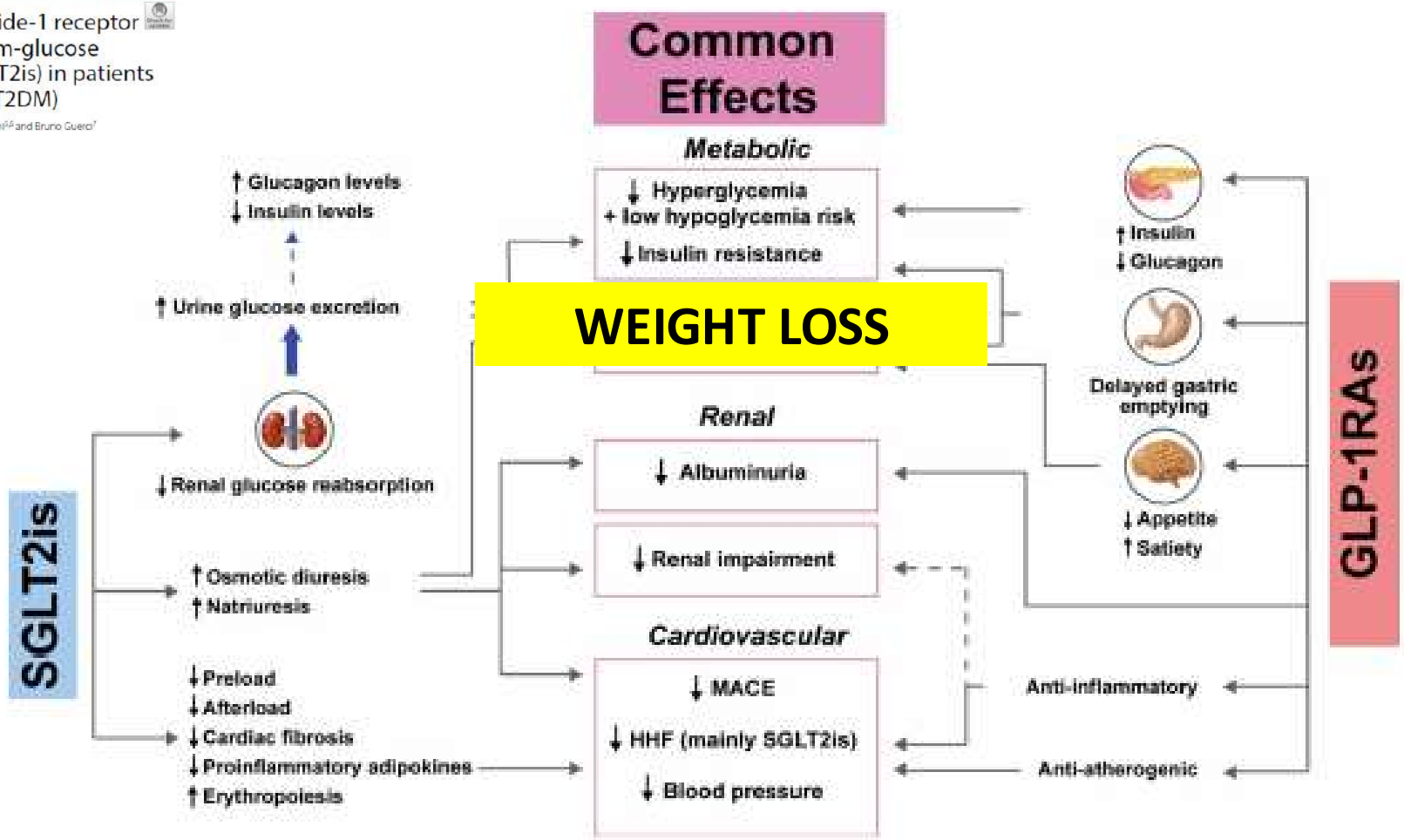
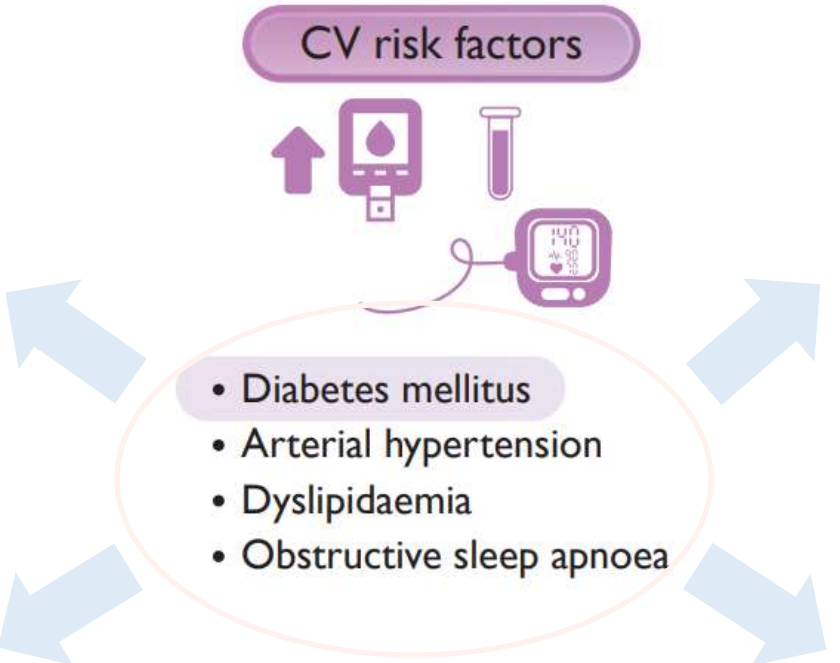



**Fig. 1** Complementary mechanisms of action of sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs). HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events. SGLT2is improve insulin secretion without increasing insulin levels. The black dotted line indicates that there is insufficient clinical evidence to support the beneficial effects of GLP-1RAs on renal impairment [87]

# Main cardiovascular consequences of obesity

**Diabetes**
**Insulin resistance**, a key factor in T2DM development manifesting long before the onset of diabetes, is also a major feature of obesity. Insulin resistance predicts the risk of developing CVD, even in the absence of diabetes, and promotes atheroma plaque formation.




**Dyslipidaemia**
Obesity is associated with an **atherogenic lipoprotein phenotype** including elevation of both fasting and post-prandial triglycerides, Apolipoprotein B (ApoB), and small dense LDL particles, and low high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) levels.
High levels of very-low-density lipoproteins (VLDL) that vehicle plasma triglycerides were found to explain 40% of the excess risk of myocardial infarction associated with higher BMI

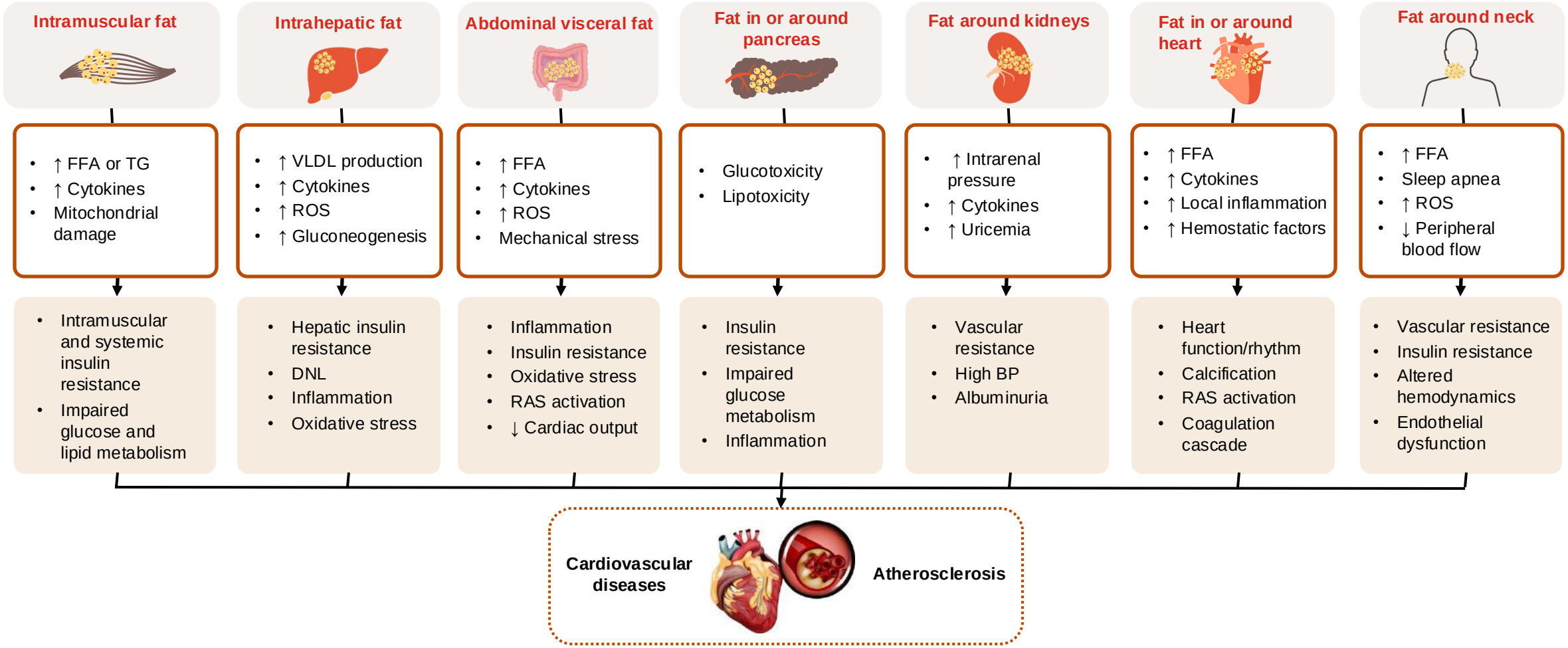
**Hypertension**
Increased BMI, from overweight to all classes of obesity is linearly related to the prevalence of hypertension.

**Obstructive sleep apnoea**
OSA per se is a risk factor implicated in the development of hypertension and the progression of HF, pulmonary hypertension, and AF overall reflecting how obesity exerts multiple direct and indirect deleterious CV effects.

Koskinas KC. Obesity and cardiovascular disease: an ESC clinical consensus statement. European Heart Journal (2024) 00, 1–36

# Linking Ectopic Fat Deposition and Cardiovascular Disease

**Mechanisms of different ectopic fats related with atherosclerosis and cardiovascular diseases**




BP=Blood Pressure; DNL=De Novo Lipogenesis; FFA=Free Fatty Acid; RAS=Renin-Angiotensin System; ROS=Reactive Oxygen Species; TG=Triglyceride; VLDL=Very Low-density Lipoprotein.
Data from Lim S, Meigs JB. *Arterioscler Thromb Vasc Biol*. 2014;34(9):1820-1826.

# Weight loss and improved health

## Towards greater weight loss and overall health improvement[1–5]

| 0–5% | 5–10% | 10–15% | ≥15% |
|---|---|---|---|
| Hypertension[1] | Urinary stress incontinence[1] | MASH[1] | Cardiovascular[1] disease |
| Hyperglycaemia[1] | Prevention of T2D[1] | OSAS[1] | MASH[1] |
| | PCOS[1] | GERD[1] | T2D remission[1,3,5] |
| | Dyslipidaemia[1] | Knee OA[1] | CV mortality[1,4] |
| | Asthma/Airway disease[1] | | HFpEF[1,4,5] |
| | MAFLD[1] | | |

Weight loss

- CV, cardiovascular; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome

1. Garvey WT, et al. Endocr Pract 2016;22(Suppl. 3): 1–203; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4(11): 913–921; 3. Lean ME, et al. Lancet. 2018;391(10120): 541–551; 4. Benraoune F and Litwin SE. Curr Opin Cardiol. 2011;26(6): 555–561; 5. Sundström J, et al. Circulation. 2017;135(17): 1577–1585.

# GLP1-RA e Obesità

**Terapia del sovrappeso e dell'obesità resistenti al trattamento comportamentale nella popolazione adulta con comorbidità metaboliche**

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

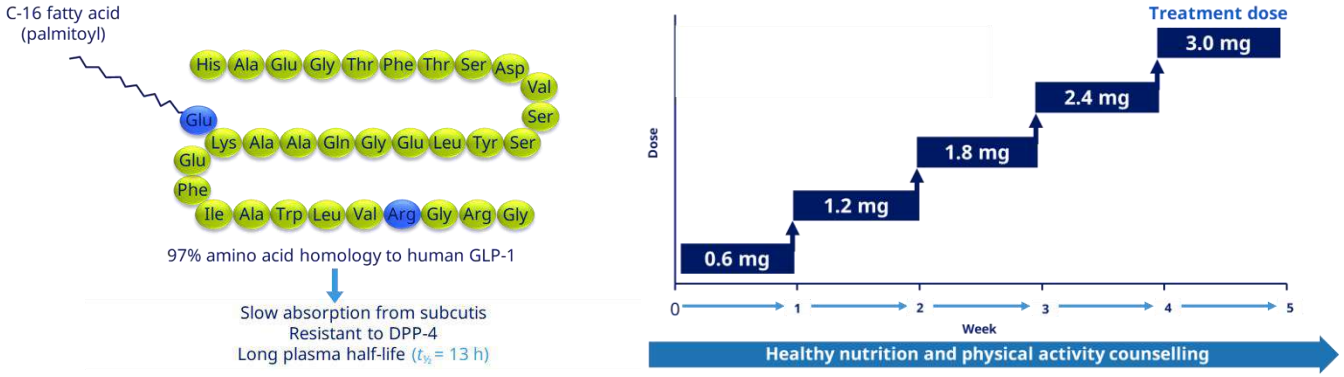
**Linea guida pubblicata nel Sistema Nazionale Linee Guida**

Roma, 24 gennaio 2023

| Qualità delle prove | Raccomandazioni | Forza della raccomandazione |
|---|---|---|
| Bassa | 1. Nella popolazione di pazienti adulti con **BMI > 27 kg/m2 e ≤ 40 kg/m2** con comorbilità metaboliche correlate al peso, resistente alle modificazioni dello stile di vita, il panel suggerisce di implementare ulteriori interventi in aggiunta a dieta e attività fisica | Condizionata (debole) a favore dell'intervento |
| Moderata | 1.1. Nei pazienti diabetici e pre-diabetici il panel raccomanda di utilizzare **Semaglutide 2.4 mg/settimana**. | Forte a favore dell'intervento |
| Bassa | 1.2. Nei pazienti diabetici e pre-diabetici il panel suggerisce di utilizzare **Liraglutide 3 mg/die**. | Condizionata (debole) a favore dell'intervento |
| Moderata | 1.3. Nei pazienti con NAFLD il panel raccomanda di utilizzare **Semaglutide 2.4 mg/ settimana**. | Forte a favore dell'intervento |
| Moderata | 1.4. Nei pazienti in cui la riduzione delle comorbilità renda necessaria una maggior perdita di peso, tra le terapie farmacologiche il panel raccomanda di utilizzare **Semaglutide 2.4 mg/ settimana**. | Forte a favore dell'intervento |
| Bassa | 1.5. Nei pazienti dislipidemici con ipertrigliceridemia e con alimentazione ipercalorica e iperlipidica il panel suggerisce di utilizzare **Orlistat**. | Condizionata (debole) a favore dell'intervento |
| Bassa | 1.6. Nei pazienti con alimentazione emotiva il panel suggerisce di utilizzare **Naltrexone/Bupropione**. | Condizionata (debole) a favore |

# Liraglutide e Obesità

## Liraglutide 3.0 mg
Structure and Dose escalation




## SCALE Obesity and Prediabetes trial
Liraglutide 3.0 mg for weight management (56 weeks)

**Aim** Efficacy and safety of liraglutide 3.0 mg, as adjunct to D&E, in participants with obesity or overweight plus comorbidities, without diabetes

| Key findings | Liraglutide 3.0 mg vs placebo |
|---|---|
| Change in body weight (%) | -9.2 vs -3.5, p<0.0001 |

| Key secondary endpoints | Liraglutide 3.0 mg vs placebo |
|---|---|
| Waist circumference (cm) | -8.2 vs -3.9, p<0.001 |
| Systolic blood pressure (mmHg) | -4.2 vs -1.5, p<0.001 |
| C-reactive protein | -37.8% vs -10.1%, p<0.001 |
| Visceral adipose tissue (VAT) (%) * | -12.49% vs -1.63%, p<0.0001 |
| Cardiometabolic variables & HRQoL | Beneficial effects with liraglutide for blood pressure and other cardiometabolic variables and with improvement in HRQoL |

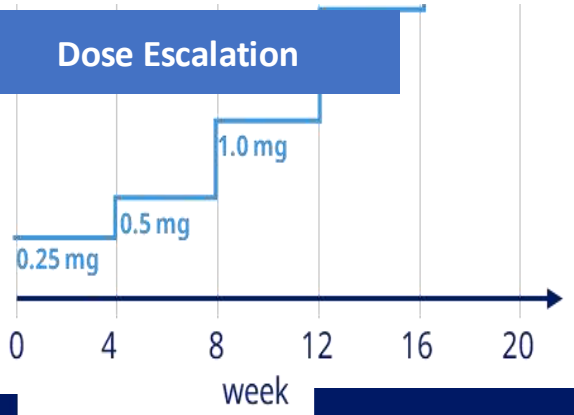
*BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference*
*Pi-Sunyer et al. N Engl J Med 2015;373:11–22*
**Neeland et al. The Lancet Diabetes & Endocrinology 2021; 9(9): 595-605. 46 weeks randomized trial*

# Semaglutide e Obesità

## SEMAGLUTIDE

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]


## Dose Escalation




## Population

*Overweight*

**BMI ≥ 27 kg/m²**

*+ ≥ 1 comorbidities [such as dysglycaemia (prediabetes or T2D), hypertension, dyslipidaemia, OSAS or CV disease]*

*es. h: 1.70 m, w: 78 kg*

*Obesity*

**BMI ≥ 30 kg/m²**

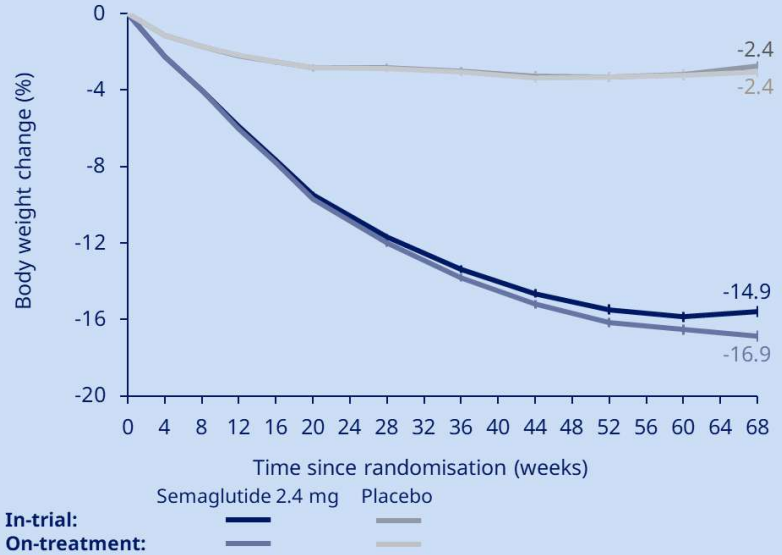
*es. h: 1.70 m, w: 87 kg*

## Change in body weight

STEP 1

**Observed body weight change over time**

(Mean at baseline: 105.3 kg)




## Health benefits beyond body weight and BMI

Persistent improvements in cardiometabolic parameters were showed in the semaglutide treatment arm*

| 68 weeks | Waist circumference | Systolic BP | Diastolic BP | LDL cholesterol | Triglycerides |
|---|---|---|---|---|---|
| **STEP 1** | **-13.5 cm** | **-6.2 mmHg** | **-2.8 mmHg** | **-3%** | **-22%** |
| Placebo | -4.1 cm | -1.1 mmHg | -0.4 mmHg | +1% | -7% |

**Exploratory analysis**

**STEP 1**

**Proportion of participants achieving prediabetes reversion†**

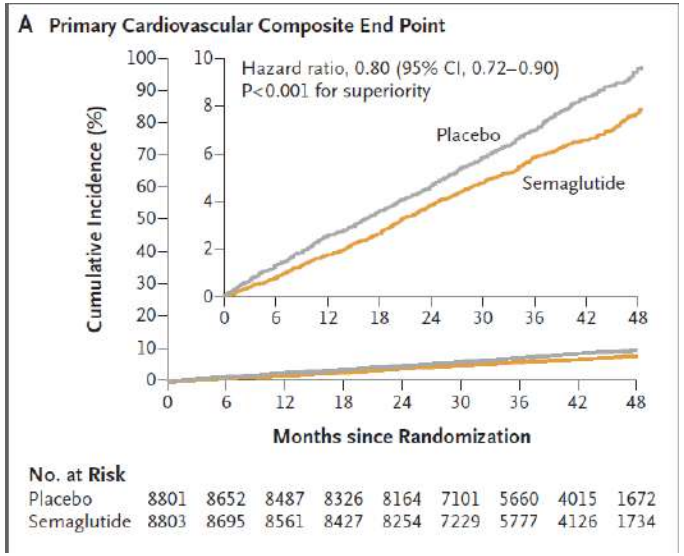

**Treatment policy estimand; †Exploratory endpoint, proportion of patients who reverted to normoglycaemia (according to American Diabetes Glycaemic category) by end of trial.*

1. Lau et al. J Med Chem 2015;58:7370–80; 2. Kapitza et al. J Clin Pharmacol 2015;55:497–504; 3. Marbury et al. Clin Pharmacokinet 2017;56:1381–90. *Wilding et al. N Engl J Med 2021;384:989-1002; 2. Davies et al. Lancet 2021;397:971-84; 3. Yuen et al. Obesity Week 2016. Oct 31–Nov 4 2016. New Orleans: T-P-3166*

# Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

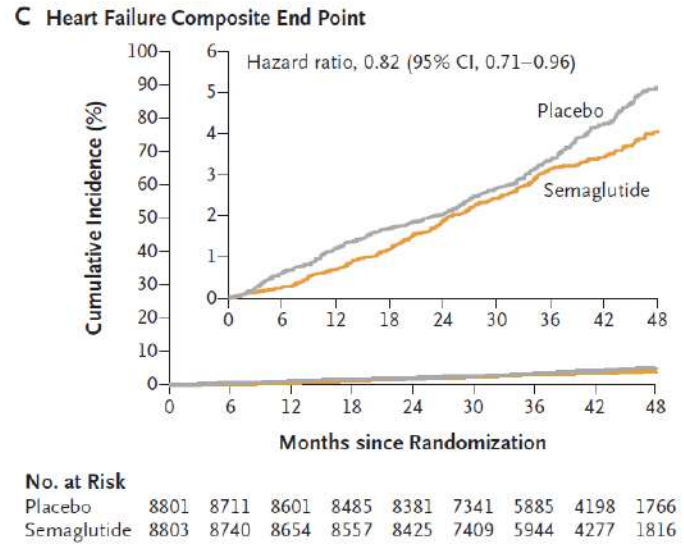
A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

Trial, multicentrico, in doppio cieco, randomizzato, ha arruolato circa 17.000 pazienti di sesso maschile e femminile con un'età superiore o uguale a 45 anni, con un BMI (indice di massa corporea) superiore o uguale a 27 kg/mq e **con almeno un evento cardiovascolare in anamnesi** (infarto del miocardio, ictus ischemico, arteriopatia obliterante degli arti inferiori), **in assenza di diabete mellito**. Lo studio ha confrontato semaglutide 2.4 mg sottocutaneo somministrato una volta alla settimana con il placebo, come aggiunta alle cure standard **per la prevenzione degli eventi cardiovascolari avversi maggiori (MACE)** per un periodo fino a cinque anni




**Una riduzione statisticamente significativa del 20% di MACE per le persone trattate con semaglutide 2.4 mg rispetto al placebo**. L'endpoint primario dello studio è stato definito come l'esito composito della prima comparsa di MACE, definito come morte cardiovascolare, infarto miocardico non fatale o ictus non fatale.

Questo studio è il primo ad aver dimostrato che un farmaco utilizzato per il trattamento e la cura dell'obesità riduce il rischio cardiovascolare dei pazienti trattati.



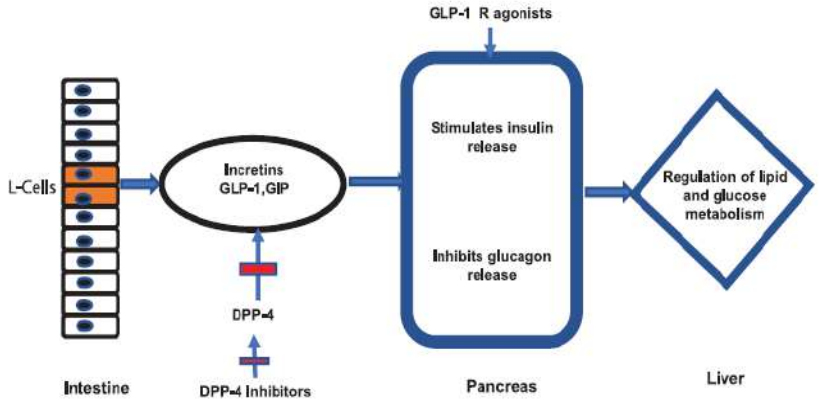
# SGLT2i e GLP1 RA MASLD/ LIVER DISORDERS

## HEPATIC BENEFITS OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS IN LIVER DISORDERS

Habib Yaribeygi[1*], Mina Maleki[2], Tannaz Jamialahmadi[3,4], Seyed Adel Moallem[5,6], Amirhossein Sahebkar[4,7,8,9*]

**Table 1:** Main interactions between SGLT2 inhibitors and hepatic complications

| | Effects of SGLT2i therapy | References |
|---|---|---|
| LFTs levels | Normalize LFT levels | Leiter et al., 2016; Seko et al., 2018; Inoue et al., 2019; Coelho et al., 2021 |
| Cirrhosis | Prevent or slow cirrhosis progression and reduces liver tissue stiffness | Saffo et al., 2020, 2021 |
| NAFLD | Reduce stored adipose tissues in the liver and normalize its composition | Aso et al., 2019; Chiang et al., 2020; Wei et al., 2021 |
| Hepatocellular carcinoma | Prevent or reduce NASH to HCC transition or HCC development | Shiba et al., 2018; Jojima et al., 2019; Hendryx et al., 2022 |




Body weight loss and glycemic control on the outcomes of patients with NAFLD. The role of new antidiabetic agents

Diego García-Compeán[a,*], Ramesh Kumar[b], Ángel Noe del Cueto-Aguilera[a], Héctor Jesús Maldonado-Garza[a], Jesús Zacarías Villarreal-Pérez[c]

## The Emerging Role of Glucagon-like Peptide-1 Receptor Agonists for the Management of NAFLD

**Chandani Patel Chavez,[1] Kenneth Cusi,[1,2] and Sushma Kadiyala[1,2]**

**Table 1.** Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]

| Author | GLP1-RA | n | Study design | Weight change[b] | Reduction in liver fat content |
|---|---|---|---|---|---|
| Vanderheiden et al, 2016 | Liraglutide | 71 | RCT | ↓2.2% | ↓31% |
| Feng et al, 2017 | Liraglutide | 87 | Open label | ↓6.4% | ↓19% |
| Petit et al, 2017 | Liraglutide | 68 | Open label | ↓4.4% | ↓19% |
| Frossing et al, 2018 | Liraglutide | 72 | RCT | ↓5.7% | ↓32% |
| Kuchay et al, 2020 | Dulaglutide | 52 | Open label | ↓2.6% | ↓20% |

Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]

| Author | GLP1-RA | n | Study design | Weight change[b] | NASH resolution |
|---|---|---|---|---|---|
| Armstrong et al, 2016 | Liraglutide | 52 | RCT | ↓4.8% | 30% |
| Newsome et al, 2020 | Semaglutide | 320 | RCT | ↓4%-12% | 19%-42% |

# SGLT2i e GLP1 RA MASLD/ LIVER DISORDERS

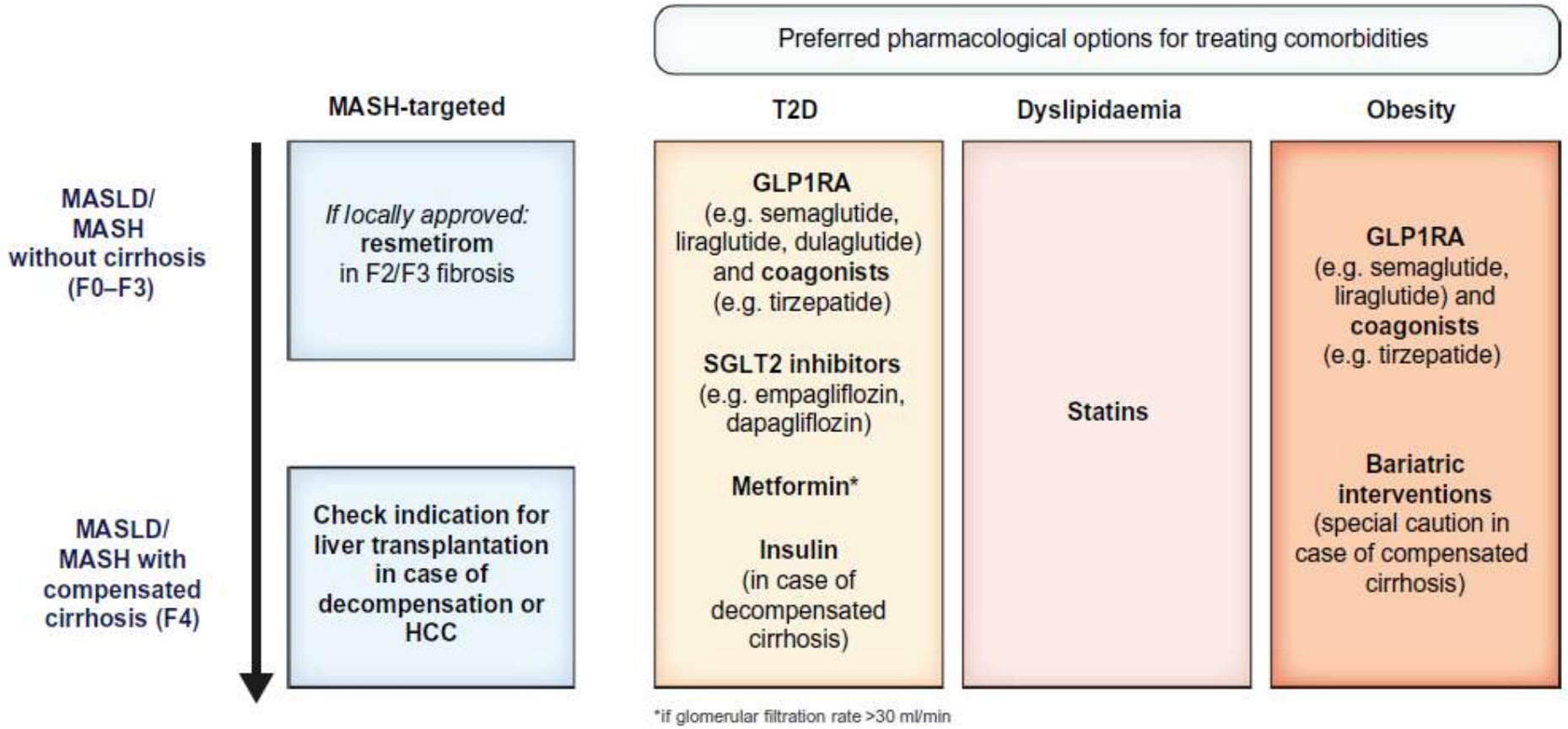
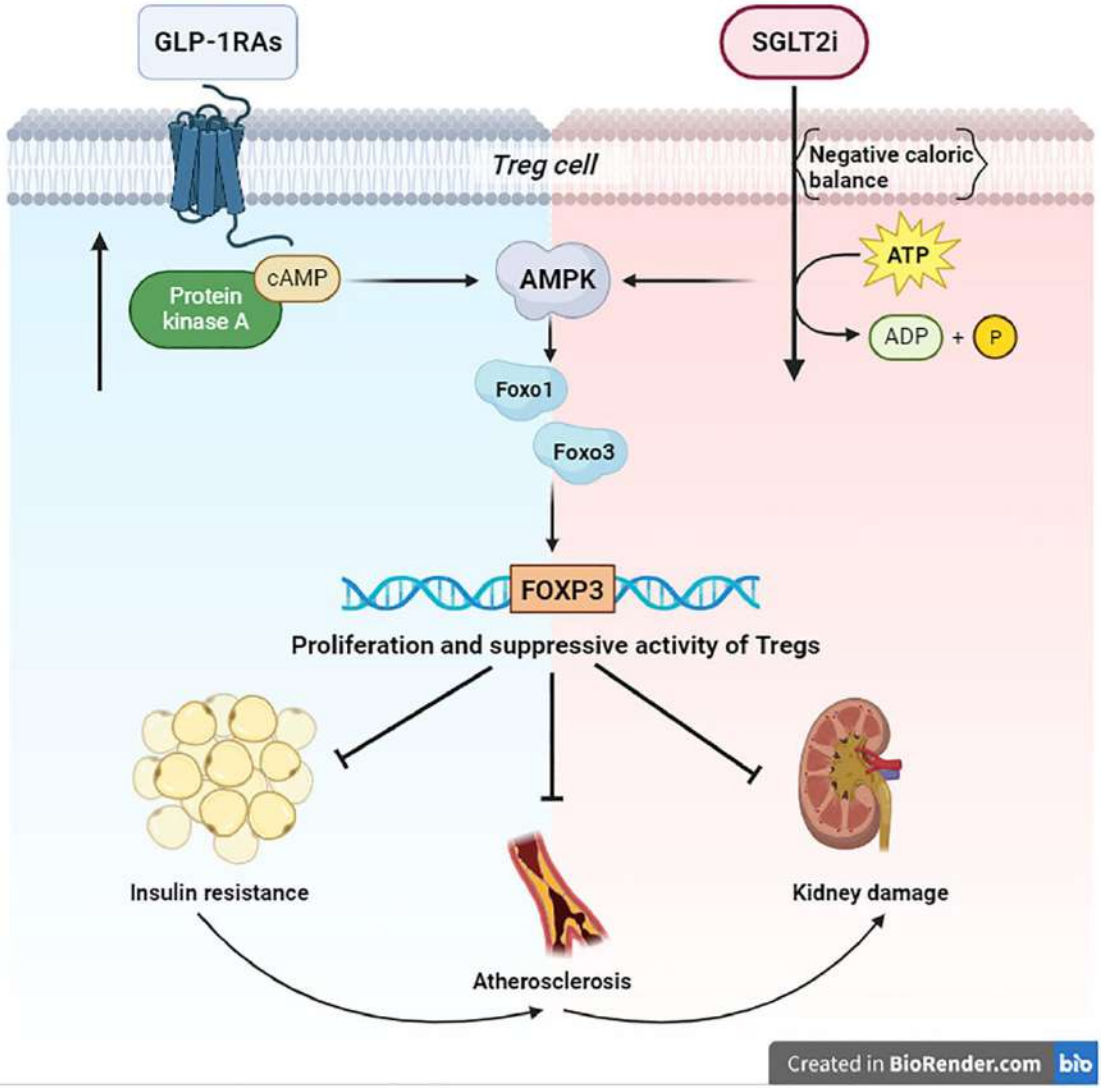



**Fig. 4** Treatment recommendations beyond lifestyle modification in MASLD/MASH. The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease. T2D, type 2 diabetes

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary

European Association for the Study of the Liver[1] · European Association for the Study of Diabetes[2] · European Association for the Study of Obesity[3]

# SGLT2i e GLP1 RA attività anti-infiammatoria




GLP-1 RAs and SGLT2i: two antidiabetic agents associated with immune and inflammation modulatory properties through the common AMPK pathway

Alessio Mazzieri[1*], Giuseppe Basta[2], Riccardo Calafiore[3,4] and Giovanni Luca[4,5]

Signaling of AMPK/FOXO/FOXP3 Both anabolic (blue zone) and catabolic (red zone) signals converge on AMPK. This kinase activates the Foxo transcriptional factors by direct phosphorylation. Specifically, Foxo1 and Foxo3 are essential for the transcription of FOXP3 and the consequential proliferation of Tregs, which are necessary to suppress the damage of chronic inflammation in T2D. BioRender.com.

# Tirzepatide

## Doppio agonista recettoriale GIP e GLP-1

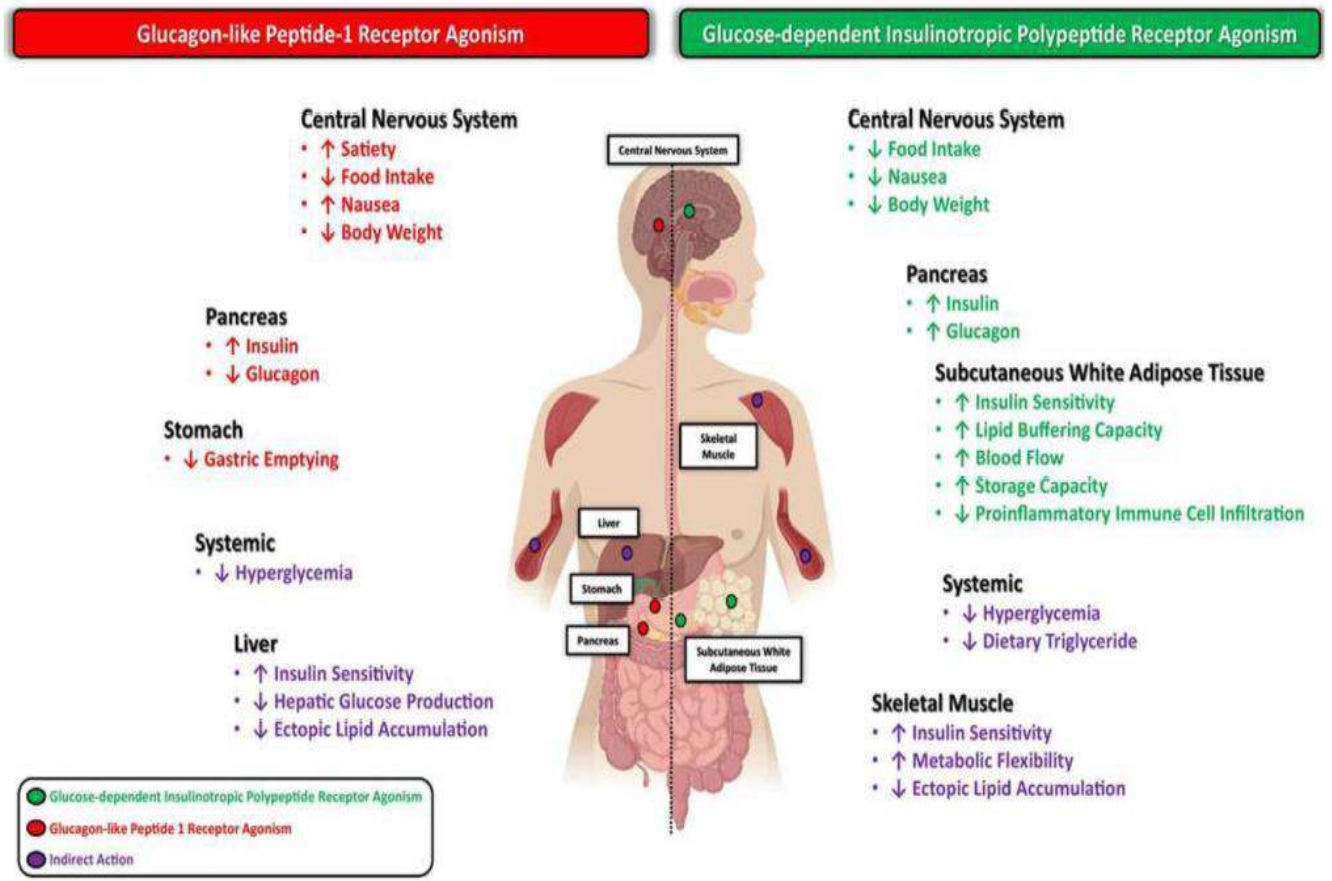



**Figure 2** Pleiotropic actions of glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) in type 2 diabetes. Reprinted from Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? Trends Endocrinol Metab. 2020;31(6):410–421. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[25] intended).

The Emerging Role of Dual GLP-1 and GIP Receptor Agonists in Glycemic Management and Cardiovascular Risk Reduction

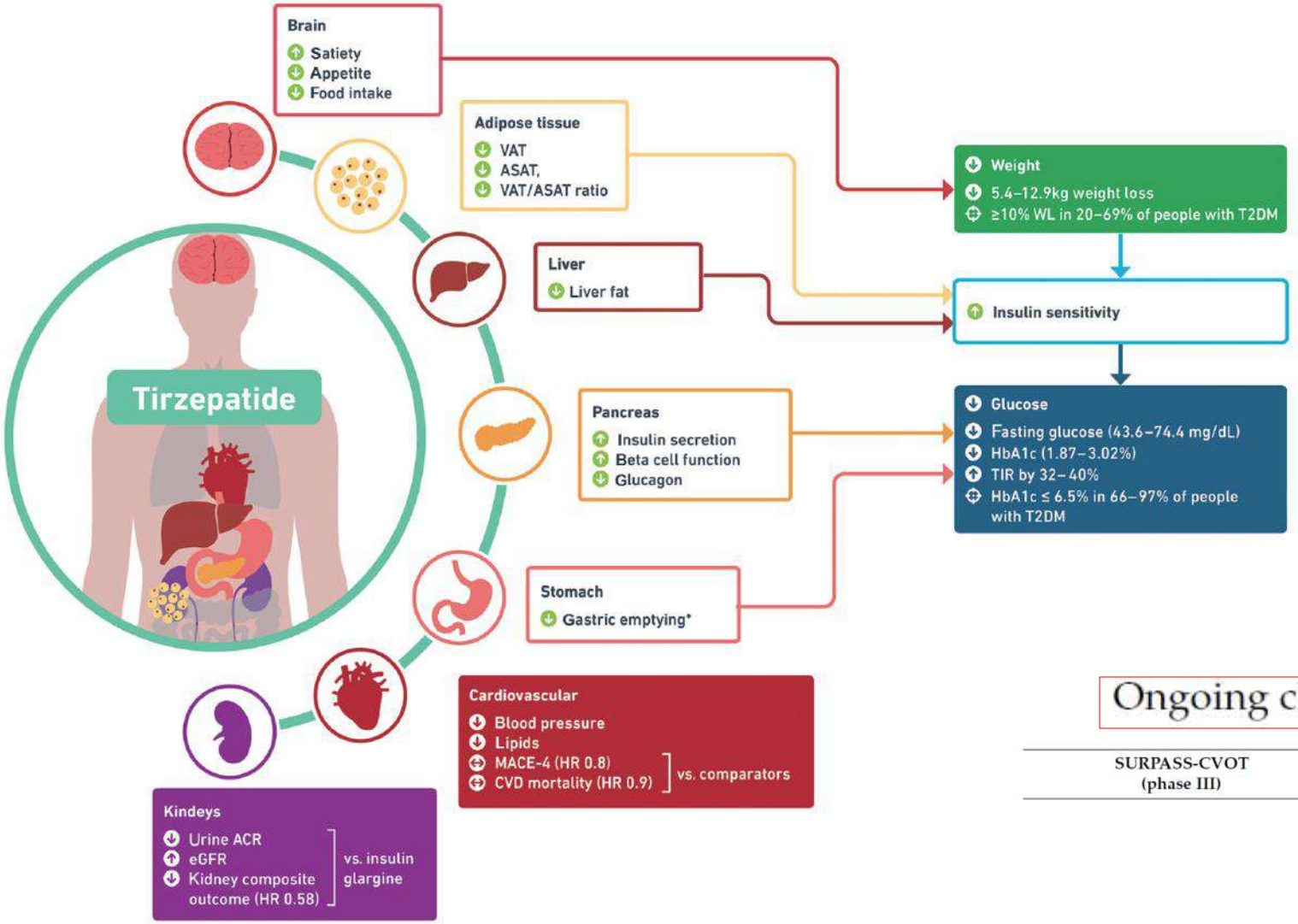
Ali A Rizvi[1], Manfredi Rizzo[2]

**Table 1** Cardiovascular Effects of GIP in Animal Models

| Animal Model | | GIPR Activation | GIPR Inhibition |
|---|---|---|---|
| **Atherosclerosis** | ApoE knockout mice | ↓Plaque formation<br>↓Macrophage foam cell formation<br>↑Plaque stability | |
| | ApoE knockout mice with diabetes | ↓Plaque formation<br>↓Macrophage foam cell formation | |
| **Restenosis** | Femoral artery wire injury (male C57BL/6 mice) | ↓Neointimal formation<br>↑endothelial regeneration | ↑Neointimal formation |
| | Femoral artery wire injury with diabetes (male db/db mice) | ↓Neointimal formation | |
| **Cardiac remodeling** | Angiotensin II infusion (male C57BL/6-background ApoE knockout mice)<br>Coronary artery ligation (male C57BL/6-background mice)<br>Transverse aortic constriction (male C57BL/6-background mice)<br>Doxorubicin injection (male C57BL/6-background mice) | ↓Cardiomyocyte enlargement<br>↓Interstitial fibrosis<br>↑Scar formation | ↓Mortality<br>↓Scar formation<br>→Left ventricular function<br>↓Cardiac atrophy<br>→ Mortality |
| **Inflammation** | Standard diet (C57BL/6 and db misty mice) | ↓Adipose tissue inflammation<br>↑Adipose tissue inflammation | |
| | High fat diet | ↓Adipose tissue inflammation<br>↑Adipose tissue expression and blood levels of adiponectin | ↑Blood and adipose tissue levels of IL-6 |
| | Diabetes (male db/db mice)<br>Gingivitis (C57BL/6-background mice)<br>Endotoxemia (C57BL/6 mice) | ↑Adipose tissue inflammation<br>↓ Blood IL-6 level | ↑Gingival inflammation |

**Notes:** Arrows: ↑, increase; →, no change; ↓ decrease. Adapted from Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease-a systematic review. *Int J Mol Sci*. 2020;21(4):1509. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[32]

# Tirzepatide




**GLP 1RA/GIP:** analisi post hoc di studi randomizzati e controllati di *outcome* metabolici (controllo glicemico e peso corporeo) con un doppio agonista recettoriale GLP-1 e *Gastric Inhibitory Polypeptide* (GIP), la tirzepatide, hanno suggerito un possibile effetto di nefroprotezione sia in termini di riduzione dell'albuminuria che di rallentamento della perdita di eGFR

## Efficacy and Safety of Tirzepatide in Type 2 Diabetes and Obesity Management

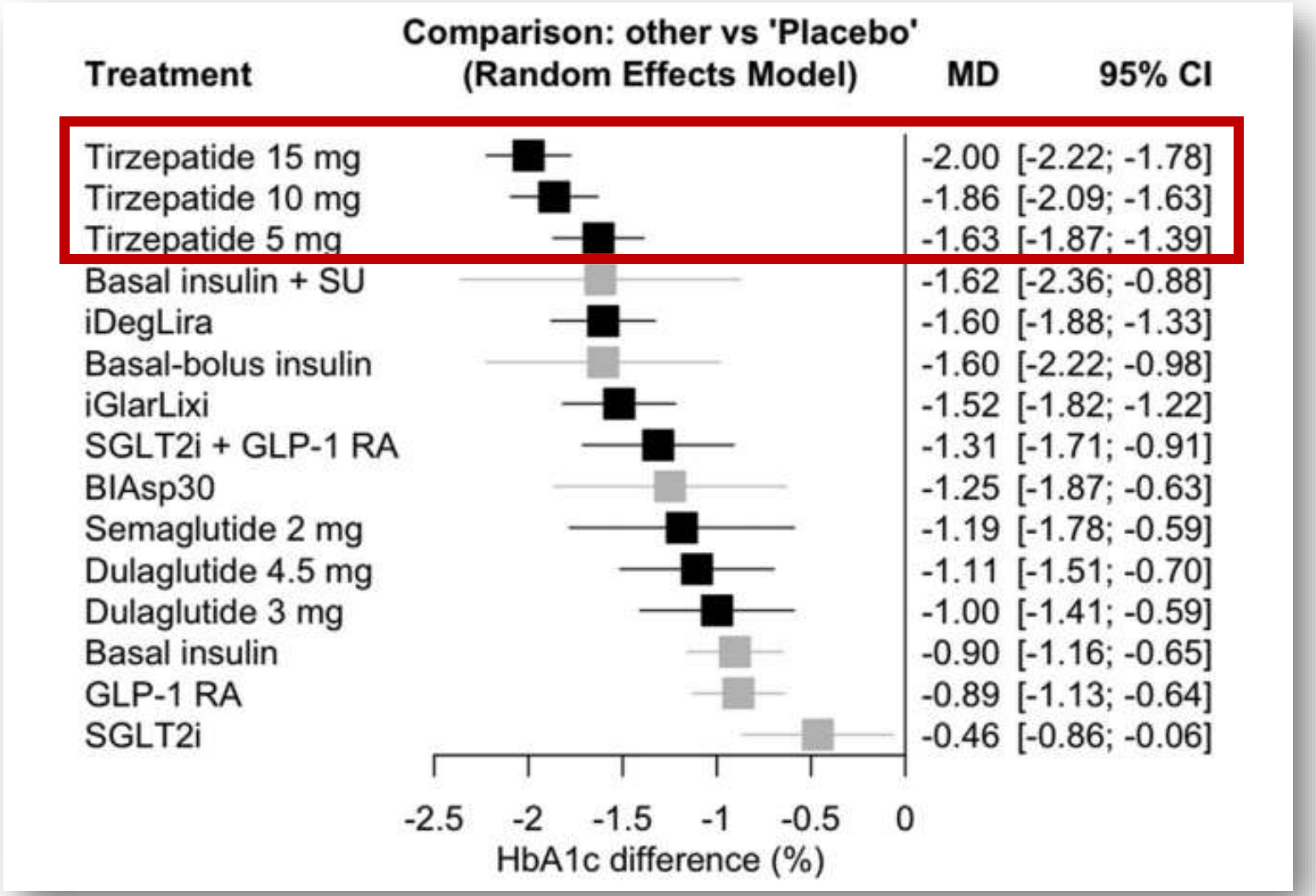
Rachel Sinha[1], Dimitris Papamargaritis[1,2,*], Jack A. Sargeant[1,2], Melanie J. Davies[1,2]

[1]Diabetes Research Centre, University of Leicester College of Life Sciences, Leicester; [2]National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre, University Hospital of Leicester NHS Trust and the University of Leicester, Leicester, UK

## Ongoing clinical trials testing Tirzepatide.

| | |
|---|---|
| **SURPASS-CVOT (phase III)** | The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes. |

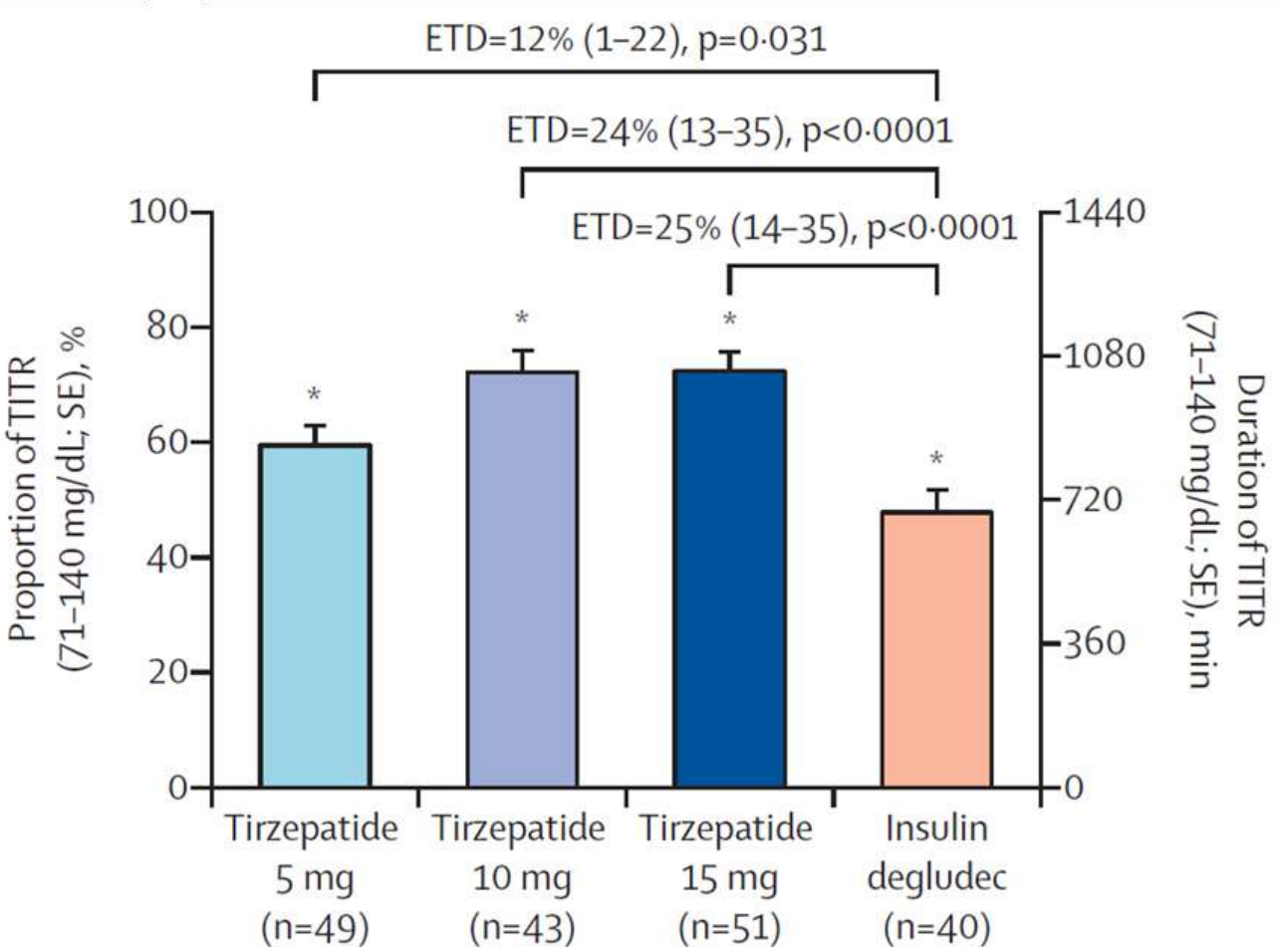
# Tirzepatide in the context of T2DM treatment: effect on HbA1c




Caruso I, Giorgino F et al. . EClinicalMedicine. 2023 Sep 12;64:102181.

# Tirzepatide allows more stringent targets of glycemic variability as measured by Time in Tight Target Range (TITR) 71-140 mg/dL

SURPASS-3 CGM




†††p<0.0001 versus baseline within the treatment group.

Note: CGM analysis dataset was used for analysis. Data are least squares mean ± standard errors. ETD are least squares mean (95% CI). Values in parentheses are in minutes.

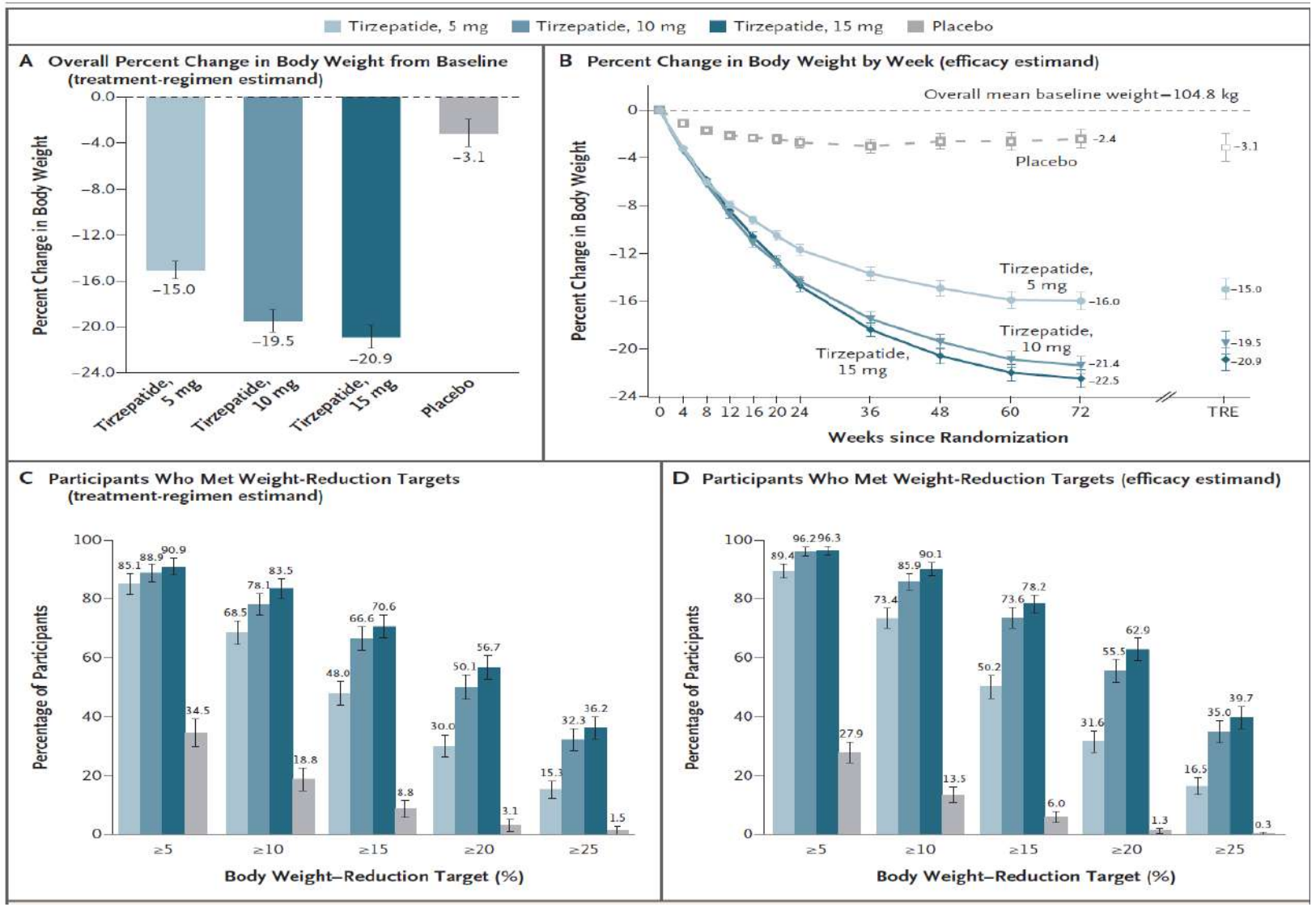
CGM = continuous glucose monitoring; CI = confidence interval; ETD = estimated treatment difference; LSM = least squares mean; SE = standard error; TITR = time in tight target range; TZP=tirzepatide.

Battelino T, et al. *Lancet Diabetes Endocrinol.* 2022;10(6):407-417.

# Tirzepatide ed Obesità

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*




Jastreboff AM et al. *N Engl J Med*. 2022 Jul 21;387(3):205-216.

# SURMOUNT-OSA Endpoints

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity
Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., +5 , for the SURMOUNT-OSA Investigators*Author Info & Affiliations
Published June 21, 2024
DOI: 10.1056/NEJMoa2404881

## Primary Endpoint[1,2]

Change in AHI (Apnoea-Hypopnoea Index) from baseline to Week 52

## Key Secondary Endpoints[1,2]

**From baseline to Week 52:**

- Percentage change in AHI
- Percentage of participants with clinically meaningful change in AHI[a]
- Percentage of participants with OSA remission or mild nonsymptomatic OSA[b]
- Change in SASHB
- Percentage change in body weight
- Change in inflammatory status (hsCRP)
- Change in PROMIS Short Form Sleep-Related Impairment 8a[c]
- Change in PROMIS Short Form Sleep Disturbance 8b[c]

**From baseline to Week 48[d]:**

- Change in systolic BP

1. Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881
2. https://clinicaltrials.gov/study/NCT05412004 (Accessed April 17, 2024).

# SURMOUNT-OSA

The NEW ENGLAND JOURNAL of MEDICINE

## Tirzepatide for Obstructive Sleep Apnea and Obesity

### A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity by A. Malhotra et al. (published June 21, 2024)

**In two trials, researchers assessed the efficacy and safety of tirzepatide for the treatment of adults with obstructive sleep apnea and obesity.**

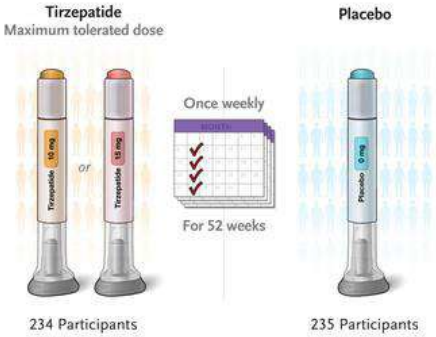
**Obstructive sleep apnea** is characterized by repetitive pharyngeal collapse during sleep, resulting in apneas and hypopneas. It is also an independent risk factor for cardiovascular disease.

#### WHY WERE THE TRIALS DONE?

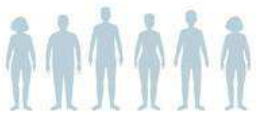
Excess adiposity is a major reversible risk factor for obstructive sleep apnea and its complications. Tirzepatide — a long-acting agonist of the glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor — has been shown to reduce body weight. Whether tirzepatide can treat obstructive sleep apnea is unknown.

#### HOW WERE THE TRIALS CONDUCTED?

In two trials, 469 adults with moderate-to-severe obstructive sleep apnea and obesity were assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo subcutaneously once weekly for 52 weeks. Trial 1 enrolled participants who were not receiving positive airway pressure (PAP) therapy. Trial 2 enrolled those who were receiving PAP therapy. The primary end point was the change from baseline in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep).




#### PARTICIPANTS



**WHO**

Trial 1 (no PAP therapy):
234 adults
Mean age, 48 years
Men: 67%; Women: 33%

Trial 2 (PAP therapy):
235 adults
Mean age, 52 years
Men: 72%; Women: 28%

**CLINICAL STATUS**

Apnea–hypopnea index, at least 15 events per hour (mean, approximately 50)

Body-mass index, at least 30 (mean, 39)

No type 1 or type 2 diabetes

#### TRIAL DESIGN

- PHASE 3
- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- DURATION: 52 WEEKS
- LOCATION: 60 SITES ACROSS 9 COUNTRIES





The NEW ENGLAND JOURNAL of MEDICINE

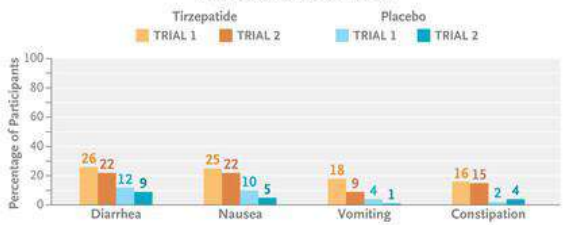
#### RESULTS

In both trial 1 and trial 2, tirzepatide led to a significantly greater reduction in the AHI at week 52 than placebo.

All key secondary end points also favored tirzepatide over placebo, including the percent change in body weight and changes in systolic blood pressure and high-sensitivity C-reactive protein concentration.

**Change in the Apnea–Hypopnea Index**


**Most Common Adverse Events**




The most common adverse events with tirzepatide were gastrointestinal; most were mild to moderate in severity.

#### LIMITATIONS AND REMAINING QUESTIONS

- Long-term cardiovascular outcomes could not be assessed, given the design and relatively short duration of the trials.
- The trials excluded participants who did not have obesity and therefore did not analyze the effect of tirzepatide in people with overweight or normal body-mass index.
- The trials were not designed to assess whether the results differed according to participants' symptoms at baseline.

#### CONCLUSIONS

**In adults with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide given once weekly led to a significantly greater reduction in the apnea–hypopnea index at 52 weeks than placebo.**

**LINKS:** FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

#### FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT05412004

Full citation: Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med 2024;391:1193-205. DOI: 10.1056/NEJMoa2404881

# SYNERGY-NASH

The NEW ENGLAND JOURNAL of MEDICINE

## Tirzepatide for MASH with Liver Fibrosis

A PLAIN LANGUAGE SUMMARY

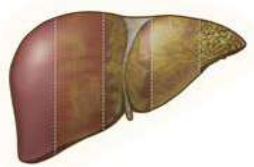
Based on the NEJM publication: Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis by R. Loomba et al. (published June 8, 2024)

**In this trial, researchers assessed the efficacy and safety of once-weekly tirzepatide in persons with metabolic dysfunction–associated steatohepatitis (MASH) and moderate or severe fibrosis.**

**MASH**, formerly known as NASH (nonalcoholic steatohepatitis), is a progressive liver disease characterized by excess fat in the liver, hepatic inflammation, and hepatocyte injury, with or without fibrosis.

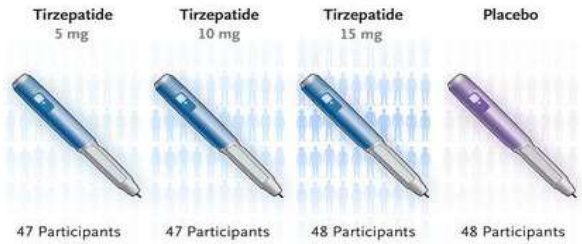
### WHY WAS THE TRIAL DONE?

MASH is associated with liver-related complications and death. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to reduce liver fat and improve biomarkers of MASH and fibrosis in persons with type 2 diabetes. The efficacy and safety of tirzepatide in persons with MASH and moderate or severe fibrosis are unclear.



### HOW WAS THE TRIAL CONDUCTED?

190 adults with a body-mass index (BMI) between 27 and 50, histologically confirmed MASH, and moderate or severe fibrosis received once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at week 52.




### PARTICIPANTS

| | |
|---|---|
| WHO | 190 participants |
| | 18 to 80 years of age |
| | Women: 57%; Men: 43% |
| CLINICAL STATUS | Biopsy-confirmed MASH |
| | Stage 2 or 3 fibrosis |
| | BMI, 27 to 50 |
| | With or without type 2 diabetes mellitus |

### TRIAL DESIGN

- PHASE 2
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 10 COUNTRIES







### RESULTS

The percentage of participants who had resolution of MASH without worsening of fibrosis was significantly higher in all three tirzepatide groups than in the placebo group.

**Resolution of MASH and No Worsening of Fibrosis**

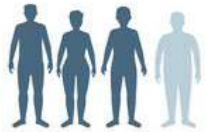
P<0.001 for all three comparisons


Gastrointestinal events were the most common adverse events with tirzepatide and were mostly mild or moderate in severity.

**Adverse Events**


### FIBROSIS STAGE

The percentage of participants who had an improvement (decrease) of at least one fibrosis stage without worsening of MASH (a key secondary end point) also favored the tirzepatide groups.



### LIMITATIONS AND REMAINING QUESTIONS

- The small sample size did not provide adequate statistical power to evaluate the effect of tirzepatide on fibrosis.
- The trial was too short to assess the effect of tirzepatide on major adverse liver outcomes.
- Persons with MASH that had progressed to cirrhosis were not included in the trial.

### CONCLUSIONS

**In participants with MASH and moderate or severe fibrosis, once-weekly tirzepatide at a dose of 5 mg, 10 mg, or 15 mg was more effective than placebo for resolution of MASH without worsening of fibrosis.**

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

### FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04166773

Full citation: Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299-310. DOI: 10.1056/NEJMoa2401943

# SUMMIT Trial

Tirzepatide reduced a composite of heart failure outcomes that included time to first occurrence of urgent HF visit, HF hospitalization, oral diuretic intensification, and CV death (HR 0.62; 95% CI 0.41 - 0.95) at a median follow-up period of 104 weeks compared with placebo, and it improved heart failure symptoms and physical limitations as measured by the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) at the 1-year mark.

The KCCQ-CSS improved by 24.8 points for those randomized to tirzepatide (5, 10, or 15 mg) and by 15 points in the placebo arm.

## Dual Primary Endpoints

**Occurrence of the composite endpoint of CV death and/or HF events (urgent HF visit, HHF, and ODI) over time**

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

## Key Secondary Endpoints

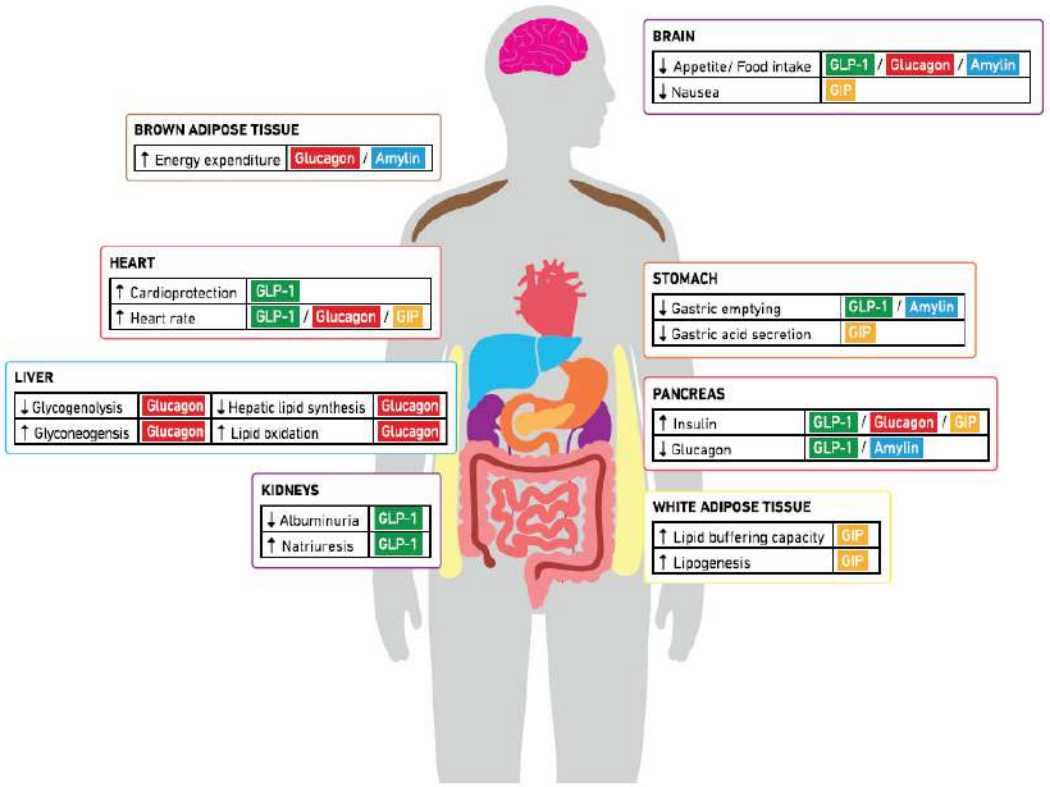
- Change from baseline to Week 52 in exercise capacity, as measured by 6-MWD
- Change from baseline to Week 52 in hs-CRP
- Percent change from baseline to Week 52 in body weight

**Topline Primary Endpoint Results**

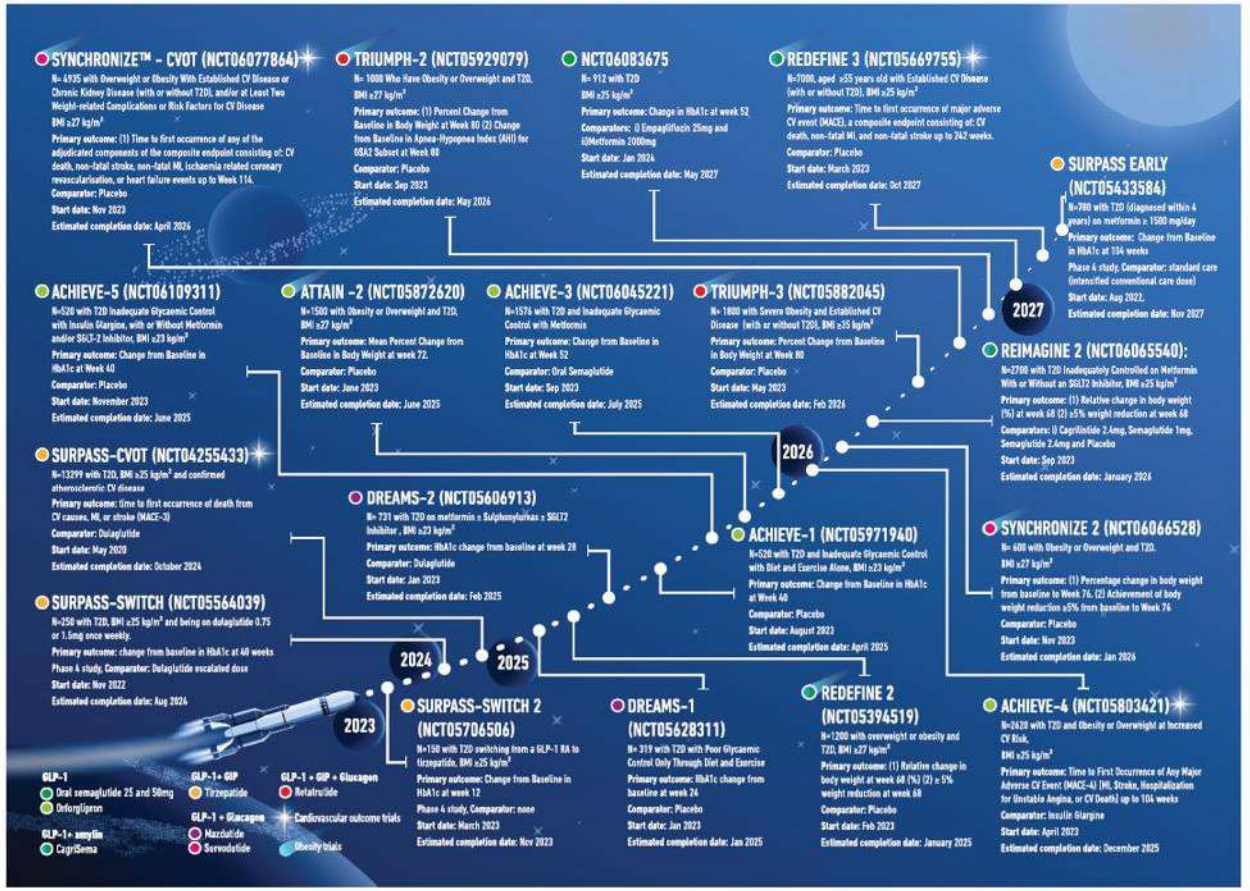
| | | | |
|---|---|---|---|
| Relative risk reduction of time-to-first occurrence of heart failure outcomes (median follow up of 104 weeks) | | -38%<br>Hazard Ratio=0.62<br>95% CI 0.41 to 0.95; P=0.026 | |
| | | **Efficacy Estimand** | **Treatment-Regimen Estimand** |
| Improvements in heart failure symptoms and physical limitations from baseline as measured by the mean change from baseline of KCCQ-CSS | **Tirzepatide MTD** | 24.8 points | 19.5 points |
| | **Placebo** | 15.0 points | 12.7 points |

- CV=Cardiovascular; HF=Heart Failure; HFpEF=Heart Failure With Preserved Ejection Fraction; HHF=Hospitalisation for Heart Failure; hsCRP=High-Se Cardiomyopathy Questionnaire – Clinical Summary Score; ODI=Oral Diuretic Intensification; NYHA=New York Heart Association; TZP=Tirzepatide; 6-M
- https://clinicaltrials.gov/ct2/show/NCT04847557 (Accessed July 07, 2024).

# Incretins: Dual and Triple agonists for DM2 and/or Obesity, ongoing trials




Actions of entero-pancreatic hormones on different organs.
GIP: glucose-dependent insulinotropic polypeptide, GLP-1: glucagon-like peptide-1.




The journey of evidence for the novel molecules for type 2 diabetes and/or obesity – the ongoing phase 3 and phase 4 clinical trials.
BMI: body mass index, CV: cardiovascular, GLP-1: glucagon-like peptide-1, HbA1c: glycated hemoglobin, MACE: Major Adverse Cardiovascular Event, MI: myocardial infarction, RA: Receptor Agonist, SGLT-2: sodium glucose-cotransporter-2, T2D: type 2 diabetes.

Oral glucagon-like peptide-1 receptor agonists and combinations of entero-pancreatic hormones as treatments for adults with type 2 diabetes: where are we now?

Prathima Gogineni*, Eka Melson*, Dimitris Papamargaritis and Melanie Davies

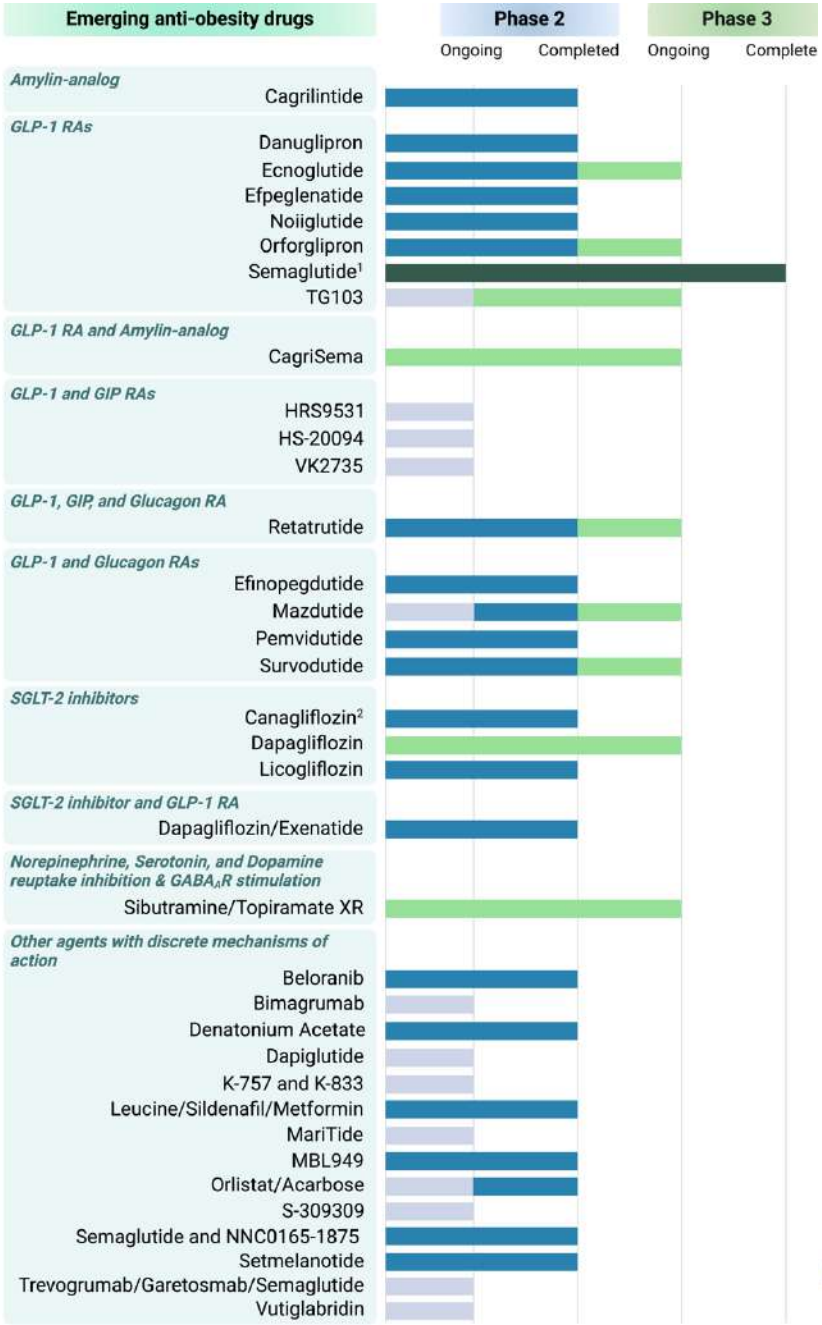
Diabetes Research Centre, University of Leicester College of Life Sciences, Leicester, UK

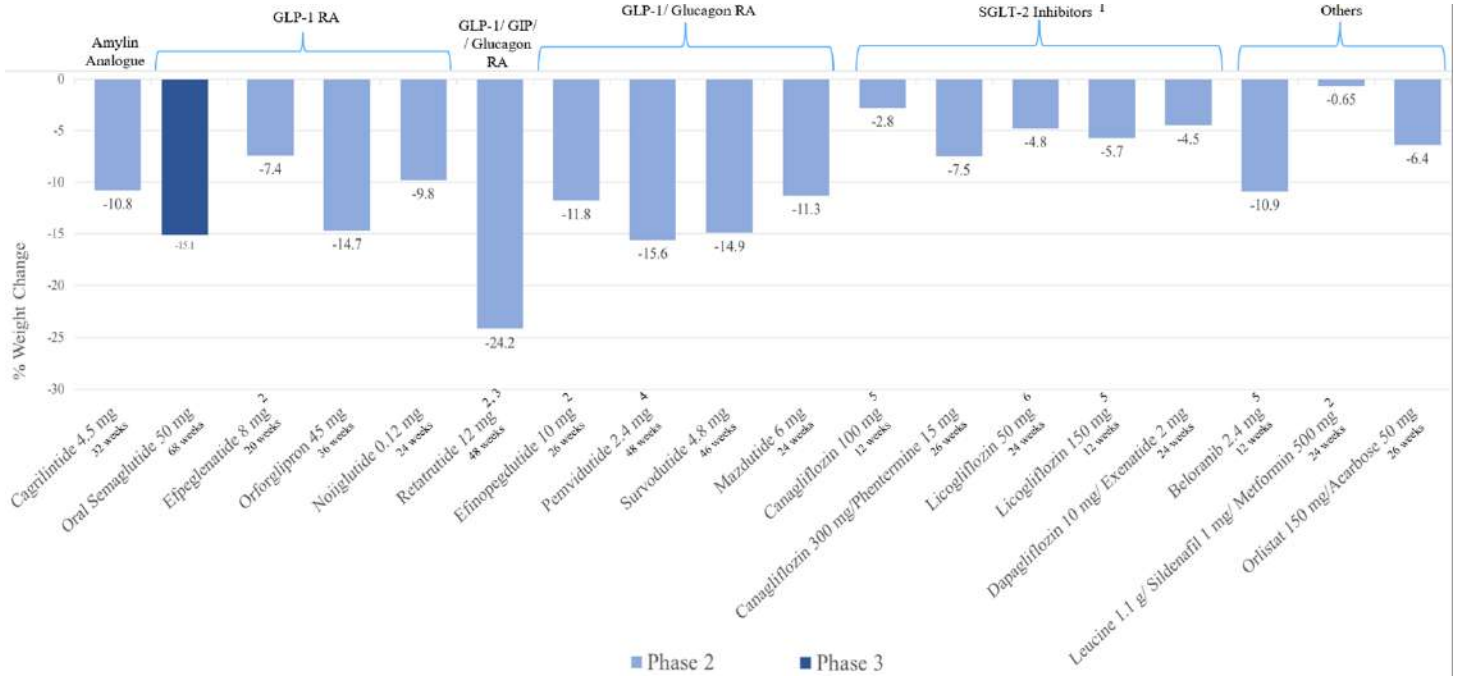
# Emerging anti-obesity drugs

Pharmrev Fast Forward. Published on 20 September 2024 as DOI 10.1124/pharmrev.123.001045 This article has not been copyedited and formatted. The final version may differ from this version.

Emerging Pharmacotherapies for Obesity: A Systematic Review

- SGLT2i
- GLP1 RA
- Doppi e Tripli agonisti incretinici
- SGLT2i+ GLP1 RA




Ongoing Phase 2 | Completed Phase 2 | Ongoing Phase 3 | Completed Phase 3

# ns-MRA

Nonsteroidal mineralocorticoid receptor antagonists (MRAs) are a new class of drugs developed to address the medical need for effective and safer treatment to protect the kidney and the heart in patients with diabetic kidney disease (DKD). There are several drugs within this class at varying stages of clinical development. Finerenone is the first nonsteroidal MRA approved for treating patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)

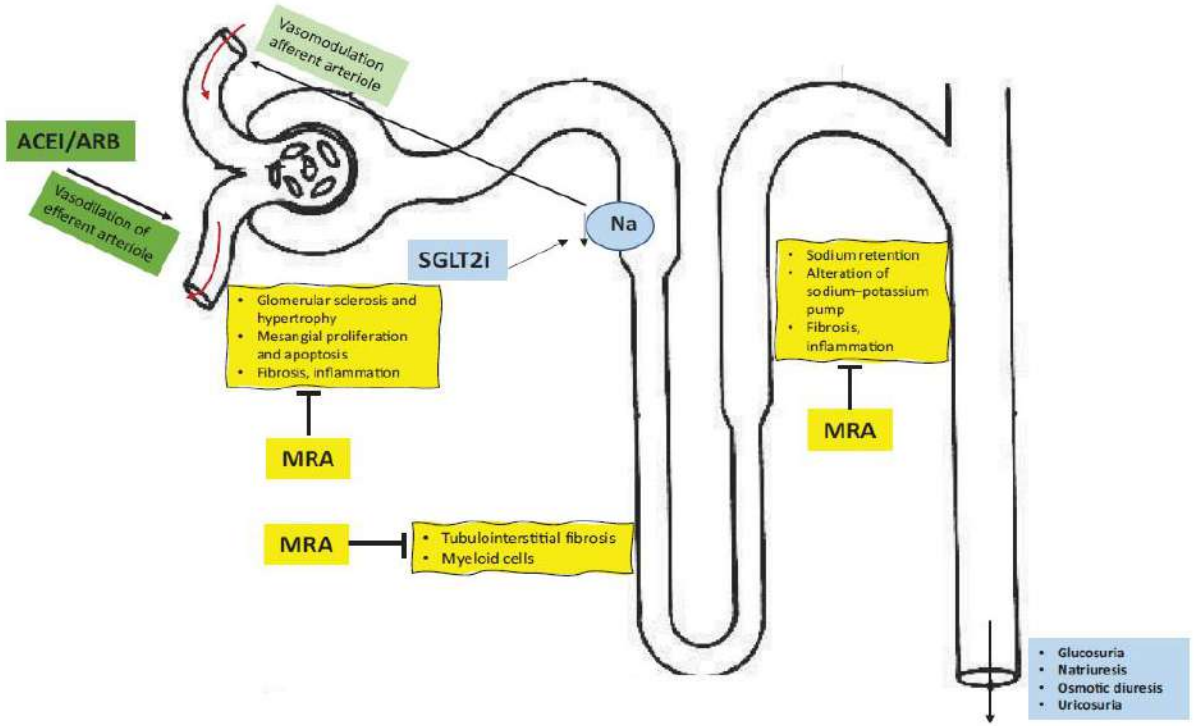


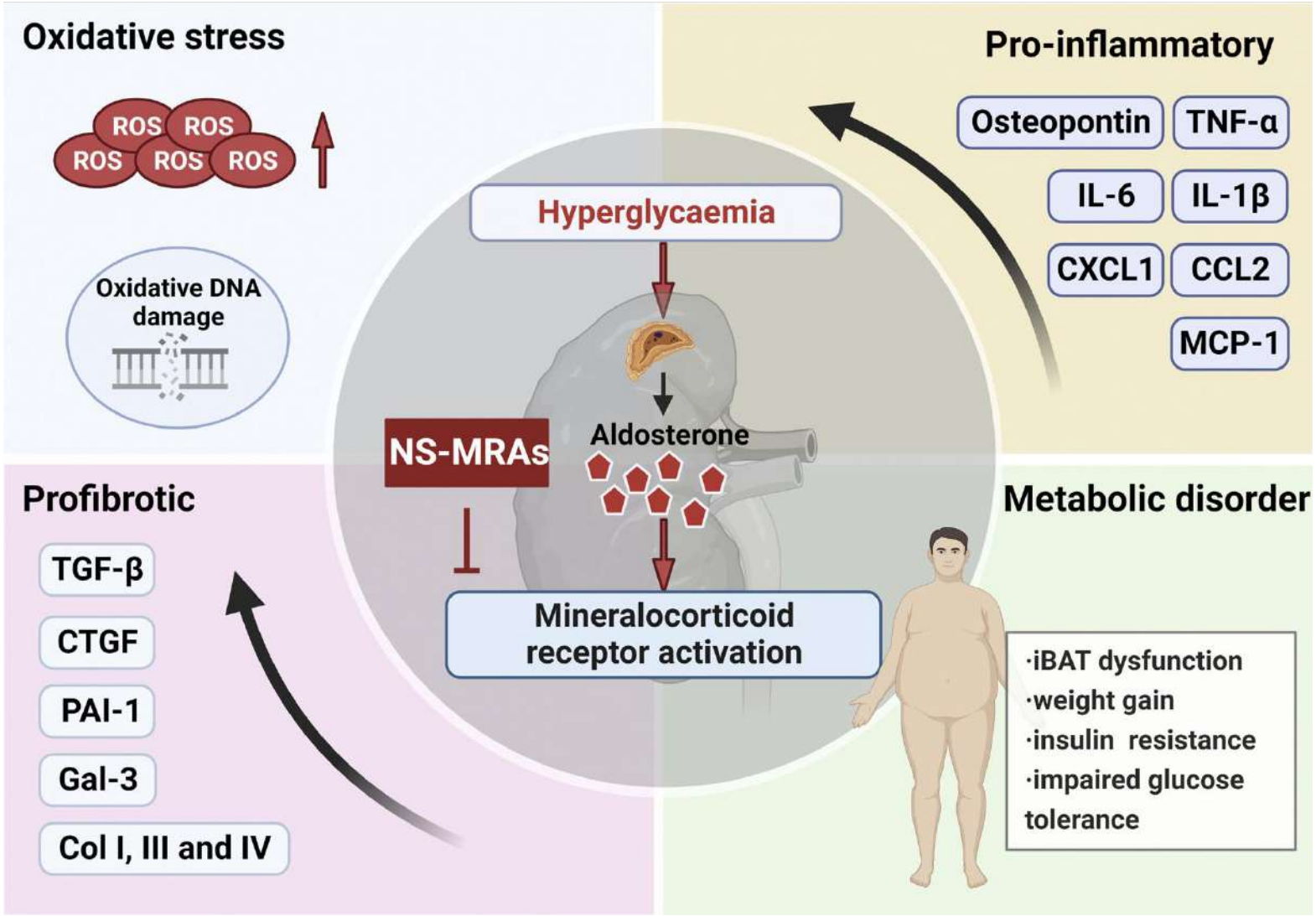

Figure 1. Mechanisms of action of ACE inhibitors/ARB, SGLT2 inhibitors and MRA on kidneys. ARB: angiotensin receptor blockers; ACE: angiotensin converting enzyme; SGLT2: sodium-glucose cotransporter type 2; MRA: mineralocorticoid receptor antagonists.

| Drugs | Therapeutic mechanisms for albuminuria in DKD | References |
|---|---|---|
| Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers | 1. The glomerular pressure is decreased due to the relative relaxation of the efferent arterioles<br>2. The reduction of glomerular albumin leakage is achieved by decreasing the surface area of the filtration barrier through glomerular contraction<br>3. Exerting an anti-inflammatory effect and decreasing proteinuria | 1. Lovshin et al. (2018)<br>2. Nistala et al. (2021)<br>3. Cantero-Navarro et al. (2021); Crowley et al. (2024) |
| SGLT2 inhibitors | 1. Block the reabsorption of sodium and glucose by SGLT2, and condense the afferent arterioles<br>2. Increase podocyte autophagy, reduce podocyte lipid content, and protect podocyte<br>3. Inhibition of YAP/TAZ activation and CYP4A/20-HETE signaling to alleviate tubulointerstitial fibrosis or glomerulosclerosis | 1. Muskiet et al. (2019); Warren et al. (2019); Hartman et al. (2020); Kogot-Levin et al. (2020); Wang et al. (2021a); González-Albarrán et al. (2022); Kim and Kim (2022); Salvatore et al. (2022)<br>2. DeFronzo et al. (2021); Chen et al. (2022); Durcan et al. (2022)<br>3. Dia et al. (2023); Feng et al. (2023) |
| Nonsteroidal mineralocorticoid receptor antagonists | 1. Mitigate the pathological alterations of glomerular and tubular injury by attenuating renal inflammation and fibrosis<br>2. Alleviate intraglomerular pressure through reduction of glomerular hyperfiltration | 1. Agarwal et al. (2021); Barrera-Chimal et al. (2022a)<br>2. Barrera-Chimal et al. (2022a); Kim et al. (2023); Ortiz et al. (2023) |

**Cardiorenal benefits of finerenone: protecting kidney and heart**

José R. González-Juanatey[a], Jose Luis Górriz[b], Alberto Ortiz[c], Alfonso Valle[d], Maria Jose Soler[e] and Lorenzo Facila[f]

# Iperglicemia e Attivazione recettore mineralcorticoidi




In the progression of DKD is that the diabetic environment induces local production of aldosterone in the kidney and triggers hyperactivation of MR.

Mechanistically, diabetic kidney damage is triggered by the following four pathways, and NS-MRAs can block and delay its disease progression.

First, NS-MRAs alleviate oxidative stress by attenuating oxidative DNA damage and reducing the production of reactive oxygen species (ROSs).

The second major mechanism, NS-MRAs reduce the upregulation of proinflammatory mediators, including tumor necrosis factor alpha (TNF-a), osteopontin, interleukin 6 (IL-6), interleukin-1beta (IL-1b), plasminogen activator inhibitor 1 (CXCL1), CC-chemokine ligand 2 (CCL2), and monocyte chemoattractant protein- 1 (MCP-1).

Simultaneously, this effect leads to reduced collagen deposition and fibrosis in the tubulointerstitium, such as transforming growth factorb TGF-b), connective tissue growth factor (CTGF), plasminogen activator inhibitor 1 (PAI-1), galectin-3 (Gal-3), collagen I, III, and IV (Col I, III, and IV).

Other effects of alleviation of metabolic disorders with NS-MRAs in the renal diabetic models include improvement of iBAT dysfunction, weight gain, insulin resistance,and glucose tolerance. Image created with BioRender and published with permission. DKD, diabetic kidney disease; MR, mineralocorticoid receptor.

Therapeutic perspective: evolving evidence of nonsteroidal mineralocorticoid receptor antagonists in diabetic kidney disease

Lan Yao,[1,2] Xianhui Liang,[1,2] and Pei Wang[1,2]
[1]Blood Purification Center, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China and [2]Research Institute of Nephrology, Zhengzhou University, Zhengzhou, People's Republic of China

**Cardiorenal benefits of finerenone: protecting kidney and heart**

José R. González-Juanatey[a], Jose Luis Górriz[b], Alberto Ortiz[c], Alfonso Valle[d], Maria Jose Soler[e] and Lorenzo Facila[f]

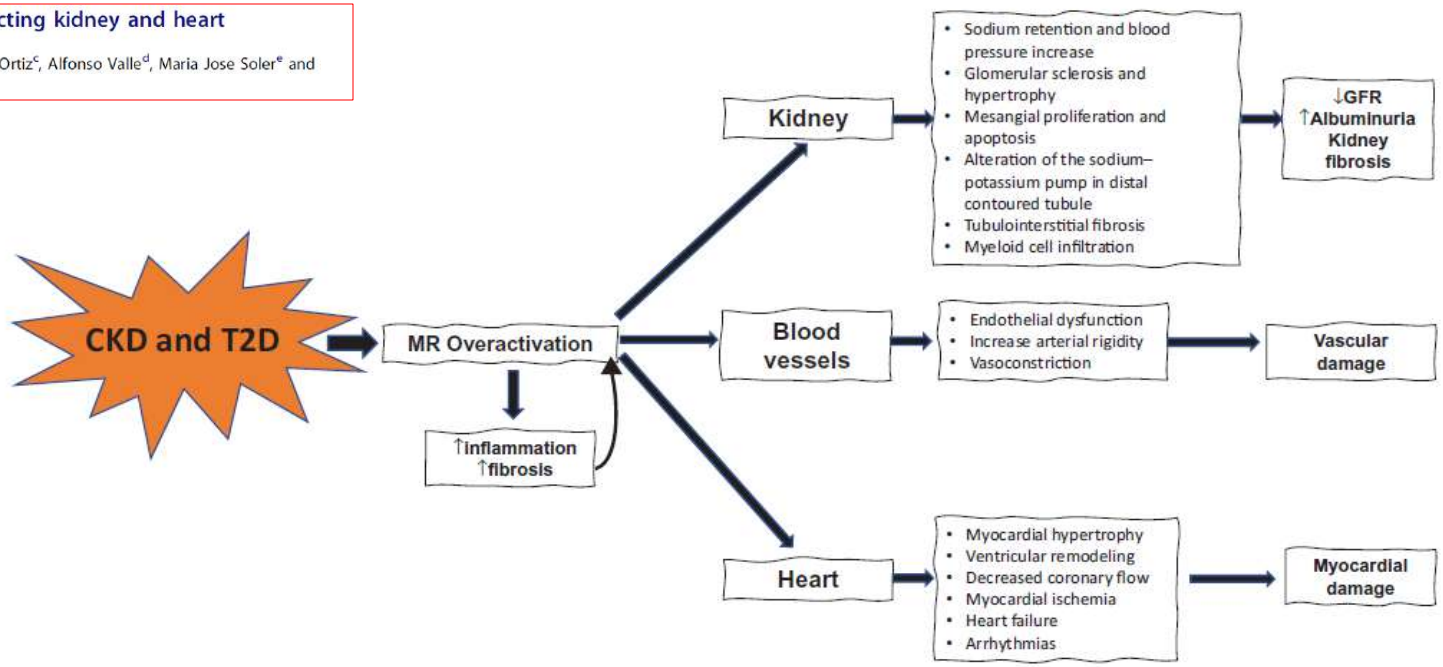
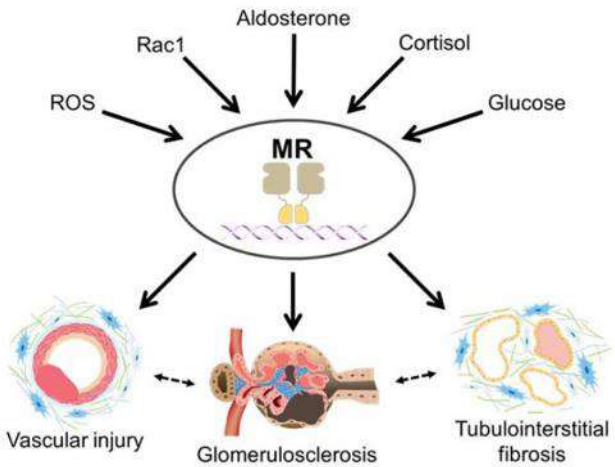



**Figure 2.** Consequences of hyperactivation of the mineralocorticoid receptor in persons with chronic kidney disease and diabetes. MR: mineralocorticoid receptor; T2D: type 2 diabetes. Figure was made with reference data [4,19–22,32,33].




| Target cells | Pathological consequences |
|---|---|
| Vascular smooth muscle cells | Vascular remodeling |
| Podocytes | Gloemrulosclerosis and impaired glomerular filtration barrier |
| Mesangial cells | Cell proliferation and extracellular matrix accumulation |
| Endothelial cells | Endothelial dysfunction and increased sieving coefficient |
| Immune cells | Imbalance between M1 and M2 macrophages and upregulation of inflammatory cytokines |
| Fibroblasts | Cell proliferation and extracellular matrix accumulation |

**Figure 1.** Mechanisms that trigger MR overactivity and the diverse pathological consequences. ROS, reactive oxygen species; MR, mineralocorticoid receptor.

Review

**Mineralocorticoid Receptor Antagonists for Preventing Chronic Kidney Disease Progression: Current Evidence and Future Challenges**

Wataru Fujii and Shigeru Shibata *

# Finerenone

| | Steroidal MRAs | | Finerenone |
|---|---|---|---|
| |  Spironolactone |  Eplerenone |  Finerenone |
| Structural properties | Flat (steroidal) | Flat (steroidal) | Bulky (nonsteroidal) |
| Potency to MR | +++ | + | +++ |
| Selectivity to MR | + | ++ | +++ |
| CNS penetration | + | + | - |
| Sexual side effects | ++ | (+) | - |
| Half-life | > 20 hours | 4-6 hours | 2-3 hours |
| Active metabolites | ++ | - | - |
| Effect on BP | +++ | ++ | + |

Figure 3. A table summarizing comparison between steroidal MRAs (spironolactone and eplerenone) and nonsteroidal MRA finerenone [37]. Figure (by Kintscher, Bakris, and Kolkhof) reused under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license. BP, blood pressure; CNS, central nervous system; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist.

ESC European Society of Cardiology
European Heart Journal (2022) 43, 2931–2945
https://doi.org/10.1093/eurheartj/ehac299
STATE OF THE ART REVIEW
*Heart failure and cardiomyopathies*

## Non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease

**Arjun K. Pandey[1], Deepak L. Bhatt[2], Francesco Cosentino[3], Nikolaus Marx[4], Ori Rotstein[5], Bertram Pitt[6], Ambarish Pandey[7], Javed Butler[8], and Subodh Verma[9]***

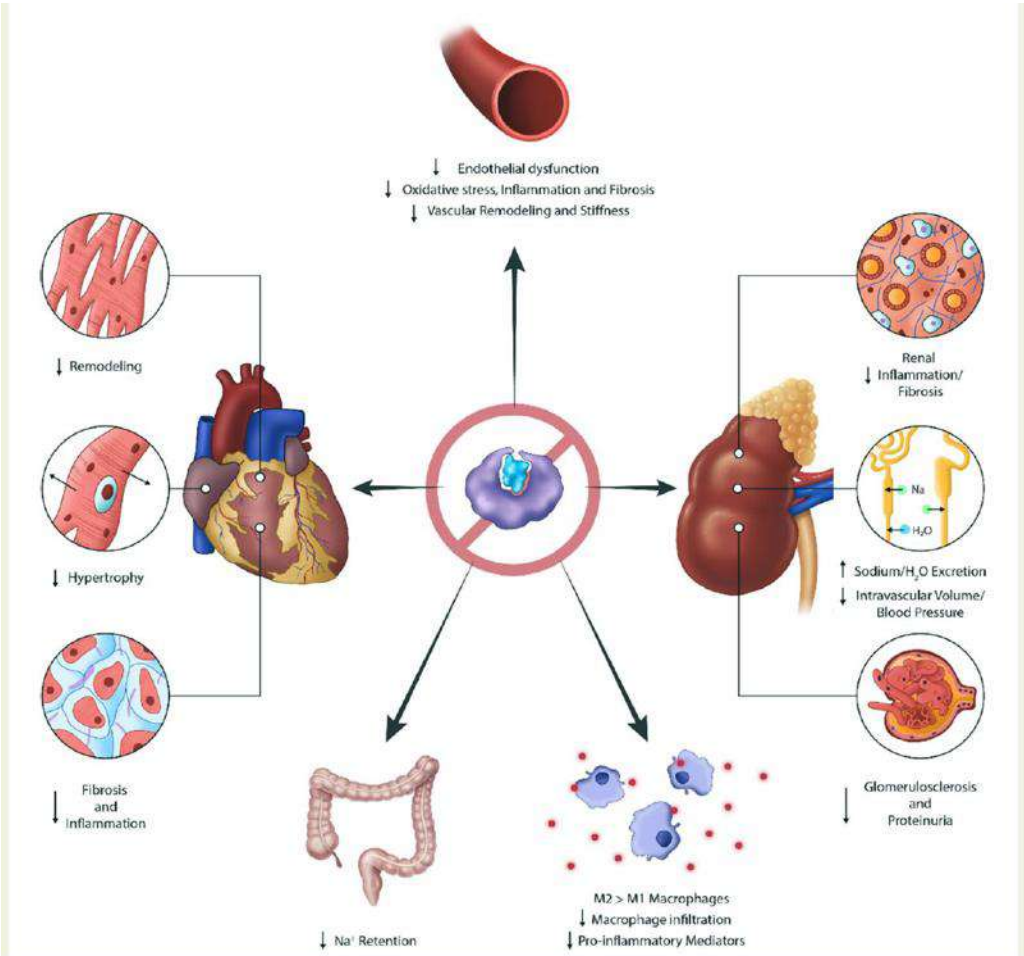
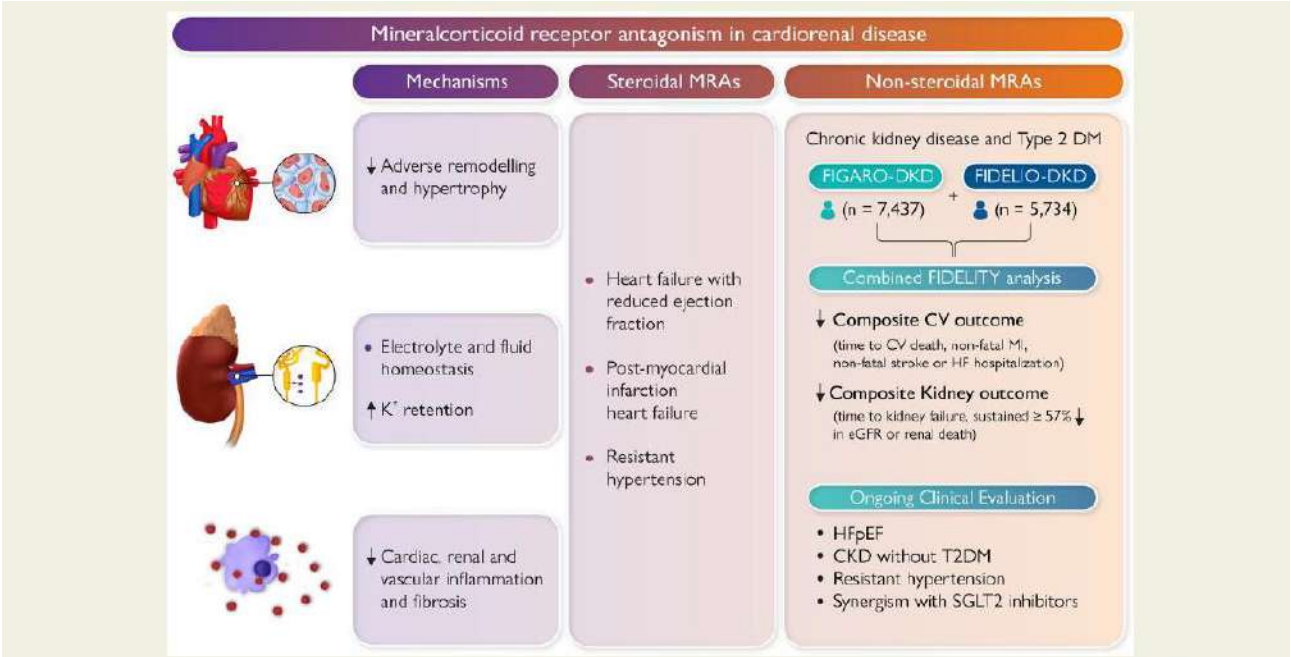



**Figure 2** Effects of mineralocorticoid receptor inhibition across various organ systems. Mineralocorticoid receptor antagonism with steroidal or non-steroidal agents affects many organ systems. Mineralocorticoid receptor antagonists reduce sodium and fluid retention in the renal tubules and gastrointestinal tract. Mineralocorticoid receptor antagonists have beneficial anti-inflammatory, anti-remodelling, and anti-fibrotic properties in the kidneys, heart, and vasculature.




Non-steroidal mineralocorticoid antagonists (MRAs) reduce adverse remodelling, inflammation, and fibrosis in the heart, kidneys, and vasculature. Finerenone has been shown to improve cardiovascular and kidney outcomes in patients with chronic kidney disease and Type 2 diabetes. Non-steroidal MRAs are currently being investigated in other settings such as heart failure.

ESC European Heart Journal (2023) 44, 2931–2945 https://doi.org/10.1093/eurheartj/ehac299
STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

**Non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease**

Arjun K. Pandey[1], Deepak L. Bhatt[2], Francesco Cosentino[3], Nikolaus Marx[4], Ori Rotstein[5], Bertram Pitt[6], Ambarish Pandey[7], Javed Butler[8], and Subodh Verma[9]*

**Cardiorenal benefits of finerenone: protecting kidney and heart**

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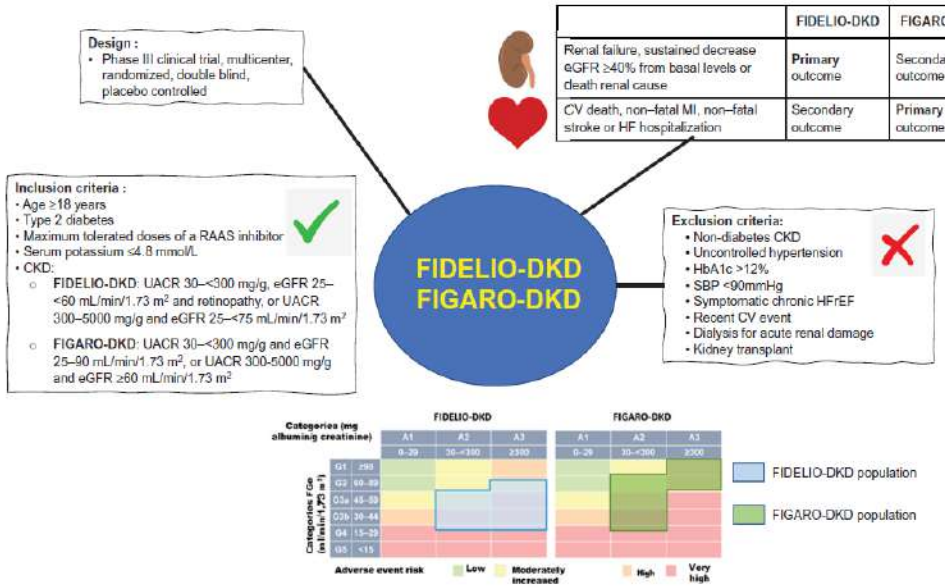


| | FIDELIO-DKD | FIGARO-DKD |
|---|---|---|
| Renal failure, sustained decrease eGFR ≥40% from basal levels or death renal cause | Primary outcome | Secondary outcome |
| CV death, non–fatal MI, non–fatal stroke or HF hospitalization | Secondary outcome | Primary outcome |

**Table 3.** Main results of the FIDELIO-DKD, FIGARO-DKD studies and the combined FIDELITY analysis.

| | FIDELIO-DKD HR (95% CI) | FIGARO-DKD HR (95% CI) | FIDELITY HR (95% CI) |
|---|---|---|---|
| Composite CV primary variable[a] | 0.86 (0.75–0.99) | 0.87 (0.76–0.98) | 0.86 (0.78–0.95) |
| CV death | 0.86 (0.68–1.08) | 0.90 (0.74–1.09) | 0.88 (0.76–1.02) |
| Myocardial infarction non-fatal | 0.80 (0.58–1.09) | 0.99 (0.76–1.31) | 0.91 (0.74–1.12) |
| Non-fatal stroke | 1.03 (0.76–1.38) | 0.97 (0.74–1.26) | 0.99 (0.82–1.21) |
| Heart failure hospitalization | 0.86 (0.68–1.08) | 0.71 (0.56–0.90) | 0.78 (0.66–0.92) |

CI: 95% confidence interval; CV: cardiovascular; HR: Hazard ratio. Table was prepared with data from references [29–31].
[a]Time to first CV death, nonfatal myocardial infarction, non-fatal stroke, or heart failure hospitalization.

L'analisi combinata dei due studi (FIDELITY) ha dimostrato una diminuzione significativa del rischio di un outcome composito CV (MACE e ospedalizzazione per scompenso cardiaco) e di un outcome composito renale; in particolare la **riduzione del rischio di progressione della CKD** era del 23% e **dell'inizio della dialisi** del 20%.

# KDIGO/ESC e ns-MRA

**Recommendation 3.8.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 $m^2$, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.**

Practice Point 3.8.1: Nonsteroidal MRA are most appropriate for adults with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Practice Point 3.8.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.8.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 26).

Practice Point 3.8.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 3.8.5: A steroidal MRA may be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among people with a low GFR.

Practice Point 3.8.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.8.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 26).

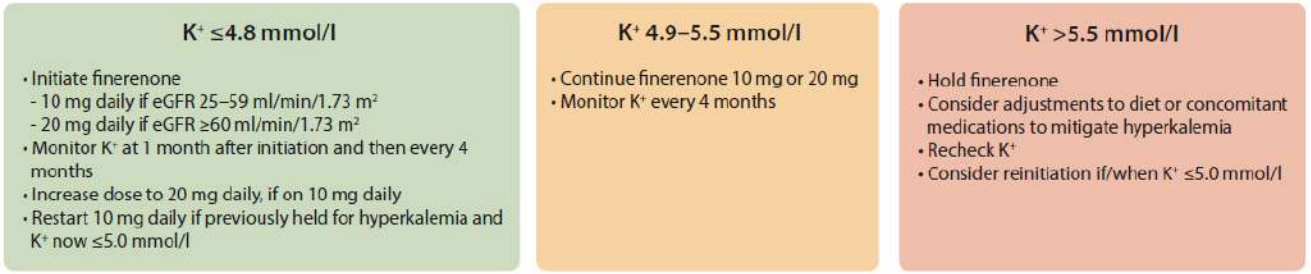


**Figure 26| Serum potassium monitoring during treatment with a nonsteroidal mineralocorticoid receptor antagonist (MRA) (finerenone).** Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD). The Work Group considers these potassium thresholds to be conservative, and it may be considered appropriate to continue MRAs in people with potassium of 5.5–6.0 mmol/l. This algorithm could be used for steroidal MRA. The US Food and Drug Administration (FDA) has approved initiation of $K^+ < 5.0$ mmol/l. This figure is guided by trial design and the FDA label and may be different in other countries. Serum creatinine/estimated glomerular filtration rate (eGFR) should be monitored concurrently with serum potassium. Reproduced from Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int.* 2022;102:S1–S127.[23]

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

## Focused update 2023 delle linee guida ESC 2021 per la diagnosi e il trattamento dello scompenso cardiaco acuto e cronico

Tabella 4 delle raccomandazioni – **Raccomandazioni per la prevenzione dello scompenso cardiaco nei pazienti con diabete mellito di tipo 2 e malattia renale cronica**

| Raccomandazioni | Classe[a] | Livello[b] |
|---|---|---|
| Nei pazienti con T2DM e CKD[c] è raccomandato il trattamento con inibitori di SGLT2 per ridurre il rischio di ospedalizzazione per HF e di morte CV[35]. | I | A |
| Nei pazienti con T2DM e CKD[c] è raccomandato il trattamento con finerenone per ridurre il rischio di ospedalizzazione per HF[10,11,34,40]. | I | A |

# Elementi da definire nel prossimo futuro

- **Ruolo delle Terapie di Associazione negli algoritmi terapeutici** in particolare in termini di RCV, protezione renale, calo ponderale, effetti epatici, etc.
Esempi:
GLP1- RA e Sglt2i
Dual or triple incretin agonist e Sglt2i
Ns- MRA e Sglt2i
Ns-MRA e GLP1-RA

- **Sostenibilità dell'aumento dei costi della spesa farmaceutica**

**- Diversi medici specialisti** (Cardiologo-Nefrologo-Diabetologo-Internista) e **MMG valutano il paziente** e possono/potranno prescrivere diverse classi di farmaci, il punto critico è che dovrebbero **essere fornite indicazioni allineate** che ad oggi talvolta putroppo non lo sono