
# Obesità e diabete mellito tipo 2: come affrontare la sfida

*Cesare Miranda*

*SSD Endocrinologia e Mal.del Metabolismo*

*Pordenone- ASFO*

- Il dr. …CESARE MIRANDA…. dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

-…NOVO NORDISK……

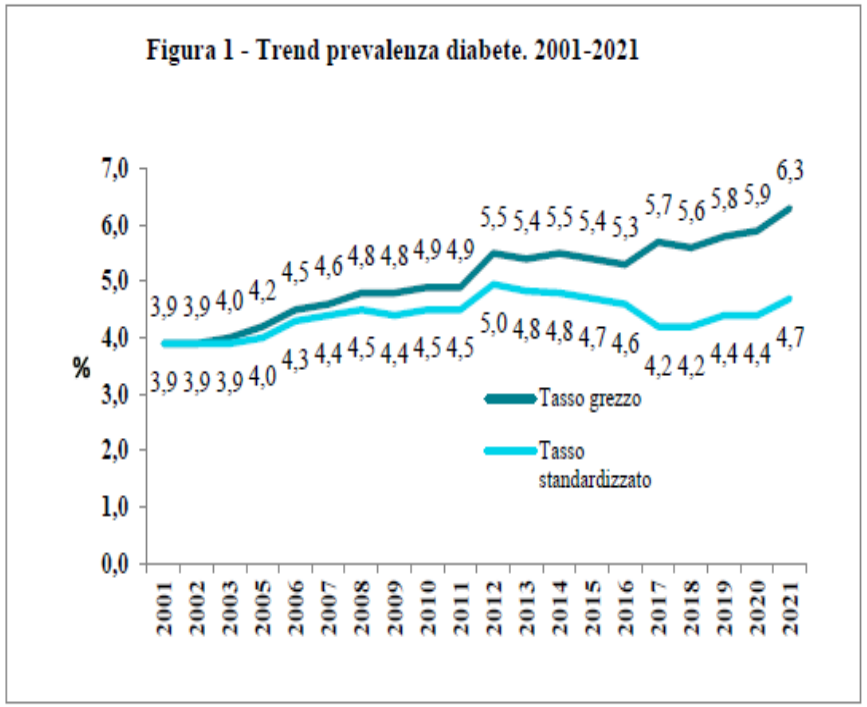
-……..

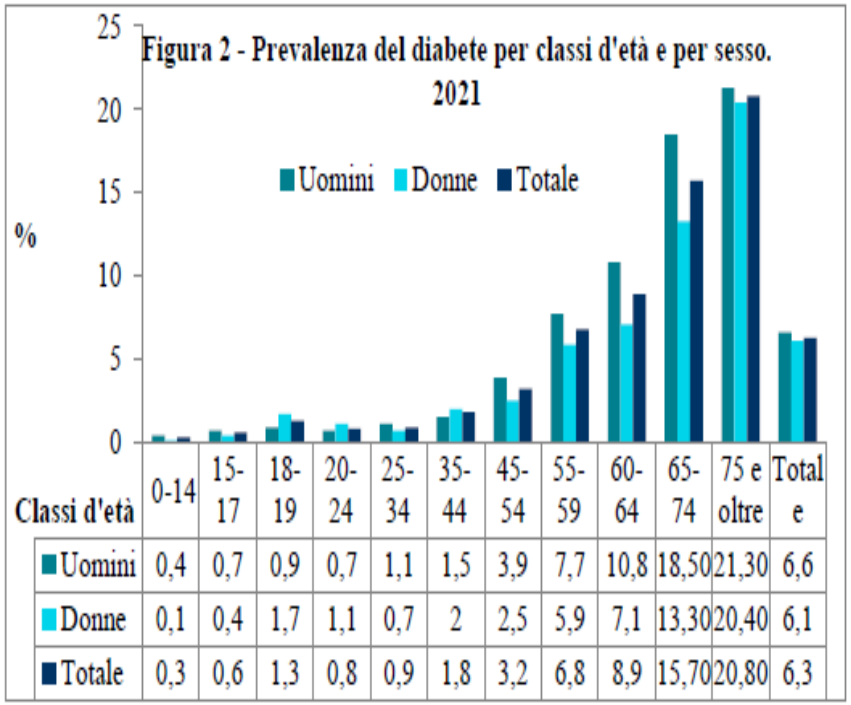
-……..

-…….

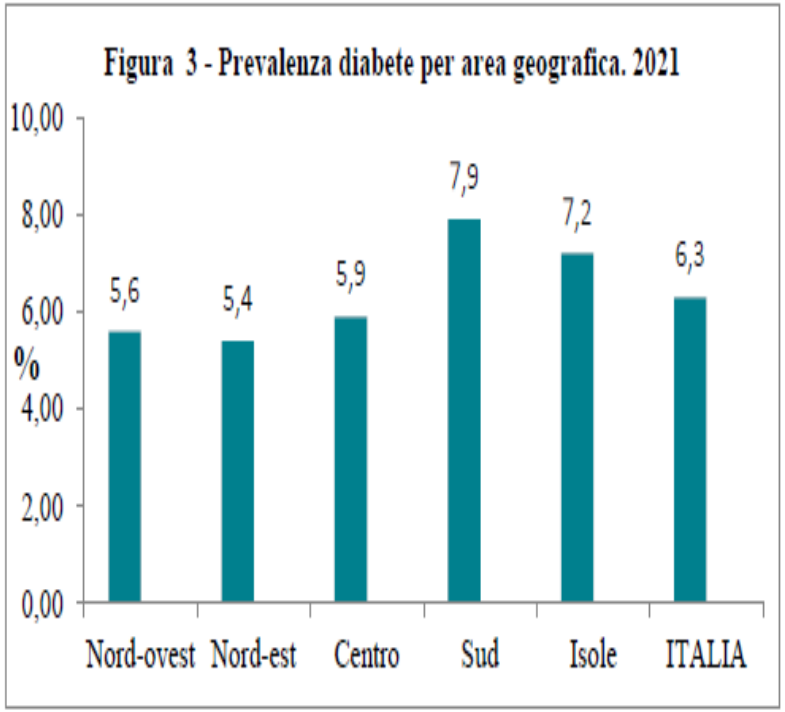
- *Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

# Prevalenza del Diabete in Italia



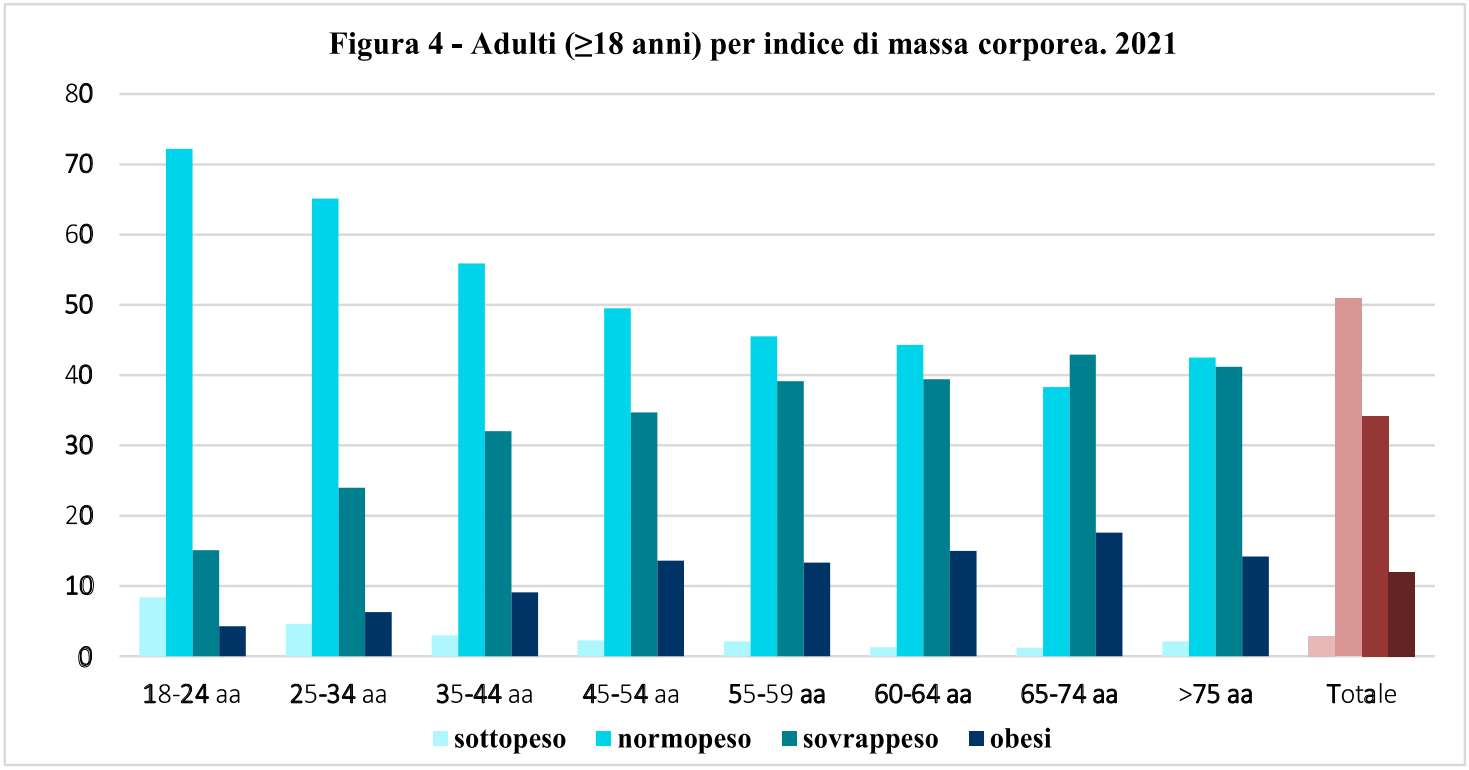




| Classi d'età | 0-14 | 15-17 | 18-19 | 20-24 | 25-34 | 35-44 | 45-54 | 55-59 | 60-64 | 65-74 | 75 e oltre | Totale |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Uomini | 0,4 | 0,7 | 0,9 | 0,7 | 1,1 | 1,5 | 3,9 | 7,7 | 10,8 | 18,50 | 21,30 | 6,6 |
| Donne | 0,1 | 0,4 | 1,7 | 1,1 | 0,7 | 2 | 2,5 | 5,9 | 7,1 | 13,30 | 20,40 | 6,1 |
| Totale | 0,3 | 0,6 | 1,3 | 0,8 | 0,9 | 1,8 | 3,2 | 6,8 | 8,9 | 15,70 | 20,80 | 6,3 |




**17th Italian Barometer Diabetes Report 2024**

# Prevalenza dell'eccesso ponderale in Italia

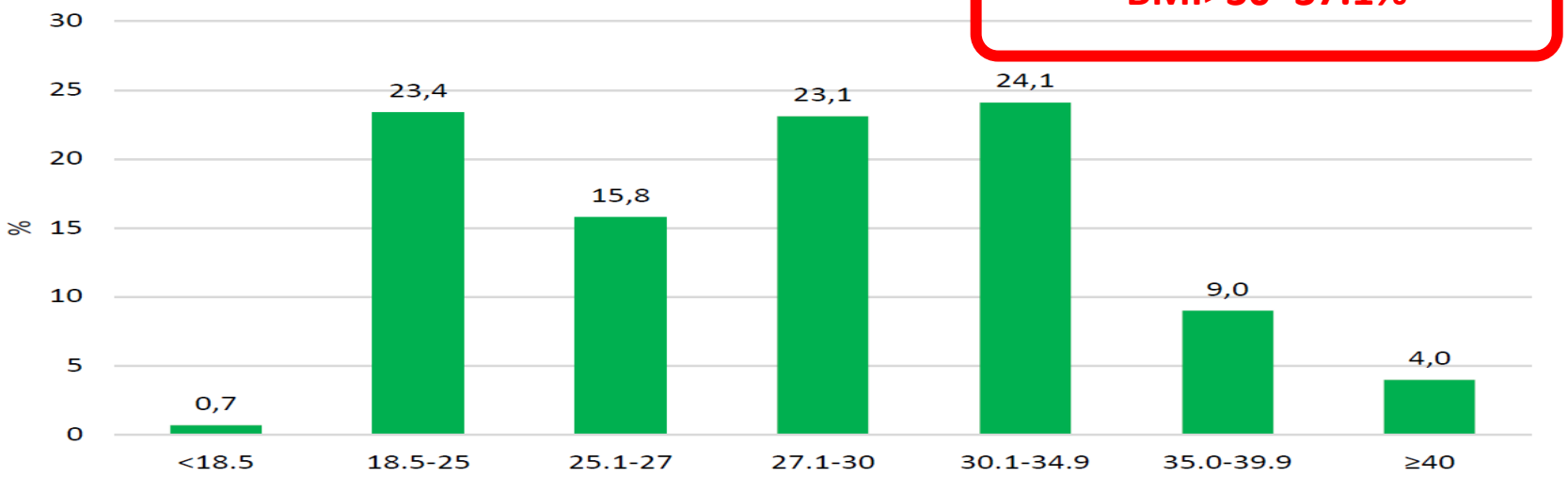




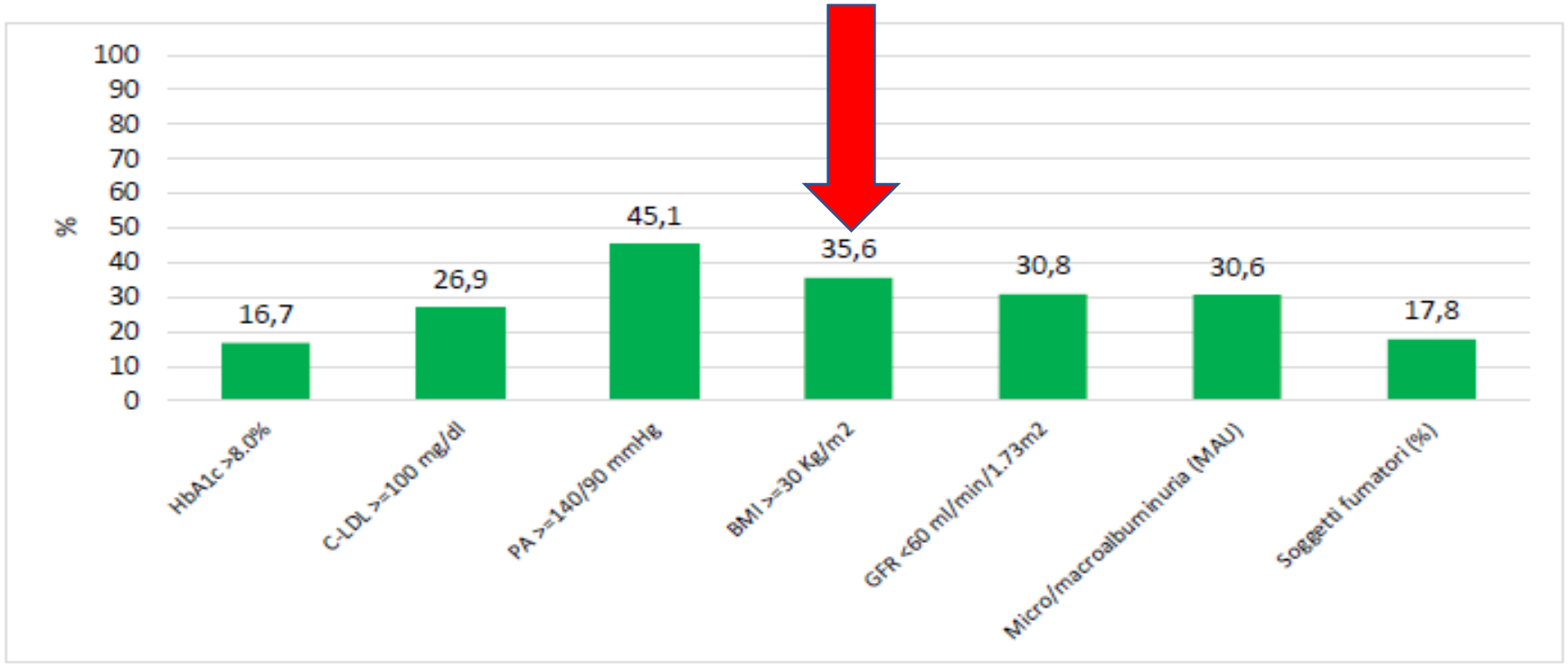
**17th Italian Barometer Diabetes Report 2024**


## Andamento per 7 classi del BMI (%)

**BMI>30=37.1%**







# Caratteristiche dei paziente DMT2- Annali Regionali AMD 2022 - FVG

Livelli medi del BMI (Kg/m²)

| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BMI (Kg/m²) | 29,7± 5,2 | 29,8± 5,3 | 29,7± 5,3 | 29,7± 5,4 | 29,8± 5,4 | 29,7± 5,4 | 29,6± 5,4 | 29,5± 5,4 | 29,5± 5,4 | 29,4± 5,5 | 29,6± 5,5 |

| Kg/m² | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0-18,4 | 0,3 | 0,3 | 0,3 | 0,3 | 0,4 | 0,4 | 0,5 | 0,5 | 0,5 | 0,5 | 0,4 |
| 18,5-25,0 | 16,5 | 16,9 | 16,9 | 17,3 | 17,9 | 17,9 | 18,3 | 19,2 | 19,4 | 20,5 | 19,7 |
| 25,1-27,0 | 15,2 | 14,2 | 15,0 | 15,0 | 14,6 | 14,8 | 15,0 | 15,2 | 15,2 | 15,2 | 15,2 |
| 27,1-30,0 | 25,8 | 25,3 | 25,0 | 24,6 | 24,1 | 23,9 | 23,6 | 23,3 | 23,7 | 23,4 | 23,2 |
| 30,1-34,9 | 27,7 | 28,3 | 27,7 | 27,7 | 27,6 | 27,9 | 27,8 | 27,2 | 26,5 | 25,9 | 26,3 |
| 35,0-39,9 | 10,4 | 10,7 | 10,6 | 10,5 | 11,0 | 10,7 | 10,5 | 10,2 | 10,4 | 10,1 | 10,4 |
| ≥40 | 4,0 | 4,2 | 4,4 | 4,5 | 4,5 | 4,4 | 4,4 | 4,3 | 4,2 | 4,3 | 4,7 |

**BMI >30= 41,4%**

# Obesità: cambio di paradigma

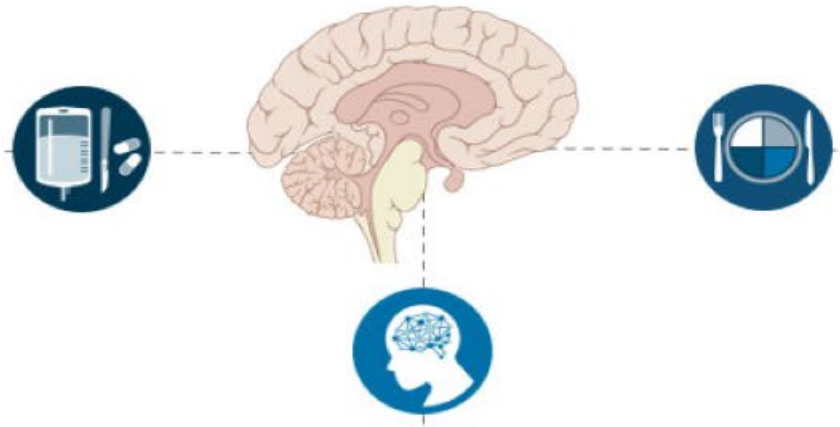

Rueda-Clausen CF, Poddar M, Lear SA, Poirier P, Sharma AM. Canadian Adult Obesity Clinical Practice Guidelines: Assessment of People Living with Obesity.
Available from:https://obesitycanada.ca/guidelines/nutrition. Accessed 11/11/2024

# Ruolo del cervello nel controllo dell'appetito

**Homeostatic system[1,2]**

- **CCK, GLP-1, OXM, and other hormones** increase satiety
- **Ghrelin** increases hunger

**Medication and surgery**



**Executive function[4]**

- **Behavioral interventions** to empower sustainable control of eating

**Lifestyle**

**Hedonic system[3]**

- **Dopamine** controls wanting, motivation/ drive to eat
- **Opioid and cannabinoid receptors** control liking, or the pleasure associated with food

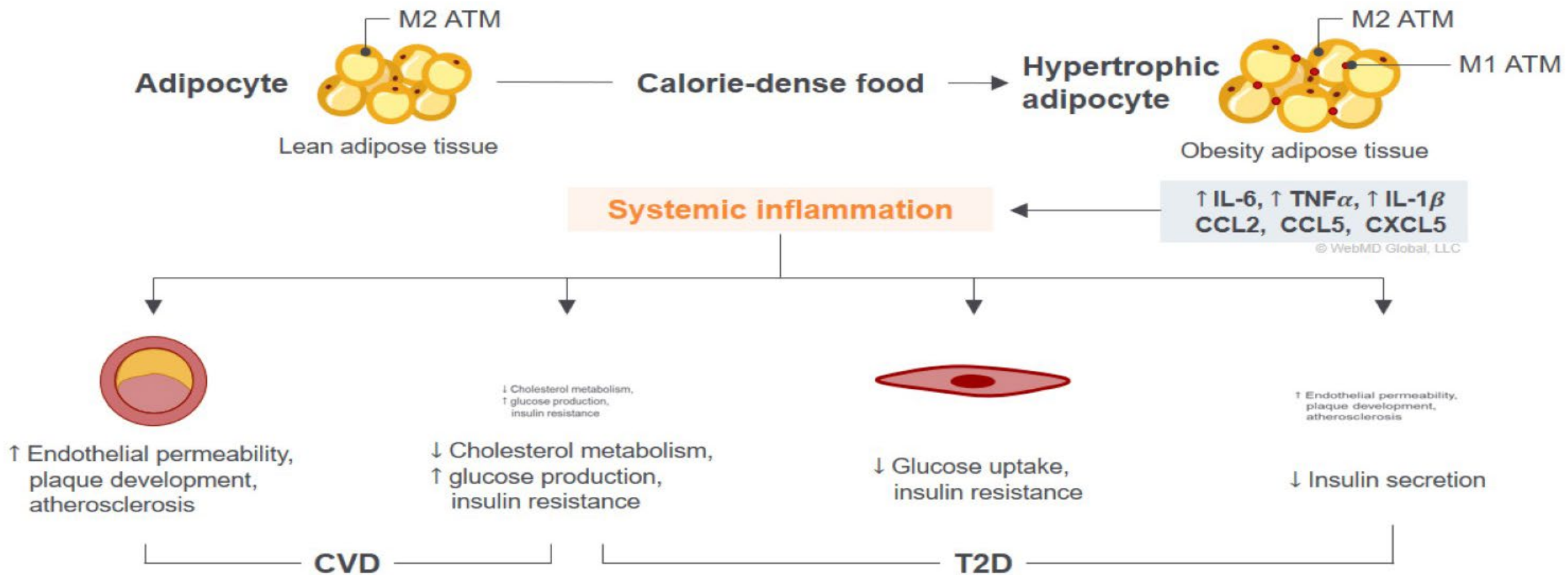
**Psychology**



OXM, oxyntomodulin.

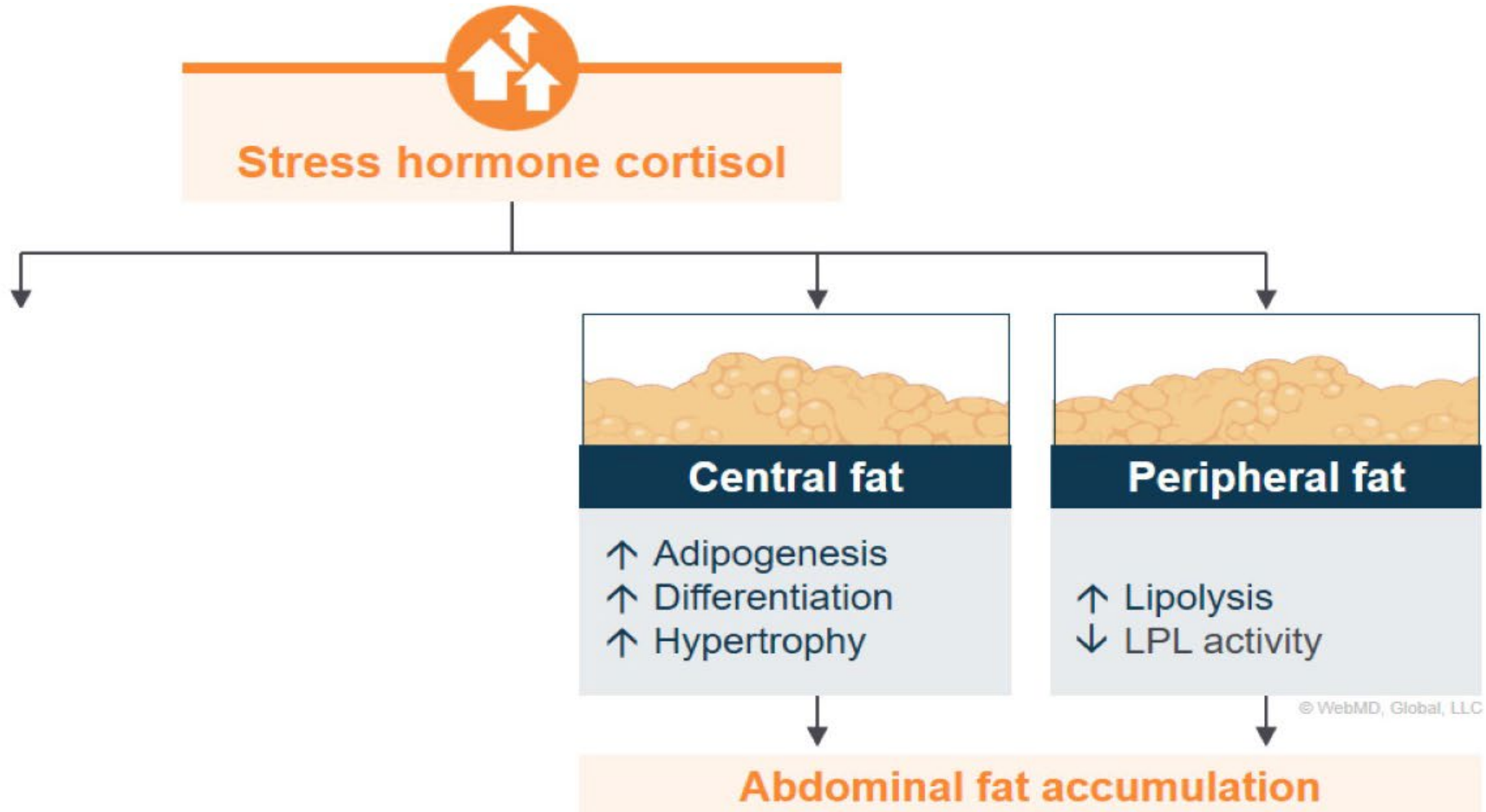
1. Badman MK, et al. Science. 2005;307:1909-1914; 2. van Bloemendaal L, et al. Diabetes. 2014;63:4186-4196; 3. Berridge KC, et al. Brain Res. 2010;1350:43-64; 4. Vallis M. Clin Obes. 2019;9:e12299.

# Conseguenze dell'infiammazione del tessuto adiposo nell'obesità



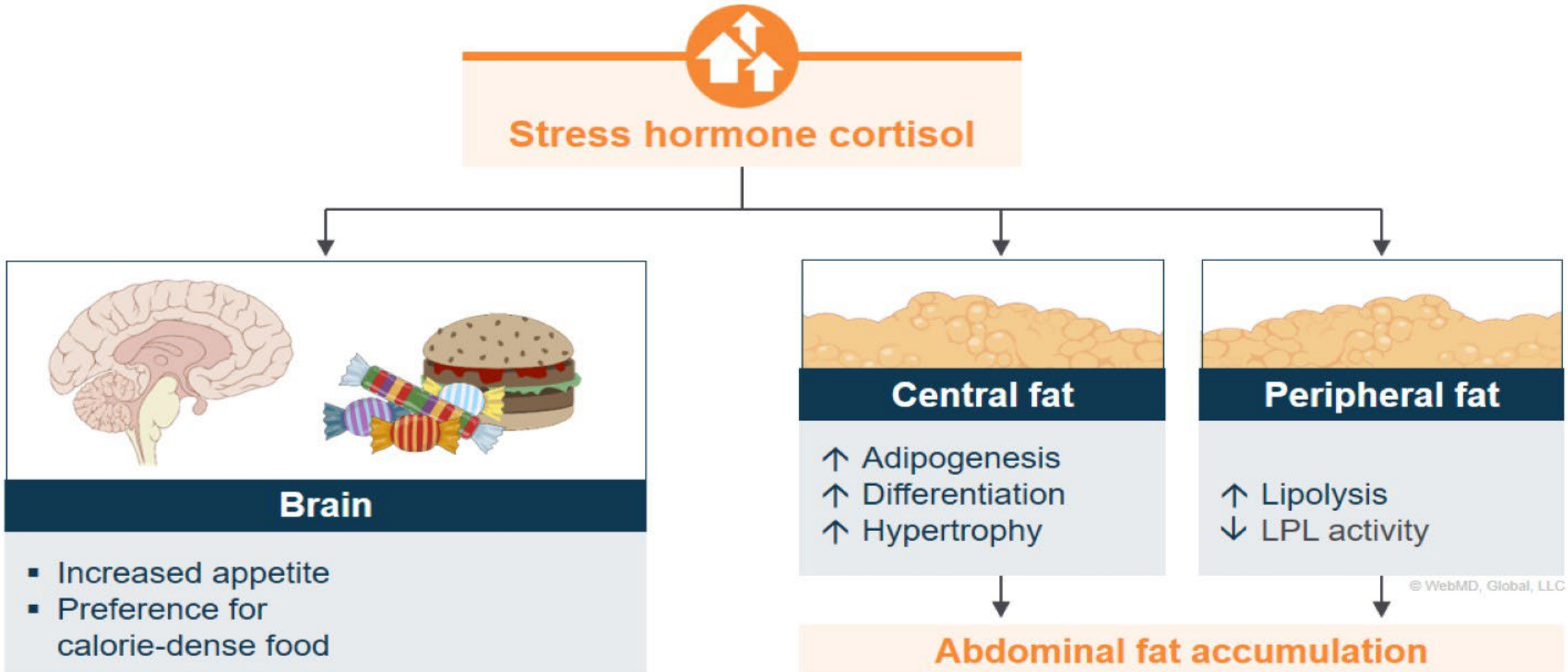

CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; TNF, tumor necrosis factor; M1 ATM, classically activated adipose tissue macrophages; M2 ATM, alternatively activated adipose tissue macrophages.
Yao L, et al. J Immunol Res. 2014;2014:181450.

# Il ruolo dello stress




LPL, lipoprotein lipase.
Fardet L, et al. Drugs. 2014;74:1731-1745; Van der Valk ES, et al. Curr Obes Rep. 2018;7:193-203.

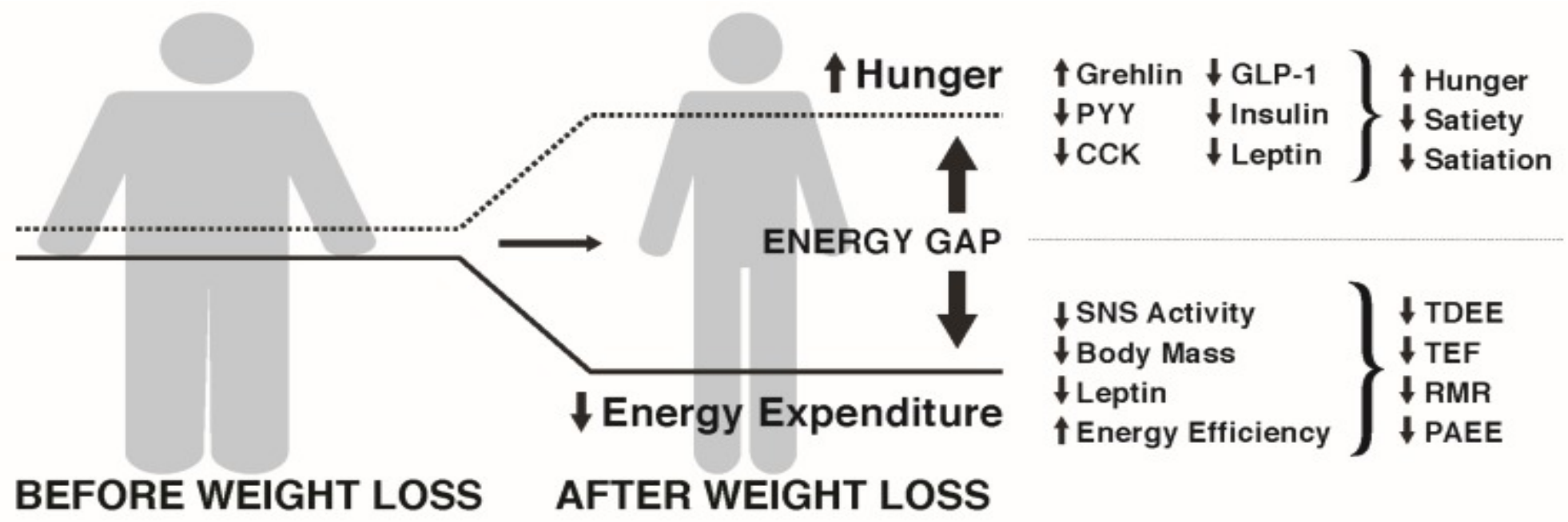
# Il ruolo dello stress




LPL, lipoprotein lipase.

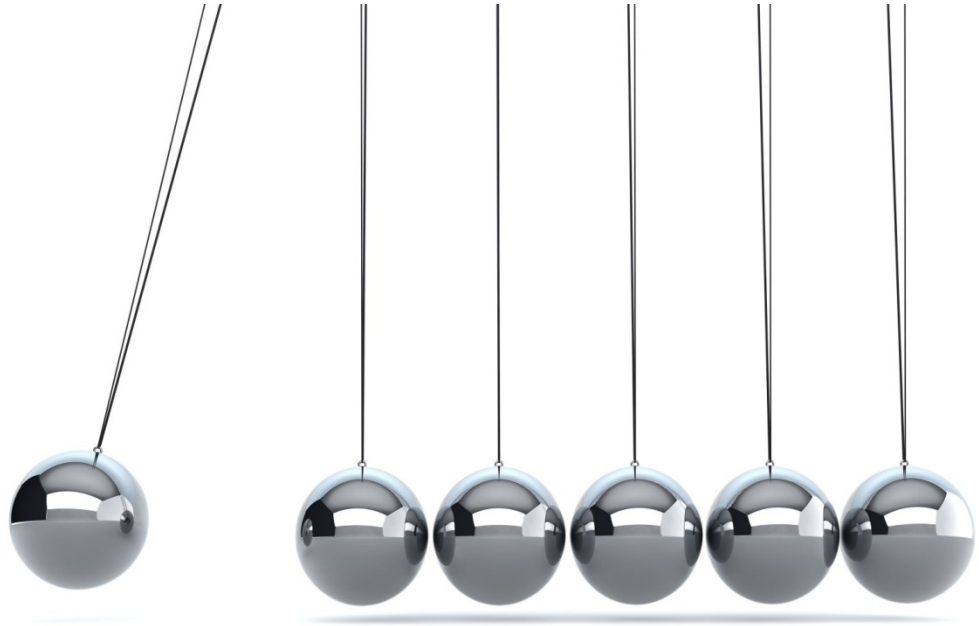
Fardet L, et al. Drugs. 2014;74:1731-1745; Van der Valk ES, et al. Curr Obes Rep. 2018;7:193-203.

# Perché si riprende peso dopo averlo perso ?

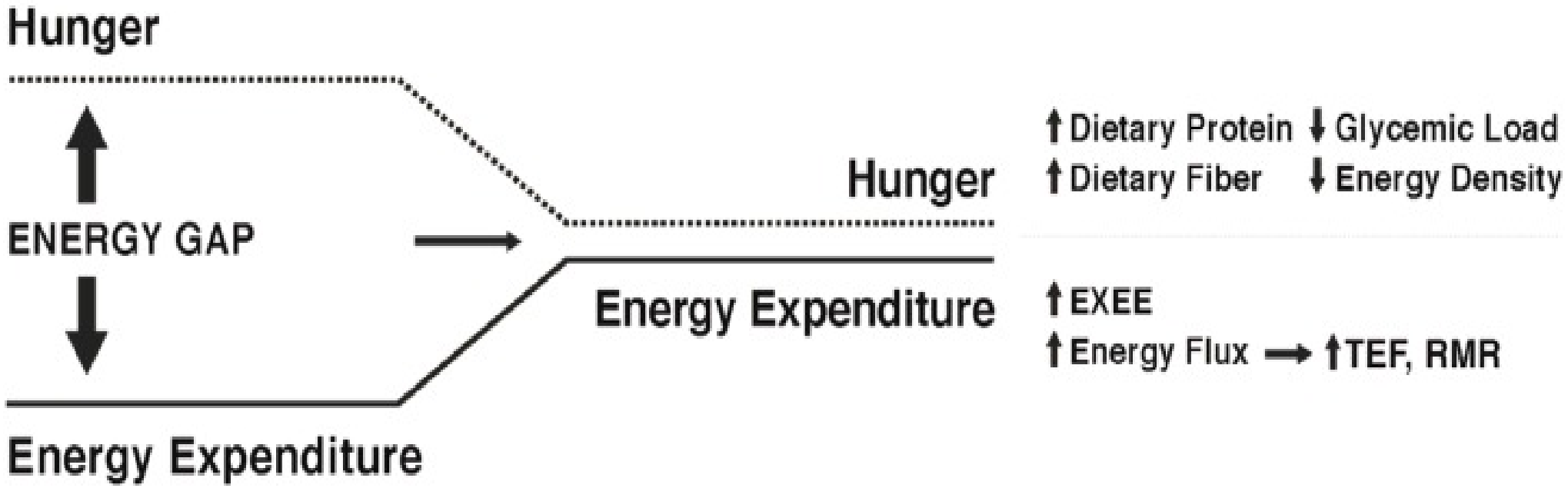



Melby CL, Paris HL, Foright RM, Peth J. Attenuating the Biologic Drive for Weight Regain Following Weight Loss: Must What Goes Down Always Go Back Up? Nutrients. 2017 May 6;9(5):468. doi: 10.3390/nu9050468. PMID: 28481261; PMCID: PMC5452198.

# E’ una legge della fisica

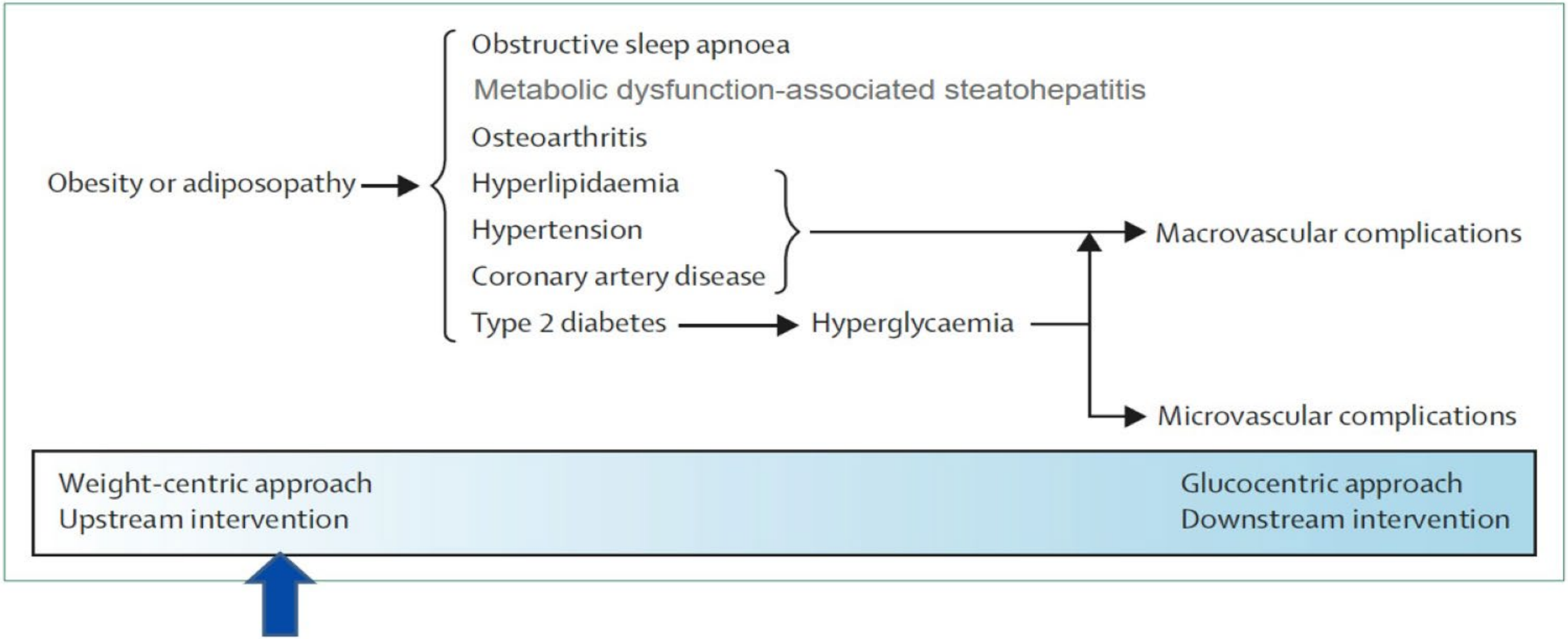



# Come fare per mantenere la perdita di peso a lungo termine?



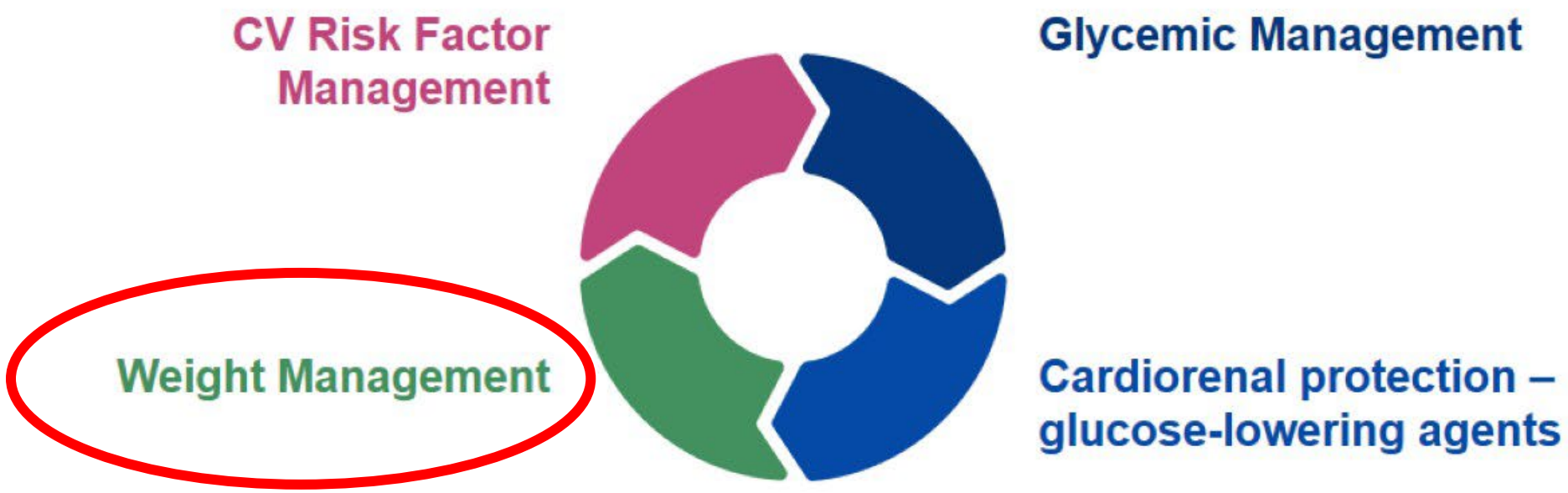

Melby CL, Paris HL, Foright RM, Peth J. Attenuating the Biologic Drive for Weight Regain Following Weight Loss: Must What Goes Down Always Go Back Up? Nutrients. 2017 May 6;9(5):468. doi: 10.3390/nu9050468. PMID: 28481261; PMCID: PMC5452198.

# Perdita di Peso=Un approccio Olistico al trattamento del DM tipo 2




Lingvay I, et al. Lancet. 2022;399:394-405.

# Prevezione delle Complicanze




CV, cardiovascular.
Davies MJ, et al. Diabetes Care. 2022;45:2753-2786; Davies MJ, et al. Diabetologia. 2022;65:1925-1966.

# La Perdita di Peso come target dell'intervento terapeutico

**Weight reduction is seen as a strategy to improve glycemic management and reduce the risk for weight-related complications**

**A weight loss of 5% to 15% should be a primary target in management for many people living with T2D**

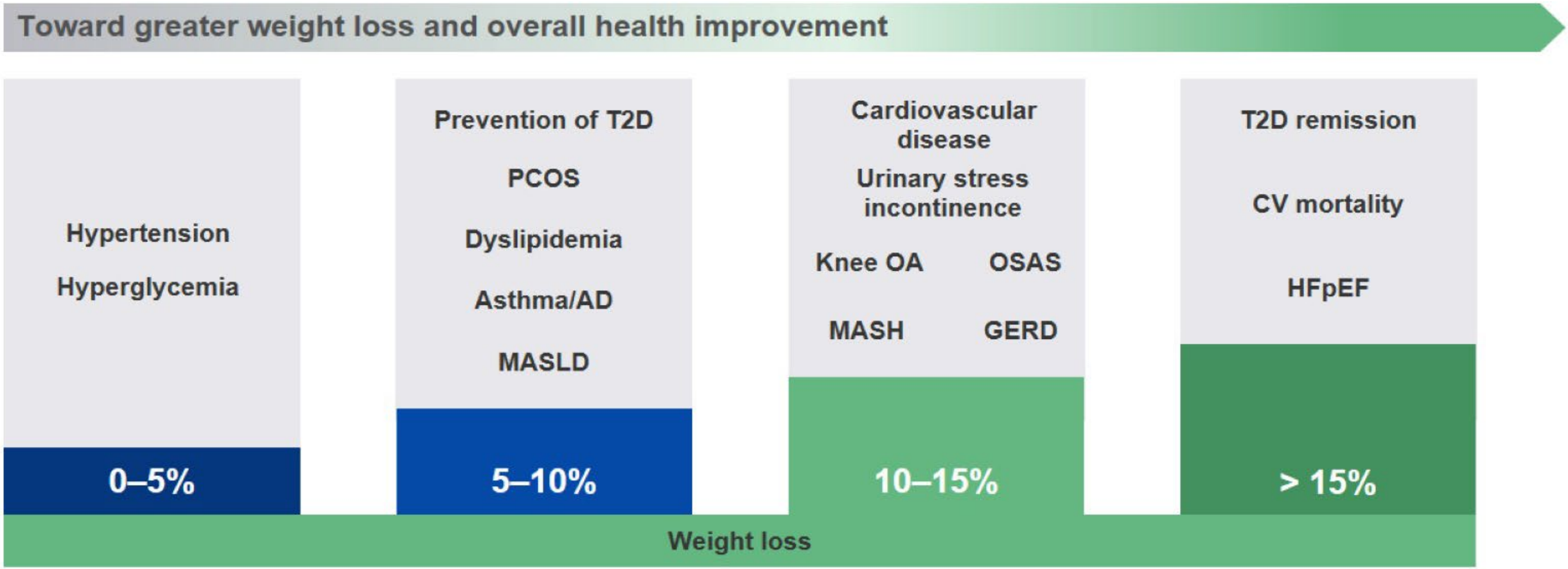
**A higher magnitude of weight loss confers better outcomes**

- A 5% to 10% loss confers metabolic improvement
- A loss of 10% to 15% or more of body weight can have a disease-modifying effect

**Weight loss may exert benefits that extend beyond glycemic management**

Davies MJ, et al. Diabetes Care. 2022;45:2753-2786; Davies MJ, et al. Diabetologia. 2022;65:1925-1966.

# Gli effetti della perdita di peso sulle comorbidità




AD, airway disease; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides.

Garvey WT, et al. Endocr Pract. 2016;22 suppl 3:1-203; Look AHEAD Research Group, et al. Lancet Diabetes Endocrinol. 2016;4:913-921; Lean ME, et al. Lancet. 2018;391:541-551; Benraouane F, et al. Curr Opin Cardiol. 2011;26:555-561; Sundström J, et al. Circulation. 2017;135:1577-1585.

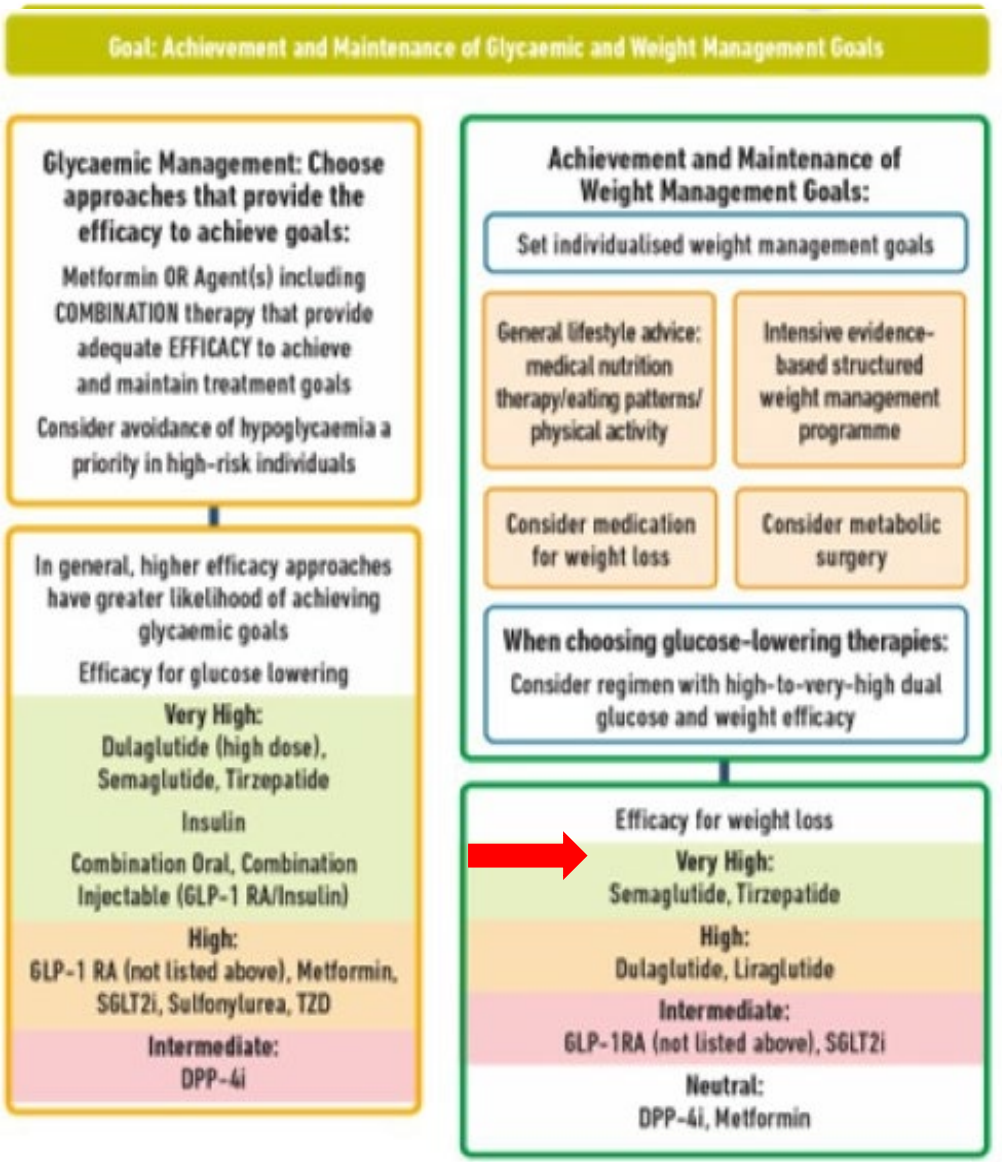
# Use of Glucose-Lowering Medications in the Management of T2D

**Agents with very high efficacy for glycemic control *and* weight loss:**

Semaglutide

OR

Tirzepatide

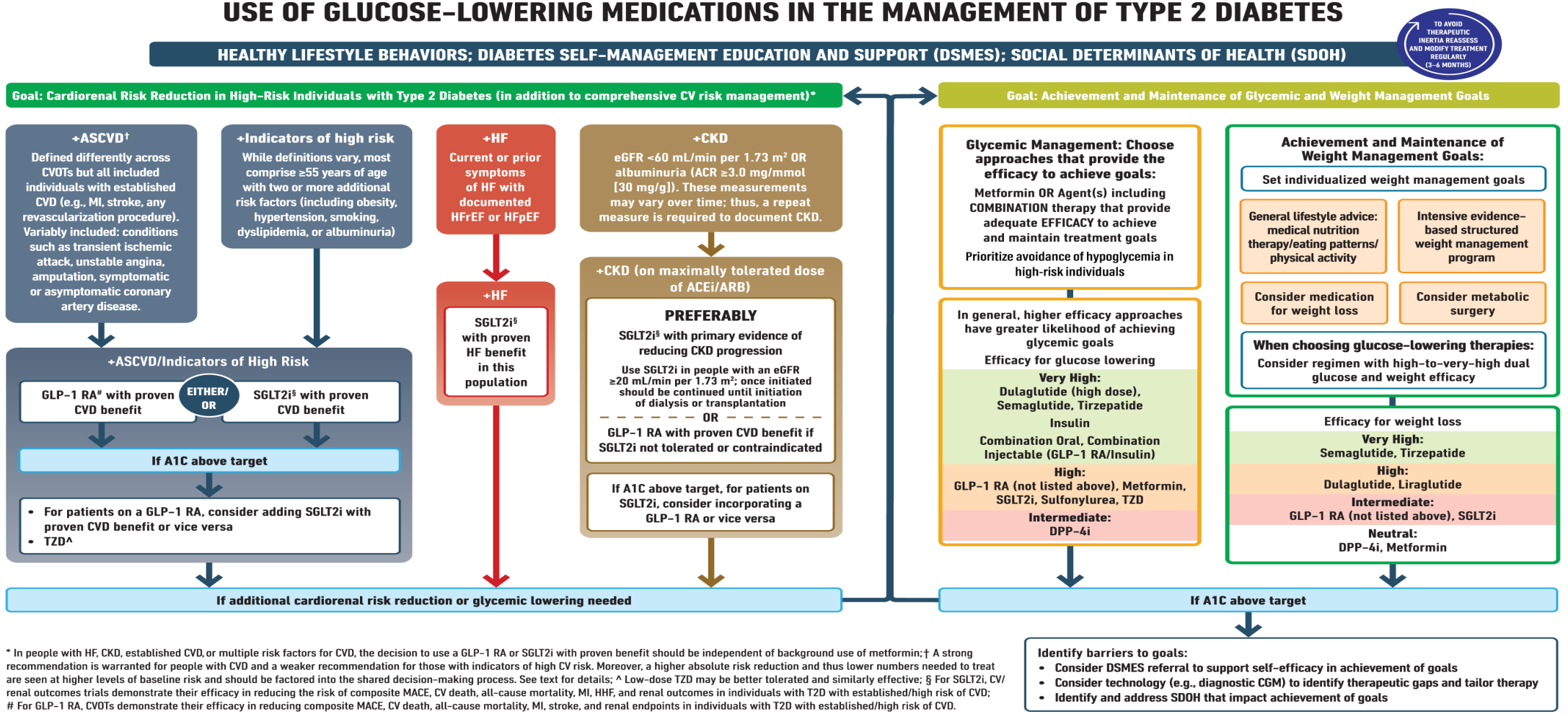



Davies MJ, et al. Diabetes Care. 2022;45:2753-2786; Davies MJ, et al. Diabetologia. 2022;65:1925-1966.

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

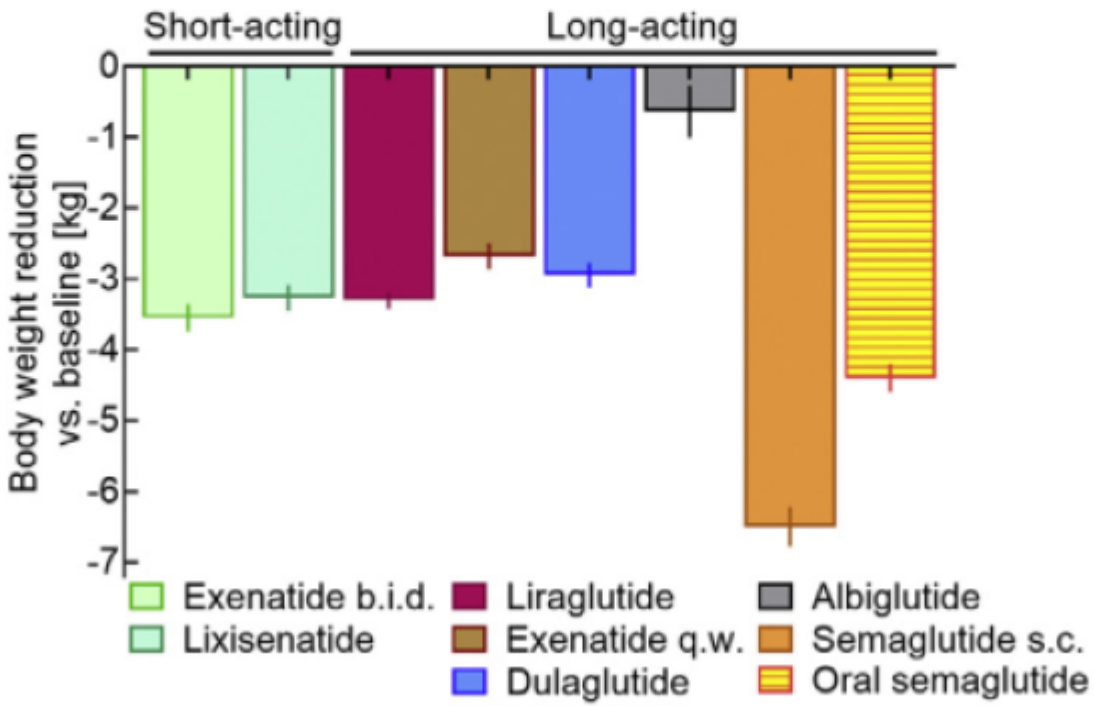
Diabetes Care. 2023;47(Supplement_1):S158-S178. doi:10.2337/dc24-S009

# USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

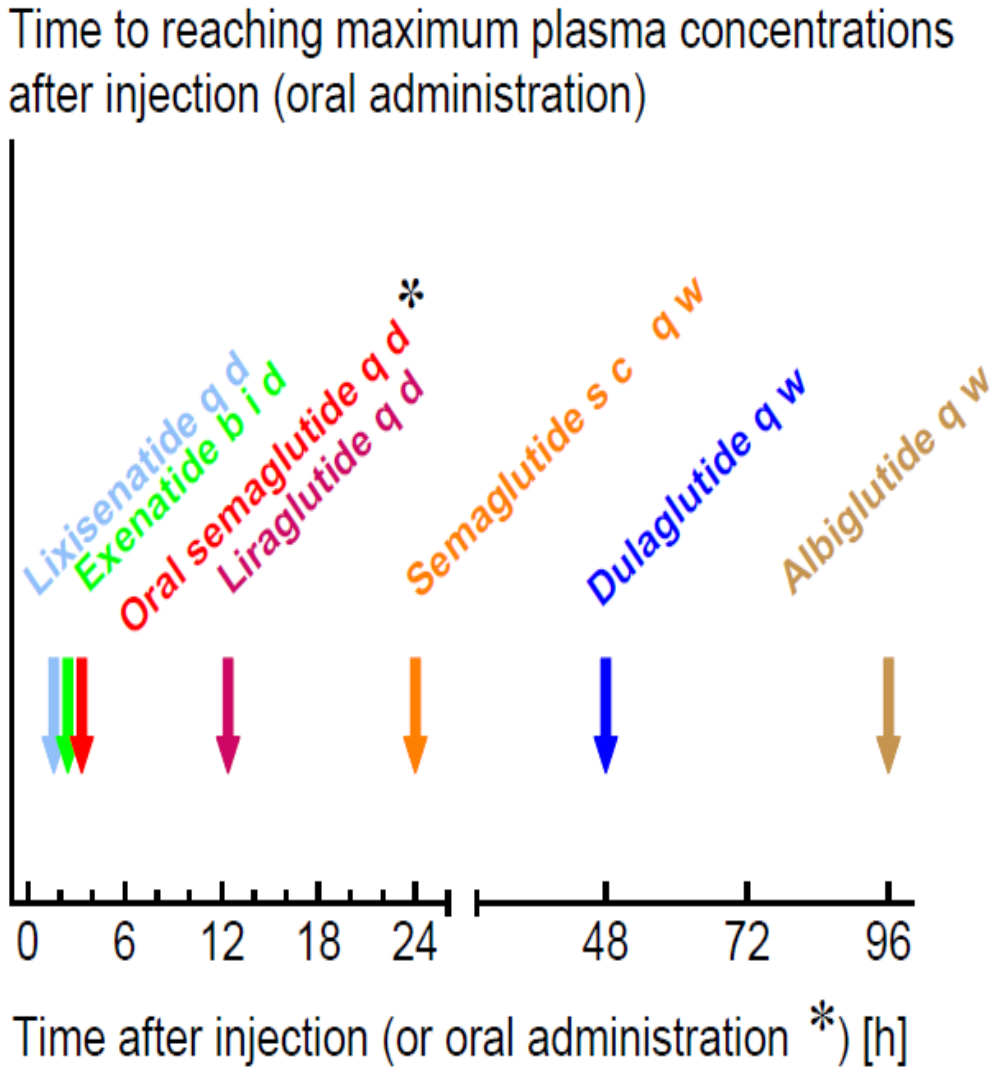


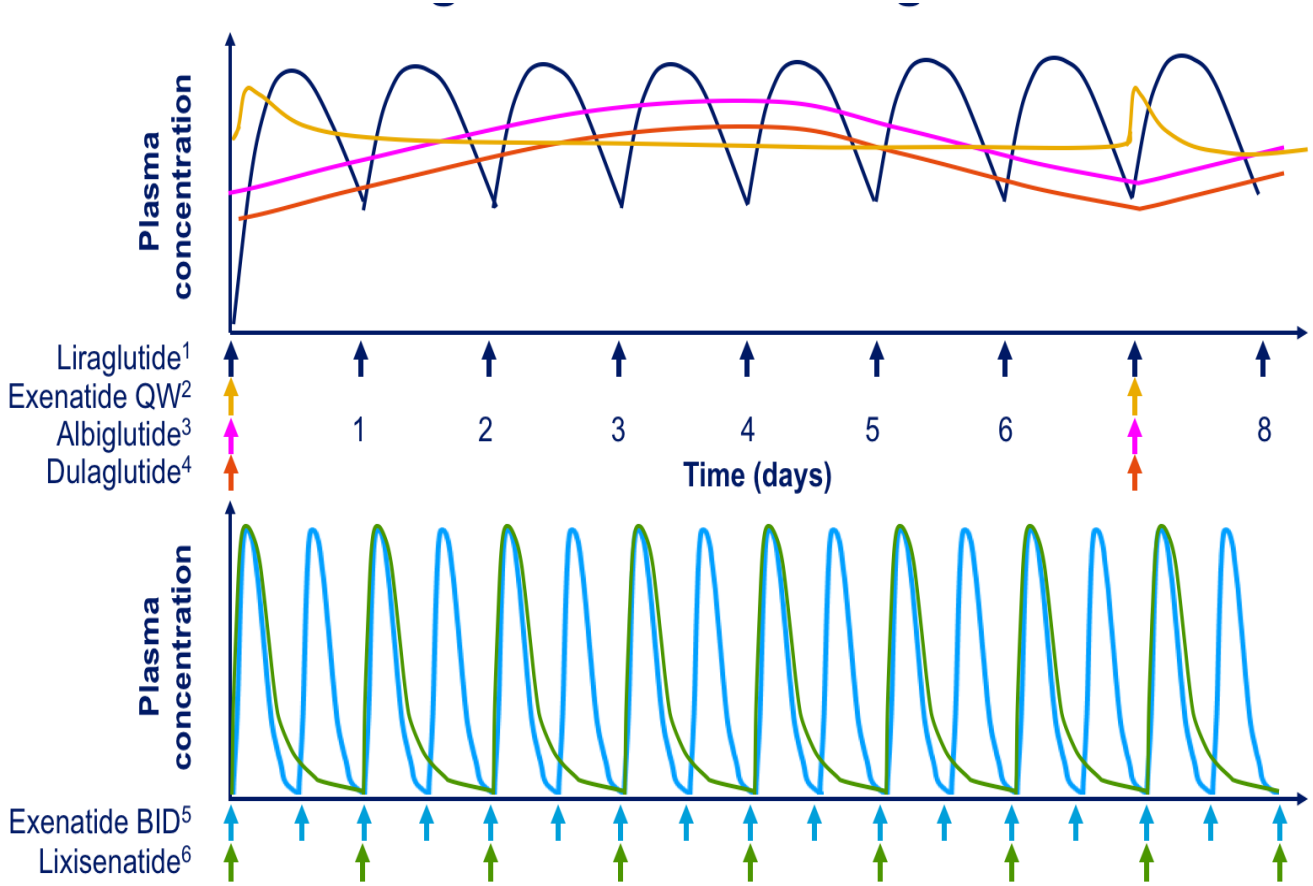

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/ renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

# Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing body weight




Adattato da Nauck M et al Mol Metabol 2020



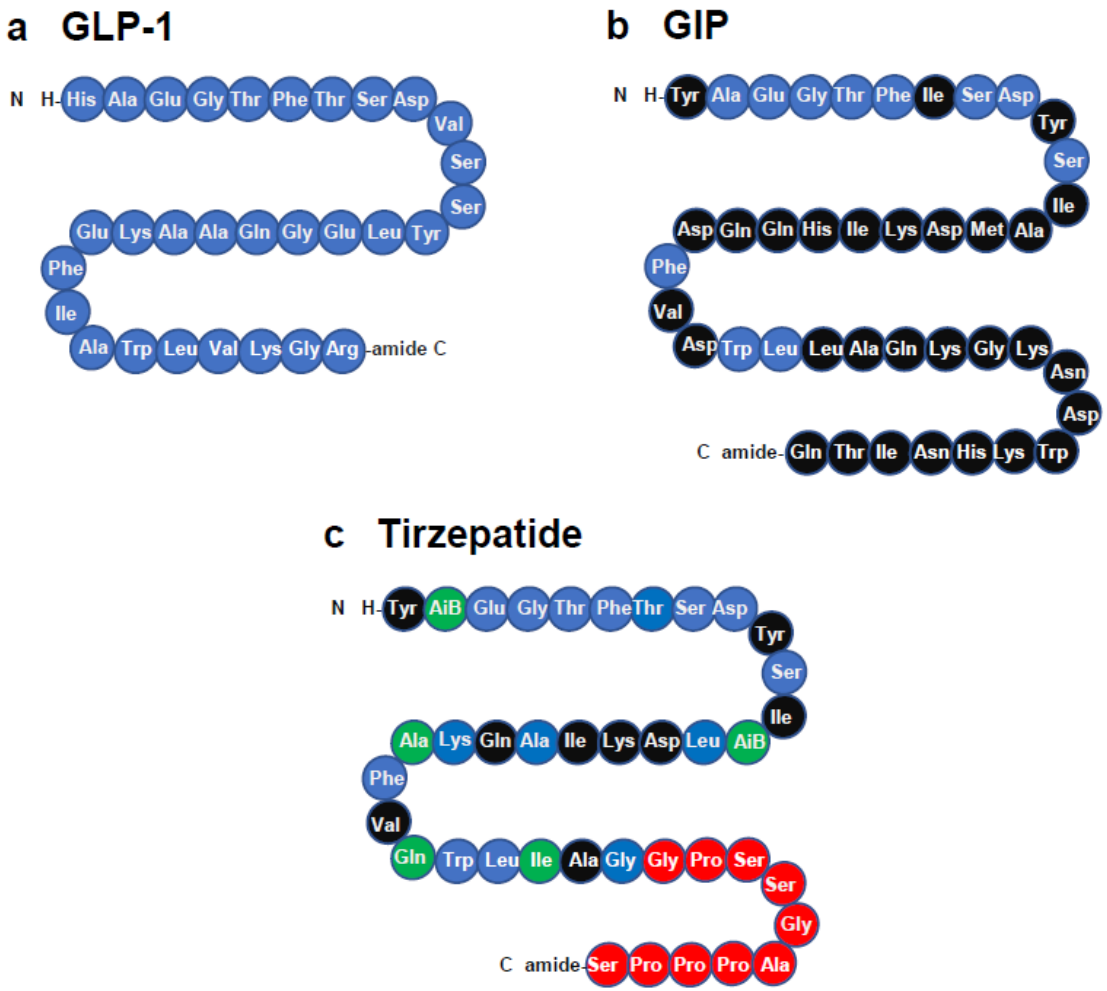




BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; QW, once weekly

1. Elbrønd *et al. Diabetes Care* 2002;25:1398–404; 2. Fineman *et al. Clin Pharmacokinet* 2011;50:65–74; 3. Bush *et al. Diabetes Obes Metab* 2009;11:498–505; 4. Kuritzky *et al. Postgrad Med* 2014;126:60–72; 5. Reddy *et al. AAPS J* 2005;7:M1285; 6. Christensen *et al. IDrugs* 2009;12:503–13

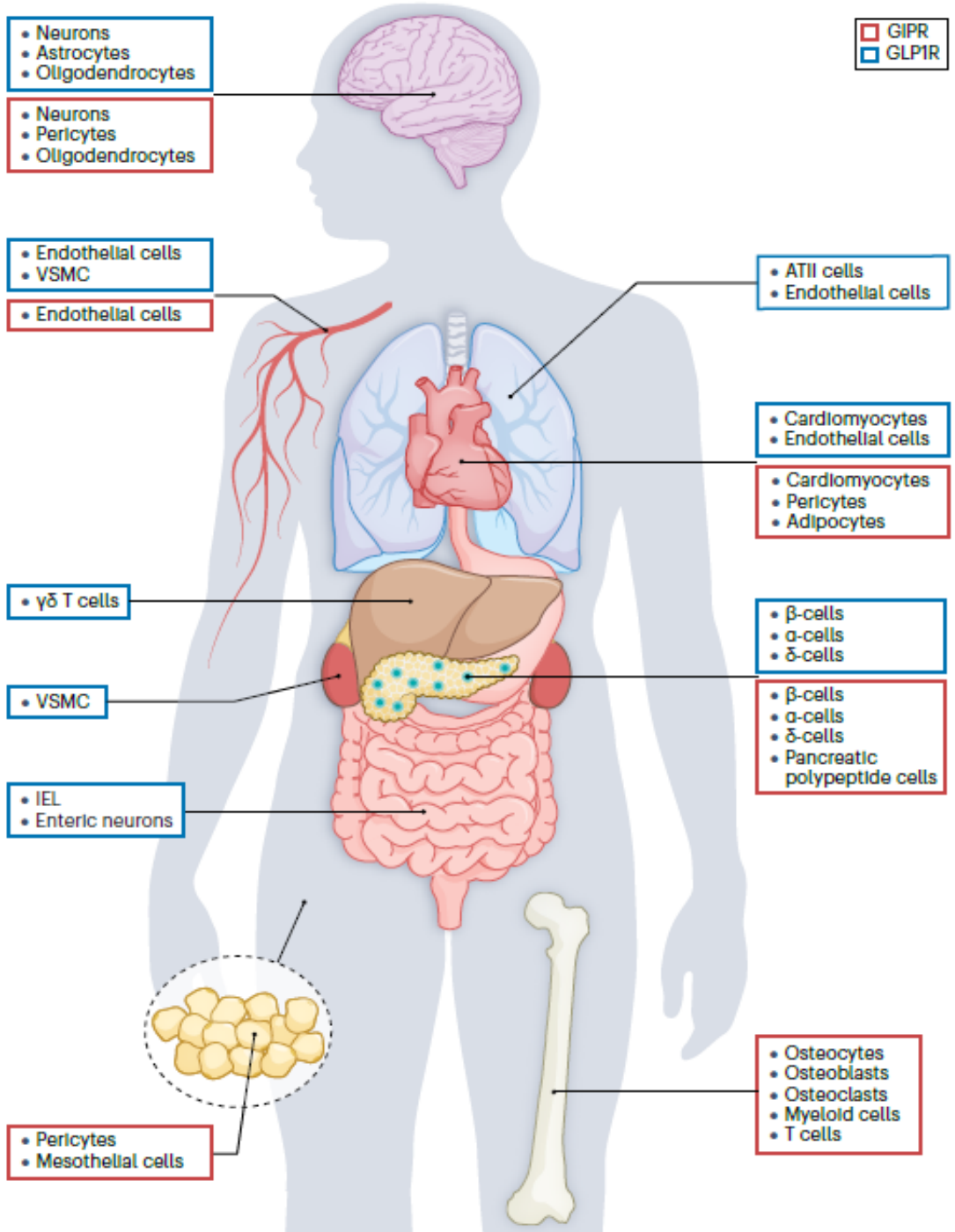
**Adattato da Nauck M et al Mol Metabol 2020**

# Structures of (a) GLP-1, (b) GIP and (c) tirzepatide




- TZP is a multifunctional peptide based on the native GIP peptide sequence, modified to bind to GIPR or GLP-1R
- TZP is a 39-amino-acid linear peptide and includes a C-20 fatty diacid moiety
- TZP has a mean half-life of ~5 days, enabling once-weekly dosing

Tschöp et al (2023) Diabetologia DOI 10.1007/s00125-023-05929-0




*Hammoud R & Drucker DJ, Nature Rev Endo 2023*

# The SURPASS Clinical Program in T2D


| Monotherapy[a] | 2-Drug Combination[b] | 2-Drug to 4-Drug Combination[c] | Open-Label RCT Phase 3[d] | Double-Blind Phase 3 RCT[e] |
|---|---|---|---|---|
| **TZP** (5 mg, 10 mg, 15 mg weekly) vs **PBO** for 40 weeks | **TZP** (5 mg, 10 mg, 15 mg weekly) **vs** **Semaglutide (GLP-1 RA)** for 40 weeks (add-on to MET) | **TZP** (5 mg, 10 mg, 15 mg weekly) vs **Insulin degludec** for 52 weeks (add-on to MET ± SGLT2i) | **TZP** (5 mg, 10 mg, 15 mg weekly) vs **Insulin glargine** for 52 weeks in patients at increased CV risk (add-on to ≥ 1 and ≤ 3 every morning MET, SGLT2i, or SU) | **TZP** (5 mg, 10 mg, 15 mg weekly) vs **PBO** for 40 weeks in patients inadequately controlled on insulin glargine ± MET |

MET, metformin; RCT, randomized controlled trial.

a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03882970; d. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03730662; e. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04039503

# The SURPASS Clinical Program in T2D

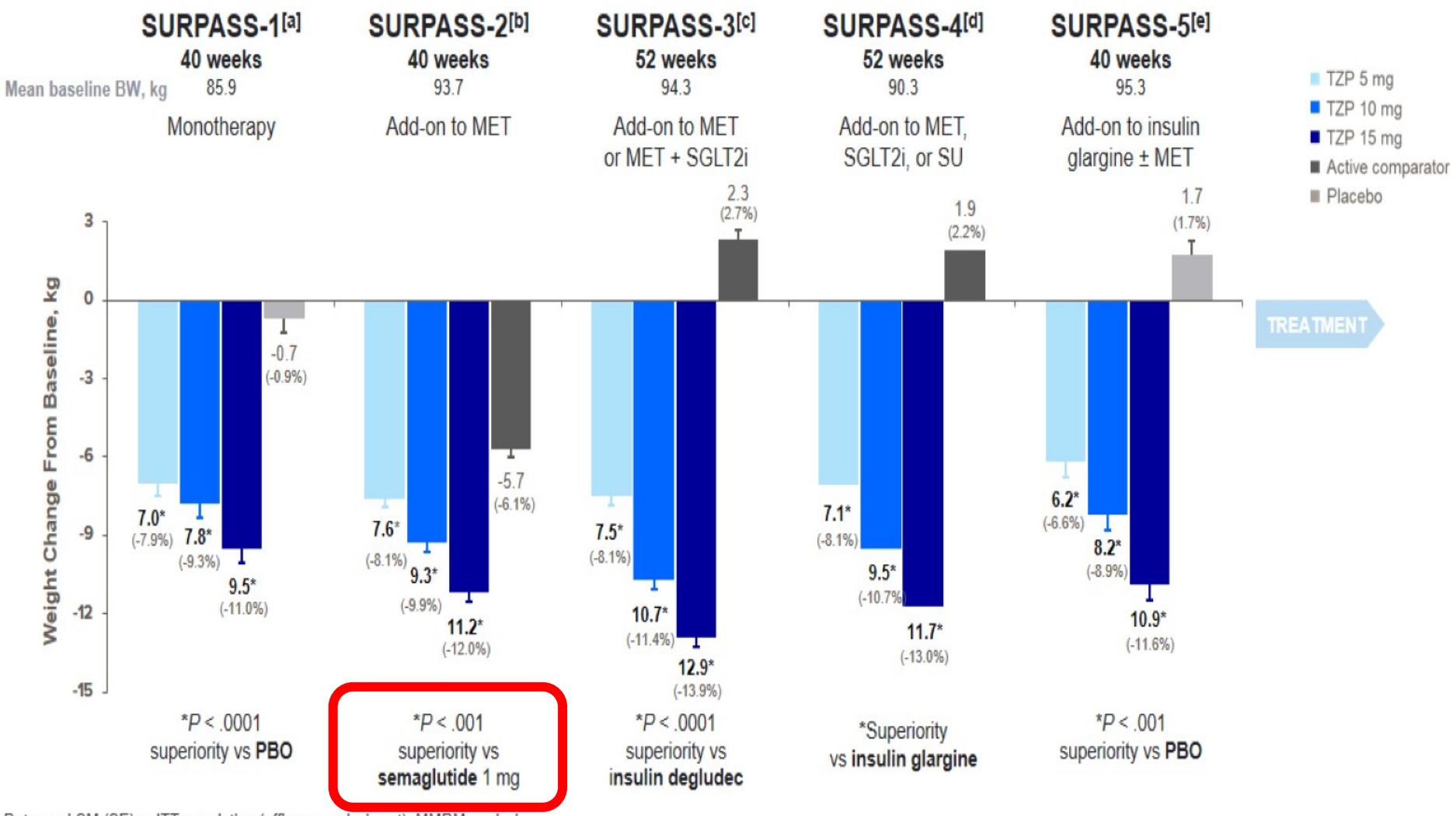

| Monotherapy[a] | 2-Drug Combination[b] | 2-Drug to 4-Drug Combination[c] | Open-Label RCT Phase 3[d] | Double-Blind Phase 3 RCT[e] | Combination With Insulin[f] |
|---|---|---|---|---|---|
| TZP (5 mg, 10 mg, 15 mg) weekly vs PBO for 40 wk | TZP (5 mg, 10 mg, 15 mg) weekly vs Semaglutide (GLP-1 RA) for 40 wk (add-on to MET) | TZP (5 mg, 10 mg, 15 mg) weekly vs Insulin degludec for 52 wk (add-on to MET ± SGLT2i) | TZP (5 mg, 10 mg, 15 mg) weekly vs Insulin glargine for 52 wk in patients at increased CV risk (add-on to ≥ 1 and ≤ 3 every morning: MET, | TZP (5 mg, 10 mg, 15 mg) weekly vs PBO for 40 wk in patients inadequately controlled on insulin glargine ± MET | TZP (5 mg, 10 mg, 15 mg) weekly vs Insulin lispro thrice daily for 40 wk in patients inadequately controlled on insulin glargine ± MET |

**SURPASS CVOT (12,500 patients; head-to-head with dulaglutide)[g]**
ONGOING

MET, metformin; RCT, randomized clinical trial.

a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03882970; d. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03730662; e. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04039503; f. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04537923; g. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04255433

# SURPASS Program
## *Key Efficacy Findings: BW*



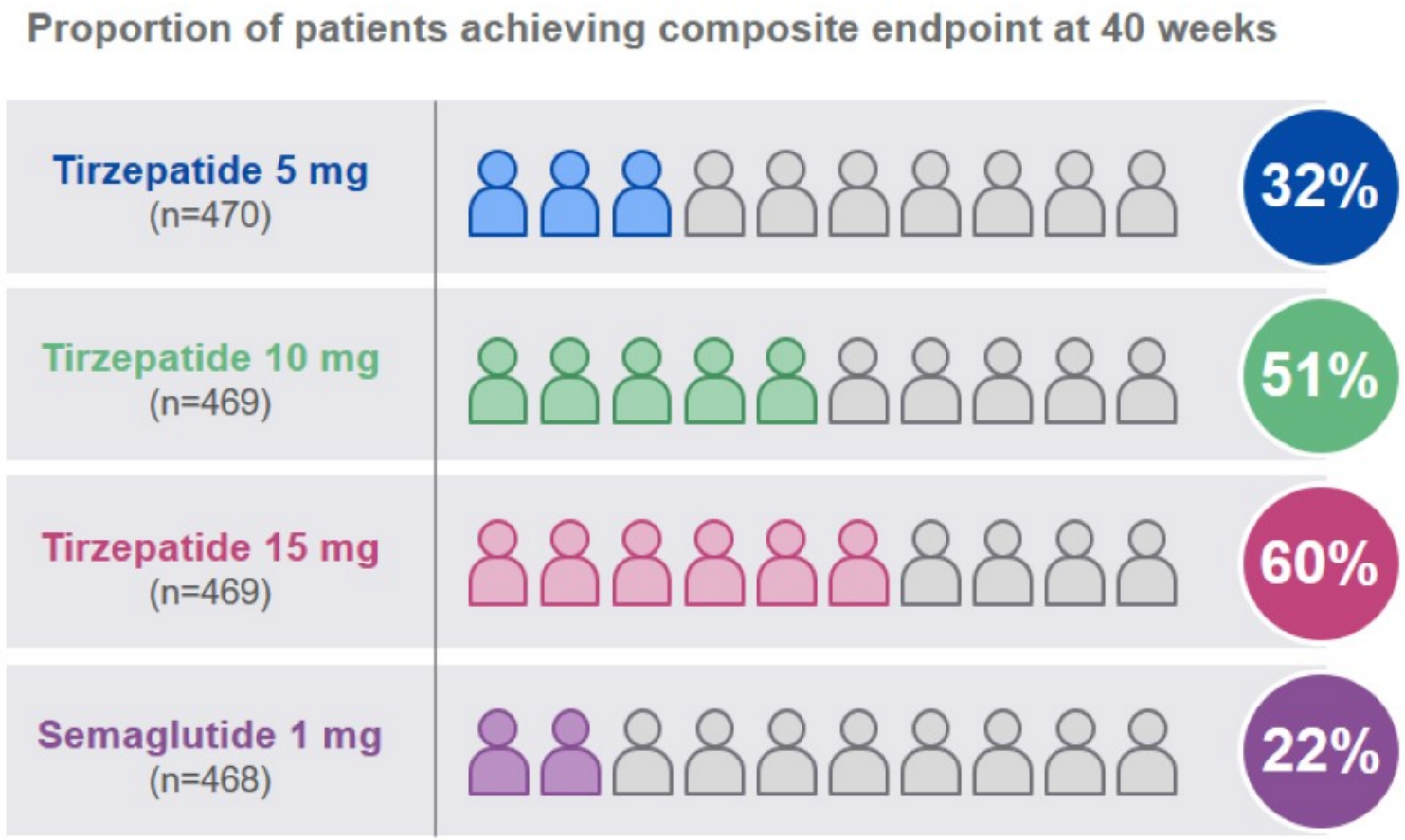

Data are LSM (SE); mITT population (efficacy analysis set); MMRM analysis.

a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Del Prato S, et al. Lancet. 2021;398:1811-182; e. Dahl D, et al. JAMA. 2022;327:534-545.

# More Patients Achieved a Composite Endpoint with Tirzepatide vs Semaglutide in SURPASS-2

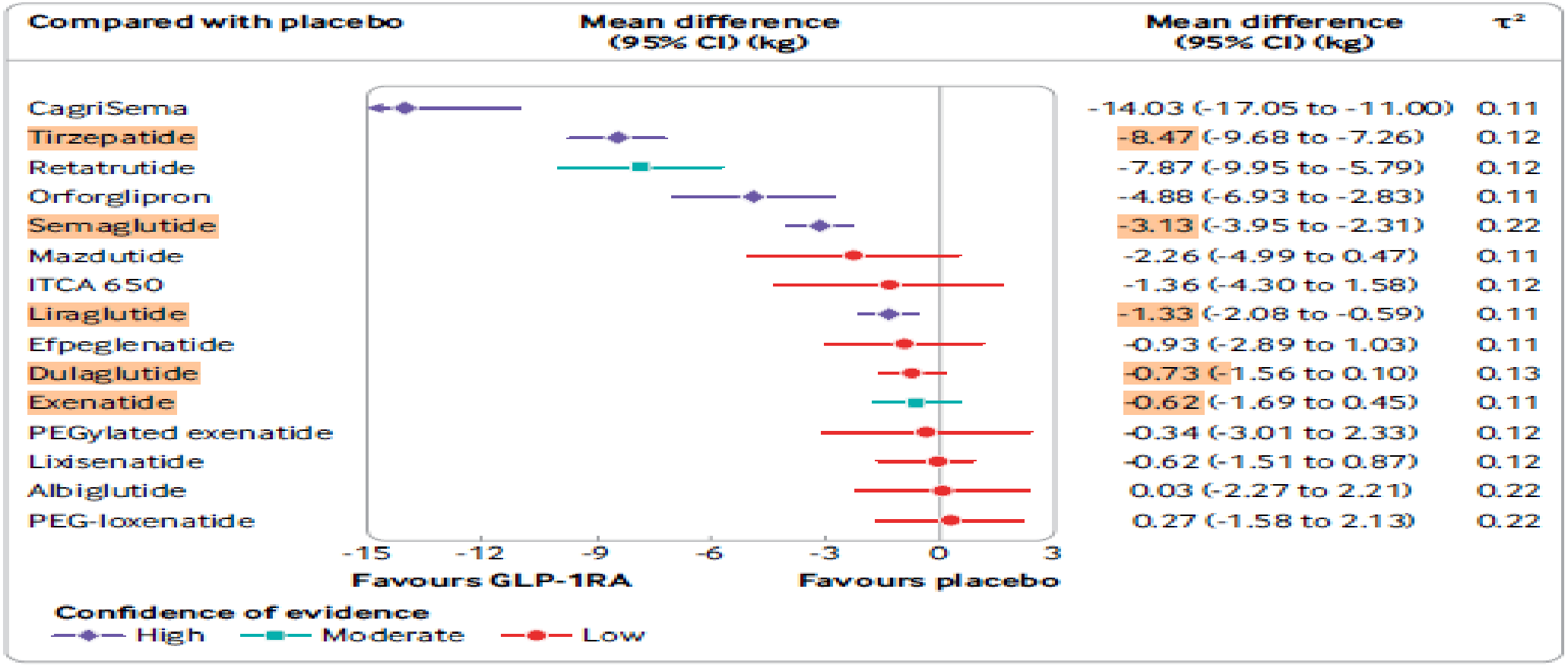
**Composite Endpoint:**

- HbA1c ≤ 6.5%
- Weight loss ≥ 10%
- No clinically significant or severe hypoglycemia



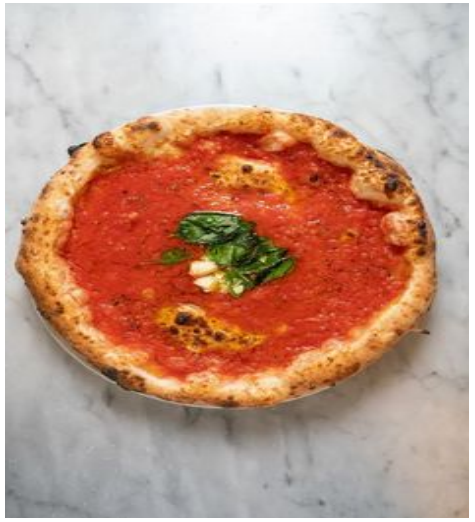

Tofe S. Presented at: 60th Annual Meeting of the EASD; September 9-13, 2024; Madrid, Spain; Frías JP, et al. N Engl J Med. 2021;385:503-515.

# Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis



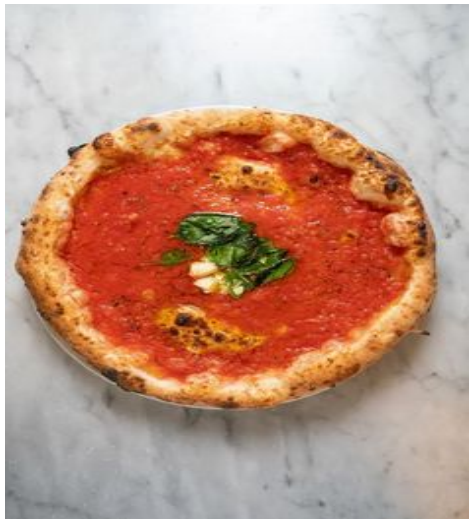

Yao H, et al BMJ. 2024 Jan 29;384:e076410. doi: 10.1136/bmj-2023-076410. PMID: 38286487; PMCID: PMC10823535.

# Menu’

| LIRAGLUTIDE | SEMAGLUTIDE INIET. | DULAGLUTIDE | SEMAGLUTIDE ORALE |
| --- | --- | --- | --- |
|  |  |  |  |

# Menu’

| LIRAGLUTIDE | SEMAGLUTIDE INIET. | DULAGLUTIDE | SEMAGLUTIDE ORALE |
|---|---|---|---|

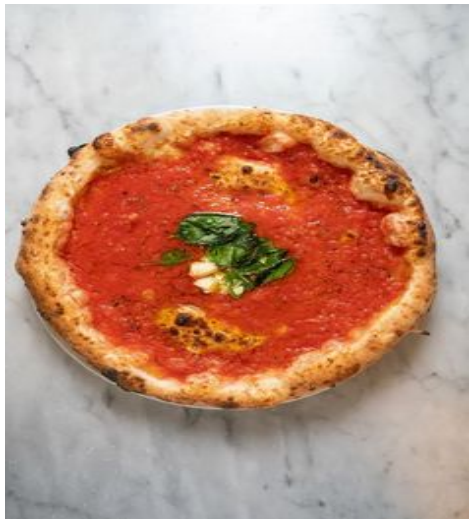






# Menu’

| LIRAGLUTIDE | SEMAGLUTIDE INIET. | DULAGLUTIDE | SEMAGLUTIDE ORALE | TIRZEPATIDE |
|---|---|---|---|---|









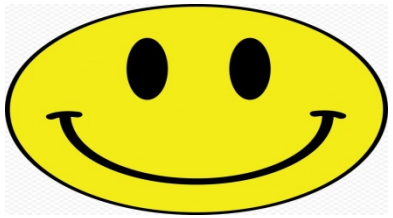
# Menu' di oggi

| LIRAGLUTIDE | SEMAGLUTIDE INIET. | DULAGLUTIDE | SEMAGLUTIDE ORALE | TIRZEPATIDE |
|---|---|---|---|---|
|  |  |  |  |  |
|  |  |  |  |  |

# Ma oggi…….

| SEMAGLUTIDE ORALE | TIRZEPATIDE |
| --- | --- |
|  |  |

**PREZZO=346,58 €**



# Tirzepatide: indicazioni

- **Tirzepatide** è un medicinale utilizzato in associazione alla dieta e all'esercizio fisico per trattare adulti affetti da **diabete di tipo 2 non adeguatamente controllato**. Può essere usato in **monoterapia (da solo) nei pazienti che non possono assumere metformina** (un altro medicinale per il diabete) o come **terapia aggiuntiva in associazione ad altri medicinali antidiabetici**.
- Tirzepatide è prescrivibile in classe di rimborsabilità Cnn-RR =farmaco in fascia C, non negoziato, soggetto a prescrizione medica da parte di qualsiasi medico del SSN.

- **Tirzepatide** è anche utilizzato in associazione alla dieta e all'esercizio fisico per aiutare le persone a perdere peso e a mantenerlo sotto controllo.
  - in soggetti con **obesità** (indice di massa corporea pari o superiore a 30 kg/m2) o **sovrappeso** (indice di massa corporea compreso tra 27 e 30 kg/m2) e con **problemi di salute correlati al peso quali diabete**, livelli insolitamente **elevati di grassi nel sangue**, **ipertensione** o **apnea ostruttiva del sonno** (frequente interruzione della respirazione durante il sonno).

# Tirzepatide: posologia

- La dose iniziale di tirzepatide è 2,5 mg una volta a settimana.
- Dopo 4 settimane, la dose deve essere aumentata a 5 mg una volta a settimana.
- Se necessario, è possibile aumentare la dose con incrementi di 2,5 mg dopo un minimo di 4 settimane con la dose in uso.
- Le dosi di mantenimento raccomandate sono 5 mg, 10 mg e 15 mg.
- La dose massima è 15 mg una volta a settimana.

# La domanda sorge spontanea……

***Come affrontare la disuguaglianza e garantire l'equità di trattamento se i farmaci sono contingentati e/o non rimborsati dal SSN?***

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

# Fair Allocation of GLP-1 and Dual GLP-1–GIP Receptor Agonists

Ezekiel J. Emanuel, Ph.D., Johan L. Dellgren, B.A., Matthew S. McCoy, Ph.D., and Govind Persad, J.D., Ph.D.

**Table 2. Fair-Allocation Framework for GLP-1 and Dual GLP-1–GIP Receptor Agonists.***

| Tier | Objective | Distribution Criteria |
|---|---|---|
| 1 | Minimize potential years of life lost by preventing excess and premature death | People with class III obesity (BMI, ≥40) and people with severe type 2 diabetes (glycated hemoglobin level, >8%) whose disease hasn't responded to alternative treatment<br>Phase 1: younger patients (e.g., <50 yr of age)<br>Phase 2: older patients |
| 2 | Prevent imminent medical complications, such as cardiovascular events | People with class II obesity (BMI, 35.0–39.9), followed by people with severe type 2 diabetes (glycated hemoglobin level, >8%)<br>Phase 1: younger patients<br>Phase 2: older patients |
| 3 | Prevent future medical complications, such as cardiovascular events | People with class I obesity (BMI, 30.0–34.9), followed by people with type 2 diabetes (glycated hemoglobin level, >7%) whose disease hasn't responded to alternative treatment<br>Phase 1: younger patients<br>Phase 2: older patients |
| 4 | Improve quality of life and social and emotional health | People with overweight (BMI, 25.0–29.9) or type 2 diabetes (glycated hemoglobin level, >7%) who aren't eligible under another tier<br>Phase 1: younger patients<br>Phase 2: older patients |

# *Grazie*

- ***«Il saggio non dice tutto quello che pensa, ma pensa tutto quello che dice».***

***Aristotele.***