

LA GESTIONE DEL SOGGETTO OBESO CON E SENZA DIABETE

Da Kennedy ad Obama: dal sogno alle opportunità terapeutiche

Terza Sessione – “The best is yet to come”

Opportunità di terapia farmacologica

Moderatori: R. Fornengo, A.R. Pia

TORINO

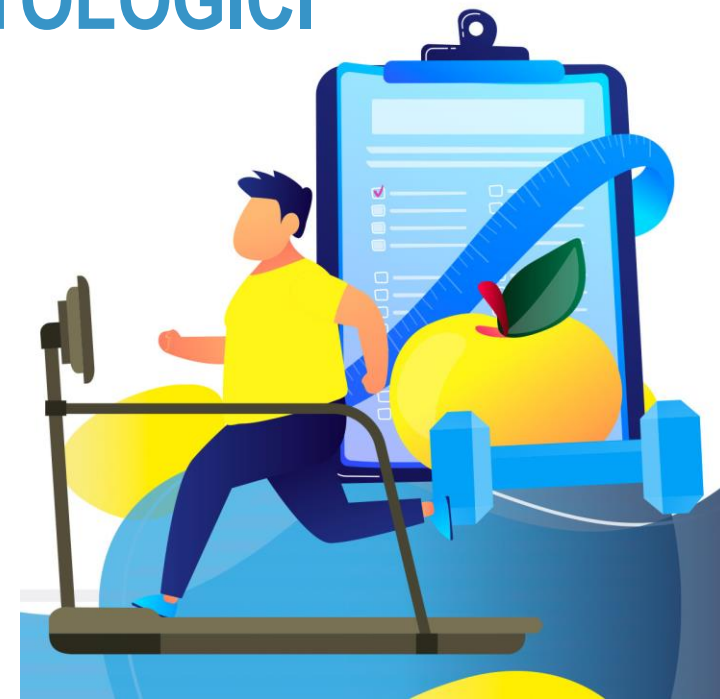
12 aprile 2025

EFFETTO SUL PESO DEI FARMACI DIABETOLOGICI

Gianluca Margiotta

S.C. di Diabetologia ed Endocrinologia Territoriale ASL CN1

gianluca.margiotta@aslcn1.it

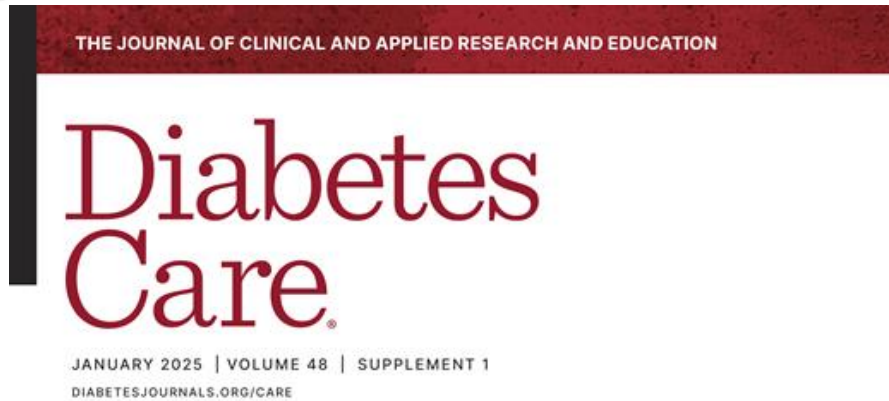


**Art. 76 comma 4 dell'Accordo Stato-Regioni in tema di
"Formazione Continua nel settore Salute"**

*Dichiaro di non aver avuto, nei due anni
precedenti l'evento formativo di oggi, rapporti
di natura finanziaria e lavorativa con imprese
commerciali operanti in ambito sanitario*



INTRODUZIONE, OVVERO IL "PESO" DEL PESO



Standards of Care in Diabetes 2025

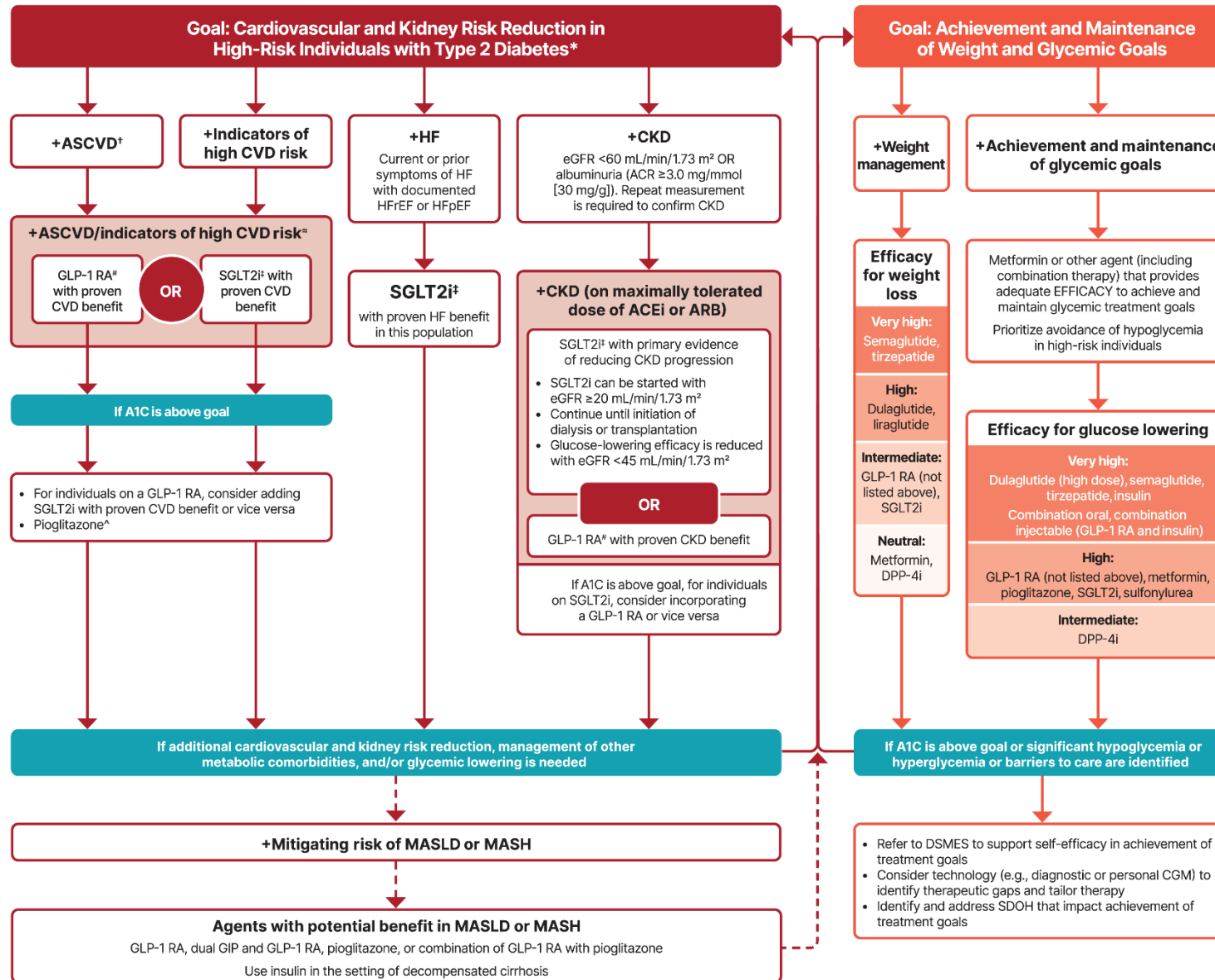


8.4 In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management. **(A)**

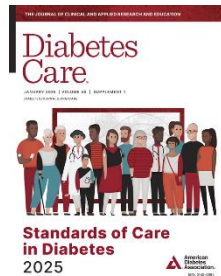
American Diabetes Association Professional Practice Committee; 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025. *Diabetes Care* 1 January 2025; 48 (Supplement_1): S167–S180. <https://doi.org/10.2337/dc25-S008>

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH

To avoid
therapeutic
inertia, reassess
and modify
treatment
regularly
(3–6 months)

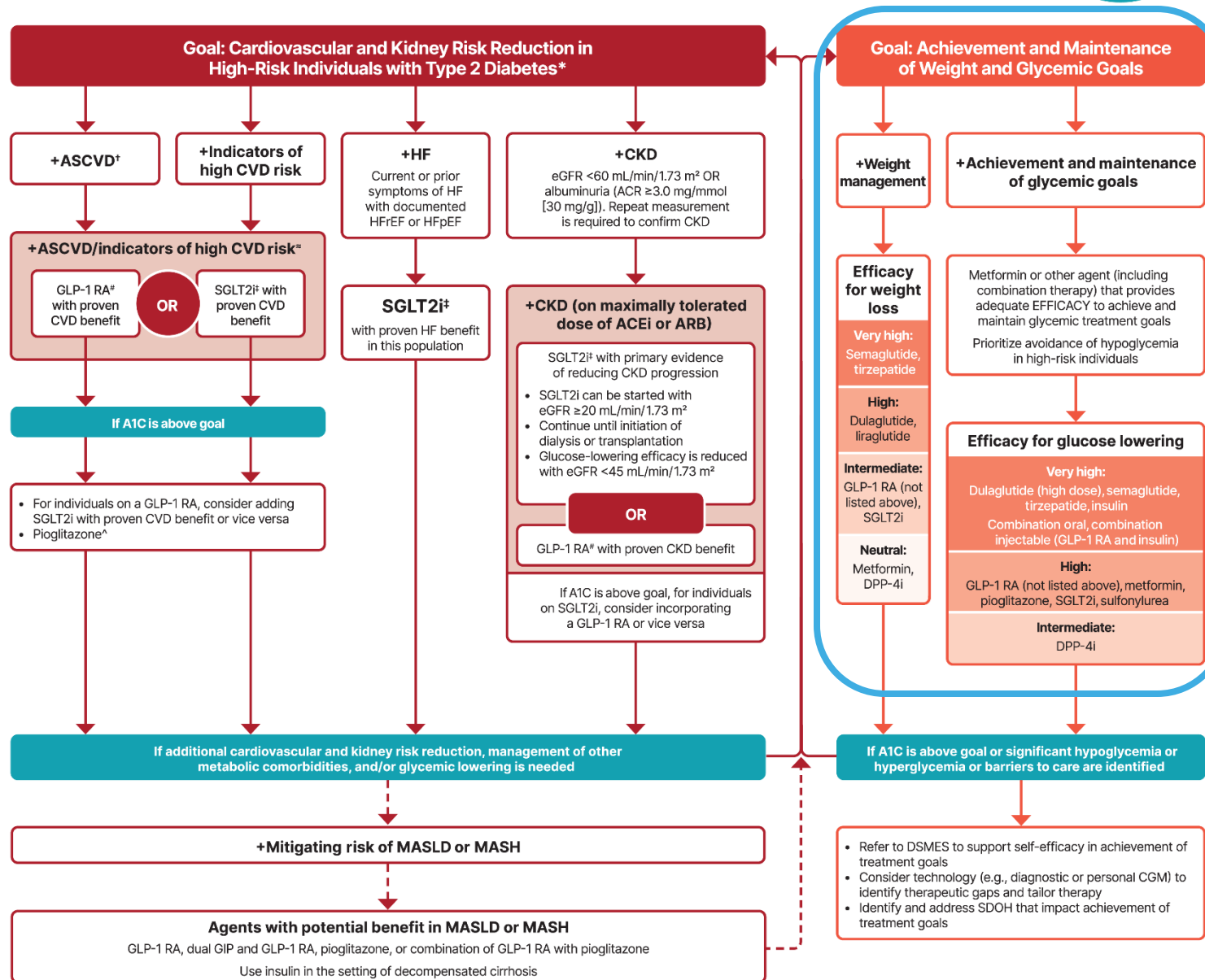


American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care* 1 January 2025; 48 (Supplement_1): S181–S206. <https://doi.org/10.2337/dc25-S009>

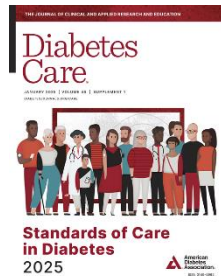


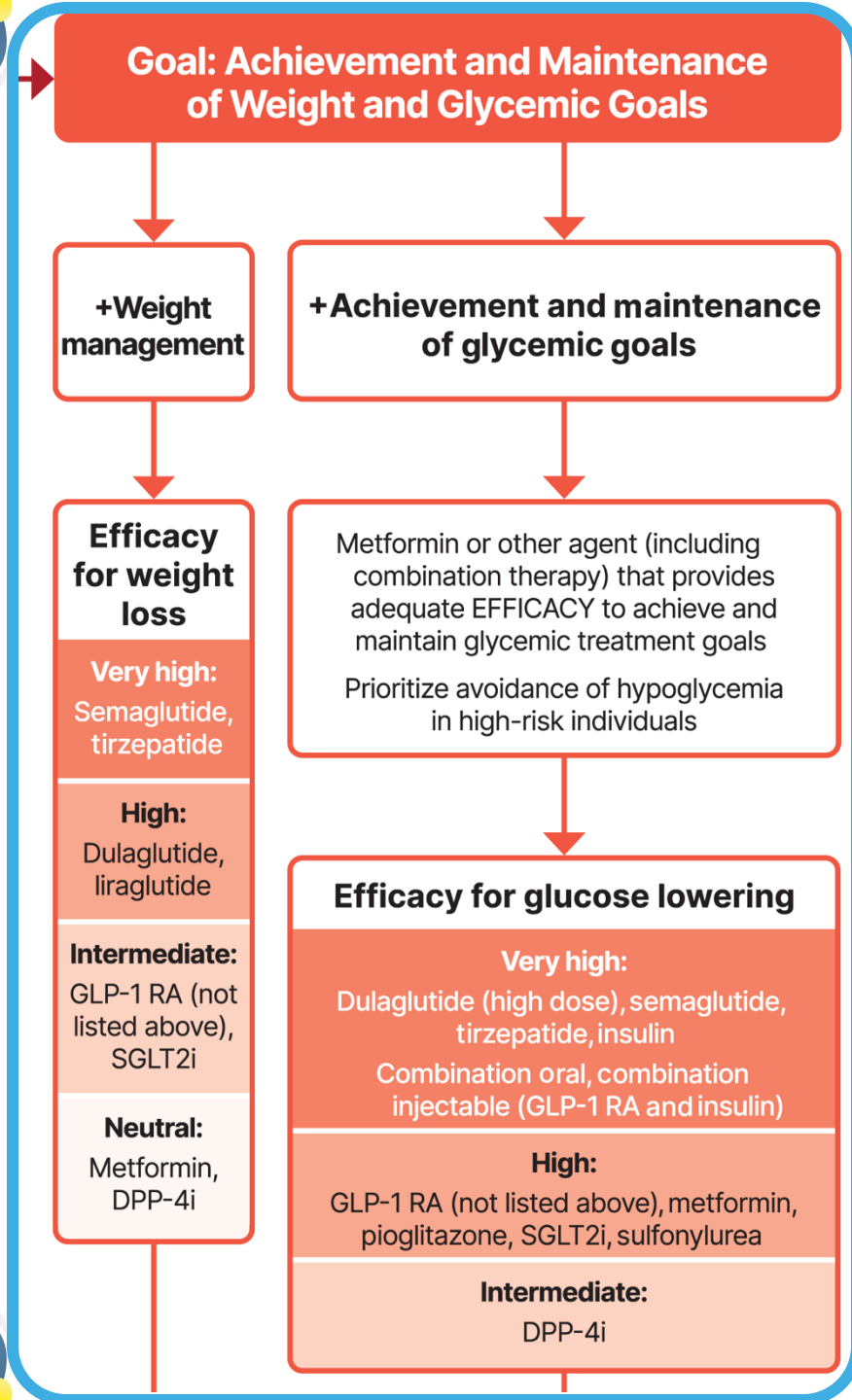
HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH

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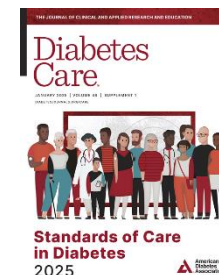
American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care* 1 January 2025; 48 (Supplement_1): S181–S206. <https://doi.org/10.2337/dc25-S009>





8.5 Provide weight management treatment, aiming for any magnitude of weight loss. Weight loss of 3–7% of baseline weight improves glycemia and other intermediate cardiovascular risk factors. **(A)**

Sustained loss of >10% of body weight usually confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **(B)**



American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care* 1 January 2025; 48 (Supplement_1): S181–S206. <https://doi.org/10.2337/dc25-S009>

SVOLGIMENTO, OVVERO METTIAMO LA TROPPIA "CICCIA" AL FUOCO

1) FARMACI CON EFFETTO NEUTRO SUL PESO

- Metformina
- iDPP4

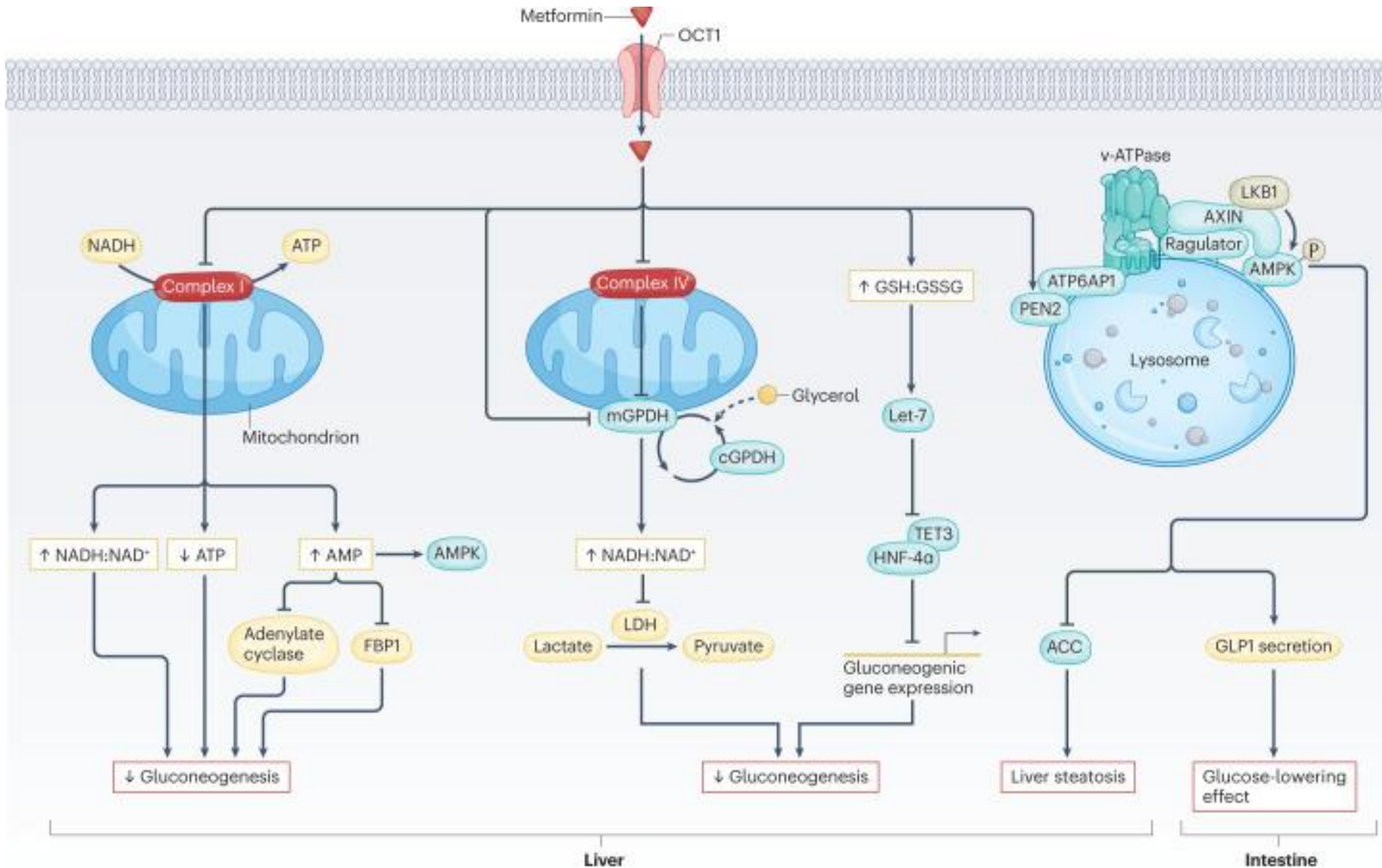
2) FARMACI CON EFFETTO DI INCREMENTO DEL PESO

- Insulina
- Sulfaniluree
- Glitazoni

3) FARMACI CON EFFETTO DI CALO DEL PESO

- iSGLT2
- GLP1-RA
- GLP1-RA/GIP

FARMACI CON EFFETTO "NEUTRO" SUL PESO: METFORMINA



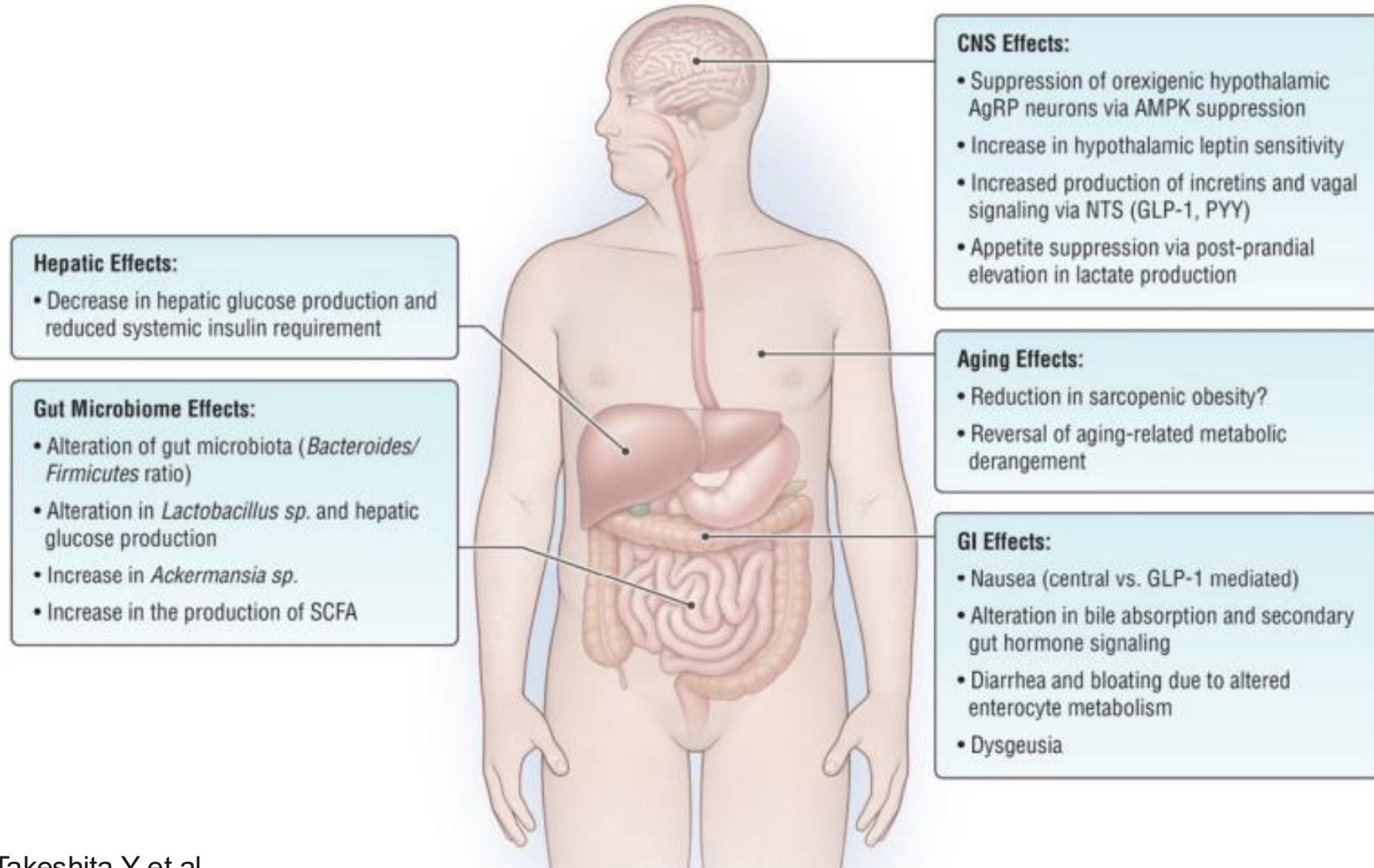
Foretz M et al.

Metformin: update on mechanisms of action and repurposing potential.

Nat Rev Endocrinol. 2023 Aug;19(8):460-476. doi: 10.1038/s41574-023-00833-4.

FARMACI CON EFFETTO "NEUTRO" SUL PESO: METFORMINA

Regulation of Obesity, Appetite, and Weight Loss by Metformin

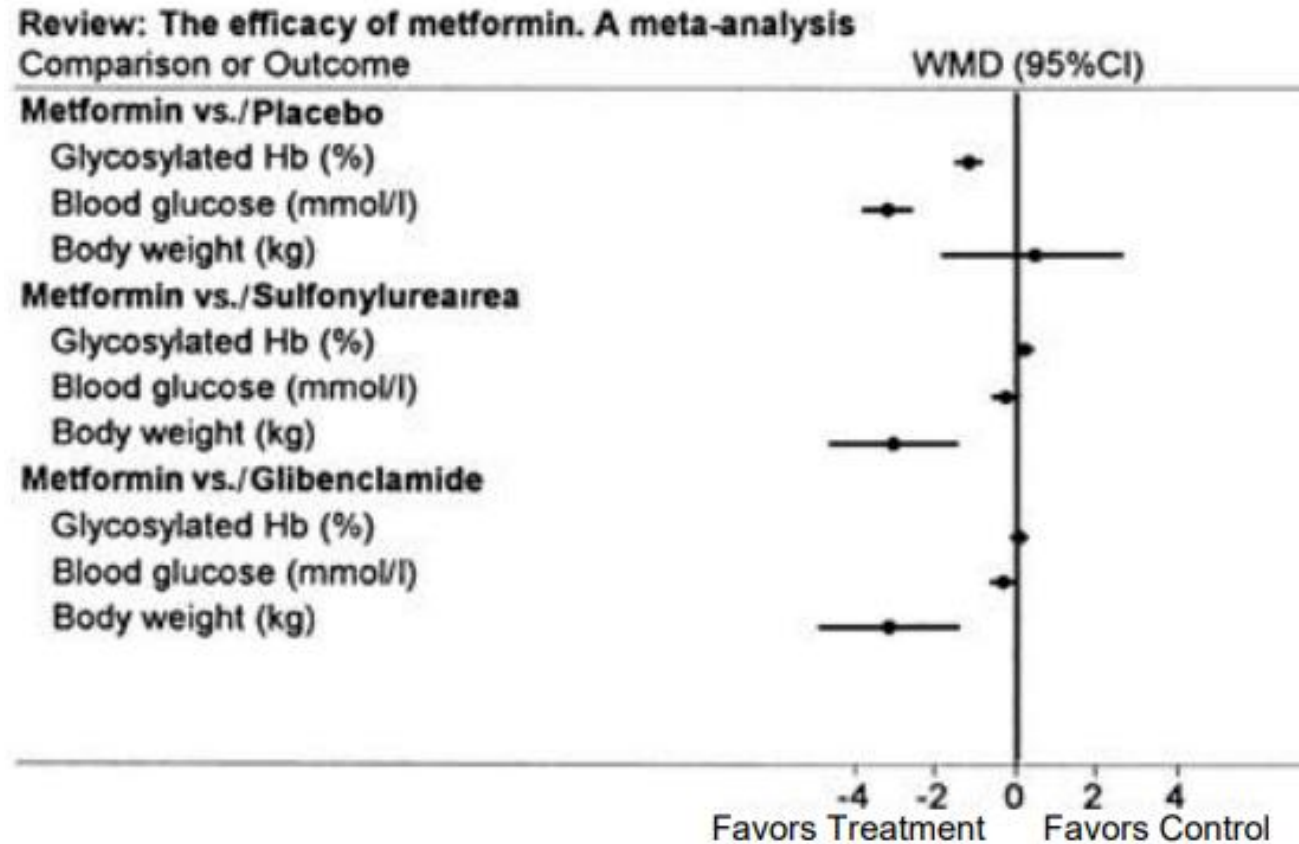


Takeshita Y et al.

Effects of metformin and alogliptin on body composition in people with type 2 diabetes.

J Diabetes Investig. 2019 May;10(3):723-730. doi: 10.1111/jdi.12920.

FARMACI CON EFFETTO "NEUTRO" SUL PESO: METFORMINA



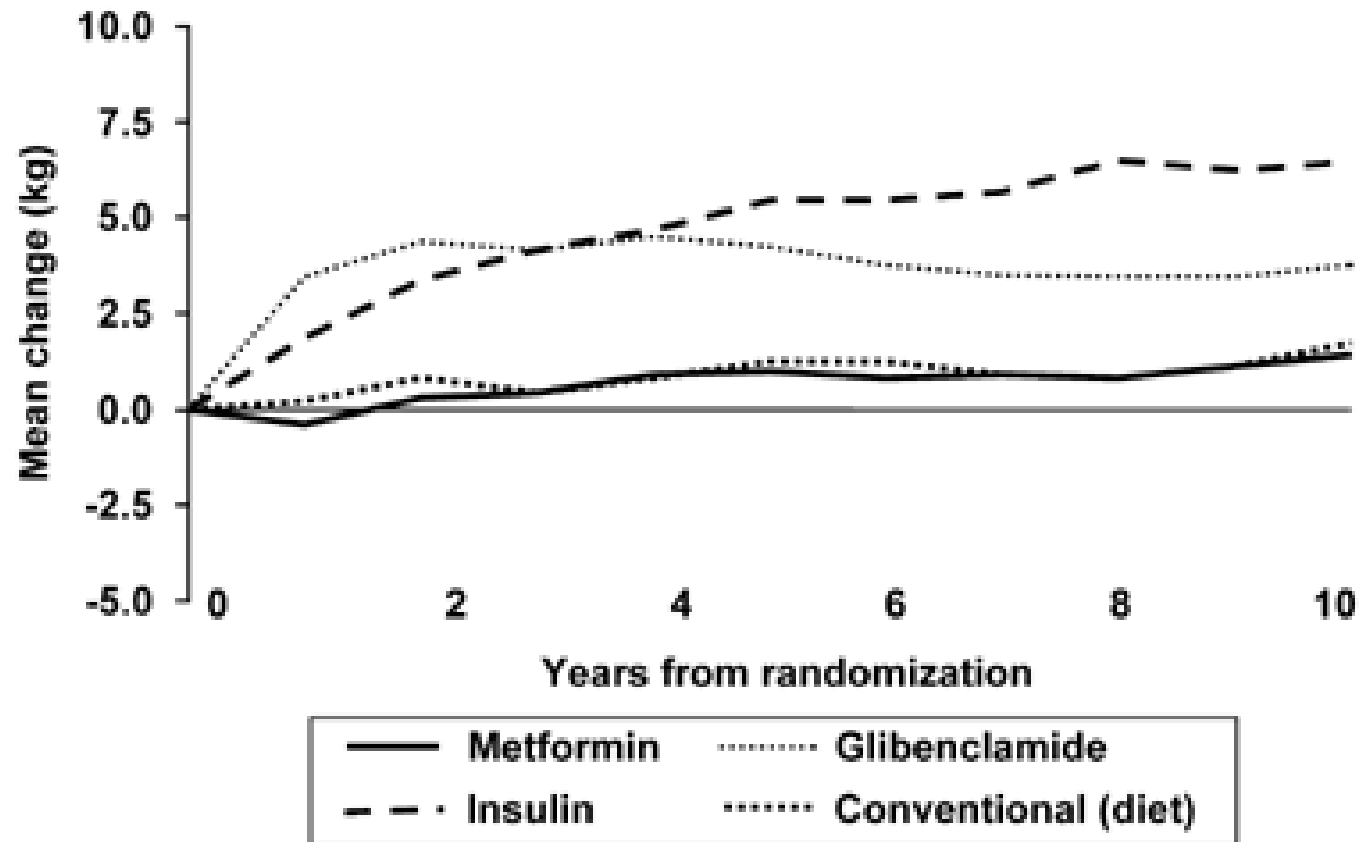
Johansen K.

Efficacy of metformin in the treatment of NIDDM. Meta-analysis.

Diabetes Care. 1999 Jan;22(1):33-7. doi: 10.2337/diacare.22.1.33.

FARMACI CON EFFETTO "NEUTRO" SUL PESO: METFORMINA

EFFETTO DELLA METFORMINA SUL PESO NEI DIABETICI



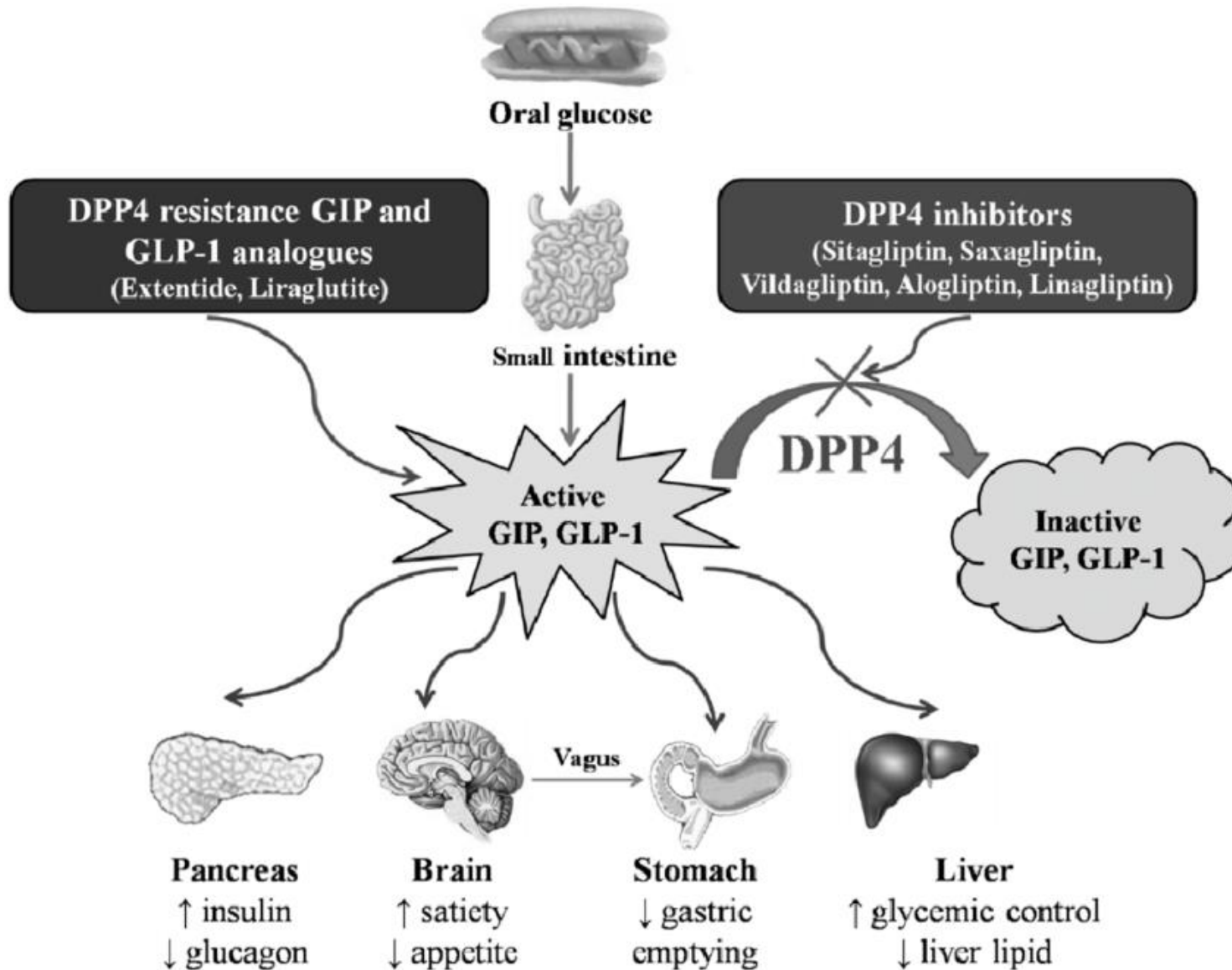
UK Prospective Diabetes Study (UKPDS)

Golay A.

Metformin and body weight.

Int J Obes (Lond). 2008 Jan;32(1):61-72. doi: 10.1038/sj.ijo.0803695.

FARMACI CON EFFETTO NEUTRO SUL PESO: iDPP4

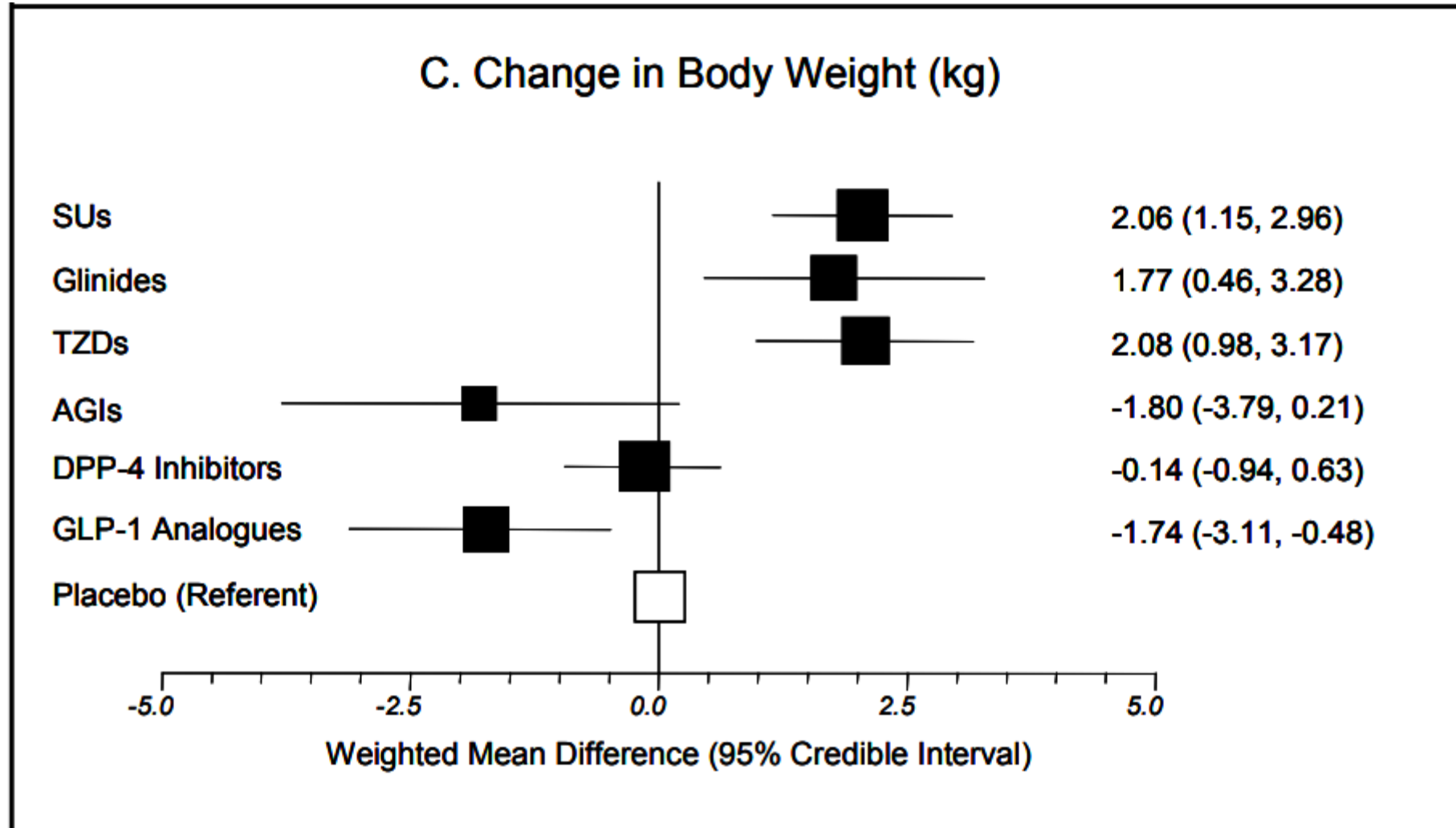


Janardhan S et al.

Dipeptidyl peptidase IV inhibitors: a new paradigm in type 2 diabetes treatment.

Curr Drug Targets. 2014 Jun;15(6):600-21. doi: 10.2174/1389450115666140311102638.

FARMACI CON EFFETTO NEUTRO SUL PESO: iDPP4

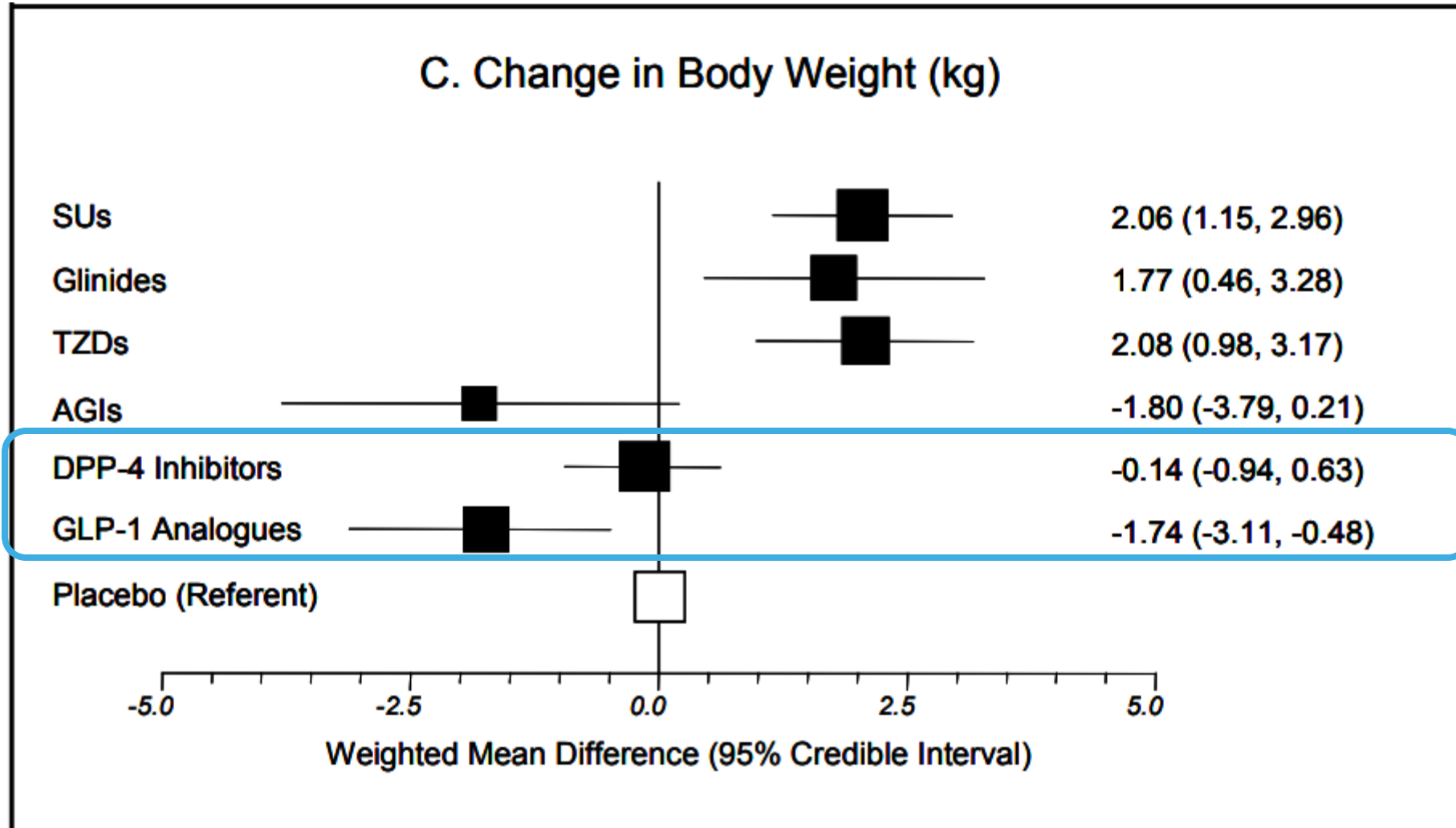


Phung OJ et al.

Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes.

JAMA. 2010 Apr 14;303(14):1410-8. doi: 10.1001/jama.2010.405.

FARMACI CON EFFETTO NEUTRO SUL PESO: iDPP4



Phung OJ et al.

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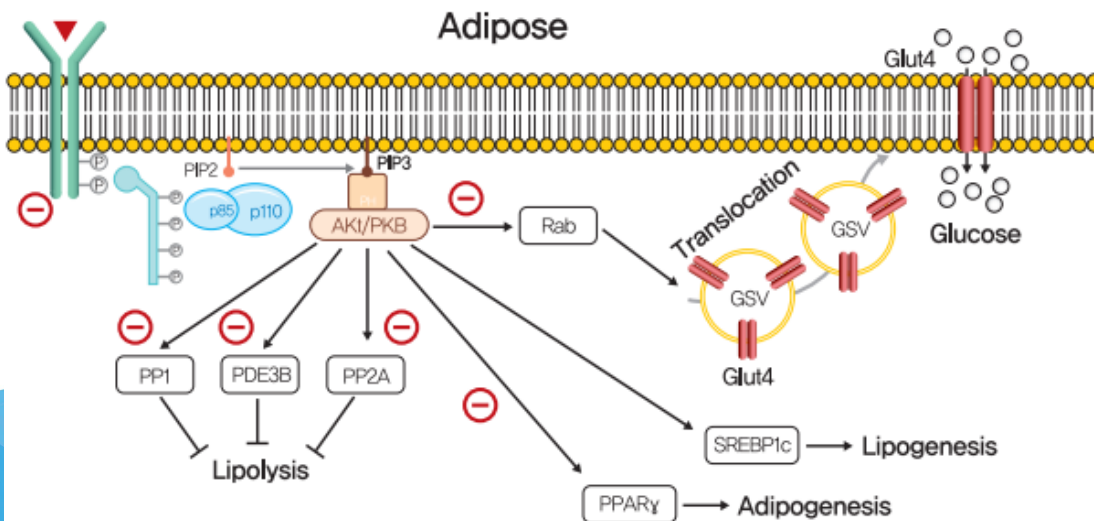
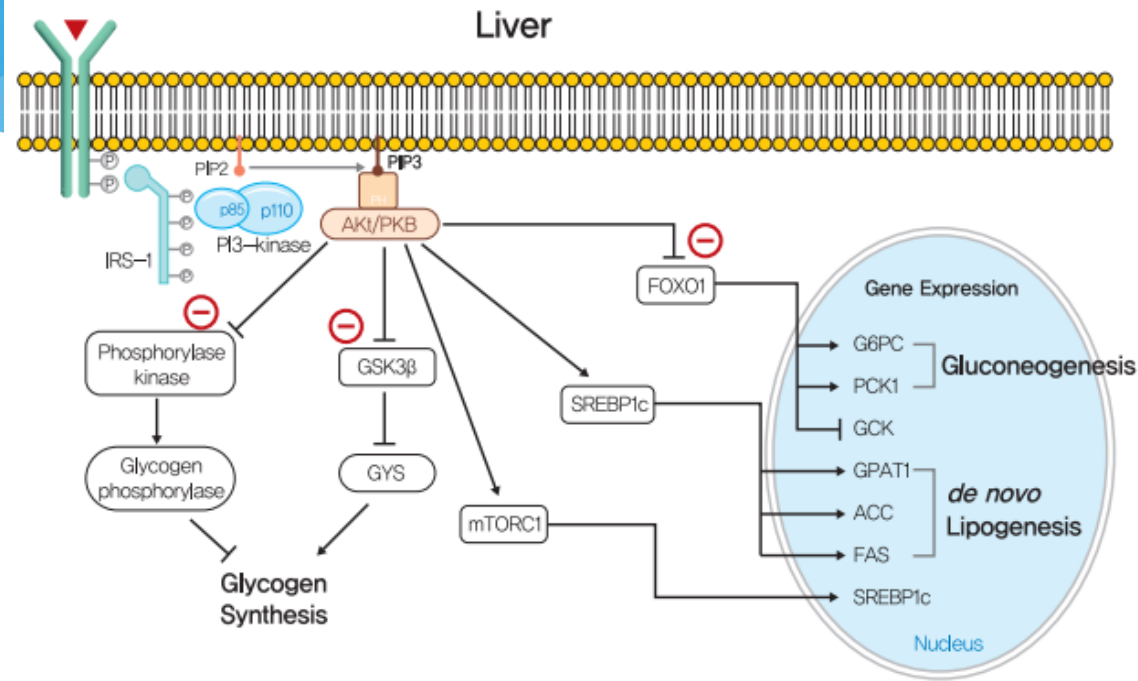
FARMACI CON EFFETTO NEUTRO SUL PESO: iDPP4

- DPP-4 inhibitors increase active GLP-1 concentrations by 2 or 3 times the concentration at baseline.
However, the stimulation of GLP-1 receptor activity with GLP-1RA is several times higher than with DPP-4 inhibitors.
- The long half-life of GLP-1RA, particularly those products administered once-daily or once-weekly, may also contribute to increased efficacy.

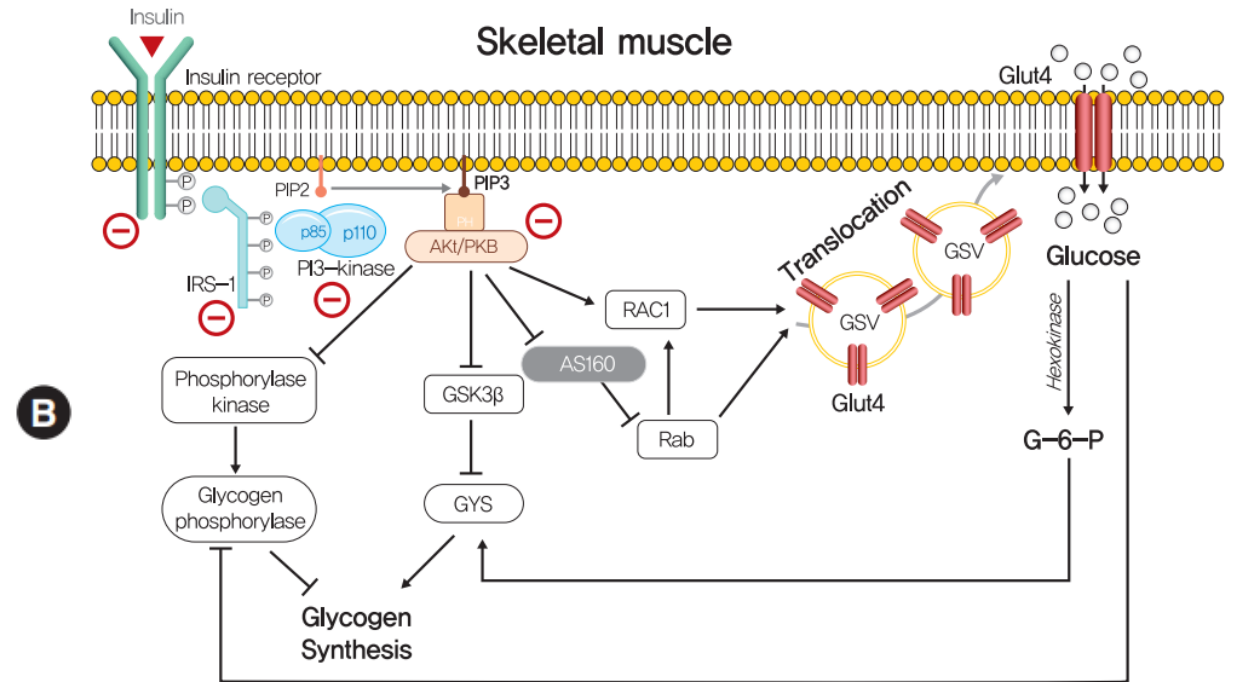
Gilbert MP et al

GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials.
Front Endocrinol (Lausanne). 2020 Apr 3;11:178. doi: 10.3389/fendo.2020.00178.

EFFETTO INCREMENTO SUL PESO: INSULINA



⊖ reduced in fat-induced insulin resistance condition



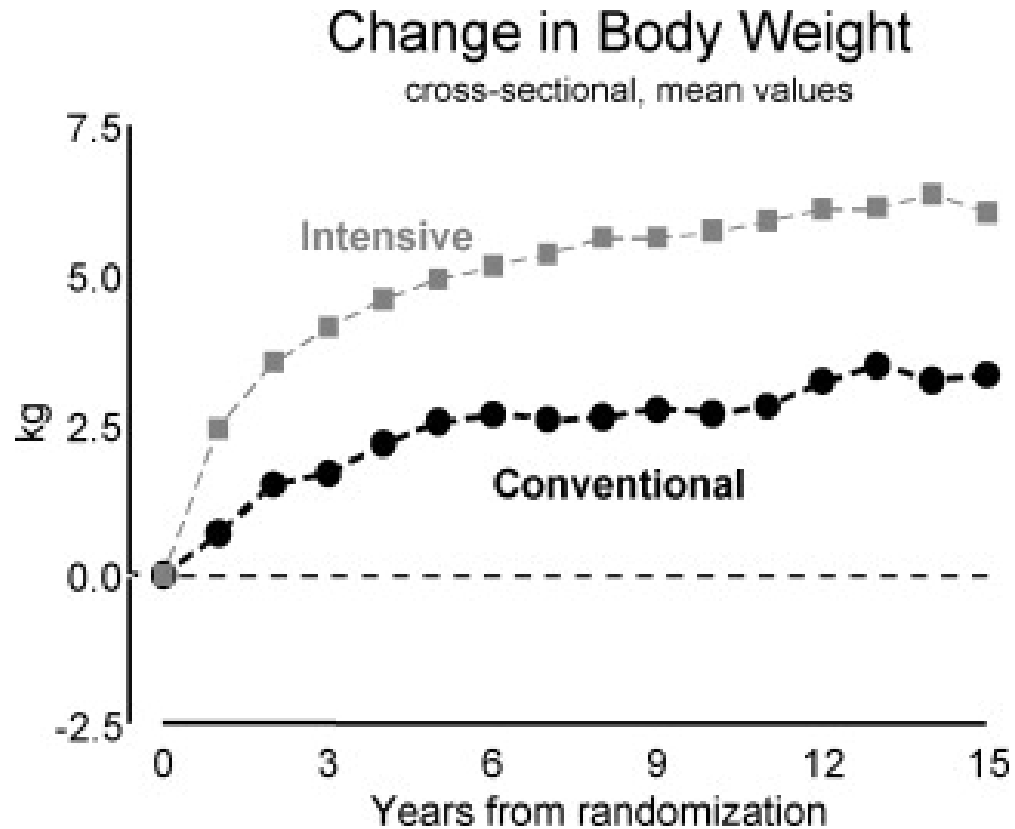
C

Lee SH et al.

Insulin Resistance: From Mechanisms to Therapeutic Strategies.

Diabetes Metab J. 2022 Jan;46(1):15-37. doi: 10.4093/dmj.2021.0280

EFFETTO INCREMENTO SUL PESO: INSULINA



Mechanisms of weight gain with insulin treatment:

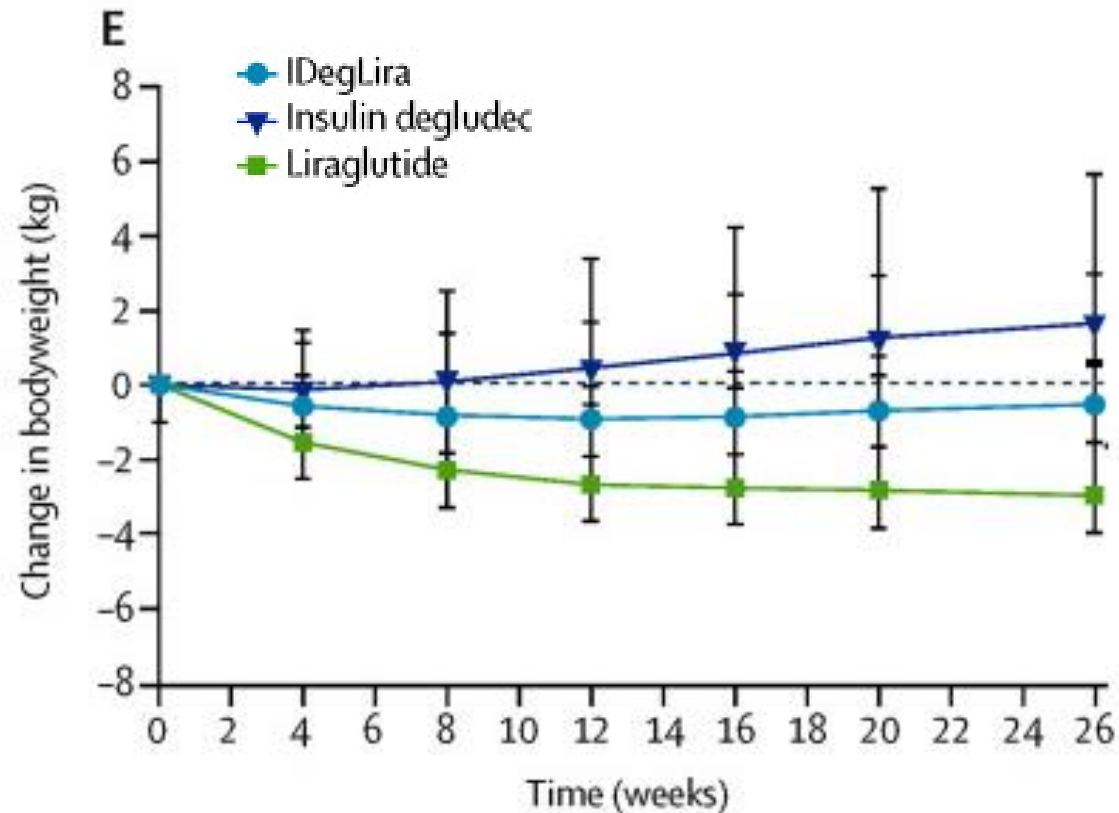
- Anabolic effects of insulin, especially when insulin is given in high doses to overcome insulin resistance
- Elimination of glycosuria with consequent retention of calories
- Appetite stimulation by hypoglycemia, and increased freedom to eat when hyperglycemia is averted or offset by insulin therapy

Heller S.

Weight gain during insulin therapy in patients with type 2 diabetes mellitus.

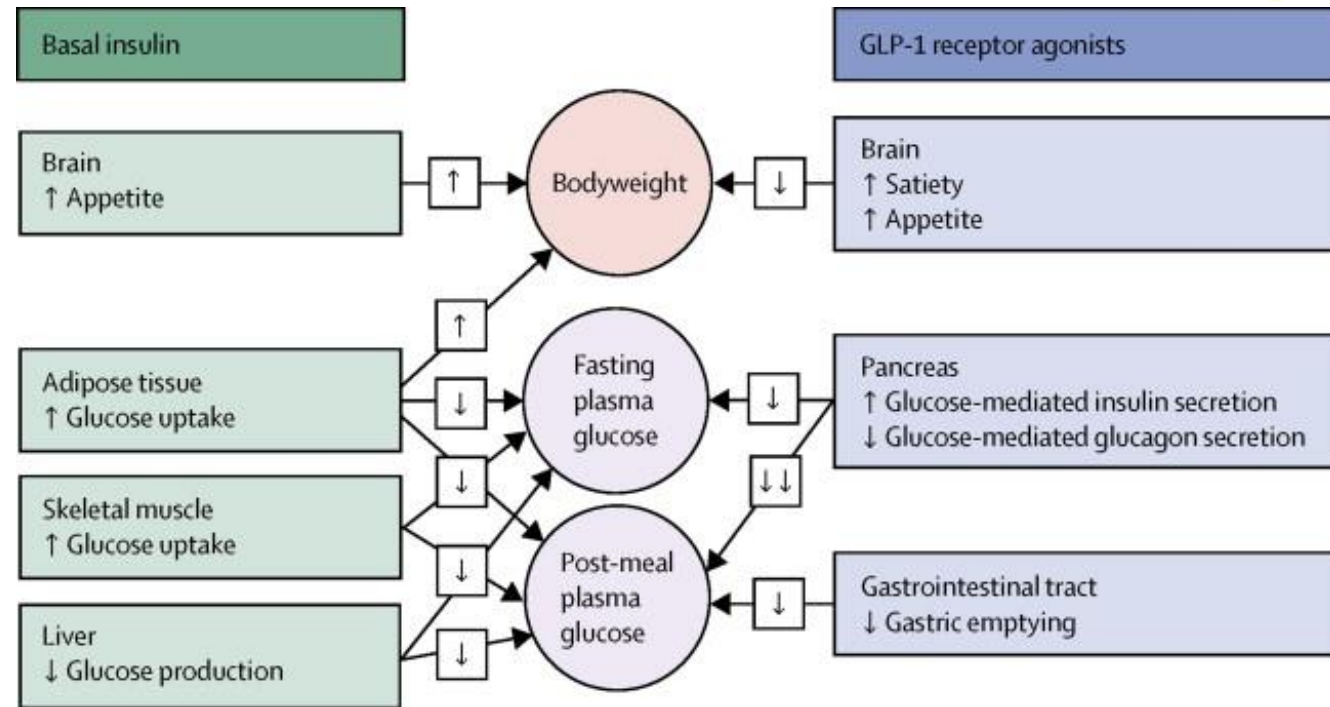
Diabetes Res Clin Pract. 2004 Sep;65 Suppl 1:S23-7. doi: 10.1016/j.diabres.2004.07.005.

EFFETTO INCREMENTO SUL PESO: INSULINA ...e se nell'insulina aggiungiamo un GLP1-RA



Gough SC et al.

Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes.
Lancet Diabetes Endocrinol. 2014 Nov;2(11):885-93. doi: 10.1016/S2213-8587(14)70174-3.

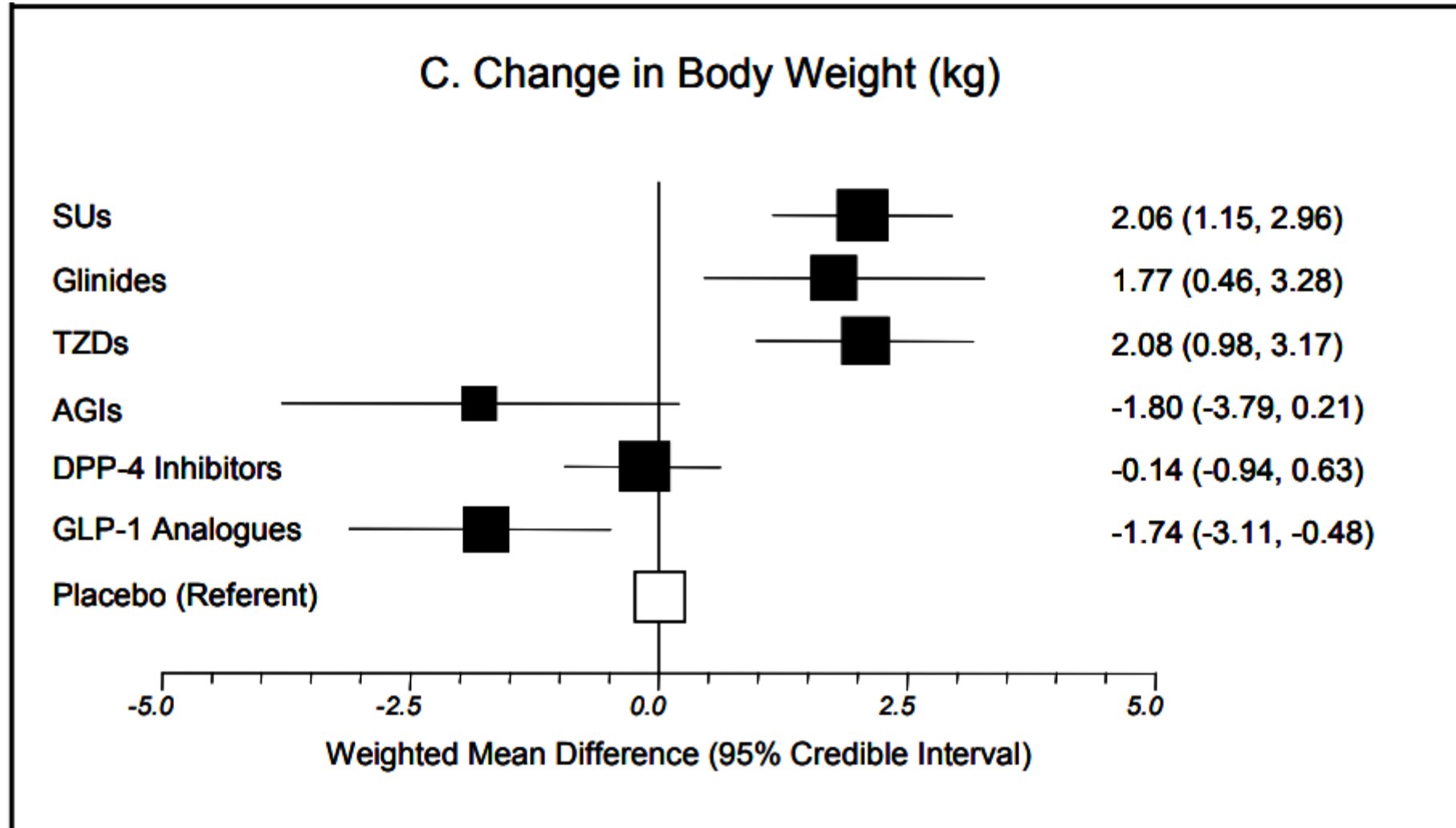


Del Prato S.

Fixed-ratio combination of basal insulin and GLP-1 receptor agonist: is two better than one?

Lancet Diabetes Endocrinol. 2014 Nov;2(11):856-8. doi: 10.1016/S2213-8587(14)70185-8.

EFFETTO INCREMENTO SUL PESO: SULFANILUREE E GLINIDI

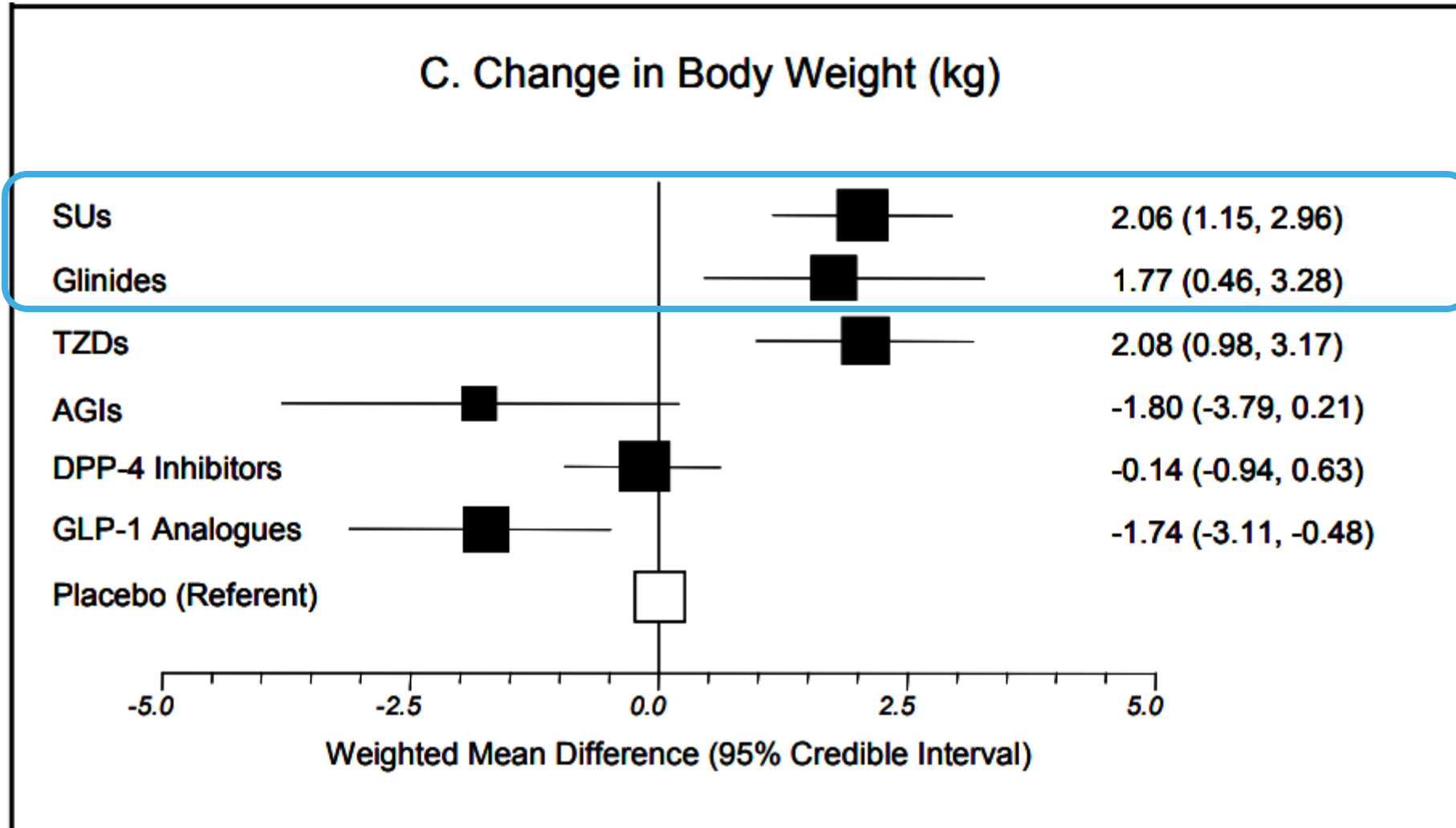


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JAMA. 2010 Apr 14;303(14):1410-8. doi: 10.1001/jama.2010.405.

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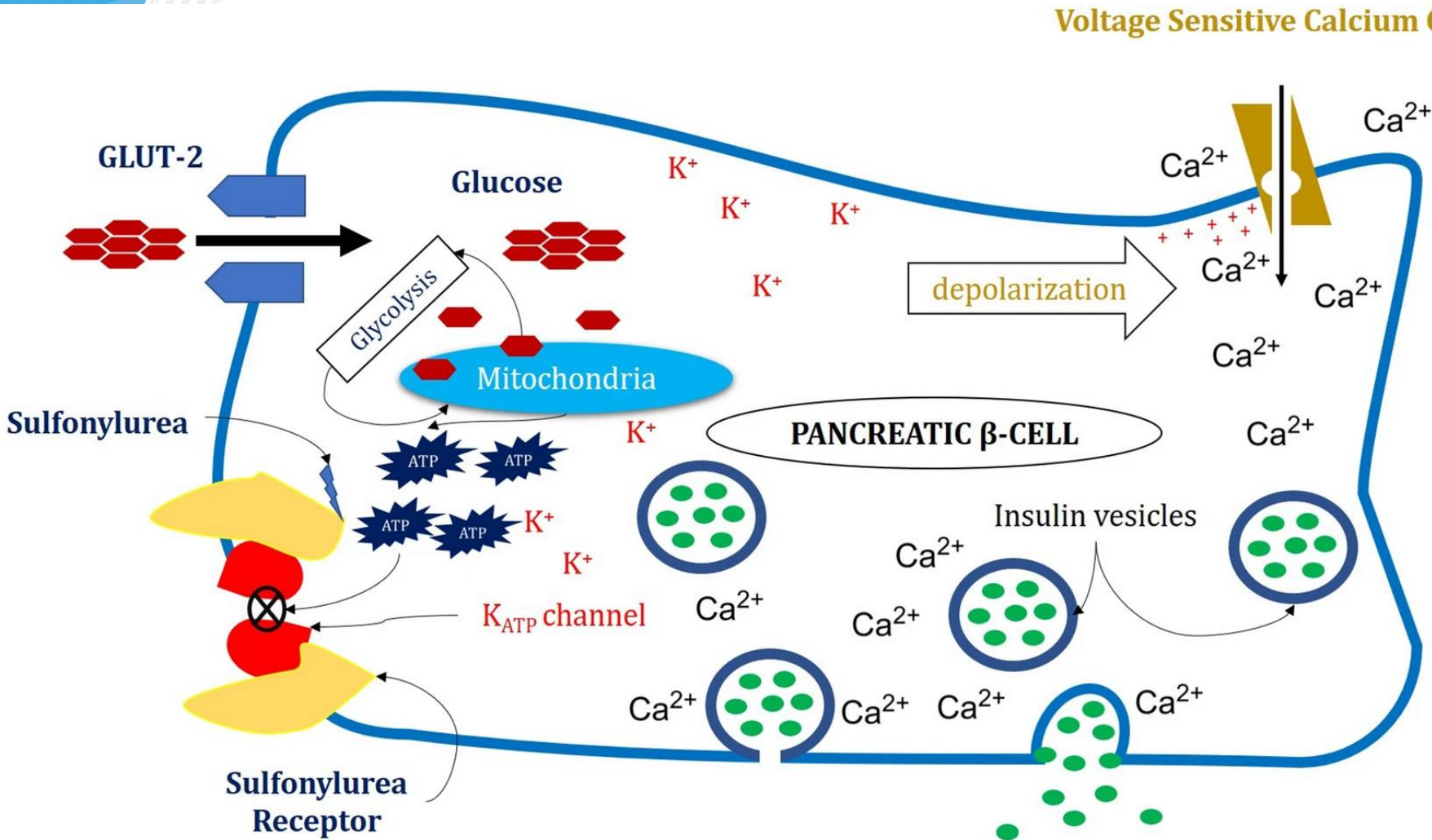


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JAMA. 2010 Apr 14;303(14):1410-8. doi: 10.1001/jama.2010.405.

EFFETTO INCREMENTO SUL PESO: SULFANILUREE E GLINIDI



The weight gain associated with sulfonylureas use is described to be most likely a result of increased caloric intake associated with effort to avoid hypoglycemia, in addition to the effect of increased insulin levels in the body.

Ghusn W et al.
Weight-centric treatment of type 2 diabetes mellitus.

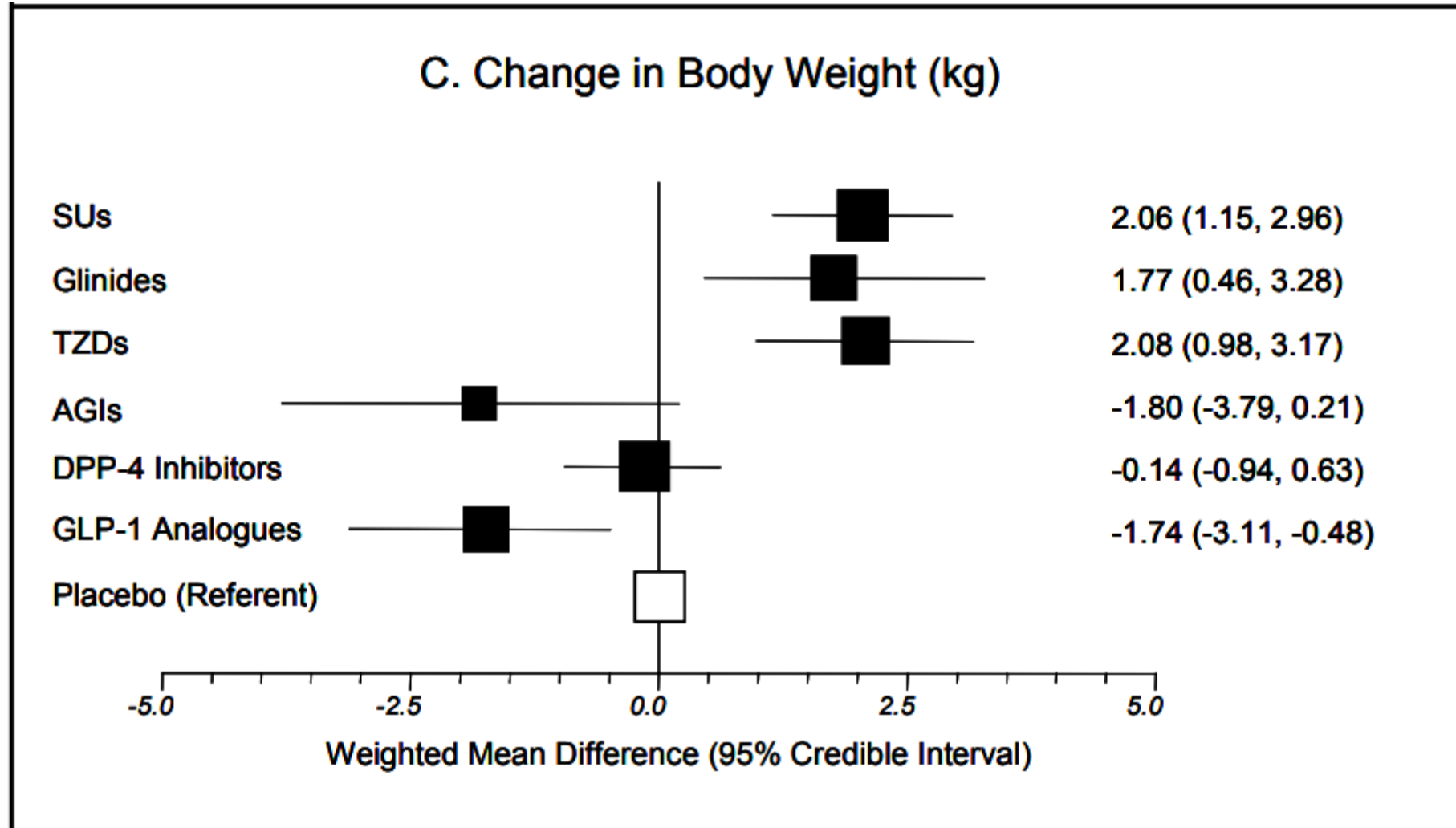
Obes Pillars. 2022 Nov 24;4:100045. doi: 10.1016/j.obpill.2022.100045.

Al-Saleh Y et al.

Sulfonylureas in the Current Practice of Type 2 Diabetes Management: Are They All the Same? Consensus from the Gulf Cooperation Council (GCC) Countries Advisory Board on Sulfonylureas.

Diabetes Ther. 2021 Aug;12(8):2115-2132. doi: 10.1007/s13300-021-01059-1

EFFETTO INCREMENTO SUL PESO: GLITAZONI

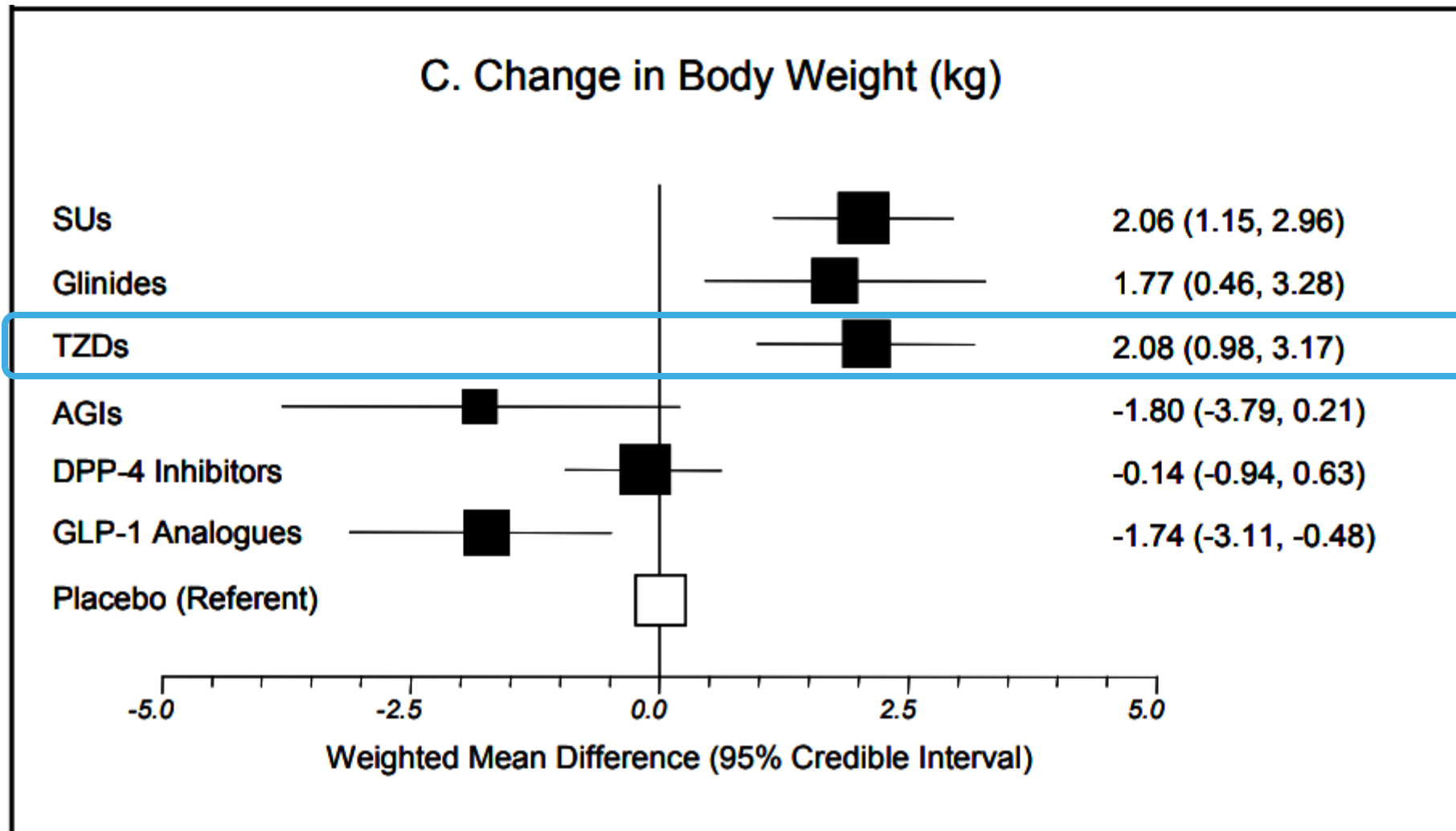


Phung OJ et al.

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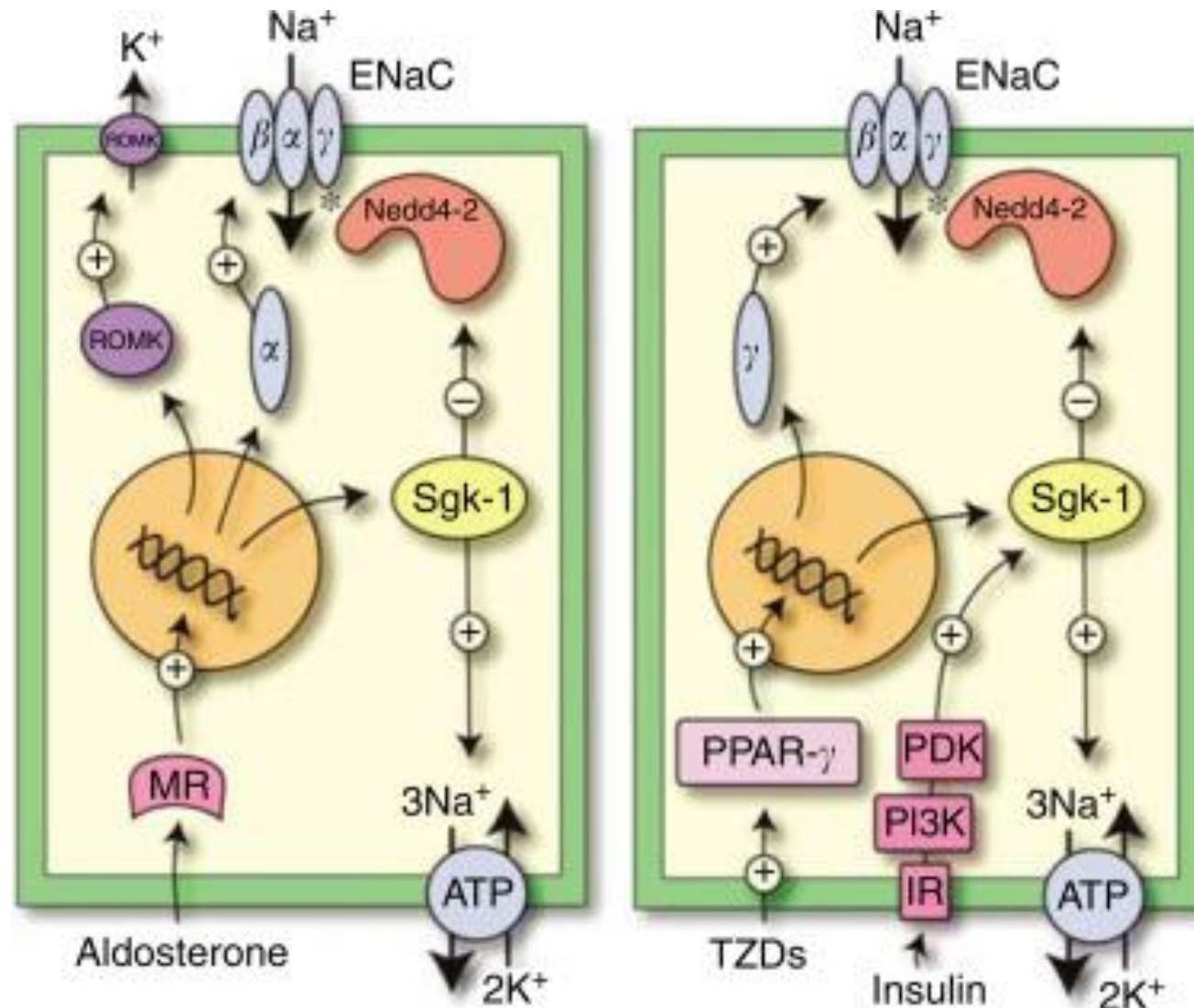


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JAMA. 2010 Apr 14;303(14):1410-8. doi: 10.1001/jama.2010.405.

EFFETTO INCREMENTO SUL PESO: GLITAZONI



Possible Causes of Weight Gain with Thiazolidinediones:

- Fat cell proliferation
- Increased appetite
- Decreased leptin production
- Decreased glycosuria
- Lack of compliance with diet
- Fluid retention

Fonseca V.

Effect of thiazolidinediones on body weight in patients with diabetes mellitus.

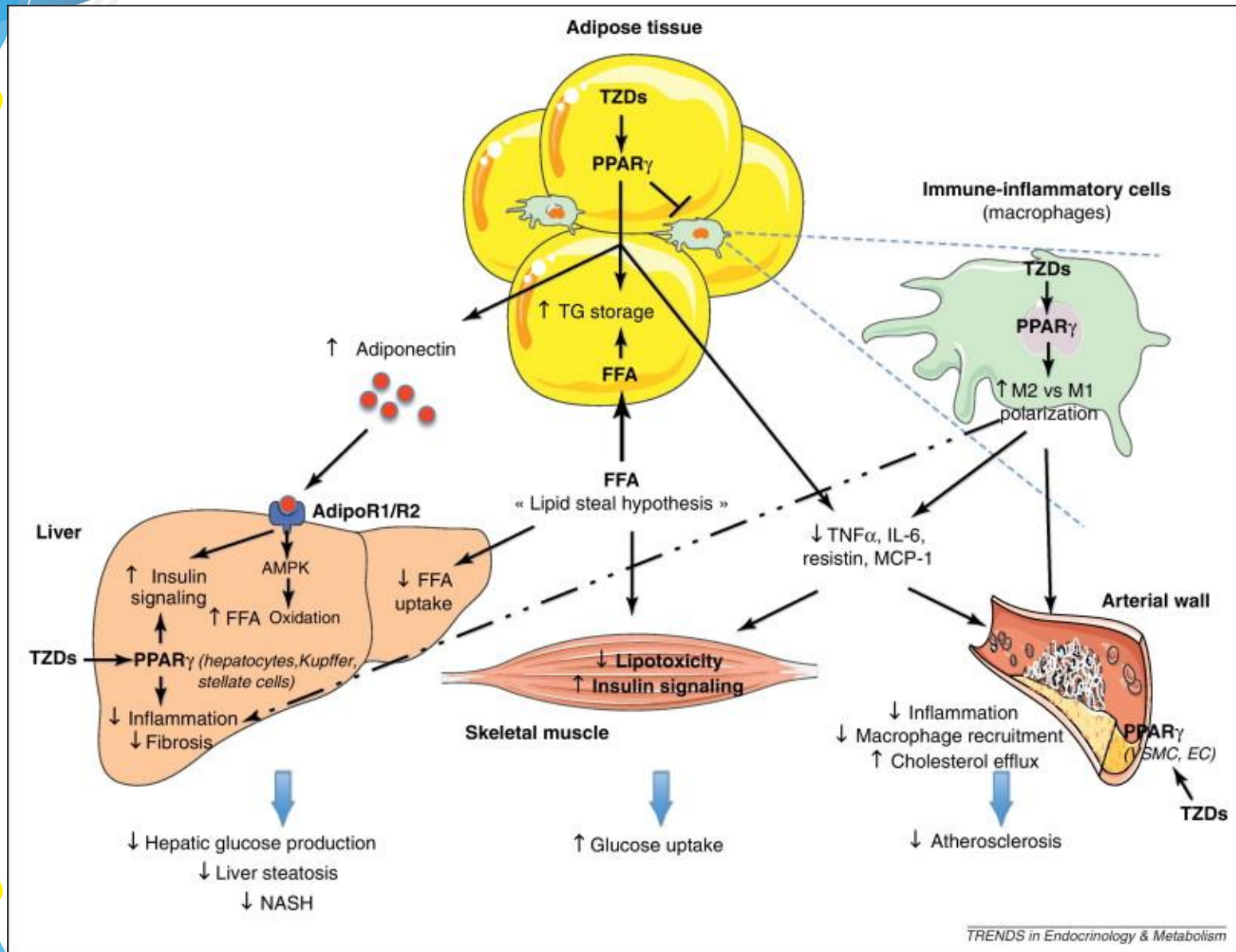
Am J Med. 2003 Dec 8;115 Suppl 8A:42S-48S.
doi: 10.1016/j.amjmed.2003.09.005

Kiryluk K et al.

Thiazolidinediones and fluid retention.

Kidney Int. 2007 Sep;72(6):762-8. doi: 10.1038/sj.ki.5002442.

EFFETTO INCREMENTO SUL PESO: GLITAZONI



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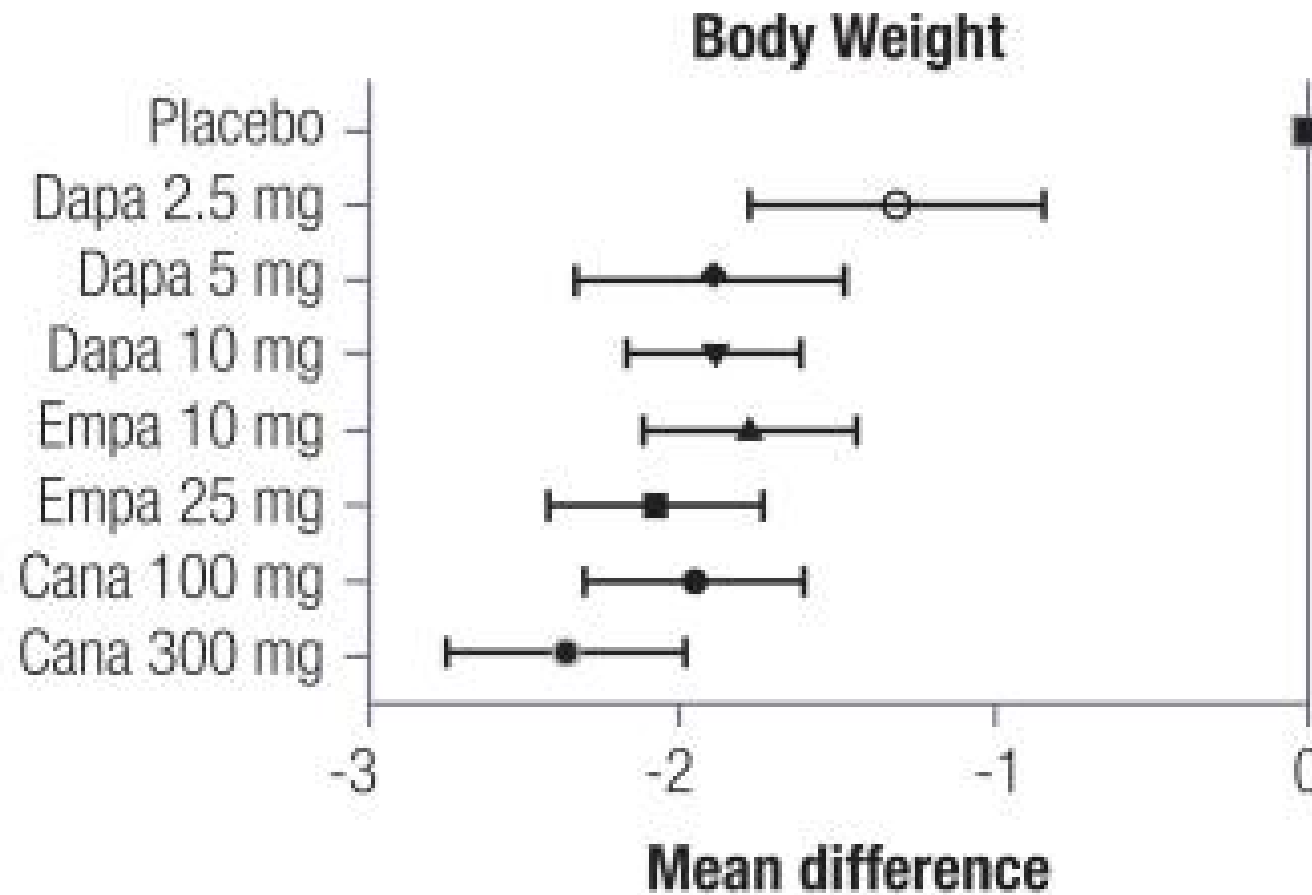
Am J Med. 2003 Dec 8;115 Suppl 8A:42S-48S.
doi: 10.1016/j.amjmed.2003.09.005

Cariou B et al.

Thiazolidinediones and PPAR γ agonists: time for a reassessment.

Trends Endocrinol Metab. 2012 May;23(5):205-15. doi: 10.1016/j.tem.2012.03.001.

EFFETTO RIDUZIONE DEL PESO: iSGLT2

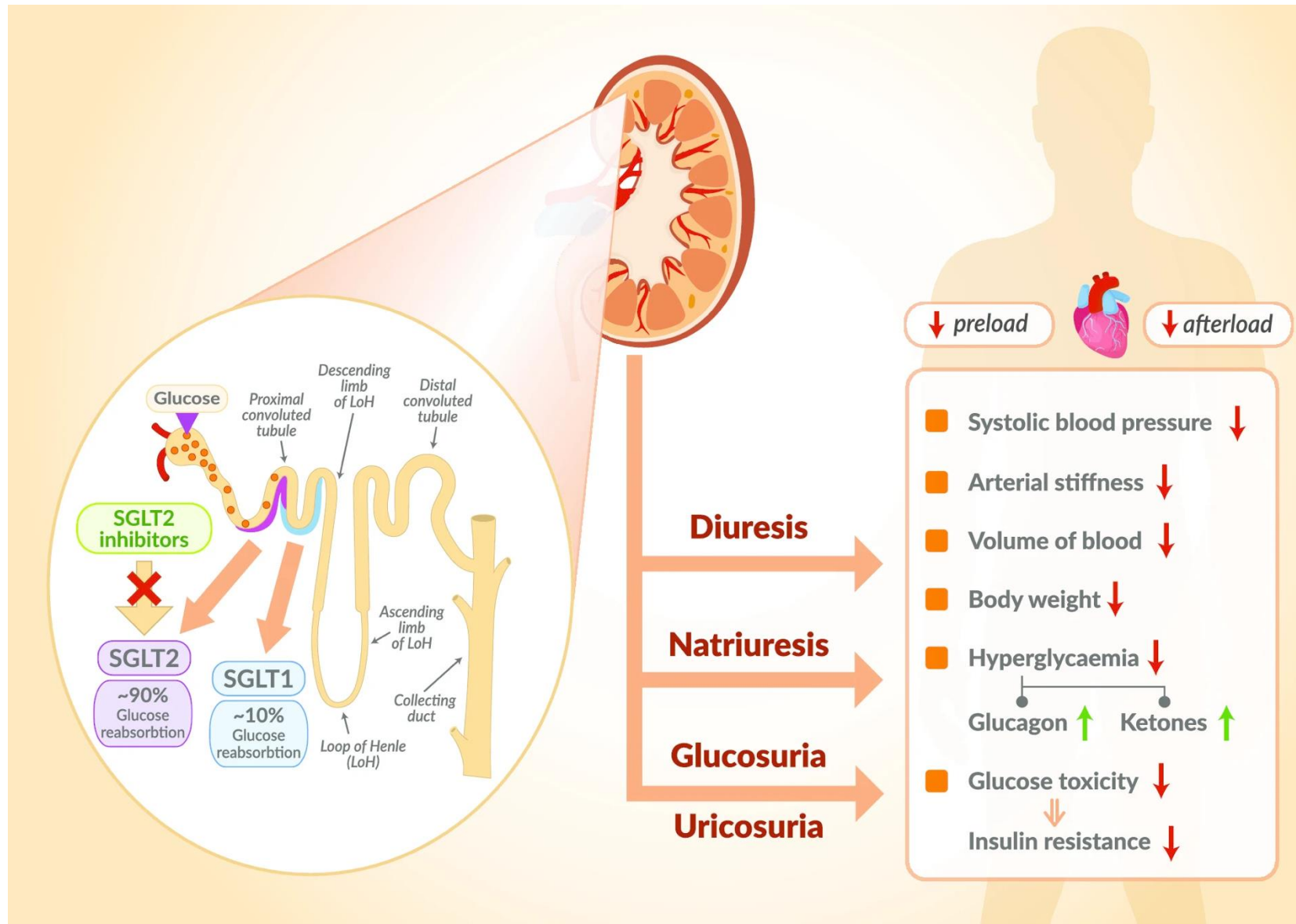


Pinto LC et al.

Dose-ranging effects of SGLT2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis.

Arch Endocrinol Metab. 2022 Mar 8;66(1):68-76. doi: 10.20945/2359-3997000000440.

EFFETTO RIDUZIONE DEL PESO: iSGLT2



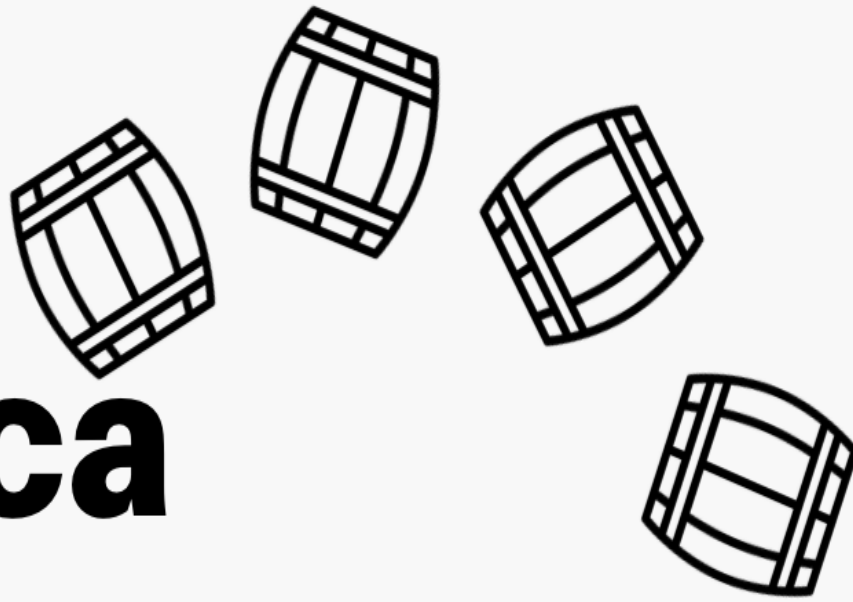
Dutka M et al.

Sodium glucose cotransporter 2 inhibitors: mechanisms of action in heart failure.

Heart Fail Rev. 2021 May;26(3):603-622. doi: 10.1007/s10741-020-10041-1.

EFFETTO RIDUZIONE DEL PESO: GLP1-RA e GLP1-RA/GIP

**Scarica
Barile.**



EFFETTO RIDUZIONE DEL PESO: GLP1-RA e GLP1-RA/GIP



Terza Sessione – “The best is yet to come” Opportunità di terapia farmacologica

Moderatori: R. Fornengo, A.R. Pia

- 14.00 Effetto sul peso dei farmaci diabetologici
G. Margiotta
- 14.20 Agonisti GLP-1 e doppi agonisti:
ruolo nel paziente diabetico e non diabetico
M. Pellegrino
- 14.40 La remissione del diabete: un sogno divenuto realtà
M. Valenzano
- 15.00 Discussione sui temi trattati
Discussants: R. Fornengo, A.R. Pia
- 15.20 Conclusioni e Take Home Messages
F. Garino, E. Pergolizzi

SINOSSI, OVVERO ARRIVIAMO ALL'OSSO DELLA QUESTIONE

Profiles of Antidiabetic Medications



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra- indicated if eGFR < 30 mL/min/ 1.73 m ²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/ min/1.73 m ² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF CARDIAC ASCVD	Neutral	See #1	See #2	See #3	Neutral	Moderate May Reduce Stroke Risk	Neutral Possible ASCVD Risk	Neutral Benefit	Neutral Safe	CHF Risk Neutral	Neutral
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

■ Few adverse events or possible benefits
 ■ Likelihood of adverse effects
 ■ Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

Garber AJ, Abrahamson
 MJ, Barzilay JI, et al.
AACE/ACE
comprehensive type 2
diabetes
management
algorithm
 2018. Endocr Pract.
 2018;24:91–120

SINOSSI, OVVERO ARRIVIAMO ALL'OSSO DELLA QUESTIONE

Profiles of Antidiabetic Medications



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
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Profiles of Antidiabetic Medications



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN					INSULIN
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain					Gain
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate	
CHF						Moderate	Neutral	Neutral	Neutral	CHF Risk		
CARDIAC ASCVD												Neutral
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

■ Few adverse events or possible benefits
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EPILOGO, OVVERO IL "BILANCIO" CON LA REALTÀ



SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ



Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

Linea guida pubblicata nel Sistema Nazionale Linee Guida

Roma, 26 luglio 2021

Aggiornamento 23 febbraio 2023

5. Terapia farmacologica

<i>Nessun evento cardiovascolare, non scompenso cardiaco, eGFR ≥ 60 ml/min</i>	<i>Nessun evento cardiovascolare, non scompenso cardiaco, eGFR < 60 ml/min</i>	<i>Pregresso evento cardiovascolare, non scompenso cardiaco</i>	<i>Scompenso cardiaco</i>
Metformin	Metformin ¹ SGLT2i	Met. GLP1RA SGLT-2i	SGLT2i
SGLT2i GLP1RA	GLP1RA		Met. ² GLP1RA
DPP4i Acar. Pio. Ins.	DPP4i Acar. Pio. Ins.	DPP4i Acar. Pio. Ins.	DPP4i ³ Acar. Insulin

E IL PESO? DOV'È?

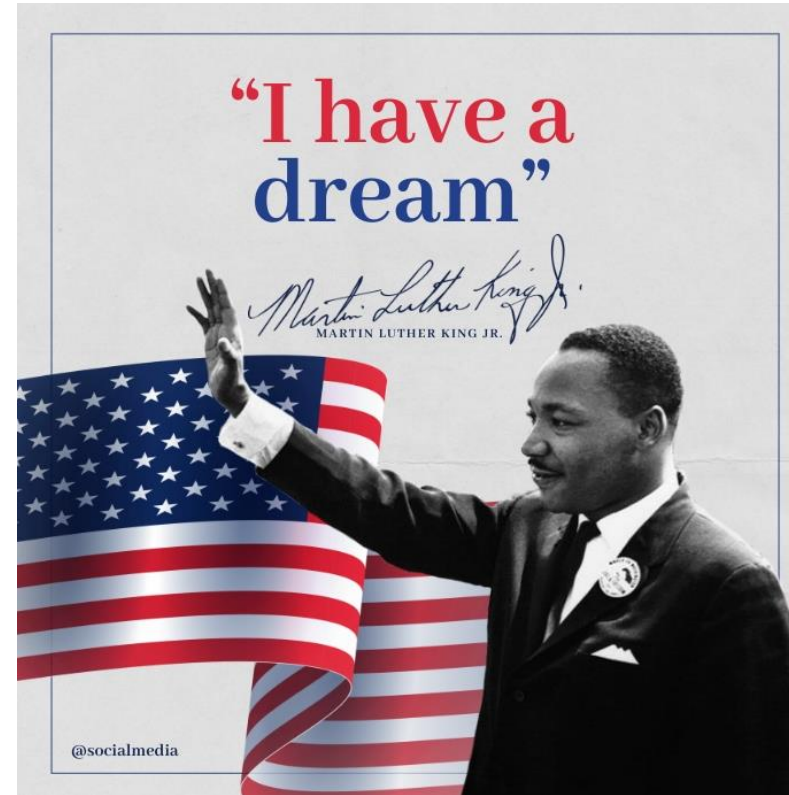
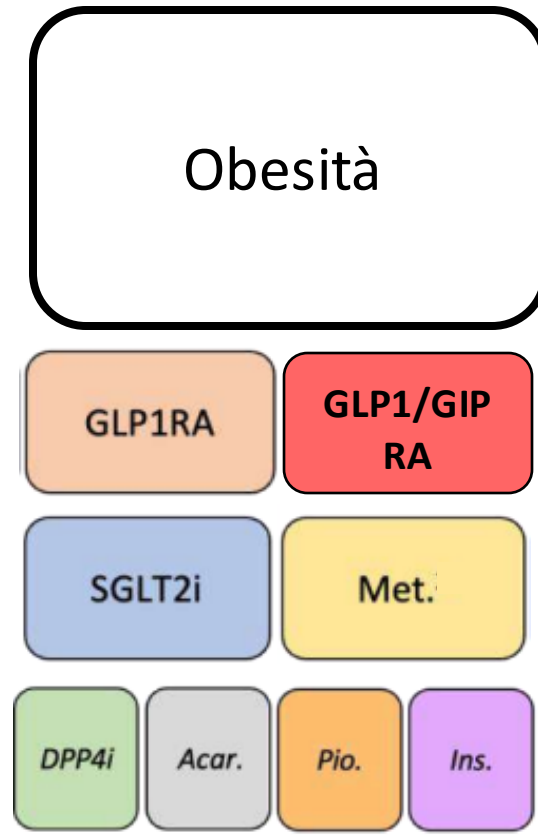
**“I have a
dream”**

Martin Luther King Jr.
MARTIN LUTHER KING JR.



@socialmedia

...IL "QUINTO QUARTO"



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**GRAZIE PER
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