



CONGRESSO REGIONALE
AMD-SID LAZIO

II DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA



ROMA - 7/8 OTTOBRE 2022 - HOTEL QUIRINALE

Update delle terapie per la diabesi

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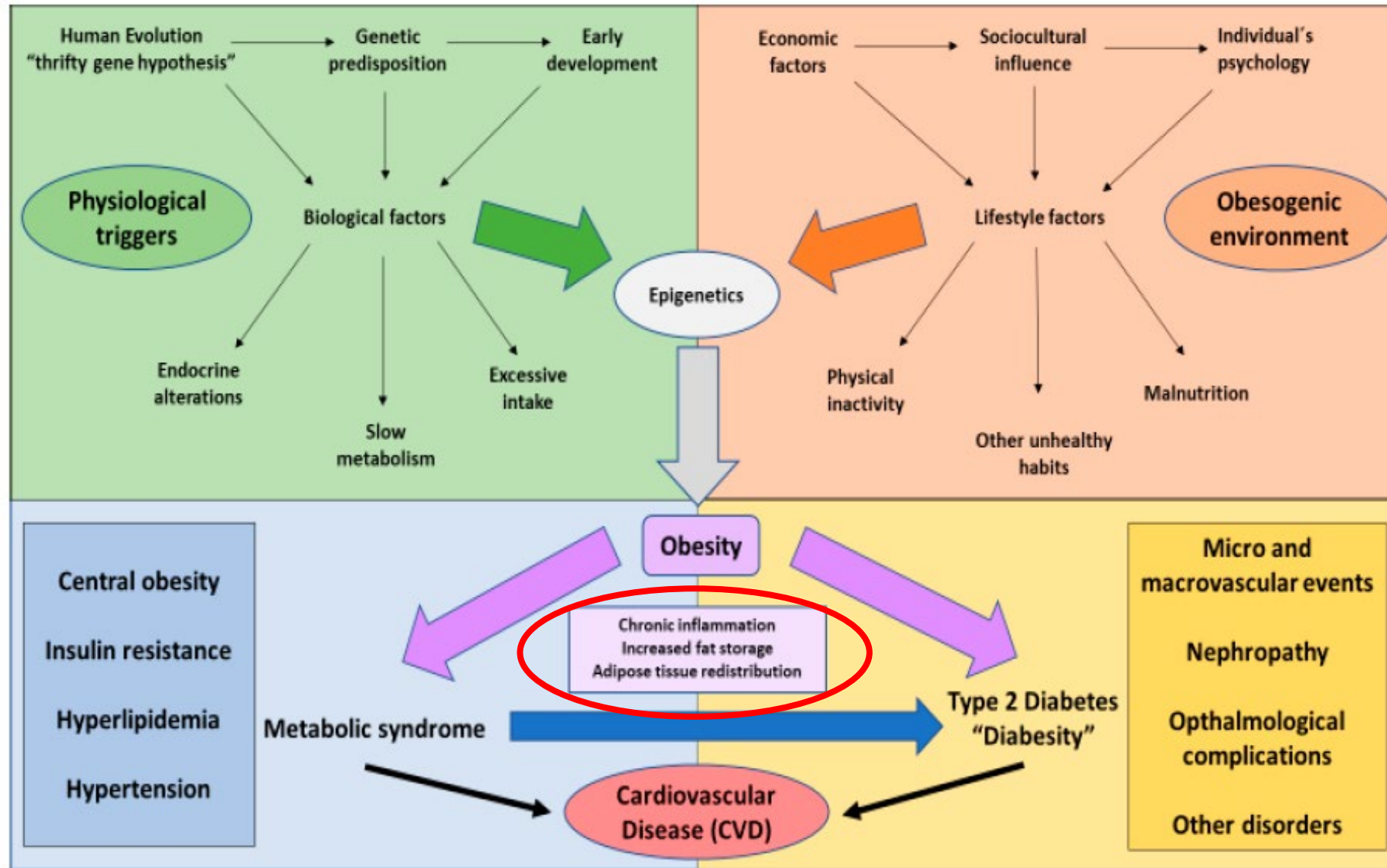
Roma, 7-8 ottobre 2022

La dr.sa Danila Capoccia 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.).

Percorso che porta dall'obesità alla diabesità



Più dell'80% dei pazienti diabetici sono sovrappeso/obesi

3 possibili meccanismi per spiegare la stretta relazione tra queste 2 condizioni:

- Infiammazione cronica
- Lipotossicità (generata dall'accumulo di grasso ectopico)
- Rilascio di adipokine dal tessuto adiposo

AGENDA

Diabesità

- ✓ Update sull'efficacia di vecchi e nuovi farmaci
- ✓ Update sul ruolo degli endocannabinodi e sul ruolo de microbiota
- ✓ Update sul ruolo della chirurgia metabolica

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Anti-diabetic drugs and weight loss in patients with type 2 diabetes

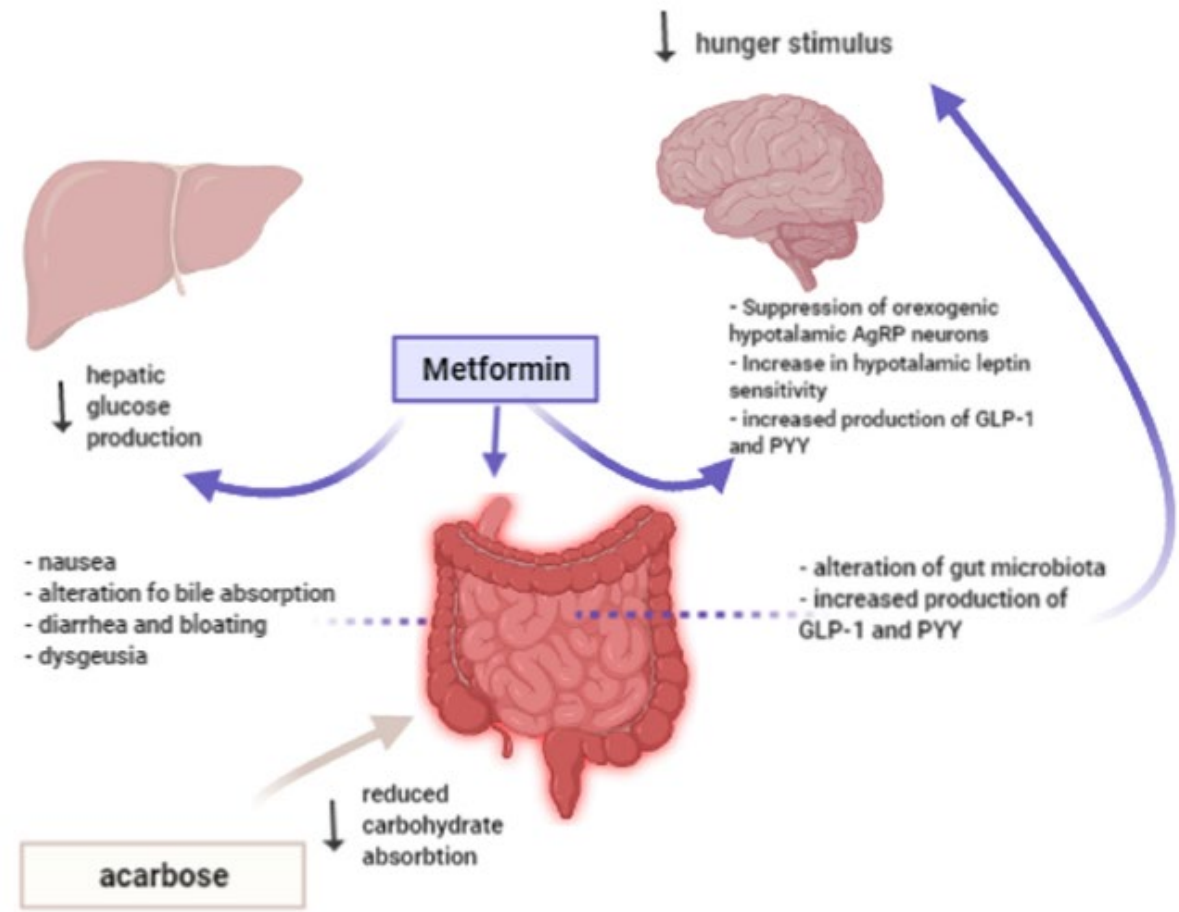
Pharmacological Research 171 (2021) 105782

Review

I farmaci antidiabetici posso essere divisi in 3 gruppi sulla base della loro efficacia sul calo ponderale:

- **Lieve efficacia** (< 3%): metformina, acarbosio, empagliflozin, exenatide
- **Modesta efficacia** (tra 3 e 5%): canagliflozin, ertugliflozin, dapagliflozin, dulaglutide
- **Forte efficacia** (> 5%): liraglutide, semaglutide, *tirzepatide*

MECCANISMI D'AZIONE DELLA METFORMINA E ACARBOSIO
LEGATI AL CALO PONDERALE



La **metformina** agisce sulla perdita di peso attraverso i suoi effetti collaterali gastrointestinali, attraverso un effetto centrale di soppressione dell'appetito e attraverso il suo effetto insulino-sensibilizzante con il vantaggio che la sua aggiunta alla terapia insulinica può mitigare l'aumento di peso

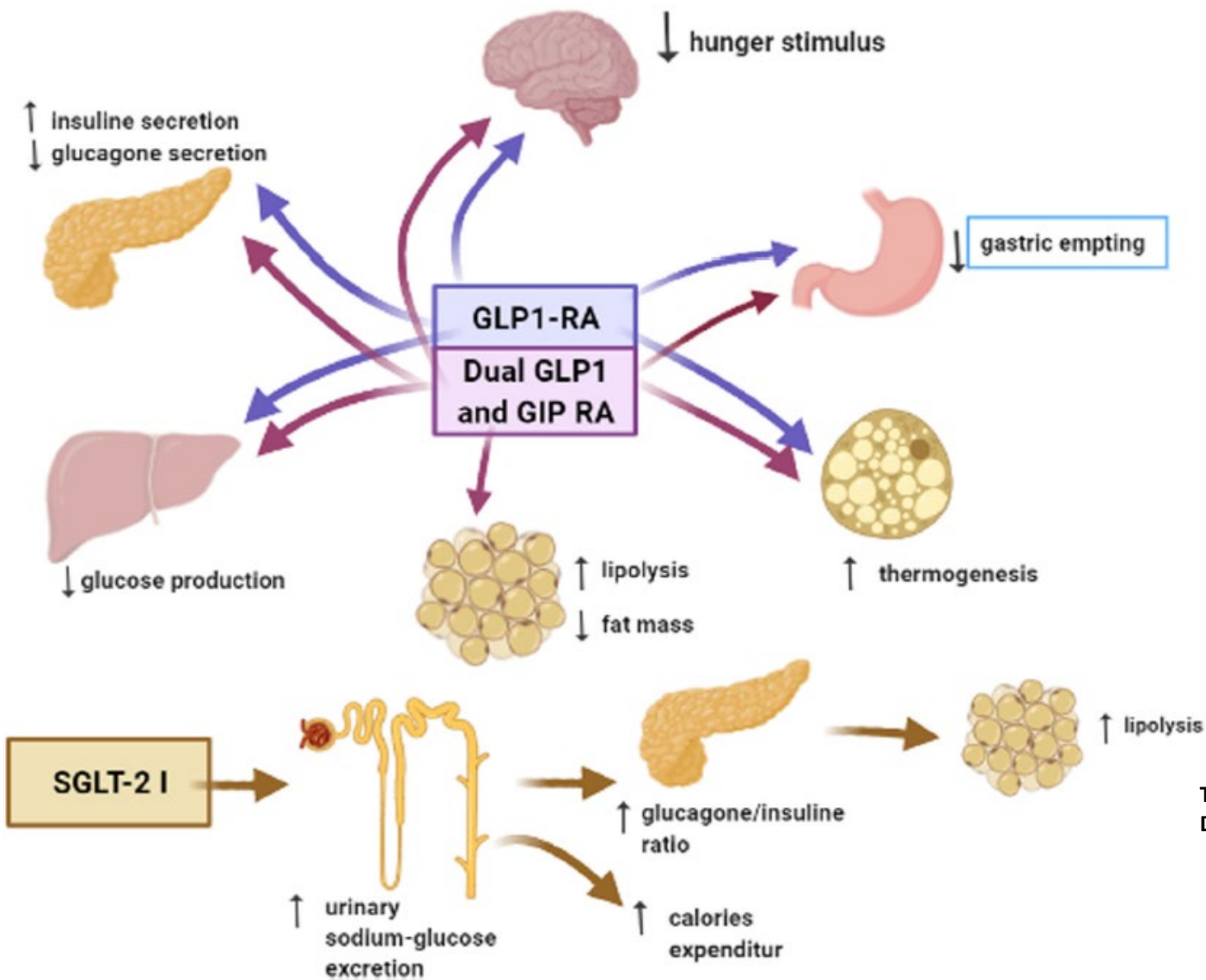
L'**acarbosio** provoca una riduzione nell'assorbimento intestinale del glucosio, inducendo così una riduzione dell'apporto calorico giornaliero

Principali studi relativi alla perdita di peso
nei pazienti diabetici trattati con
metformina e inibitori dell'α-glucosidasi

Drug	Study	Dose (mg)	Average weight loss (Kg)	% weight loss vs. baseline	Observation interval (weeks)
Metformin	Stumvoll et al.	2550 per day	-2.7 ± 1.3	-2.8%	16
	Kahn et al.	500 per day	-2.9 (CI -3.4; -2.3)	-3.2%	260
	DeFronzo et al.	2550 per day	-0.6 ± 0.3	-0.6%	29
	Holman et al.	2550 per day	+1.5 (no CI provided)	+1.7%	312
Acarbose	Wolever et al.	200 three times per day	-0.4 ± 0.3	-0.4%	52

Lieve efficacia (< 3.2%): metformina, acarbosio

MECCANISMI D'AZIONE DEGLI SGLT2-i E GLP1-RA
LEGATI AL CALO PONDERALE



		GLP-1	GIP
Pancreas	Beta cells	↑Insulin synthesis	↑Insulin synthesis
		↑Insulin secretion	↑Insulin secretion
		↑Cell proliferation	↑Cell proliferation
		↑Glucose sensing	↑Glucose sensing
Brain	Alpha cells	↓Glucagon secretion	↑Glucagon secretion
		↑Satiety	
Gastrointestinal		↓Appetite	
		↓GI motility	
Adipose tissues		↓Gastric emptying	
			↑Lipolysis
			↑Fatty acid synthesis
			?Anti-lipogenic effect

The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type 2 Diabetes: The SURPASS Clinical Trials. *Diabetes Ther.* 2020

Principali studi relativi alla perdita di peso nei pazienti diabetici trattati con SGLT2- inibitori

Drug	Study	Dose (mg)	Average weight loss (Kg)	% weight loss vs. baseline	Observation interval (weeks)
Empagliflozin	EMPA-REG Study	25 per day	-2.0 ± 0.5	-2.5%	24
		10 per day	-1.6 ± 0.4	-1.9%	24
		25 per day	-1.5 ± 0.2	NA	24
Ertugliflozin	VERTIS SITA2 study	5 per day	-3.4 ± 0.4	NA	26
		15 per day	-3.0 ± 0.4	NA	26
	VERTIS FACTORIAL	5 per day	-2.7 ± 0.4	- 3.0%	26
		15 per day	-3.7 ± 0.4	- 4.2%	26

Lieve efficacia (< 3.2%): empagliflozin

Modesta efficacia (tra 3.2 e 5%): canagliflozin, ertugliflozin, dapagliflozin

Drug	Study	Dose (mg)	Average weight loss (Kg)	% weight loss vs. baseline	Observation interval (weeks)
Canagliflozin	Stenl�f et al.	100 per day	-1.9 ± 0.3	-2.2%	26
		300 per day	-2.9 ± 0.7	-3.3%	26
	CANVAS study	100 per day	-1.6 ± 0.1	-1.8%	188
		100 per day	-2.3 (no CI provided)	-2.6%	12
	Rosenstock et al.	300 per day	- 3.0 (no CI provided)	-3.4%	12
Dapagliflozin	Ferrarini et al.	5 per day	-2.8 ± 0.5	-3.2%	24
		10 per day	-3.2 ± 0.5	-3.4%	24
		10 per day	-3.2 ± 0.4	NA	52
	Nauck et al.	10 per day	-1.8 ± 0.2	NA	218
		10 per day	-1.8 ± 0.2	NA	218
	Bailey et al.	5 per day	-2.9 ± 0.5	-3.4%	24
		10 per day	-1.5 ± 0.2	-1.8%	102
		10 per day	-2.7 ± 0.5	-3.1%	24
		10 per day	-1.4 ± 0.3	-1.6%	102
	Bolinder et al.	10 per day	-4.5 ± 0.9	-4.9%	52

Principali studi relativi alla perdita di peso nei pazienti diabetici trattati con GLP1 analoghi

Drug	Study	Dose (mg)	Average weight loss (Kg)	% Weight loss vs. baseline	Observation interval (weeks)	Drug	Study	Dose (mg)	Average weight loss (Kg)	% Weight loss vs. baseline	Observation interval (weeks)	
Exenatide	Vilsbøll et al.	10 µg per day	-2.8 ± 1-3	NA	20	Semaglutide	SUSTAIN1	0.5 per week	-3.7 ± 0.8	- 4.1%	30	
	Buse et al.	10 µg per day	-1.6 ± 0.3	- 1.7%	26			1.0 per week	-4.5 ± 0.8	- 4.9%	30	
	De Fronzo et al.	10 µg per day	-2.8 ± 0.5	- 2.8%	30		SUSTAIN2	0.5 per week	-4.3 (No CI provided)	- 4.8%	56	
		5 µg per day	-1.6 ± 0.4	- 1.6%	26			1.0 per week	-6.1 ± 1.0	- 6.8%	56	
Liraglutide	Vilsbøll et al.	1.2 per day	-2.2 ± 1.3	NA	20		SUSTAIN3	1.0 per week	-5.6 (No CI provided)	- 5.8%	56	
	Wadden et al.	3.0 per day	-8.4 ± 7.3	- 7.5%	56		SUSTAIN4	0.5 per week	-3.5 ± 0.4	- 3.7%	30	
	Davies et al.	3.0 per day	-6.4 (No CI provided)	- 6.0%	56			1.0 per week	-5.2 ± 0.5	- 5.6%	30	
		1.8 per day	-5.0 (No CI provided)	- 4.7%	56			SUSTAIN6	0.5 per week	-3.6 (No CI provided)	- 3.9%	104
Dulaglutide	Wysham et al.	1.50 per week	-1.3 ± 0.3	- 1.4%	26			1.0 per week	-4.9 (No CI provided)	- 5.3%	104	
		0.75 per week	+0.2 ± 0.3	+ 0.2%	26		Sema orale	PIONEER	14.0 daily	-4.2 (No CI provided)	- 4.8%	190
	Nauck et al.	1.50 per week	-3.0 ± 0.2	- 3.4%	52		Tirzepatide	Frias et al.	5 per day	-2.1 (no CI provided)	- 2.3%	26
		0.75 per week	-2.6 ± 0.2	- 3.0%	52			10 per day	-4.4 (no CI provided)	- 4.7%	26	
								15 per day	-6.2 (no CI provided)	- 7.0%	26	

Lieve efficacia (< 3%):
exenatide

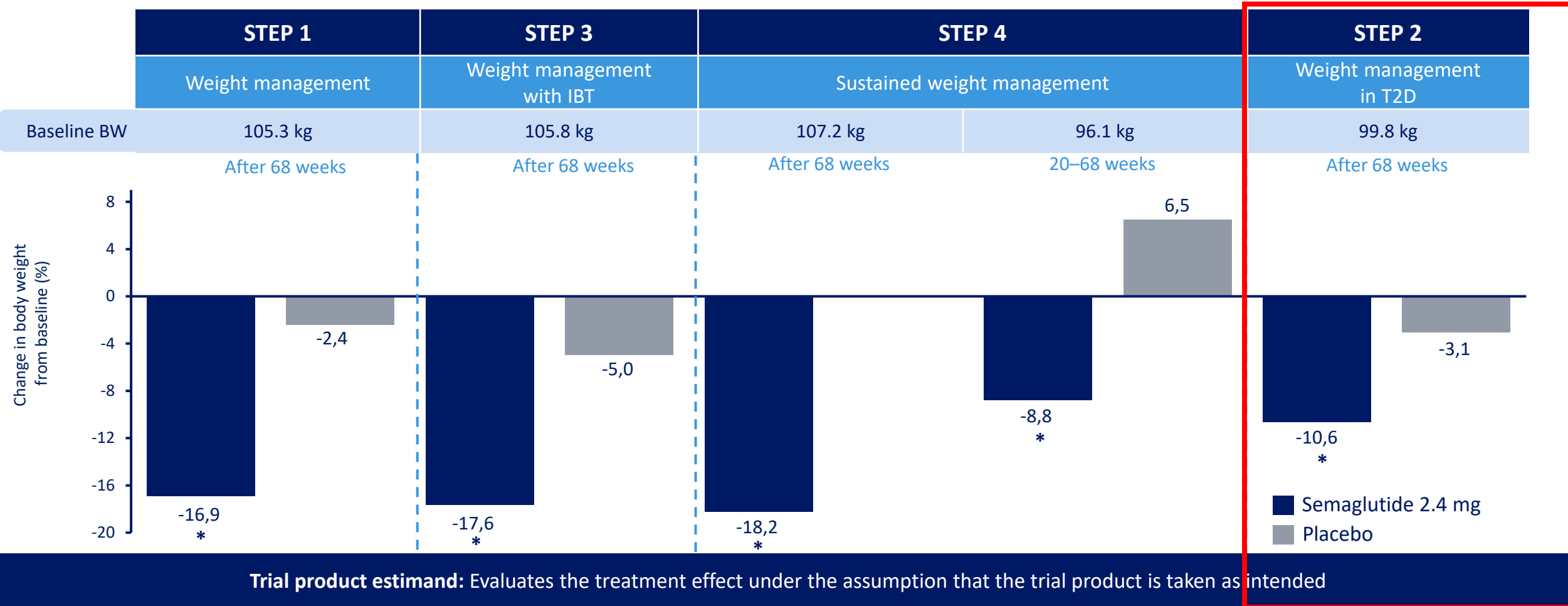
Modesta efficacia (tra 3.2 e 5%):
dulaglutide

Forte efficacia (> 5%):
liraglutide, semaglutide, *tirzepatide*

SEMAGLUTIDE 2,4 mg

Perdita di peso negli studi STEP

Semaglutide 2.4 mg once-weekly in participants with overweight or obesity



*Statistically significant vs placebo.

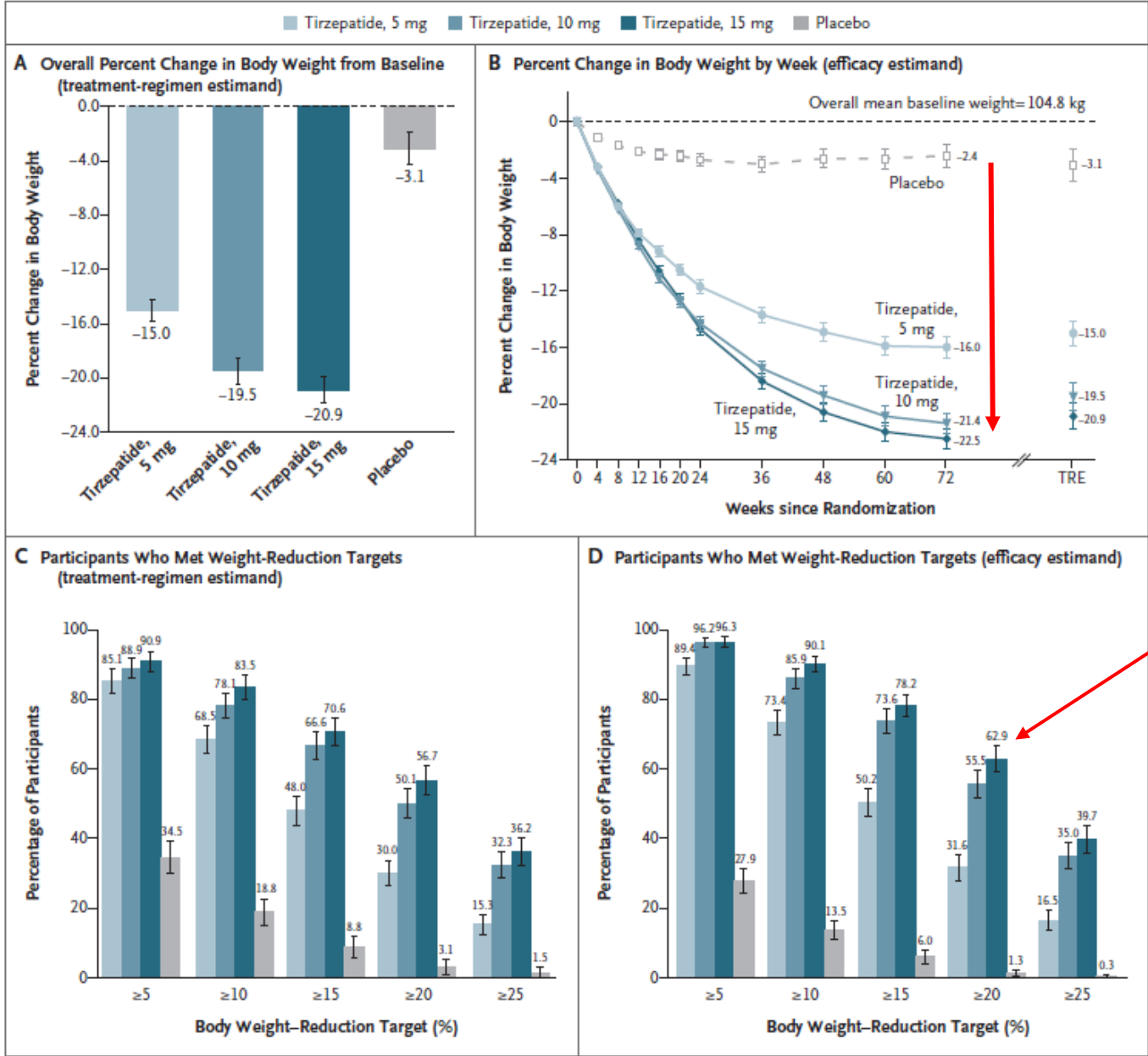
BW, body weight; IBT, intensive behavioural therapy.

Wilding et al. N Engl J Med 2021;384:989-1002; Davies et al. Lancet 2021;397:971-84.; Wadden et al. JAMA 2021;325:1403-13; Rubino et al. JAMA. 2021;325:1414-25.

Tirzepatide Once Weekly for the Treatment of Obesity

N ENGL J MED 387;3 NEJM.ORG JULY 21, 2022 SURMOUNT-1

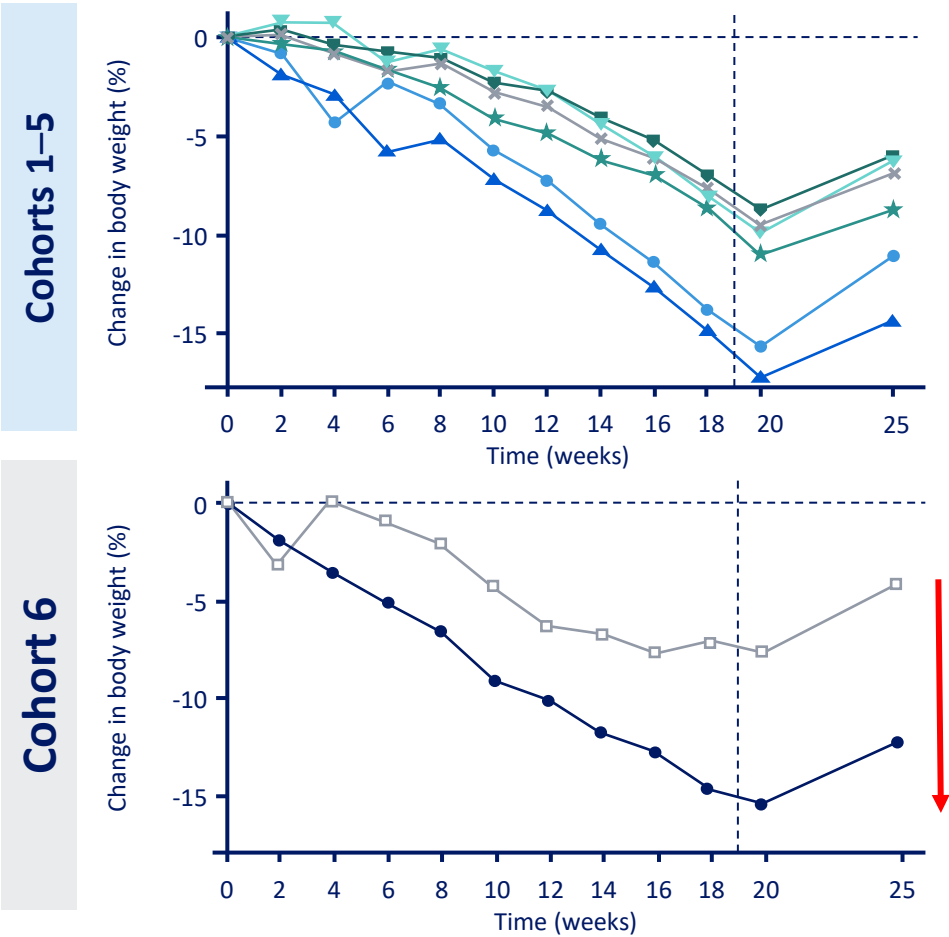
TIRZEPATIDE



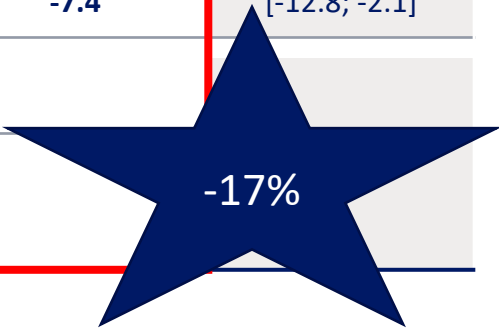
Oltre il 50% dei pazienti ha un calo ponderale superiore al 20%

Cagrilintide/Semaglutide

Observed mean change from baseline (%)



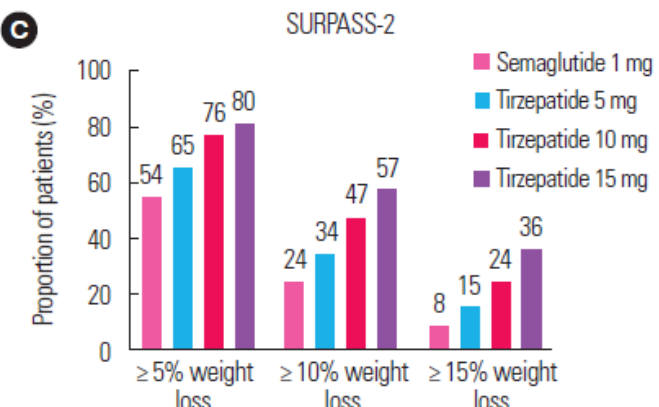
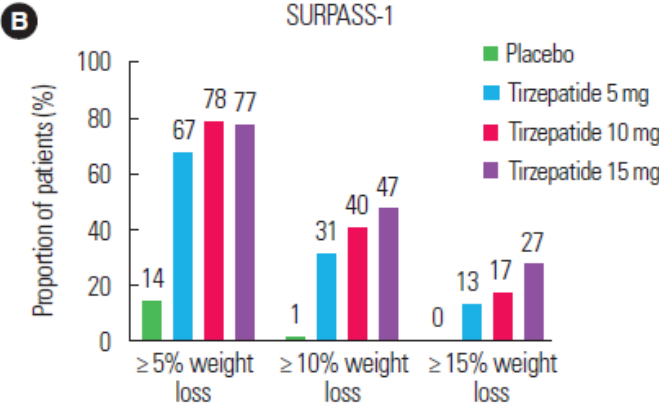
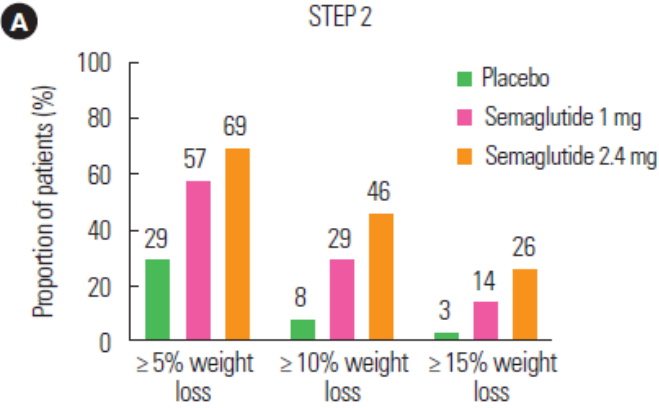
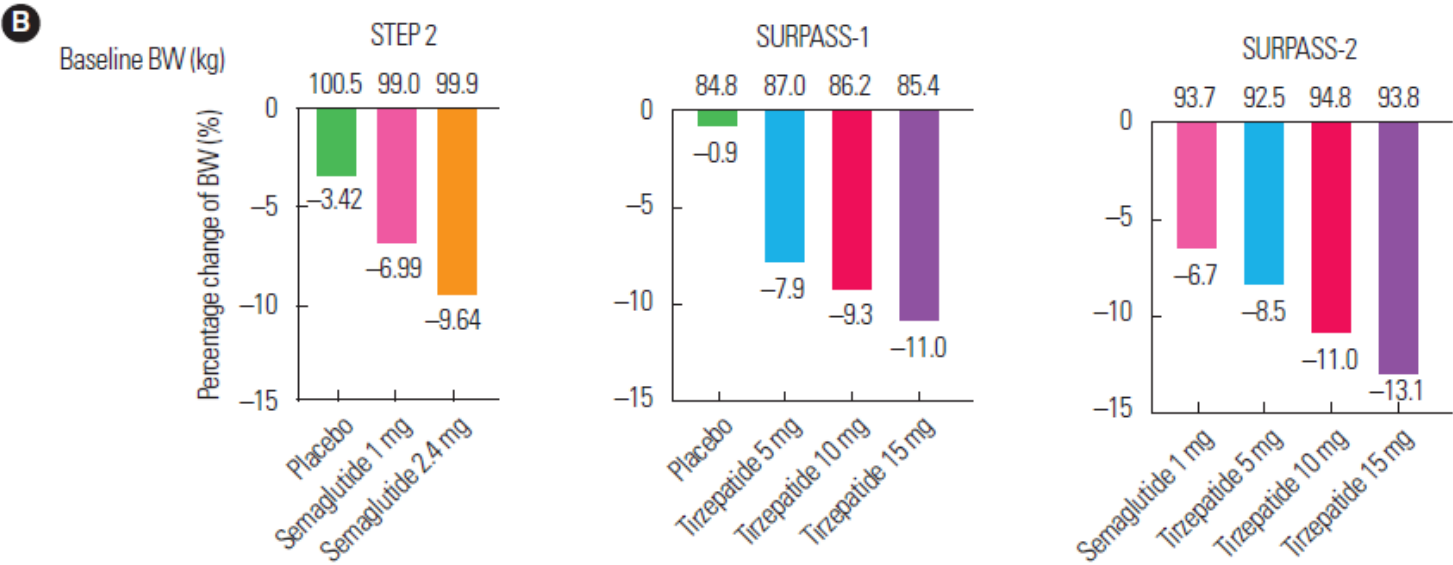
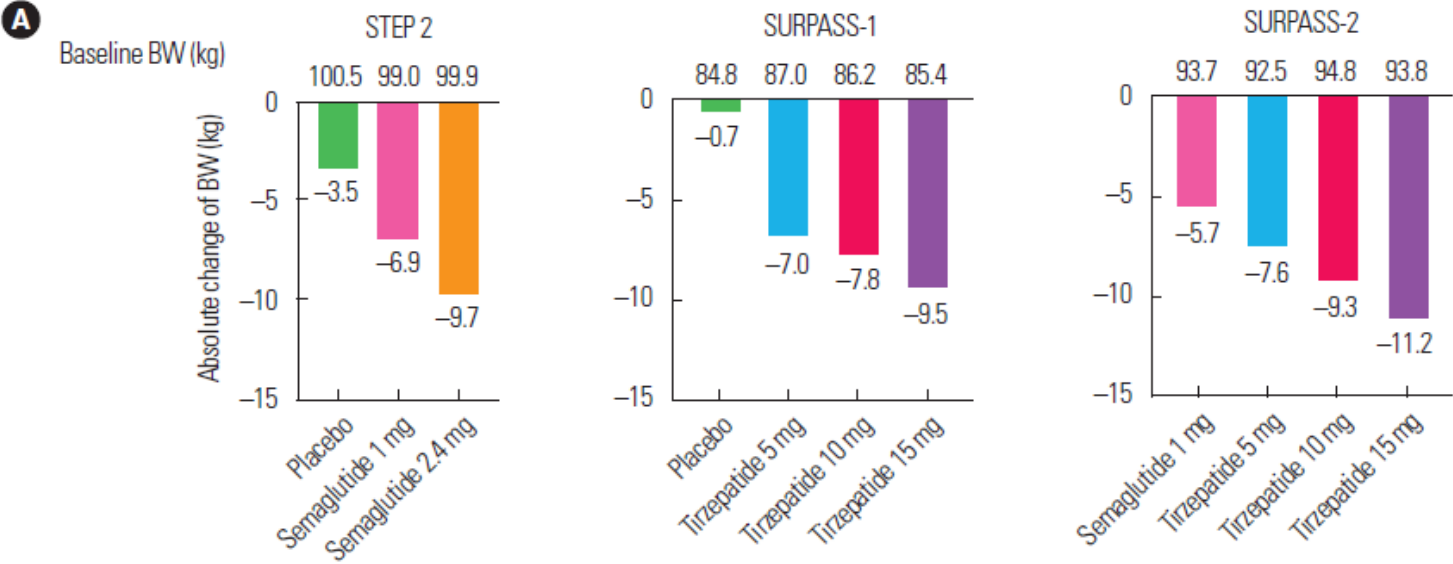
	Mean estimate	Treatment difference vs placebo, sema 2.4 mg	95% CI
Cagri 0.16 mg, Sema 2.4 mg	-8.3	1.4	[-2.6; 5.4]
Cagri 0.3 mg, Sema 2.4 mg	-10.0	-0.3	[-4.1; 3.6]
Cagri 0.6 mg, Sema 2.4 mg	-10.6	-0.9	[-5.0; 3.3]
Cagri 1.2 mg, Sema 2.4 mg	-15.7	-6.0	[-9.9; -2.0]
Cagri 2.4 mg, Sema 2.4 mg	-17.1	-7.4	[-11.2; -3.5]
Cagri 4.5 mg, Sema 2.4 mg	-15.4	-7.4	[-12.8; -2.1]
Placebo, Sema 2.4 mg	-9.8		
Placebo, Sema 2.4 mg (comparator for cagri 4.5 mg, sema 2.4 mg arm)	-8.0		



Mean observed changes in bodyweight with cagrilintide 0.16–4.5 mg in combination with semaglutide 2.4 mg from baseline by treatment week
Vertical reference lines represent first and last dosing of cagrilintide and semaglutide. Data for participants receiving treatment with placebo in combination with semaglutide 2.4 mg were pooled across cohorts; subset analyses of placebo groups for cohorts 1–5 (n=20) and cohort 6 (n=4) did not identify any differences in baseline characteristics
Cagri, cagrilintide; CI, confidence intervals; sema, semaglutide.
Enebo et al. Lancet. 2021 May 8;397(10286):1736-1748.

The Upcoming Weekly Tides (Semaglutide vs. Tirzepatide) against Obesity: STEP or SURPASS?

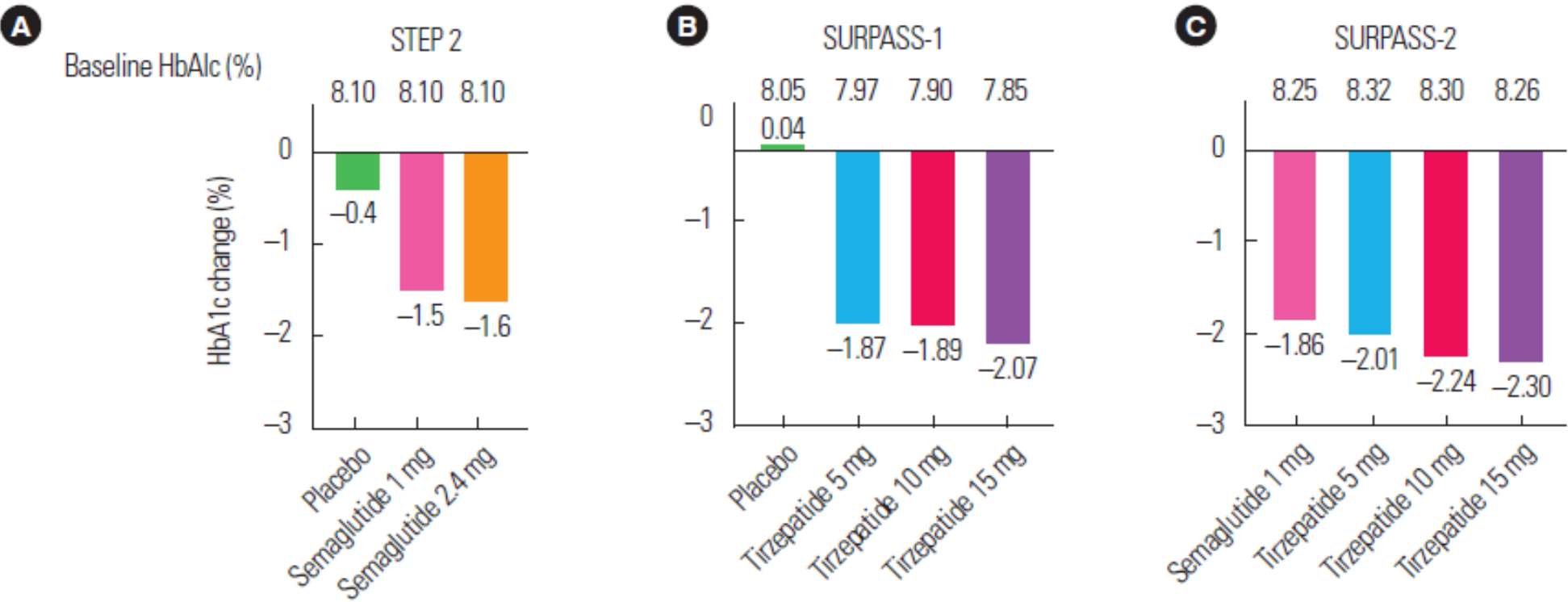
Journal of Obesity & Metabolic Syndrome 2022;31:28-36 **Review**



The Upcoming Weekly Tides (Semaglutide vs. Tirzepatide) against Obesity: STEP or SURPASS?

Journal of Obesity & Metabolic Syndrome 2022;31:28-36 [Review](#)

Contrariamente all'efficacia sul calo ponderale che è dose-dipendente, sia in STEP2, in SURPASS 1 e in SURPASS 2, l'aumento di dose determina solo un lieve miglioramento del compenso glicemico



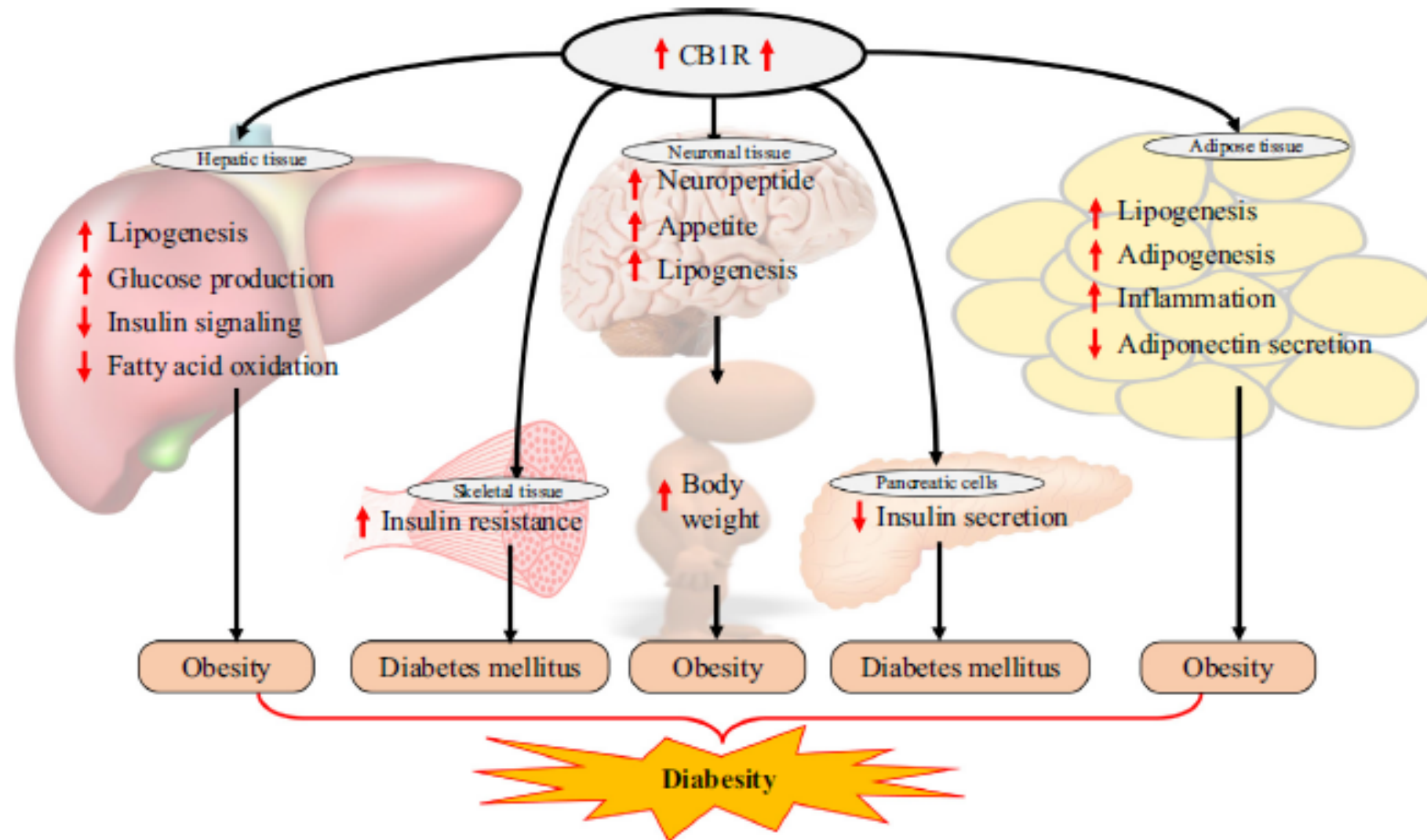
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- ✓ Update sull'efficacia di vecchi e nuovi farmaci
- ✓ Update sul ruolo degli endocannabinodi e sul ruolo de microbiota
- ✓ Update sul ruolo della chirurgia metabolica

Targeting the endocannabinoid system in diabetes: Fact or fiction?

Drug Discovery Today d Volume 26, Number 7, July 2021



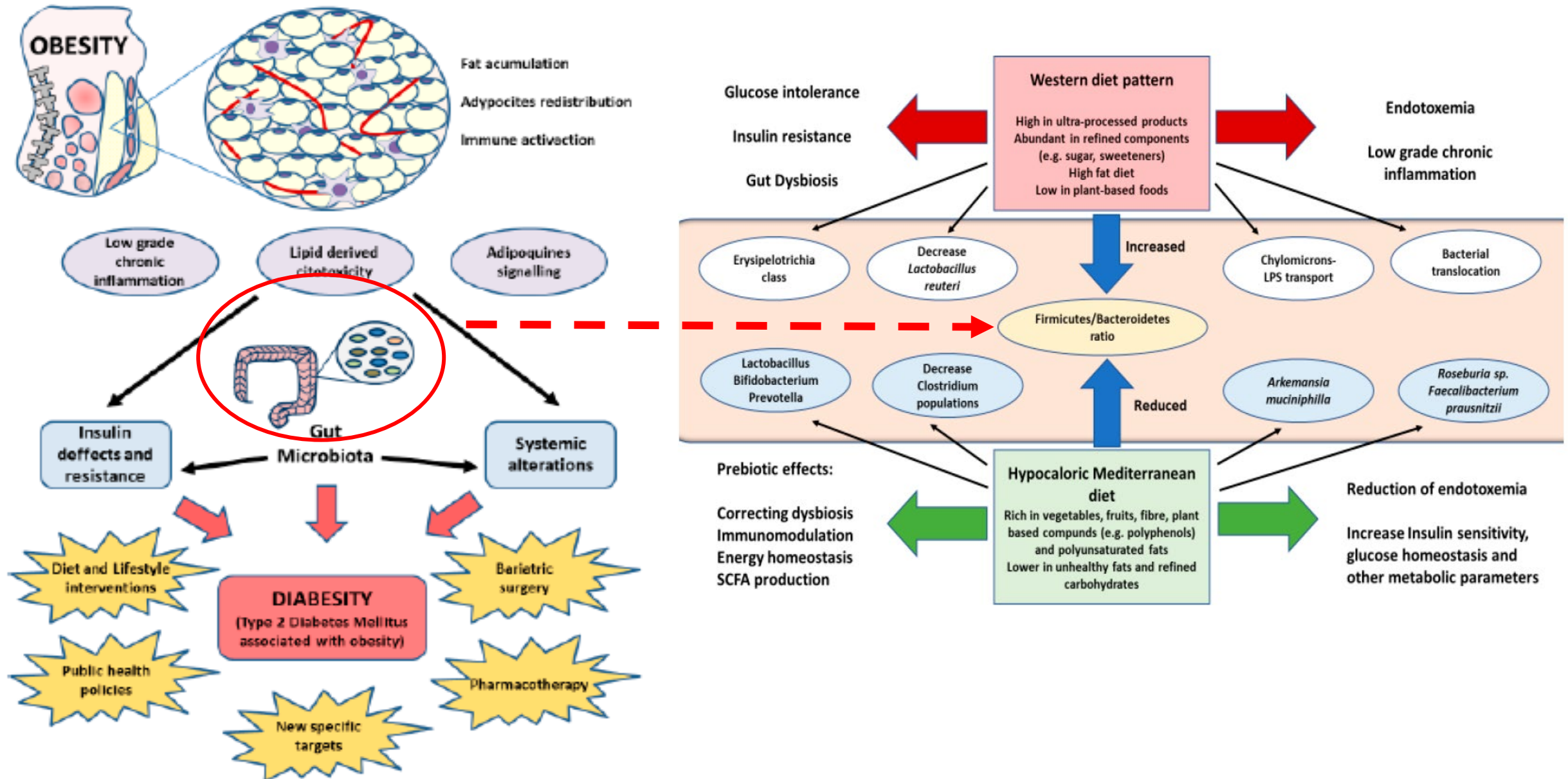
Second-generation CB1R antagonist/inverse agonists.

Sr No.	CB1R antagonist	Characteristics	Pharmacological potential	Remarks
1	URB447	Mixed CB1R/CB2R antagonism potential	Reduced food intake and body weight gain in mice compared with rimonabant	Has polar surface area (PSA) or topological polar surface area (tPSA)
2	D4	Hydroxypiperidine derivative	Peripheral restriction; reduced body weight gain	Lower lipophilicity and higher PSA
3	TM38837	Possible structural analog of D4	No psychiatric side effects owing to decreased ability to cross the blood–brain barrier	Shows improved safety and pharmacokinetic properties over rimonabant in Phase I
4	AM6545	Rimonabant derivative with an alkynyl chain off the 4-aryl group	Improved leptin sensitivity and improved the metabolic profile of mice with diet-induced obesity	Brain/plasma ratio remained low administration; limited oral bioavailability
5	Compound 11	2,3-diarylpyrrole based compound with polar surface area	Weak CB1 inverse agonist with high binding affinity and selectivity	Brain to plasma ratio is ' , oral bioavailability
6	BPR697	Inverse agonist of CB1R	Limited brain penetrance; peripheral restriction	Brain/plasma ratio
7	BPR0912	Inverse agonist of CB1R	Induced food intake independent weight loss; reduced hepatic steatosis; peripheral restriction	Brain/plasma ratio; can modify gene expression in white and brown adipose tissue
8	BPRCB1184	Pyrazole ring derivative	Dose-dependent weight-loss rate at early phase; significantly reduced hepatic triglyceride	Improved brain–plasma ratio of
9	Compound 13	Benzhydrylpiperazines derivative	Have comparable body weight-loss efficacy	Brain/plasma ratio is 1.0; have racemic compound as 13R and 13S
10	Compounds 8j and 8k	Pyrazolyl CB1R ligands	High CB1R affinities and peripherally restricted properties	Have high tPSA values
11	JD5006	N-methyl group of SLV-319	Support minimal blood–brain penetration; low membrane permeability and	Polar moieties consisting of natural and unnatural amino acid derivatives
12	JD5037	N-methyl group of SLV-319	Improve glucose tolerance, insulin resistance, and liver weight, and enzymes	Prevent β -cell loss by preventing the CB1R mediated transmigration of macrophages
13	Compound 23	1,1-dioxo-thiomorpholino derivative	Limited brain penetration; peripheral restriction	Lower CB1R affinity; act as brain efflux transporters
14	Compound 14g	6-alkoxy-5-aryl-3-pyridinecarboxamides derivative	Partial agonist of CB1R outside the brain; significantly reduced body weight gain; increased leptin level	Low brain to plasma ratio compared with rimonabant
15	VD60	3,4,22,3-demethoxycarbonyl-1-hydroxymethyl-4-methyl-5-vindoline 3,4-thiophene derivative	Peripherally restricted CB1R antagonist; potent peripheral anti-fibrotic agent	Low brain side effects; acts as antagonist/inverse agonist
16	Compounds 13 and 31	1,5-diaryl-1H-pyrazole-4-carboxamide derivative	Potent CB1R antagonistic with high selectivity for peripheral tissues and exhibited anti-obesity effects	Brain: plasma exposure rates of compounds 13 and 31 were about 3% and 0.4%, respectively
17	TXX-522	Partial agonist/inverse agonist	Potent anti-obesity effect; ameliorated insulin resistance in high-fat diet-induced obese mice	Has good oral bioavailability; improved brain–plasma ratio of 0.02
18	AJ5012 and AJ5018	Peripherally restricted CB1R antagonist with a high degree of CB1R/CB2R selectivity	Potency to reduce body weight; improved hormonal/metabolic abnormalities; no CNS-mediated neurobehavioral effects	Brain–plasma concentration ratio is ~ 0.1 , which was much lower than that of rimonabant; no anxiogenic response
19	Compound 38	Piperidine ring derivative	Peripherally restricted analogs; high CB1R/CB2R selectivity	Good oral absorption and favorable clearance upon oral dosing in rats; brain–plasma ratio is about 0.03
20	Compound 2p	Inverse agonism of the hCB1R receptor	Suppressed the basal signaling through hCB1R; reduced hepatic lipid accumulation	Long plasma half-life and low clearance
21	Compound 6a	Potent CB1R inverse agonist 6-benzhydryl-4-aminoquinoline-2-one derivative	Acts as anti-diabetic agent Potent and selective CB1R inverse agonists; improved peripheral selectivity; attenuated obesity and improved insulin sensitivity	Brain–plasma ratio of 0.05 and tPSA of 59 Brain–plasma ratio of 0.024 and high tPSA; excellent <i>in vivo</i> metabolic stability; long half-life (both oral and iv dosing); low clearance and low volume of distribution
22	Compound 5 and 36	Cinnoline derivatives	CB1R inverse agonists	Low brain side effects; act as antagonists/inverse agonists
23	Compound 47	Quinazoline derivative	CB1R inverse agonists; good CB1R affinity and selectivity over CB2R	Designed as non-brain penetrant

Diabetes is a global epidemic, and we have an **urgent need for novel cannabinoids** that could have promising effects against obesity and T2DM **without any psychiatric and non-psychiatric adverse effects.**

Diverse categories of cannabinoids, including natural and synthetic agonists, inverse agonists, partial agonists, antagonists, neutral agonists, peripherally restricted antagonists and allosteric modulators, have been investigated as possible therapeutics, and second- and third-generation CB1R antagonists show particular promise for the treatment of diabetes.

Type 2 Diabetes Mellitus Associated with Obesity (Diabetes). The Central Role of Gut Microbiota and Its Translational Applications. *Nutrients* 2020



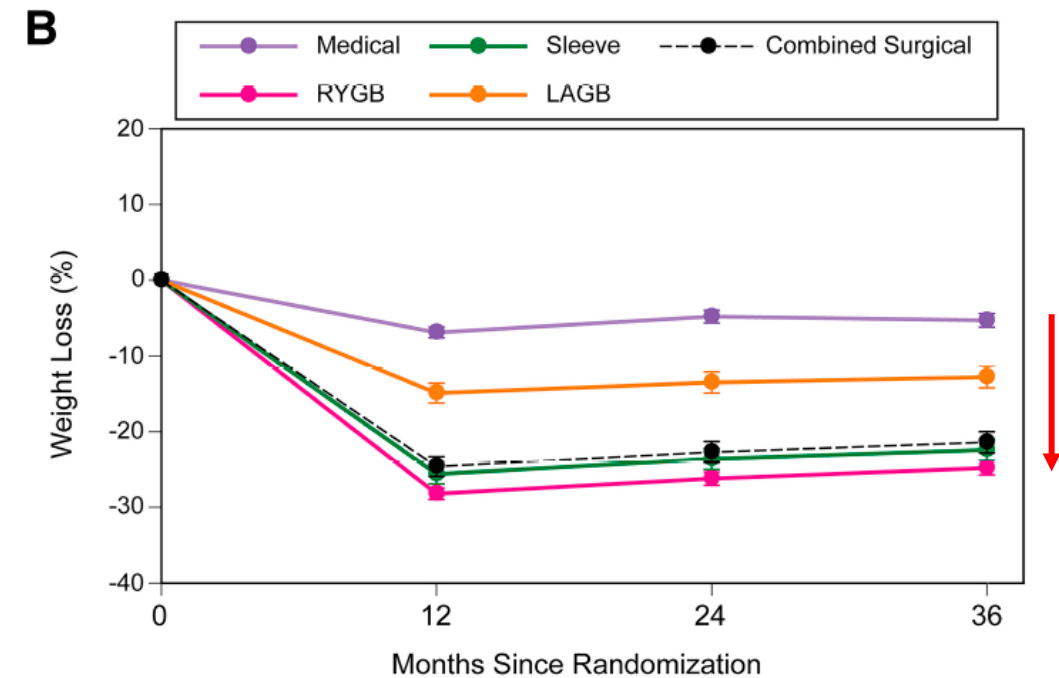
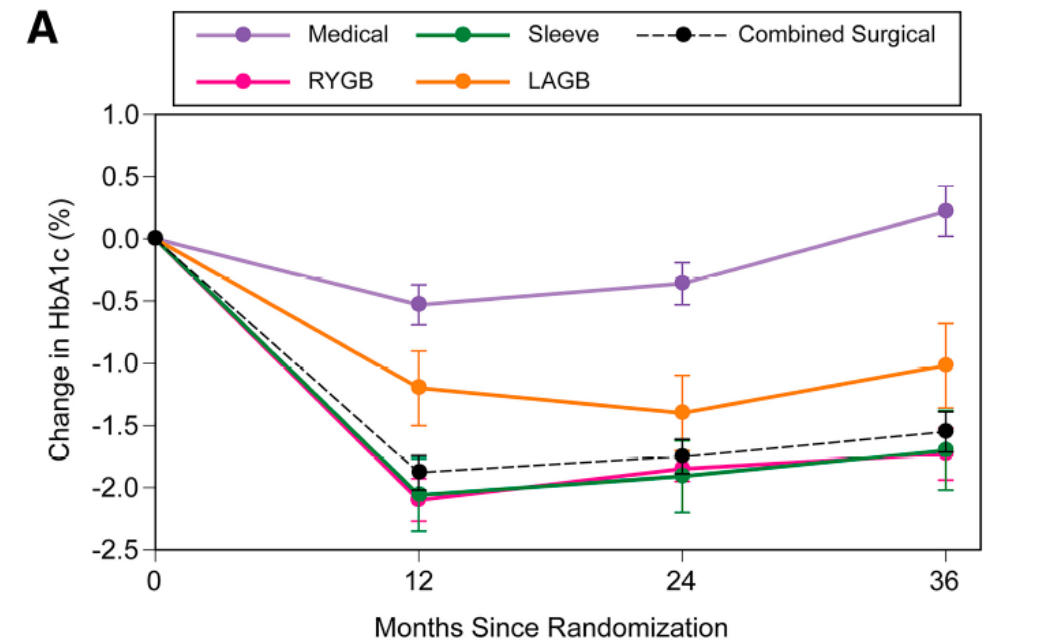
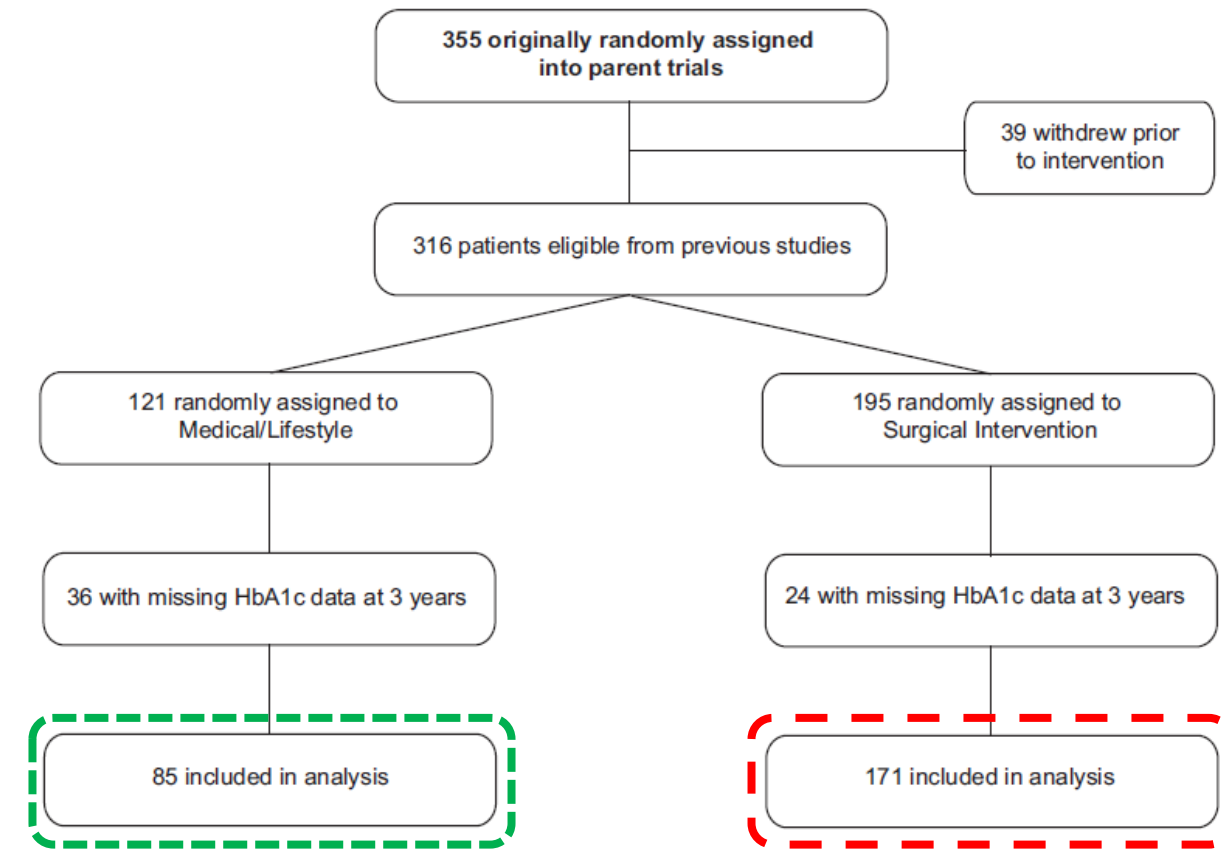
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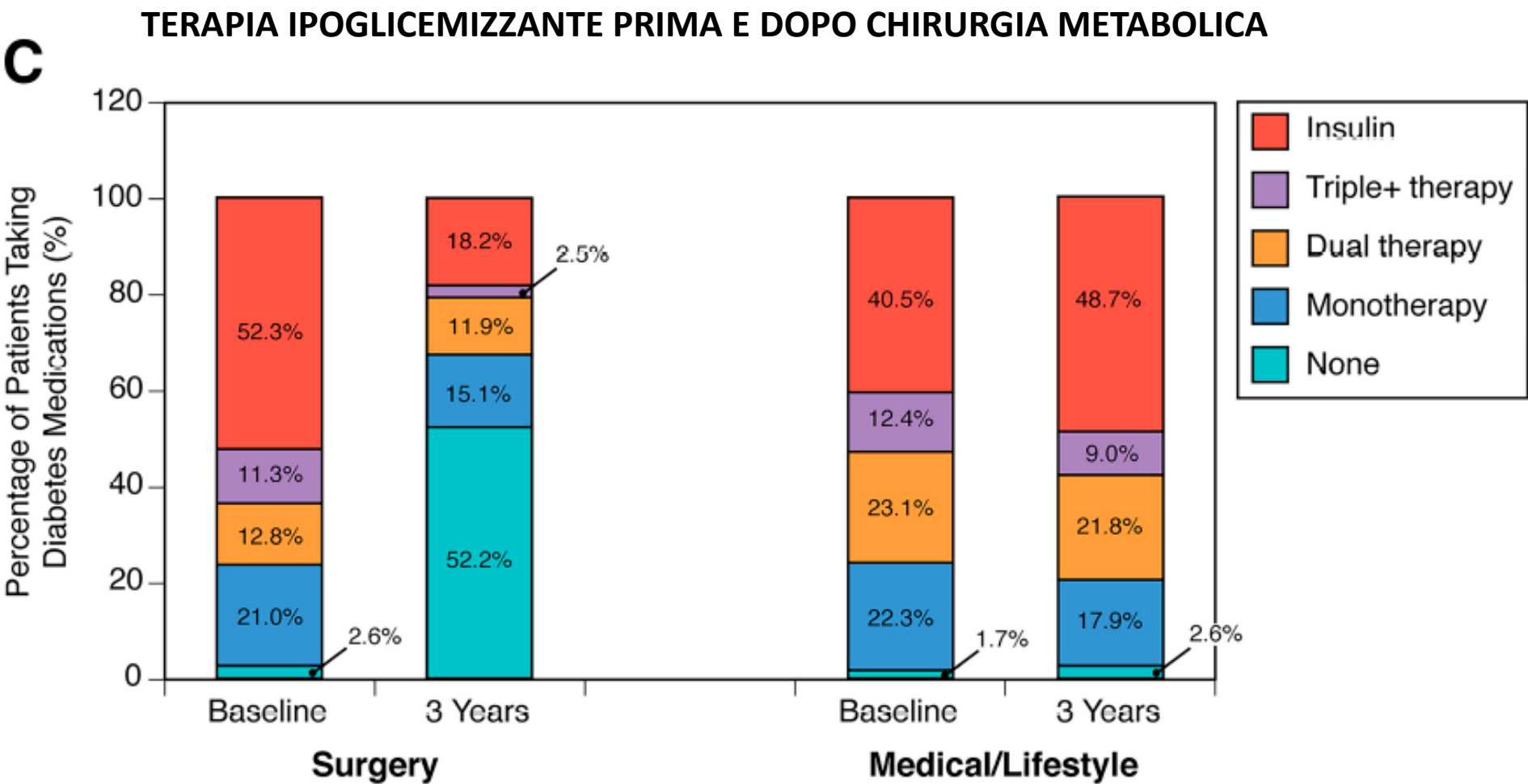
Diabetes Remission in the Alliance of Randomized Trials of Medicine Versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D)

Diabetes Care 2022;45:1574–1583 | <https://doi.org/10.2337/dc21-2441>



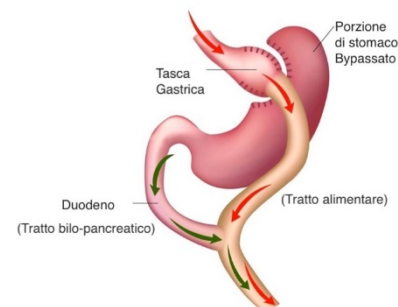
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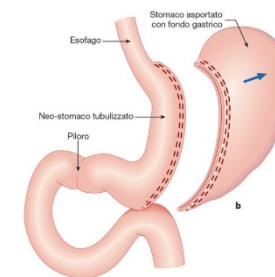


Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy for Remission of Type 2 Diabetes

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 3, 922–933



VS



10 studi inclusi, 778 pazienti.

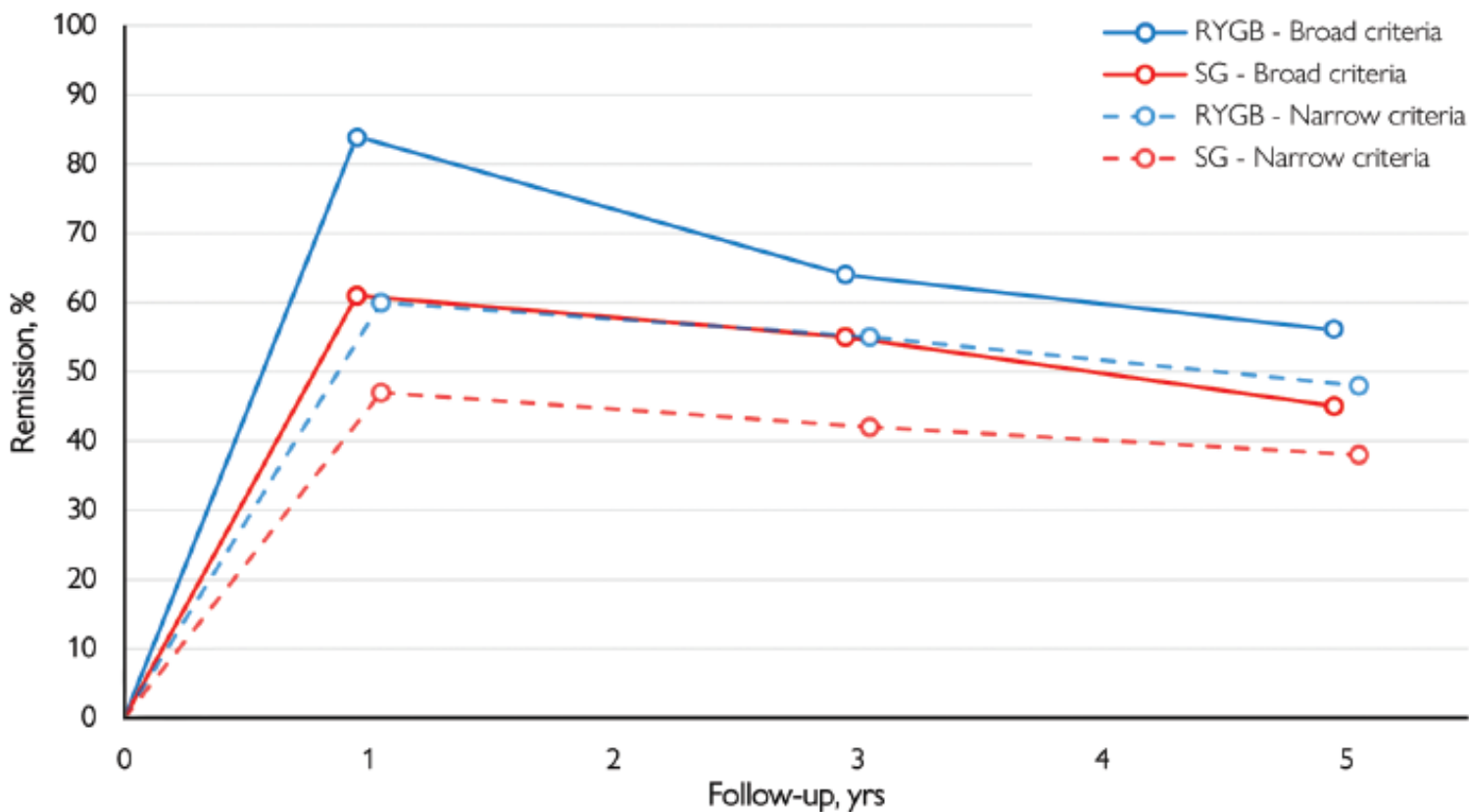


Figure 2. Prevalence of remission of type 2 diabetes after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) at each follow-up according to criteria for remission.

Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy for Remission of Type 2 Diabetes

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 3, 922–933

Criteri per la remissione del diabete dopo chirurgia metabolica

CRITERI MENO STRINGENTI

CRITERI PIU' STRINGENTI

Table 2. Broad and narrow criteria for remission of type 2 diabetes adopted for data extraction

First author, y	Broad criteria for remission	Narrow criteria for remission
Lee, 2011 (23)	HbA _{1c} < 6.5% (48 mmol/mol) and FPG < 126 mg/dL without therapy	NA
Schauer, 2017 (24-26)	HbA _{1c} ≤ 6.5% (48 mmol/mol) without pharmacologic therapy	HbA _{1c} ≤ 6.0% (42 mmol/mol) without pharmacologic therapy
Peterli, 2018 (27-29)	NA	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 100 mg/dL for at least 1 y without pharmacologic therapy or ongoing procedures
Yang, 2015 (30)	HbA _{1c} ≤ 6.5% (48 mmol/mol) without pharmacologic therapy	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 126 mg/dL without pharmacologic therapy
Casajoana, 2017 (31)	HbA _{1c} < 6.5% (48 mmol/mol) and FPG 100-125 mg/dL for 1 y without therapy	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 100 mg/dL without therapy for 1 y
Kalinowski, 2017 (32)	NA	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 100 mg/dL without pharmacologic therapy
Murphy, 2018 (33)	HbA _{1c} < 6.5% (48 mmol/mol) without pharmacologic therapy	HbA _{1c} < 6.0% (42 mmol/mol) without pharmacologic therapy
Ruiz-Tovar, 2018 (34)	HbA _{1c} < 6.5% [48 mmol/mol) and FPG < 126 mg/dL without pharmacologic therapy	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 100 mg/dL without pharmacologic therapy
Salminen, 2018 (35)	HbA _{1c} < 6.5% (48 mmol/mol) and FPG 100-125 mg/dL for at least 1 y without pharmacologic therapy or ongoing procedures	HbA _{1c} < 6.0% (42 mmol/mol) and FPG < 100 mg/dL for at least 1 y without pharmacologic therapy or ongoing procedures
Hofsø, 2019 (36)	HbA _{1c} < 6.5% (48 mmol/mol) without pharmacologic therapy	HbA _{1c} ≤ 6.0% (42 mmol/mol) without pharmacologic therapy

REMISSIONE COMPLETA

- HbA1c < 6%
- Glicemia a digiuno < 100 mg/dl

CONCLUSIONI

- I farmaci antidiabetici raccomandati oggi dalle linee guida hanno una buona efficacia sulla riduzione del peso corporeo
- Ci sono farmaci in arrivo molto promettenti
- Si apre la strada a nuove scoperte relativamente ad endocannabinoidi e microbiota
- Rimane indiscusso il ruolo della chirurgia metabolica sul trattamento della diabesià