SGLT2i, GLP1ras, GLP1-GIP e Finerenone: oltre la glicemia
NUOVI ORIZZONTI TERAPEUTICI

Chiara Gottardi
SC Patologie Diabetiche
ASUGI-Trieste-

Per anni abbiamo «navigato lungo coste note, in un perimetro **GLUCOCENTRICO**»

Esigenza di perseguire il target GLICEMICO

UKPDS: HbA_{1c} è un fattore di rischio cardiovascolare indipendente

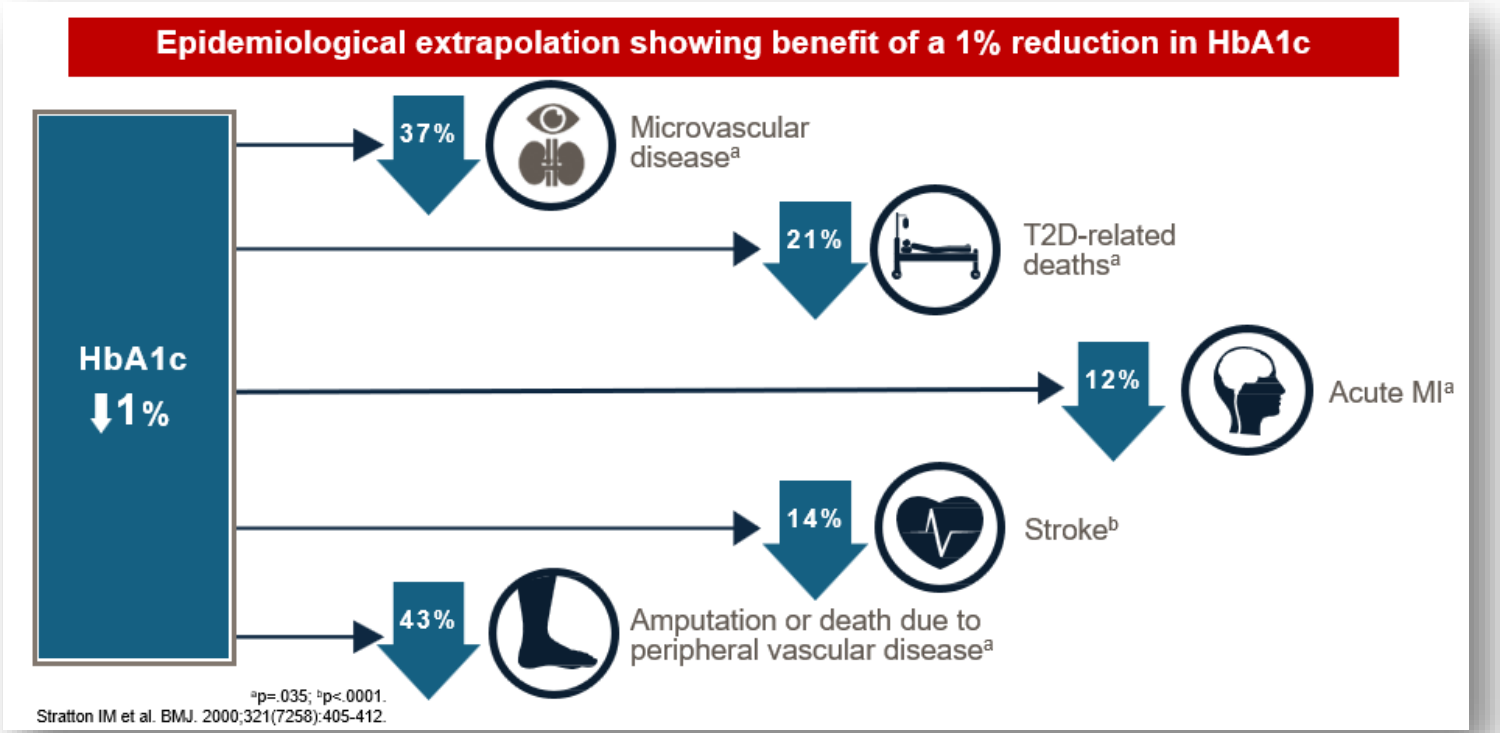
The deadly 'quartet' became the deadly 'quintet'

		p
↑	LDL cholesterol	<0.0001
↓	HDL cholesterol	0.0001
↑	Systolic blood pressure	0.0065
+	Smoking	(0.056)
↑	Haemoglobin A_{1c}	0.0022

Stepwise selection of major risk factors for 280 coronary artery disease events in 2,693 UKPDS patients @ 10 years

UKPDS 23. BMJ 1998;316:823-8

UKPDS: Un controllo glicemico intensivo PRECOCE riduce il rischio a lungo termine di complicanze croniche nel diabete di tipo 2



Nel 2008 *a seguito del ritiro dal commercio del rosiglitazone, a causa dell'aumentato rischio di infarto miocardico, l'FDA ha imposto l'esecuzione di* ***studi sugli esiti cardiovascolari*** *per i farmaci per il diabete* ***(CVOTs)****, per valutarne il profilo di* ***SICUREZZA***

Prof. ARCANGELO GHISLERI

TESTO-ATLANTE

DI GEOGRAFIA STORICA GENERALE E D'ITALIA IN PARTICOLARE

MONDO ANTICO

Parte I - ORIENTE E GRECIA

CON TAVOLE CON RELATIVO TESTO A FRONTE

PER LA IV CLASSE GINNASIALE

UTILE COME LIBRO DI CONSULTAZIONE AD OGNI COLTA PERSONA

Bago Domenico
IIa Ginnasiale A

23.ª RISTAMPA

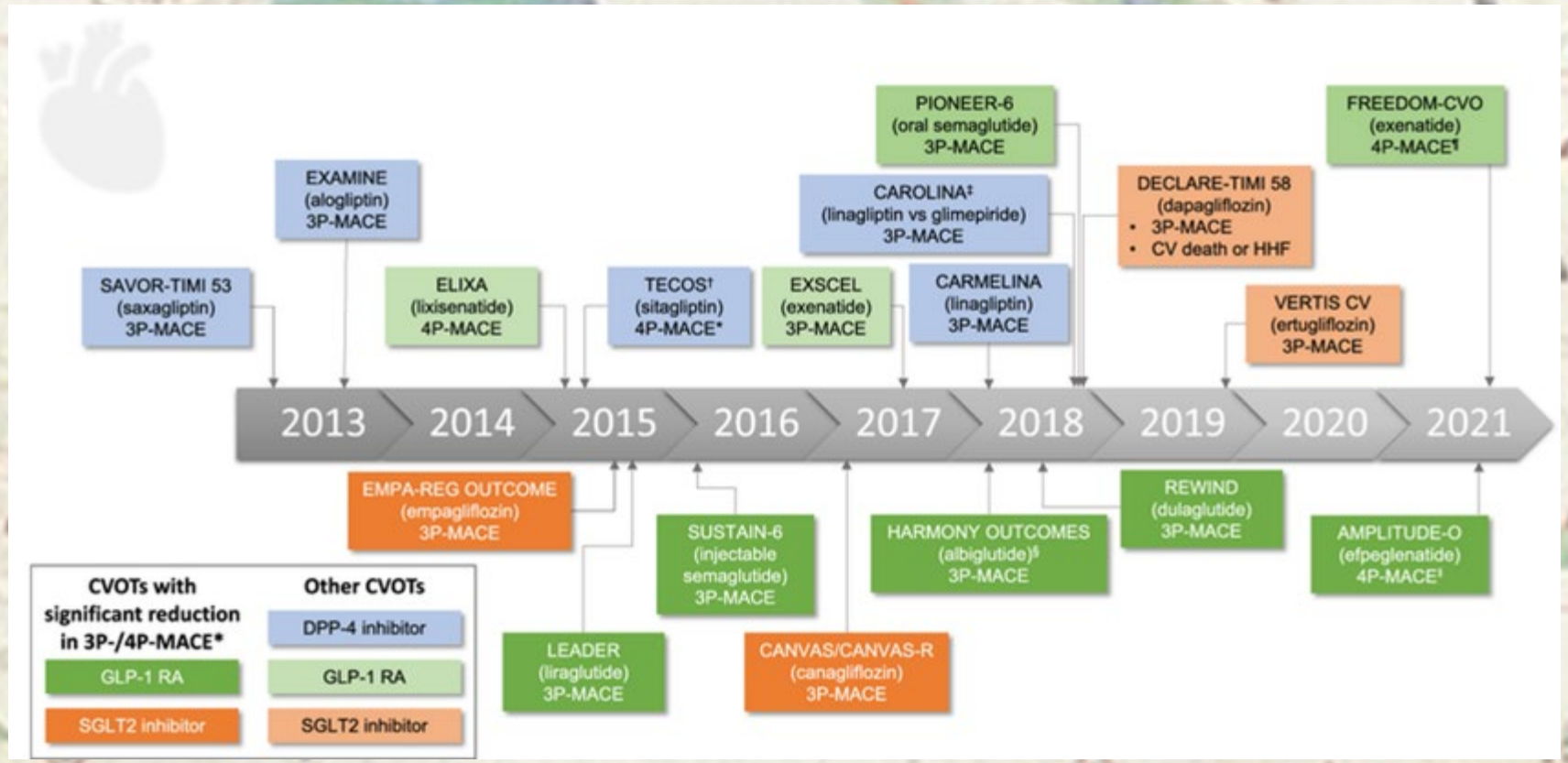
nuovamente riveduta dall'Autore

…**Colombo** scopre un continente che non cercava…

Questi studi hanno dimostrato che alcuni farmaci ipoglicemizzanti, come gli inibitori **SGLT2** e gli agonisti del recettore **GLP-1**, non solo hanno un **profilo cardiovascolare sicuro,** ma forniscono anche **significativi benefici cardiorenali**

...Indipendentemente dalla glicemia...

Nascita del concetto di **protezione d'organo**



IL BENEFICIO CARDIORENALE

..parlando di SGLT2i...

Beneficio CV

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

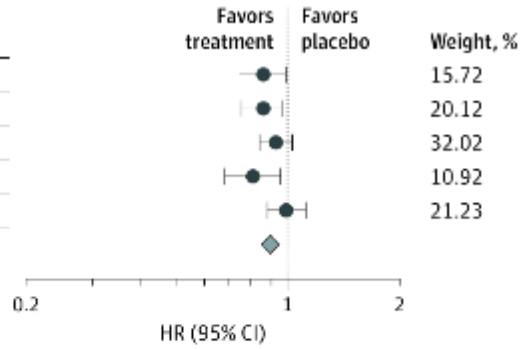
C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, B. Charbonnel, R. Frederich, S. Gallo, F. Cosentino, W.J. Shih, I. Gantz, S.G. Terra, D.Z.I. Cherney, and D.K. McGuire, for the VERTIS CV Investigators*

CVOTs: studi ad Hoc per valutare la **sicurezza** CV degli ipoglicemizzanti, con evidenza di beneficio CV vs placebo

Effects of SGLT2i on Major Adverse Cardiovascular Events

A Overall MACEs

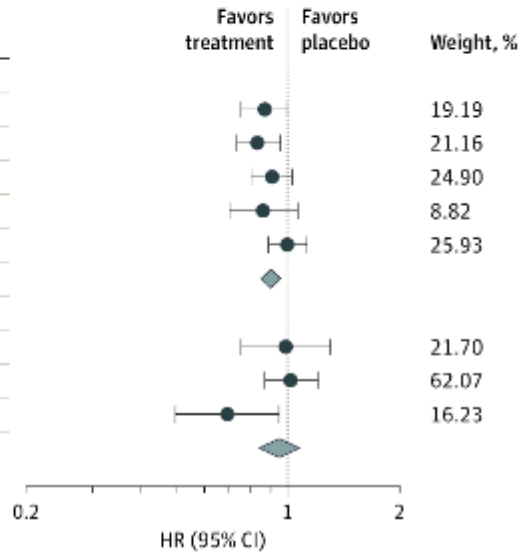
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)



-10%

B MACEs by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

Gli stessi studi hanno dimostrato una riduzione dello SCC

Effects of SGLT2i on HHF

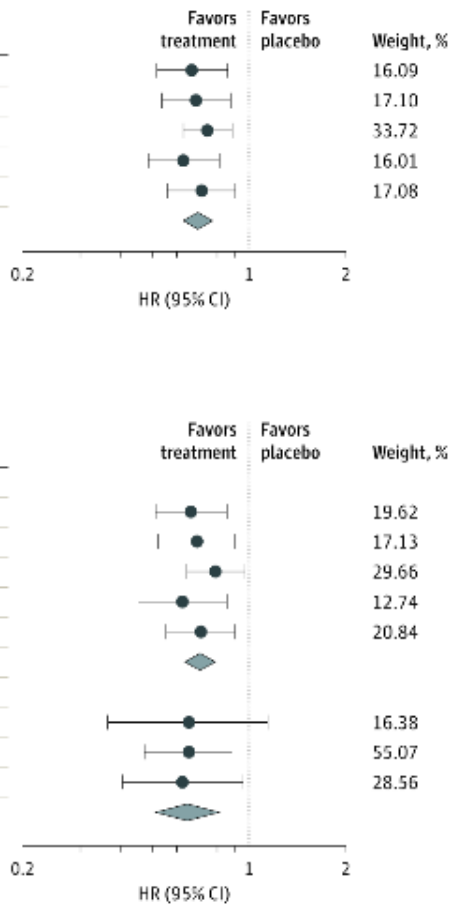
Beneficio SCC

A Overall HHF

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model ($Q = 1.39$; $df = 4$; $P = .85$; $I^2 = 0.0\%$)					0.68 (0.61-0.76)

B HHF by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model ($Q = 1.97$; $df = 4$; $P = .74$; $I^2 = 0.0\%$)					0.70 (0.62-0.78)
Patients without ASCVD					
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)
Fixed-effects model ($Q = 0.03$; $df = 2$; $P = .99$; $I^2 = 0.0\%$)					0.63 (0.50-0.80)



- 32%

JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

Da qui studi con end point primario su SCC

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Kober, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

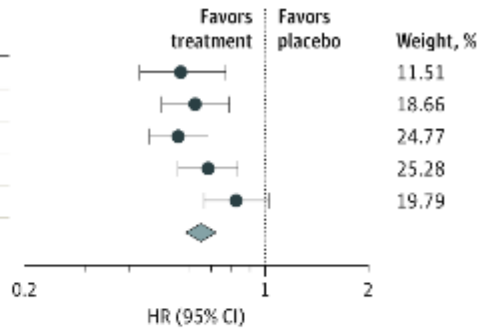
Heart Failure Trials: disegnati per valutare **l'efficacia** di SGLT2-i su pazienti con **SCC** diabetici e non diabetici

Gli stessi studi hanno dimostrato un beneficio renale

Effects of SGLT2i on Kidney-Related Outcomes

A Overall kidney outcomes

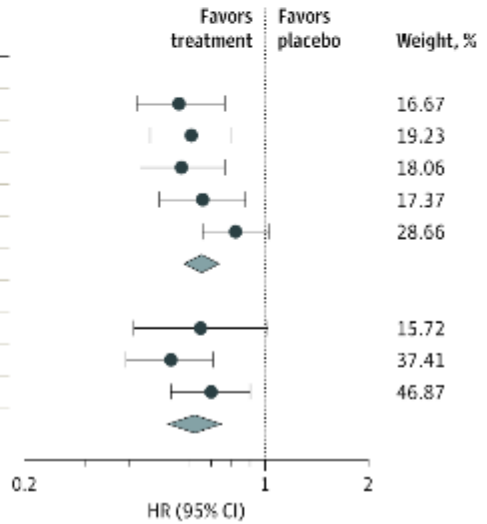
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; P = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



- 38%

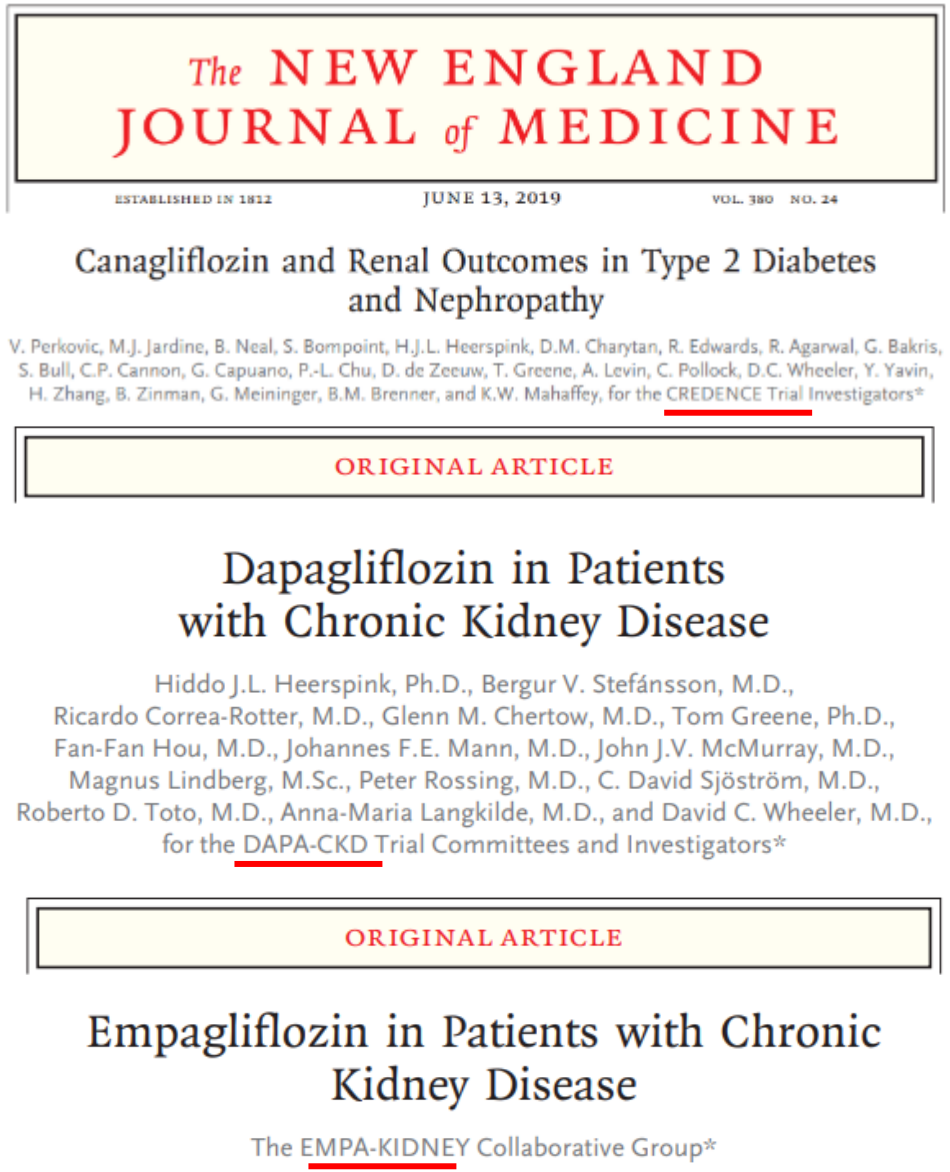
B Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; P = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; P = .40; I^2 = 0.0%)					0.60 (0.50-0.73)



Beneficio RENALE

JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

Da qui studi con end point primario su rischio di progressione CKD

Kidney Outcome Trials:
disegnati per valutare **l'efficacia** di SGLT2-i sulla progressione della **malattia renale** anche in pz non diabetici

..parlando di GLP1ar...

The NEW ENGLAND JOURNAL of MEDICINE
JULY 28, 2016

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

THE LANCET

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Prof Hertzel C Gerstein, MD [a] · Prof Helen M Colhoun, MD [b] · Prof Gilles R Dagenais, MD [c] · Rafael Diaz, MD [d] · Mark Lakshmanan, MD [e] · Prof Prem Pais, MD [f] · et al. Show more

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial

Darren K. McGuire MD [1] | Rodica P. Busui MD [2] | John Deanfield MD [3] | Silvio E. Inzucchi MD [4] | Johannes F. E. Mann MD [5,6] | Nikolaus Marx MD [7] | Sharon L. Mulvagh MD [8] | Neil Poulter FRCP [9] | Mads D. M. Engelmann MD [10] | G. Kees Hovingh MD [10] | Maria Sejersten Ripa MD [10] | Mette Gislum MSc [10] | Kirstine Brown-Frandsen MD [10] | John B. Buse MD [11]

Outcome CV

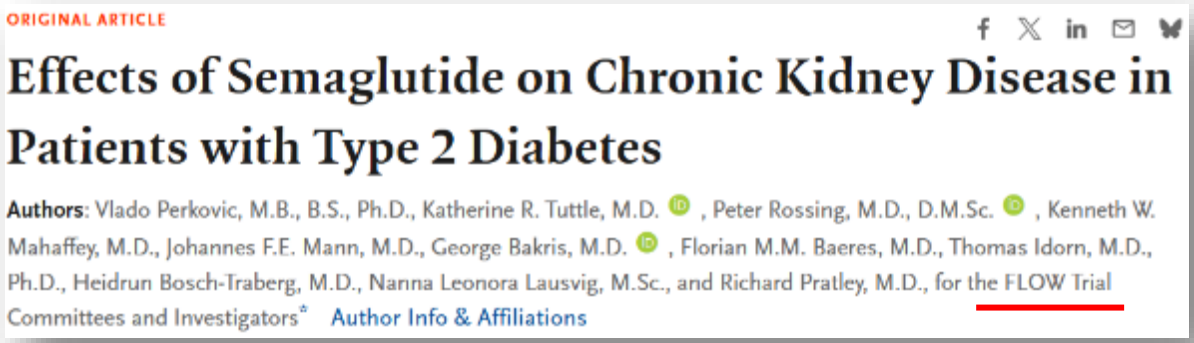
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

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

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

Ouctome SCC



ORIGINAL ARTICLE

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

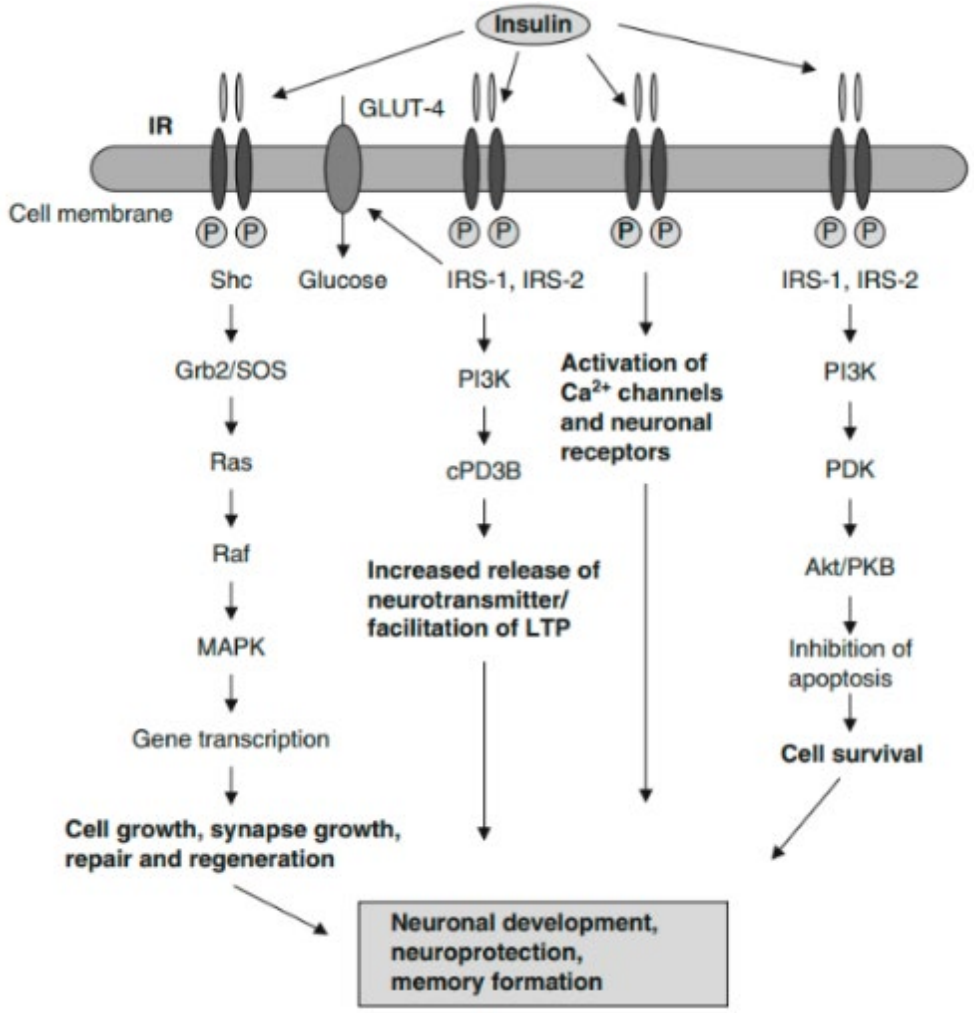
Authors: Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators* Author Info & Affiliations

Ouctome renali


...Vespucci comprese che le terre scoperte non erano le Indie, ma un vero e proprio *nuovo* continente, che chiamò America...
...Così i GLP1 e SGLT2i ci hanno permesso di ampliare l'orizzonte terapeutico con dimostrazione di risvolti su neuroprotezione, MASLD, peso, placca aterosclerotica e infiammazione

NEUROPROTEZIONE

Ruolo dell'Insulina nel SNC



Fattore di crescita: ruolo nella crescita e nella sopravvivenza delle cellule.

I neuroni esprimono recettori dell'insulina la cui attivazione induce

- germogliazione dendritica
- attivazione delle cellule staminali neuronali
- crescita cellulare generale
- riparazione e neuroprotezione

Potenti effetti neuroprotettivi contro i fattori di stress

Migliora le funzioni cerebrali come l'attenzione, la formazione della memoria e gli aspetti cognitivi

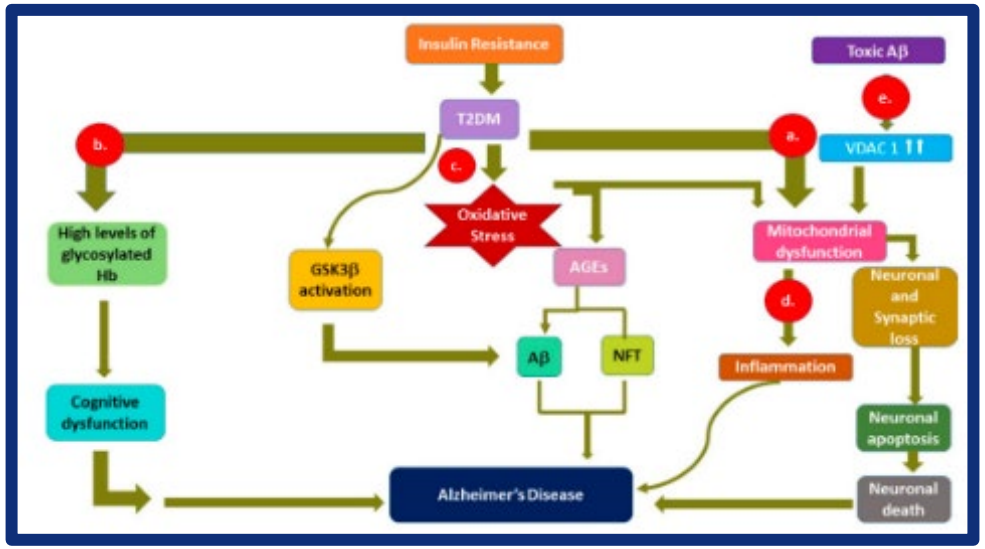
INSULINO-RESISTENZA CEREBRALE

Mancata risposta delle cells all'insulina

CK pro-infiammatorie

- Aumento dello stress ossidativo
- Difettosa attivazione della cascata enzimatica

Alterazione della neuroplasticità

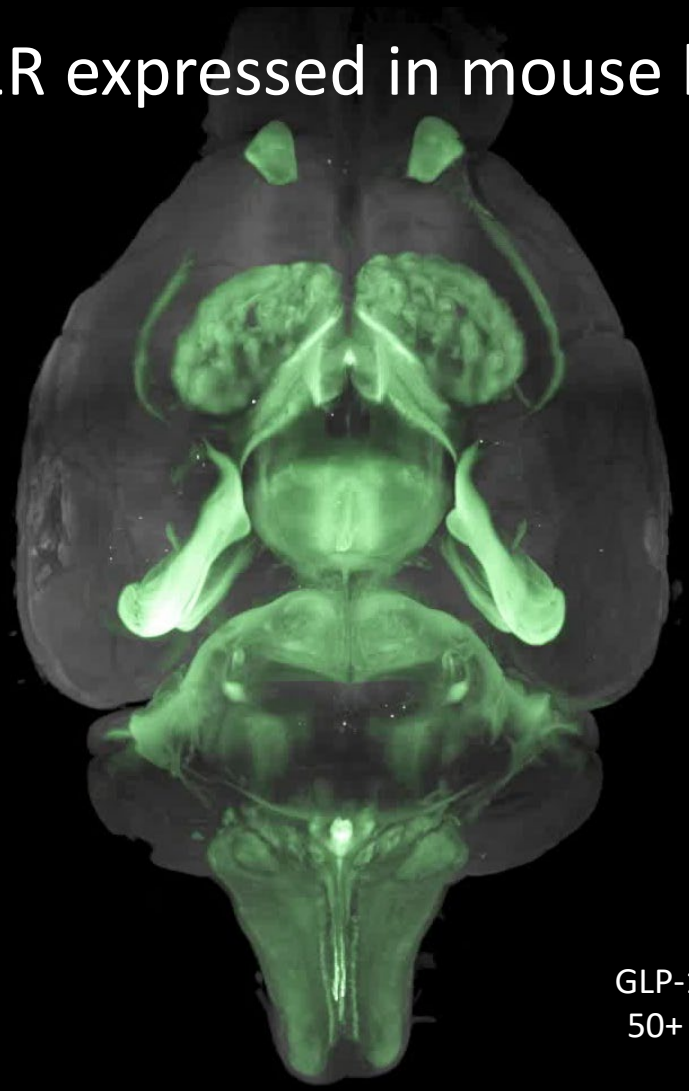


L'alterazione del segnale insulinico dovuta **CK ed AGE**

- promuove la **generazione di beta amiloide** tra le sinapsi e iperfosforilazione di tau
- Amiloide solubile altera la trasduzione dell'insulina con cascate di eventi che portano a **danno mitocondriale** e a **morte cellulare**

R. Kandimalla et al. / Biochimica et Biophysica Acta 1863 (2017) 1078–1089

GLP-1R expressed in mouse brain



GLP-1R identified in 50+ brain regions[1]

Areas in neon green reflect GLP-1 receptor expression
Jensen et al. Endocrinology 2017;159:665–675

GLP-1R espresso principalmente nell'ippocampo e nella neocorteccia

GLP-1R ippocampale coinvolto nell'**apprendimento** e nella **memoria**

- I topi con deficit di GLP-1R hanno un fenotipo caratterizzato da un deficit di apprendimento che viene ripristinato dopo il trasferimento del gene GLP-1R dell'ippocampo

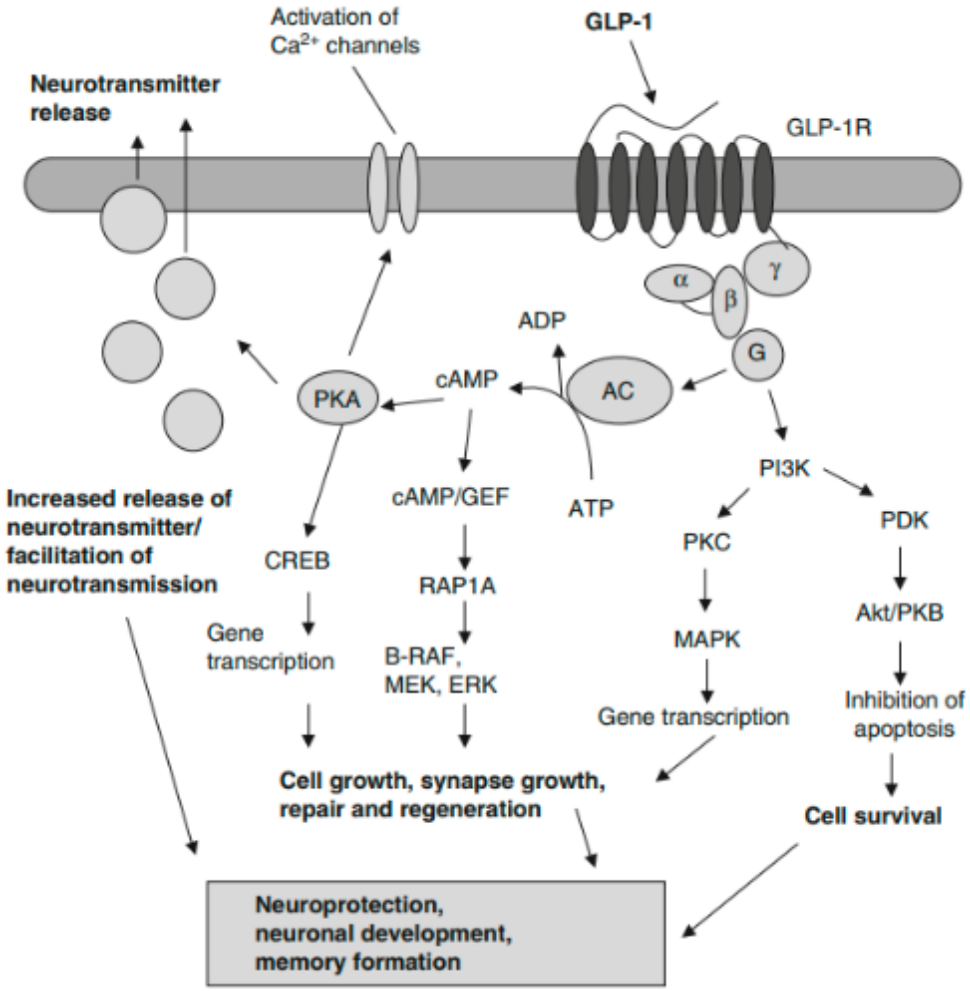
- I ratti che sovraesprimono il GLP-1R dell'ippocampo mostrano un miglioramento dell'apprendimento e della memoria

GLP-1R, glucagon-like peptide 1 receptor
During MJ et al. Nat Med 2003;9:1173–1179

Potential Role of Glucagon-Like Peptide-1 (GLP-1) in Neuroprotection

Christian Hölscher

CNS Drugs 2012; 26 (10): 871-882



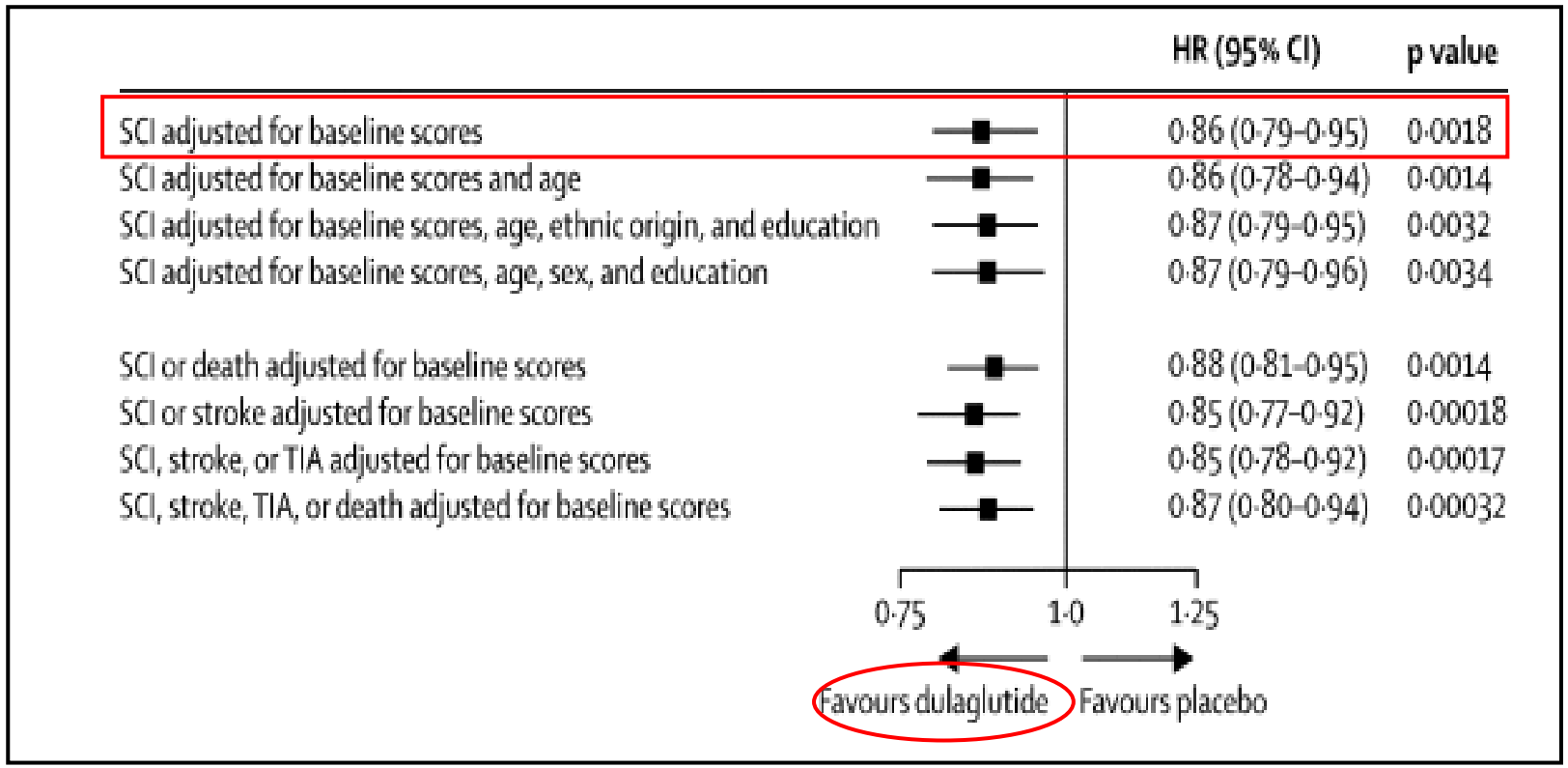
Il GLP-1 **ha proprietà simili all'insulina** in qualità di **fattore di crescita** ed ha dimostrato di ridurre una serie di processi degenerativi.

In studi preclinici il GLP-1 e gli analoghi attraversando la barriera ematoencefalica

- proteggono la formazione della **memoria** o l'attività **motoria**
- proteggono le **sinapsi** e le funzioni sinaptiche
- potenziano la **neurogenesi**
- riducono **l'apoptosi**
- proteggono i neuroni dallo **stress ossidativo**
- riducono la formazione della **placca**

Effetto nel SNC di modelli murini di AD, PD, SLA, SM, ictus su risposta infiammatoria cronica di malattie degenerative.

Dulaglutide mostra un impatto positivo su diversi indicatori di **declino cognitivo:** post hoc analisi dello studio **REWIND**



Funzione cognitiva valutata al baseline e nel FU con degli SCORE nei due gruppi DULA/PLAC

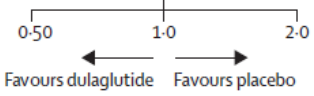
Dulaglutide riduce il rischio di decadimento cognitivo sostanziale (SCI) del 14% rispetto al placebo (HR 0·86, 95% CI 0·79–0·95; p=0·0018).

Substantive cognitive impairment **(SCI = decadimento congitivo sostanziale), definito come prima evidenza di variazione di punteggio di MoCA (Montreal Cognitive Assessment test) o di DSST (Digit Symbol Substitution Test) di almeno −1.5 devizioni standard.**

Cukierman-Yaffeet al. Lancet Neurol 2020; 19: 582–90

...indipendentemente dalla storia di ictus o malattia cardiovascolare...

	Dulaglutide		Placebo		Baseline-adjusted HR (95% CI)	$p_{interaction}$
	Events/patients (%)	Events/100 patient-years	Events/patients (%)	Events/100 patient-years		
Age						
>70 years	326/1128 (29%)	6·06	340/1086 (31%)	6·66	0·83 (0·71–0·97)	
≤70 years	579/3328 (17%)	3·41	604/3286 (18%)	3·63	0·89 (0·79–1·00)	0·23
Sex						
Female	472/2081 (23%)	4·59	494/2027 (24%)	4·97	0·96 (0·84–1·09)	
Male	433/2375 (18%)	3·59	450/2345 (19%)	3·82	0·79 (0·69–0·90)	0·032
Education						
>12 years	218/1731 (13%)	2·37	218/1733 (13%)	2·39	0·86 (0·71–1·04)	
<12 years	679/2717 (25%)	5·17	721/2633 (27%)	5·73	0·88 (0·79–0·97)	0·77
CVD						
No previous CVD	555/2815 (20%)	3·89	602/2783 (22%)	4·32	0·85 (0·76–0·96)	
Previous CVD	297/1373 (22%)	4·37	288/1351 (21%)	4·33	0·90 (0·76–1·06)	0·88
Stroke or TIA						
No previous stroke or TIA	802/4065 (20%)	3·92	828/3975 (21%)	4·17	0·87 (0·79–0·96)	
Previous stroke or TIA	103/388 (27%)	5·60	115/393 (29%)	6·15	0·90 (0·68–1·18)	0·95
HbA_{1c}						
>8·1%	237/1061 (22%)	4·54	257/1061 (24%)	4·99	0·83 (0·69–0·99)	
≤8·1%	668/3386 (20%)	3·91	685/3299 (21%)	4·15	0·87 (0·79–0·98)	0·70
Baseline log ACR						
≤–0·062	256/1388 (18%)	3·58	248/1342 (19%)	3·61	1·01 (0·85–1·21)	
–0·062 to –1·35	278/1421 (20%)	3·88	304/1389 (22%)	4·34	0·85 (0·72–1·01)	
>1·35	321/1363 (24%)	4·89	334/1358 (25%)	5·16	0·80 (0·69–0·94)	0·072
Baseline eGFR						
≥60 mL/min per 1·73 m^2	653/3405 (19%)	3·78	681/3315 (21%)	4·09	0·86 (0·77–0·96)	
<60 mL/min per 1·73 m^2	220/938 (24%)	4·88	232/945 (25%)	5·12	0·85 (0·71–1·03)	0·90
Standardised baseline MoCA						
>–1 unit	507/3755 (14%)	2·60	523/3674 (14%)	2·75	0·89 (0·78–1·00)	
≤–1 unit	390/693 (56%)	13·98	416/692 (60%)	15·5	0·87 (0·76–1·00)	0·63
Standardised baseline DSST						
>–1 unit	578/3866 (15%)	2·9	599/3784 (16%)	3·08	0·85 (0·76–0·96)	
≤–1 unit	312/567 (55%)	13·68	331/569 (58%)	14·88	0·89 (0·77–1·04)	0·92
Overall	**905/4456 (20%)**	**4·05**	**944/4372 (22%)**	**4·35**	**0·86 (0·79–0·95)**	



Cukierman-Yaffeet al. Lancet Neurol 2020; 19: 582–90

evoke and evoke+: two large global phase 3a trials will assess the efficacy and safety of Semaglutide in early AD

1840 patients in each trial

Age: 55–85 years (both inclusive)

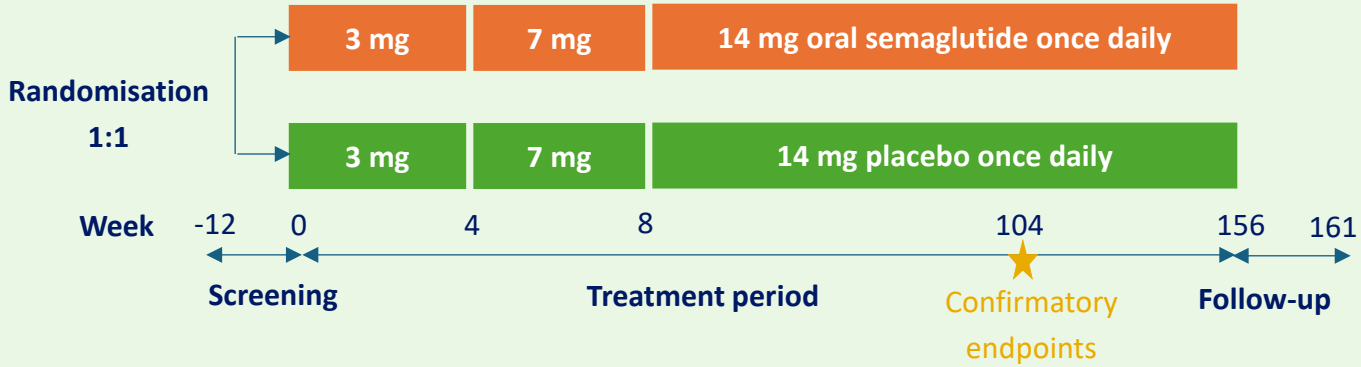
MCI or mild dementia both of the Alzheimer's type

- 80% MCI and 20% mild dementia
- Amyloid positive (PET or lumbar puncture)

800+ sites in **40** countries

evoke — evaluation of oral semaglutide in early Alzheimer's disease

evoke+ — evaluation of oral semaglutide in early Alzheimer's disease



Modifica del CLINICAL DEMENTIA RATING dal baseline alla sett 104

TEMPO DI PROGRESSION DA MCI A AD

molecules

MDPI

Review

Neuroprotective Effect of SGLT2 Inhibitors

Agnieszka Pawlos, Marlena Broncel *, Ewelina Woźniak and Paulina Gorzelak-Pabiś

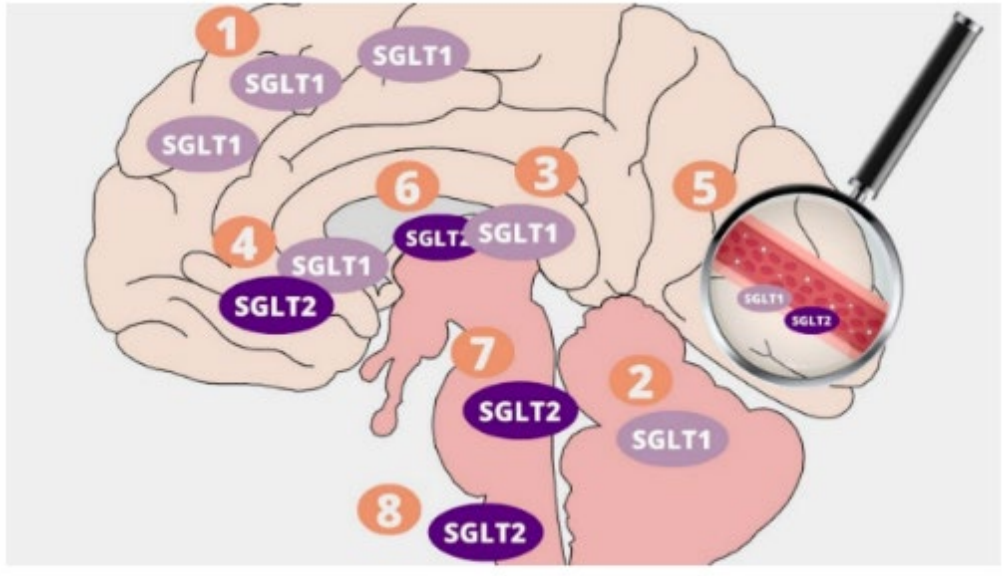


Figure 1. Distribution of SGLT1 and SGLT2 receptors in the Central Nervous System: 1. Pyramidal cells of brain cortex; 2. Purkinje cerebellum cells; 3. Hippocampus pyramidal and granular cells; 4. Hypothalamus; 5. Microvessels; 6. Amygdala; 7. Periaqueductal grey; 8. Dorsomedial medulla—nucleus of the solitary tract (NTS).

SGLT: aree responsabili dei processi di **apprendimento**, dell'assunzione di **cibo**, dell'omeostasi **dell'energia** e della **regolazione autonomica** centrale

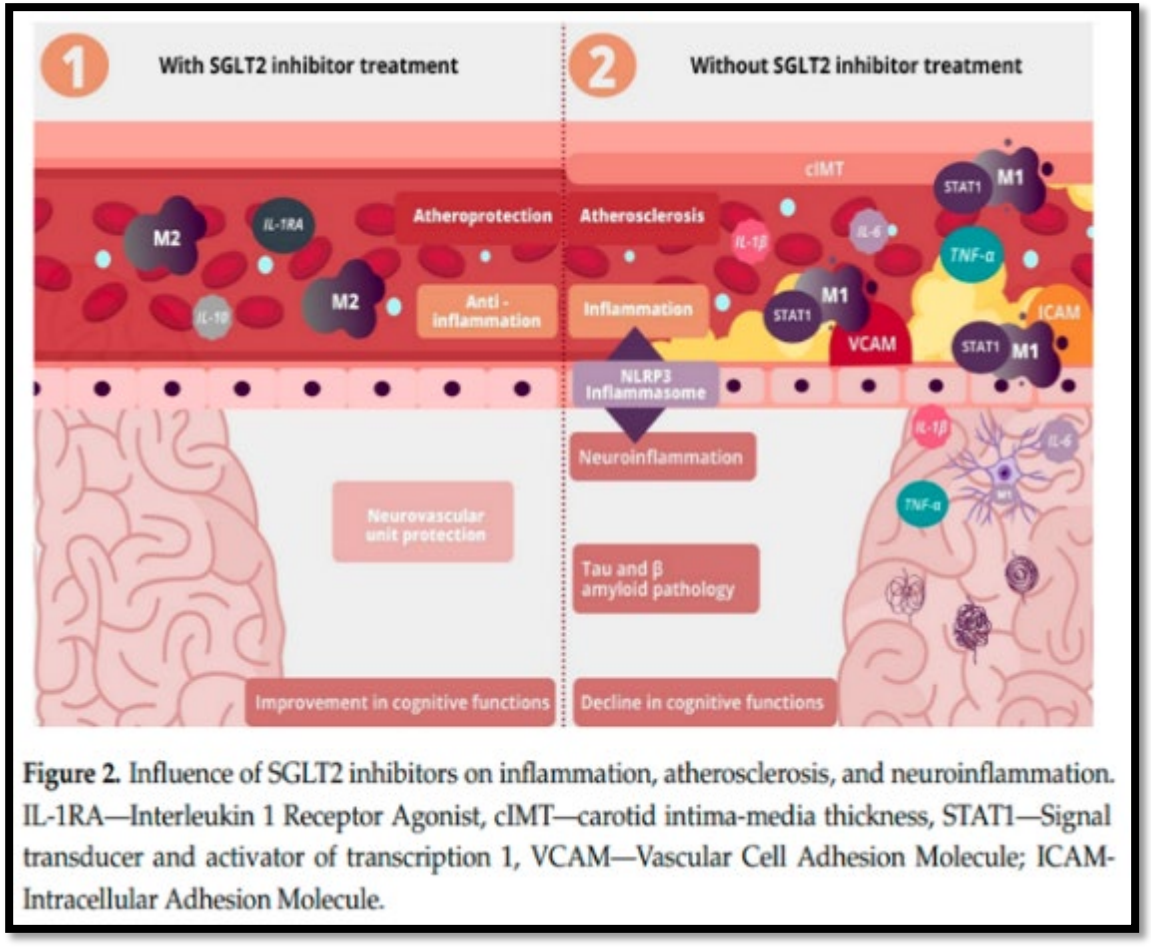


Figure 2. Influence of SGLT2 inhibitors on inflammation, atherosclerosis, and neuroinflammation. IL-1RA—Interleukin 1 Receptor Agonist, cIMT—carotid intima-media thickness, STAT1—Signal transducer and activator of transcription 1, VCAM—Vascular Cell Adhesion Molecule; ICAM-Intracellular Adhesion Molecule.

SGLT1i Protezione contro **ISCHEMIA e DANNO CEREBRALE DA RIPERFUSIONE**

SGLT2i : funz **antinfiammatoria e antiaterosclerotica**

Ruolo nella regolazione di mTOR

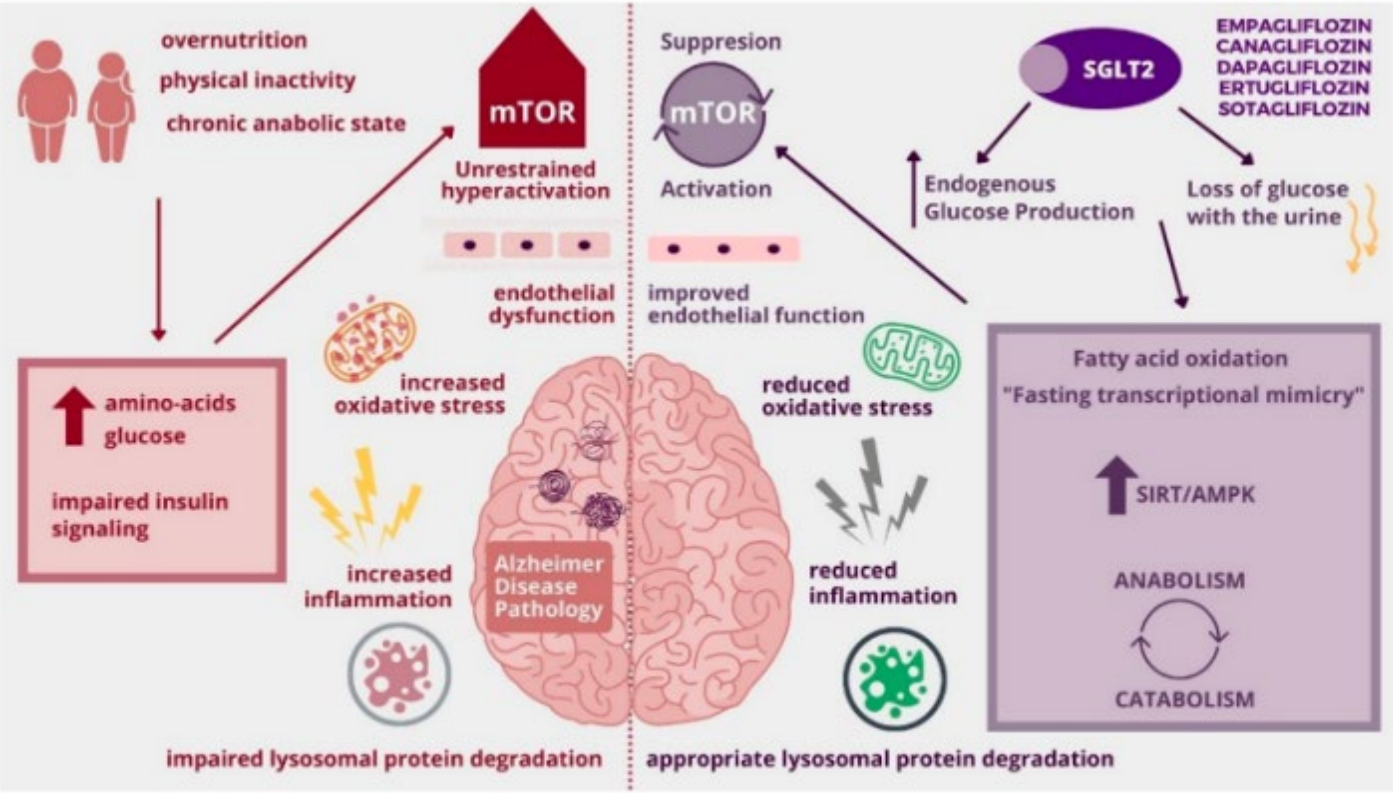


Figure 3. Influence of SGLT2 inhibitors on unrestrained activation of mTOR (mechanistic/mammalian target of rapamycin). AMPK-AMP-activated protein kinase, SIRT-Sirtuin.

Proteina chinasi che regola

- crescita, proliferazione e sopravvivenza cellulare

- Sintesi e trascrizione delle proteine

Con attivazione eccessiva

↓

Crescita incontrollata delle cellule (cancro, invecchiamento, neurodegenerazione)

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journal homepage: www.elsevier.com/locate/yfrne

Review article

Sodium-glucose cotransporter-2 inhibitors and their potential role in dementia onset and cognitive function in patients with diabetes mellitus: a systematic review and meta-analysis

Yea Jin Youn [a,1], Seungyeon Kim [b,1], Hyun-Jeong Jeong [c], Young-Mi Ah [c,*], Yun Mi Yu [d,e,*]

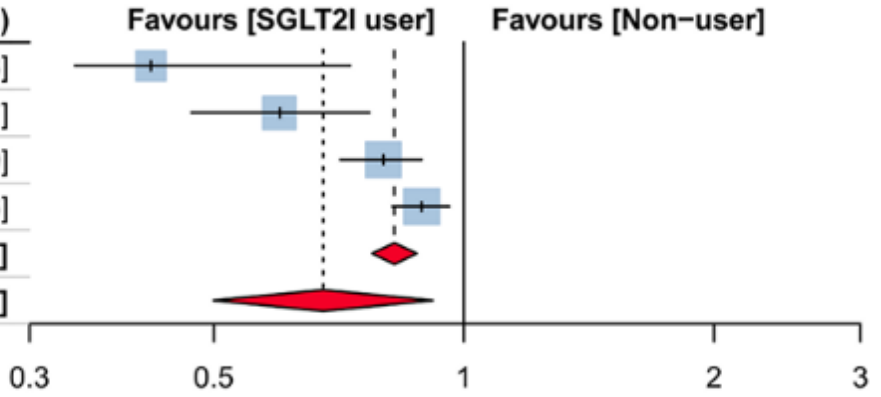
OP incidenza della demenza per tutte le cause, tra cui il morbo di Alzheimer, la demenza vascolare e la demenza a corpi di Lewy.

OS valutare il cambiamento nei punteggi della funzione cognitiva nel gruppo di utenti con inibitori SGLT-2 rispetto a quello nel gruppo non utilizzatore.

DEMENTIA INCIDENCE RISK

A. Hazard ratio

Study	Weight (fixed)	Weight (random)	HR (95% CI)
Mui 2021	2.6%	19.8%	0.42 [0.34; 0.73]
Proietti 2023	6.3%	24.2%	0.60 [0.47; 0.77]
Wu 2023	29.8%	27.7%	0.80 [0.71; 0.89]
Siao 2022	61.3%	28.3%	0.89 [0.82; 0.96]
Fixed effects model	**100.0%**	--	**0.82 [0.78; 0.88]**
Random effects model	--	**100.0%**	**0.68 [0.50; 0.92]**



Heterogeneity: $\chi^2_3 = 22.23$ ($P < .001$), $I^2 = 87\%$

Y.J. Youn et al. Frontiers in Neuroendocrinology 73 (2024) 101131

COGNITIVE SCORE CHANGES

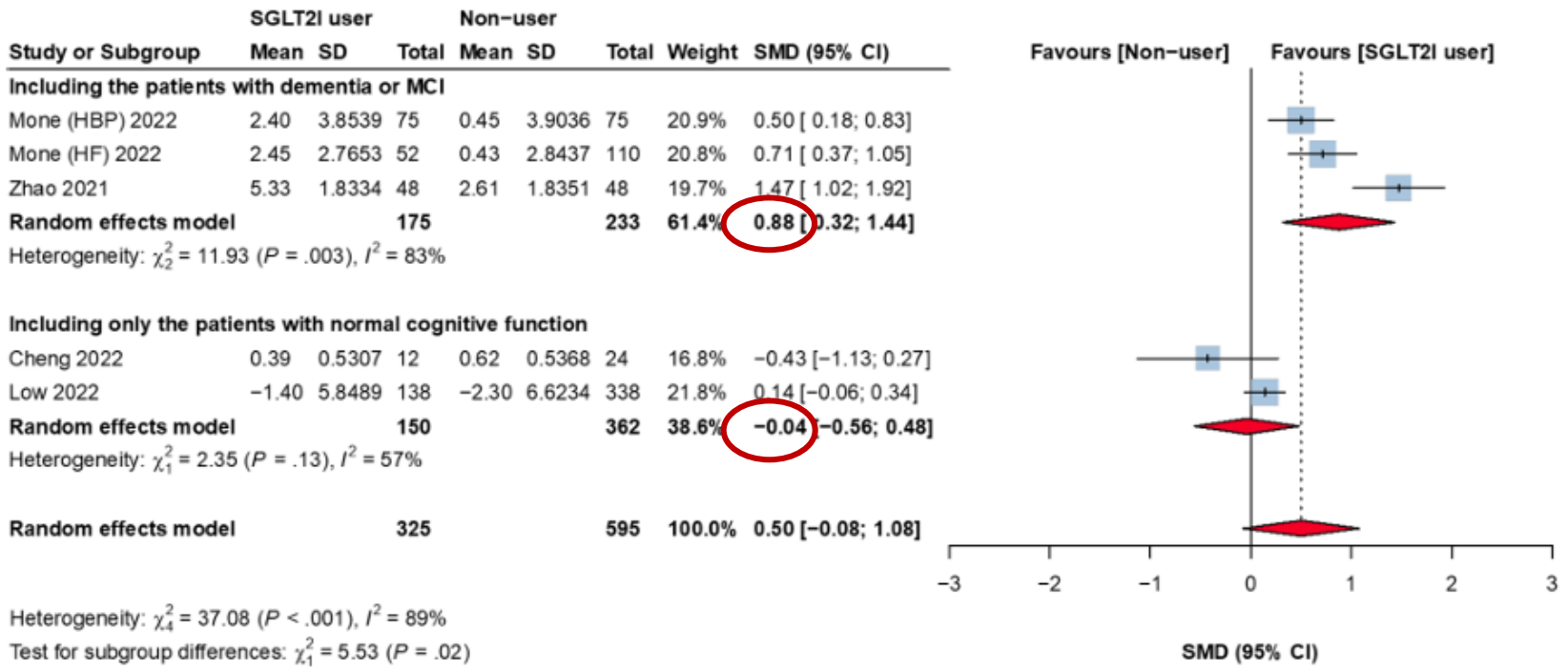


Fig. 3. Forest plot of cognitive function score changes with sodium-glucose cotransporter 2 inhibitors.

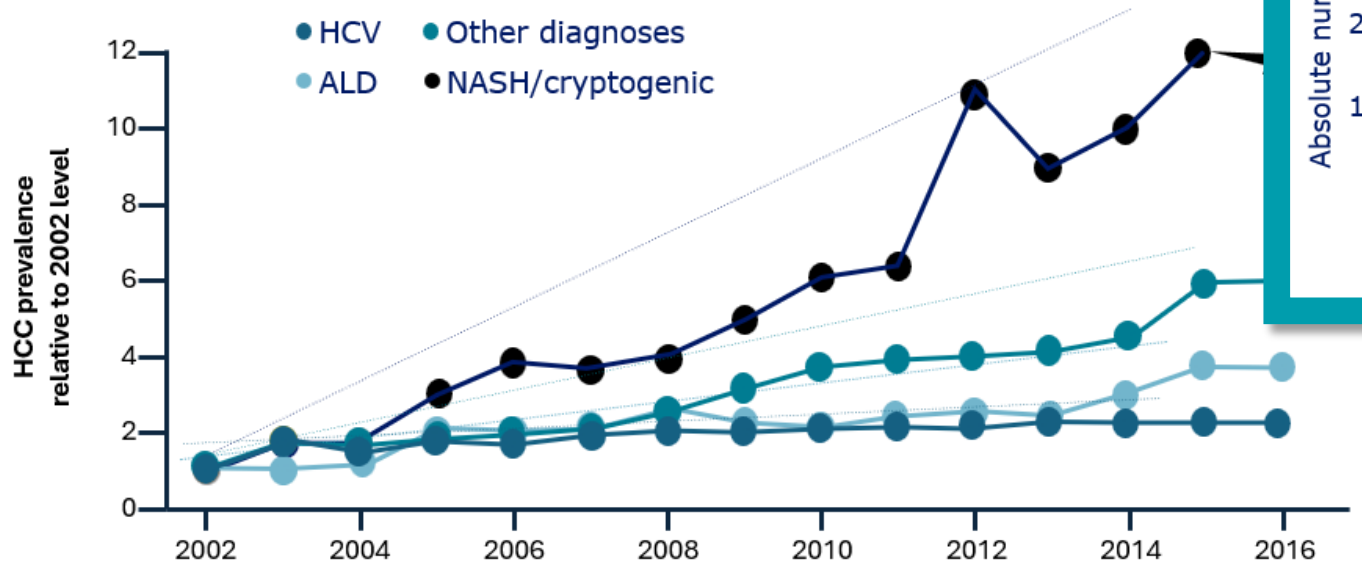
Y.J. Youn et al. Frontiers in Neuroendocrinology 73 (2024) 101131

EPATOPROTEZIONE

MASLD
(Metabolic dysfunction–associated steatotic liver disease)

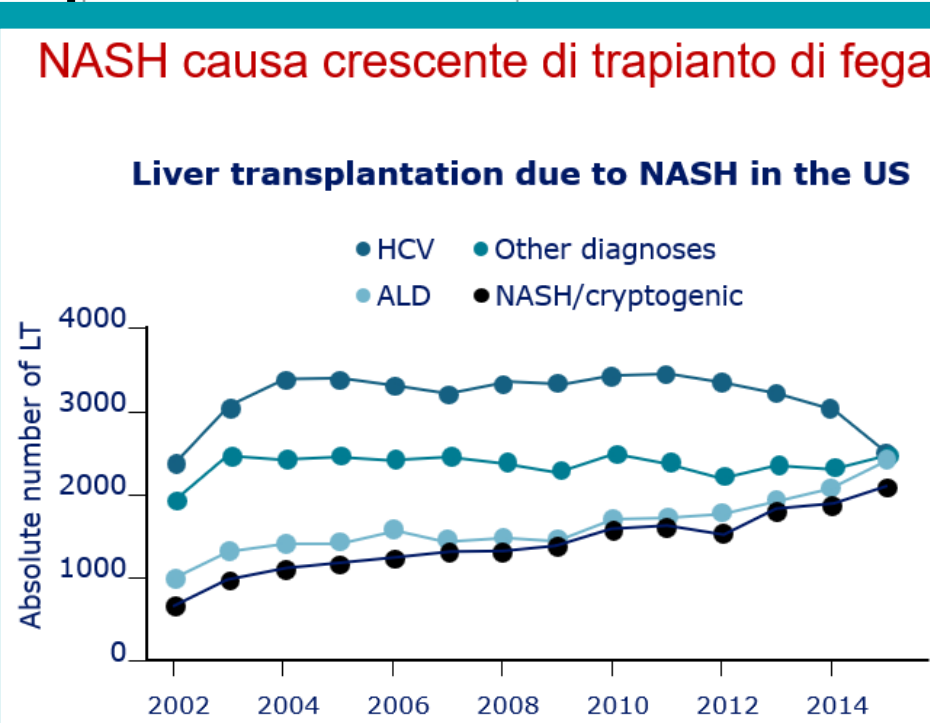
Steatosis with ≥1 cardiometabolic risk factors:
- Prediabetes or diabetes
- Overweight or obesity
- Dyslipidemia (or on lipid-lowering therapy)
- Hypertension (or on BP-lowering medication)

Prevalenza di HCC nei pazienti con NASH in aumento



Younossi Z et al. *Clin Gastrolenterol Hepatol* 2018;17:748–55.

NASH causa crescente di trapianto di fegato



Younossi ZM et al. *Clin Gastroenterol Hepatol.* 2019;17:748–755.

Figure 2. Natural History of Steatotic Liver Disease and MASLD.
Factors related to insulin resistance and metabolic dysfunction, diet and environmental exposures, and genetic and epigenetic factors are the main drivers of MASLD development and its progression throughout the entire spectrum of liver disease (Panel A). Female sex and hormonal factors can also modulate the development and progression of MASLD (Panel B). Ranges for years for disease progression and percentage of patients are approximations. HCV denotes hepatitis C virus.

Targher et al.NEJM August 14, 2025 393;7

Complicanze extraepatiche

Approximate increase in the risk of new-onset adv

Type 2 diabetes (i

Fatal or nonf

A

C

Extr

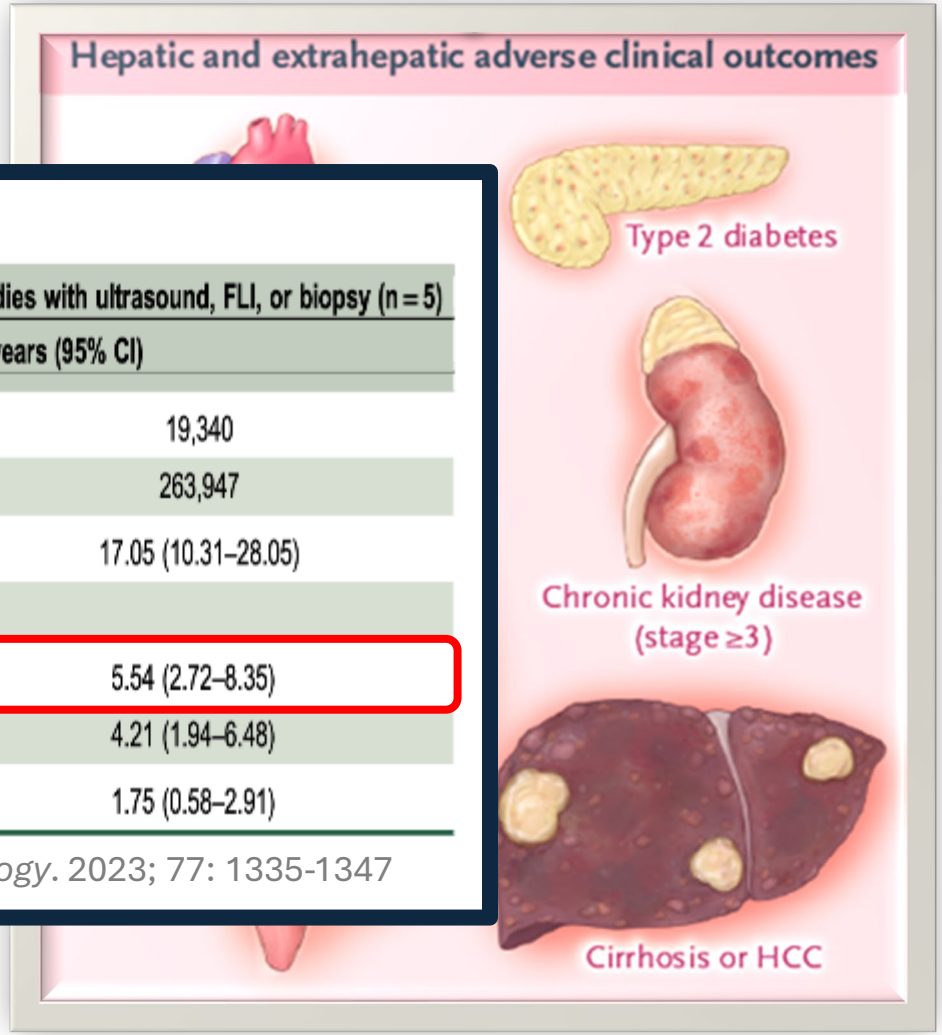
Cir

TABLE 4 All-cause and cause-specific mortality rate among NAFLD patients

	Studies with ultrasound or FLI (n = 3)	Studies with ultrasound, FLI, or biopsy (n = 5)
	Rate per 1000 person-years (95% CI)	
Total NAFLD cases	8153	19,340
Total person-years	104,470	263,947
All-cause mortality	12.6 (6.68–23.67)	17.05 (10.31–28.05)
Cause-specific death		
Cardiac specific	4.20 (1.34–7.05)	5.54 (2.72–8.35)
Extrahepatic cancer specific	2.83 (0.78–4.88)	4.21 (1.94–6.48)
Liver specific	0.92 (0.00–2.21)	1.75 (0.58–2.91)

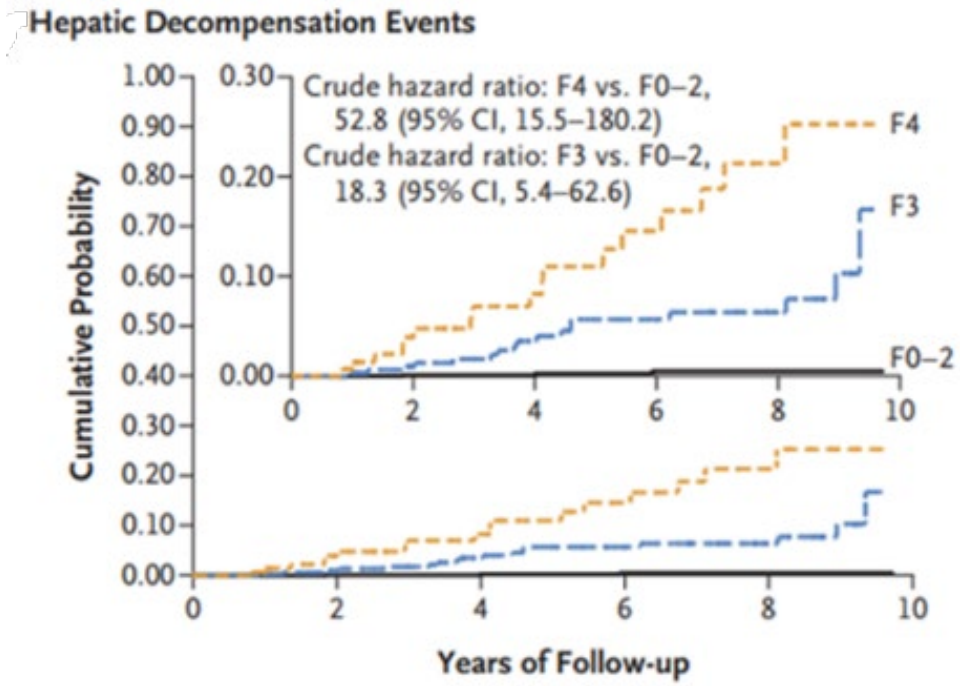
Abbreviation: FLI, fatty liver index.

Younossi ZM et al. *Hepatology*. 2023; 77: 1335-1347

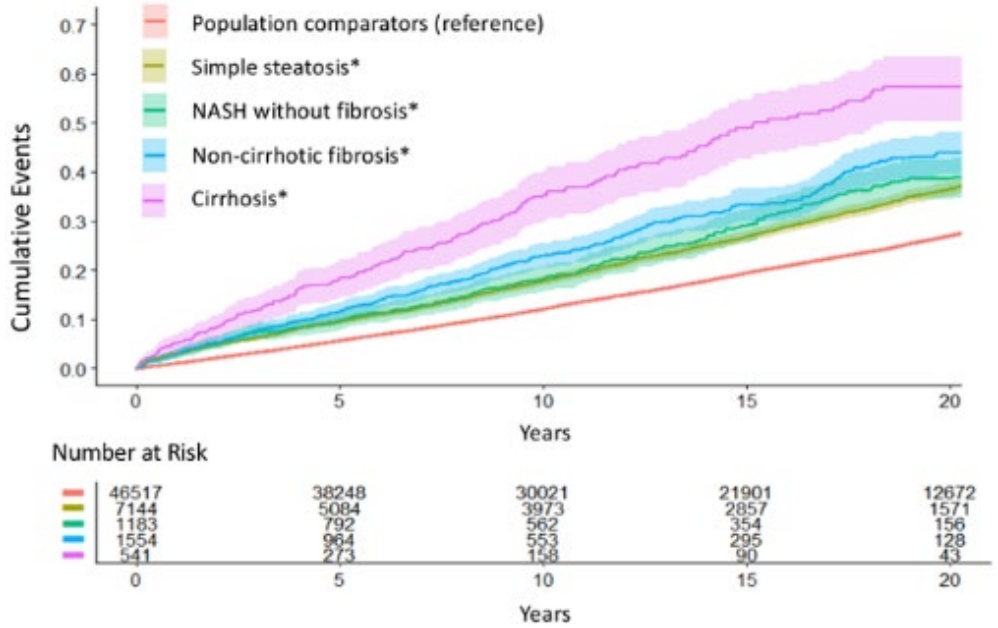


Targher et al.NEJM August 14, 2025 393;7

Stadio della fibrosi come fattore prognostico più rilevante



studio prospettico multicentrico su 1773 pazienti con MASLD sottoposti a biopsia (seguito per una mediana di 4 annI)
L'incidenza di **complicanze epatiche** per 100 anni-persona è **aumentata con lo stadio di fibrosi** (da F0 a F2 vs. F3 vs. F4).



Studio di coorte basato su pz con MASLD comprovata da biopsia (seguito per una mediana di 13,6 anni)
I pz con MASLD avevano **MACE incidenti più elevati** rispetto ai controlli: 24,3 contro 16,0/1000 anni-persona (aHR 1,73), **con la più alta incidenza osservata nella cirrosi.**

Edited from Sanyal et al, NEJM 2021; Simon TG et al, Gut 2022

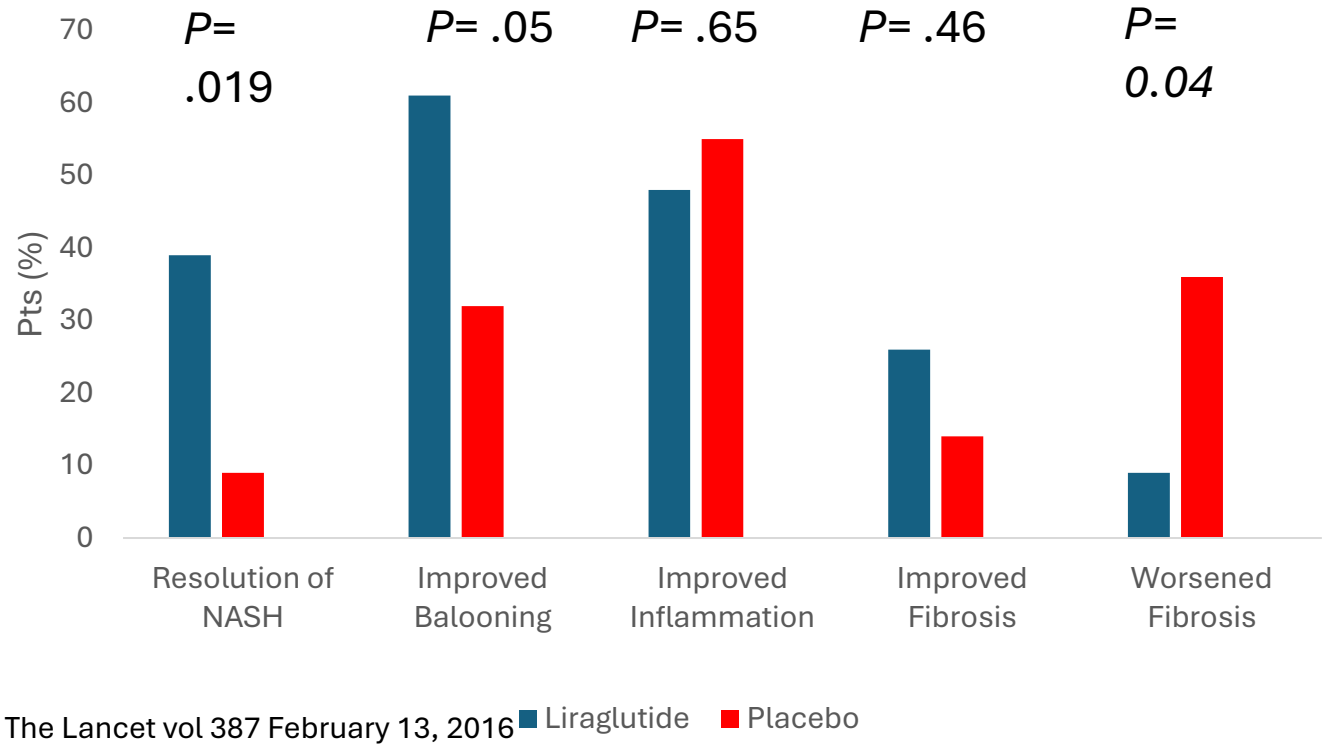
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team*, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome

26 paz

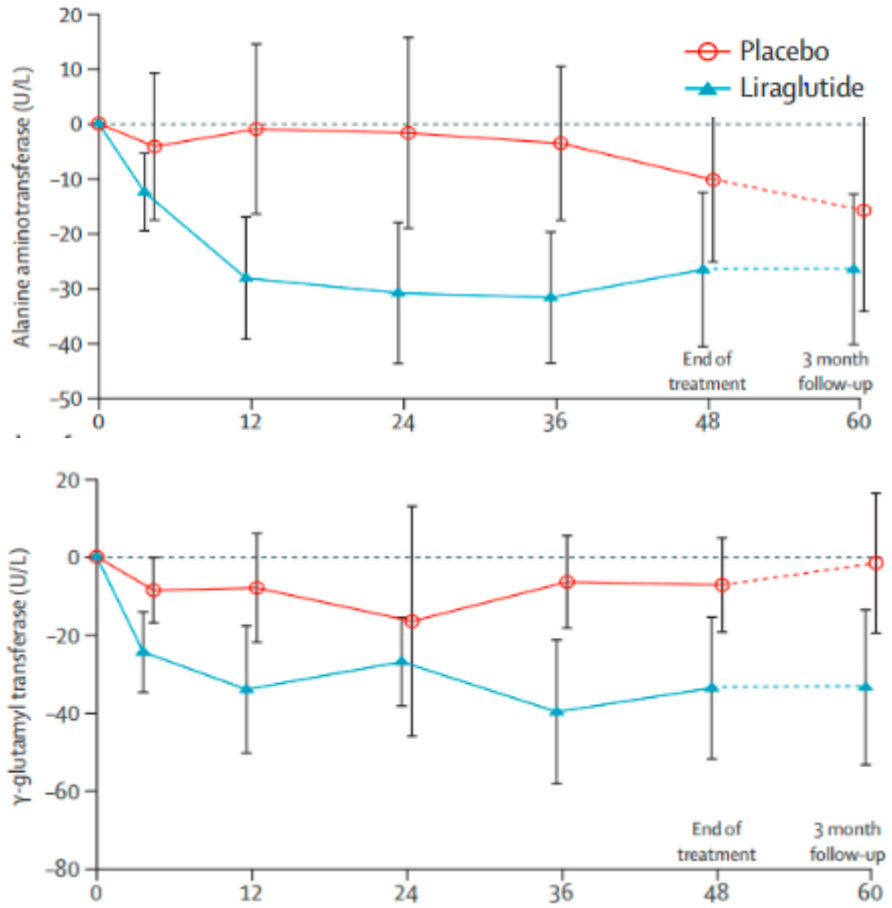
Liraglutide

26 paz Placebo

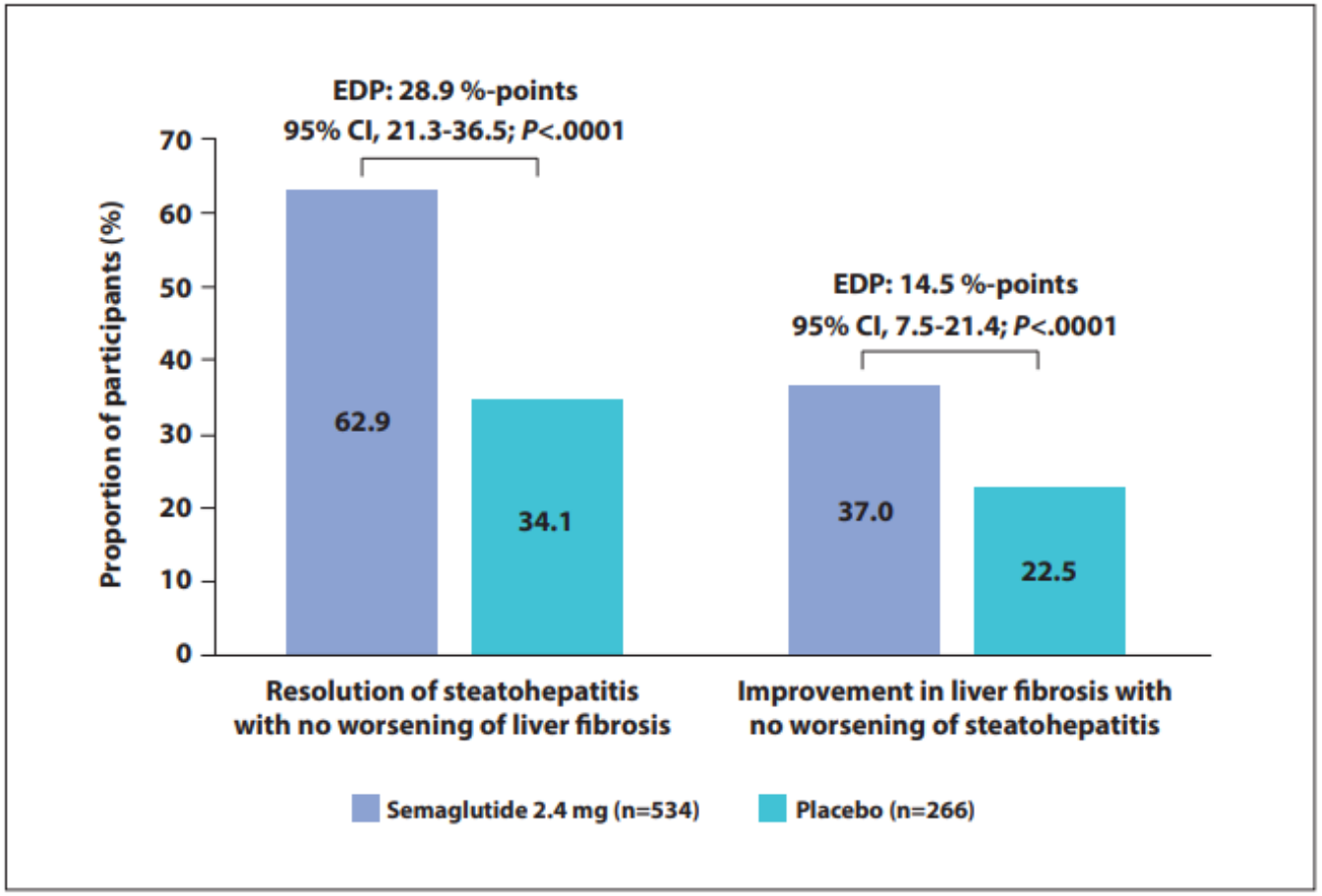


The Lancet vol 387 February 13, 2016

- 9/23 (39%) con **LIRA**: risoluzione alla bio di NASH Vs 2/22 (9%) in PL (RR 4·3 [95% CI 1·0–17·7]; p=0·019).
- 2/23 (9%) con **LIRA** vs 8/22 (36%) in PL hanno avuto progressione della fibrosi (0.2 [0.1-1.0]; p=0.04



Phase 3 ESSENCE Trial: Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis



- Miglioramento statisticamente significativo e superiore della **fibrosi epatica** senza peggioramento della steatoepatite, nonché la **risoluzione della steatoepatite** senza peggioramento della fibrosi epatica con Sema 2,4 mg vs placebo.

- Alla settimana 72 **il 37,0%** delle persone trattate con Sema 2,4 mg ha ottenuto un **miglioramento della fibrosi epatica** senza peggioramento della steatoepatite rispetto al 22,5% del placebo.

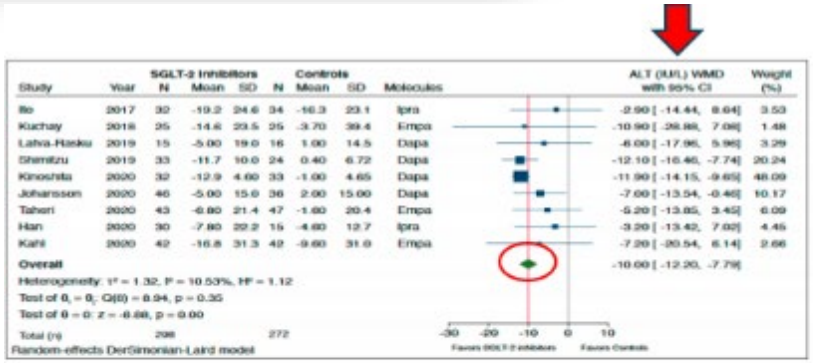
- Il **62,9%** delle persone trattate con Sema 2,4 mg ha raggiunto la **risoluzione della steatoepatite** senza peggioramento della fibrosi epatica rispetto al 34,1% del placebo.

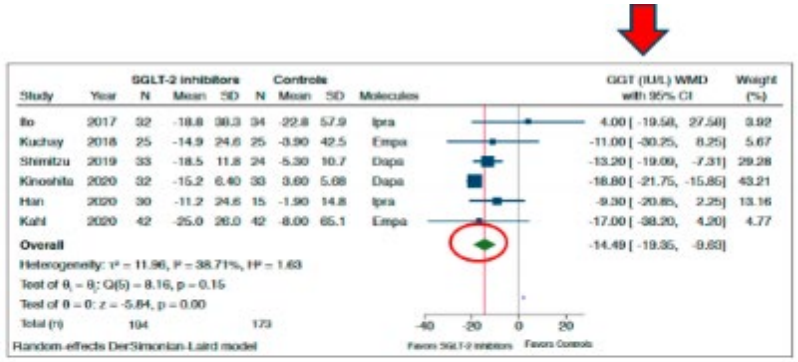
Review

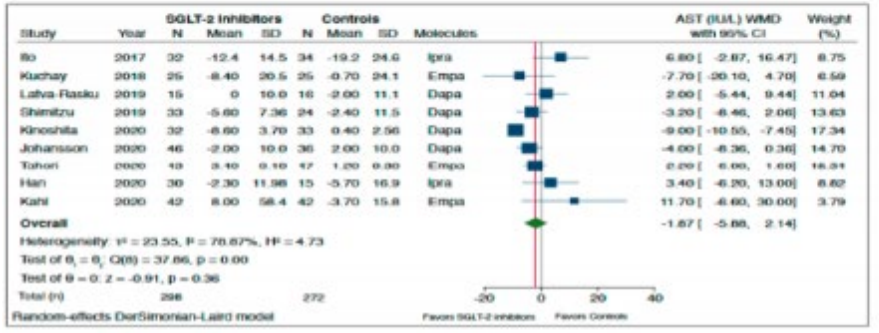
Sodium-Glucose Cotransporter-2 Inhibitors for Treatment of Nonalcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials

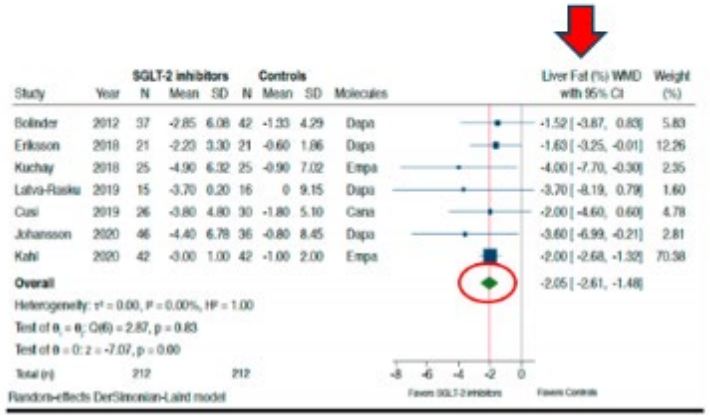
Alessandro Mantovani, Graziana Petracca, Alessandro Csermely, Giorgia Beatrice and Giovanni Targher *

- 12RCT : dapagliflozin (n =6), empagliflozin (n = 3), ipragliflozin (n = 2), canagliflozin (n = 1)
- 850 soggetti sovrappeso o obesi con NAFLD (90% con DM2)
- 24 sett
- Outcome primario: modifica degli enzimi e della steatosi





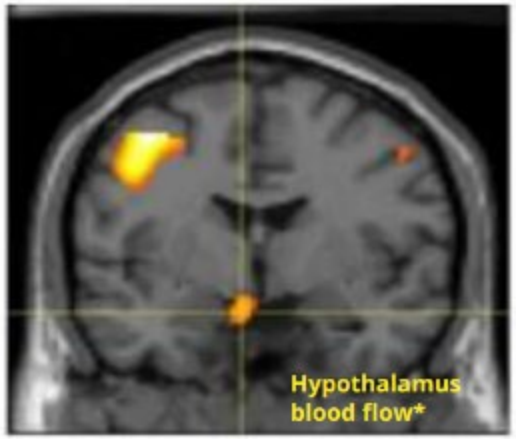


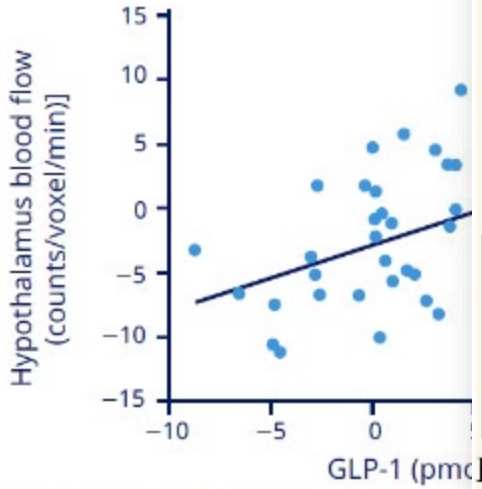


Metabolites 2021, 11, 22

EFFETTI SUL PESO

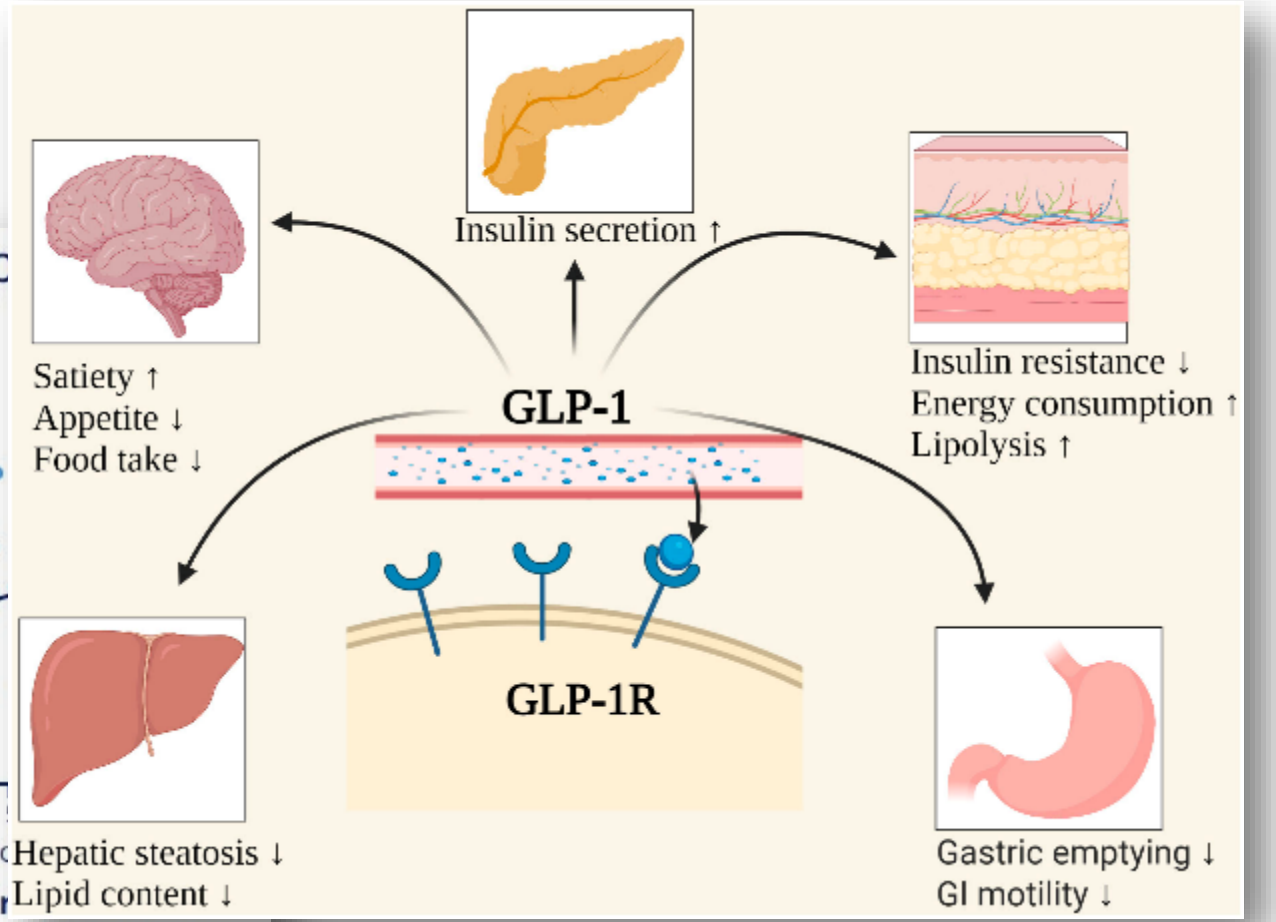
GLP-1 activates areas of the brain involved in app regulation





Peak post-prandial increases in plasma GLP-1 concentrations are cor increases in regional cerebral blood flow in the hypothalamus

*Post-prandial change in regional cerebral blood flow captured by PET scan.
GLP-1, glucagon-like peptide-1; PET, positron emission tomograph.
Pannacciulli et al. NeuroImage 2007;35:511–7.



Diabetes Care
American Diabetes Association

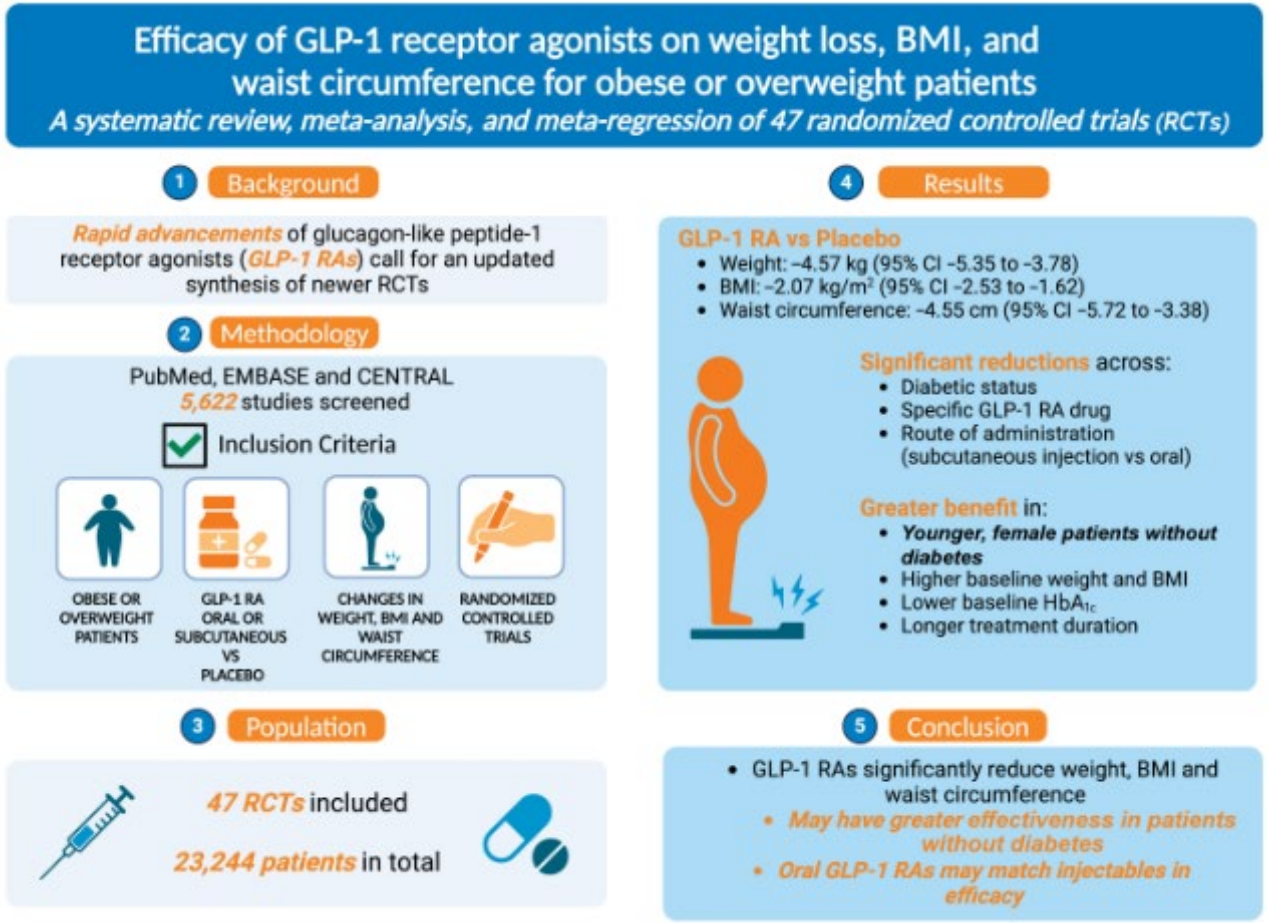
Efficacy of GLP-1 Receptor Agonists on Weight Loss, BMI, and Waist Circumference for Patients With Obesity or Overweight: A Systematic Review, Meta-analysis, and Meta-regression of 47 Randomized Controlled Trials

Hon Jen Wong, Bryan Sim, Yao Hao Teo, Yao Neng Teo, Mark Y. Chan, Leonard L.L. Yeo, Pei Chia Eng, Benjamin Y.Q. Tan, Naveed Sattar, Mayank Dalakoti, and Ching-Hui Sia

Diabetes Care 2025;48(2):292–300 | https://doi.org/10.2337/dc24-1678

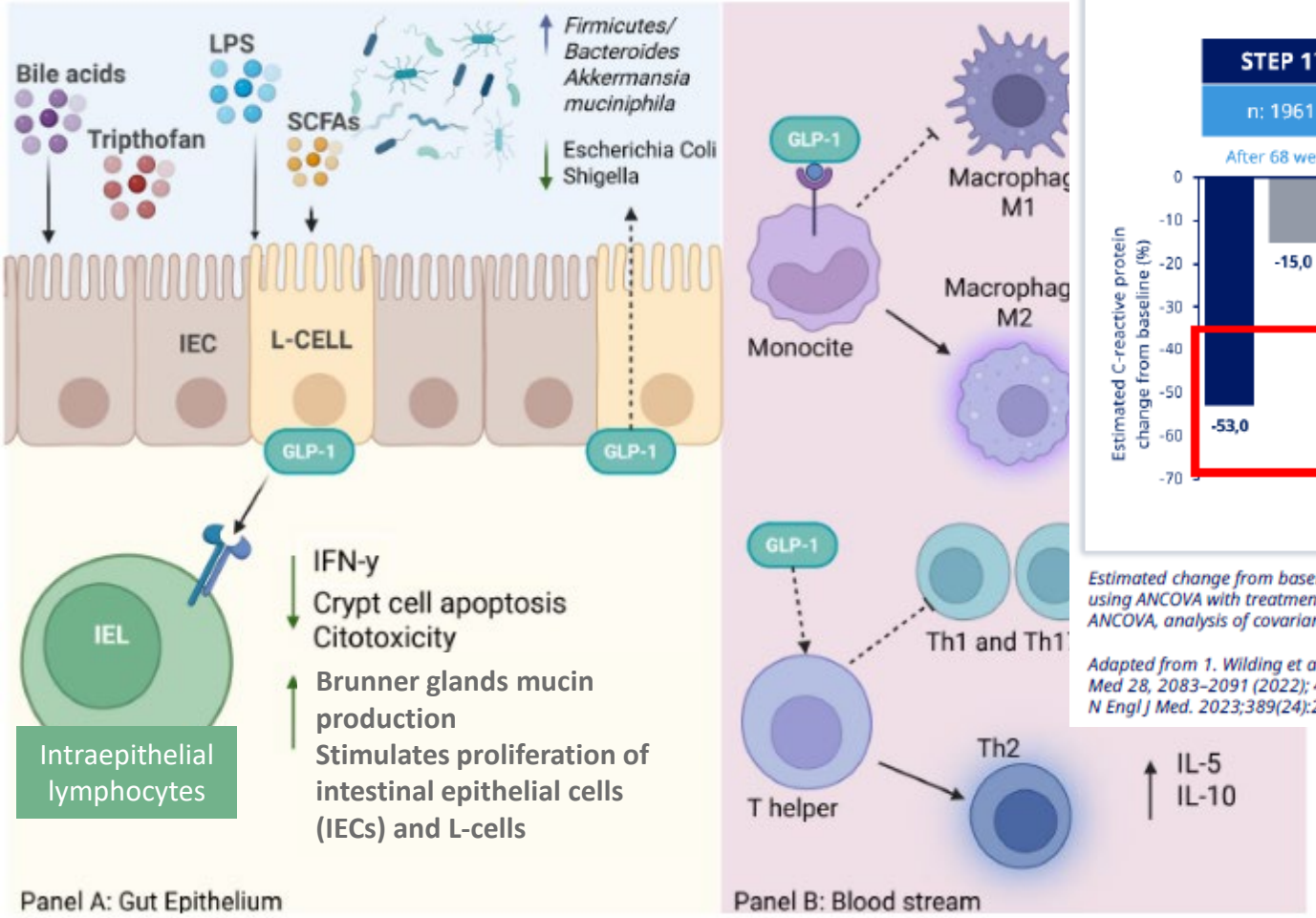
Examined the weight loss efficacy of GLP-1 RAs in populations with diabetes and overweight or obesity versus populations without diabetes but with overweight or obesity and whether there are differences in weight loss efficacy of oral versus injected GLP-1 RAs.

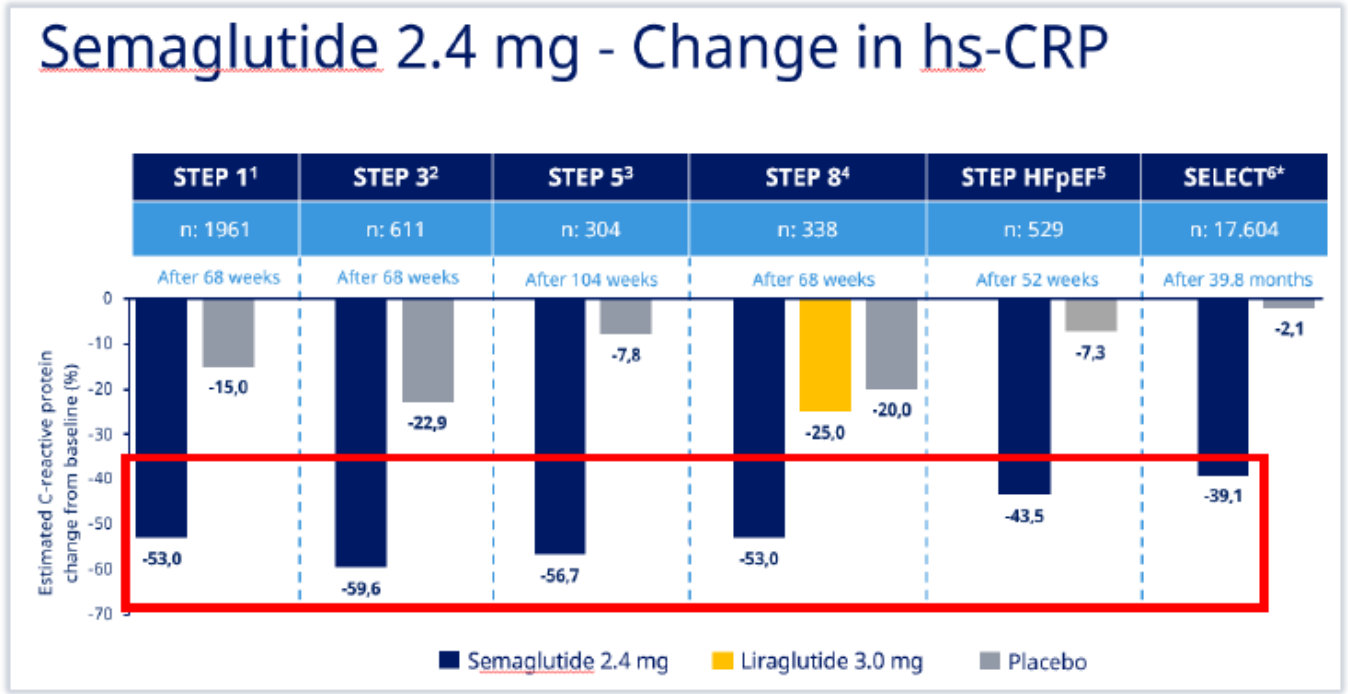
Oral GLP-1 RAs may be as effective as injected GLP-1 RAs
GLP-1 RAs could be more effective in younger female patients without diabetes but with higher baseline weight/BMI but lower baseline HbA1c.



EFFETTI SULLA PLACCA E SU INFIAMMAZIONE

Infiammazione





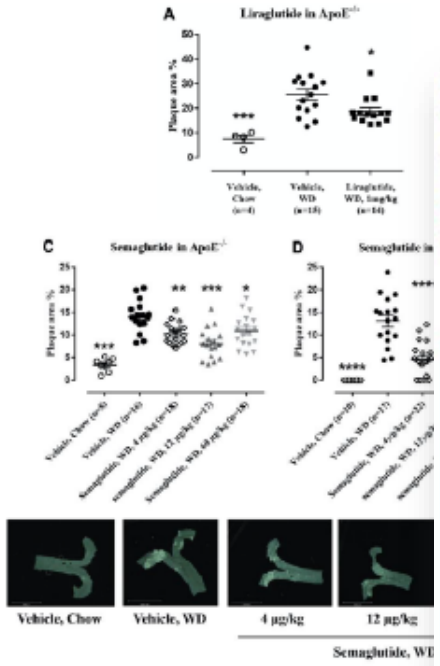
*Estimated change from baseline for treatment policy estimand. *Relative changes from baseline (log-transformed before analysis) to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.*
ANCOVA, analysis of covariance; hsCRP, high-sensitivity C-reactive protein.

Adapted from 1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 3. Garvey et al. Nat Med 28, 2083–2091 (2022); 4. Rubino et al. JAMA 2022; 327(2): 138-150; 5. Kosiborod MN, et al. N Engl J Med. 2023;389(12):1069-1084. 6. Lincoff AM, et al. N Engl J Med. 2023;389(24):2221-2232.

Migliorisi et al. Frontiers in Immunology Jul 2025

Semaglutide has anti-atherosclerotic effects

Attenuation of plaque lesion area in mouse models of atherosclerosis is independent of dose



GLP-1R activation

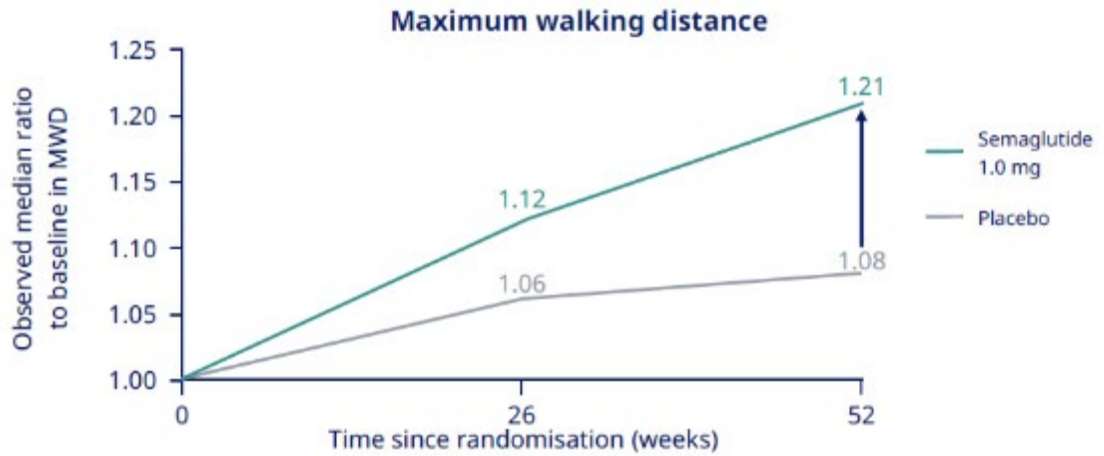
OW Semaglutide improved MWD by 13% compared to placebo

Ratio to baseline at week 52

Semaglutide demonstrated a **13% MWD improvement** compared to placebo on top of SoC [ETR **1.13** (95% CI, 1.06–1.21; p=0.0004)]

Median improvement
26.4 m (95% CI, 11.8–40.9)

Mean improvement*
39.9 m (95% CI, 13.9–66.0)



*Mean difference in MWD for semaglutide versus placebo were derived from an analysis using the trial product estimand.
CI, confidence interval; ETR, estimated treatment ratio; **MWD, maximum walking distance**; SoC, standard of care
Bonaca MP et. al. Lancet 2025: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)00509-4/fulltext.

Studio STRIDE

PLACCA ATEROSCLEROTICA

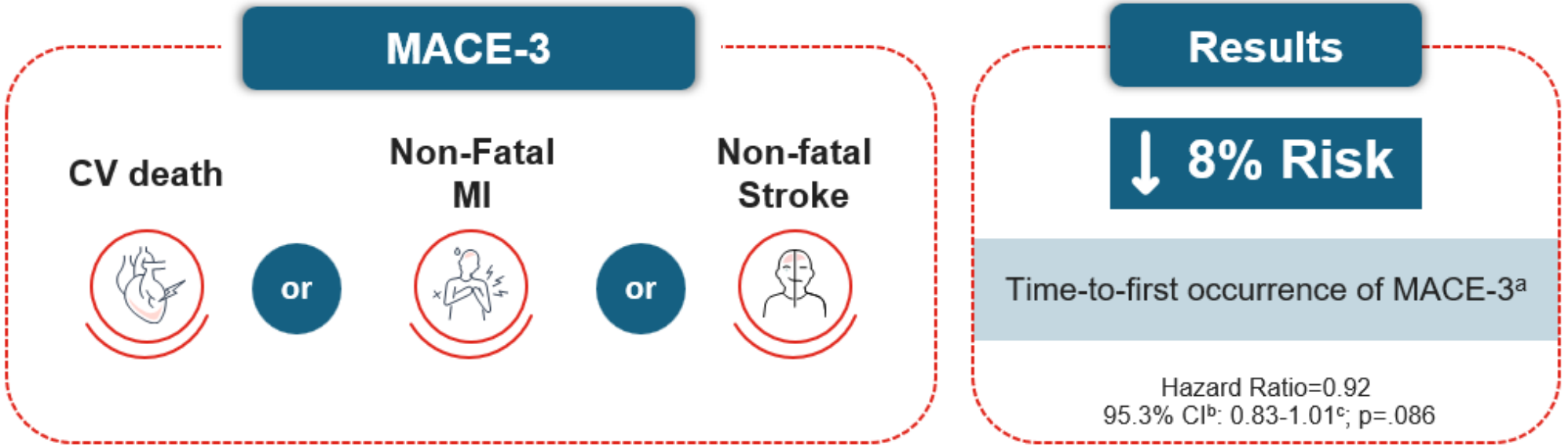
…Magellano guidò la prima spedizione per la circumnavigazione del globo…

Con la Tirzepatide abbiamo ulteriormente allargato i confini metabolici dimostrando, oltre ad una sua importante efficacia su tutti gli aspetti sovra-esposti, anche effetti su **controllo lipidico e pressorio**

PROTEZIONE CV

La tirzepatide ha dimostrato un tasso non inferiore di MACE-3 rispetto a dulaglutide

Primary Outcome of SURPASS-CVOT



La tirzepatide ha dimostrato risultati coerenti in tutti e tre i componenti dell'endpoint composito MACE-3

[a]Time-to-first event analysis using Cox proportional hazard model. [b]95.3% CI reported due to type 1 error rate adjusted for efficacy interim analysis. [c]Boundary for non-inferiority statistical significance <1.05.
CI=Confidence Interval; CV=Cardiovascular; CVOT=Cardiovascular Outcomes Trial; MACE-3=3-Point Major Adverse Cardiovascular Event; MI=Myocardial Infarction.

https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction (Accessed July 31, 2025).

NEUROPROTEZIONE

RESEARCH Open Access

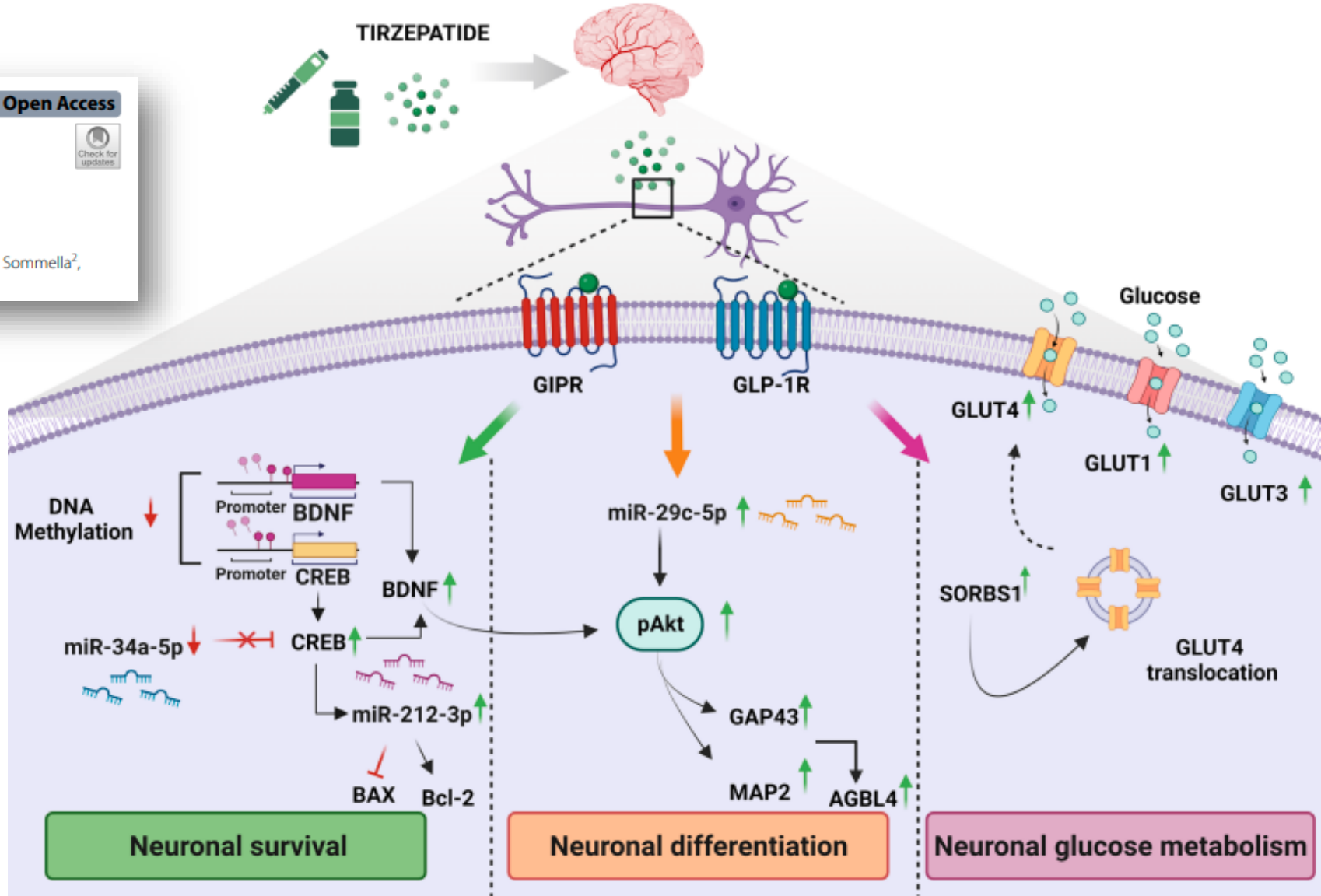
Tirzepatide prevents neurodegeneration through multiple molecular pathways

Rosaria Anna Fontanella[1†], Puja Ghosh[1†], Ada Pesapane[1], Fatemeh Taktaz[1], Armando Puocci[1], Martina Franzese[1], Maria Federica Feliciano[1], Giovanni Tortorella[1], Lucia Scisciola[1*], Eduardo Sommella[2], Concetta Ambrosino[3,4], Giuseppe Paolisso[1,5] and Michelangela Barbieri[1]

Effetto di **TIRZE** su markers di

- Crescita
- Apoptosi
- Differenziazione
- Insulino resistenza

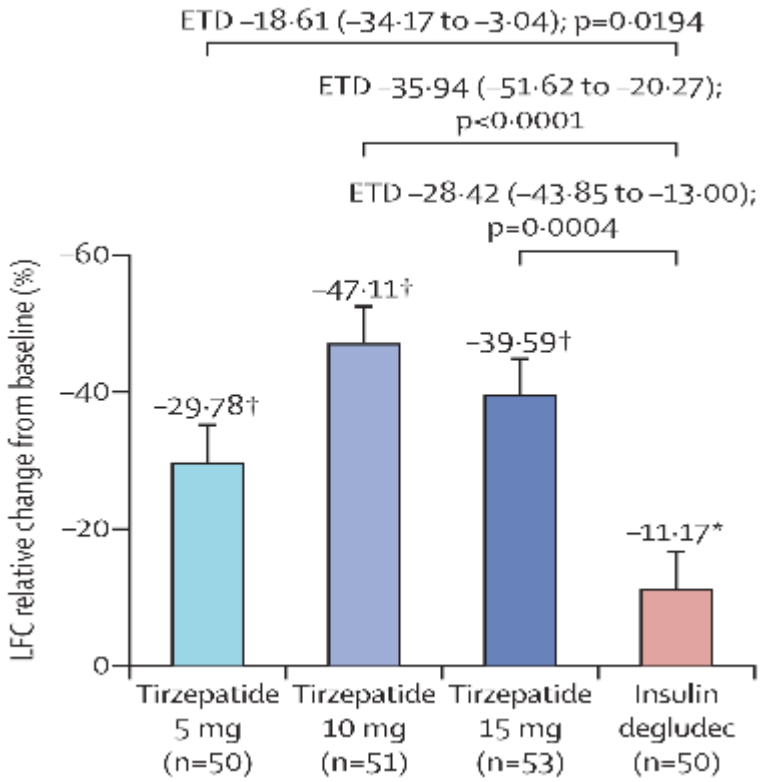
In **neuroblastoma cell line** esposta a [gluc] normale o alta

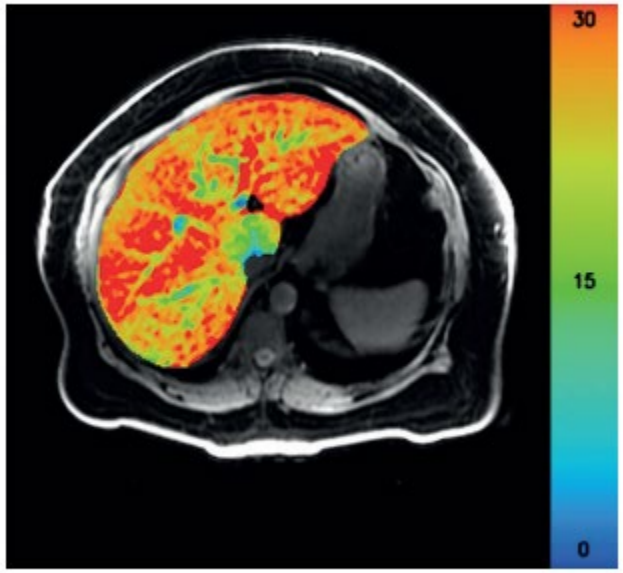


Fontanella et al. Journal of Translational Medicine (2024) 22:114

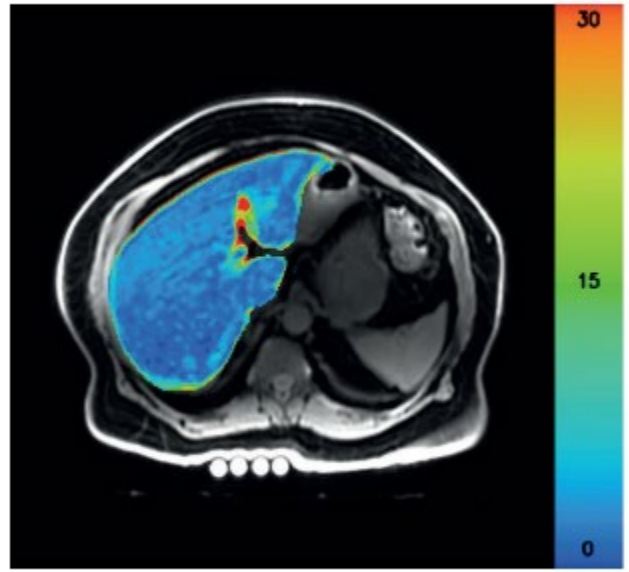
MASLD

SURPASS-3 MRI: Tirzepatide Reduces Fat Liver Content





LFC at baseline: 27·3%



LFC at week 52: 2·6%

ETD, estimated treatment difference; LFC, liver fat content; * p<0·05; †p<0·0001; ‡ p<0·01, vs baseline.

Gastaldelli A, et al, Lancet Diabetes Endocrinol 2022

The NEW ENGLAND JOURNAL of MEDICINE

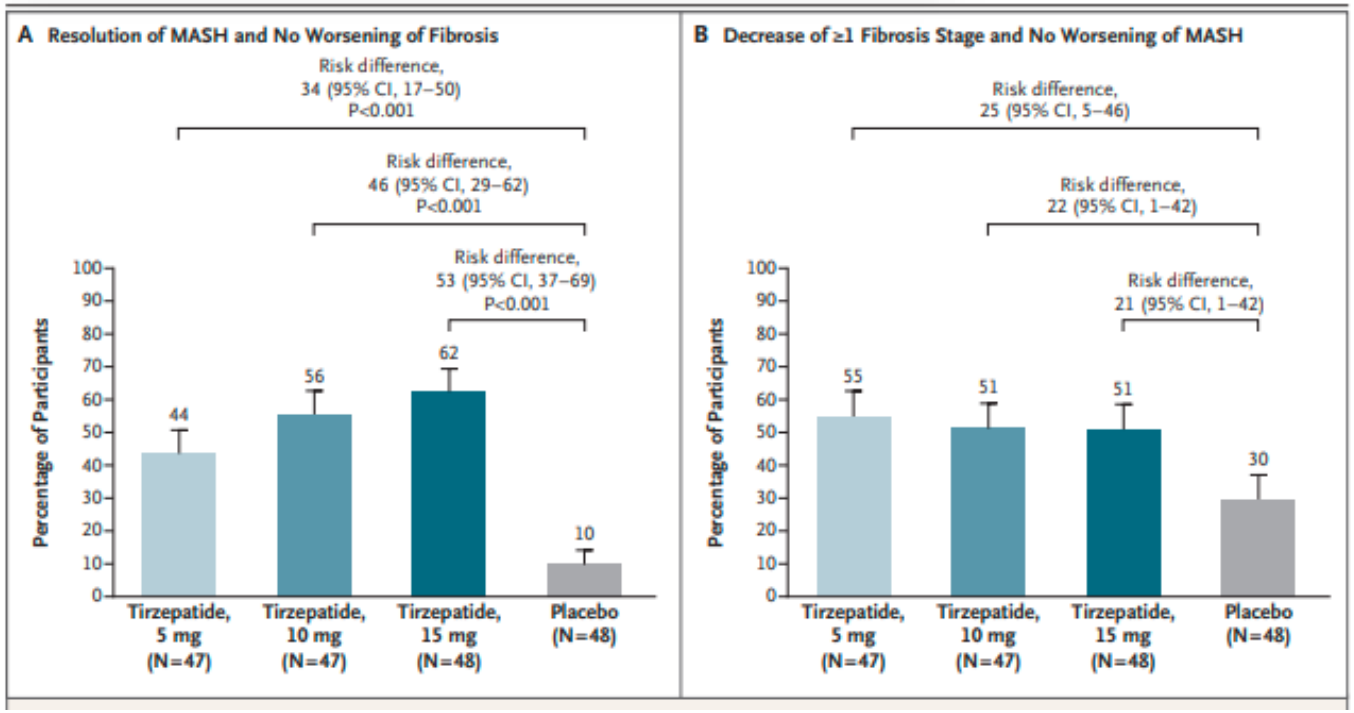
ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

Studio di fase 2 controllato con placebo che ha coinvolto **190 partecipanti con MASH confermata da biopsia e fibrosi in stadio F2 o F3 (moderata o grave).**

sc tirzepatide (5 mg, 10 mg, or 15 mg) o placebo per 52 sett.

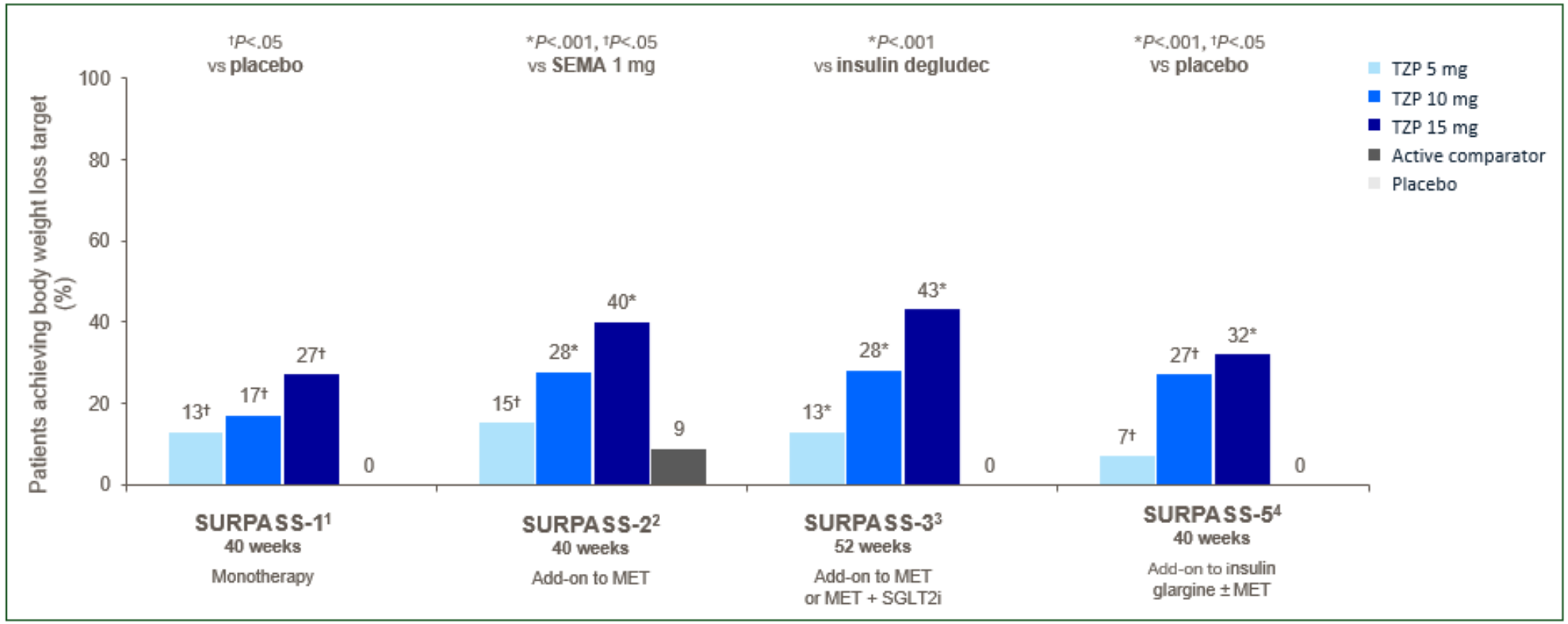


- **Endpoint primario** era la risoluzione della MASH senza peggioramento della fibrosi a 52 settimane.
- **Endpoint secondario** chiave era un miglioramento (diminuzione) di almeno uno stadio di fibrosi senza peggioramento della MASH

Tirze è più efficace del placebo per quanto riguarda la risoluzione della MASH senza peggioramento della fibrosi

PESO

Up to 43% of Patients Achieving ≥15% Weight Loss
Efficacy Estimand



- Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
- MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

Rosenstock J et al, Lancet, 2021; Frias JP et al, N Eng J Med,,2021; Ludvik B et al, Lancet 2021; Del Prato S et al., Lancet 2021; Dahl D et al, JAMA 2022

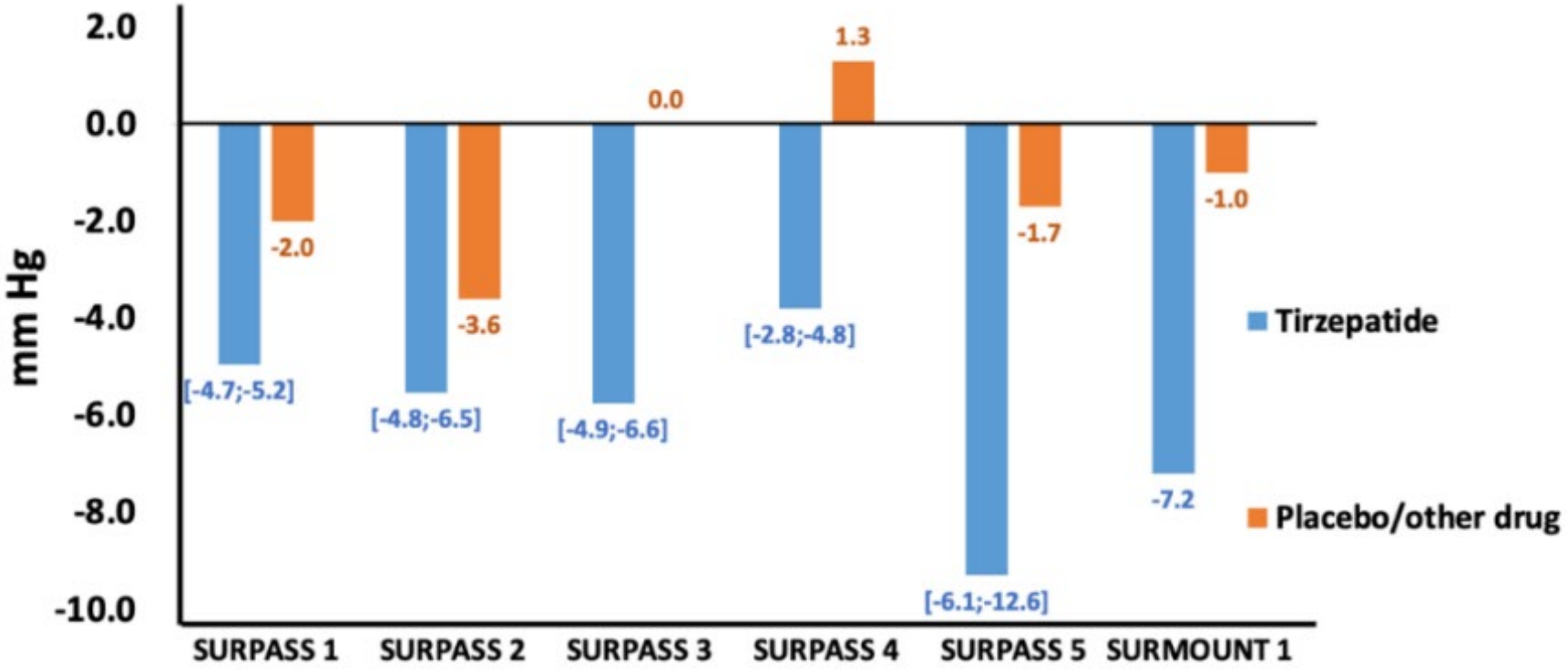
SBP

Riduzione PAS

Effetto in parte legato alla **perdita di peso**

- Miglioramento della **funzione endoteliale**
- Riduzione dell'**infiammazione** e della **rigidità arteriosa**

Mean variations in systolic blood pressure (SBP) with Tirzepatide vs. placebo/other drugs

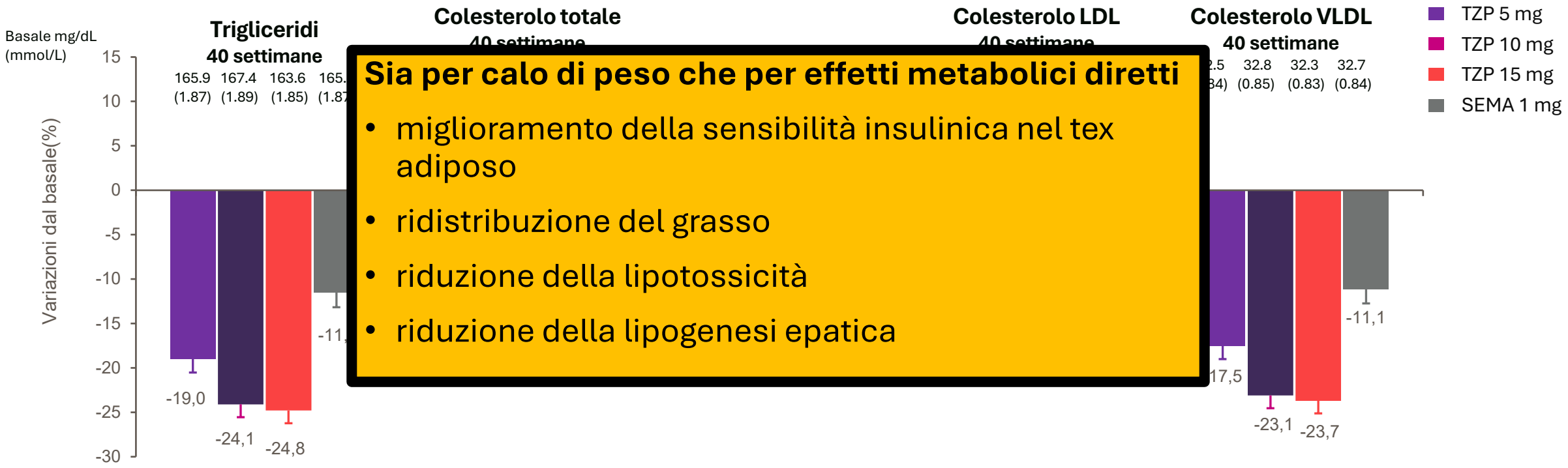


Int. J. Mol. Sci. 2022, 23, 14631

LIPIDI

Tirzepatide migliora il profilo lipidico sierico a 40 settimane (SURPASS-2)

Tirzepatide ha aumentato i livelli di colesterolo HDl e diminuito i livelli di colesterolo VLDL e LDL rispetto a sema 1 mg



Sia per calo di peso che per effetti metabolici diretti

- miglioramento della sensibilità insulinica nel tex adiposo
- ridistribuzione del grasso
- riduzione della lipotossicità
- riduzione della lipogenesi epatica

I dati sono percentuali medie stimate (SE) dall'analisi MMRM utilizzando la trasformazione logaritmica; popolazione mITT (set di analisi di efficacia).
HDL = lipoproteine ad alta densità; LDL = lipoproteine a bassa densità; MET = metformina; mITT = popolazione "intent-to-treat" modificata; MMRM = modello misto a misure ripetute; SEMA = semaglutide; TZP = tirzepatide; VLDL = lipoproteine a densità molto bassa..

Frias JP, et al. N Engl J Med. 2021

OSAS

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

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., Richard J. Schwab, M.D., Julia P. Dunn, M.D., Sujatro Chakladar, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Josef Bednarik, M.D., for the SURMOUNT-OSA Investigators*

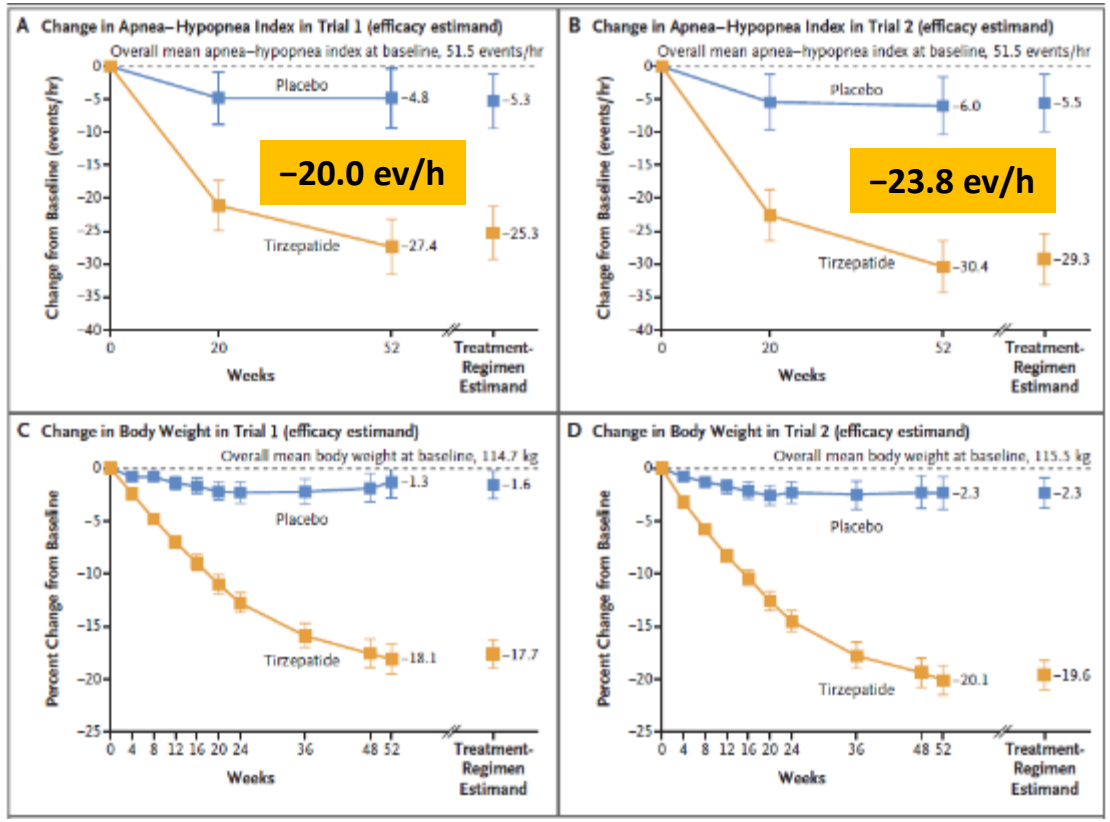


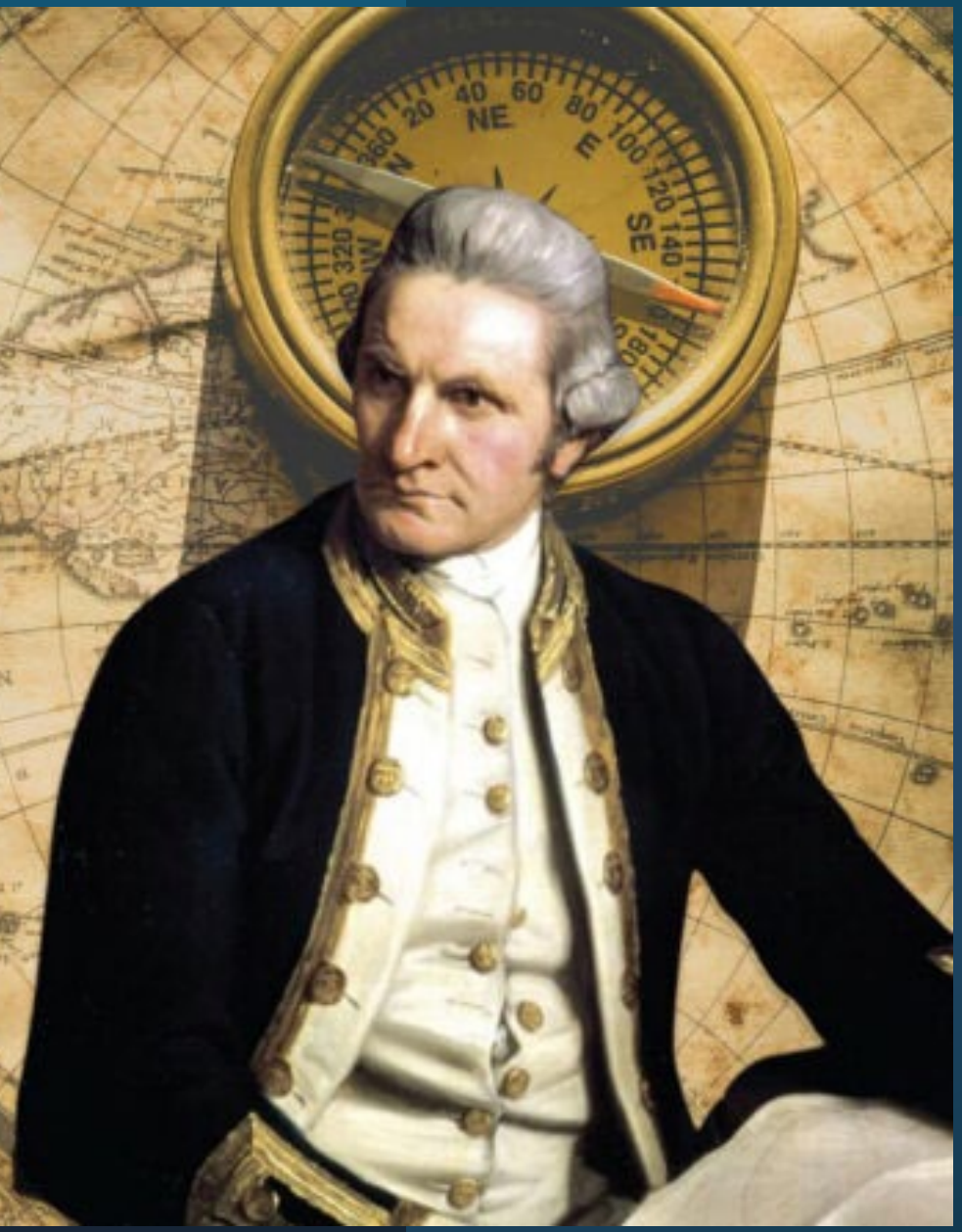
Table 3. Pooled Trial 1 and Trial 2 Patient-Reported Outcomes.*

Variable	Tirzepatide (N=234)	Placebo (N=233)	Estimated Treatment Difference (95% CI)	P Value
Change in PROMIS Sleep-related Impairment T score	−7.5 (−8.8 to −6.3)	−3.6 (−4.9 to −2.3)	−3.9 (−5.7 to −2.2)	<0.001
Change in PROMIS Sleep Disturbance T score	−5.7 (−6.8 to −4.7)	−2.7 (−3.8 to −1.6)	−3.1 (−4.5 to −1.5)	<0.001

N Engl J Med 391;13 nejm.org October 3, 2024

James Cook con la sua abilità cartografica e navale, contribuì in modo significativo **all'espansione delle conoscenze** geografiche del suo tempo e portò alla creazione di **mappe molto precise**

Così il **Finerenone**, che agisce su cuore e rene modulando l'infiammazione e la fibrosi, ha **completato la mappa** con la **protezione d'organo profonda**



Meccanismo d'azione

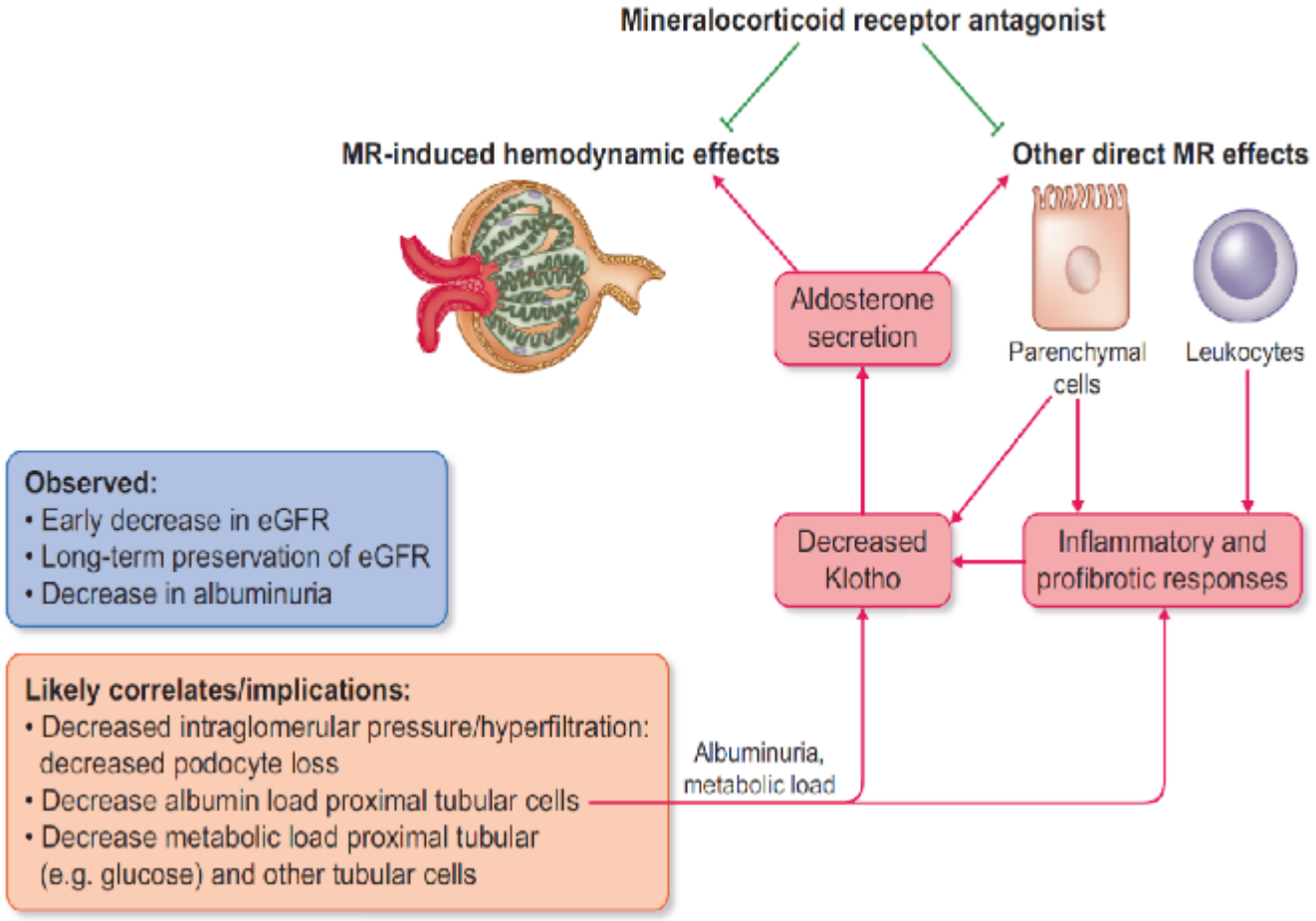
Antagonista selettivo del recettore dei mineralcorticoidi (MRA)

Inibisce il recettore dei mineralcorticoidi legandosi a questo recettore, impedendo all'aldosterone di attivarne i processi patologici.

Azione anti-infiammatoria e anti-fibrotica: Bloccando l'azione dell'aldosterone, il farmaco inibisce la produzione di sostanze pro-infiammatorie e pro-fibrotiche

Effetti emodinamici: A livello renale, riduce il riassorbimento di sodio e acqua, e aumenta il riassorbimento di potassio, contribuendo anche a una riduzione della pressione arteriosa.

Protezione renale e cardiaca: Protegge reni e cuore da infiammazione e fibrosi, rallentando la progressione della malattia renale cronica e riducendo il rischio di eventi cardiovascolari.



FINERENONE, ALBUMINURIA AND KIDNEY/CARDIOVASCULAR OUTCOMES

	FIDELIO-DKD Finerenone in reducing kiDnEy faiLure and disease prOgression in DKD	FIGARO-DKD Finerenone in reducinG cArdiovascular moRtality and mOrbidity in DKD
Patients	Mainly Stage 3-4 CKD	Mainly Stage 1-2 CKD
1 Primary outcome	↓ 18% decrease in CKD progression (HR 0.82; 95% CI 0.73–0.93)	↓ 13% decrease in CV mortality and morbidity (HR 0.87; %95 CI 0.76–0.98)
2 Secondary outcome	↓ %14 decrease in CV mortality and morbidity (HR 0.86; 95% CI 0.75–0.99)	↓ %13 decrease in CKD progression (HR 0.87; %95 CI 0.76–1.01) (not significant)
Safety	Favorable safety profile: small and manageable hyperkalemia risk with minimal clinical effect	

NNT a 3 anni: 42

...OGGI...

- Visione e percezione della diabetologia come terra di **INTEGRAZIONE**

…OGGI…

- Visione e percezione della diabetologia come terra di **INTEGRAZIONE**

- …Volta al **MODIFY DISEASE** con una medicina cardiometabolica PERSONALIZZATA E PRECOCE

…Grazie per l’attenzione…