SID
Società Italiana di Diabetologia
fondata dal 1964

Diagnosi precoce e trattamento efficace della patologia cardionefrometabolica: dalla teoria alla pratica

Milano, 4/5 luglio 2025

Agonismo (multi)recettoriale nel diabete di tipo 2: più ce n'è meglio è?

Angelo Avogaro

Studioso Senior

Università di Padova

- **CONFLITTI DI INTERESSE DI ANGELO AVOGARO**

- **In qualità di RELATORE, ai sensi dell'art.76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:**

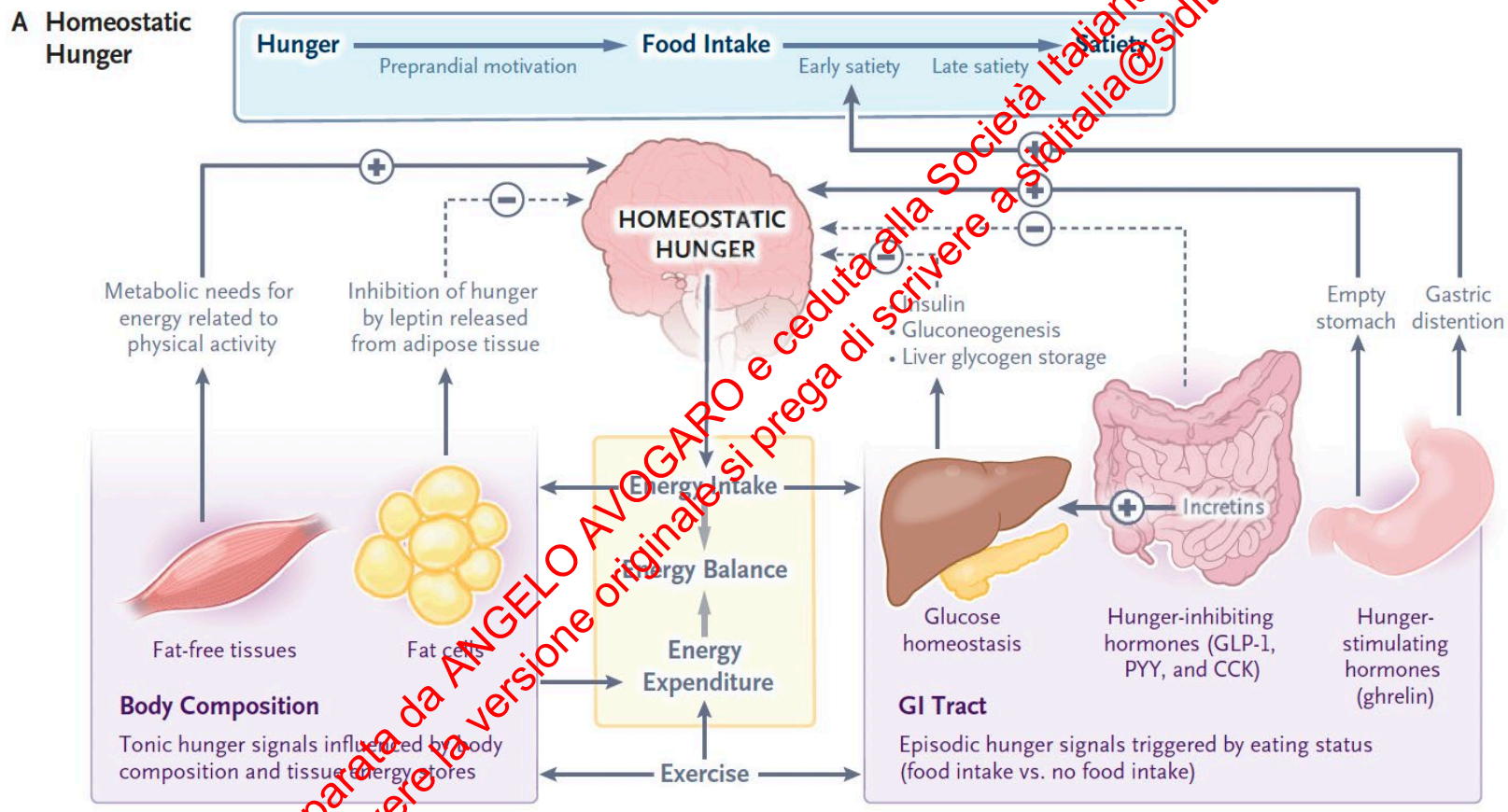
- **Novo, Lilly, Sanofi, Astrazeneca, Boehringher, Amgen, Daikii Sankio, MSD, Amarin, Bruno Farmaceutici, Neopharmed Gentili**

La Fame

Fame omeostatica innescata dalla privazione di energia per mantenere l'equilibrio energetico

Fame edonica legata all'assunzione di cibo guidata dal piacere e dalla necessità di gratificazione.

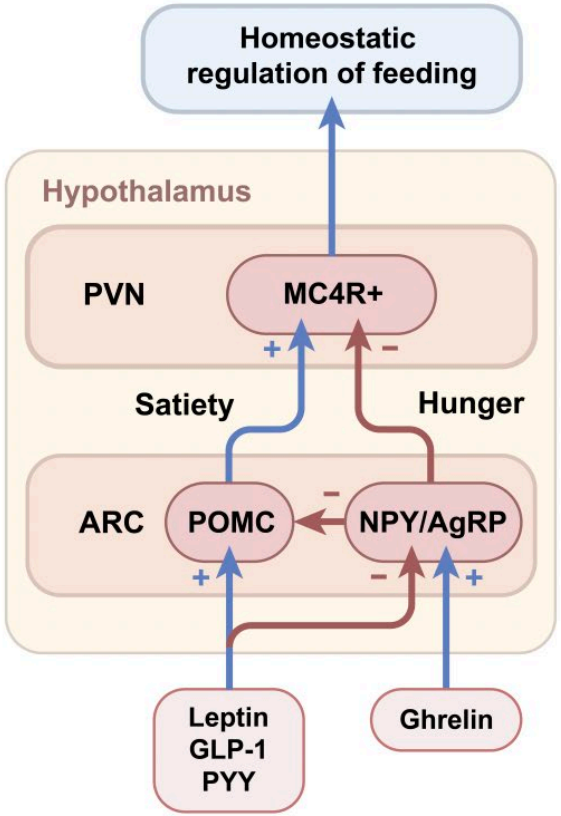
Fame Omeostatica

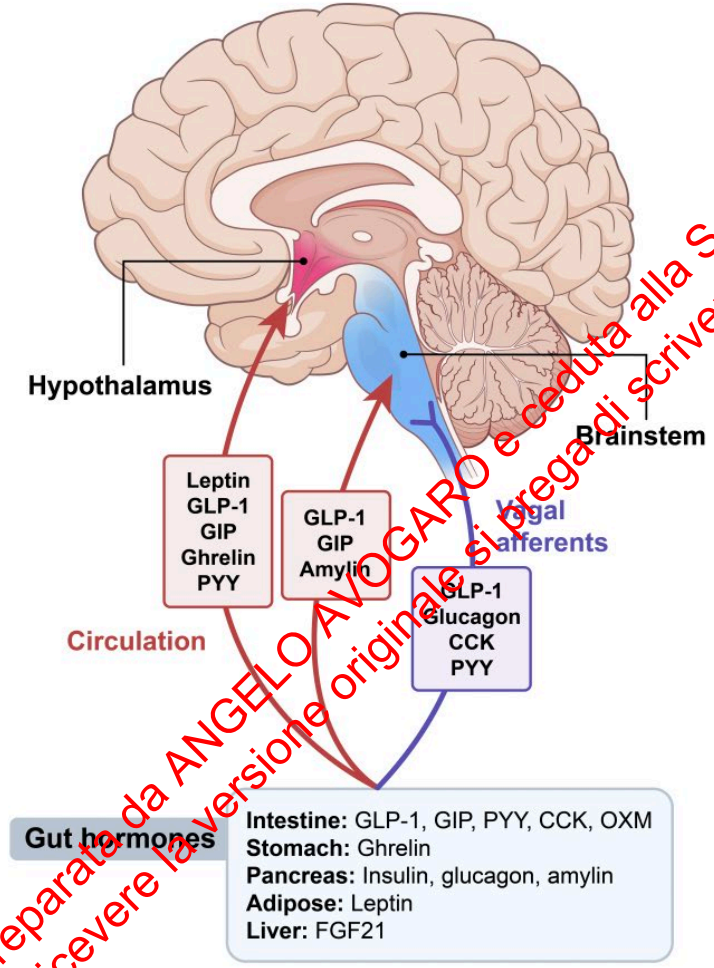


Fasano NEJM 2025

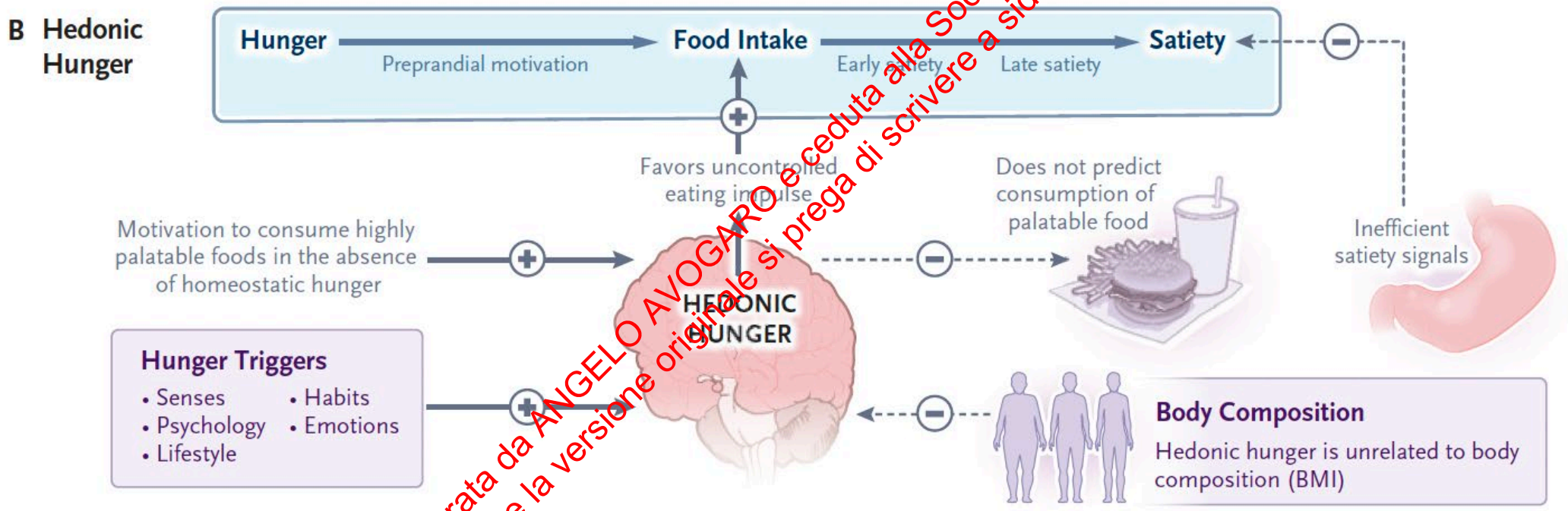
Hormonal Gut–Brain Signaling for the Treatment of Obesity

Roh et al. IJMS 2024





Fame Edonica



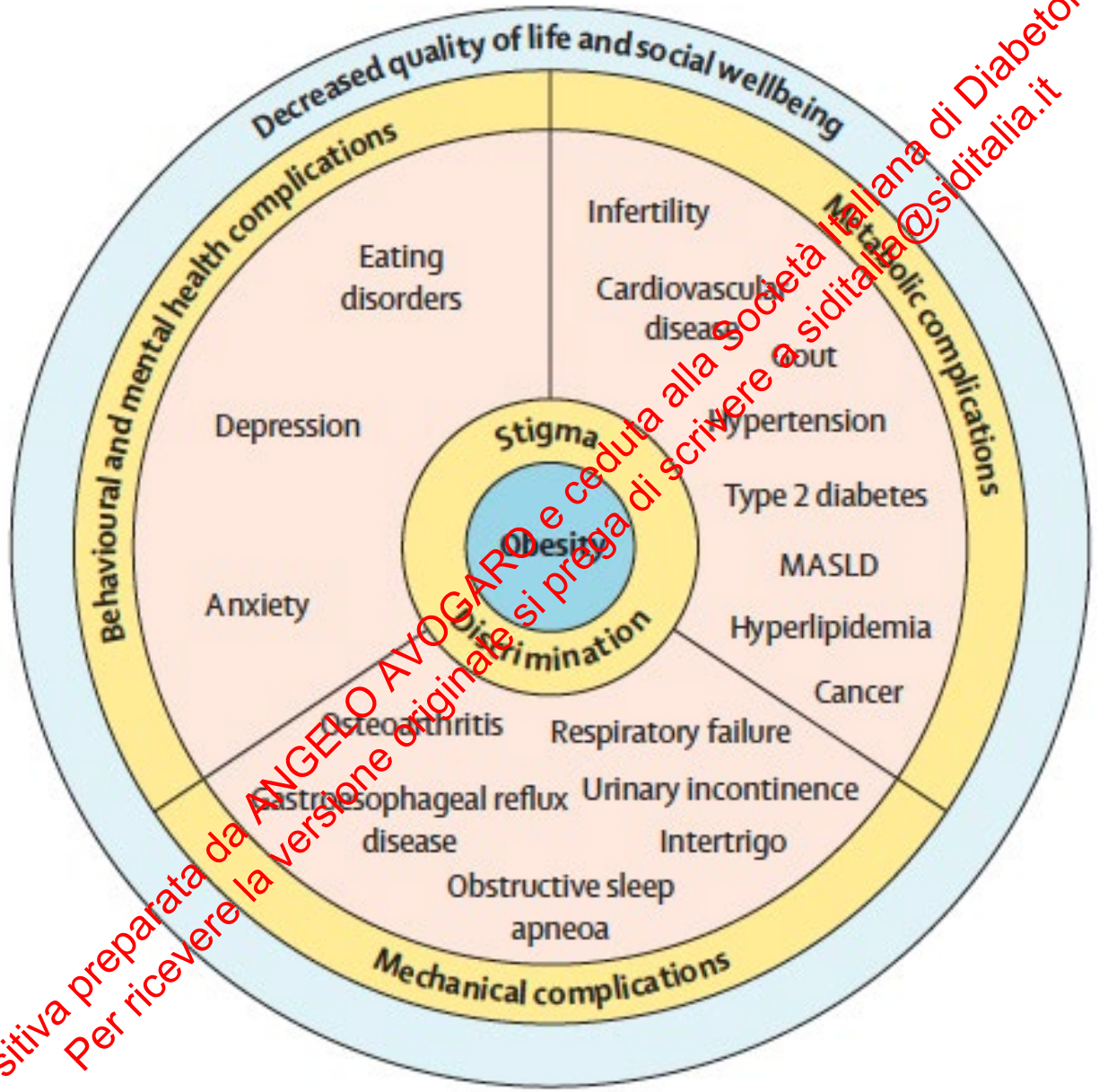
Fasano NEJM 2025

Effetti del Microbiota sulla fame

1. Ridotta diversità del microbiota: Stimolazione
2. Probiotici: Soppressione
3. Ac. Grassi a catena corta: Soppressione
4. Succinato di derivazione batterica: Stimolazione
5. Indolo: Soppressione
6. GABA di derivazione batterica: Stimolazione

Obesity in adults

Ildiko Lingvay, Ricardo V Cohen, Carel W le Roux, Priya Sumithran

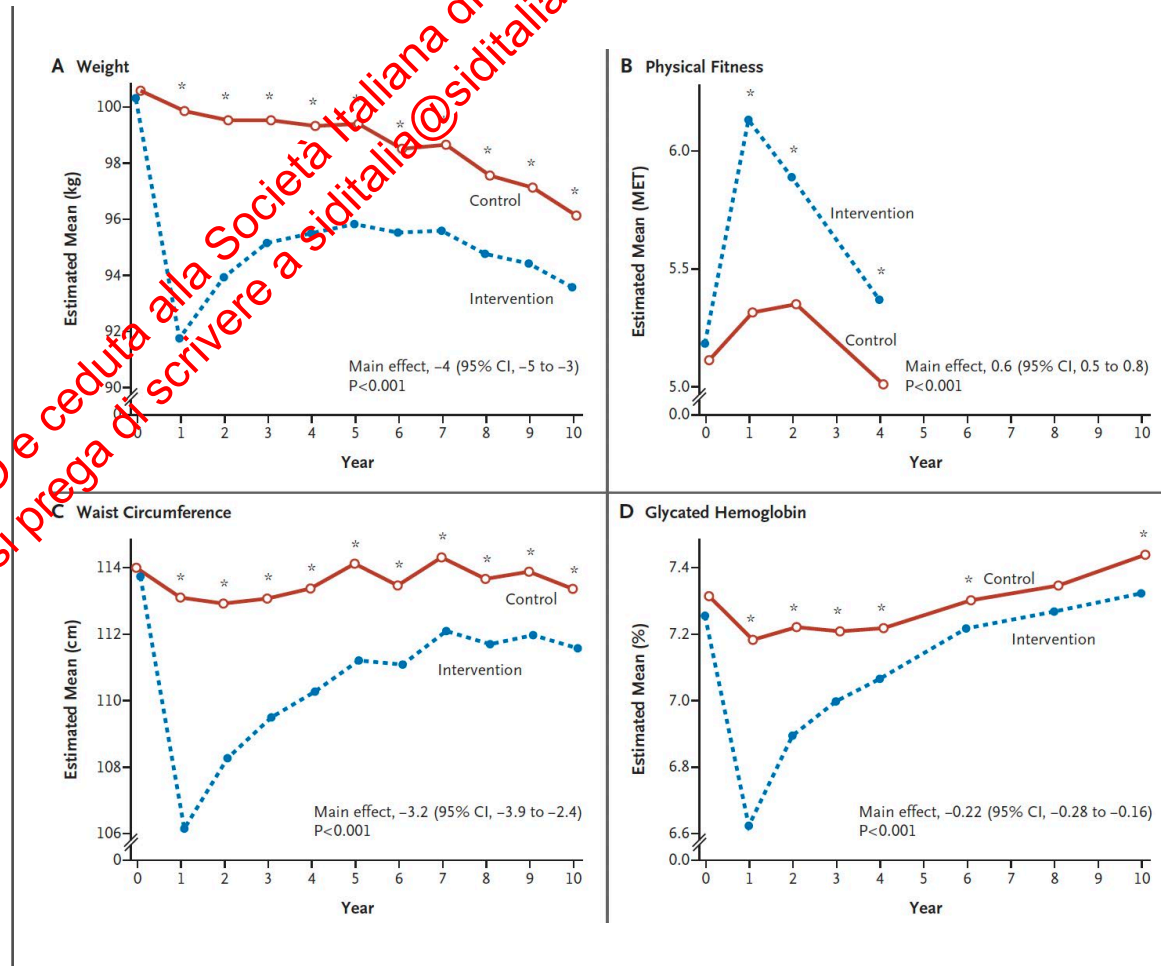


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*



Hormonal Fluctuations

Metabolic Adjustments

Thyroid Hormone Variations

Adipose Tissue and Inflammation

Behavioral and Environmental Influences

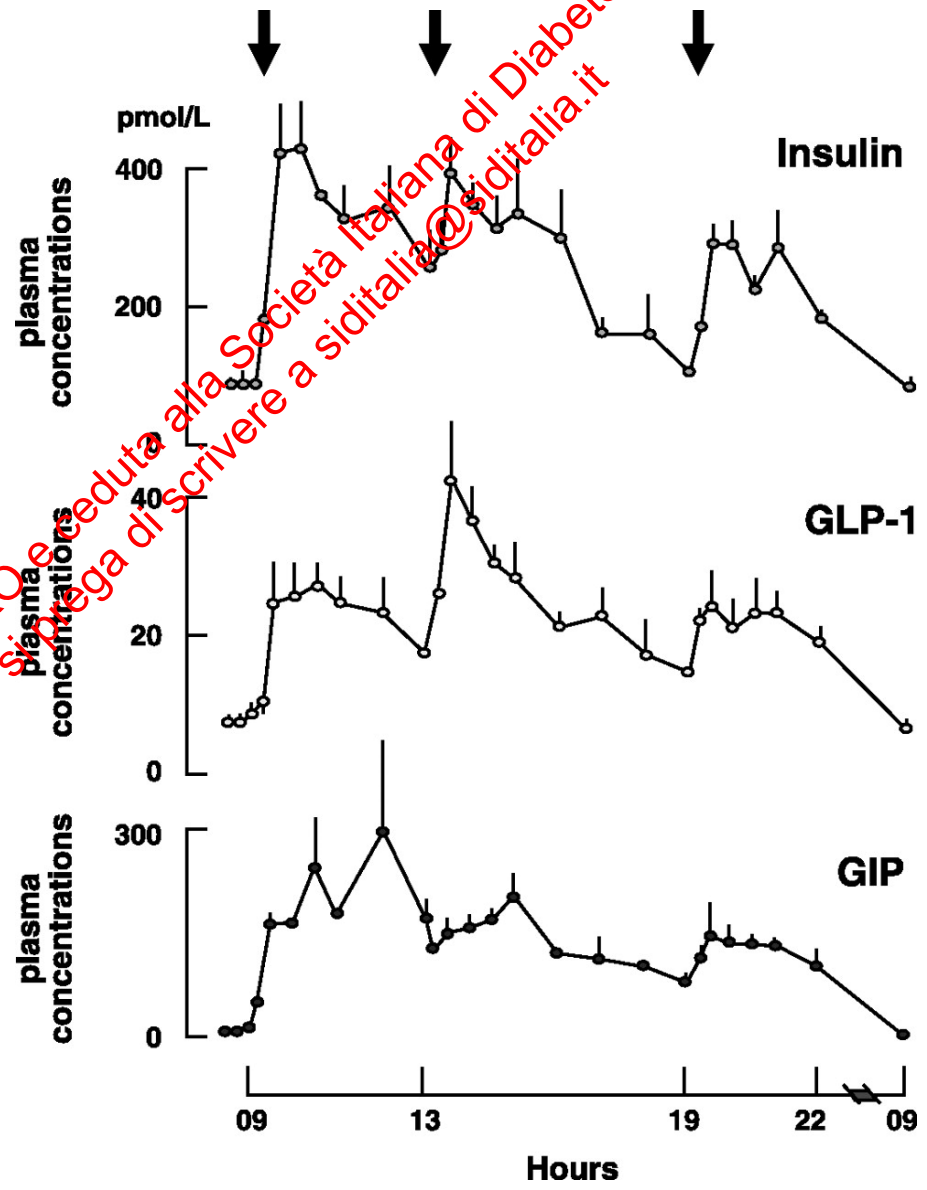
Psychological Influences

Microbiome Impact

Weight regain:

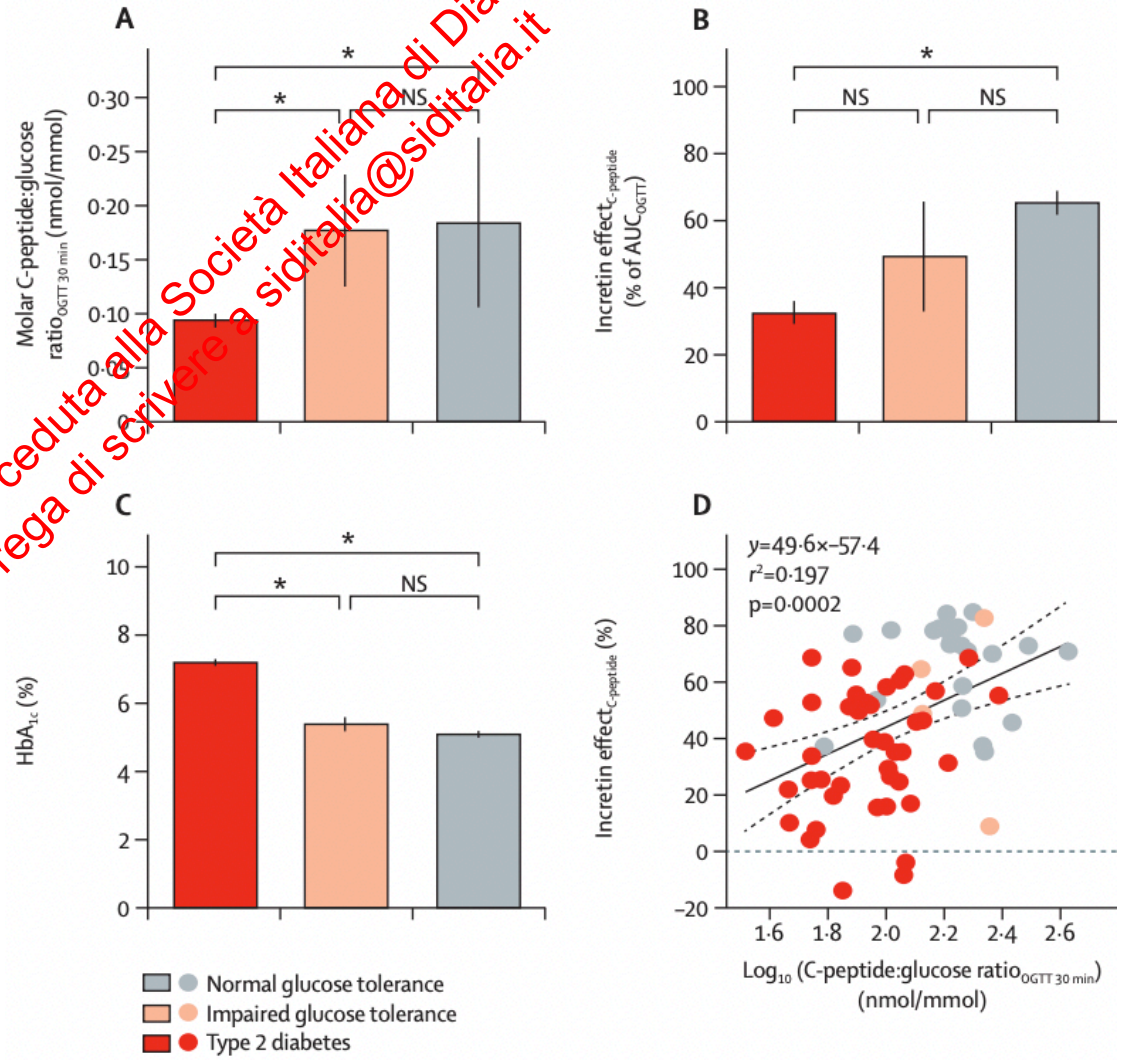
- Only about 20% of individuals who achieve significant weight loss are able to maintain it long-term
- In the "Biggest Loser" television program, participants who initially lost an average of 58 kg over 30 weeks had regained an average of 70% of that weight (41 kg) six years later
- After discontinuing once-weekly semaglutide (2.4 mg) in the STEP 1 trial (following 68 weeks of treatment that resulted in a mean weight loss of 17.3%), participants regained 11.6% of their weight over the subsequent 52 weeks

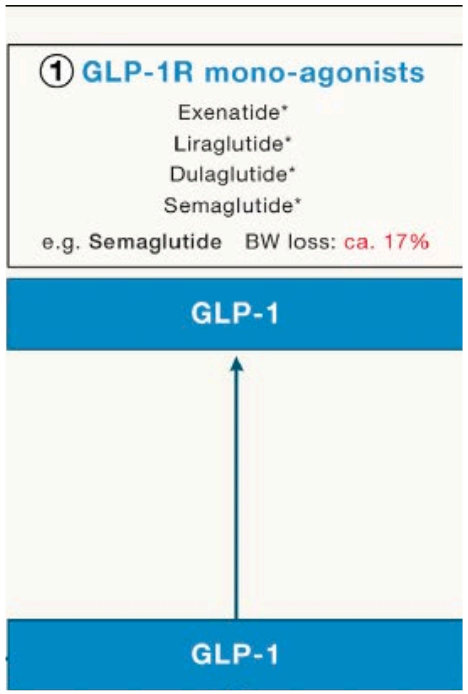
Plasma concentrations of insulin, GLP-1 (total), and gastric inhibitory peptide (GIP; total) during the day time in healthy subjects.



The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions

Michael A Nauck, Juris J Meier



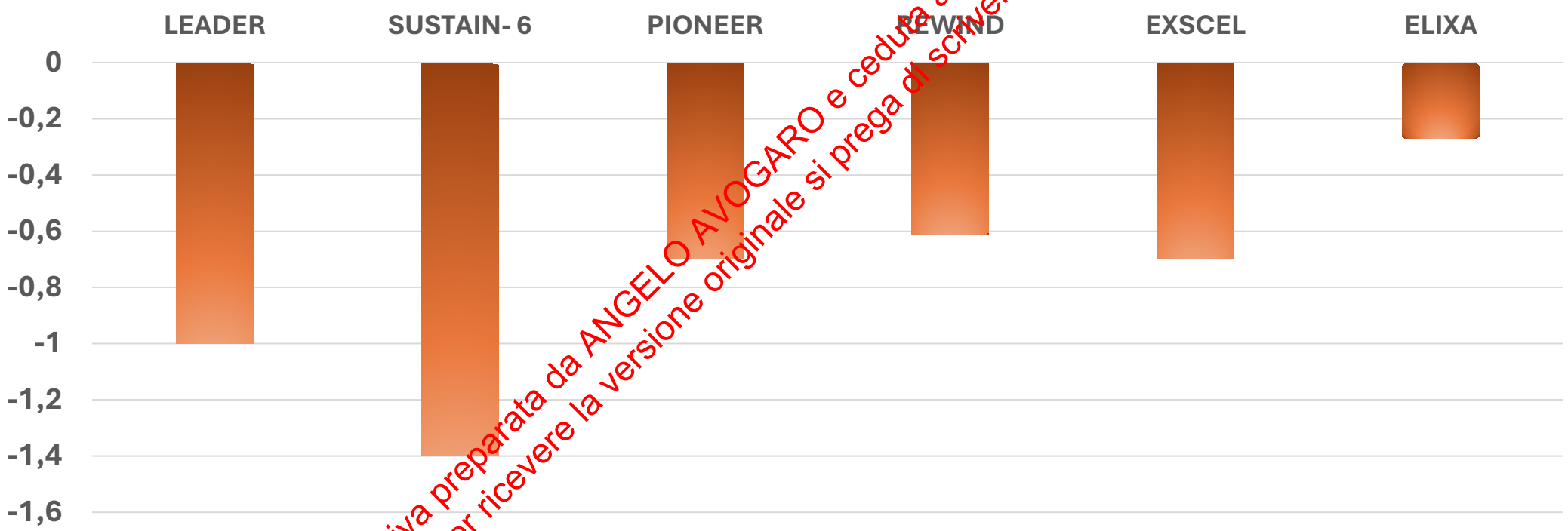


Cell
Leading Edge
Review

Transforming obesity: The advancement of multi-receptor drugs

Christine M. Kusminski,[1] Diego Perez-Tilve,[2] Timo D. Müller,[3,4] Richard D. DiMarchi,[5] Matthias H. Tschöp,[6,7] and Philipp E. Scherer[1,*]
[1]Touchstone Diabetes Center, The University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[2]Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[3]Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Munich, Munich, Germany
[4]German Center for Diabetes Research (DZD) and Walther-Straub Institute of Pharmacology and Toxicology, Ludwig-Maximilians-University (LMU) Munich, Munich, Germany
[5]Department of Chemistry, Indiana University, Bloomington, IN, USA
[6]Helmholtz Munich, Munich, Germany
[7]Division of Metabolic Diseases, Department of Medicine, Technische Universität, Munich, Germany
*Correspondence: philipp.scherer@utsouthwestern.edu
https://doi.org/10.1016/j.cell.2024.06.003

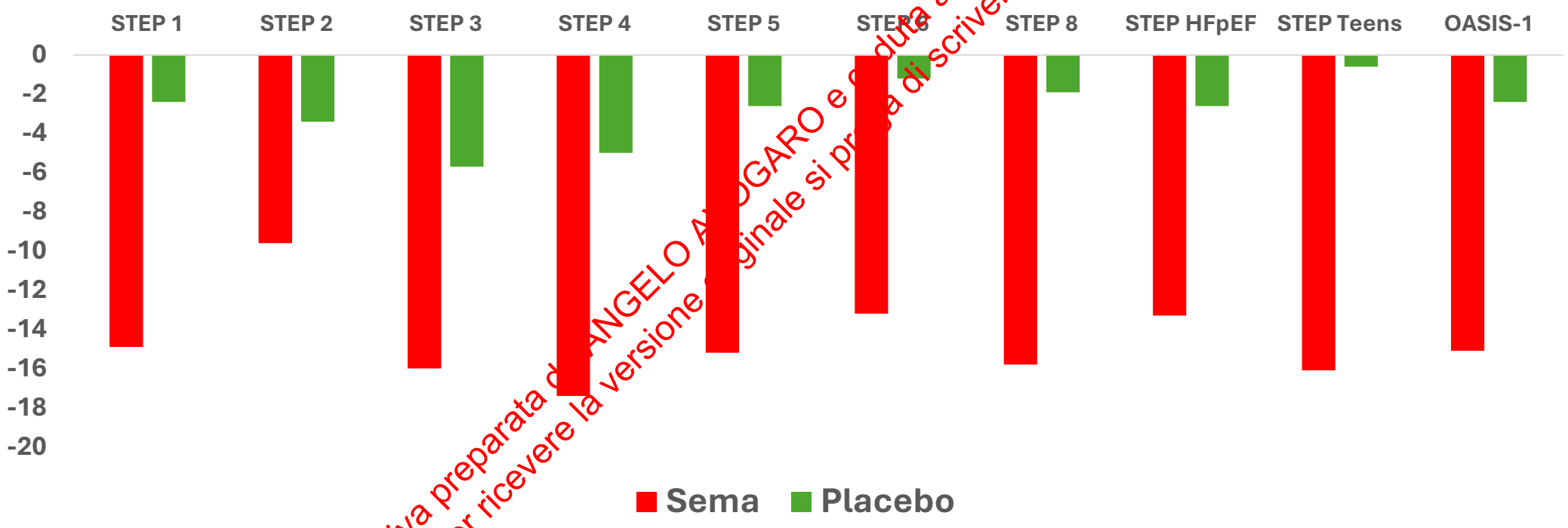
Riduzione percentuale della Emoglobina Glicata nei CVOT

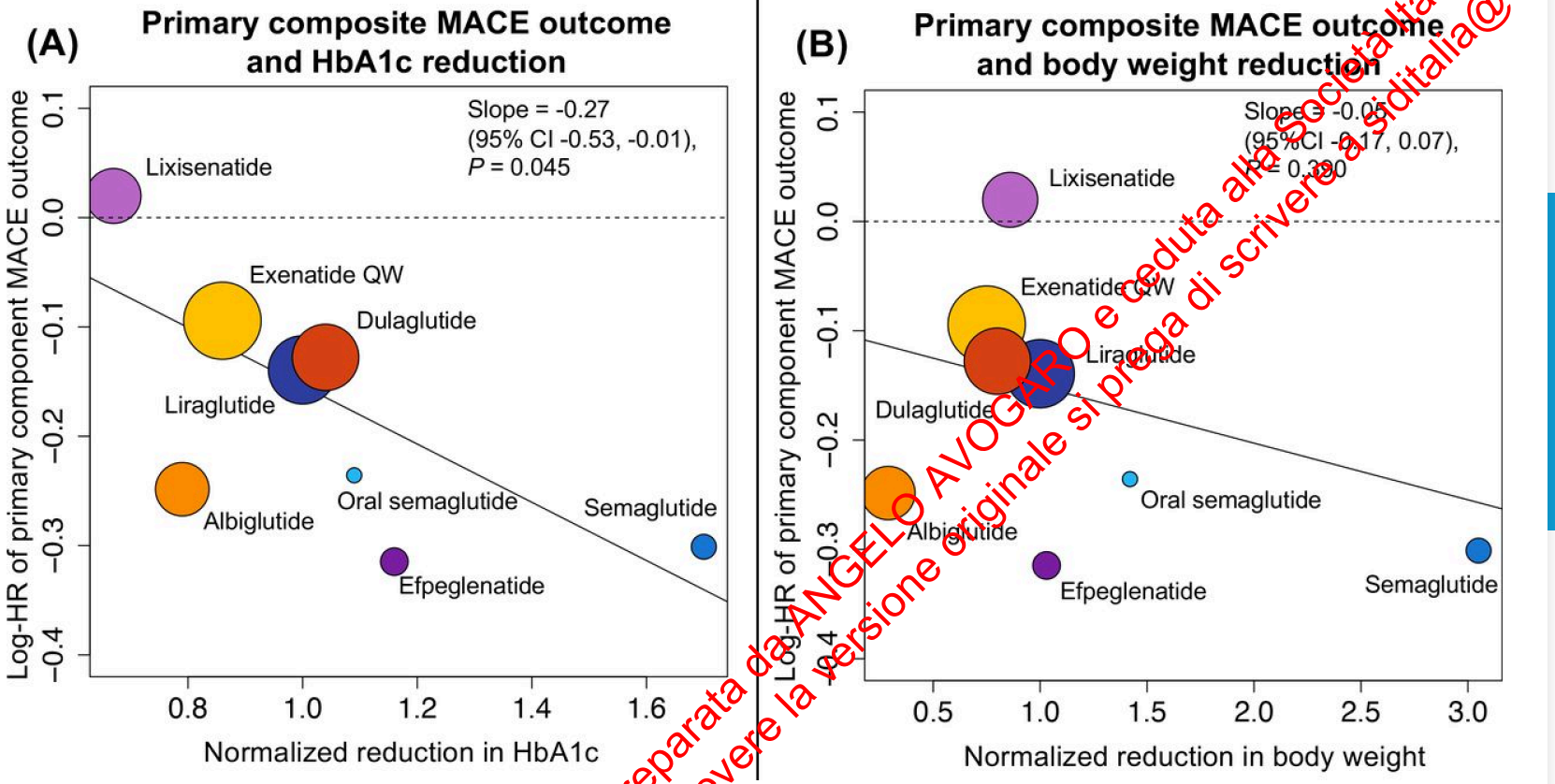


Riduzione di peso nei CVOT

Studio (farmaco)	Popolazione	Durata	Riduzione peso
LEADER (liraglutide 1,8 mg/die)	T2D ad alto rischio CV	~3,8 anni	–2,3 kg in più rispetto a placebo (~3–4 %)
SUSTAIN-6 (semaglutide settimanale)	T2D ad alto rischio CV	2 anni	–3,7 kg (≈4 %) vs placebo
EXSCEL (exenatide XL settimanale)	T2D ad alto rischio CV	~3,2 anni	≈–2 kg vs placebo
Harmony Outcomes (albiglutide)	T2D ad alto rischio CV	~3,6 anni	≈–2 kg vs placebo
REWIND (dulaglutide 1,5 mg settimanale)	T2D, incluso con rischio CV	~5 anni	≈–3 kg in più rispetto a placebo
PIONEER 6 (semaglutide orale)	T2D con rischio CV/CKD	~1,6 anni	≈–2 kg vs placebo

Riduzione percentuale del peso corporeo con Semaglutide iniettiva o orale





GLP-1 oltre la riduzione di peso: protezione CV

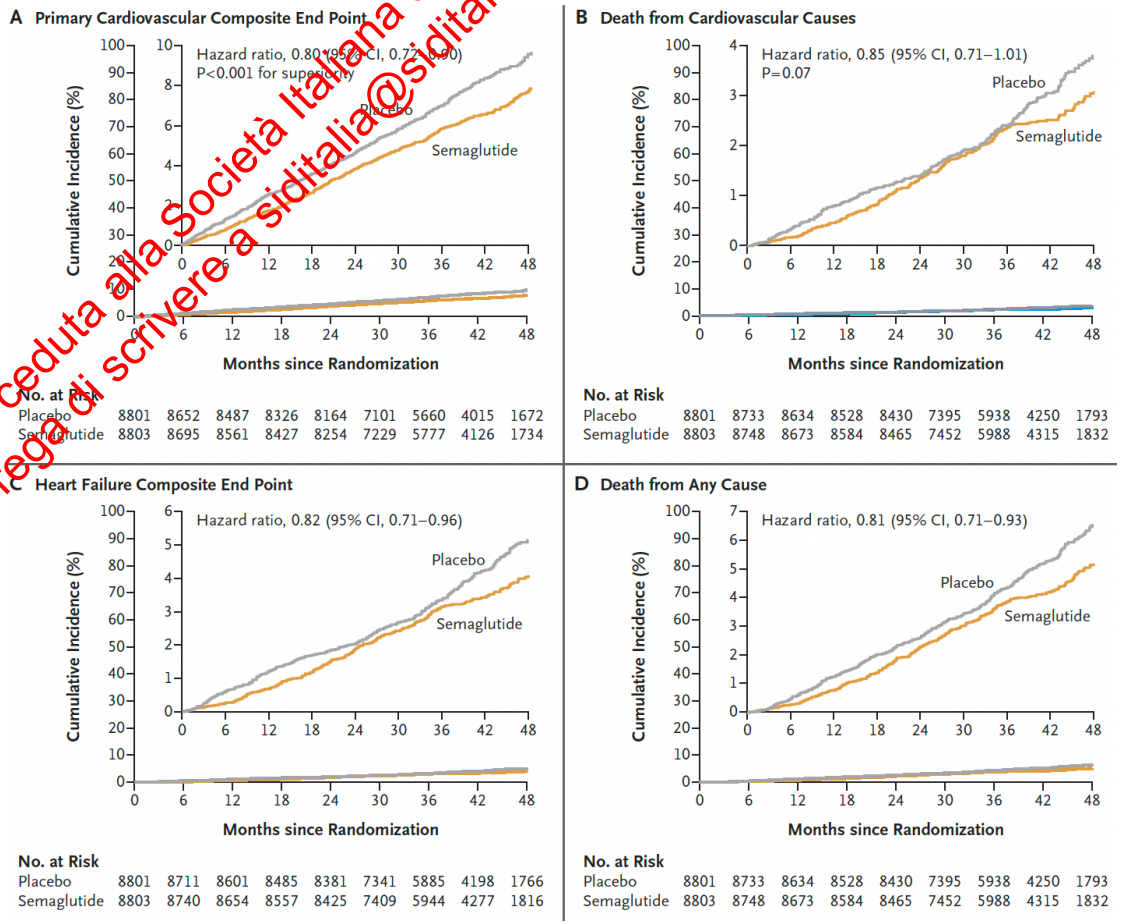
Yoshiji et al. DOM 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

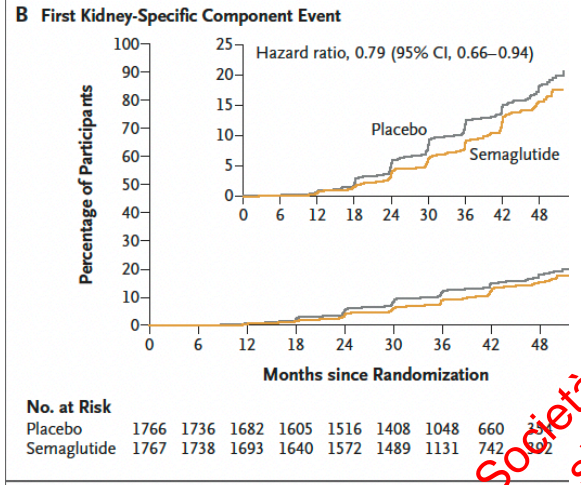
A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H.,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

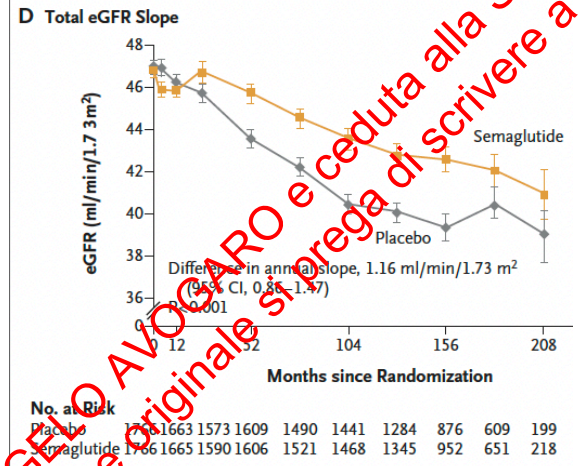


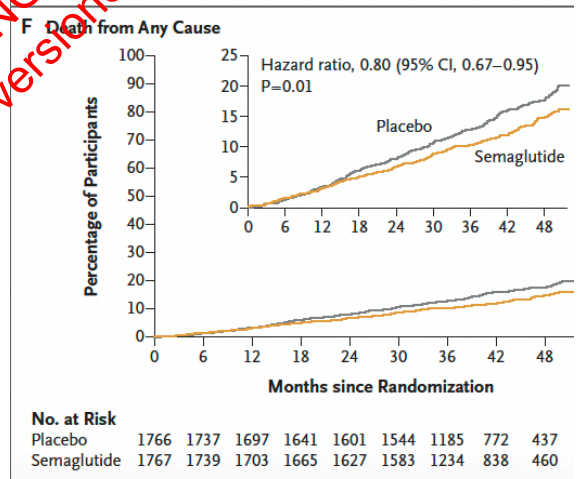
ORIGINAL ARTICLE

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

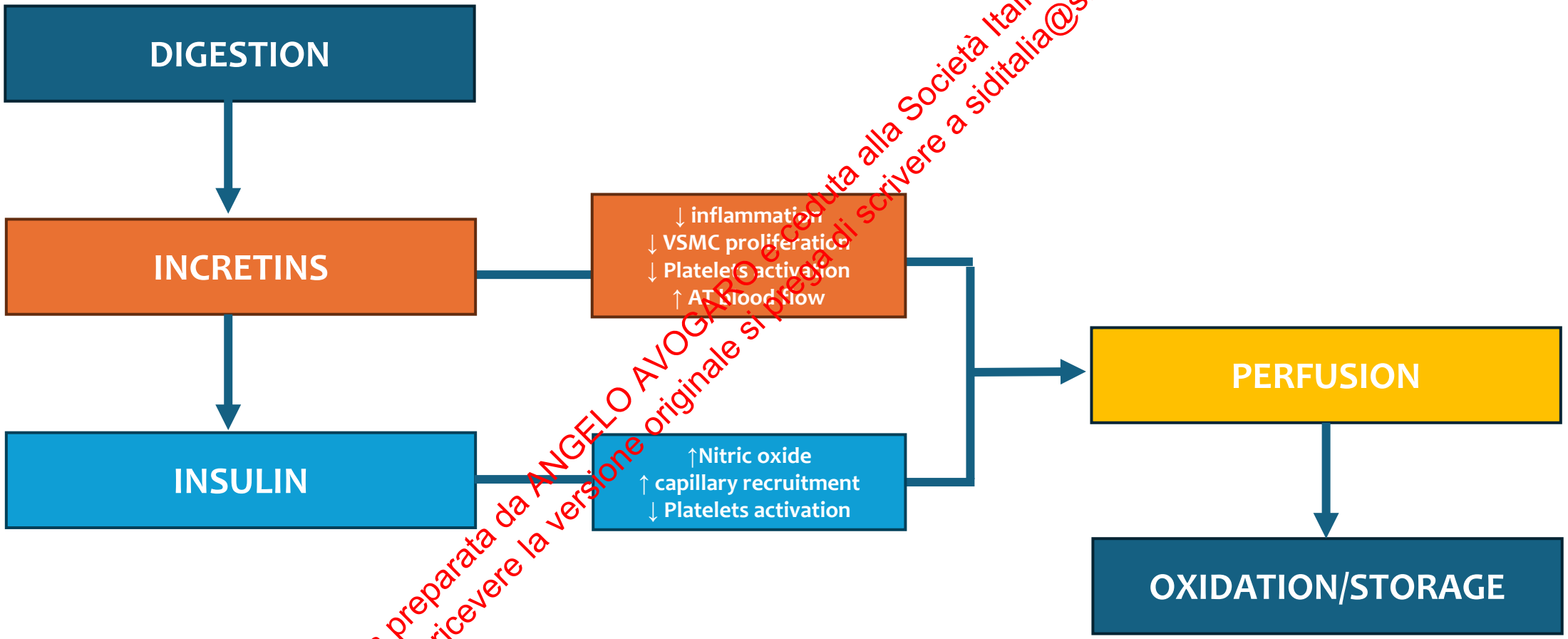
Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D.,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



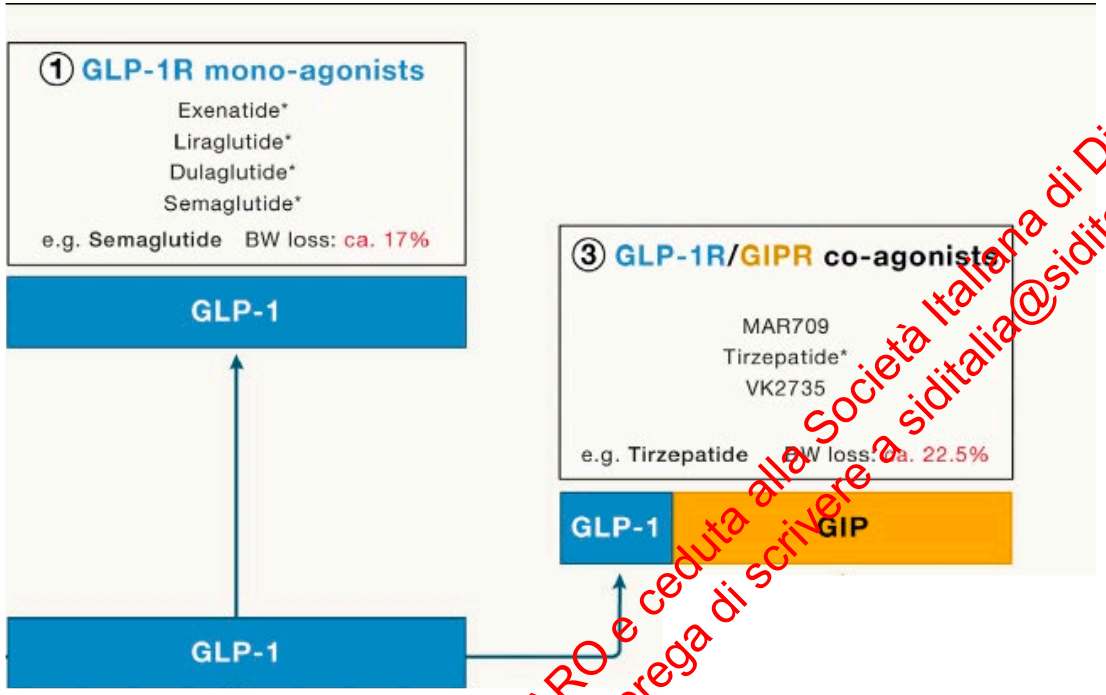




Incretins improve the Digestion/Oxidation coupling



Avogaro & Fadini. Lancet DE 2025 in press



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Transforming obesity: The advancement of multi-receptor drugs

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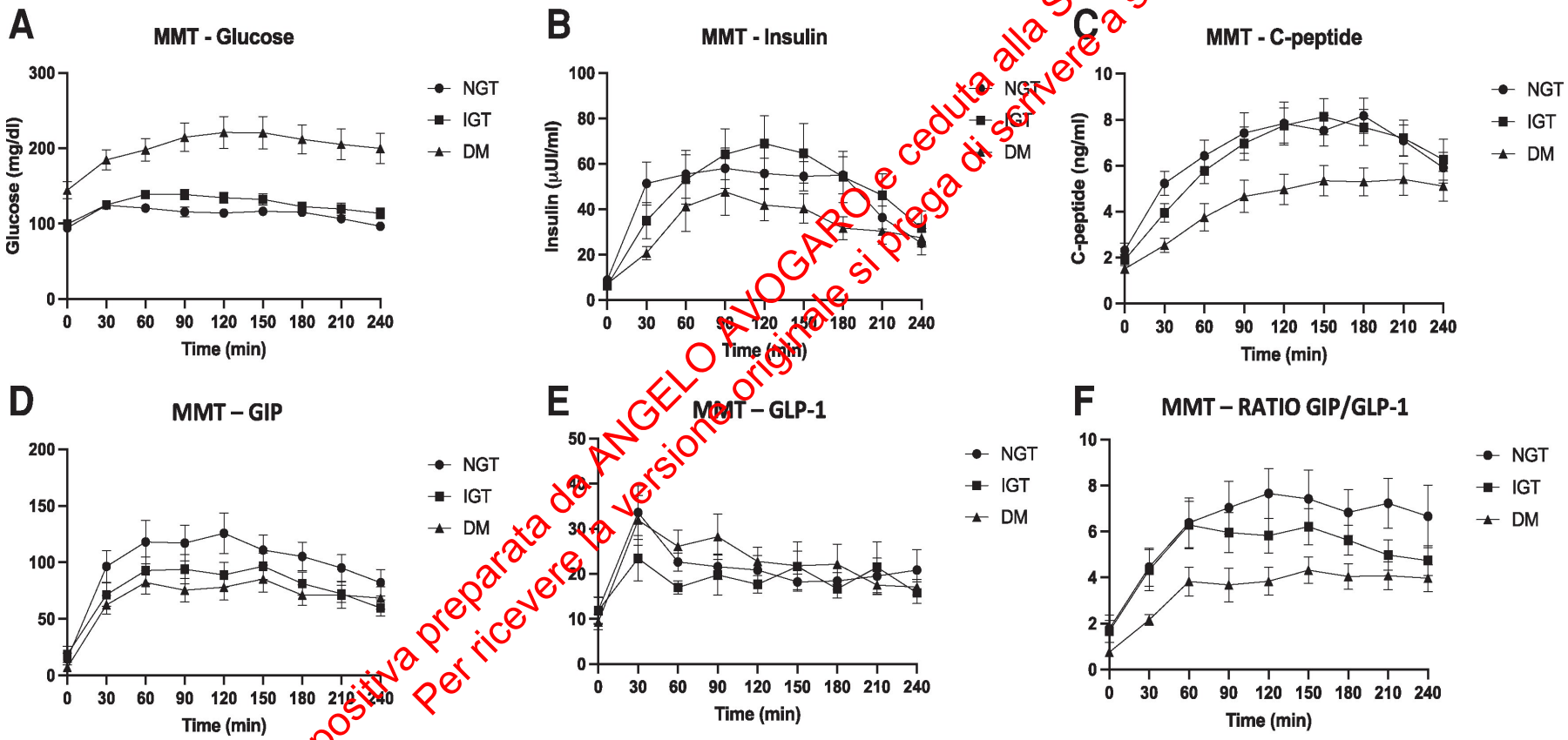
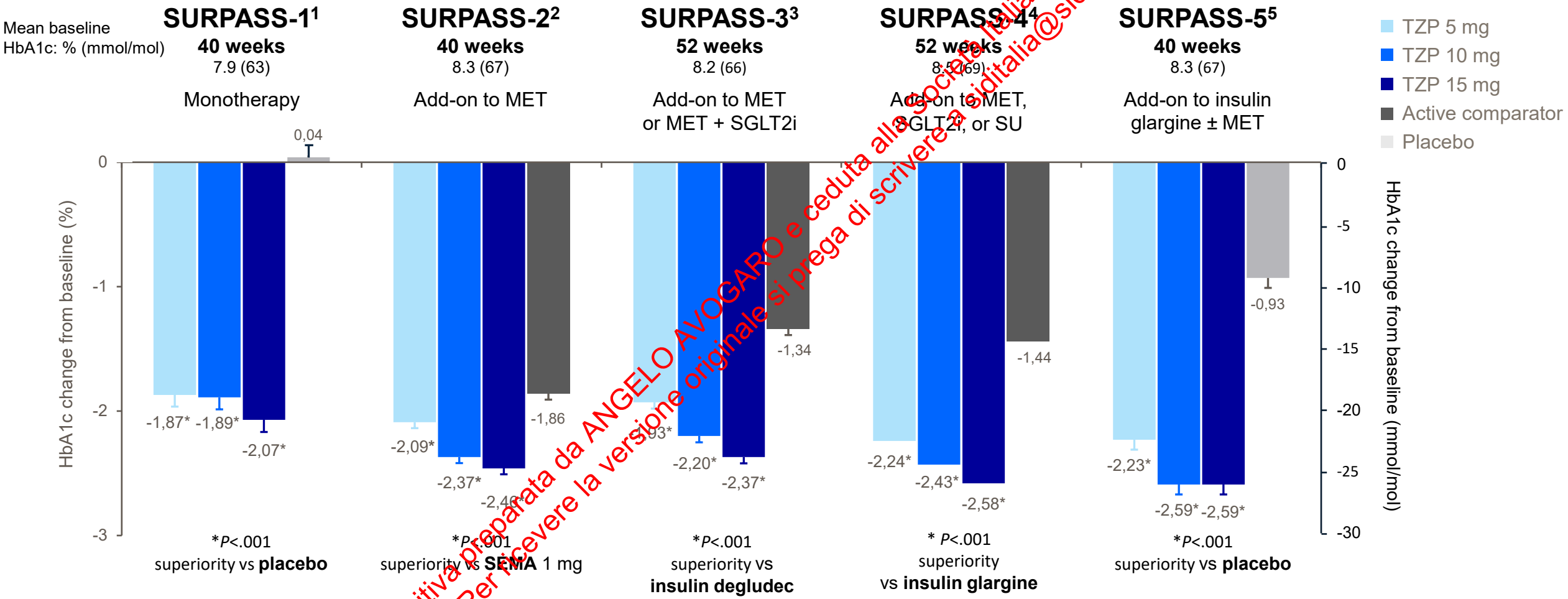
The Journal of Clinical Endocrinology & Metabolism, 2025, **00**, 1–7
https://doi.org/10.1210/clinem/dgaf210
Advance access publication 12 May 2025
Clinical Research Article

Altered GIP/GLP-1 Secretion Ratio is Associated With Impaired β Cell Function in Humans

Gianfranco Di Giuseppe,[1,2] Giulia Gliozzo,[2] Gea Ciccarelli,[1,2] Lorenzo Carciero,[2] Michela Brunetti,[1,2] Laura Soldovieri,[1,2] Giuseppe Quero,[2,3] Francesca Cinti,[1,2] Enrico Celestino Nista,[2,4] Sara Sofia De Lucia,[2,4] Antonio Gasbarrini,[2,4] Sergio Alfieri,[2,3] Alfredo Pontecorvi,[1,2] Andrea Mari,[5] Bolette Hartmann,[6] Jens Juul Holst,[7] Andrea Giaccari,[1,2] and Teresa Mezza[1,2,4]



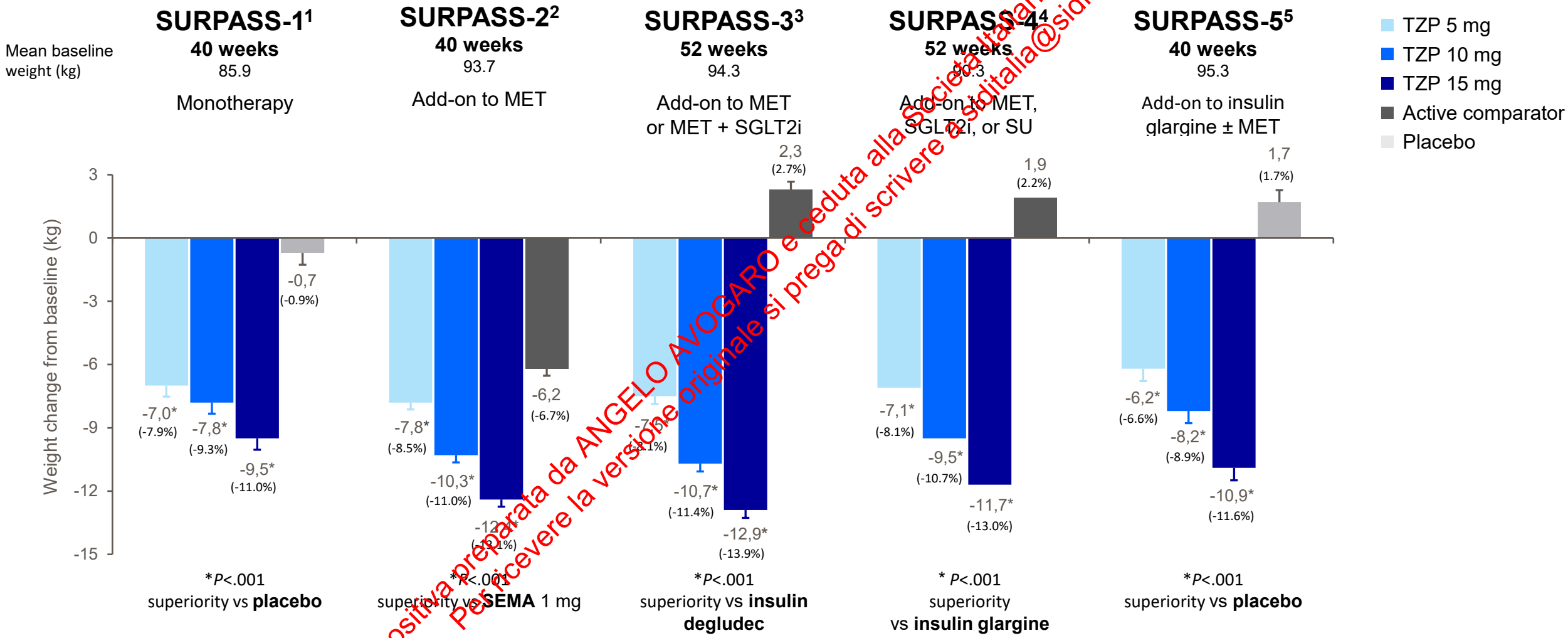
HbA1c Change From Baseline to Primary Endpoint



Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.
HbA1c = glycated haemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Body Weight Change From Baseline to Primary Endpoint



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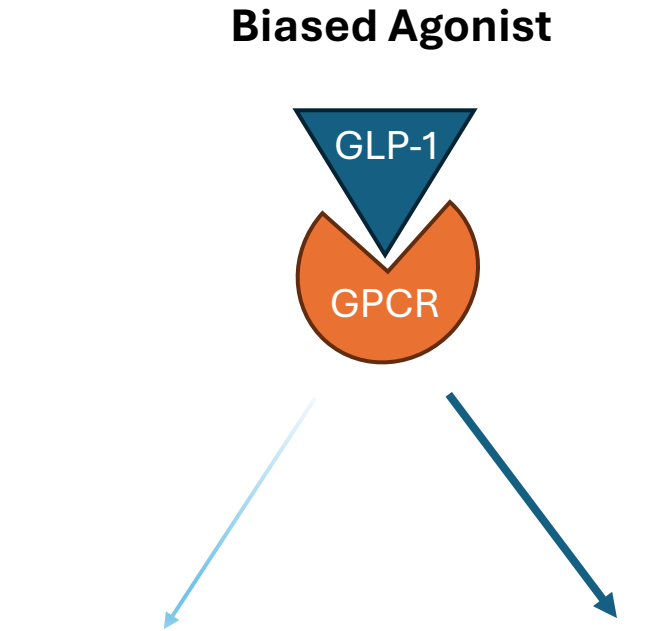
Commentary

MOLECULAR METABOLISM

"Let's Stay Together"; GIP and GLP-1 dual agonism in the treatment of metabolic disease

Richard D. DiMarchi [1]

Il perché di un bias



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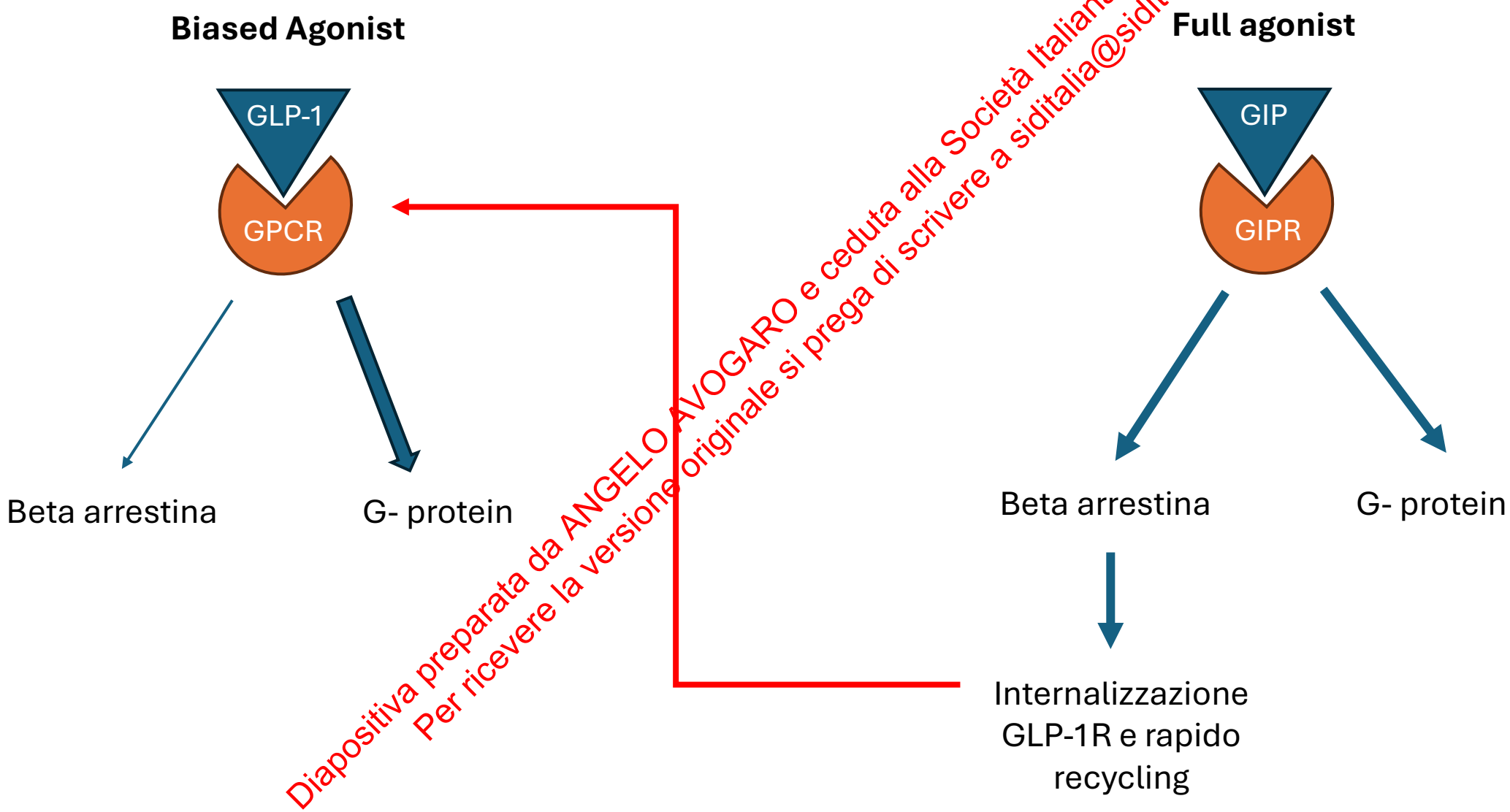
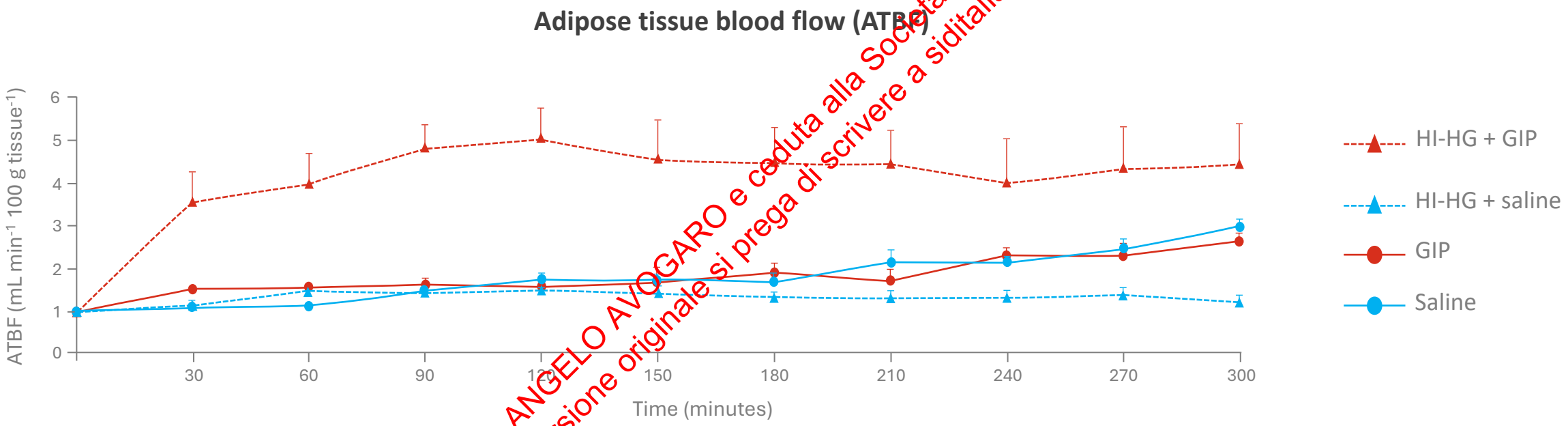


GIP enhances blood flow in the adipose tissue in high glucose high insulin clamp in healthy subjects

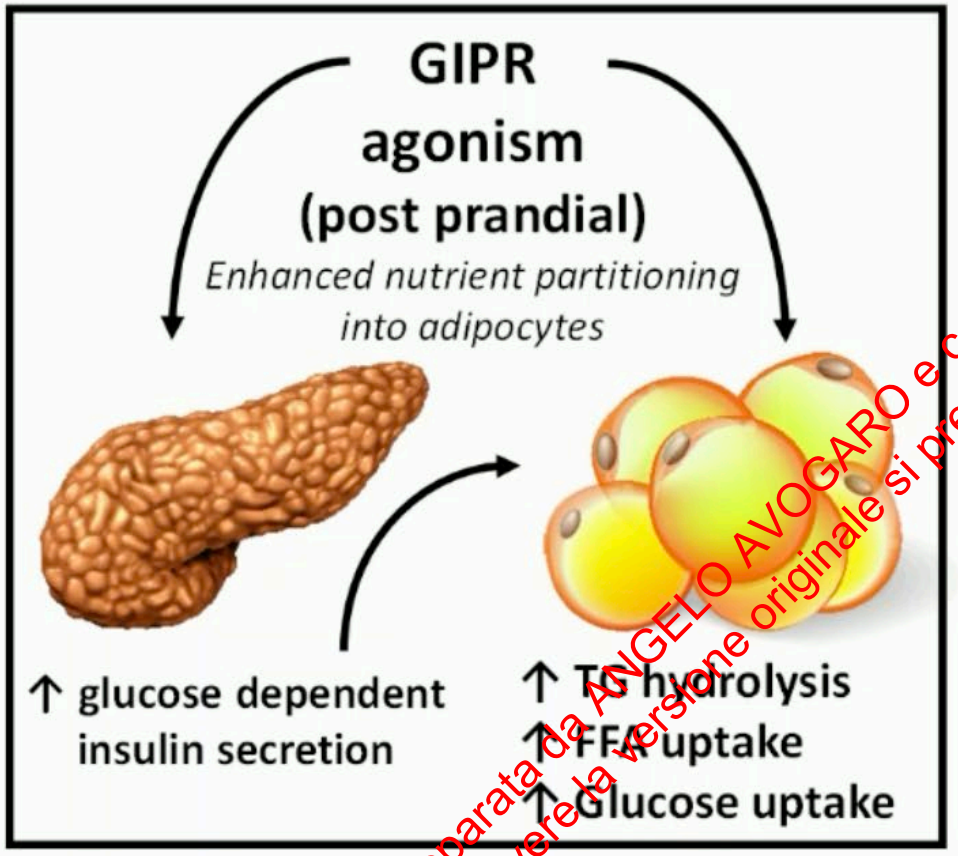


30–300 minutes after commencement of infusions

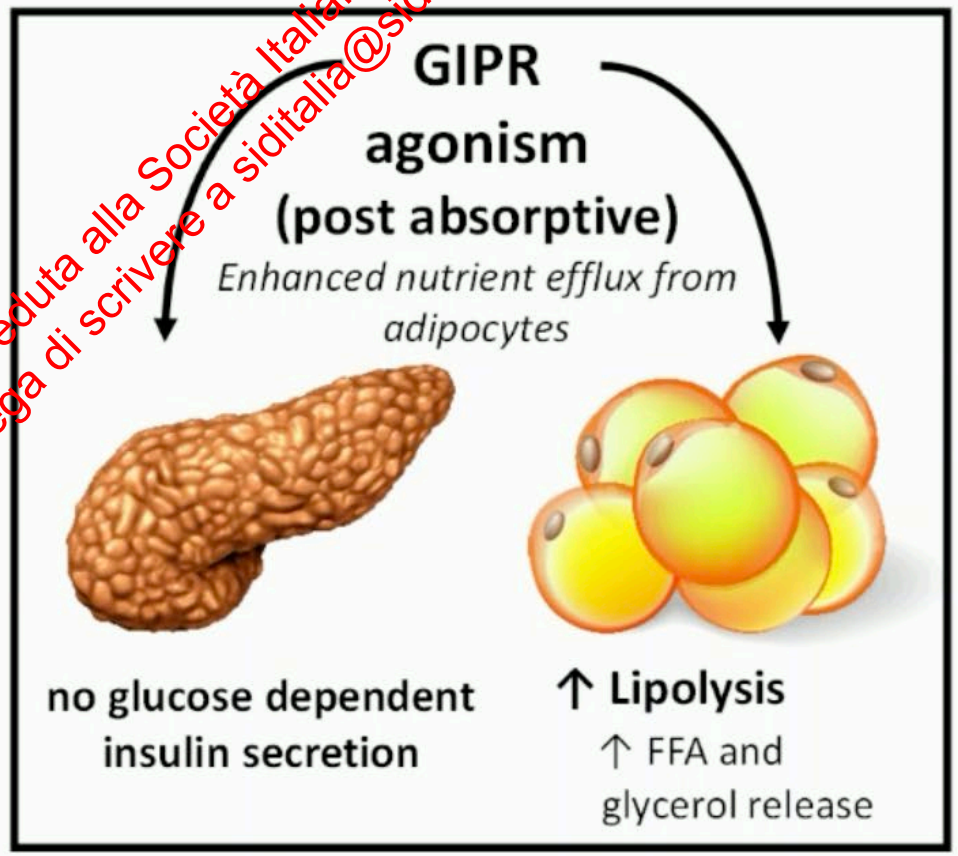
HI:hyperinsulinemic; HG: hyperglycemic; GIP= Glucose-dependent insulinotropic polypeptide

Asmar M et al. Diabetes 2010;59(9): 2160–2163

Proposed model



Long-acting GIPR agonism regulation of plasma lipids and glucose under post-prandial/hyperglycemic conditions



Long-acting GIPR agonism regulation of plasma lipid metabolism under postabsorptive/fasted conditions

Sia l’agonismo che l’antagonismo del recettore GIP (GIPR), combinati con l’agonismo del recettore GLP-1 (GLP-1R), portano a una perdita di peso simile

Agonismo del GIPR:

Aumenta la secrezione e la sensibilità all’insulina e riduce l’infiammazione.

Attenua gli effetti avversi (come nausea) causati dall’agonismo del GLP-1R attraverso l’azione su neuroni GABAergici nel SNC.

Campbell & Drucker Diabetes 2025

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Attenua gli effetti avversi (come nausea) causati dall’agonismo del GLP-1R attraverso l’azione su neuroni GABAergici nel SNC.

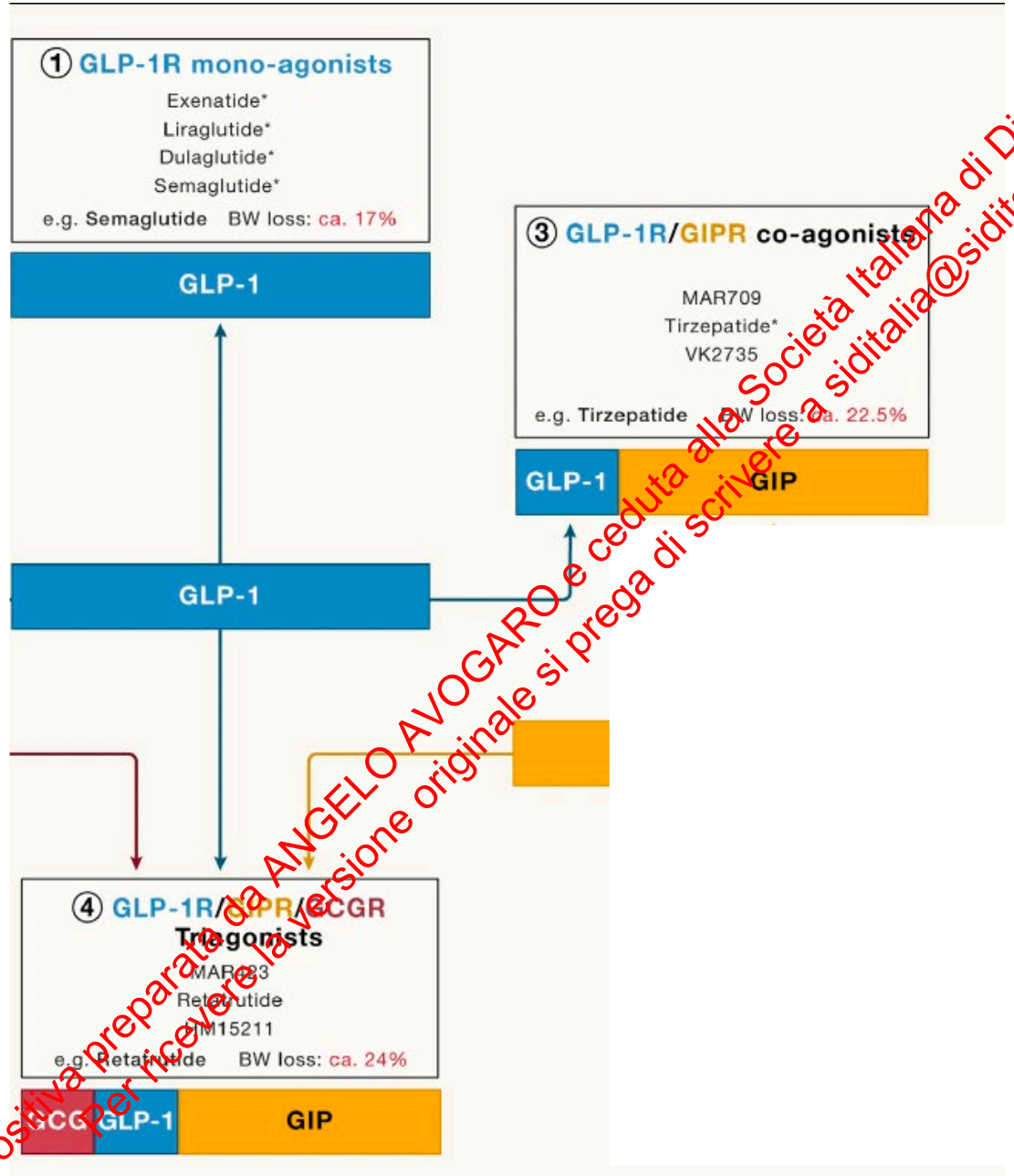
Antagonismo del GIPR:

Riproduce i benefici osservati in studi genetici con perdita di funzione del GIPR.

Può "disinibire" i circuiti GLP-1R, migliorando l’effetto anoressizzante

L’agonismo prolungato del GIPR potrebbe causare **desensibilizzazione** del recettore, comportandosi quindi come un antagonista

Campbell & Drucker Diabetes 2025



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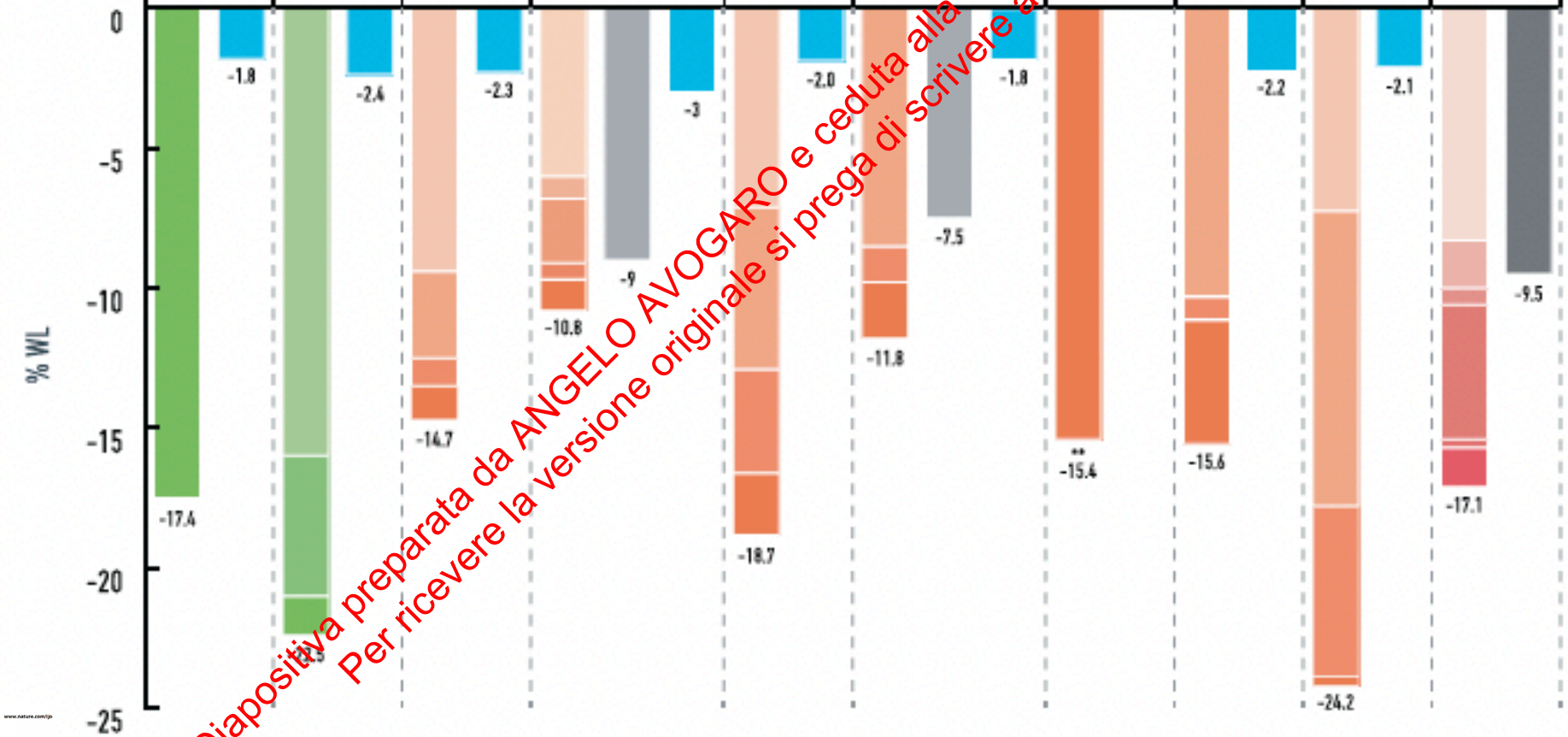
[7]Division of Metabolic Diseases, Department of Medicine, Technische Universität, Munich, Germany
*Correspondence: philipp.scherer@utsouthwestern.edu
https://doi.org/10.1016/j.cell.2024.06.003

	Oral Semaglutide[A]	Tirzepatide[A]	Orforglipron[A]	Cagrilintide[A]	Survodutide[A]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.6/10mg OW	9mg OW	1.2/[illegible].4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	60	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	32	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 - 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg

A



KEY:
- Phase 3
- Phase 2
- Phase 1
- Placebo
- Active Comparator

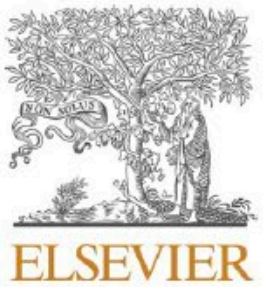
Lowest dose → Highest dose

International Journal of Obesity www.nature.com/ijo
REVIEW ARTICLE OPEN
Clinical Research

What is the pipeline for future medications for obesity?

Eka Melson[1,4], Uzma Ashraf[1,4], Dimitris Papamargaritis[1,2,3] and Melanie J. Davies[1,2]

European Journal of Pharmacology 985 (2024) 177095



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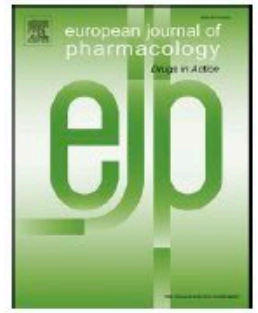
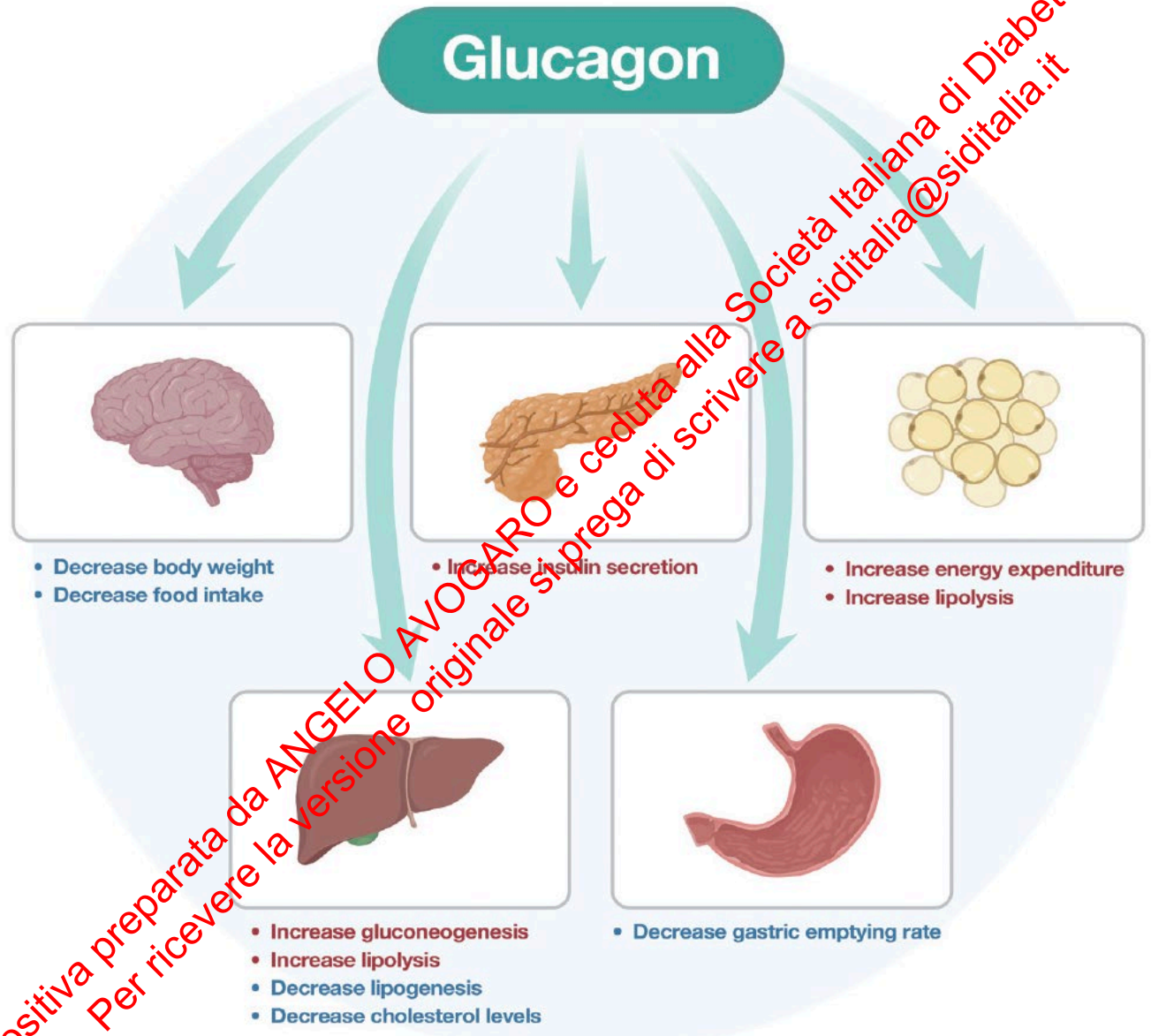


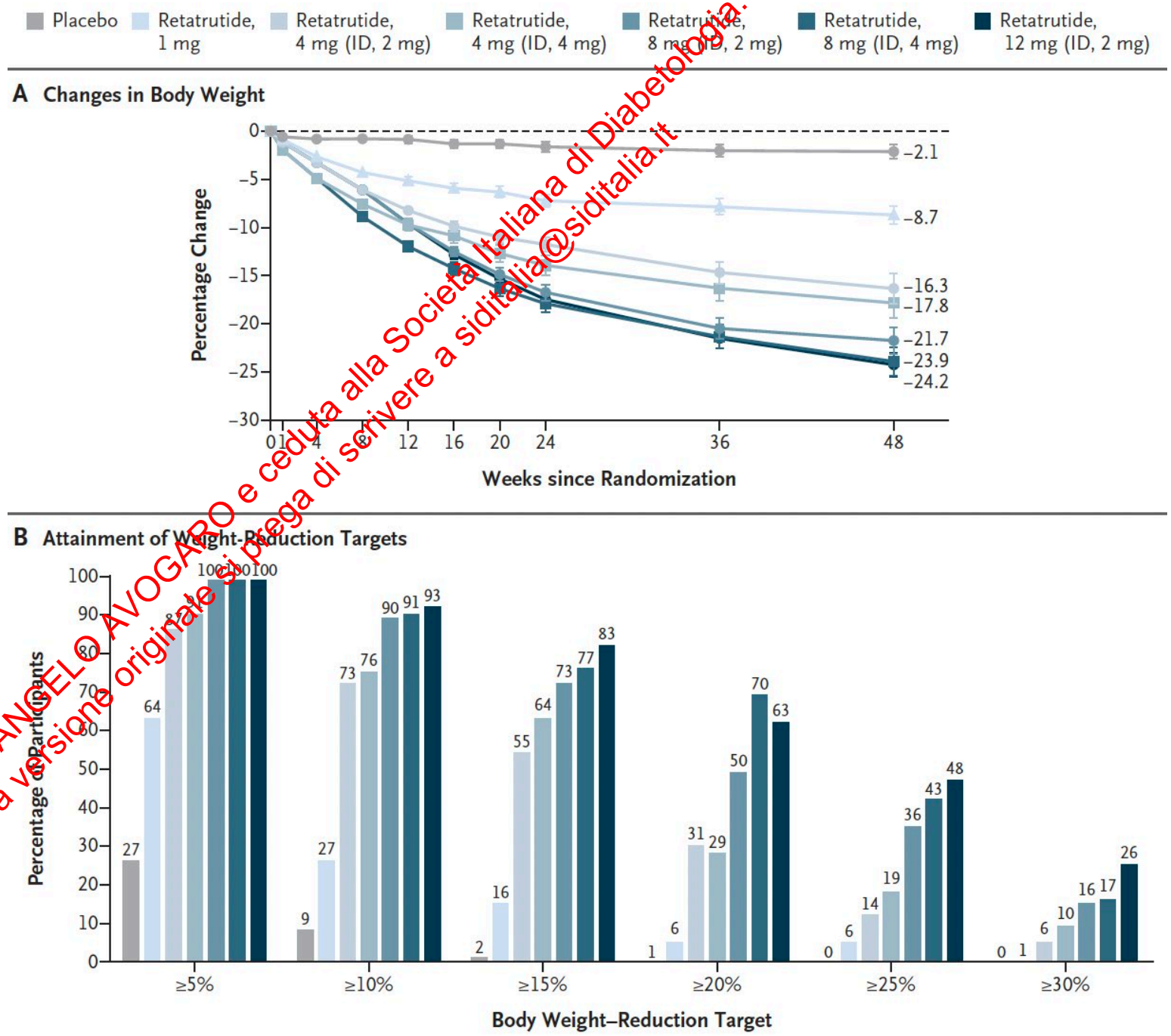
The power of three: Retatrutide's role in modern obesity and diabetes therapy



ORIGINAL ARTICLE

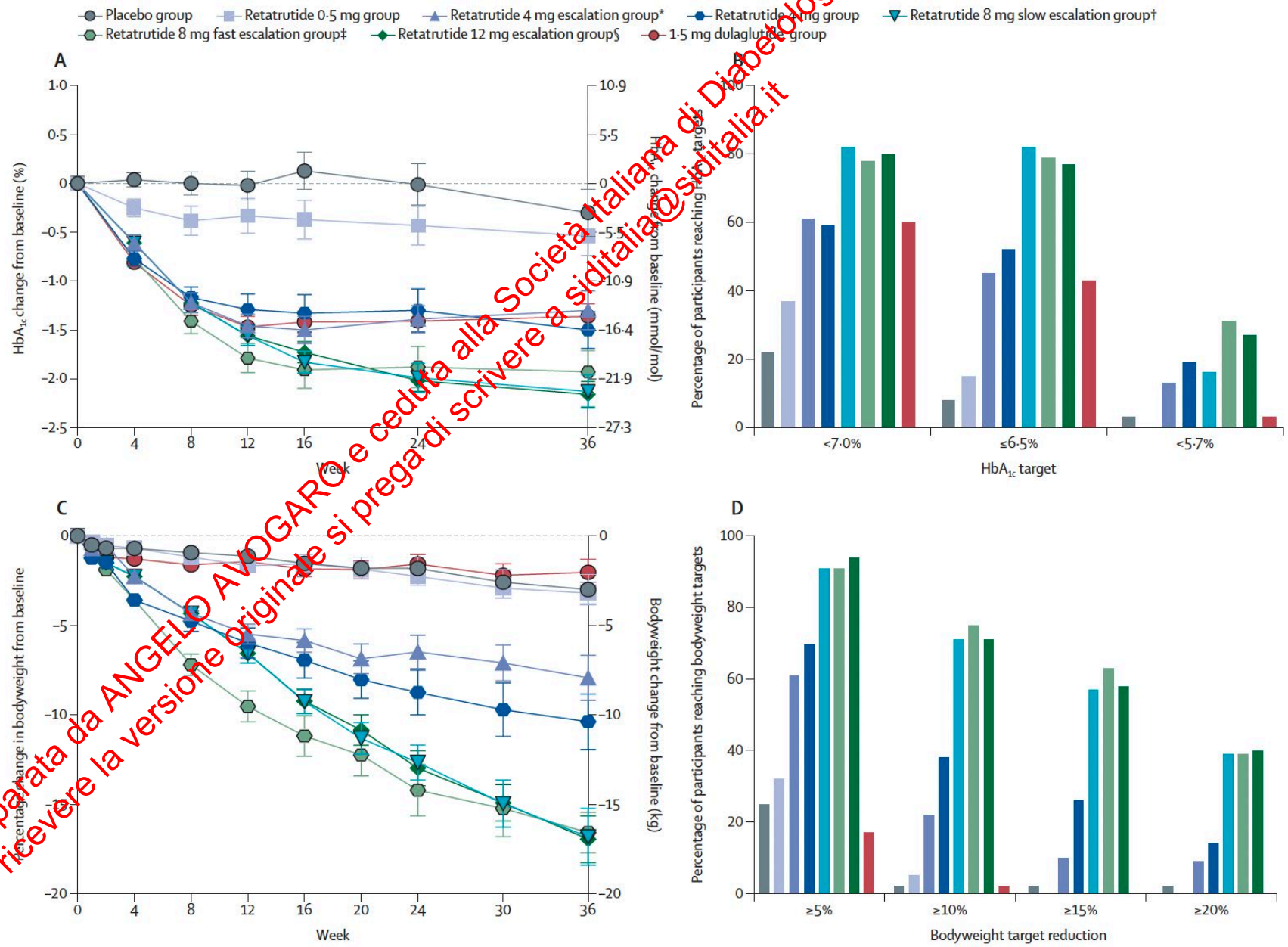
Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*



Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

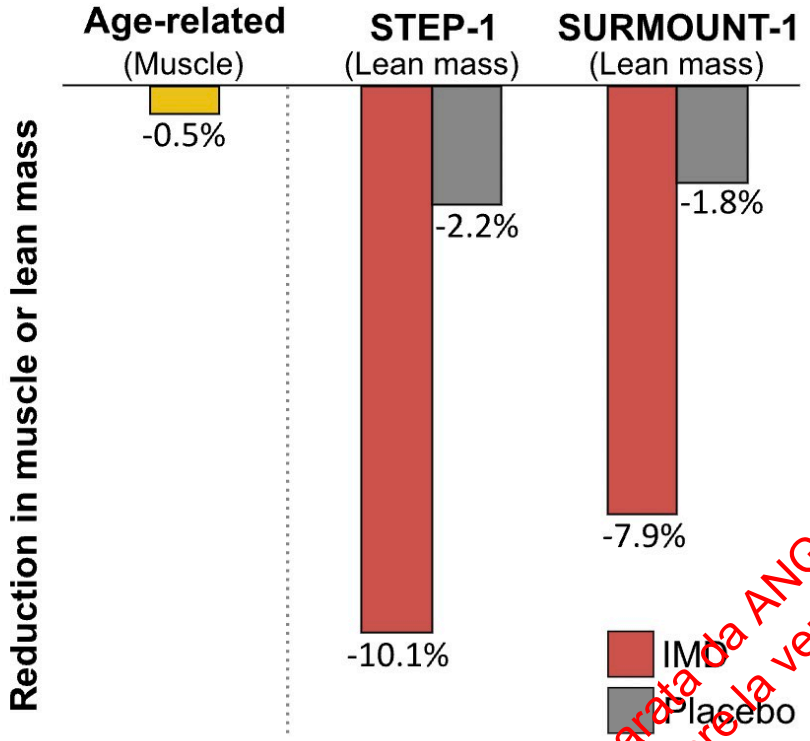
Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

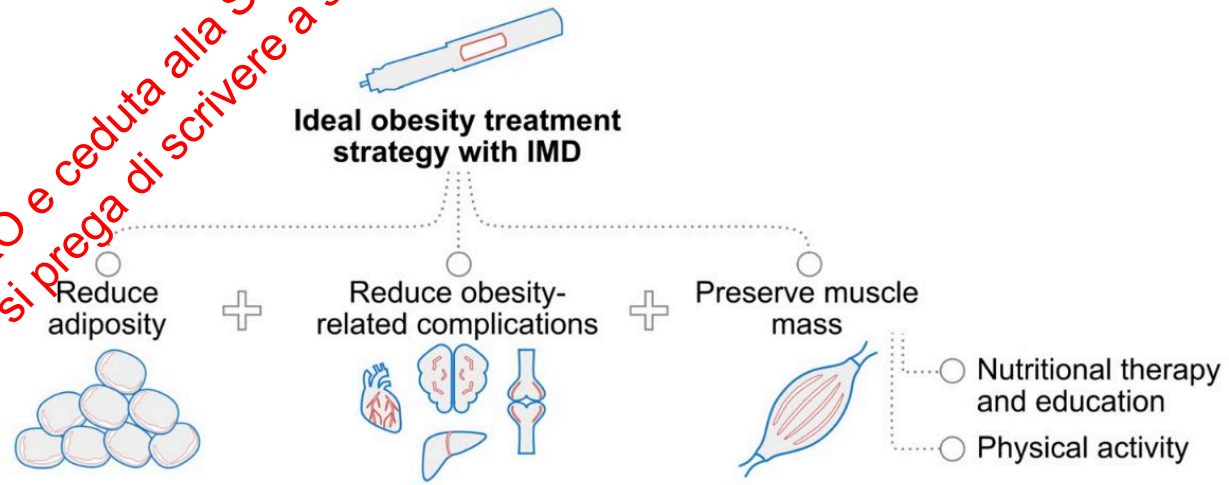


REVIEW
Obesity Management / Intervention

Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity

Jeffrey I. Mechanick[1] | W. Scott Butsch[2] | Sandra M. Christensen[3] | Osama Hamdy[4] | Zhaoping Li[5] | Carla M. Prado[6] | Steven B. Heymsfield[7]





Conclusioni

- L’agonismo mono-recettoriale del GLP-1R rappresenta un approccio terapeutico fondamentale per ridurre il rischio cardio-reno-metabolico
- L’approccio bi-recettoriale appare molto più efficiente nel controllo dei parametri metabolici e, da dati preliminari, non inferiore rispetto al placebo nel ridurre il rischio CV
- L’approccio tri-recettoriale sembra possedere la stessa efficacia nel migliorare i parametri metabolici ma nulla si può affermare sulla tollerabilità a lungo termine
- Nel perseguire il calo ponderale non deve essere assolutamente ignorato il mantenimento della massa magra