Congresso Regionale
SID-AMD
Sezione Marche

Universo incretine: dai diversi GLP-1 RA ai doppio e triplo agonisti per la cura del diabete

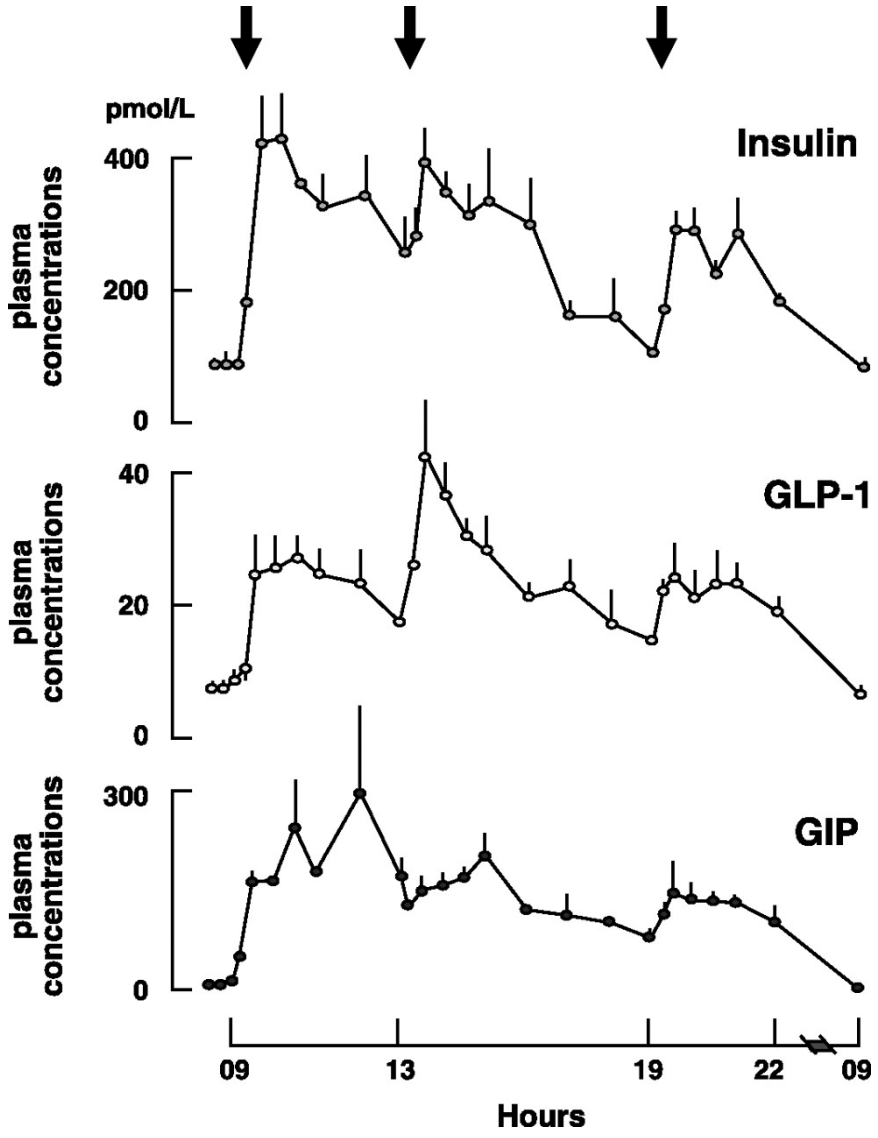
Angelo Avogaro. UNIPD.

ALLEANZA PER IL DIABETE

Conflitti di interesse di Angelo Avogaro

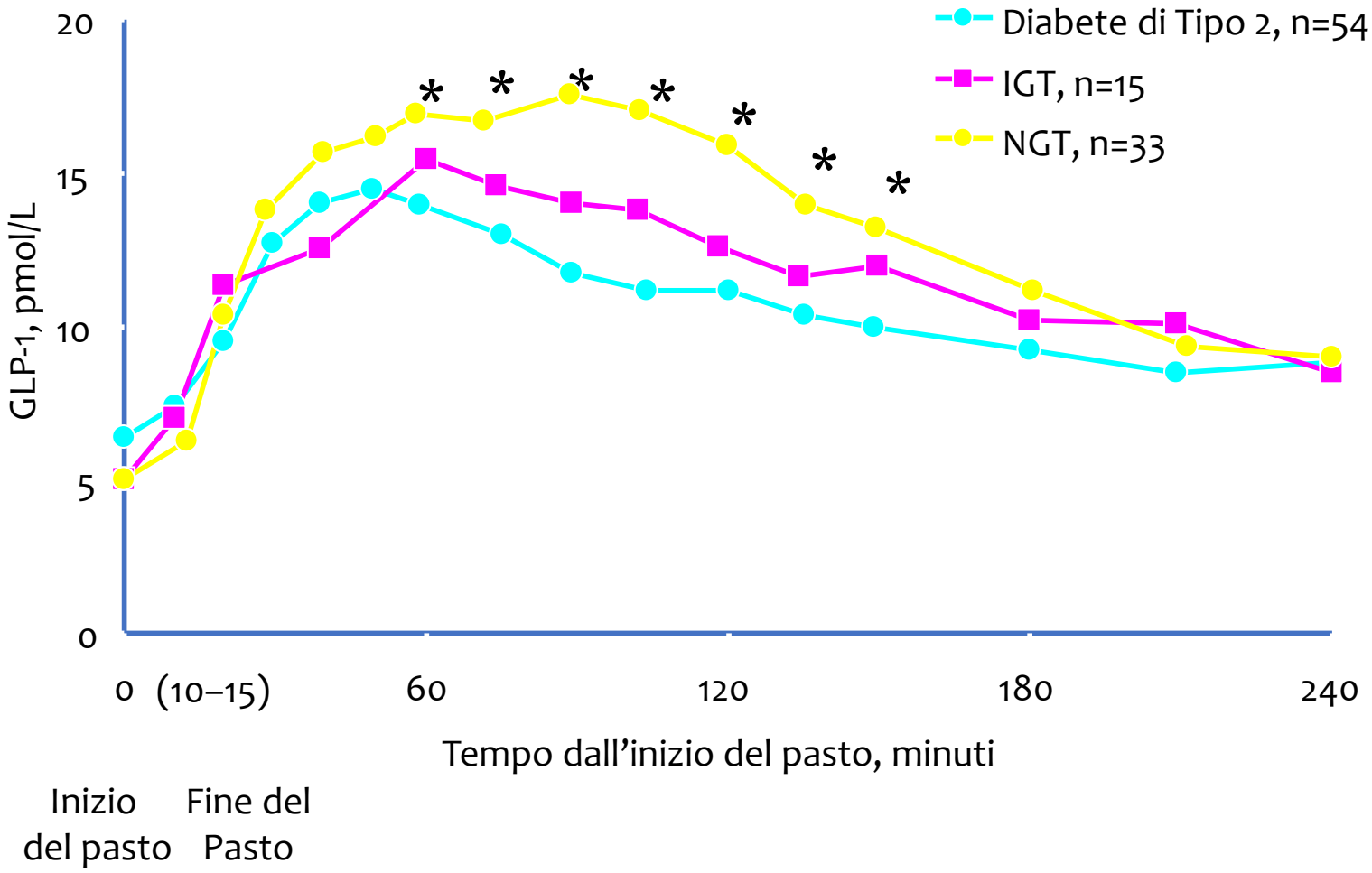
- Dichiaro di aver ricevuto negli ultimi 2 anni compensi dalle seguenti aziende:
- Pharma International Company, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Bruno Farmaceutici, Mundipharma, Neopharmed, Amgen, Servier, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda.

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



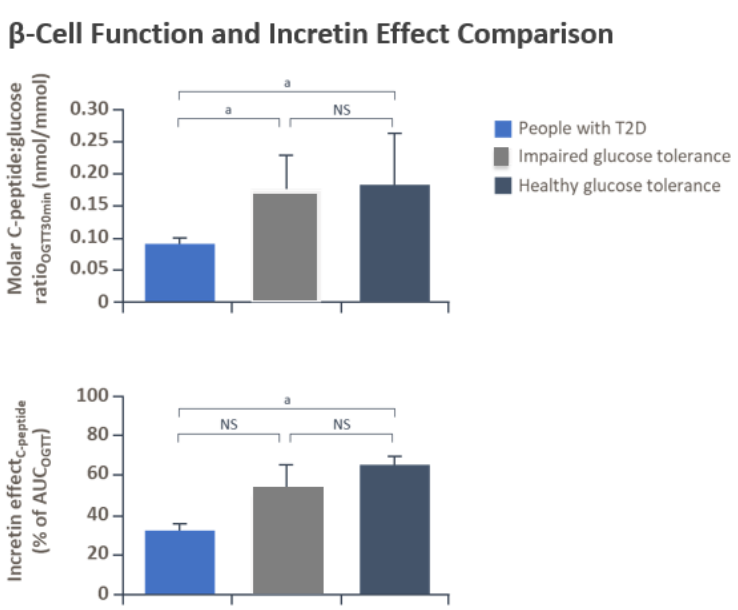
Jens Juul Holst Physiol Rev 2007;87:1409-1439

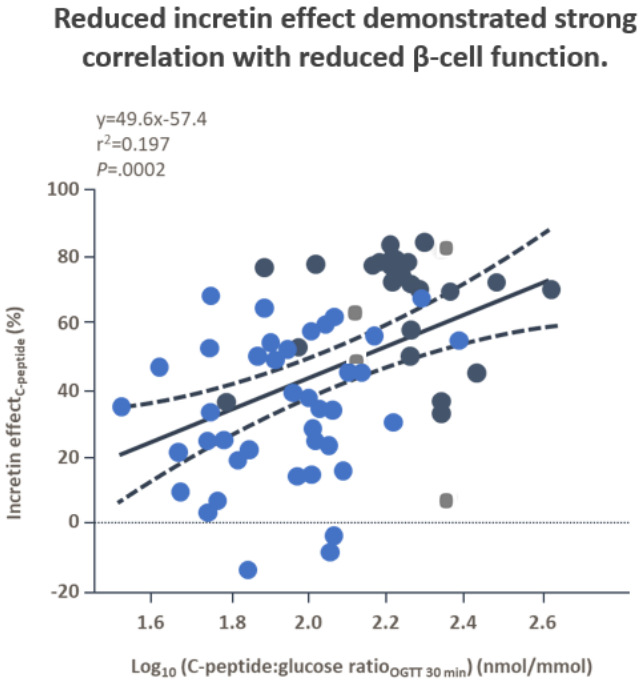
Ridotti livelli post-prandiali del GLP-1 in pazienti con Diabete di tipo 2



*P<0.05, Diabete di Tipo 2 vs NGT.

The Reduced Incretin Effect Associates With Reduced β-Cell Function in People With T2D[1]





[a]Significant difference (*P*<.05).

Fig. 3 ref.1

1.Nauck MA, Meier JJ. *Lancet Diabetes Endocrinol*. 2016;4(6):525-536.

(a) GLP-1,

(b) exenatide,

(c) lixisenatide,

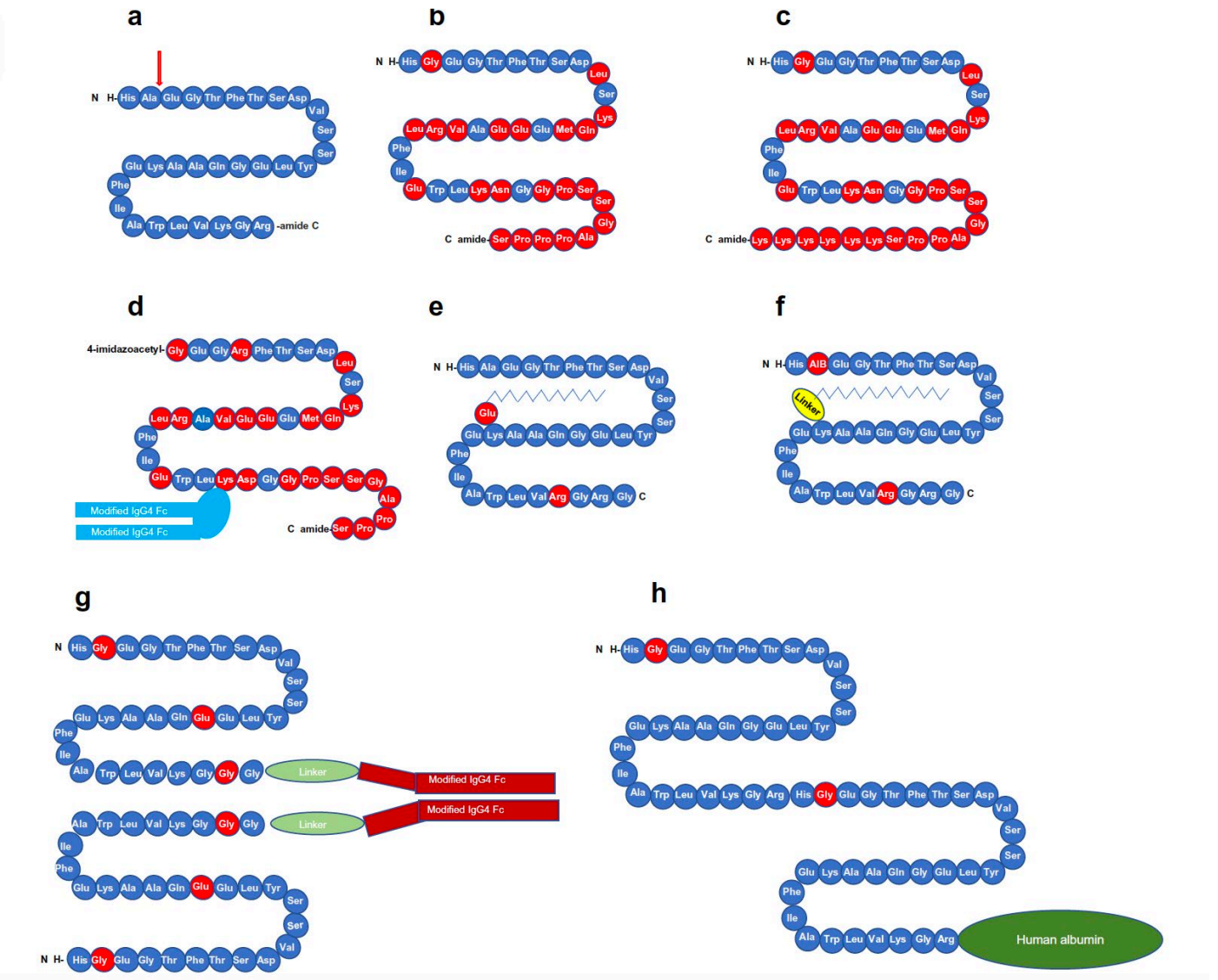
(d) efpeglenatide,

(e) liraglutide,

(f) semaglutide,

(g) dulaglutide,

(h) albiglutide.



GLP-1 receptor agonists have multifactorial effects beyond glycaemic control

Heart
- ↑ Contractility
- ↑ Cardiac function
- ↑ Myocyte survival
- ↑ Cardioprotection
- ↑ Glucose utilization
- ↑ Vasodilatation
- ↑ Glucose reuptake
- ↑ Left ventricle function
- ↑↓→ Blood pressure
- ↑↓→ Heart rate
- ↑ ANP production

Pancreas
- ↑ Insulin secretion
- ↑ Insulin biosynthesis
- ↓ Glucagon secretion
- ↑ Beta cell proliferation
- ↑ Beta cell survival
- ↓ Apoptosis

Bone
- ↑ Osteogenesis
- ↑ Bone mass

GI tract
- ↓ Gastric emptying
- ↓ GI motility

Kidney
- ↑ Diuresis
- ↑ Natriuresis
- ↓ Albuminuria
- ↓ Renal inflammation

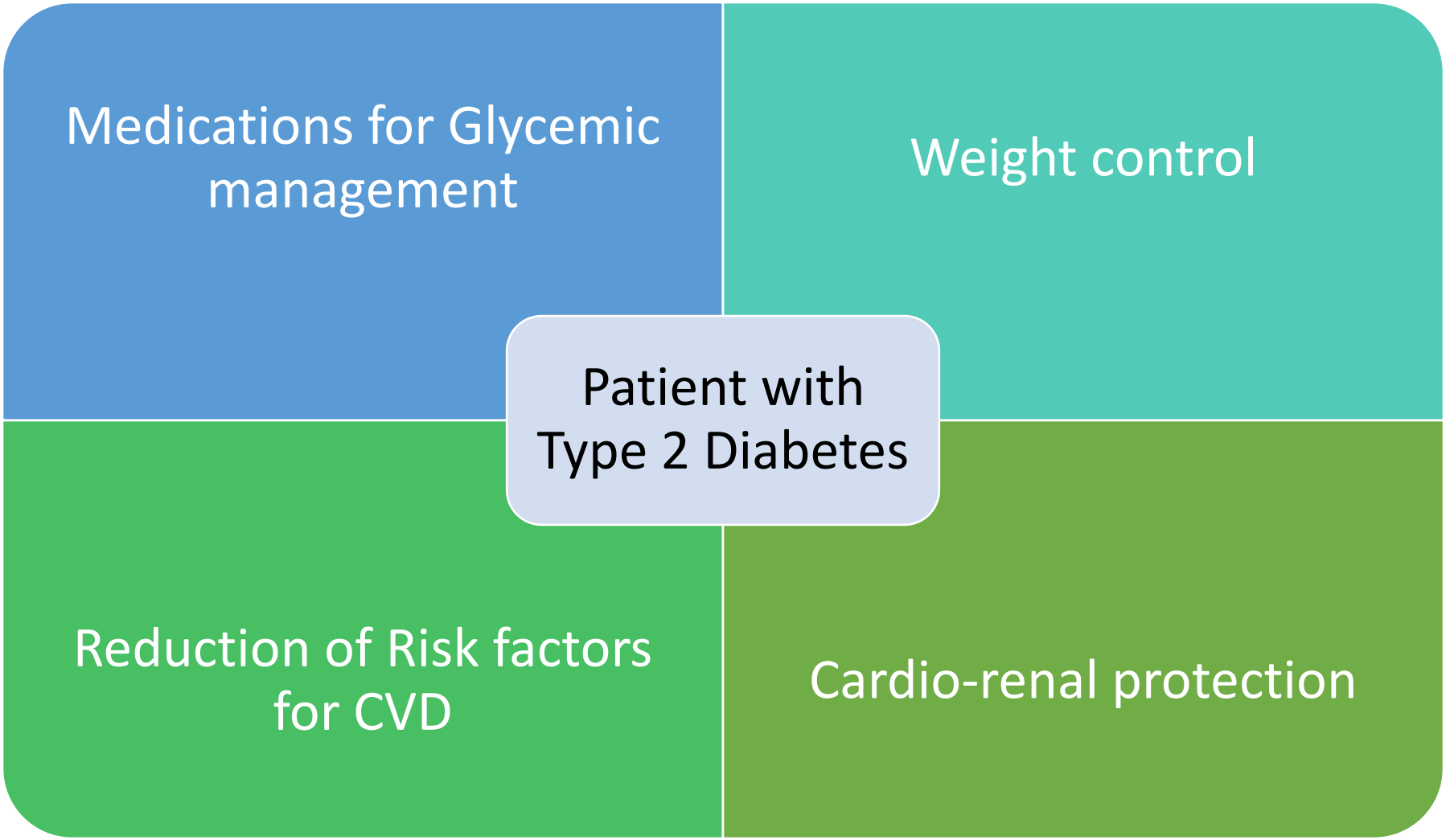
Brain
- ↓ Food intake
- ↓ Water intake
- ↑ Memory and learning ability
- ↑ Neuroprotection
- ↓ Inflammation
- ↓ Rewarding behaviour
- ↓ Palatability
- ↓ Apoptosis

Liver
- ↓ Endogenous glucose production
- ↓ Steatosis

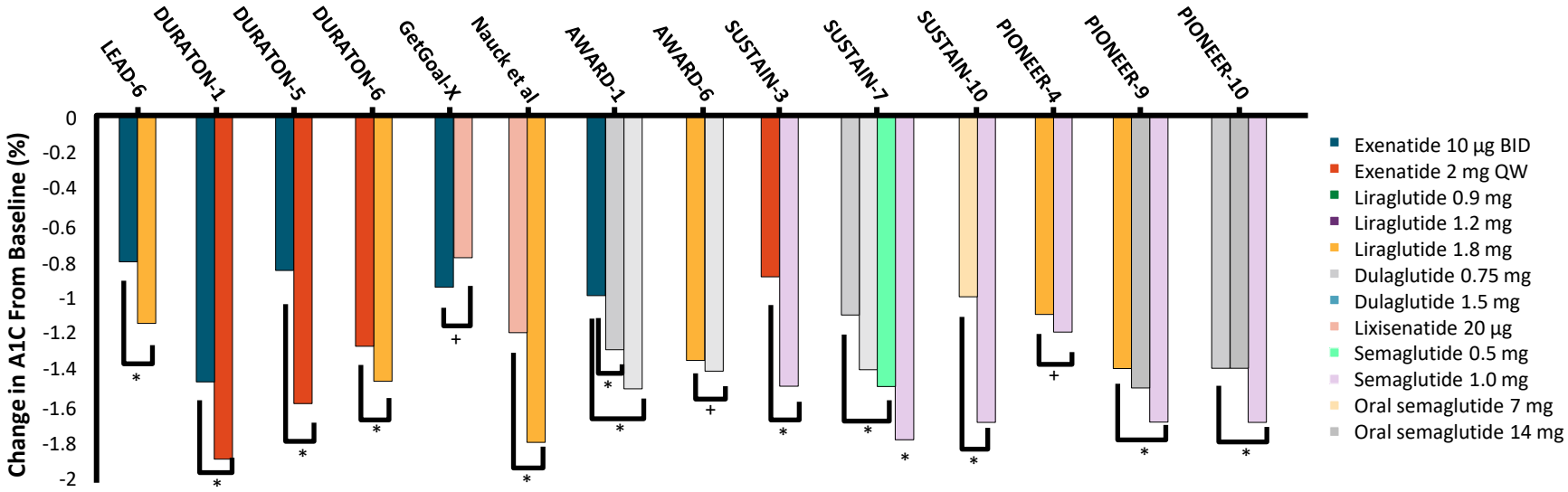
Muscle
- ↑ Insulin sensitivity
- ↑ Glucose reuptake

GLP-1RA, glucagon-like peptide-1 receptor agonist; ANP, atrial natriuretic peptide.

1. Müller TD, et al. Mol Metab. 2019;30:72-130; 2. Tsimihodimos V, et al. Eur J Pharmacol. 2018;818:103-109.

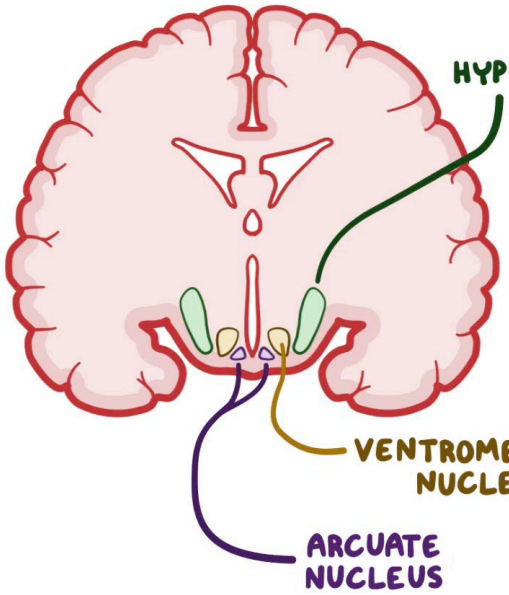

Medications for Glycemic management
Weight control
Patient with Type 2 Diabetes
Reduction of Risk factors for CVD
Cardio-renal protection

GLP-1 RA Comparative Studies in T2D: Change in A1C



*P <.05. †P <.05, meeting predefined noninferiority margin.

Figure adapted from: Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be made. Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117. Capehorn. Diabetes Metab. 2020;46:100. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501. Pratley. Lancet. 2019;394:39. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care. 2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:392. Yamada. Lancet Diabetes Endocrinol. 2020;8:377.



LATERAL HYPOTHALAMIC AREA

- FEEDING CENTER
  - ↓
  - SENSATION of **HUNGER**

VENTROMEDIAL NUCLEI

- SATIETY CENTER

ARCUATE NUCLEUS

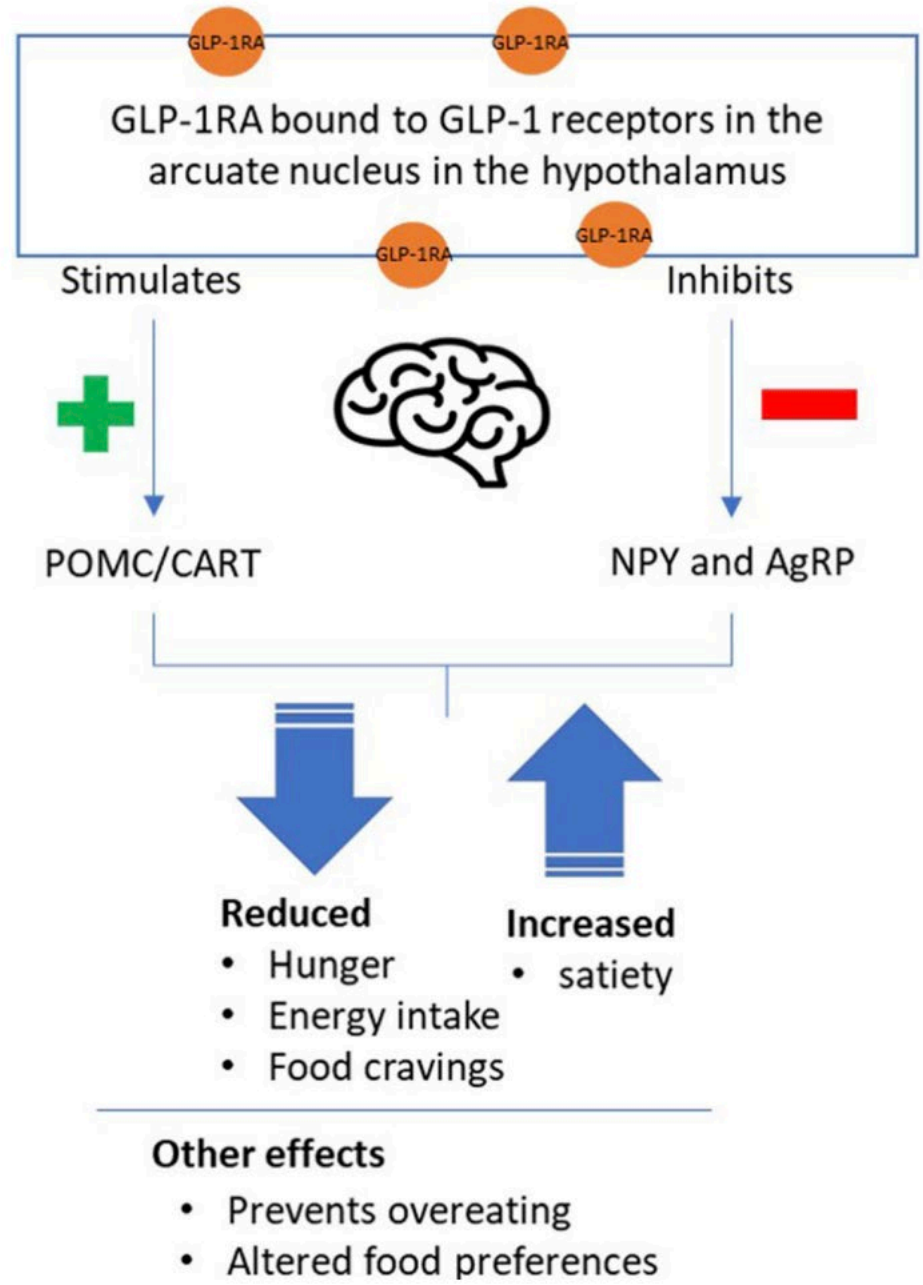
- SWITCHBOARD
  - RECEIVES SIGNALS from the **GI TRACT**
  - REGULATES the **FEEDING CENTER** & **SATIETY CENTER**

Adv Ther (2021) 38:2821–2839
https://doi.org/10.1007/s12325-021-01710-0

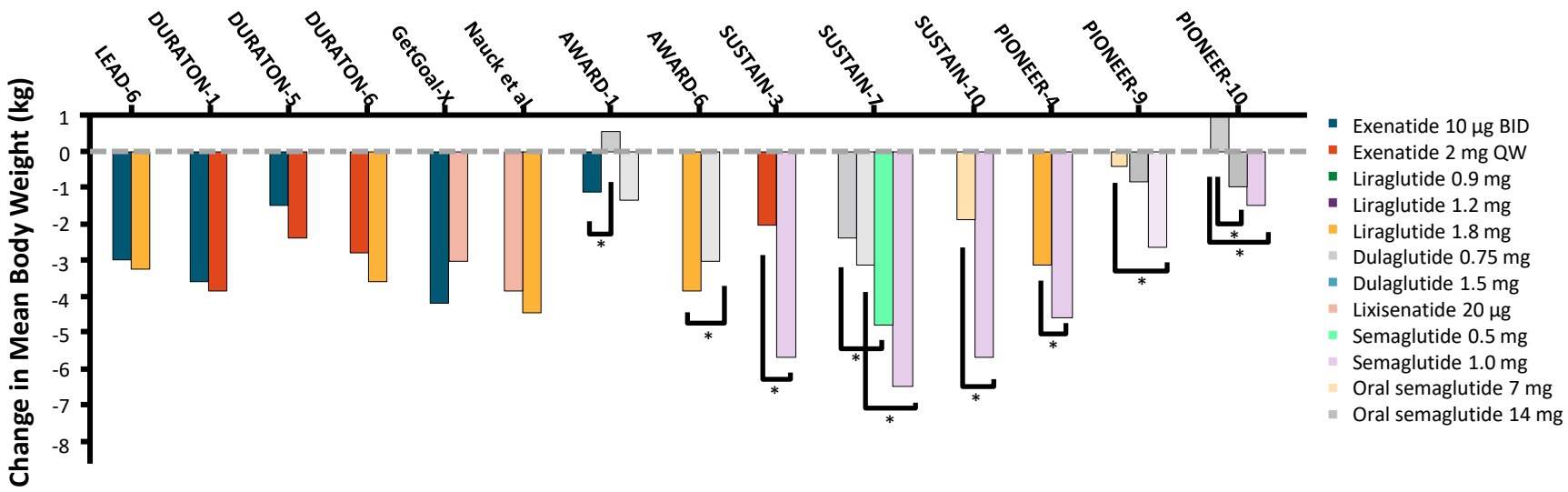
REVIEW

Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists

Jamy Ard · Angela Fitch · Sharon Fruh · Lawrence Herman



Trials of GLP-1 RAs in T2D: Changes in Body Weight



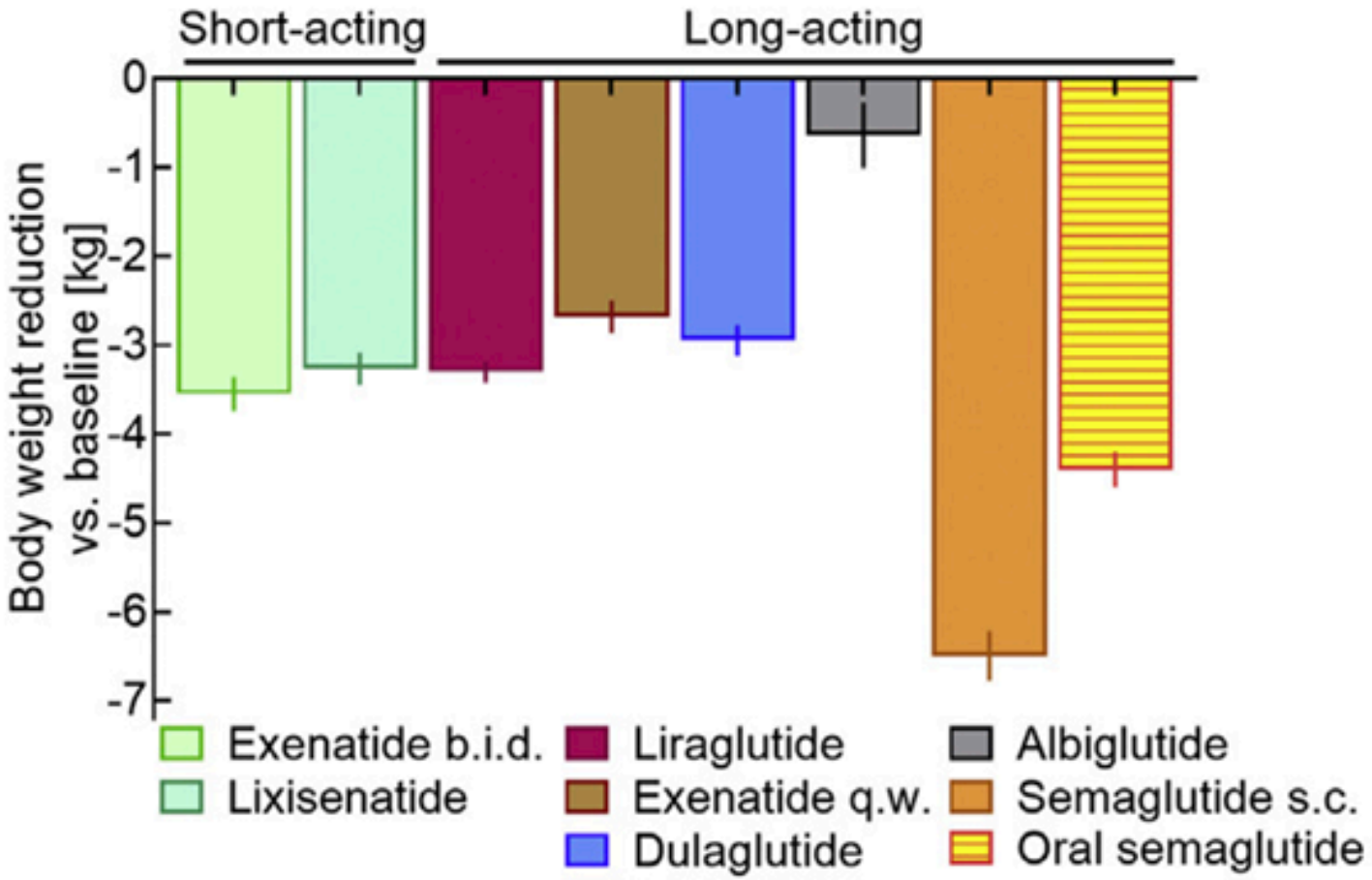
*P <.05.

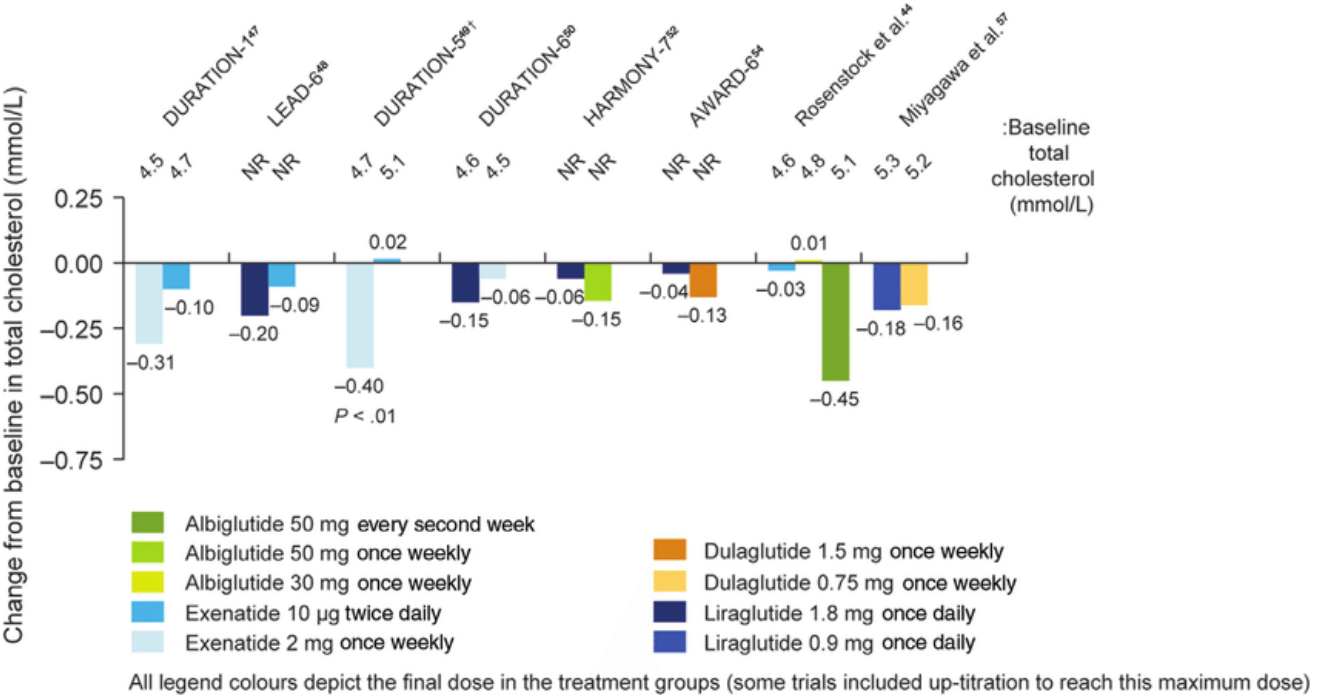
Figure adapted from: Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be n
Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117.
Capehorn. Diabetes Metab. 2020;46:100. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501.
Pratley. Lancet. 2019;394:39. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care.
2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:392. Yamada. Lancet Diabetes Endocrinol. 2020;8:377.

MOLECULAR
METABOLISM

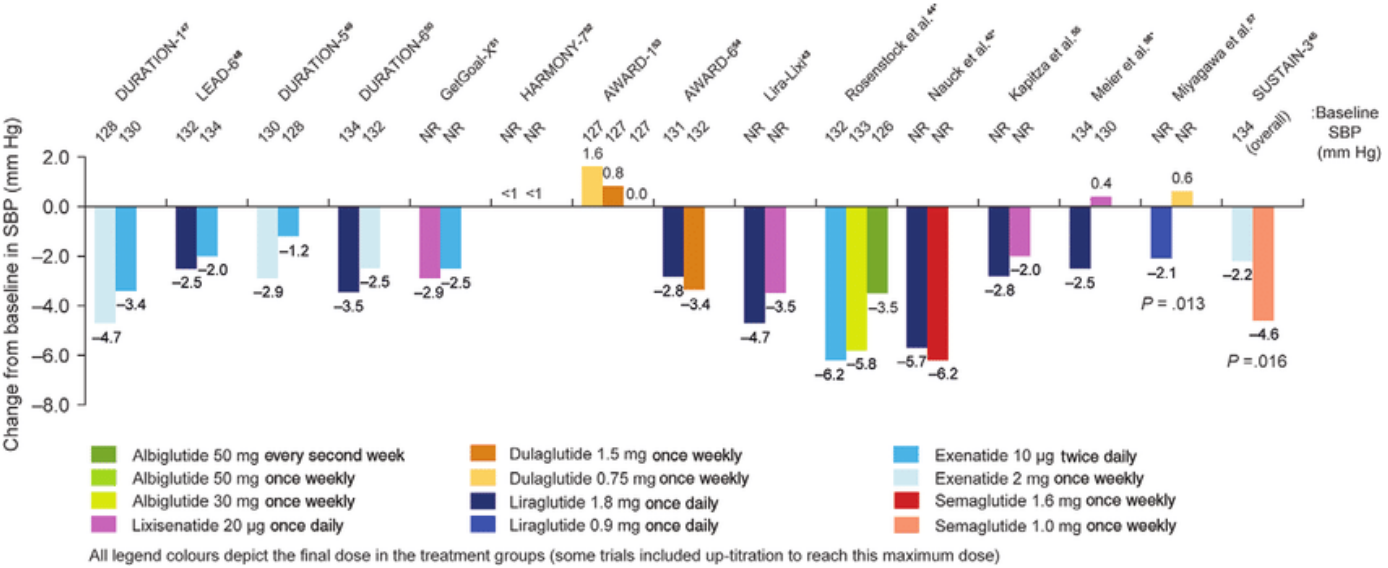
GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art

Michael A. Nauck*, Daniel R. Quast, Jakob Wefers, Juris J. Meier



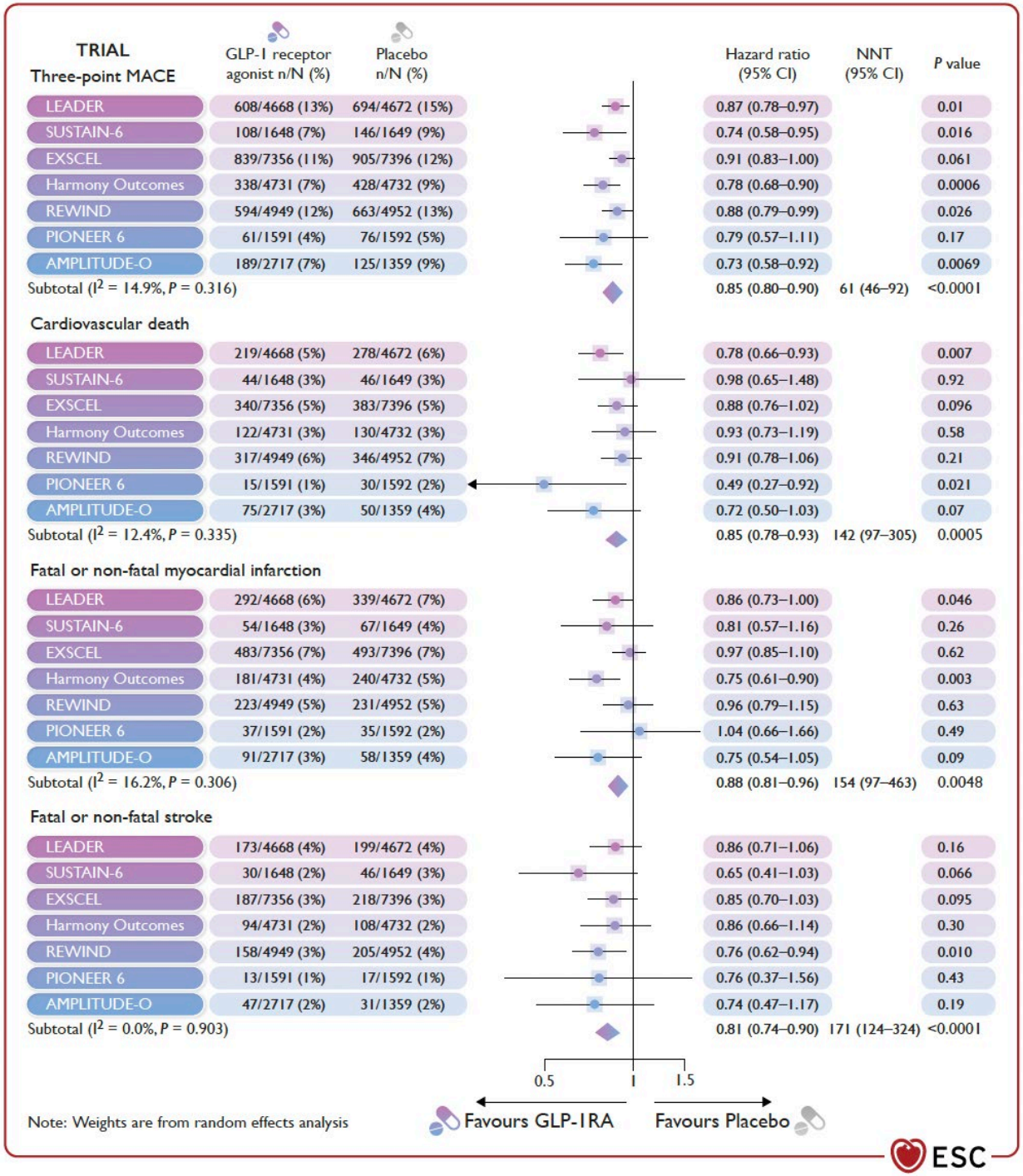


All legend colours depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose)



All legend colours depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose)

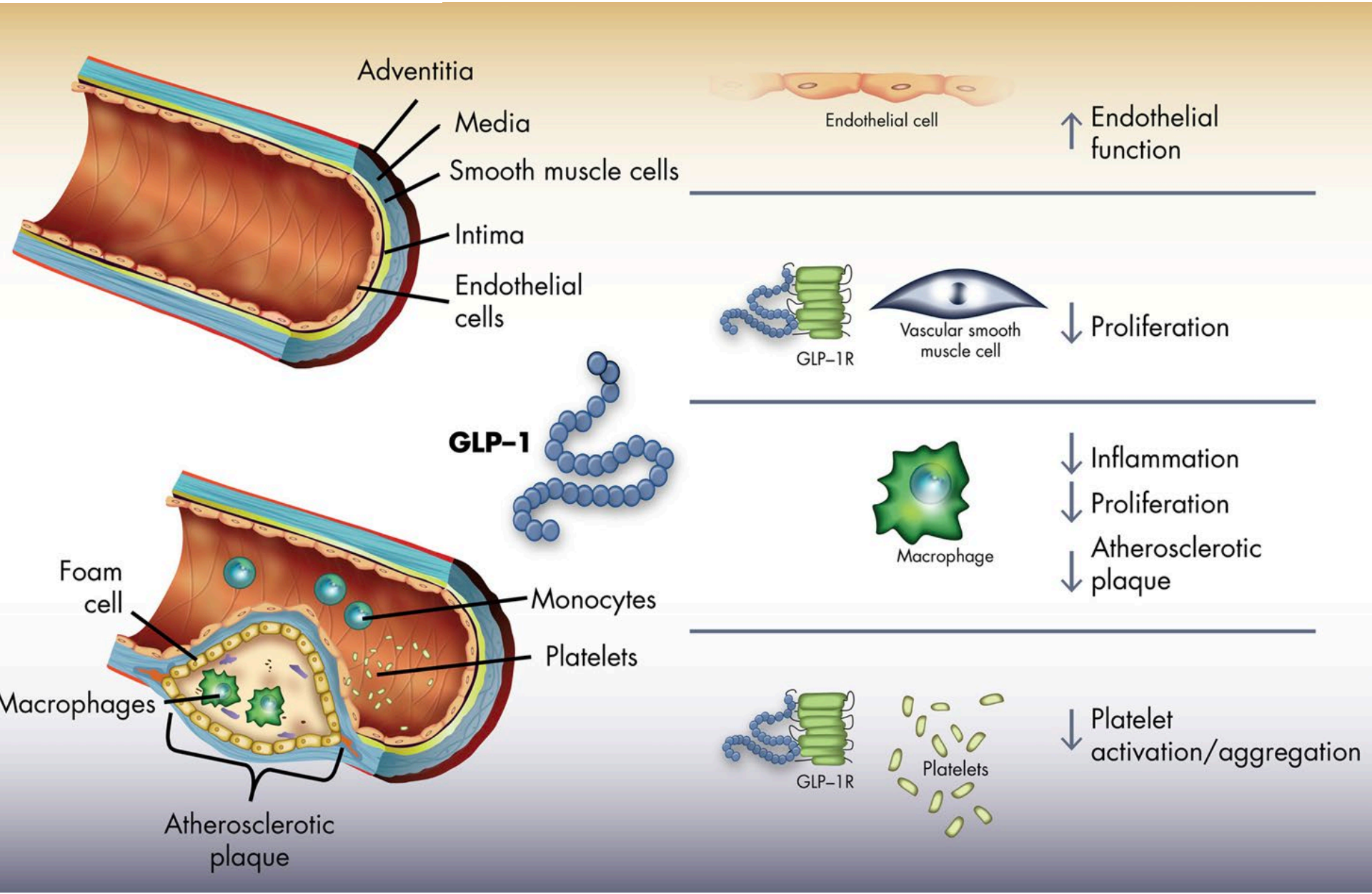
Dalsgaard et al. DOM 2017


TRIAL
GLP-1 receptor agonist n/N (%)
Placebo n/N (%)
Hazard ratio (95% CI)
NNT (95% CI)
P value
Three-point MACE
LEADER 608/4668 (13%) 694/4672 (15%) 0.87 (0.78–0.97) 0.01
SUSTAIN-6 108/1648 (7%) 146/1649 (9%) 0.74 (0.58–0.95) 0.016
EXSCEL 839/7356 (11%) 905/7396 (12%) 0.91 (0.83–1.00) 0.061
Harmony Outcomes 338/4731 (7%) 428/4732 (9%) 0.78 (0.68–0.90) 0.0006
REWIND 594/4949 (12%) 663/4952 (13%) 0.88 (0.79–0.99) 0.026
PIONEER 6 61/1591 (4%) 76/1592 (5%) 0.79 (0.57–1.11) 0.17
AMPLITUDE-O 189/2717 (7%) 125/1359 (9%) 0.73 (0.58–0.92) 0.0069
Subtotal (I^2 = 14.9%, P = 0.316) 0.85 (0.80–0.90) 61 (46–92) <0.0001
Cardiovascular death
LEADER 219/4668 (5%) 278/4672 (6%) 0.78 (0.66–0.93) 0.007
SUSTAIN-6 44/1648 (3%) 46/1649 (3%) 0.98 (0.65–1.48) 0.92
EXSCEL 340/7356 (5%) 383/7396 (5%) 0.88 (0.76–1.02) 0.096
Harmony Outcomes 122/4731 (3%) 130/4732 (3%) 0.93 (0.73–1.19) 0.58
REWIND 317/4949 (6%) 346/4952 (7%) 0.91 (0.78–1.06) 0.21
PIONEER 6 15/1591 (1%) 30/1592 (2%) 0.49 (0.27–0.92) 0.021
AMPLITUDE-O 75/2717 (3%) 50/1359 (4%) 0.72 (0.50–1.03) 0.07
Subtotal (I^2 = 12.4%, P = 0.335) 0.85 (0.78–0.93) 142 (97–305) 0.0005
Fatal or non-fatal myocardial infarction
LEADER 292/4668 (6%) 339/4672 (7%) 0.86 (0.73–1.00) 0.046
SUSTAIN-6 54/1648 (3%) 67/1649 (4%) 0.81 (0.57–1.16) 0.26
EXSCEL 483/7356 (7%) 493/7396 (7%) 0.97 (0.85–1.10) 0.62
Harmony Outcomes 181/4731 (4%) 240/4732 (5%) 0.75 (0.61–0.90) 0.003
REWIND 223/4949 (5%) 231/4952 (5%) 0.96 (0.79–1.15) 0.63
PIONEER 6 37/1591 (2%) 35/1592 (2%) 1.04 (0.66–1.66) 0.49
AMPLITUDE-O 91/2717 (3%) 58/1359 (4%) 0.75 (0.54–1.05) 0.09
Subtotal (I^2 = 16.2%, P = 0.306) 0.88 (0.81–0.96) 154 (97–463) 0.0048
Fatal or non-fatal stroke
LEADER 173/4668 (4%) 199/4672 (4%) 0.86 (0.71–1.06) 0.16
SUSTAIN-6 30/1648 (2%) 46/1649 (3%) 0.65 (0.41–1.03) 0.066
EXSCEL 187/7356 (3%) 218/7396 (3%) 0.85 (0.70–1.03) 0.095
Harmony Outcomes 94/4731 (2%) 108/4732 (2%) 0.86 (0.66–1.14) 0.30
REWIND 158/4949 (3%) 205/4952 (4%) 0.76 (0.62–0.94) 0.010
PIONEER 6 13/1591 (1%) 17/1592 (1%) 0.76 (0.37–1.56) 0.43
AMPLITUDE-O 47/2717 (2%) 31/1359 (2%) 0.74 (0.47–1.17) 0.19
Subtotal (I^2 = 0.0%, P = 0.903) 0.81 (0.74–0.90) 171 (124–324) <0.0001
0.5
1
1.5
Note: Weights are from random effects analysis
Favours GLP-1RA
Favours Placebo
ESC

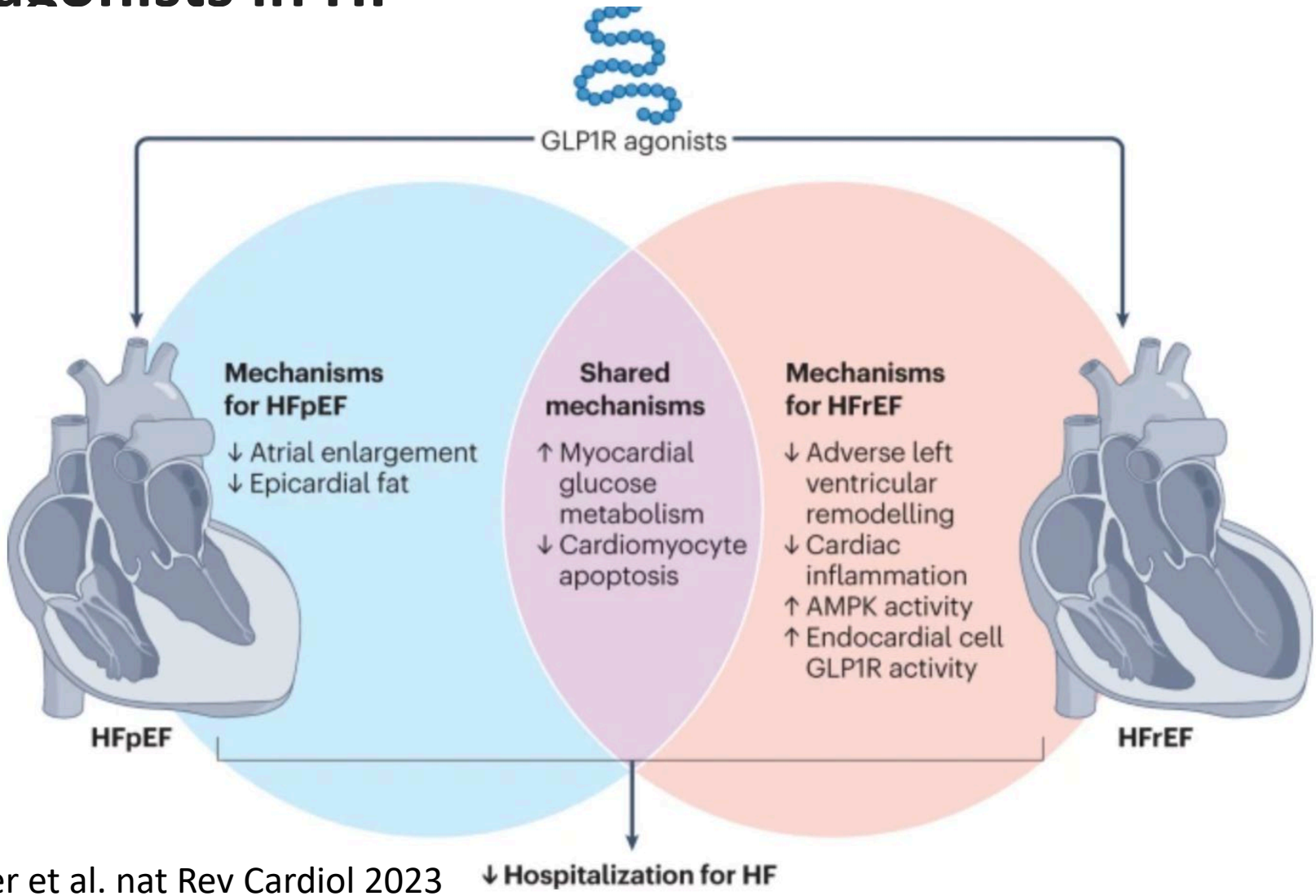
Il ruolo delle Incretine

Vascular Biology of Glucagon Receptor Superfamily Peptides: Mechanistic and Clinical Relevance

Gemma Pujadas and Daniel J. Drucker



Actions and potential mechanisms of GLP1R agonists in HF



Ussher et al. nat Rev Cardiol 2023

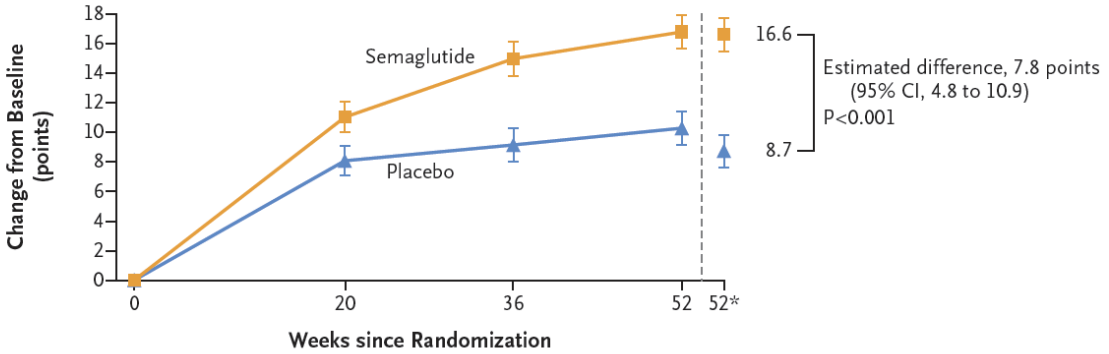
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

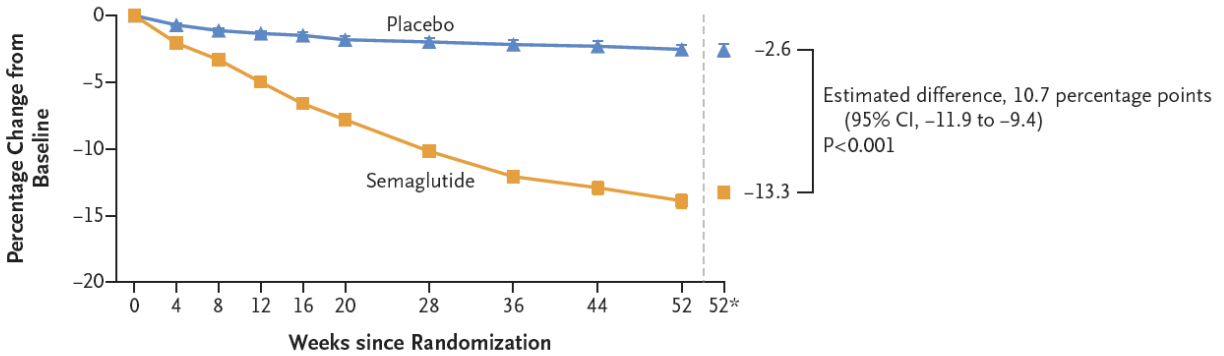
M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, 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*

A Change in KCCQ-CSS



No. of Participants					
Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

B Change in Body Weight



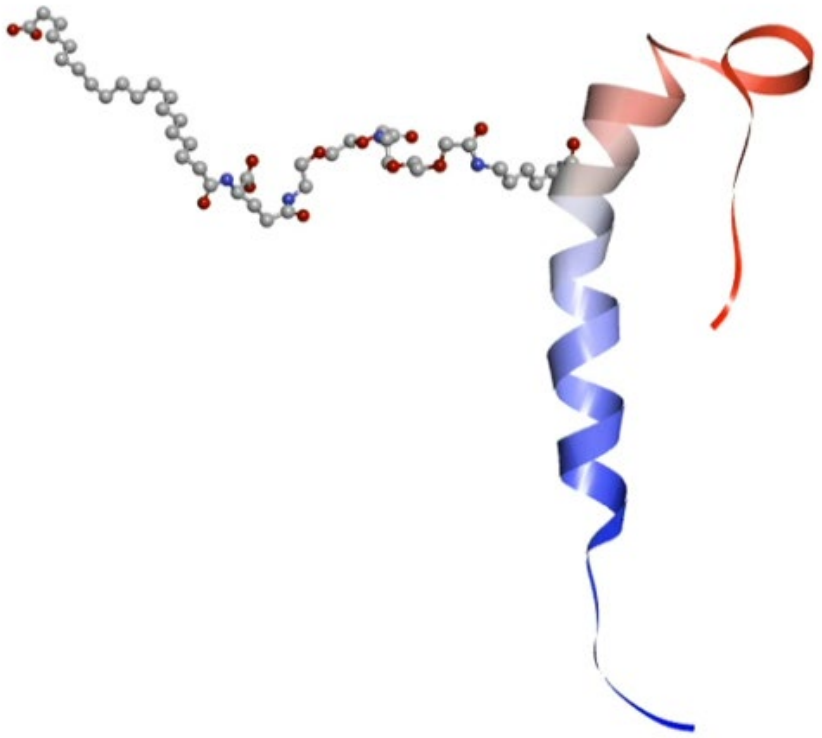
No. of Participants											
Semaglutide	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

Il Futuro: doppio, triplo, etc…

	GLP-1RA	GIPRA
TIRZEPATIDE	✔	✔

Tirzepatide Is a Dual GIPR / GLP-1R Agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of approximately 5 days (116.7 hours), enabling once-weekly dosing

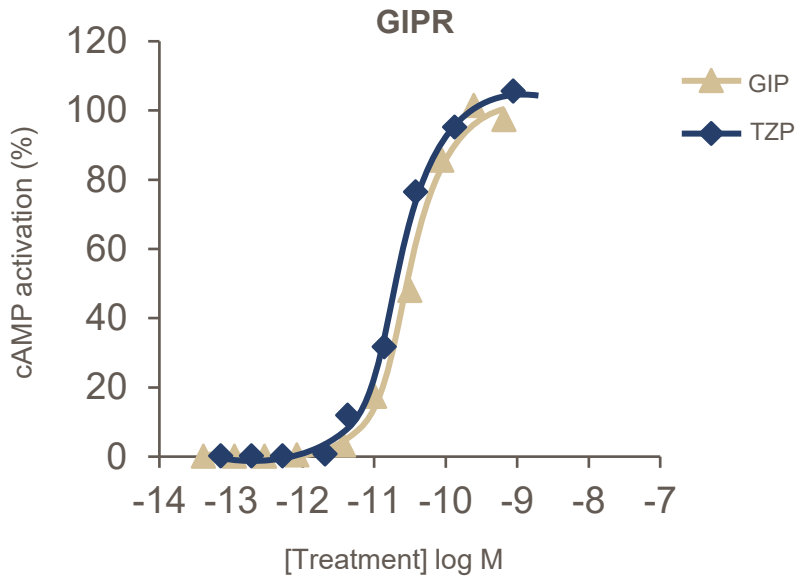


GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor.

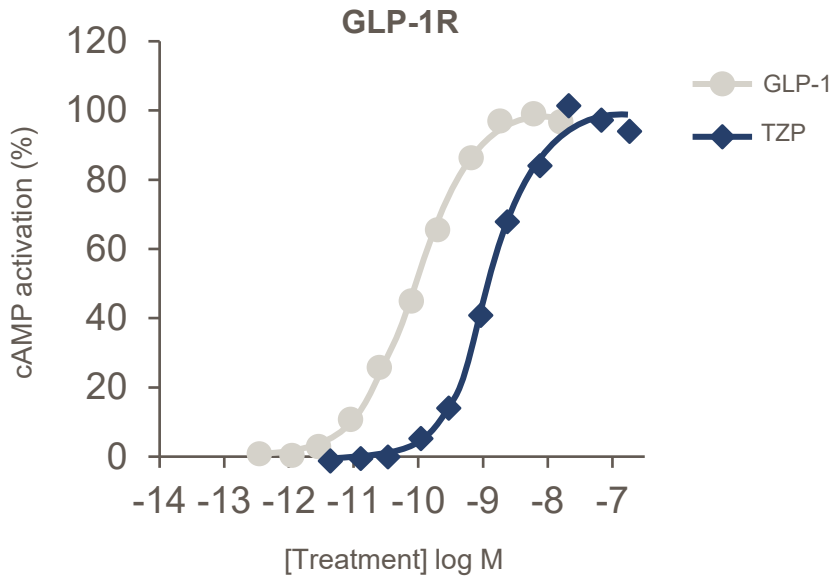
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

Tirzepatide is a Potent GIPR / GLP-1R unimolecular Dual Agonist

In vitro, tirzepatide has a potency for the GIPR similar to native GIP.*



Potency for the GLP-1R is slightly weaker than native GLP-1.*

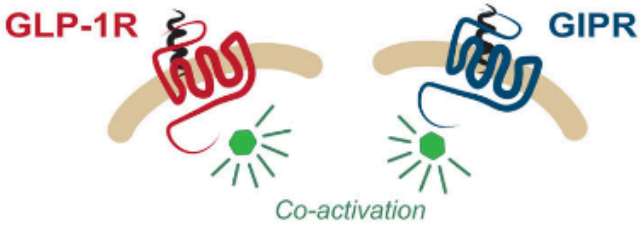


*In overexpressed HEK cells.
cAMP = cyclic adenosine monophosphate; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide-1; GLP-1R = glucagon-like peptide-1 receptor; HEK = human endometrial adenocarcinoma; TZP = tirzepatide.
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

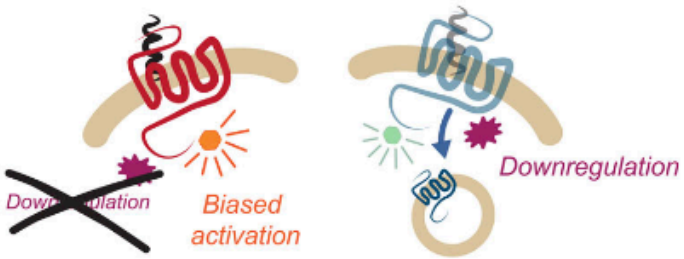
Tirzepatide actions in humans

Three hypotheses

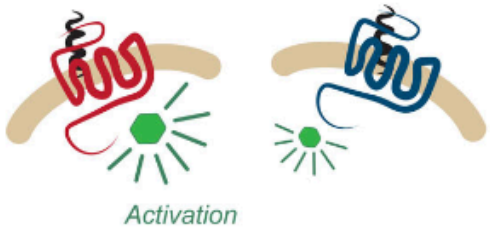
1: GLP-1R–GIPR *co-agonist*?



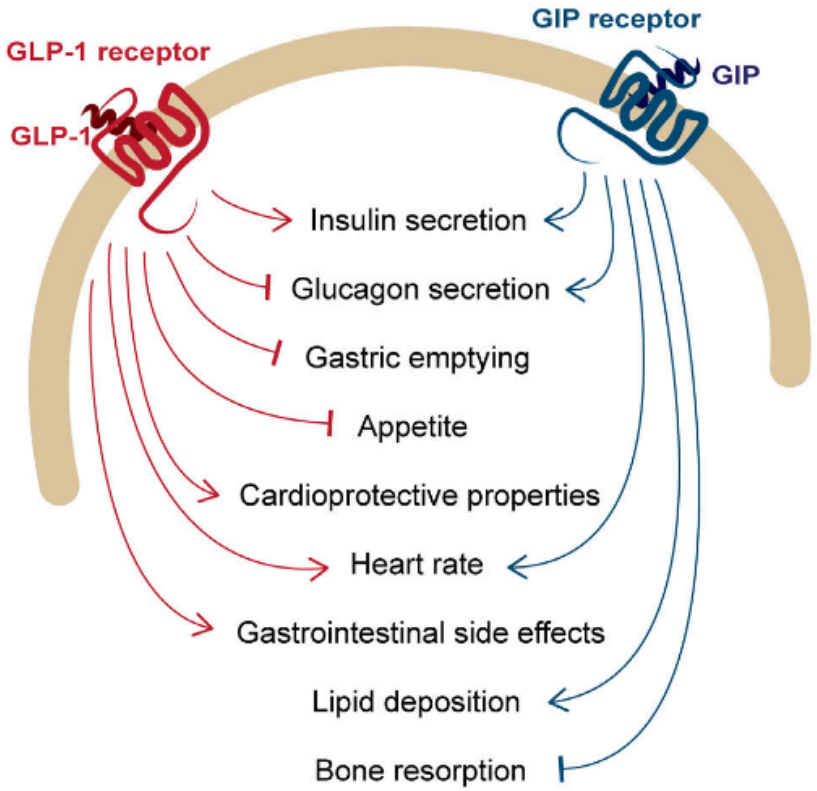
2: Biased agonist of GLP-1R and *functional antagonist* of GIPR?



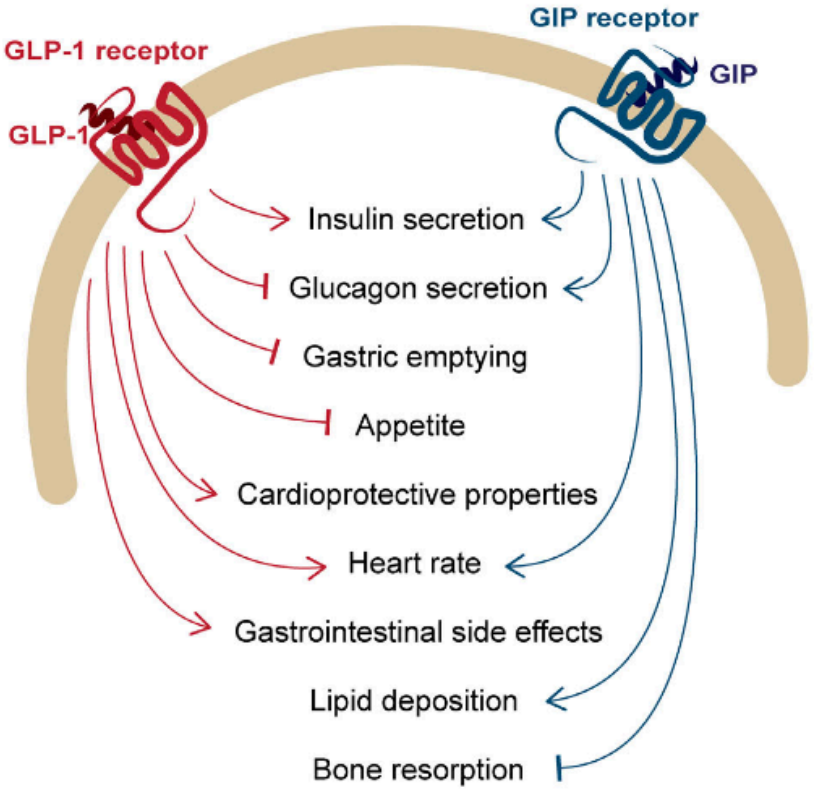
3: GLP-1R '*super-agonist*'?



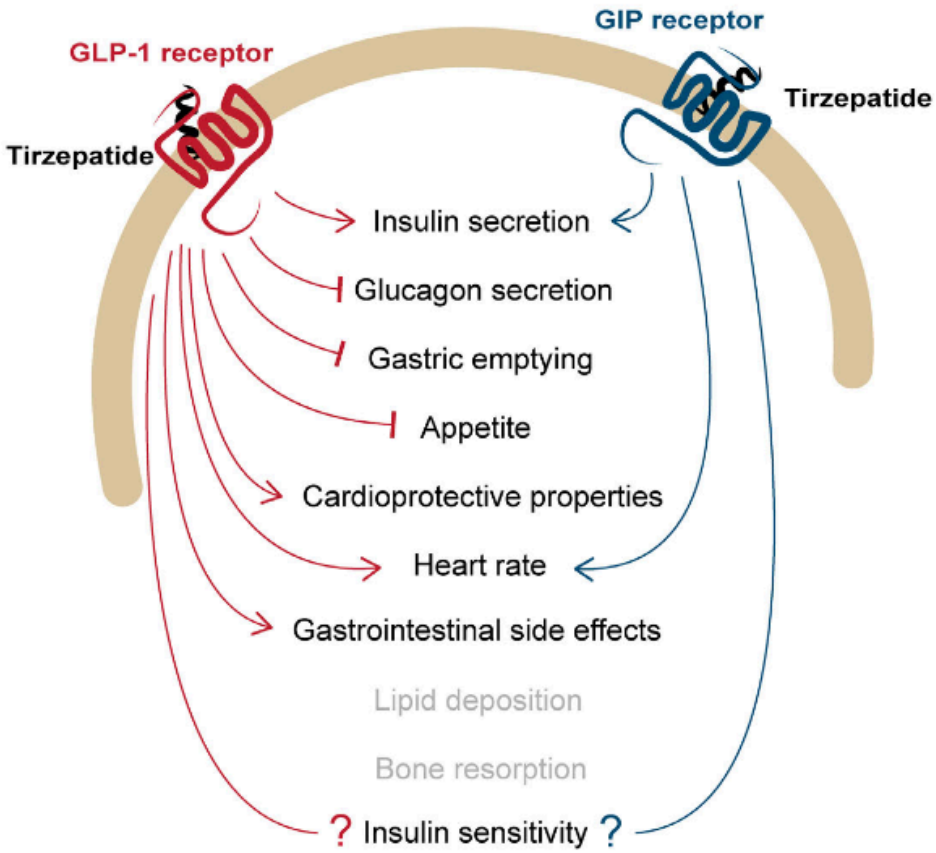
Current results of GLP-1 and GIP receptor activation in humans



Current results of GLP-1 and GIP receptor activation in humans



Current results of tirzepatide treatment in humans

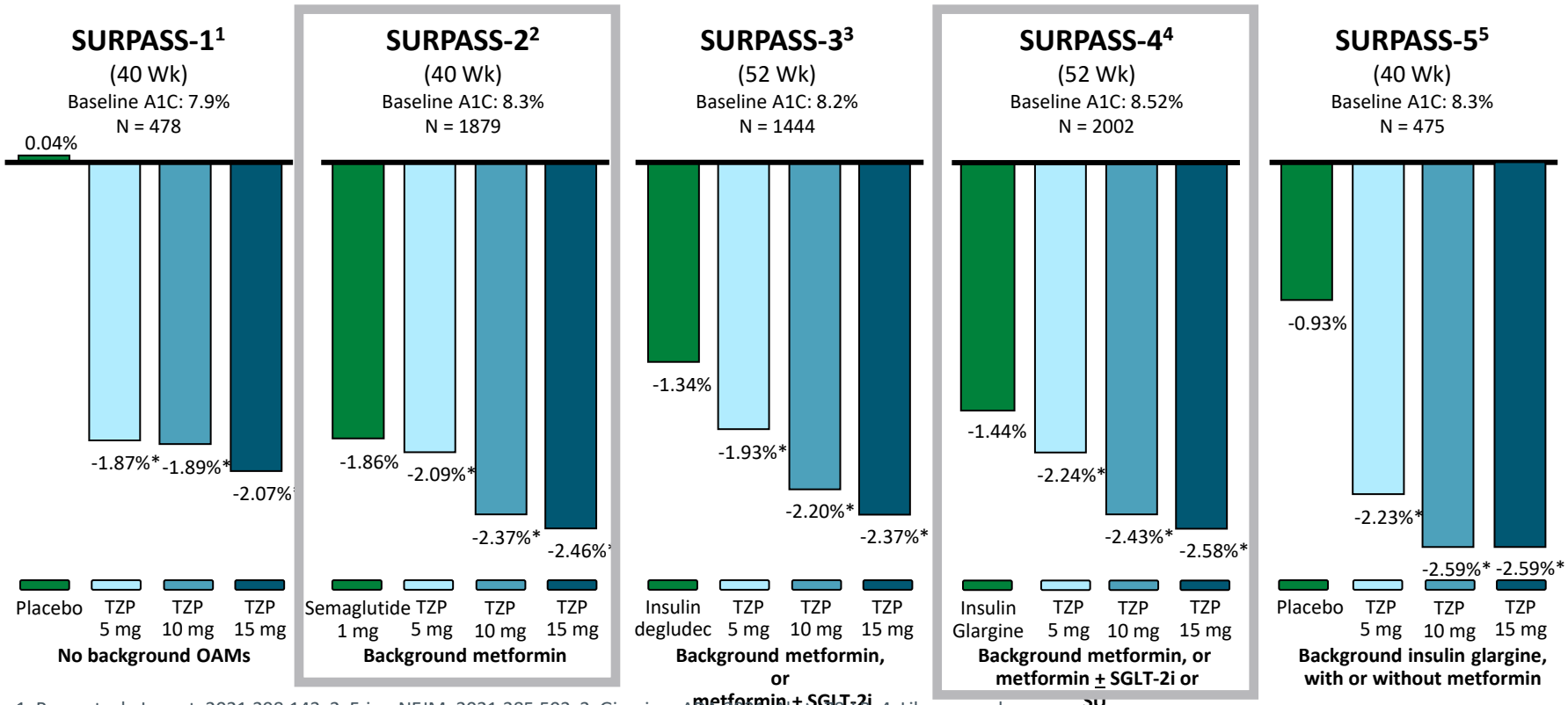


Overview of the SURPASS Studies

Study	Design	N	Background Therapy	Comparator	Mean Baseline Characteristics		
					A1C, %	Duration of Diabetes, Yr	BMI, kg/m^2
SURPASS-1[1]	Blinded	478	None	Placebo	7.94	4.7	31.9
SURPASS-2[2]	Open label	1879	Metformin	Semaglutide	8.28	8.6	34.2
SURPASS-3[3]	Open label	1444	Metformin ± SGLT-2i	Degludec	8.17	8.4	33.5
SURPASS-4[4]	Open-label	2000	Metformin ± SGLT2 or SU	Glargine	8.52	11.8	NR
SURPASS-5[5]	Blinded	475	Glargine ± metformin	Placebo	8.31	13.3	33.4
SURPASS-CVOT[6]	Blinded	12,500 (planned)	Any	Dulaglutide	NR	NR	NR

1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;[Epub]. 3. Ludvik. ADA 2021. Abstr 78-LB.
4. Lily news release. investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 5. Dahl. ADA 2021. Abstr 80-LB. 6. NCT04255433.

SURPASS: Tirzepatide Reduces A1C in Type 2 Diabetes

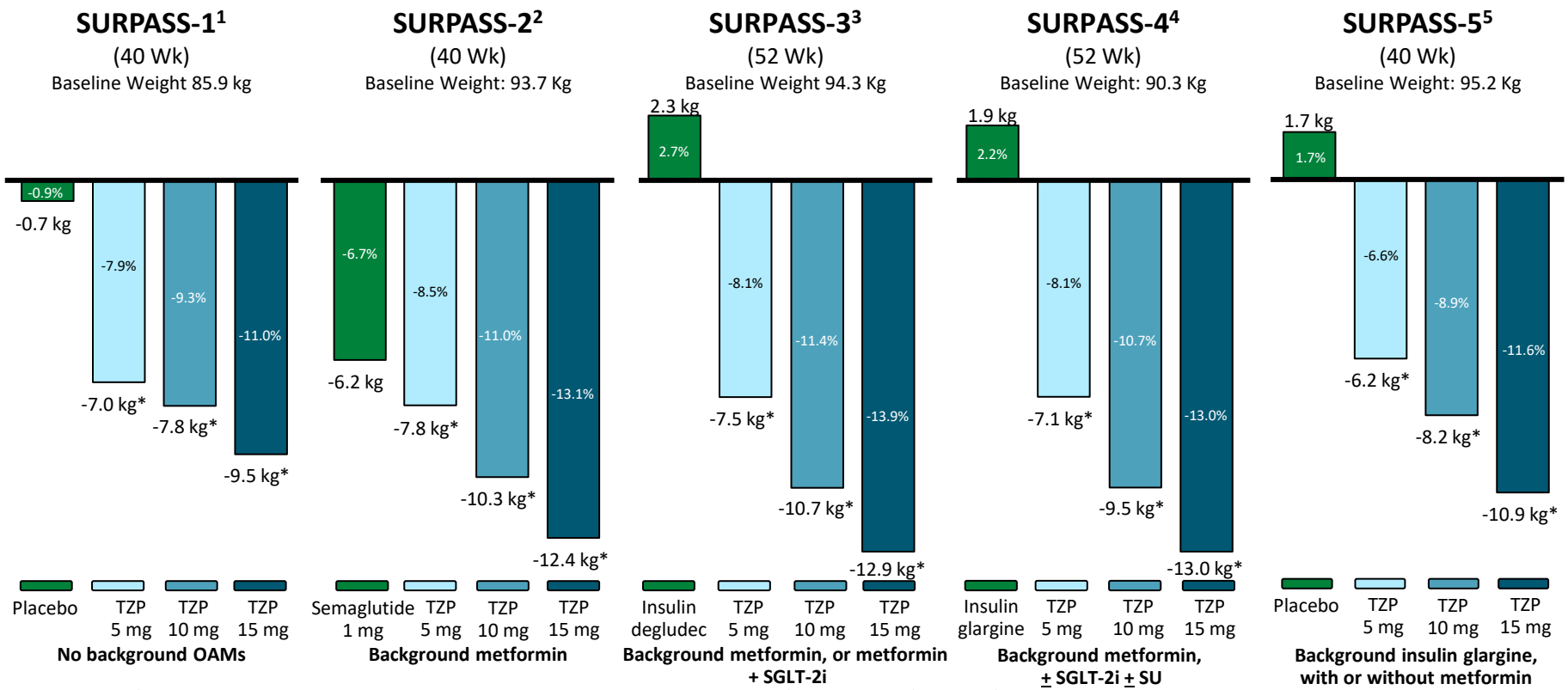


1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;385:503. 3. Giorgino. ADA 2021. Abstr 78-LB. 4. Lily news release. investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 5. Dahl. ADA 2021. Abstr 80-LB.

* Denotes statistical significance to comparator.

Slide credit: clinicaloptions.com

SURPASS: Weight Loss With Tirzepatide in T2D



1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;385:503. 3. Giorgino. ADA 2021. Abstr 78-LB. 4. Lily news release. investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 5. Dahl. ADA 2021. Abstr 80-LB.

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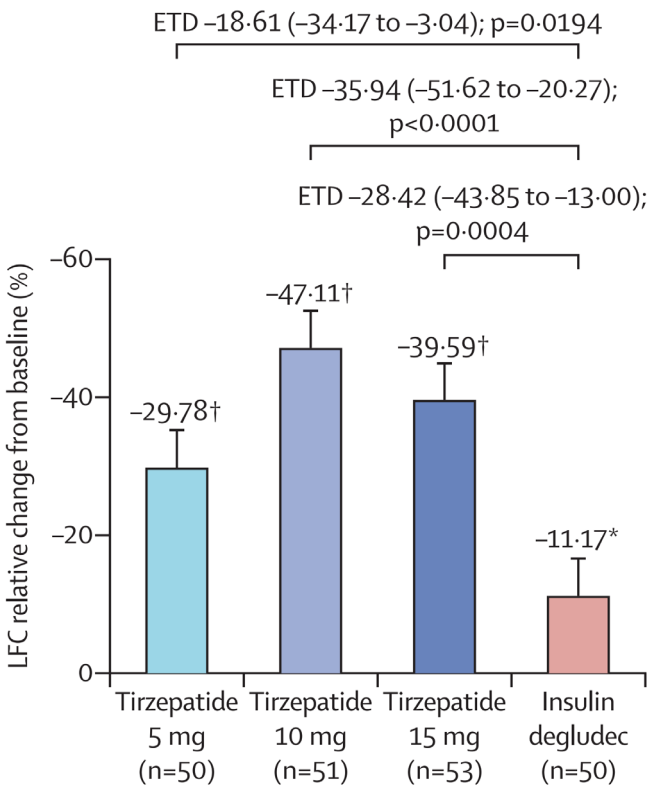
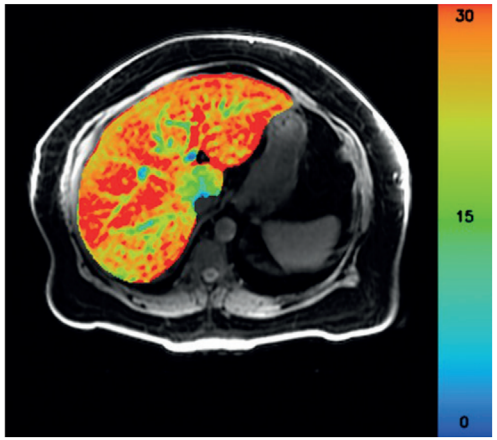
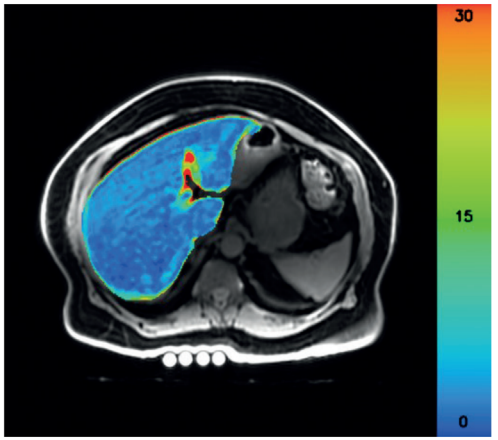
Slide credit: clinicaloptions.com

SURPASS-3 MRI: Tirzepatide Reduces Fat Liver Content





LFC at baseline: 27·3%

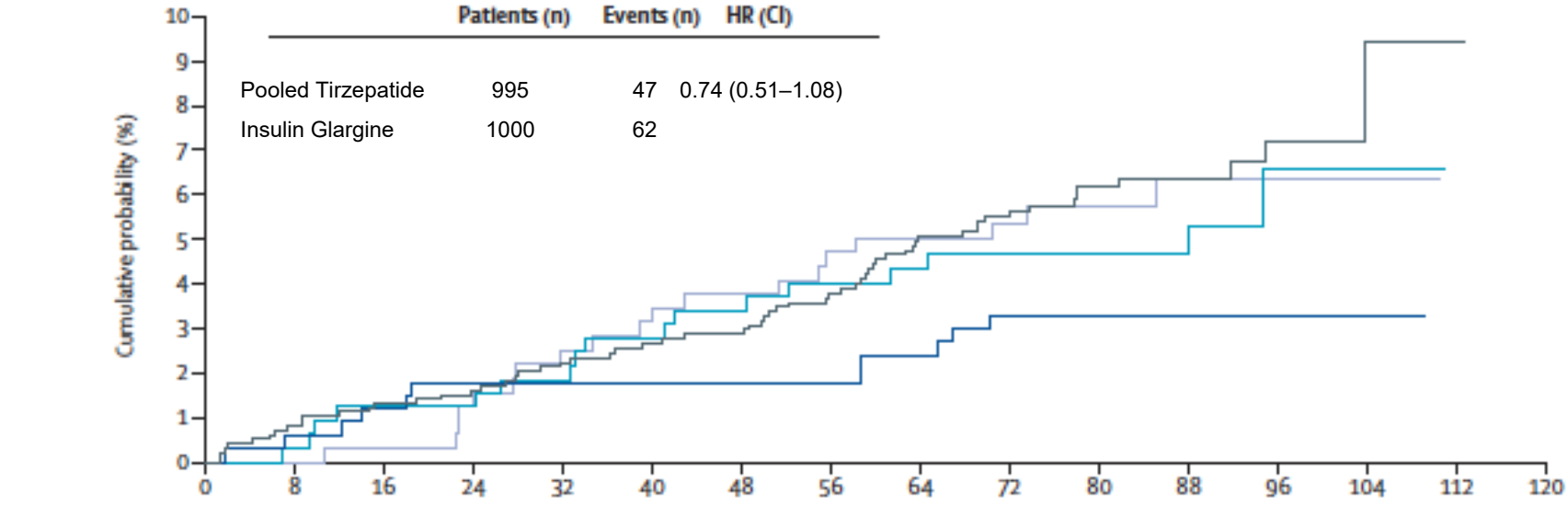


LFC at week 52: 2·6%

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

SURPASS 4 - Kaplan-Meier Plot of Time to First Occurrence



Number at risk

Tirzepatide 5 mg	329	328	322	315	310	307	304	299	297	264	203	128	60	15	0	0
Tirzepatide 10 mg	328	325	321	319	317	314	312	307	305	280	211	137	62	12	0	0
Tirzepatide 15 mg	338	335	332	329	329	328	327	326	321	288	217	144	66	18	0	0
Glargine	1000	982	971	961	947	937	932	916	892	794	584	392	172	37	1	0

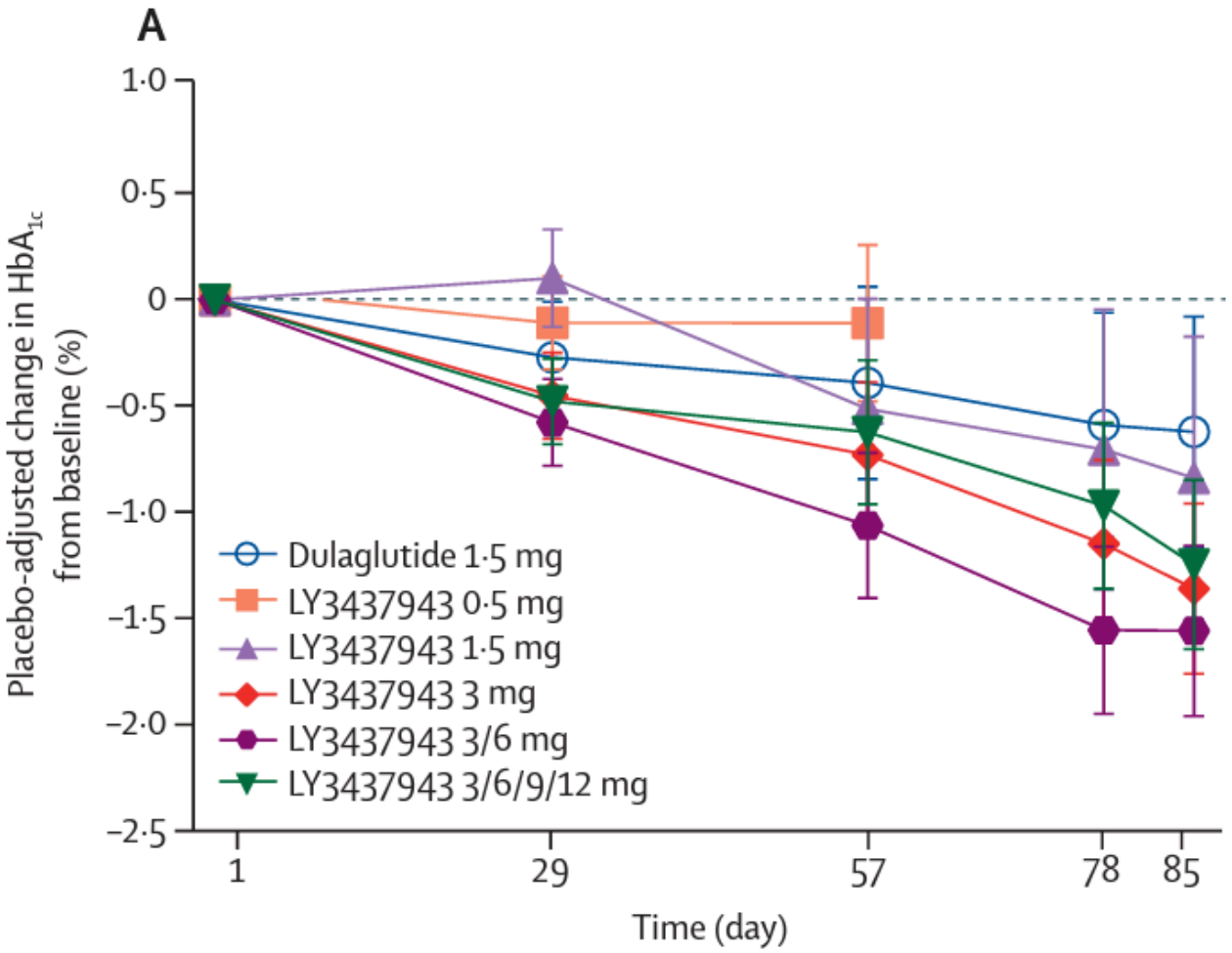
Del Prato S et al ***Lancet*** 2021*;* 398:1811-1824

Il Futuro: doppio, triplo, etc…

	GLP-1RA	GIPRA	GLUCAGONE RA	OSSINTOMODULINA	AMILINA
TIRZEPATIDE	✓	✓			
COTADUTIDE	✓		✓		
PEGAPAMODUTIDE				✓	
MAZDUTIDE				✓	
EFINOPEGDUTIDE				✓	
PEMVIDUTIDE	✓		✓		
CAGRISEMA	✓				✓
RETATRUTIDE	✓	✓	✓		

LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial

Shweta Urva, Tamer Coskun*, Mei Teng Loh, Yu Du, Melissa K Thomas, Sirel Gurbuz, Axel Haupt, Charles T Benson, Martha Hernandez-Illas, David A D'Alessio, Zvonko Milicevic*

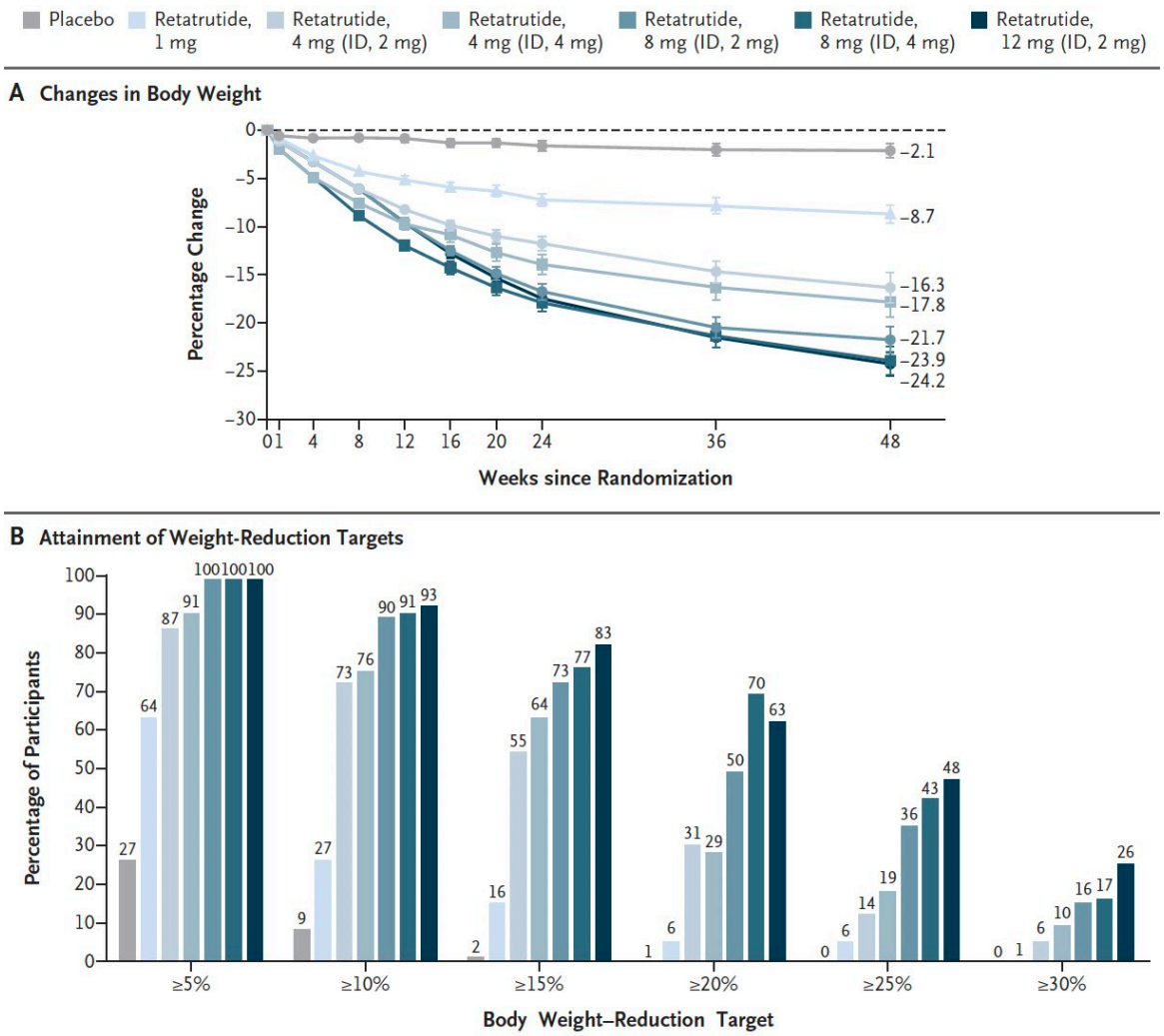


The NEW ENGLAND JOURNAL of MEDICINE

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*



Clinical trials https://doi.org/10.1038/s41591-023-02538-7

A revolution in obesity treatment

Ildiko Lingvay & Shubham Agarwal