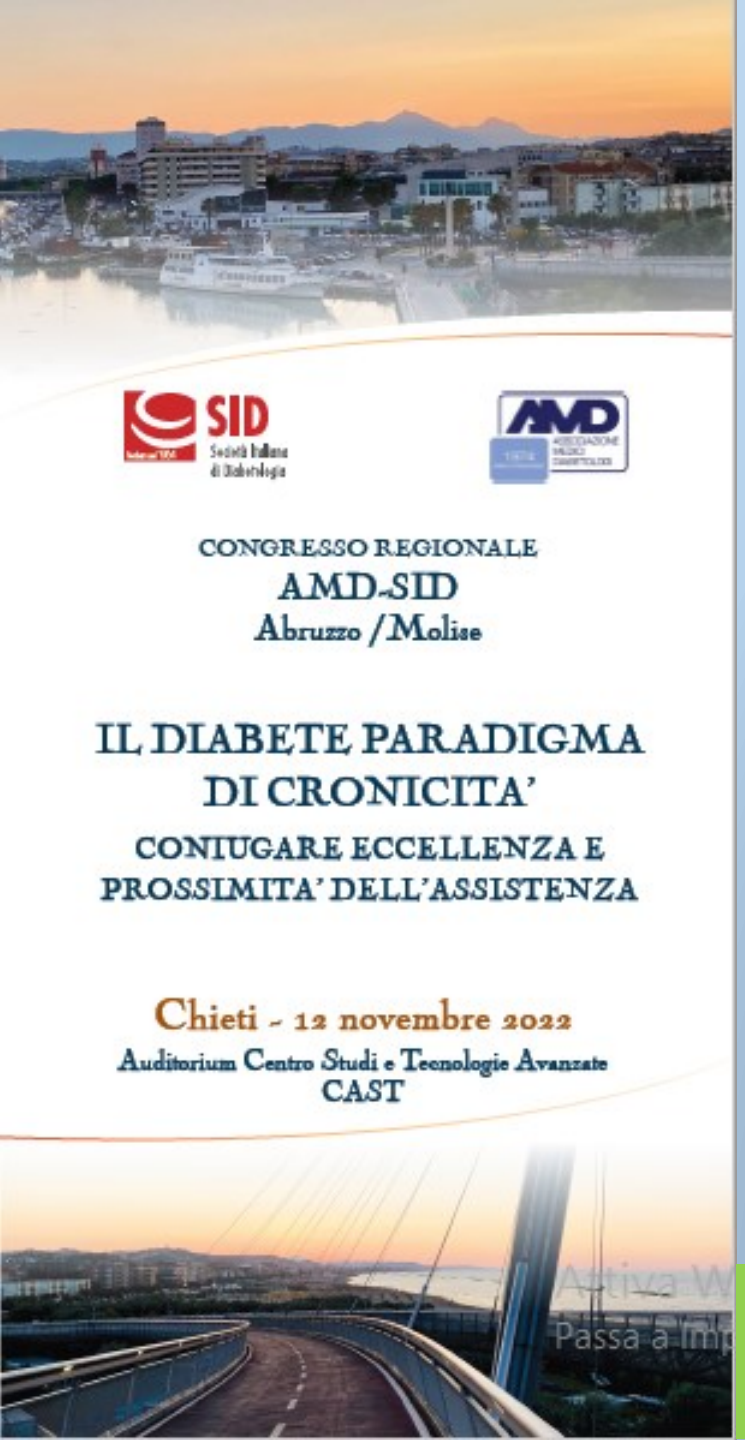
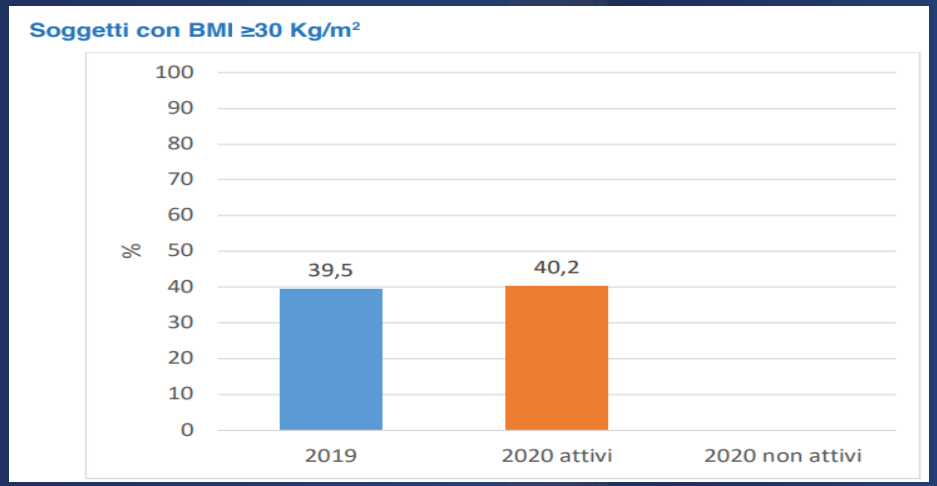
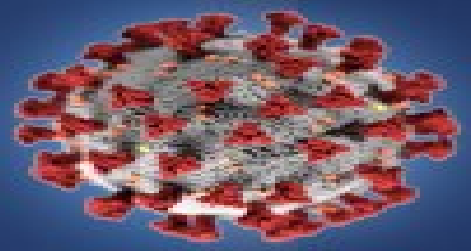


Terapia del Diabete Mellito Tipo 2 oltre la glicemia: le promesse dei nuovi farmaci sull'Obesità

Dott. Angelo Cosimo Gioia
U.O.C. Medicina P.O. Popoli-Servizio di Diabetologia

Annali AMD 2021





Andamento per 7 classi del BMI (%)

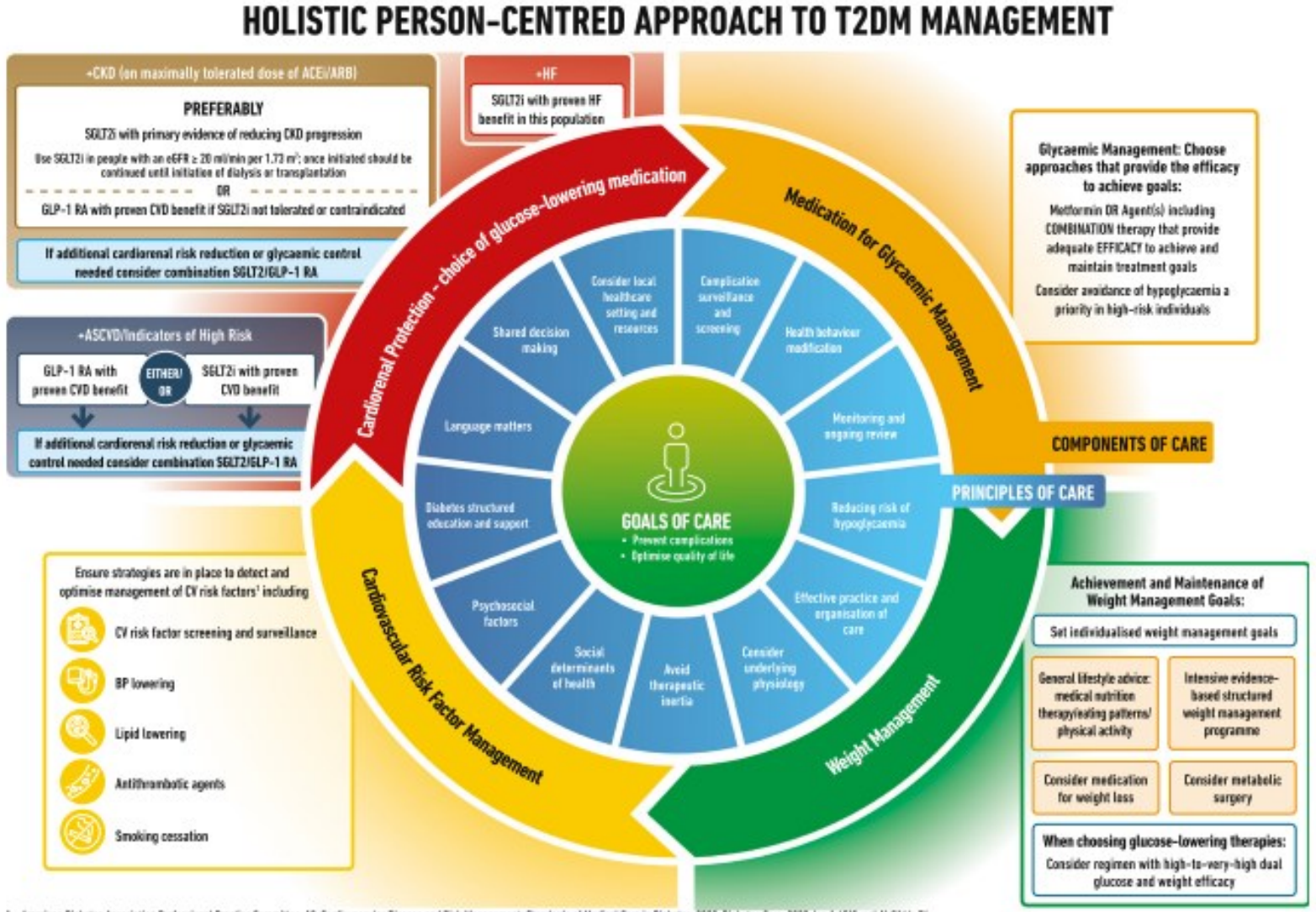
CLASSI BMI (kg/m²)	2019	2020 ATTIVI	2020 NON ATTIVI
<18,5	0,5	0,5	-
18,5-25	21,0	20,5	-
25,1-27,0	15,5	15,3	-
27,1-30,0	23,6	23,6	-
30,1-34,9	25,5	25,7	-
35,0-39,9	9,6	9,9	-
≥40,0	4,3	4,5	-

DIABETE DI TIPO 2

Diabetologia (2022) 65:1925–1966
https://doi.org/10.1007/s00125-022-05787-2

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

DIABETES RESEARCH AND CLINICAL PRACTICE 177 (2021) 108904

Contents available at ScienceDirect

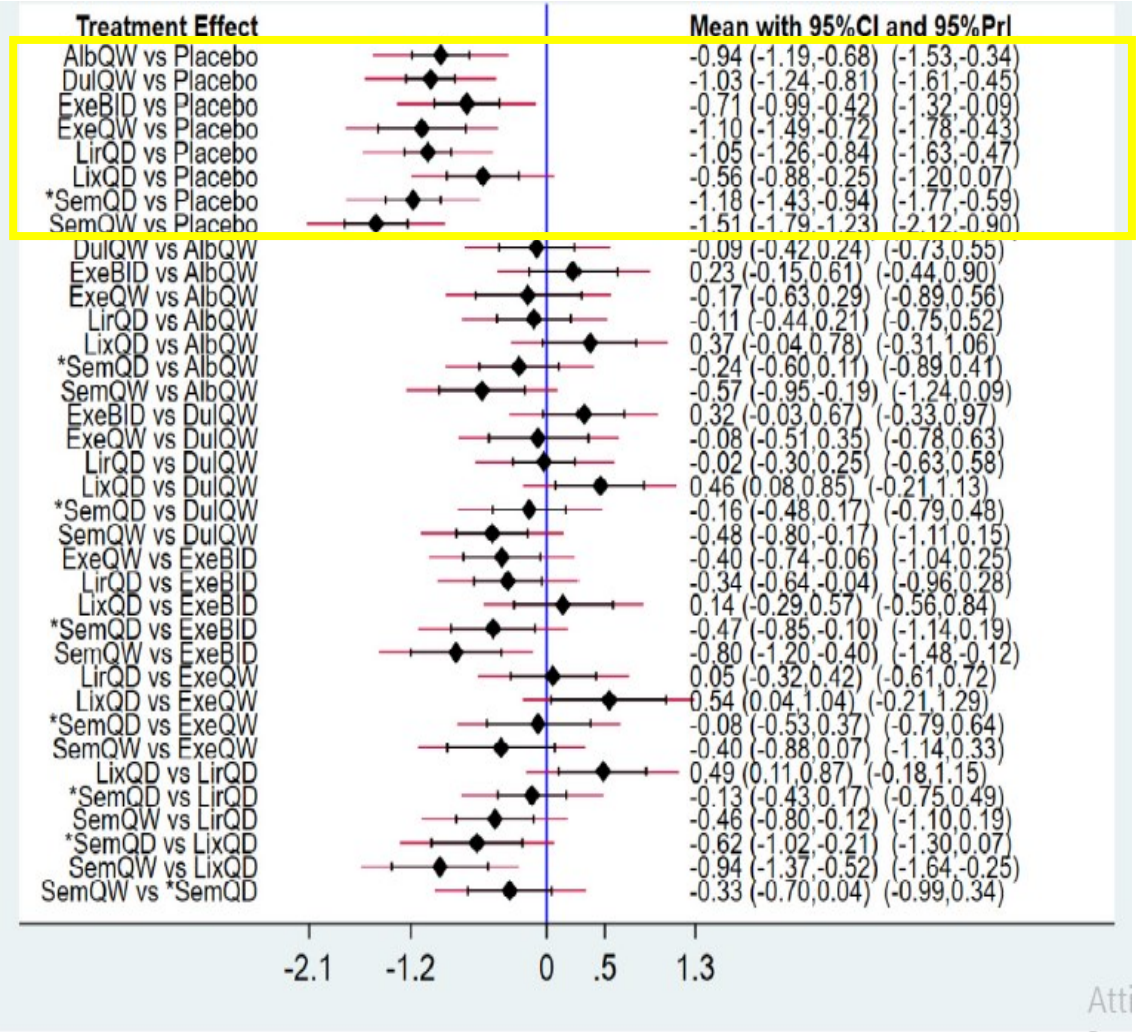
Diabetes Research and Clinical Practice

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

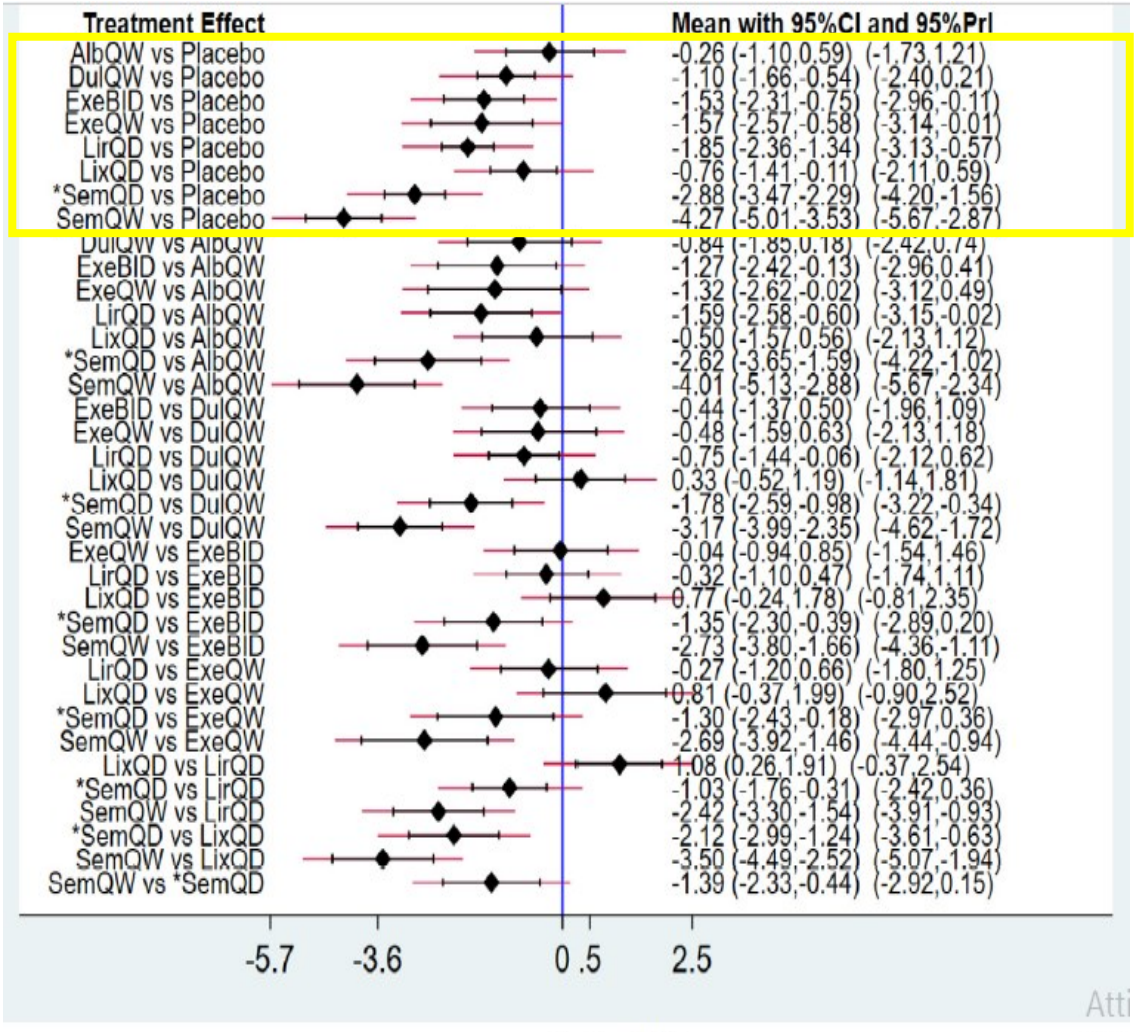
International Diabetes Federation

Review

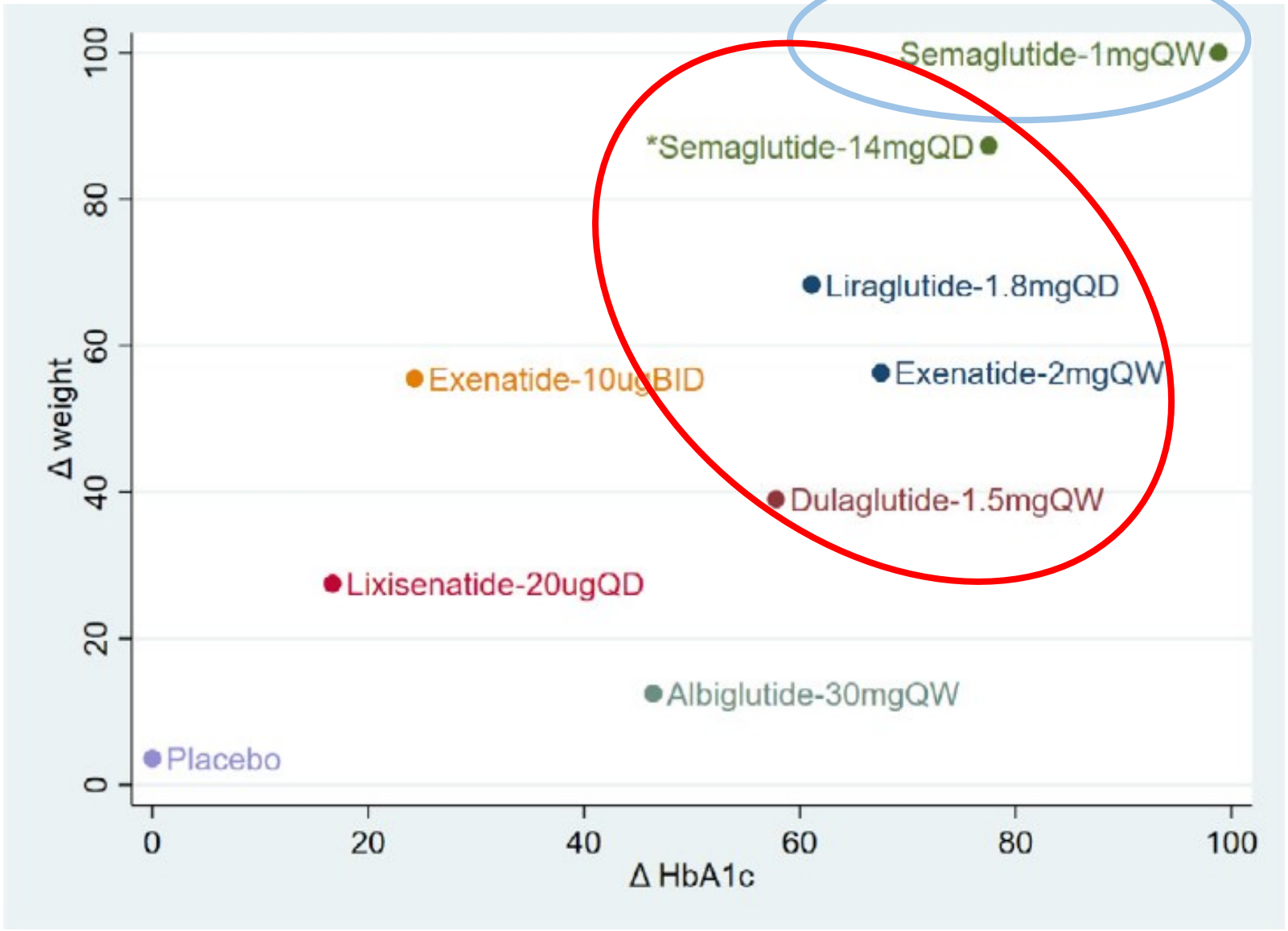
Comparative efficacy and safety of 8 GLP-1RAs in patients with type 2 diabetes: A network meta-analysis



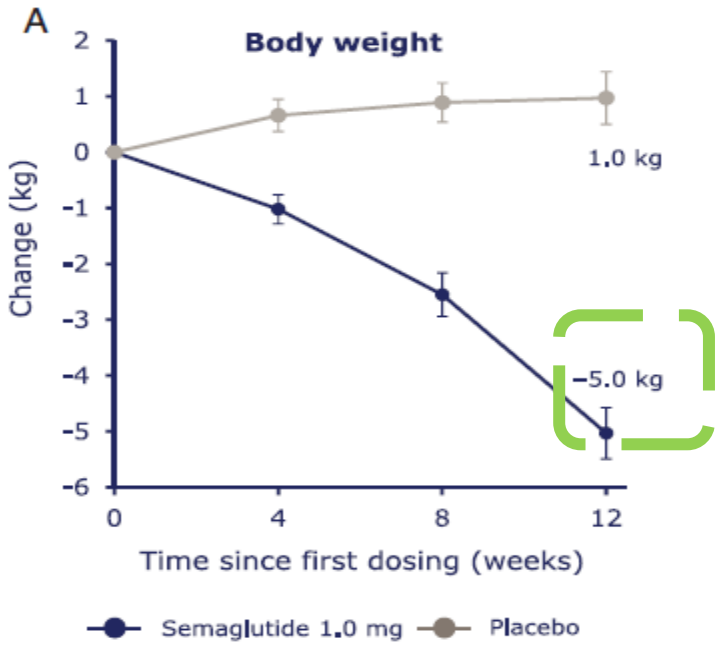
a Δ HbA_{1c}

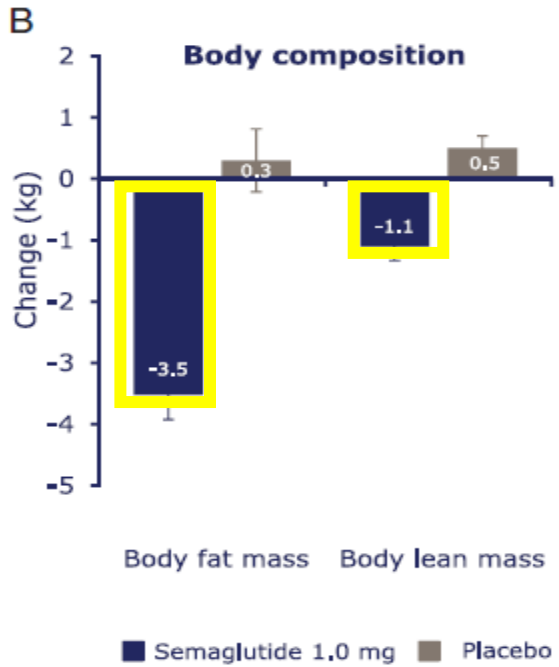


b Δ weight



Diabetes Research and Clinical Practice 177 (2021)





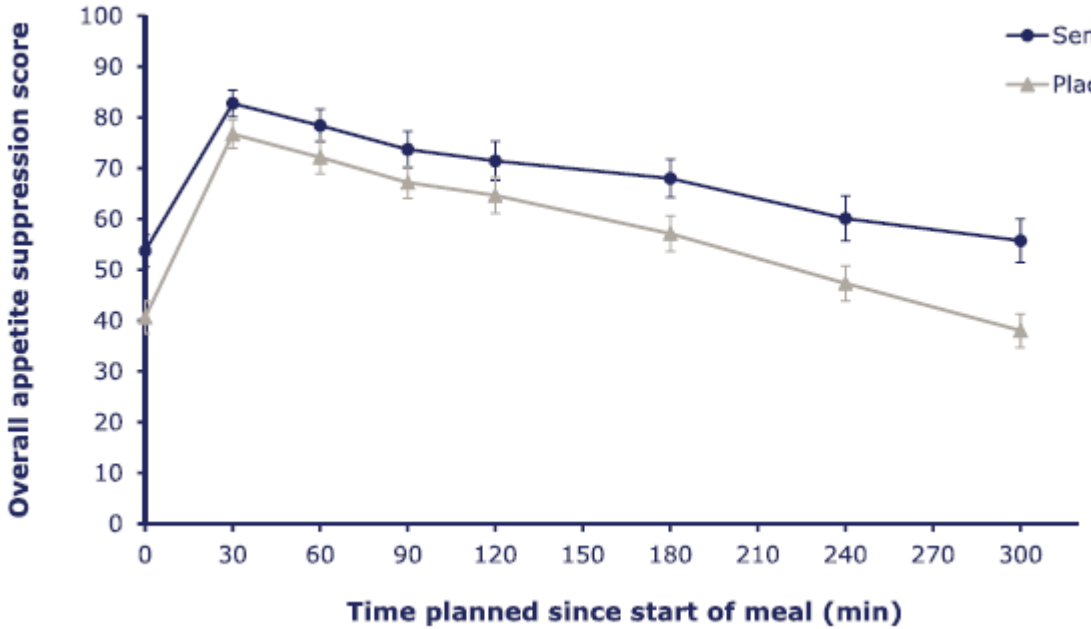
Received: 6 December 2016 | Revised: 27 February 2017 | Accepted: 1 March 2017
DOI: 10.1111/dom.12932

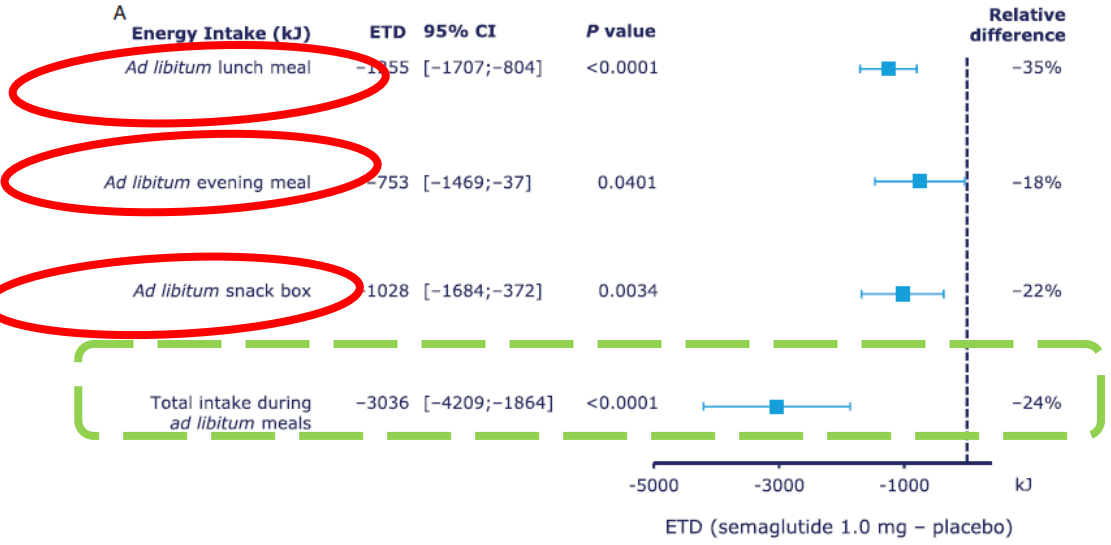
WILEY

ORIGINAL ARTICLE

Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity

John Blundell PhD[1] | Graham Finlayson PhD[1] | Mads Axelsen MD[2] | Anne Flint PhD[2] | Catherine Gibbons PhD[1] | Trine Kvist PhD[2] | Julie B. Hjerpsted PhD[2]





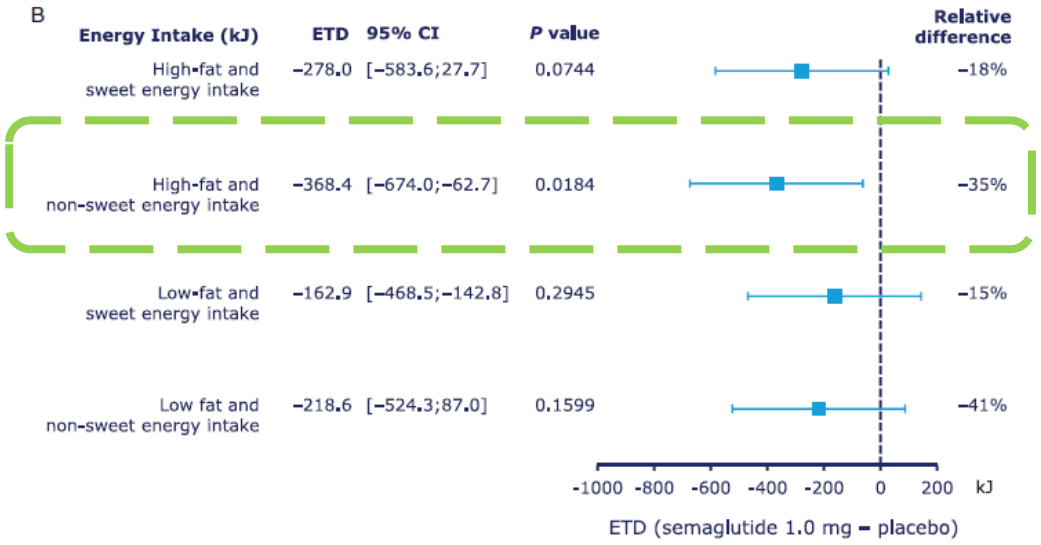


TABLE 1 Energy and food intake during *ad libitum* meals and duration of *ad libitum* lunch

	FAS	N	Estimated mean [95% CI]	ETD[1] [95% CI]	P value
Ad libitum lunch					
Energy intake (kJ)					
Placebo	28	28	3634 [3132; 4136]		
Semaglutide 1.0 mg	30	28	2378 [1876; 2881]	−1255 [−1707; −804]	P < .0001
Food intake (g)					
Placebo	28	28	645 [556; 735]		
Semaglutide 1.0 mg	30	28	424 [334; 514]	−221 [−301; −142]	P < .0001
Duration (min)					
Placebo	28	28	122 [10.5; 13.9]		
Semaglutide 1.0 mg	30	28	107 [9.0; 12.4]	−1.5 [−2.4; −0.6]	P = .0018
Ad libitum evening meal					
Energy intake (kJ)					
Placebo	28	28	4214 [3618; 4809]		
Semaglutide 1.0 mg	30	28	3461 [2865; 4057]	−753 [−1469; −36.6]	P = .0401
Food intake (g)					
Placebo	28	28	557 [481; 634]		
Semaglutide 1.0 mg	30	28	446 [369; 522]	−112 [−201; −22.3]	P = .0164
Ad libitum evening snack box					
Energy intake (kJ)					
Placebo	28	28	4573 [3967; 5178]		
Semaglutide 1.0 mg	30	28	3545 [2939; 4150]	−1028 [−1684; −372]	P = .0034
Food intake (g)					
Placebo	28	28	257 [223; 290]		
Semaglutide 1.0 mg	30	28	200 [166; 233]	−57.3 [−94.0; −20.6]	P = .0035
Total intake during *ad libitum* meals					
Energy intake (kJ)					
Placebo	28	28	12421 [11214; 13627]		
Semaglutide 1.0 mg	30	28	9384 [8178; 10591]	−3036 [−4209; −1864]	P < .0001
Food intake (g)					
Placebo	28	28	1459 [1315; 1604]		
Semaglutide 1.0 mg	30	28	1069 [925; 1213]	−391 [−505; −276]	P < .0001

Abbreviation: FAS, full analysis set.

[1] Semaglutide 1.0 mg − placebo.

Diabetes Obes Metab. 2017;19:1242–1251

ESC European Society of Cardiology
European Heart Journal (2020) 41, 255–323
doi:10.1093/eurheartj/ehz486

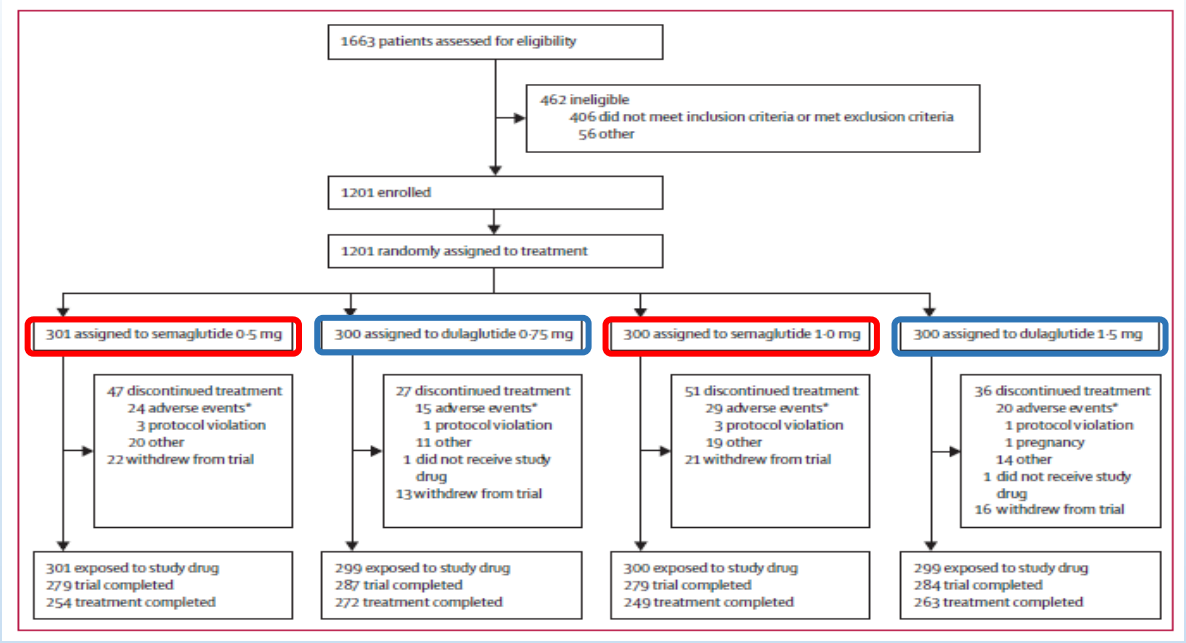
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Recommendations for glucose-lowering treatment for patients with diabetes

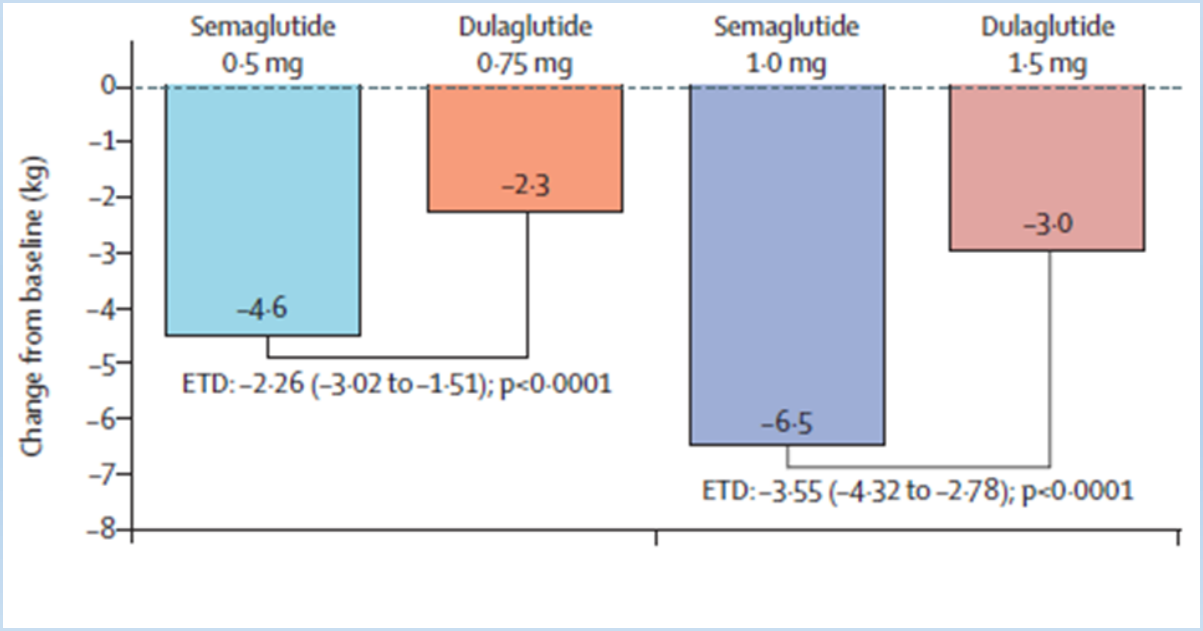
Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

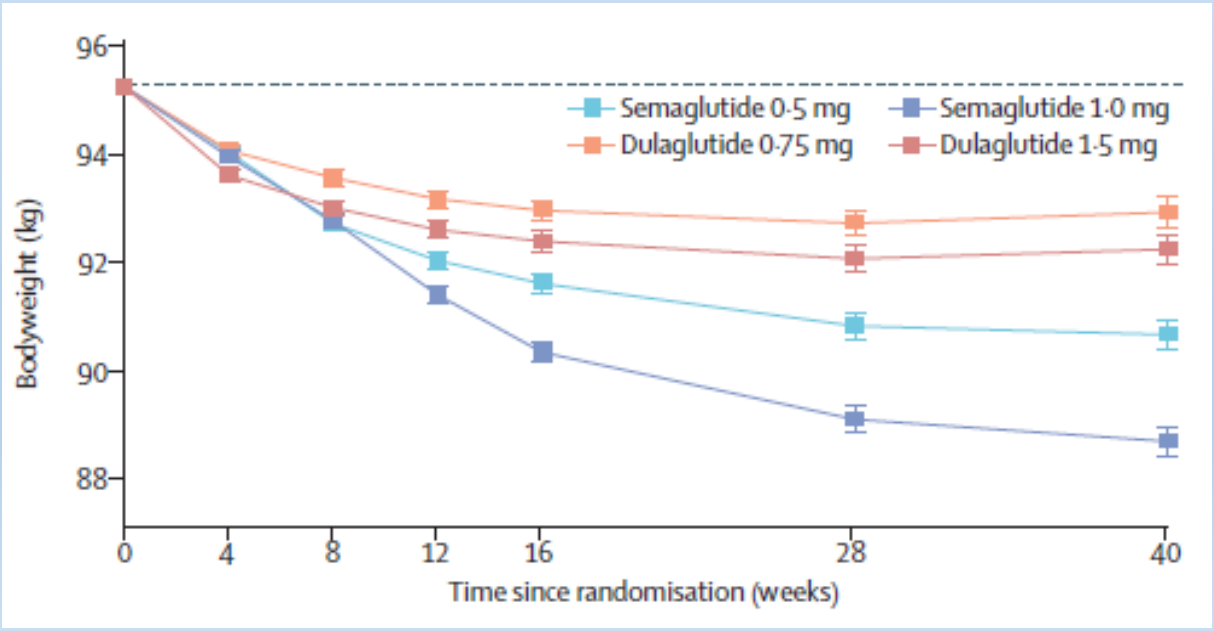
Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

Richard E Pratley, Vanita R Aroda, Ildiko Lingvay, Jörg Lüdemann, Camilla Andreassen, Andrea Navarria, Adie Viljoen, on behalf of the SUSTAIN 7 investigators



BMI medio nei 4 gruppi: 33 Kg/m^2





Received: 13 August 2021 | Revised: 5 October 2021 | Accepted: 5 October 2021
DOI: 10.1002/oby.23331

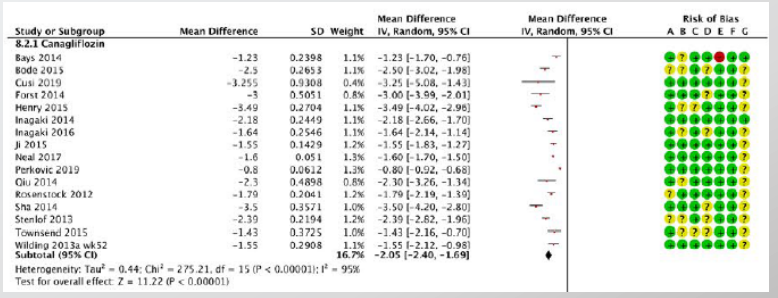
Obesity
THE OBESITY SOCIETY
WILEY

ORIGINAL ARTICLE

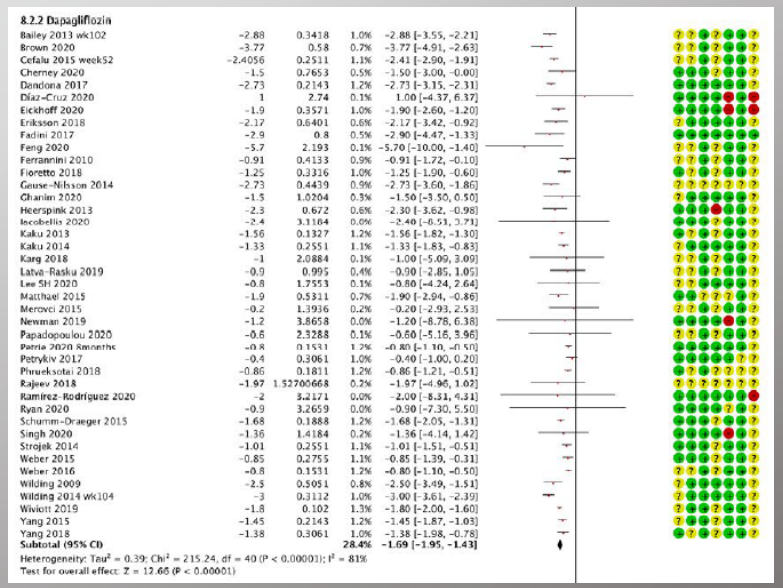
Clinical Trials and Investigations

SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials

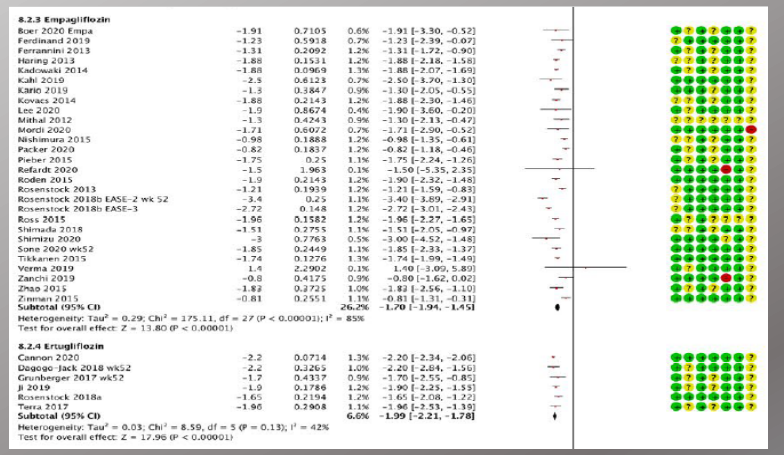
VARIZIONI DI PESO DA SGLTi



Canagliflozin -2,05

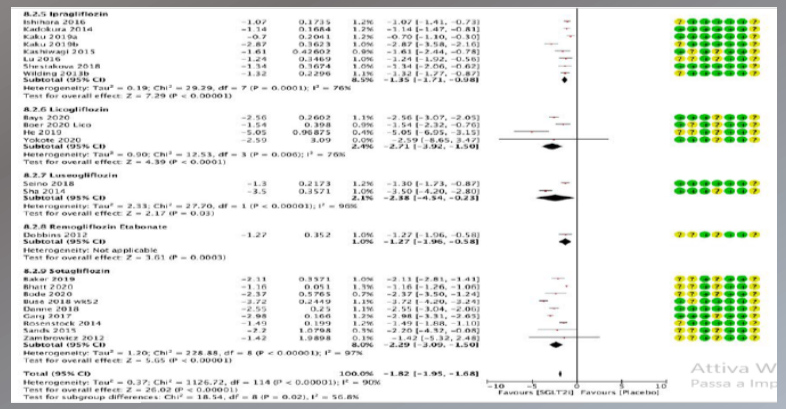


Dapagliflozin -1,69



Empagliflozin -1,70

Ertugliflozin -1,99



Ipragliflozin -1,35

Licogliflozin -2,71

Luseogliflozin -2,38

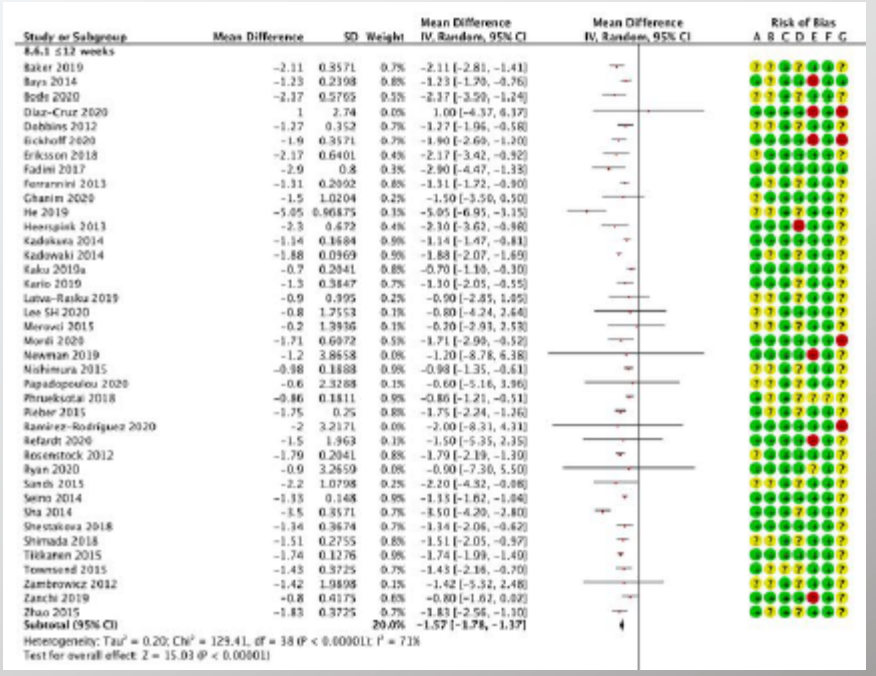
Remogliflozin -1,27

Sotagliflozin -2,29

TOTALE -1,82

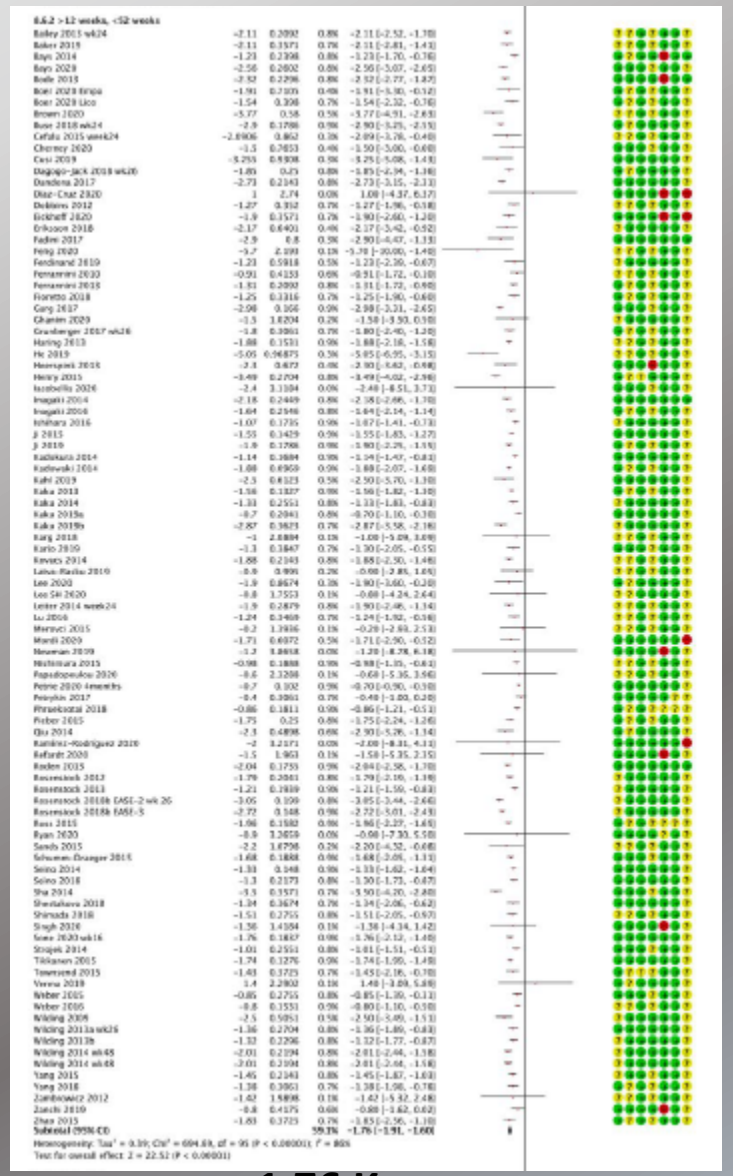
VARIZIONI DI PESO DA SGLTi E DURATA DEL FOLLOW-UP

<12 SETTIMANE



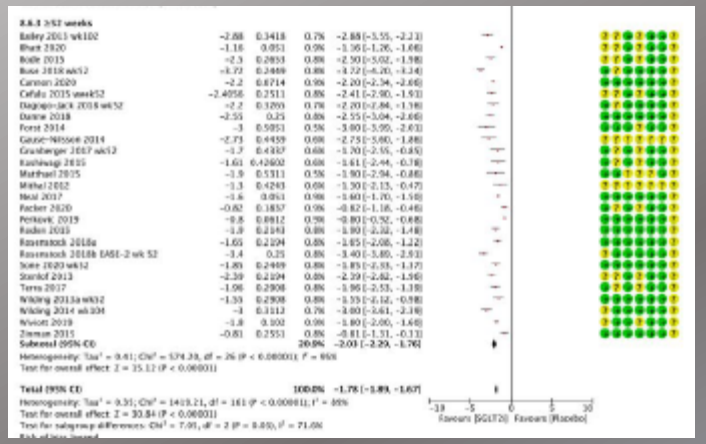
-1,57 Kg

12-52 SETTIMANE



-1,76 Kg

>52 SETTIMANE

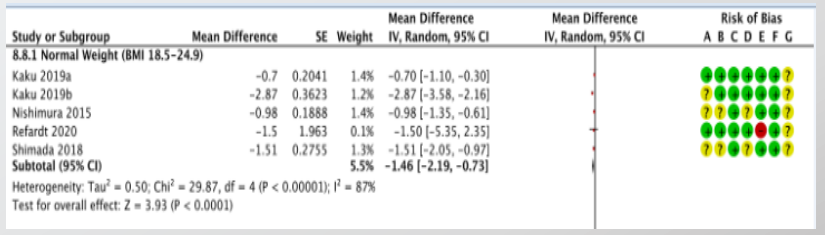


-2,03 Kg

Obesity (Silver Spring). 2022;30:117–128

VARIZIONI DI PESO DA SGLTi E GRADO DI BMI

BMI 18,5-24,9

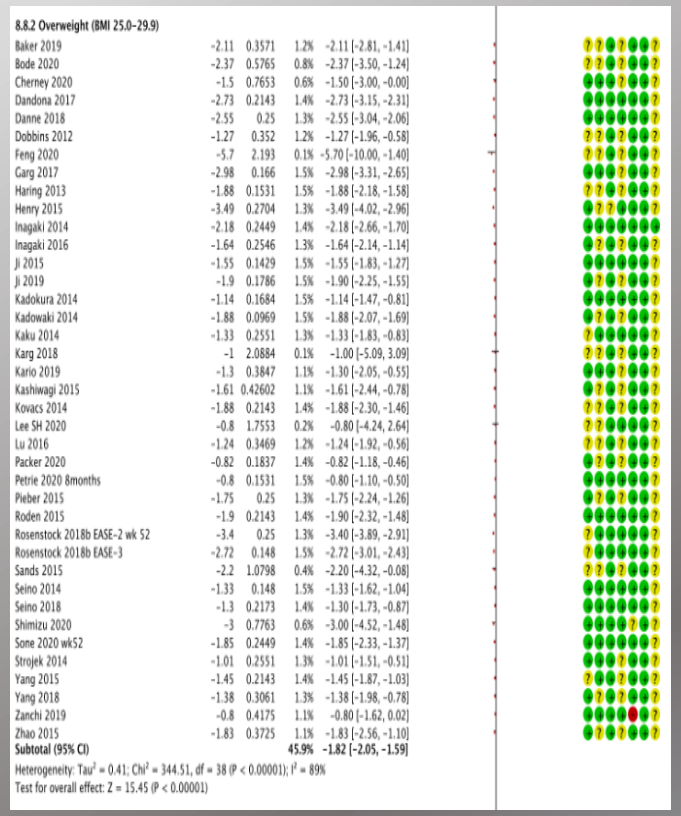


Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
8.8.1 Normal Weight (BMI 18.5–24.9)				
Kaku 2019a	−0.7	0.2041	1.4%	−0.70 [−1.10, −0.30]
Kaku 2019b	−2.87	0.3623	1.2%	−2.87 [−3.58, −2.16]
Nishimura 2015	−0.98	0.1888	1.4%	−0.98 [−1.35, −0.61]
Refardt 2020	−1.5	1.963	0.1%	−1.50 [−5.35, 2.35]
Shimada 2018	−1.51	0.2755	1.3%	−1.51 [−2.05, −0.97]
Subtotal (95% CI)			**5.5%**	**−1.46 [−2.19, −0.73]**

Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 29.87$, df = 4 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: $Z = 3.93$ ($P < 0.0001$)

-1,46 Kg p<0,001

BMI 25-29,9

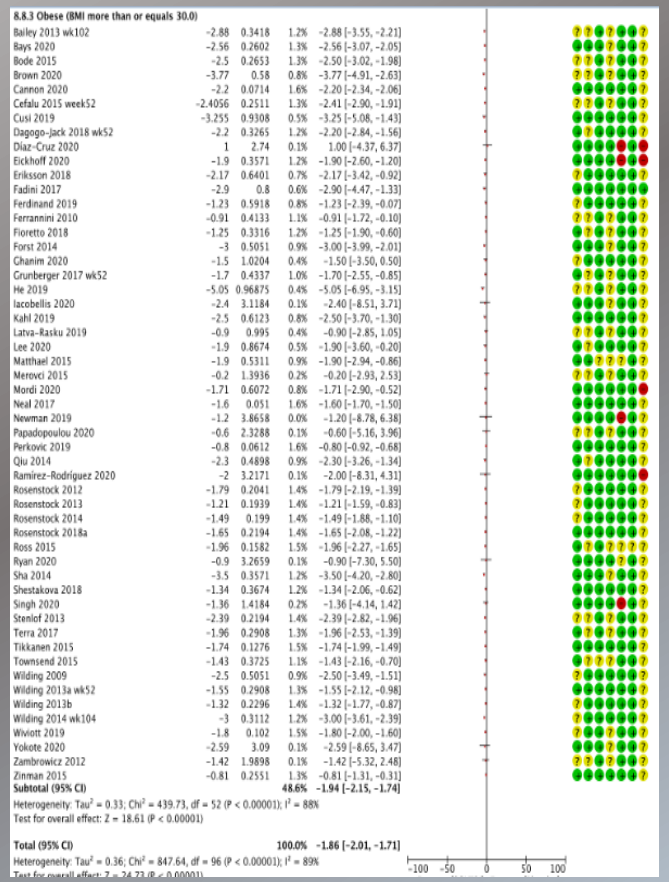


8.8.2 Overweight (BMI 25.0–29.9)				
Baker 2019	−2.11	0.3571	1.2%	−2.11 [−2.81, −1.41]
Bode 2020	−2.37	0.5765	0.8%	−2.37 [−3.50, −1.24]
Cherney 2020	−1.5	0.7653	0.6%	−1.50 [−3.00, −0.00]
Dandona 2017	−2.73	0.2143	1.4%	−2.73 [−3.15, −2.31]
Danne 2018	−2.55	0.25	1.3%	−2.55 [−3.04, −2.06]
Dobbins 2012	−1.27	0.352	1.2%	−1.27 [−1.96, −0.58]
Feng 2020	−5.7	2.193	0.1%	−5.70 [−10.00, −1.40]
Garg 2017	−2.98	0.166	1.5%	−2.98 [−3.31, −2.65]
Haring 2013	−1.88	0.1531	1.5%	−1.88 [−2.18, −1.58]
Henry 2015	−3.49	0.2704	1.3%	−3.49 [−4.02, −2.96]
Inagaki 2014	−2.18	0.2449	1.4%	−2.18 [−2.66, −1.70]
Inagaki 2016	−1.64	0.2546	1.3%	−1.64 [−2.14, −1.14]
Ji 2015	−1.55	0.1429	1.5%	−1.55 [−1.83, −1.27]
Ji 2019	−1.9	0.1786	1.5%	−1.90 [−2.25, −1.55]
Kadokura 2014	−1.14	0.1684	1.5%	−1.14 [−1.47, −0.81]
Kadowaki 2014	−1.88	0.0969	1.5%	−1.88 [−2.07, −1.69]
Kaku 2014	−1.33	0.2551	1.3%	−1.33 [−1.83, −0.83]
Karg 2018	−1	2.0884	0.1%	−1.00 [−5.09, 3.09]
Kario 2019	−1.3	0.3847	1.1%	−1.30 [−2.05, −0.55]
Kashiwagi 2015	−1.61	0.42602	1.1%	−1.61 [−2.44, −0.78]
Kovacs 2014	−1.88	0.2143	1.4%	−1.88 [−2.30, −1.46]
Lee SH 2020	−0.8	1.7553	0.2%	−0.80 [−4.24, 2.64]
Lu 2016	−1.24	0.3469	1.2%	−1.24 [−1.92, −0.56]
Packer 2020	−0.82	0.1837	1.4%	−0.82 [−1.18, −0.46]
Petrie 2020 8months	−0.8	0.1531	1.5%	−0.80 [−1.10, −0.50]
Pieber 2015	−1.75	0.25	1.3%	−1.75 [−2.24, −1.26]
Roden 2015	−1.9	0.2143	1.4%	−1.90 [−2.32, −1.48]
Rosenstock 2018b EASE-2 wk 52	−3.4	0.25	1.3%	−3.40 [−3.89, −2.91]
Rosenstock 2018b EASE-3	−2.72	0.148	1.5%	−2.72 [−3.01, −2.43]
Sands 2015	−2.2	1.0798	0.4%	−2.20 [−4.32, −0.08]
Seino 2014	−1.33	0.148	1.5%	−1.33 [−1.62, −1.04]
Seino 2018	−1.3	0.2173	1.4%	−1.30 [−1.73, −0.87]
Shimizu 2020	−3	0.7763	0.6%	−3.00 [−4.52, −1.48]
Sone 2020 wk52	−1.85	0.2449	1.4%	−1.85 [−2.33, −1.37]
Strojek 2014	−1.01	0.2551	1.3%	−1.01 [−1.51, −0.51]
Yang 2015	−1.45	0.2143	1.4%	−1.45 [−1.87, −1.03]
Yang 2018	−1.38	0.3061	1.3%	−1.38 [−1.98, −0.78]
Zanchi 2019	−0.8	0.4175	1.1%	−0.80 [−1.62, 0.02]
Zhao 2015	−1.83	0.3725	1.1%	−1.83 [−2.56, −1.10]
Subtotal (95% CI)			**45.9%**	**−1.82 [−2.05, −1.59]**

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 344.51$, df = 38 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 15.45$ ($P < 0.00001$)

-1,82 Kg<0,001

BMI >30



8.8.3 Obese (BMI more than or equals 30.0)				
Bailey 2013 wk102	−2.88	0.3418	1.2%	−2.88 [−3.55, −2.21]
Bays 2020	−2.56	0.2602	1.3%	−2.56 [−3.07, −2.05]
Bode 2015	−2.5	0.2653	1.3%	−2.50 [−3.02, −1.98]
Brown 2020	−3.77	0.58	0.8%	−3.77 [−4.91, −2.63]
Cannon 2020	−2.2	0.0714	1.6%	−2.20 [−2.34, −2.06]
Cefalu 2015 week52	−2.4056	0.2511	1.3%	−2.41 [−2.90, −1.91]
Cusi 2019	−3.255	0.9308	0.5%	−3.25 [−5.08, −1.43]
Dagogo-Jack 2018 wk52	−2.2	0.3265	1.2%	−2.20 [−2.84, −1.56]
Diaz-Cruz 2020	1	2.74	0.1%	1.00 [−4.37, 6.37]
Eickhoff 2020	−1.9	0.3571	1.2%	−1.90 [−2.60, −1.20]
Eriksson 2018	−2.17	0.6401	0.7%	−2.17 [−3.42, −0.92]
Fadini 2017	−2.9	0.8	0.6%	−2.90 [−4.47, −1.33]
Ferdinand 2019	−1.23	0.5918	0.8%	−1.23 [−2.39, −0.07]
Ferrannini 2010	−0.91	0.4133	1.1%	−0.91 [−1.72, −0.10]
Fioretto 2018	−1.25	0.3316	1.2%	−1.25 [−1.90, −0.60]
Forst 2014	−3	0.5051	0.9%	−3.00 [−3.99, −2.01]
Ghanim 2020	−1.5	1.0204	0.4%	−1.50 [−3.50, 0.50]
Grunberger 2017 wk52	−1.7	0.4337	1.0%	−1.70 [−2.55, −0.85]
He 2019	−5.05	0.96875	0.4%	−5.05 [−6.95, −3.15]
Iacobellis 2020	−2.4	3.1184	0.1%	−2.40 [−8.51, 3.71]
Kahl 2019	−2.5	0.6123	0.8%	−2.50 [−3.70, −1.30]
Latva-Rasku 2019	−0.9	0.995	0.4%	−0.90 [−2.85, 1.05]
Lee 2020	−1.9	0.8674	0.5%	−1.90 [−3.60, −0.20]
Matthael 2015	−1.9	0.5311	0.9%	−1.90 [−2.94, −0.86]
Merovci 2015	−0.2	1.3936	0.2%	−0.20 [−2.93, 2.53]
Mordi 2020	−1.71	0.6072	0.8%	−1.71 [−2.90, −0.52]
Neal 2017	−1.6	0.051	1.6%	−1.60 [−1.70, −1.50]
Newman 2019	−1.2	3.8658	0.0%	−1.20 [−8.78, 6.38]
Papadopoulou 2020	−0.6	2.3288	0.1%	−0.60 [−5.16, 3.96]
Perkovic 2019	−0.8	0.0612	1.6%	−0.80 [−0.92, −0.68]
Qiu 2014	−2.3	0.4898	0.9%	−2.30 [−3.26, −1.34]
Ramírez-Rodríguez 2020	−2	3.2171	0.1%	−2.00 [−8.31, 4.31]
Rosenstock 2012	−1.79	0.2041	1.4%	−1.79 [−2.19, −1.39]
Rosenstock 2013	−1.21	0.1939	1.4%	−1.21 [−1.59, −0.83]
Rosenstock 2014	−1.49	0.199	1.4%	−1.49 [−1.88, −1.10]
Rosenstock 2018a	−1.65	0.2194	1.4%	−1.65 [−2.08, −1.22]
Ross 2015	−1.96	0.1582	1.5%	−1.96 [−2.27, −1.65]
Ryan 2020	−0.9	3.2659	0.1%	−0.90 [−7.30, 5.50]
Sha 2014	−3.5	0.3571	1.2%	−3.50 [−4.20, −2.80]
Shestakova 2018	−1.34	0.3674	1.2%	−1.34 [−2.06, −0.62]
Singh 2020	−1.36	1.4184	0.2%	−1.36 [−4.14, 1.42]
Stenlof 2013	−2.39	0.2194	1.4%	−2.39 [−2.82, −1.96]
Terra 2017	−1.96	0.2908	1.3%	−1.96 [−2.53, −1.39]
Tikkanen 2015	−1.74	0.1276	1.5%	−1.74 [−1.99, −1.49]
Townsend 2015	−1.43	0.3725	1.1%	−1.43 [−2.16, −0.70]
Wilding 2009	−2.5	0.5051	0.9%	−2.50 [−3.49, −1.51]
Wilding 2013a wk52	−1.55	0.2908	1.3%	−1.55 [−2.12, −0.98]
Wilding 2013b	−1.32	0.2296	1.4%	−1.32 [−1.77, −0.87]
Wilding 2014 wk104	−3	0.3112	1.2%	−3.00 [−3.61, −2.39]
Wiviott 2019	−1.8	0.102	1.5%	−1.80 [−2.00, −1.60]
Yokote 2020	−2.59	3.09	0.1%	−2.59 [−8.65, 3.47]
Zambrowicz 2012	−1.42	1.9898	0.1%	−1.42 [−5.32, 2.48]
Zinman 2015	−0.81	0.2551	1.3%	−0.81 [−1.31, −0.31]
Subtotal (95% CI)			**48.6%**	**−1.94 [−2.15, −1.74]**

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 439.73$, df = 52 ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: $Z = 18.61$ ($P < 0.00001$)

Total (95% CI)			**100.0%**	**−1.86 [−2.01, −1.71]**

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 847.64$, df = 96 ($P < 0.00001$); $I^2 = 89\%$

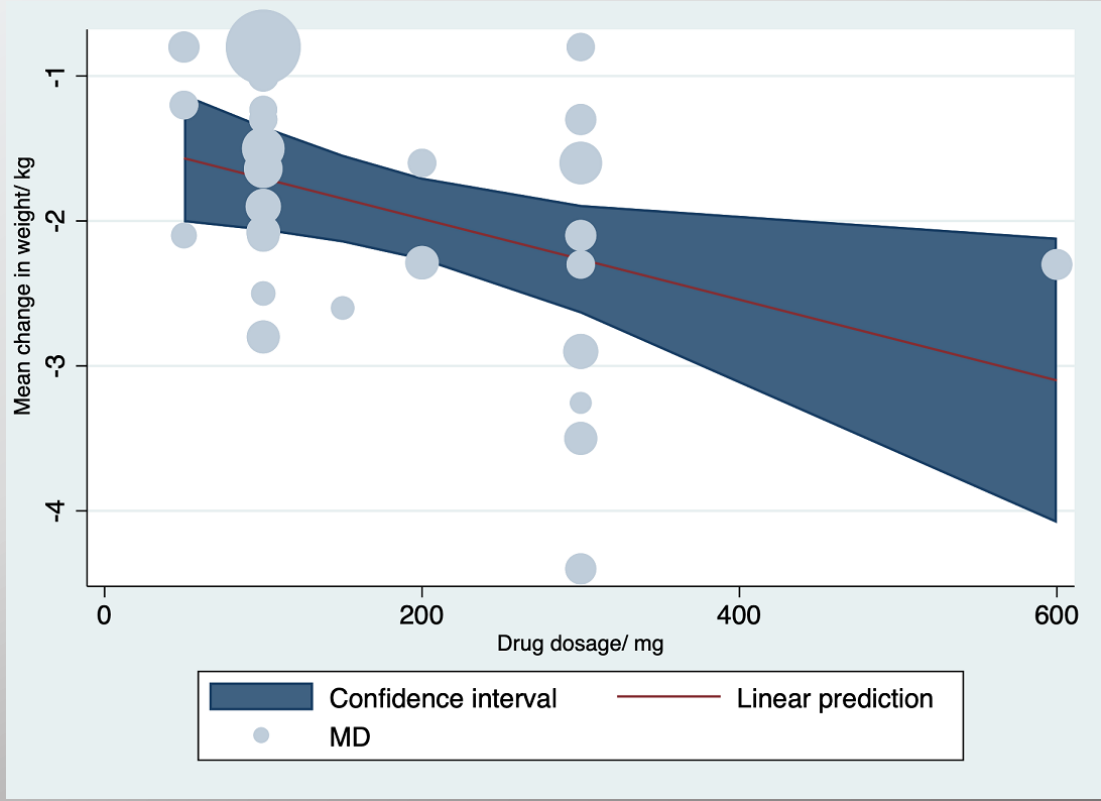
−100 −50 0 50 100

-1,94 Kg p <0,001

Obesity (Silver Spring). 2022;30:117–128

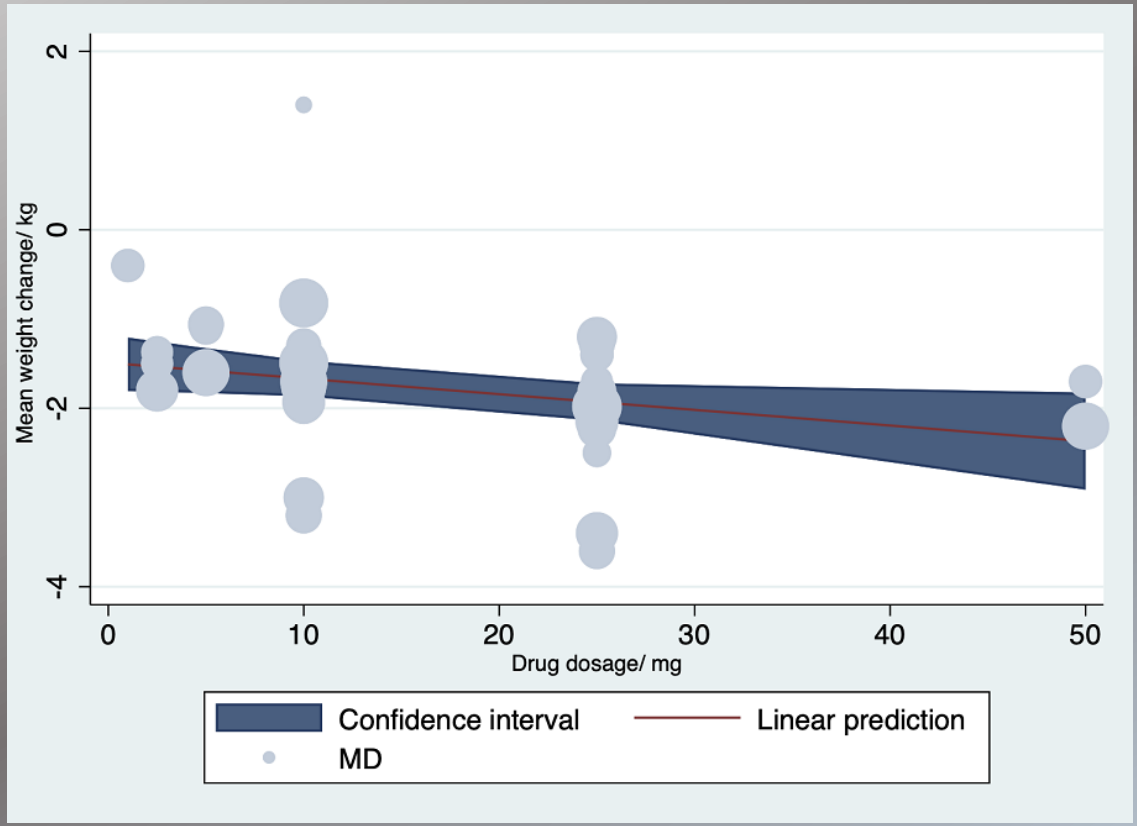
VARIZIONI DI PESO DA SGLTi E DOSE DIPENDENZA

CANAGLIFLOZIN



ogni incremento di dose di 5 mg
riduzione del peso di 0,0139Kg p 0,02

EMPAGLIFLOZIN



ogni incremento di dose di 5 mg
riduzione del peso di 0,0878Kg p 0,03

Obesity (Silver Spring). 2022;30:117–128

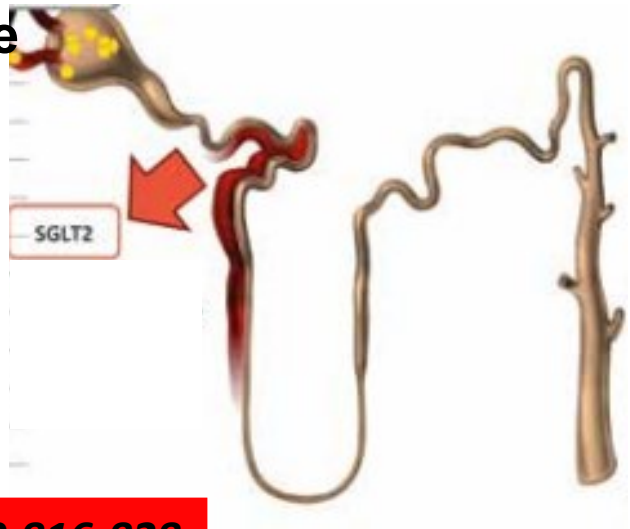
LIMITI E PROPOSITI NELLA PERDITA DI PESO DA SGLT2i

Ipotesi:
SGLT2→75 g glucosuria die→300 Kcal/die=1,3 MJ
15 MJ→ ~0,5 Kg di peso/settimana
Tesi
Perdita di peso dopo 24 settimane

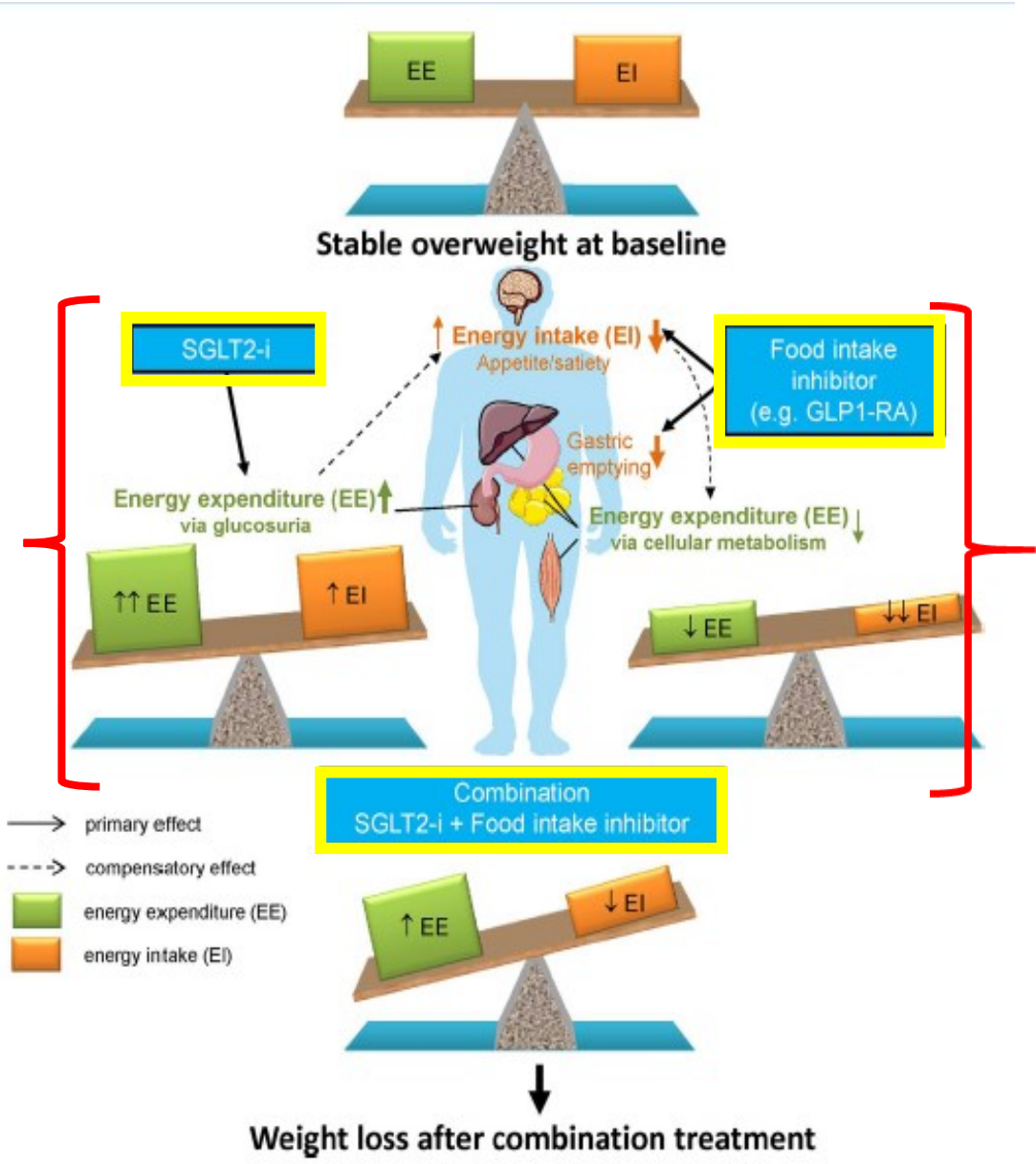
Risoluzione
1,3 Mj x 7 giorni= 9,1 Mj
9,1 Mj x 24 settimana= 218,4 Mj

15 Mj: 0,5 Kg= 218,4 Mj : x → *7,28 Kg*

Glucose



Obesity Reviews. 2019;20:816-828

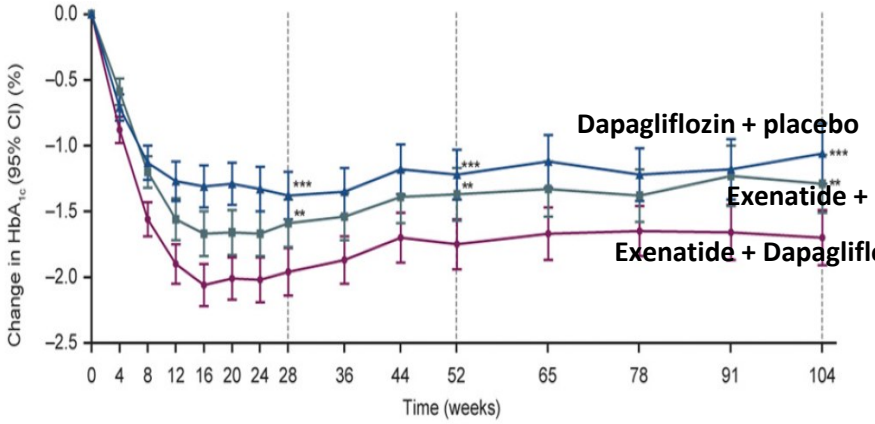


Drugs (2019) 79:219-230

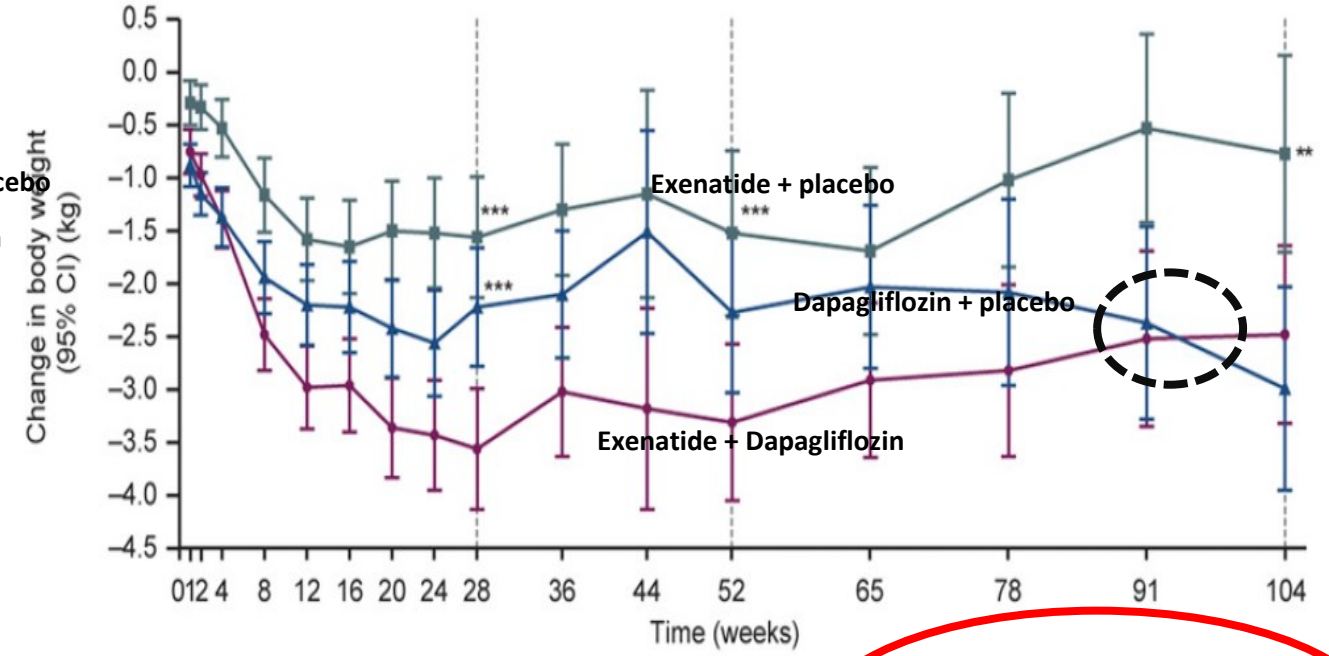
Exenatide plus Dapagliflozin in the DURATION-8 Study

Exenatide QW plus dapagliflozin — Exenatide QW plus placebo — Dapagliflozin plus placebo

Weight, mean (SD), kg	91.8 (22.2)	89.8 (20.2)	91.1 (19.7)
BMI, mean (SD), kg/m^2	33.2 (6.8)	32.0 (5.9)	33.0 (6.1)



Exenatide QW plus dapagliflozin, *n*	223	212	209	201	197	198	193	185	150	133	118	96	85	67
Exenatide QW plus placebo, *n*	225	213	209	203	192	189	184	175	140	116	94	77	69	50
Dapagliflozin plus placebo, *n*	225	220	219	216	209	207	196	187	147	117	98	77	61	43



Exenatide QW plus dapagliflozin, *n*	223	213	209	202	200	198	194	185	150	133	119	96	85	68
Exenatide QW plus placebo, *n*	224	214	209	203	196	191	184	175	142	116	94	78	70	50
Dapagliflozin plus placebo, *n*	226	220	220	217	211	207	196	187	147	117	99	77	61	43

Diabetes Care Volume 43, October 2020

Mettiamo caso che ogni mese prendi un cinghiale: a gennaio una freccia un cinghiale, febbraio una freccia un cinghiale, poi arriva dicembre, tiri la tua freccina e trovi due cinghiali. Ti è mai successo? Si chiama tredicesima.

Glucagon-like Peptide-1 Receptor Agonism

Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

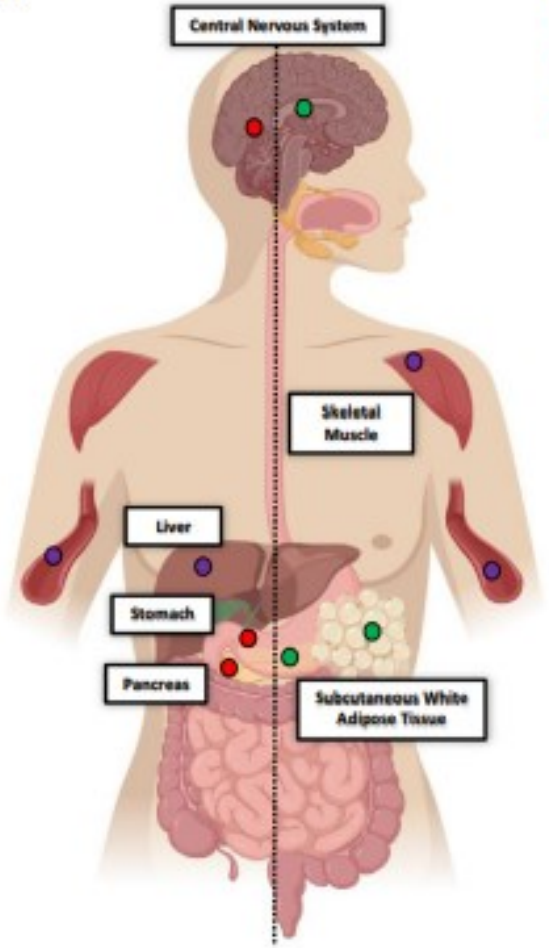
Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

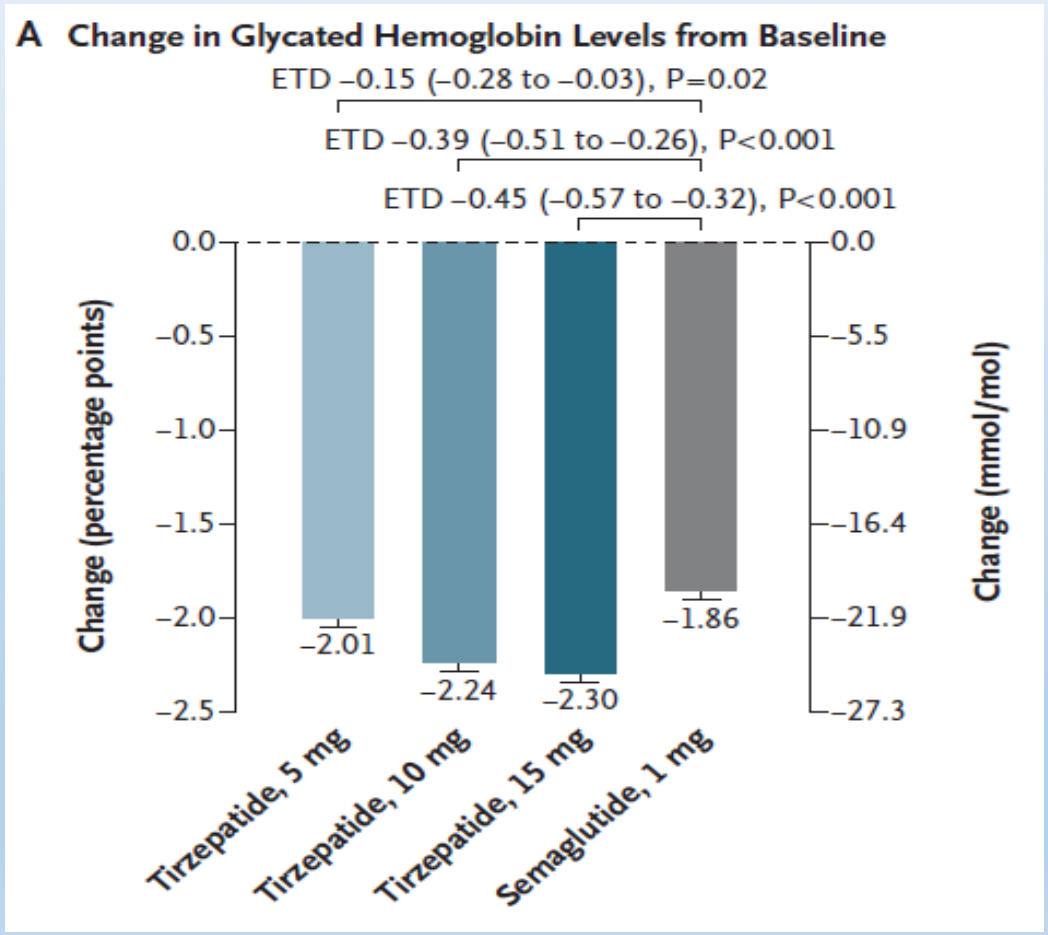
Trends in Endocrinology & Metabolism, June 2020, Vol. 31, No. 6

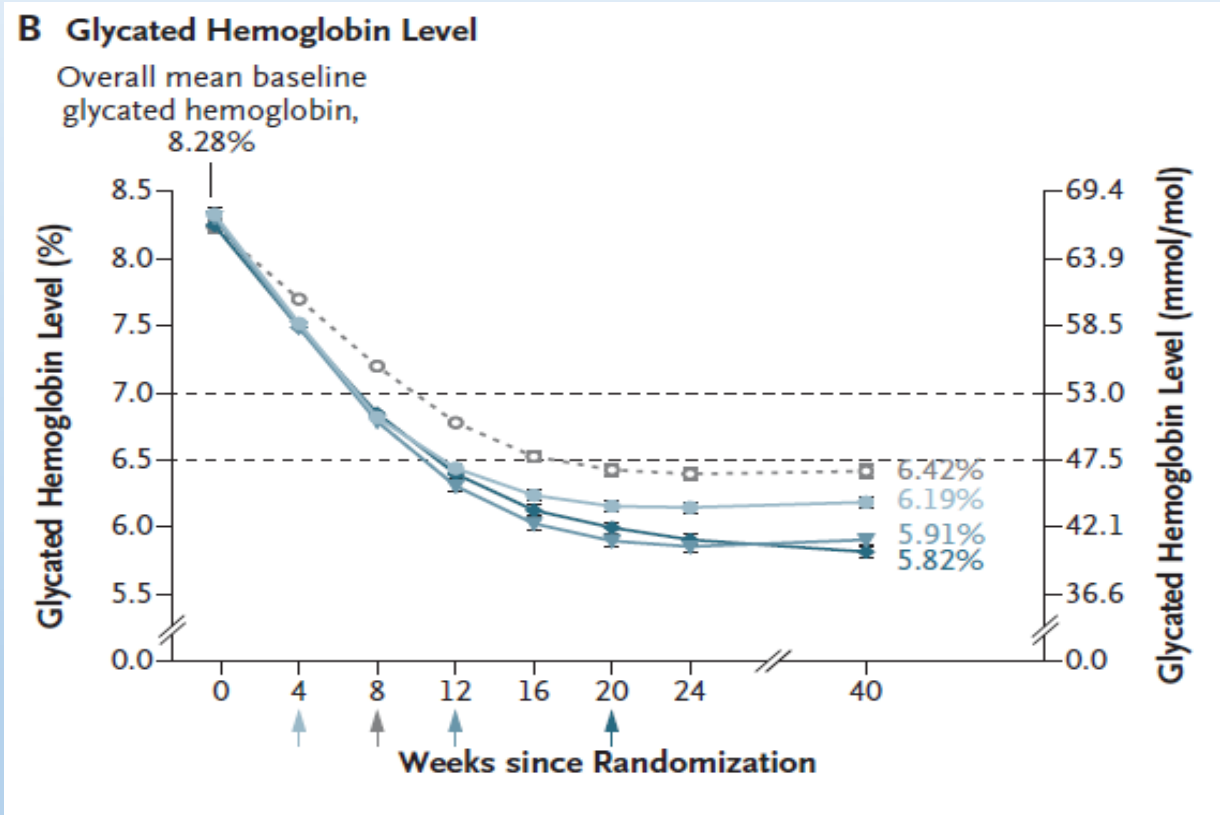
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

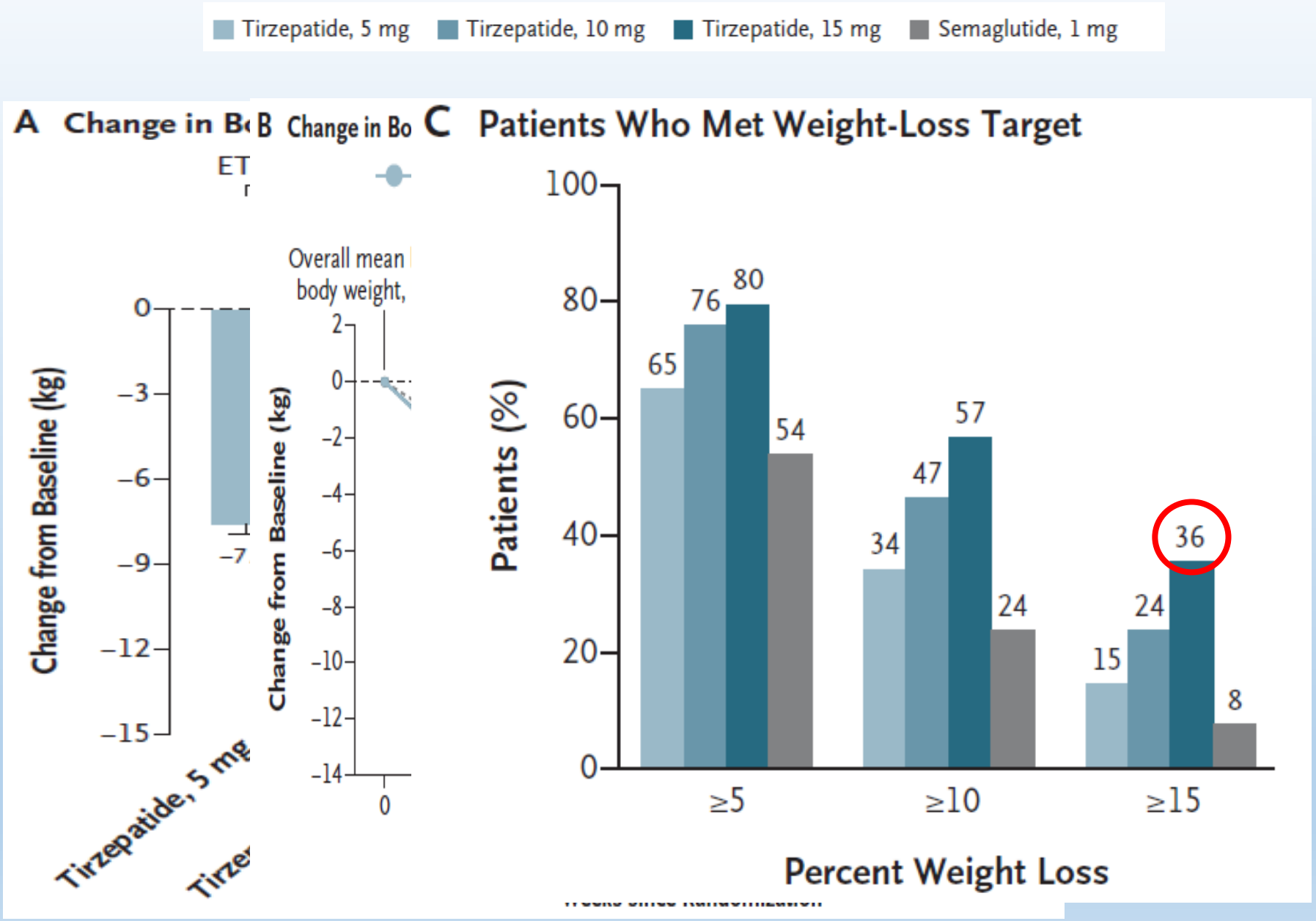
Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

BMI‡	33.8±6.85	34.3±6.60	34.5±7.11	34.2±7.15
Weight — kg	92.5±21.76	94.8±22.71	93.8±21.83	93.7±21.12
Waist circumference — cm	108.06±14.81	110.55±16.05	109.55±15.60	109.04±14.90





SURPASS-2 N ENGL J MED 385;6 AUGUST 5, 2021



SURPASS-2 N ENGL J MED 385;6 AUGUST 5, 2021

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularisation procedure). Variably included: conditions such as transient ischaemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+CKD

eGFR < 60 ml/min per 1.73 m² OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+ASCVD/Indicators of High Risk

GLP-1 RA^ with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If HbA_{1c} above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

SGLT2i§ with proven HF benefit in this population

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycaemic lowering needed

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals

Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management programme

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If HbA_{1c} above target

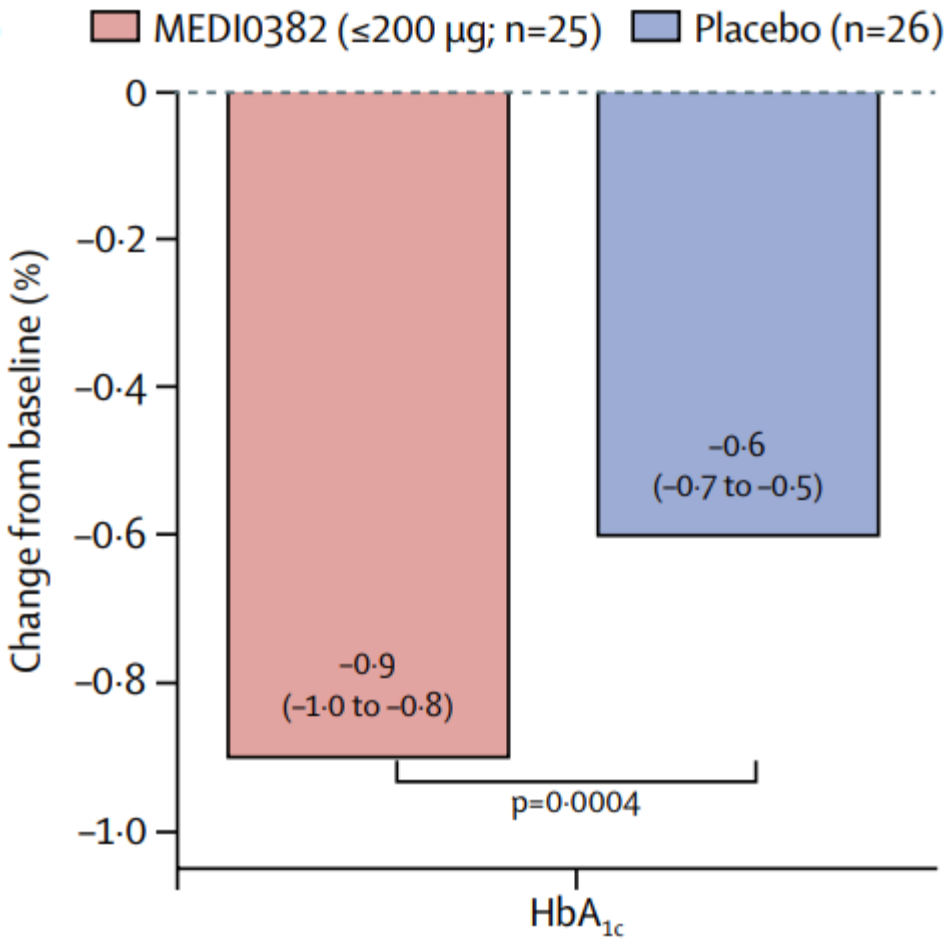
Identify barriers to goals:

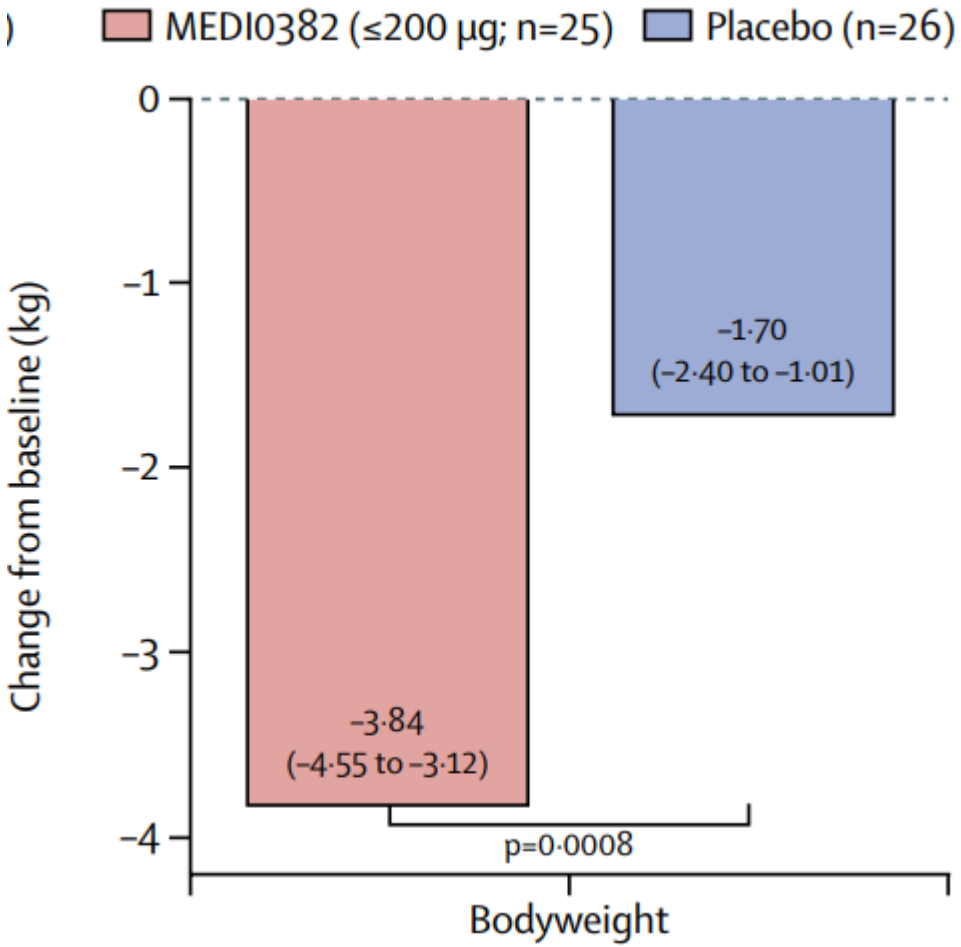
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

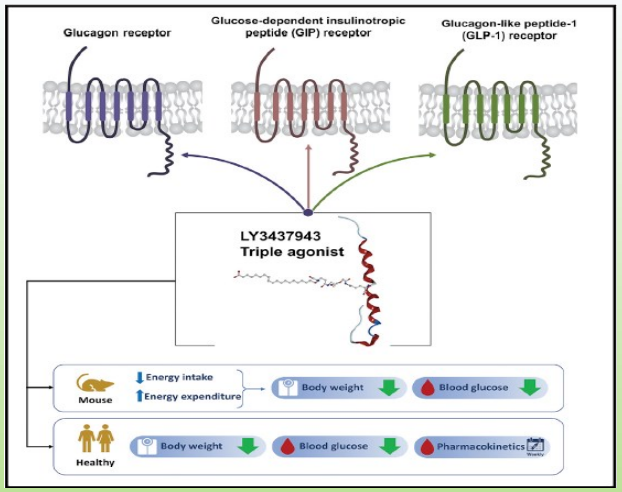
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD;

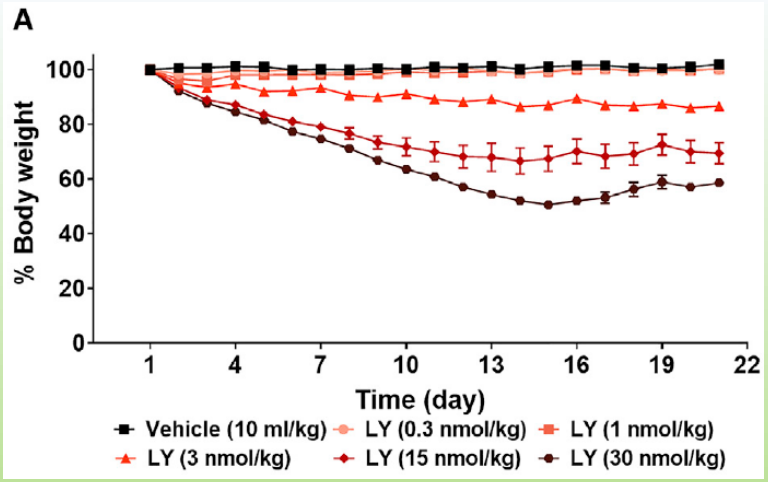
MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study

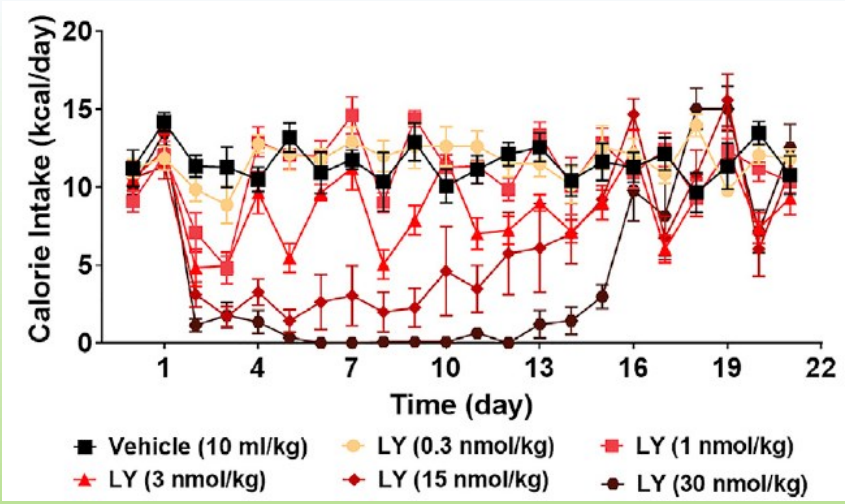


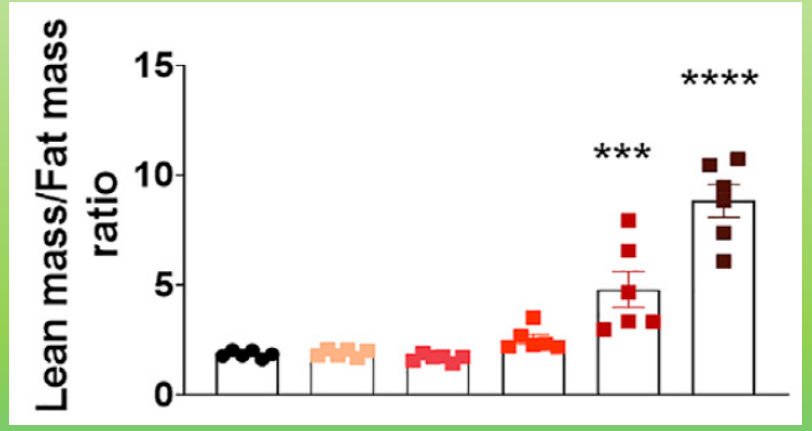


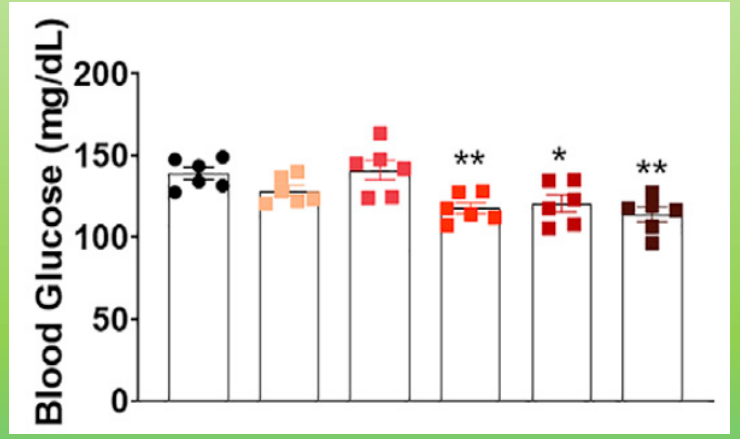
Lancet 2018; 391: 2607–18

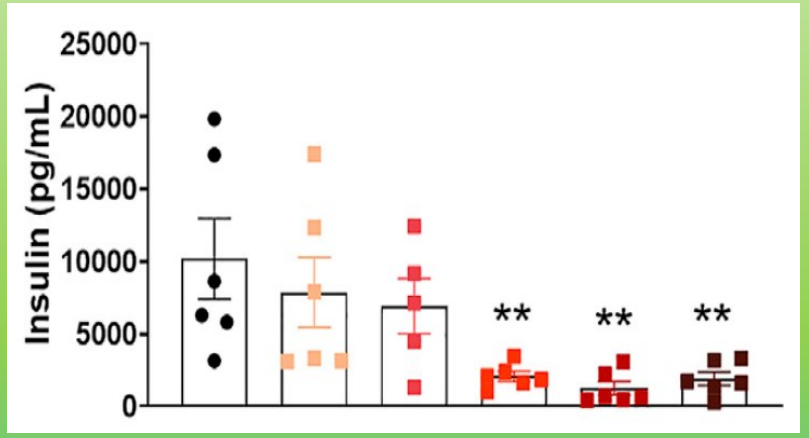




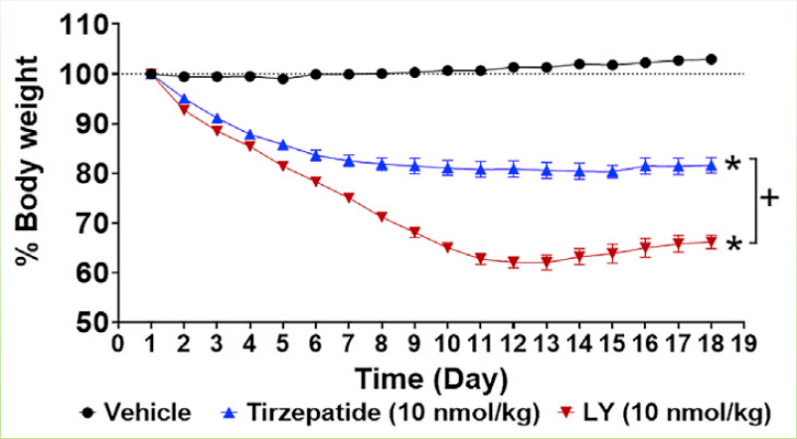


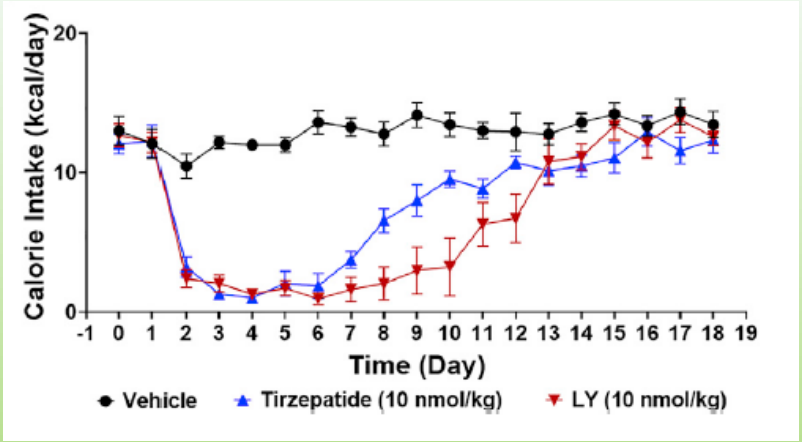


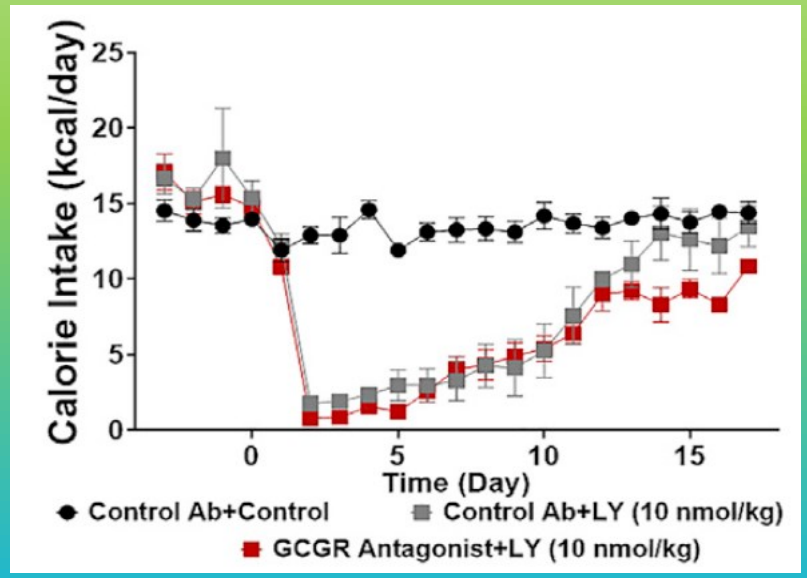


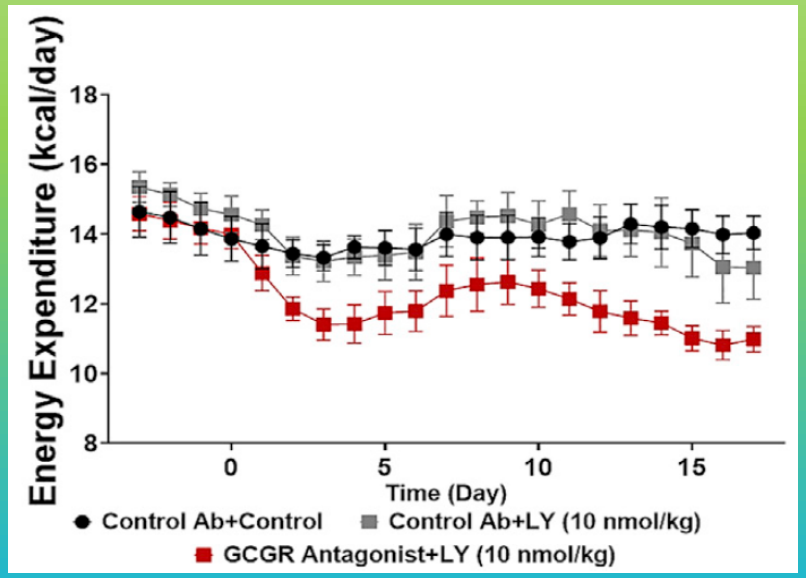


Cell Metabolism 34, 1234–1247 September 6, 2022









Cell Metabolism 34, 1234–1247 September 6, 2022

Grazie per l'attenzione