SID Società Italiana di Diabetologia

ROMA | 21 MAGGIO 2019

Terapia con analoghi del GLP-1: quando e perché

Analoghi del GLP-1 nei pazienti sovrappeso ed obesi

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Il /la dr./sa Lucia Frittitta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

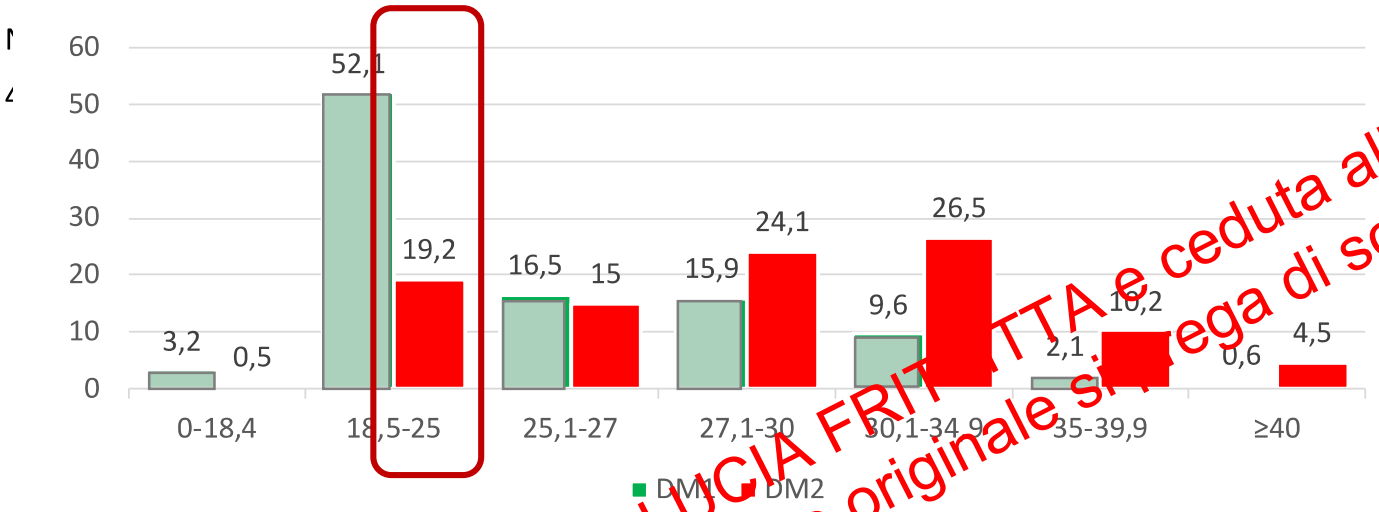
- Astra Zeneca
- Eli-Lilly
- Novo-Nordisk
- Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

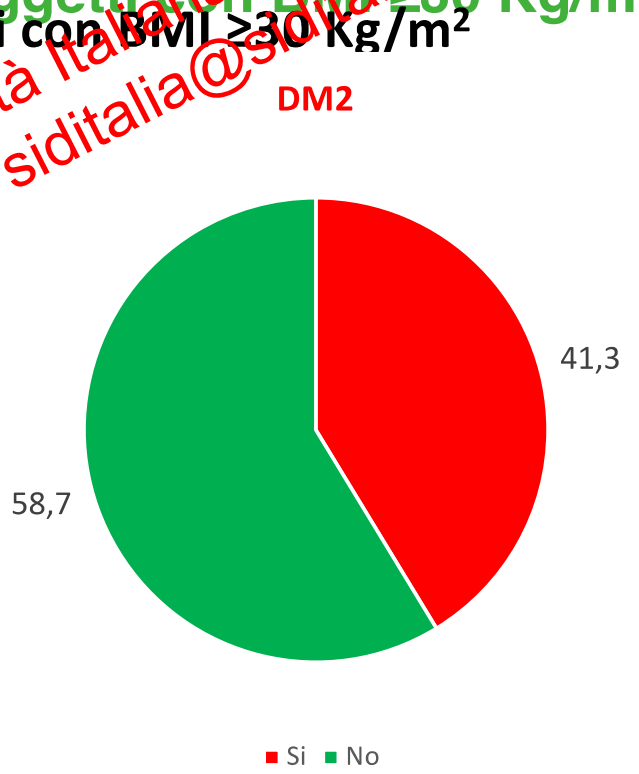
Annali AMD 2018

Andamento per 7 classi del BMI (%)

44.8% un target su tre, mentre il 12.1% non raggiunge nessun target.



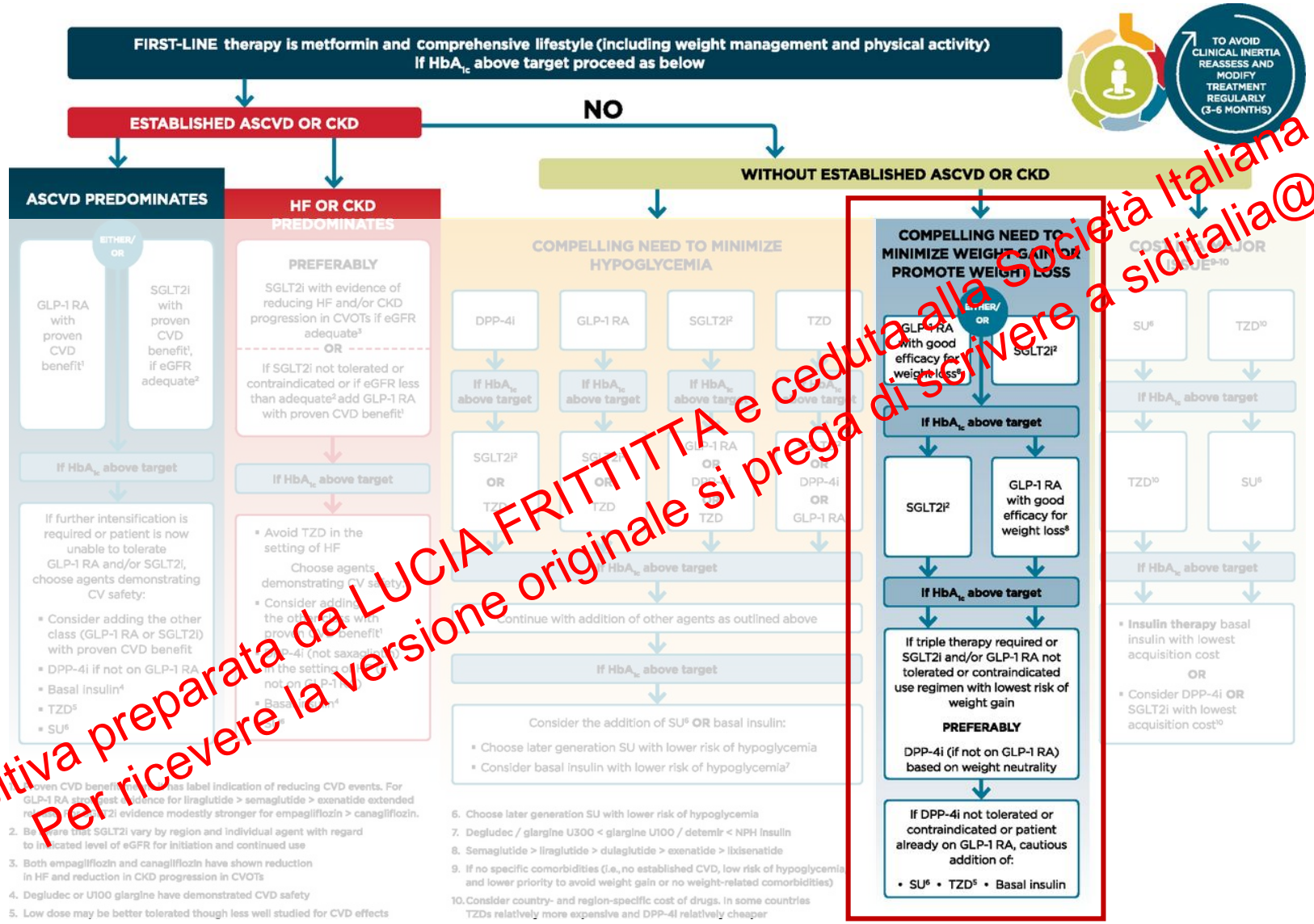
Soggetti con BMI ≥30 Kg/m²



Livelli medi del BMI (Kg/m²)

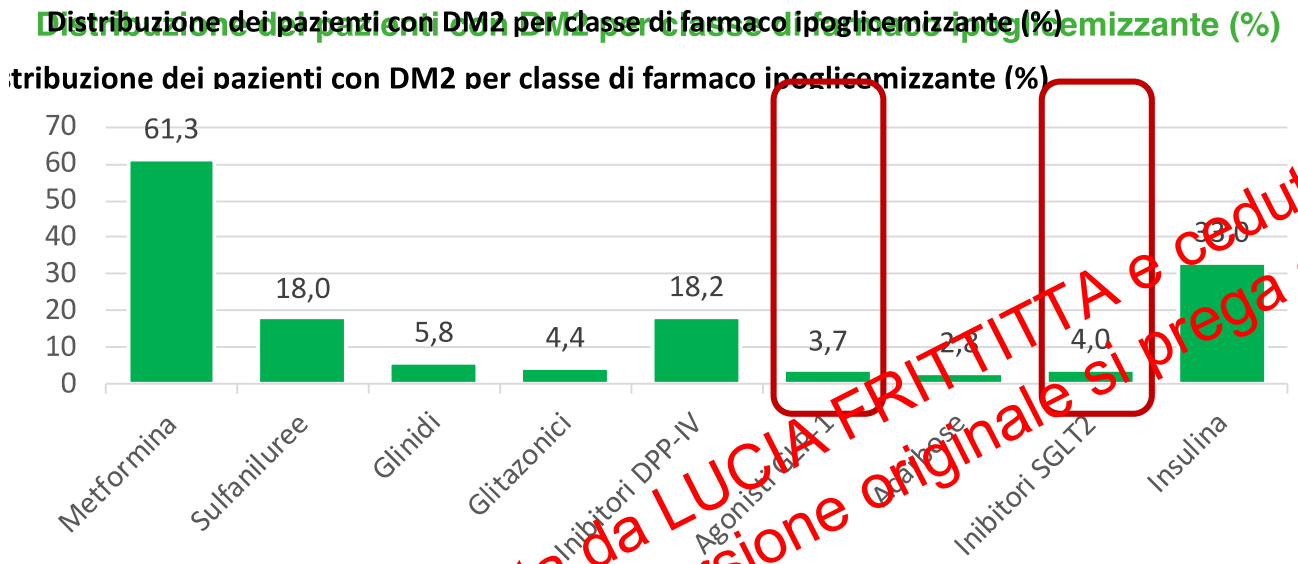
	DM1 Media ± ds	DM2 Media ± ds
BMI	25,1 ± 4,4	29,6 ± 5,5

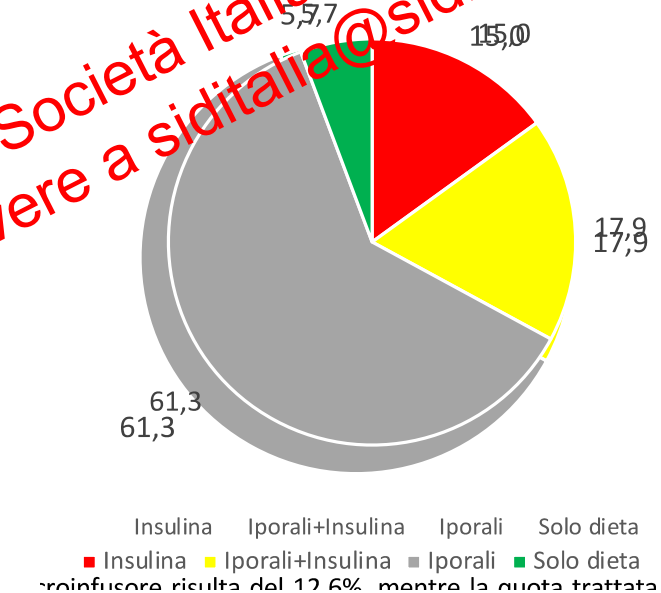
Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Dia Care 2019;42:S90-S102

Terapia per il diabete



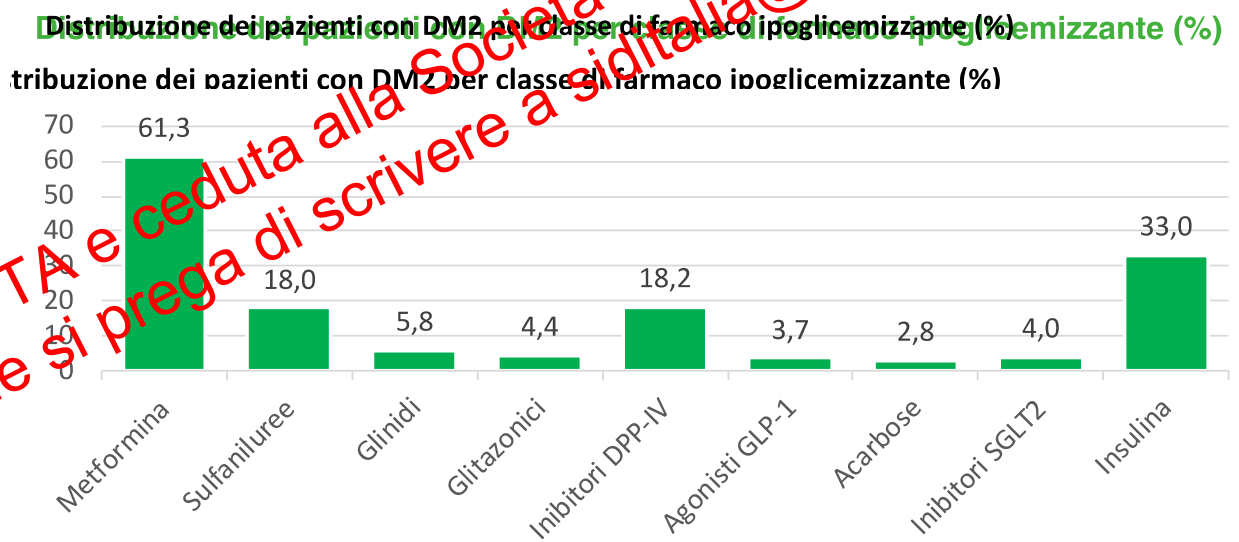


Il 29.4% dei soggetti utilizza insulina basale, il 22.3% insulina rapida e l'1.1% insulina premiscelata.

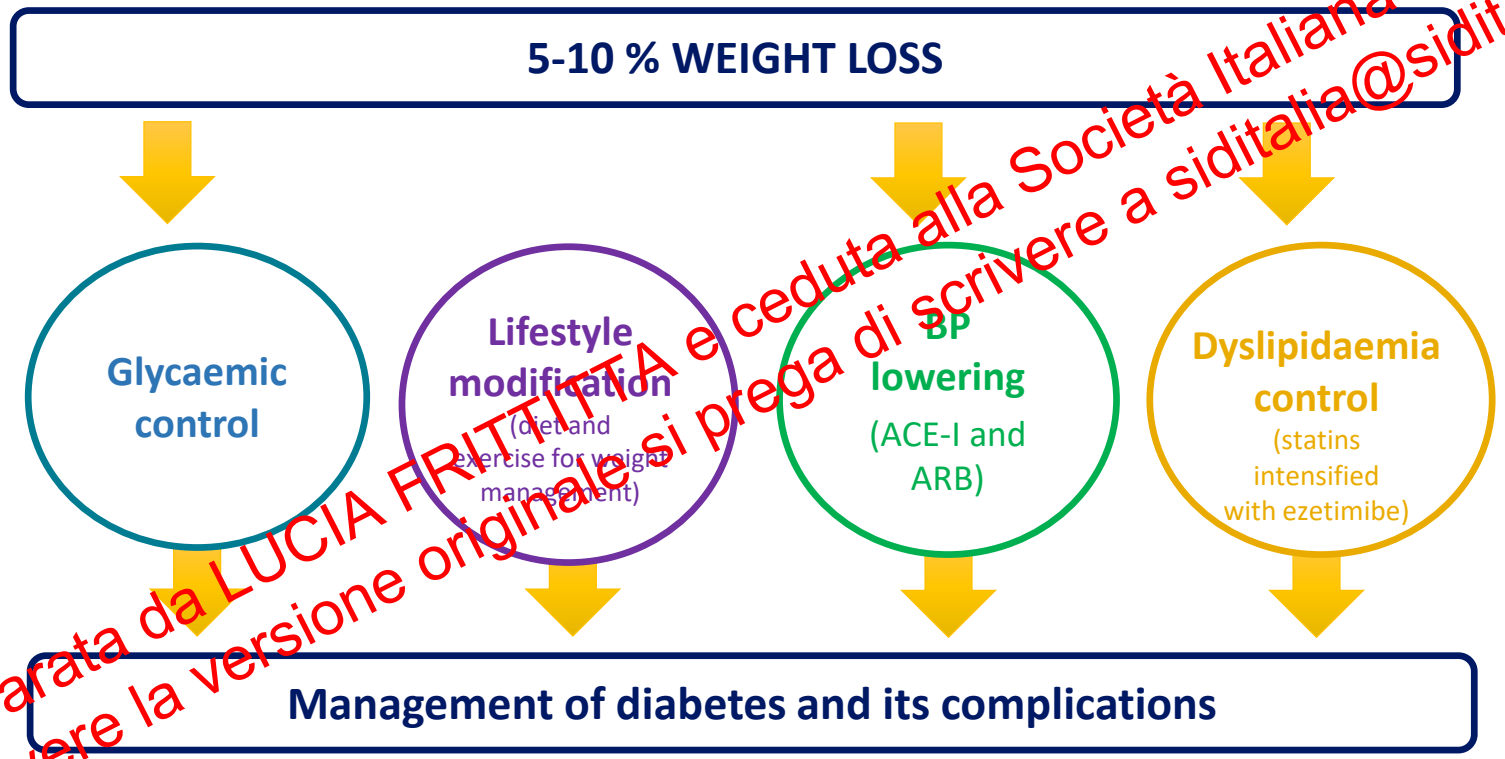
Studio Arno

Descrizione	Trattati (n=516.073)	% Trattati*	% spesa sul totale
Iperglicemici orali o iniettabili	446.320	86,5	50
Metformina	321.009	62,2	9,4
Sulfoniluree	99.127	19,2	3,8
Glinidi (Repaglinide)	45.942	8,9	2,8
Metformina e sulfoniluree	42.527	8,2	1,9
Metformina e Inibitori DPP-4	35.942	7	10
Inibitori DDP-4	25.991	5	7
Inibitori alfa-glicosidasi (Acarbosio)	19.210	3,7	1,2
Metformina e pioglitazone	14.245	2,8	3
Analoghi GLP-1	12.447	2,4	7,2
Glitazoni (Pioglitazone)	9.582	1,9	1
Inibitori SGLT-2	7.236	1,4	1,4
Metformina e inibitori SGLT-2	4.425	0,9	0,8
Glimepiride e pioglitazone	1.361	0,3	0,3
Pioglitazone e alogliptin	1.009	0,2	0,2
Insuline umane	3.345	1	0,7
Insuline ad azione rapida	4.114	0,8	0,5
Insuline ad azione intermedia	1.314	0,3	0,1
Insuline ad azione intermedia e azione rapida miscelate	736	0,1	0,1
Analoghi dell'Insulina	134.409	26	49,4
Analoghi ad azione rapida	100.132	19,4	27,6
Analoghi ad azione intermedia e azione rapida miscelati	12.547	2,4	2,6
Analoghi ad azione intermedia	6.656	1,3	1
Analoghi ad azione lenta	105.998	20,5	18,2
Totale	516.073	-	100,0

Annali



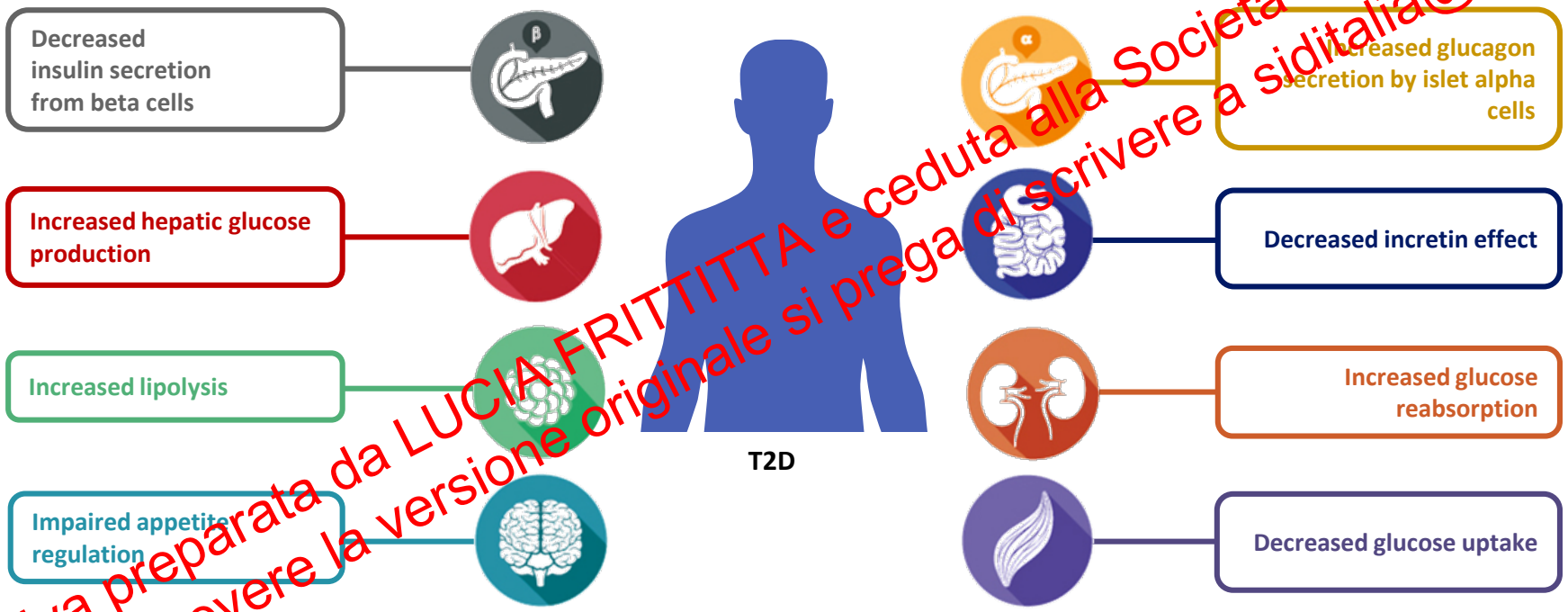
Multifactorial approach improves outcomes



- Primary prevention methods only - platelet inhibition recommended as secondary prevention.
- *Physical activity of moderate to vigorous intensity, spread over at least 3 days/week. †ADA guidelines suggest 40 mg/dL for men, 50 mg/dL for women. American Diabetes Association. *Diabetes Care* 2019;42(Suppl. 1):S1–S3.

Various parameters impact T2D pathophysiology

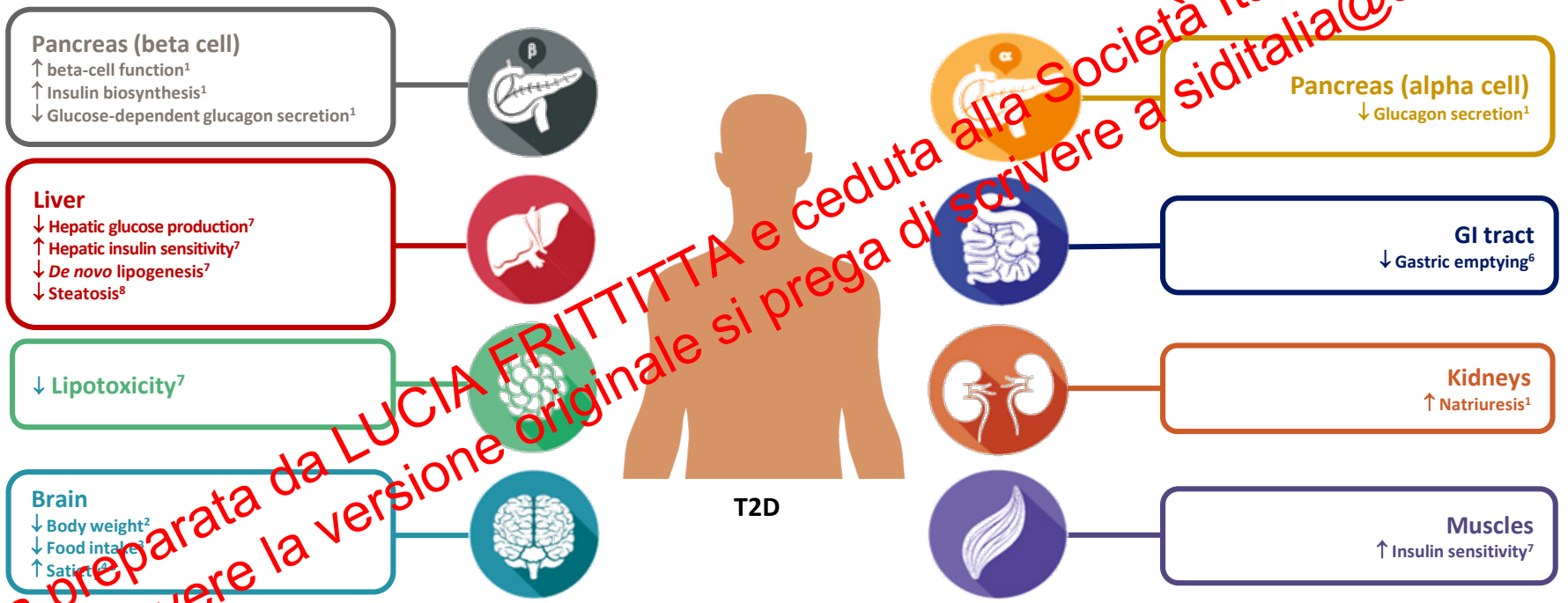
- THE ‘OMINOUS OCTET’



Adapted from DeFronzo RA. *Diabetes* 2009;58:773–95 and DeFronzo RA et al. *Nat Rev Dis Primers* 2015;1:15019.

GLP-1RAs have multifactorial effects

- PHARMACOLOGICAL EFFECTS OF GLP-1RAs



1. Campbell JE, DJ Drucker. *Cell Metab* 2013;17:819–37; 2. Baggio LL, Drucker DJ. *J Clin Invest* 2014;124:4223–6; 3. Bagger JI et al. *J Clin Endocrinol Metab* 2015;100:4541–52; 4. Flint A et al. *J Clin Invest* 1998;101:515–20; 5. Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51; 6. Tong J, D'Alessio D. *Diabetes* 2014;63:407–9; 7. Armstrong MJ et al. *J Hepatol* 2016;64:399–408; 8. Armstrong MJ et al. *Lancet* 2016;387:679–90.

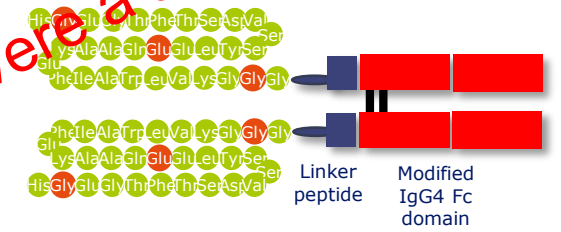
GLP-1RAs vary in molecular structure and size

Exendin-based GLP-1RAs	Human GLP-1 analogues	
	Small	Large

Exenatide *(4.19 kDa, 53% homology)*

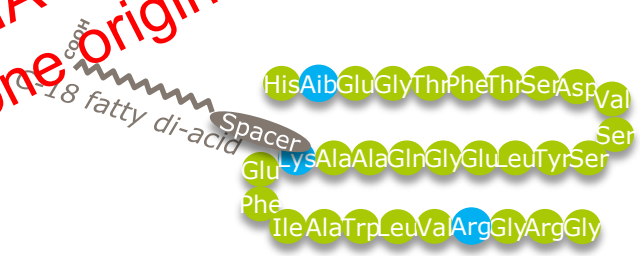
Liraglutide *(3.75 kDa, 97% homology)*

Dulaglutide *(~63 kDa, 90% homology)*

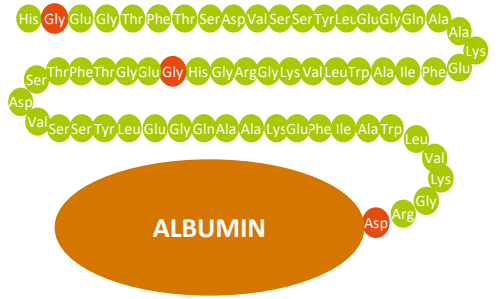


Lixisenatide *(4.86 kDa, ~50% homology)*

Semaglutide *(4.11 kDa, 94% homology)*



Albiglutide*



*Withdrawn from market.

PK profiles of approved GLP-1RAs

Increasing protraction

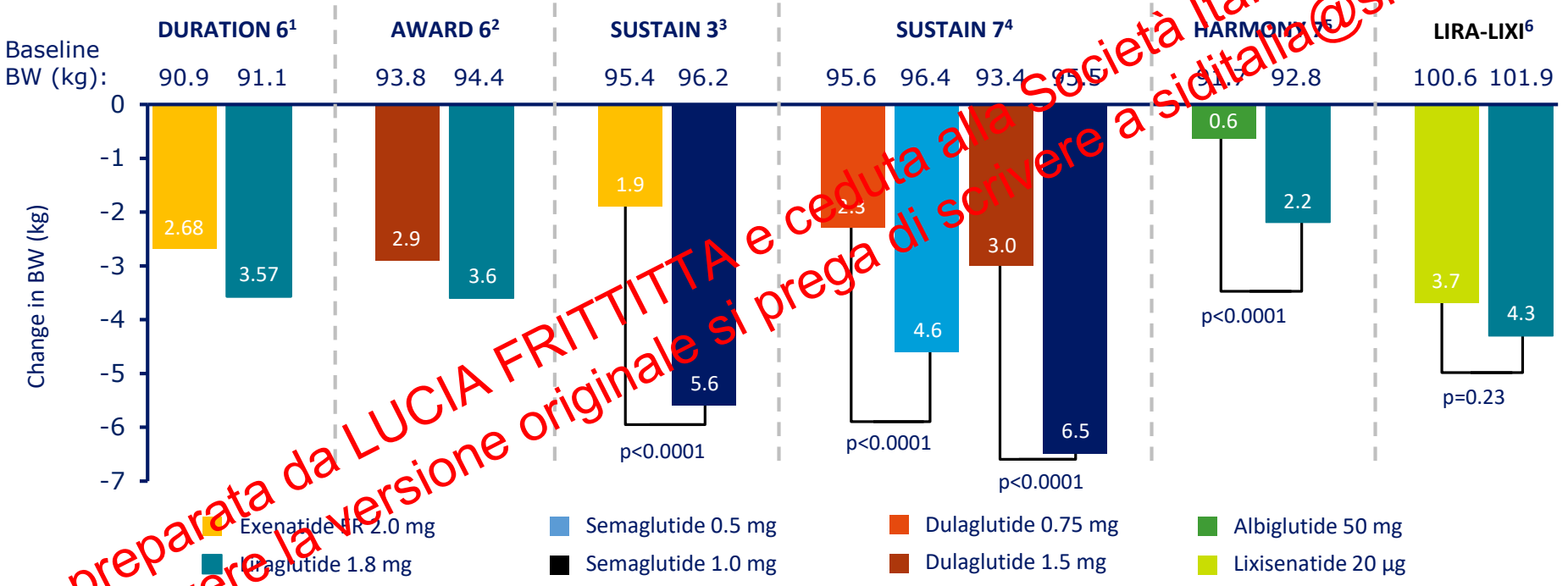
Agent	$t_{1/2}$	t_{max}
Exenatide BID[1]	2.4 h	0.6 h
Lixisenatide OD[2]	3 h	1–3.5 h
Liraglutide OD[3]	13 h	8–12 h
Dulaglutide OW[4]	~4 days	24–48 h
Exenatide OW[5]	7–14 days	6–7 weeks
Semaglutide OW[6]	~7 days	1–3 days

Short acting

Long acting

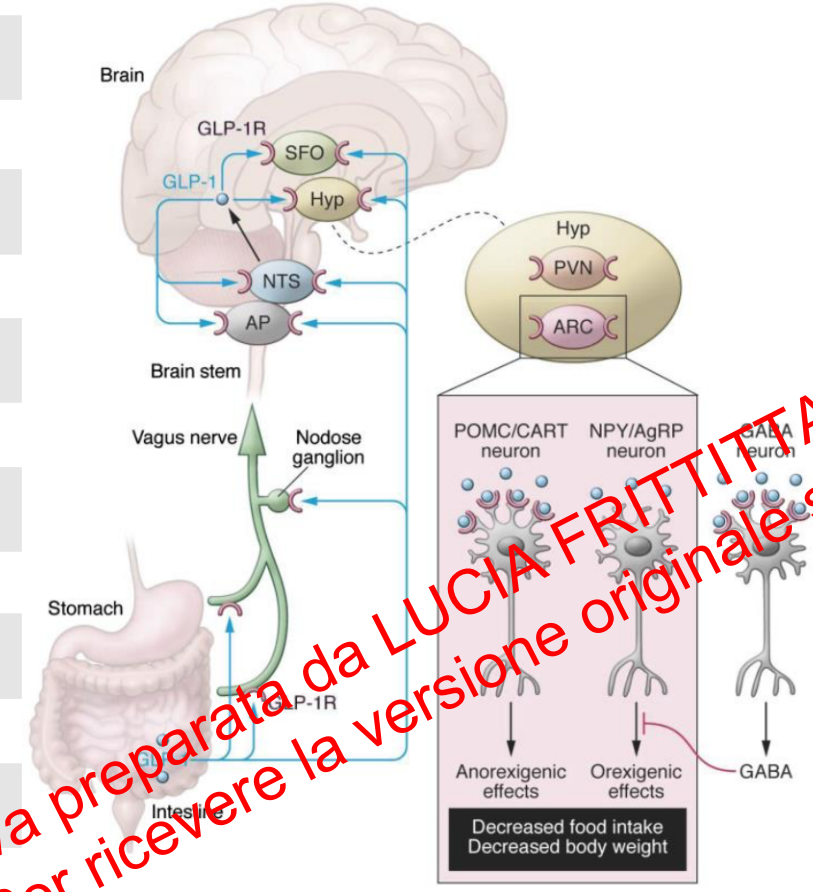
GLP-1RAs reduce Body Weight

- RESULTS FROM COMPARATIVE TRIALS



- 1. Buse JB et al. *Lancet* 2013;381:117–24; 2. Dungan KM et al. *Lancet* 2014;384:1349–57; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258–66; 4. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Pratley RE et al. *Lancet Diabetes Endocrinol* 2014;2:289–97; 6. Nauck M et al. *Diabetes Care* 2016;39:1501–9.

Liraglutide for Weight Loss



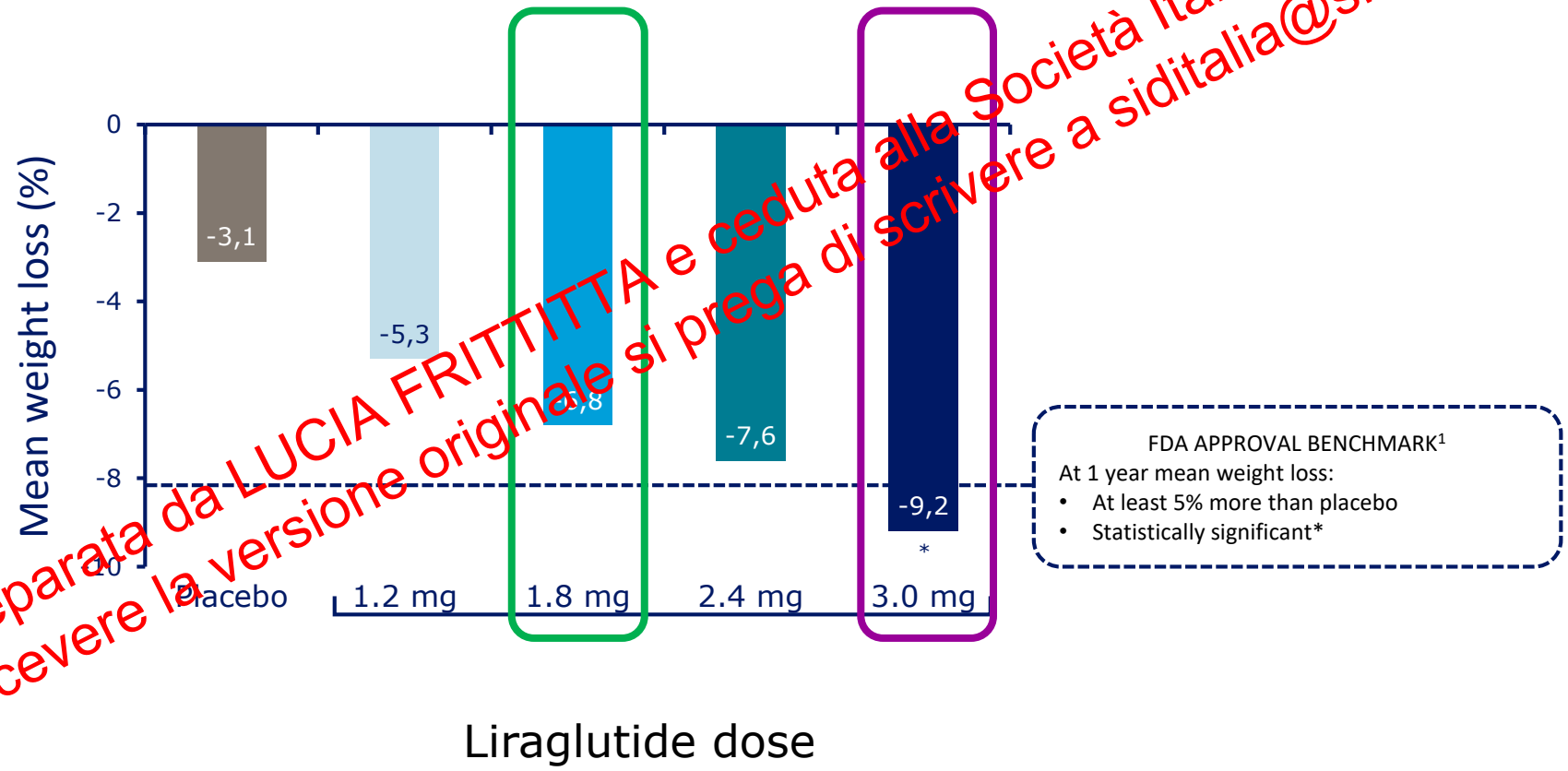
Liraglutide

- Modified human glucagon like peptide-1(GLP-1) to increase albumin binding
- Released slowly from fat
- Receptors present in the vagus, brain stem, multiple areas of the CNS
- Activation of Pro-opio melanocortin (POMC) neurons
- Inhibition of Neuropeptide Y (NPY) neurons

Baggio LL., Drucker D., JCI 2014 (PMID: 25202976)

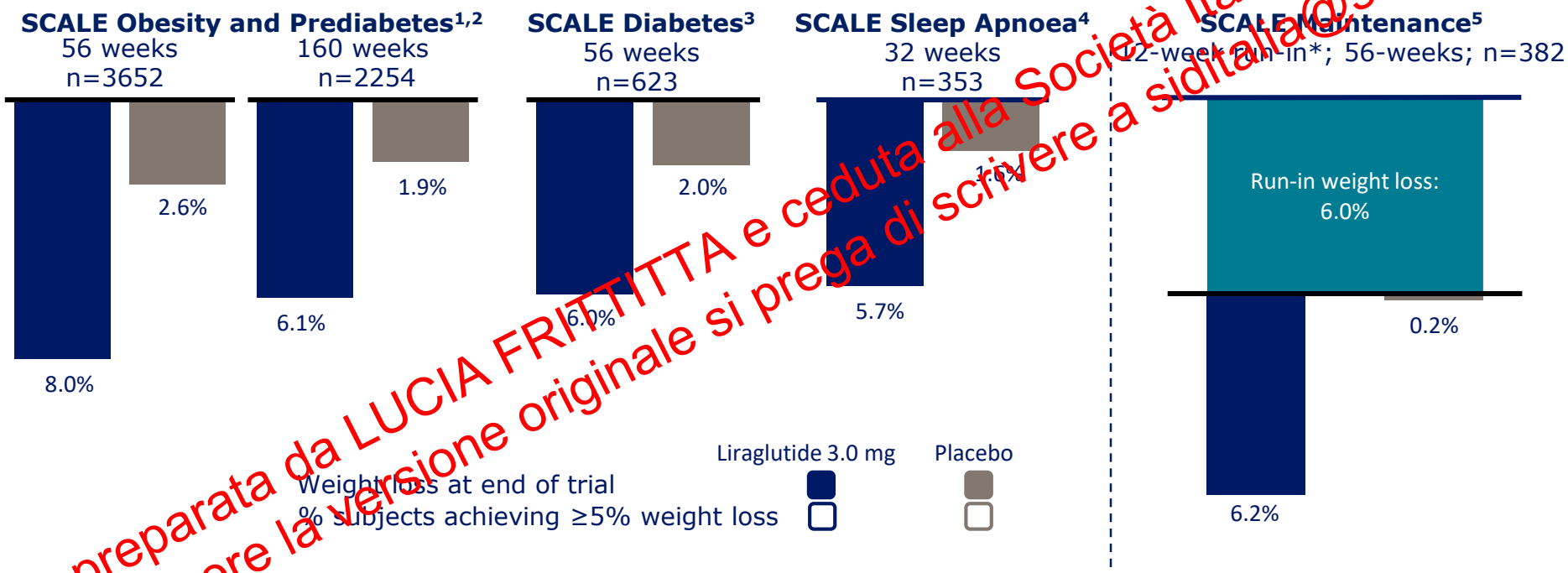
Mean weight loss at 1 year

Phase 2 dose-ranging study



*p<0.05 vs. placebo

Weight loss across SCALE trials



Data are observed means; last observation carried forward at end of trial; N, number of individuals contributing to the analysis
*Low calorie diet (total energy intake 1200–1400 kcal/day)

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. le Roux *et al. Lancet* 2017;389:1399–409; 3. Davies *et al. JAMA* 2015;314:687–99;
4. Blackman *et al. Diabetologia* 2014;57(Suppl. 1):Abstract 184-OR; 5. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

SCALE Efficacy

Key efficacy outcomes with liraglutide 3.0 mg

SCALE Obesity and Prediabetes[1,2]

-8.0%

change in body weight after 1 year

80%

reduction in the risk of T2D over 3 years

SCALE Diabetes[3]

-6.0%

change in body weight after 56 weeks

-1.3%

change in HbA_{1c} from baseline

SCALE Maintenance[4]

81%

maintained ≥5% weight loss after 1 year

6.2%

additional weight loss with liraglutide 3.0 mg*

SCALE Sleep Apnoea[5]

-12.2

events p/h vs. 6.1 with placebo

-5.7%

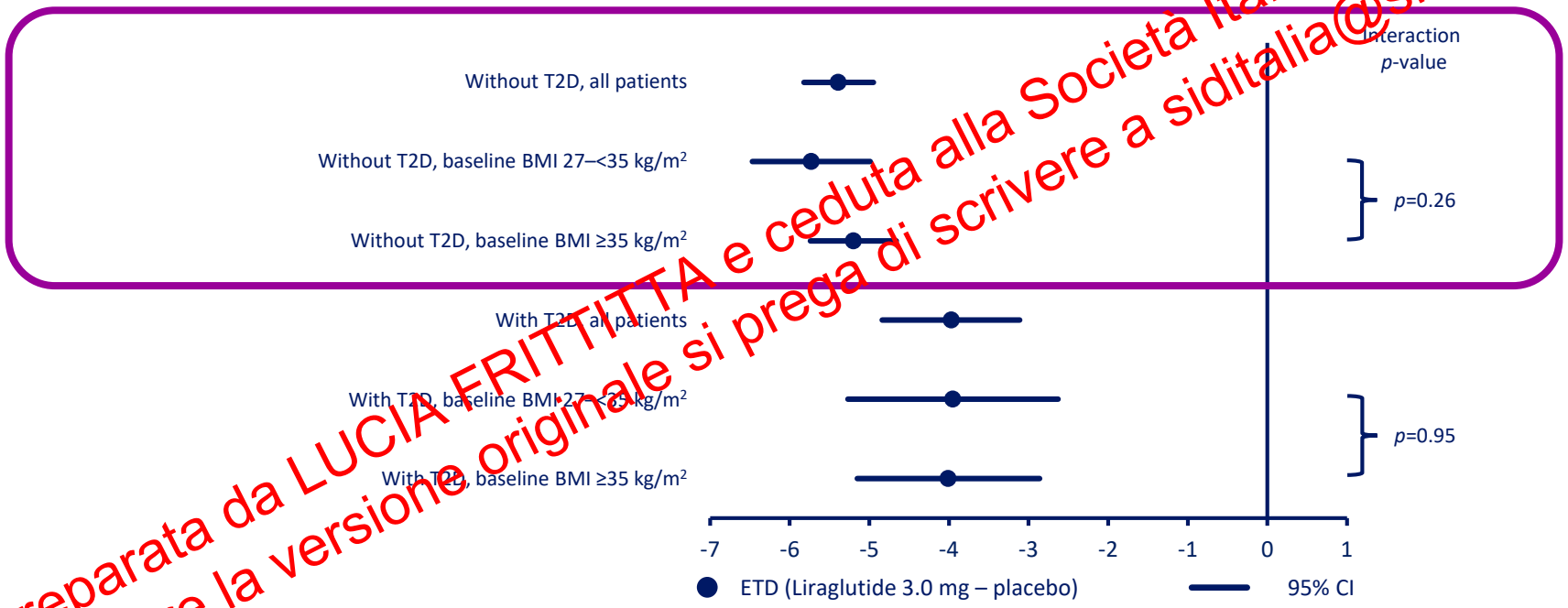
change in body weight after 32 weeks

*following lifestyle intervention induced weight loss of ≥5% over a 12 week run in period

1. Pi-Sunyer *et al*. *N Engl J Med* 2015;373:11–22; 2. le Roux *et al*. *Lancet* 2017;389:1399–409; 3. Davies *et al*. *JAMA* 2015;314:687–99;
4. Wadden *et al*. *Int J Obes (Lond)* 2013;37:1443–51; 5. Blackman *et al*. *Int J Obes (Lond)* 2016;40:1310–19

Change from baseline in body weight (%)

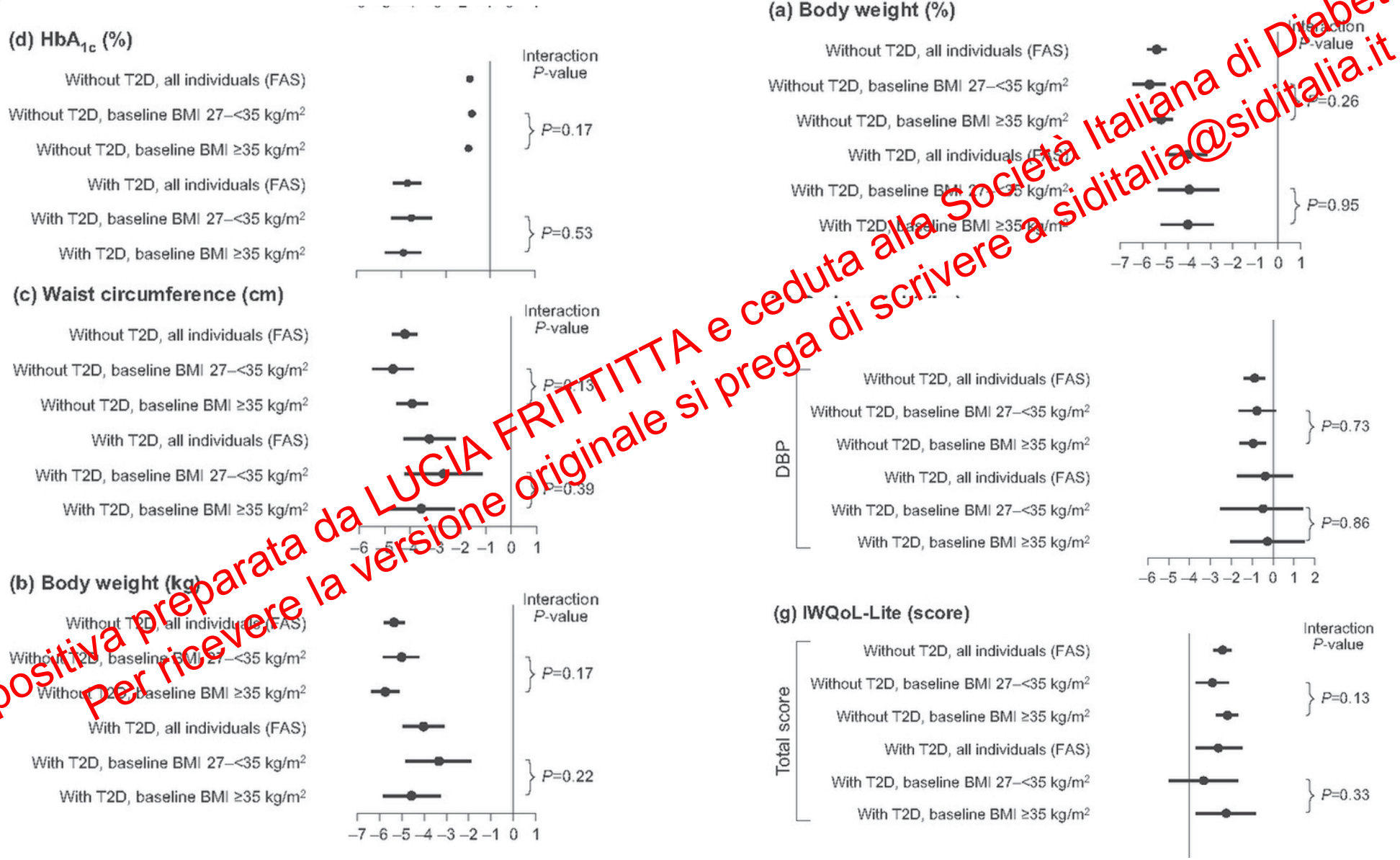
SCALE Obesity and Prediabetes and SCALE Diabetes



Full analysis set. Analysis of covariance, with last observation carried forward. *P*-values are based on test of interaction between treatment effect and baseline BMI subgroup and reflect the evidence of a difference in treatment effect between BMI subgroups
CI, confidence interval; ETD, estimated treatment difference

Le Roux *et al. Obes Facts* 2017;10:531–44

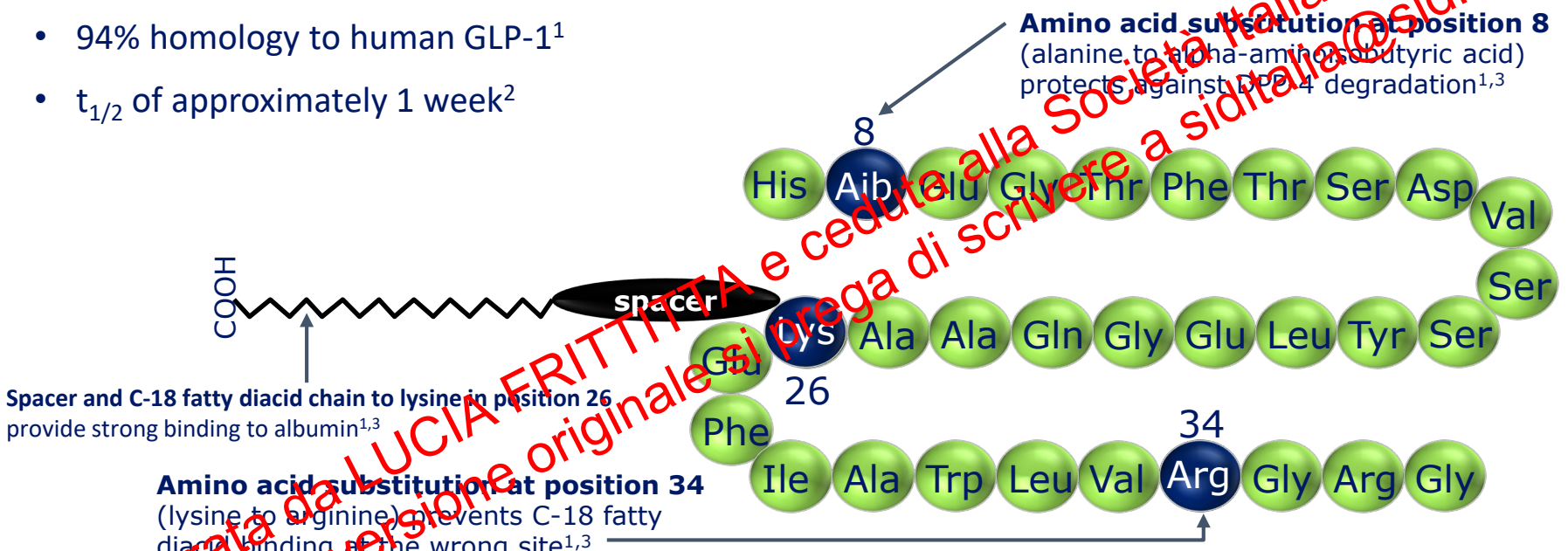
Efficac of Liraglutide 3.0 mg in Individuals with BMI above and below 35 kg/m2



Le Roux *et al. Obes Facts* 2017;10:531–44

Semaglutide is a human GLP-1 analogue

- 94% homology to human GLP-1[1]
- $t_{1/2}$ of approximately 1 week[2]

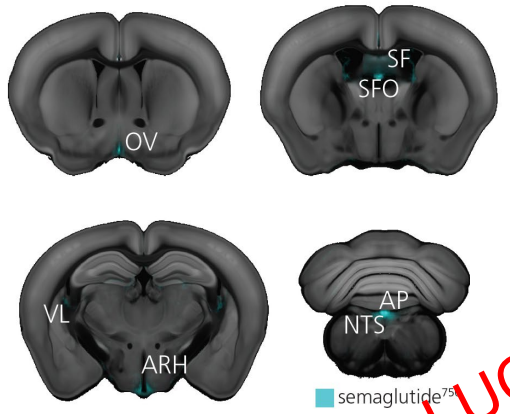


- DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, half-life.

1. Lau J et al. *J Med Chem* 2015;58:7370–80; 2. Kapitza C et al. *J Clin Pharmacol* 2015;55:497–504; 3. Lund A et al. *Eur J Intern Med* 2014;25:407–14.

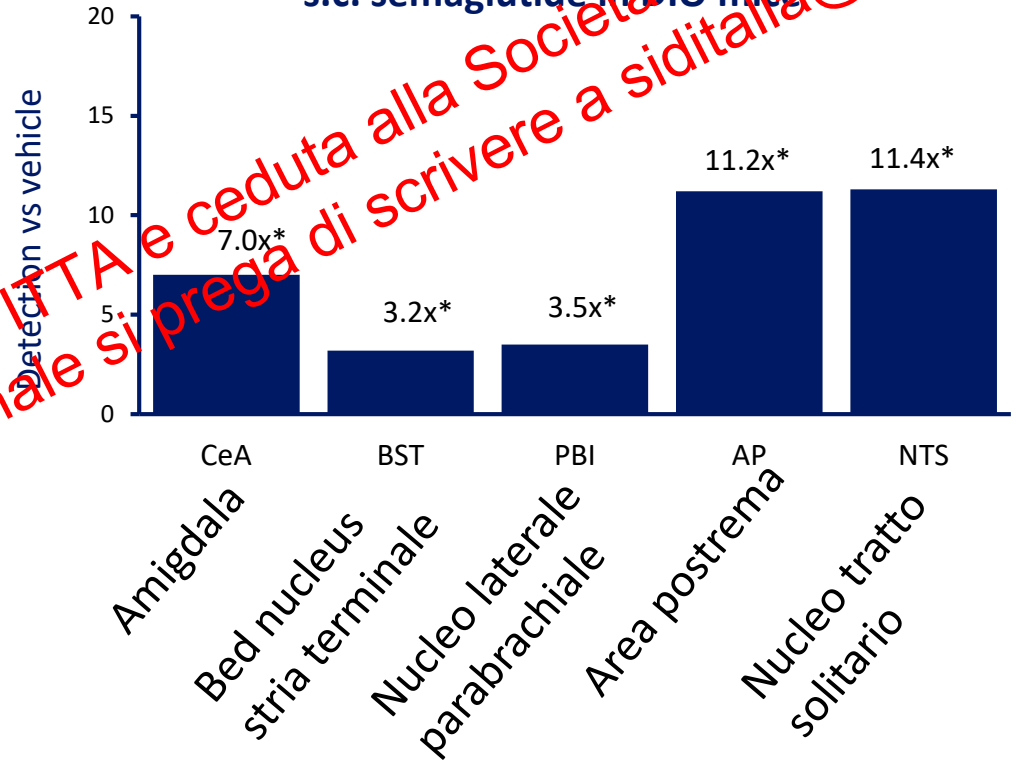
Semaglutide accesses and activates regions of the brain involved in reward behaviour and food intake

Semaglutide[750] signal following intravenous injection in C57BL/6 mice[1]



*p≤0.0001.

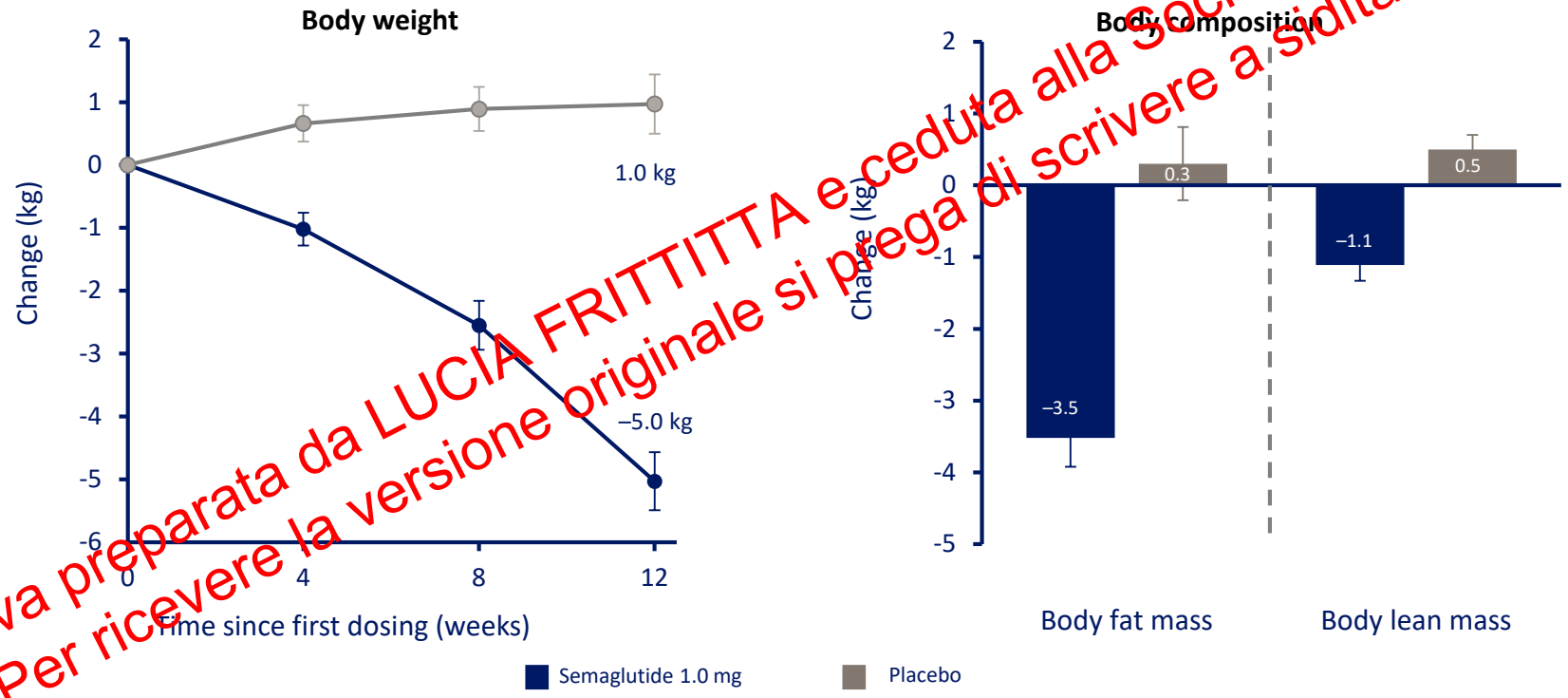
Neuronal activation following s.c. semaglutide in DIO mice[1]



2. Rui L. *Rev Endocr Metab Disord* 2013;14:387–407.

Primary mechanism of weight loss

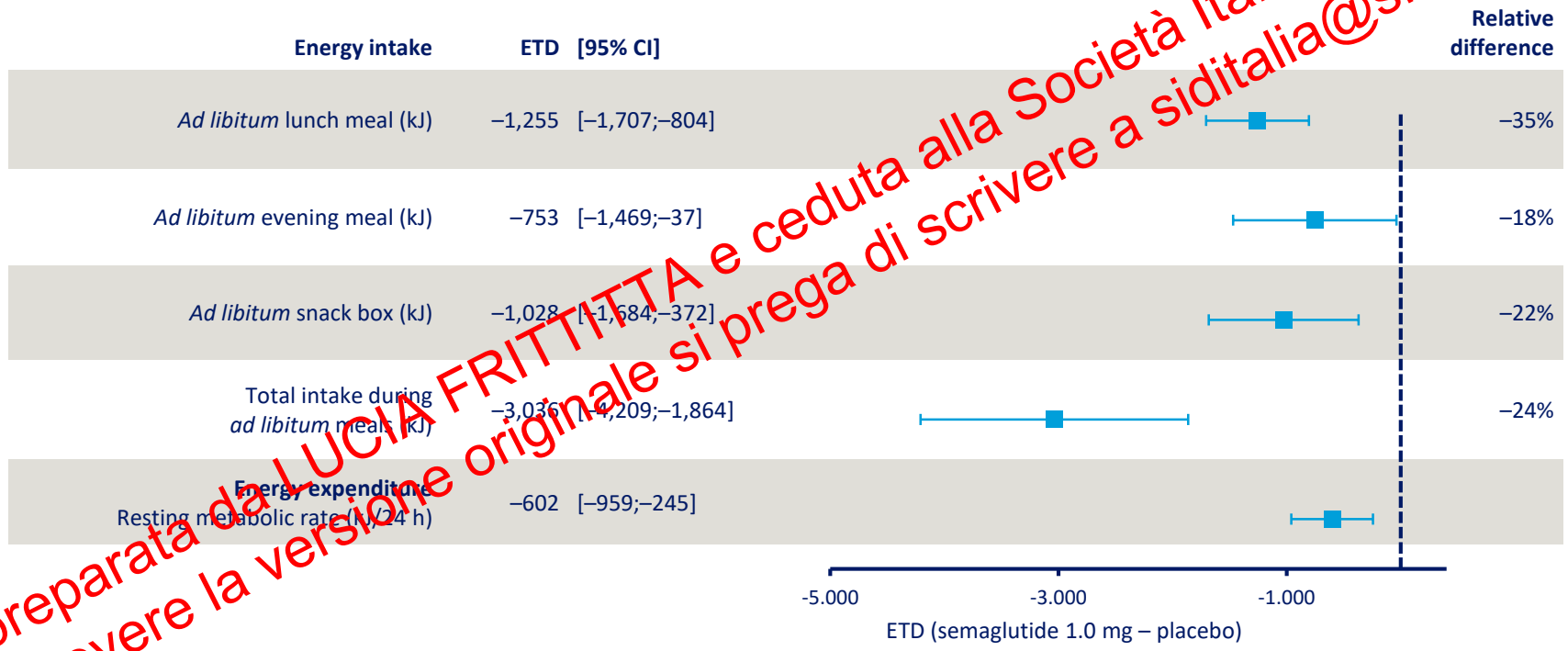
Semaglutide reduces fat mass



Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51.

Semaglutide treatment for 12 weeks in obese subjects

Semaglutide reduces energy intake and expenditure



Relative difference: ETD / estimated mean for placebo x 100%. Data for 24-h resting metabolic rate are from a post hoc statistical analysis

Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51.

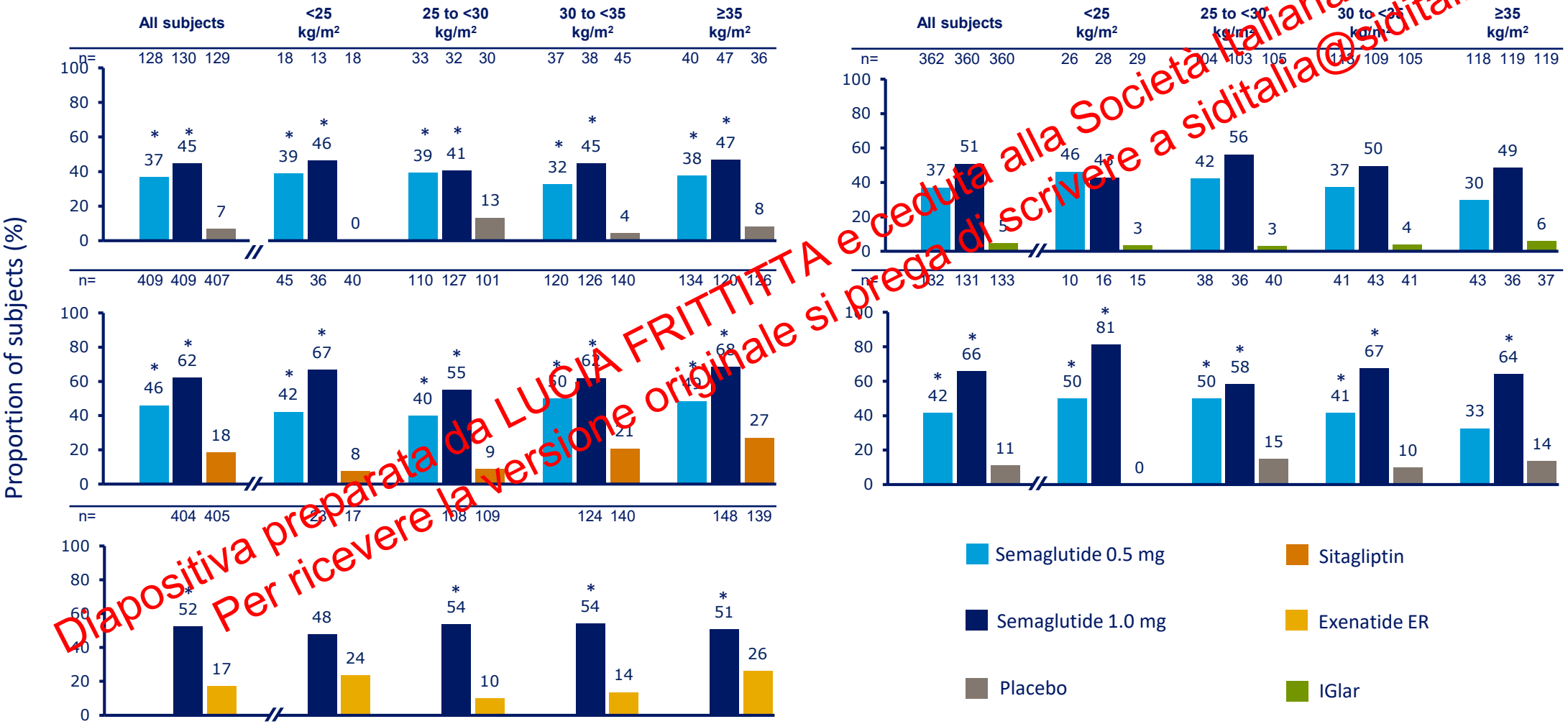
Baseline characteristics

	SUSTAIN 1: Semaglutide vs placebo 30 weeks	SUSTAIN 2: Semaglutide vs sitagliptin 100 mg 56 weeks	SUSTAIN 3: Semaglutide vs exenatide ER 2.0 mg 56 weeks	SUSTAIN 4: Semaglutide vs IGlar 30 weeks	SUSTAIN 5: Semaglutide add-on to insulin vs placebo 30 weeks
Baseline characteristics, mean (SD)†					
Age, years	53.7 (11.3)	55.1 (10.0)	56.6 (10.7)	56.5 (10.4)	58.8 (10.1)
Males, %	54.3	50.6	55.3	53.0	56.1
Diabetes duration, years	4.2 (5.5)	6.6 (5.1)	9.2 (6.3)	8.6 (6.3)	13.3 (7.8)
Body weight, kg	91.9 (23.8)	89.5 (20.3)	95.8 (21.5)	93.5 (21.8)	91.7 (21.0)
HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)
HbA_{1c}, mmol/mol	64.5 (9.8)	64.8 (10.1)	67.7 (10.4)	65.8 (9.7)	67.9 (9.2)
FPG, mg/dL	175.5 (48.2)	169.4 (40.7)	189.0 (48.7)	175.3 (51.2)	155.9 (53.7)
BMI, kg/m^2	32.9 (7.7)	32.5 (6.2)	33.8 (6.7)	33.0 (6.5)	32.2 (6.2)

Adapted from Table 1. †Values are mean (SD) unless otherwise indicated.
BMI, body mass index; exenatide ER, exenatide extended release; FPG, fasting plasma glucose; IGlar, insulin glargine; SD, standard deviation.

Proportion of subjects achieving ≥5% weight loss by baseline BMI

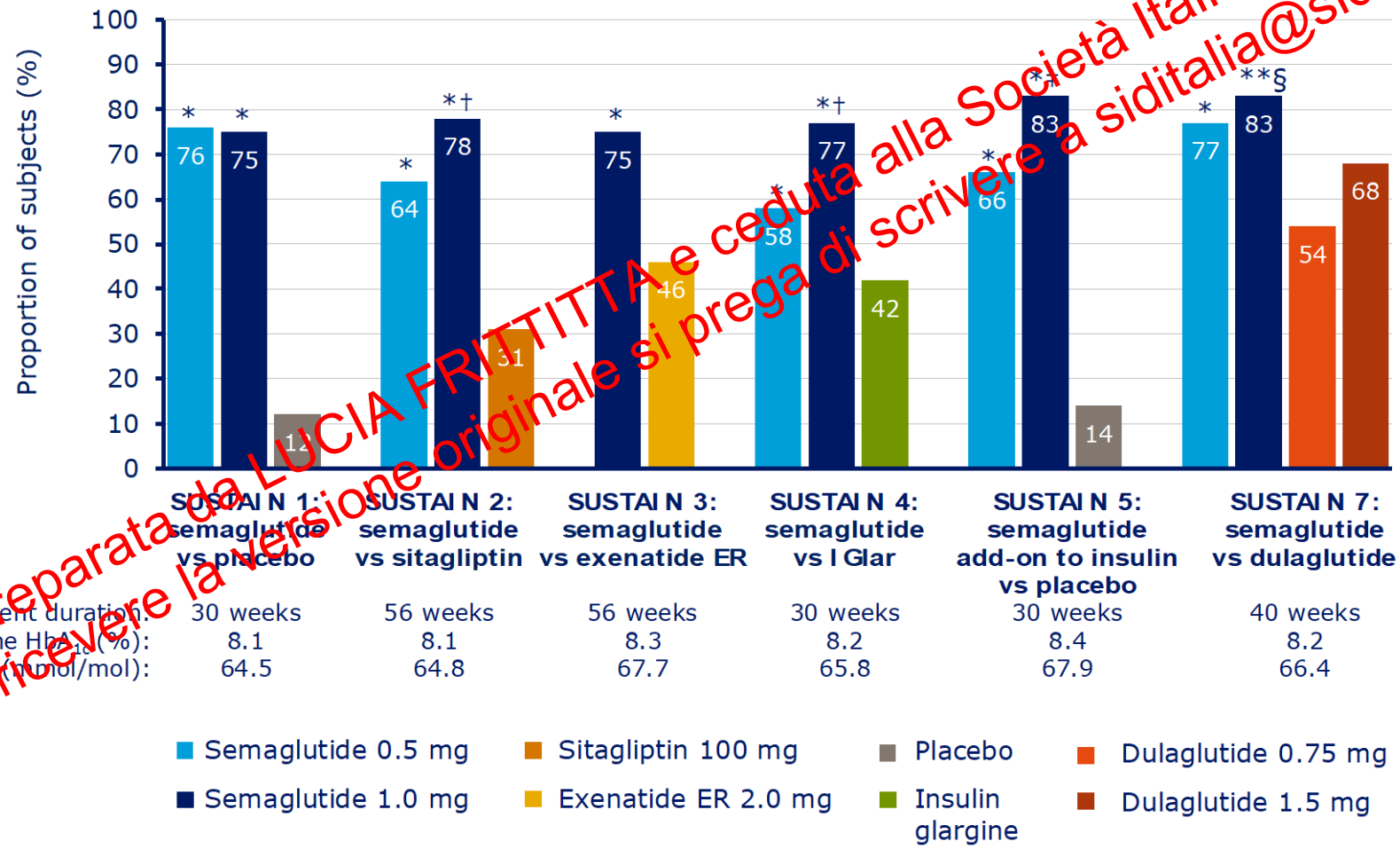
Sustain 1-5



Change in body weight by nausea or vomiting

5 trials

Proportion of subjects achieving an HbA1c reduction of ≥1.0% (SUSTAIN 1–5 and 7)

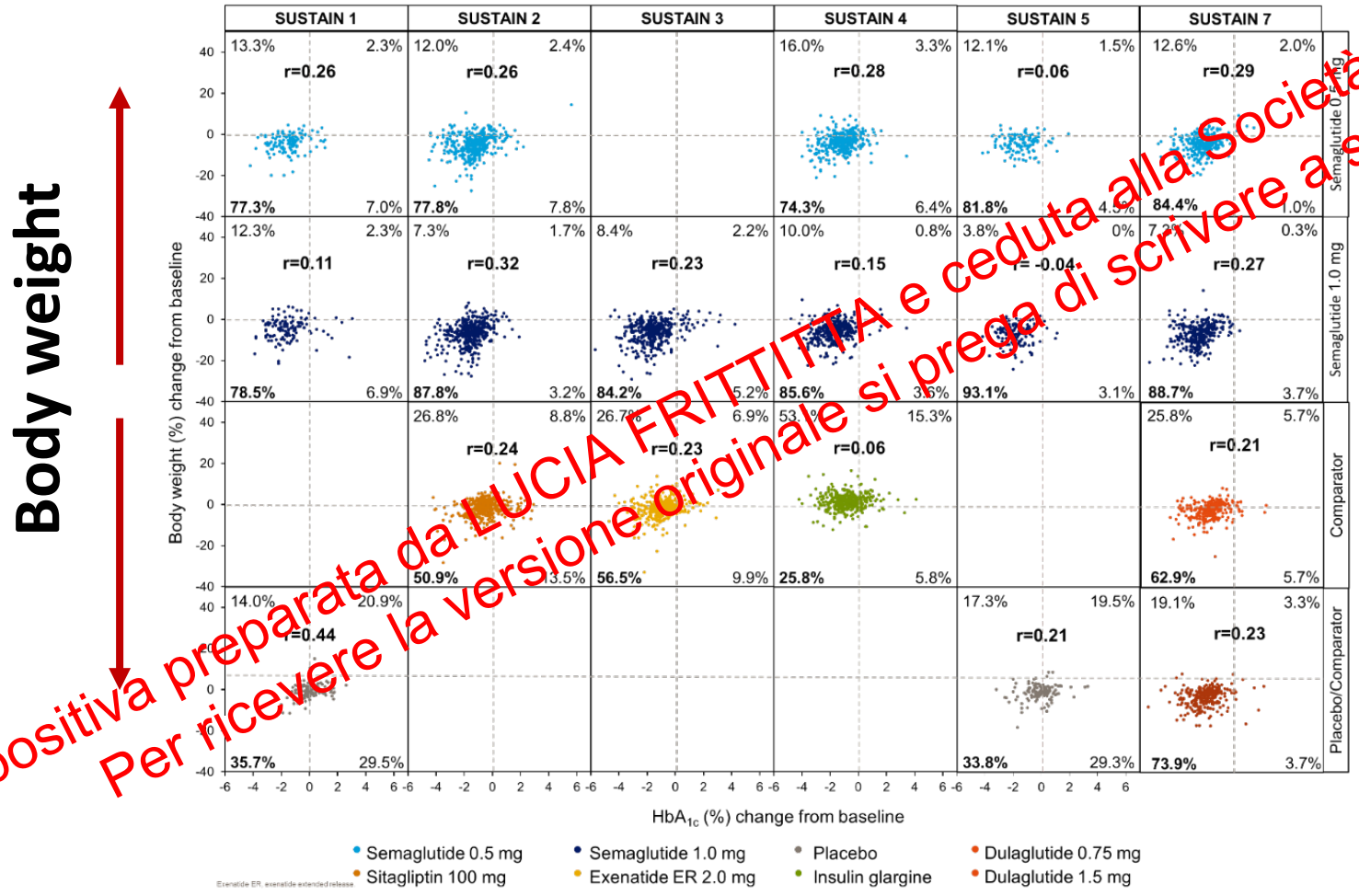


1. Rodbard HW et al. Endocr Practice, 2019

Change in HbA_{1c} and body weight

- SUSTAIN 1–5 AND 7[1,2]

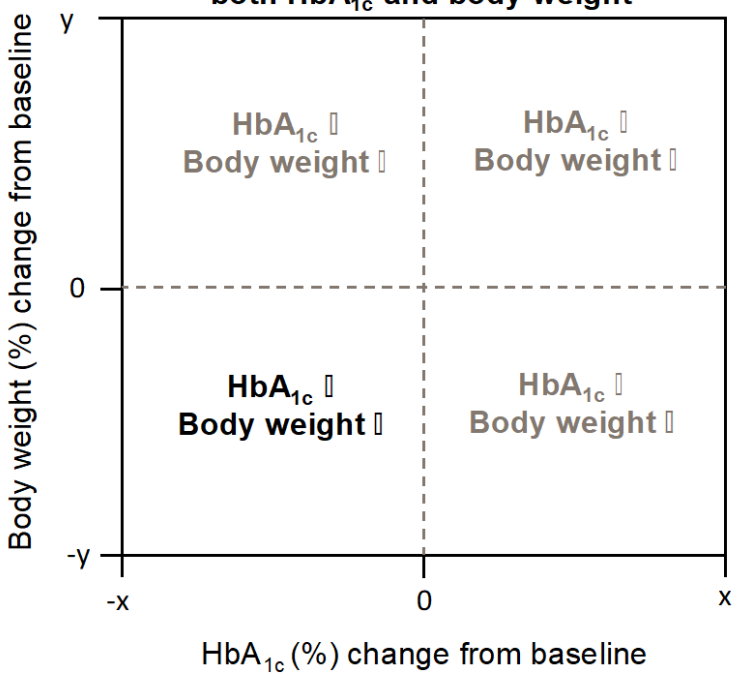
Vs. Pbo Sita Ex LAR Glar +glar /pbo Dula



Body weight

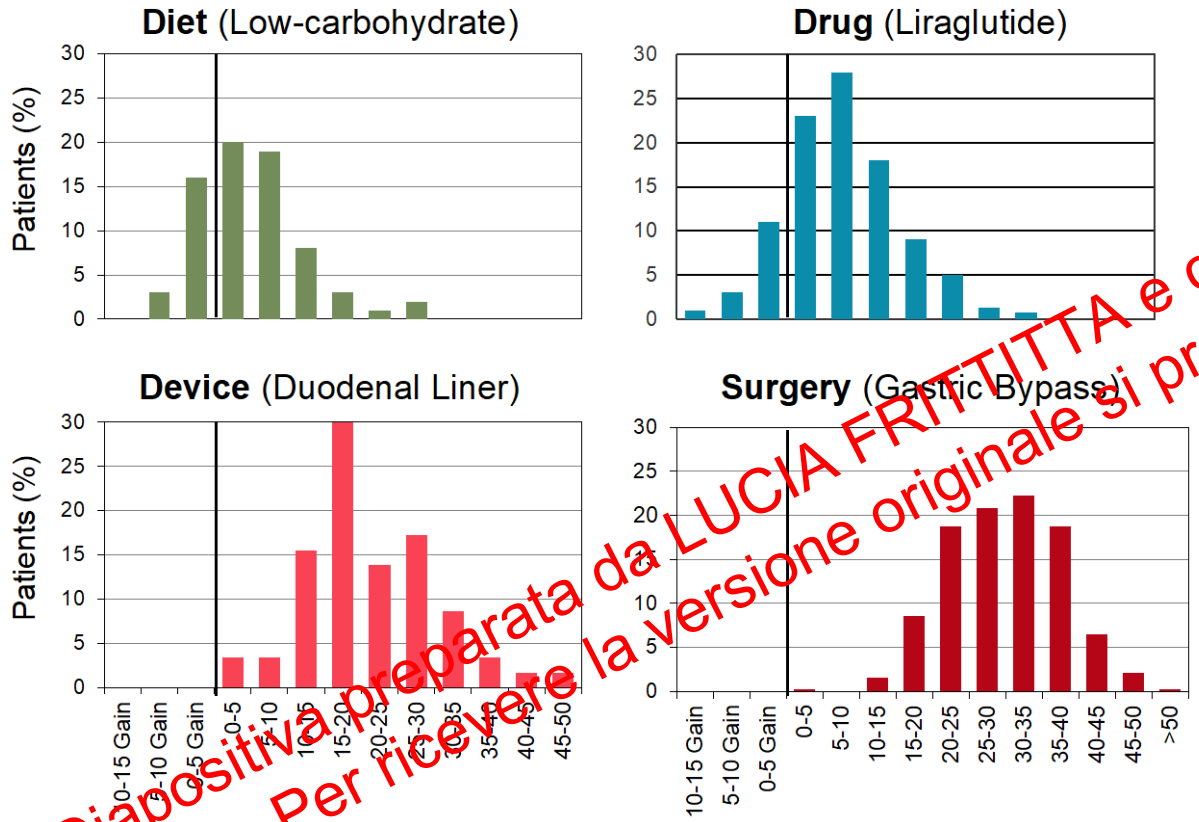
HbA1c

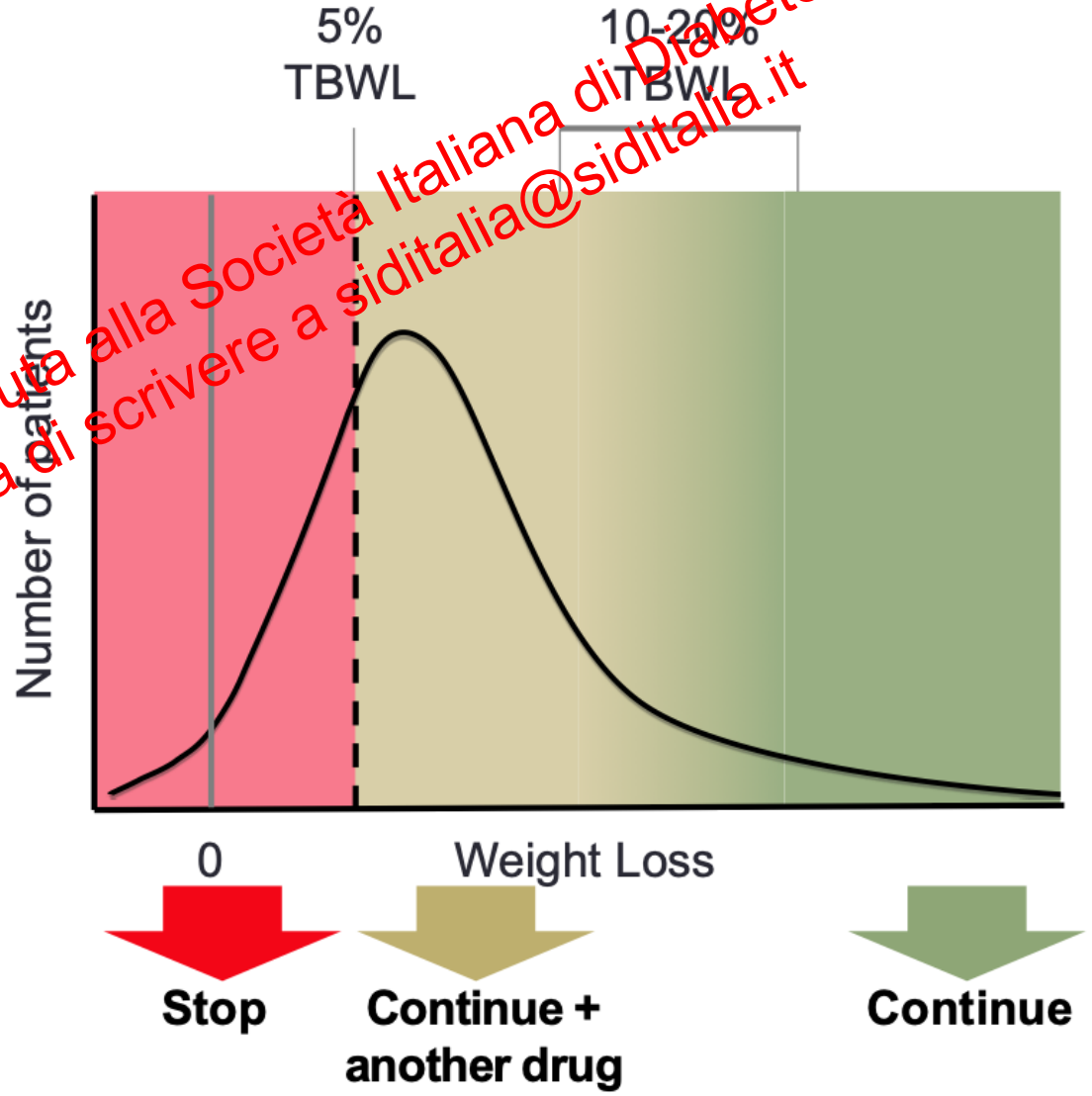
Graphic representation of scatter plot quadrants. Ideally, individual subjects would cluster in the lower left quadrant, indicating a reduction in both HbA_{1c} and body weight



1. Rodbard HW et al. Endocr Practice, . 2019

Weight Loss Varies Widely Among Patients

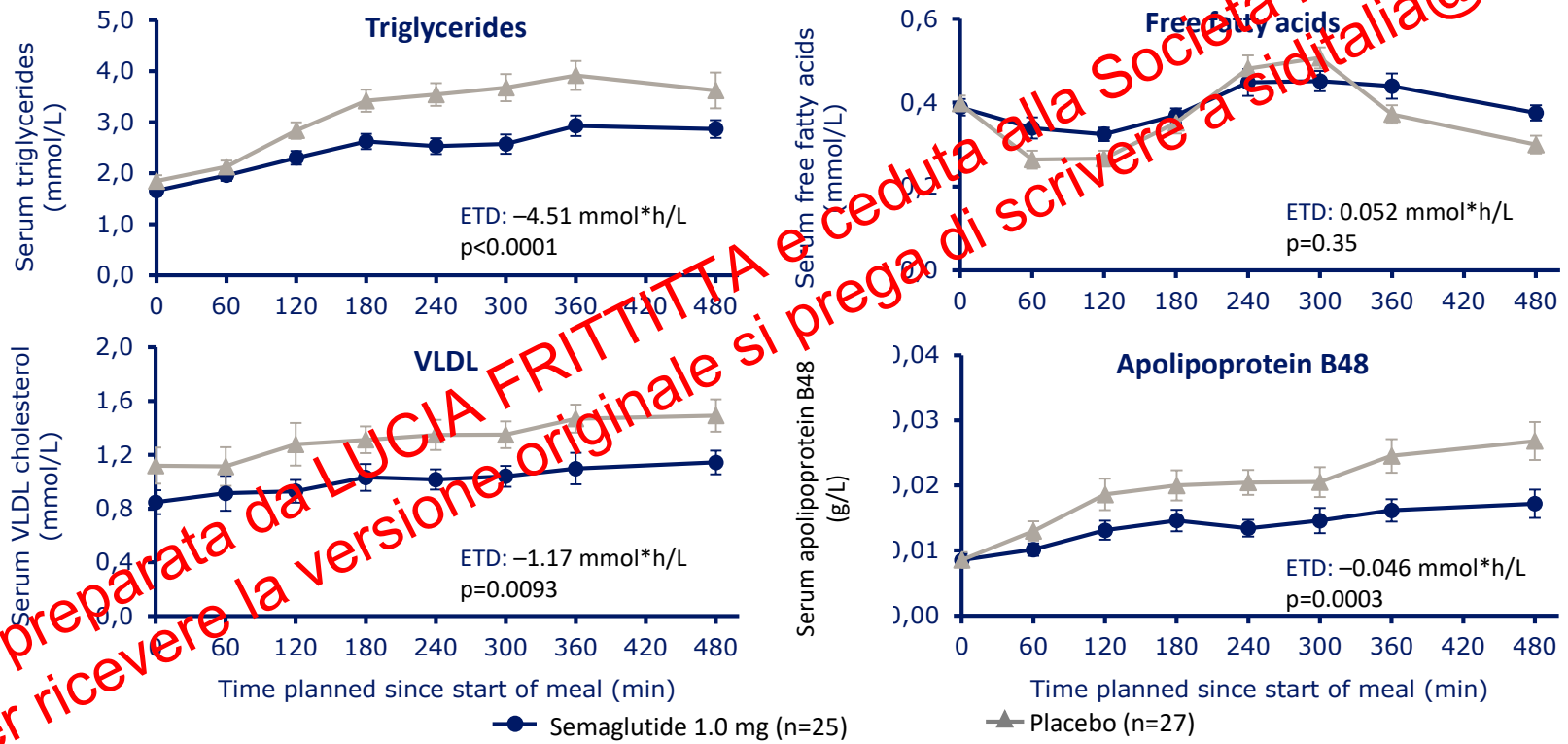




Kaplan LM

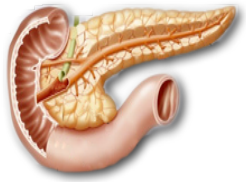
Semaglutide improves postprandial lipid profile

- SUBJECTS WITH OBESITY AT FAT-RICH BREAKFAST



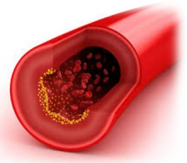
Hjerpsted JB et al. *Diabetes Obes Metab* 2018;20:610–9.

Summary of semaglutide mechanism of action



Semaglutide increases insulin secretion and beta-cell responsiveness, and suppresses hepatic glucose output in a glucose-dependent manner

Energy intake, food consumption and body weight are reduced with semaglutide vs placebo



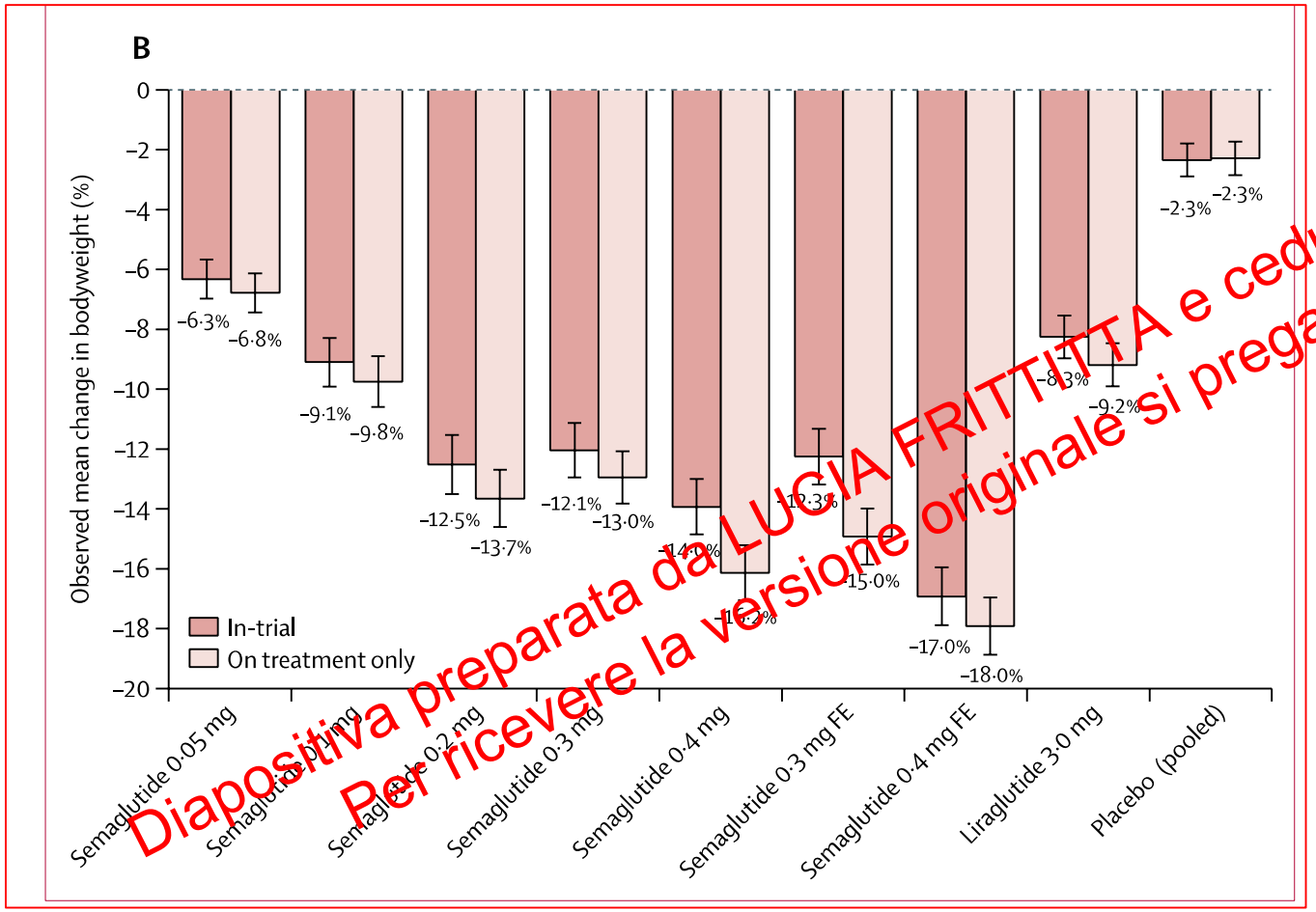
Semaglutide lowers postprandial lipids and attenuates plaque lesion progression in atherosclerotic mouse models

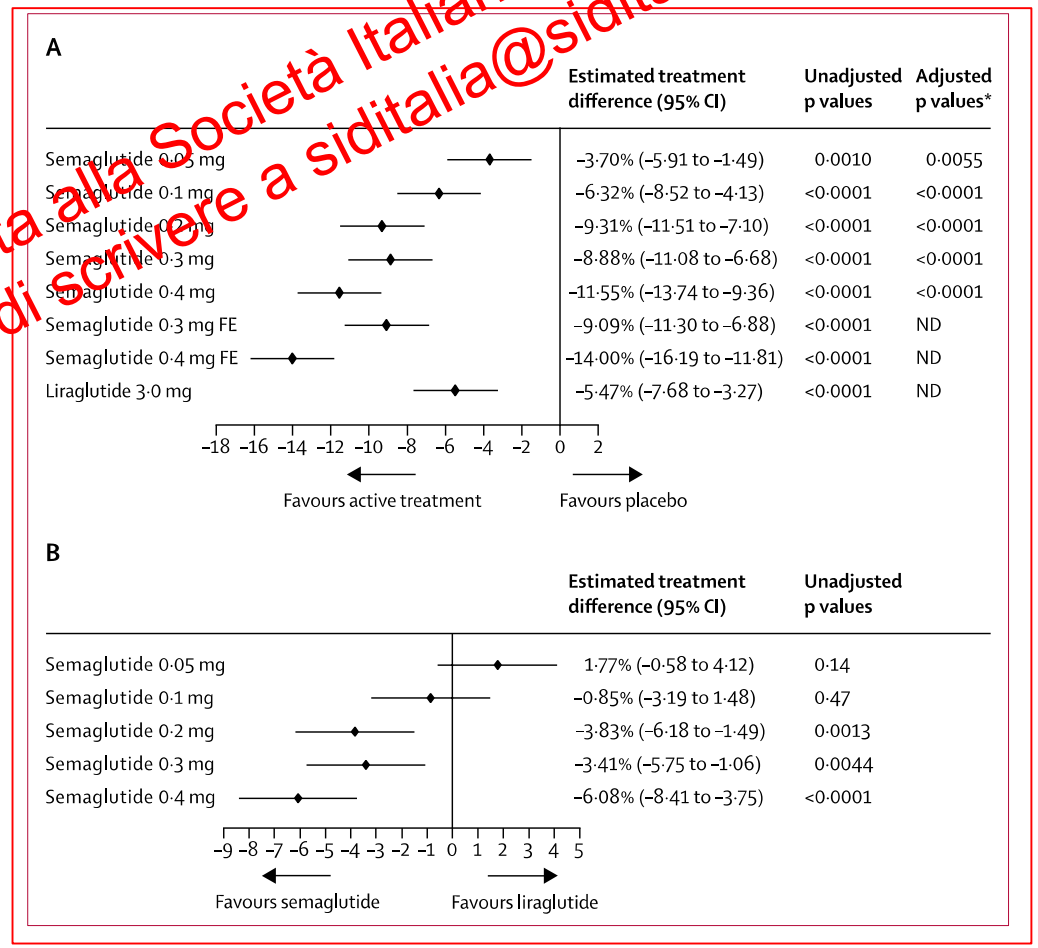
AE

The GI AE rate was higher with semaglutide than comparators

Kapitza C et al. *Diabetologia* 2017;60:1390–9; 2. Korsatko S et al. *Diabetes Obes Metab* 2018;20:2565–73; 3. Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51. 4. Hjerpsted JB et al. *Diabetes Obes Metab* 2018;20:610–9; 5. Rakipovski G et al. *JACC Basic Transl Sci* 2018;3:844–57.

Semaglutide induce weight loss in a dose dependent manner





O'Neil PA, Lancet 2018

Adverse Events

	Semaglutide 0·05 mg (n=103)	Semaglutide 0·1 mg (n=102)	Semaglutide 0·2 mg (n=103)	Semaglutide 0·3 mg (n=103)	Semaglutide 0·4 mg (n=102)	Semaglutide 0·3 mg FE (n=102)	Semaglutide 0·4 mg FE (n=103)	Liraglutide 3·0 mg (n=103)	Placebo pooled (n=136)
Most common events†									
Nausea	32 (31%)	42 (41%)	45 (44%)	43 (42%)	49 (48%)	55 (54%)	50 (49%)	46 (45%)	24 (18%)
Diarrhoea	20 (19%)	25 (25%)	35 (34%)	27 (26%)	39 (38%)	28 (27%)	28 (27%)	29 (28%)	16 (12%)
Constipation	13 (13%)	22 (22%)	26 (25%)	18 (17%)	24 (24%)	19 (19%)	29 (28%)	24 (23%)	6 (4%)
Nasopharyngitis	16 (16%)	23 (23%)	19 (18%)	15 (15%)	19 (19%)	16 (16%)	20 (19%)	16 (16%)	16 (12%)
Vomiting	8 (8%)	18 (18%)	24 (23%)	11 (11%)	18 (18%)	21 (21%)	23 (22%)	11 (11%)	6 (4%)
Decreased appetite	8 (8%)	17 (17%)	13 (13%)	13 (13%)	14 (14%)	18 (18%)	20 (19%)	12 (12%)	5 (4%)
Headache	7 (7%)	15 (15%)	10 (10%)	10 (10%)	21 (21%)	14 (14%)	11 (11%)	15 (15%)	15 (11%)
Eructation	4 (4%)	8 (8%)	14 (14%)	8 (8%)	7 (7%)	17 (17%)	10 (10%)	6 (6%)	1 (1%)
Events of special interest									
Gastrointestinal disorders	64 (62%)	72 (71%)	72 (70%)	72 (70%)	84 (82%)	84 (82%)	78 (76%)	77 (75%)	52 (38%)
Gallbladder disorders	2 (2%)	2 (2%)	3 (3%)	3 (3%)	6 (6%)	7 (7%)	2 (2%)	0	5 (4%)
Hepatic events	2 (2%)	3 (3%)	2 (2%)	2 (2%)	1 (1%)	3 (3%)	0	2 (2%)	9 (7%)
Injection-site reactions	7 (7%)	9 (9%)	6 (6%)	5 (5%)	8 (8%)	8 (8%)	10 (10%)	10 (10%)	10 (7%)
Allergic reactions	5 (5%)	9 (9%)	7 (7%)	3 (3%)	8 (8%)	8 (8%)	3 (3%)	13 (13%)	10 (7%)
Neoplasms (EAC confirmed in-trial)‡	3 (3%)	1 (1%)	3 (3%)	0	4 (4%)	0	1 (1%)	3 (3%)	4 (3%)
Hypoglycaemic episodes	1 (1%)	4 (4%)	4 (4%)	5 (5%)	9 (9%)	8 (8%)	10 (10%)	4 (4%)	8 (6%)
Acute pancreatitis (EAC confirmed on-treatment)	1 (1%)	0	0	0	0	2 (2%)	0	0	1 (1%)

Conclusioni

It is possible the reorientation of the anti diabetic treatment regimen to promote secondary weight loss could have a major impact on the natural history of early type 2 diabetes with respect to the progression of retinopathy, nephropathy, and neuropathy, as well as the overall cumulative burden of type 2 diabetes treatments, including the need for insulin.

Prophylactic use of GLP1 receptor agonists in conjunction with diet and lifestyle changes in overweight adults with the goal of reducing adiposity and reducing incident type 2 diabetes might be one of the largest opportunities to influence public health in the future.

Aaron Y Kluger, Peter A McCullough, Lancet 2018