SID Società Italiana di Diabetologia

ROMA | 29 OTTOBRE 2019

ANALOGHI DEL GLP-1: STATO DELL'ARTE E PROSPETTIVE FUTURE

Possiamo puntare ancora di più sul calo ponderale?

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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:

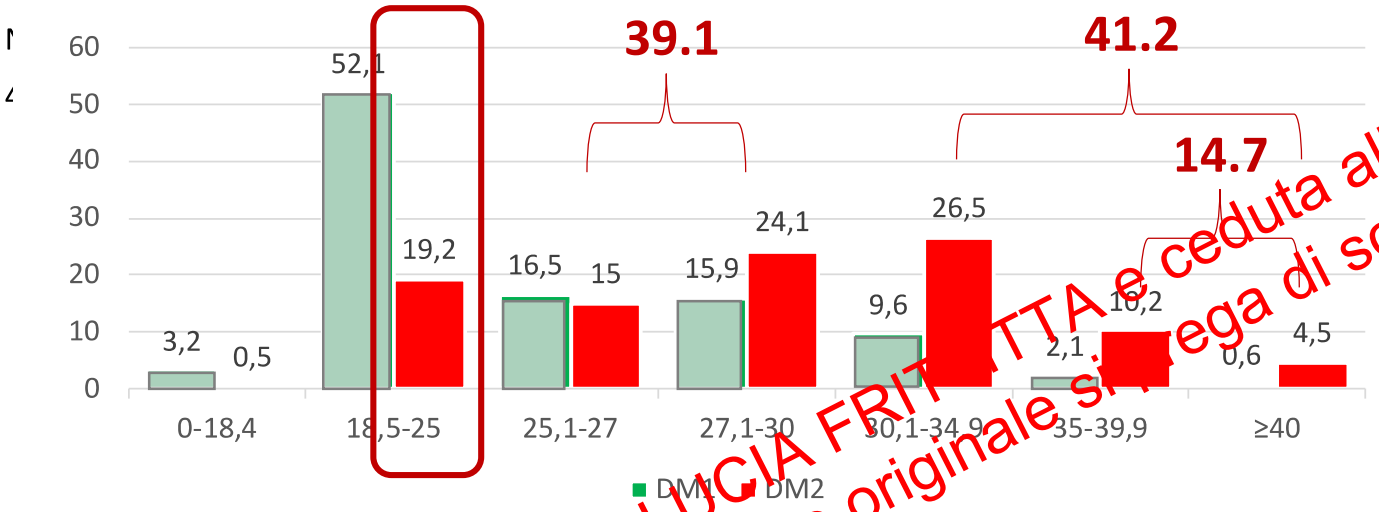
- Astra Zeneca
- Eli-Lilly
- Novo- Nordisk
- Sanofi

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.).

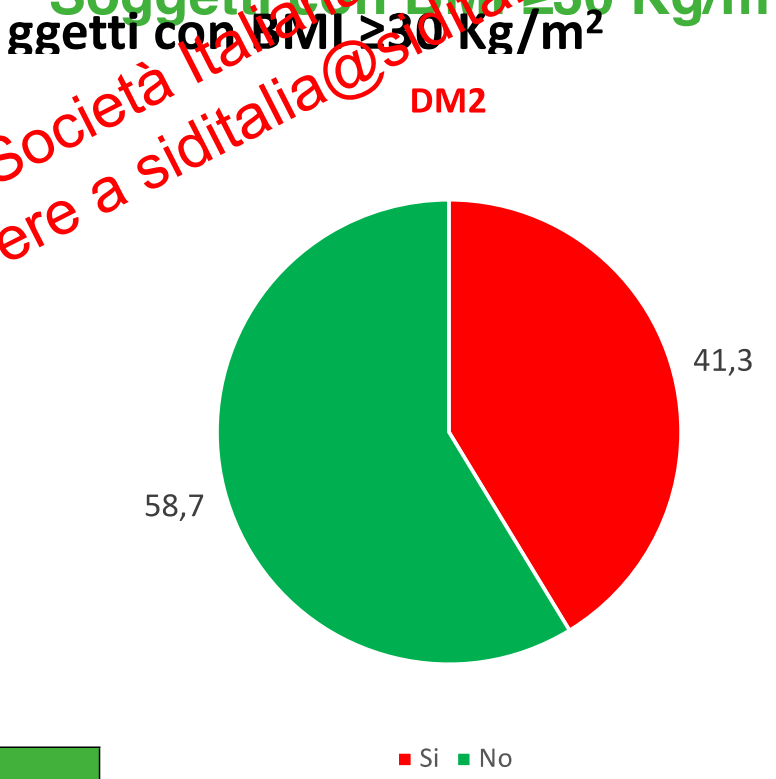
Annali AMD 2018

Andamento per 7 classi del BMI (%)

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



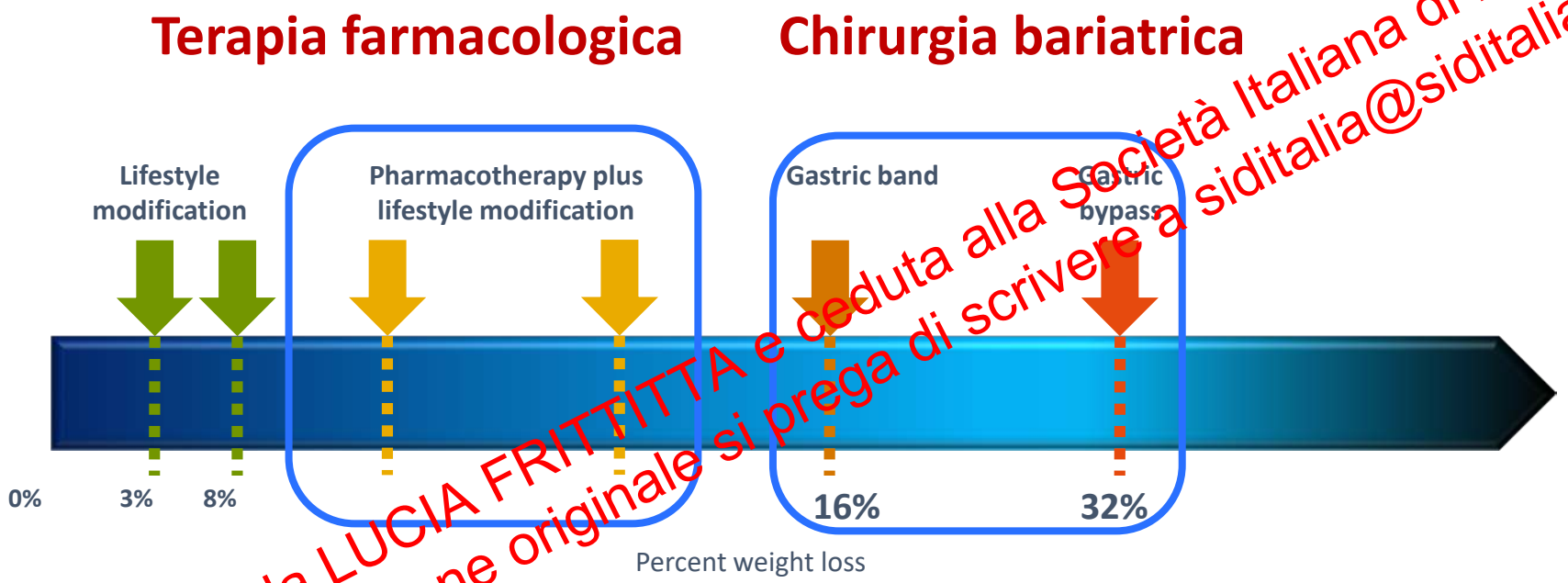
Soggetti con BMI ≥30 Kg/m²



Livelli medi del BMI (Kg/m²)

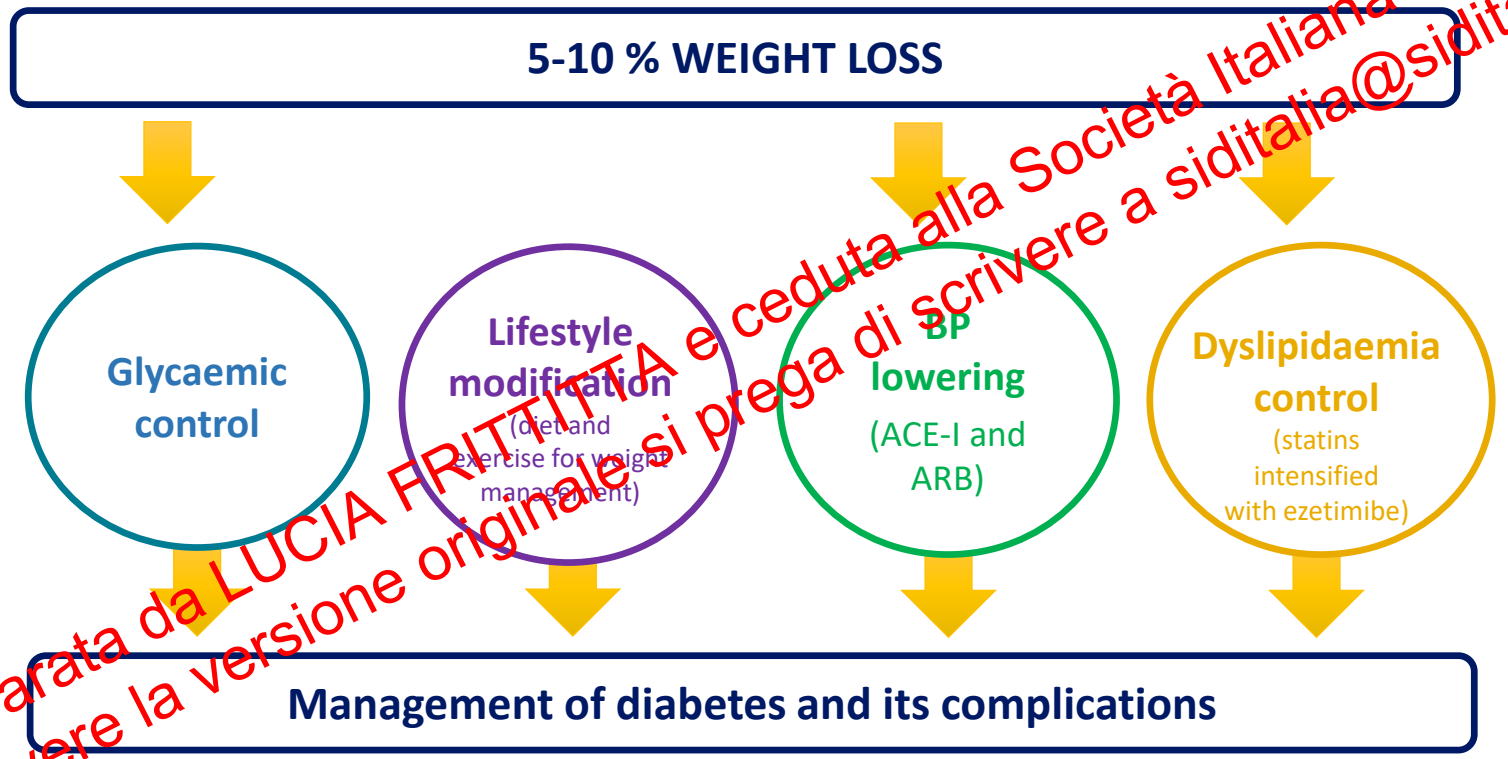
	DM1 Media ± ds	DM2 Media ± ds
BMI	25,1 ± 4,4	29,6 ± 5,5

Treatment options for people with obesity



BMI≥ 25 BMI≥ 35

Multifactorial approach improves outcomes



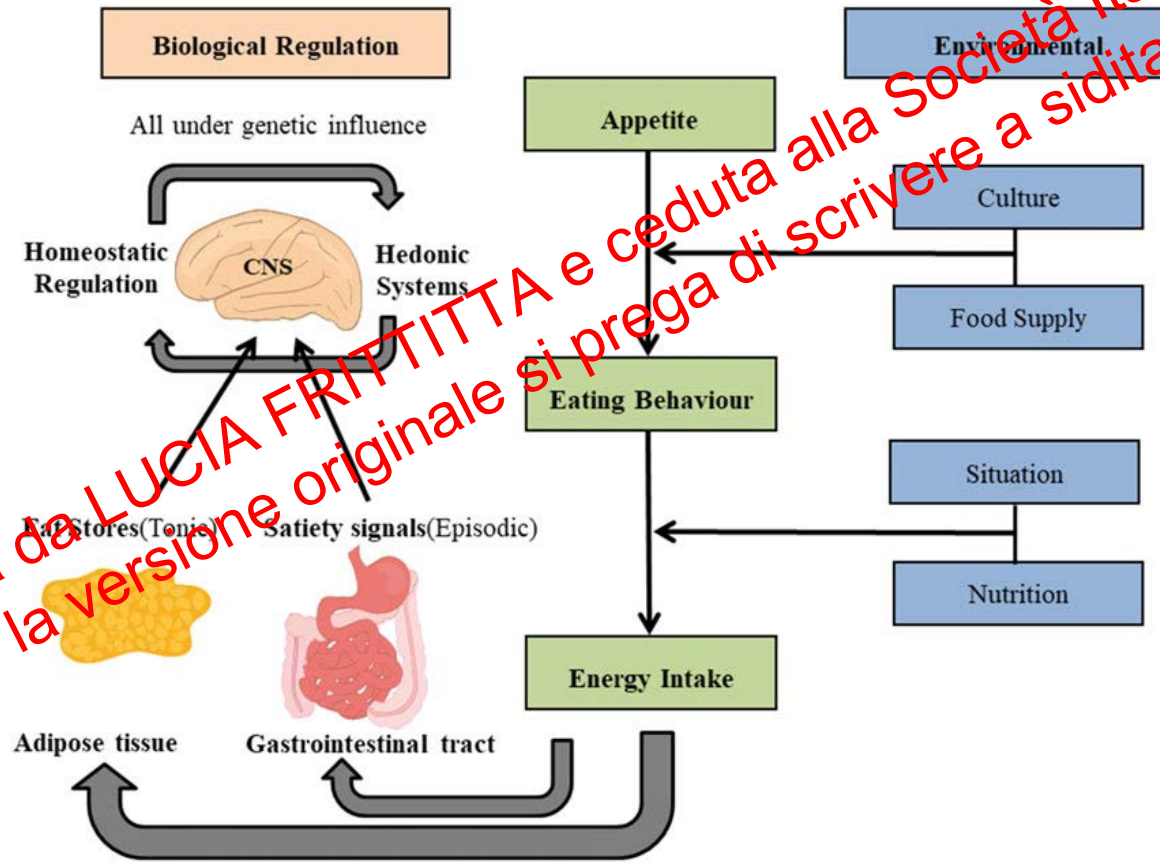
- Primary prevention methods only - platelet inhibition recommended as secondary prevention.
- *Physical activity of moderate to vigorous intensity, spread over at least 3 days/week. †ADA guidelines suggest 40 mg/dL for men, 50 mg/dL for women. American Diabetes Association. *Diabetes Care* 2019;42(Suppl.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

Personalise medicine: getting the right treatment to the right patient at the right time

What Differs Among Different Obesity Subtypes

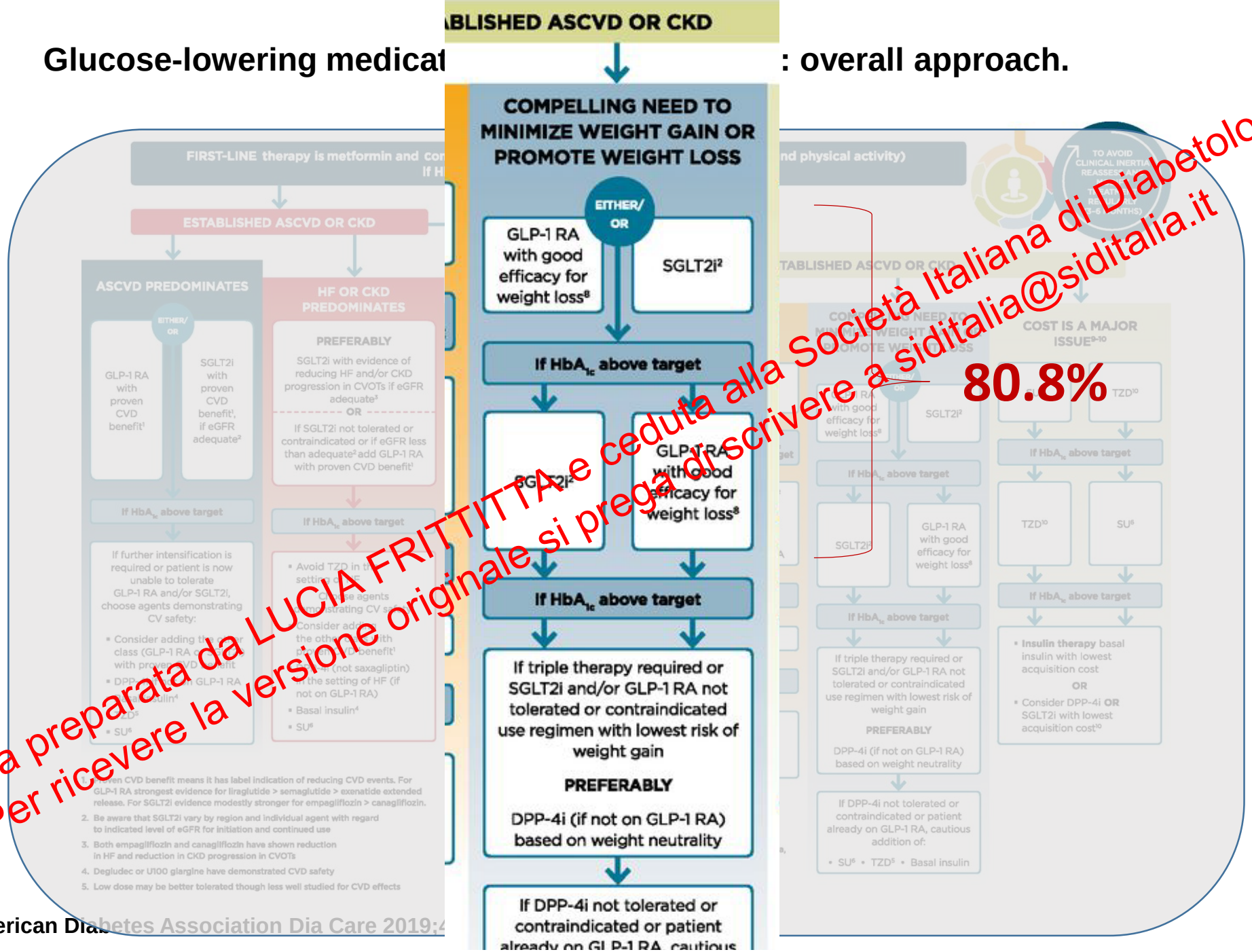
- Timing of obesity onset
- Fat location and distribution
- Metabolic consequences
- Phenotypic differences
  - Hunger
  - Satiety
  - Reward-based eating
  - Energy expenditure
- Response to environmental causes
  - Eating
  - Exercise
  - Stress
  - Sleep deprivation
  - Circadian disruption
- Response to therapies

Interaction between biology and environment in the control of energy intake in body weight



Obesity Reviews. 2019;1–13.

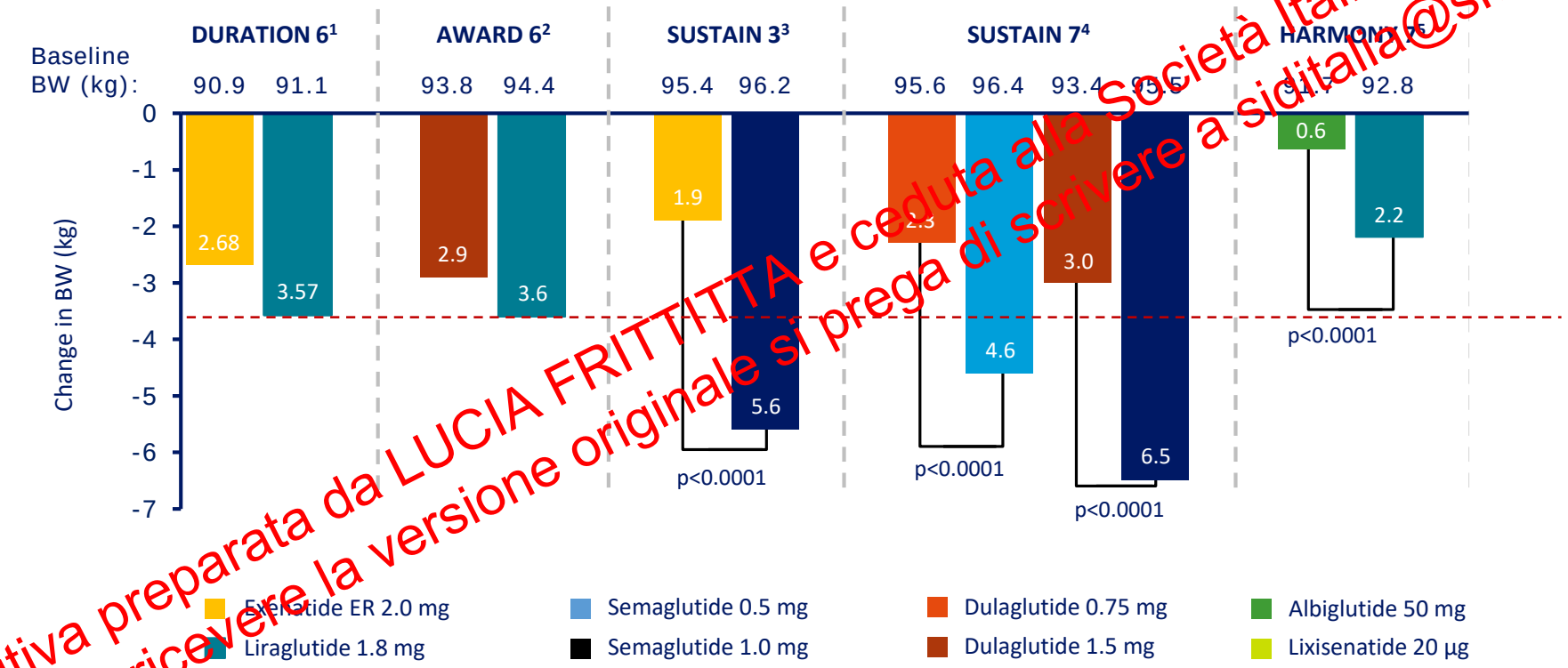
Glucose-lowering medicat : overall approach.



American Dia betes Association Dia Care 2019;4

GLP-1RAs reduce Body Weight

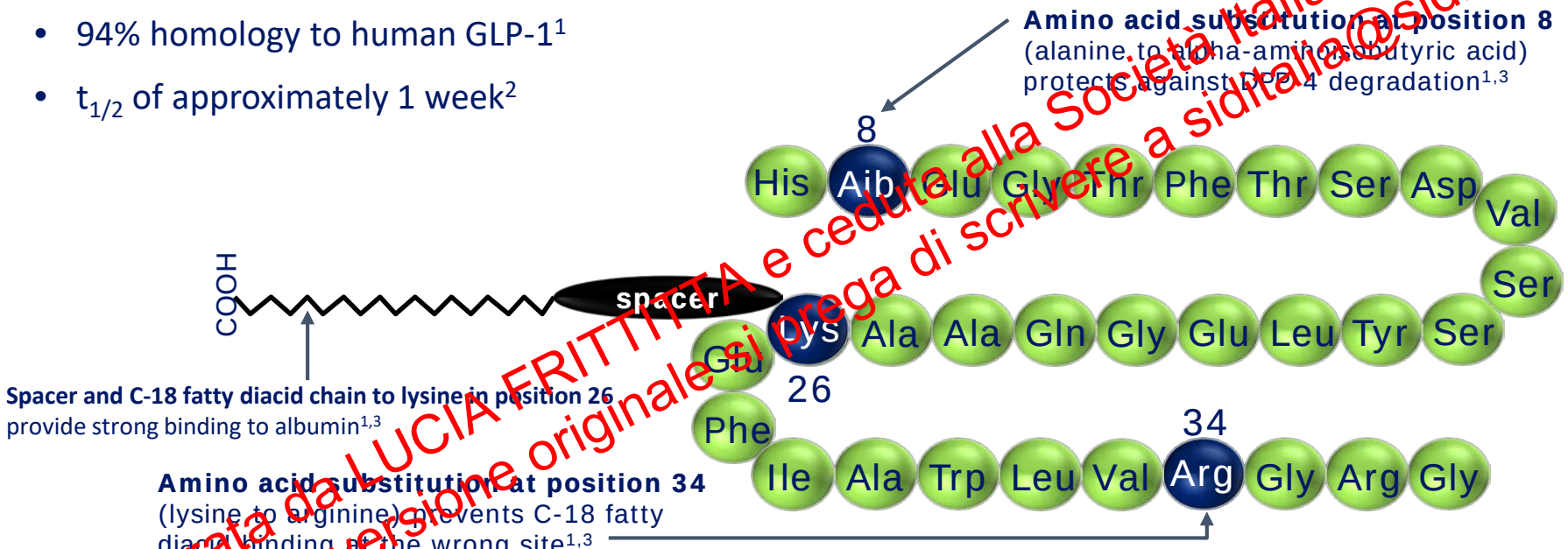
- RESULTS FROM COMPARATIVE TRIALS



- 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.

Semaglutide is a human GLP-1 analogue

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

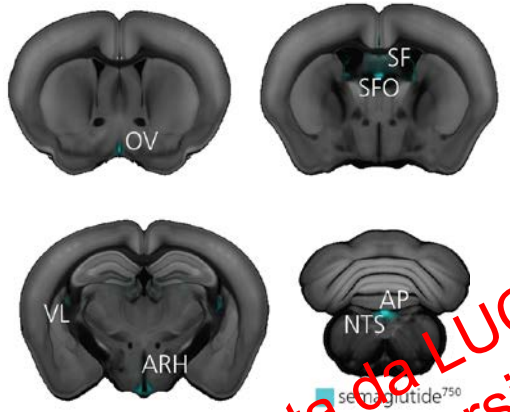


- DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, half-life.

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.

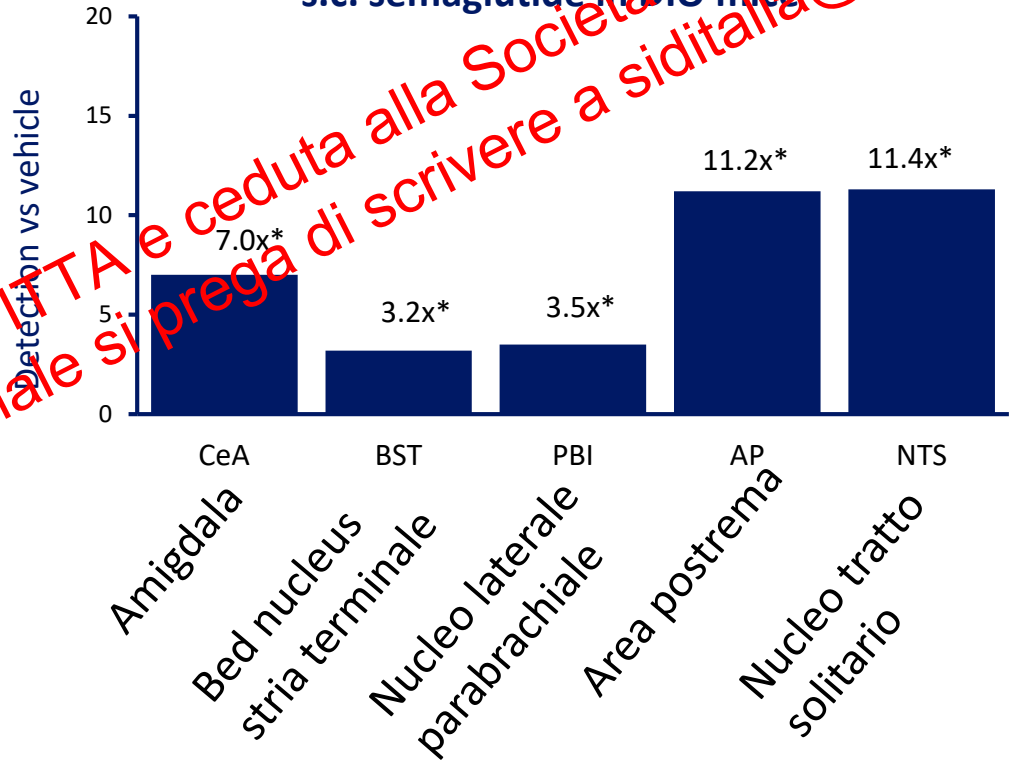
Semaglutide accesses and activates regions of the brain involved in reward behaviour and food intake

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



*p≤0.0001.

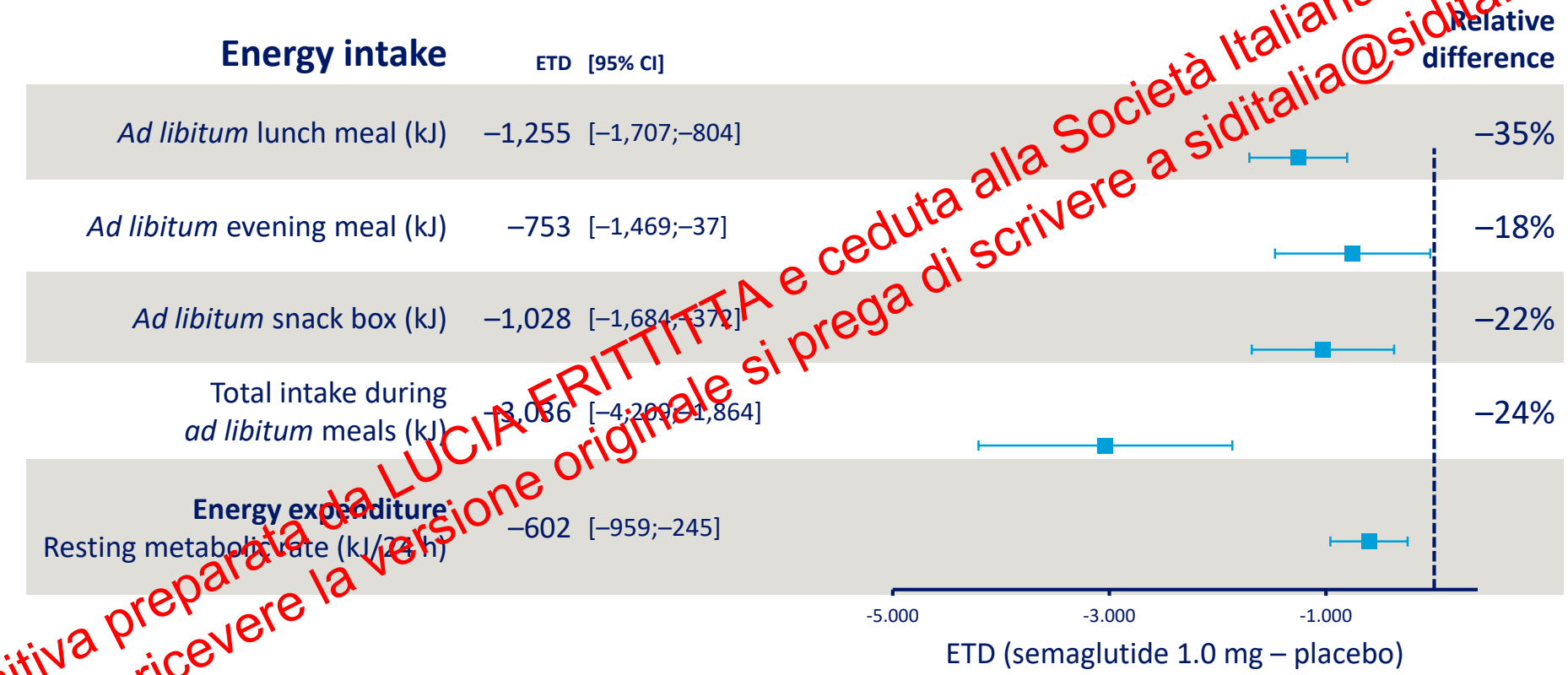
Neuronal activation following s.c. semaglutide in DIO mice[2]



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

Semaglutide treatment for 12 weeks in obese subjects

Semaglutide reduces energy intake and expenditure

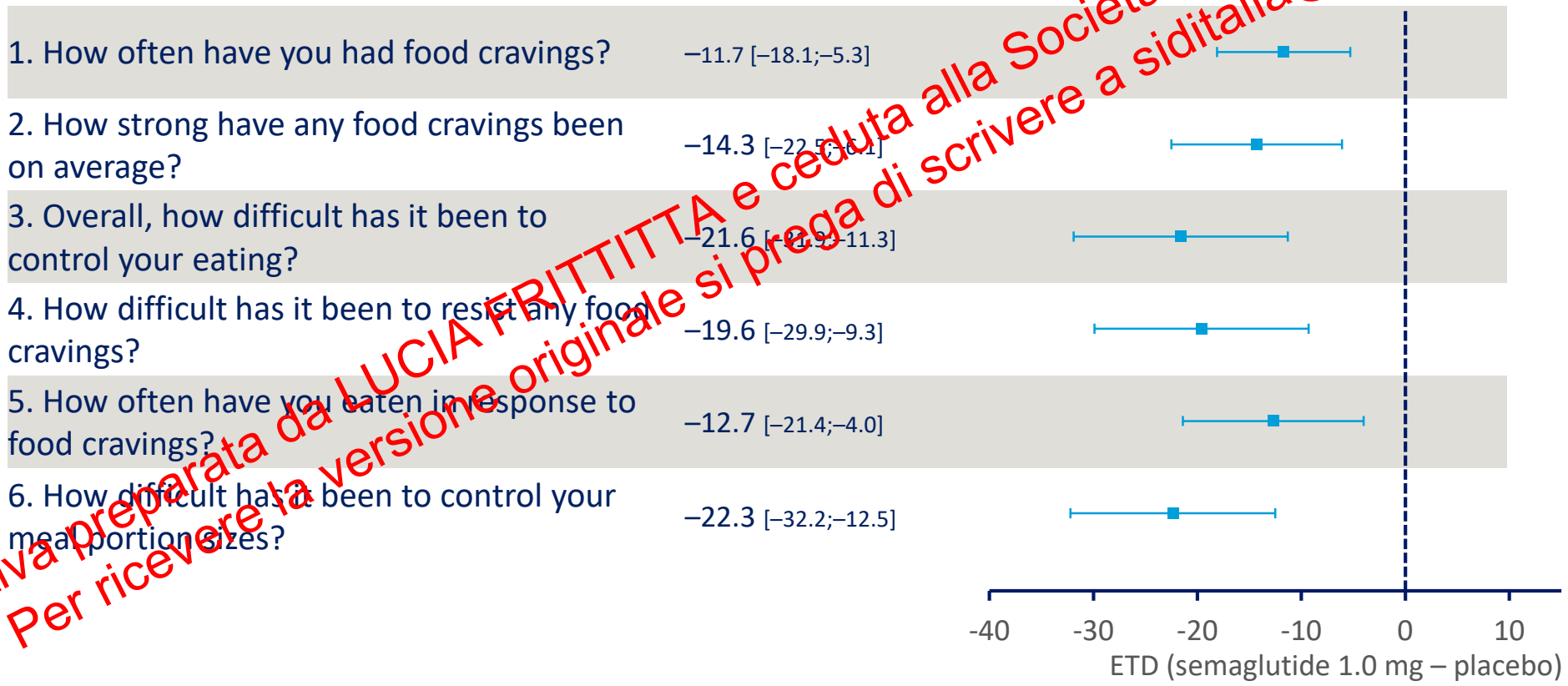


Relative difference: ETD / estimated mean for placebo x 100%. Data for 24-h resting metabolic rate are from a post hoc statistical analysis

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

Semaglutide improves control of eating and food cravings

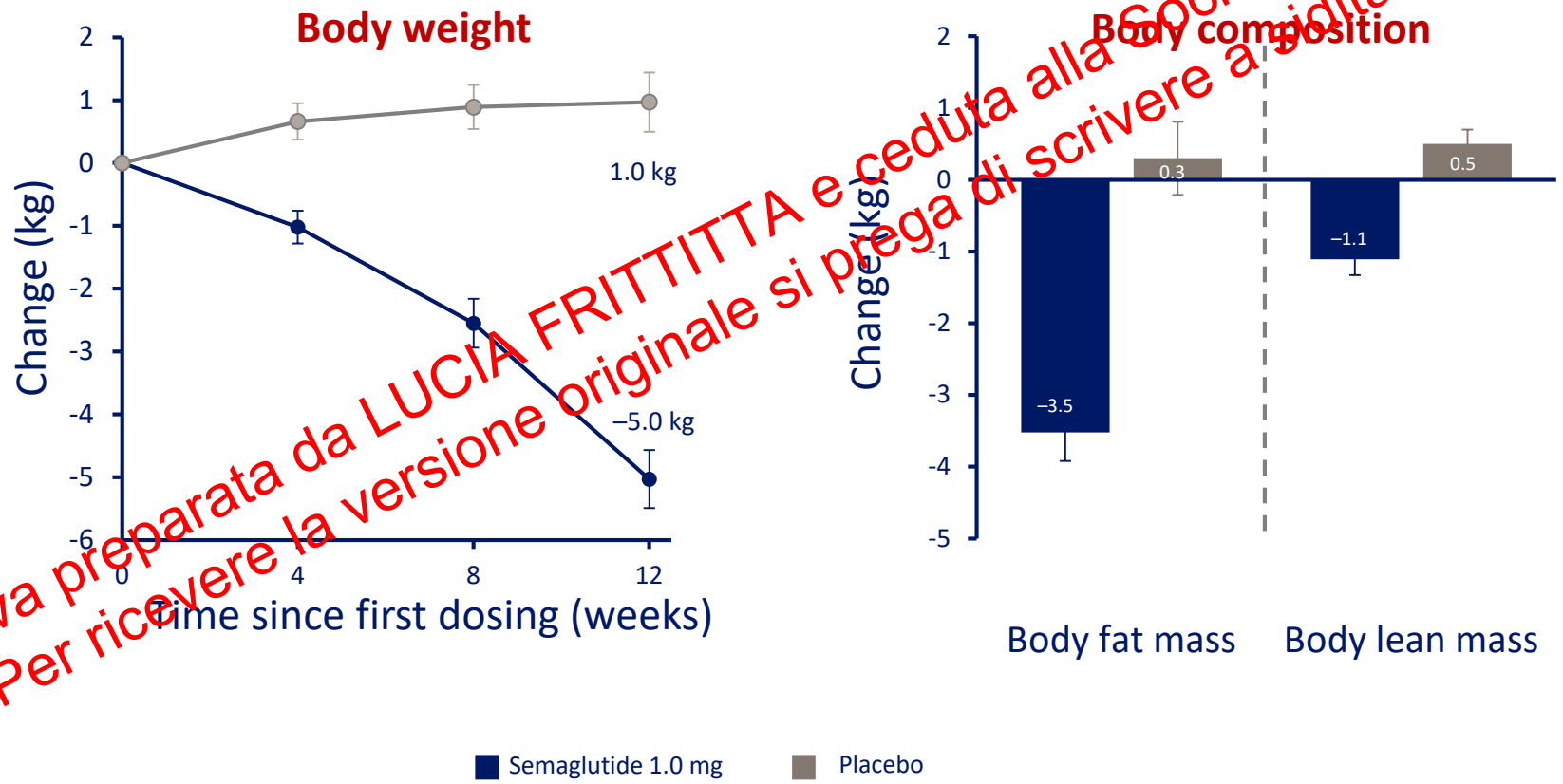
- CONTROL OF EATING QUESTIONNAIRE*



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

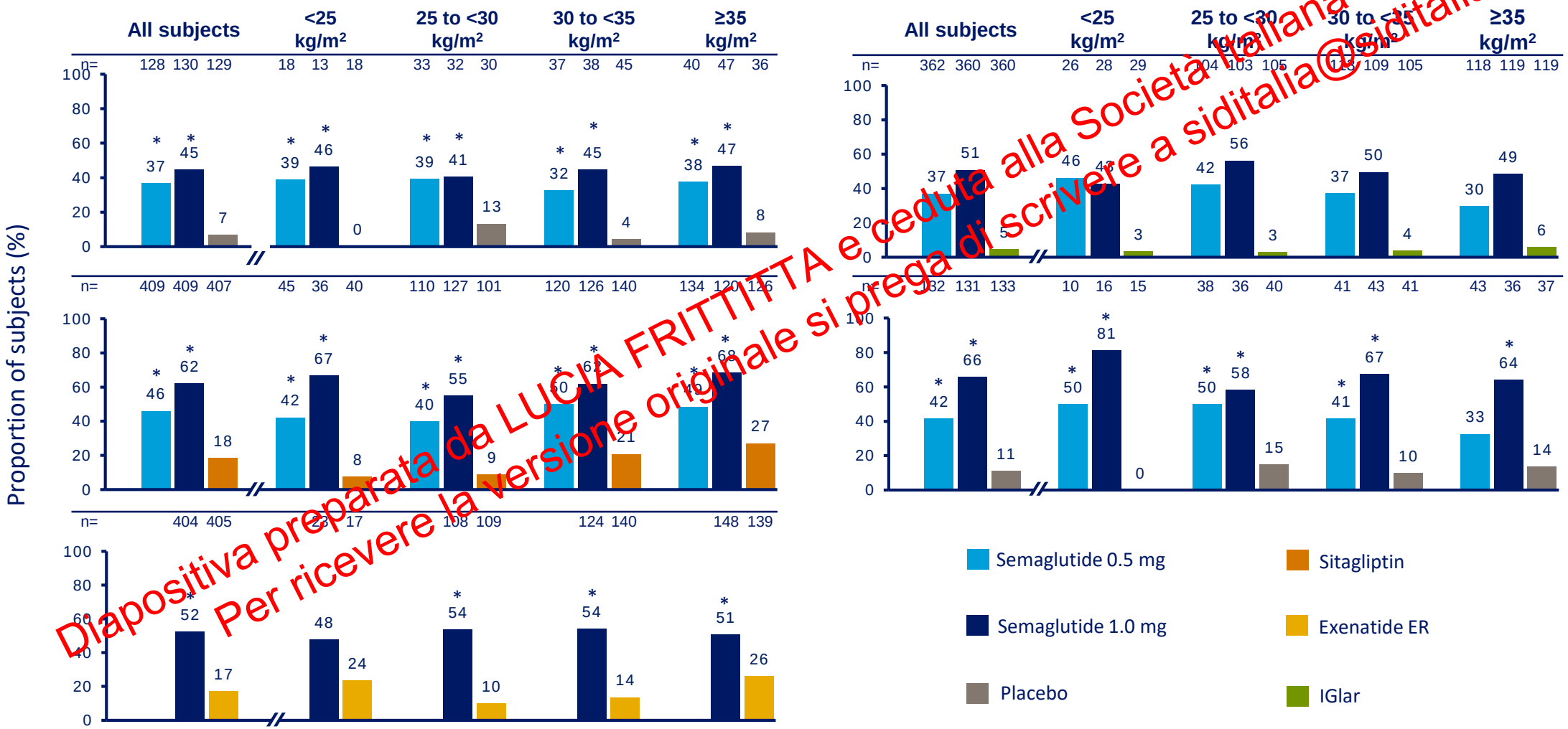
Primary mechanism of weight loss

Semaglutide reduces fat mass



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

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



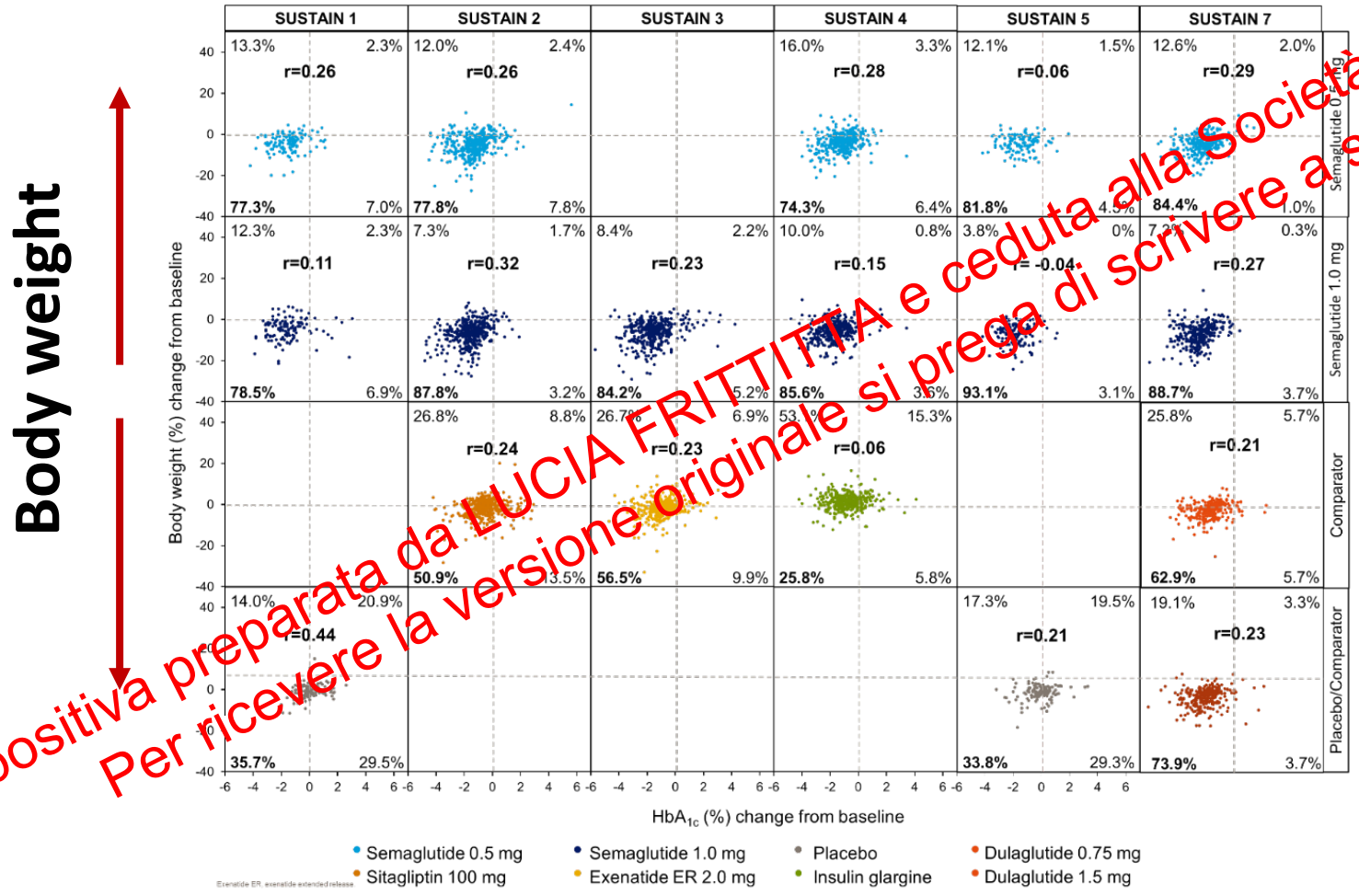
Change in body weight by nausea or vomiting

5 trials

Change in HbA_{1c} and body weight

- SUSTAIN 1–5 AND 7

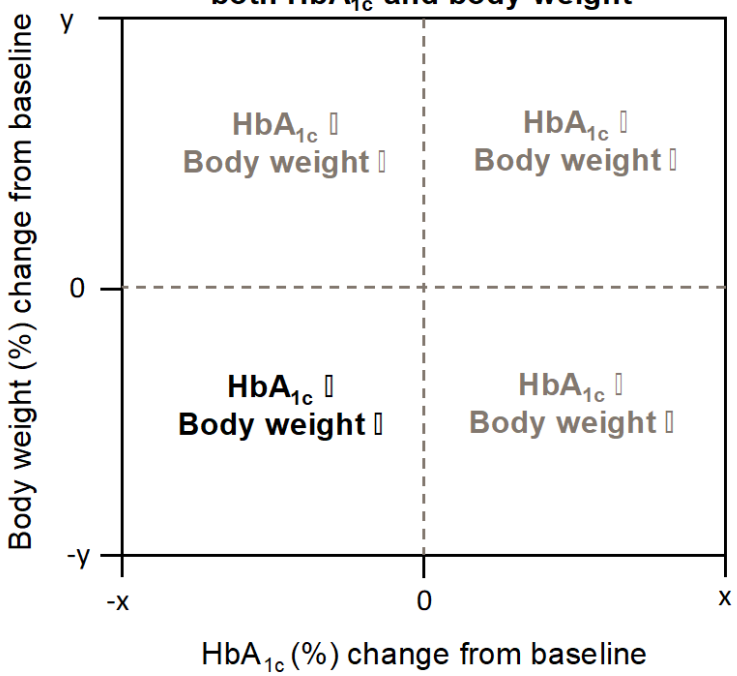
Vs. Pbo Sita Ex LAR Glar +glar /pbo Dula



Body weight

HbA1c

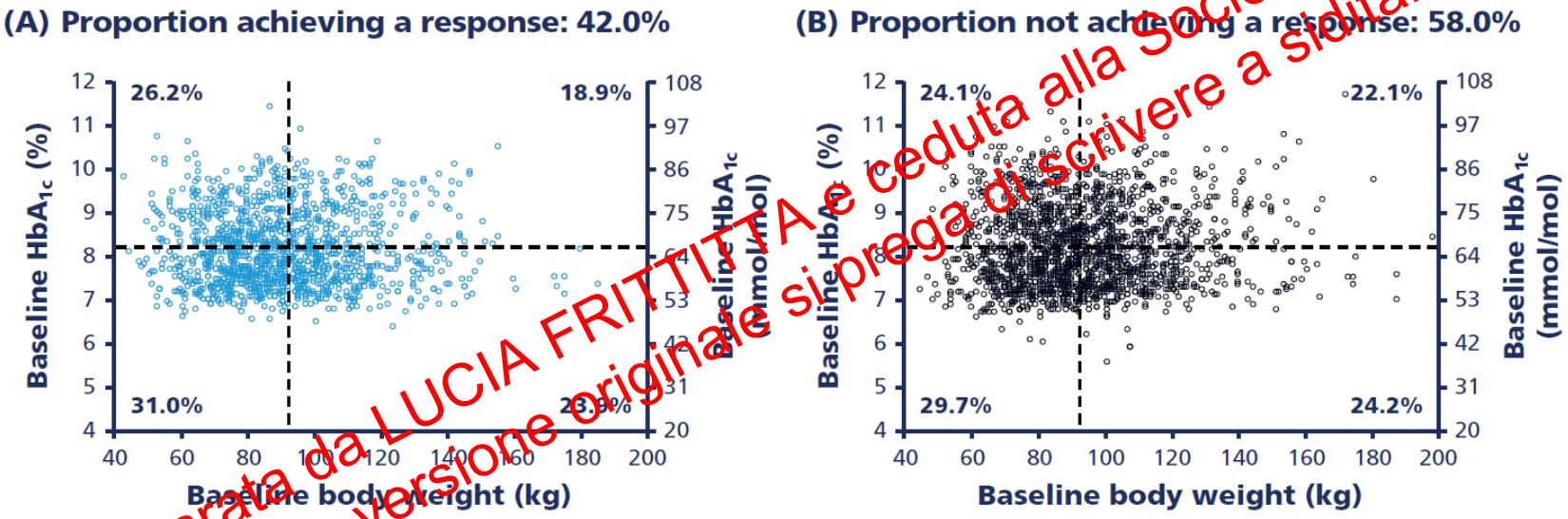
Graphic representation of scatter plot quadrants. Ideally, individual subjects would cluster in the lower left quadrant, indicating a reduction in both HbA_{1c} and body weight



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

Proportion of semaglutide-treated subjects achieving or not ≥1.0% HbA_{1c} reduction and ≥5.0% body weight loss by baseline HbA_{1c} and body weight

SUSTAIN 1–5 AND 7



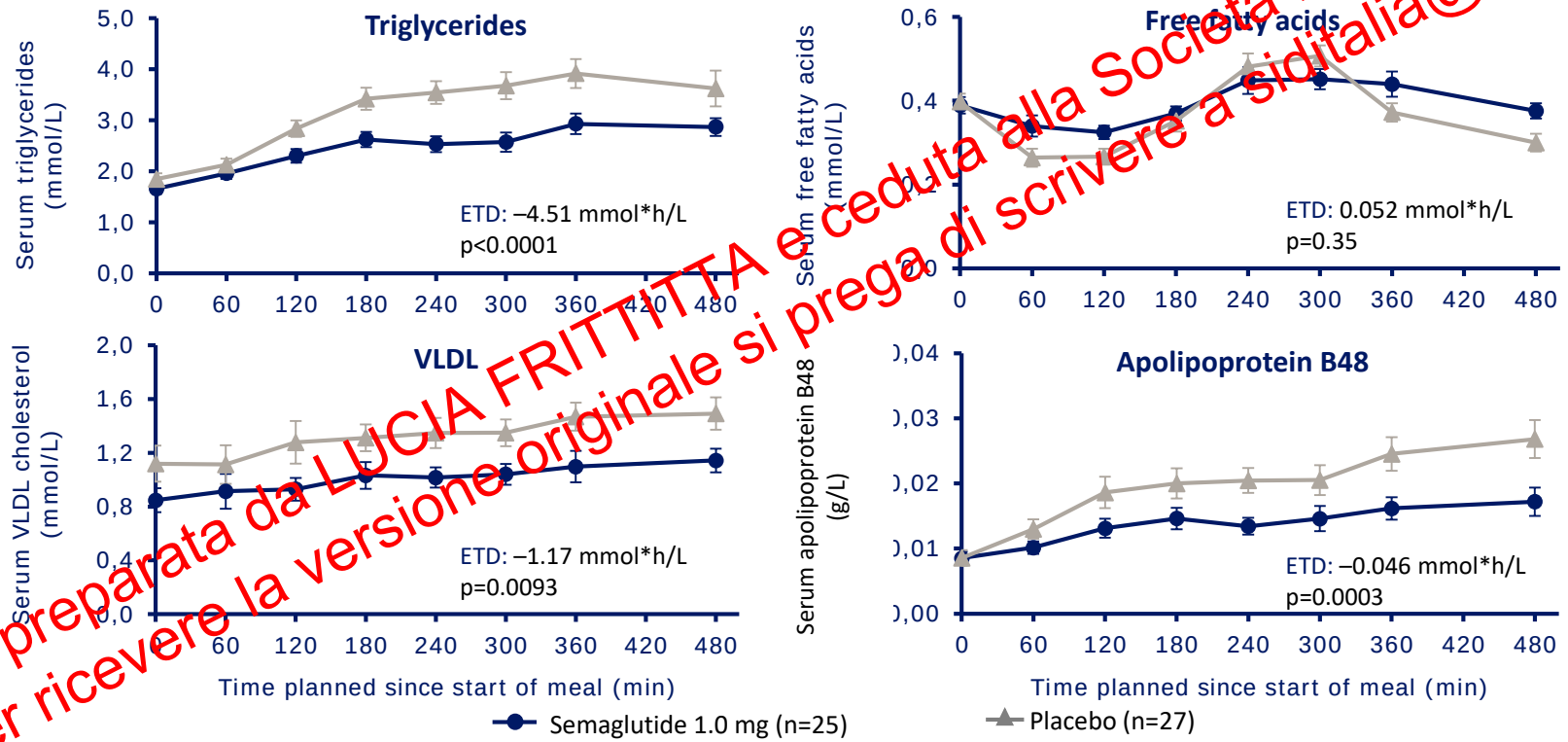
Across the SUSTAIN 1–5 and 7 trials, semaglutide once weekly provided clinically meaningful responses in composite and individual endpoints of ≥1.0% HbA_{1c} reduction and/or ≥5.0% body weight loss, across a range of baseline HbA_{1c} and body weight values

Dashed lines indicate mean baseline values for HbA_{1c} (8.2%/66 mmol/mol) and body weight (93.3 kg). ADA, American Diabetes Association.

Aroda VR et al. Presentation at the 79th ADA Scientific Sessions, 7–11 June 2019, San Francisco, CA, USA. Poster 1003-P.

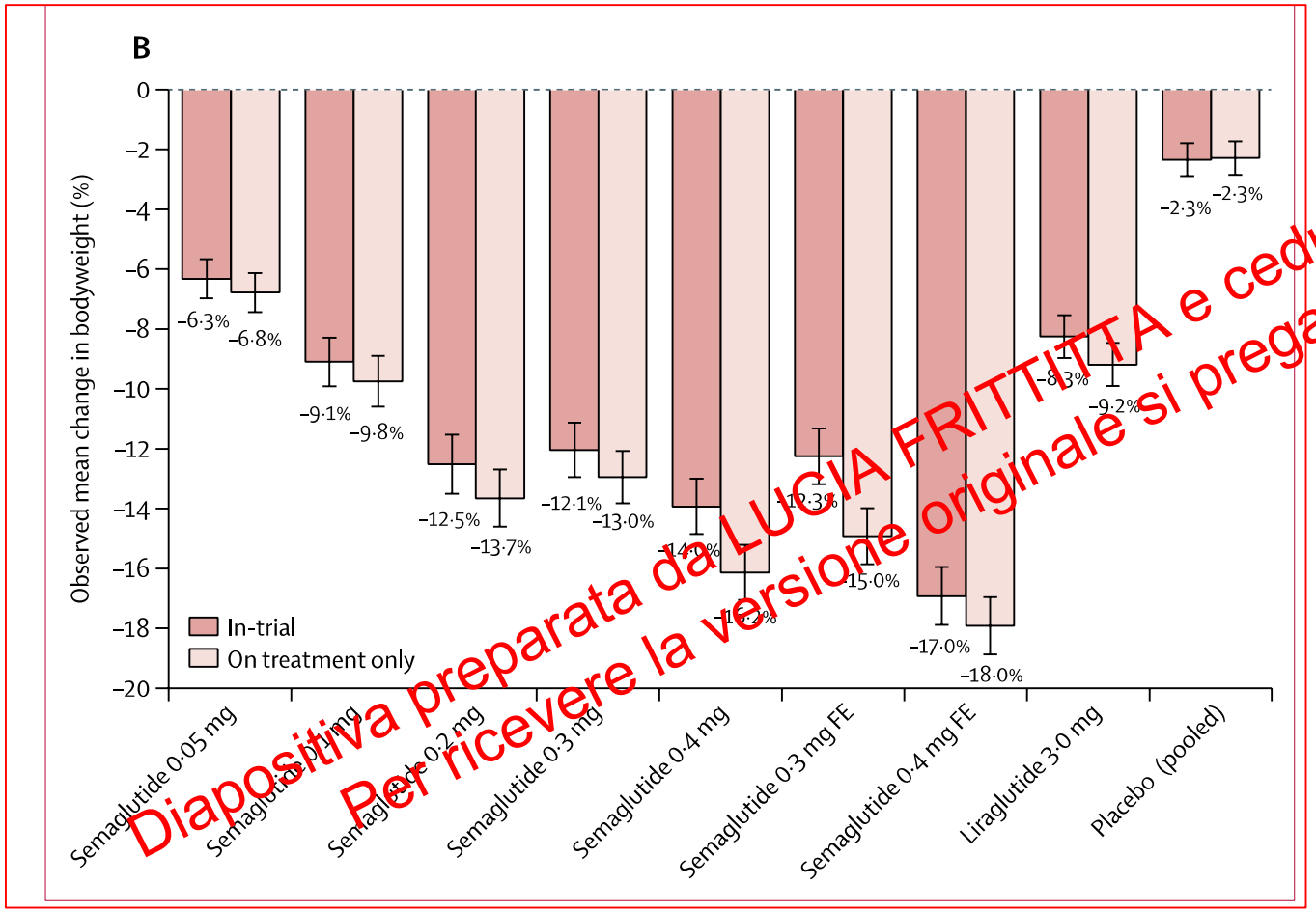
Semaglutide improves postprandial lipid profile

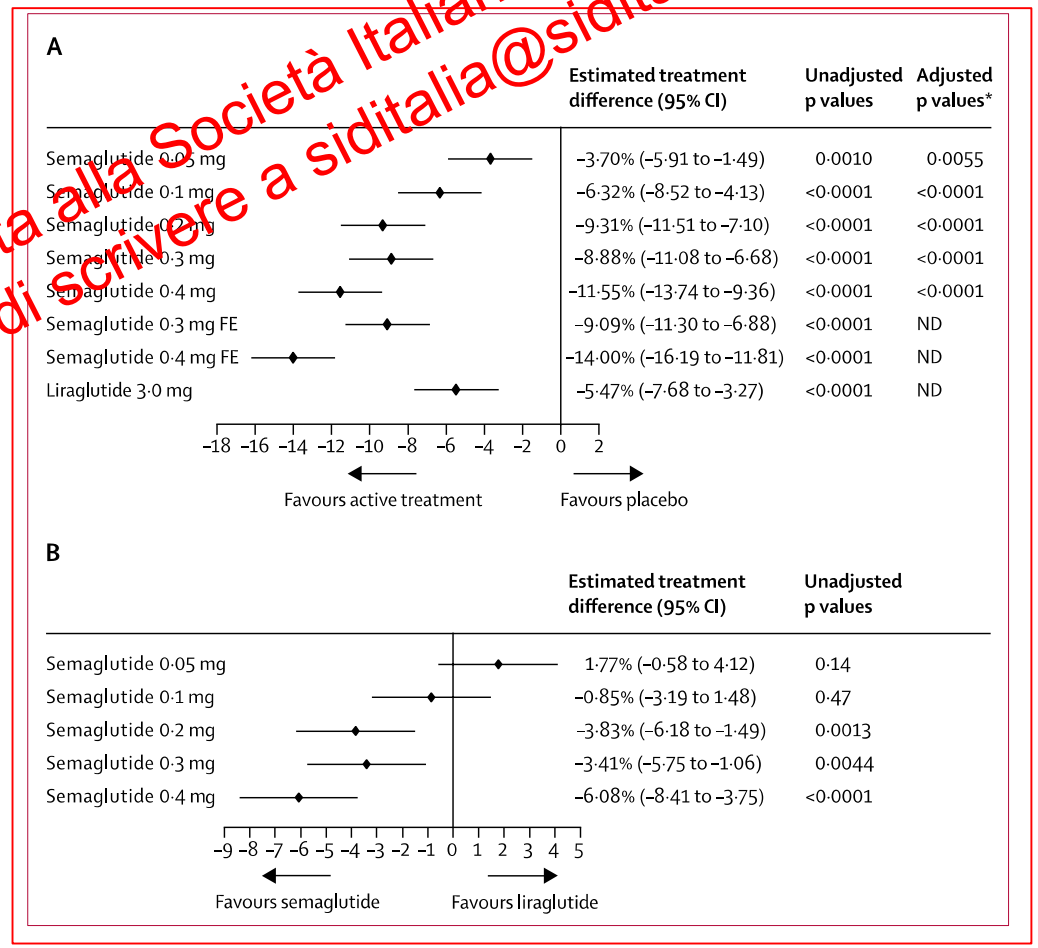
- SUBJECTS WITH OBESITY AT FAT-RICH BREAKFAST



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

Semaglutide induce weight loss in a dose dependent manner in obese patients

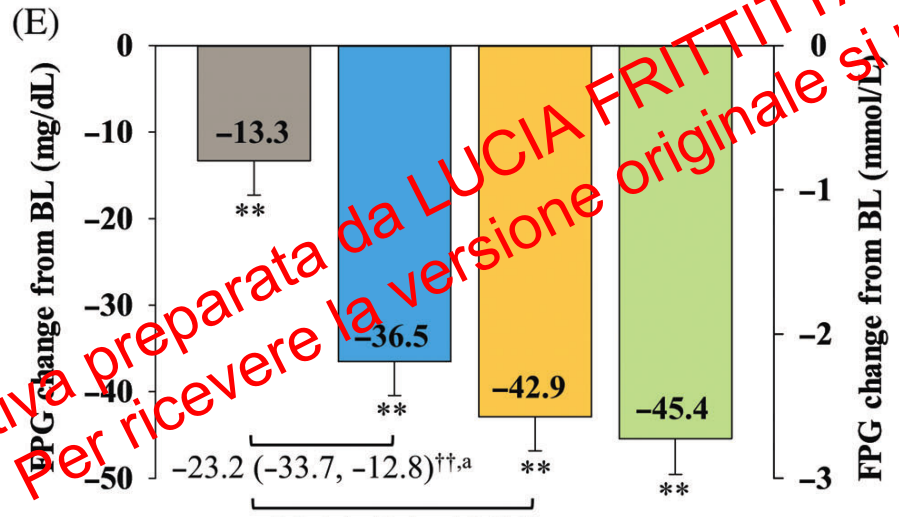




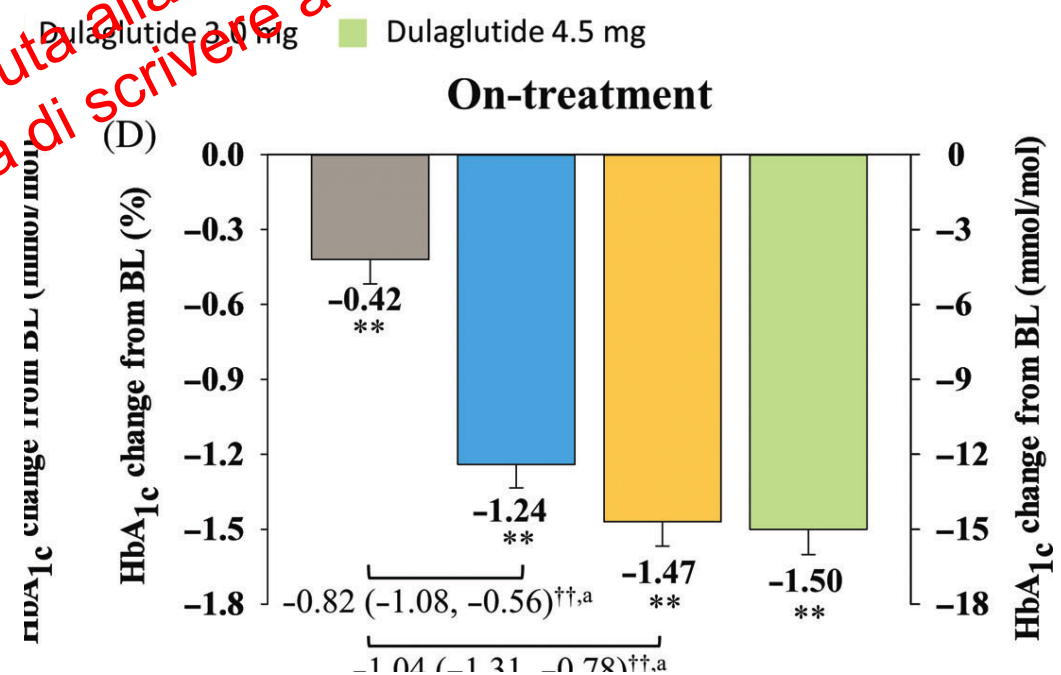
O'Neil PA, Lancet 2018

Dulaglutide induce weight loss in a dose dependent manner in diabetic patients

HbA1c

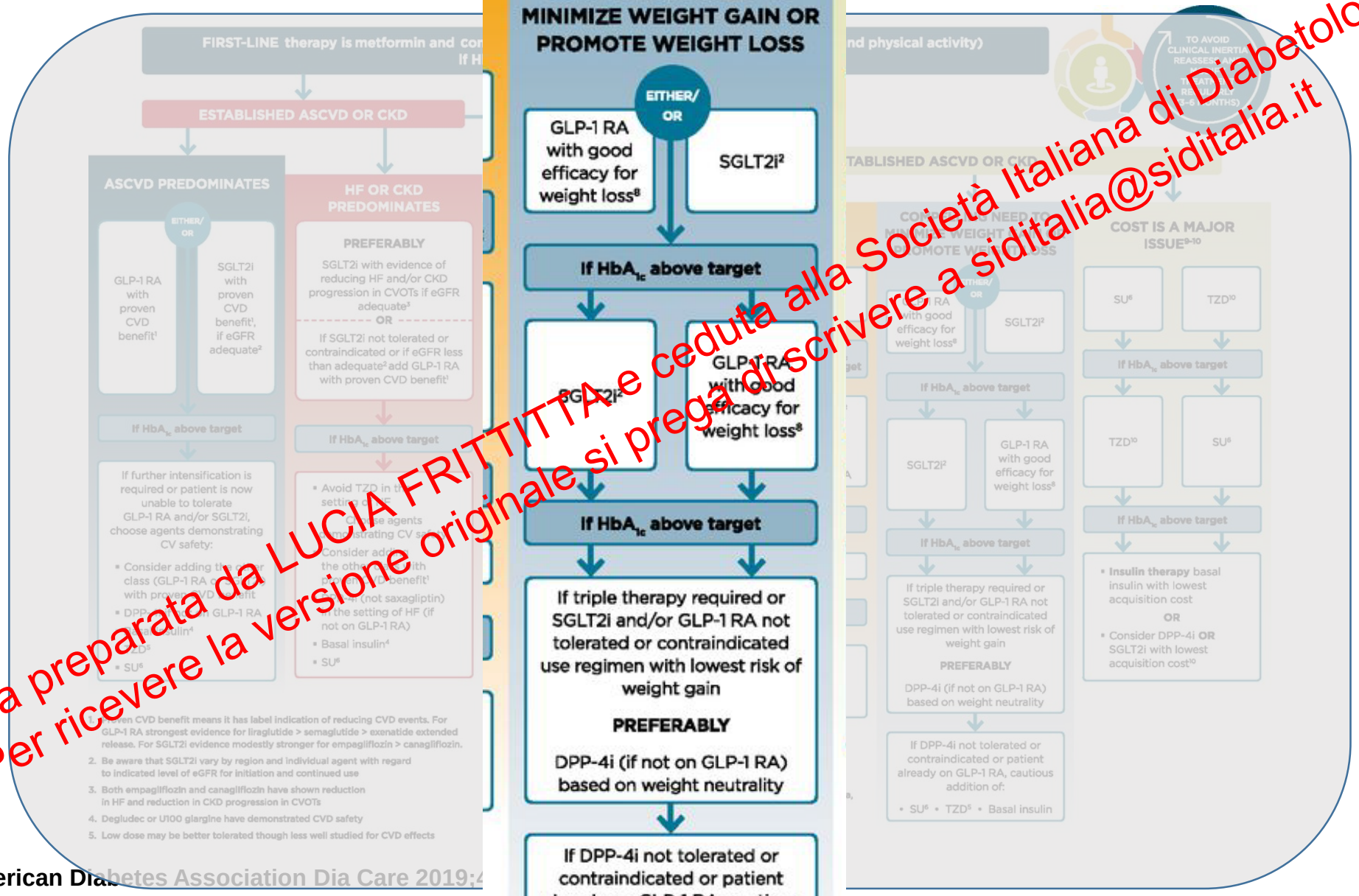


Weight Loss



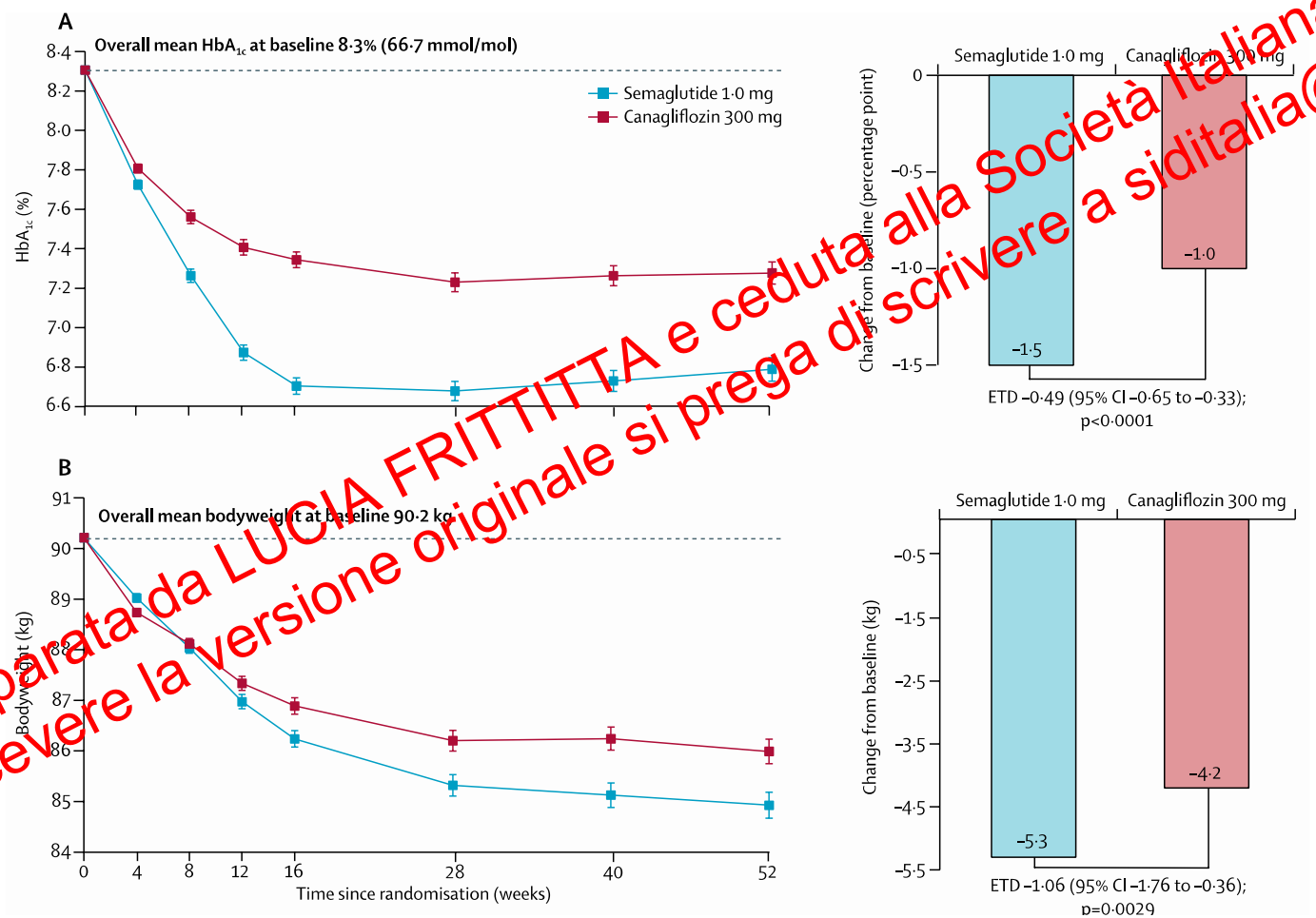
Diabetes Obes Metab. 2019;21:2048–2057.

Glucose-lowering medicat : overall approach.



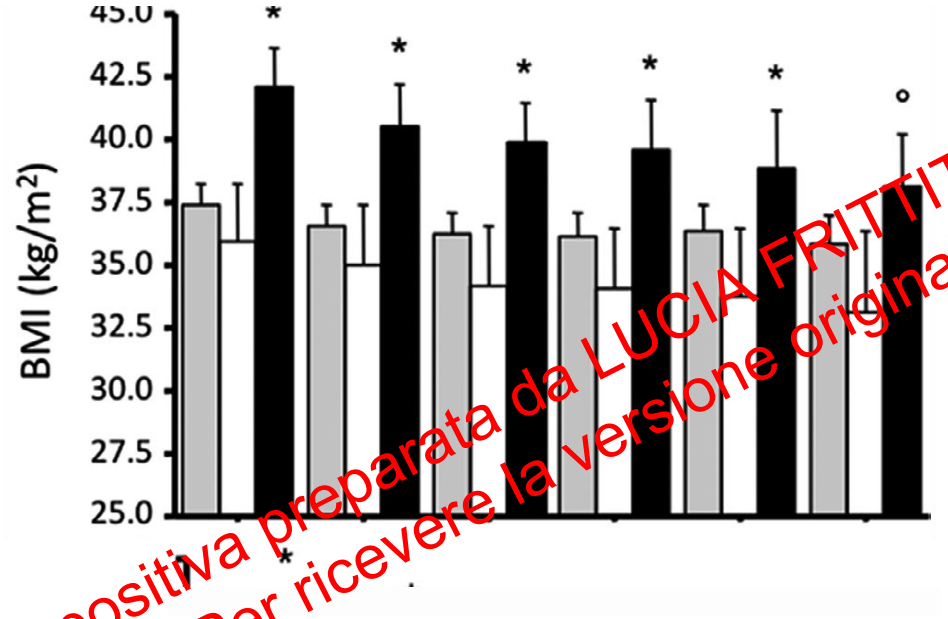
American Diabetes Association Dia Care 2019;4

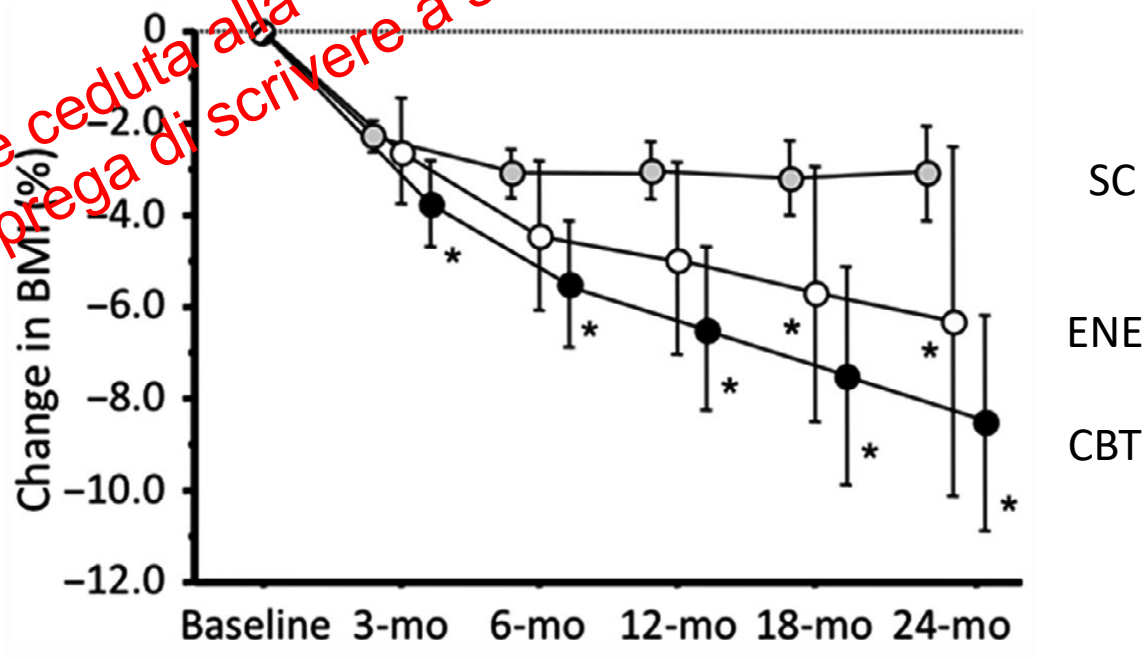
Efficacy and safety of once-weekly semaglutide versus daily canagliflozin in T2DM (SUSTAIN 8)



Lancet Diabetes Endocrinol 2019

Combination of GLP-1-Ra and behavioural treatment in T2DM: synergistic effects on body weight

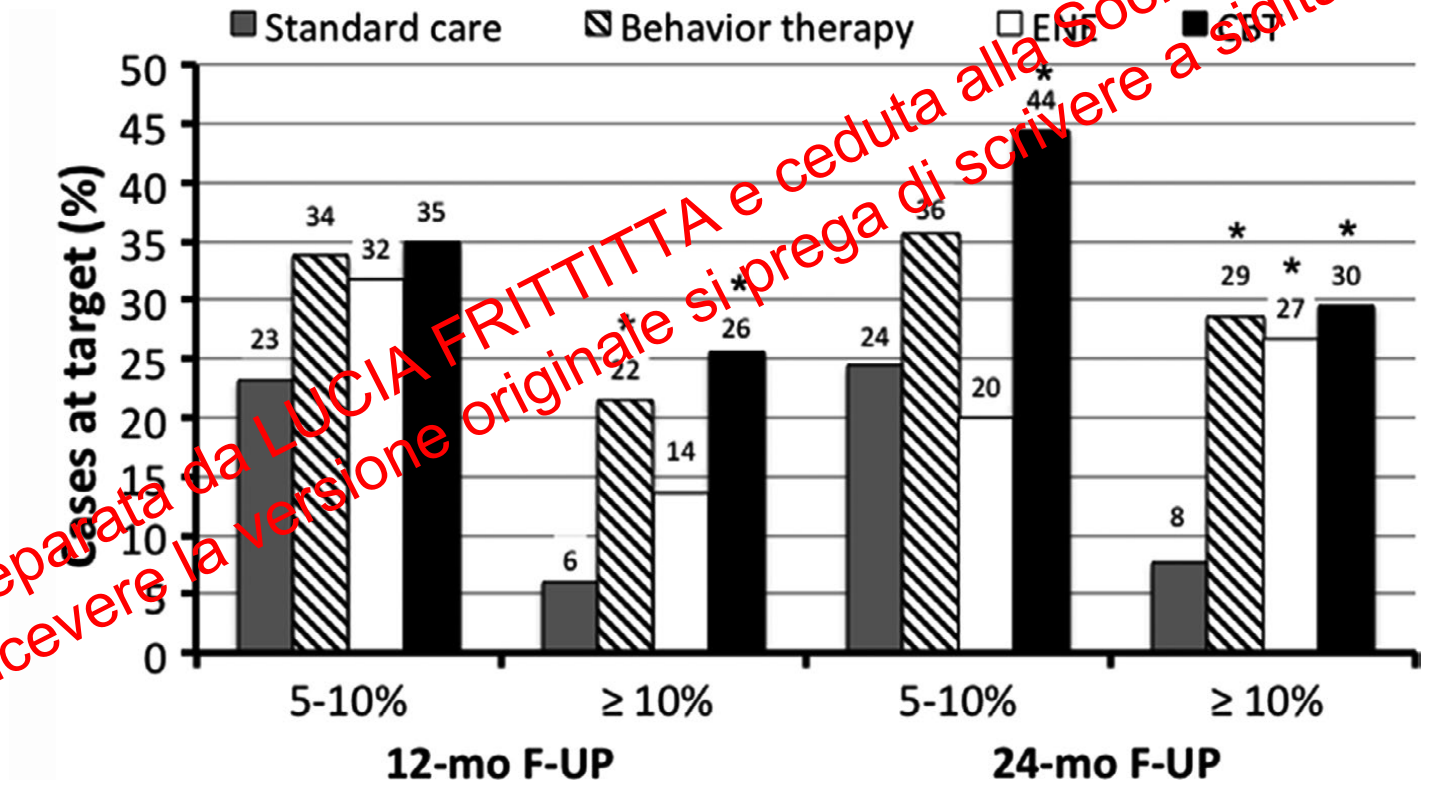




Type of GLP-1RA (%)
Exenatide BID 11.5; Liraglutide 54.9; Exenatide ER 14.3; Dulaglutide 19.3

Endocrinol Diab Metab. 2019

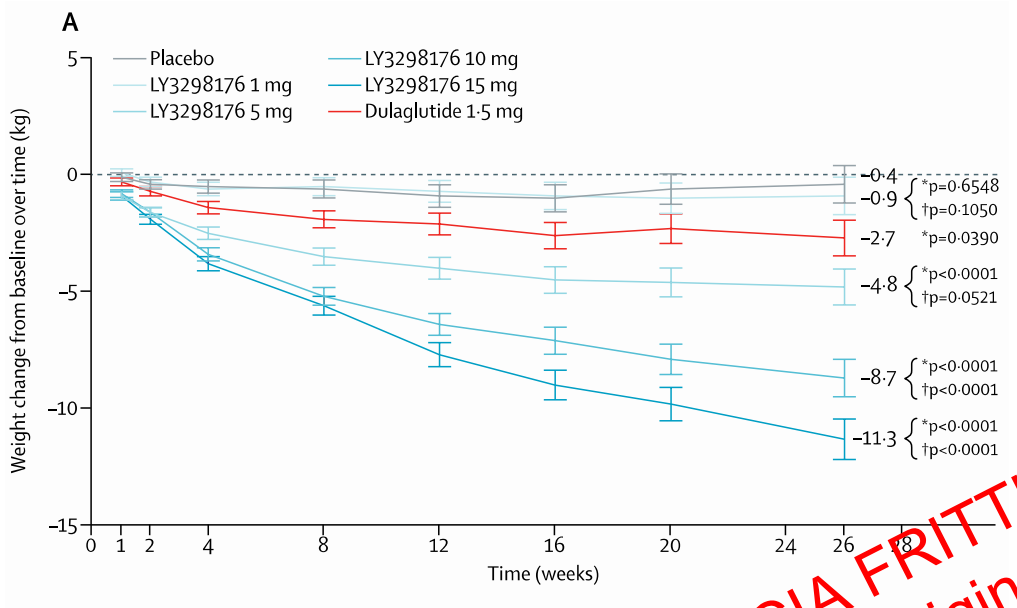
Combination of GLP-1-Ra and behavioural treatment in T2DM: synergistic effects on body weight

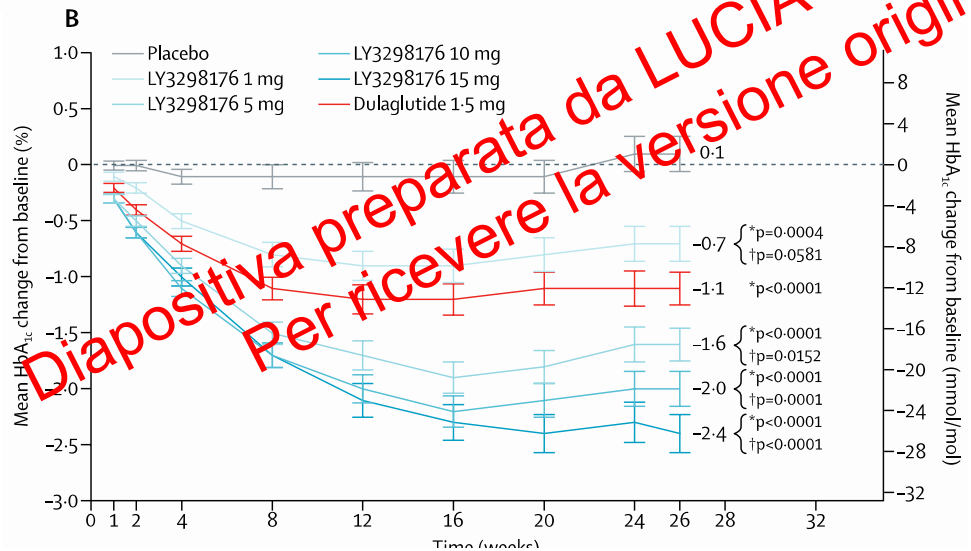


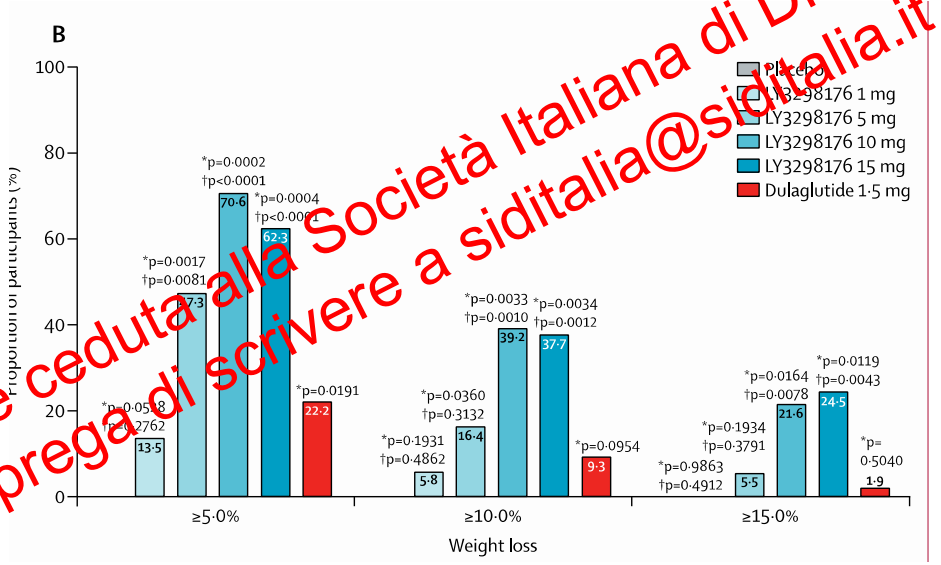
Type of GLP-1RA (%)
Exenatide BID 11.5; Liraglutide 54.9; Exenatide ER 14.3; Dulaglutide 19.3

Endocrinol Diab Metab. 2019

Dual GIP and GLP-1 receptor agonist in patients with T2DM







	Placebo (n=51)	1 mg LY3298176 (n=52)	5 mg LY3298176 (n=55)	10 mg LY3298176 (n=51)	15 mg LY3298176 (n=53)	1·5 mg dulaglutide (n=54)
Any treatment-emergent adverse events	27 (52·9%)	26 (50·0%)	40 (72·7%)	40 (78·4%)	45 (84·9%)	40 (74·1%)
Participants with at least one treatment-emergent adverse event						
Mild	15 (29·4%)	15 (28·8%)	18 (32·7%)	15 (29·4%)	20 (37·7%)	23 (42·6%)
Moderate	11 (21·6%)	7 (13·5%)	18 (32·7%)	22 (43·1%)	17 (32·1%)	11 (20·4%)
Severe	1 (2·0%)	4 (7·7%)	4 (7·3%)	3 (5·9%)	8 (15·1%)	6 (11·1%)
Serious adverse events	2 (3·9%)	2 (3·8%)	1 (1·8%)	3 (5·9%)	2 (3·8%)	3 (5·6%)
Fatal adverse events	1 (2·0%)	0	0	0	0	0
Adverse events leading to treatment discontinuation	2 (3·9%)	2 (3·8%)	5 (9·1%)	3 (5·9%)	13 (24·5%)	6 (11·1%)
Adverse events leading to study discontinuation	1 (2·0%)	1 (1·9%)	0	1 (2·0%)	2 (3·8%)	2 (3·7%)

Lancet, 2018

Conclusioni (1)

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.

Aaron Y Kluger, Peter A McCullough, Lancet 2018

Conclusioni (2)

The use of GLP1 receptor agonists in conjunction with diet and lifestyle changes in overweight adults with the goal of reducing adiposity and reducing progression of 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