Effetti glicemici ed extraglicemici di GLP1RA (vs SGLT2i?): what-is e what-if

Emanuela Orsi

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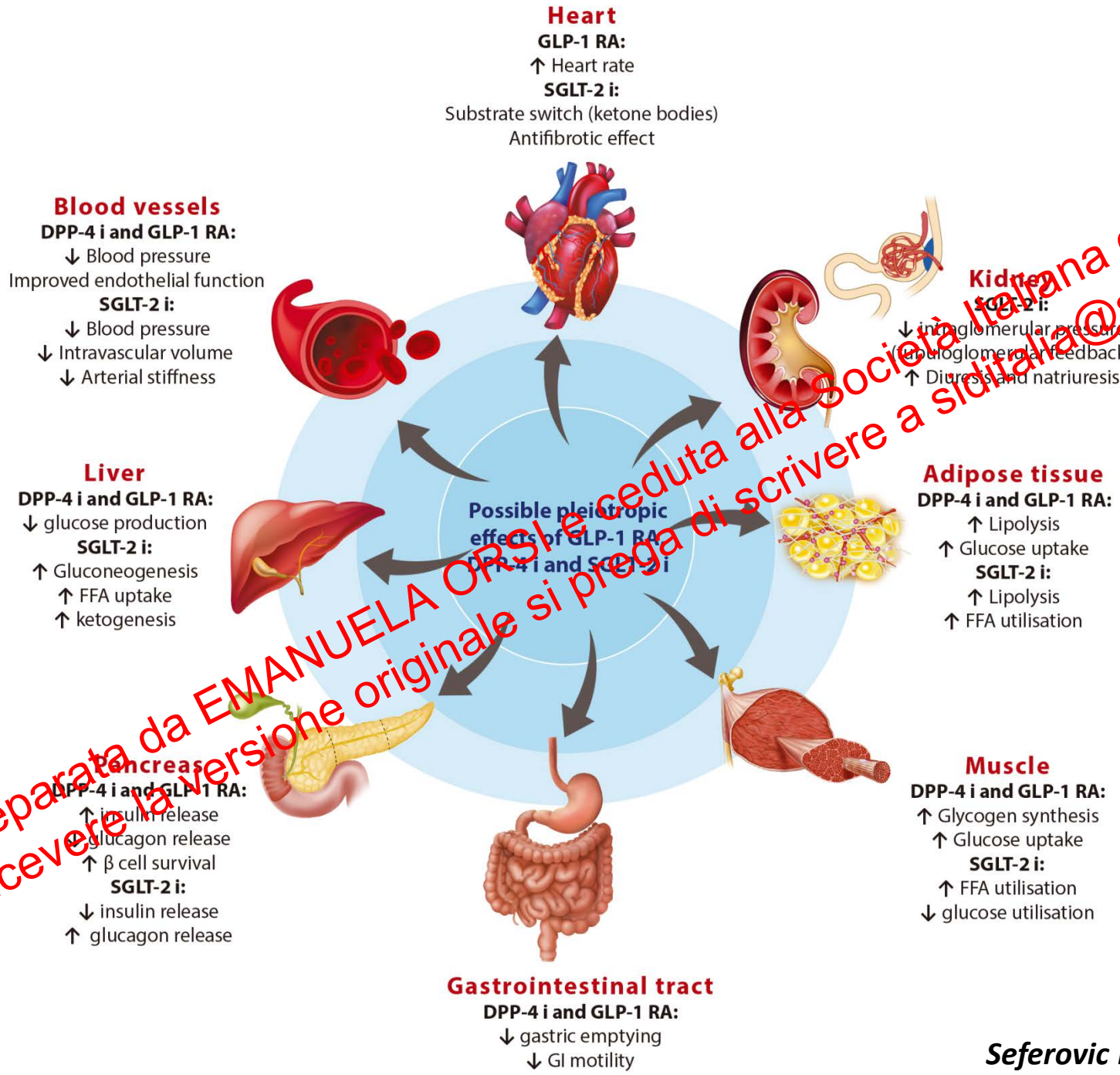
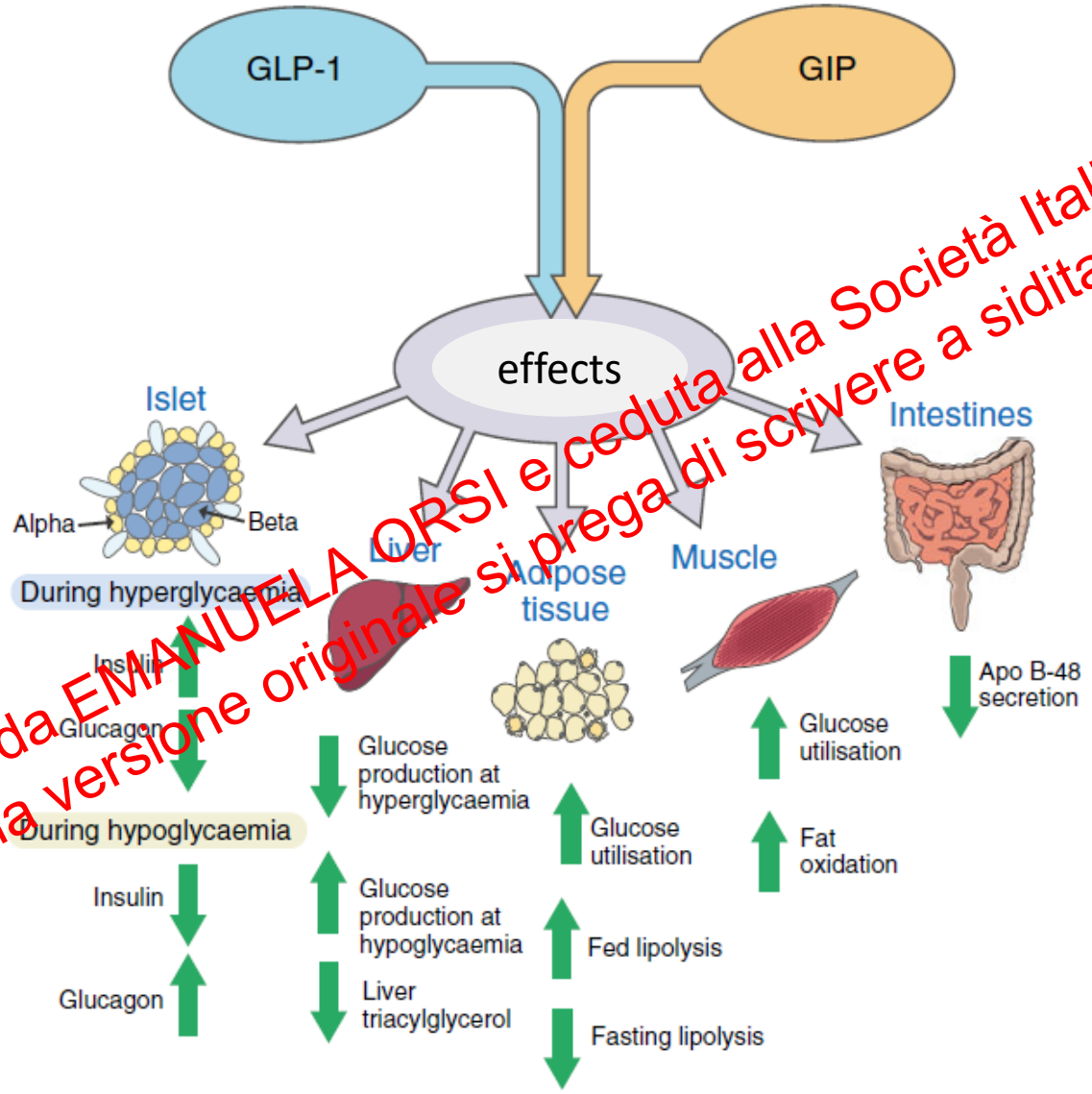
Conflitti di interesse

- Eli Lilly
- Novo Nordisk



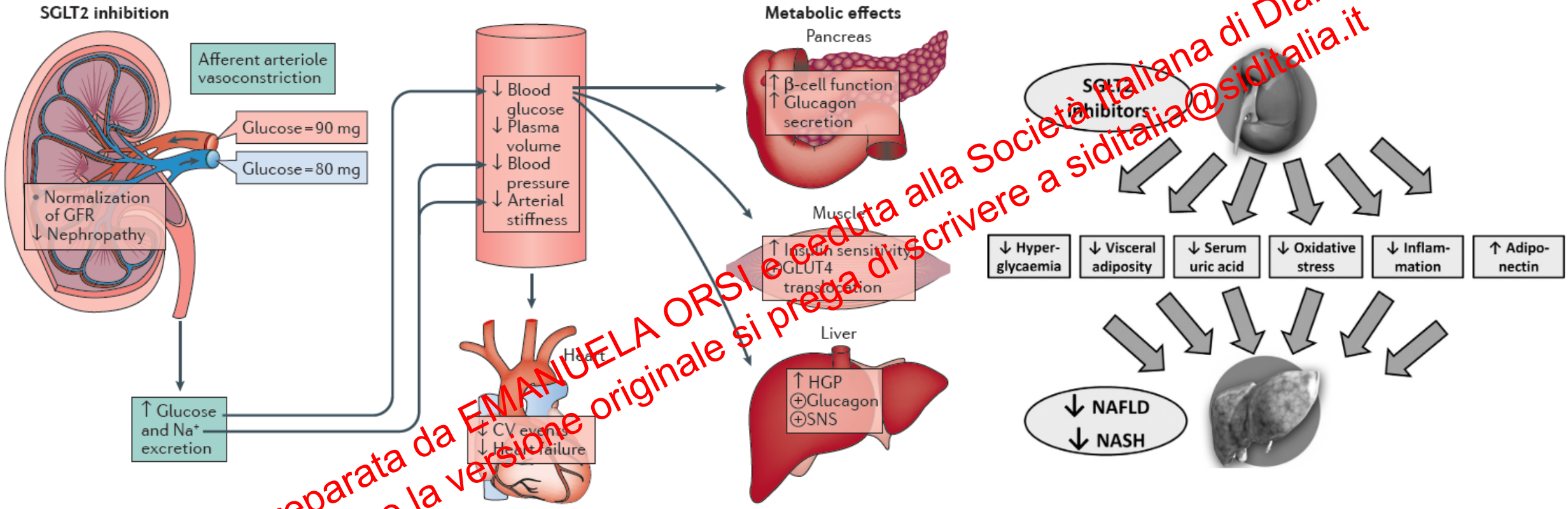
Seferovic PM etal, Eur J Heart Fail, 2020

Metabolic effects of GLP 1 and GIP



Modified from: Ahren B & Foley JE, Diabetologia, 2016

Metabolic effects of SGLT2 inhibition



DeFronzo RA et al, Nat Rev Nephrol, 2017
Sheen AJ, Diabetes Metab, 2019

Agenda

- GLP1 RA (vs SGLT2i ?) e controllo glicemico
- GLP1 RA (vs SGLT2i ?) e peso corporeo
- GLP1 RA (vs SGLT2i ?) e NAFLD

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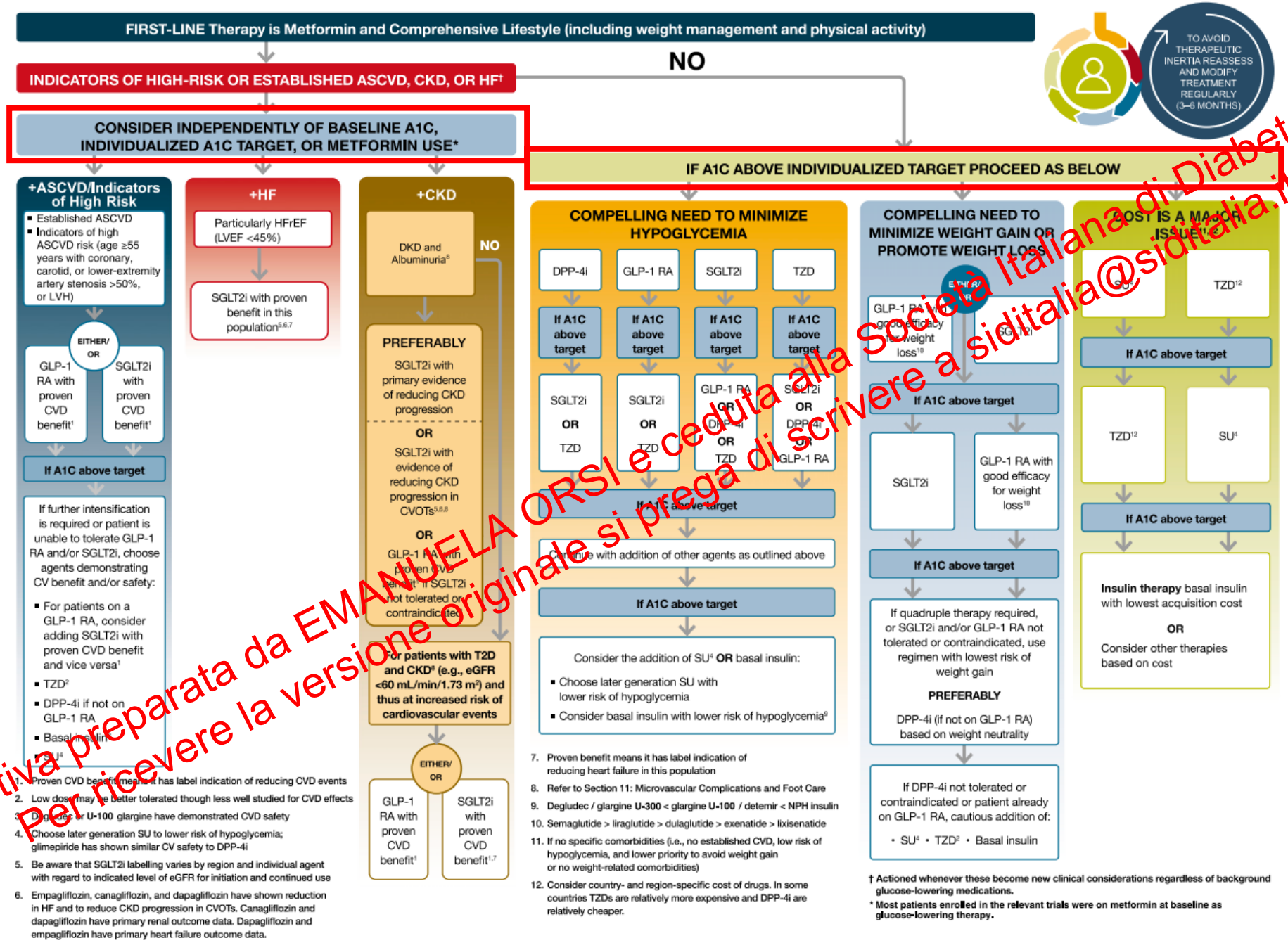
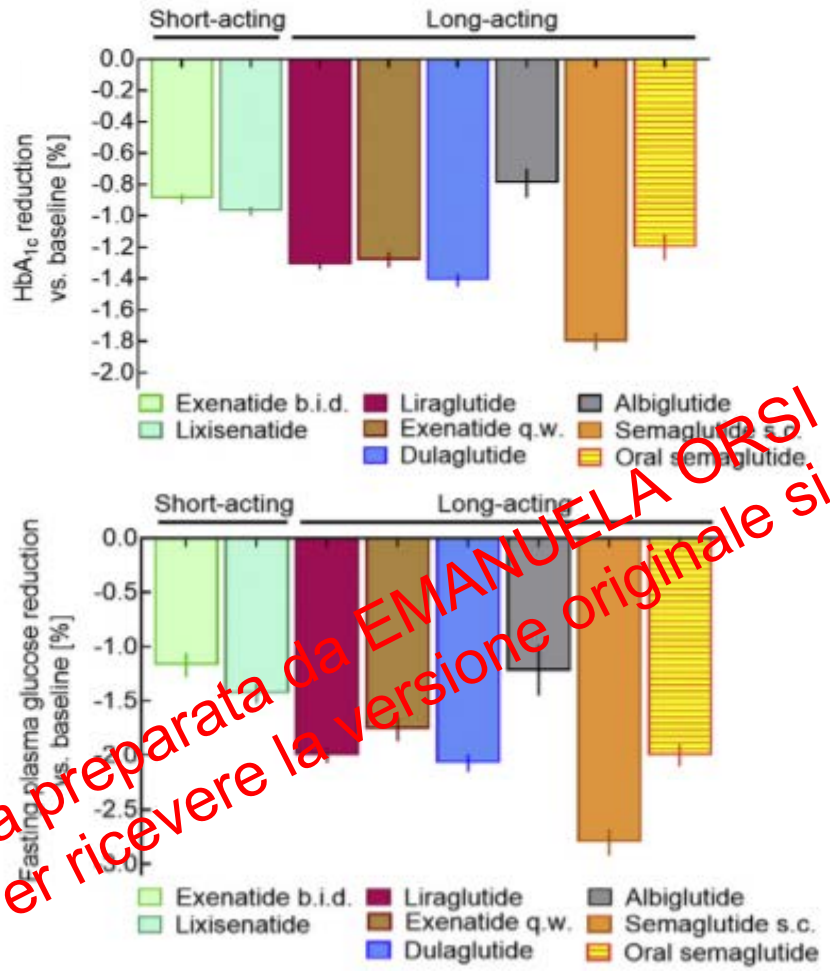
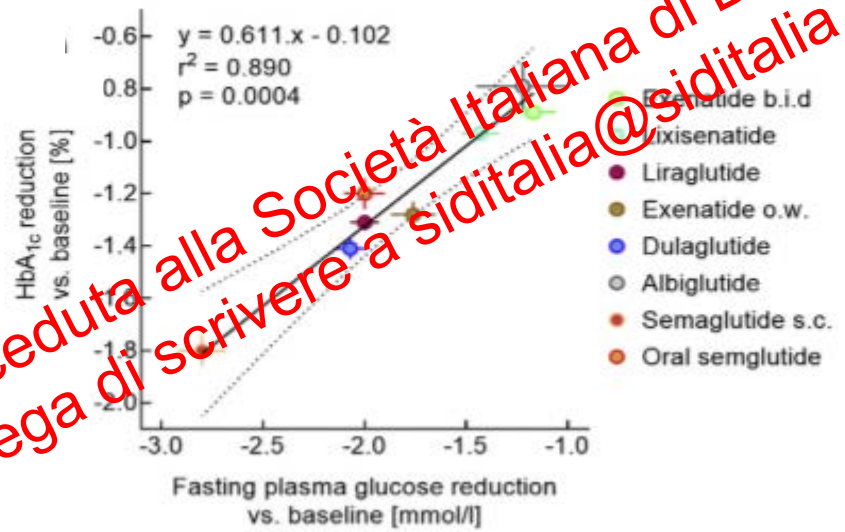


Standard of Medical Care, ADA 2021

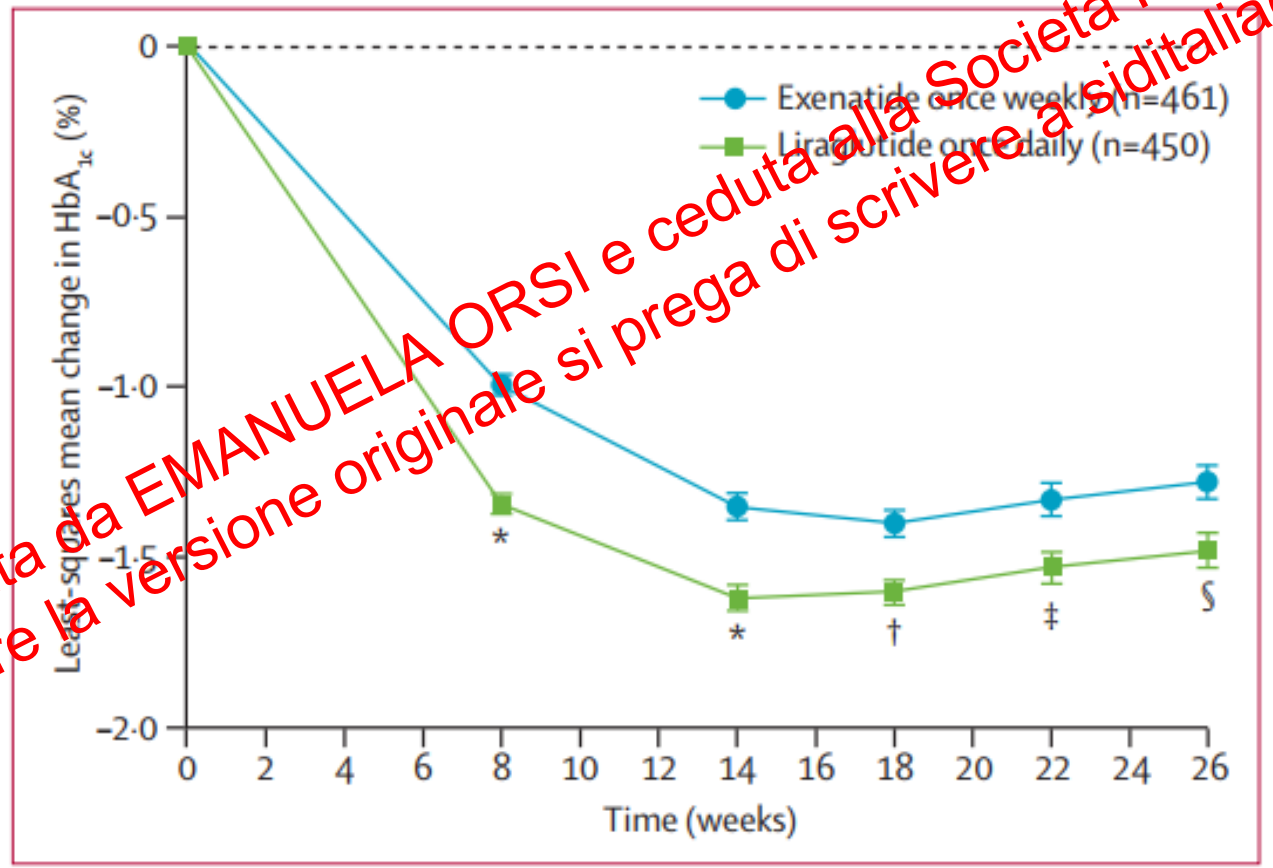
Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing HbA1C and fasting plasma glucose





Nauck MA et al, Mol Metabol, 2020

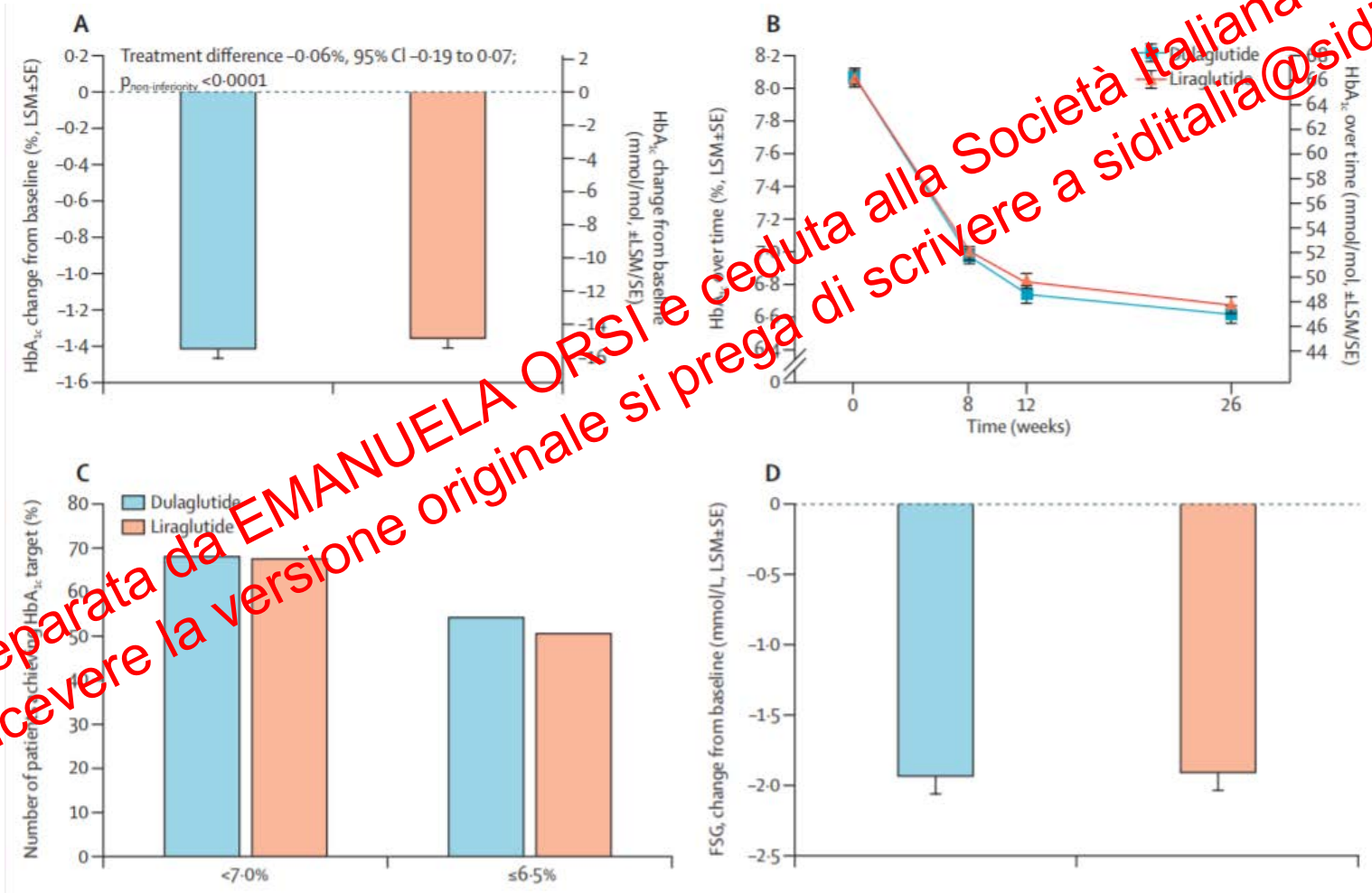
Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study



*p<0·0001.
†p=0·0005.
‡p=0·0012.
§p=0·0018

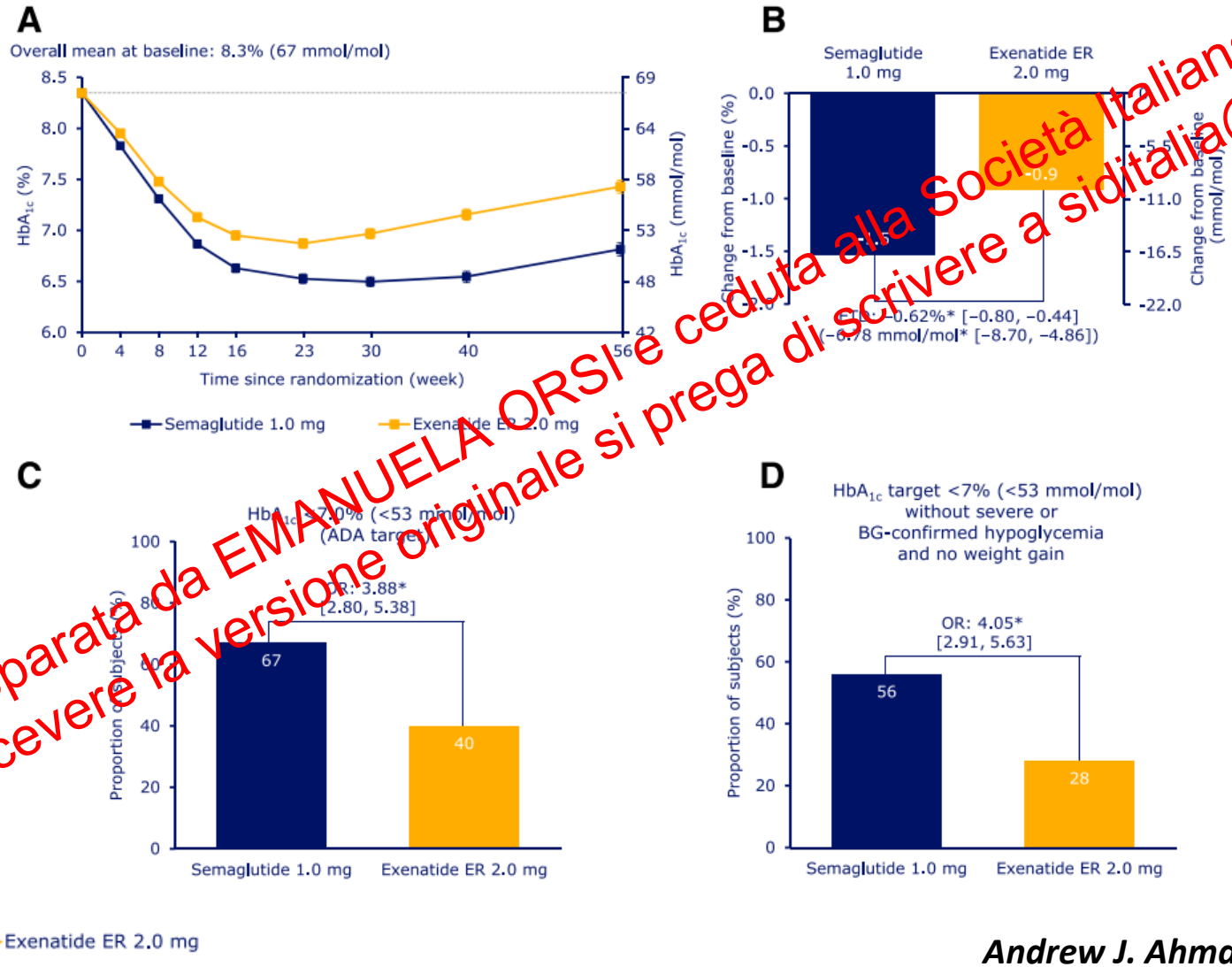
Buse JB et al, Lancet, 2013

Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial



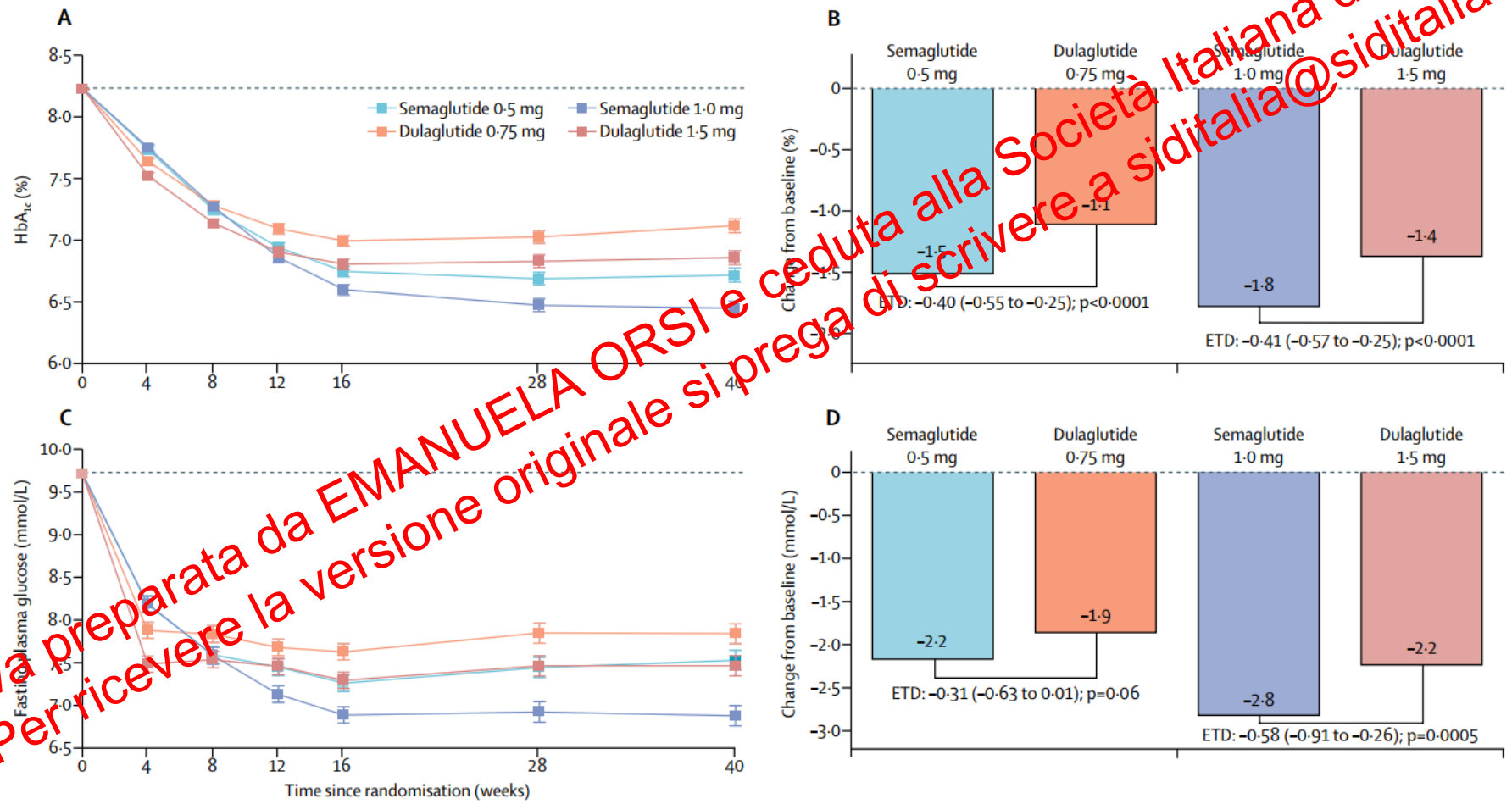
Dungan KM et al, Lancet, 2014

Efficacy and Safety of OnceWeekly Semaglutide Versus Exenatide Extended Release (ER) in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial



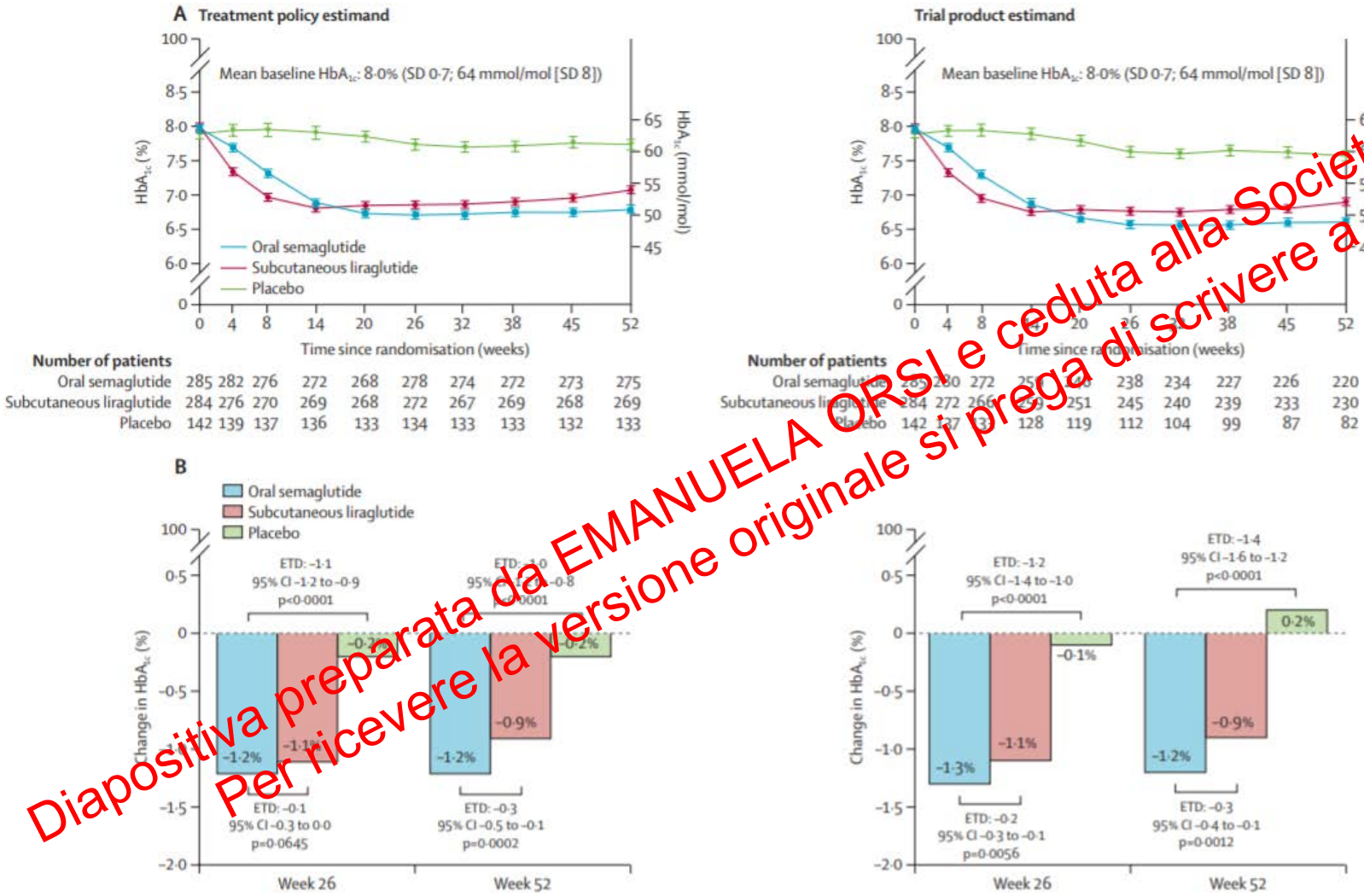
Andrew J. Ahmann AJ et al, Diabetes Care, 2017

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



Pratley RE et al, Lancet Diabetes Endocrinol, 2018

Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial

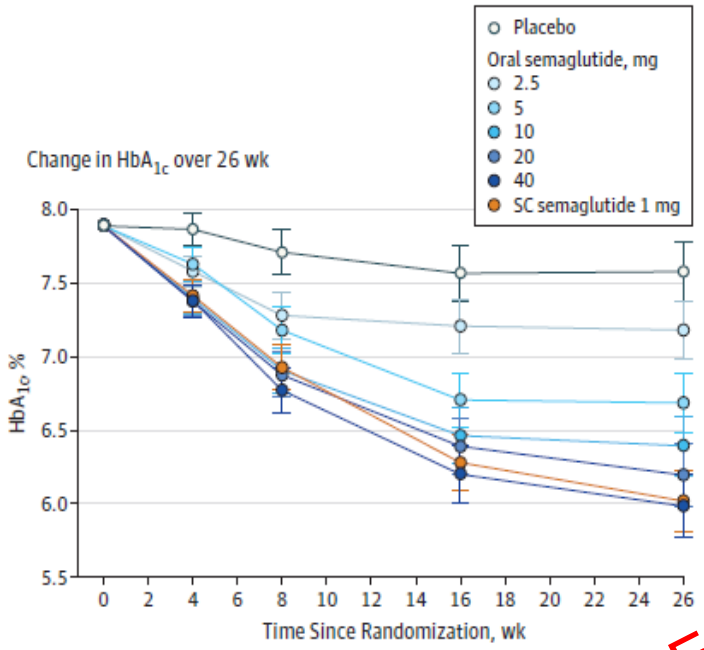


Treatment policy: study drug with discontinuation or rescue medication

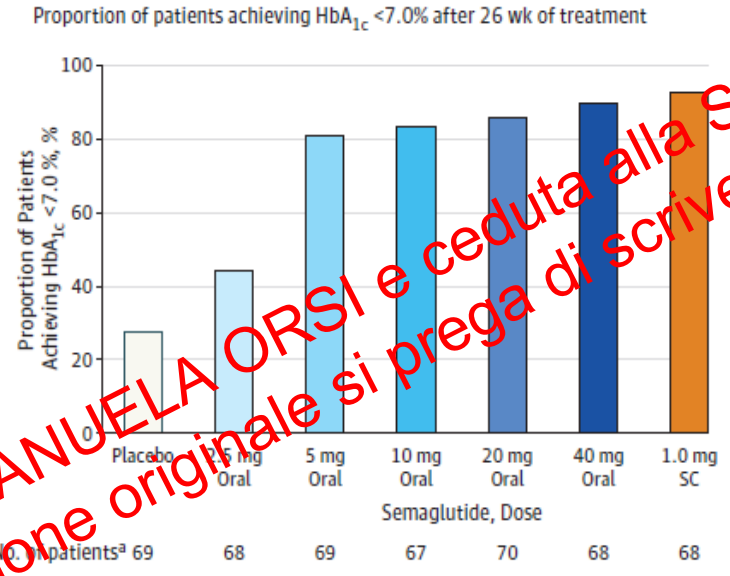
Trial product: study drug without rescue medication

Pratley R et al, Lancet, 2019

Oral Semaglutide vs sc semaglutide: Efficacy Among Patients With Type 2 Diabetes and Insufficient Glycemic Control



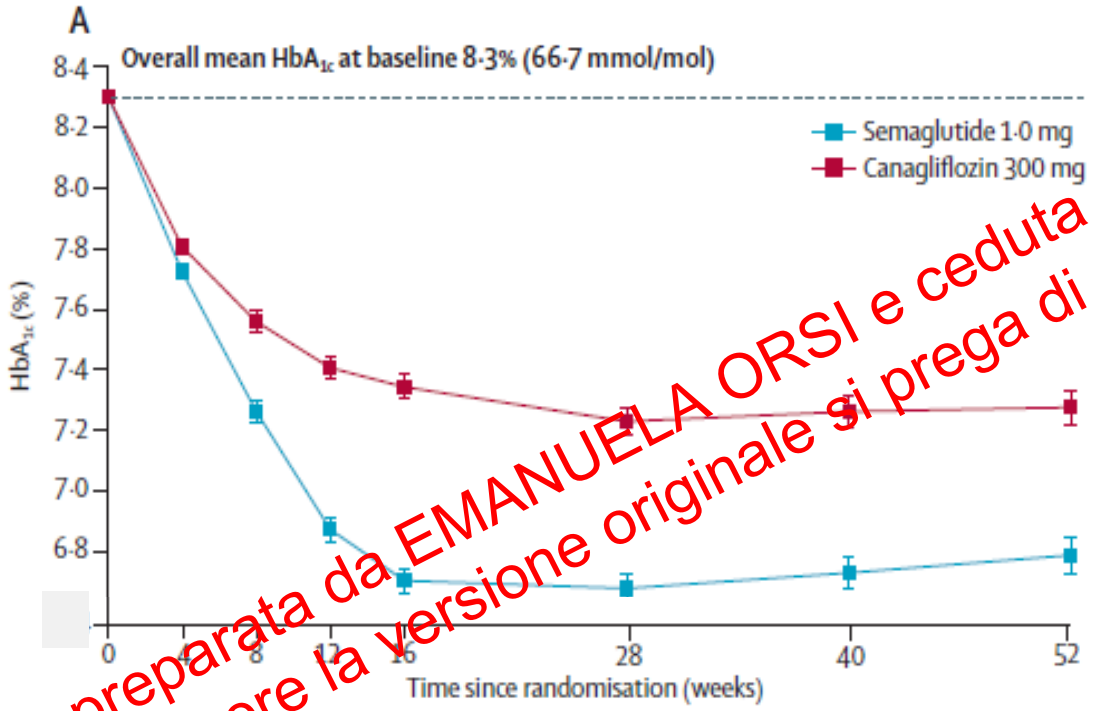
No. of patients[a]					
Placebo	69	69	64	57	51
Oral semaglutide, mg					
2.5	68	68	64	61	56
5	69	69	63	61	58
10	66	66	61	61	57
20	70	70	60	53	48
40	68	68	63	55	46
SC semaglutide 1 mg	67	67	66	61	48

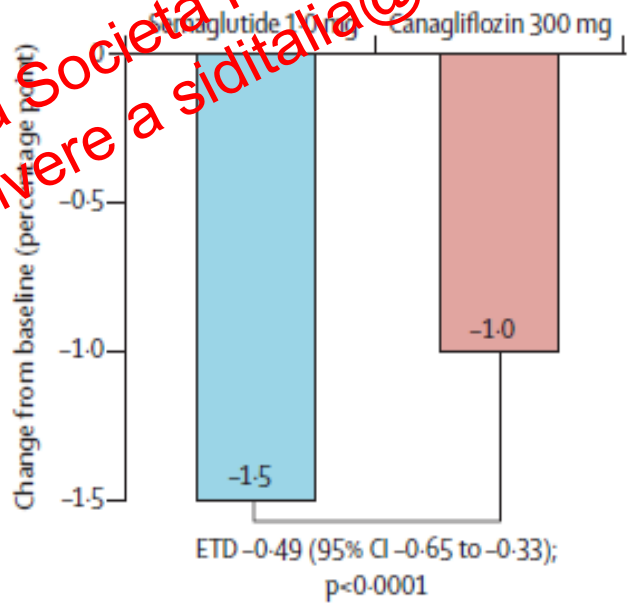


No. of patients[a]	69	68	69	67	70	68	68

Davies M et al, JAMA, 2017

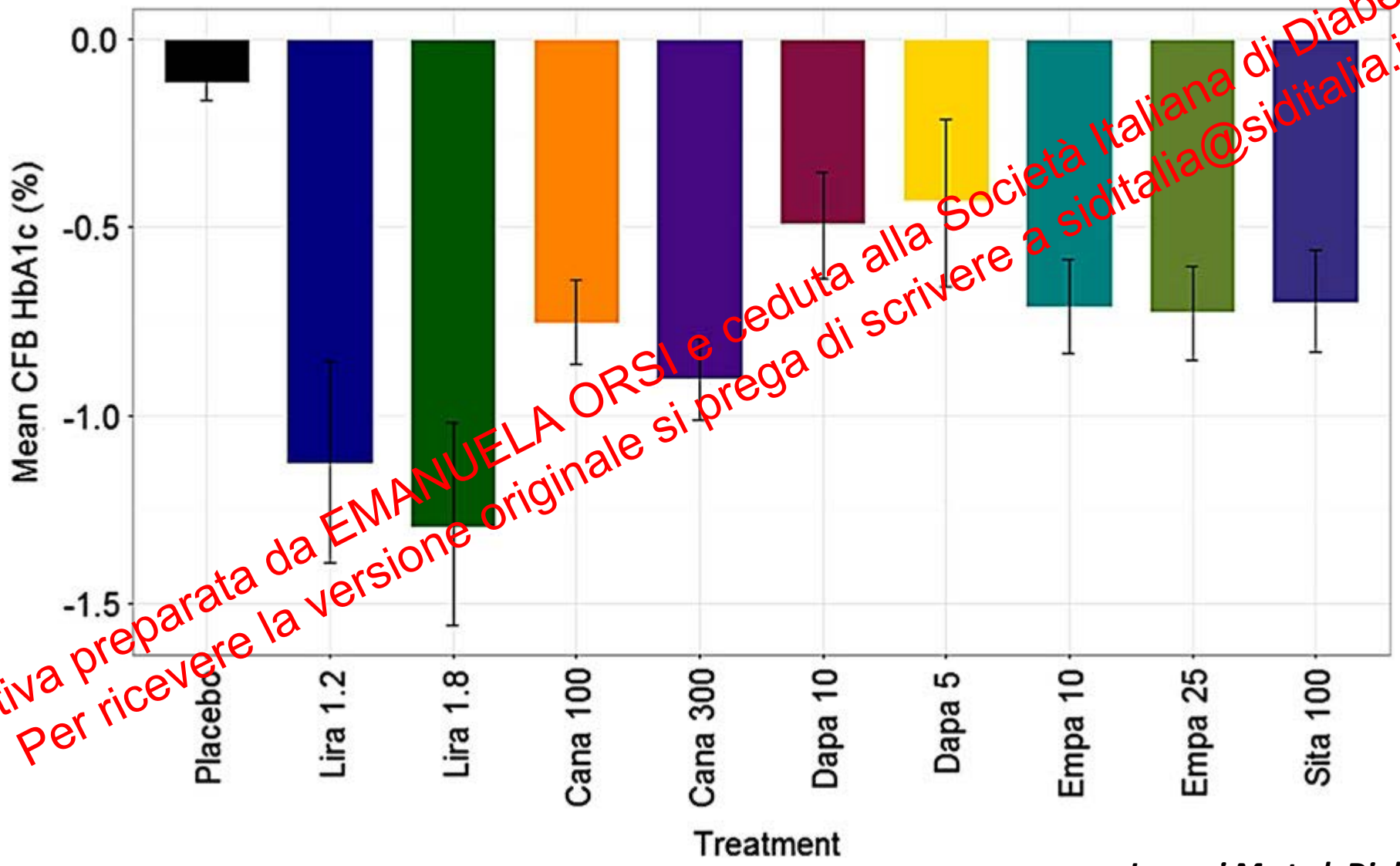
Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8)





Lingvay I et al, Lancet Diabetes Endocrinol, 2019

Liraglutide Versus SGLT-2 Inhibitors in People with Type 2 Diabetes: A Network Meta-Analysis



Lorenzi M et al, Diabetes Ther, 2017

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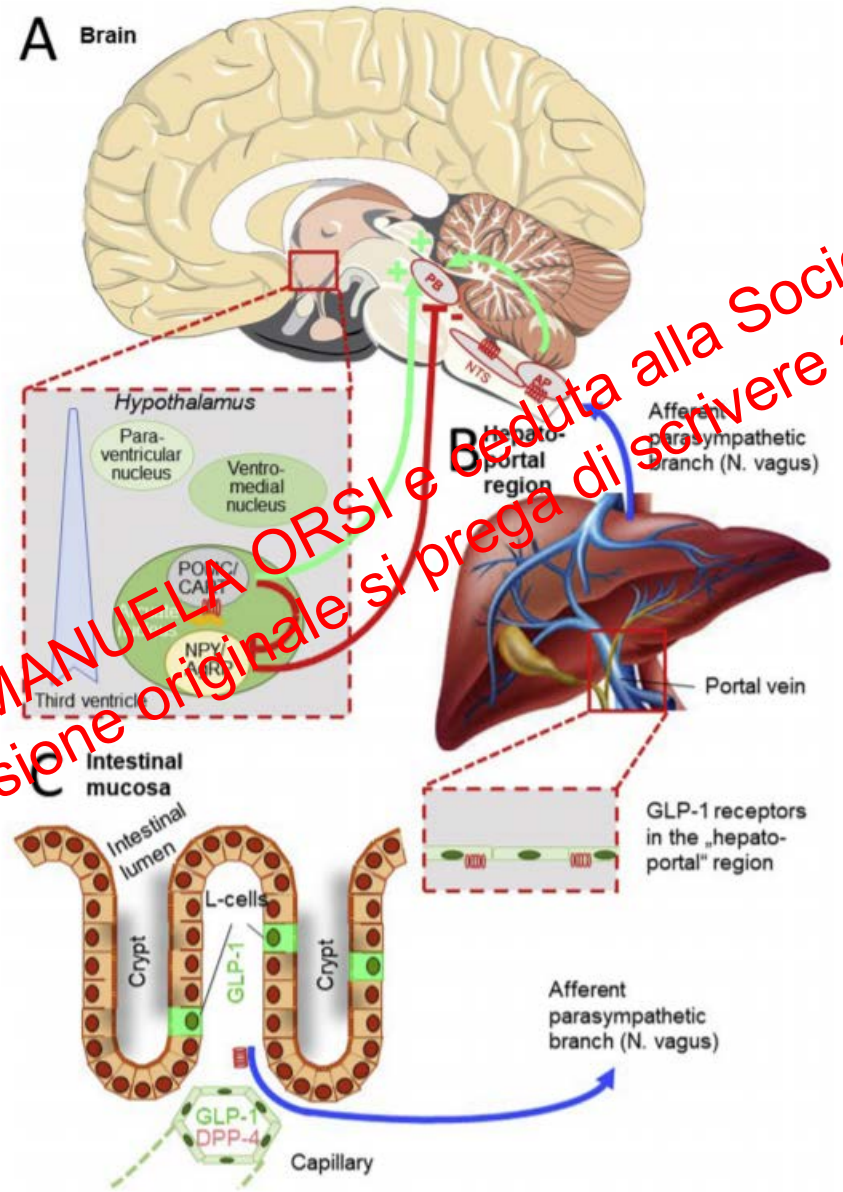
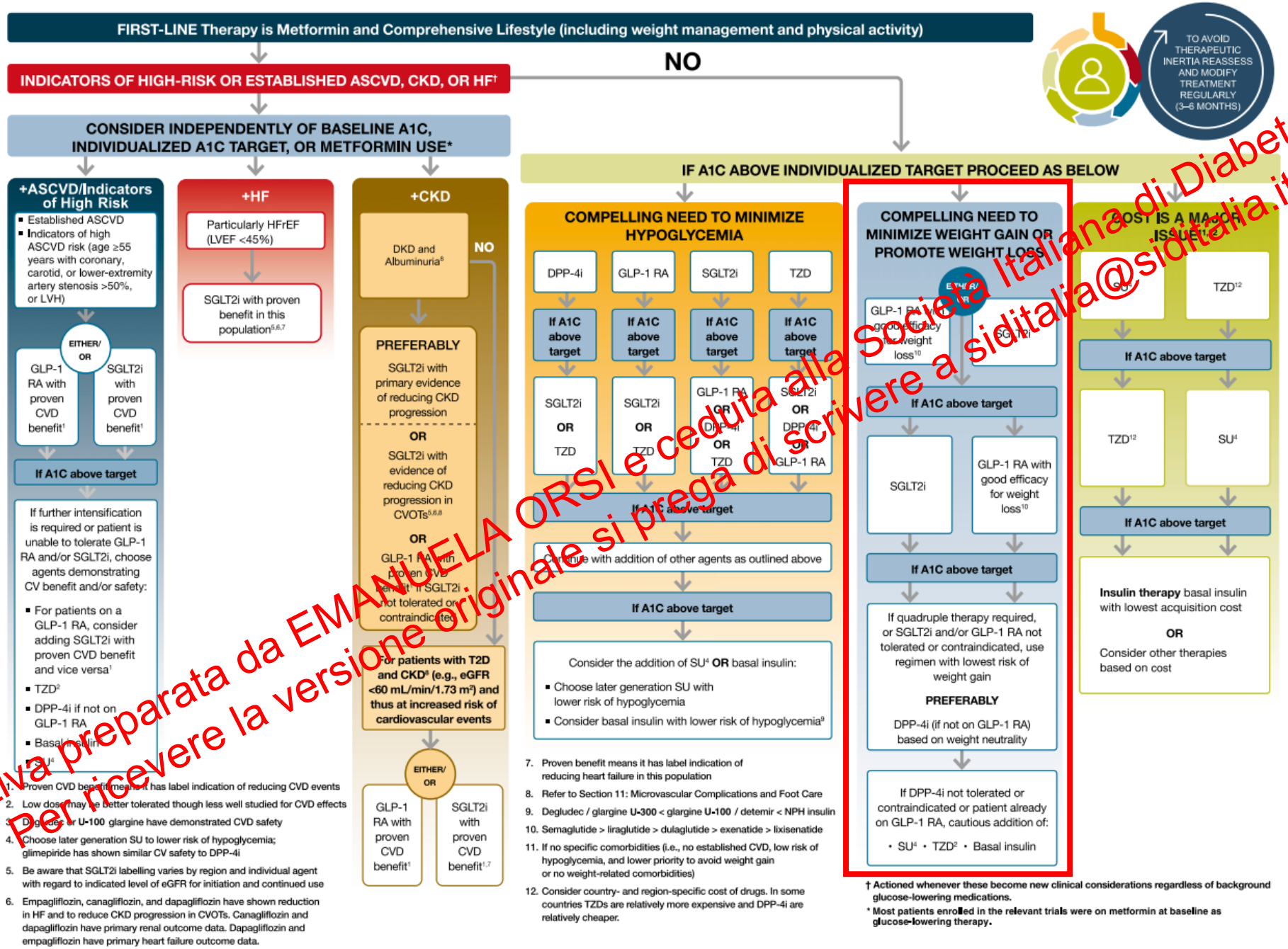
GLP1 and GLP1 RA: regulation of energy intake and expenditure

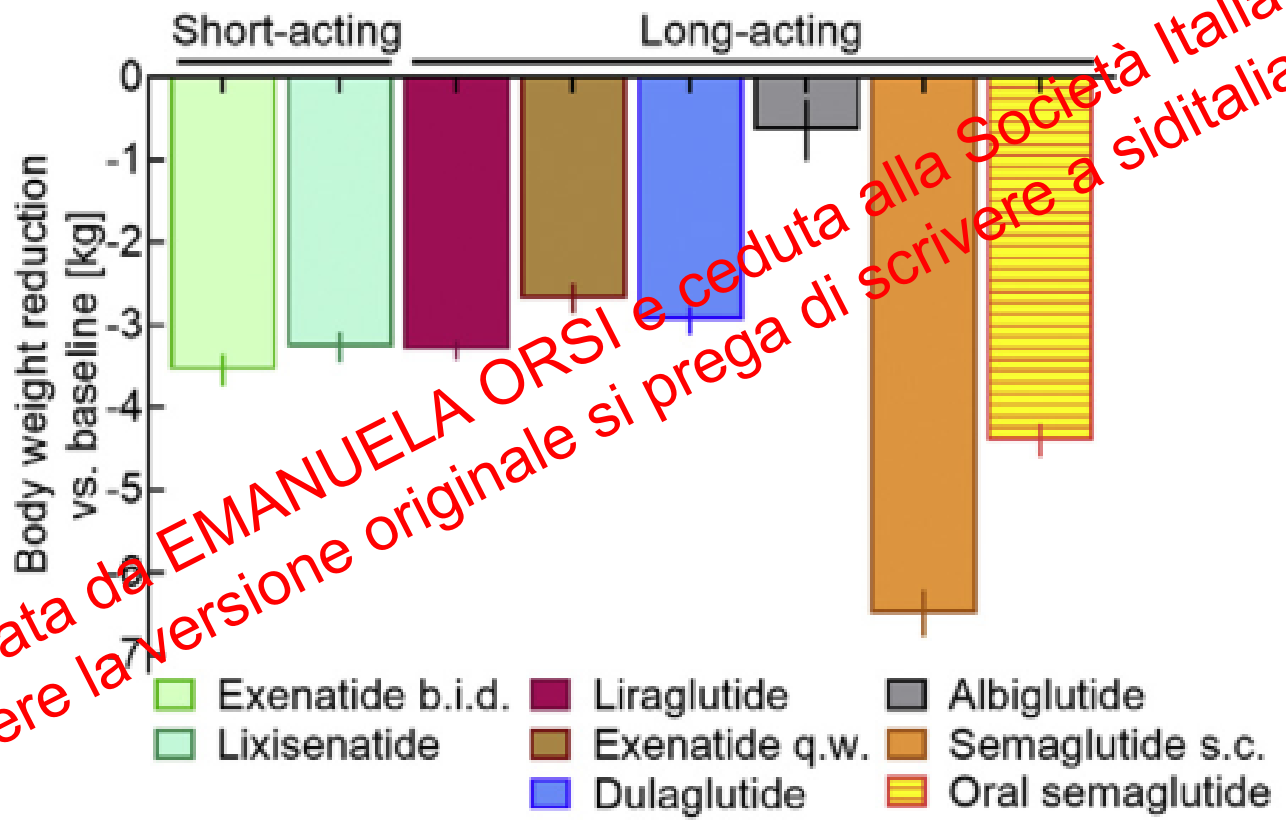


Nauck MA et al, Mol Metabol, 2020



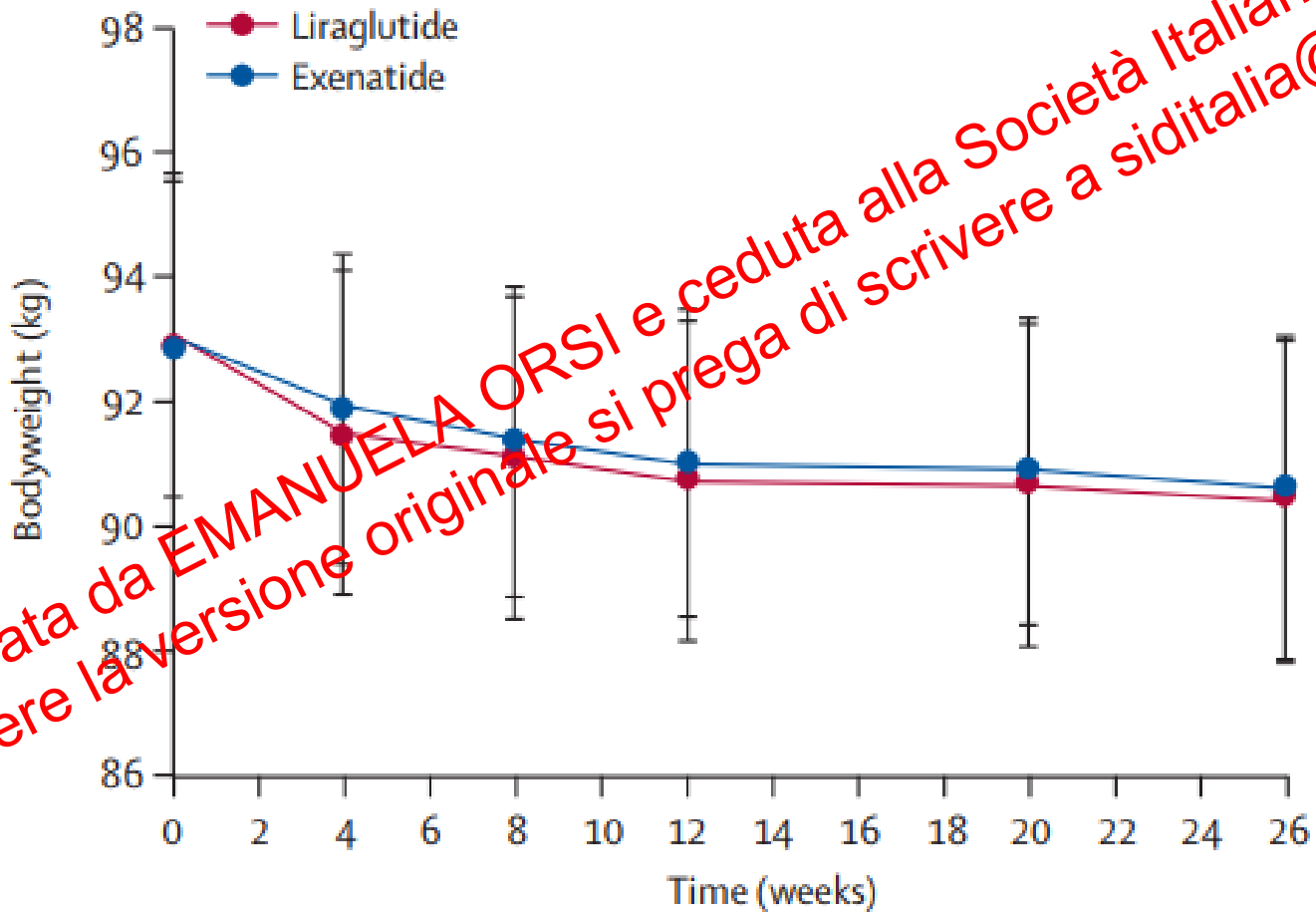
Standard of Medical Care, ADA 2021

Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing body weight



Nauck MA et al, Mol Metabol, 2020

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)



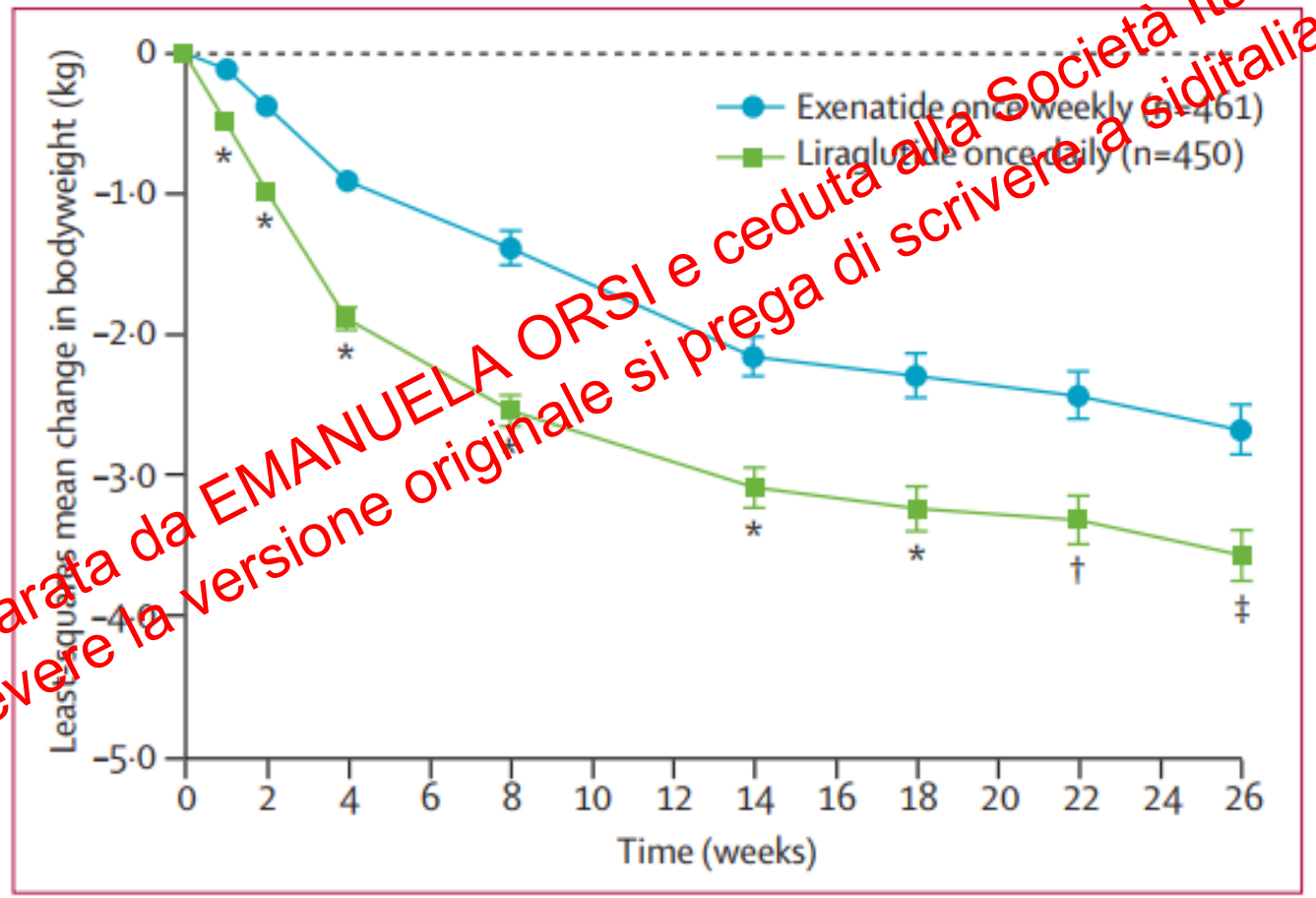
p=0.22

Buse JB et al, Lancet, 2009

Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes

Nauck M et al, Diabetes Care, 2016

Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study



*p<0·0001
†p=0·0002
‡p=0·0005

Buse JB et al, Lancet, 2013

Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial

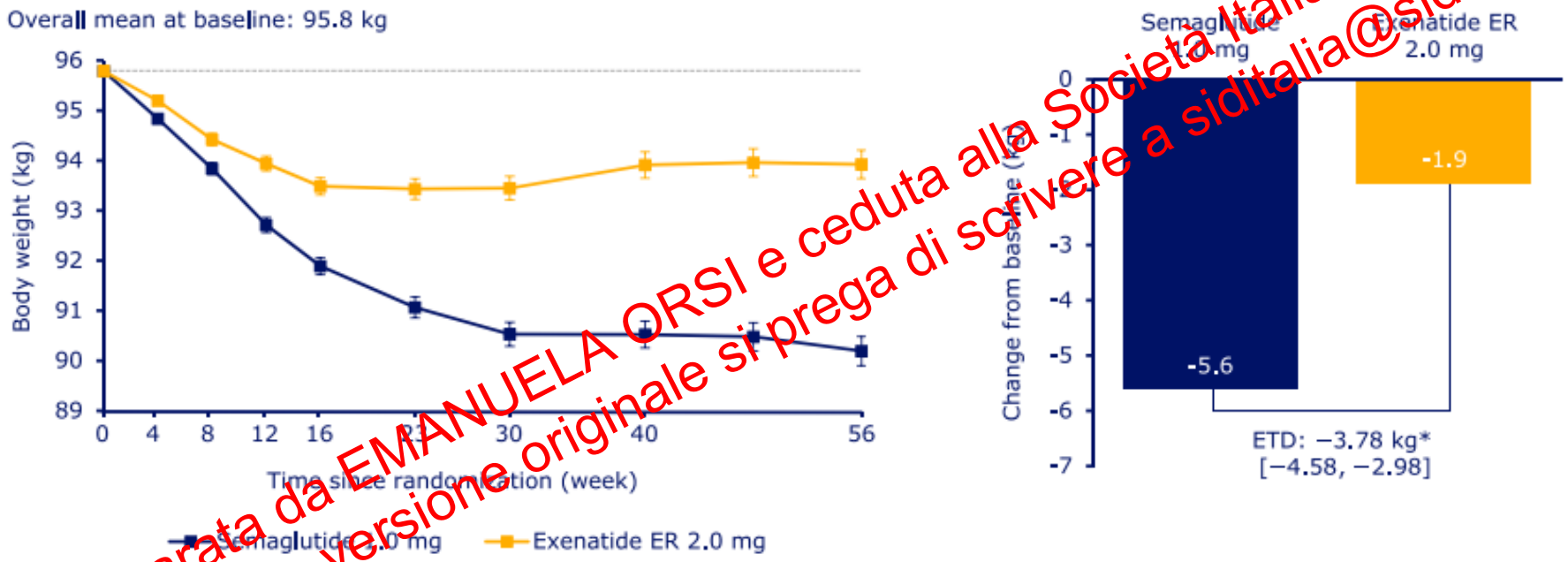
	Dulaglutide (n=299)			Liraglutide (n=300)			Dulaglutide *vs* liraglutide	
	Baseline	Change from baseline to week 26	p value	Baseline	Change from baseline to week 26	p value	Mean difference	p value
HbA_{1c} (%)	8·1% (0·8)	−1·42% (0·05)	<0·0001	8·1% (0·8)	−1·36% (0·05)	<0·0001	−0·06% (−0·19 to 0·07)	<0·0001*
HbA_{1c} (mmol/mol)	65 (8·8)	−16 (0·55)	<0·0001	65 (8·8)	−15 (0·55)	<0·0001	−0·66 (−2·08 to 0·77)	<0·0001*
Fasting serum glucose concentration (mmol/L)	9·3 (2·2)	−1·93 (0·12)	<0·0001	9·2 (2·3)	−1·90 (0·12)	<0·0001	−0·03 (−0·32 to 0·25)	0·83
Postprandial plasma glucose concentration (mmol/L)	10·7 (0·1)	−2·56 (0·09)	<0·0001	10·6 (0·1)	−2·43 (0·09)	<0·0001	−0·13 (−0·36 to 0·10)	0·26
Bodyweight (kg)	93·8 (18·2)	−2·90 (0·22)	<0·0001	94·4 (19·0)	−3·61 (0·22)	<0·0001	0·71 (0·17 to 1·26)	0·011

Data are least-squares mean (SE) or mean difference (95% CI). HbA_{1c}=glycated haemoglobin. *p value is for non-inferiority of dulaglutide versus liraglutide.

Table: **Comparison of trial outcome measures between dulaglutide and liraglutide**

Dungan KM et al, Lancet, 2014

Efficacy and Safety of OnceWeekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial



Andrew J. Ahmann AJ et al, Diabetes Care, 2017

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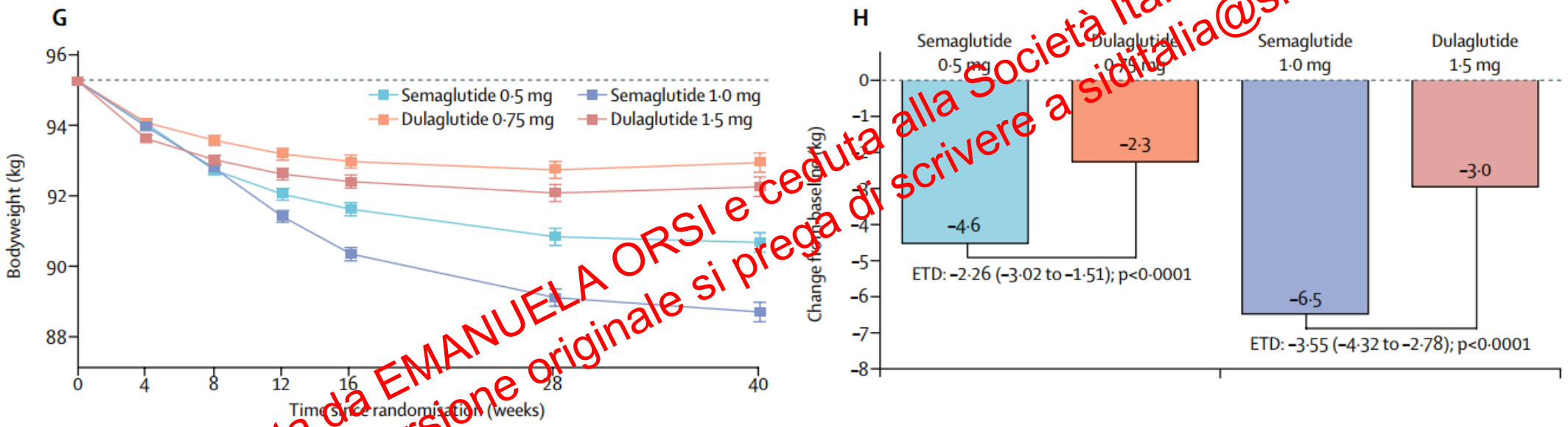

Pratley RE et al, Lancet Diabetes Endocrinol, 2018

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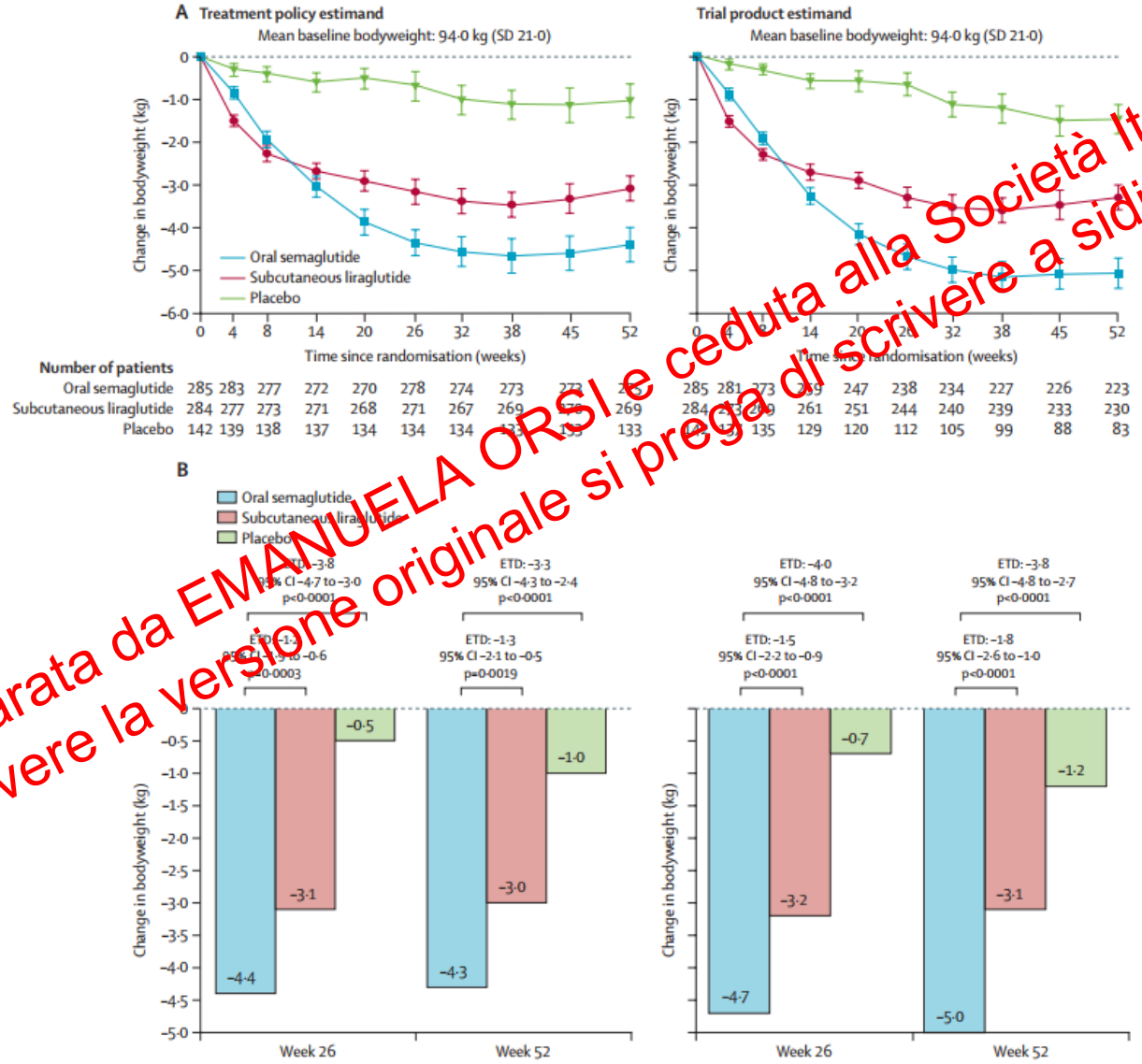
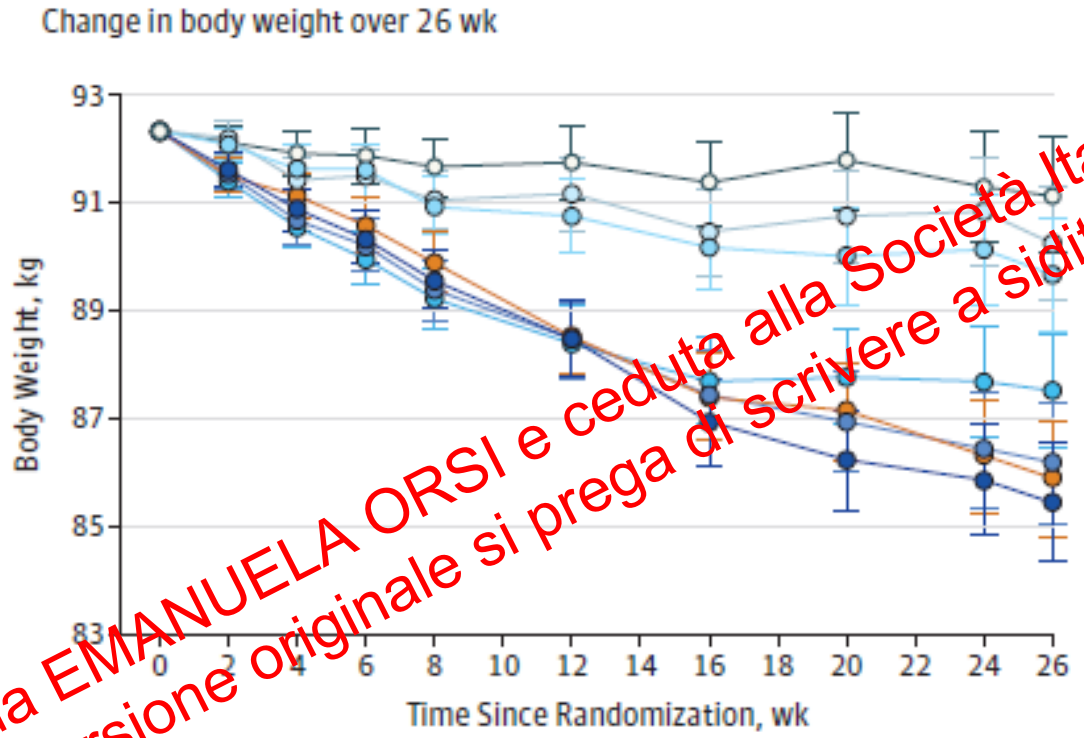


Richard Pratley R et al, Lancet, 2019

Oral Semaglutide vs sc Semaglutide : Body Weight Among Patients With Type 2 Diabetes and Insufficient Glycemic Control



No. of patients[a]					
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Oral semaglutide, mg					
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20	70	66	57	51	47
40	71	66	63	50	46
SC semaglutide 1 mg					
	69	66	65	57	46

Davies M et al, JAMA, 2017

Medication approved by the FDA for the treatment of obesity

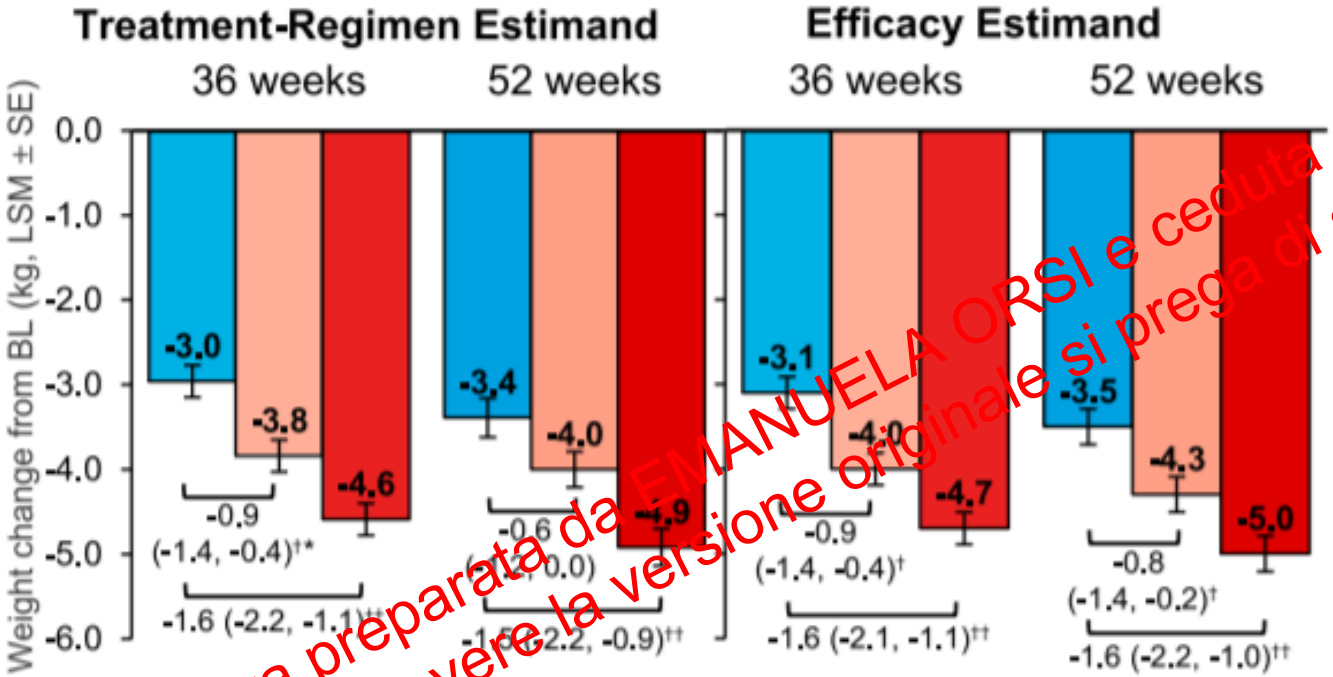
Table 8.2—Continued

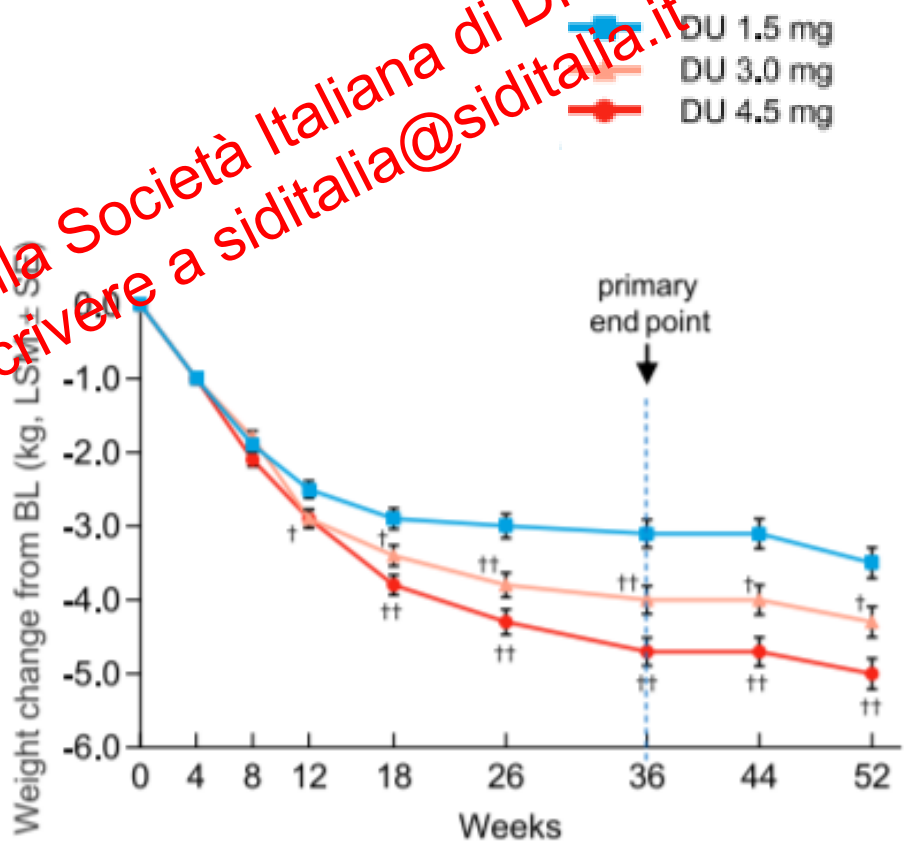
Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (118)	National Average Drug Acquisition Cost (30-day supply) (119)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (120–124)	Possible safety concerns/ considerations (120–124)
				Treatment arms	Weight loss (% loss from baseline)		
Glucagon-like peptide 1 receptor agonist							
Liraglutide (16)**	3 mg q.d.	$1,557	$1,243	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in patients with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined

All medications are contraindicated in women who are or may become pregnant. Women of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general obese adult population. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (127). ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ||Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance.

Standard of Medical Care, ADA 2021

Award 11: Change in body weight





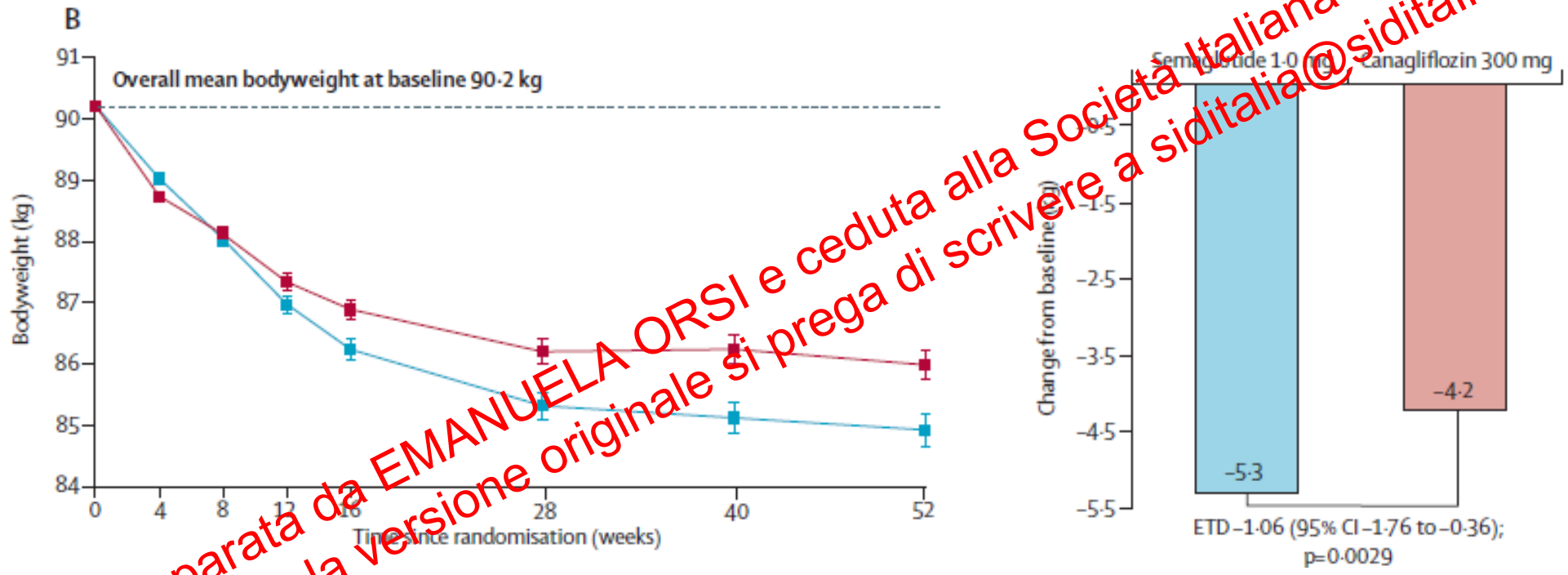
†P < 0.05

††P <0.001

*

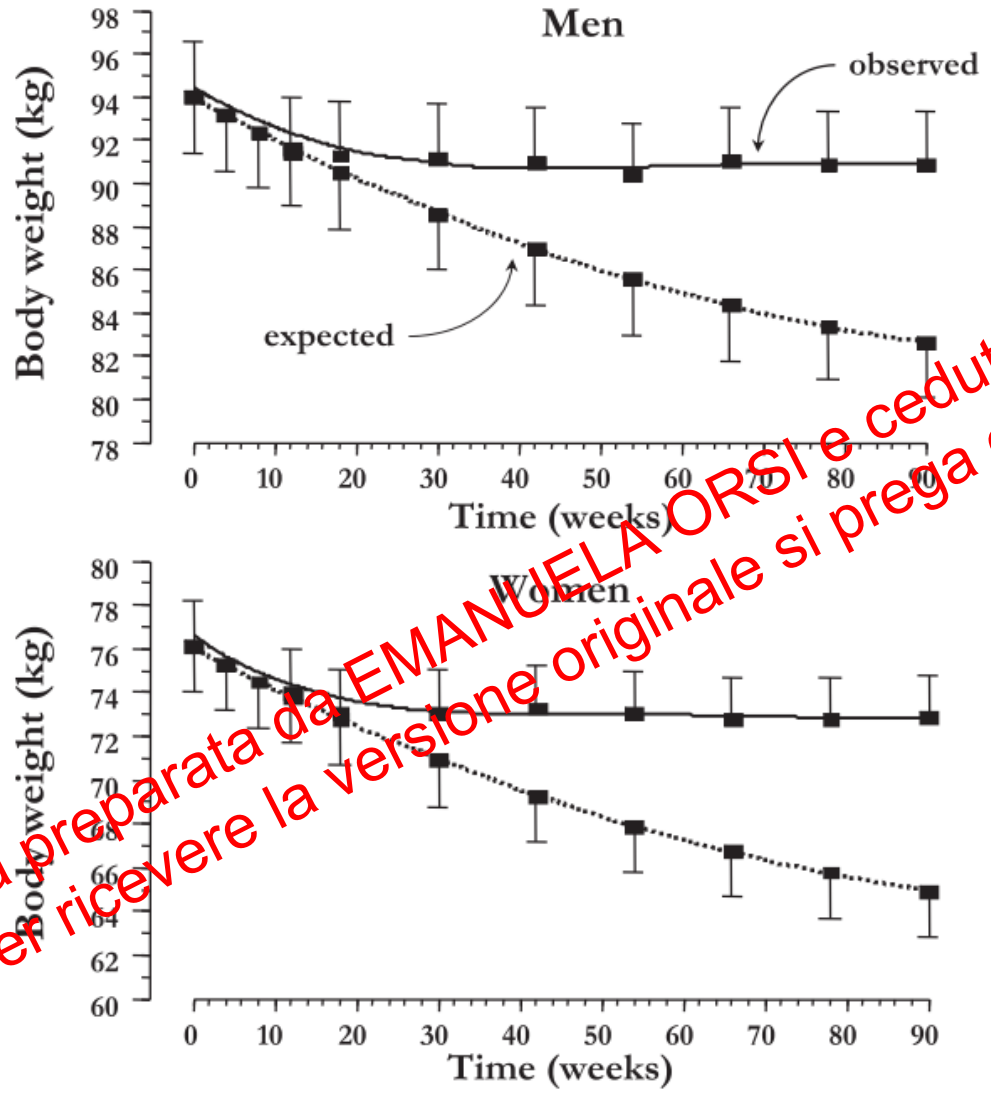
Frias JB et al, Diabetes Care, 2021

Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8)



Lingvay I et al, Lancet Diabetes Endocrinol, 2019

Time course of observed and predicted (by glycosuria) weight loss in men and women with T2DM treated with empagliflozin (25 mg/day) for 90 weeks



Chronic glycosuria elicits an adaptive increase in energy intake

Ferrannini G et al, Diabetes Care, 2015

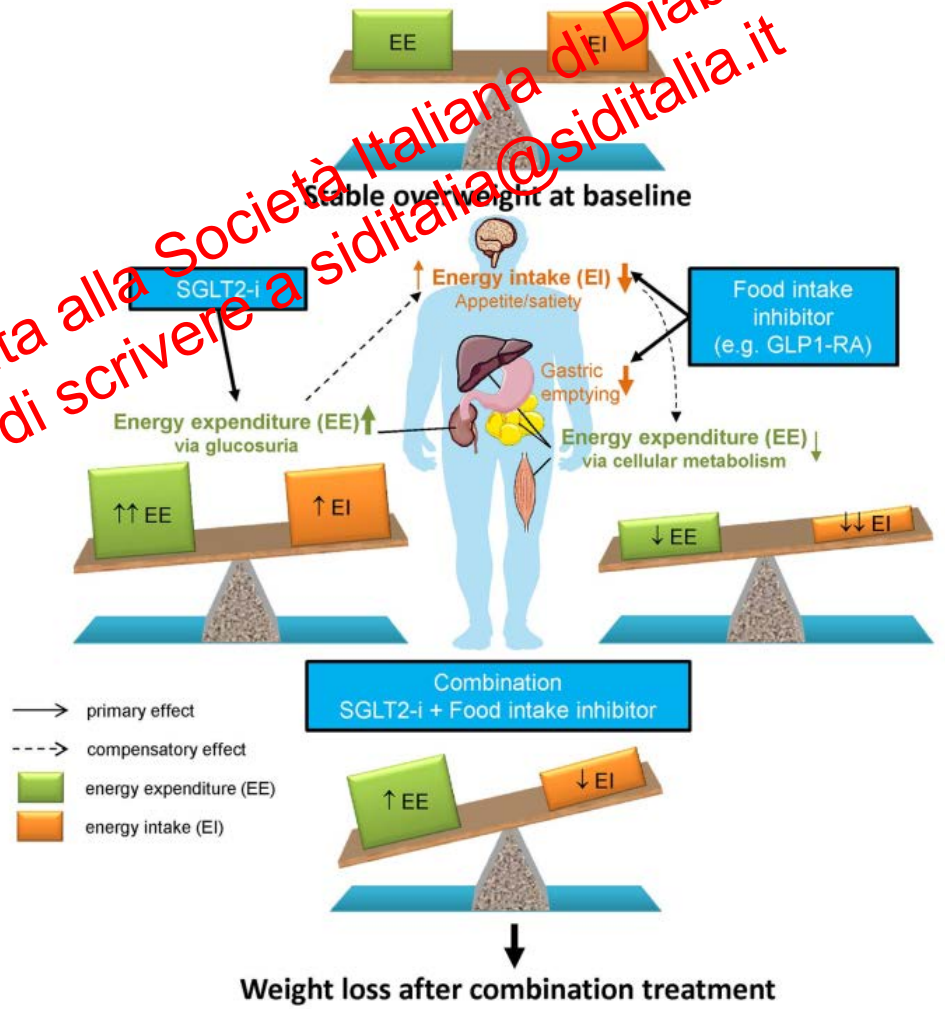
Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity

Key Points

With the increasing prevalence of obesity and associated co-morbidities, including impaired glucose tolerance and type 2 diabetes mellitus, novel treatment strategies are needed.

SGLT2 inhibitor monotherapy does not provide sufficient weight loss for successful treatment of obesity.

Co-administration of SGLT2 inhibitors together with agents that reduce food intake target complementary mechanisms and represent an effective weight loss therapy.



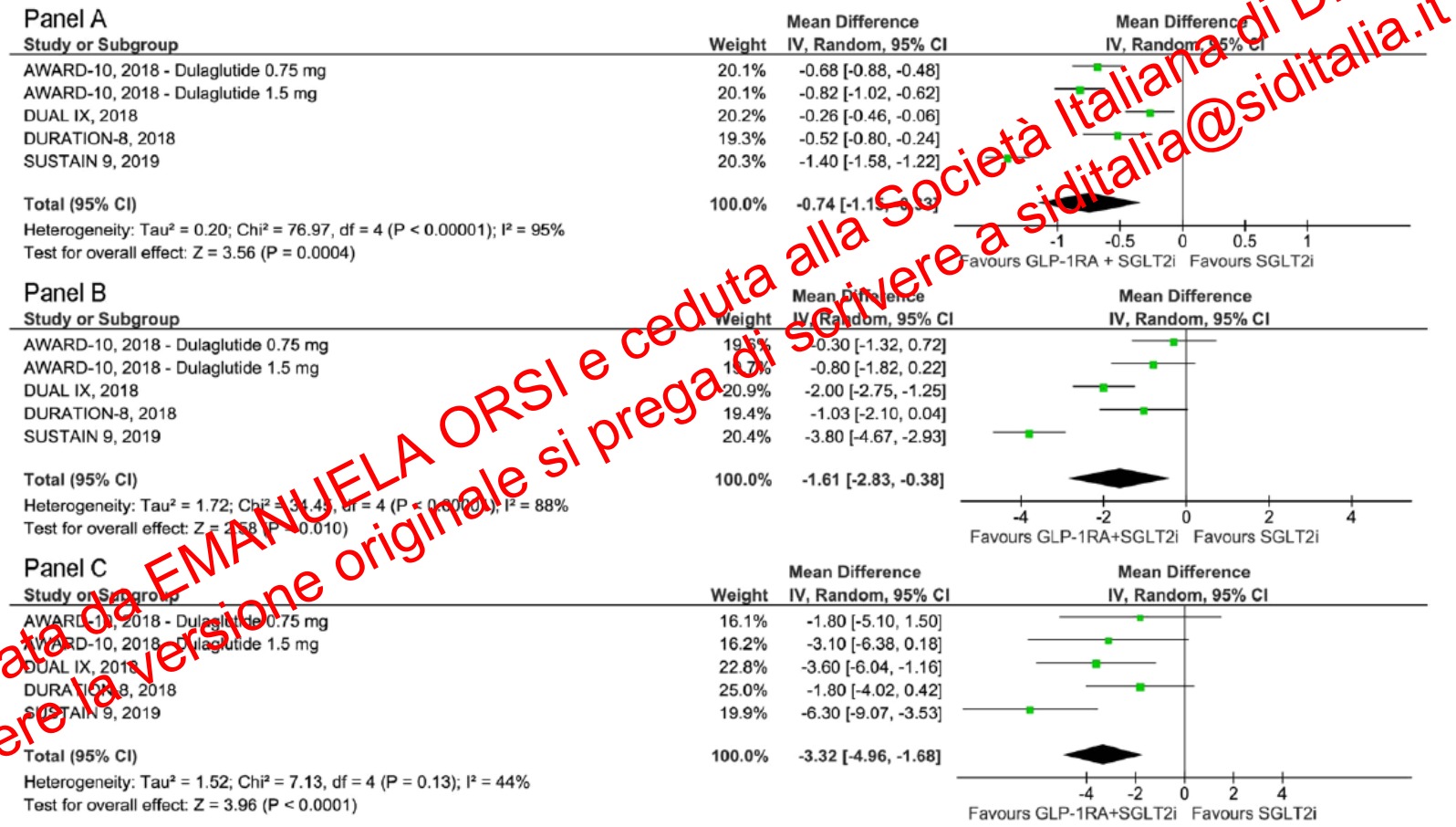
Pereira MJ, Drugs, 2019

Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis

HbA1c

Body Weight

Blood Pressure



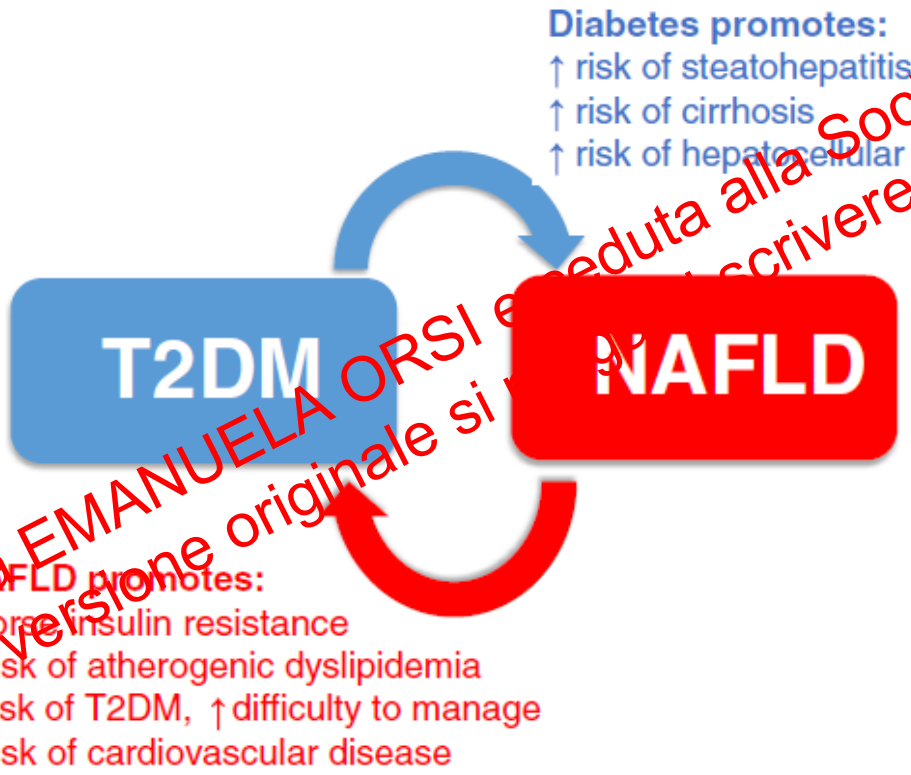
AWARD 10 Dulaglutide QW + SGLT2i
DUAL IX iDegLira QD + SGLT2i
DURATION 8 Exenatide QW + Dapagliflozin
SUSTAIN 9 Semaglutide QW + SGLT2i

Castellana M et al, Scientific Reports, 2019

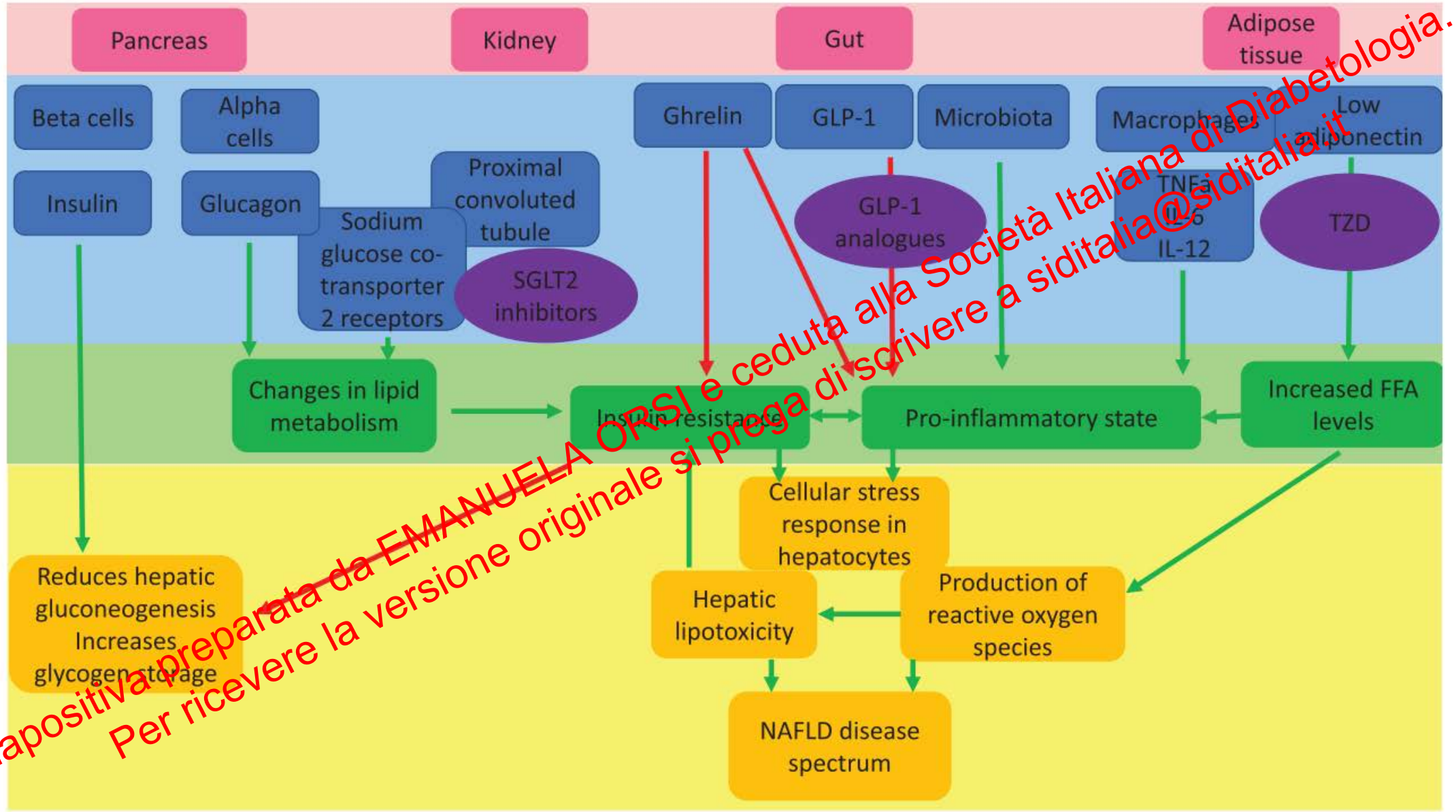
Agenda

- GLP1 RA (vs SGLT2i ?) e controllo glicemico
- GLP1 RA (vs SGLT2i ?) e peso corporeo
- GLP1 RA (vs SGLT2i ?) e NAFLD

Relationship between T2DM and NAFLD. Both conditions share underlying pathophysiological mechanisms that exacerbate each other and promote worse disease and comorbid conditions



Budd J & Cusi K, Curr Diab Rep, 2020



Vincent RK et al, Diabetes Obes Metab, 2020

Treatment Approach for Nonalcoholic Steatohepatitis and Nonalcoholic Fatty Acid Liver Diseases

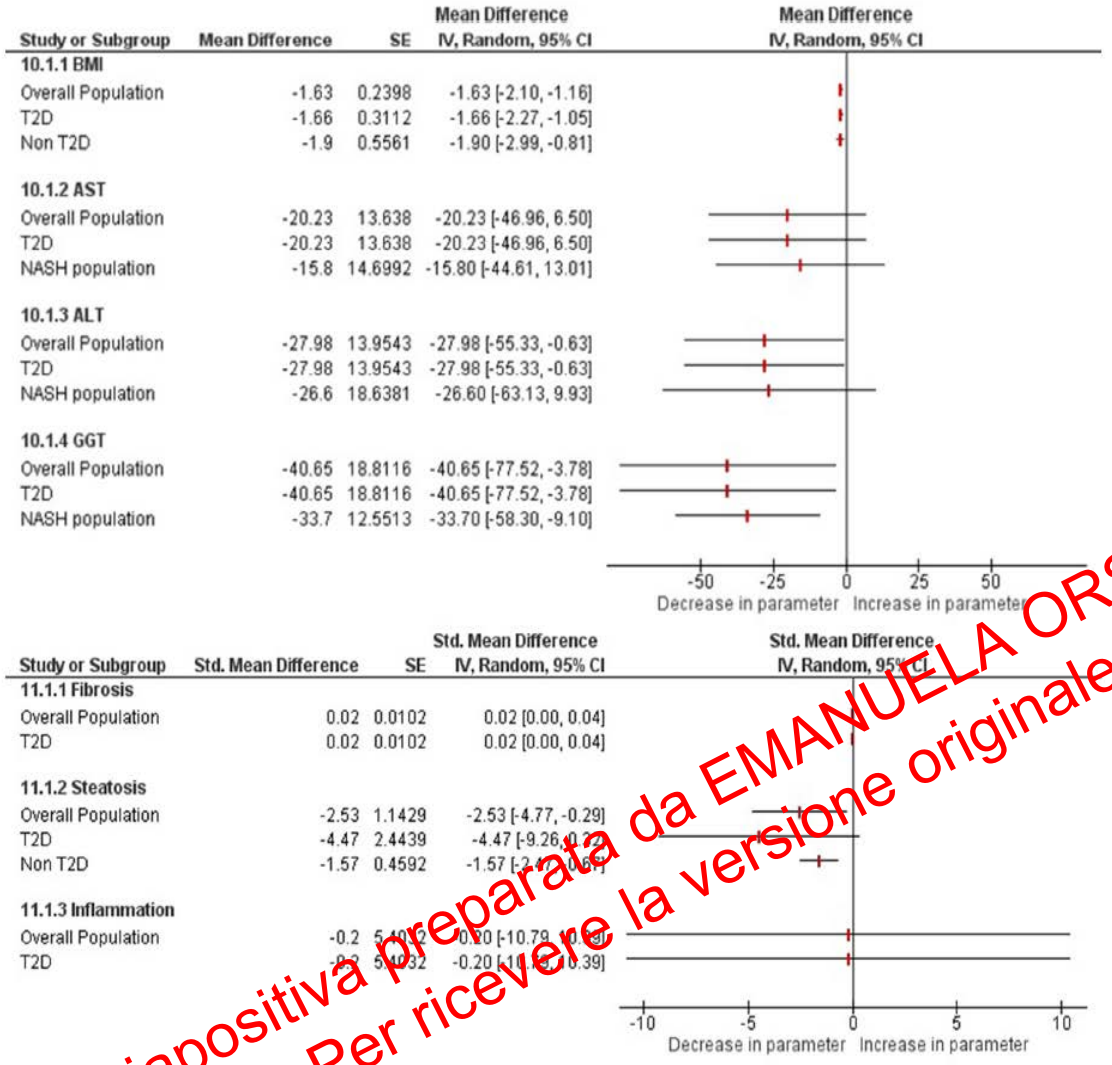
	NAFLD	Suspected NASH	Biopsy-proven NASH	NASH cirrhosis
Obtain baseline liver function tests including CBC, transaminases (AST/ALT), bilirubin, alkaline phosphatase, creatinine, INR	✓	✓	✓	✓
Medical optimization of comorbid conditions:				
Control of type 2 diabetes, hypertension, and dyslipidemia	✓	✓	✓	✓
Cardiovascular optimization				
Statin therapy as indicated by ACC/AHA guidelines				
Intensive lifestyle modification with goal of 7%-10% weight loss				
Caloric restriction	✓	✓	✓	✓
Aerobic exercise regimen				
Minimize alcohol use	✓	✓	✓	✓
Minimize added fructose intake	✓	✓	✓	✓
If patients are unable to achieve weight loss goal and may be otherwise eligible, refer for bariatric surgery evaluation	May consider, particularly for patients with BMI >35 or BMI >30 and type 2 diabetes	✓	✓	✓
Consider pioglitazone for patients with or without diabetes (30 mg/d)			✓	
For patients without diabetes, consider vitamin E (800 IU/d)			✓	
Consider eligibility for clinical trial participation		✓	✓	✓
Initiate screening for hepatocellular carcinoma per AASLD guidelines				✓
Initiate screening for esophageal varices per AASLD guidelines				✓
Consider evaluation for liver transplant if clinically decompensated				✓

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACC/AHA, American College of Cardiology and American Heart Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CBC, complete blood cell count; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[a] Check marks indicate that the treatment strategy should be used.

Sheka AC et al JAMA, 2020

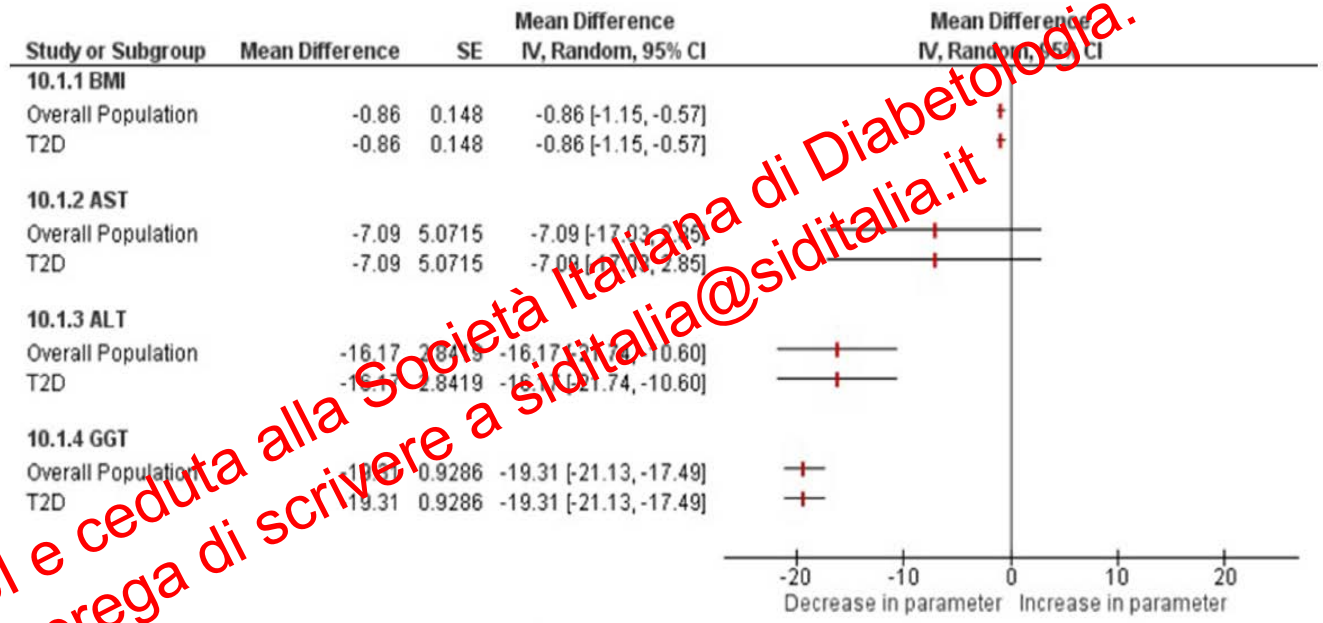
GLP 1 RA and NAFLD



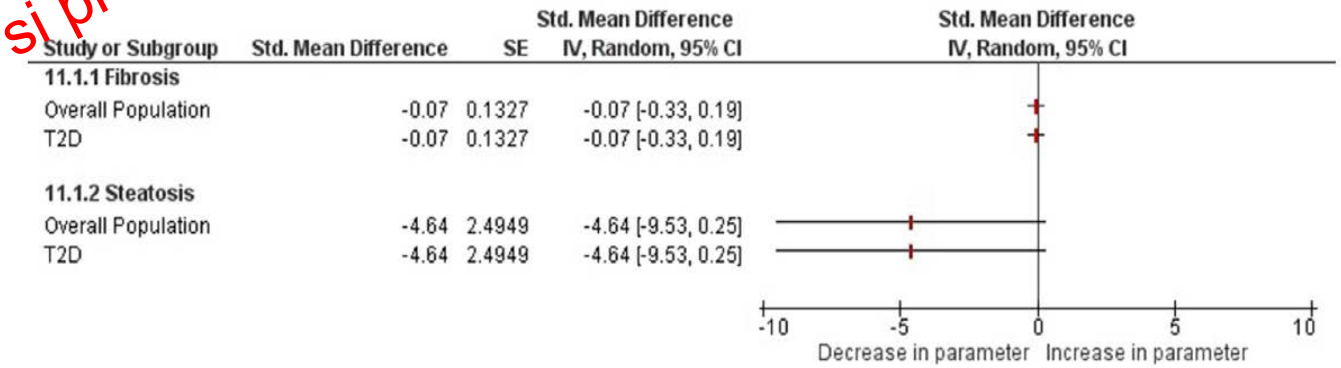
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
10.1.1 BMI			
Overall Population	-1.63	0.2398	-1.63 [-2.10, -1.16]
T2D	-1.66	0.3112	-1.66 [-2.27, -1.05]
Non T2D	-1.9	0.5561	-1.90 [-2.99, -0.81]
10.1.2 AST			
Overall Population	-20.23	13.638	-20.23 [-46.96, 6.50]
T2D	-20.23	13.638	-20.23 [-46.96, 6.50]
NASH population	-15.8	14.6992	-15.80 [-44.61, 13.01]
10.1.3 ALT			
Overall Population	-27.98	13.9543	-27.98 [-55.33, -0.63]
T2D	-27.98	13.9543	-27.98 [-55.33, -0.63]
NASH population	-26.6	18.6381	-26.60 [-63.13, 9.93]
10.1.4 GGT			
Overall Population	-40.65	18.8116	-40.65 [-77.52, -3.78]
T2D	-40.65	18.8116	-40.65 [-77.52, -3.78]
NASH population	-33.7	12.5513	-33.70 [-58.30, -9.10]

Study or Subgroup	Std. Mean Difference	SE	Std. Mean Difference IV, Random, 95% CI
11.1.1 Fibrosis			
Overall Population	0.02	0.0102	0.02 [0.00, 0.04]
T2D	0.02	0.0102	0.02 [0.00, 0.04]
11.1.2 Steatosis			
Overall Population	-2.53	1.1429	-2.53 [-4.77, -0.29]
T2D	-4.47	2.4439	-4.47 [-9.26, 0.32]
Non T2D	-1.57	0.4592	-1.57 [-2.47, -0.67]
11.1.3 Inflammation			
Overall Population	-0.2	5.1012	-0.20 [-10.79, 10.39]
T2D	-0.2	5.1032	-0.20 [-10.79, 10.39]

SGLT-2 inhibitors and NAFLD



Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
10.1.1 BMI			
Overall Population	-0.86	0.148	-0.86 [-1.15, -0.57]
T2D	-0.86	0.148	-0.86 [-1.15, -0.57]
10.1.2 AST			
Overall Population	-7.09	5.0715	-7.09 [-17.03, 2.85]
T2D	-7.09	5.0715	-7.09 [-17.03, 2.85]
10.1.3 ALT			
Overall Population	-16.17	2.8419	-16.17 [-21.74, -10.60]
T2D	-16.17	2.8419	-16.17 [-21.74, -10.60]
10.1.4 GGT			
Overall Population	-19.31	0.9286	-19.31 [-21.13, -17.49]
T2D	-19.31	0.9286	-19.31 [-21.13, -17.49]



Study or Subgroup	Std. Mean Difference	SE	Std. Mean Difference IV, Random, 95% CI
11.1.1 Fibrosis			
Overall Population	-0.07	0.1327	-0.07 [-0.33, 0.19]
T2D	-0.07	0.1327	-0.07 [-0.33, 0.19]
11.1.2 Steatosis			
Overall Population	-4.64	2.4949	-4.64 [-9.53, 0.25]
T2D	-4.64	2.4949	-4.64 [-9.53, 0.25]

Kumar J et al, Dig Liver Dis, 2021

Effects of diabetes medications in NAFLD

Author	CVD risk	Effect on liver fat	Effect on liver histology
Pioglitazone	↓	↓	Improved
GLP-1RAs			
Liraglutide	↓	↓	Improved
Semaglutide	↓	↓	Improved
SGLT2 inhibitors			
Dapagliflozin	↓	↓	?
Empagliflozin	↓	↓	?
Canagliflozin	↓		?
DPP-IV inhibitors			
Sitagliptin	Neutral	Unchanged	?
Vildagliptin	Neutral	mild↓	?
Metformin	?*	Unchanged	Neutral
Insulin	?**	↓	?

GLP-1RA: glucagon-like peptide-1 receptor agonist

SGLT2 inhibitors: sodium-glucose cotransporter-2 inhibitors

DPP-IV inhibitors: dipeptidyl peptidase-4 inhibitors

*The effect of metformin on atherosclerosis and cardiovascular disease in human remains controversial

**The effect of insulin on atherosclerosis and cardiovascular disease in human remain controversial

Budd J & Cusi K, Curr Diab Rep, 2020

Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial)

Changes in clinical and biochemical variables

Variable	Control (SE) ($n = 25$)	Dulaglutide (SE) ($n = 27$)	Mean between-group difference (95% CI)	p value
Body weight, kg	−2.0 (0.7)	−4.3 (0.5)	−2.3 (−4.1, −0.6)	0.01*
BMI, kg/m^2	−0.68 (0.3)	−1.5 (0.2)	−0.8 (−1.43, −0.19)	0.01*
FPG, mmol/l	−2.6 (2.8)	−3.6 (3.5)	−0.9 (−2.7, 0.8)	0.296
HbA_{1c}, mmol/mol	−13.7 (2.4)	−17.4 (1.8)	−3.7 (−9.6, 2.3)	0.218
HbA_{1c}, %	−1.3 (0.2)	−1.6 (0.2)	−0.3 (−0.9, 0.2)	0.222
Total bilirubin, μmol/l	−1.8 (3.4)	−0.9 (4.3)	−0.9 (−1.3, 3.1)	0.407
AST, U/l	−7.3 (3.8)	−16.6 (3.4)	−9.3 (−19.5, 1.0)	0.075
ALT, U/l	−13.9 (5.0)	−26.4 (5.5)	−13.1 (−24.4, 2.5)	0.1
GGT, U/l	−6.3 (4.6)	−19.4 (3.4)	−13.1 (−24.4, −1.8)	0.025*
Alkaline phosphatase, U/l	−5.6 (3.4)	−10.2 (4.2)	−4.6 (−15.5, 6.3)	0.401
Triacylglycerols, mmol/l	−0.2 (1.0)	−0.5 (0.7)	−0.3 (−0.8, 0.2)	0.187
HDL-cholesterol, mmol/l	−0.0 (0.2)	−0.1 (0.2)	−0.1 (−0.1, 0.2)	0.391
LDL-cholesterol, mmol/l	−0.4 (0.9)	−0.2 (0.6)	0.1 (−0.3, 0.6)	0.592
Serum urea, mmol/l	0.1 (1.0)	0.3 (1.1)	0.3 (−0.3, 0.9)	0.271
Serum creatinine, mmol/l	3.6 (11.2)	−1.9 (9.3)	−5.5 (−11.2, 0.3)	0.06
Serum uric acid, mmol/l	0 (0.1)	0 (0.1)	0 (−0.1, 0)	0.11
Urine protein/creatinine ratio	−0.0 (0.01)	−0.15 (0.05)	−0.15 (−0.26, −0.04)	0.01*

Baseline and change (absolute and relative) in liver fat content (LFC), pancreatic fat content (PFC) and in liver stiffness measurement (LSM)

	Control ($n = 25$)	Dulaglutide ($n = 27$)	Between-group difference, % (95% CI)	p value
MRI-PDFF assessment				
Baseline LFC, % (mean±SD)	17.1 ± 7.7	17.9 ± 7.2	–	–
Week 24 LFC, % (mean±SD)	14.8 ± 6.5	12.0 ± 6.6	–	–
Absolute LFC change, % (SE)	−2.3 (1.2)	−5.8% (1.0)	−3.5 (−6.6, −0.4)	0.025*
Relative LFC change, % (SE)	−5.7 (7.9)	−32.1 (4.3)	−26.4 (−44.2, −8.6)	0.004*
Baseline PFC, % (mean±SD)	8.8 ± 6.7	9.3 ± 7.0	–	–
Week 24 PFC, % (mean±SD)	8.1 ± 5.1	7.2 ± 4.5	–	–
Absolute PFC, % change (SE)	−0.7 (0.5)	−2.1 (0.7)	−1.4 (−3.2, 0.3)	0.106
Relative PFC change, % (SE)	−0.2 (5.2)	−11.4 (6.6)	−11.2 (−28.3, 5.8)	0.192
LSM by VCTE				
Baseline LSM, kPa (mean±SD)	9.0 ± 4.3	10.8 ± 5.1	–	–
Week 24 LSM, kPa (mean±SD)	8.9 ± 4.9	9.3 ± 4.3	–	–
Absolute LSM change, kPa (SE)	−0.12 (0.63)	−1.43 (0.56)	−1.31 (−2.99, 0.37)	0.123
Relative LSM change, kPa (SE)	2.04 (25.7)	−9.1 (25.7)	−11.2 (−25.5, 3.5)	0.124

Kuchay MS et al, Diabetologia, 2020

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

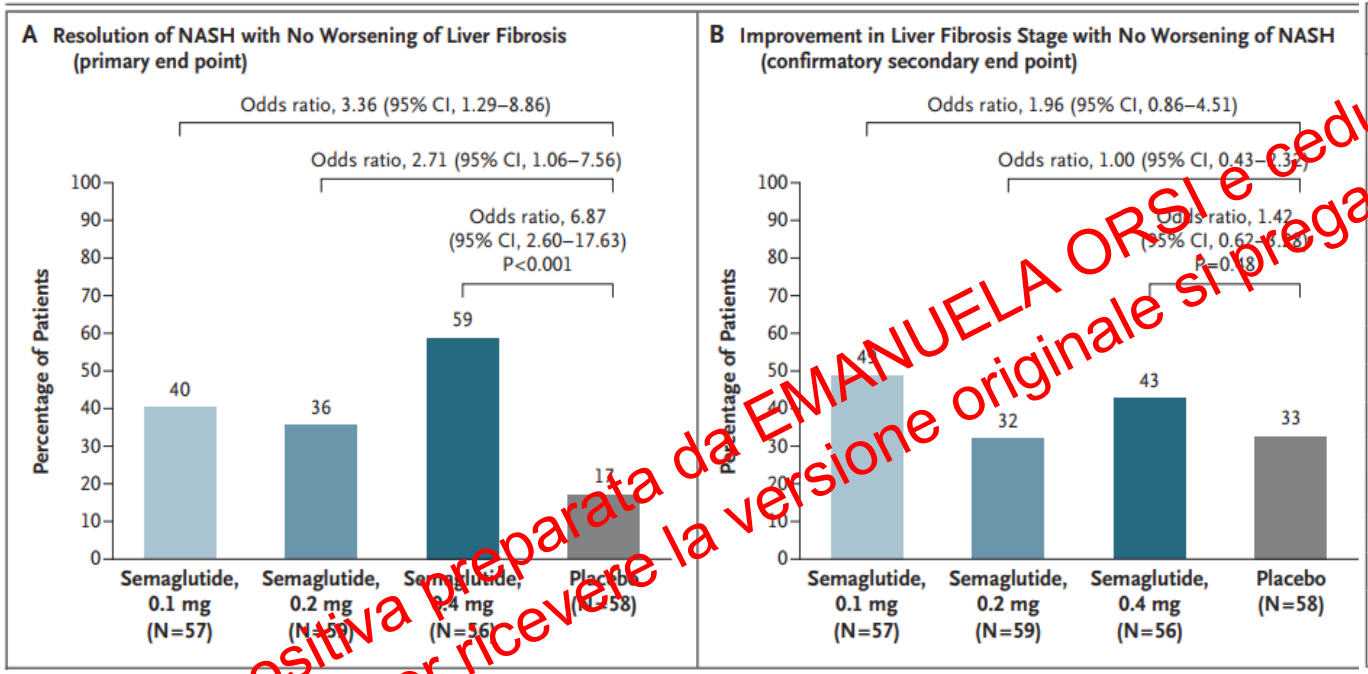


Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	−0.34	−0.39	−0.56	0.01
Body weight — %	−4.84	−8.91	−12.51	−0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	−0.63	−1.07	−1.15	−0.01

Newsome PN et al, NEJM, 2020

GLP 1 RA (vs SGLT 2?) outcome

Outcome	GLP-1 receptor antagonists	SGLT2 inhibitors
A1c reduction (%)	0.7–1.7	0.32–1.17
Target of BG lowering	Shorter acting, mostly postprandial BG; longer acting, target fasting and postprandial BG	Fasting and postprandial BG
Hypoglycemia risk	Low	Low
Weight loss (kg)	2–5	1.5–3.0
Systolic blood pressure reduction (mmHg)	2–5	3–5
Cardiovascular outcomes	Unclear benefit in primary and secondary prevention	Reduction in CV death in patients with known ASCVD; unclear benefit in primary prevention
Potential adverse effects	Gastrointestinal upset, pancreatitis/pancreatic cancers, thyroid tumors/cancers, long-term safety not established	Genitourinary infections, diabetic ketoacidosis, bone fractures, long-term safety not established
Administration	Subcutaneous injections, twice daily to once weekly; may require reconstitution and use of prefilled pens	Oral, once daily
Cost/day (US $)[72]	13.56–21.37	12.10
Cost/QALY[a64-p9]	EXEN BID vs IG: dominate to £30,000 EXEN QW vs IG: £9,400–£13,000	DAPA vs SITA: £6,800 DAPA vs MET: £2,700

Gurgle HE et al, Vasc Health Risk Manag, 2016

Glucagon-like Peptide-1 Receptor Agonism

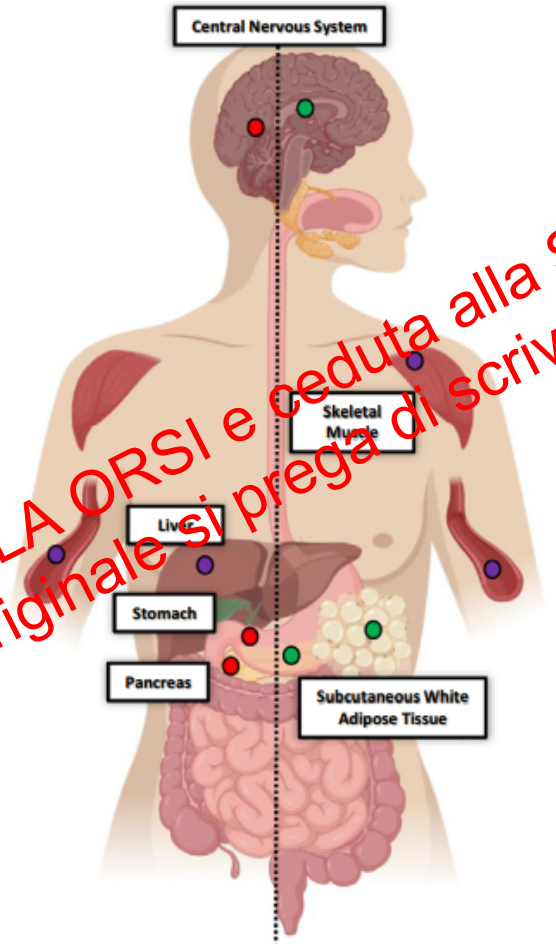
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

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



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Glucagon-like Peptide 1 Receptor Agonism

Indirect Action

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

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

Pancreas
- ↑ Insulin
- ↑ Glucagon

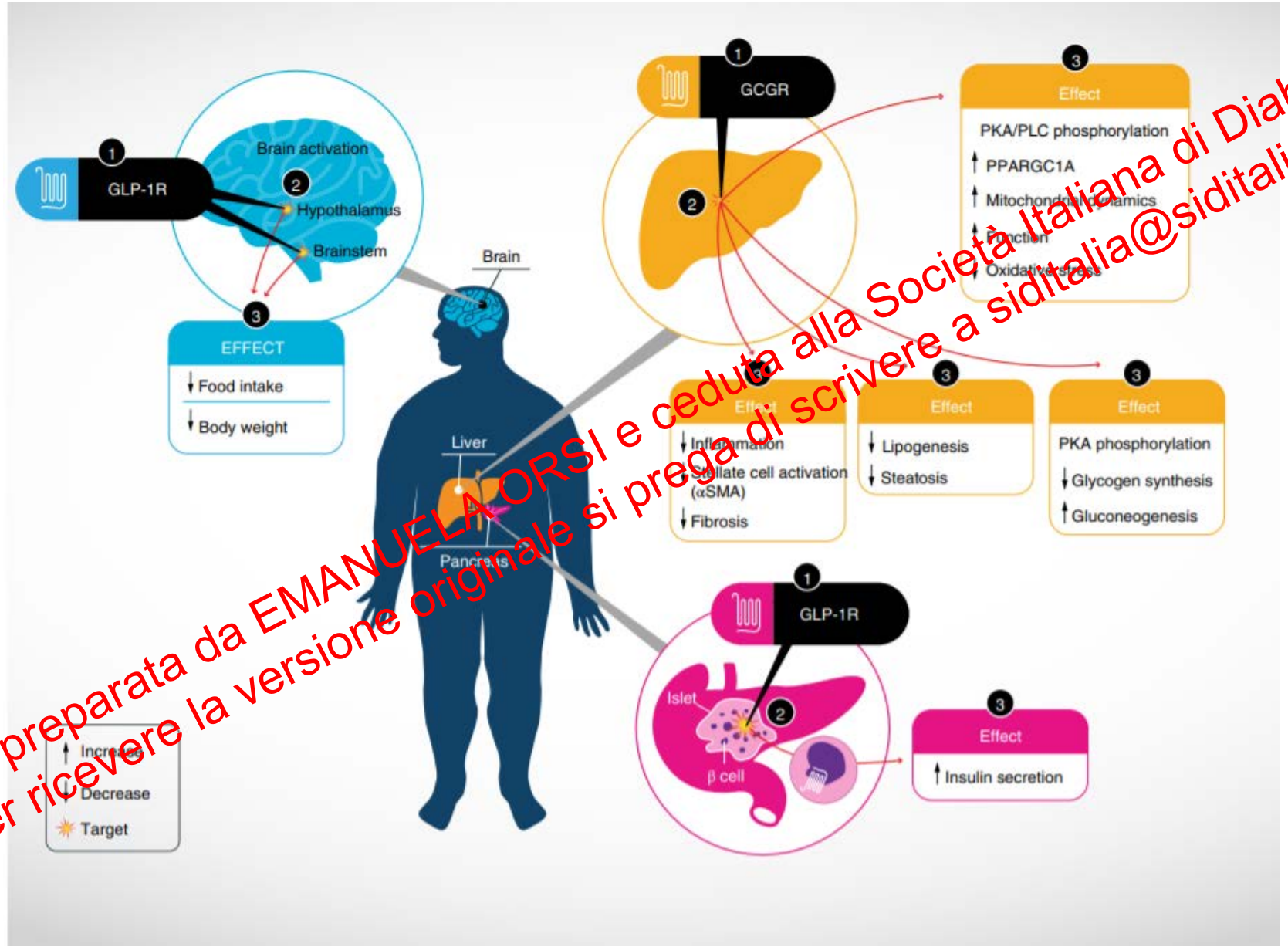
Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

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

Samms RJ et al, Trends in Endocrinology & Metabolism, 2020

Cotadutide: a Dual Receptor Glucagon-Like Peptide-1 and Glucagon Agonist



Boland ML et al, Nat Metab, 2020

What is

What if

Metabolic effects

EBM

Real life studies

Guidelines

Grazie per l'attenzione