Analoghi del GLP-1 nei pazienti sovrappeso ed obesi

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Università degli Studi di Torino

Conflitto di interessi

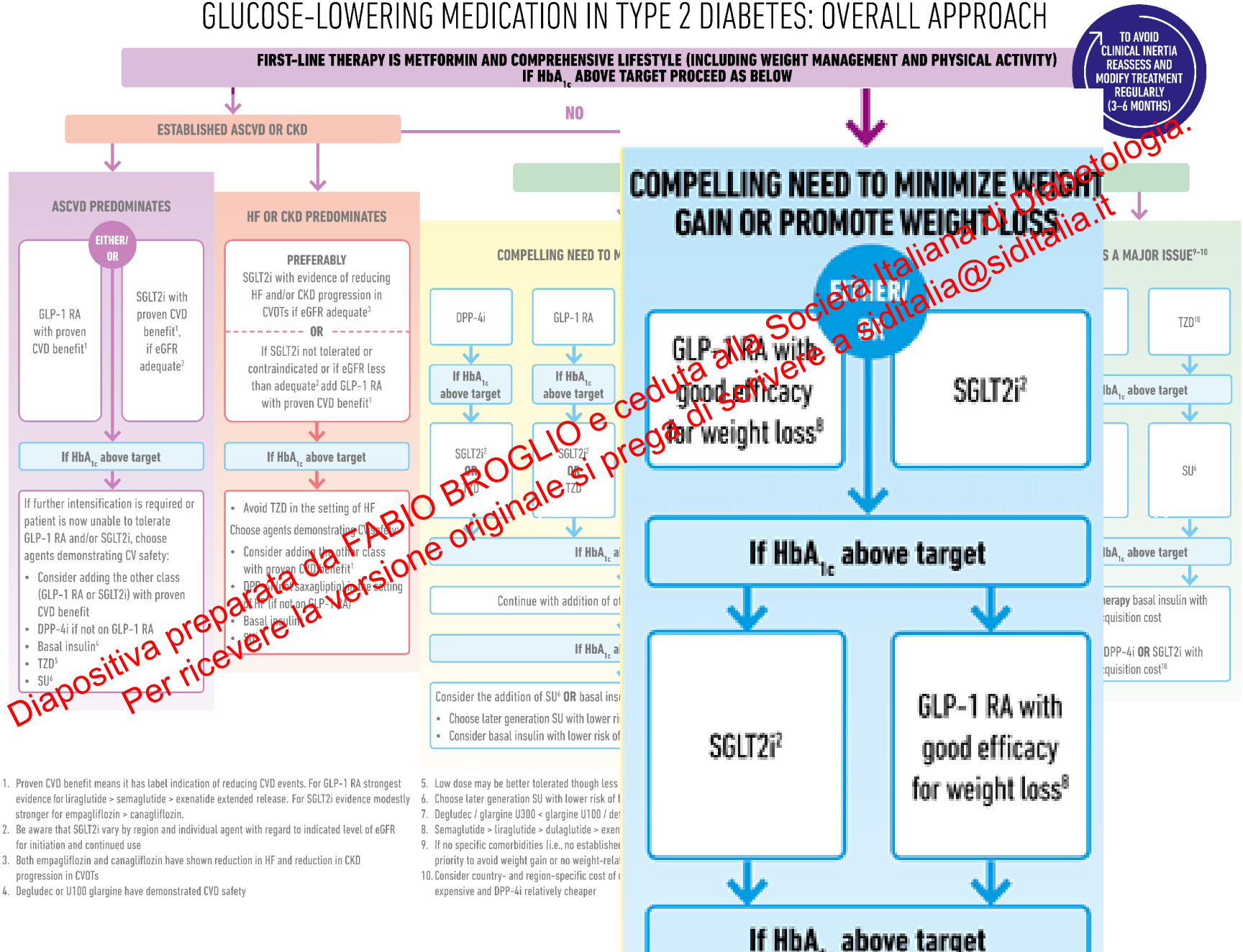
Negli ultimi due anni, F. Broglio ha ricevuto compensi per relazioni e/o consulenze da:

AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, Novartis, Novo Nordisk, Roche Diabetes Care e Sanofi.

La struttura di appartenenza di F. Broglio ha ricevuto donazioni, finanziamenti per ricerca o compensi per trial clinici da:

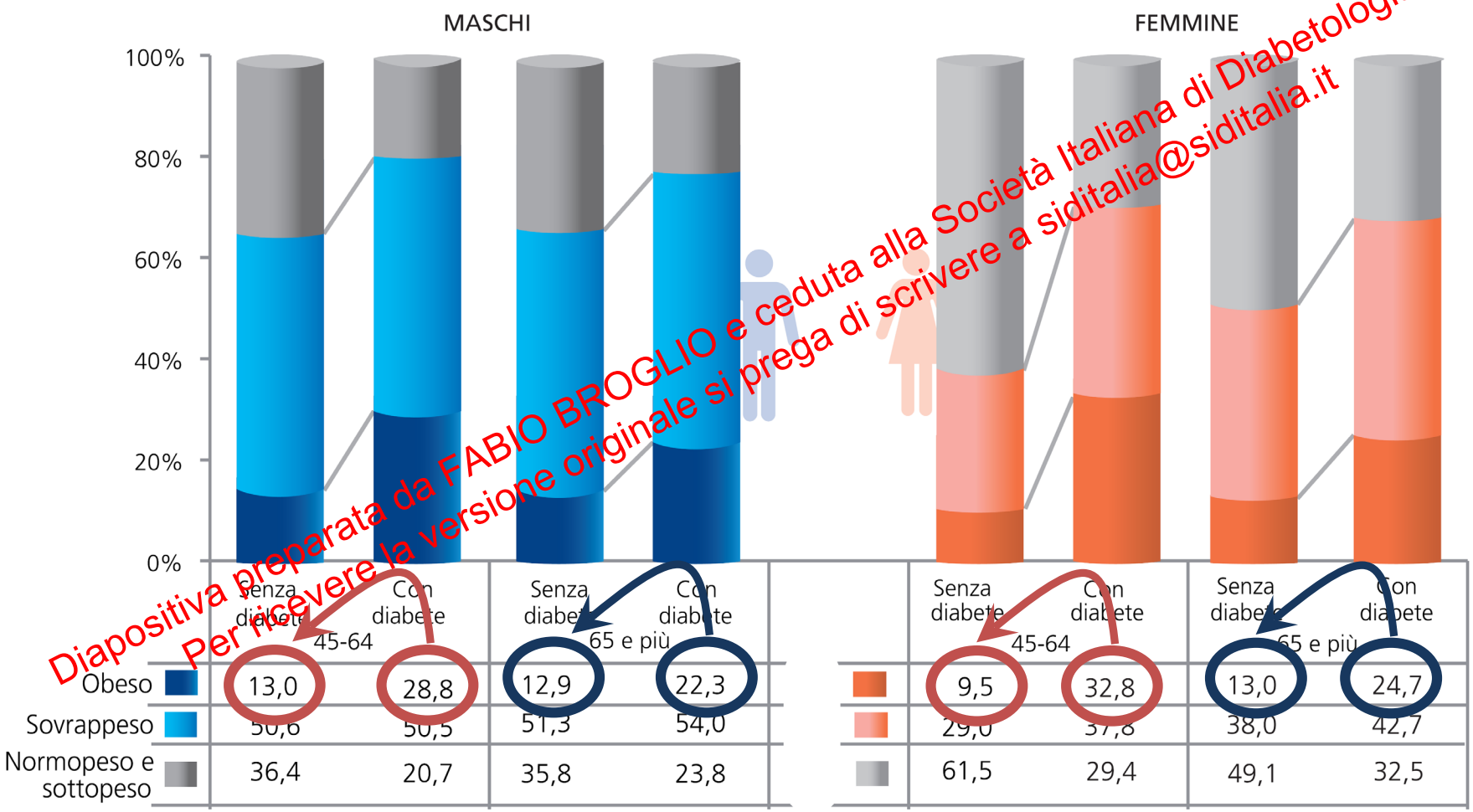
AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, Novo Nordisk e Sanofi.

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less
6. Choose later generation SU with lower risk of
7. Degludec / glargine U300 < glargine U100 / de
8. Semaglutide > liraglutide > dulaglutide > exen
9. If no specific comorbidities (i.e., no establishe priority to avoid weight gain or no weight-rela
10. Consider country- and region-specific cost of expensive and DPP-4i relatively cheaper

Percentuale di soggetti obesi in relazione a presenza di diabete



Italian Diabetes & Obesity Barometer Report, 2018

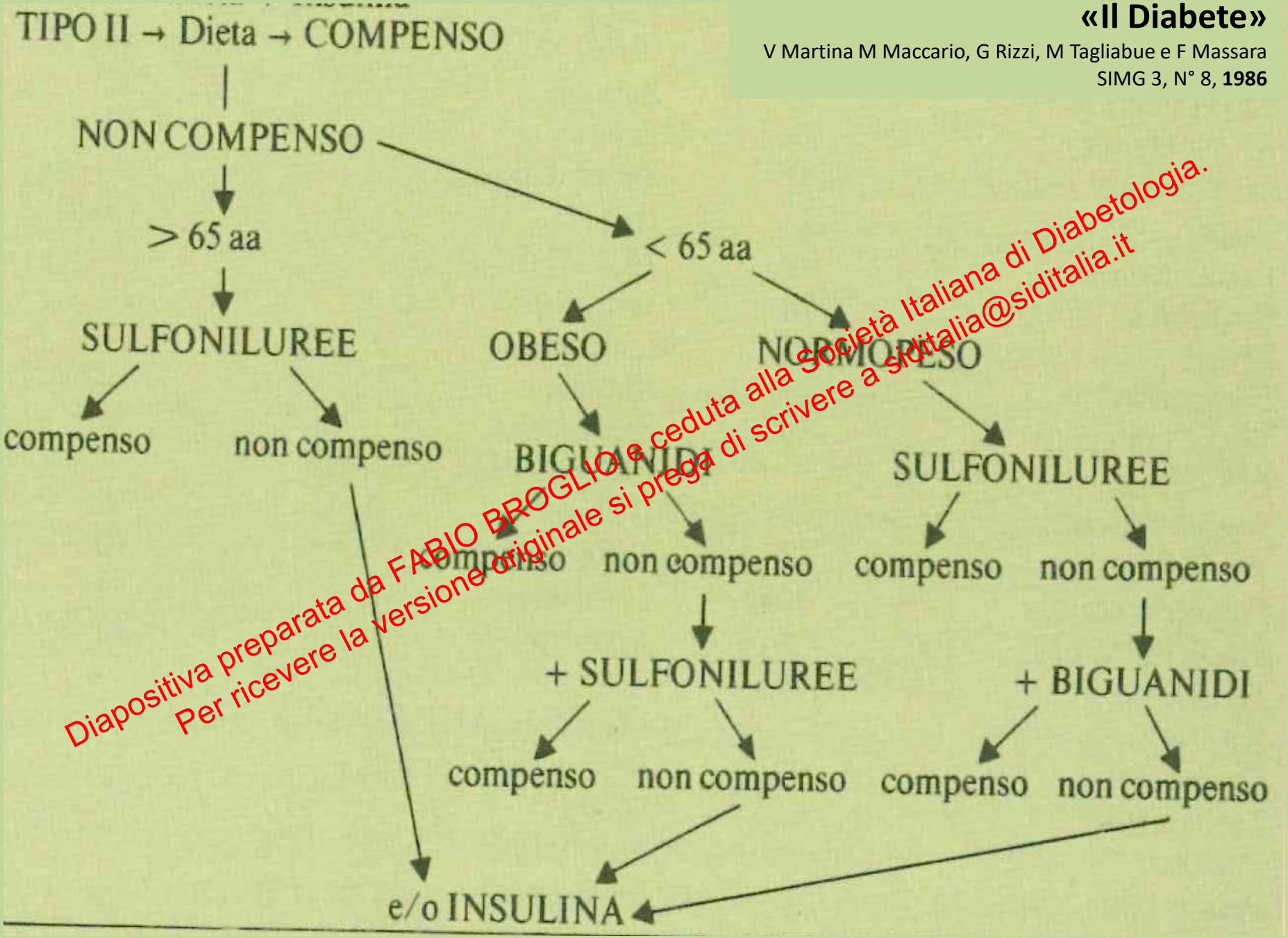
Consequences of Obesity in Diabetes

- Increases the risk of cardiovascular comorbidities
  - Hypertension
  - Dyslipidemia
  - Atherosclerosis
- May limit ability to engage in physical activity and reduces quality of life
- Impacts on the responsiveness to antidiabetic drugs
  - Increases insulin resistance
  - Impairs beta cell function

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

«Il Diabete»

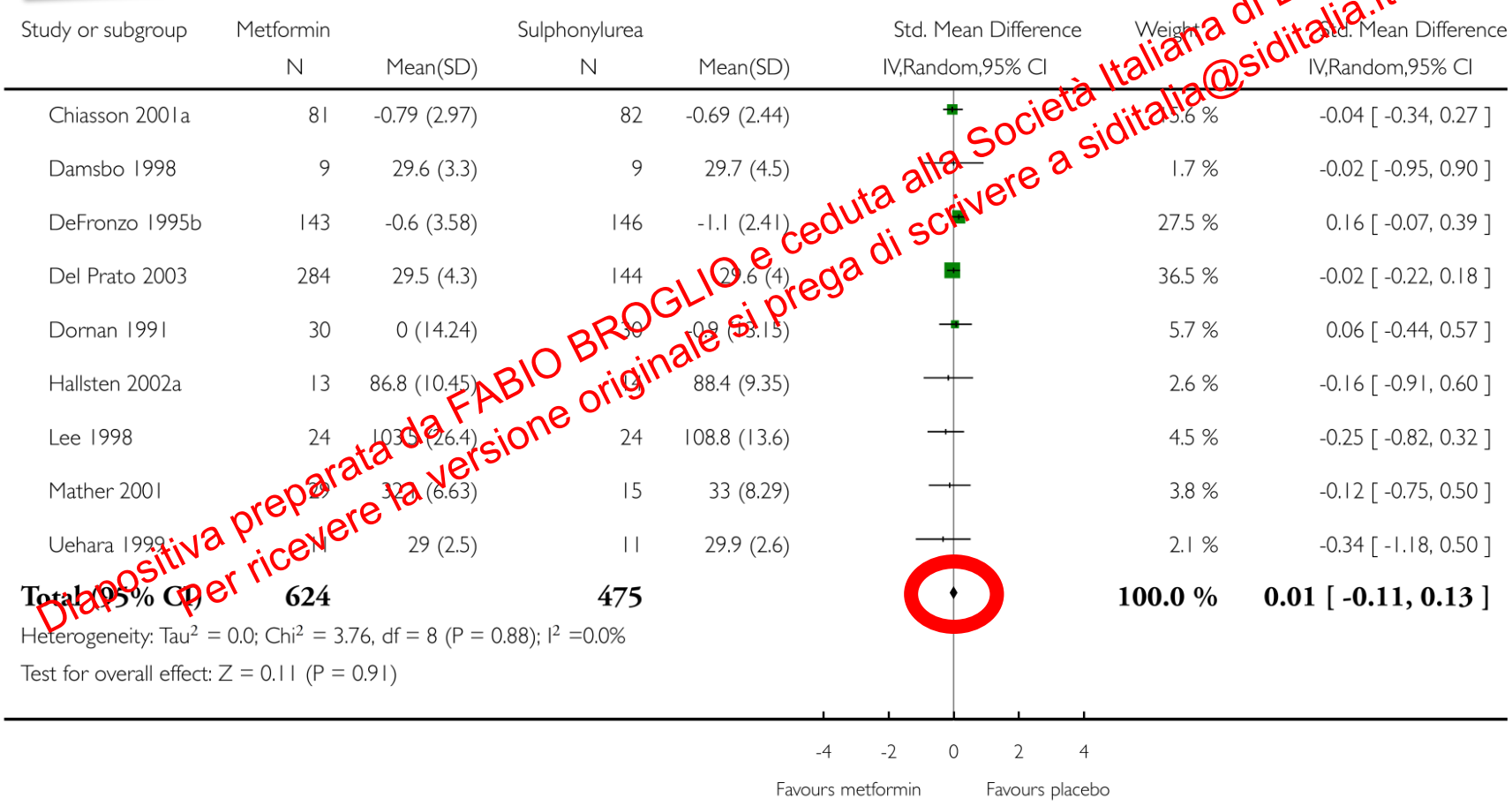
V Martina M Maccario, G Rizzi, M Tagliabue e F Massara
SIMG 3, N° 8, **1986**



Metformin monotherapy for type 2 diabetes mellitus (Review)

Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D

BMI



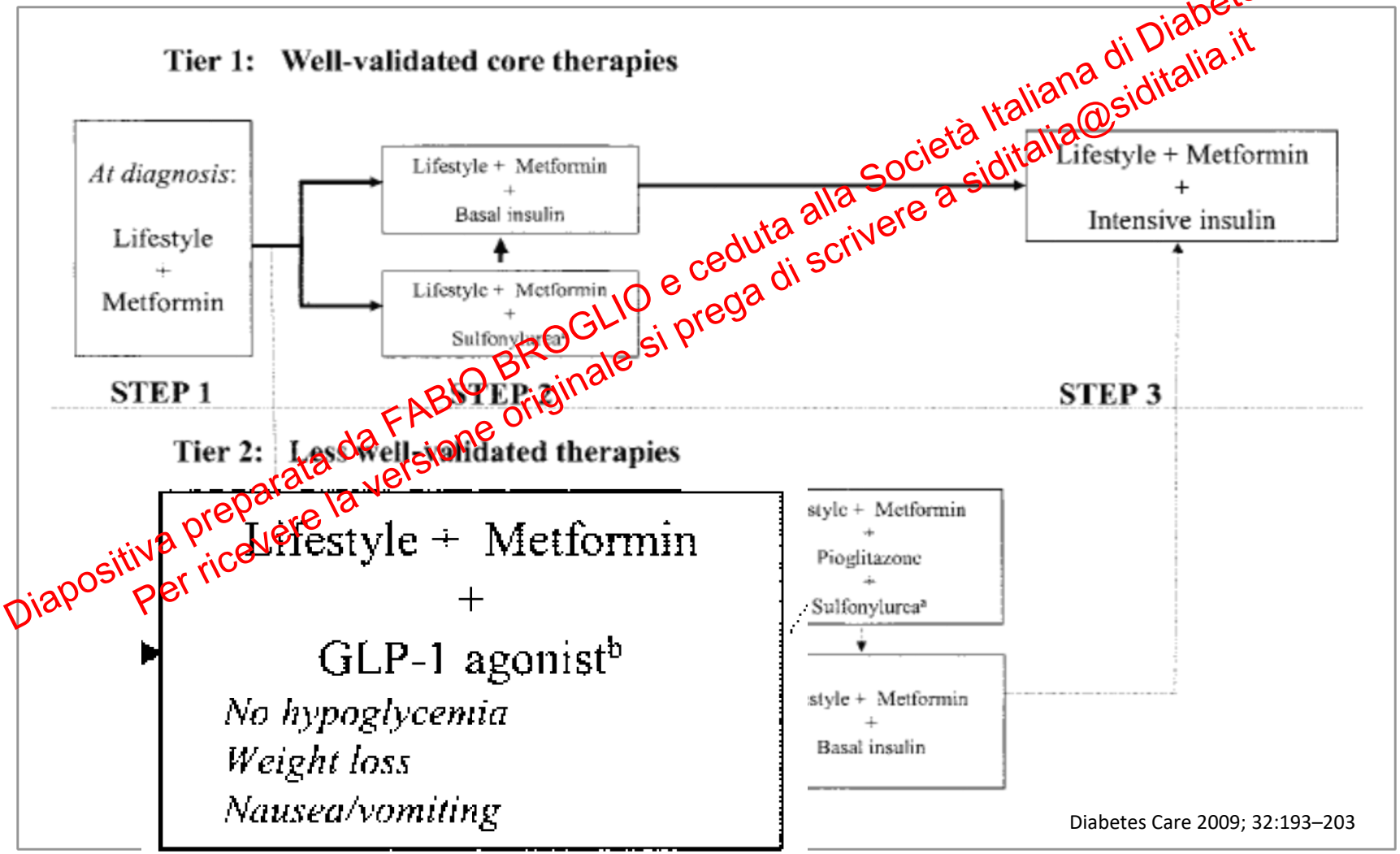
Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002966.

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

2009

A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

David M. Nathan, MD[1]
John B. Buse, MD, PHD[2]
Mayer B. Davidson, MD[3]
Ele Ferrannini, MD[4]
Rury R. Holman, FRCP[5]
Robert Sherwin, MD[6]
Bernard Zinman, MD[7]



Diabetes Care 2009; 32:193–203

GLP-1 mimetic (exenatide)

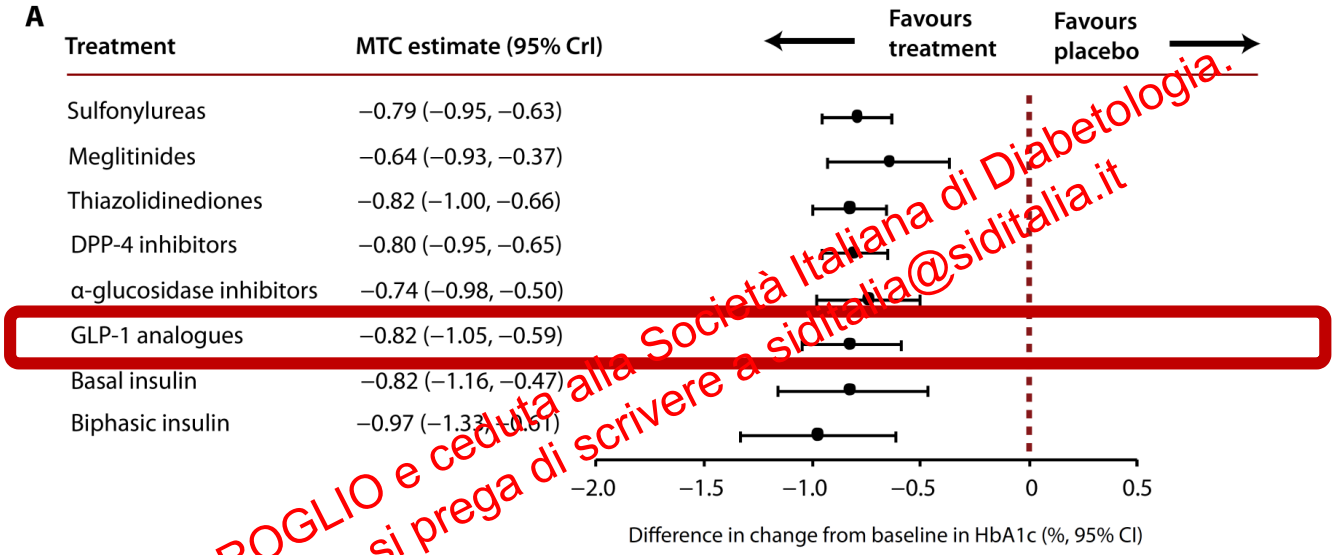
1.1.14 Consider adding a GLP-1 mimetic as **third-line therapy** to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has

- a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight,
- a BMI < 35.0 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

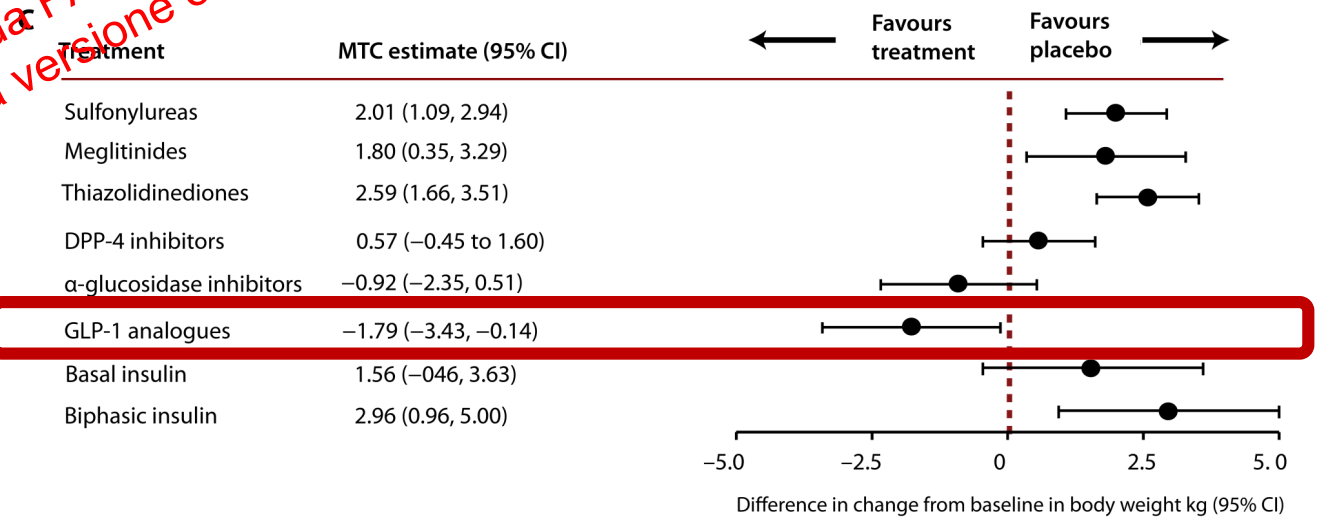
Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis

Brendan McIntosh, Chris Cameron, Sumeet R. Singh, Changhua Yu, Tarun Ahuja, Nicky J. Welton, Marshall Dahl

HbA1c



weight



Open Medicine 2011;5(1):e35

A Meta-Analysis of the Effect of Glucagon-Like Peptide-1 (7–36) Amide on *Ad Libitum* Energy Intake in Humans

C. VERDICH, A. FLINT, J.-P. GUTZWILLER, E. NÄSLUND, C. BEGLINGER, P. M. HELLSTRÖM, S. J. LONG, L. M. MORGAN, J. J. HOLST, AND A. ASTRUP

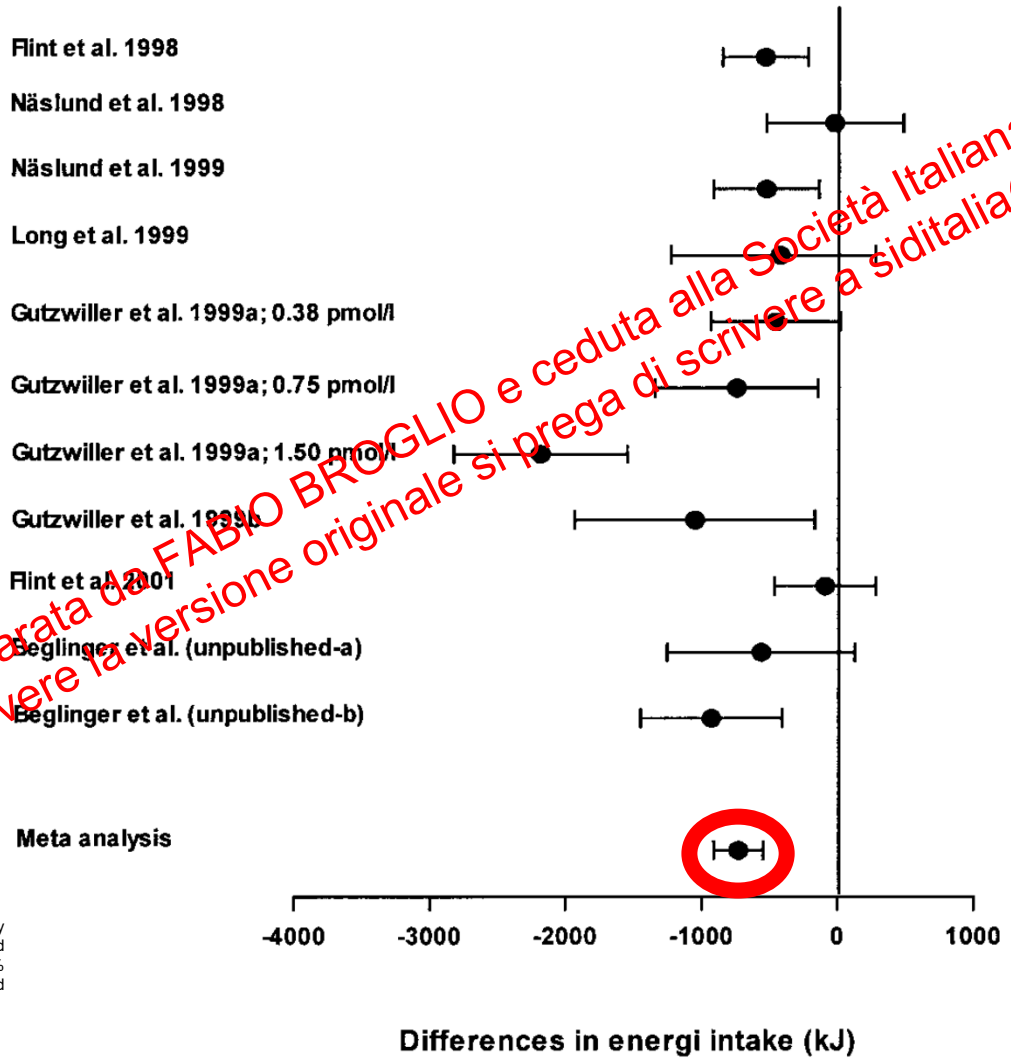
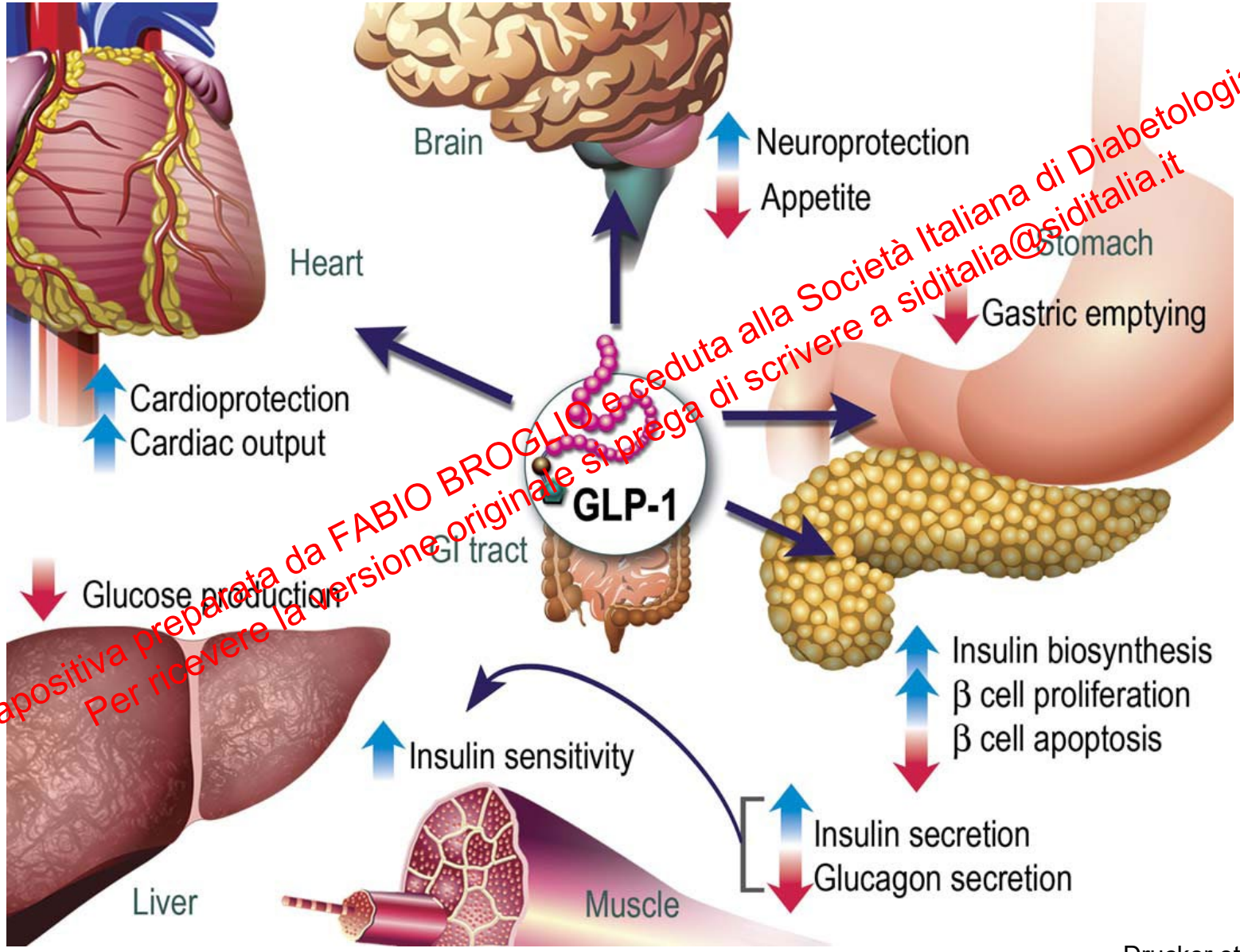


FIG. 1. The difference in ad libitum energy intake (kJ) between the placebo day and the day of GLP-1 infusion. Mean and 95% CI are shown for the original studies and for the meta-analysis.

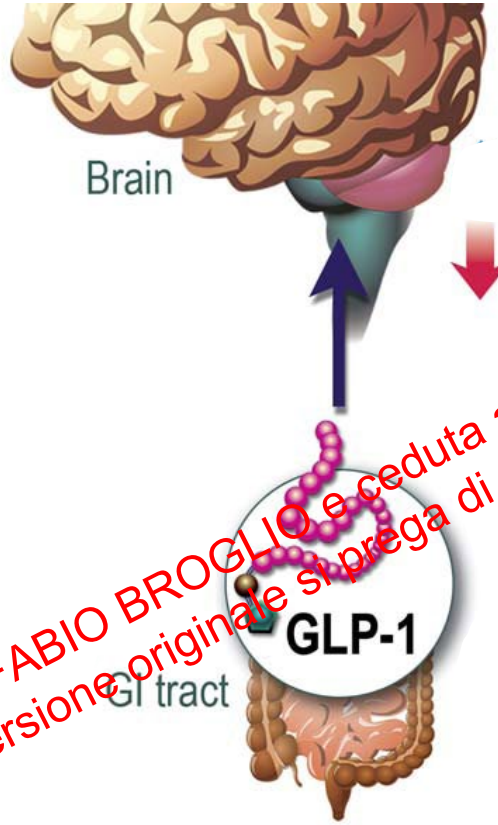
J Clin Endocrinol Metab 86: 4382–4389, 2001

Azioni extra-pancreatiche del GLP-1



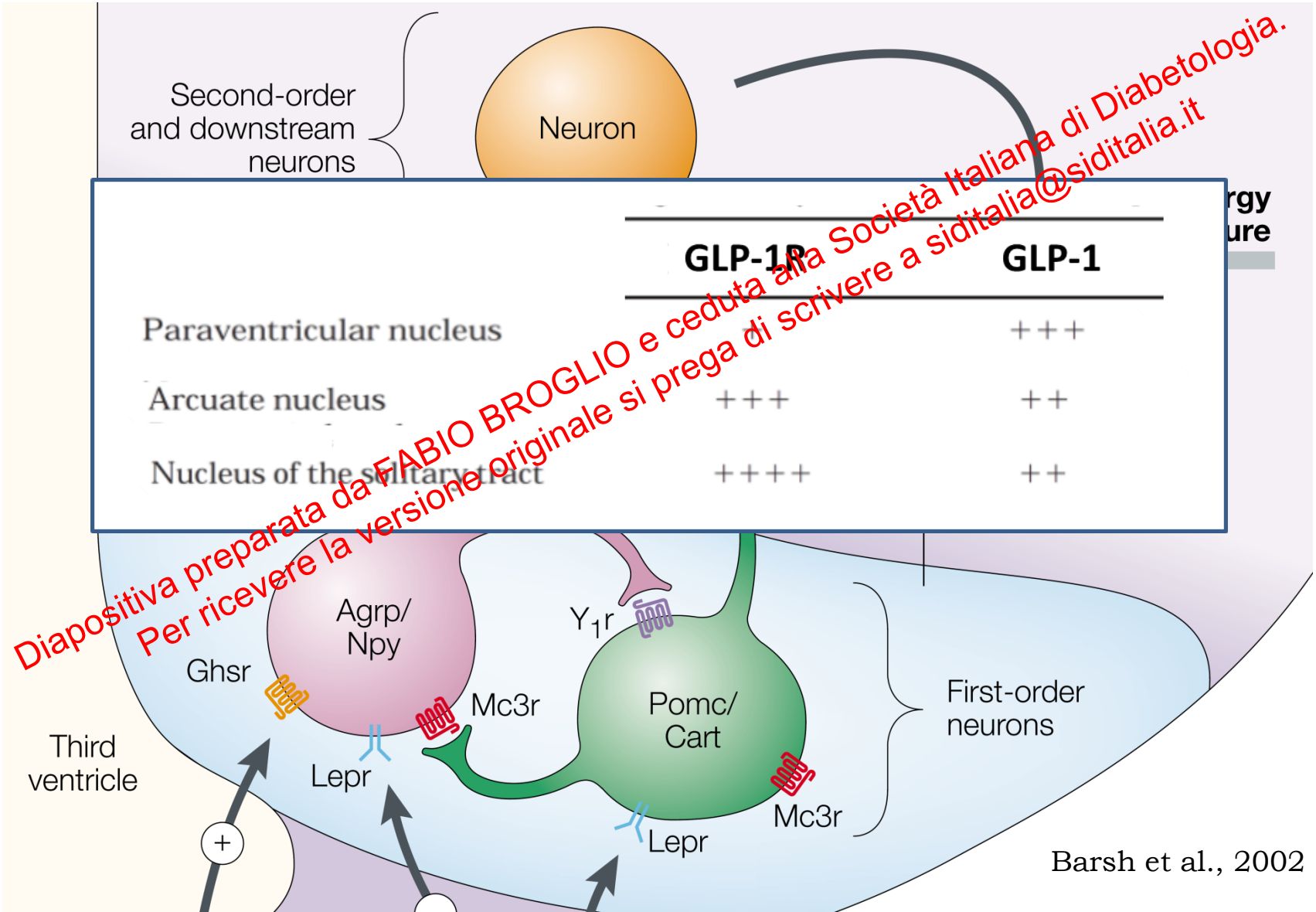
Drucker et al., 2006

Azioni extra-pancreatiche del GLP-1



Drucker et al., 2006

L'ipotalamo come centro della regolazione del bilancio energetico



	GLP-1R	GLP-1
Paraventricular nucleus	++	+++
Arcuate nucleus	+++	++
Nucleus of the solitary tract	++++	++

Barsh et al., 2002

Central Administration of Glucagon-Like Peptide-1 Activates Hypothalamic Neuroendocrine Neurons in the Rat*

PHILIP J. LARSEN, MADS TANG-CHRISTENSEN, AND DAVID S. JESSOP

ARC

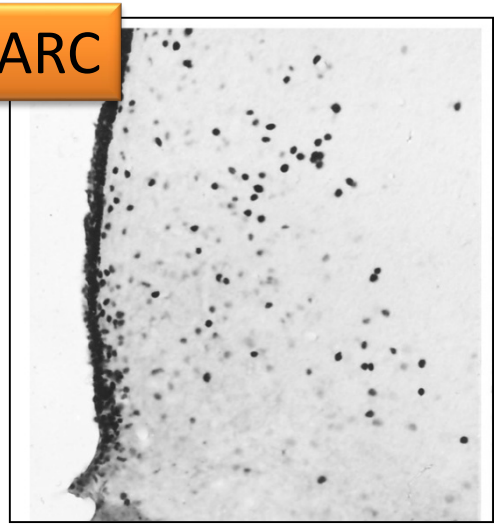


FIG. 5. GLP-1 induced c-*fos expression in the arcuate nucleus and circumventricular areas. The photomicrographs emonstrate c-fos-immunoreactive* nuclei in the arcuate nucleus from a rat given an icv injection of GLP-1 alone. Numerous c-*fos-immunoreactive cell bodies are seen in the area postrema and the surrounding subpostreme* region of the nucleus of the solitary tract (D). *Scale bars 5 100 mm (A–C) and 200 mm (D).*

PVN

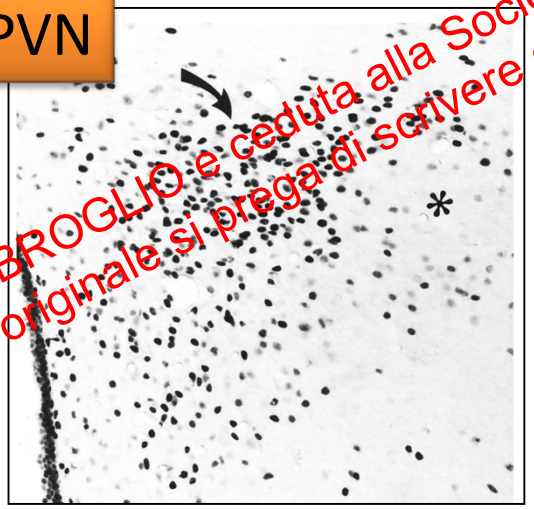
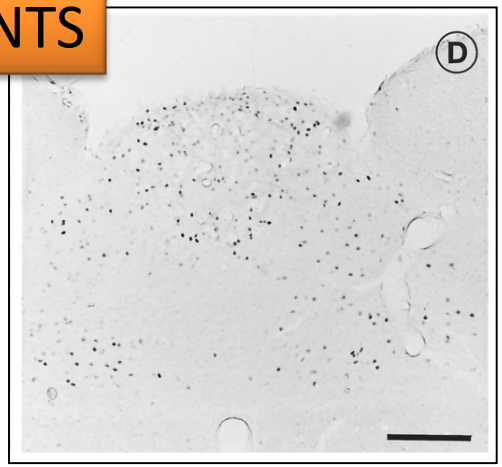


FIG. 4. Photomicrographs demonstrating c-*fos-immunoreactive nuclei in the hypothalamic paraventricular* (90 min after icv injection of GLP-1 alone (A and C) or GLP-1 preceded by a dose of exendin-(9–39) given 10 min earlier (B and D)

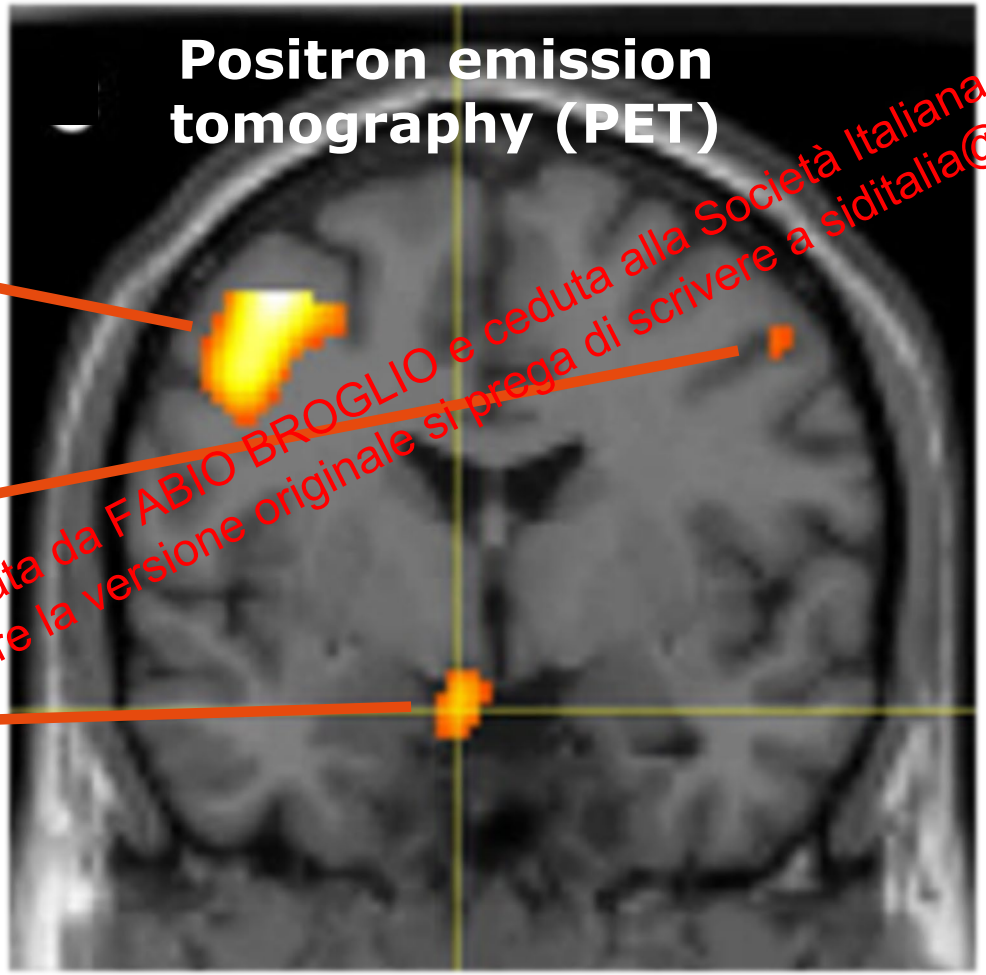
NTS



Endocrinology 138: 4445–4455, 1997

Postprandial glucagon-like peptide-1 (GLP-1) response is positively associated with changes in neuronal activity of brain areas implicated in satiety and food intake regulation in humans

Nicola Pannacciulli[a,*], Duc Son N.T. Le[a], Arline D. Salbe[a], Kewei Chen[b], Eric M. Reiman[b,c], Pietro A. Tataranni[a], and Jonathan Krakoff[a]



Post-meal GLP-1 response is associated with activation of areas of the human brain that are implicated in the regulation of eating behaviour

Neuroimage 2007;35:511–517

A role for glucagon-like peptide-1 in the central regulation of feeding

M. D. Turton, D. O'Shea, I. Gunn, S. A. Beak, C. M. B. Edwards, K. Meeran, S. J. Choi, G. M. Taylor, M. M. Heath, P. D. Lambert, J. P. H. Wilding, D. M. Smith, M. A. Ghatei, J. Herbert* & S. R. Bloom†

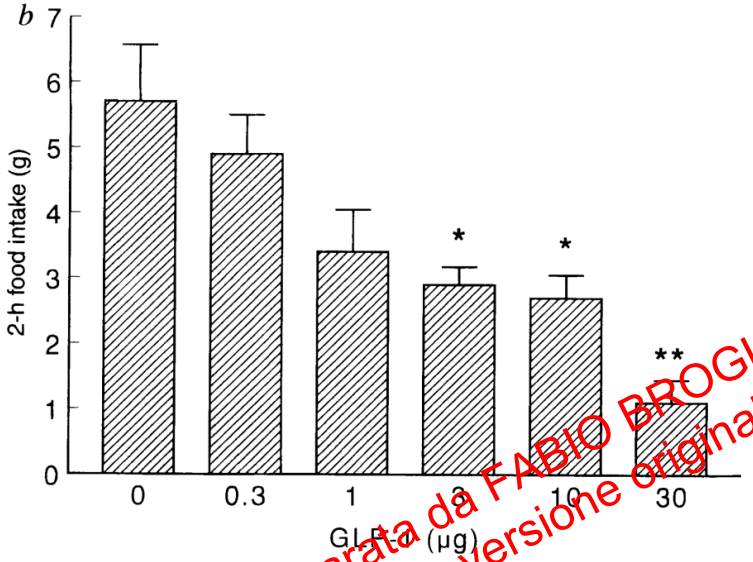
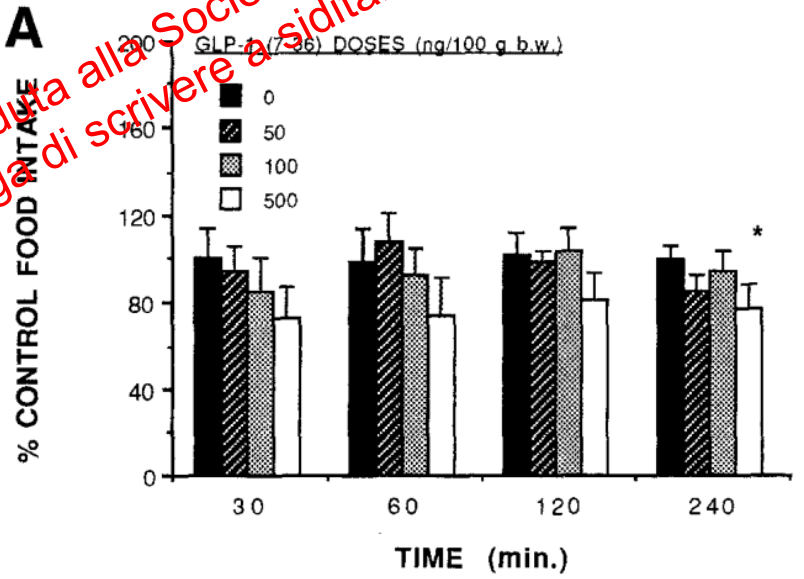


FIG. 1 *a*, Reduction in 2-h food intake in rats ($n = 7$–8 per group) injected ICV with GLP-1 or 0.9% saline (10 μl) at the onset of the dark phase ($F(3,27) = 10.6$, $P < 0.001$). (GLP-1 versus control, *$P < 0.001$). *b*, reduction in 2-h food intake in 24-h fasted rats ($n = 6$–7 per group) injected ICV with GLP-1 or 0.9% saline (10 μl) ($F(5,34) = 8.0$, $P < 0.001$). (GLP-1 versus control: $^{\dagger}P < 0.05$, **$P < 0.01$).

Nature. 1996 Jan 4;379(6560):69-72.

Peripheral Versus Central Effects of Glucagon-Like Peptide-1 Receptor Agonists on Satiety and Body Weight Loss in Zucker Obese Rats

Fernando Rodriquez de Fonseca, Miguel Navarro, Elvira Alvarez, Isabel Roncero, Julie A. Chowen, Olivia Maestre, Raquel Gómez, Raúl M. Muñoz, Olivia Eng, and Enrique Blázquez



Effects of peripheral (SC) administration of (A) GLP-1 (7-36) amide (0, 50, 100, or 500 ng/100 g BW) or (B) exendin-4 (0, 5, 50, or 250 ng/100 g BW) on food intake in food-deprived Wistar rats. Values are the mean ± SEM percentage of cumulative food intake during 4 consecutive intervals for 10-12 determinations per group after acute administration of the peptide. *P < .05, Newman-Keuls, v control group. Absolute

Metabolism, Vol 49, No 6 (June), 2000: pp 709-717

The inhibitory effects of peripheral administration of peptide $YY_{3–36}$ and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal–brainstem–hypothalamic pathway

Caroline R. Abbott[1], Mariana Monteiro[1], Caroline J. Small, Arshia Sajedi, Kirsty L. Smith, James R.C. Parkinson, Mohammad A. Ghatei, Stephen R. Bloom*

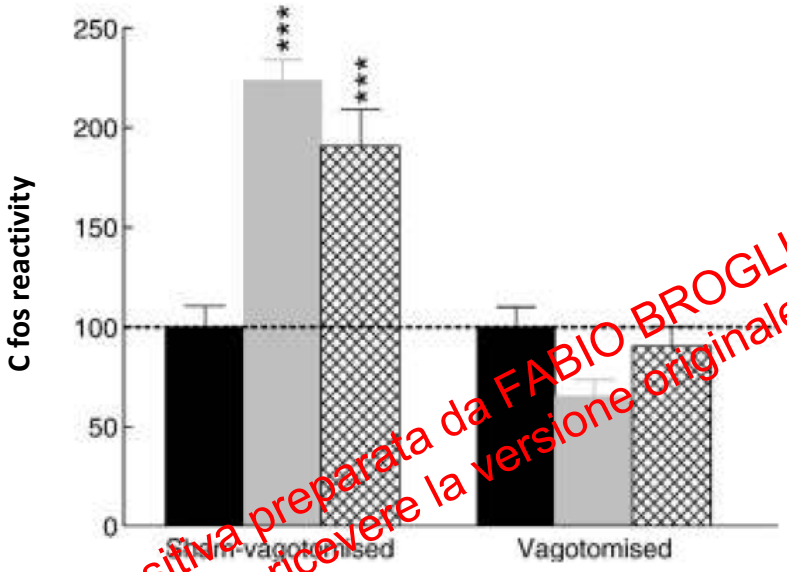


Fig. 3. Expression of fos-like immunoreactivity in the hypothalamic arcuate nucleus of satiated sham-vagotomised and vagotomised rats (n = 3–4/ group) in response to ip administration of saline (black bars), 10 nmol/kg PYY3–36 (grey bars) or 100 nmol/kg GLP-1 (hatched bars). Expressed as mean F SEM % saline, ***P b 0.001 vs. saline.

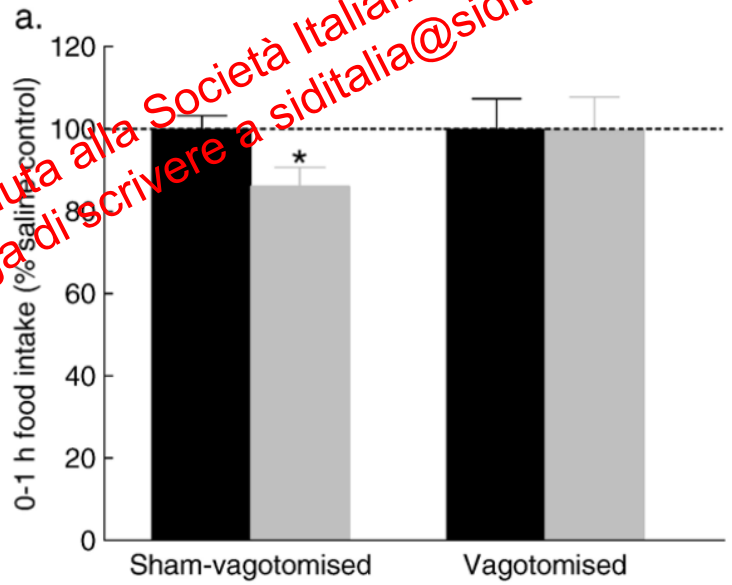
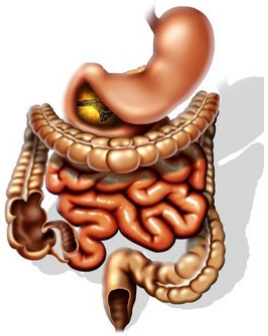


Fig. 1. The effect of a single ip injection of saline (black bars) or 10 nmol/ kg PYY3–36 (grey bars) on 0–1 h food intake when administered during the early light phase to 24 h fasted (a) sham-vagotomised or vagotomised or (b) sham-transectioned or transectioned rats (*n = 12–15/group). Expressed as* mean F SEM % saline control, **P b 0.05 vs. saline.*

Brain Research 1044 (2005) 127– 131

Azioni centrali e gastrointestinali del GLP-1 sul controllo alimentare

GLP-1



svuotamento gastrico

?

sazietà

assunzione calorica

Glucagon-like peptide-1: a potent regulator of food intake in humans

J-P Gutzwiller, B Göke, J Drewe, P Vinzens, S Ketterer, D Handschin, R Winterhalder, D Conen, C Beglinger

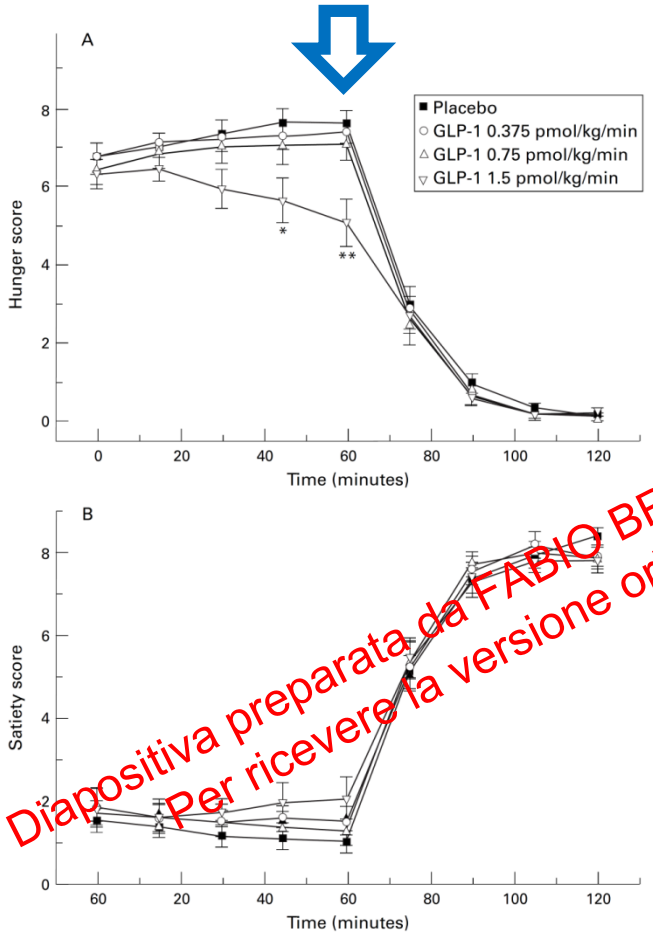


*Figure 2 Subjective sensations of hunger (A) and fullness (B) experienced by healthy male subjects before and after food intake during intravenous infusion of 5% glucose (placebo) or one dose (0.375, 0.75, or 1.5 pmol/kg/min) of human glucagon-like peptide-1. Results are expressed as mean and SEM (n = 16). *p<0.05, **p<0.01 v control.*

Gut 1999;44:81–86

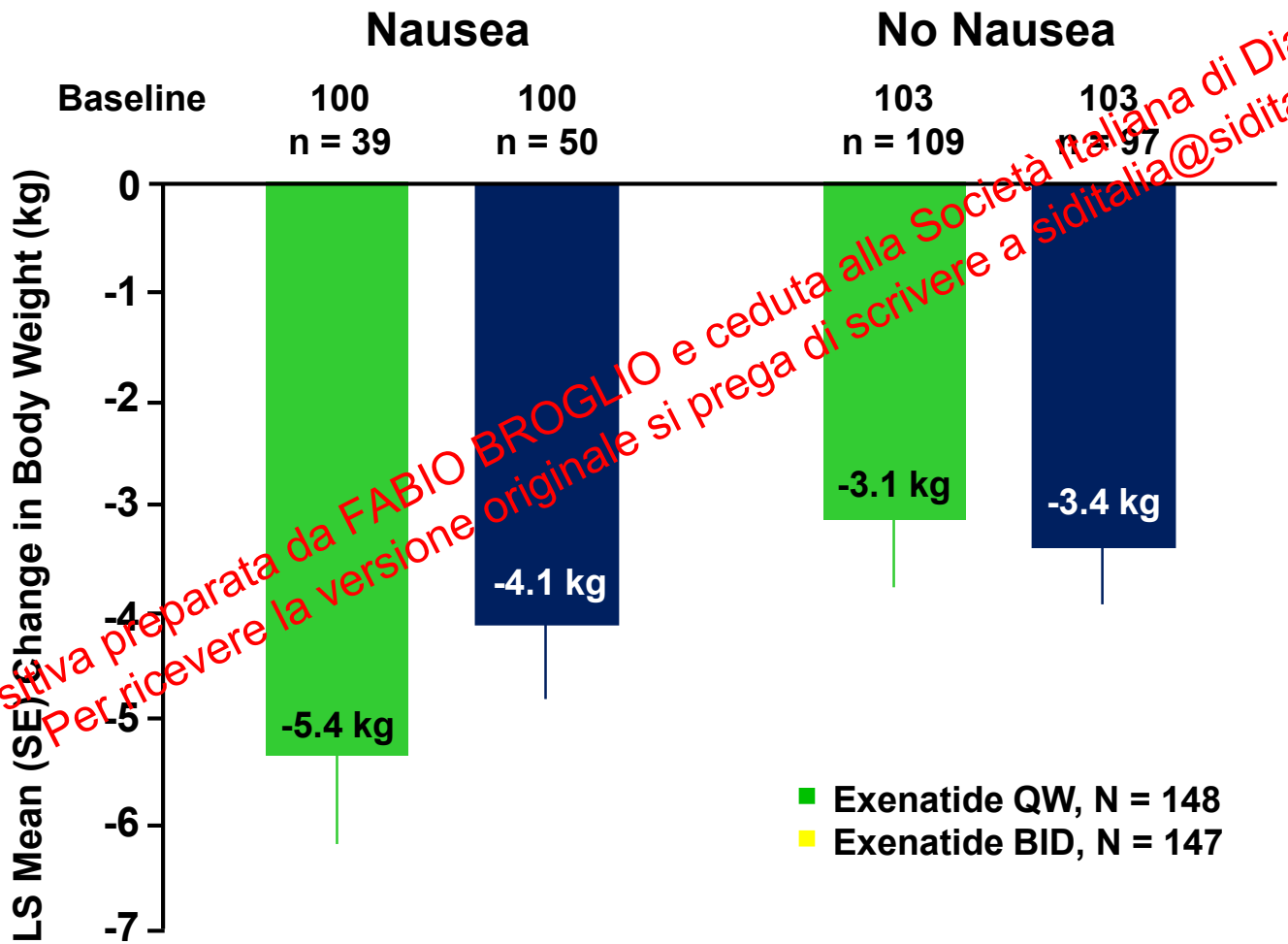
A Meta-Analysis of the Effect of Glucagon-Like Peptide-1 (7–36) Amide on *Ad Libitum* Energy Intake in Humans

C. VERDICH, A. FLINT, J.-P. GUTZWILLER, S. NASLUND, C. BEGLINGER, P. M. HELLSTRÖM, S. J. LONG, L. M. MORGAN, J. J. HOLST, AND A. ASTRUP

No correlation was seen between the reduction in Δpeak and AUC acetaminophen and the reduction in *ad libitum* intake during GLP-1 infusion.

J Clin Endocrinol Metab 86: 4382–4389, 2001

Effetti sul peso corporeo in funzione della comparsa di nausea



*at least one episode

Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis

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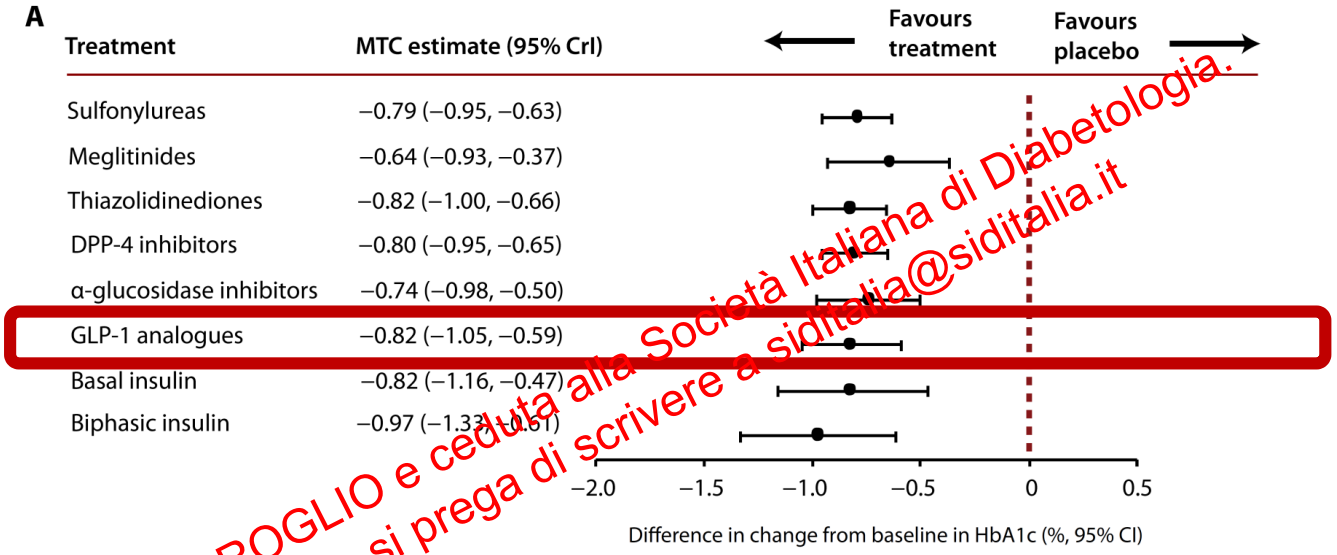
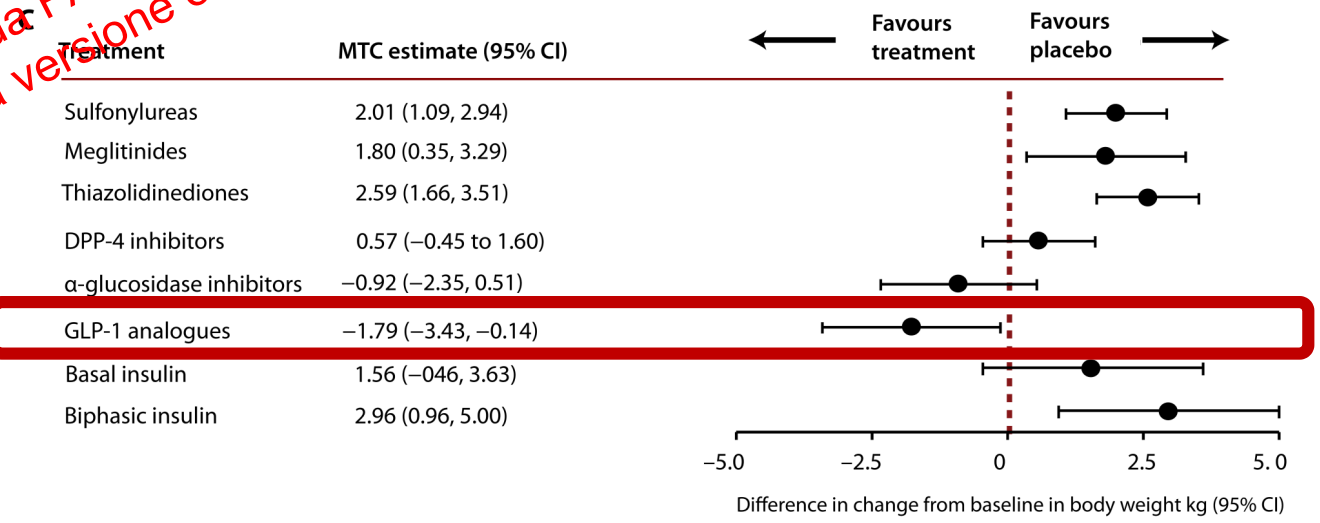
HbA1c



weight



Open Medicine 2011;5(1):e35

GLP-1 receptor agonists: a review of head-to-head clinical studies

Jennifer M. Trujillo, Wesley Nuffer and Samuel L. Ellis

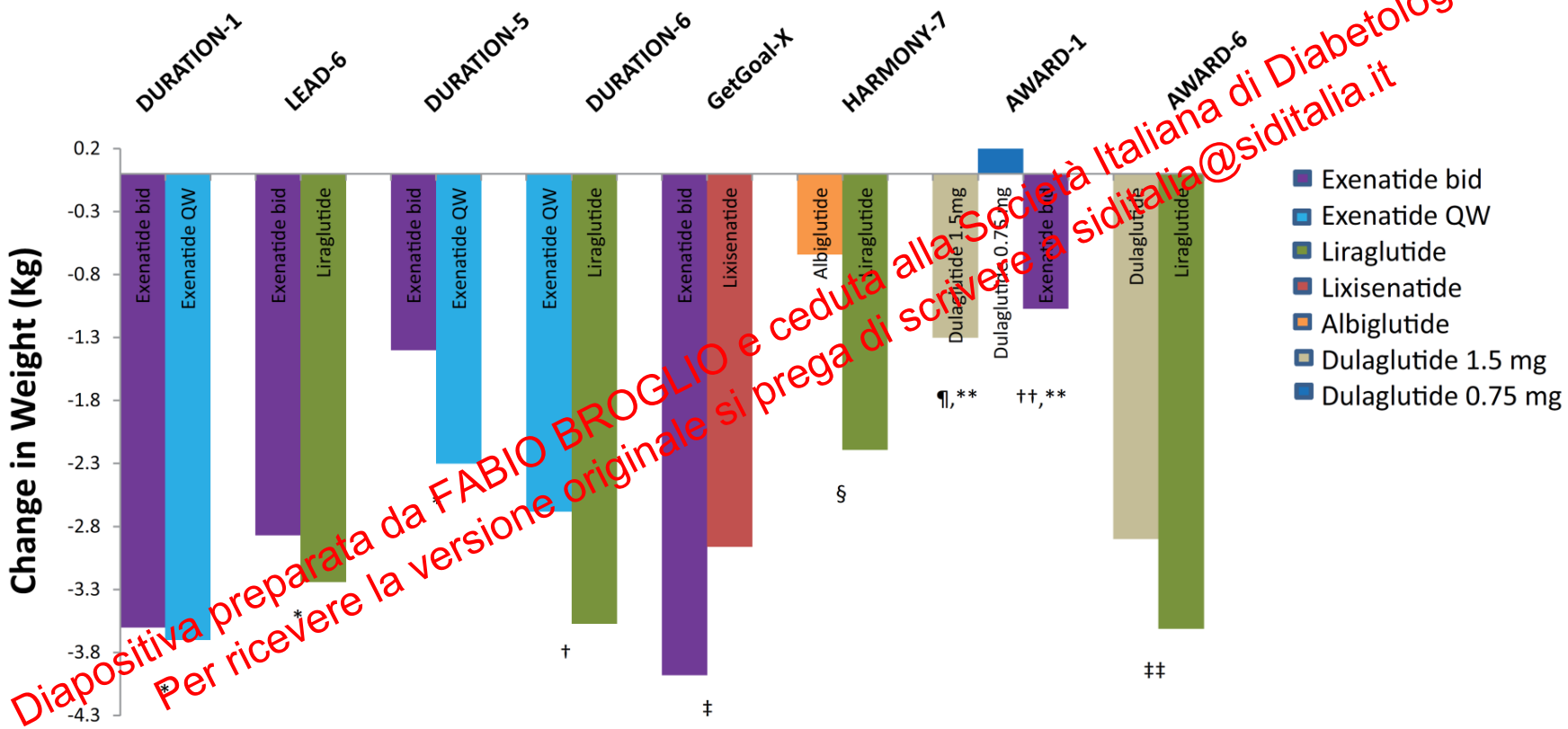


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies. *p-values are for statistical superiority (unless noted for noninferiority); *p = not significant, †p = 0.0005, ‡p-value not reported* for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), *§p < 0.0001, ¶ p < 0.001 versus dulaglutide 0.75 mg, **p = not significant between dulaglutide 1.5 mg versus exenatide bid, ‡‡p = 0.011.*

Long-term management of type 2 diabetes with glucagon-like peptide-1 receptor agonists

Hamish Courtney[1]
Rahul Nayar[2]
Chinnadorai Rajeswaran[3]
Ravi Jandhyala[4]

Table 1 Currently approved GLP-1RAs and corresponding summary of currently available published data from prospective studies reporting long-term efficacy and safety data

Name	Marketed name	Number of … duration of:			icacy and safety data after a treatment			
		76–82 weeks	1(…ks	156 weeks	208 week			weeks
Albiglutide QW	Tanzeum (US), Eperzan (EU)		1					
Dulaglutide QW	Trulicity	1	1					
Exenatide BID	Byetta	3		1	1			
Exenatide QW	Bydureon		1	2		1	1	1
Liraglutide QD	Victoza		2					
Lixisenatide QD	Adlyxin (US), Lyxumia (EU)	3						

Abbreviations: BID, twice daily; EU, Europ… Union; GLP-1RA, glucagon-li… …e-1 receptor agonist; QD, once daily; QW, once weekly; US, United States.

Dulaglutide (104w)
Δ peso: -2.9 kg

Exenatide QW (364w)
Δ peso: -3.9 kg

Liraglutide (104w)
Δ peso: -3.0 kg

Lixisenatide (76w)
Δ peso: -3.8 kg

Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng*, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran

Weight gain

change in weight (kg) at the end of intervention

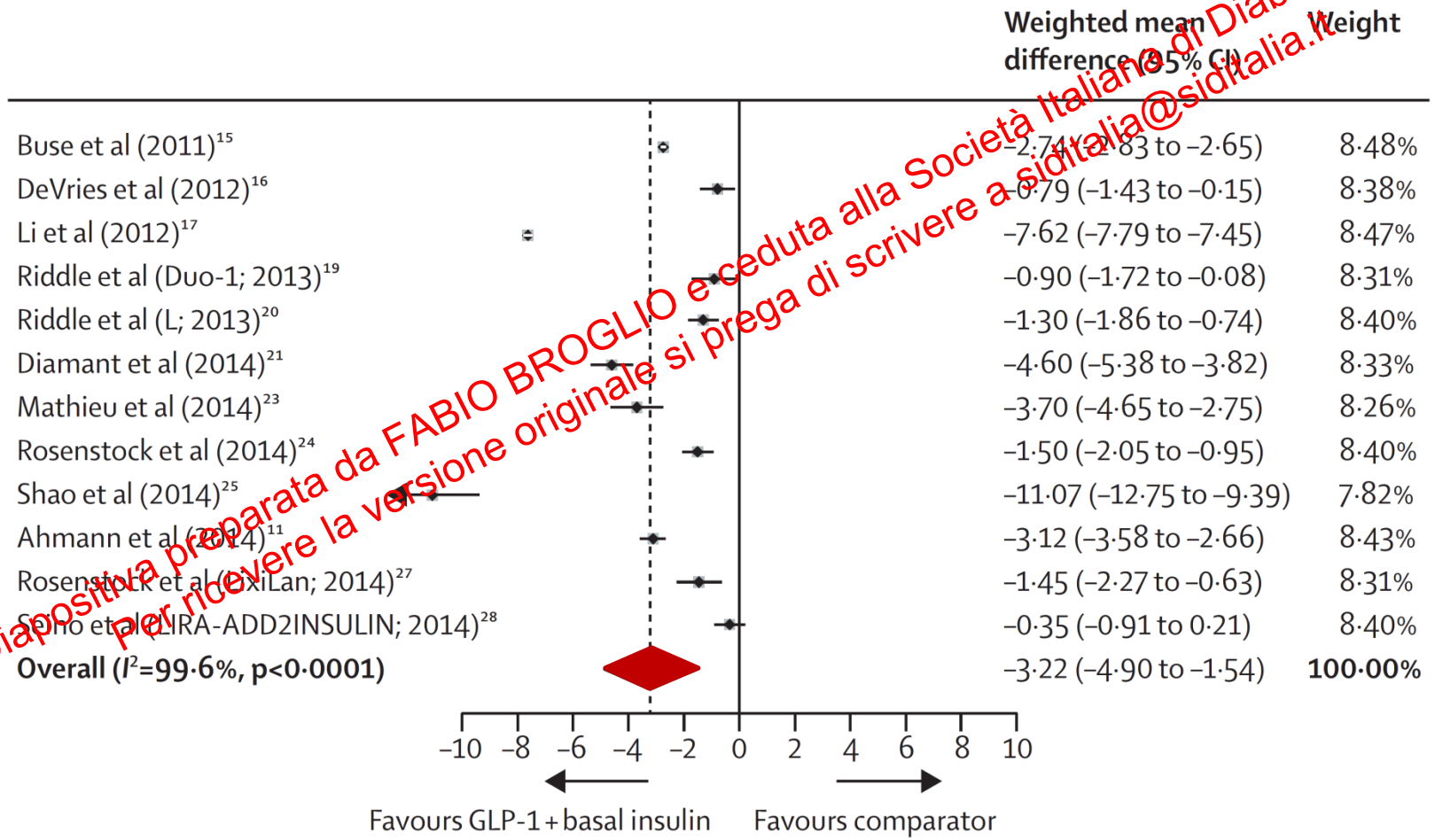


Figure 3: Meta-analyses of glucagon-like peptide-1 (GLP-1) agonist and basal insulin combination treatment versus other anti-diabetic treatments, comparing hypoglycaemia and change in weight Outcomes assessed are (C) change in weight (kg) at the end of intervention,

Lancet 2014; 384: 2228–34

Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng*, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran

Weight gain

change in weight (kg) at the end of intervention

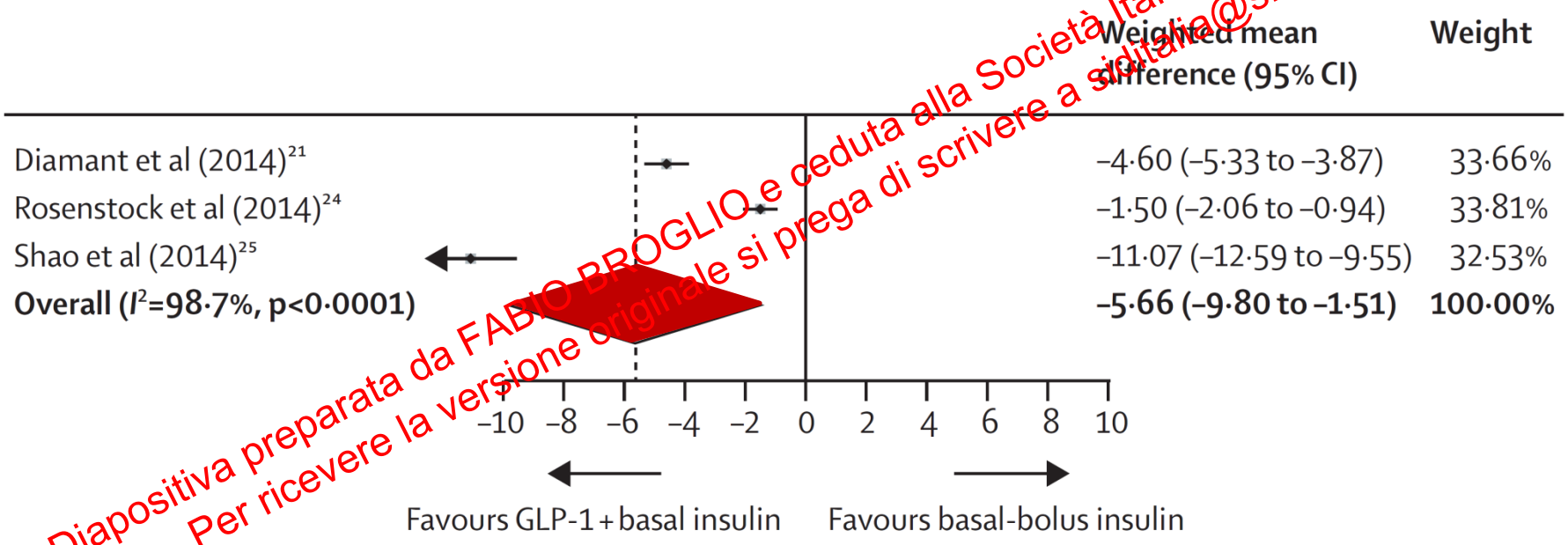


Figure 3: Meta-analyses of glucagon-like peptide-1 (GLP-1) agonist and basal insulin combination treatment versus other anti-diabetic treatments, comparing hypoglycaemia and change in weight Outcomes assessed are change in weight (kg) at the end of intervention in studies that compared combination treatment with basal-bolus insulin treatment. For each estimate, the grey shaded area is the weight of the estimate in proportion to the overall eff ect.

Lancet 2014; 384: 2228–34

Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes

*Stephen C L Gough, Bruce Bode, Vincent Woo, Helena W Rodbard, Sultan Linjawi, Pernille Poulsen, Lars H Damgaard, John B Buse, on behalf of the NN9068-3697 (DUAL-I) trial investigators**

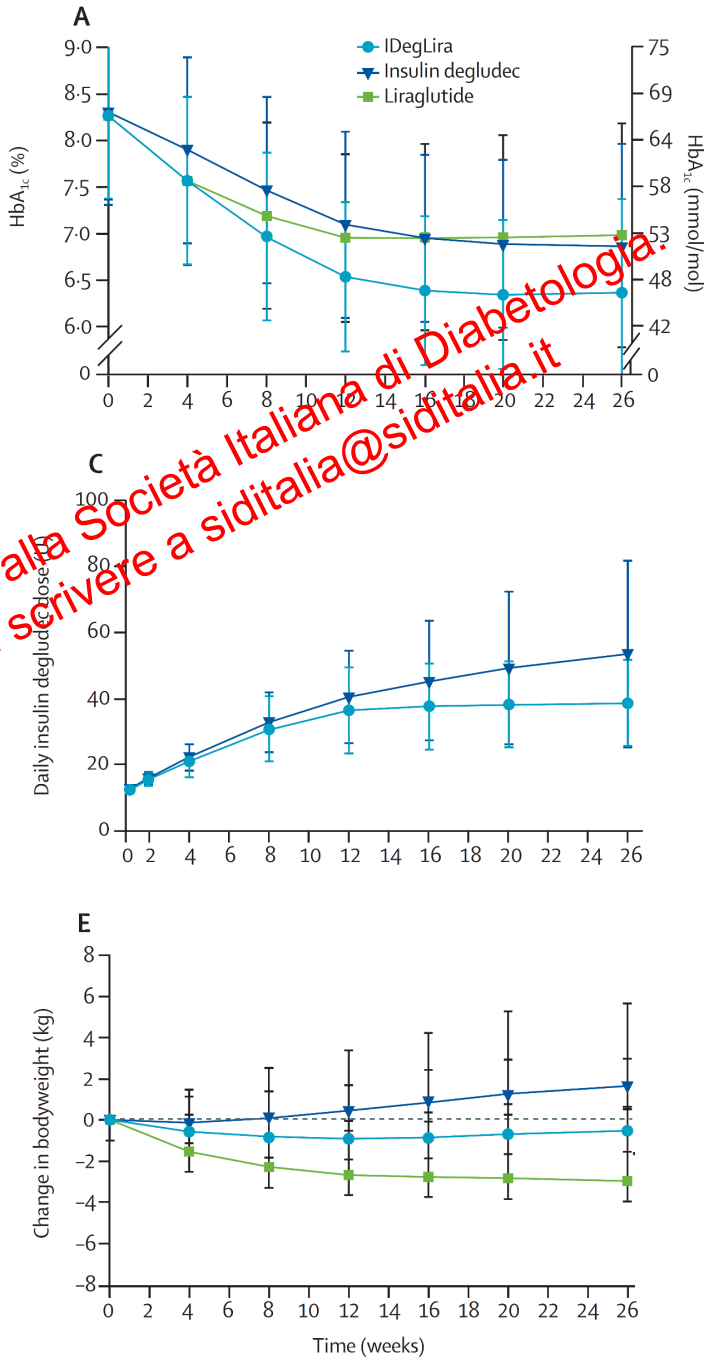


Figure 2: Glycaemic efficacy, doses, bodyweight, and cumulative hypoglycaemia over 26 weeks Mean HbA1c (A), fasting plasma glucose (B), insulin degludec dose (C), liraglutide dose (D), and change in bodyweight (E), plus cumulative mean number of hypoglycaemic episodes per patient (F). Error bars show SDs.

Lancet Diabetes Endocrinol 2014; 2: 885–93

Liraglutide Reduces Visceral and Intrahepatic Fat Without Significant Loss of Muscle Mass in Obese Patients With Type 2 Diabetes: A Prospective Case Series

Satoshi Ishii[a], Yoshio Nagai[a, b], Yukiyoshi Sada[a], Hisashi Fukuda[a], Yuta Nakamura[a], Ren Matsuba[a], Tomoko Nakagawa[a], Hiroyuki Kato[a], Yasushi Tanaka[a]

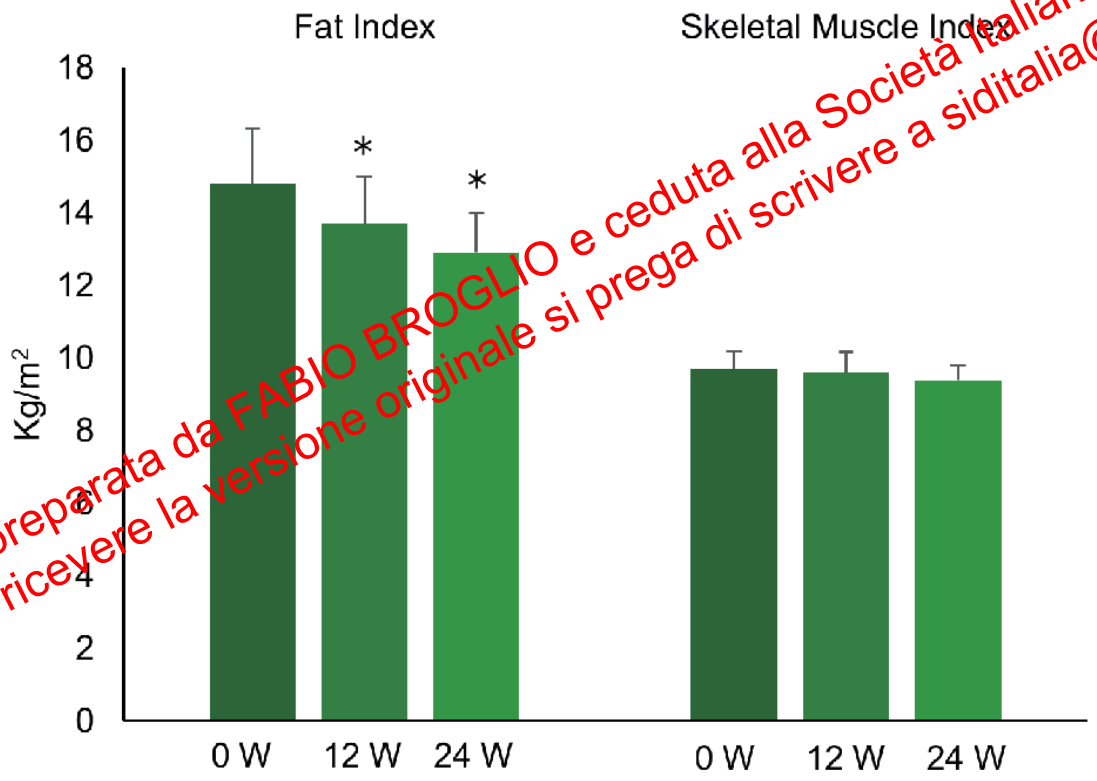


Figure 1. Changes of fat index and skeletal muscle index during the treatment with liraglutide (0.9 mg/day) in obese Japanese patients with type 2 diabetes. *P < 0.05 versus 0 week.

J Clin Med Res. 2019;11(3):219-224

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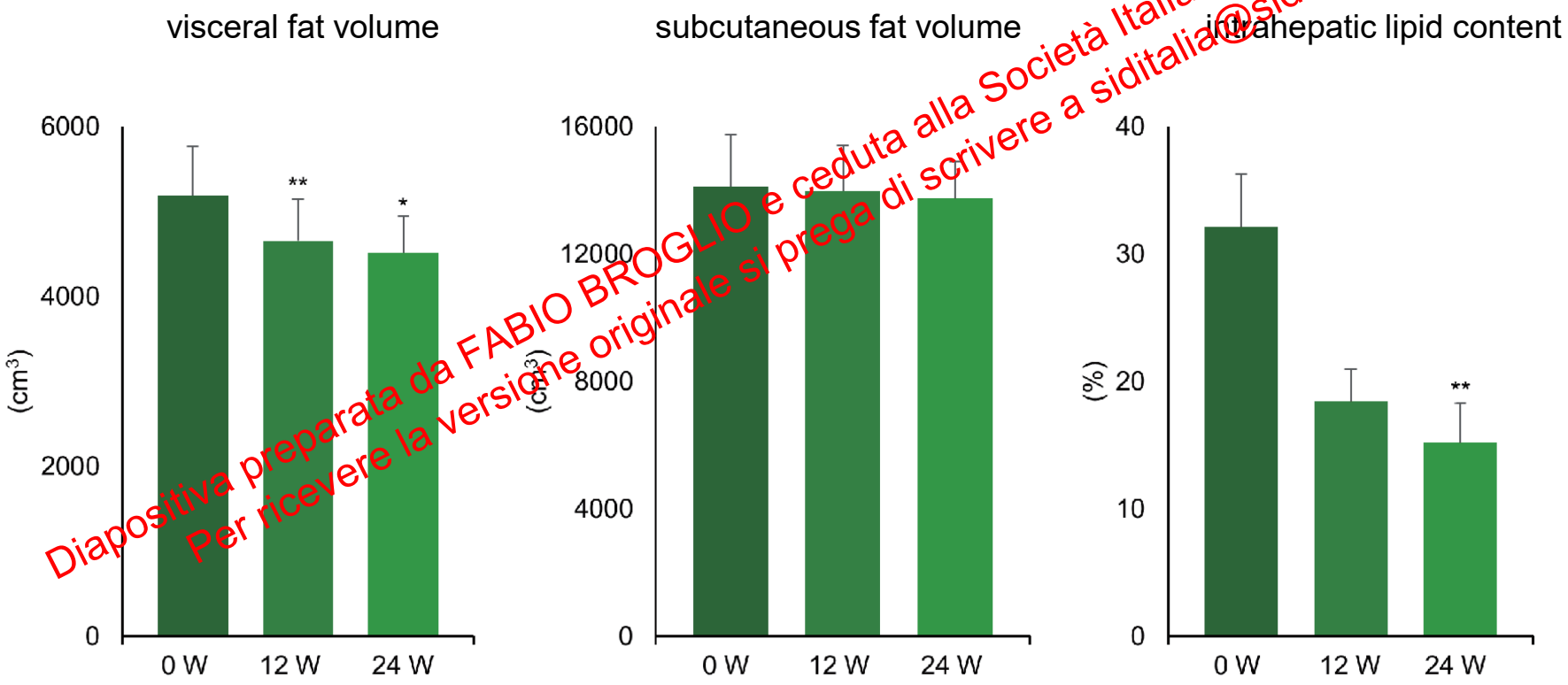

Figure 2. Changes of visceral fat volume, subcutaneous fat volume, and intrahepatic lipid content during the treatment with liraglutide (0.9 mg/day) in obese Japanese patients with type 2 diabetes. *P < 0.05, **P < 0.01 versus 0 week.

J Clin Med Res. 2019;11(3):219-224

Antiobesity efficacy of GLP-1 receptor agonist liraglutide is associated with peripheral tissue-specific modulation of lipid metabolic regulators

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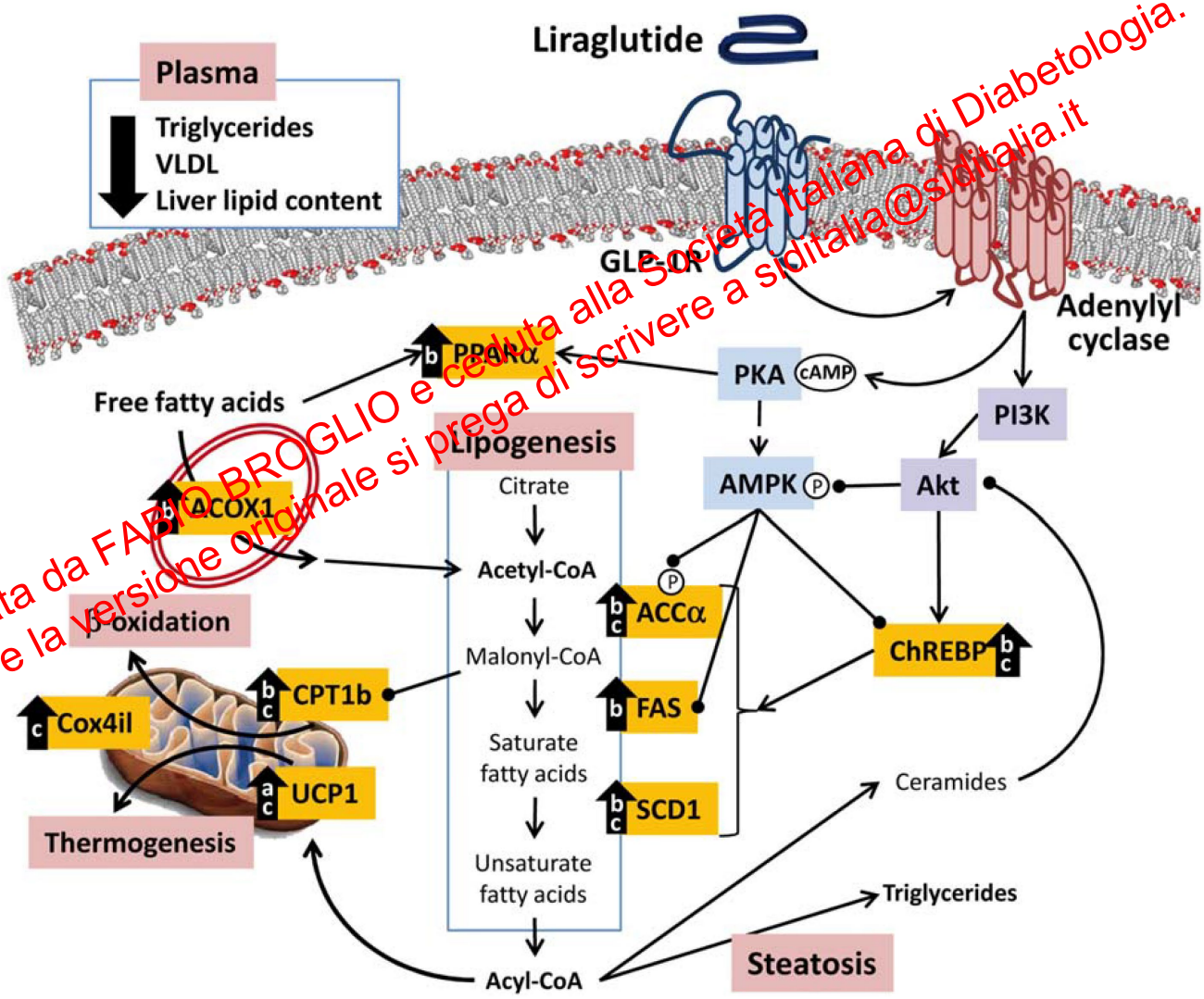
Daniel Beiroa[2,3]
Patricia Rivera[1,2]
Antonio Vargas[1,2]
Antonia Serrano[1,2]
Francisco Javier Pavón[1,2]
Joan Ballesteros[4]
Carlos Dieguez[2,3]
Rubén Nogueiras[2,3]
Fernando Rodríguez de Fonseca[1,2]
Juan Suárez[1,2*]



(a): liver
(b): skeletal muscle
(c): epididymal white adipose tissue

Scheme representing the liraglutide effect on the expression of main regulators involved in lipid metabolism, b-oxidation and thermogenesis FIG 5 in liver (a), skeletal muscle (b) and/or epididymal white adipose tissue (c).

International Union of Biochemistry and Molecular Biology
Volume 42, Number 6, November/December 2016, Pages 600–611

Gut microbiome differences between metformin- and liraglutide-treated T2DM subjects

Zhang Wang[1] | Somdutta Saha[1] | Stephanie Van Horn[2] | Elizabeth Thomas[2] | Christopher Traini[2] | Ganesh Sathe[2] | Deepak K. Rajpal[1] | James R. Brown[1]

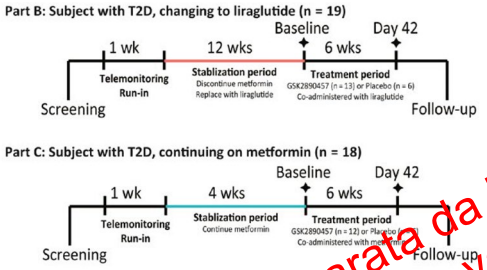
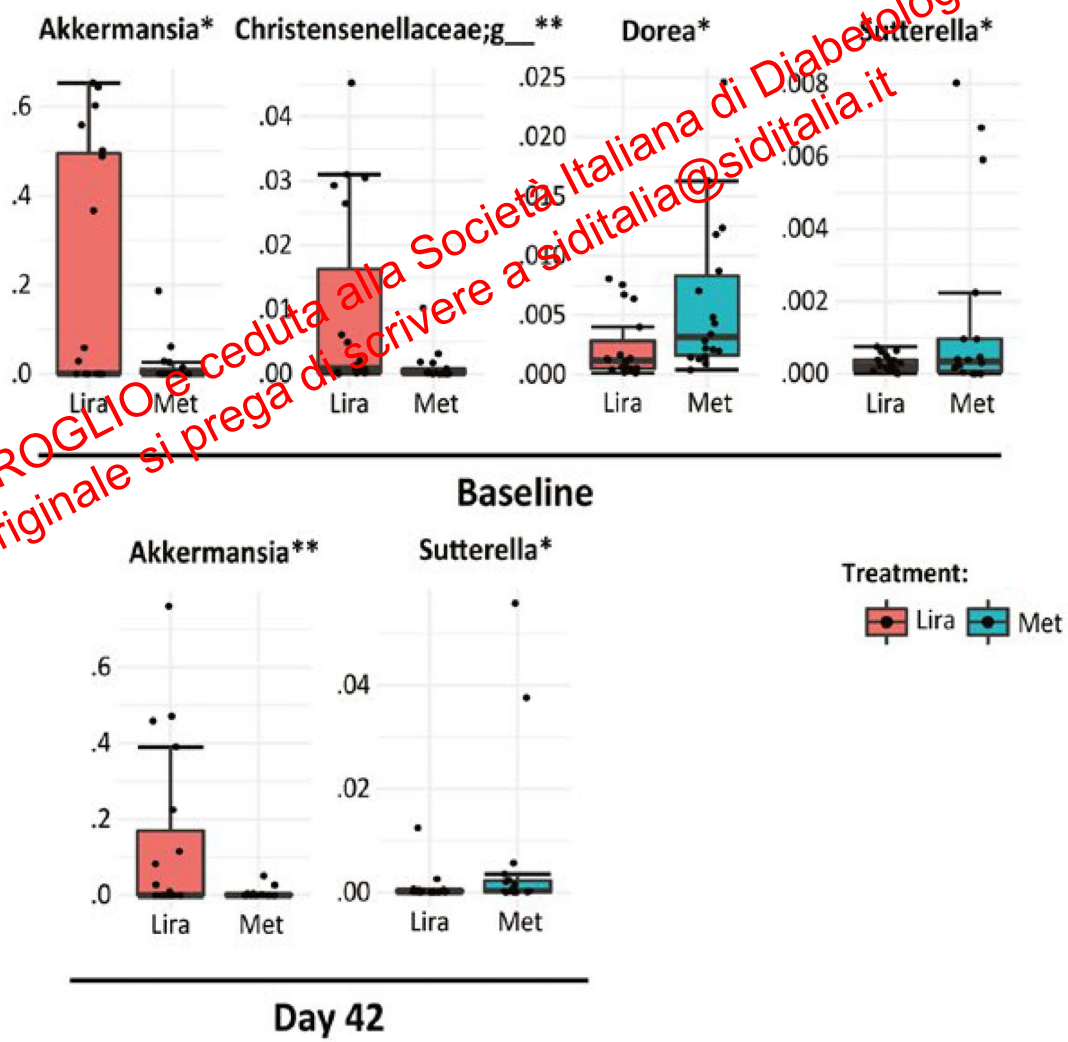


FIGURE1 Difference in microbiome composition in metformin or liraglutide-treated T2DM subjects. A, Study design and stool sampling periods at baseline and Day 42 as adapted from Hodge et al.; D, Significantly differentially represented bacterial genera between metformin and liraglutide groups, at baseline and Day 42



Endocrinol Diab Metab. 2018;1:e9. https://doi.org/10.1002/edm2.9

GLP-1 receptor agonists: a review of head-to-head clinical studies

Jennifer M. Trujillo, Wesley Nuffer and Samuel L. Ellis

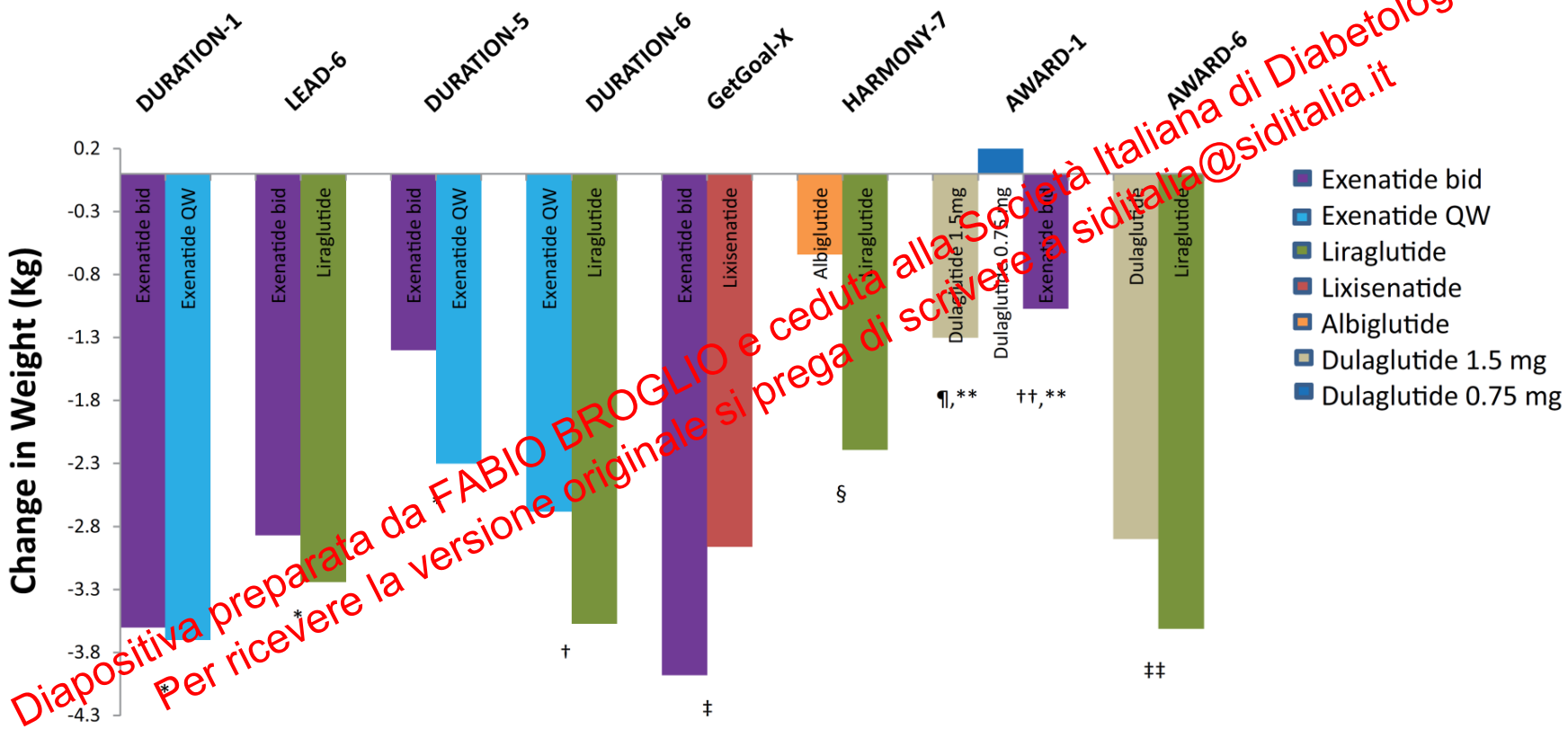


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies. *p-values are for statistical superiority (unless noted for noninferiority); *p = not significant, †p = 0.0005, ‡p-value not reported* for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), *§p < 0.0001, ¶ p < 0.001 versus dulaglutide 0.75 mg, **p = not significant between dulaglutide 1.5 mg versus exenatide bid, ‡‡p = 0.011.*

Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study

*Arne Astrup, Stephan Rössner, Luc Van Gaal, Aila Rissanen, Leo Niskanen, Mazin Al Hakim, Jesper Madsen, Mads F Rasmussen, Michael E J Lean, on behalf of the NN8022-1807 Study Group**

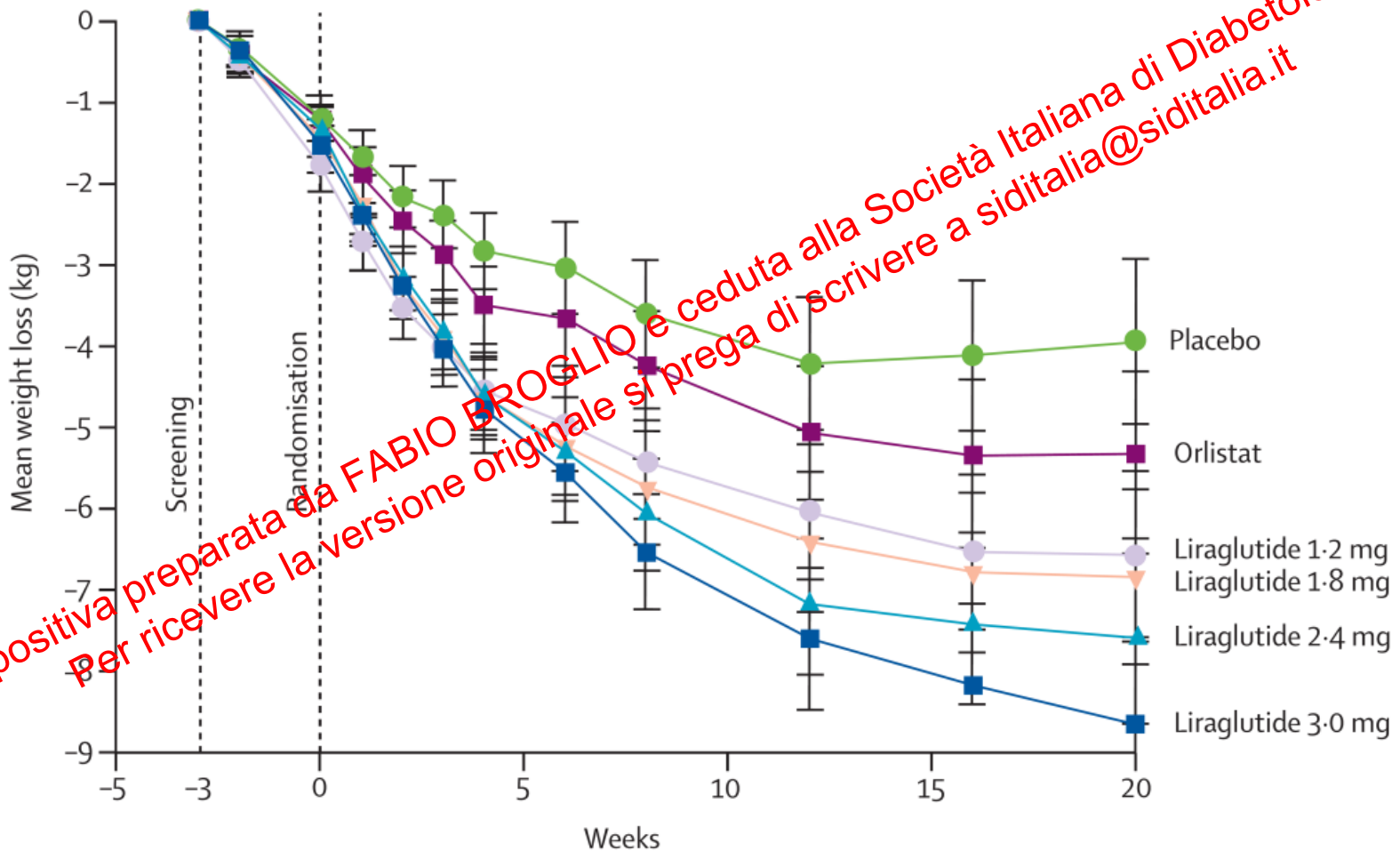


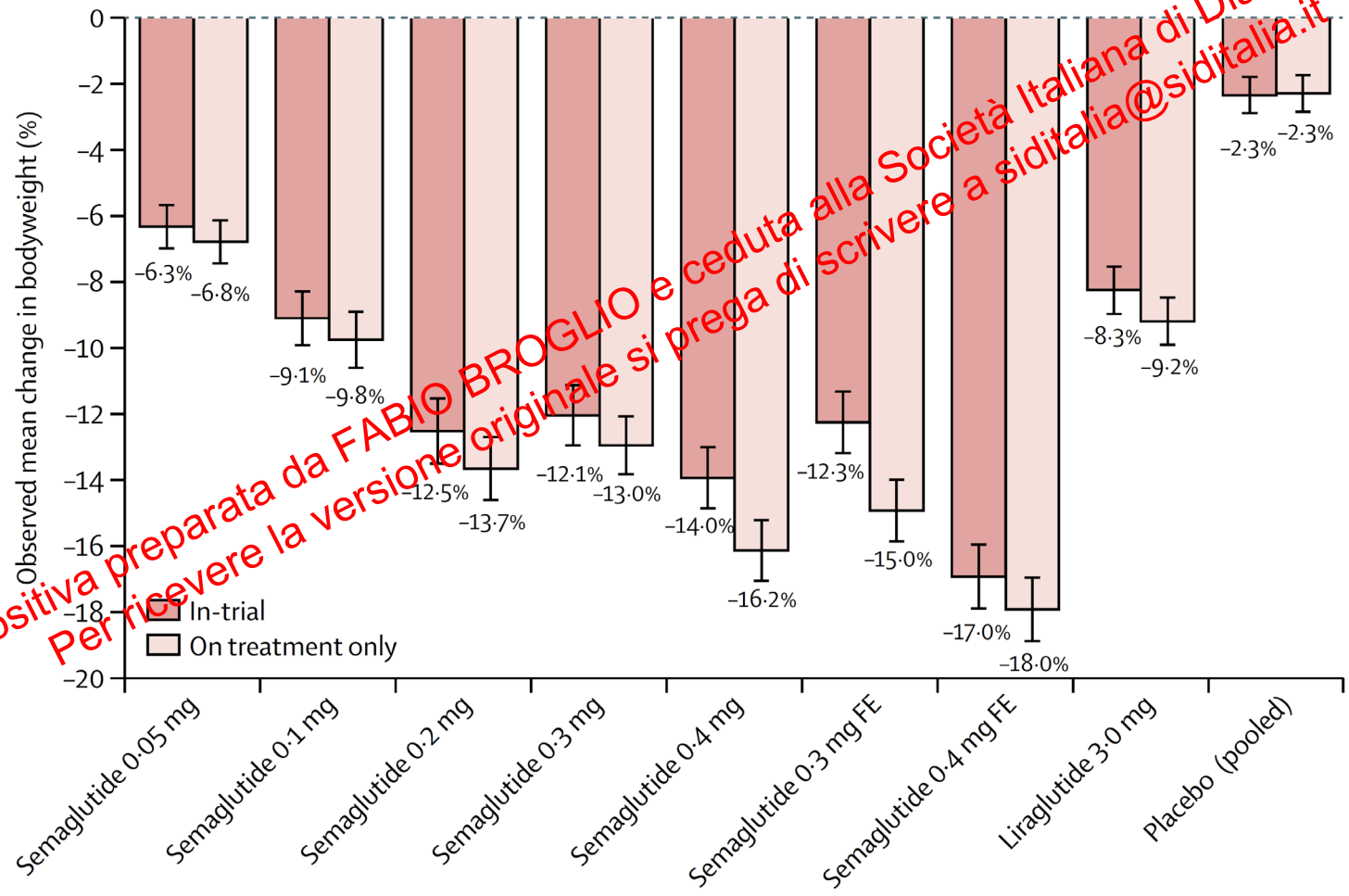
Figure 2: Change in bodyweight Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

Lancet. 2009 Nov 7;374(9701):1606-16

Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial

Patrick M O'Neil, Andreas L Birkenfeld, Barbara McGowan, Ofri Mosenzon, Sue D Pedersen, Sean Wharton, Charlotte Giwercman Carson, Cecilie Heerdegen Jepsen, Maria Kabisch, John P H Wilding

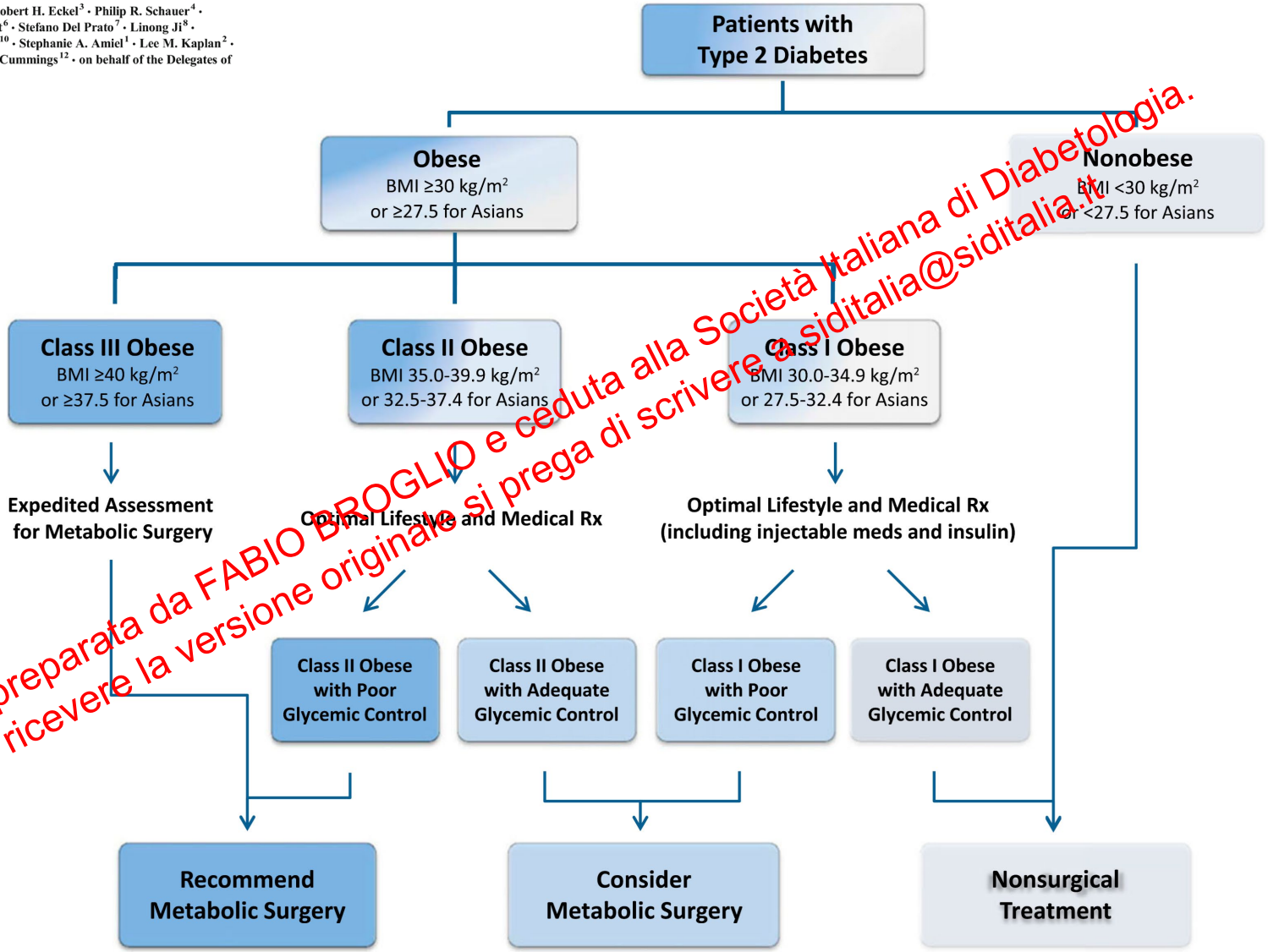
Figure 2: Estimated mean changes (A) and observed mean changes (B) in bodyweight from baseline to week 52



Lancet 2018; 392: 637–49

Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: a Joint Statement by International Diabetes Organizations

Francesco Rubino[1] · David M. Nathan[2] · Robert H. Eckel[3] · Philip R. Schauer[4] · K. George M. M. Alberti[5] · Paul Z. Zimmet[6] · Stefano Del Prato[7] · Linong Ji[8] · Shaukat M. Sadikot[9] · William H. Herman[10] · Stephanie A. Amiel[1] · Lee M. Kaplan[2] · Gaspar Taroncher-Oldenburg[11] · David E. Cummings[12] · on behalf of the Delegates of the 2nd Diabetes Surgery Summit

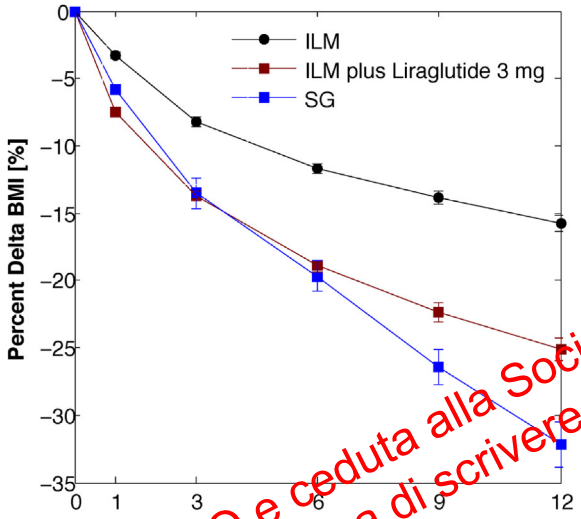


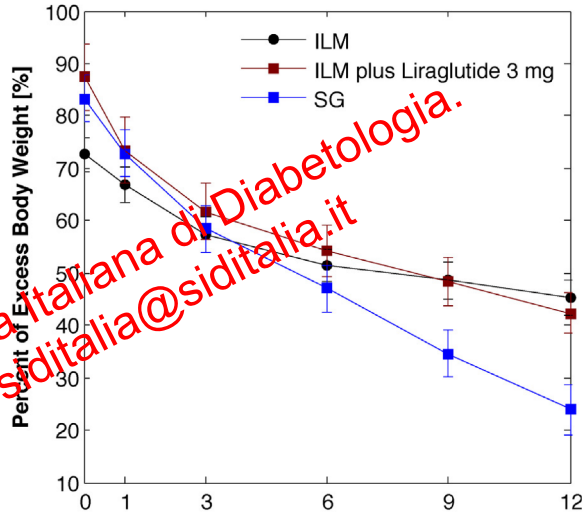
OBES SURG (2017) 27:2–21

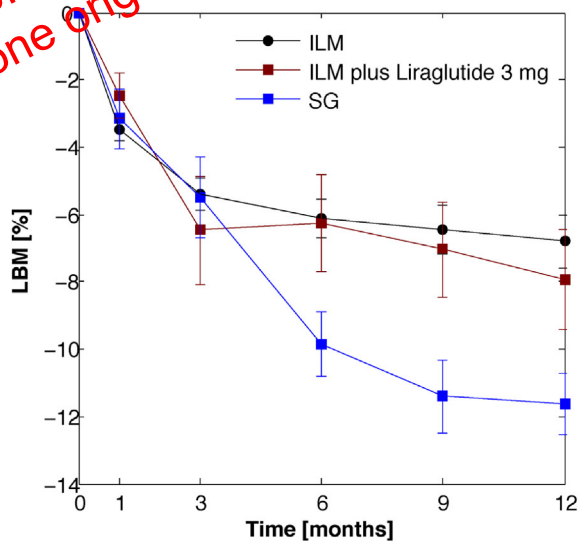
GLP1 RA o chirurgia bariatrica?

Intensive lifestyle modifications with or without liraglutide 3 mg vs. sleeve gastrectomy: A three-arm non-randomised, controlled, pilot study☆

E. Capristo [a], S. Panunzi [b], A. De Gaetano [b], M. Raffaelli [c], C. Guidone [a], A. Iaconelli [a], L. L'Abbate [b], A.L. Birkenfeld [d,e,f], R. Bellantone [c], S.R. Bornstein [d,e], G. Mingrone [a,e,*]







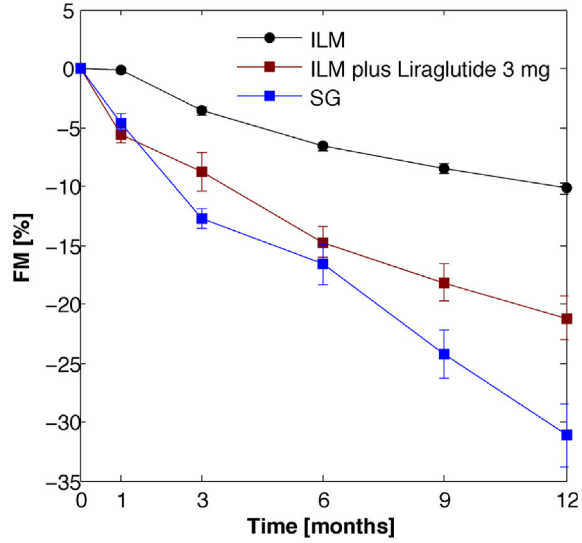
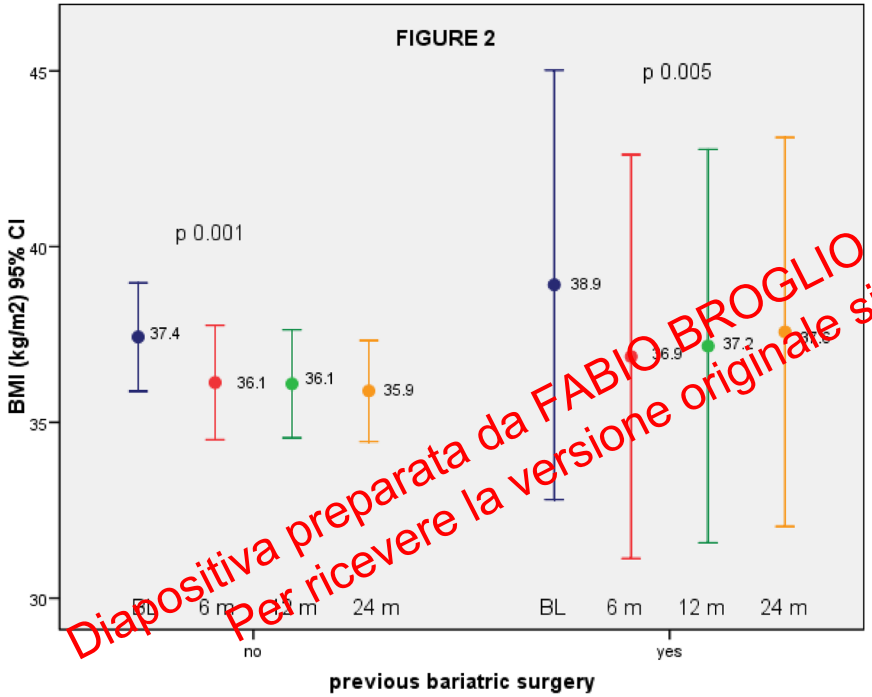


Fig. 3. Time course of percent changes from baseline in body mass index (BMI; kg/m2), body weight, lean body mass (LBM) and fat mass (FM) in the three study arms. Data are means SE (standard error). ILM: intensive lifestyle modification; SG: sleeve gastrectomy.

GLP1 RA e chirurgia bariatrica?

Effectiveness and Tolerability of Liraglutide in Patients with Type 2 Diabetes Mellitus and Obesity after Bariatric Surgery

Juan José Gorgojo-Martinez MD, Gara Feo-Ortega MD, Clara Serrano-Moreno MD



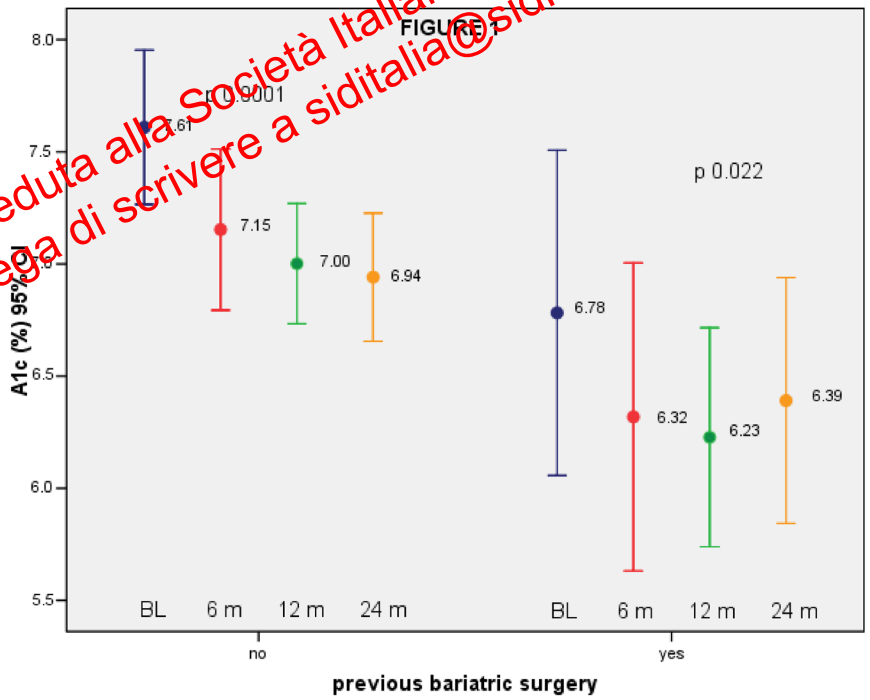


Figure 1. Changes in glycated hemoglobin after therapy with liraglutide in completers. Data are mean (95% confidence interval, CI). p value: repeated measures analysis of variance. A1c: glycated hemoglobin. BS: previous bariatric surgery. NBS: non previous bariatric surgery. Figure 2. Changes in body mass index (BMI) after therapy with liraglutide in completers. Data are mean (95% confidence interval, CI). p value: repeated measures analysis of variance. BS: previous bariatric surgery. NBS: non previous bariatric surgery.

Surgery for Obesity and Related Diseases; 12: 10, 1856-1863; 2016

Conclusioni

Nel paziente diabetico, se sovrappeso o obeso, gli analoghi del GLP-1, quando non già prescrivibili per altre indicazioni, rappresentano uno strumento efficace e duraturo anche per il controllo ponderale, indipendemente dall'effetto normoglicemizzante anche antagonizzando efficacemente l'incremento ponderale indotto da altri farmaci antidiabetici, incluso il trattamento insulinico.