SID Società Italiana di Diabetologia

BOLOGNA | 27 GIUGNO 2019

Terapia con analoghi del GLP-1: quando e perché

Analoghi GLP-1: a che punto siamo?

Enzo Bonora

Endocrinologia, Diabetologia e Metabolismo

Università e Azienda Ospedaliera Integrata di Verona

Ringraziamento

Esprimo massima gratitudine alla **Società Italiana di Diabetologia** per avermi formato, guidato, stimolato, sostenuto e gratificato in 40 anni di professione (1979-2019).

SID è la mia casa e SID è nel mio cuore.

Disclosures (last 10 years)

Advisory Boards

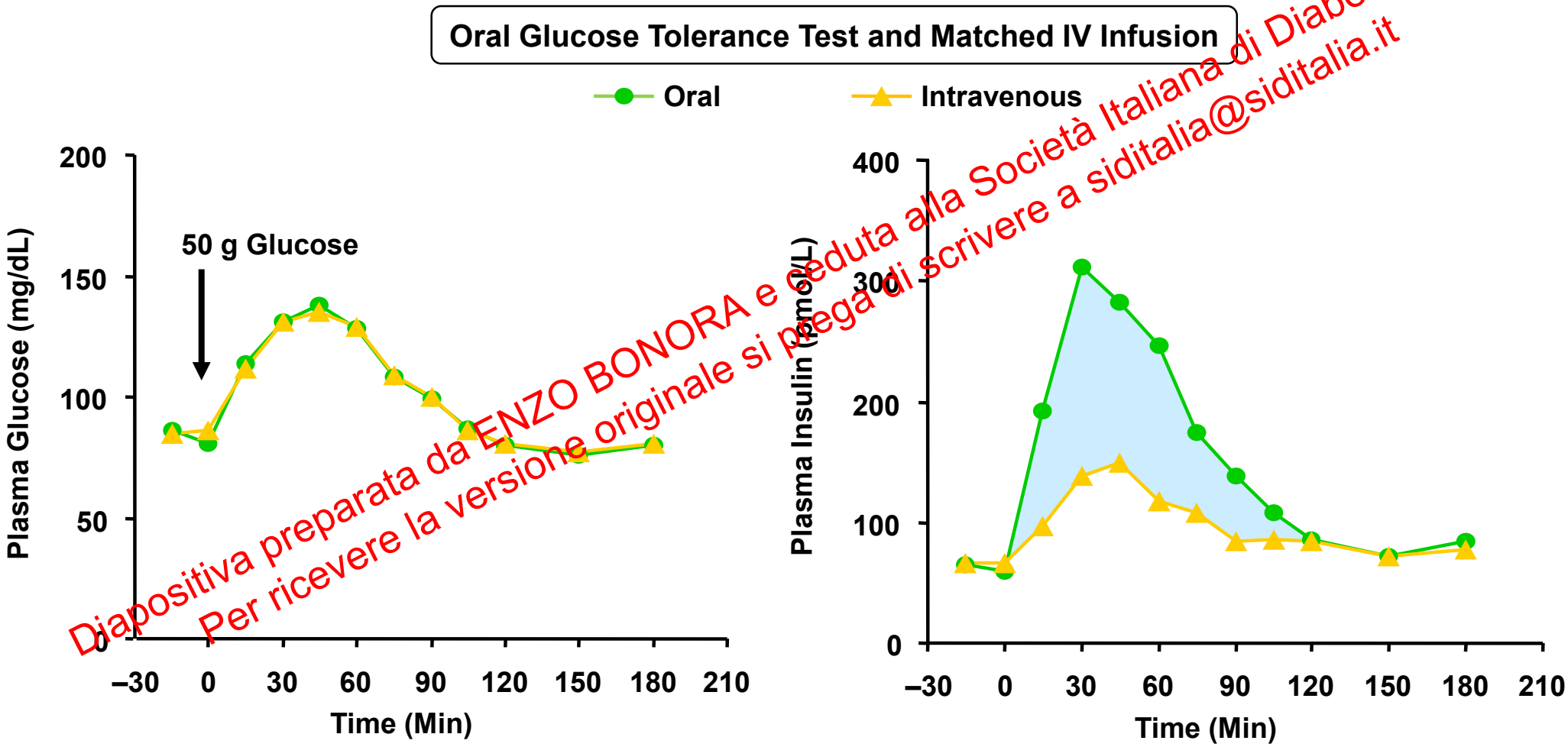
ABBOTT, ASTRAZENECA, BOEHRINGER INGELHEIM, BRISTOL-MYERS SQUIBB, BRUNO FARMACEUTICI, JANSSEN, JOHNSON&JOHNSON, LILLY, MSD, MUNDIPHARMA, NOVARTIS, NOVO NORDISK, ROCHE, SANOFI, SERVIER, TAKEDA

Research Grants

ASTRAZENECA, GENZYME, MENARINI DIAGNOSTICS, NOVO NORDISK, ROCHE DIAGNOSTICS, TAKEDA

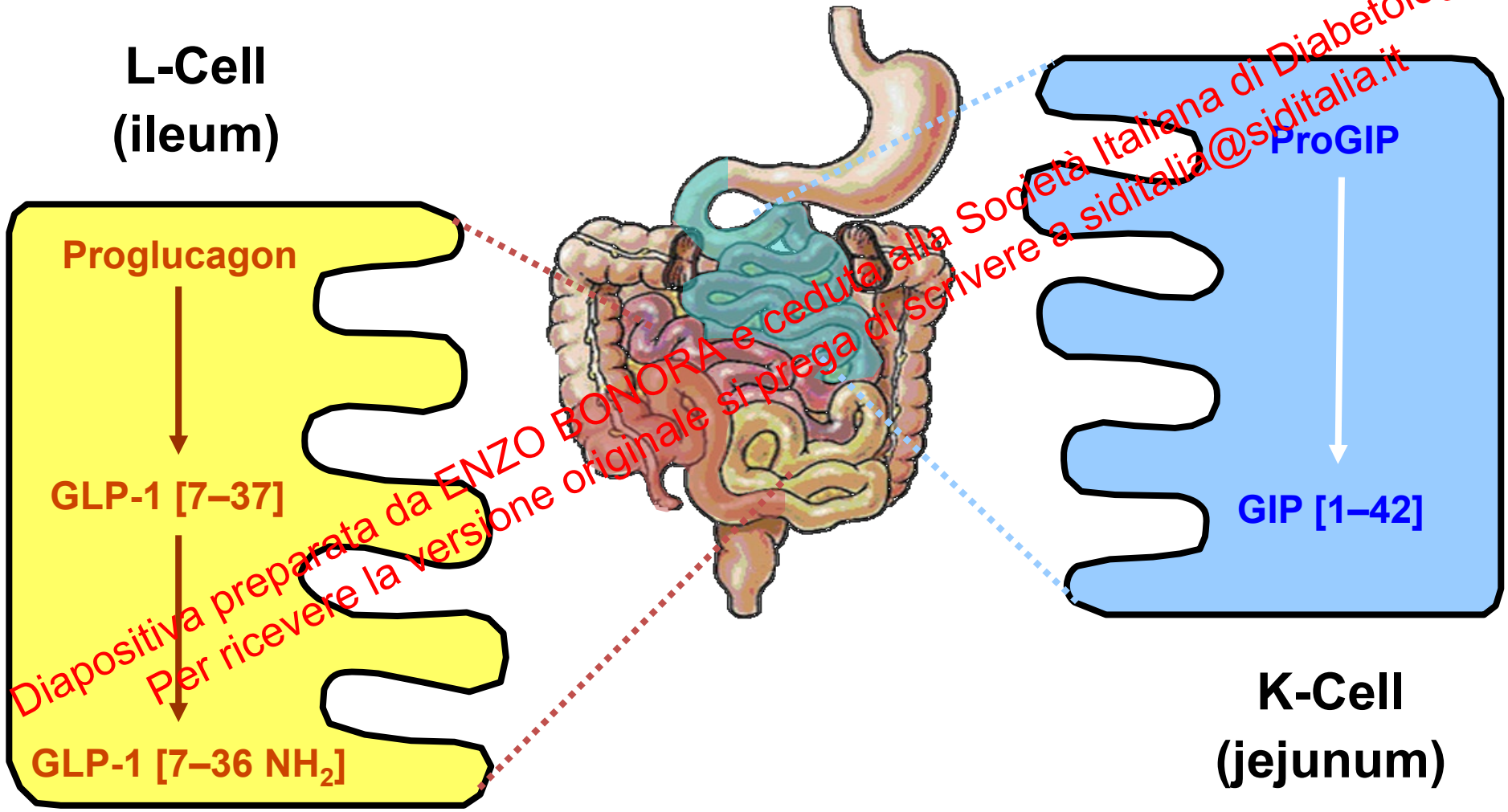
The gastrointestinal 'Incretin Effect': different responses to oral vs. intravenous glucose

Nauck MA et al - J Clin Endocrinol Metab 1986; 63: 492–498



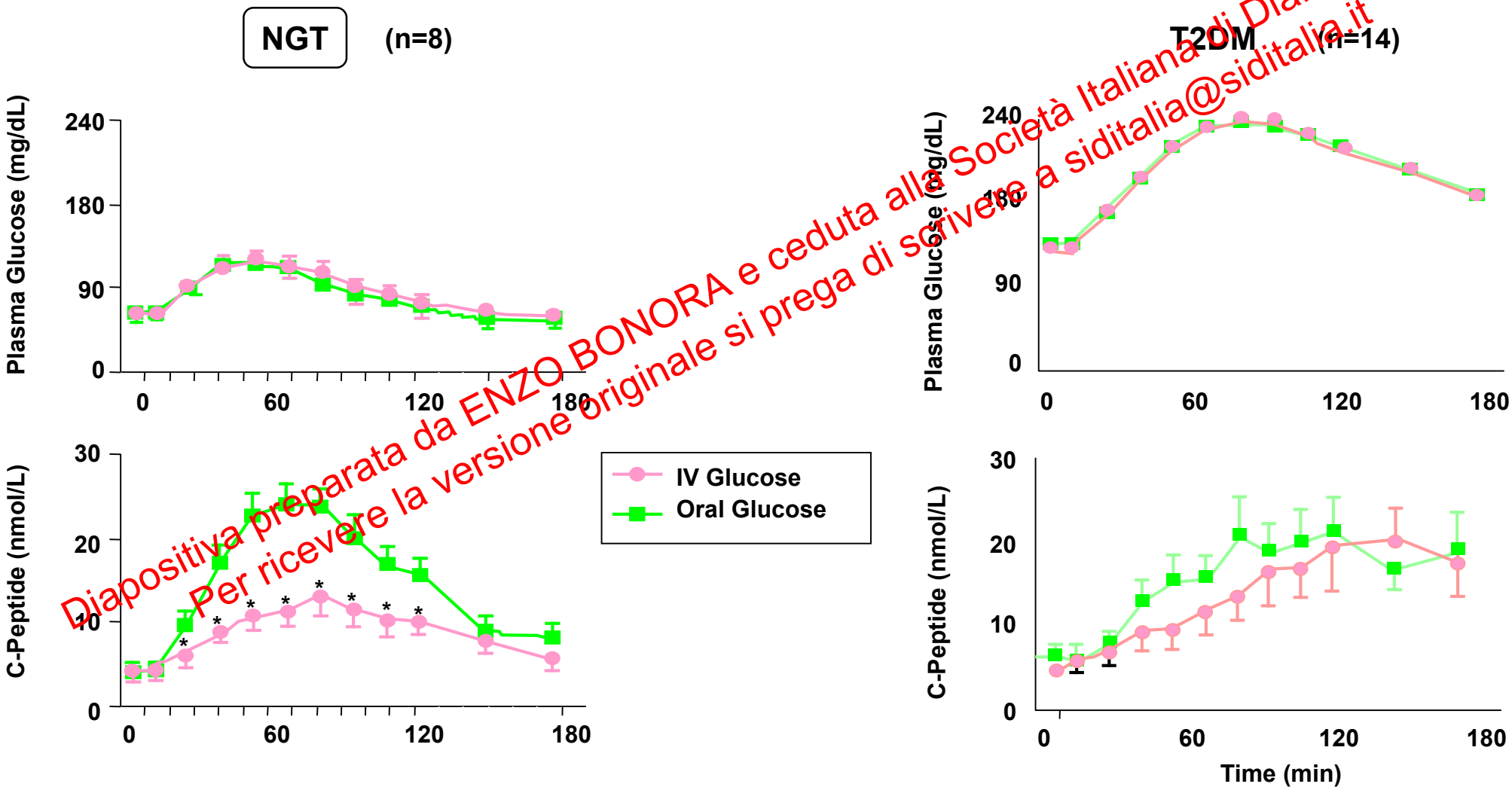
N=6

GLP-1 and GIP are synthesized and secreted from the gut in response to food intake



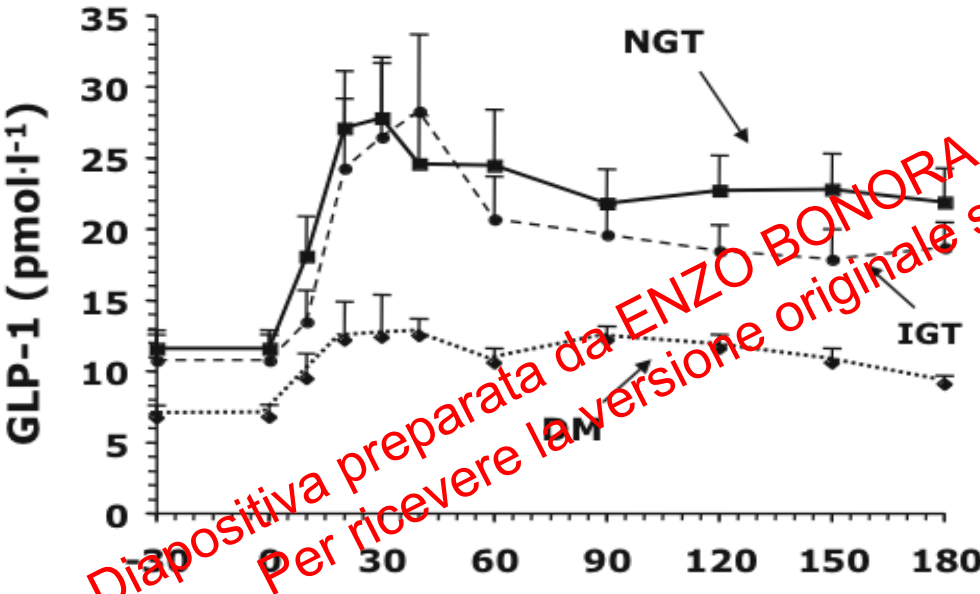
The Incretin Effect is Impaired in T2DM Leading to Reduced Beta-Cell Secretion

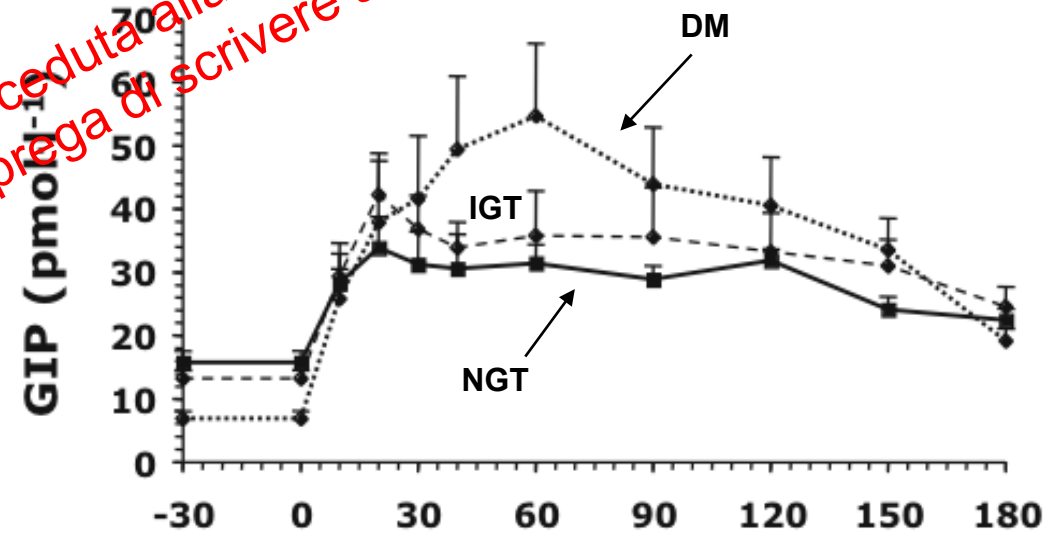
Nauck M et al - Diabetologia 1986; 29:46-52



Discordant Behaviour of GLP-1 and GIP levels during OGTT in Type 2 Diabetes

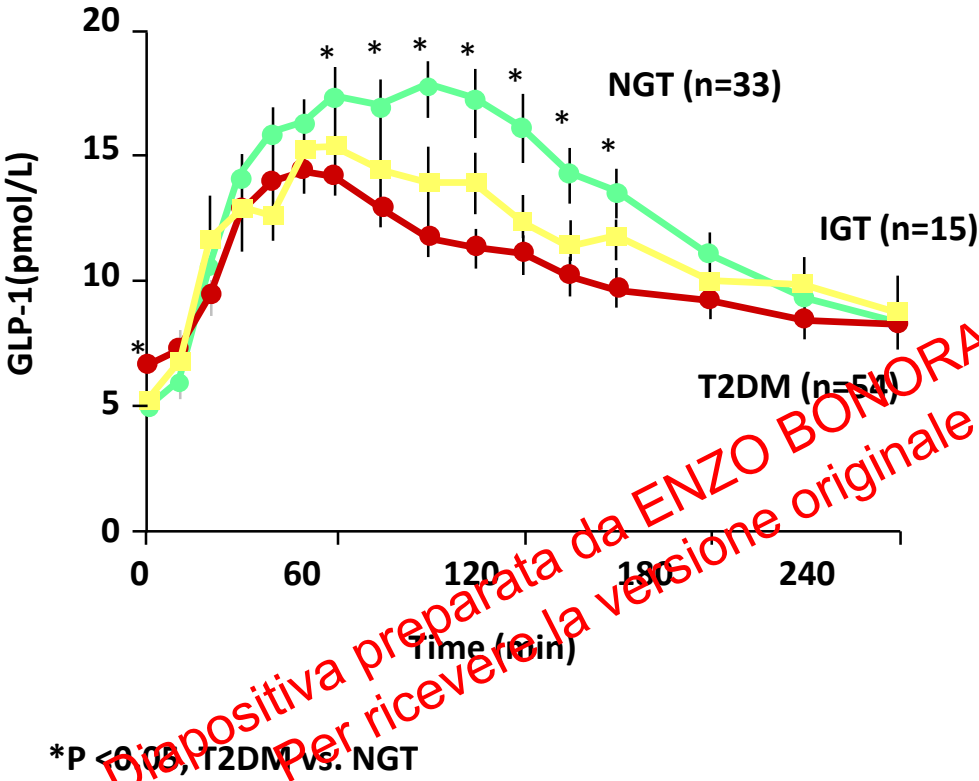
Muscelli E et al - Diabetes 2008

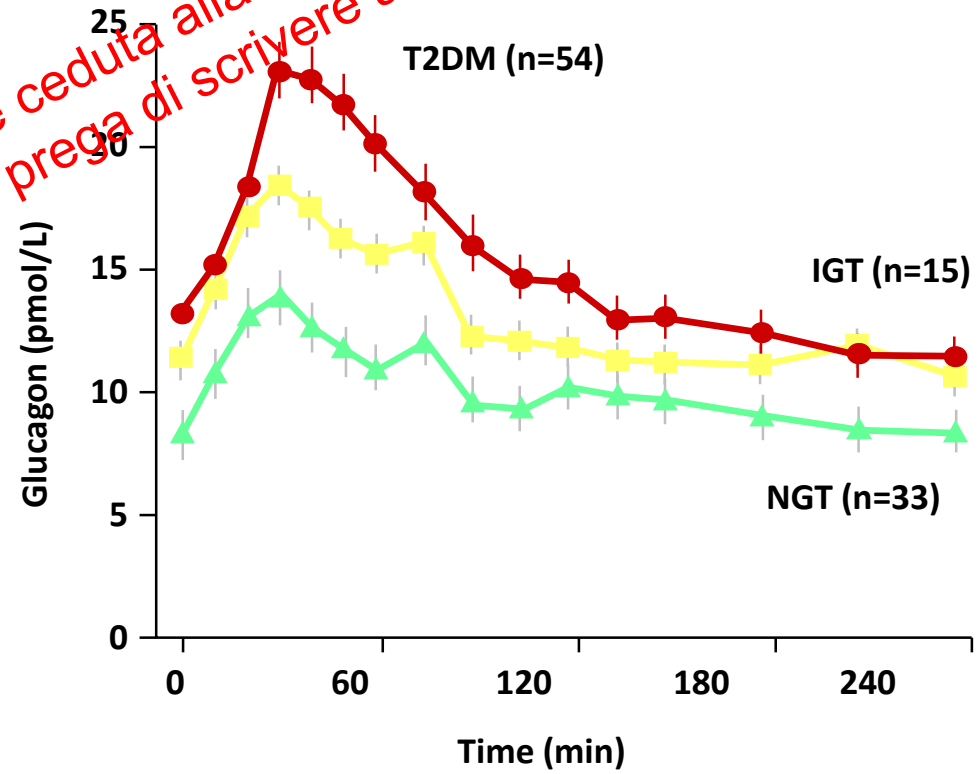




Decreased GLP-1 Response is Associated with Diminished Glucagon Suppression After Meal in T2DM

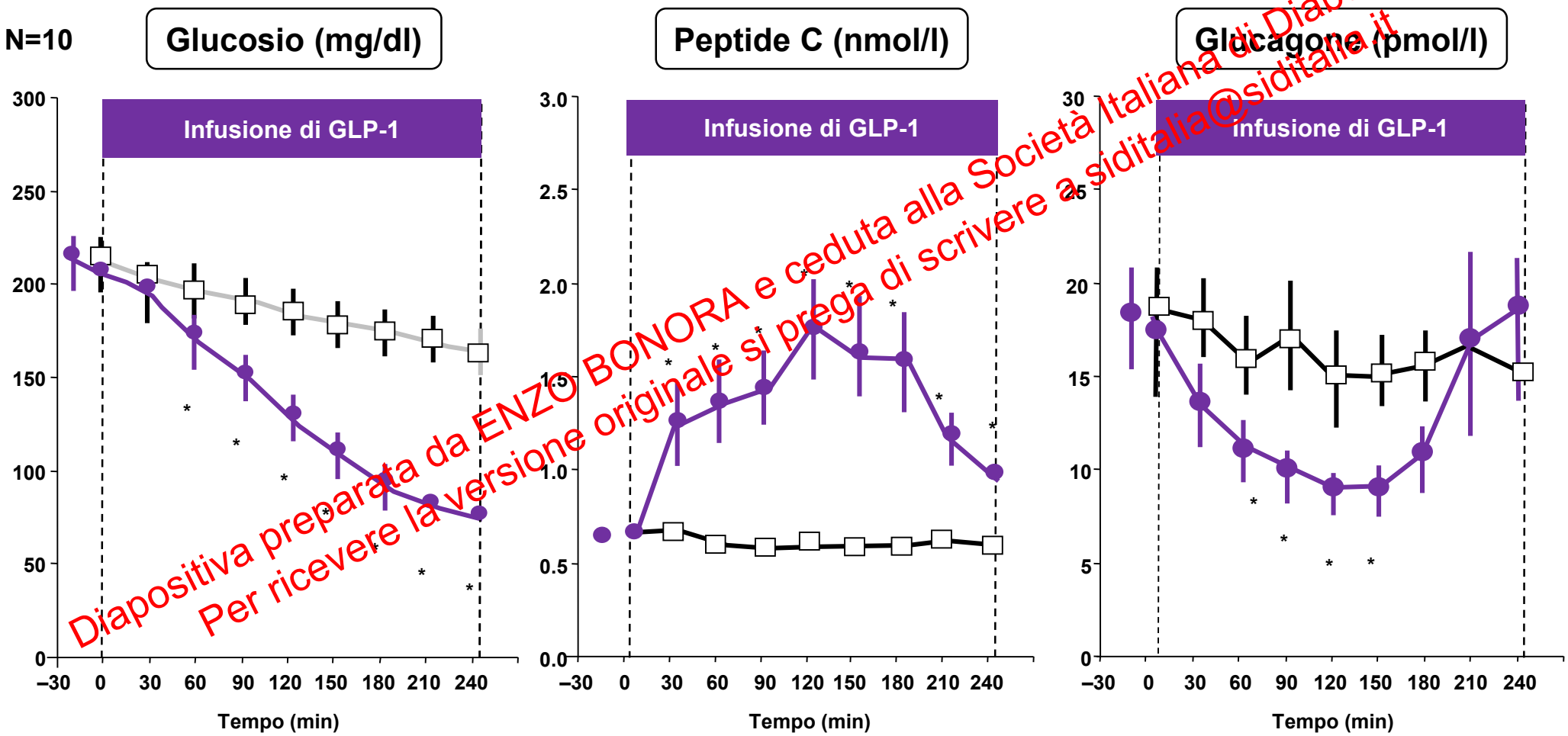
Toft-Nielsen M-B et al - J Clin Endocrinol Metab 2001; 86:3717





Il GLP-1 migliora la risposta dell'insulina e del glucagone nel T2DM

Nauck MA et al. Diabetologia 1993;36:741

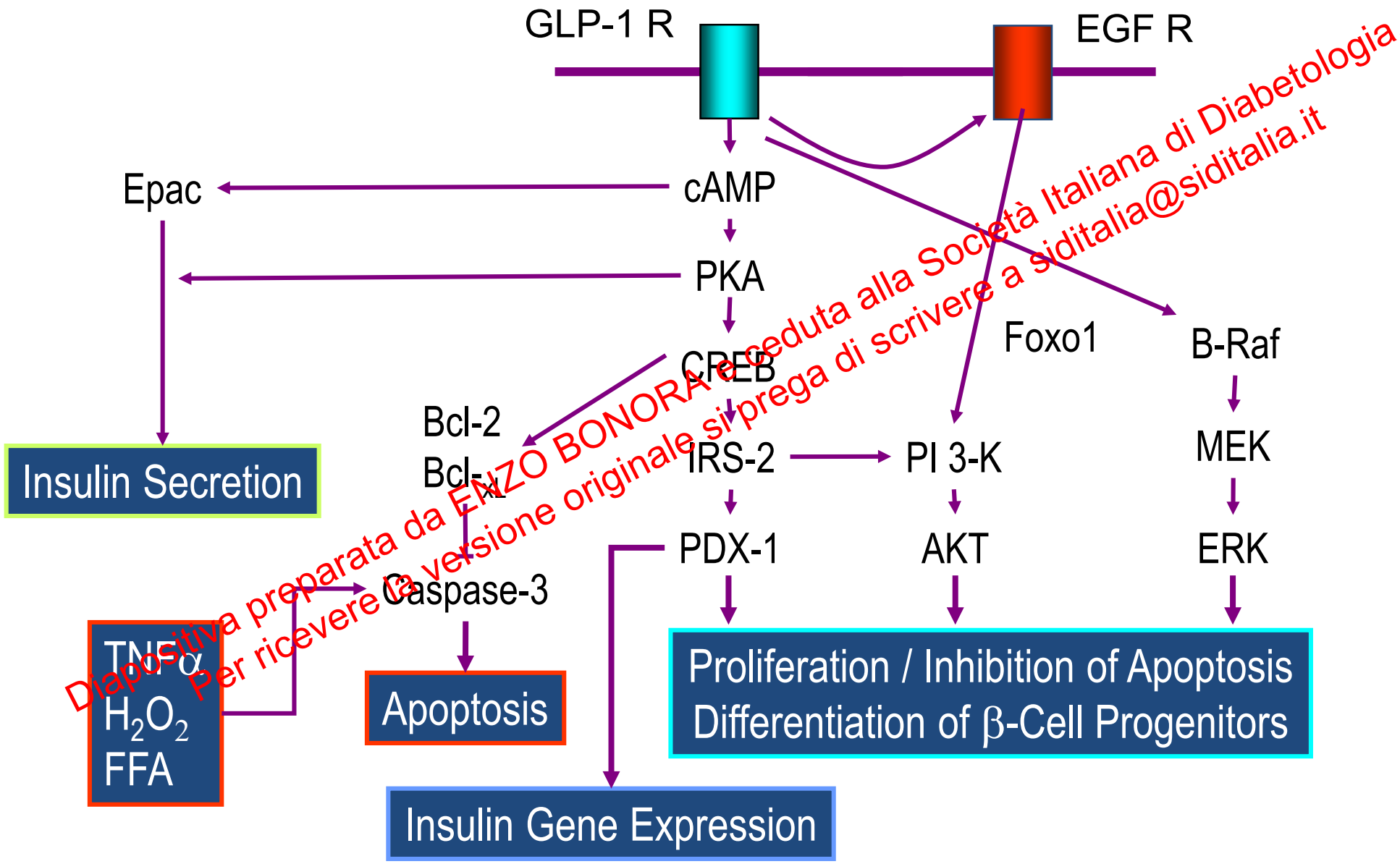


*p <0,05

†GLP-1(7-36 amide) infuso a 1,2 pmol/kg/min per 240 minuti.

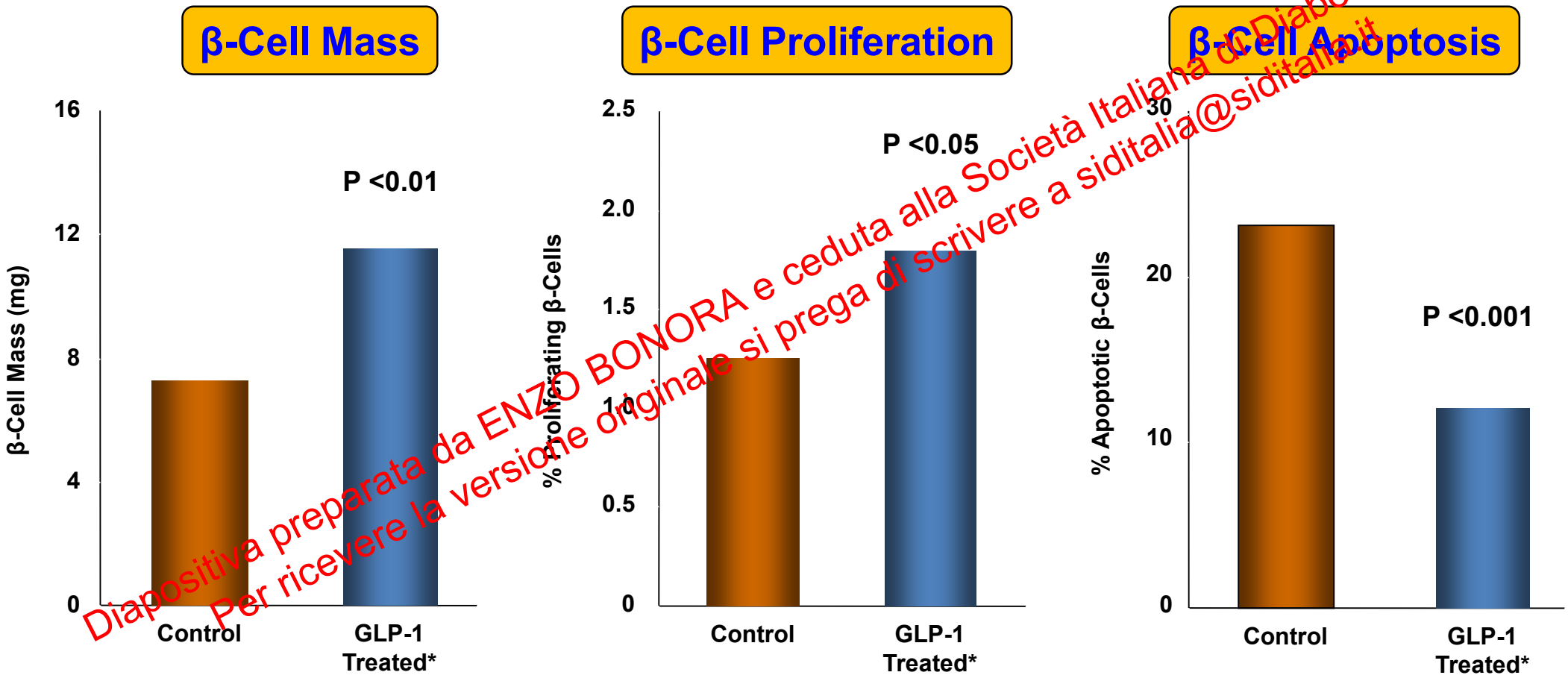
GLP-1† Placebo

Mechanism of action of GLP-1 in beta-cells



Effect of GLP-1 on the beta-cells of ZDF rats

Farilla et al - Endocrinology 143: 4397, 2002



GLP-1 infused at 30 pmol/kg/min over 2 days

GLP-1 receptors in various tissues

Korner M et al - Nucl Med 2007

TABLE 2
GLP-1 Receptor Density in Receptor-Positive Human Normal Tissues

Organ	Tissue compartment	GLP-1 receptor density*	
Central nervous system	Neurohypophysis	5,207 ± 472	(n = 6)
	Leptomeninges	1,453 ± 276	(n = 6)
Normal pancreas	Islets	1,322 ± 143	(n = 24)
	Acini	693 ± 49	(n = 9)
Chronic pancreatitis	Islets	960 ± 251	(n = 6)
	Acini	567 ± 112	(n = 6)
Duodenum	Brunner's glands	2,752 ± 522	(n = 5)
Ileum	Myenteric plexus	887 ± 285	(n = 6)
Colon	Myenteric plexus	788 ± 84	(n = 9)
Breast	Ducts and lobuli	519 ± 136	(n = 3)
Lung	Small blood vessels	636 ± 164	(n = 11)
Kidney	Large- and medium-sized arteries	674 ± 127	(n = 2)

*Mean ± SEM of receptor-positive cases (dpm/mg tissue).

Domanda per televoter

Su quale di questi organi/tessuti non sembra esercitarsi un'azione significativa di GLP-1 e dei suoi analoghi:

a) Fegato

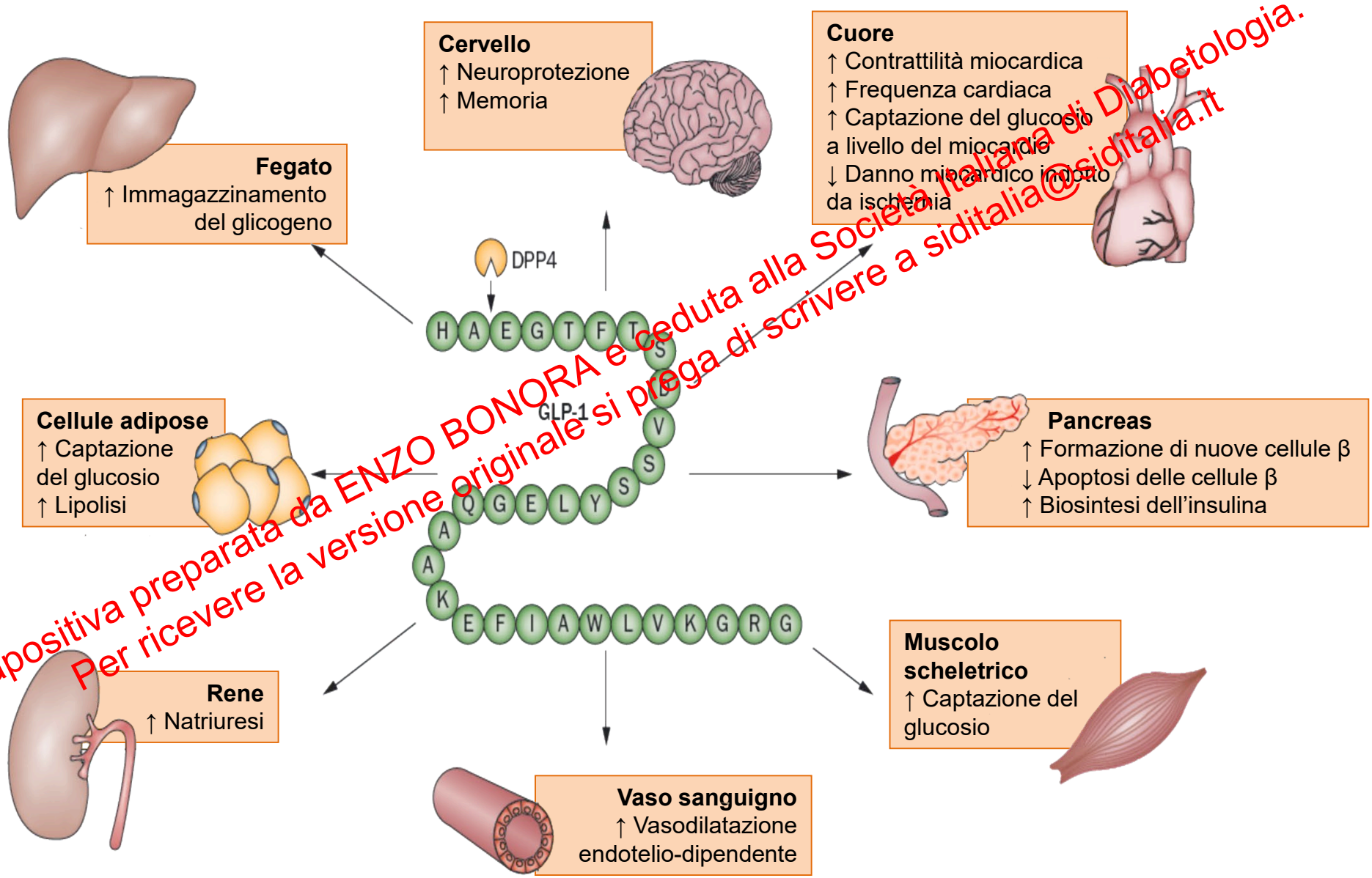
b) Tessuto adiposo

c) Polmone

d) Muscolo scheletrico

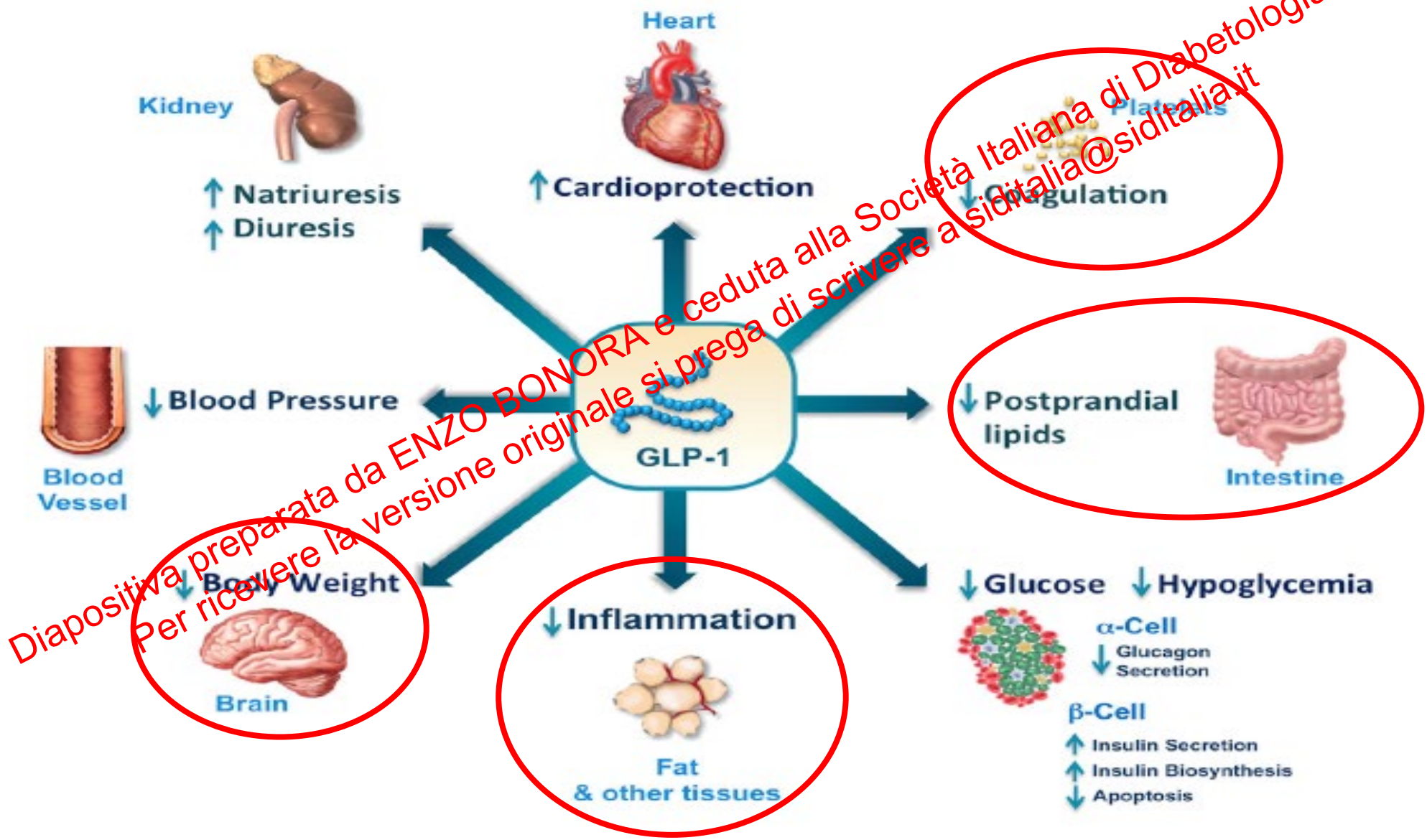
GLP-1: un ampio spettro di azioni biologiche

Meier JJ - Nat Rev Endocrinol 2012; 8:728-42



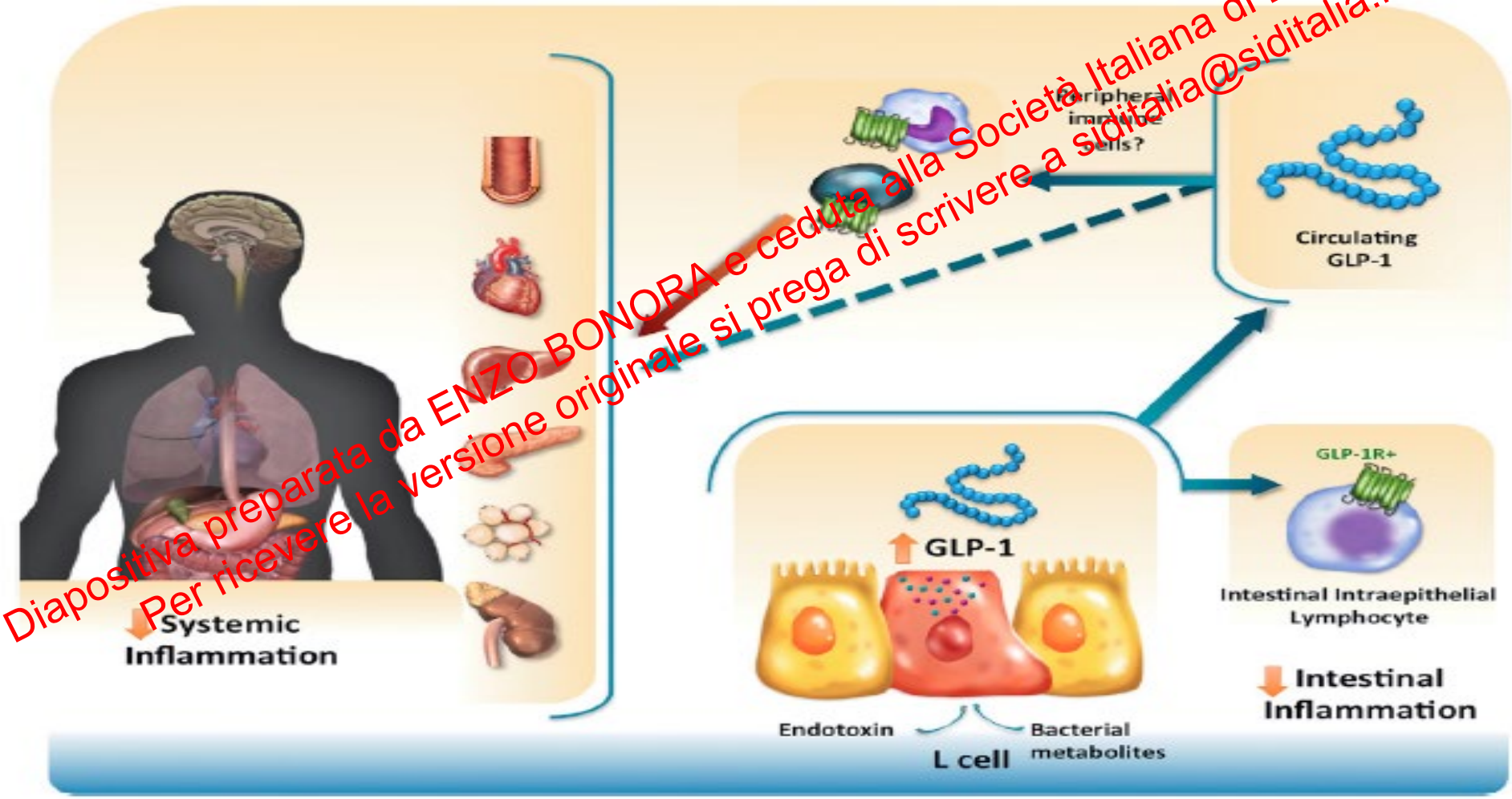
Pleiotropic effects of GLP-1

Drucker DJ - Cell Metabolism 2016; 24:15



Direct and indirect actions of GLP-1 as a local and systemic anti-inflammatory molecule

Drucker DJ - Cell Metabolism 2016; 24:15



Domanda per televoter

La perdita di peso conseguente all'uso di analoghi di GLP-1 è verosimilmente legata a:

a) Riduzione dell'introito di cibo per ritardato svuotamento gastrico

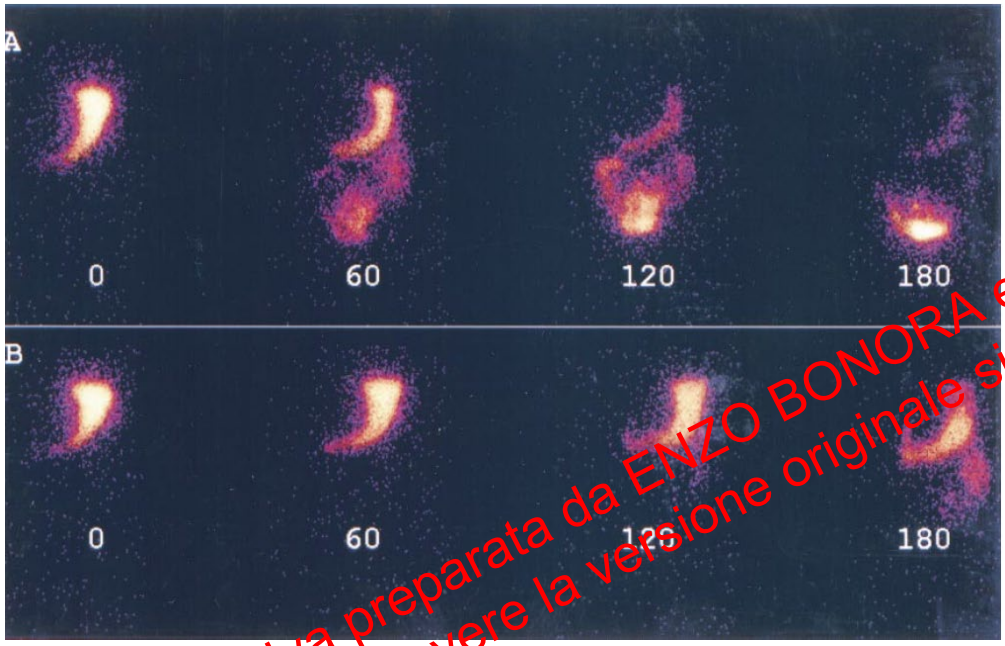
b) Azione diretta sui centri della fame e della sazietà

c) Cambiamento del microbiota con possibile effetto anti-obesità

d) Tutte le precedenti

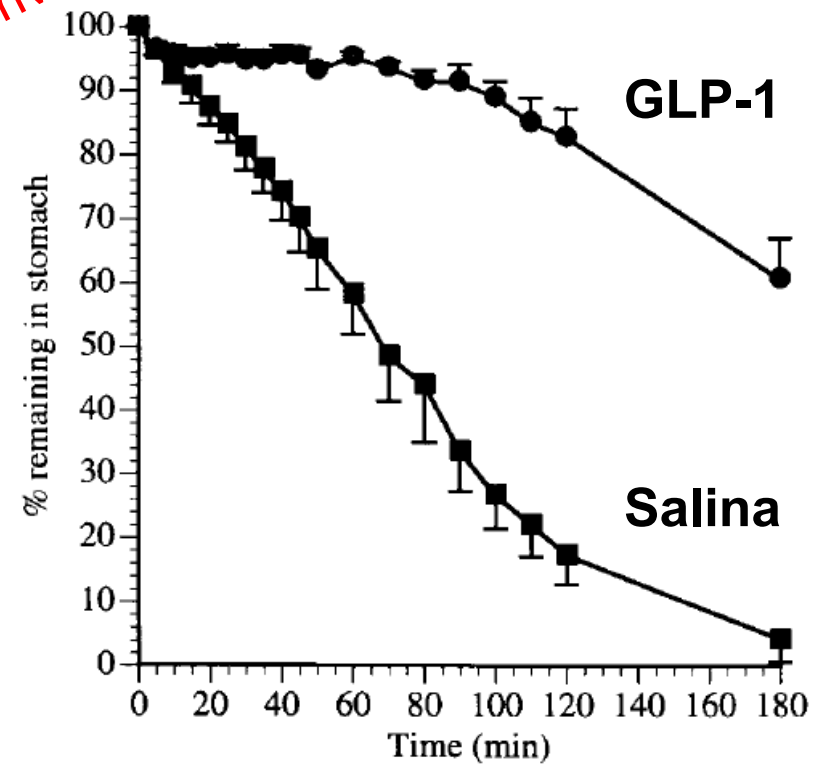
GLP-1 Decreases Gastric Emptying after Meal

Näslund et al. - Am J Physiol 1999; 277: R910-R916



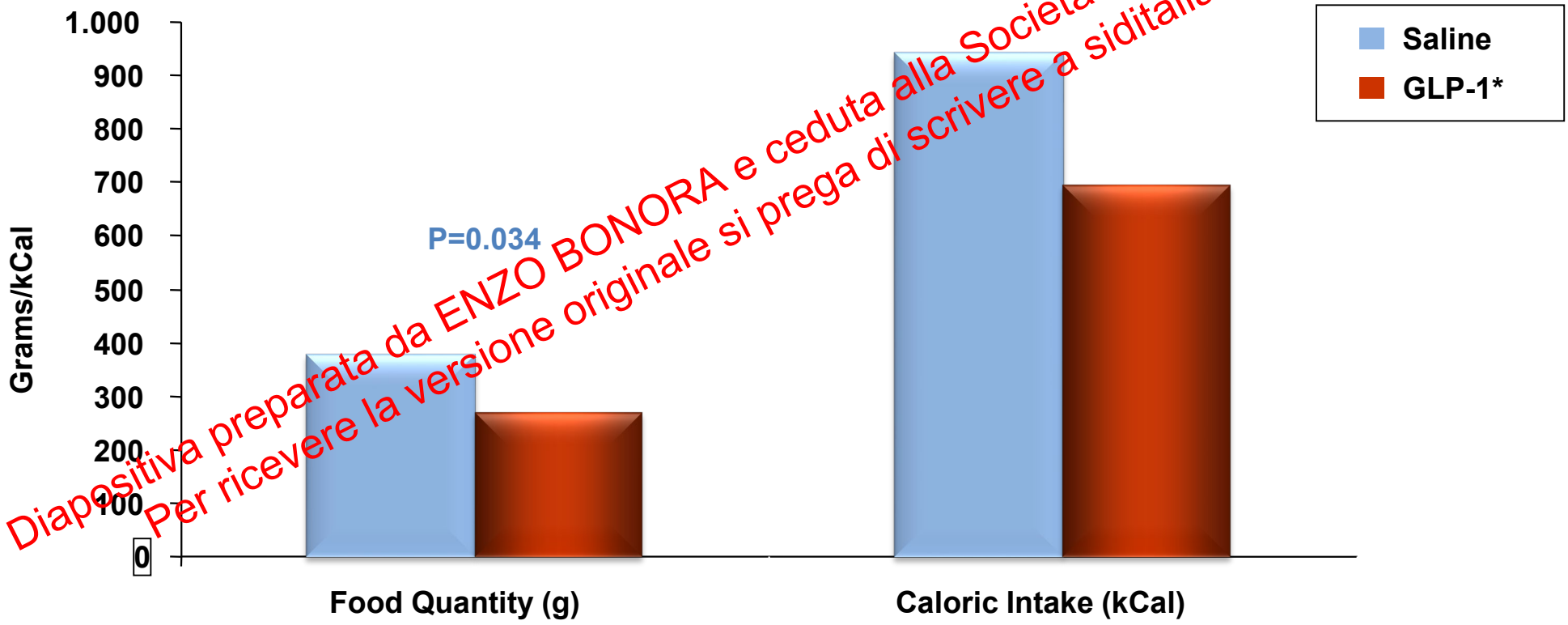
Salina

GLP-1



GLP-1 Infusion Leads to Significant Decreases in Eating Behaviors

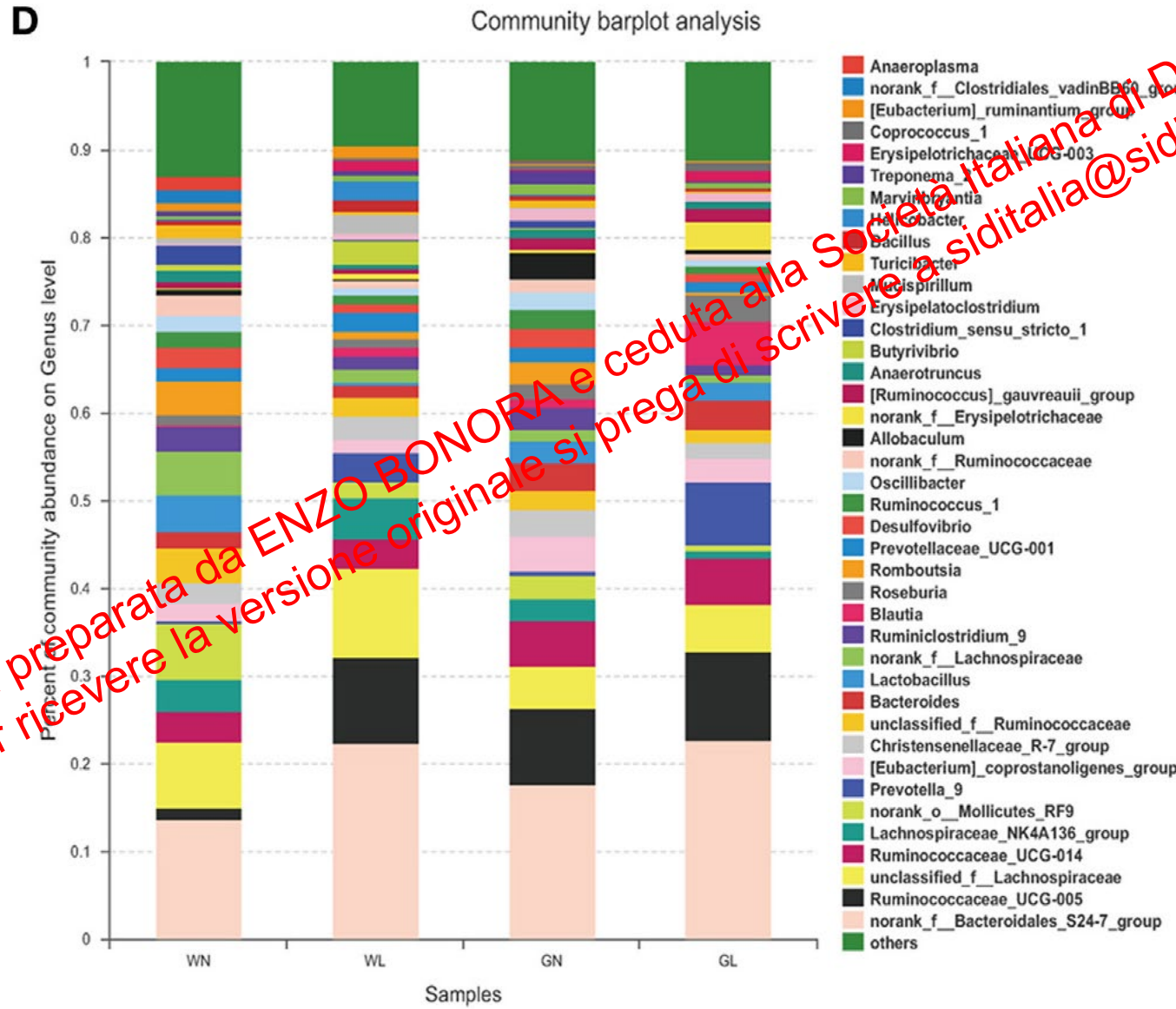
Gutzwiller JP et al - Am J Physiol 1999; 276: R1541-R1544



n=12

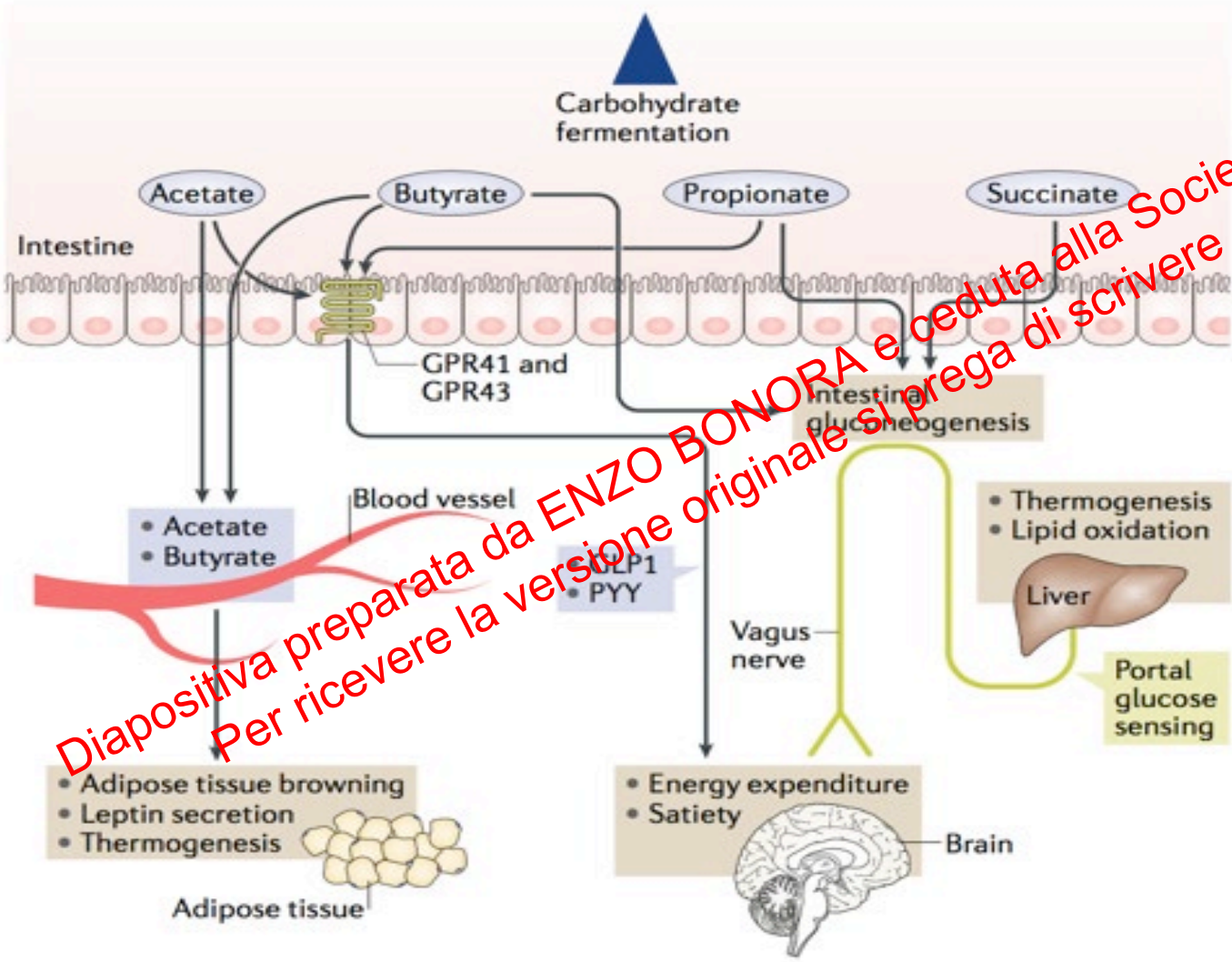
Liraglutide alters the gut microbiota of Wistar and Goto-Kakizaki rats

Zhao L et al - Front Endocrinol 2018; 9:233



Metabolites derived from carbohydrate fermentation by microbiota influences body weight

Canfora E et al - Nat Rev Endocrinol 2019

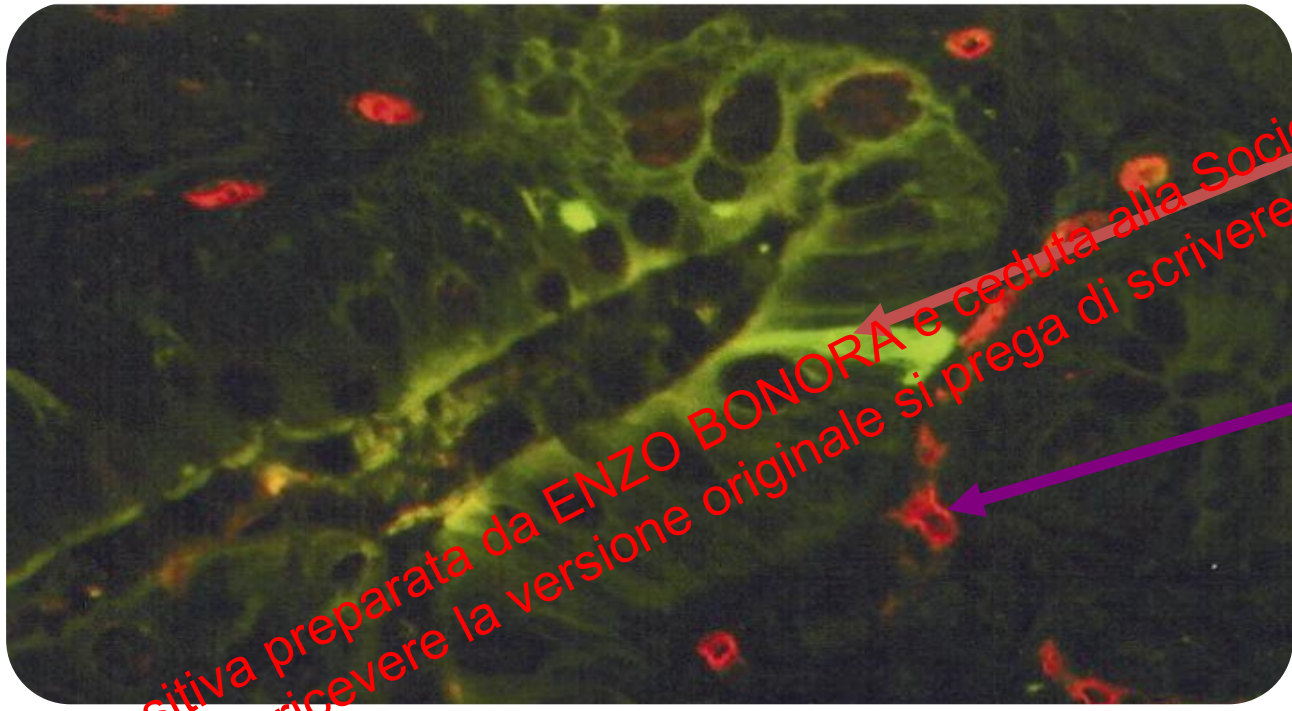


- Propionate, butyrate and succinate induce intestinal gluconeogenesis, thereby beneficially regulating energy homeostasis

- Acetate and butyrate have also been demonstrated to induce satiety via a central mechanism and to increase thermogenesis in adipose tissue and liver as well as to induce adipose tissue browning and leptin secretion

- In addition, acetate, propionate and butyrate stimulate the secretion of the satiety hormones glucagon-like peptide 1 (GLP1) and peptide YY (PYY) in a G protein-coupled receptor (GPR) dependent manner.

Native GLP-1 is Rapidly Degraded by DPP-4

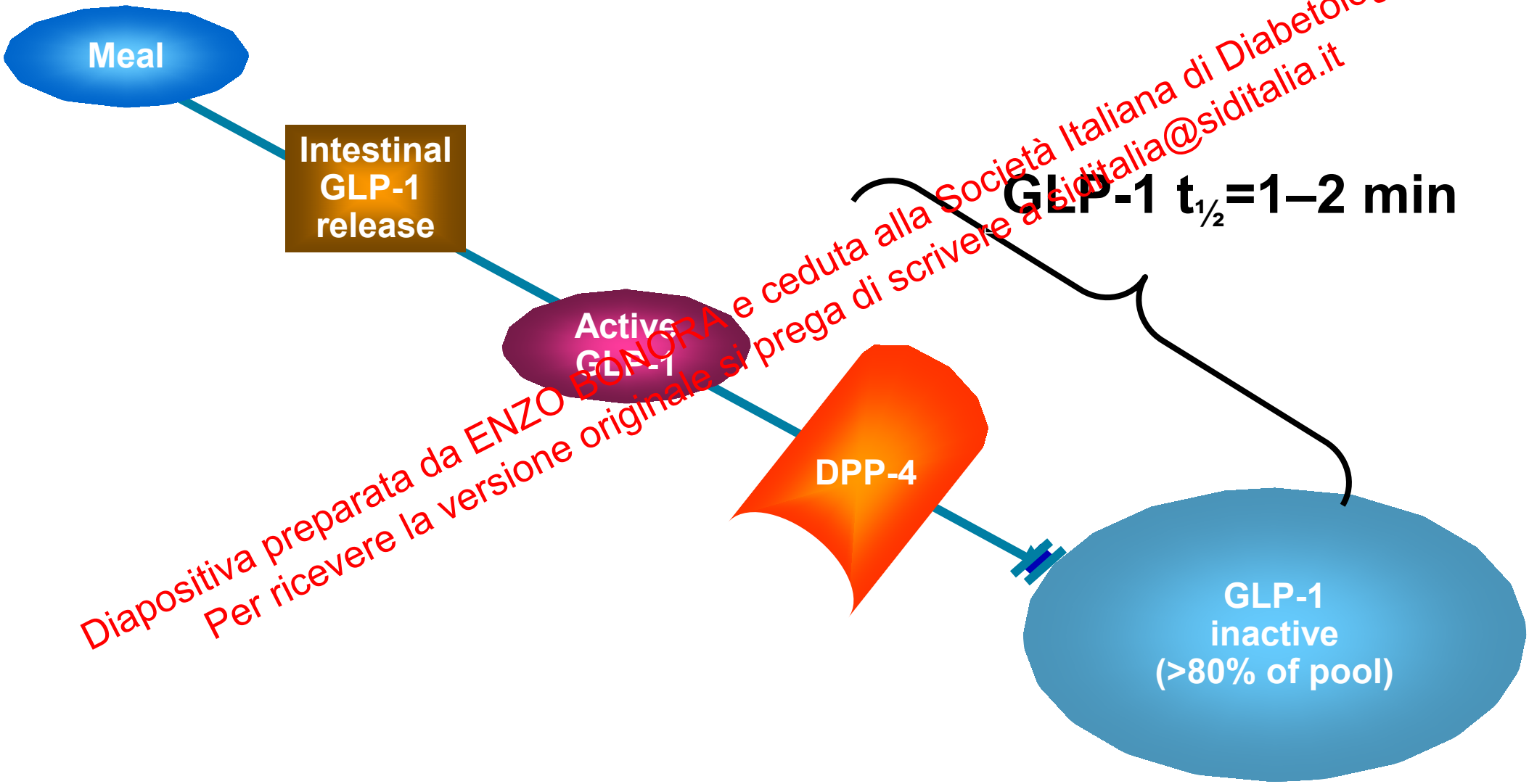


Human ileum,
GLP-1 producing
L-cells

Capillaries, DPP-4
(Di-Peptidyl
Peptidase-4)

Double immunohistochemical staining for DPP-IV (red) and
GLP-1 (green) in the human ileum

Rapid degradation of active GLP-1 by DPP-4



Development of exenatide: an incretin mimetic

Exenatide (Exendin-4)

- Synthetic version of salivary protein found in the Gila Monster.
- Approximately 50% identity with human GLP-1.

Binds to known human GLP-1 receptors on β cells *in vitro.* Resistant to DPP-IV inactivation

Exenatide	H **G** E G T F T S D **L** S **K** **Q** **M** E **E** **E** A **V** **R** **L** F I **E** W L **K** **N** G **G** P **S** **S** **G** A P P P S – NH_2
GLP-1 Human	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R – NH_2

Site of DPP-IV Inactivation

Adapted from Nielsen LL, et al. *Regulatory Peptides*. 2004;117:77-88.; Fineman MS, et al. *Diabetes Care*. 2003;26:2370-2377. Reprinted from *Regulatory Peptides*, 117, Nielsen LL, et al, Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycaemic control of type 2 diabetes, 77-88, 2004, with permission from Elsevier for English use only.

GLP-1 Receptor Agonists

Prandial
(short and prolonged acting)

- Exenatide (BID)
- Lixisenatide (daily)

Non prandial
(long and very long acting)

- Liraglutide (daily)
- Exenatide LAR (weekly)
- Dulaglutide (weekly)
- Albiglutide (weekly)
- Semaglutide (weekly)

Comparison of Prandial (Short-acting) vs. Non-prandial (Long-acting) GLP-1 RAs

Meier JJ - Nat Rev Endocrinol 2012; 8:728-742

Parameters	Prandial GLP-1 receptor agonists	Non-prandial GLP-1 receptor agonists
Compounds	Exenatide BID Lixisenatide	Liraglutide, Exenatide LAR Dulaglutide, Albiglutide Semaglutide
Half-life	2–5 hours	12h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest Reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5kg	2–5kg
Induction of nausea	20–50% attenuates slowly (weeks to many months)	20–40% attenuates quickly (~4–8weeks)

Domanda per televoter

Fra i vari agonisti del recettore GLP-1 la maggiore analogia molecolare con il GLP- 1 nativo è posseduta da:

a) Exenatide

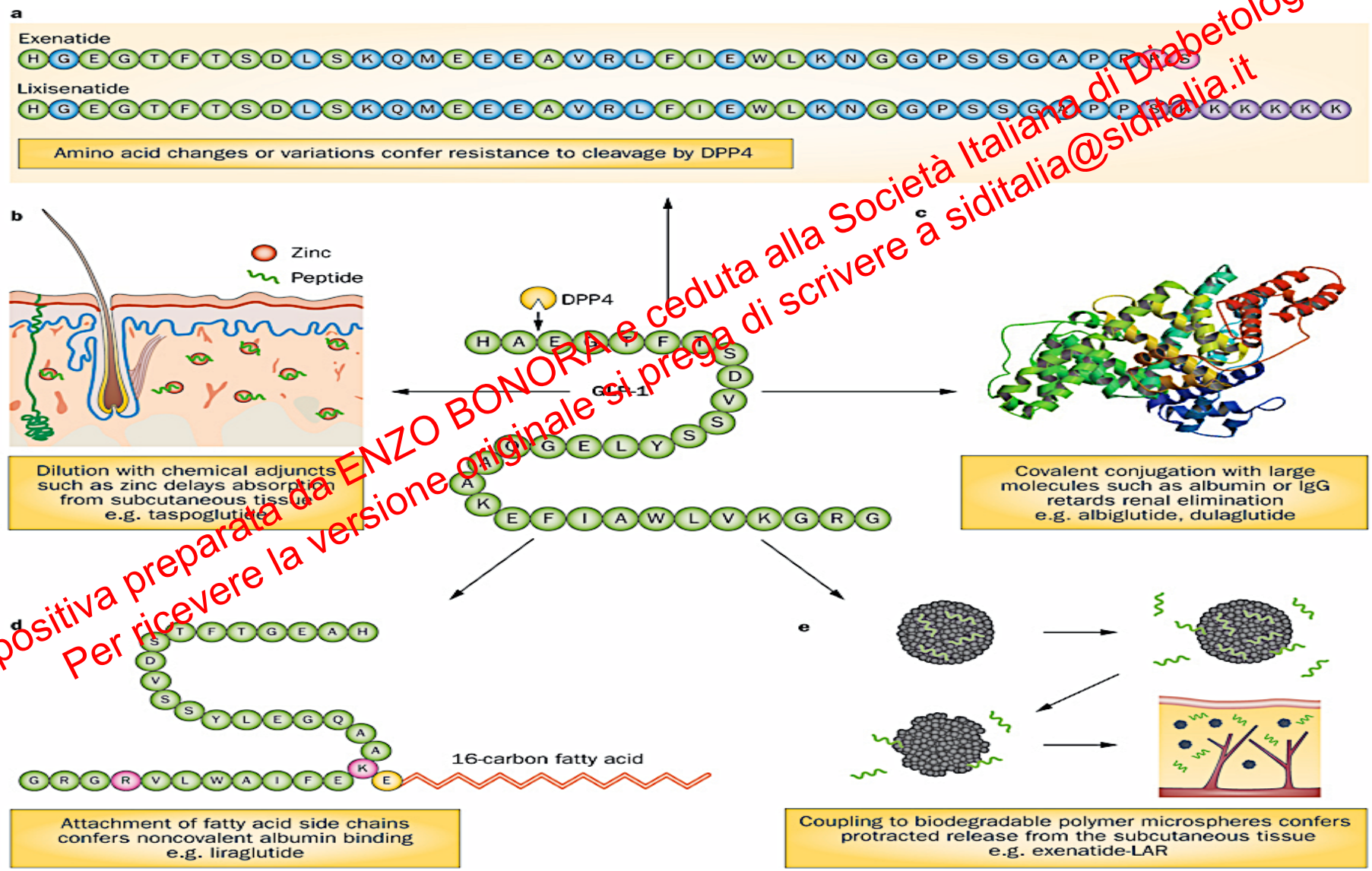
b) Lixisenatide

c) Liraglutide

d) Sono tutti molto simili

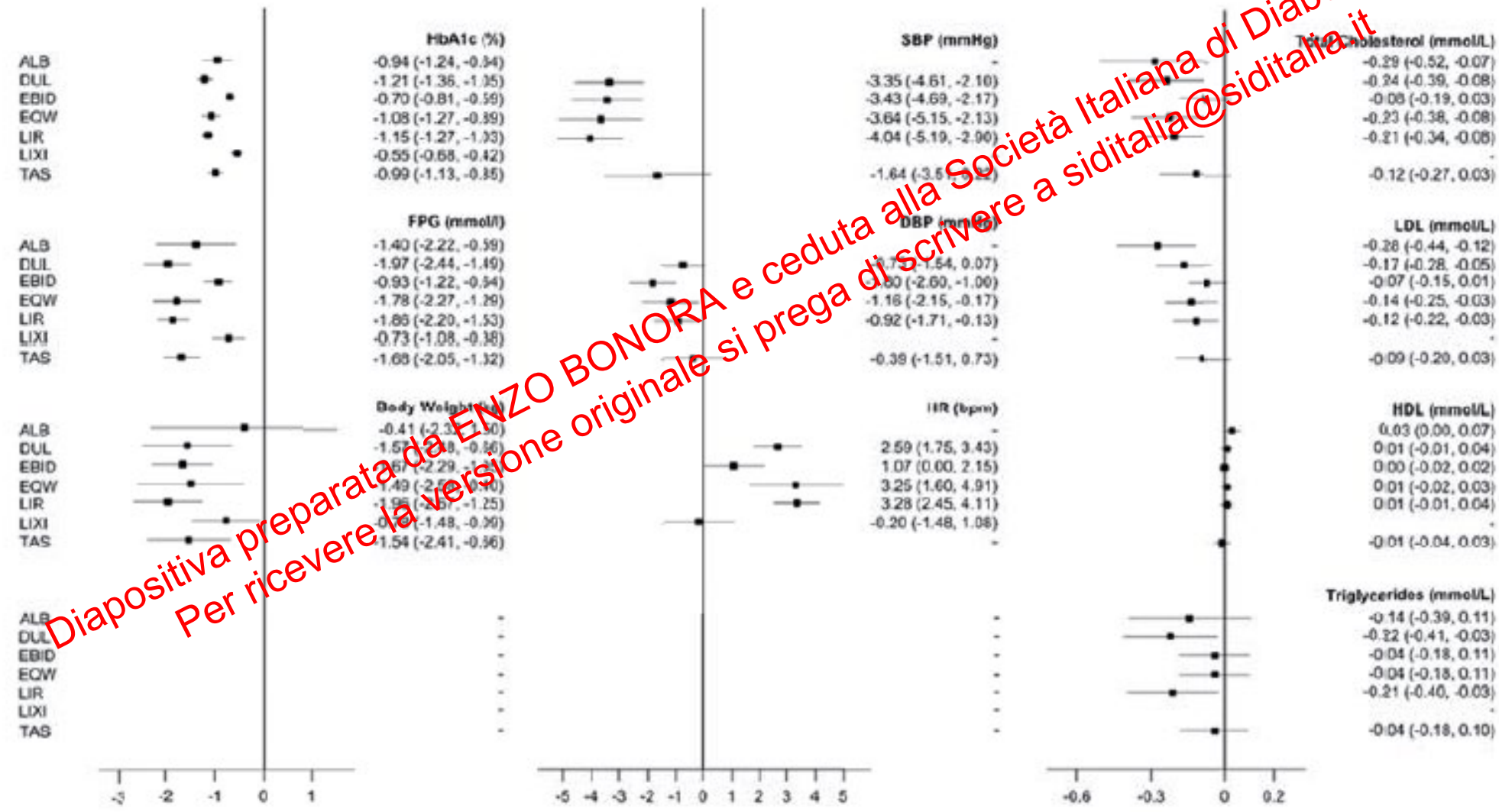
Strategies to develop GLP-1 receptor agonists

Meier JJ – Nat Rev Endocrinol 2012; 8: 728-742



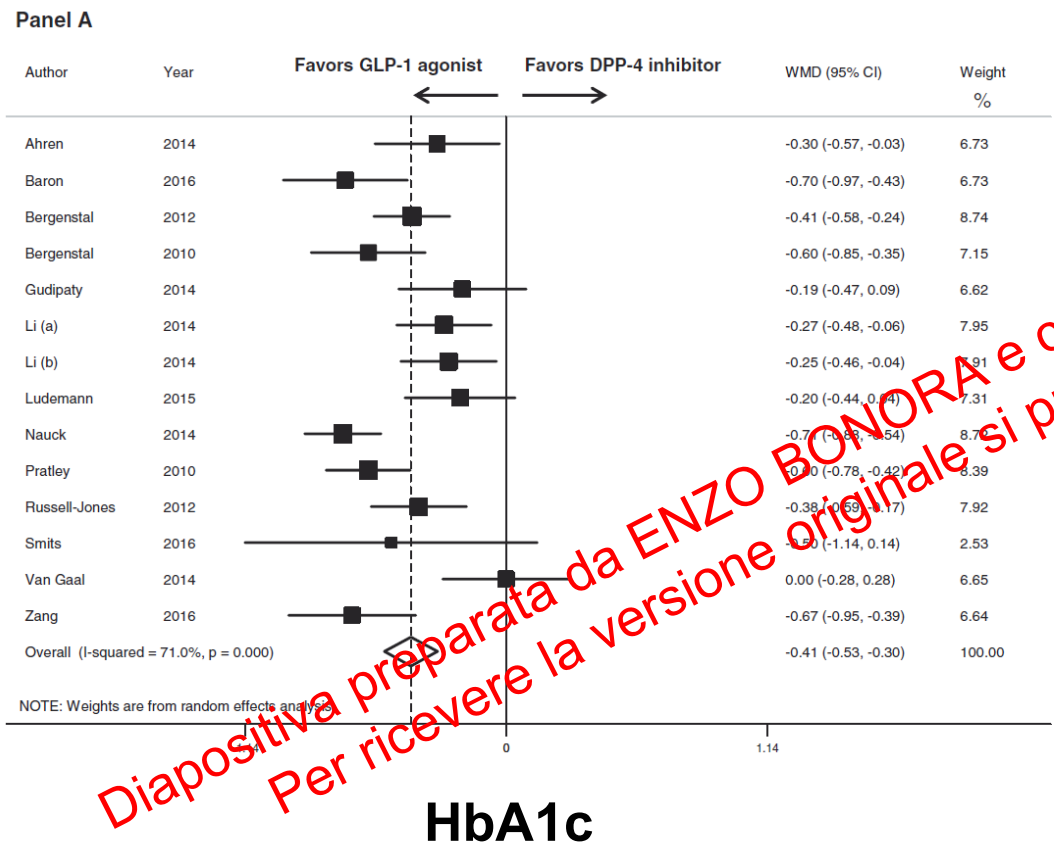
Efficacy of GLP-1RAs - A systematic review and mixed treatment comparison analysis

Hitke ZZ et al – Diab Obes Metab 2017; 19: 524



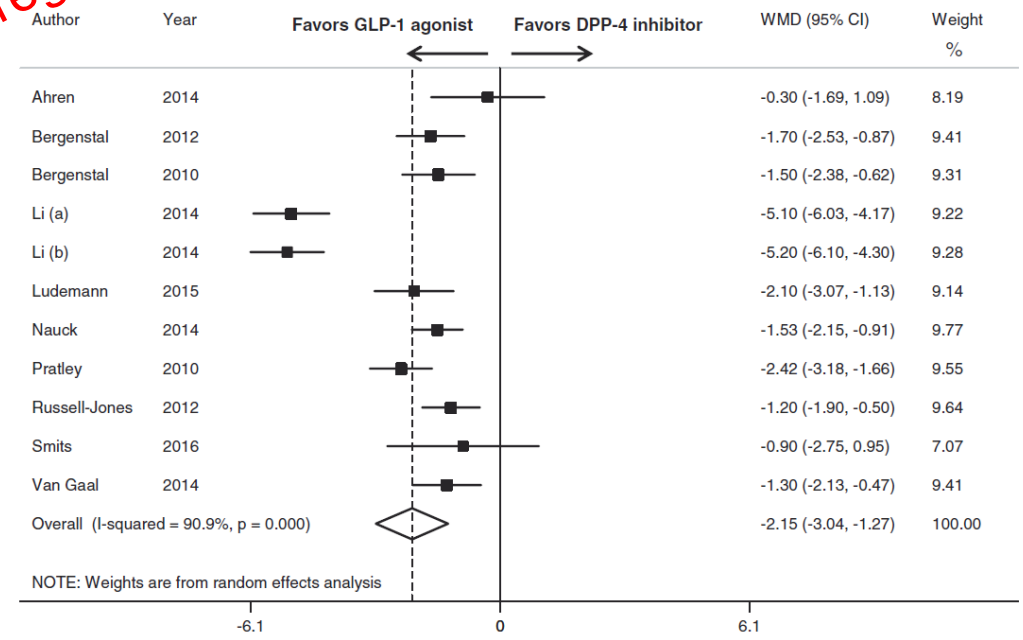
GLP-1RAs vs. DPP-4 added to metformin
Meta-analysis on the effect on HbA1c and BW

Tran S et al – Diab Obes Metab 2018; 20 (suppl 1): 68-76



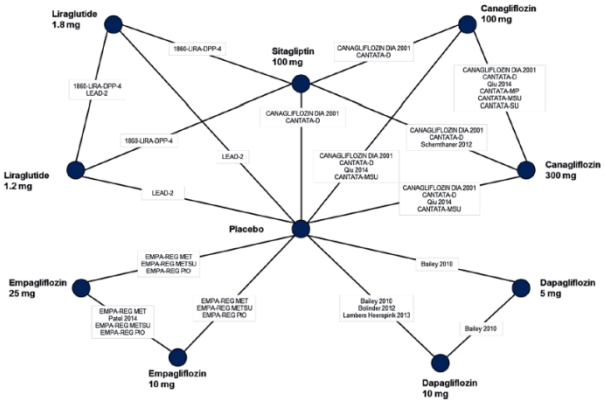
HbA1c

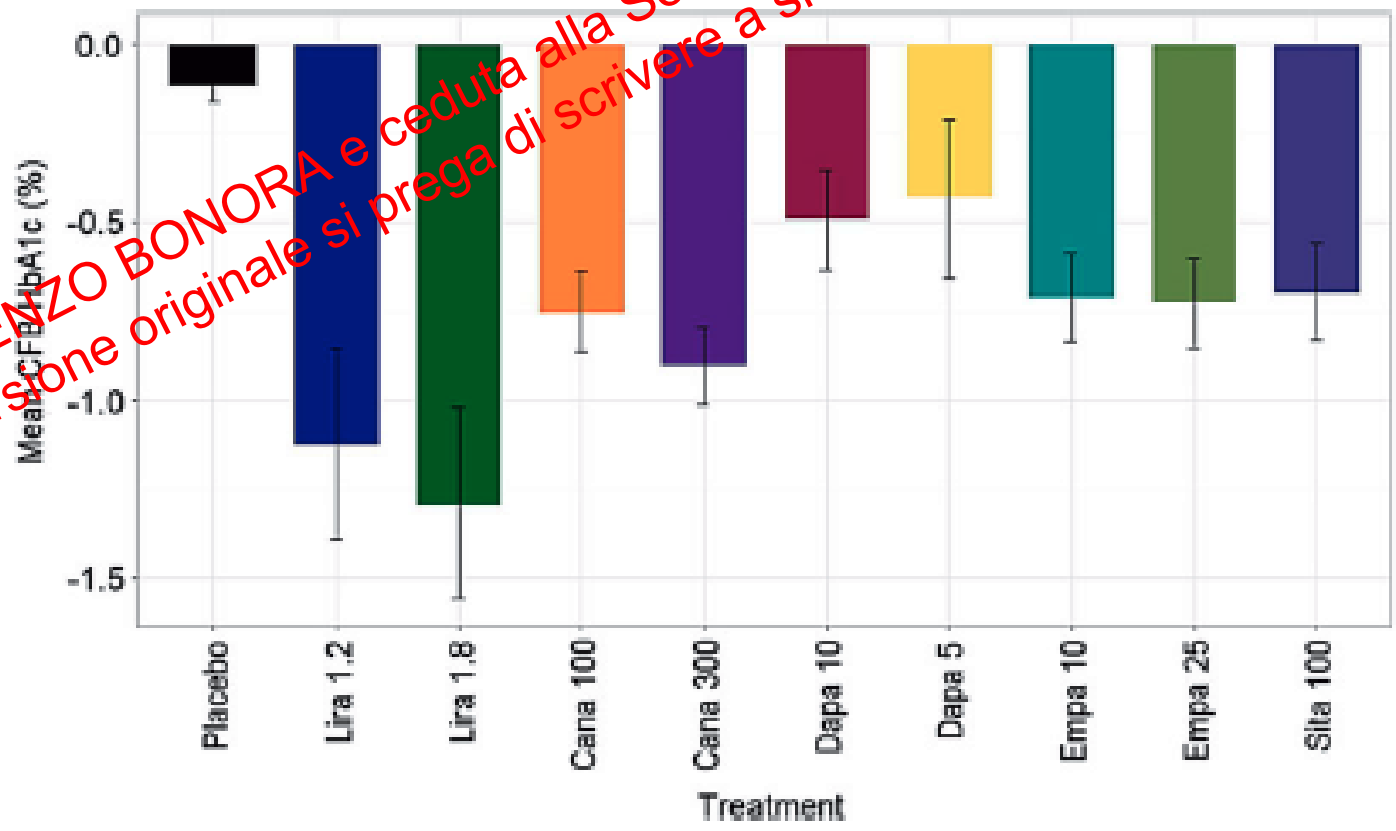
Body Weight



Effect on HbA1c of Liraglutide vs. SGLT-2
Network meta-analysis

Lorenzi M et al – Diabetes Ther 2017; 8:85



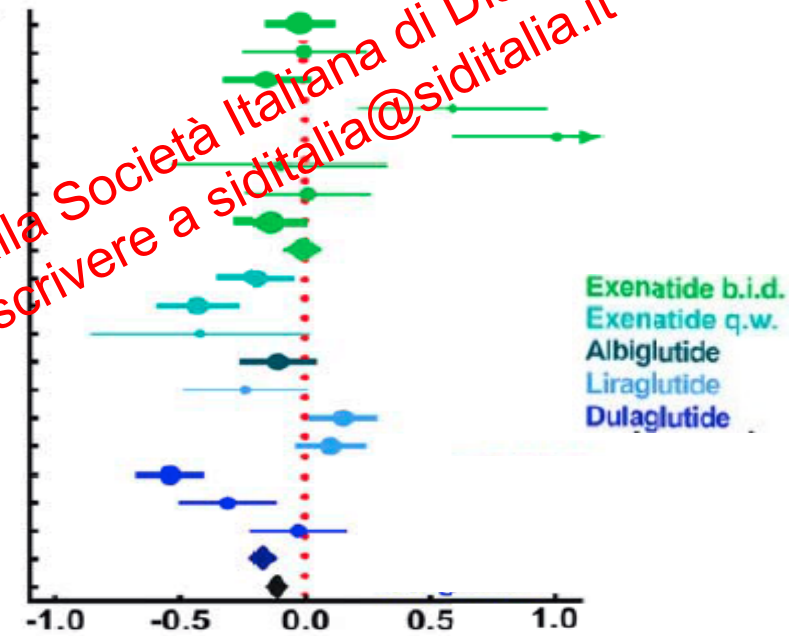


GLP-1RAs vs. insulin - Meta-analysis

Abd El Aziz MS et al – Diabet Obes Metab 2017; 19: 216

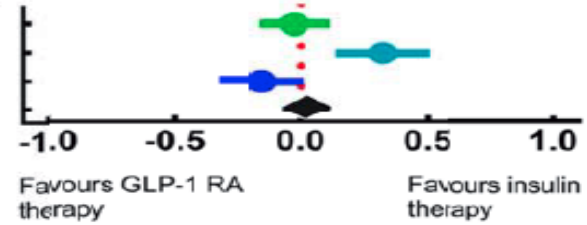
A GLP-1 RA versus insulin treatment (OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Heine et al. 2005 [44]	short	-0.02	-0.16	0.12	-0.24	0.81
Barnett et al. 2007 [33]	short	0.00	-0.25	0.25	0.00	1.00
Nauck et al. 2007 [47]	short	-0.15	-0.33	0.03	-1.63	0.10
Bergenstal et al. 2009 a [34]	short	0.59	0.21	0.97	3.02	0.0026
Bergenstal et al. 2009 b [34]	short	1.01	0.59	1.43	4.72	< 0.0001
Bunck et al. 2009 [35]	short	-0.10	-0.53	0.33	-0.46	0.65
Davies et al. 2009 [36]	short	0.01	-0.24	0.26	0.08	0.94
Gallwitz et al. 2011 [41]	short	-0.14	-0.29	0.01	-1.87	0.061
All short-acting GLP-1 RAs		**-0.02**	**-0.09**	**0.06**	**-0.39**	**0.70**
Diamant et al. 2010 [40]	long	-0.20	-0.35	-0.05	-2.57	0.010
Inagaki et al. 2012 [45]	long	-0.43	-0.60	-0.26	-5.06	< 0.0001
Davies et al. 2013 [37]	long	-0.42	-0.86	0.02	-1.87	0.061
Weissman et al. 2014 [50]	long	-0.11	-0.27	0.05	-1.39	0.16
Russell-Jones et al. 2009 [49]	long	-0.24	-0.49	0.01	-1.89	0.059
D'Alessio et al. 2015 [36]	long	0.15	0.01	0.29	2.12	0.034
Gough et al. 2015 [43]	long	0.10	-0.04	0.24	1.37	0.17
Araki et al. 2015 [32]	long	-0.51	-0.63	-0.40	-7.66	< 0.0001
Giorgino et al. 2015 a [42]	long	-0.31	-0.51	-0.12	-3.13	0.0018
Giorgino et al. 2015 b [42]	long	-0.03	-0.22	0.16	-0.30	0.76
All long-acting GLP-1 RAs		**-0.17**	**-0.22**	**-0.12**	**-6.24**	**< 0.0001**
All GLP-1 RAs		**-0.12**	**-0.16**	**-0.07**	**-5.30**	**< 0.0001**



B GLP-1 RA versus rapid-acting insulin (basal insulin + OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Diamant et al. 2014 [39]	short	-0.03	-0.17	0.11	-0.42	0.67
Mathieu et al. 2014 [46]	long	0.32	0.13	0.51	3.37	0.0008
Rosenstock et al. 2014 [48]	long	-0.16	-0.33	0.01	-1.89	0.059
All GLP-1 RAs		**0.02**	**-0.09**	**0.11**	**0.34**	**0.73**



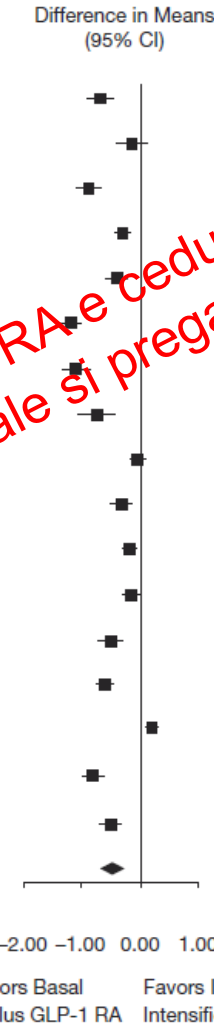
Δ Change in HbA_{1c} vs. baseline [%] (± 95 % confidence interval)

GLP-1RA added to basal insulin provides a better or not inferior glucose control vs. insulin intensification Meta-analysis

Wysham CH et al – Postgraduate Med 2017; 129: 436

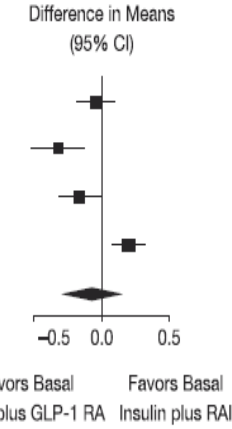
a

	Difference in Means	95% CI	p value
Buse et al.[13]	−0.69	−0.92 to −0.46	<0.0001
Li et al.[20]	−0.14	−0.41 to 0.13	0.30
Seino et al.[17]	−0.88	−1.11 to −0.65	<0.0001
Riddle et al.[15]	−0.30	−0.45 to −0.15	0.0001
Riddle et al.[14]	−0.40	−0.60 to −0.20	0.0001
Ahmann et al.[23]	−1.19	−1.39 to −0.99	<0.0001
Buse et al.[18]	−1.10	−1.35 to −0.85	<0.0001
de Wit et al.[19]	−0.74	−1.07 to −0.41	<0.0001
Diamant et al.[26]	−0.04	−0.18 to 0.10	0.59
Mathieu et al.[28]	−0.32	−0.52 to −0.12	0.002
Rosenstock et al.[16]	−0.17	−0.30 to −0.04	0.01
Rosenstock et al.[25]	−0.16	−0.32 to 0.00	0.05
Aroda et al.[43]	−0.50	−0.70 to −0.30	<0.0001
Lingvay et al.[42]	−0.59	−0.73 to −0.45	<0.0001
Rosenstock et al.[45]	0.20	0.09 to 0.31	0.0006
Seino et al.[17]	−0.81	−0.99 to −0.63	<0.0001
Yang et al.[44]	−0.51	−0.69 to −0.33	<0.0001
Overall	**−0.48**	**−0.67 to −0.30**	**<0.0001**



c

	Difference in Means	95% CI	p value
Diamant et al.[26]	−0.04	−0.18 to 0.10	0.59
Mathieu et al.[28]	−0.32	−0.52 to −0.12	0.002
Rosenstock et al.[25]	−0.16	−0.32 to 0.00	0.05
Rosenstock et al.[45]	0.20	0.9 to 0.31	0.0006
Overall	**−0.07**	**−0.29 to 0.15**	**0.5**

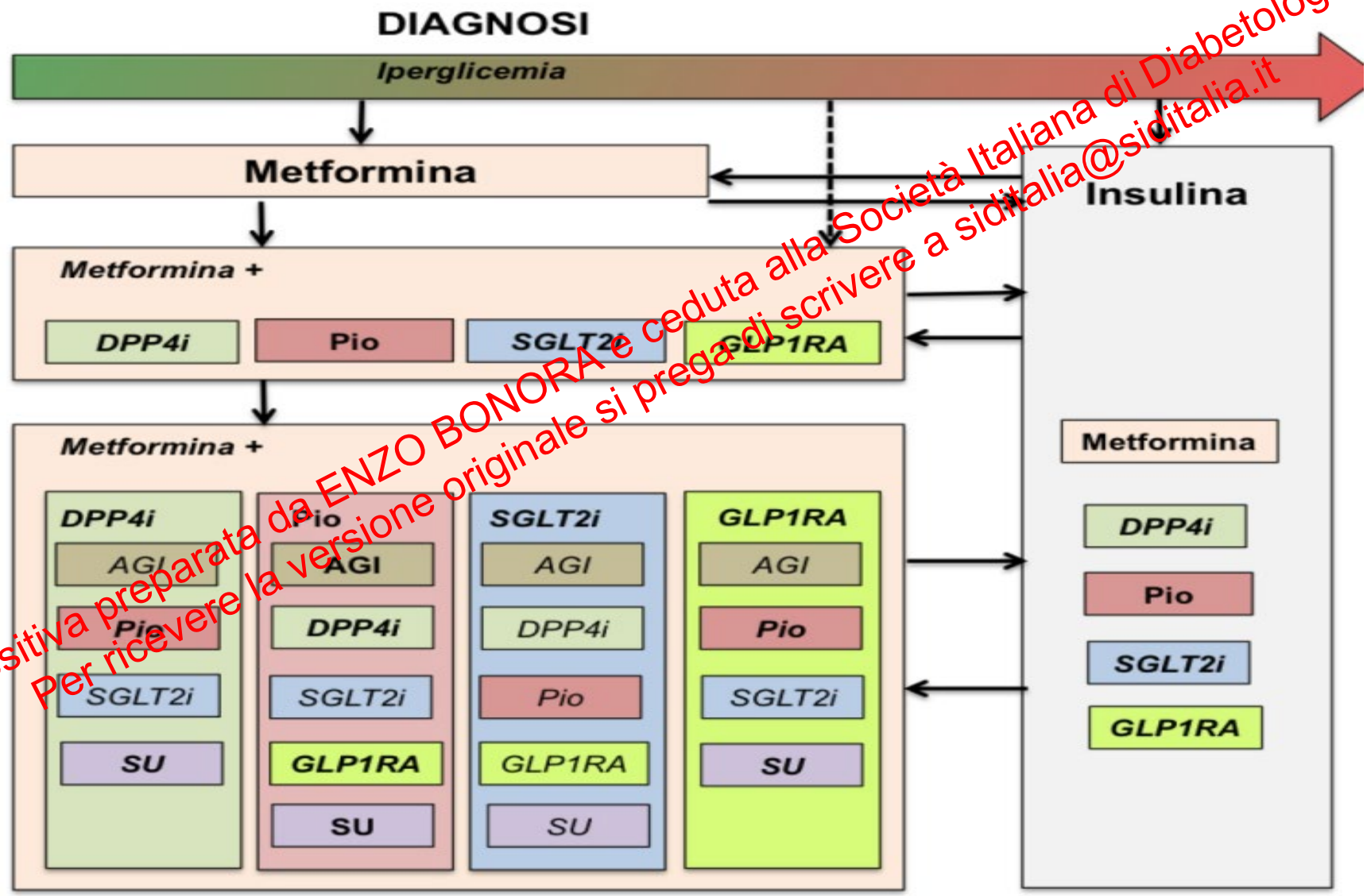


Target terapeutici nel diabete ed effetti dei GLP-1 RA

Target terapeutico	Effetti favorevoli dei GLP-1 RA
Elevata HbA1c	Sì
Iperglicemia a digiuno	Sì
Iperglicemia post-prandiale	Sì
Prevenzione dell'ipoglicemia	Sì
Eccesso ponderale	Sì
Ipertensione	Sì
Dislipidemia aterogena	Sì
Trombofilia	Sì
Cronica media infiammazione	Sì
Stress ossidativo	Sì

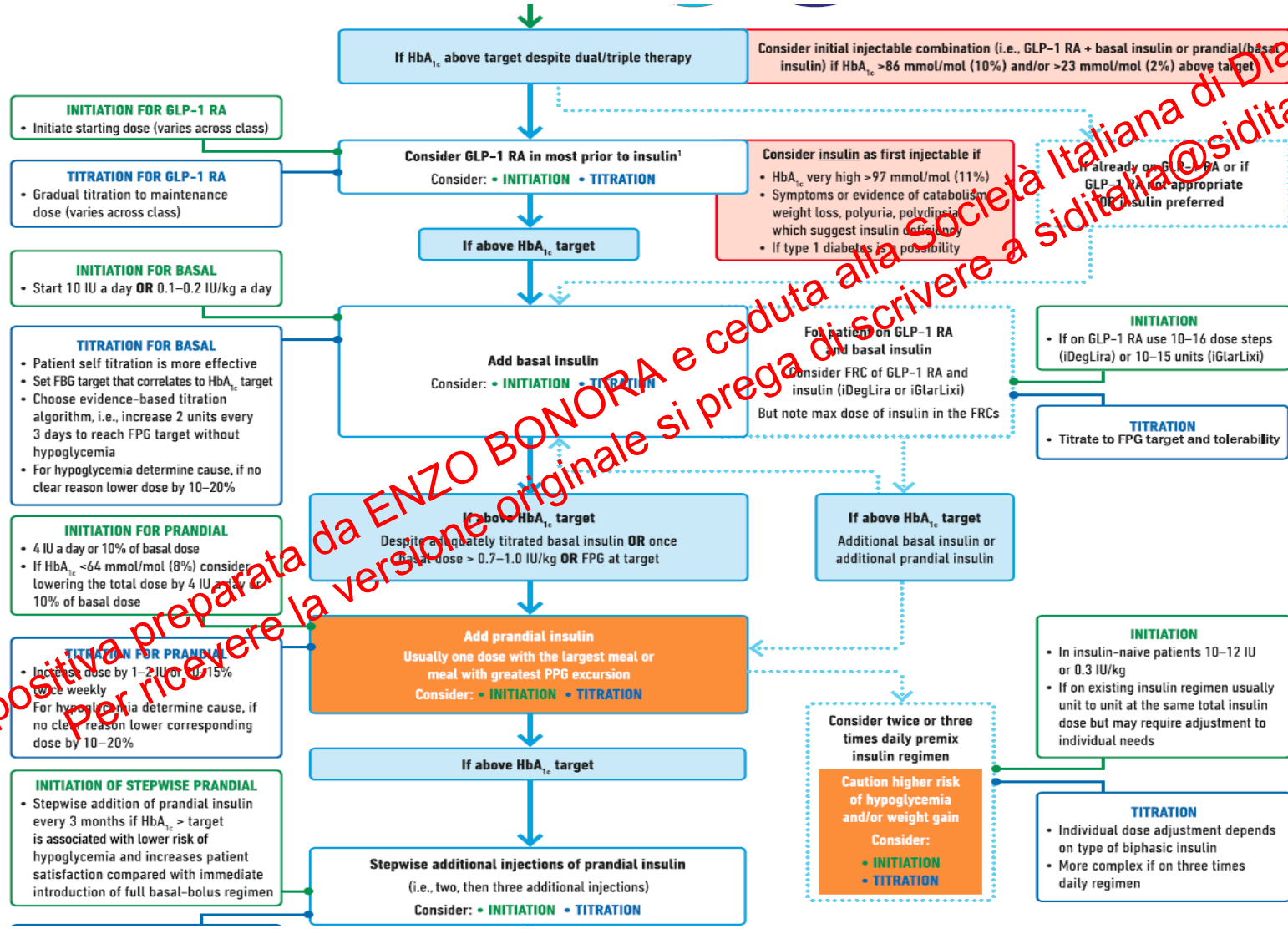
Sono indicati nella gran parte dei pazienti con diabete tipo 2

Standard Italiani per la Cura del Diabete Mellito - 2018



Algoritmo terapeutico nel diabete tipo 2: se si deve usare un farmaco iniettabile

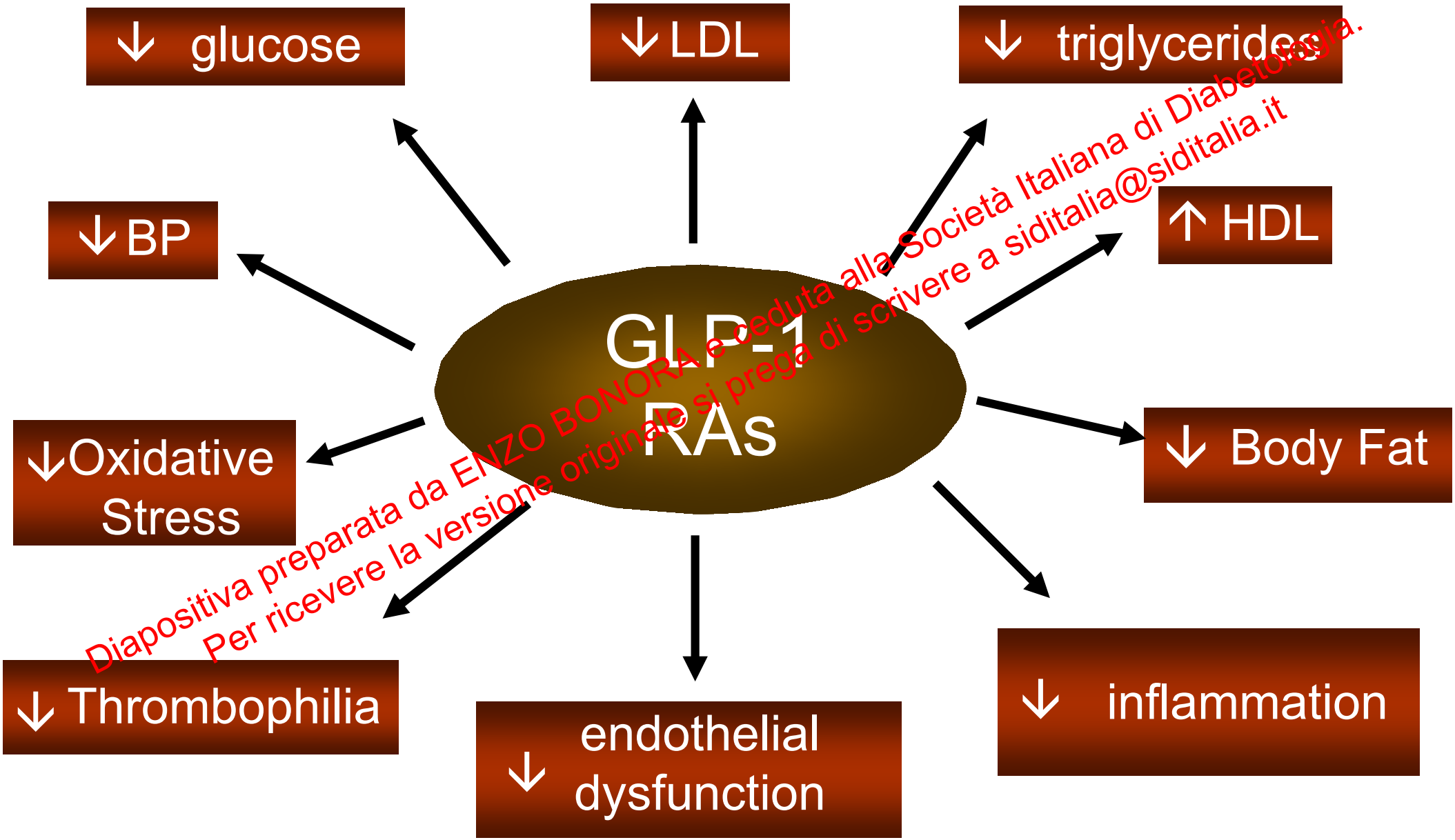
Consensus ADA-EASD 2018



Iniezione: GLP-1 RA contro terapia insulinica

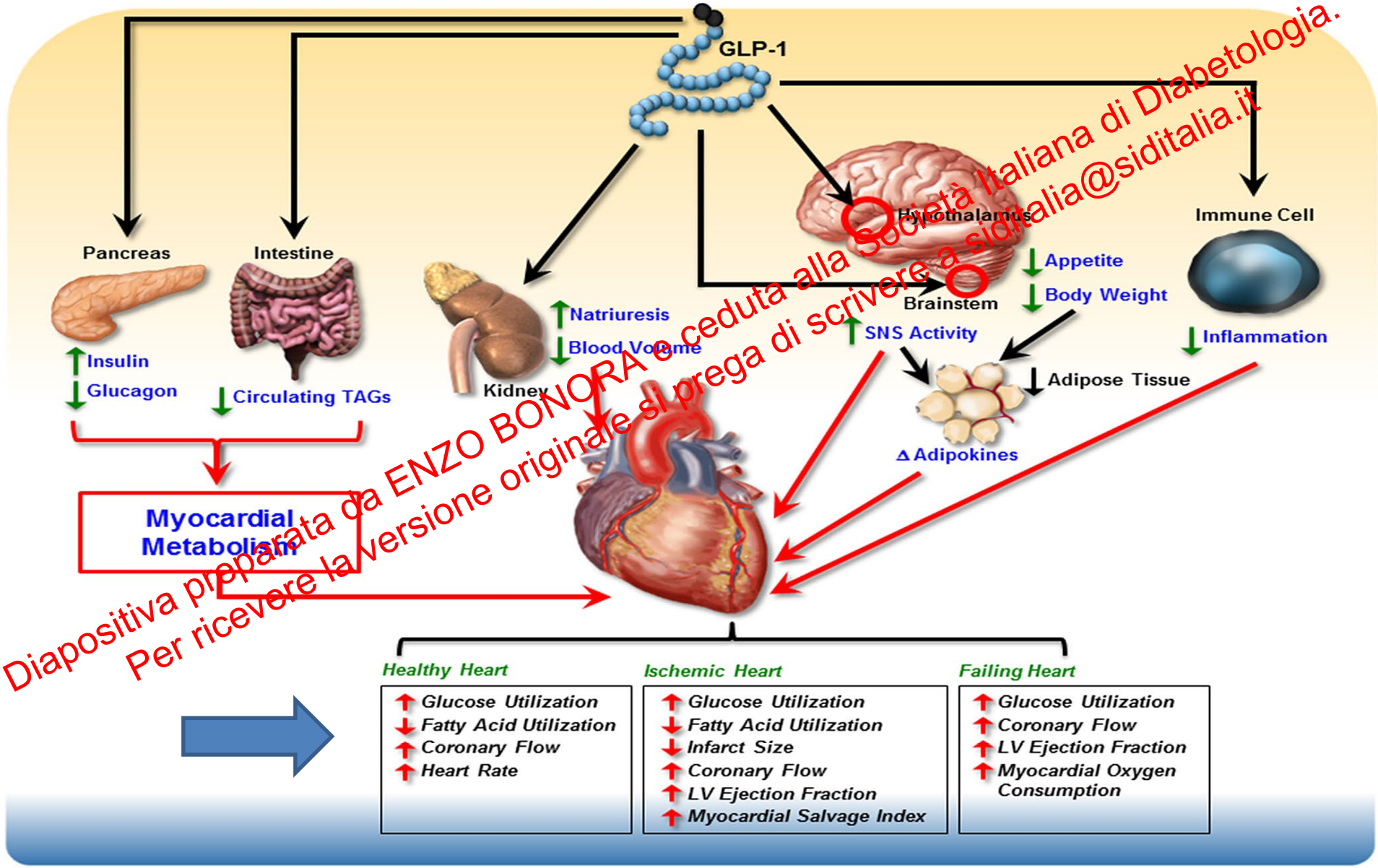
	GLP-1 RA	Insulina
Iniezioni settimanali	1 (formulazione settimanale) 7 (formulazione giornaliera)	7 (solo basale) 28 (MDI)
Iniezioni per anno	52 o 365	Possono essere fino a 1460
Titolazione dose	No o limitata a 2-3 step	Si
Flessibilità nel momento della iniezione	Sì (soprattutto nelle long acting)	No (solo con le basali lunghe)
Relazione iniezione/pasto	No (nelle long acting)	Sì con MDI
Automonitoraggio glicemico	Sporadico	Quotidiano (più volte)
Possibili lipodistrofie	No	Sì
Rischio ipoglicemia	No (tranne che quando associati a SU o insulina)	Elevato

The several beneficial effects of GLP-1 RAs



Several favorable cardiovascular effects of GLP-1RAs

Ussher JR and Drucker DJ - Circulation Research 2014; 114:1788



CVD (MACE) reduction in RCTs exploring GLP-1 RA safety or benefit in T2DM

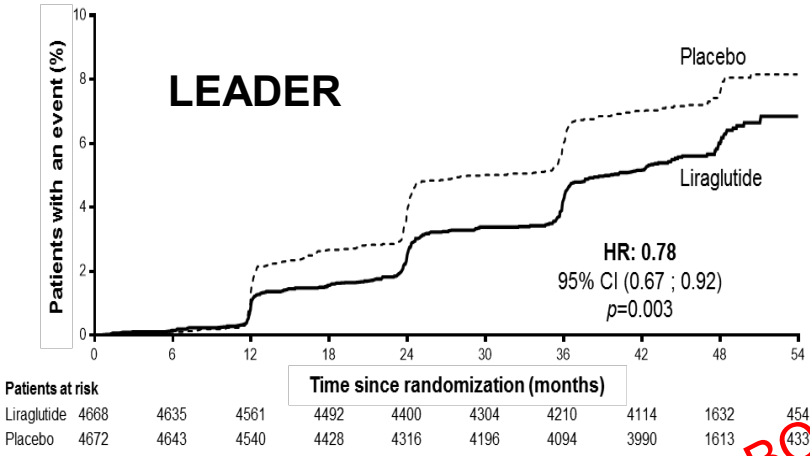
ELIXA, NEJM 2015 - LEADER, NEJM 2016 - SUSTAIN-6, NEJM 2016

EXSCEL, NEJM 2017 - HARMONY, Lancet 2018 – REWIND, Lancet 2019

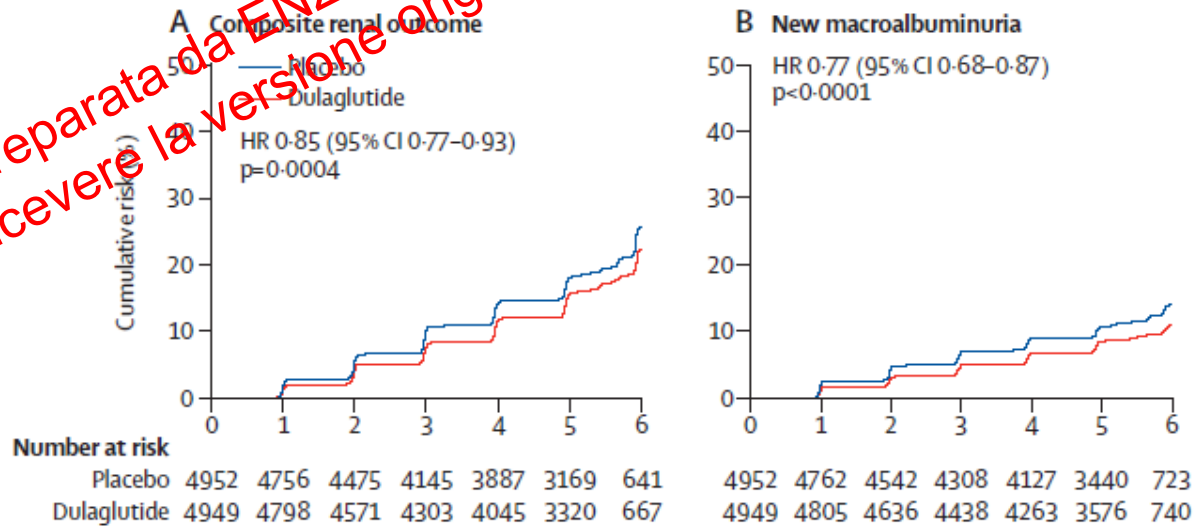
	Mean HbA1c difference (%)	HR	95% CI	P values
ELIXA (Lixisenatide vs. Placebo)	0.2	1.02	0.89-1.17	NS
LEADER (Liraglutide vs. Placebo)	0.3	0.87	0.78-0.97	**0.01**
SUSTAIN 6 (Semaglutide vs. Placebo)	0.8	0.74	0.58-0.95	**0.001**
EXSCEL (Exenatide LAR vs. Placebo)	0.4	0.91	0.83-1.00	0.06
HARMONY (Albiglutide vs. Placebo)	0.5	0.78	0.68-0.90	**0.006**
REWIND (Dulaglutide vs. Placebo	0.6	0.88	0.79-0.99	**0.026**

Not only benefits for the heart but also for the kidney with GLP-1 RA

Incidence of macroalbuminuria, doubling of serum creatinine*, ESRD, renal death



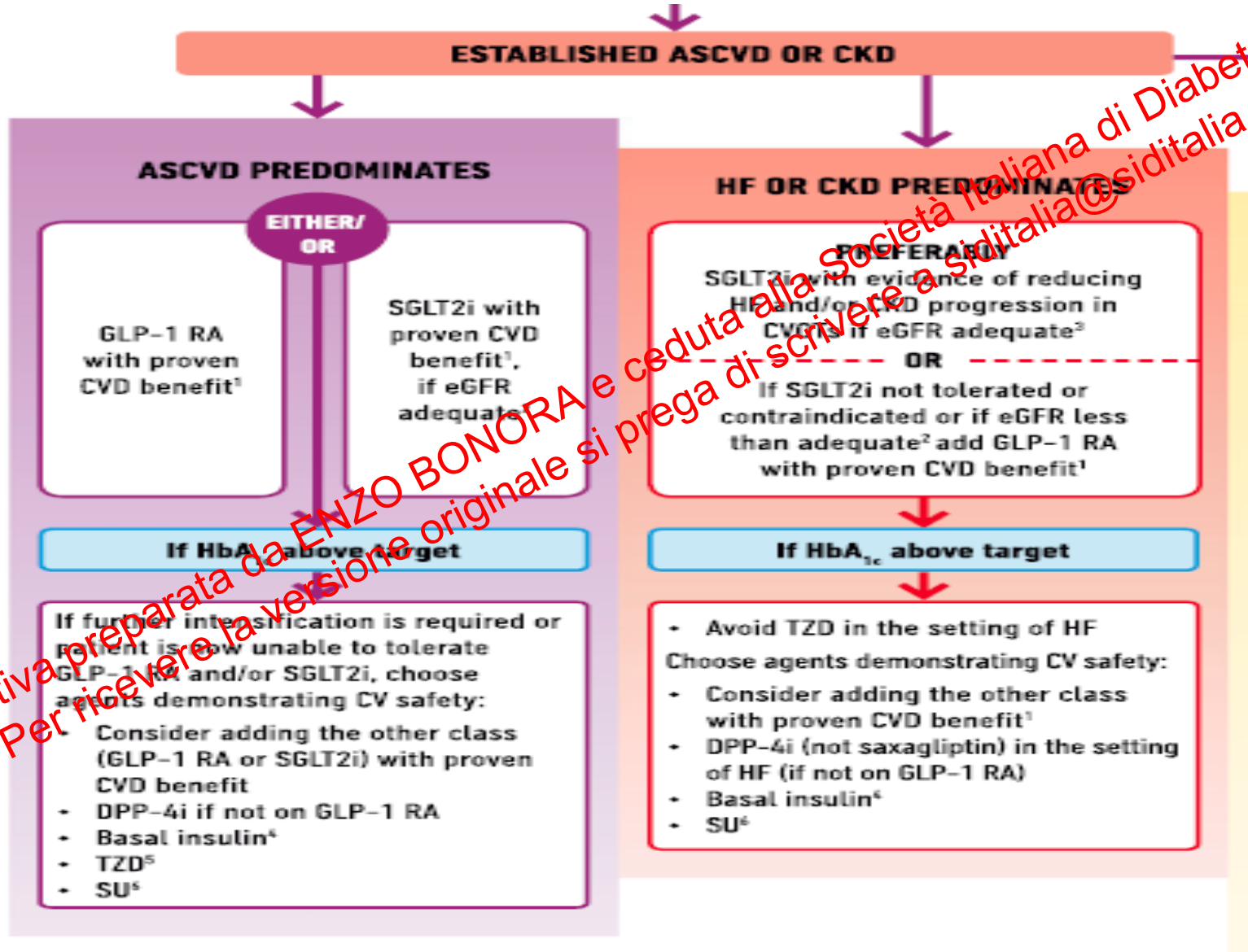
SUSTAIN 6



REWIND

Algoritmo terapeutico nel diabete tipo 2: CVD/CKD

Consensus ADA-EASD 2018



Dogma

Principio che si accoglie per vero e per giusto, senza discussione

In caso di malattia cardiovascolare, salvo controindicazioni, mancanza di indicazioni, intolleranza o effetti avversi accertati si devono usare anche SGLT-2i e/o rGLP-1RA

E probabilmente il concetto va esteso anche al paziente senza CVD accertata

A prescindere dal fatto che il paziente sia in terapia insulinica (cambio terapia!)

Virtù degli analoghi GLP-1 in diabetologia

- Efficaci nel ridurre la glicemia superiore a tutti i farmaci orali
- Efficacia confermata più a lungo rispetto ad altri farmaci antidiabete
- Efficaci nel ridurre la glicemia almeno pari, se non superiore all'insulina (alternativa alla basale, alternativa alla prandiale)
- Indicati in combinazione con MET, SU, PIO, SGLT-2, INS
- Disponibili anche in combinazioni fisse con insulina
- Esenti da un rischio diretto di ipoglicemia
- Efficaci nel ridurre il peso corporeo
- Benefici extra-glicemici (pressione, lipidi, infiammazione, ecc.)
- Prevengono gli eventi cardiovascolari maggiori
- Migliorano numerosi outcome renali (prevenzione della nefropatia)
- Possibilità di utilizzo anche con GFR nettamente ridotto (fino a 15 ml/min)
- Buona tollerabilità (soprattutto con i preparati a più lunga durata)
- Convenienti per il paziente (ancora di più con i settimanali o gli orali)

Tutto bellissimo ma sono poco utilizzati in Italia

Questa però è un'altra storia

che racconterò nel secondo incontro del corso

(ottobre 2019)