Il sistema incretinico:

l'evoluzione delle conoscenze negli ultimi 10 anni

AGOSTINO CONSOLI
DMSI & CeSI-MeT
Università d'Annunzio – CHIETI

Il Prof. Agostino Consoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbot, Astra Zeneca, Boheringer Ingelhaim , Eli Lilly, Merck Sharp & Dhome, Menarini Diagnostici, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda
(Speaker)

Astra Zeneca, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici, Merck Sharp & Dhome, Novo-Nordisk, Sanofi-Aventis.
(Advisory Board)

Astra Zeneca , Novo-Nordisk
(Consultant)

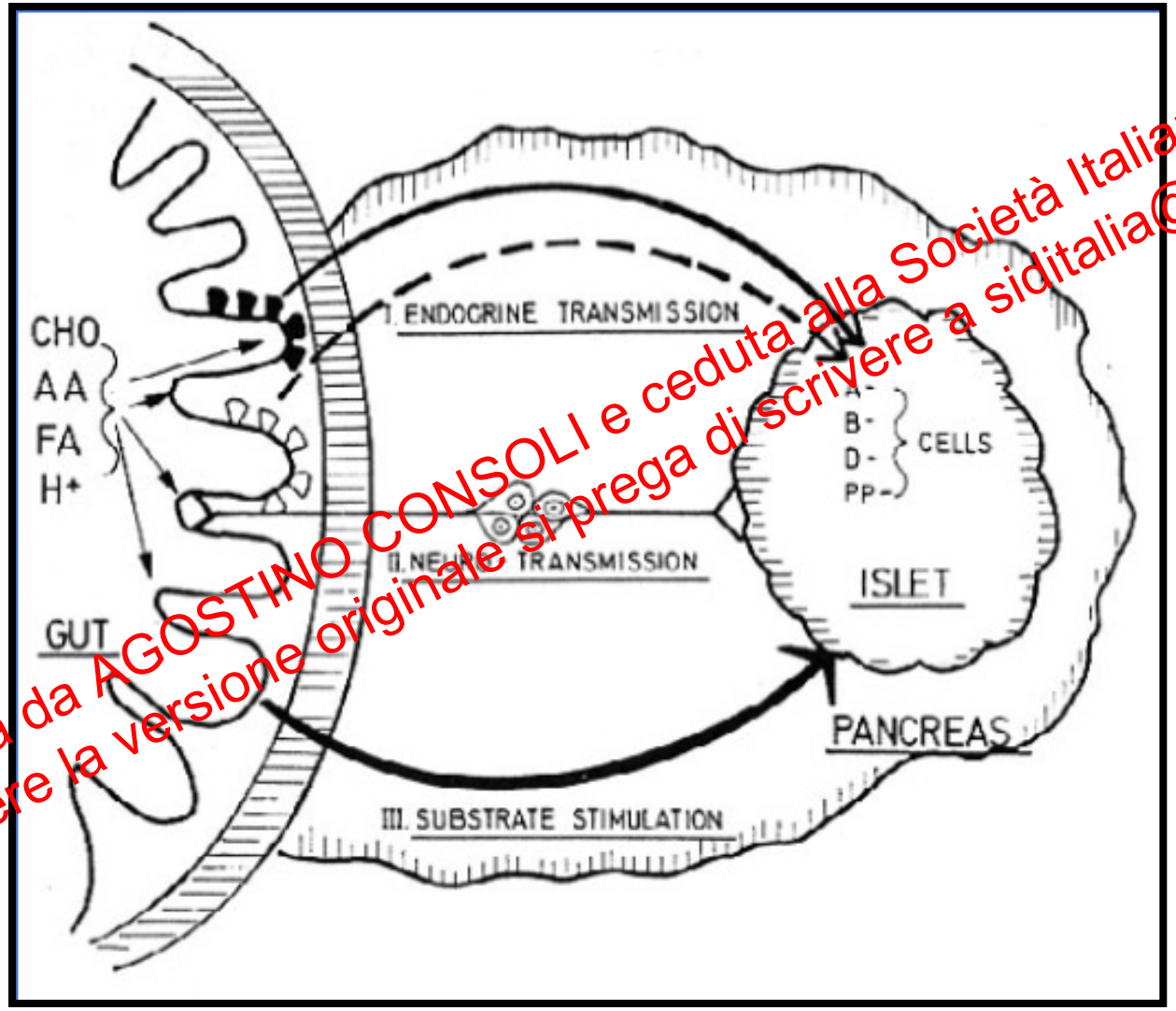
Eli Lilly, Novo-Nordisk
(Research Grant)

Ringrazio sinceramente la SID per lo straordinario contributo alla mia formazione culturale, scientifica e clinica.

Opinioni e giudizi espressi durante questa presentazione sono di mia esclusiva responsabilità e non possono essere imputati alla SID e/o ad alcuno dei suoi "officers".

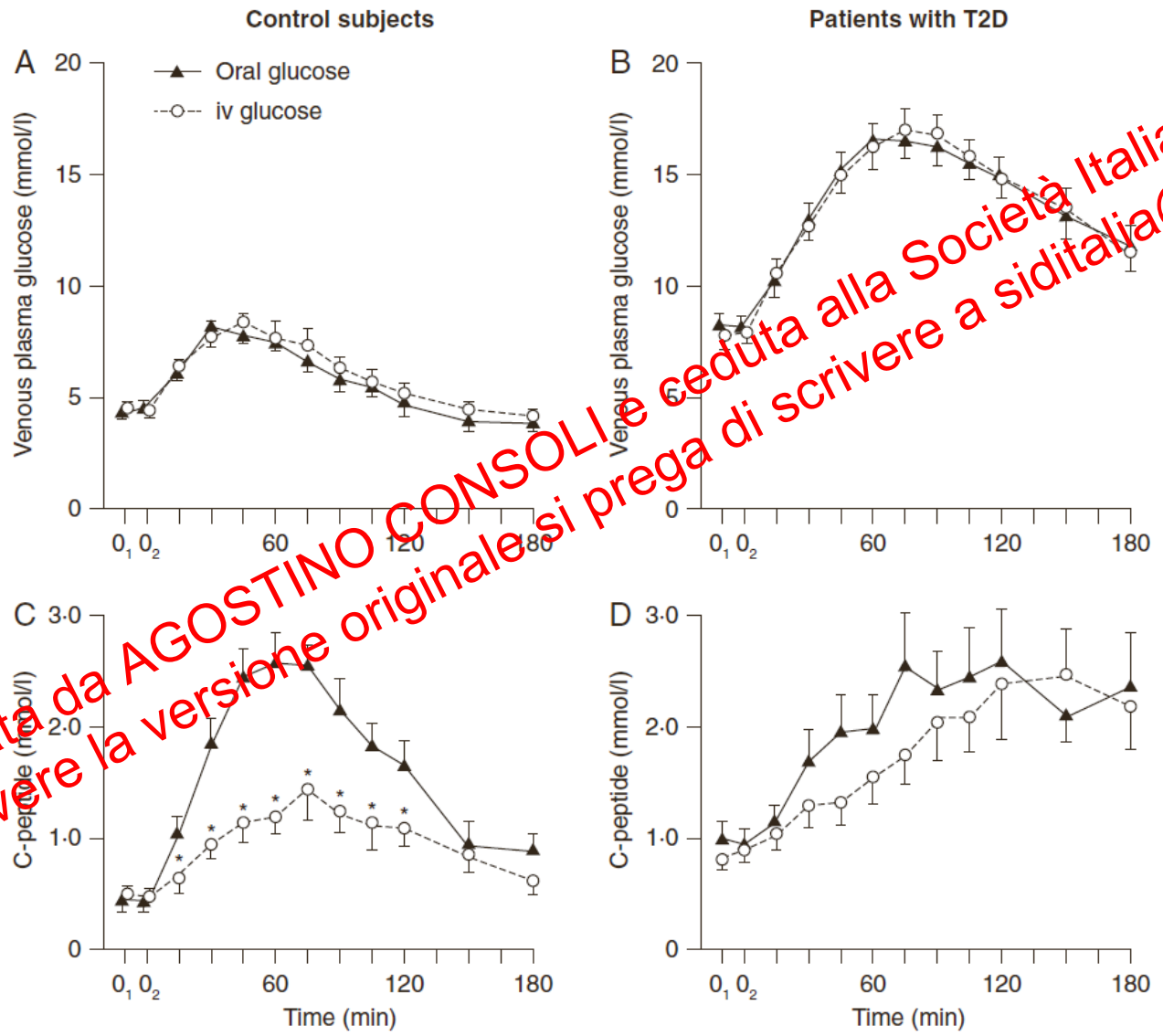
SID
Società Italiana
di Diabetologia

Entero-Insular Axis

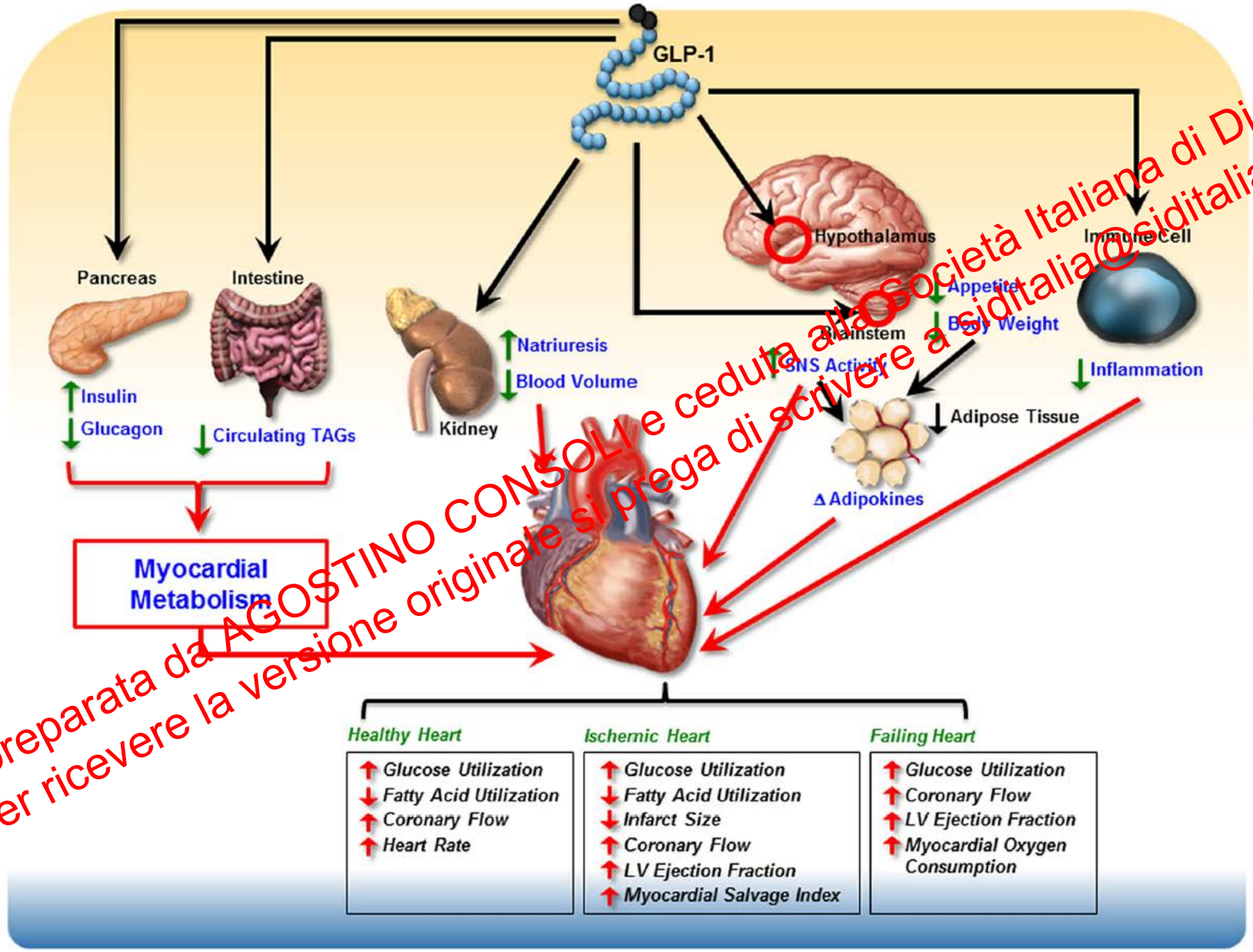


Creutzfeld, Diabetologia 1979

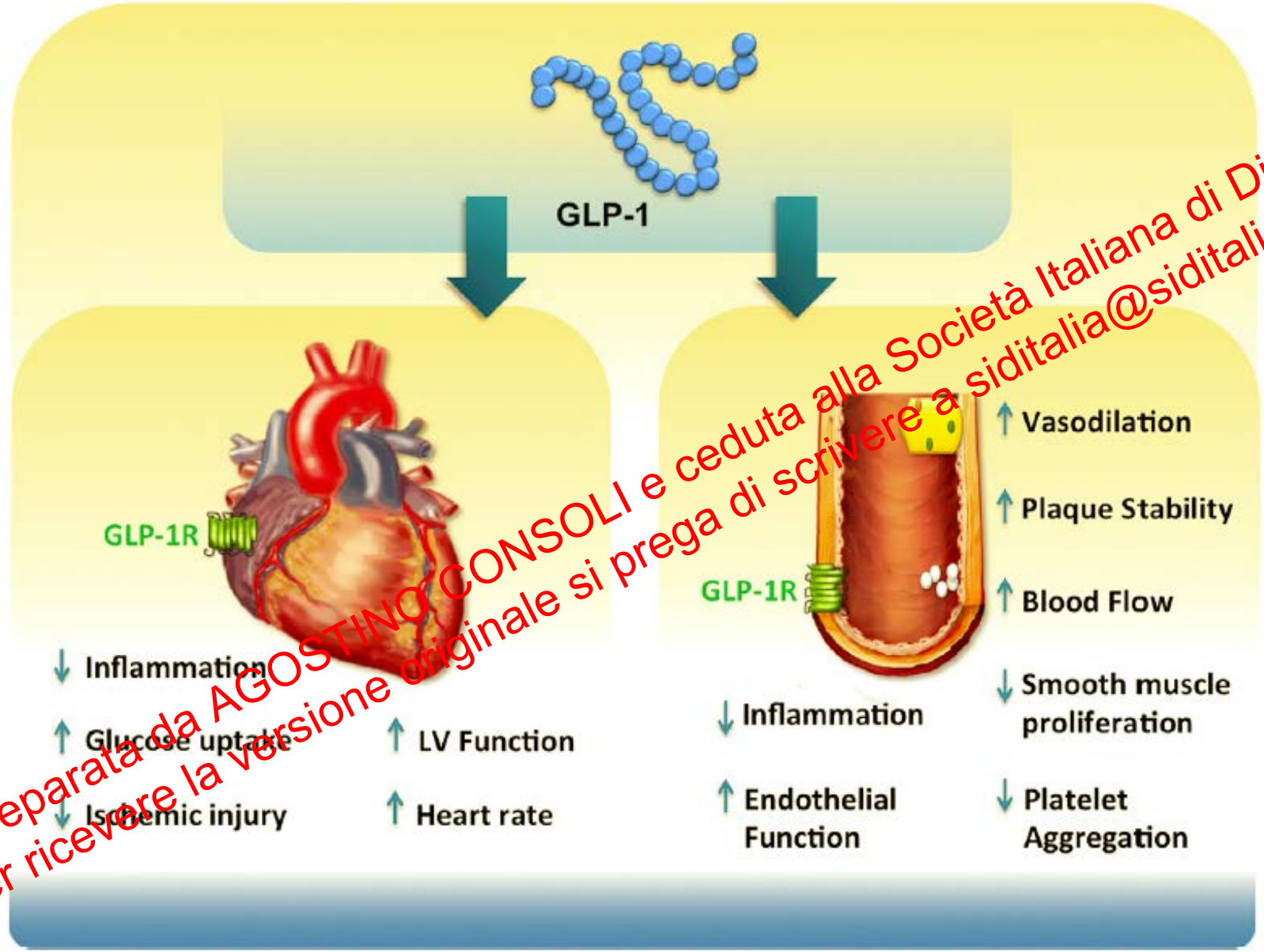
The incretin effect in control subjects and patients with T2DM



Nauck M. et al, Diabetologia 1986



Ussher & Drucker, *Circ Res*. 2014;114:1788



Ussher & Drucker, *Cell Metab* 2016;24:15

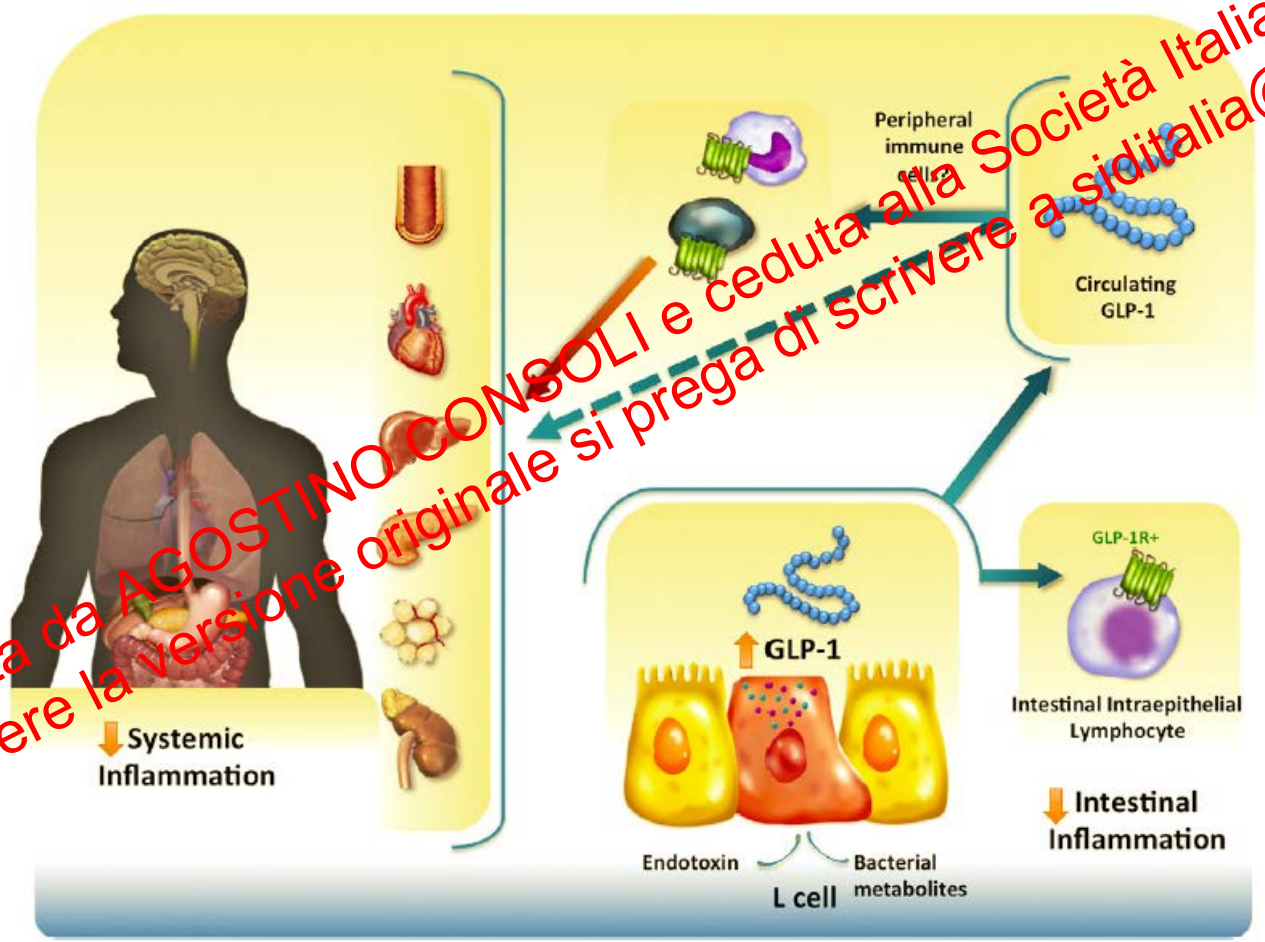
«Emerging» actions of GLP-1 on

- Inflammation
- Cardiovascular System
- Body Composition
- Beta-cell function

«Emerging» actions of GLP-1 on

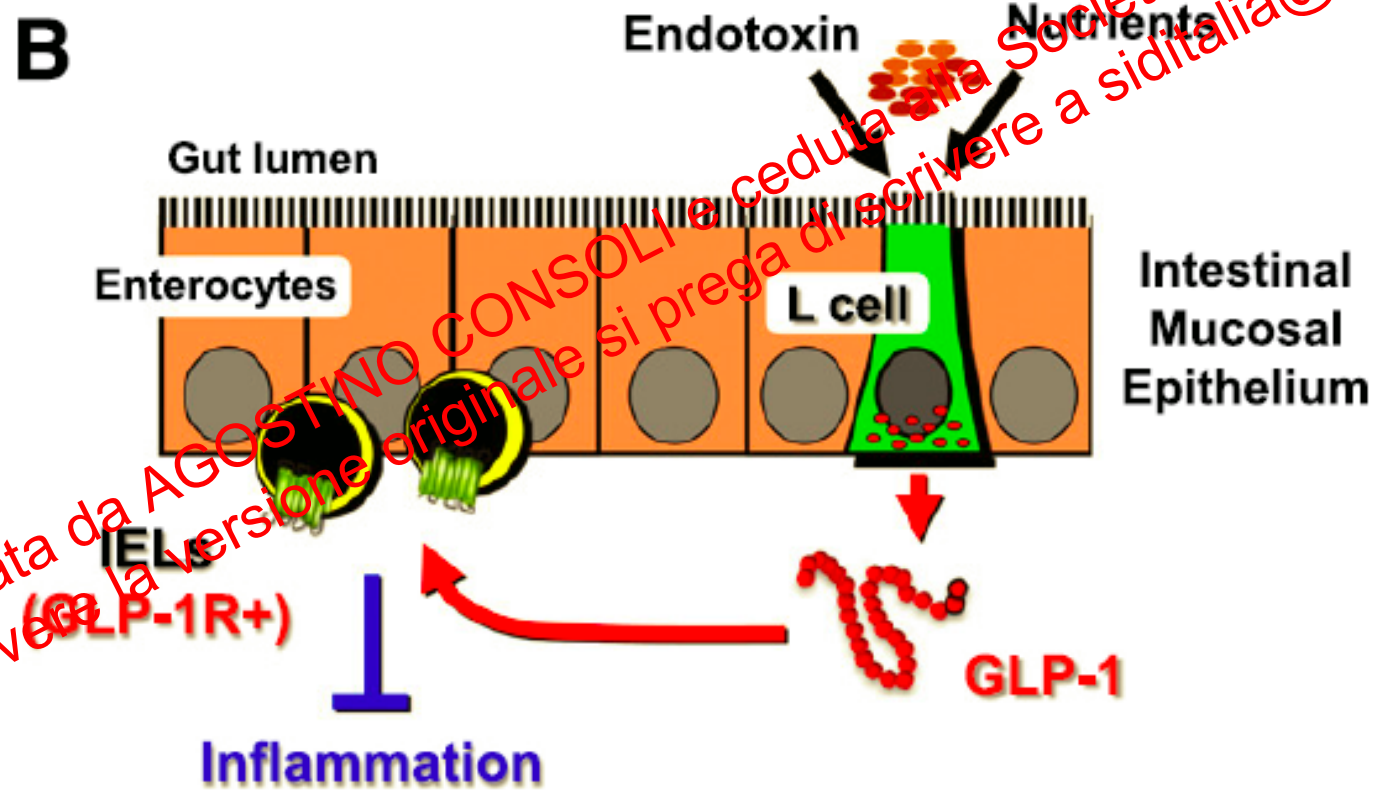
- **Inflammation**
- Cardiovascular System
- Body Composition
- Beta-cell function

GLP-1 modulates systemic and local inflammation



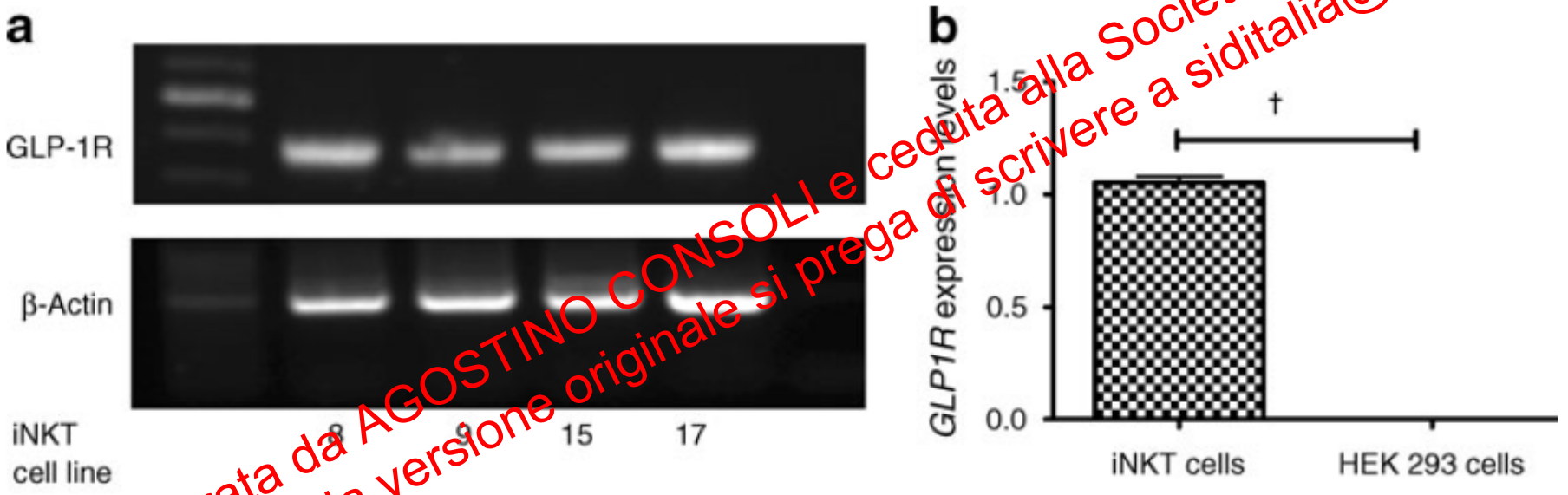
Drucker D., Cell Metabolism 2016

GLP-1 locally modulates enterocytes inflammation



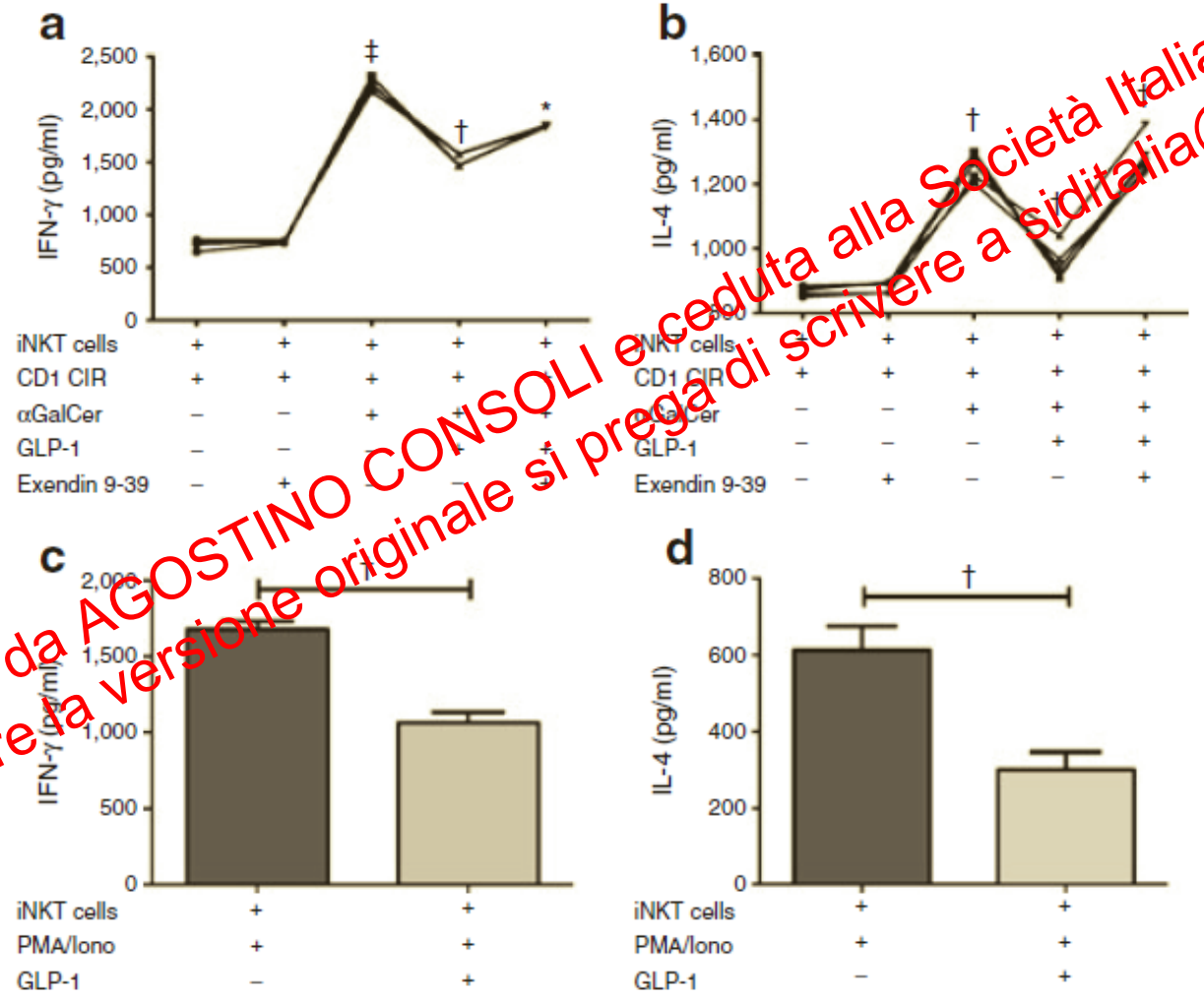
Yusta B., et al., Diabetes 2015

Natural Killer Cells Express GLP-1 receptor



Hogan AL et al, Diabetologia 2011

GLP-1 decreases stimulated cytokines secretion capacity in Natural Killer Cells

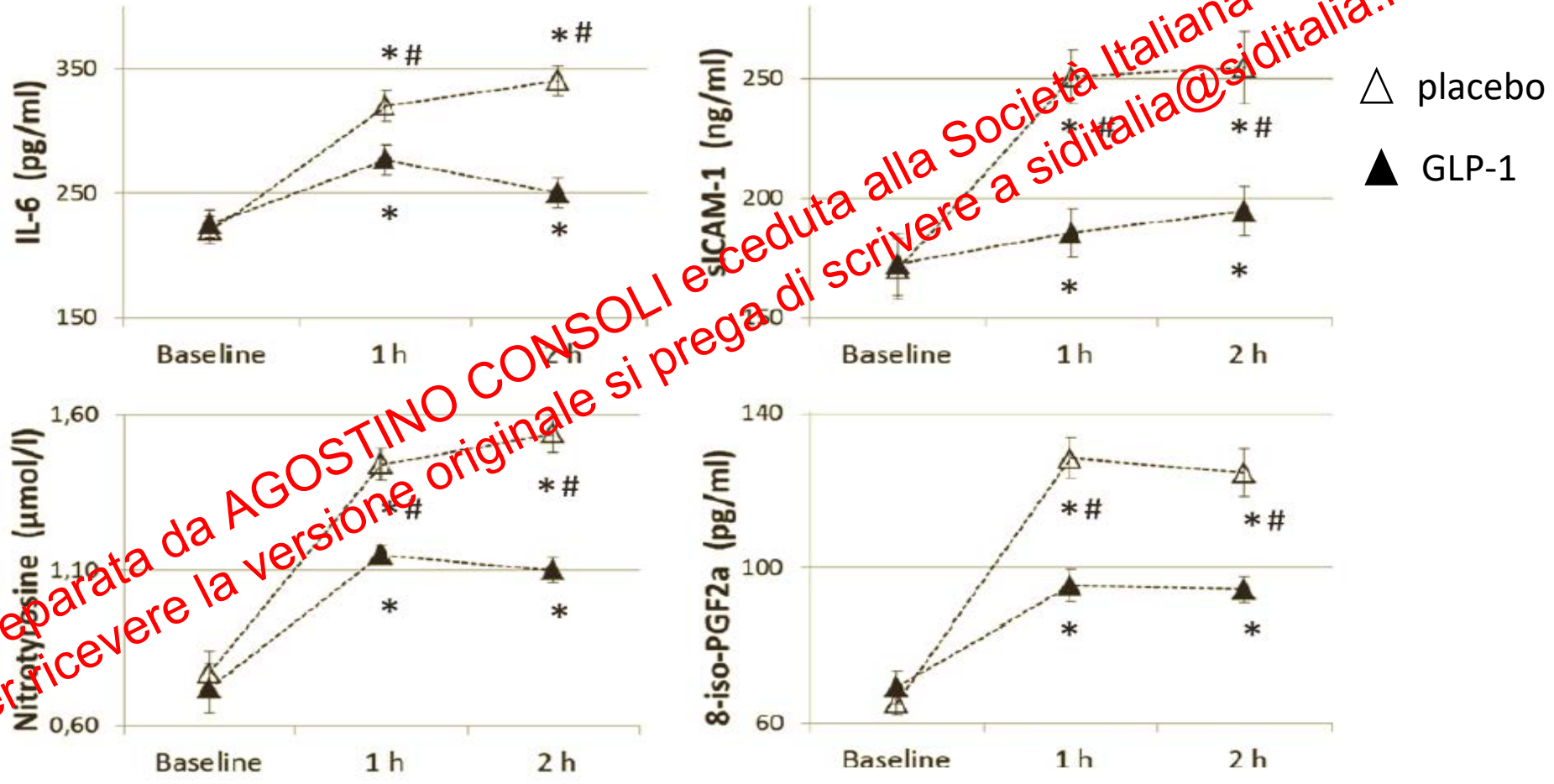


Hogan AL et al, Diabetologia 2011

NFkB nuclear translocation and TNF-alfa levels in hearts of High Fat Diet fed mice exposed to placebo or liraglutide for 7 days

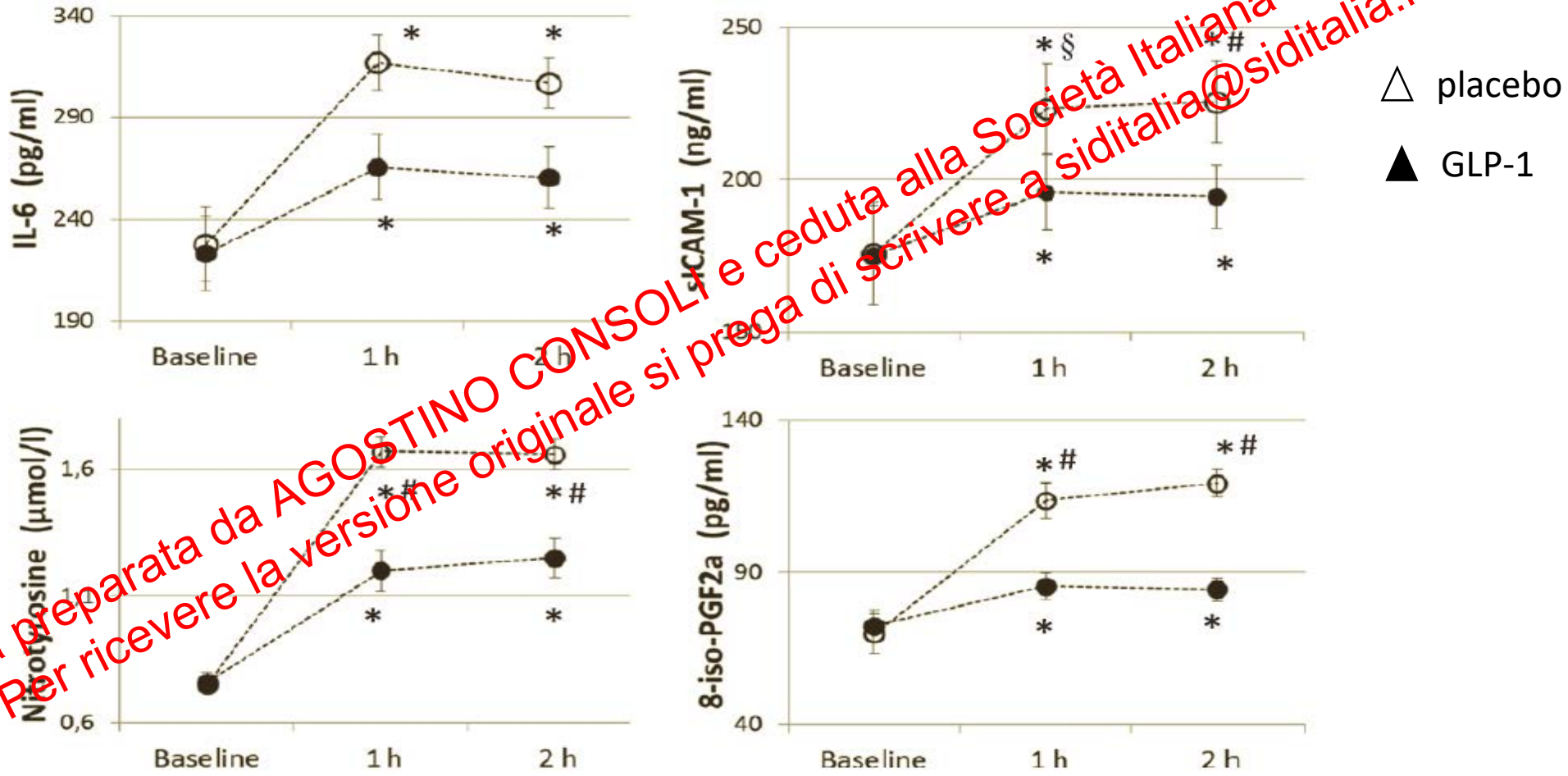
Noyan.Ashraf MH. et al., Circulation 2013

Native GLP-1 infusion mitigates hypoglicaemia induced inflammatory and oxidative stress in T1DM subjects



Ceriello A. et al., Diabetes Care 2013

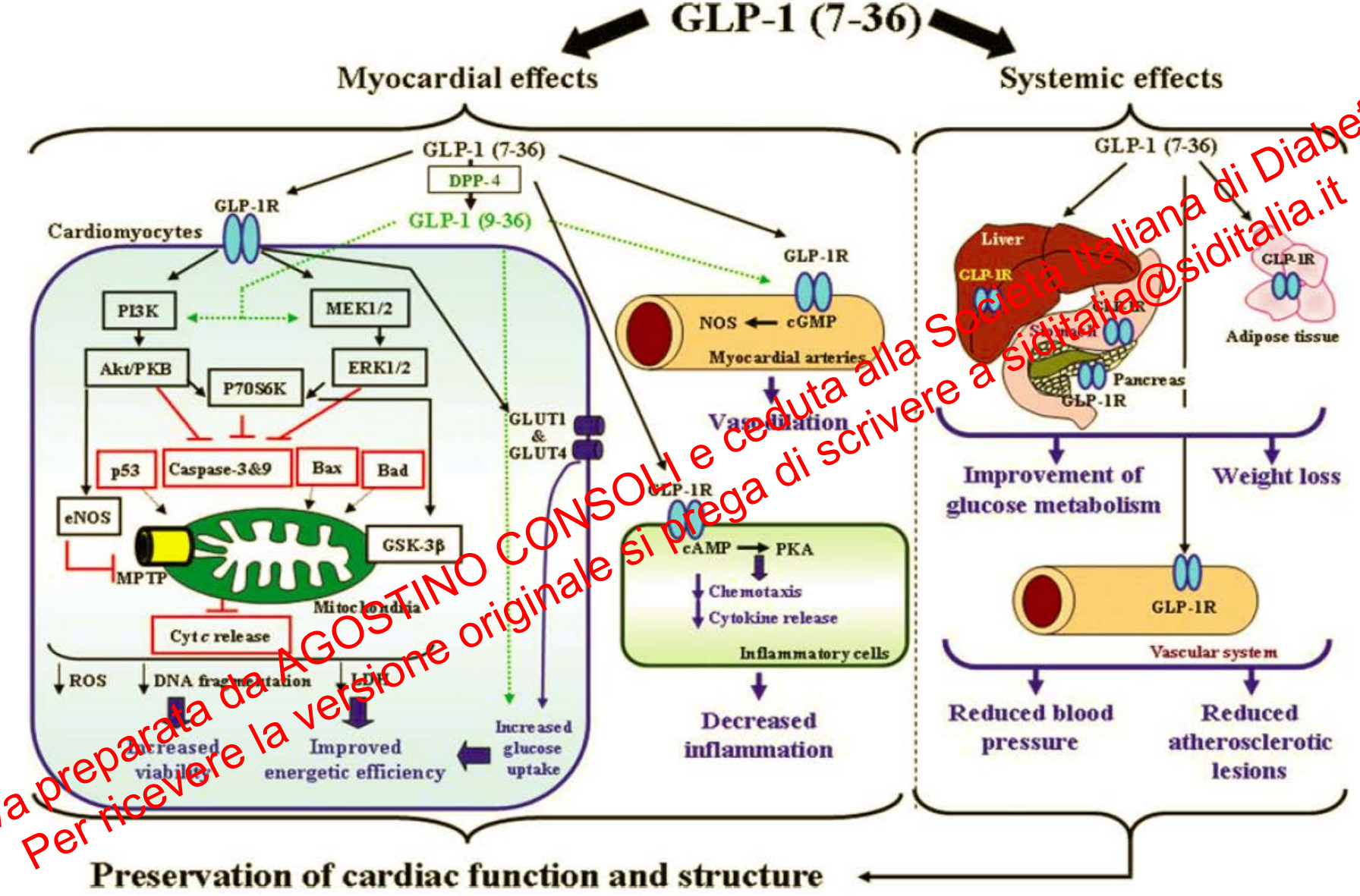
Native GLP-1 infusion mitigates hyperglicaemia induced inflammatory and oxidative stress in T1DM subjects



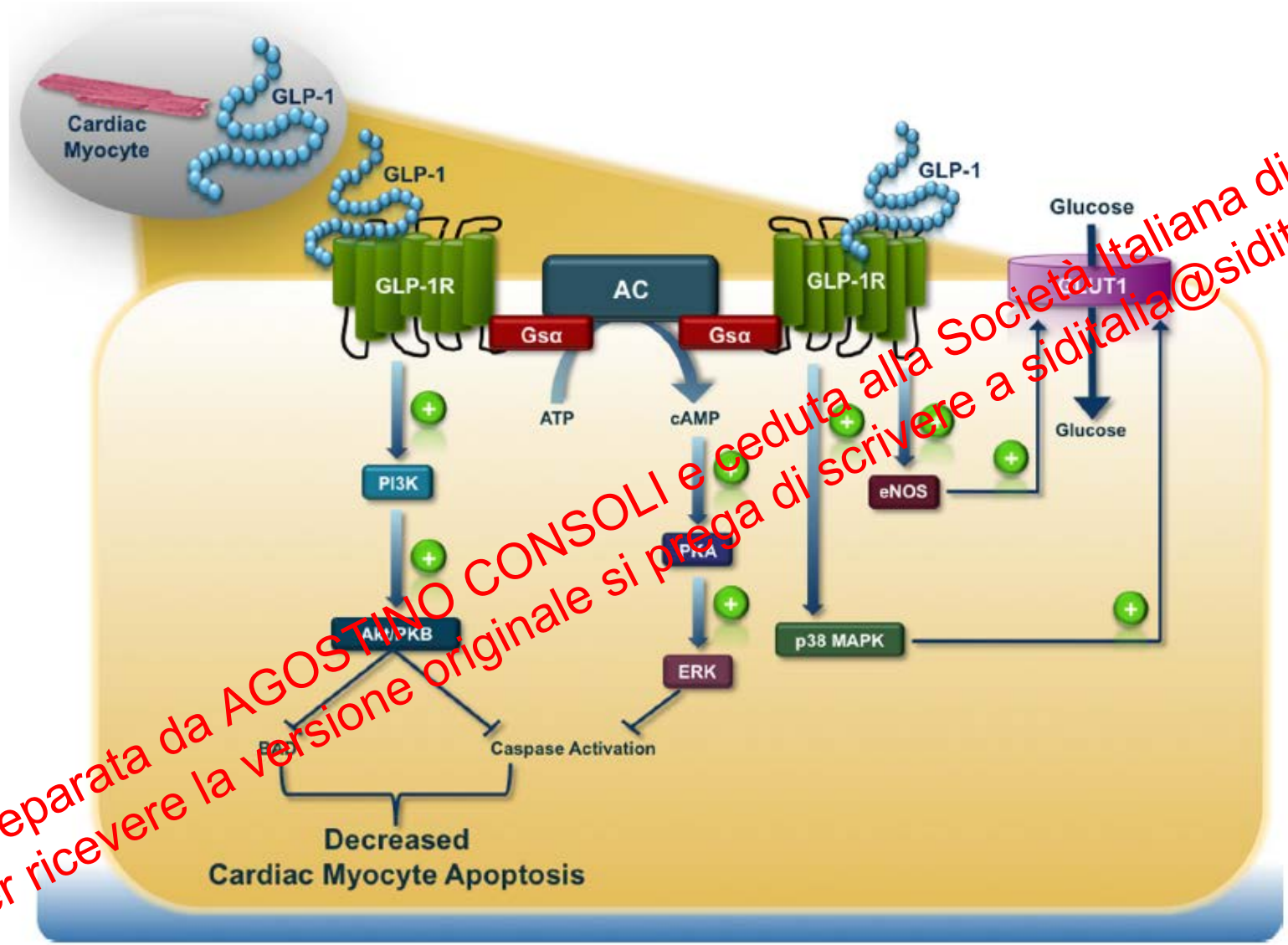
Ceriello A. et al., Diabetes Care 2013

«Emerging» actions of GLP-1 on

- Inflammation
- **Cardiovascular System**
- Central Nervous System
- Body Composition
- Beta-cell function



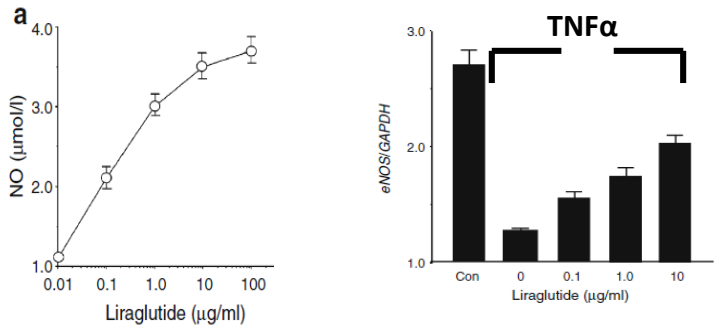
Ravassa S, et al. *Cardiovasc Res* 2012; 94:316



Ussher & Drucker, *End Rev* 2012;33:187

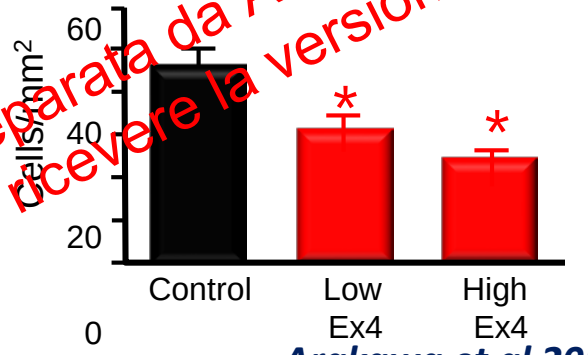
GLP1 Agonists and Endothelial Function

Liraglutide increases Nitric Oxide Levels



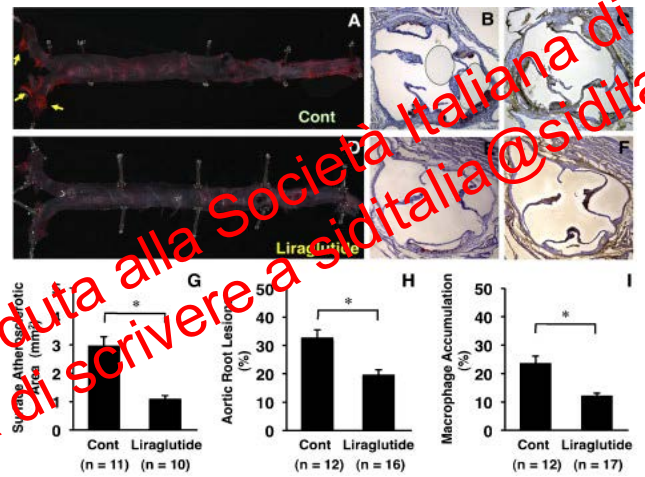
Hattori et al. 2010

Exenatide reduces monocyte adhesion to endothelial cells

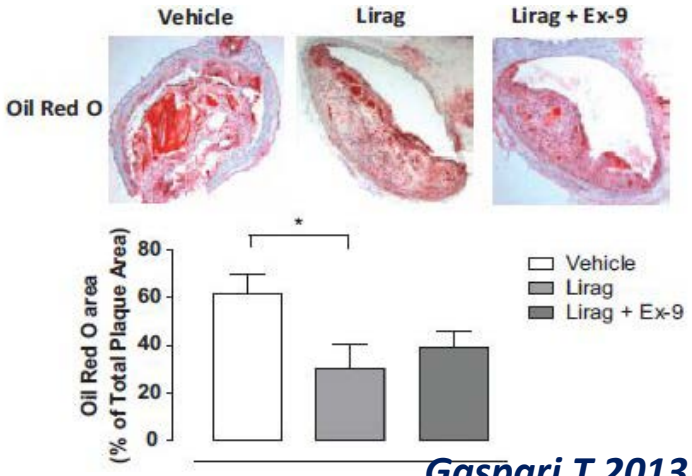


Arakawa et al 2010

Liraglutide reduces the extent of atherosclerotic lesion

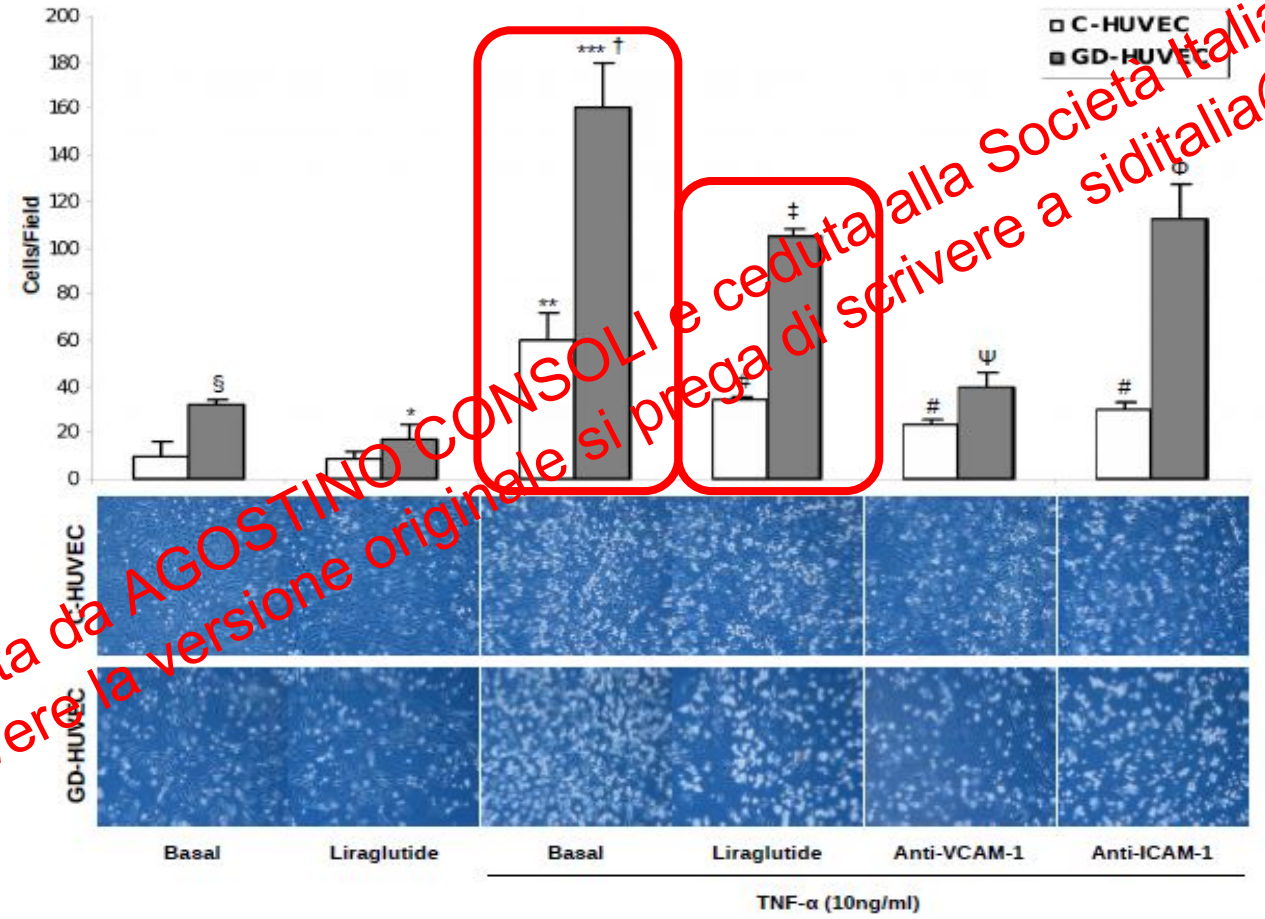


Tashiro Y 2013



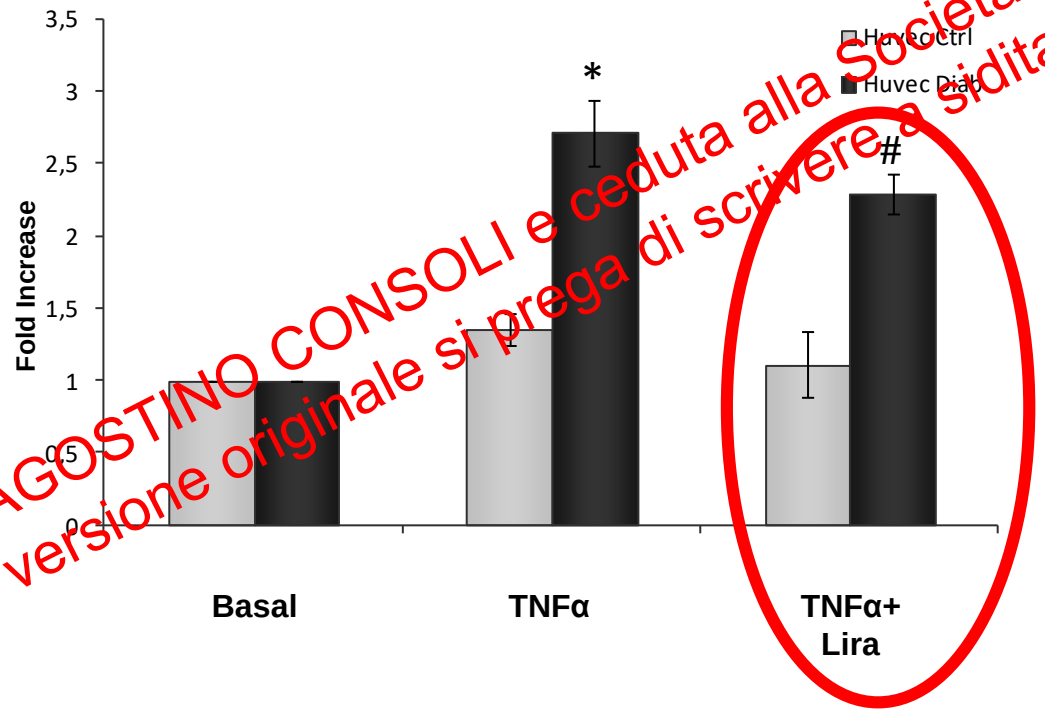
Gaspari T 2013

Liraglutide reduces monocyte adhesion to endothelial cells



Di Tomo et al., Diabetes Metab Res Rev 2017

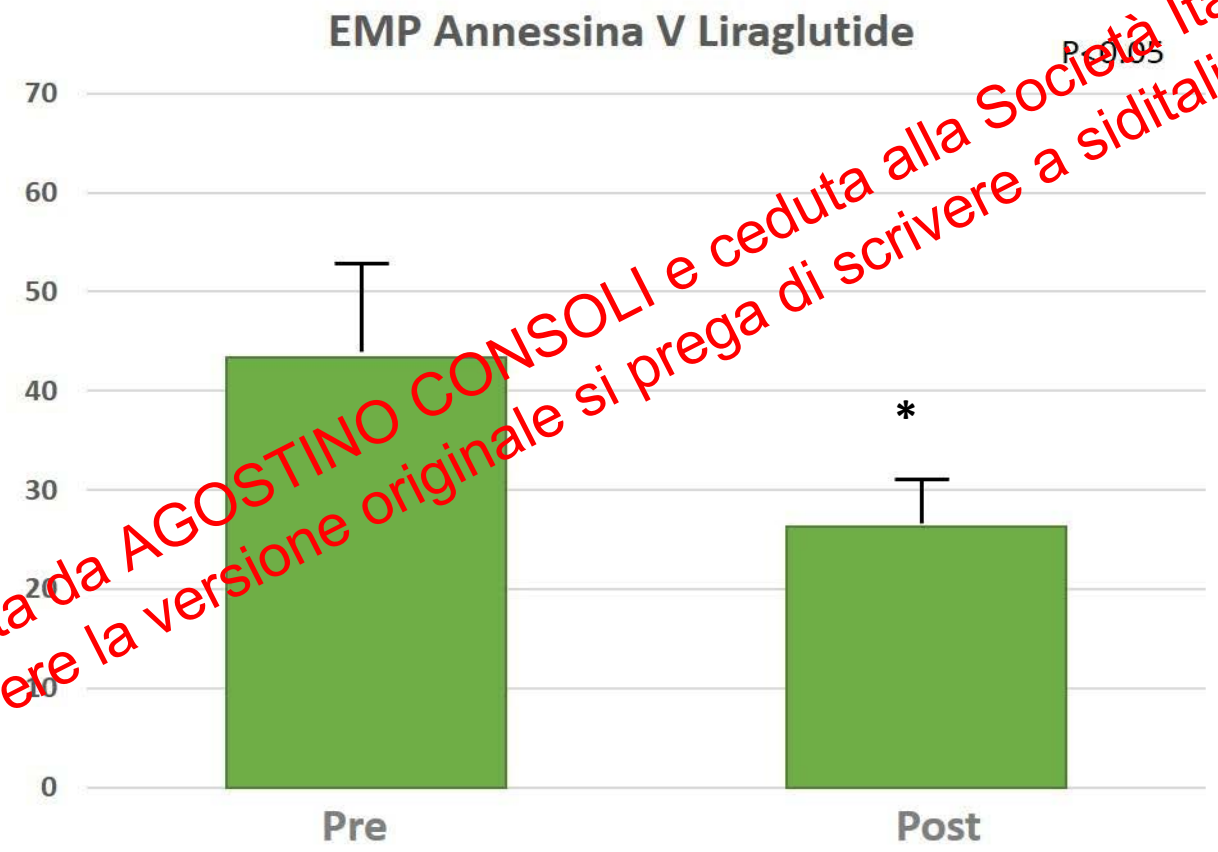
Liraglutide effects on basal and TNF-α induced Microparticles release from C- and D-HUVEC



- P > 0.05 vs control cells;
- # P< 0.05 vs diabetic untreated cells.

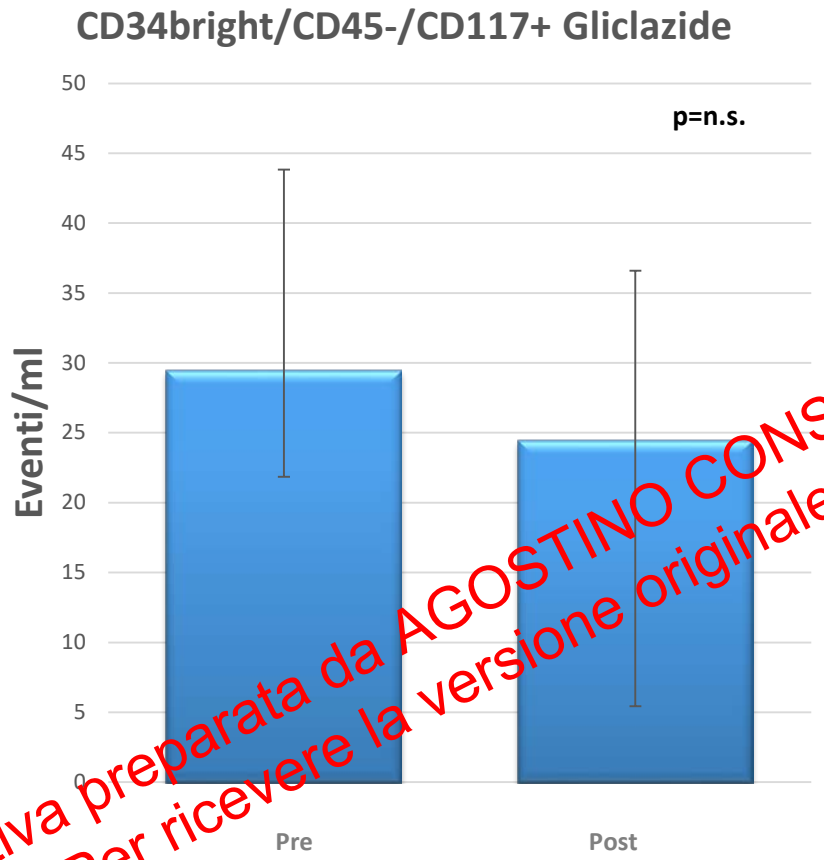
Di Tomo et al., Diabetes Metab Res Rev 2017

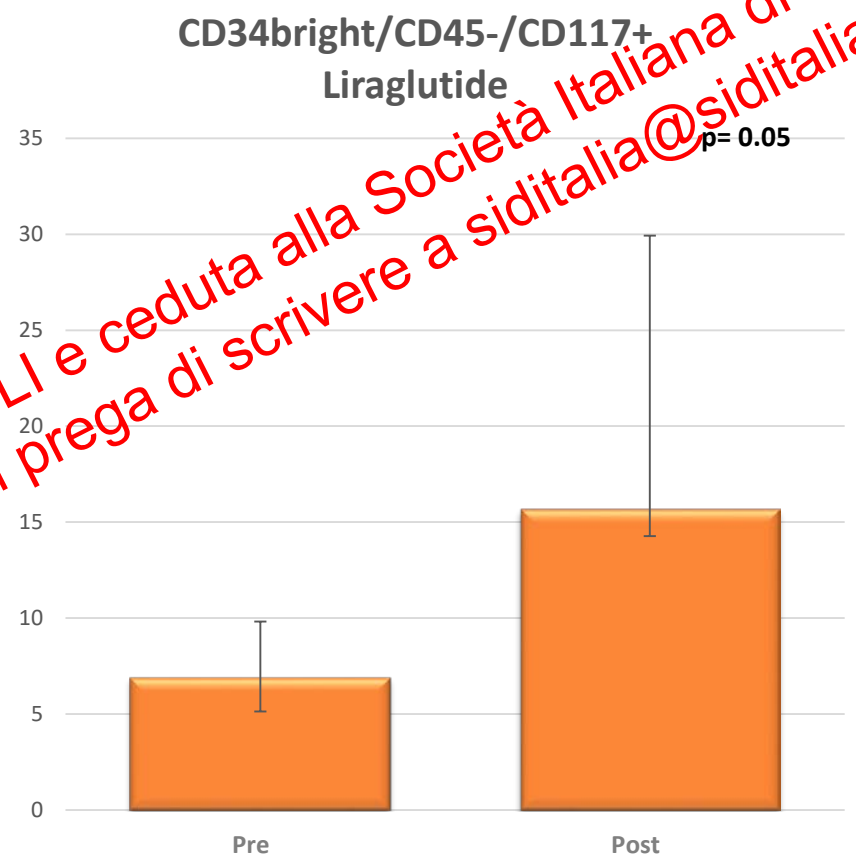
Levels of Endothelium derived Microvescicles Annexin V+ in subjects treated with liraglutide



Baldassarre MP et al., manuscript in preparation

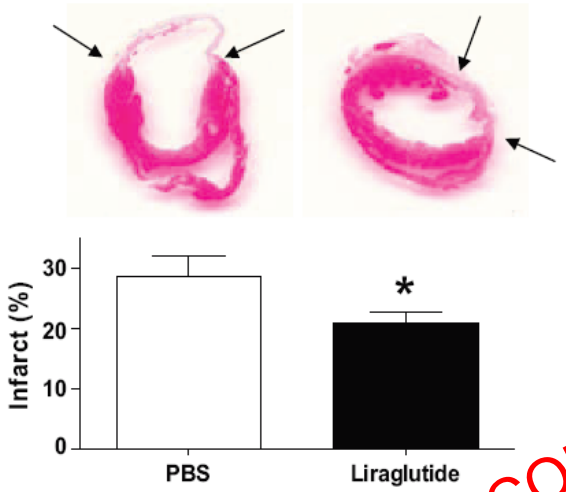
Levels of Differentiated EPC Population (CD34 bright/CD45-/CD117+)before and after Treatment with Anti-Diabetes Medications

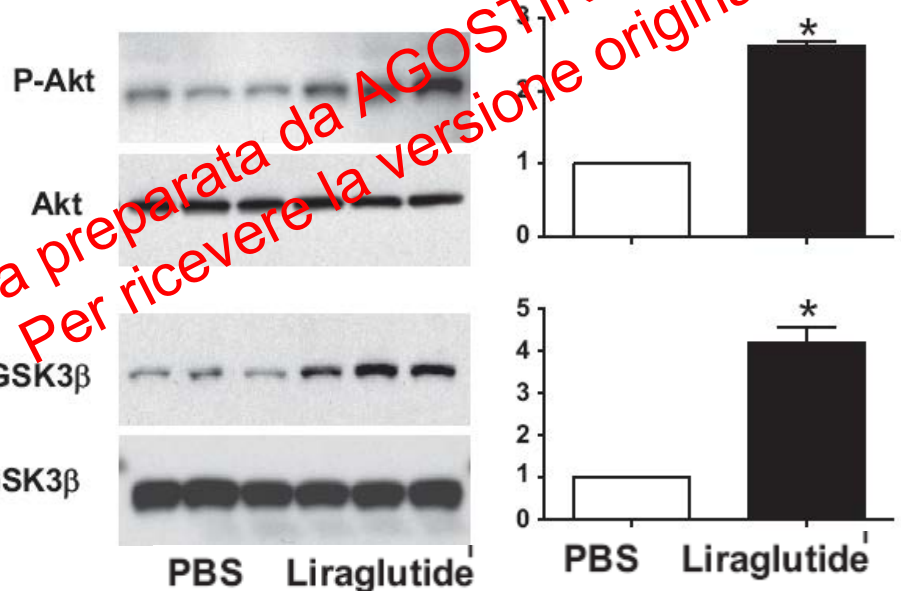


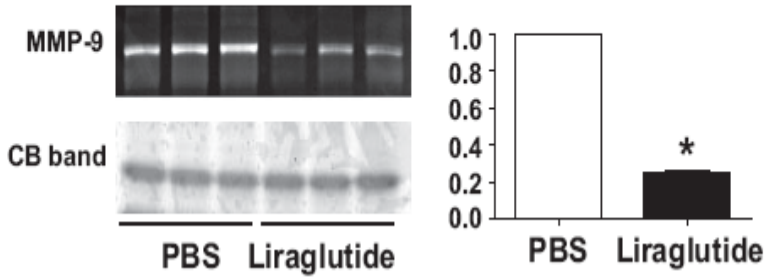


Baldassarre MP et al., manuscript in preparation

Liraglutide induced molecular changes in a mouse model of Miocardial Infarction

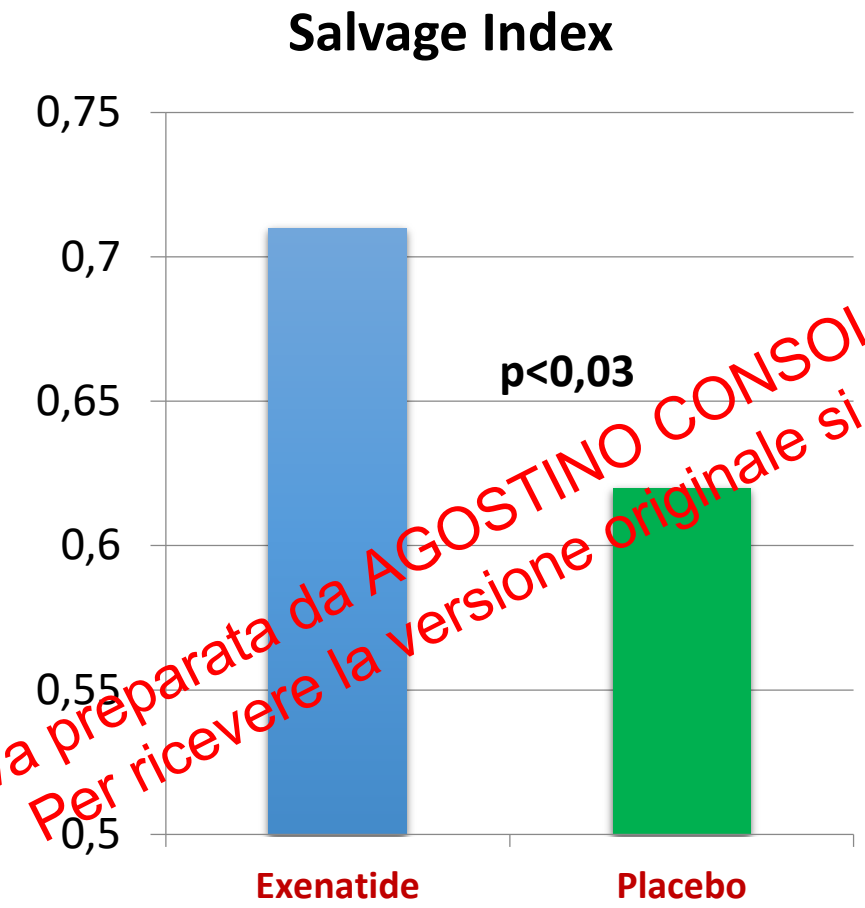


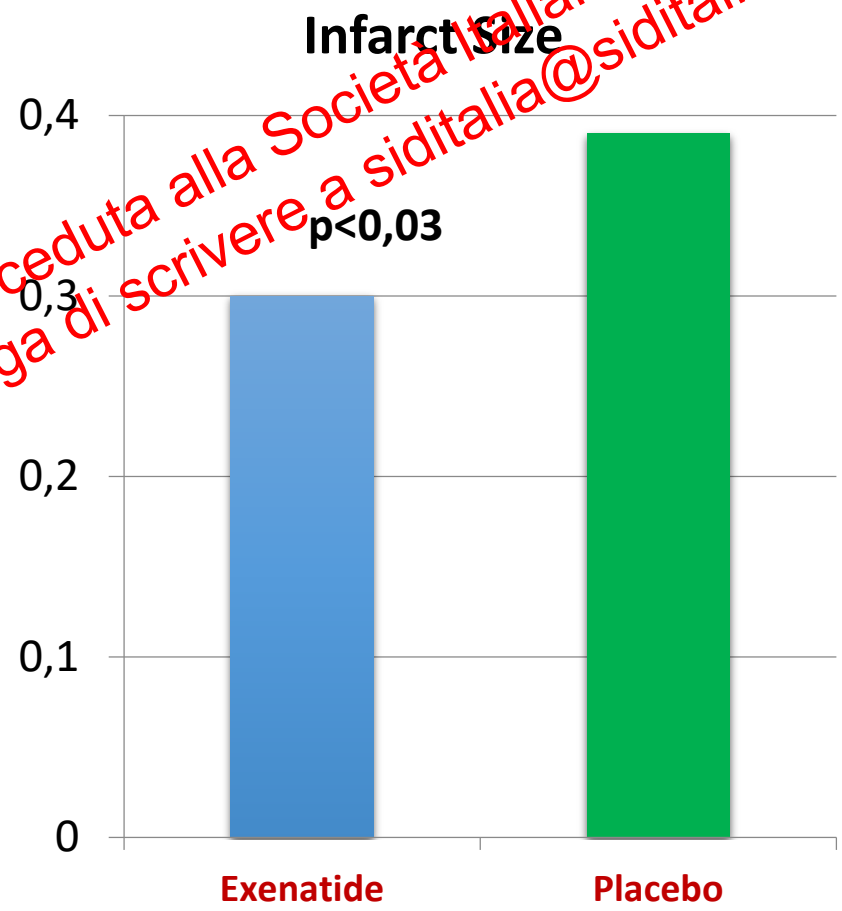




Noyan-Ashraf MH, et al. Diabetes 2009; 58:975

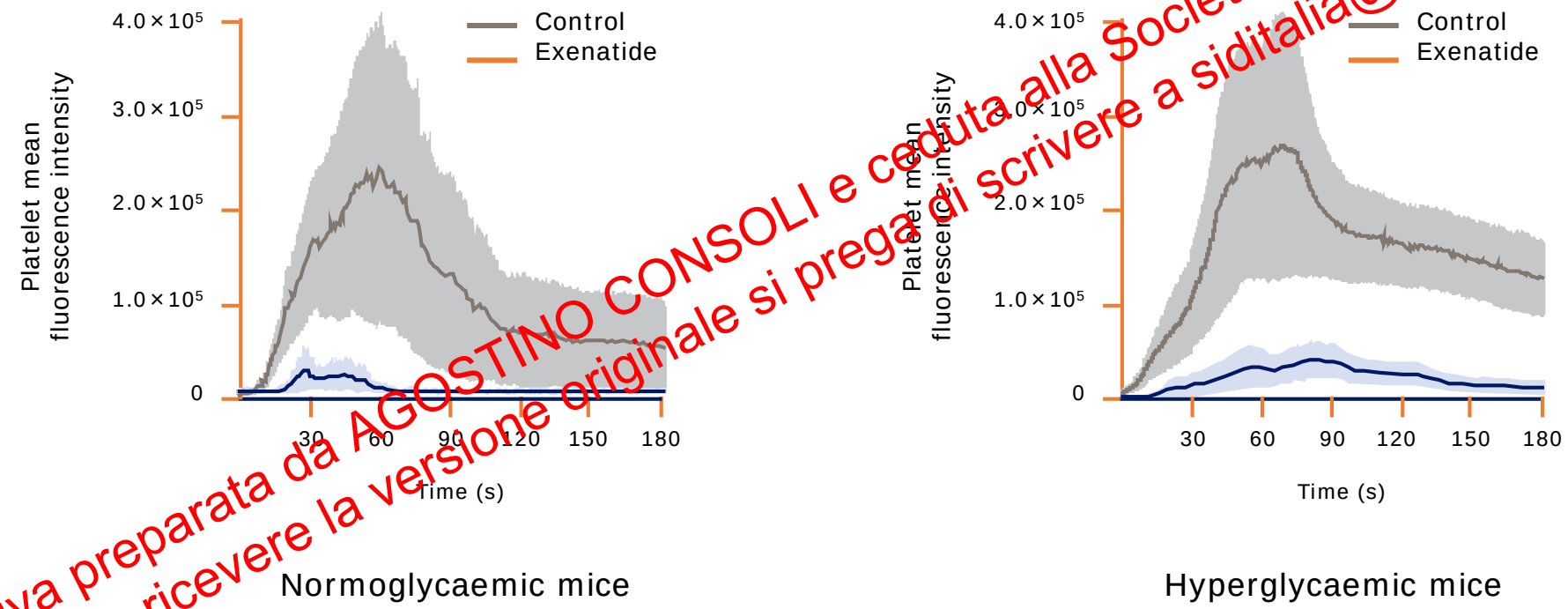
Salvage Index and Final Infarct Size in ST-segment elevation myocardial infarction treated by ballon angioplasty and exenatide or placebo infusion





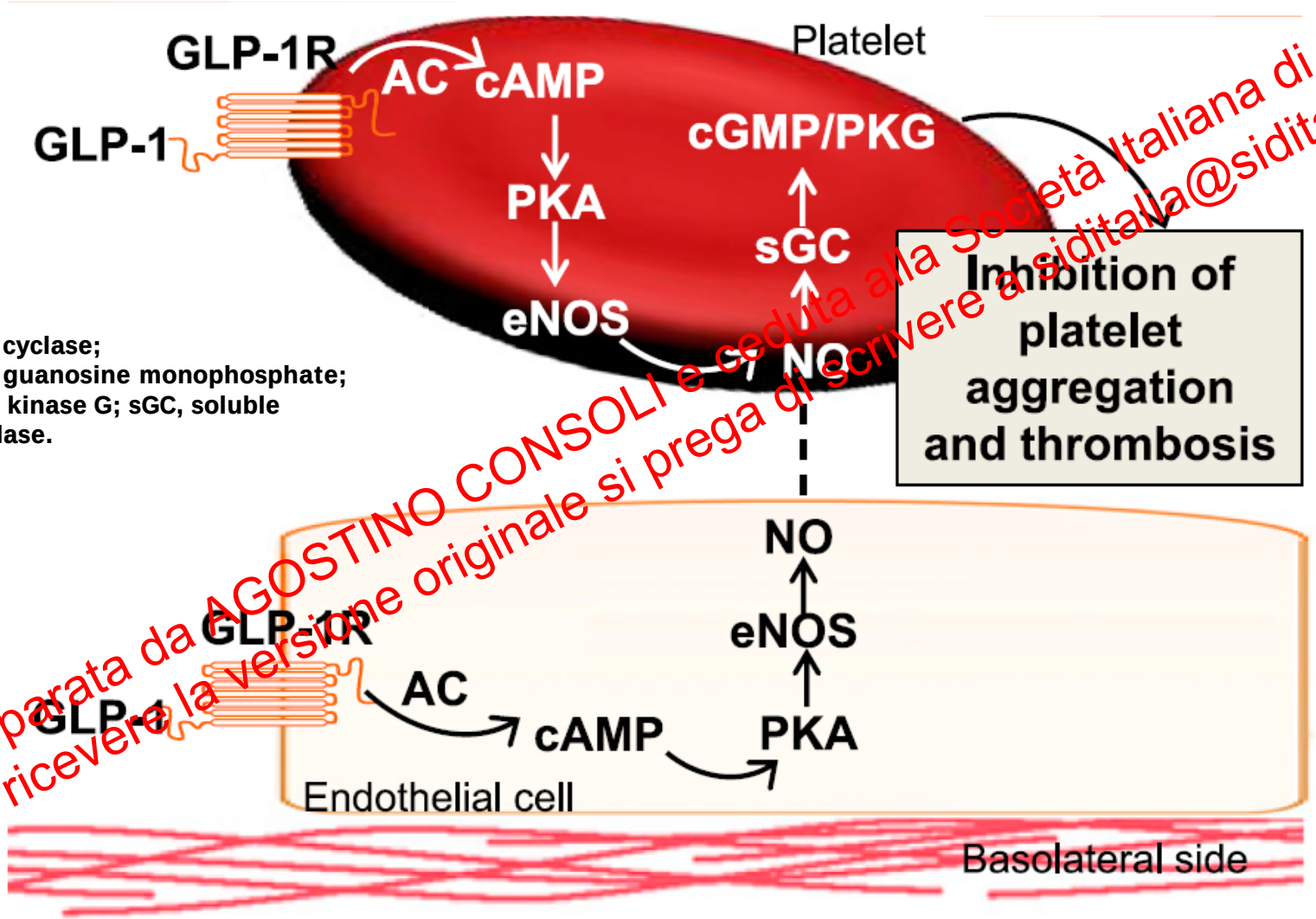
Lønborg J, et al. Eur Heart J 2012; 33:1491

GLP-1RA treatment inhibits laser-induced thrombus formation in mice



Cameron-Vendrig A et al. Diabetes 2016;65:171

Glucagon-Like Peptide 1 Receptor activation attenuates platelet aggregation and thrombosis

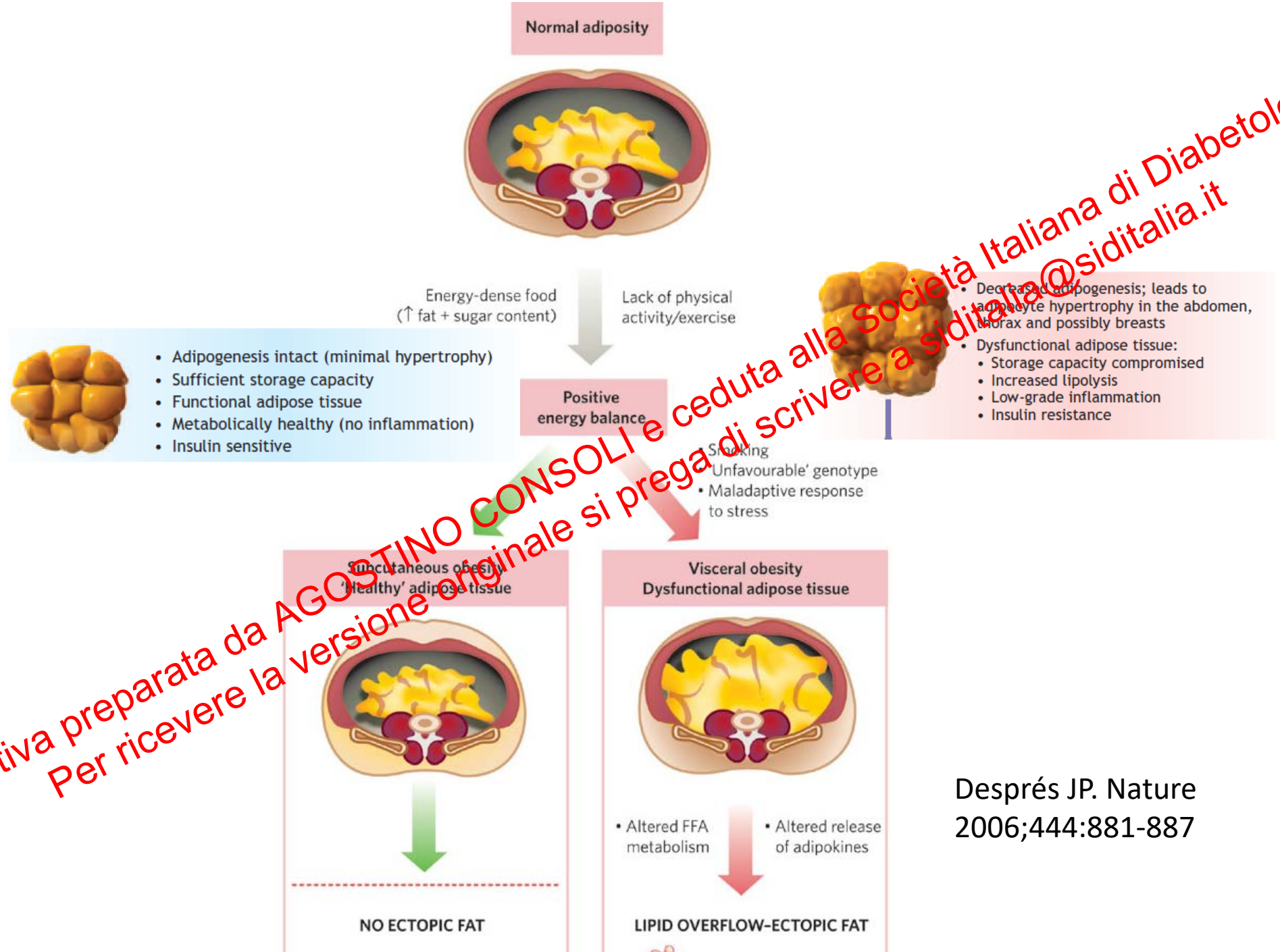


AC, adenylyl cyclase;
cGMP, cyclic guanosine monophosphate;
PKG, protein kinase G; sGC, soluble guanylyl cyclase.

Cameron-Vendrig A et al. Diabetes 2016; 65:1714

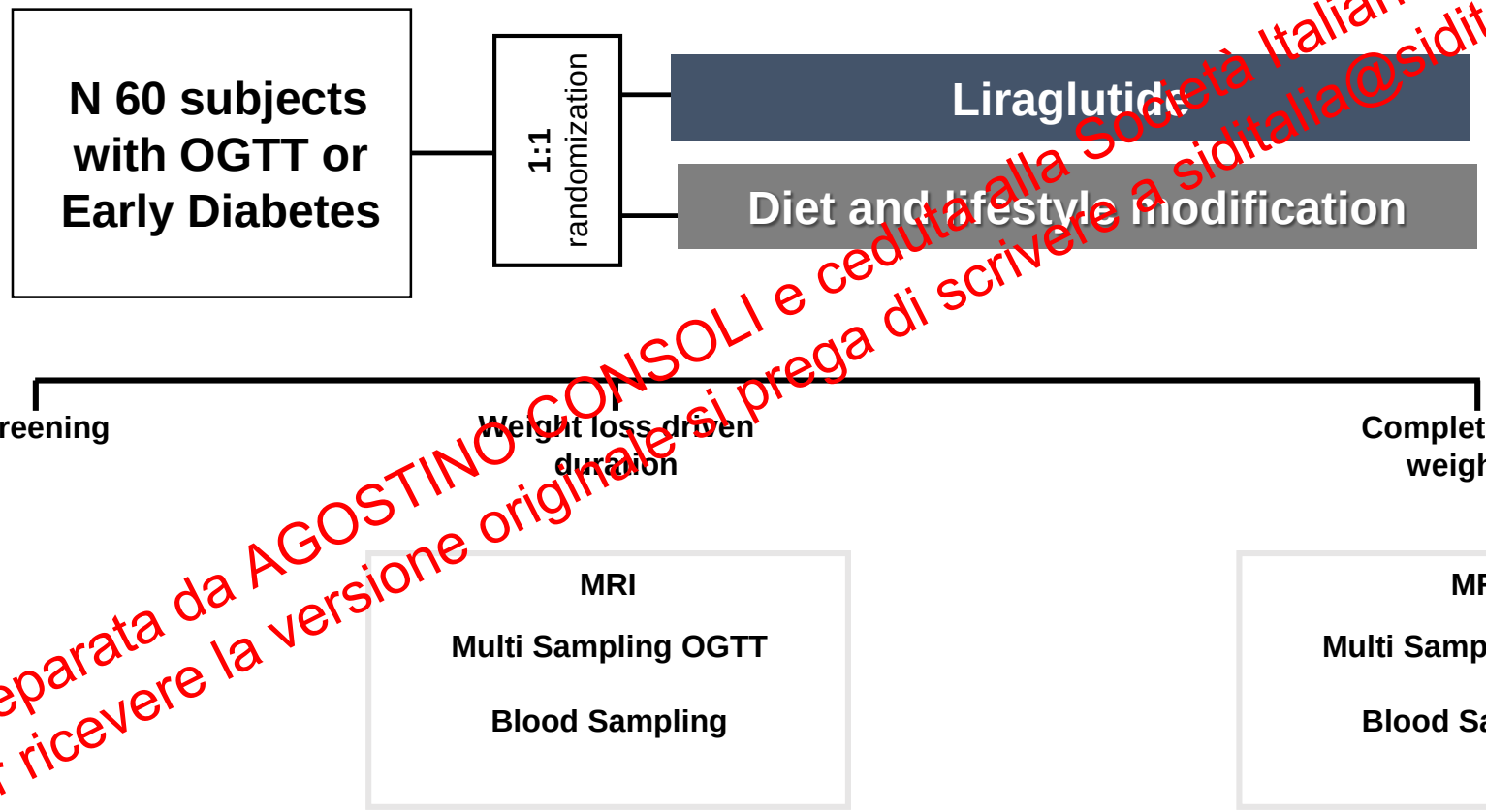
«Emerging» actions of GLP-1 on

- Inflammation
- Cardiovascular System
- **Body Composition**
- Beta-cell function

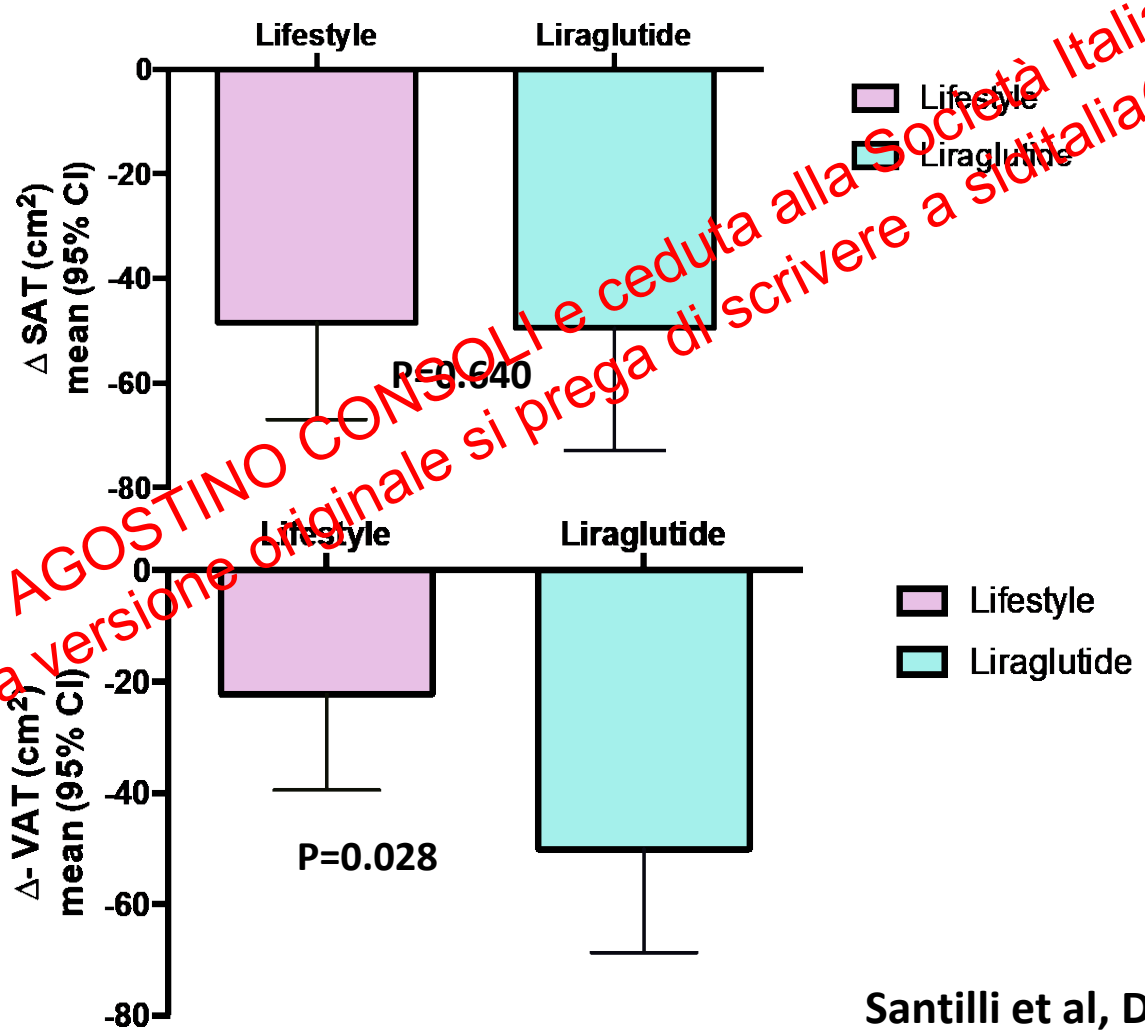


Després JP. Nature 2006;444:881-887

Study Design



Effects of Liraglutide or Lifestyle-induces weight loss on Subcutaneous and Visceral Adipose Tissue loss

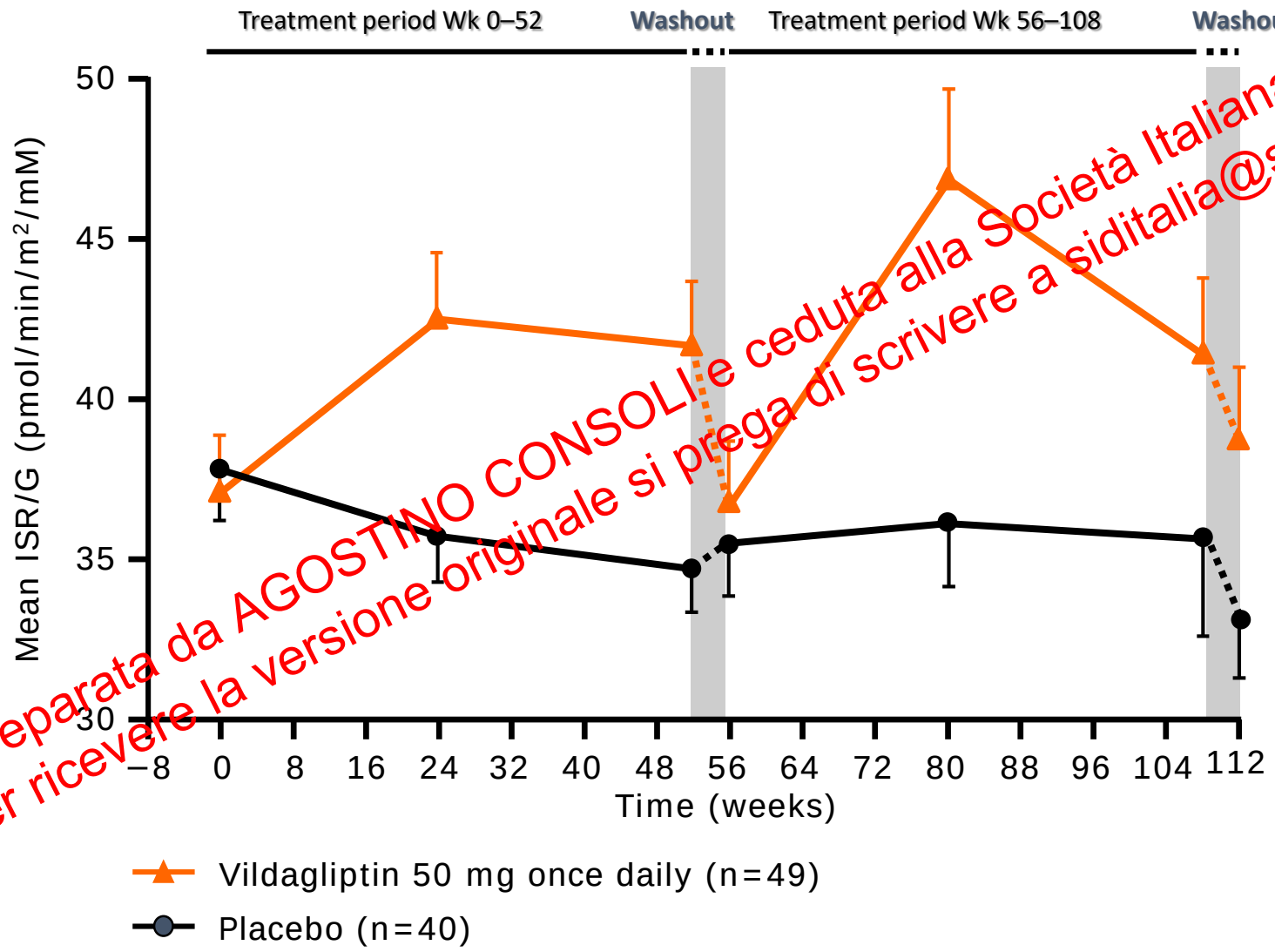


Santilli et al, Diabetes Care 2017

«Emerging» actions of GLP-1 on

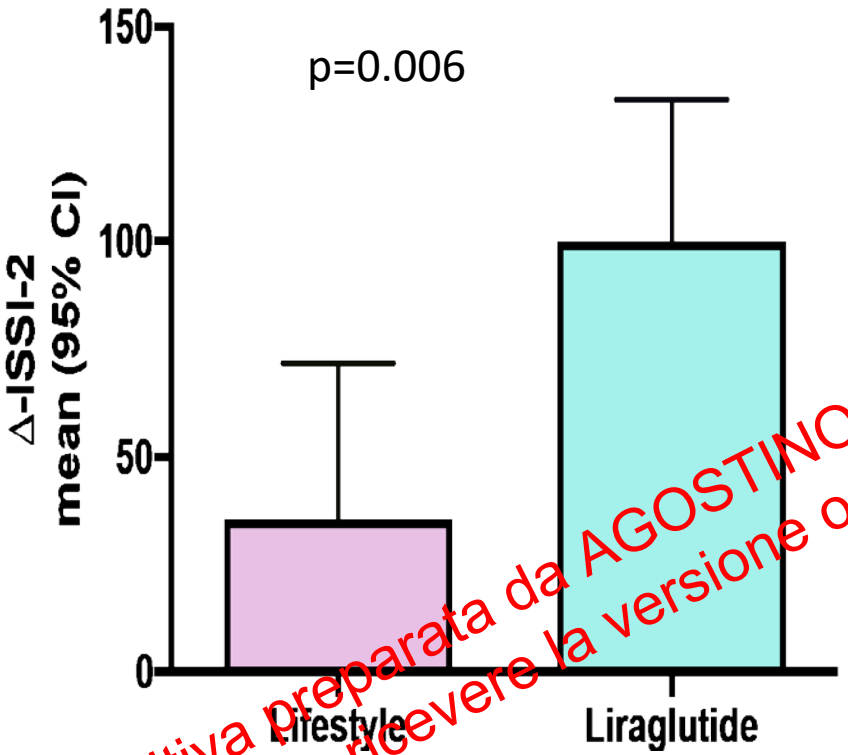
- Inflammation
- Cardiovascular System
- Body Composition
- **Beta-cell function**

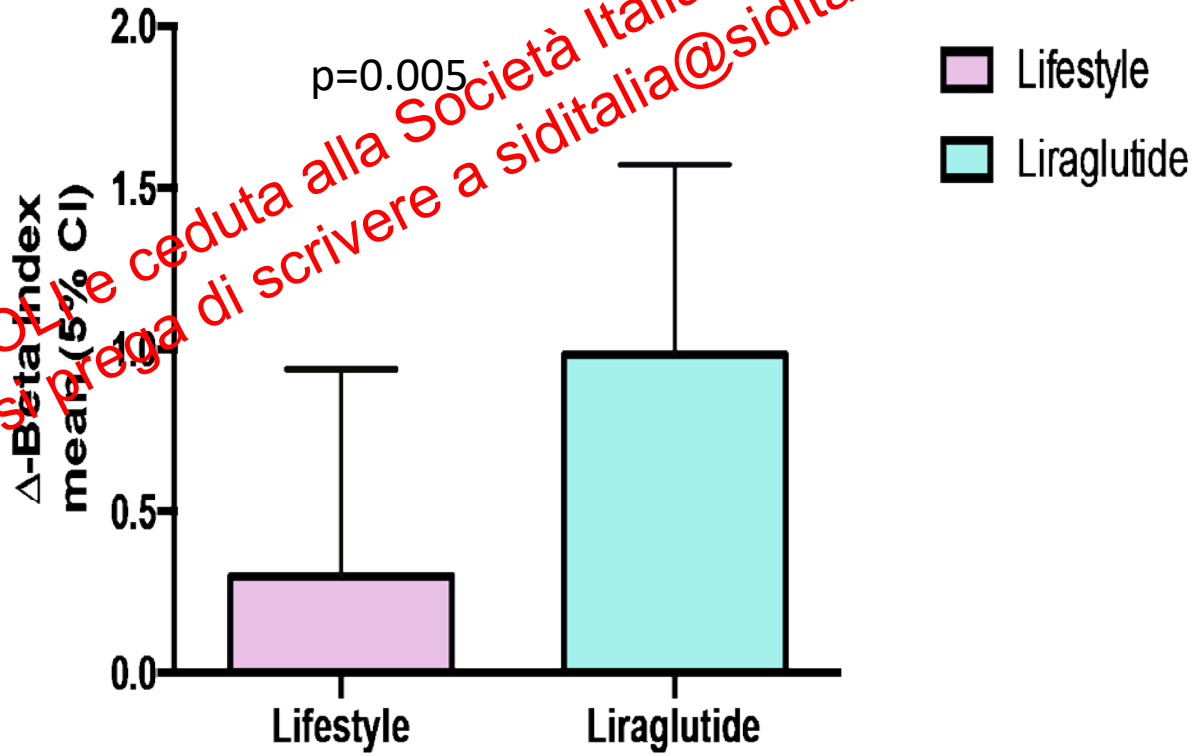
β-cell Function over 2 Years in Vildagliptin treated T2DM subjects



Scherbaum WA, et al. *Diabetes Obes Metab*. 2008

Effects of Liraglutide or Lifestyle intervention on Beta-cell function in IGT or Early T2DM subjets



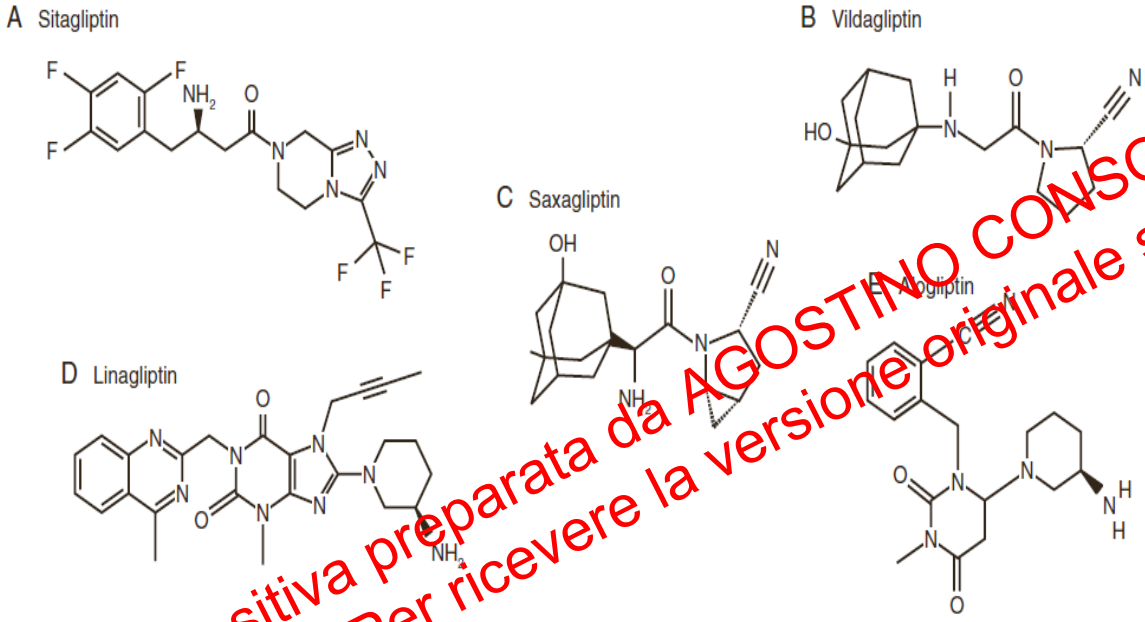


Santilli et al, Diabetes Care 2017

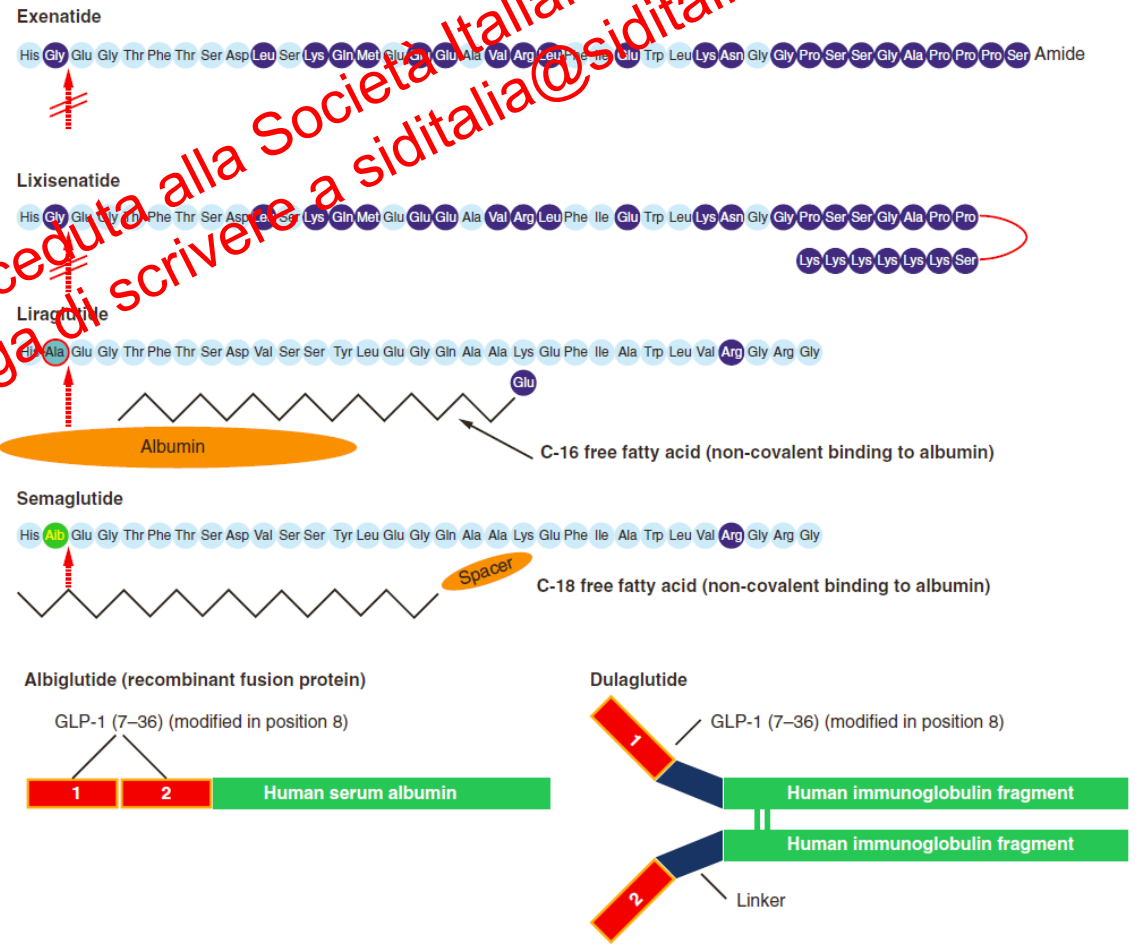
Incretin effect

TRANSLATION INTO CLINIC

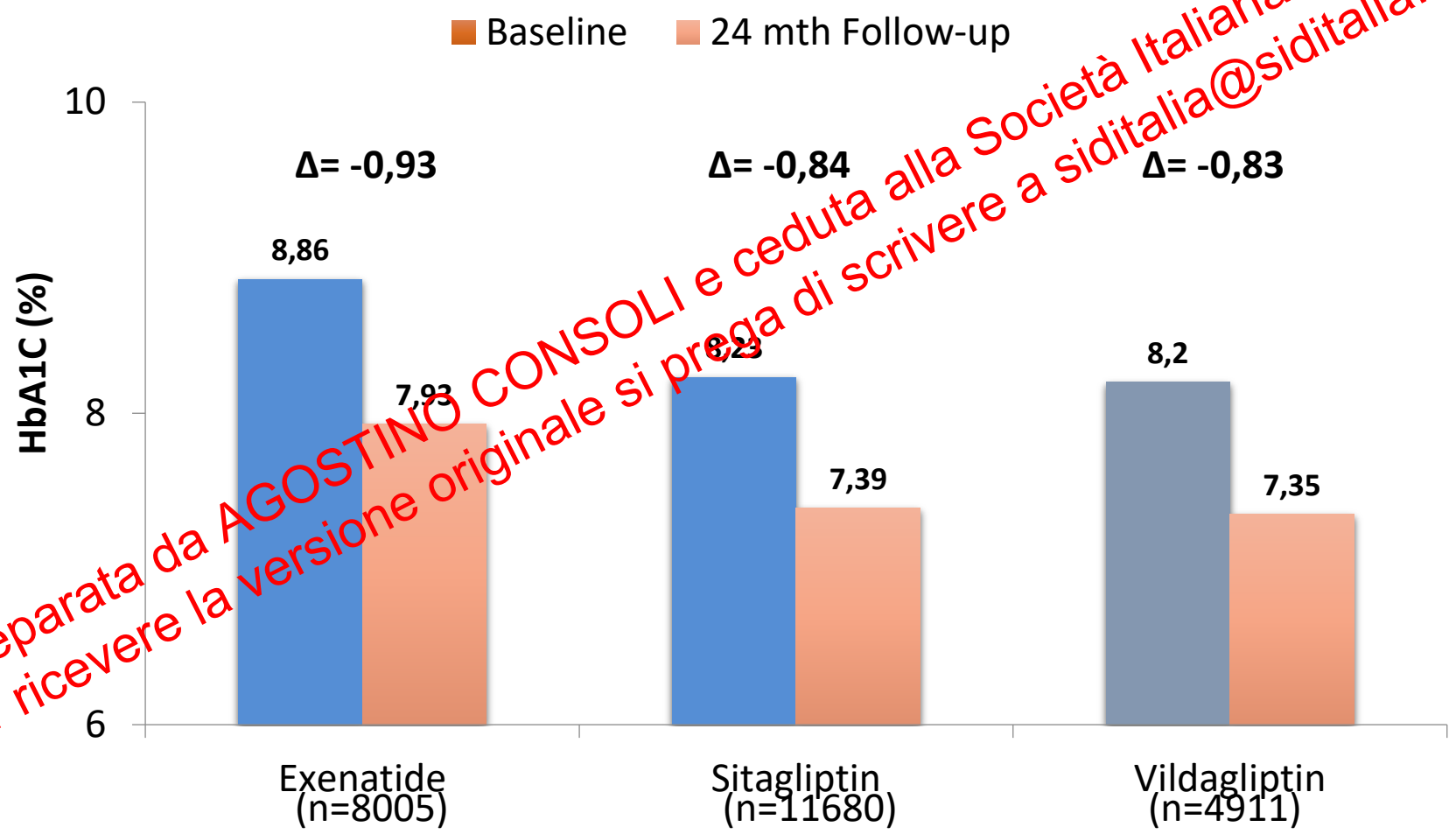
DPP-IV inhibitors



GLP-1 Rx Agonists

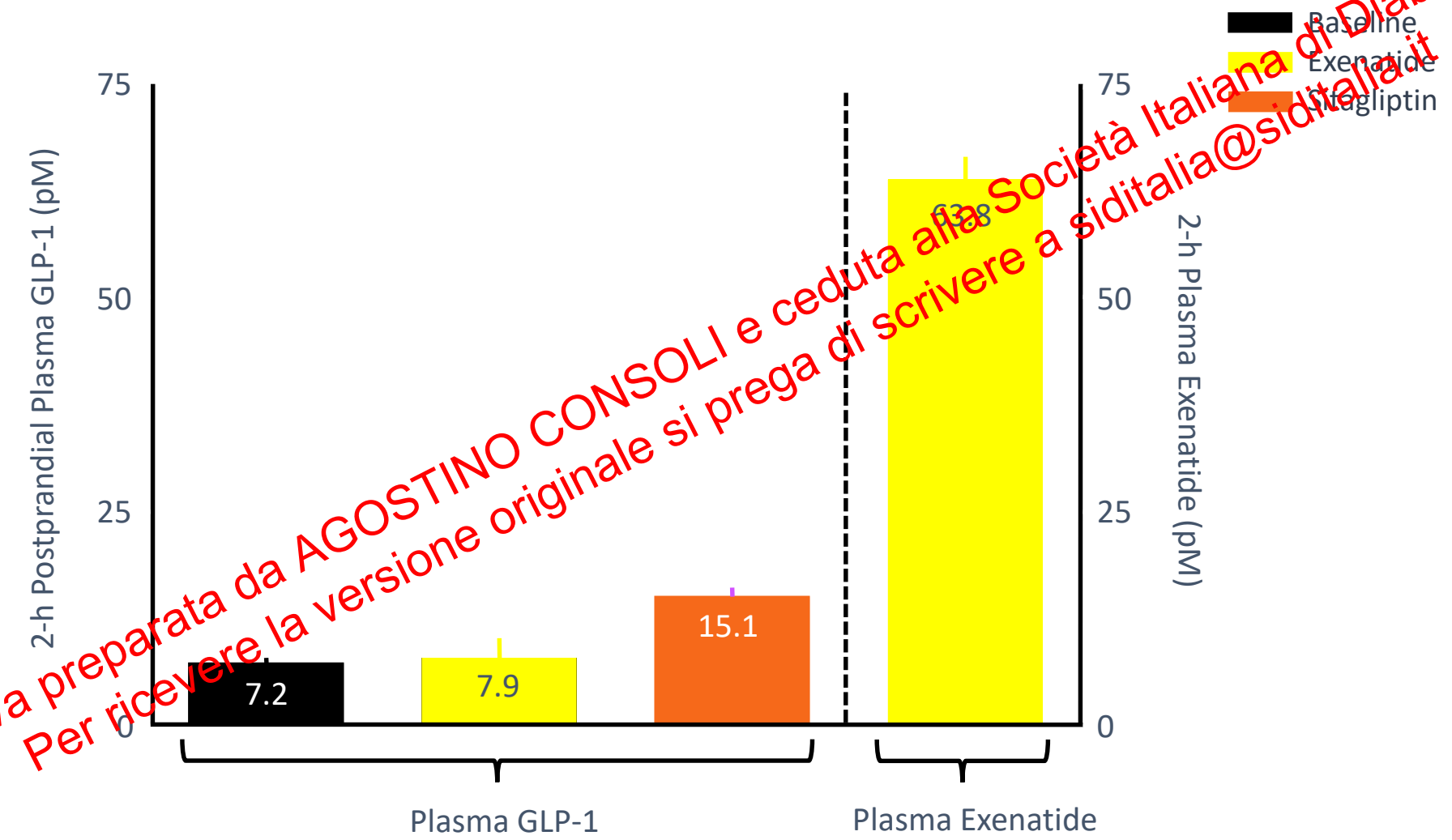


HbA1 at baseline and at 24 months follow-up in T2DM subjects enrolled in the AIFA incretin-based therapies national on-line registry



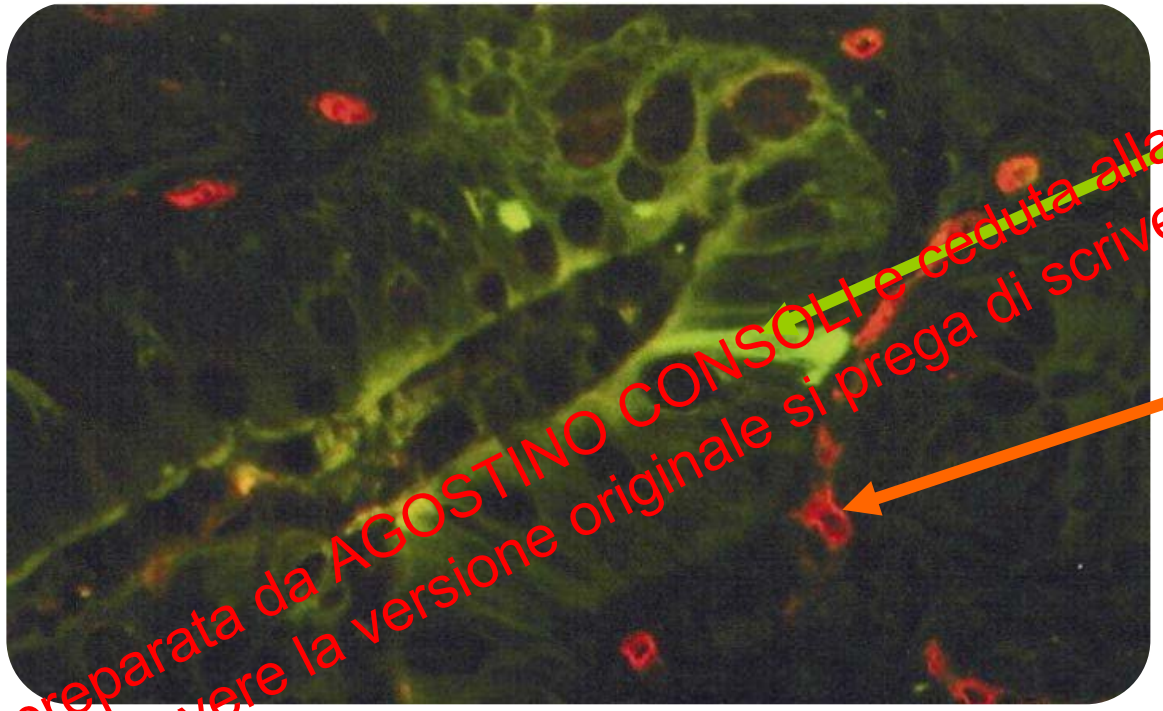
AIFA Report Jan 25 2011

GLP-1 Circulating Levels After GLP-1 RA or DPP-IV inhib administration



DeFronzo RA, *Curr Med Res Opin.* 2008;24:2943

DPP-IV is heavily expressed in the endothelial cells of the gut lining vessels



Human Ileum,
GLP-1 producing L-cells

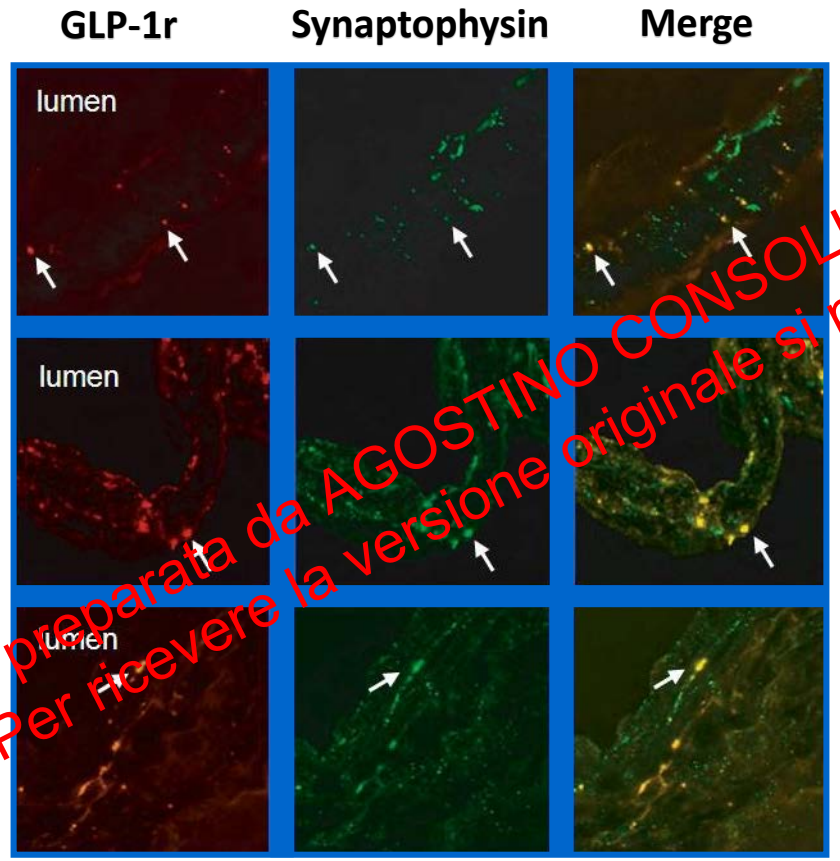
Capillaries, DPP-IV

Human Ileum: DPP-IV staining (red) and GLP-1 staining (green)

Adapted from: Hansen et al. Endocrinology 1999;140:5356–63.

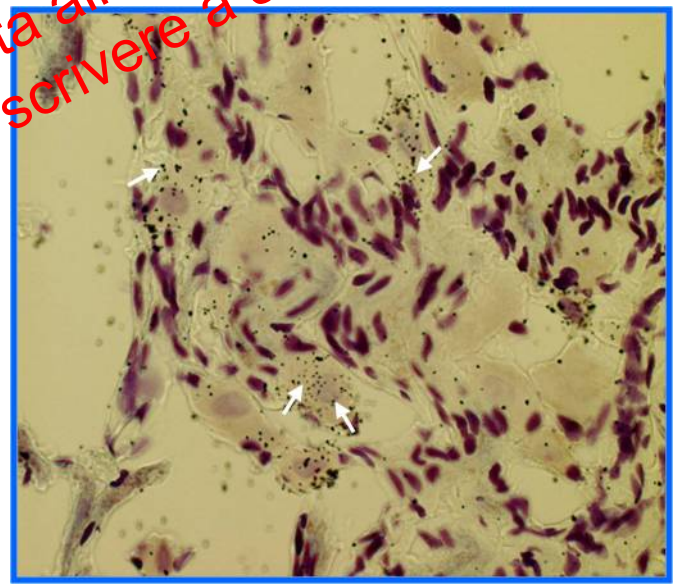
GLP-1 Receptors are Expressed on Nerve Terminals Outside the Brain

Portal vein



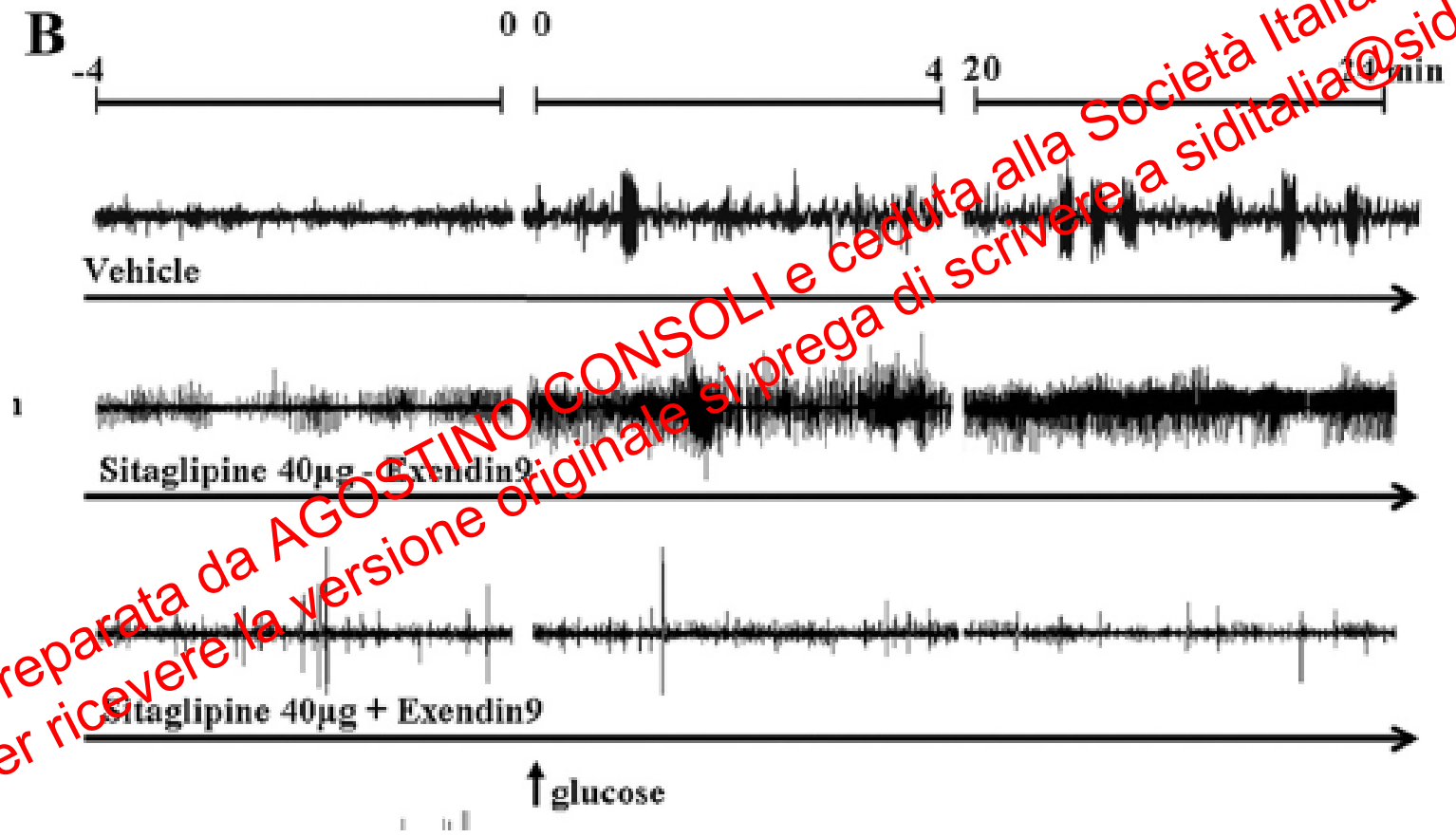
Vahl et al. Endocrinology 2007

Nodose ganglion



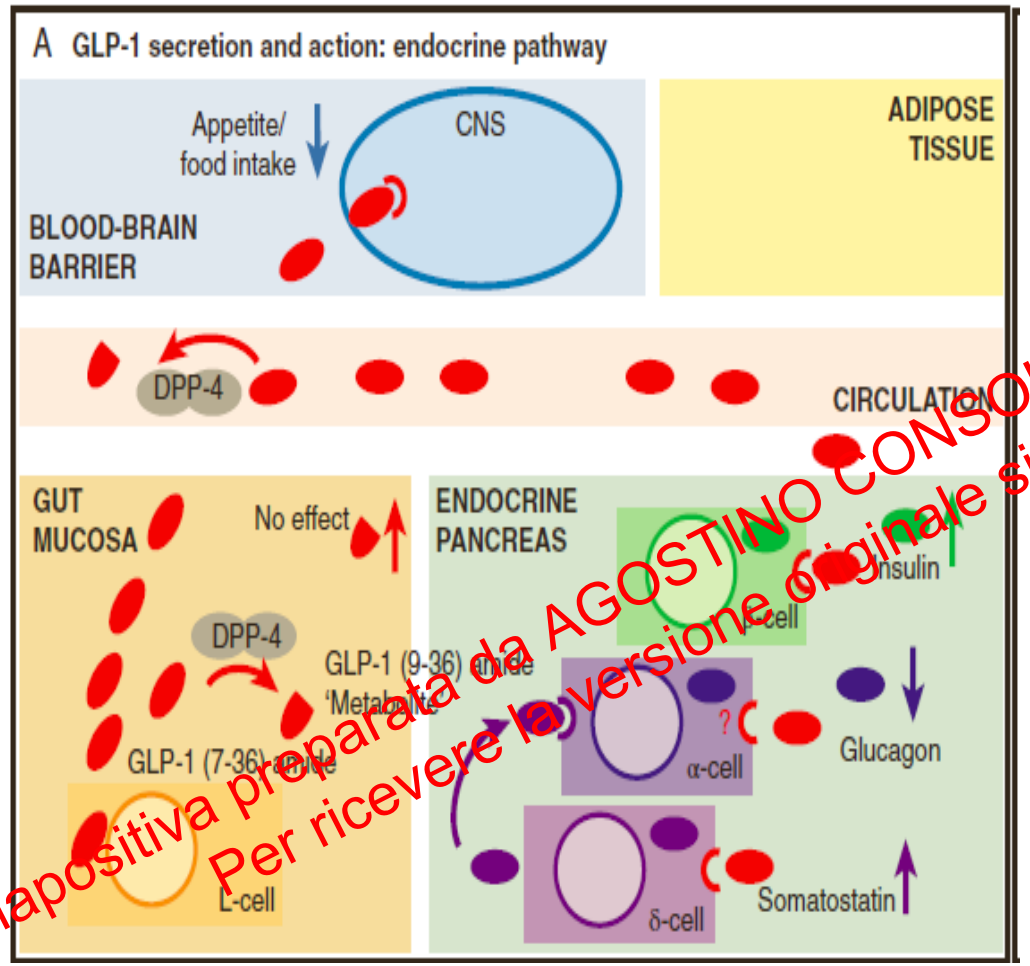
Philip Larsen, Copenhagen

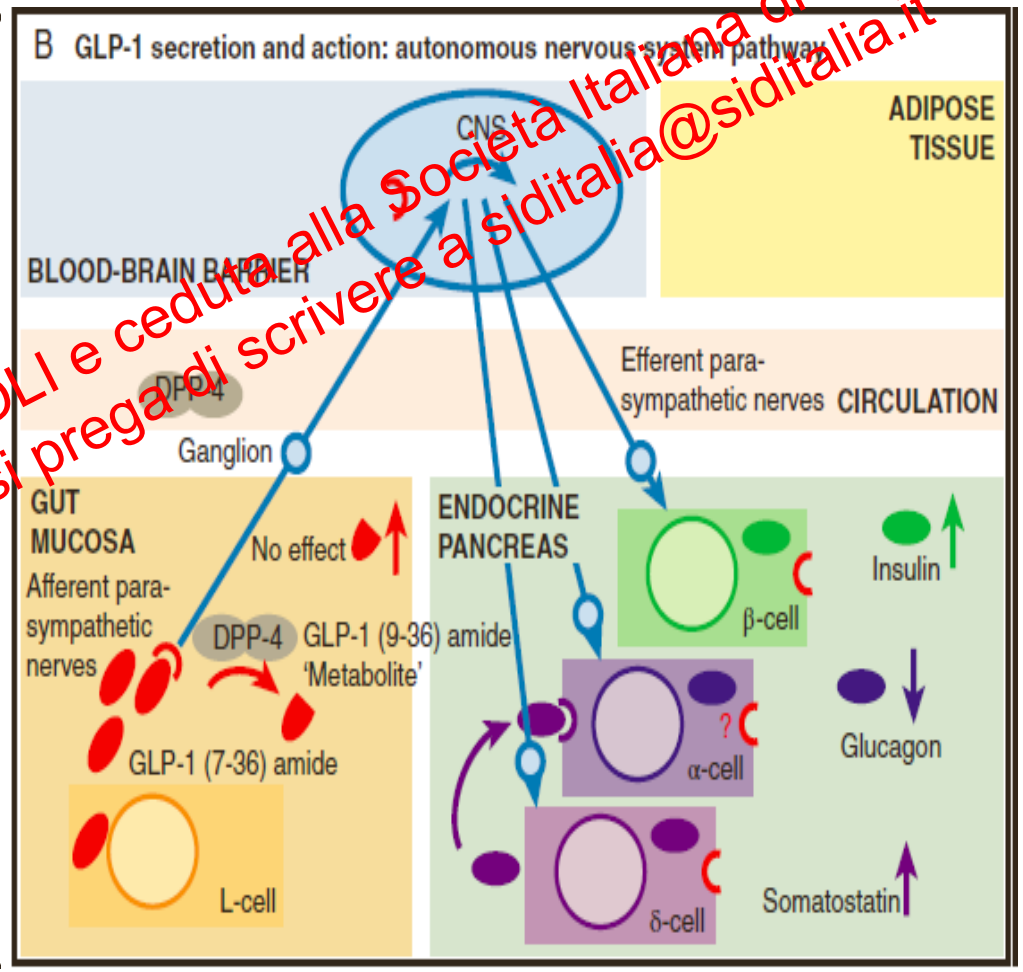
Vagal activity following glucose ingestion after vehicle or after sitagliptin in the presence or in the absence of GLP-1 Rx blockage



Waget et al., Endocrinology 2011

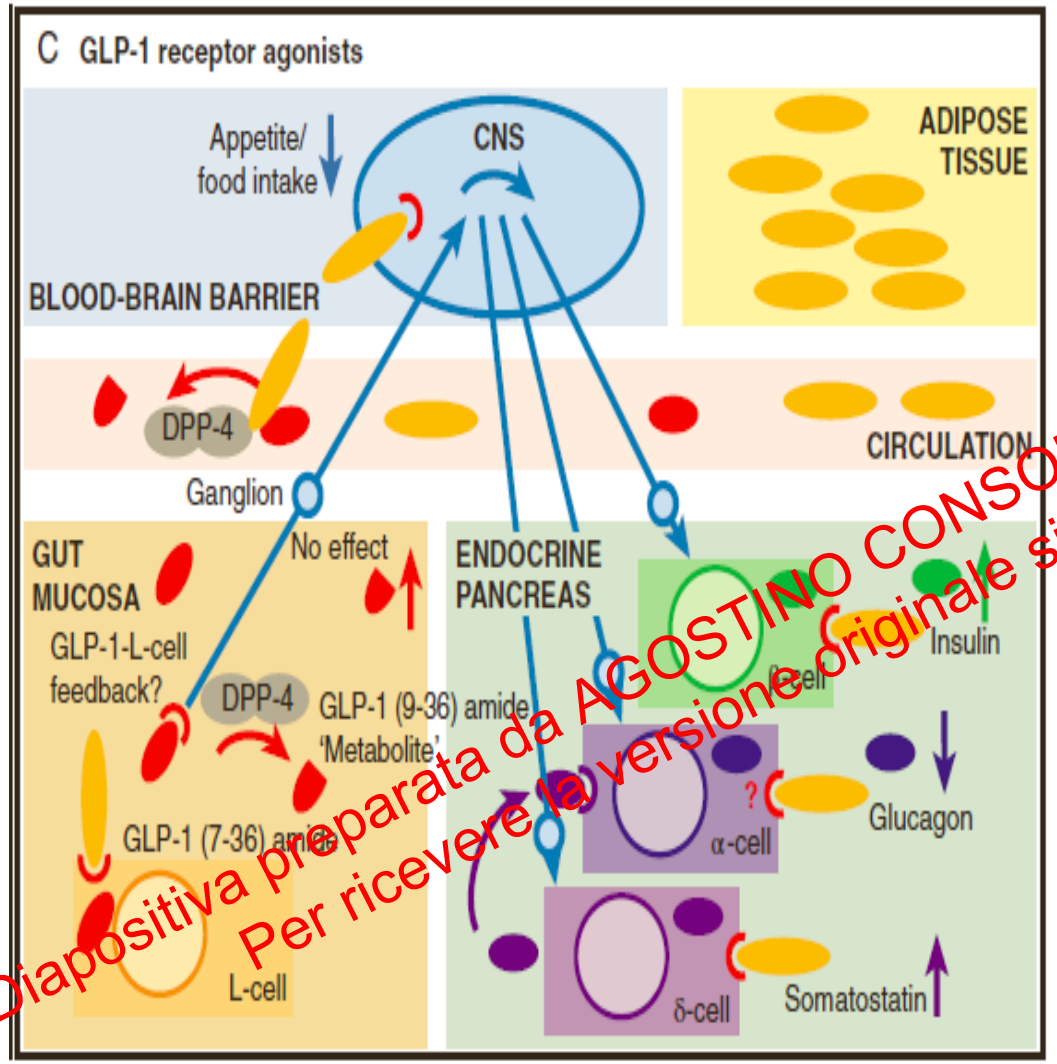
GLP-1 Mode of Action

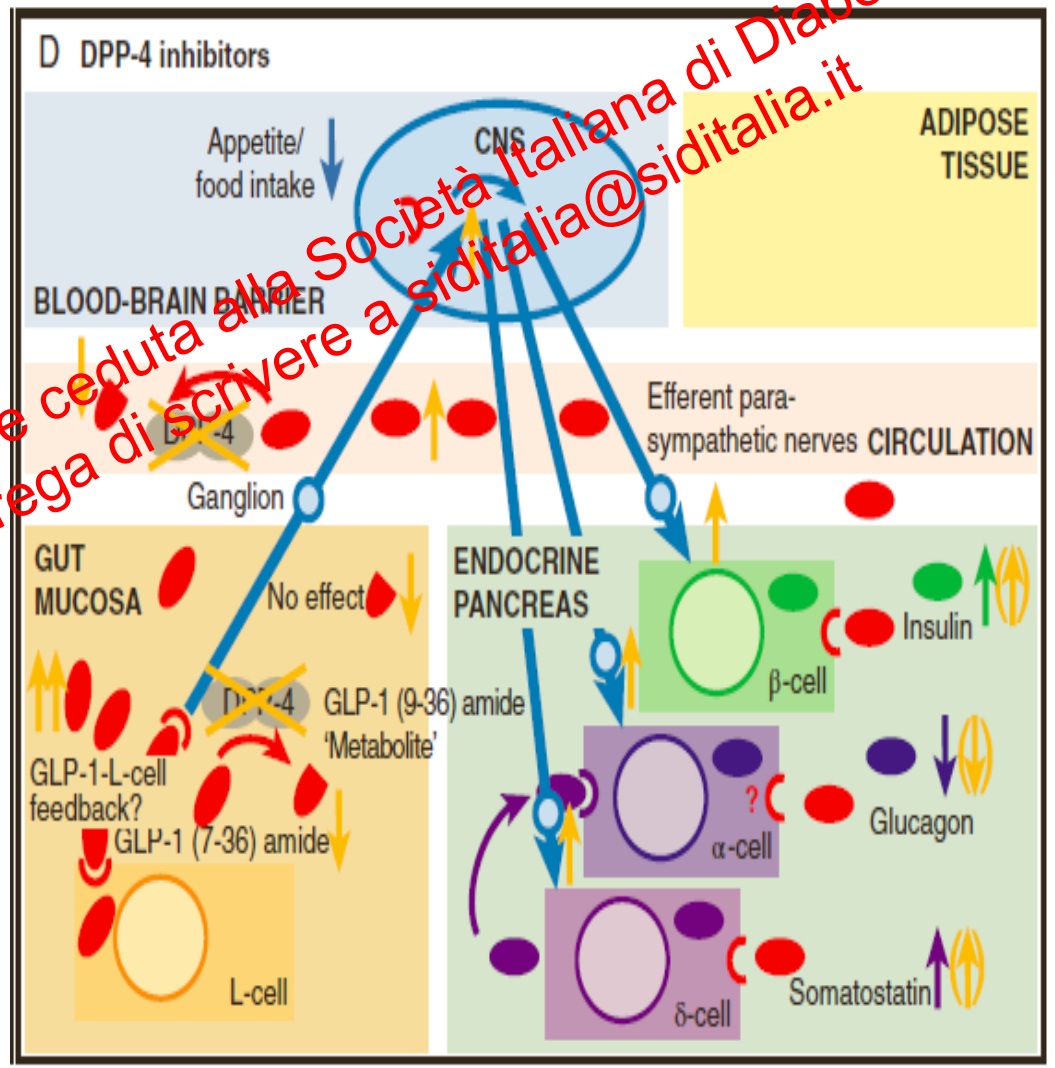




Nauck M., Diab Obes Metab 2016

GLP-1 Ras and DPP-IV inhib. Mode of Action





Nauck M., Diab Obes Metab 2016

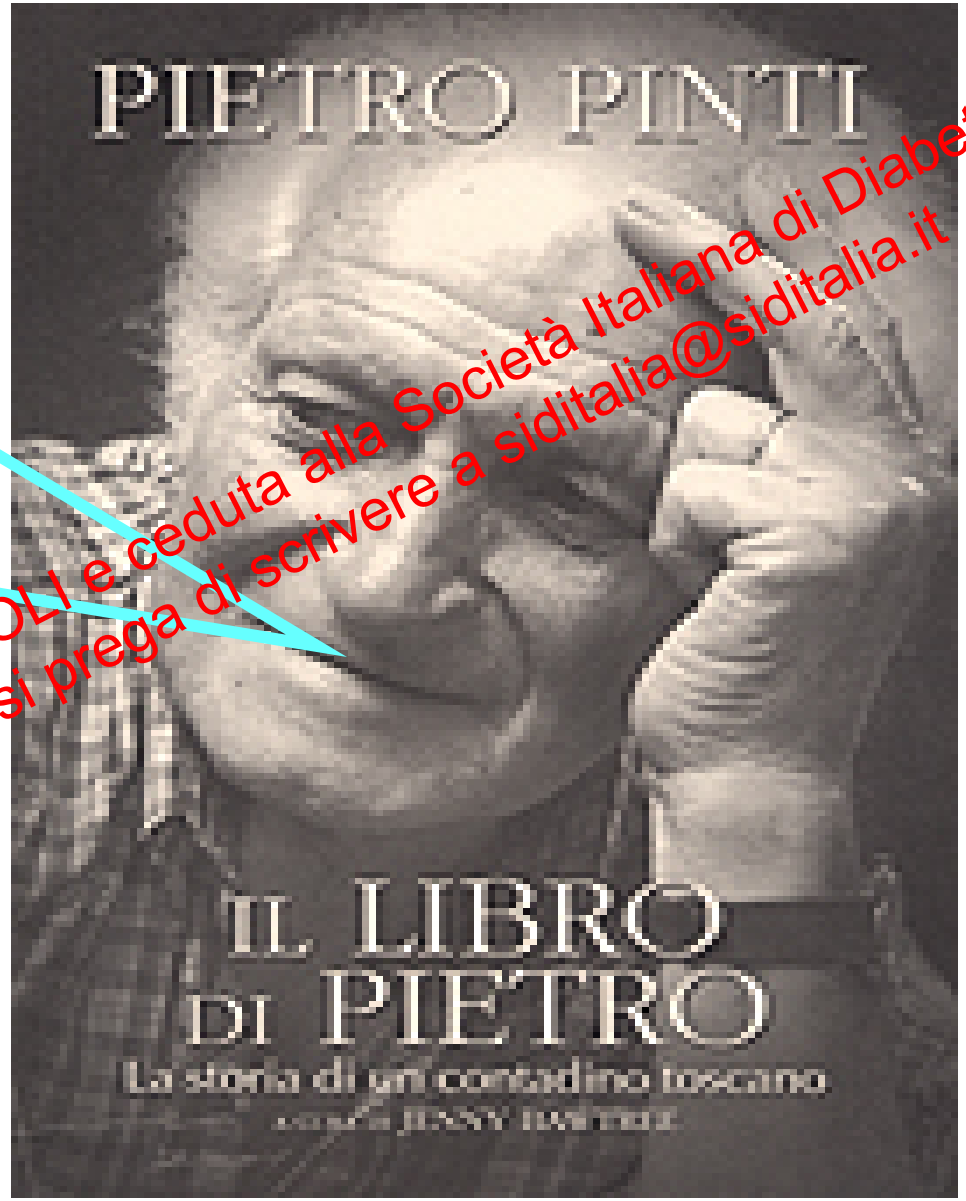
Patient characteristics	DPP-4 inhibitor therapy	GLP-1RA therapy	Therapy with other antidiabetic drugs (as specified)
Glycaemic-related			
HbA1c	0.5–1.0% above target*	1.0–1.5% above target	>1.5% above target Unsuitable: DPP-4 inhibitor Possible: GLP-1RA Preferred: insulin
FPG	0–1.7 mmol/l (0–30 mg/dl) above target [42]	1.1–3.9 mmol/l (20–70 mg/dl) above target Liraglutide > exenatide [91]	>3.9 mmol/l (70 mg/dl) above target Preferred: insulin [92] Unsuitable: DPP-4 inhibitor or GLP-1RA [8]
PPG	Δ above preprandial >3.3 mmol/l (60 mg/dl) (±elevated FBG) [42]	Δ above preprandial >3.3–5.6 (60–100 mg/dl) Exenatide > liraglutide [91]	Δ above preprandial >5.6 mmol/l (100 mg/dl) insulin – prandial or mealtime [90,92]
Necessity to avoid hypoglycaemia*	Preferred	Preferred	Unsuitable: insulin or SUs
Non-glycaemic-related			
Necessity to reduce body mass index	Preferred to insulin	Preferred to DPP-4 inhibitor	Possible: metformin, pramlintide Unsuitable: insulin, SUs and glitazones
Preference for oral treatment/injection phobia	Preferred over GLP-1RAs and insulin	Not suitable	Suitable: SUs, if DPP-4 inhibitors contraindicated
Inability or unwillingness for blood glucose self-monitoring*	—	Preferred over insulin	Unsuitable: insulin
Sensitivity to gastrointestinal events	Suitable	Not suitable	Unsuitable: metformin, acarbose
Poor compliance*	Possible: (neutral)	Preferred: long-acting GLP-1RA	Unsuitable: insulin

Nauck M., Diab Obes Metab 2016

Patient characteristics	DPP-4 inhibitor therapy	GLP-1RA therapy	Therapy with other antidiabetic drugs (as specified)
Comorbidities			
Renal insufficiency	Preferred: linagliptin	Preferred: liraglutide	Unsuitable: metformin (lactic acidosis) [28]; sulphonylureas (hypoglycaemia)
	Dose adjustment required for other DPP-4 inhibitors [27,29]	Possible: exenatide (mild/moderate renal impairment), exenatide once weekly (mild renal impairment)	
Liver disease†	Suitable (except saxagliptin)	Suitable (unlimited data)	Preferred: insulin Unsuitable: secretagogues (severe hepatic disease) [90]
Cardiovascular disease	Preferred to insulin	Preferred	Preferred: metformin, acarbose Unsuitable: intensive insulin therapy, SUs[90]
Economics			
Cost	Preferred over GLP-1RA	More costly than DPP-4 inhibitors, similar to insulin treatment (including blood glucose self-monitoring)	Preferred: metformin, SUs

Nauck M., Diab Obes Metab 2016

Male che 'un dole, .. curare 'un si pole !!



Characteristics of the “ideal” diabetes drug for a “treat to success” strategy

- **EFFICACY**
  - Reduction in HbA1c significant and non inferior to other agents
  - MOA potentially able to impact on disease progression
- **TOLERABILITY**
  - Easy administration
  - No need for titration
  - No minor drug associated ailments (GI symptoms, ankles swelling, headache, itch, etc…)
- **SAFETY**
  - No hypoglycemia risk
  - No weight gain
  - No adverse CV effects
  - No documentable adverse effects on any organ or apparatus
- **SUSTAINABILITY**
  - Affordable cost/benefit ratio