Analoghi del GLP-1 e protezione cardiovascolare

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ITALY

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)

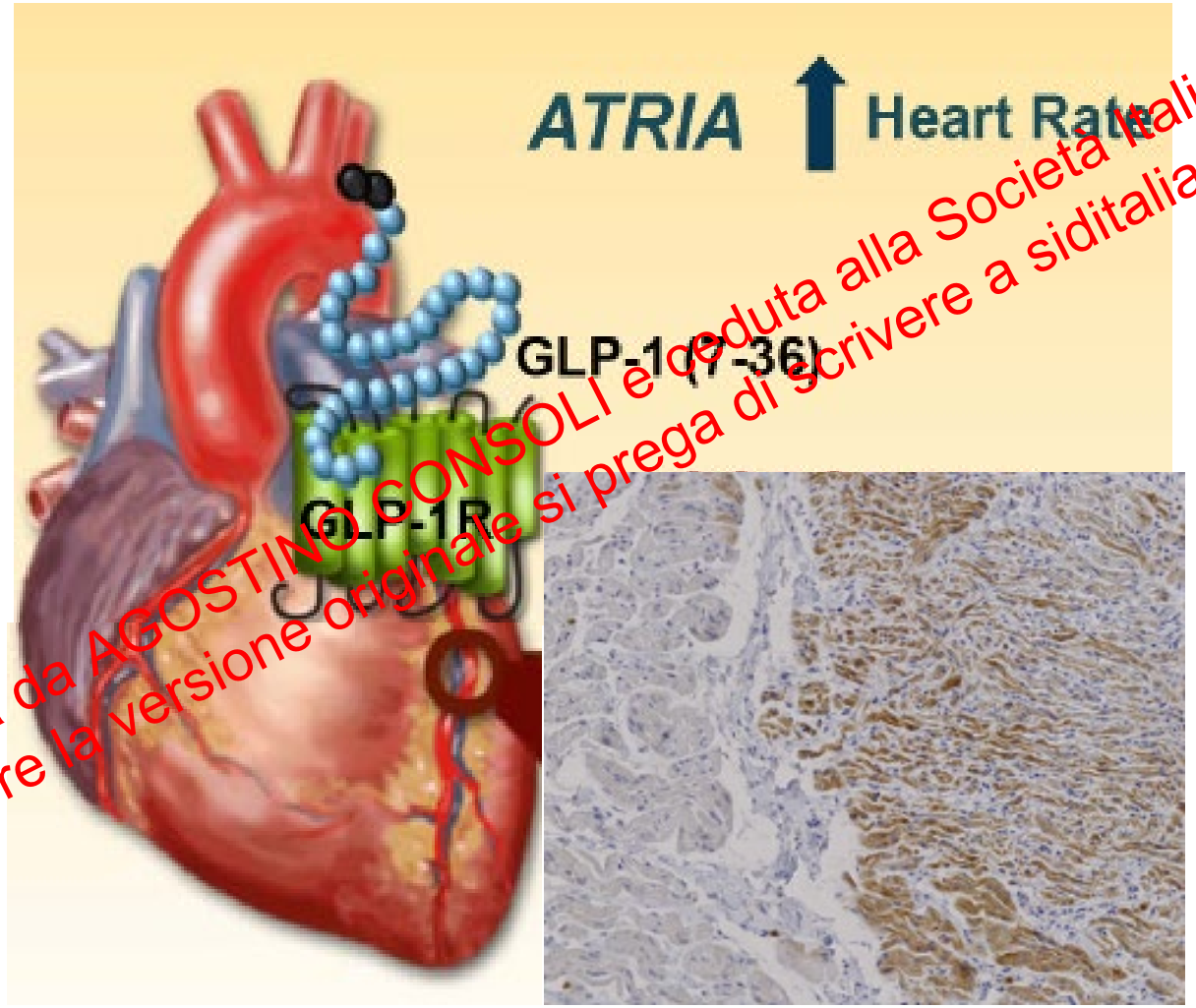
Eli Lilly, Novo-Nordisk
(Research Grant)

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

GLP-1 Rx is expressed in Seno-Atrial myocytes in human heart



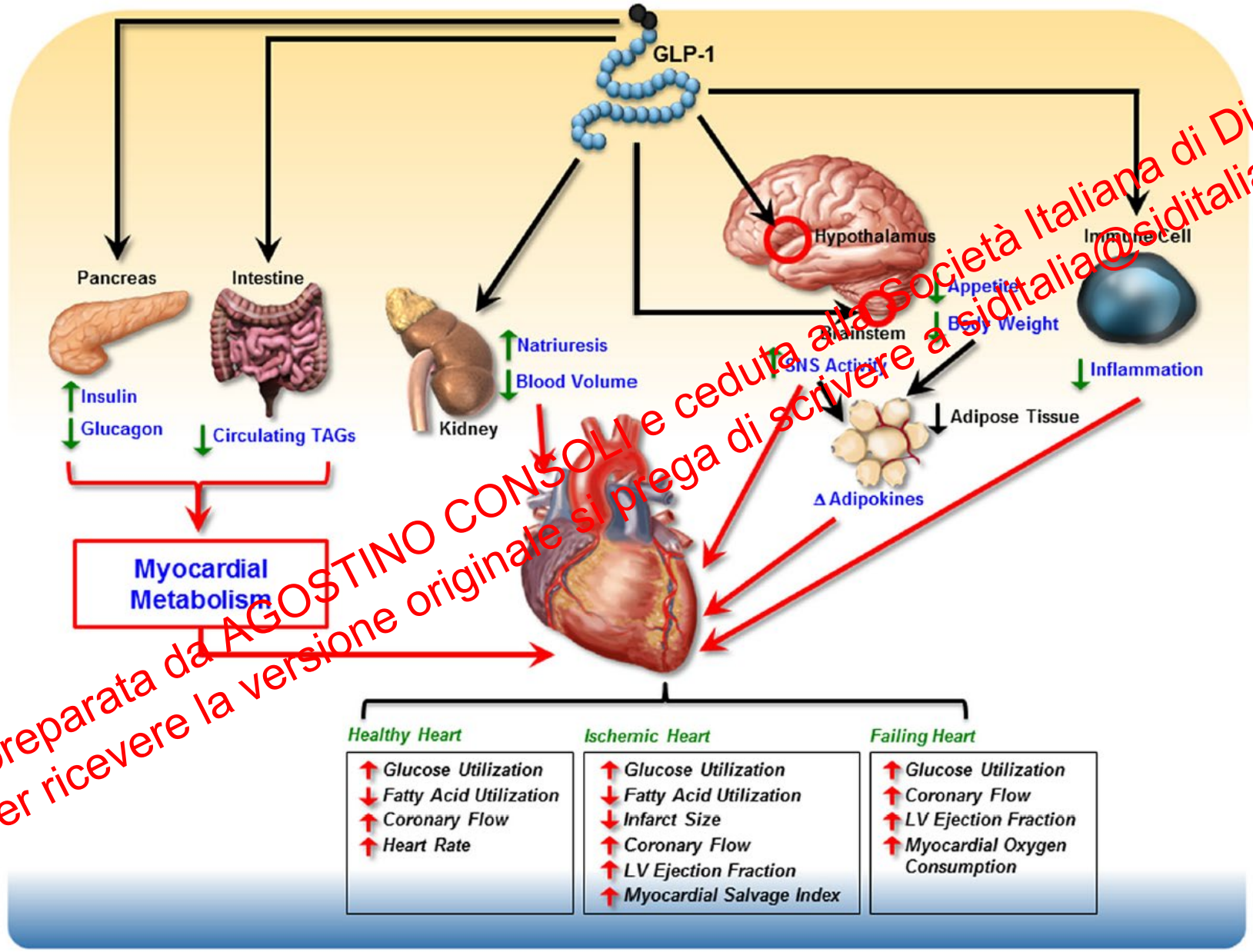
Pyke C, et al. Endocrinology 2014; 155: 1280

Increases in HR (significant) observed with the use of GLP-1 RAs

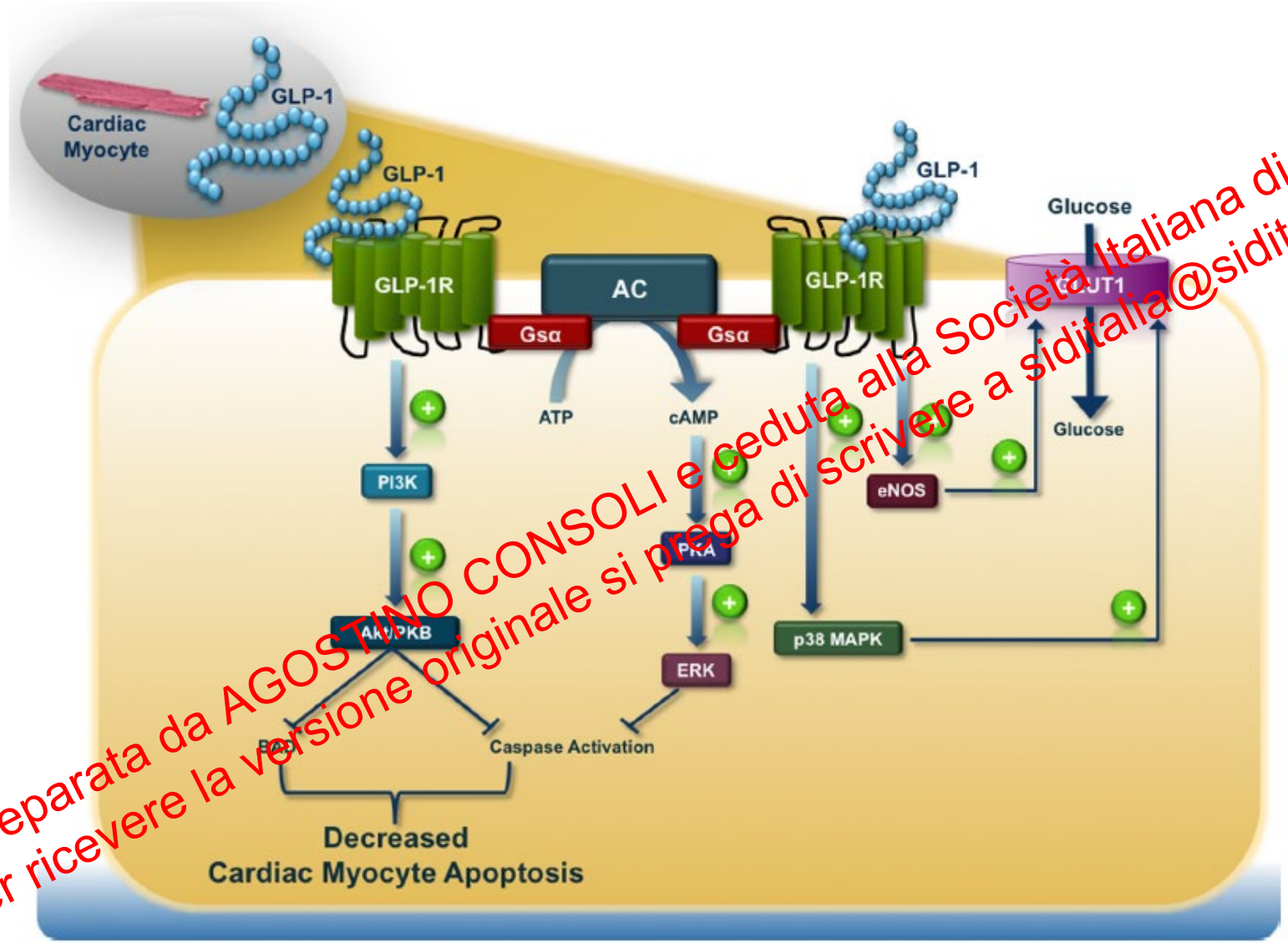
	Exenatide 10 µg BID	Exenatide 2 mg OW	Liraglutide 1.2 mg OD	Liraglutide 1.8 mg OD	Albiglutide 50 mg OW	Dulaglutide 1.5 mg OW	Lixisenatide 20 µg OD
Increase in heart rate (bpm)	**1–2**	**4**	**2–9**	**2–9**	**1–2**	**2–4**	**3**

BID, twice daily; GLP-1RA; glucagon-like peptide-1 receptor agonist; OD, once daily; OW, once weekly

Marre M et al. *Diabet Med* 2009;26:268
Nauck MA et al. *Diabetes Care* 2009;32:84
Zinman B et al. *Diabetes Care* 2009;32:1224
Buse JB et al. *Lancet* 2009;374:39
Diamant M et al. *Lancet* 2010;26;375:2234
Gill A et al. *Cardiovasc Diabetol* 2010;9:6
Eperzan Summary of Product Characteristics.
Trulicity Summary of Product Characteristics.
Meier JJ et al. *Diabetes care* 2015; 38:1263

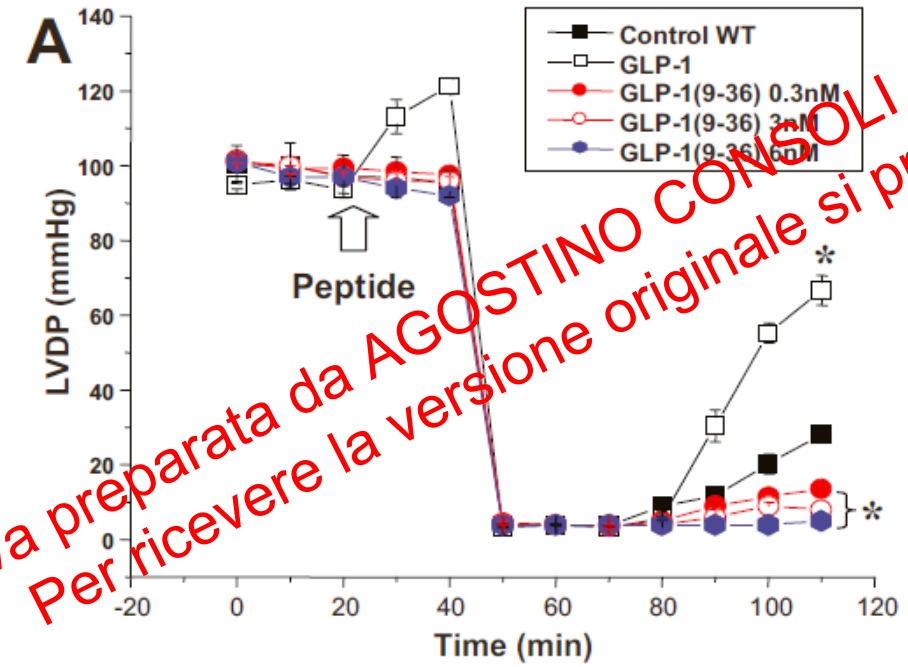


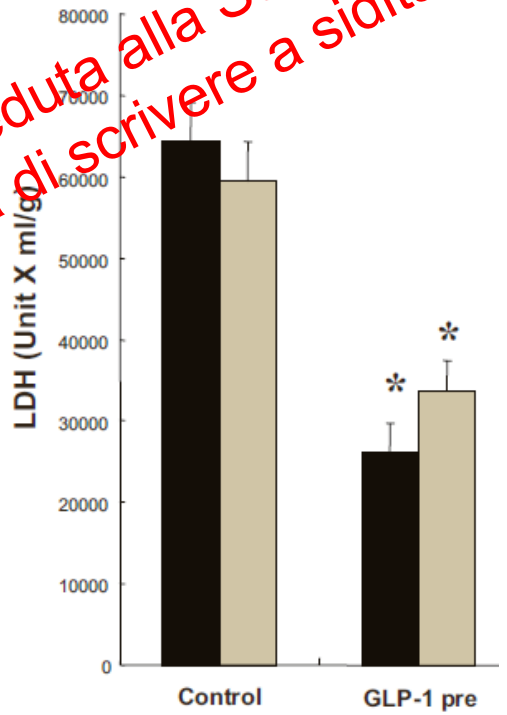
Ussher & Drucker, *Circ Res*. 2014;114:1788



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

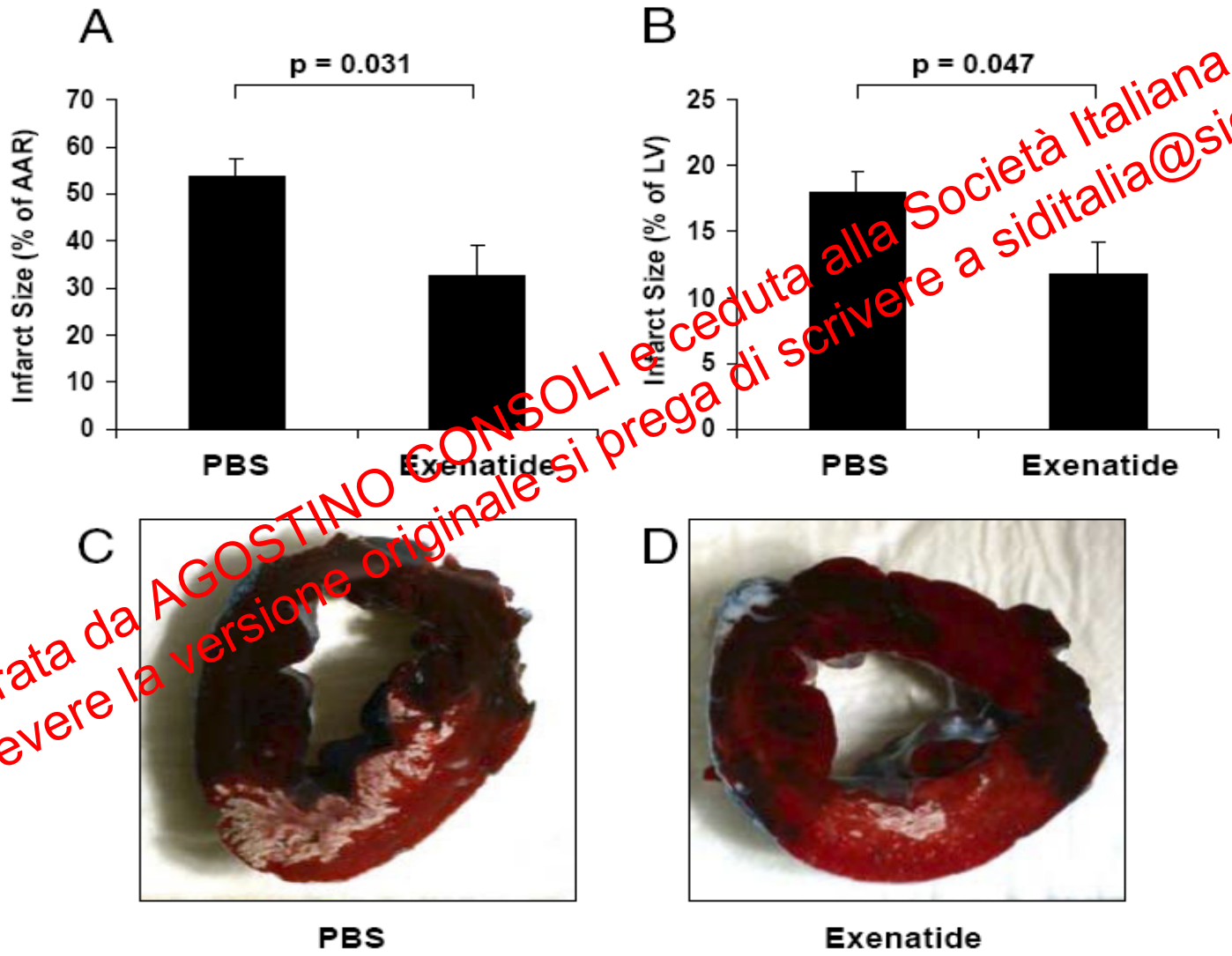
Effects of GLP-1 on recovery after ischemia/reperfusion injury in isolated murine heart





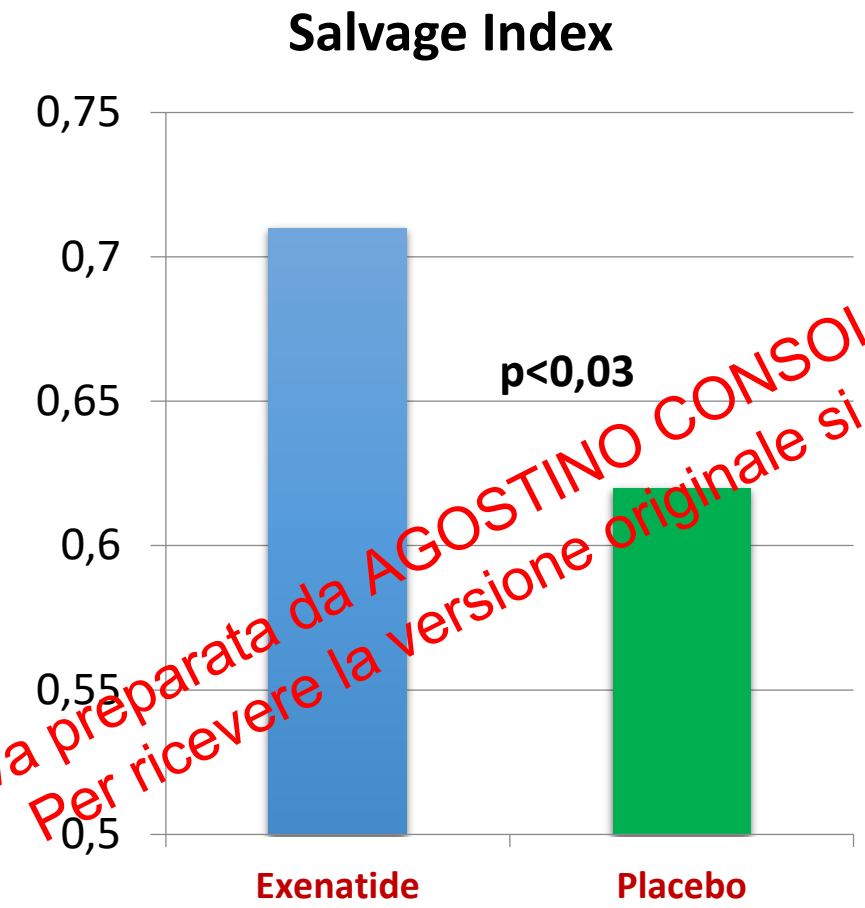
Ban K, et al. Circulation 2008, 117:2340

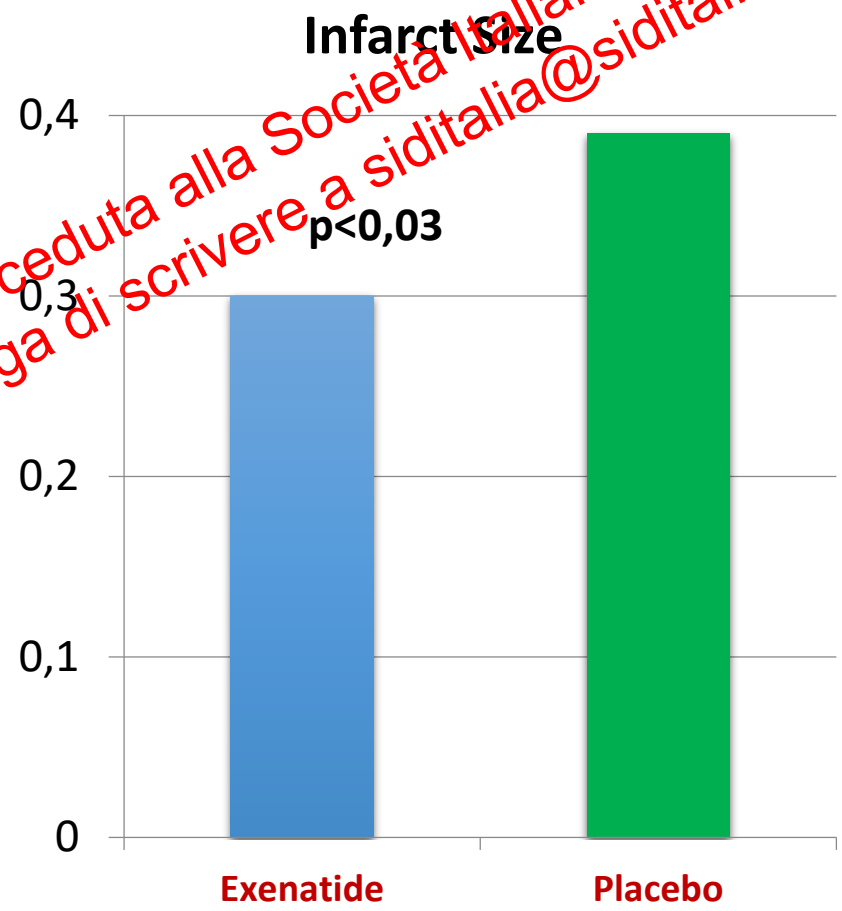
Exenatide Reduces Infarct Size in a Porcine Model of Ischemia and Reperfusion Injury



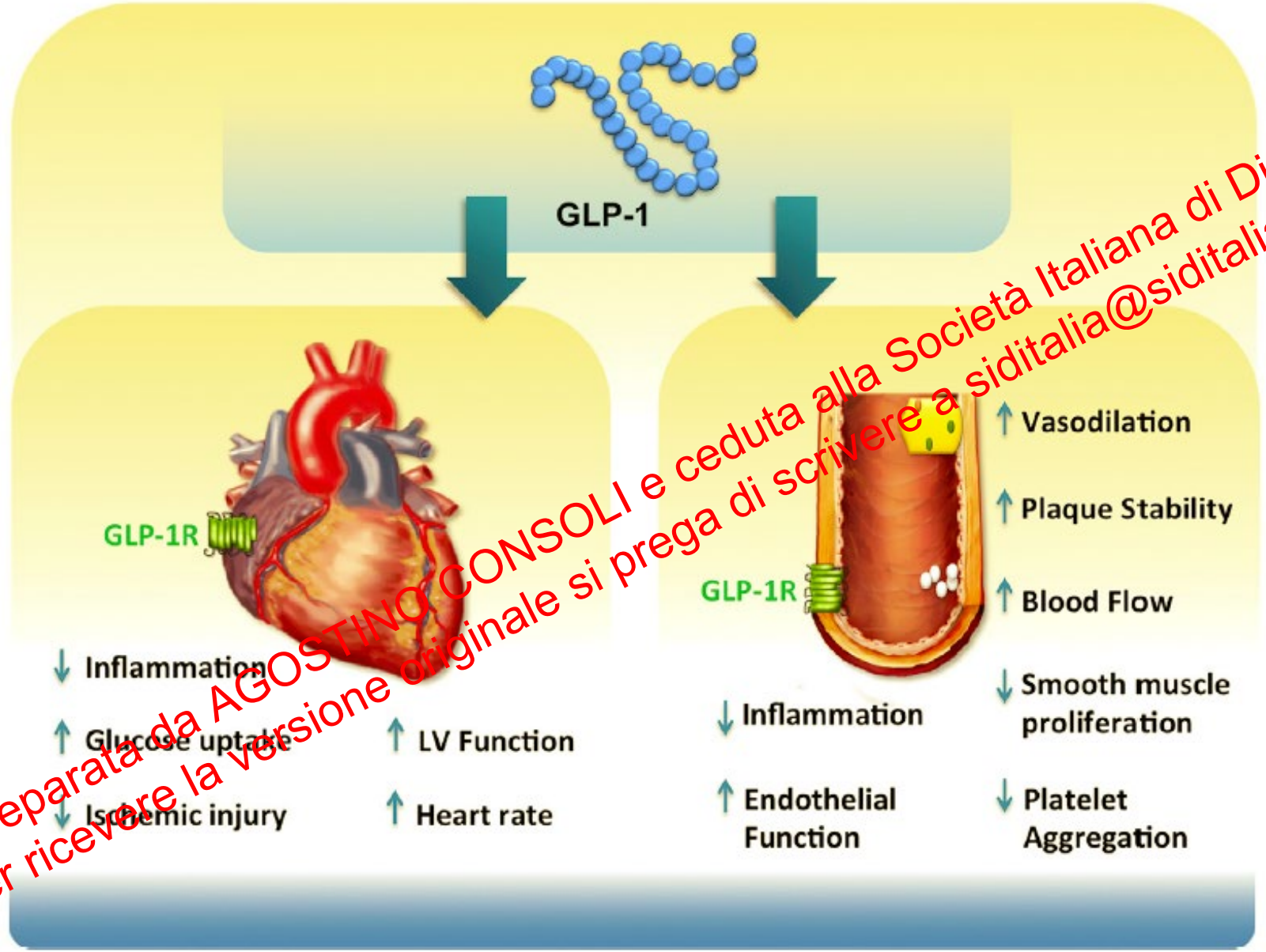
Timmers J, et al. JACC 2009, 53:501

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



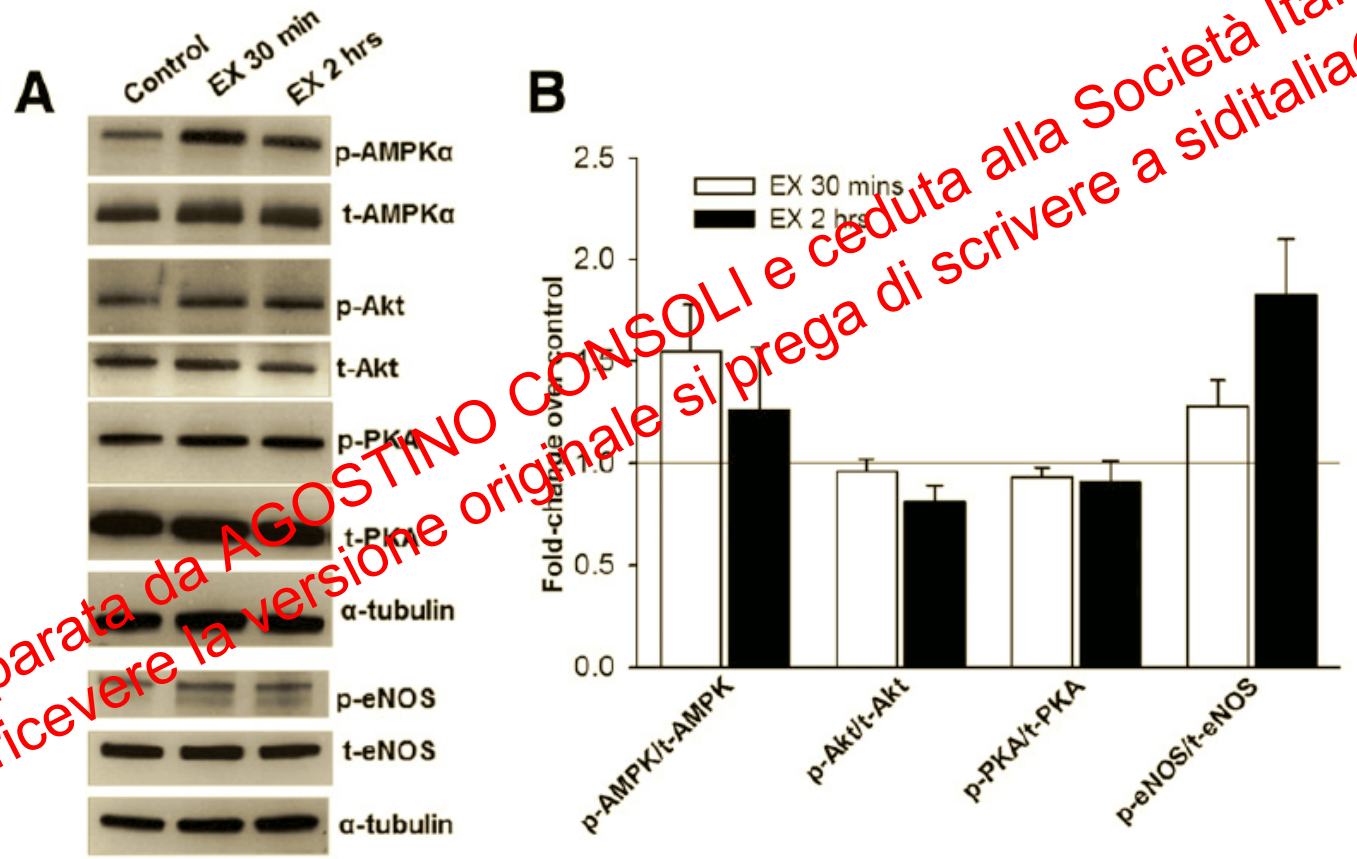


Lønborg J, et al. Eur Heart J 2012; 33:1491



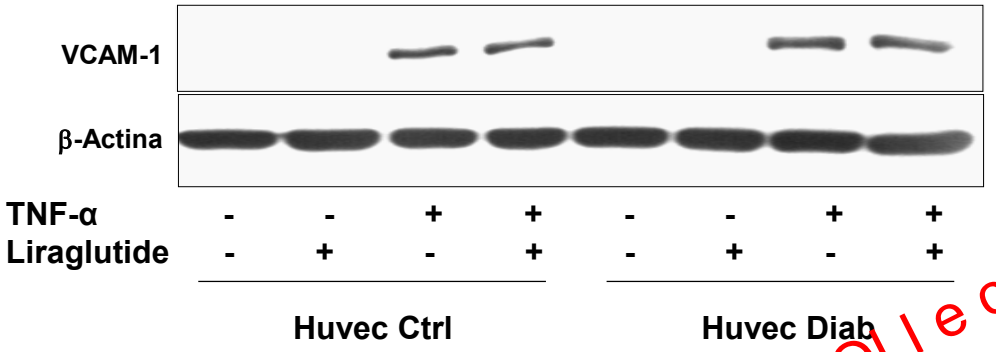
Ussher & Drucker, *Cell Metab* 2016;24:15

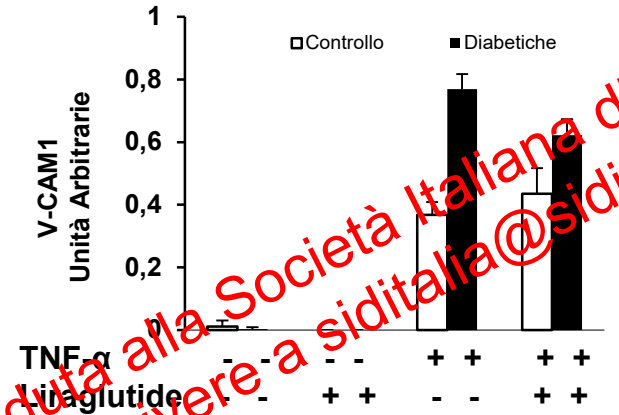
In vitro exenatide increases AMPK, Akt and eNOS phohosphorylation in human endothelial cells

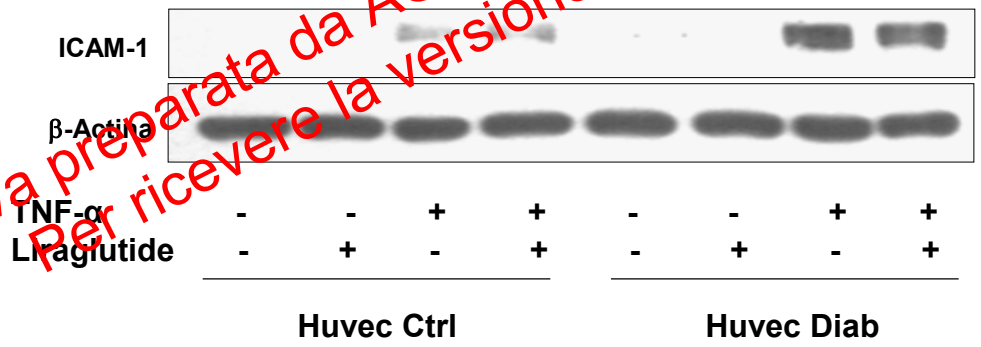


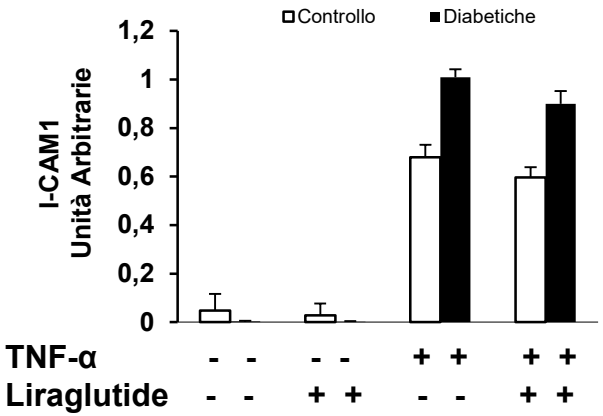
Koska et al., Diabetes 2015;64:2624

Liraglutide prevents TNFα induced VCAM-1 and ICAM-1 increased expression In HUVEC from umbelical cords of diabetic mothers



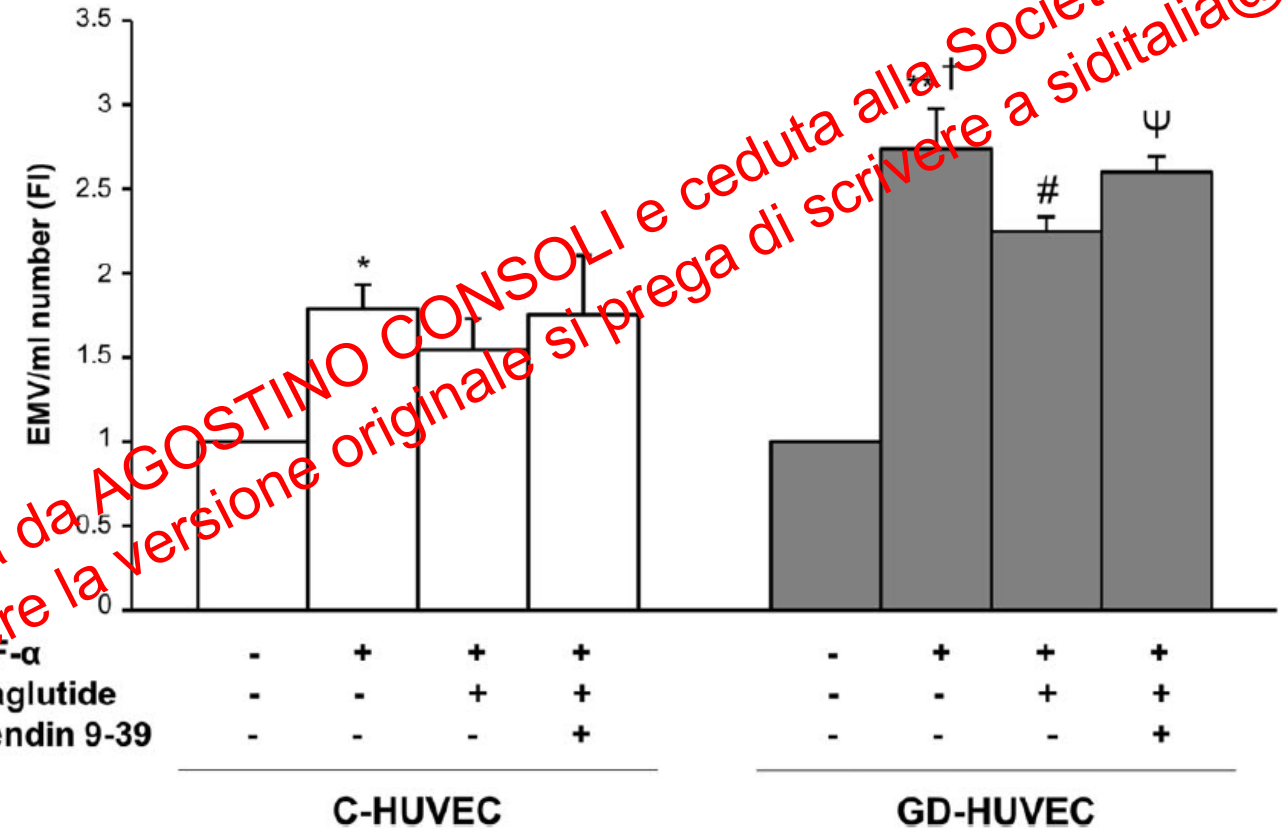






Di Tomo P, et al. Diabetes Metab Res Rev. 2017;33:e2925.

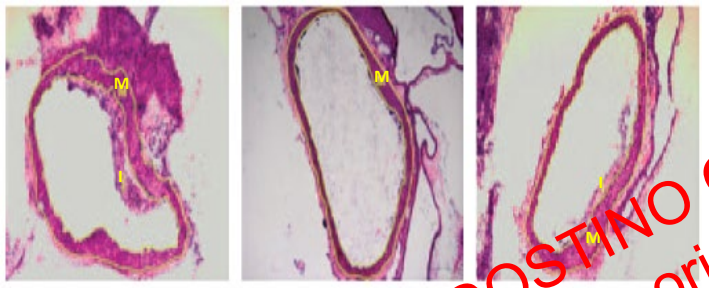
Effects of Liraglutide on Endothelial Micro Vescicles release in the culture medium in TNFα HUVEC from umbelical cords of diabetic mothers



Di Tomo P, et al. Diabetes Metab Res Rev. 2017;33:e2925.

Liraglutide inhibits progression of early, low-burden atherosclerotic lesion development in mice

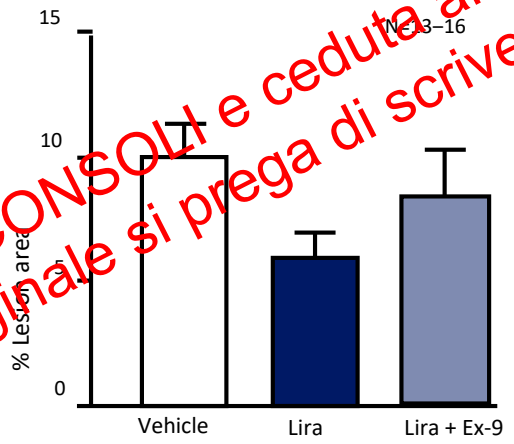
Lesion development



Vehicle | Lira | Lira + Ex-9

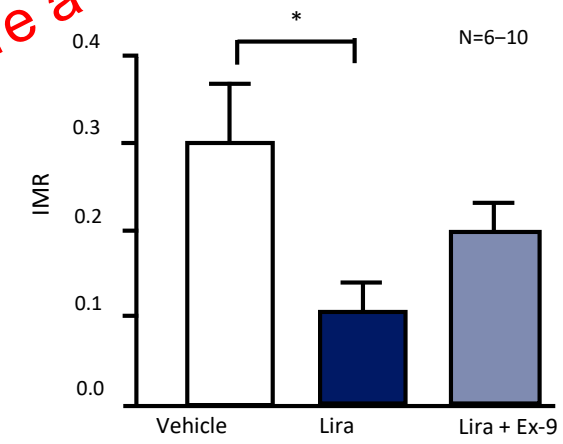
Haemotoxylin and eosin staining in the aortic arch

Lipid deposition



Oil red O staining performed in the aorta

Intima:media ratio (IMR)

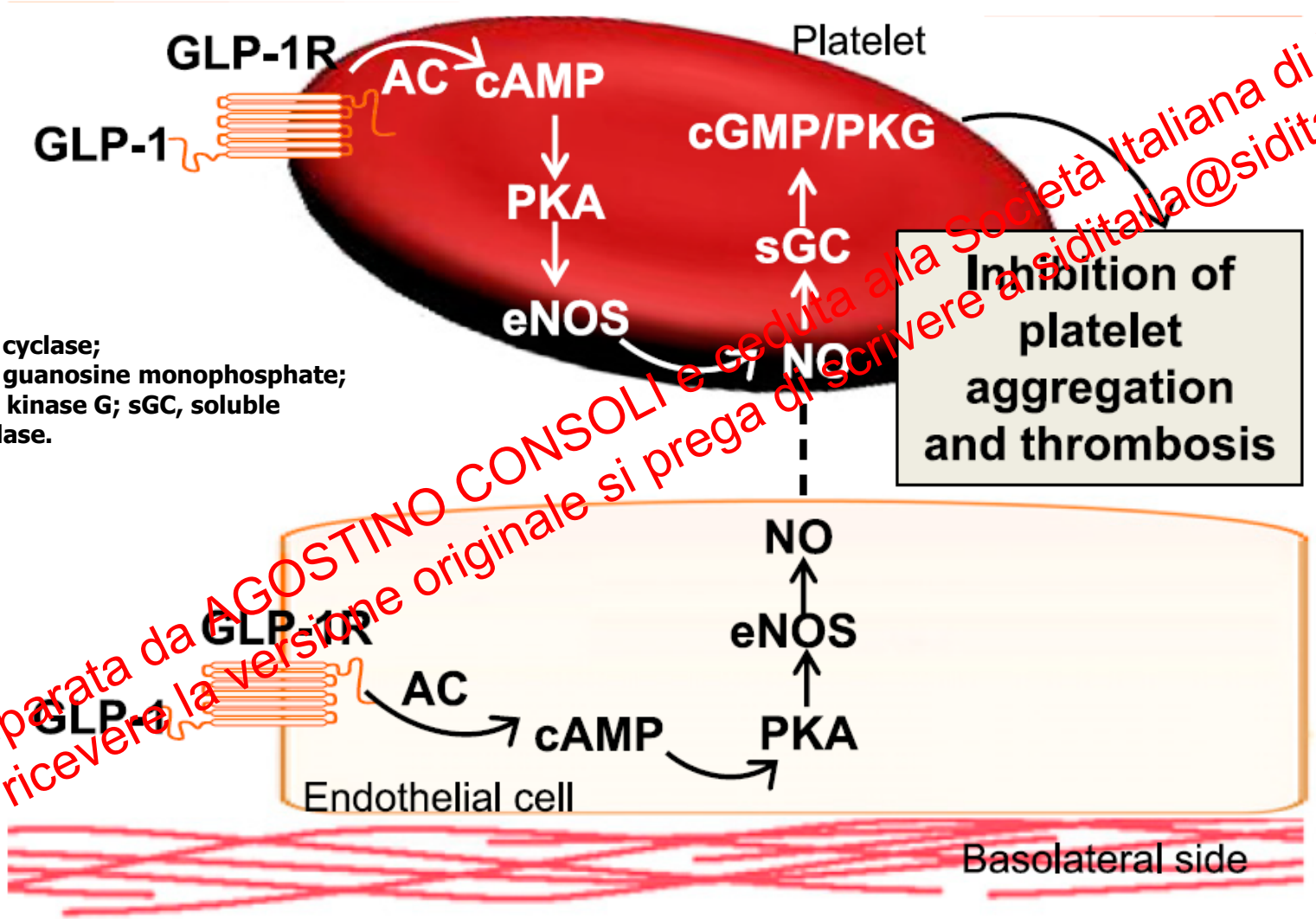


IMR analysis performed in the aortic arch

*P < 0.05 vs. vehicle by one-way ANOVA; data are mean ± SEM; performed in ApoE$^{-/-}$ mice with early, low-burden atherosclerotic lesions.
ApoE$^{-/-}$, apolipoprotein E knockout; ANOVA, analysis of variance; Ex-9, exendin-9; IMR, intima:media ratio; Lira, liraglutide; SEM, standard error of the mean.

Gaspari T et al. Diab Vasc Dis Res 2013;10:353–360

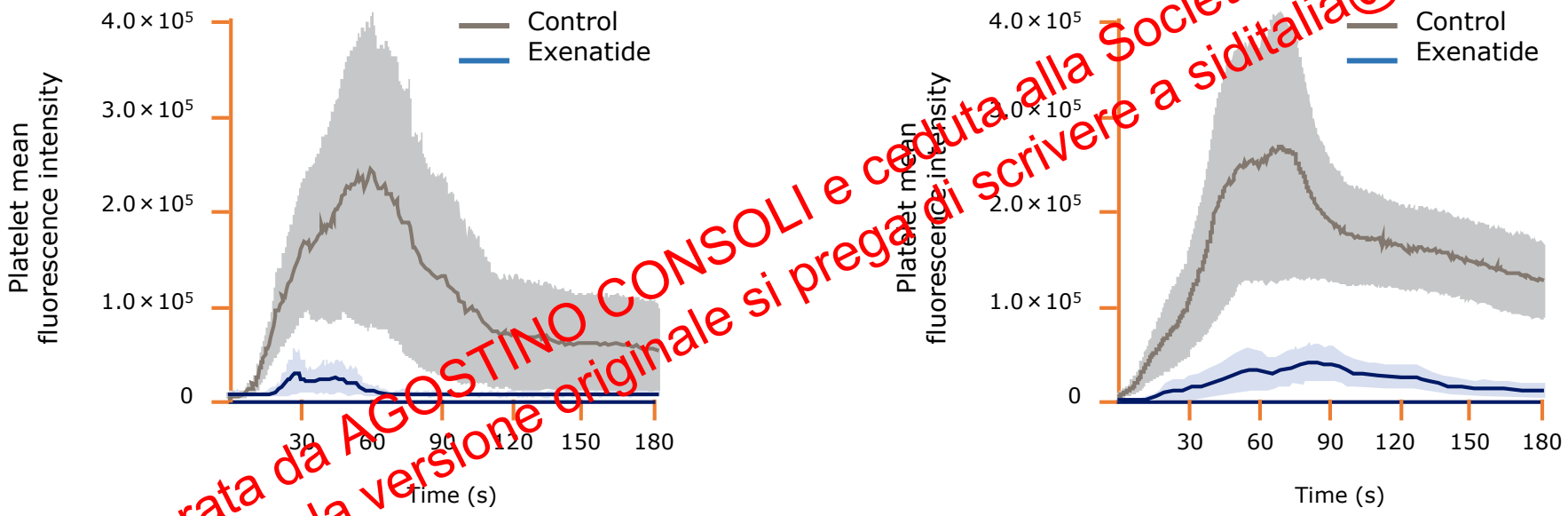
Glucagon-Like Peptide 1 Receptor activation attenuates platelet aggregation and thrombosis



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

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

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



Normoglycaemic mice

Hyperglycaemic mice

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

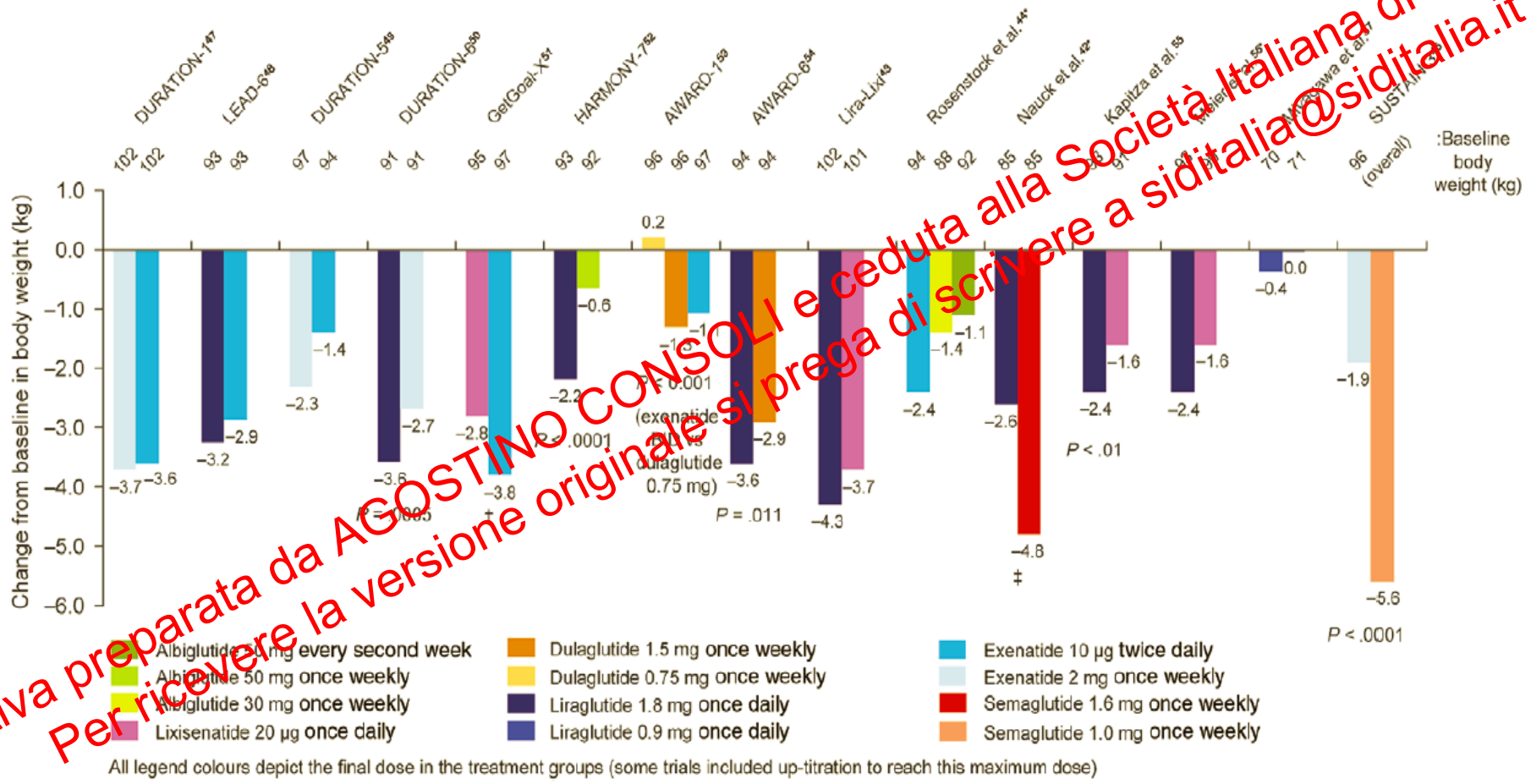
GLP-1RAs reduce body weight

Trial	No. of patients	
	GLP-1RA	Control
Bergenstal 2010	160	166
Buse 2004	129	123
Kendall 2005	241	247
Pratley 2010	221	219
Moretto 2008	78	78
Nauck 2009	242	122
Garber 2009	246	248
Diamant 2010	233	223
DeFronzo 2010	45	45
Russell Jones 2009	230	114
Heine 2005	282	267
Astrup 2009	93	98
Elkin 2010	20	20
Davies 2009	118	117
Rosenstock 2010	73	70
Zinman 2009	178	177
Ahrén 2010	96	98
Bergenstal 2009	124	124
Bunck 2009	36	33
Marre 2009	234	114
Nauck 2007	253	248
Overall; *p*=0.00*		

Change in body weight after at least 20 weeks' treatment, using random effects model.
*i.e. <0.01.
CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

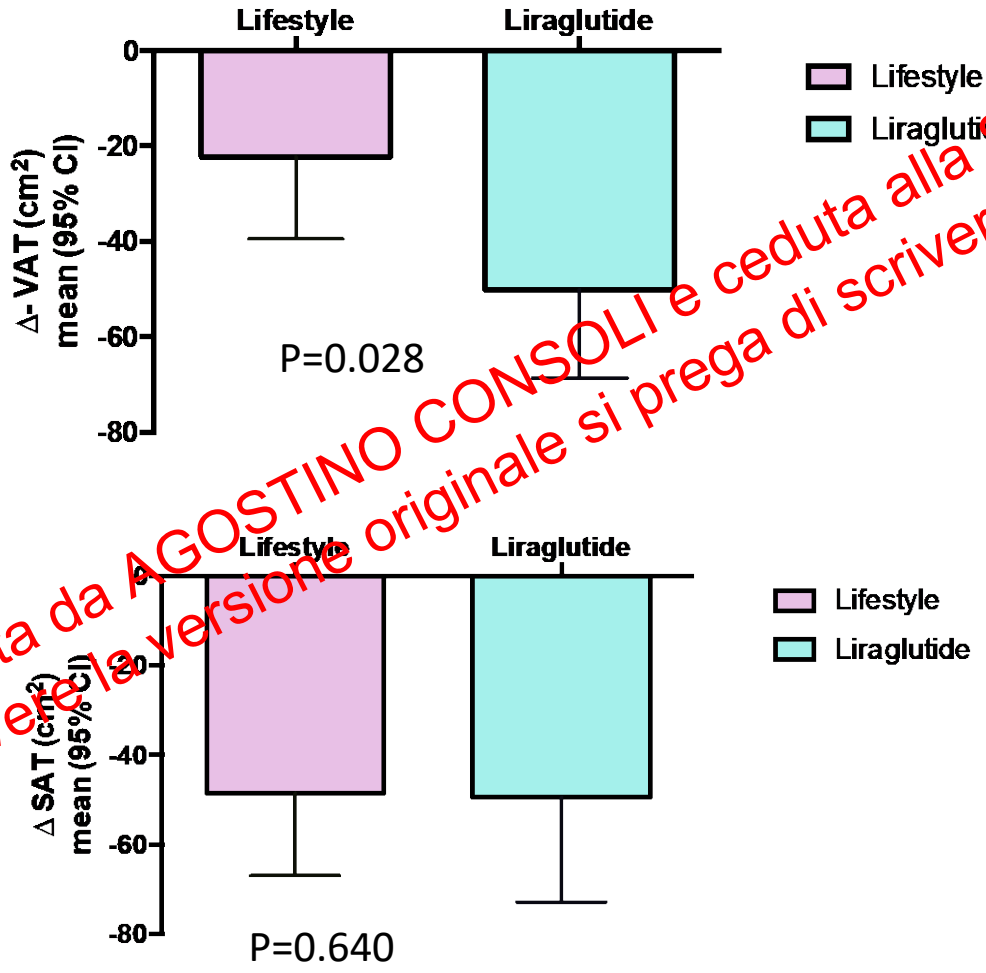
Vilsbøll T et al. Br Med J 2012;344:d7771

GLP-1RAs reduce body weight



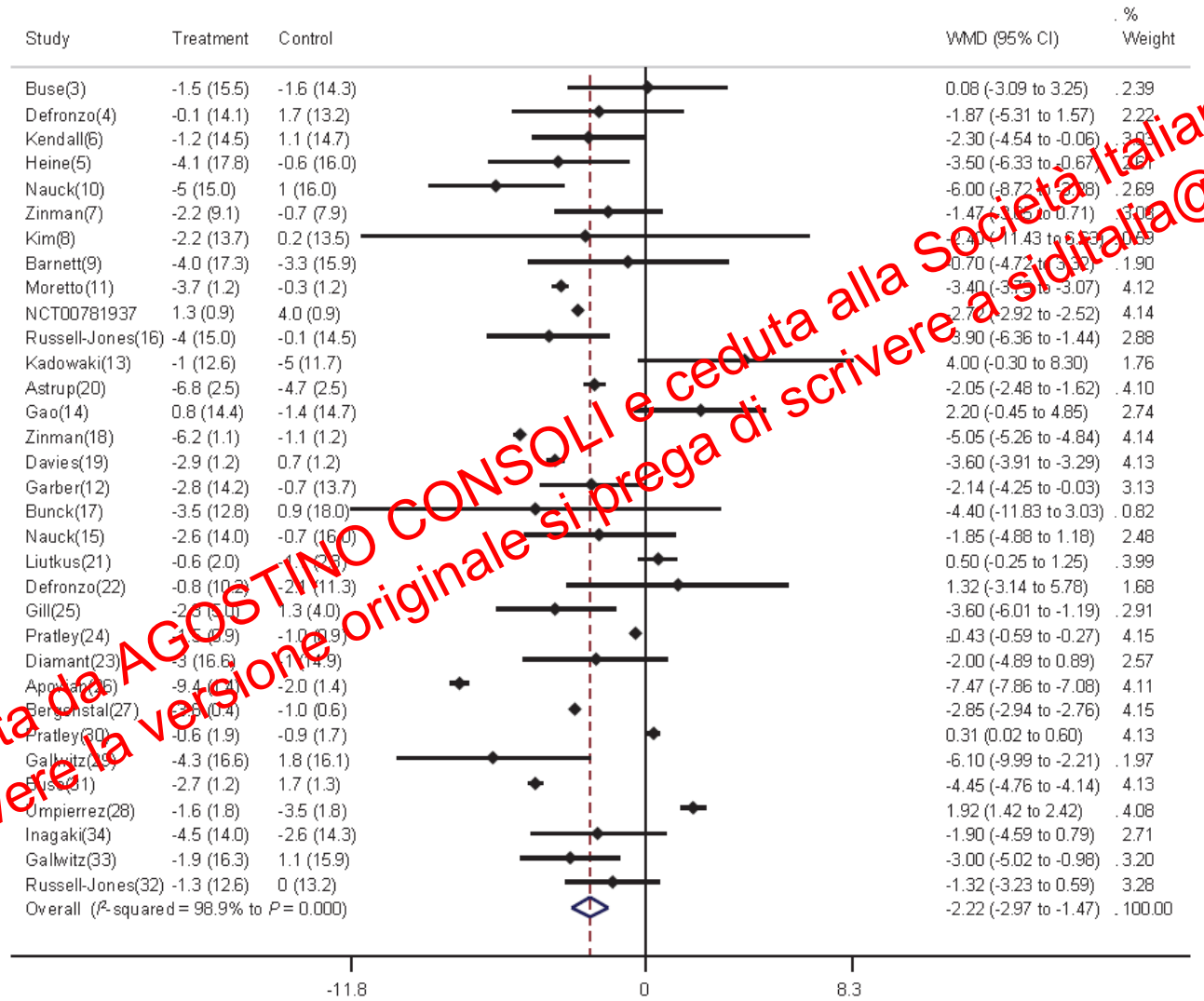
Dalsgaard NB, et al. Diabetes Obes Metab 2017; [Epub Oct 12]

Effects of Liraglutide or Lifestyle-induced weight loss on Visceral and Subcutaneous MRI determined Adipose Tissue content



Santilli F, et al. Diabetes Care 2017; 40:1556

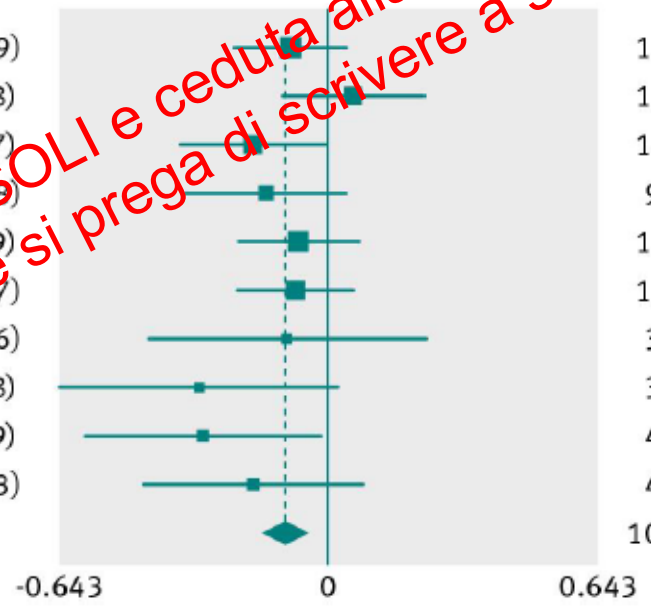
Meta-analysis of change in systolic blood pressure (mm Hg) in RCTs after at least 12 weeks of treatment with GLP-1 RA



Katout M al. Am J Hypertens 2014; 27: 130

Meta-analysis of change in total cholesterol (mmol/L) in RCTs after at least 20 weeks of treatment with GLP-1 RA

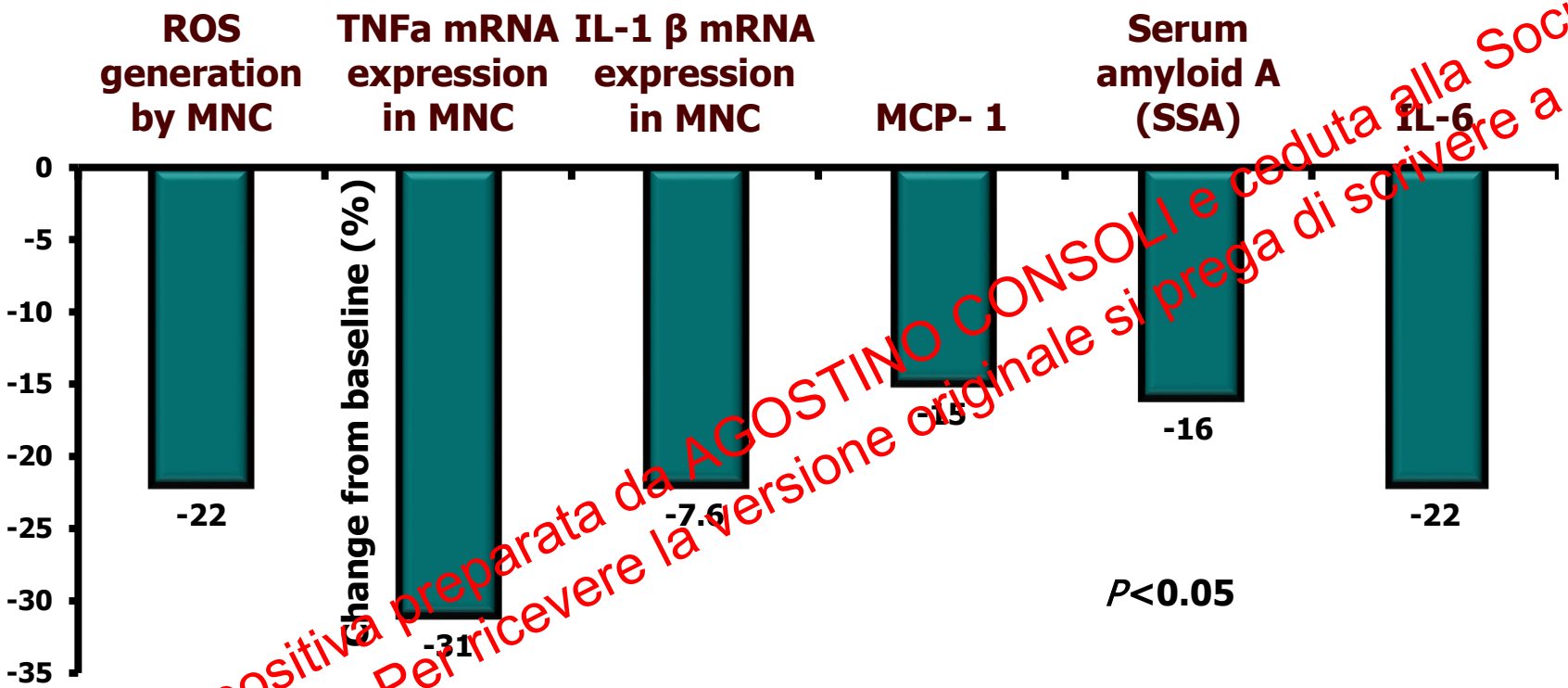
Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weight (%)	Weighted mean difference (95% CI)
Heine 2005	282	267	-0.1 (0.7)	-0.0 (0.9)	18.57	-0.09 (-0.23 to 0.05)
Bergensthal 2010	160	166	0.1 (0.7)	0.0 (0.8)	12.30	0.06 (-0.11 to 0.23)
Buse 2009	129	123	-0.1 (0.7)	0.1 (0.7)	11.22	-0.18 (-0.35 to -0.01)
Davies 2009	118	117	-0.4 (0.8)	-0.3 (0.8)	9.04	-0.15 (-0.34 to 0.04)
Kendall 2005	241	247	0.0 (0.8)	0.1 (0.9)	15.64	-0.07 (-0.22 to 0.08)
Diamant 2010	233	223	-0.1 (0.8)	-0.0 (0.7)	17.92	-0.08 (-0.22 to 0.06)
Bunck 2009	36	33	-0.3 (0.8)	-0.2 (0.6)	3.09	-0.10 (-0.43 to 0.23)
DeFronzo 2010	45	45	0.1 (0.8)	0.4 (0.8)	3.08	-0.31 (-0.64 to 0.02)
Moretto 2008	78	77	-0.1 (0.9)	0.2 (0.9)	4.24	-0.30 (-0.58 to -0.02)
Zinman 2009	178	177	-0.2 (1.2)	-0.0 (1.3)	4.90	-0.18 (-0.44 to 0.08)
Overall; P=0.468					100.00	-0.10 (-0.16 to -0.04)



Vilsbøll T, et al. Br Med J 2012; 344:d7771

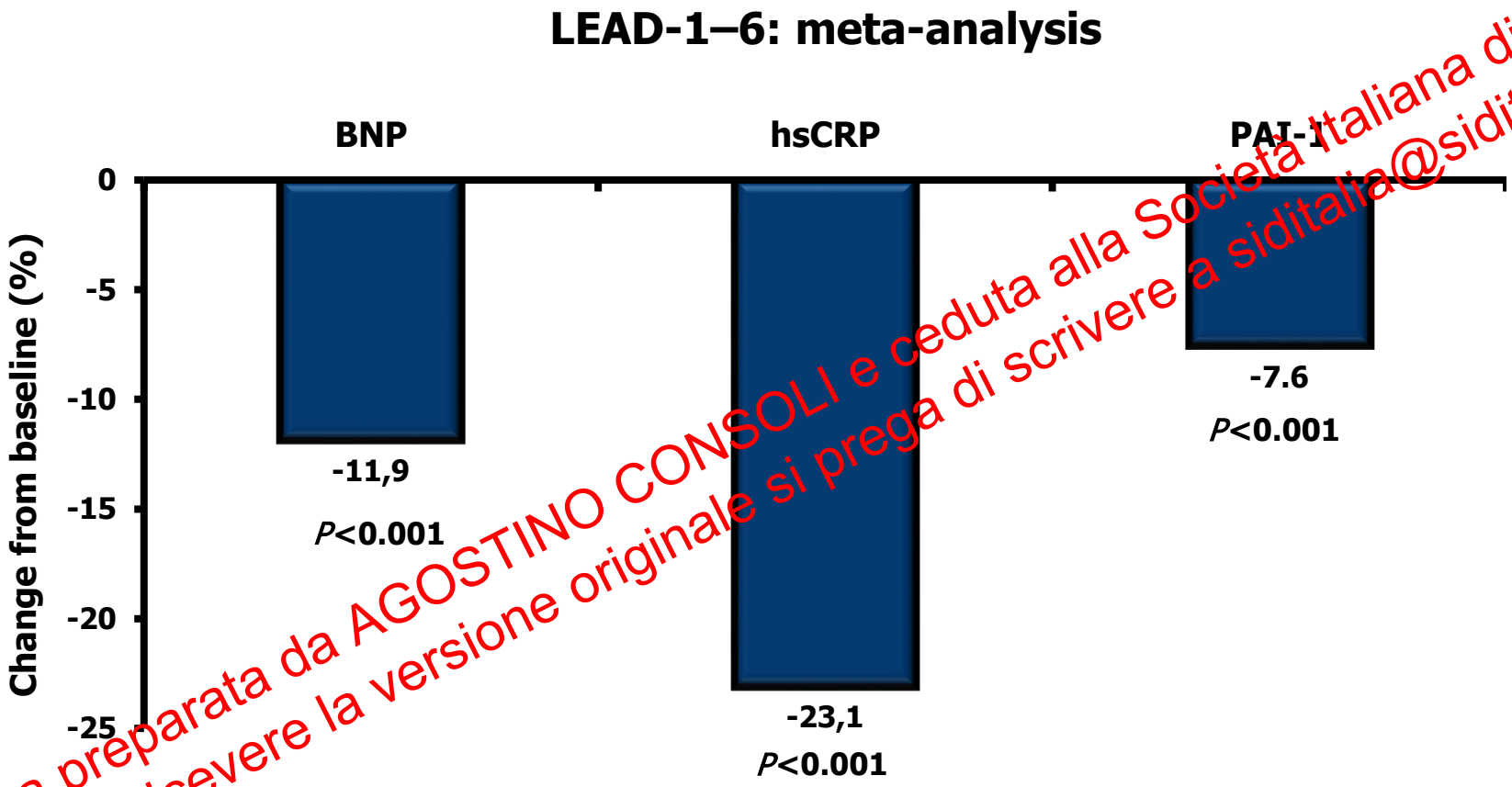
Exenatide anti-inflammatory effects in obese subjects with T2DM

Change from baseline to week 12 with exenatide 10 µg twice daily in obese T2DM patients (mean BMI = 39.8 kg/m^2)



Chaudhuri K, et al. J Clin Endocrinol Metab 2012; 97: 198

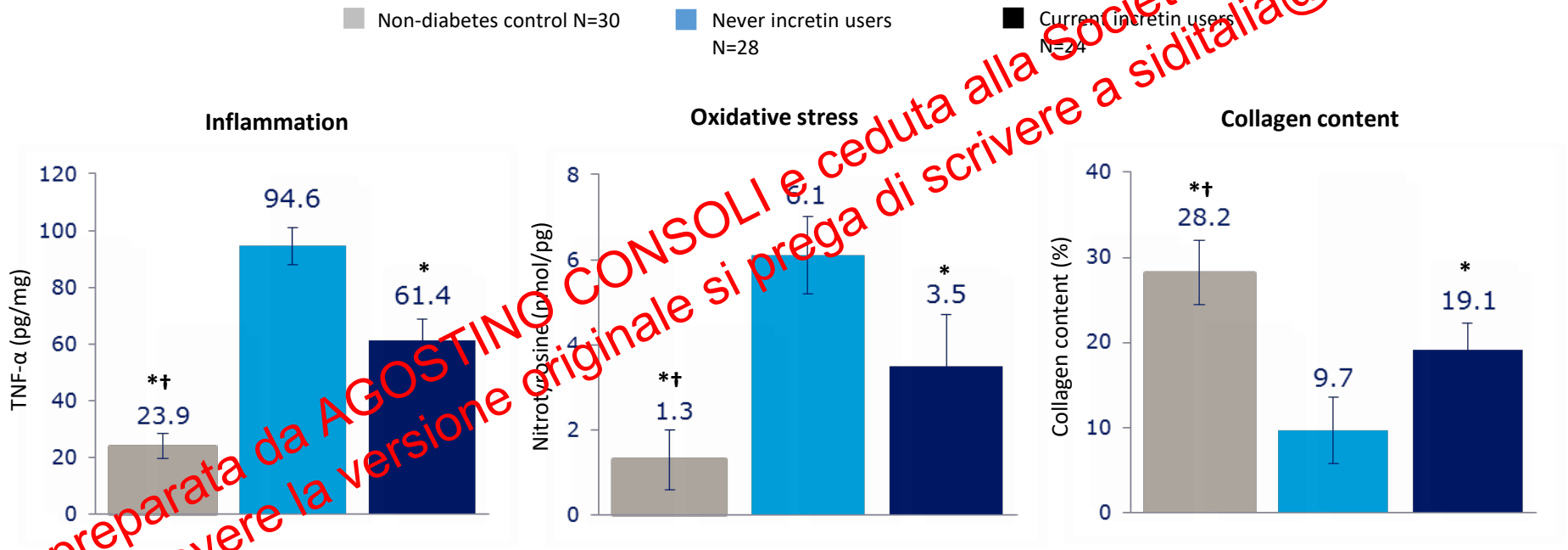
Changes in CV risk biomarkers in liraglutide treated T2DM subjects



*Change from baseline to week 26 with liraglutide 1.8 mg once daily

Plutzky J, et al. Diabetologia 2009; 52 (Suppl. 1): S299
Plutzky J, et al. Circulation 2009; 120:S397

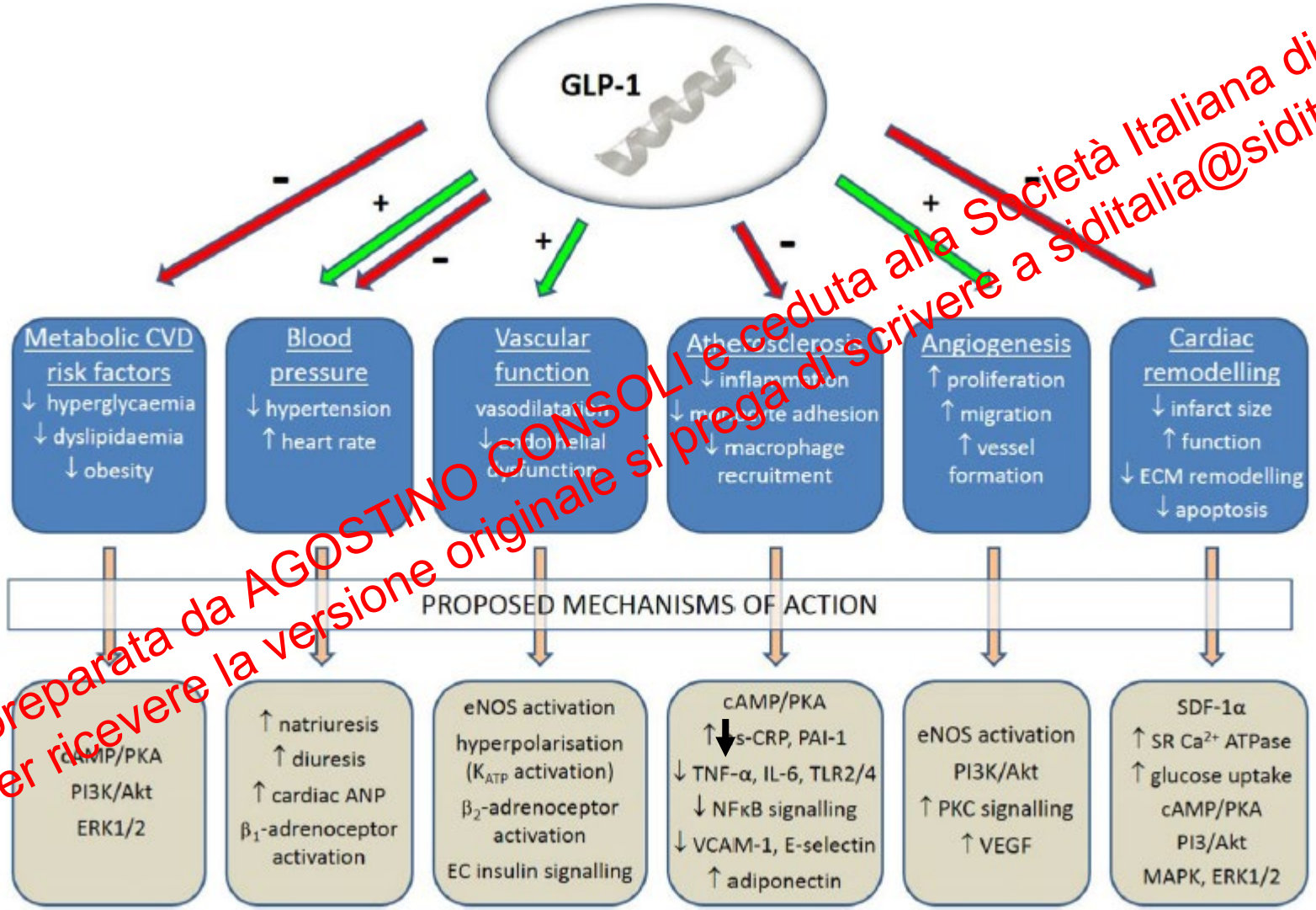
Incretin therapy improves indicators of plaque stability in patients with T2DM



*p<0.05 vs. never users group; †p<0.05 vs. current users group.
Atherosclerotic plaques from patients undergoing carotid endarterectomy; patients included patients without diabetes and patients with T2DM ± incretin therapy.
TNF-α, tumour necrosis factor-α; T2DM, type 2 diabetes mellitus.
Balestrieri ML et al. *Diabetes* 2015;64:1395–1406.

Balestrieri ML et al. *Diabetes* 2015;64:1395

Proposed mechanisms underlying the reported cardiovascular actions of GLP-1.



Tate M., BJP 2014

IN GOD WE TRUST
ALL OTHERS MUST SHOW DATA

W.E. Demings

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

N Engl J Med 2007; 356:2457

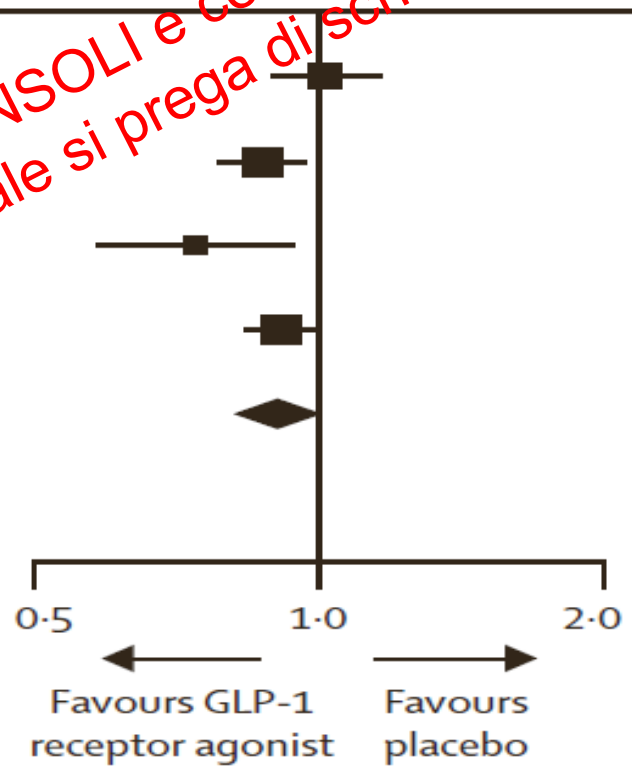
Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis

Lancet Diabetes Endocrinol 2017
Published Online
December 6, 2017

Three-point MACE

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)	0·776
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)	0·015
SUSTAIN 6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)	0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)	0·061
Overall			**0·90 (0·82–0·99)**	**0·033**

Test for heterogeneity: $p=0·11$, $I^2=50\%$



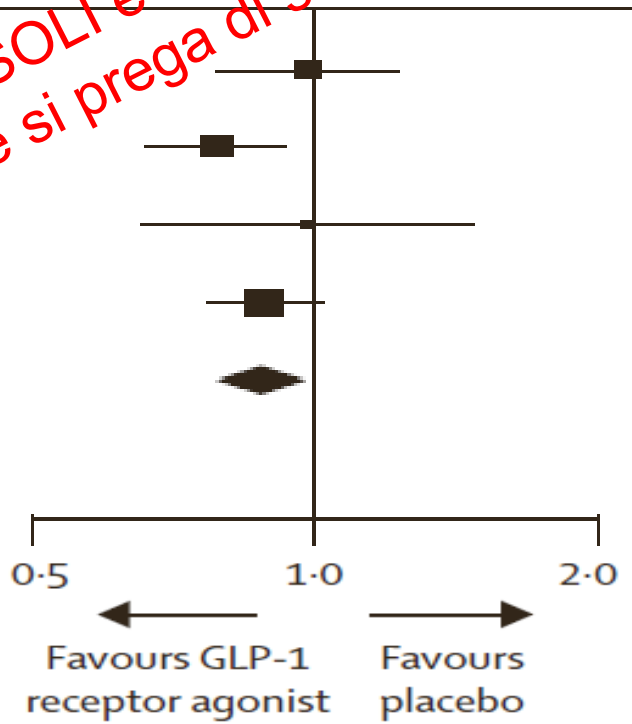
Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis

Lancet Diabetes Endocrinol 2017
Published Online
December 6, 2017

Cardiovascular mortality

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)	0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)	0·007
SUSTAIN 6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)	0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)	0·096
Overall			**0·87 (0·79–0·96)**	**0·007**

Test for heterogeneity: $p=0·43$, $I^2=0\%$



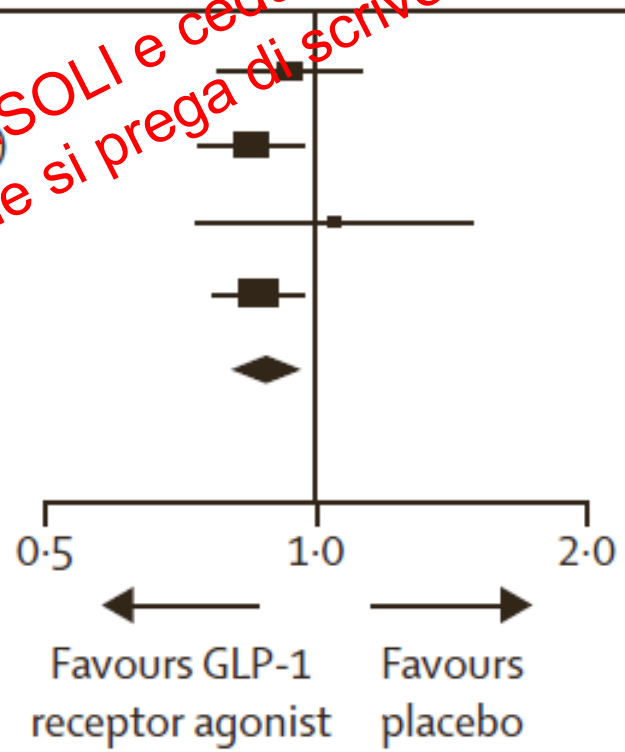
Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis

Lancet Diabetes Endocrinol 2017
Published Online
December 6, 2017

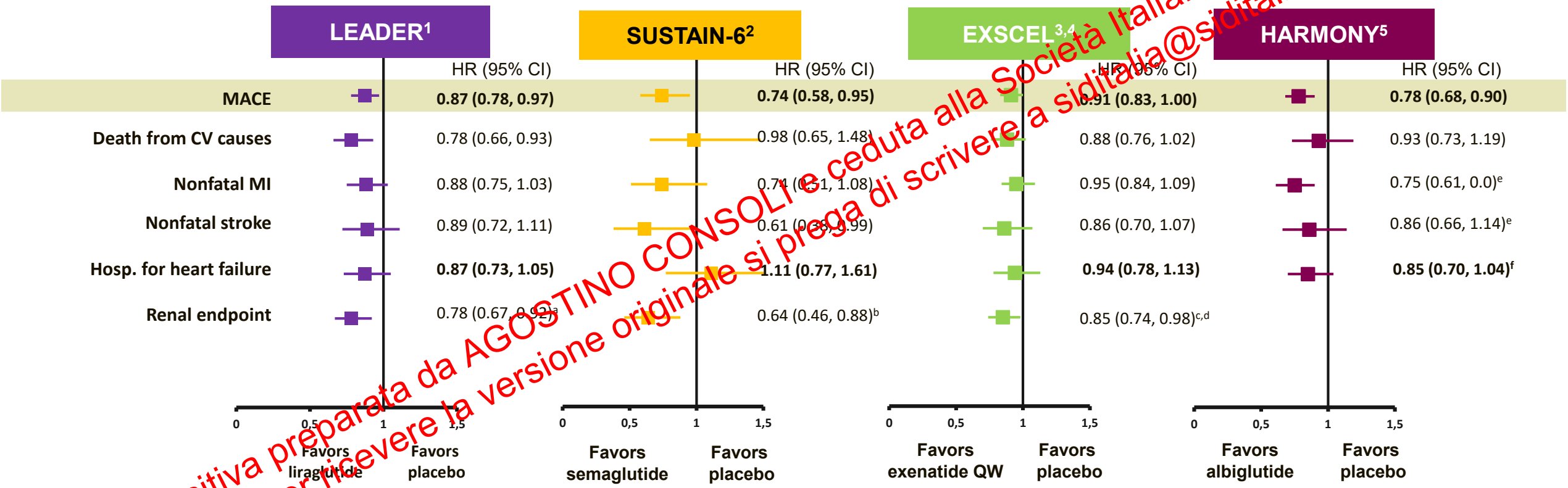
All-cause mortality

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)	0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)	0·020
SUSTAIN 6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)	0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)	0·016*
Overall			**0·88 (0·81–0·95)**	**0·002**

Test for heterogeneity: p=0·663, I^2=0%



GLP-1 Receptor Agonists -CVOTs

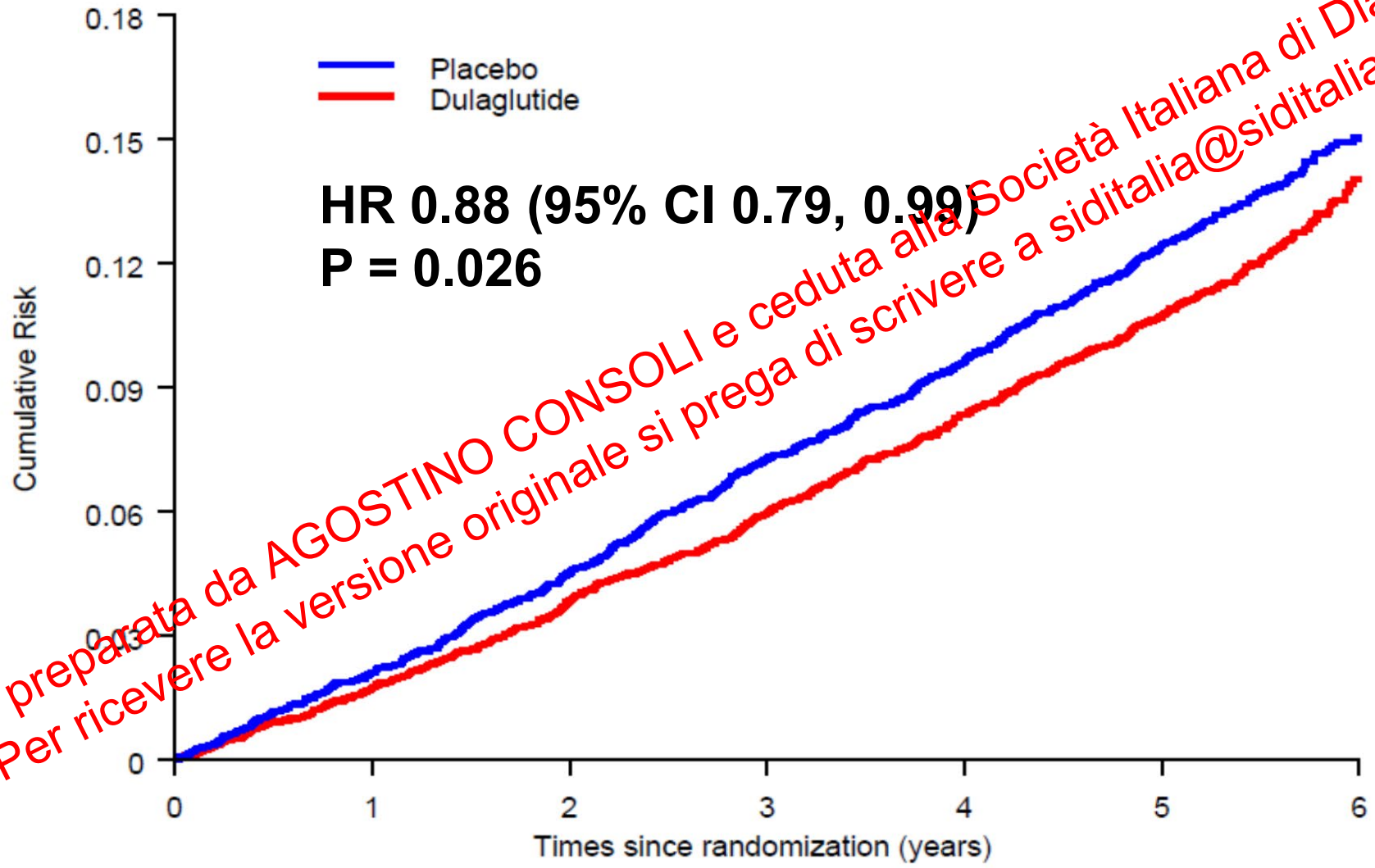


[a]New onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73 m², the need for continuous renal-replacement therapy, or death from renal disease; [b]New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml/min/1.73 m² (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; [c]40% eGFR decline, renal replacement, renal death, or new-onset macroalbuminuria; [d]Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline glycated hemoglobin, eGFR, and body-mass index [e]Includes fatal and nonfatal events; [f]Composite of CV death or hospitalization for heart failure. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; QW, once weekly

[1]Marso SP, et al. *N Engl J Med* 2016;375:311–322; [2]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844; [3]Holman RR, et al. Article and supplementary appendix. *N Engl J Med* 2017;377:1228-1239;
[4]Bethel MA, et al. Presented at: ADA 78th Scientific Sessions; June 22-26, 2018; Orlando, FL. Poster 522-P; [5]Hernandez AF, et al. Online ahead of print. *Lancet.* 2018.

Dulaglutide's Effect on the CV Composite

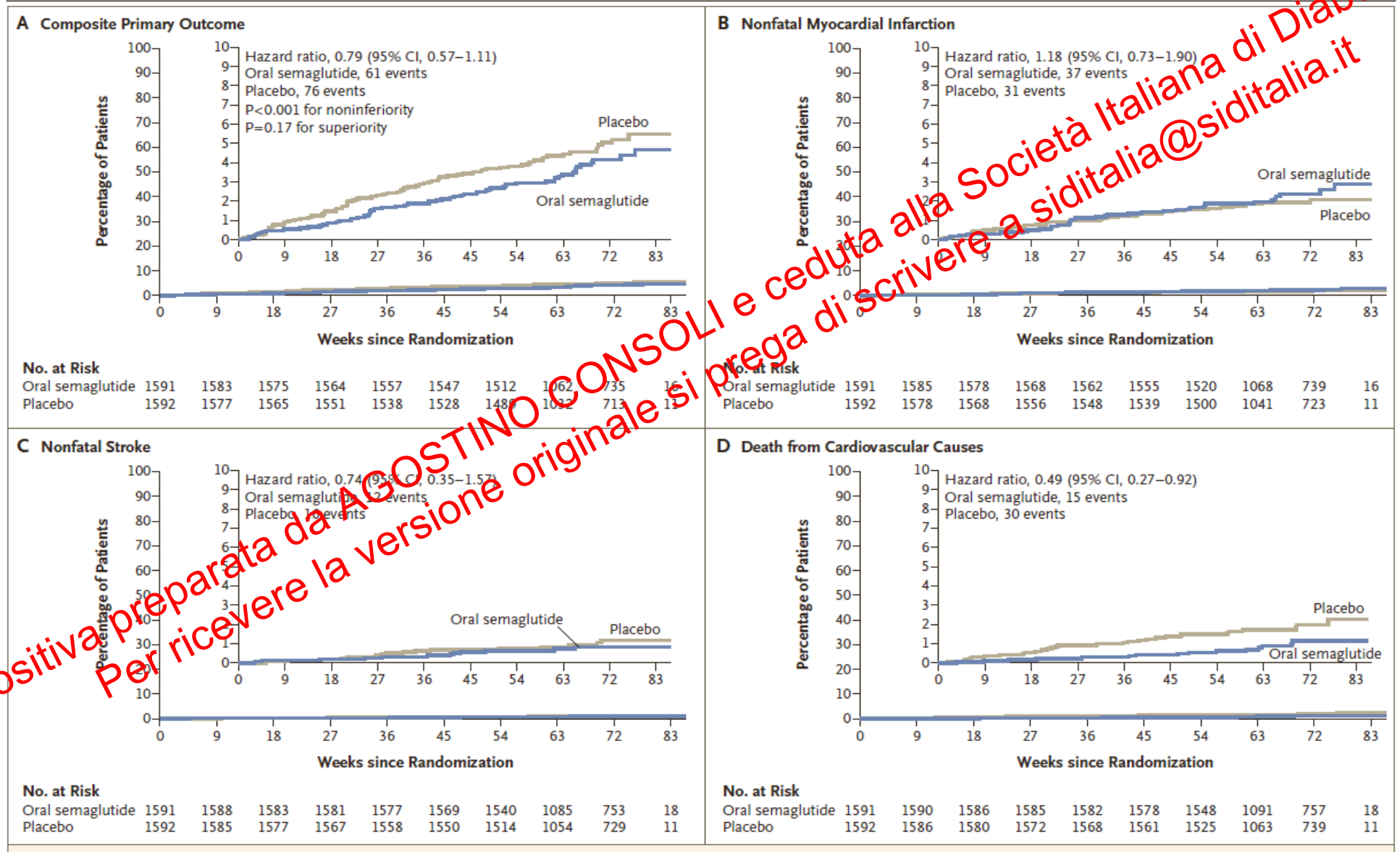
Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



No. at Risk							
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

PIONEER 6 results.

This article was published on June 11, 2019, at NEJM.org.



Solid evidence demonstrate reduction of CV events occurrence associated with the use of GLP-1 Ras in high risk T2DM subjects.

QUESTIONS

- **Is this a class effect or is it peculiar of some molecules?**
- **What is the meaning of «superiority» when in the control arm a worse glycemic control is achieved while more traditional diabetes drugs are used and in larger doses ?**
- **How much of the observed results are due to a DIRECT effect of the drug and how much to the improvement in metabolic parameters that these drugs bring about ?**

Estimated tretment difference between the active and the placebo arms in HbA1c, Body Weight and SBP

TRIAL	HbA1c (%)	Body Weight (kg)	SBP (mmHG)
EXSCEL	**- 0.53**	**- 1.27**	**- 1.57**
LEADER	**- 0.45**	**- 2.30**	**- 1.24**
SUSTAIN-6	**- 1.05**	**- 4.35**	**- 2.59**

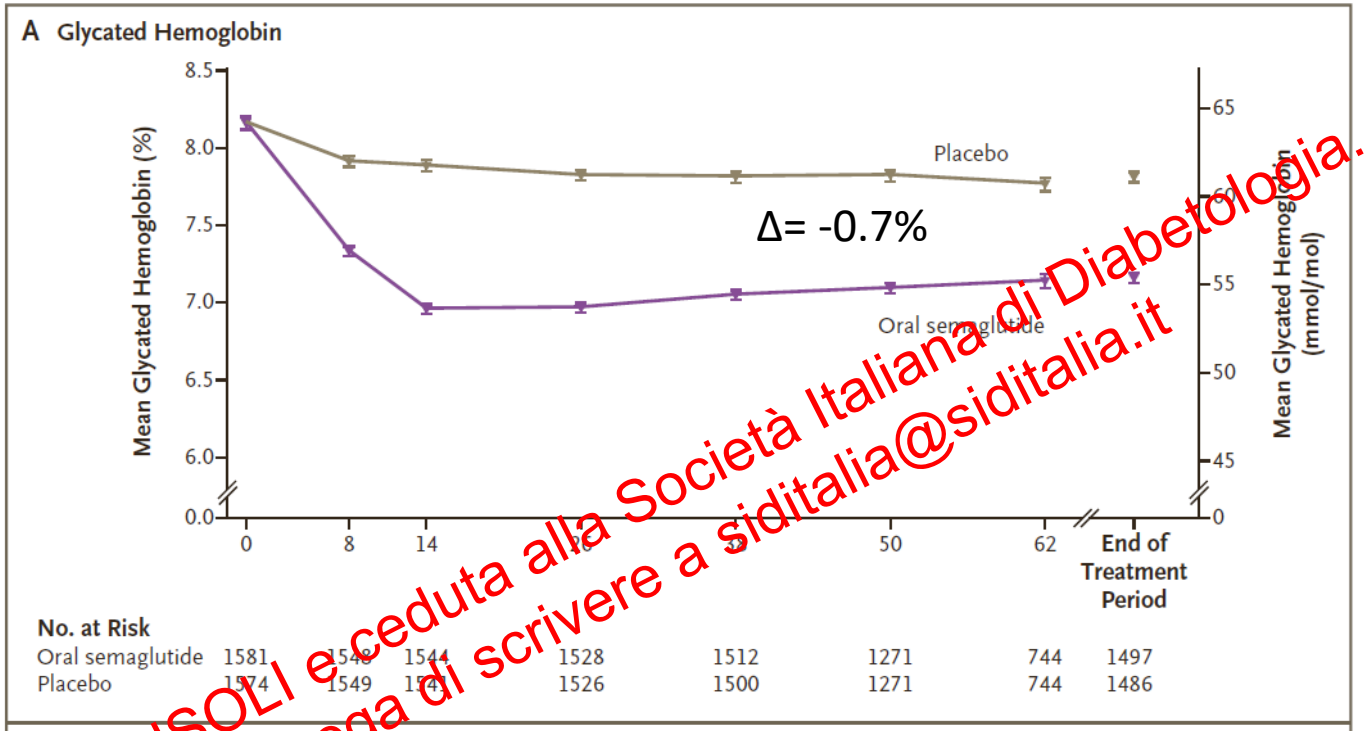
Summary of Effect on Clinical Measures

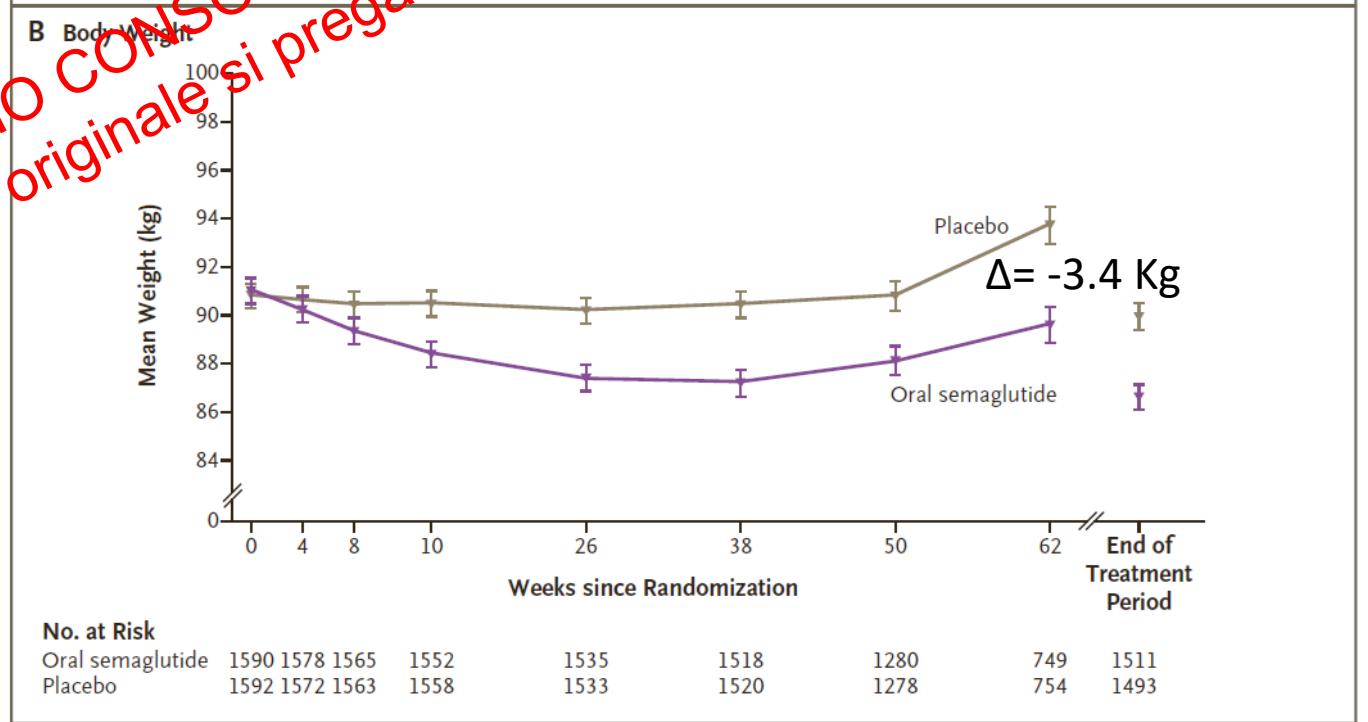
Measurement	Dulaglutide	Placebo	Difference	P
HbA1c (%)	-0.46	0.16	-0.61	<0.0001
LDL (mmol/l)	-0.15	-0.09	-0.05	0.001
Weight (kg)	-2.95	-1.49	-1.46	<0.0001
Body Mass Index	-1.08	-0.55	-0.53	<0.0001
Waist:Hip (Men)	-0.007	-0.004	-0.003	0.04
Waist:Hip (Women)	-0.005	0.0	-0.005	0.009
Systolic BP (mm Hg)	-3.15	-1.44	-1.70	<0.0001
Mean BP (mm)	-2.34	-1.85	-0.49	<0.0001
Heart Rate (bpm)	2.95	1.09	1.87	<0.0001

PIONEER 6 results.

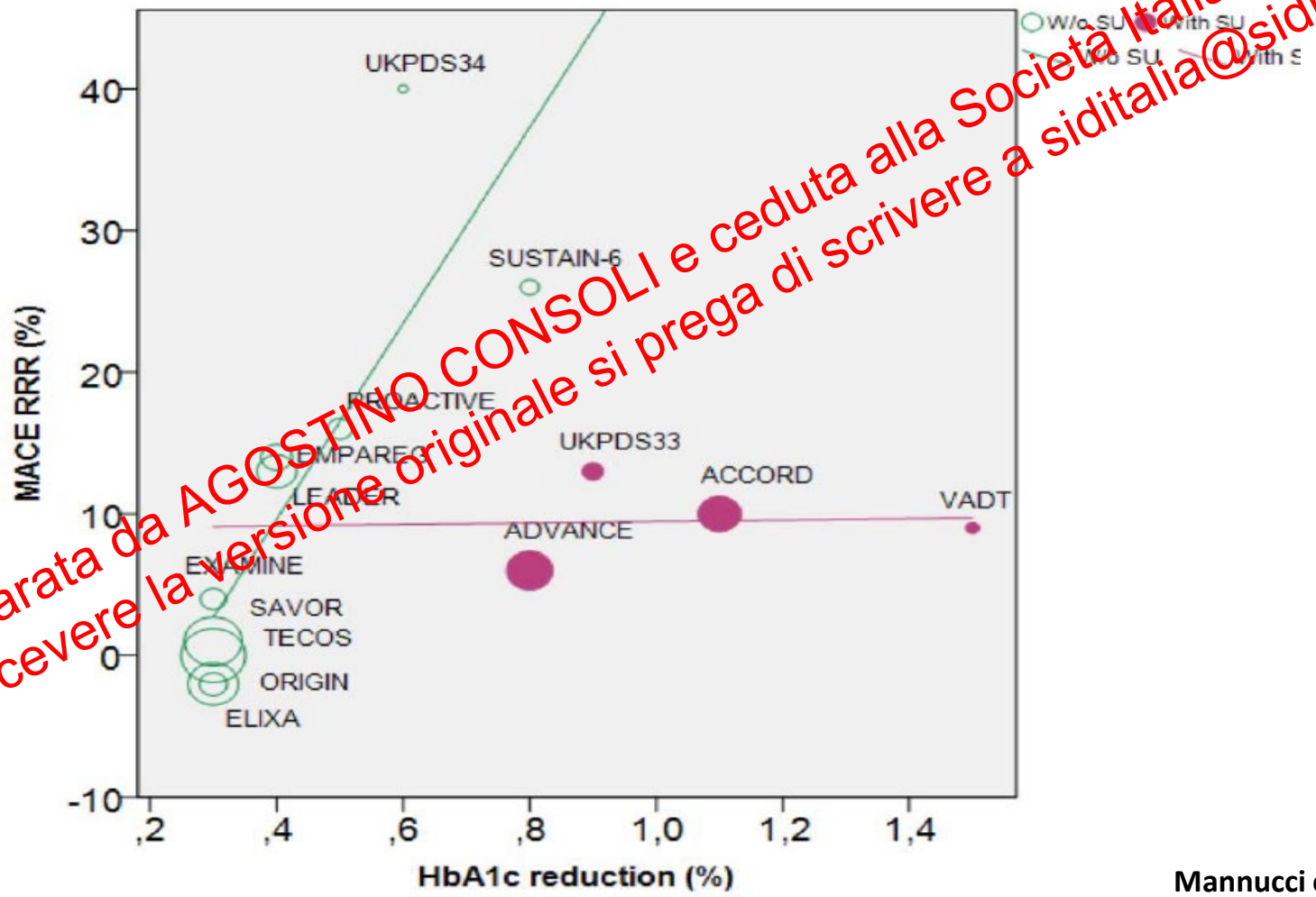
Efficacy Outcomes

This article was published on June 11, 2019, at NEJM.org.



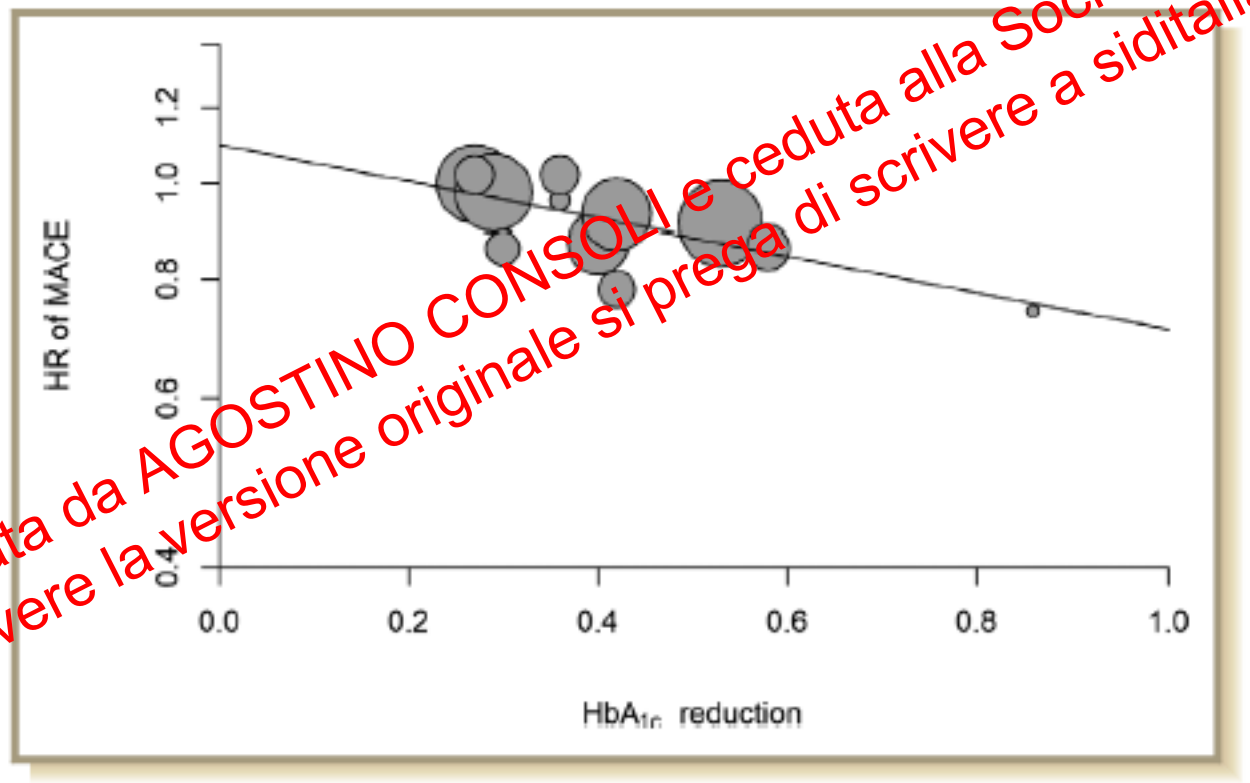


Relationships between improvement in HbA1c and MACE Risk Reduction Rate in clinical trials were sulphonylurea were or were not part of the treatment intensification strategy



Mannucci et al. NMCD 2017

Figure 1. Meta-regression analysis between reduction of HbA_{1c} and MACE risk in the 12 CVOTs. CVOT indicates cardiovascular outcome trial; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; MACE, major cardiovascular events.



Giugliano D. et al *J Am Heart Assoc.* 2019;8:e012356.

It is tempting to speculate that the results of the GLP-1 RAs Safety CVOTs offer indication that achieving a better metabolic control by means of innovative treatment strategies, avoiding increase in sulphonylureas and insulin administration and with no increase in hypoglycemia might improve outcomes also in patients with established CV disease.

HOWEVER……

- For the same degree of «metabolic amelioration» only some trials demonstrated a clear and significant reduction in outcomes

- Analyses aimed at «dissecting out» factors possibly implicated in the observed risk reduction failed to demonstrate a significant contribution of HbA1c reduction, Hypoglycemia reduction and differences in the use of other diabetes drugs

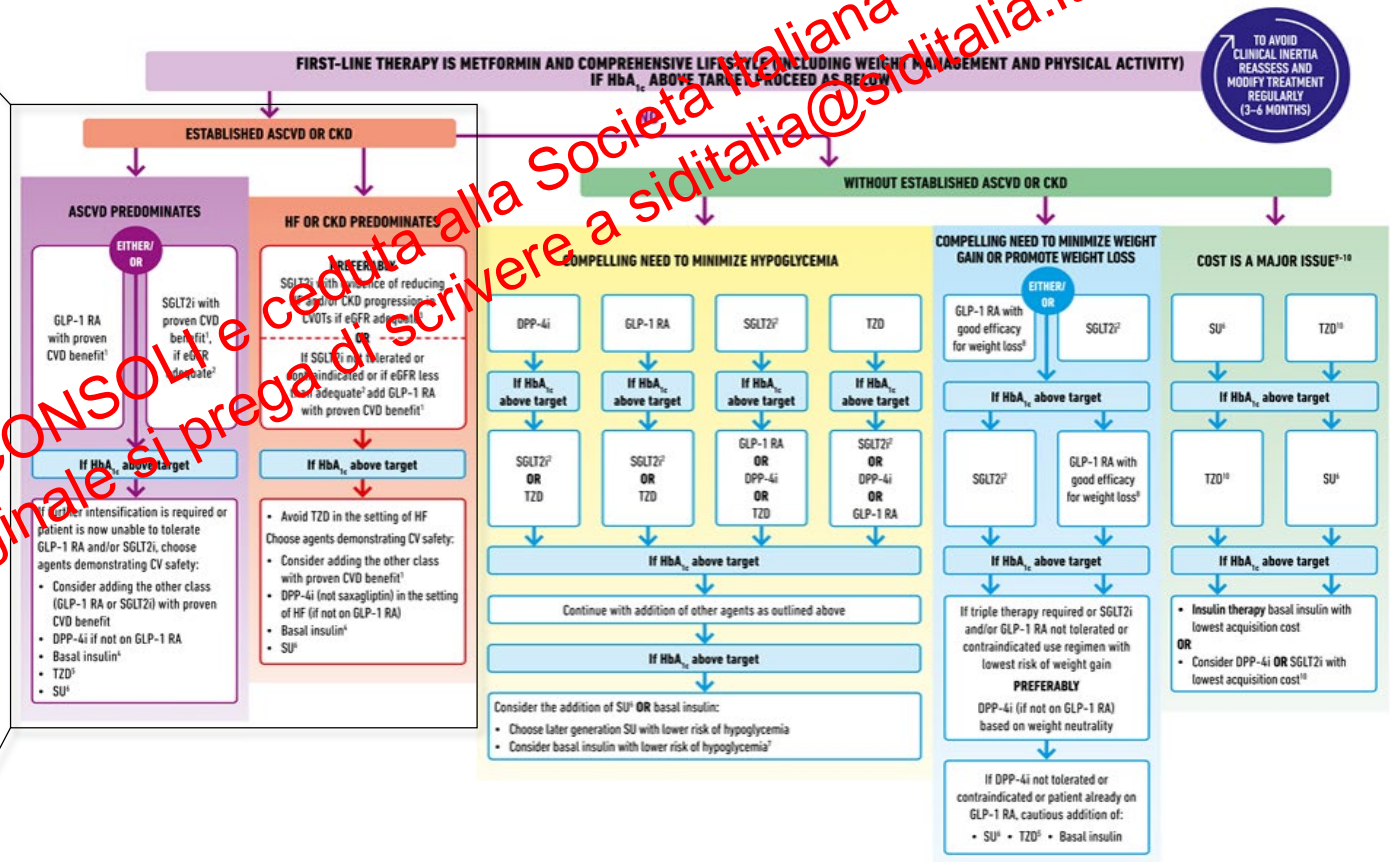
ADA-EASD Consensus Report – Oct 2018

Choice in second-line therapy in patients with established ASCVD or CKD

IMPLICATIONS OF NEW EVIDENCE FROM CVOTs

Recommendations (p6/7)

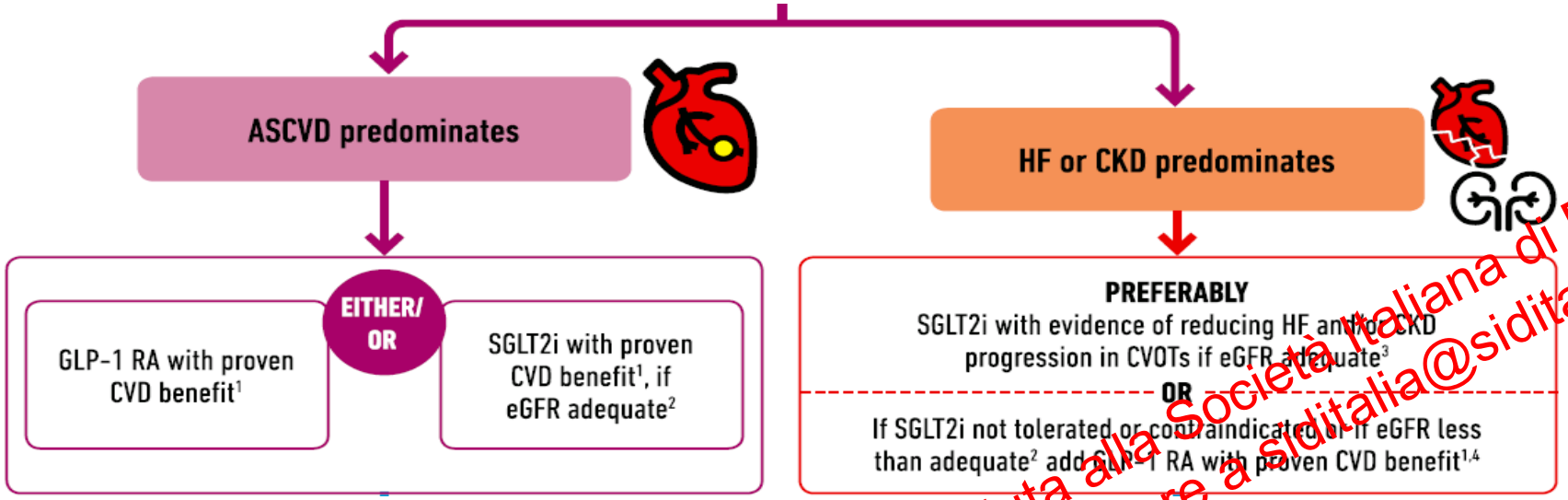
"The major change from prior consensus reports is based on **new evidence that specific SGLT2 inhibitors or GLP-1 RAs improve CV outcomes**……..therefore, an important early step in this new approach is to **consider the presence or absence of ASCVD.**"[1]



These recommendations have been also incorporated into the ADA Standards of Medical Care in Diabetes 2019[2]

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eCVD, established cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium-glucose co-transporter-2

1. Davies MJ *et al. Diabetes Care* 2018;41:2669; 2. American Diabetes Association. *Diabetes Care* 2019;42:S1



- **Pazienti diabetici di tipo 2 con malattia cardiovascolare in atto (%):**

  20 % (stima minima)

- **Pazienti diabetici di tipo 2 in trattamento con GLP-1 RA o SGLT2 inhib.**

  5.5 % (stima massima)

Injectable Therapies

which one to prefer ?

Effects on

- **HbA1c**

- **Body weight**

- **Aes (Hypoglycemia)**

Rapporto ARNO 2017: Tabella 5

Soggetti (numeri assoluti e percentuali) di trattati con i vari farmaci anti-iperglicemici

Descrizione	N. Trattati	% Trattati
Agonisti GLP-1	**12,447**	**2,4%**
Insulina Basale	**105,998**	**20,5%**