Terapia con analoghi del

GLP-1:

quando e perché

Obiettivi nel paziente con diabete tipo 2: la glicemia non basta

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Roma, 21 maggio 2019

SAPIENZA UNIVERSITÀ DI ROMA

Il sottoscritto Marco Giorgio Baroni

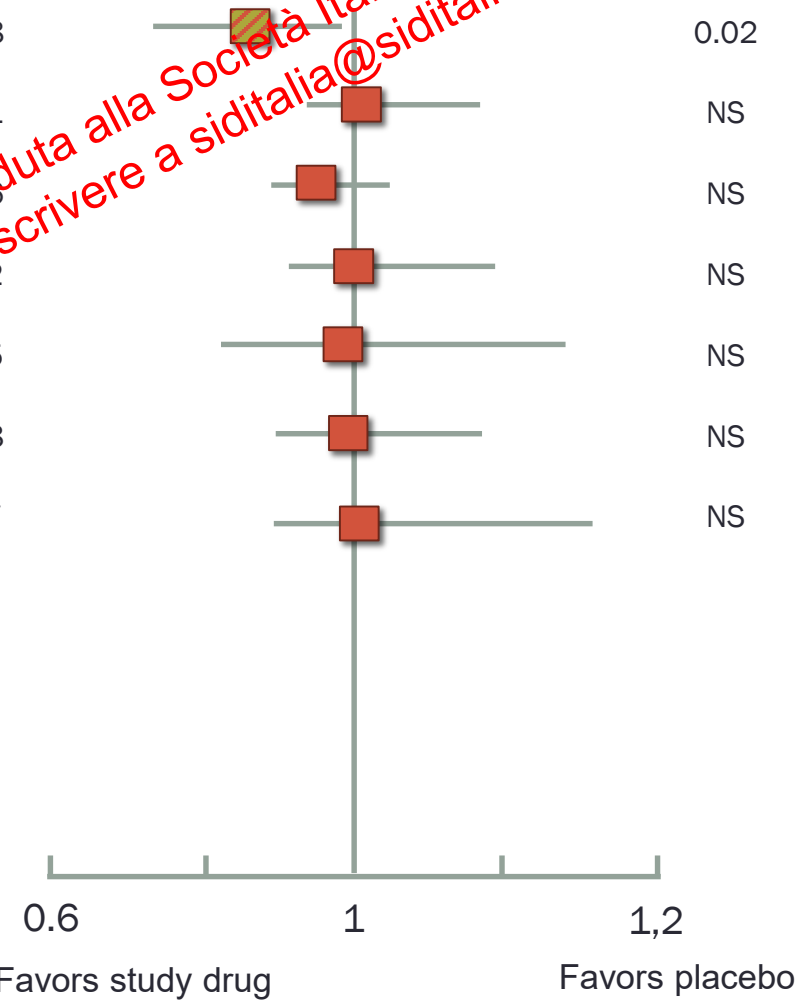
dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Novo Nordisk
- Abbott
- Mundi Pharma
- MSD

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Effect of Glucose-Lowering Drugs on 3-Point MACE* in T2DM Patients

Study	Year	Glucose-lowering drug	HR	95% CI	*P*-value
PROACTIVE	2005	Pioglitazone	0.84	0.72 - 0.98	0.02
ORIGIN	2012	Insulin glargine	1.02	0.94 - 1.11	NS
DEVOTE	2017	Insulin degludec	0.91	0.78 - 1.06	NS
SAVOR	2013	Saxagliptin	1.00	0.89 - 1.12	NS
EXAMINE	2013	Alogliptin	0.96	0.80 - 1.15	NS
TECOS	2015	Sitagliptin	0.98	0.89 - 1.08	NS
ELIXA	2015	Lixisenatide	1.02	0.89 - 1.17	NS



*CV mortality, non-fatal MI, non-fatal stroke

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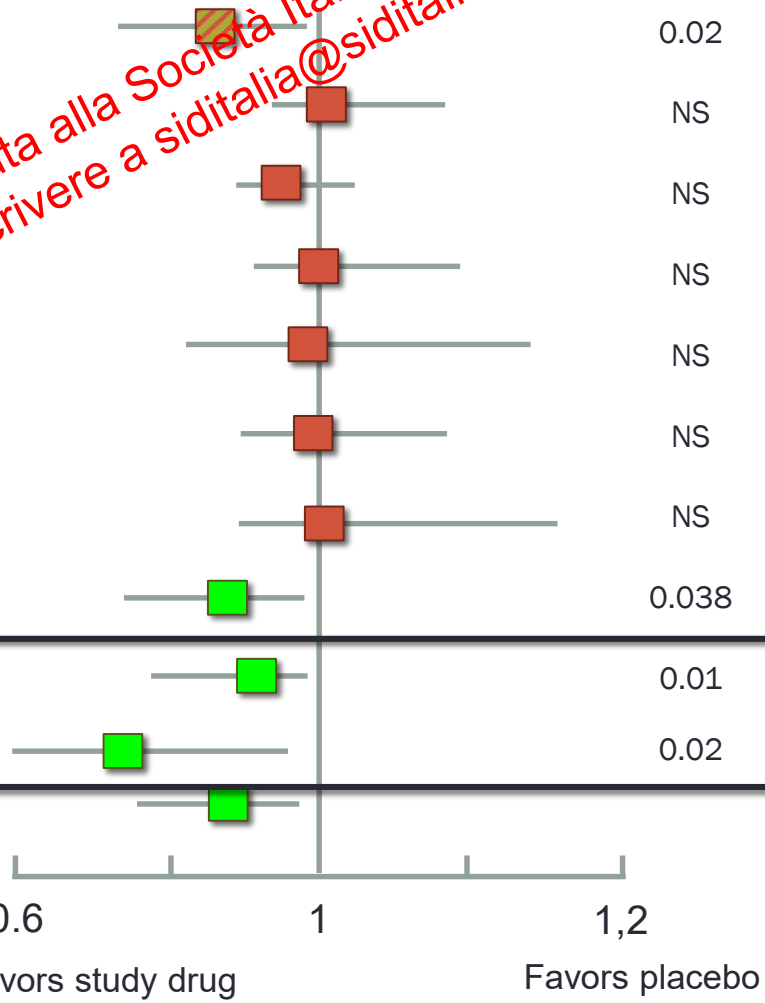
ELIXA	2015	Lixisenatide	1.02	0.89 - 1.17	NS
EMPA-REG	2015	Empagliflozin	0.86	0.74 - 0.99	0.038
LEADER	2016	Liraglutide	0.87	0.78 - 0.97	0.01
SUSTAIN-6	2016	Semaglutide	0.74	0.58 - 0.95	0.02
CANVAS	2017	Canagliflozin	0.86	0.75 - 0.97	



*CV mortality, non-fatal MI, non-fatal stroke

Effect of GLP-1 RAs on CVD outcome

A 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%

B 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%

Bethel MA et al Lancet 2018

Effect of GLP-1 RAs on CVD outcome

C Fatal and non-fatal myocardial infarction

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)	0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)	0·046
SUSTAIN 6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)	0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)	0·62
Overall			**0·94 (0·86–1·03)**	**0·18**

Test for heterogeneity: p=0·32, I^2=15%

E All-cause mortality

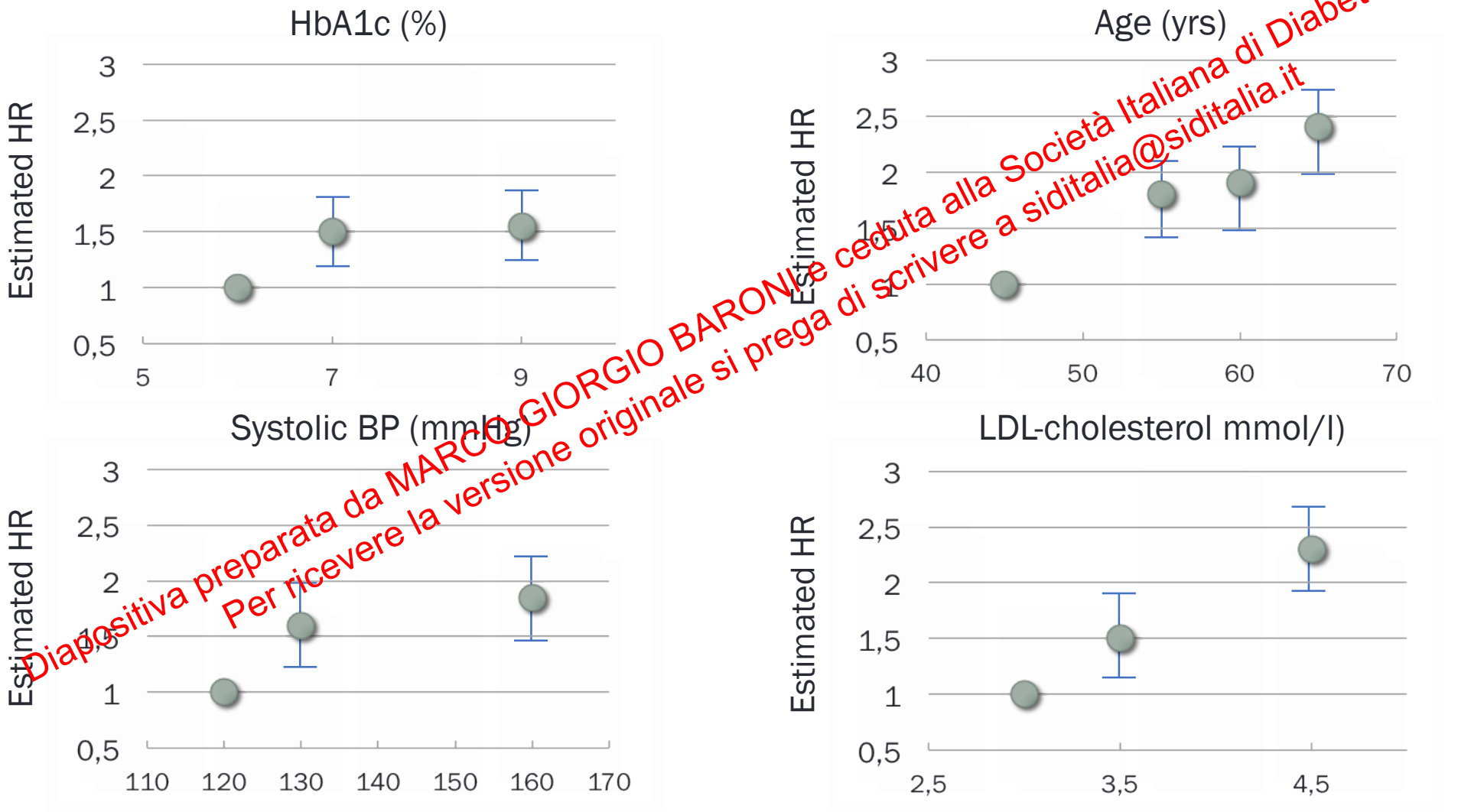
	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	211/3034 (7%)	233/3034 (7%)	0·94 (0·78–1·13)	0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)	0·020
SUSTAIN 6	60/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)	0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)	0·016*
Overall			**0·88 (0·81–0·95)**	**0·002**

Test for heterogeneity: p=0·63, I^2=0%

Bethel MA et al Lancet 2018

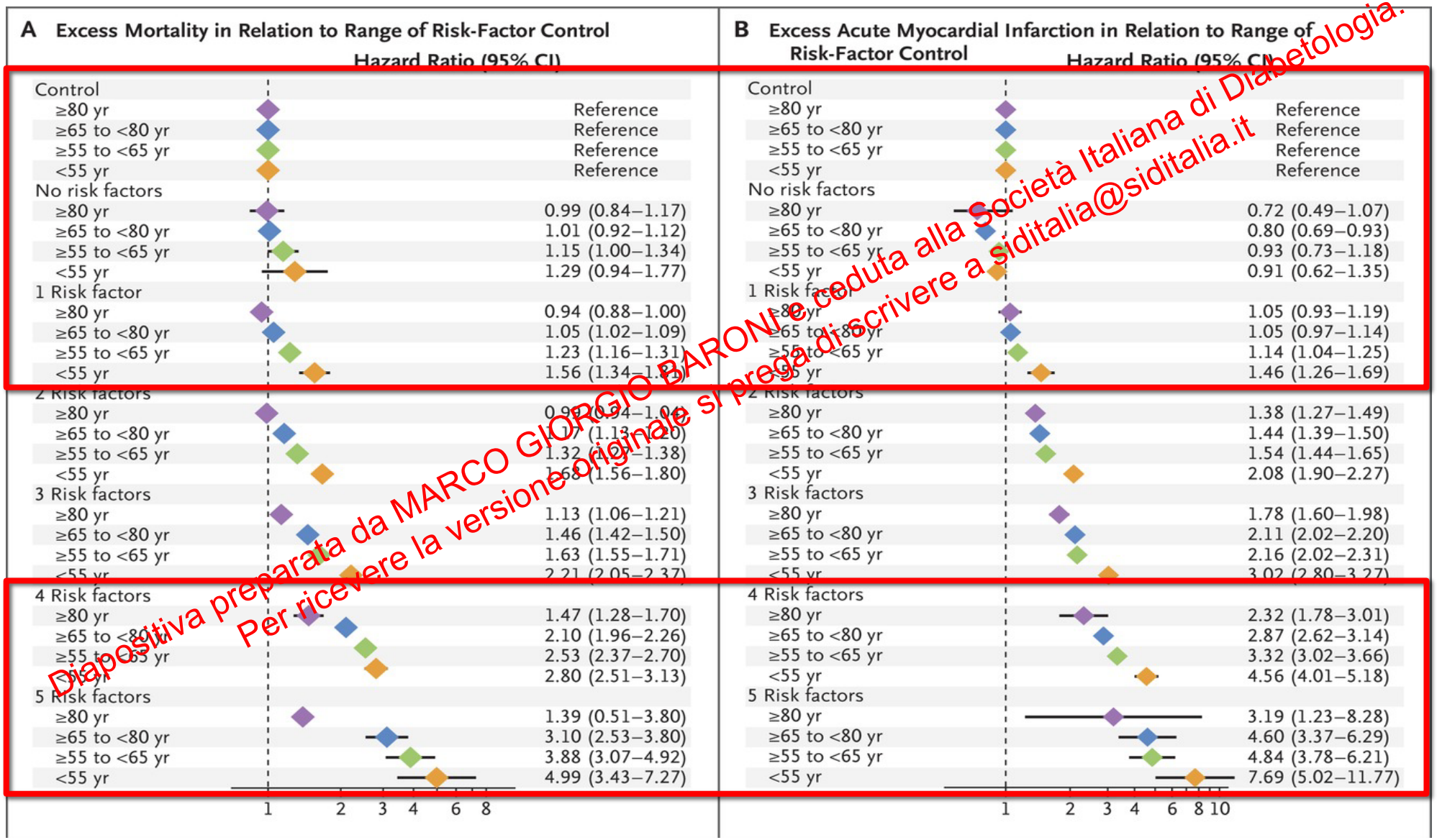
Quali meccanismi?

UKPS 23: Risk Factors for CHD



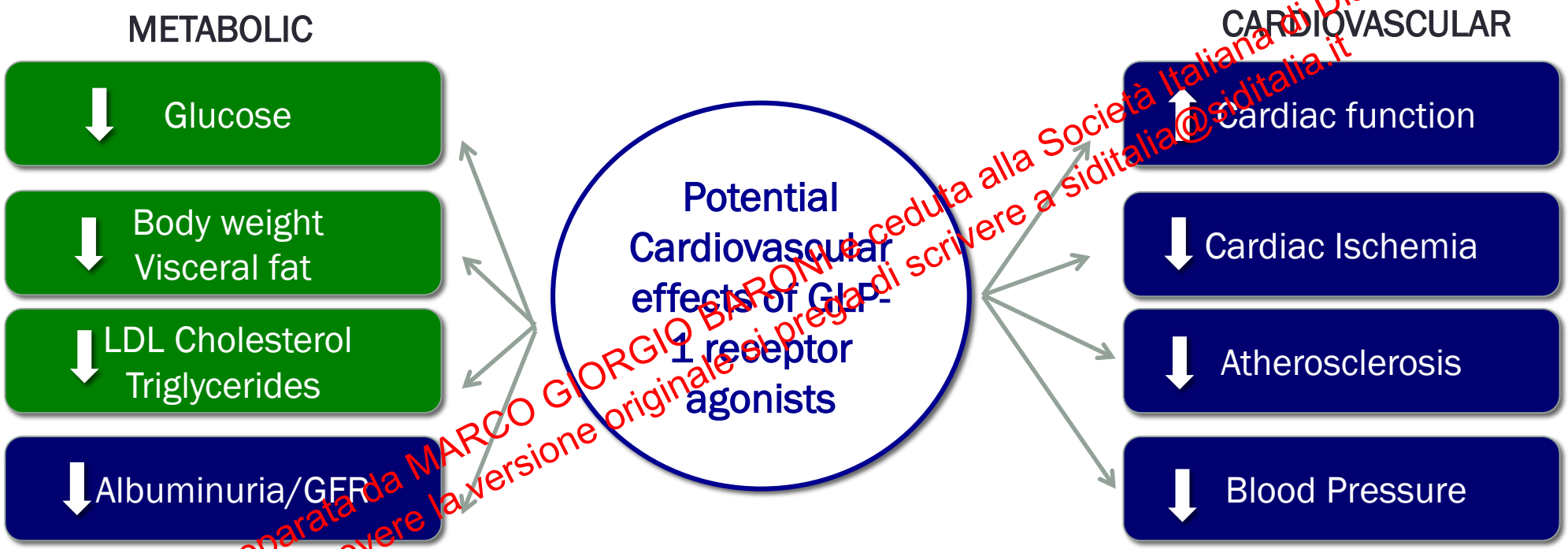
Turner RC et al ***BMJ*** 1999;316:823-828

Adjusted Hazard Ratios for Outcomes, According to Age Category and Number of Risk-Factor Variables outside Target Ranges (HbA1c, LDL, Album., BP, smoke)

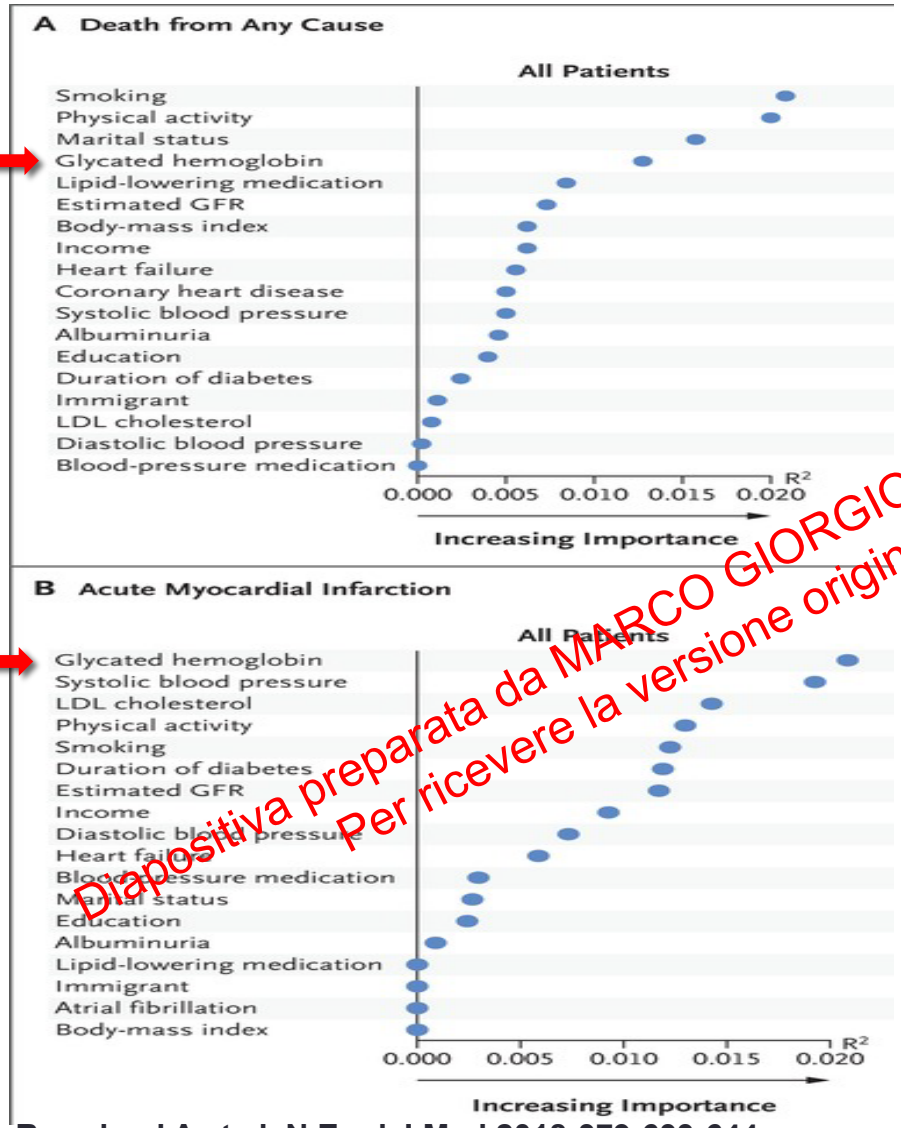


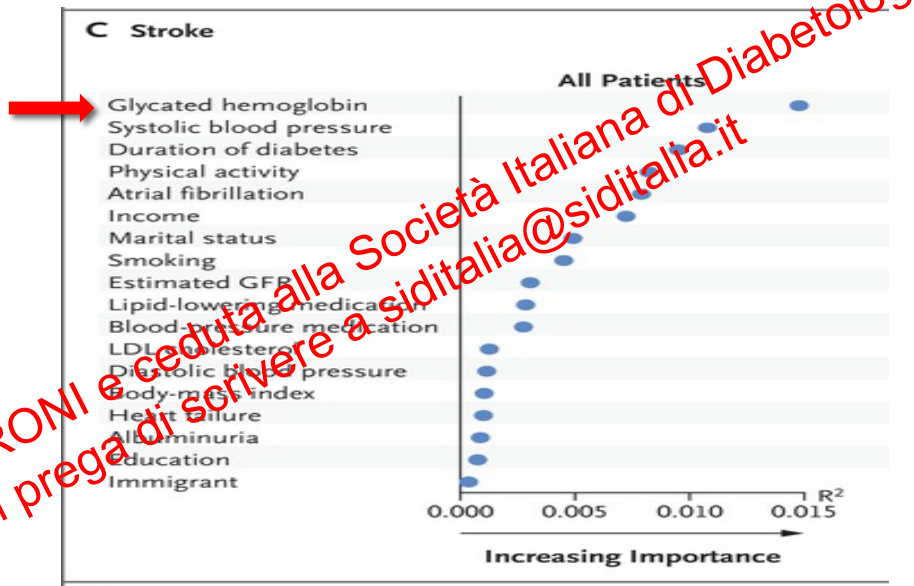
Rawshani A et al. N Engl J Med 2018;379:633-644

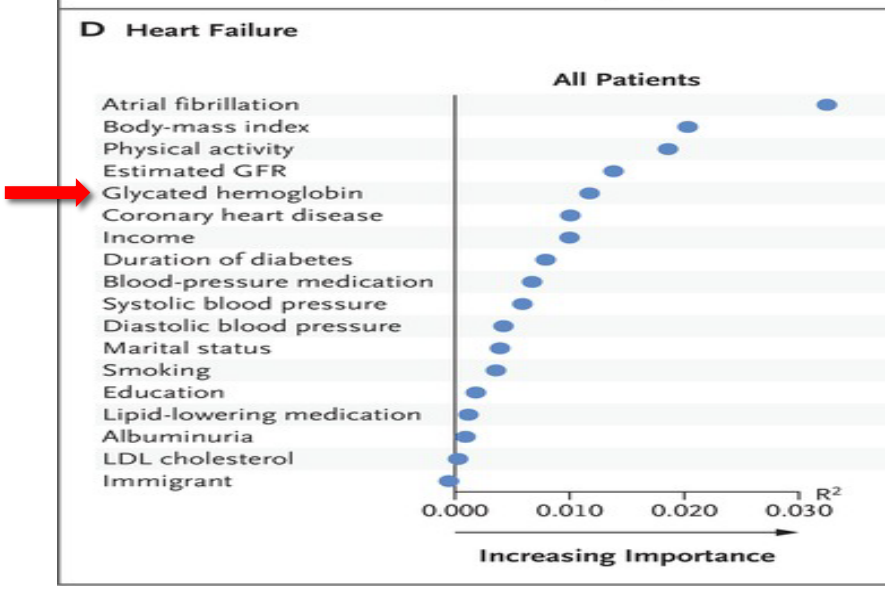
The Potential Mechanisms of Cardiovascular Benefits of Glucagon-like Peptide-1 Receptor Agonists



Relative Importance of Risk Factors for Predicting Death from Any Cause, Acute Myocardial Infarction, Stroke, and Hospitalization for Heart Failure among Patients with Type 2 Diabetes, with or without Preexisting Conditions

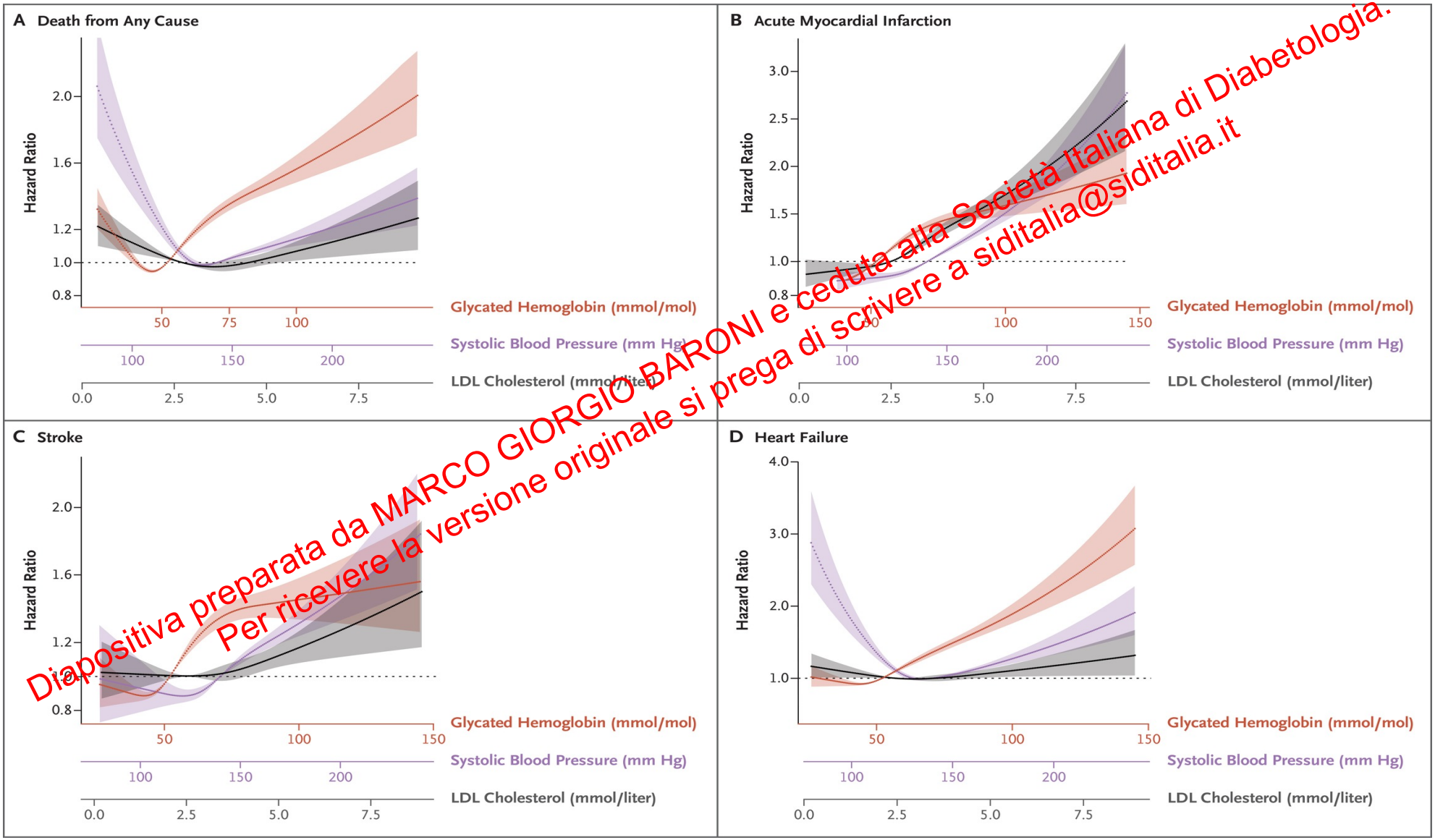






Rawshani A et al. N Engl J Med 2018;379:633-644

Association between Levels of Glycated Hemoglobin, Systolic Blood Pressure, and LDL Cholesterol and Death from Any Cause, Acute Myocardial Infarction, Stroke, and Heart Failure in Patients with Type 2 Diabetes.

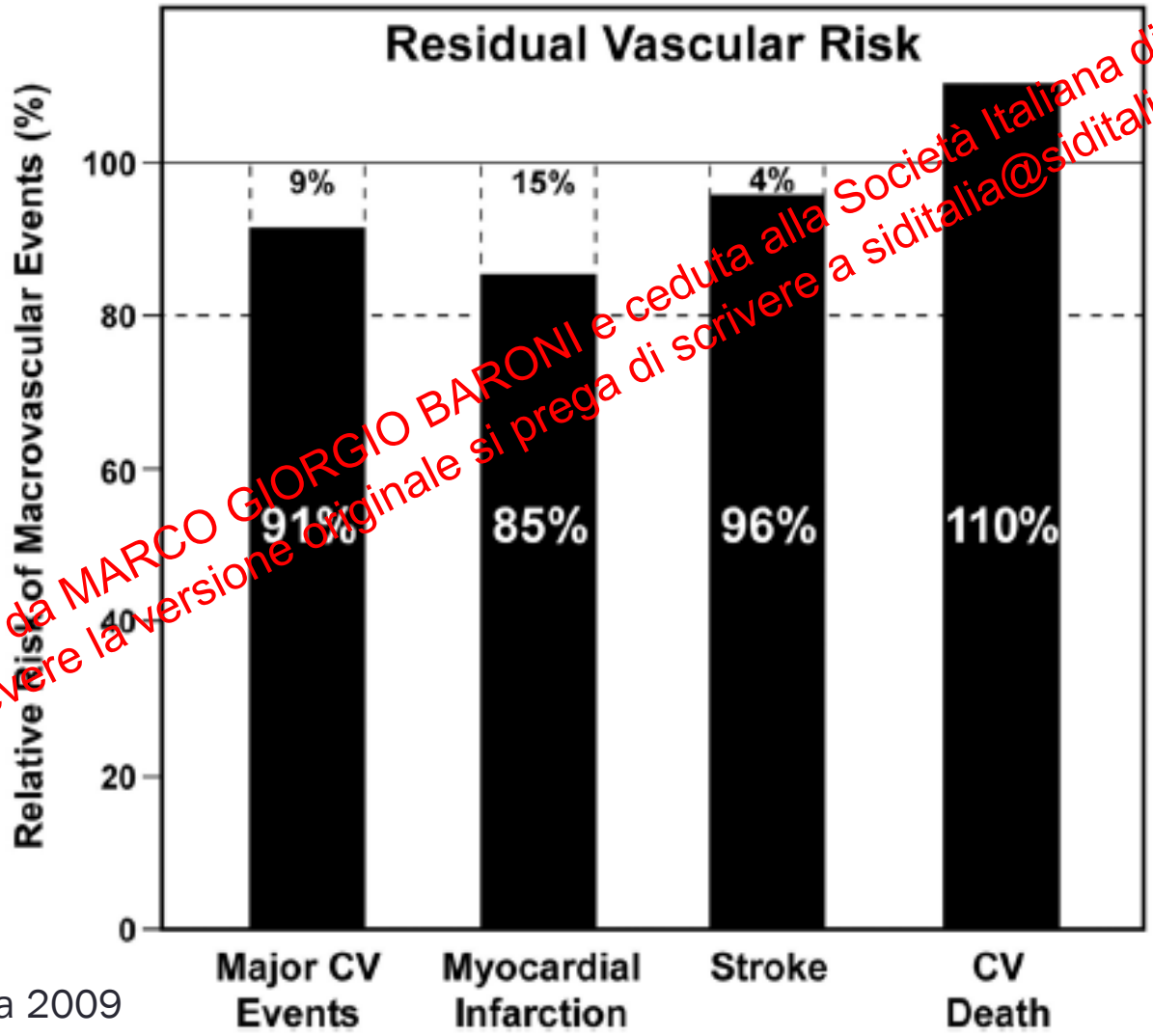


Rawshani A et al. N Engl J Med 2018;379:633-644

Quale riduzione del rischio cardiovascolare è stata ottenuta con il trattamento intensivo della glicemia?

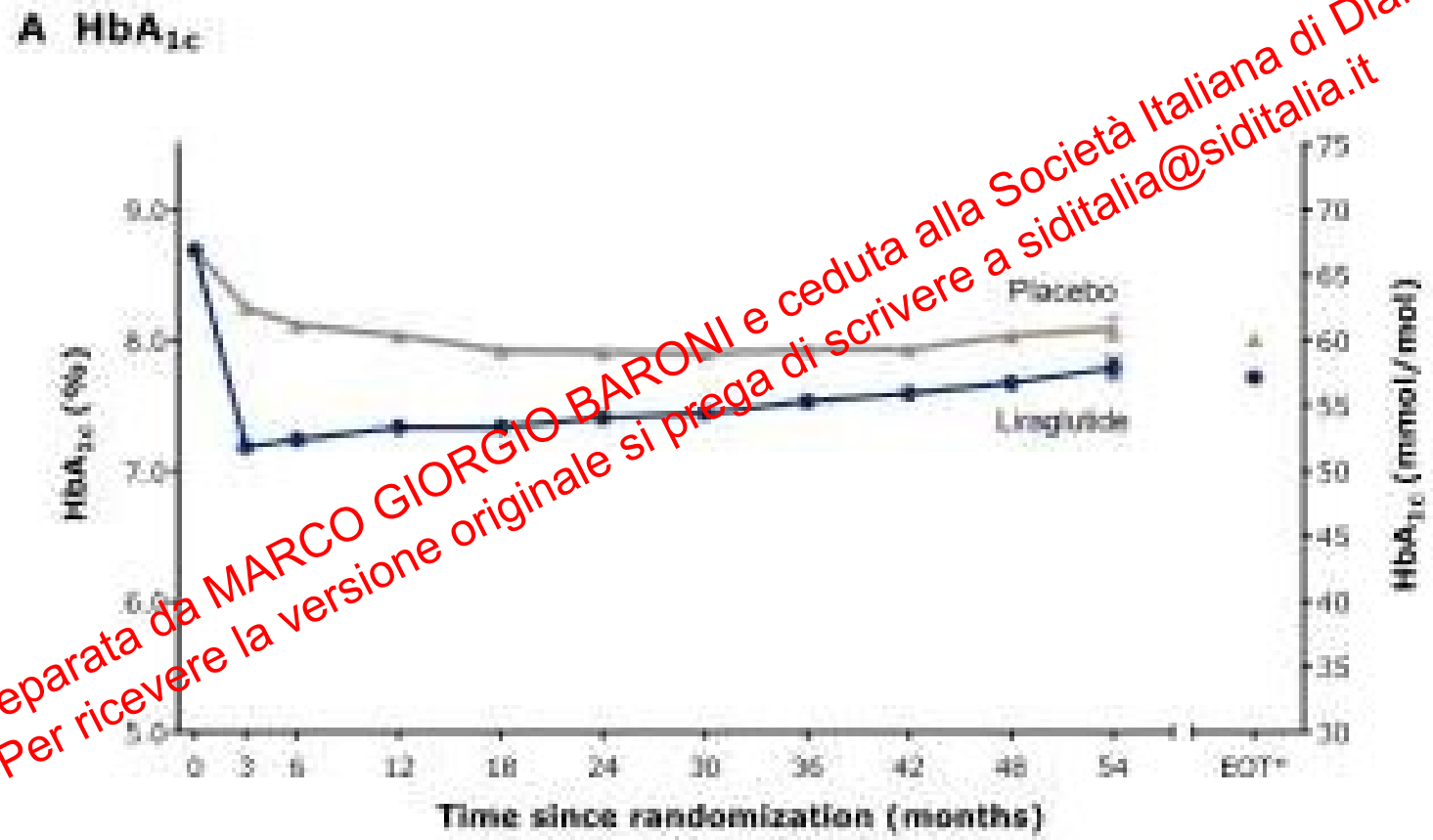
1. >30%
2. >50%
3. <10%
4. 2%

Residual vascular risk for macrovascolar complications in type 2 diabetic patients, as reported in randomized controlled trials that compared more intensive glucose control vs less intensive glucose control.



Turnbull FM et al Diabetologia 2009
Giugliano D et al. Endocrine 2018

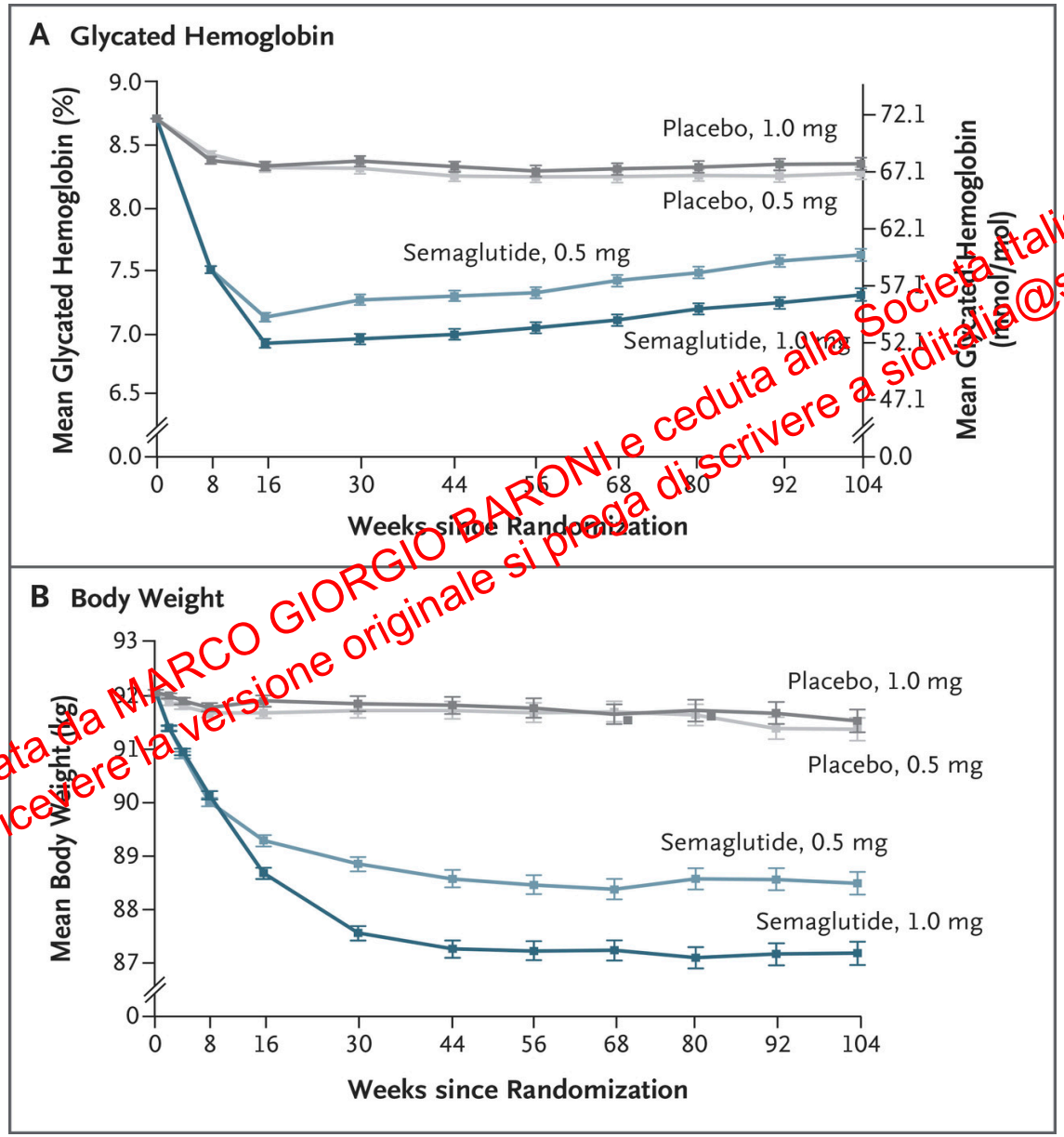
Leader: Estimated mean values from randomization to end of trial for glycated hemoglobin



Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3703
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561

Glycated Hemoglobin and Body Weight in SUSTAIN 6

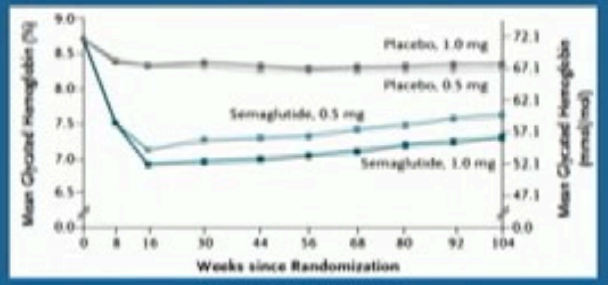


Marso SP et al. N Engl J Med 2016.

GLP-1 receptor agonists: glucose control

Impact on HbA_{1c}

Liraglutide

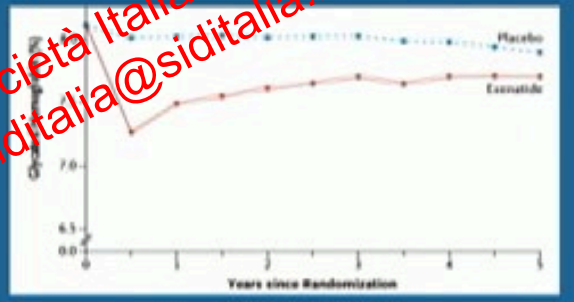


Treatment diff
– 0.4%
(95% CI – 0.45; – 0.34)
p<0.001

Semaglutide

Treatment diff
– 0.7%
(95% CI –0.80 ; –0.52)
p<0.001

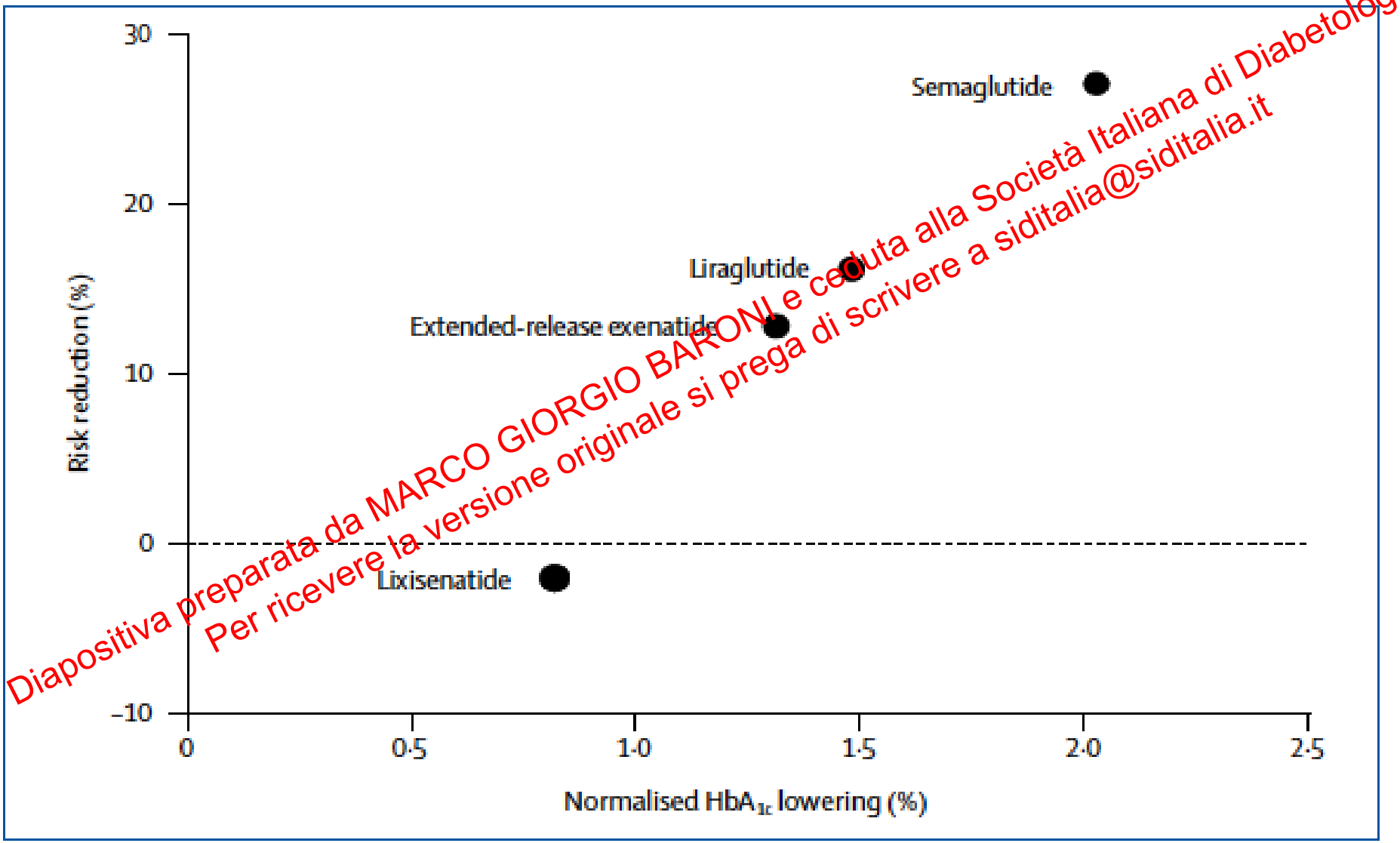
Exenatide



Treatment diff
– 0.5%
(95% CI – 0.57; – 0.50)
p<0.001

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al *N Engl J Med 2017; 1228*
Hernandez A F et al *N Engl J Med 2018; 392:1519*

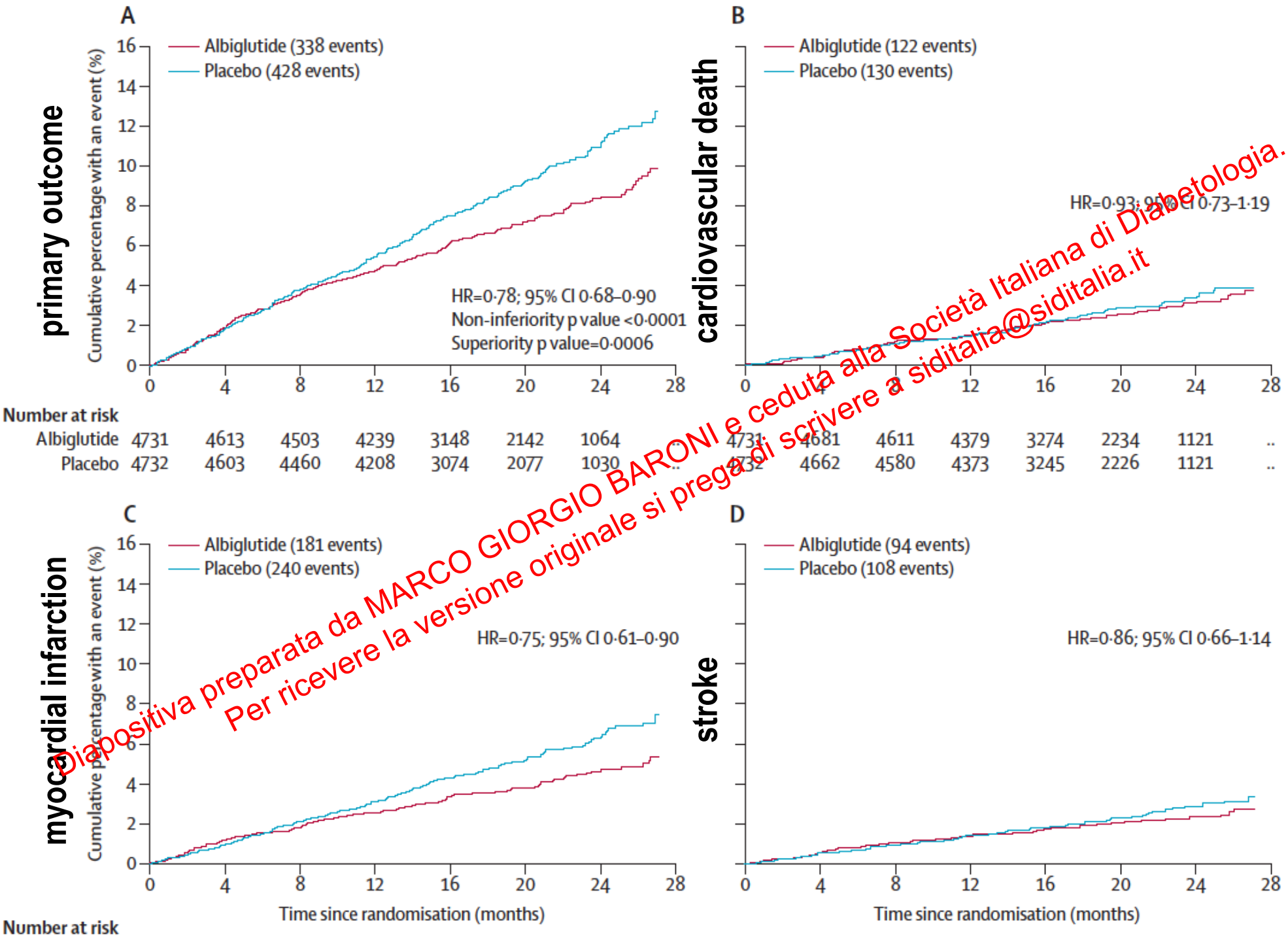
Magnitude of cardioprotection and HbA1c lowering with GLP-1 receptor agonists



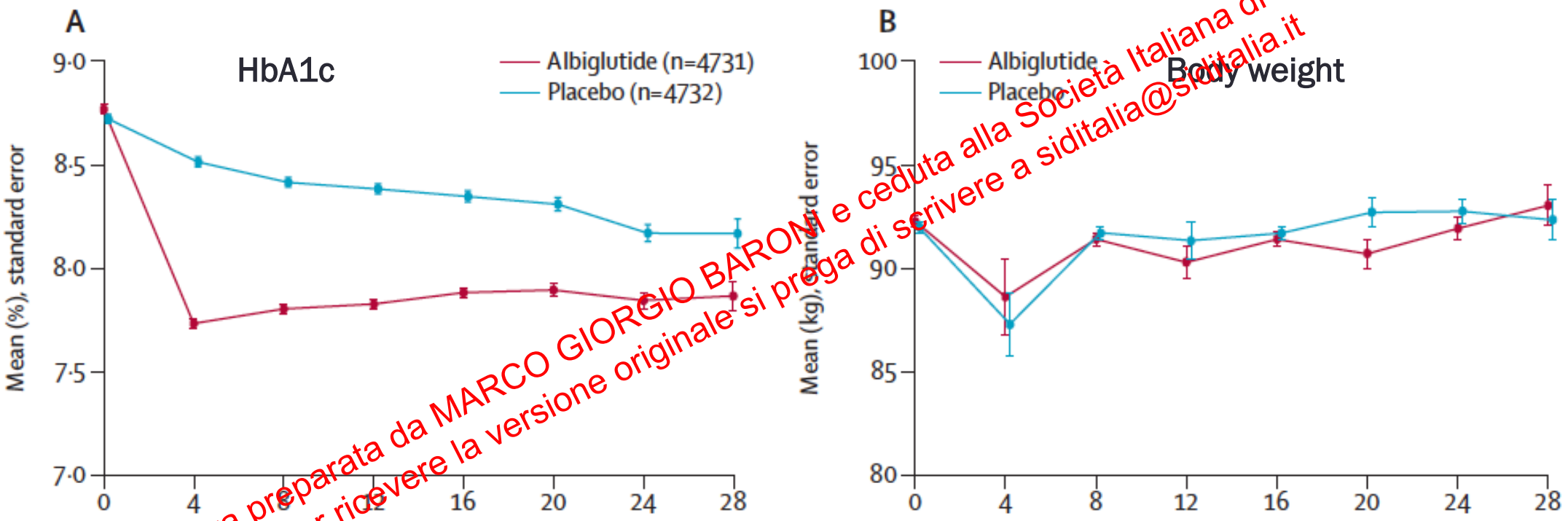
Taylor SI. GLP-1 receptor agonists: differentiation within the class. Lancet 2018

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

*Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators**



Harmony Outcomes: HbA1c and body weight



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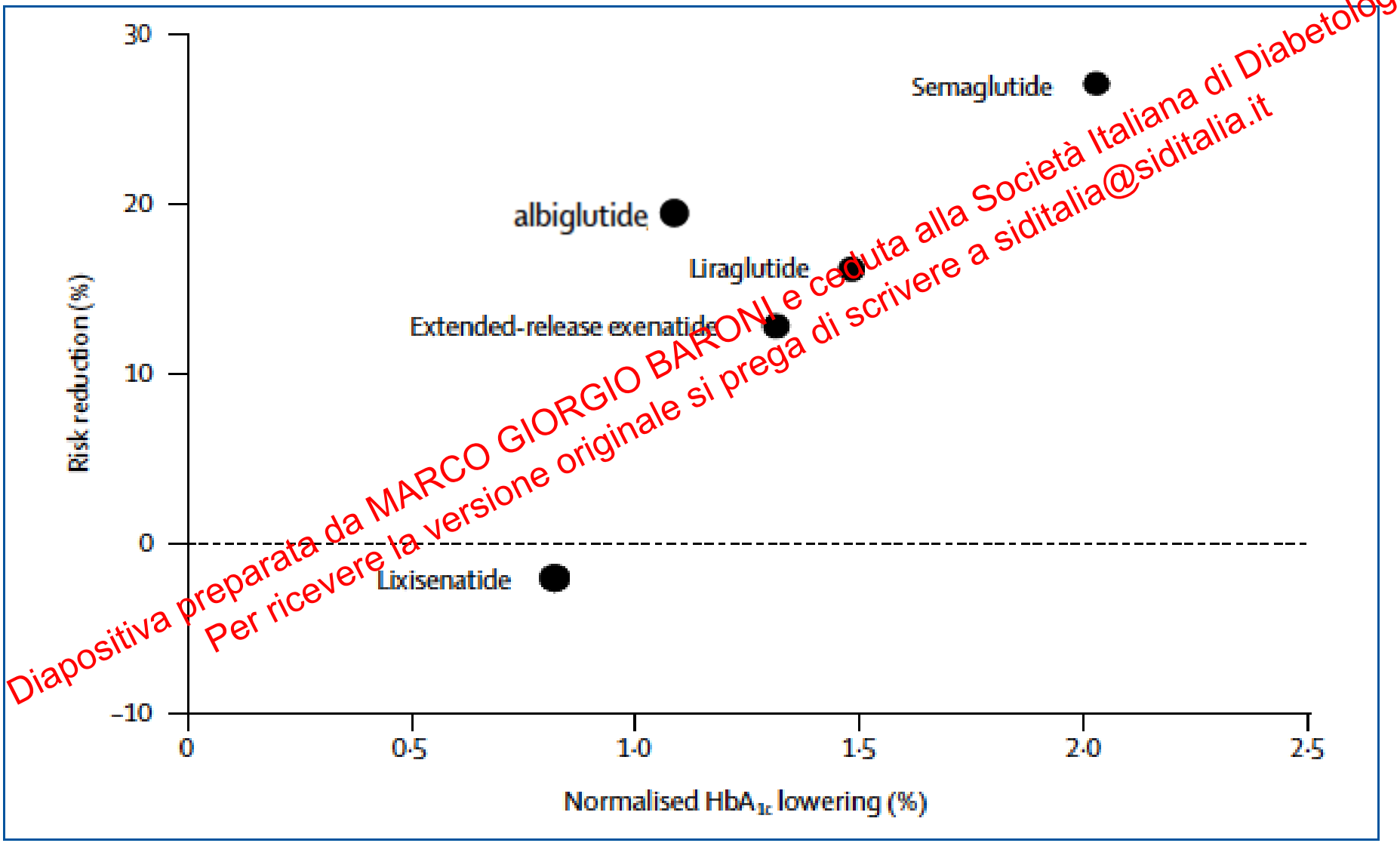
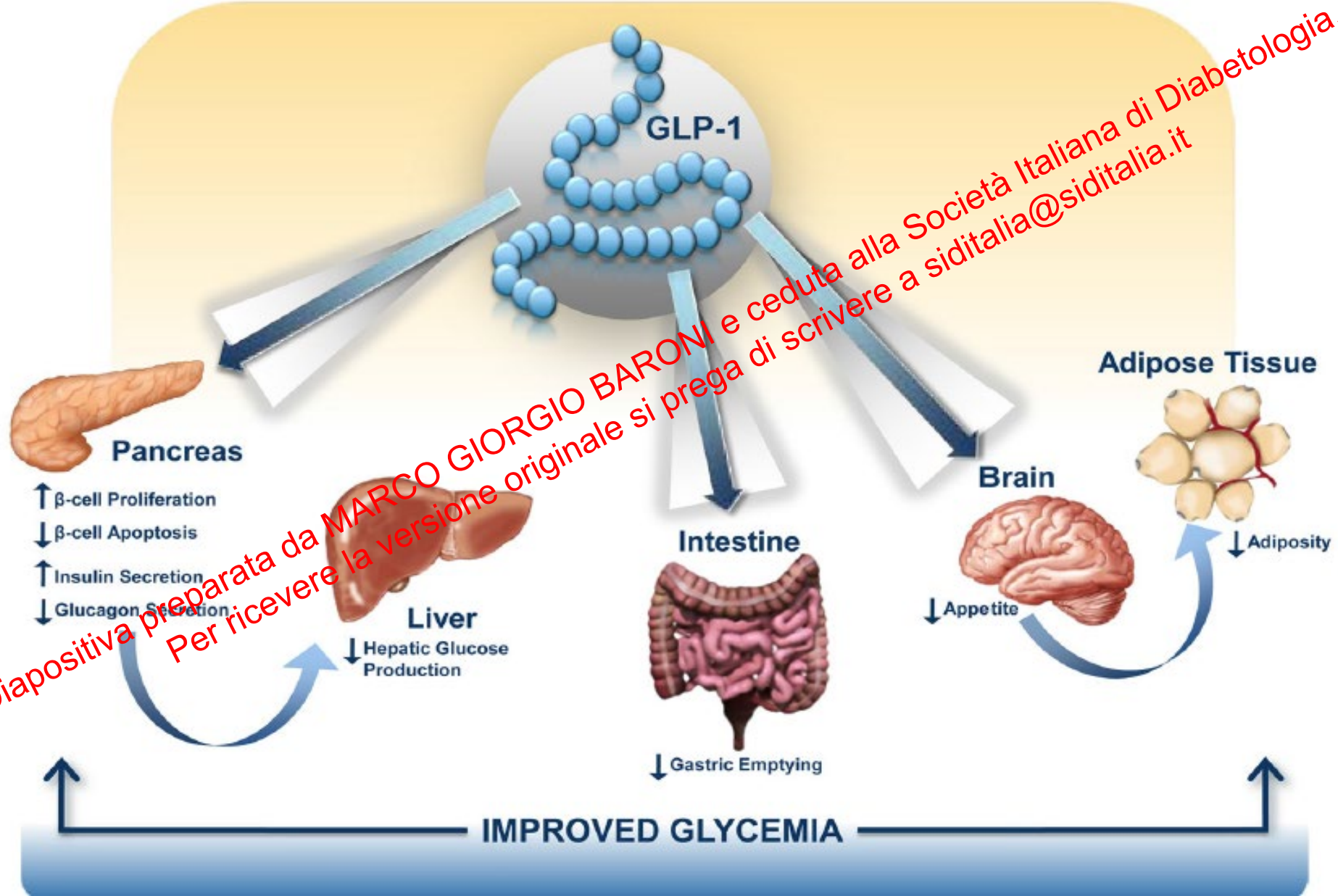


Taylor SI. GLP-1 receptor agonists: differentiation within the class. Lancet 2018

GLP-1 targets multiple organs to improve glucose control in T2DM



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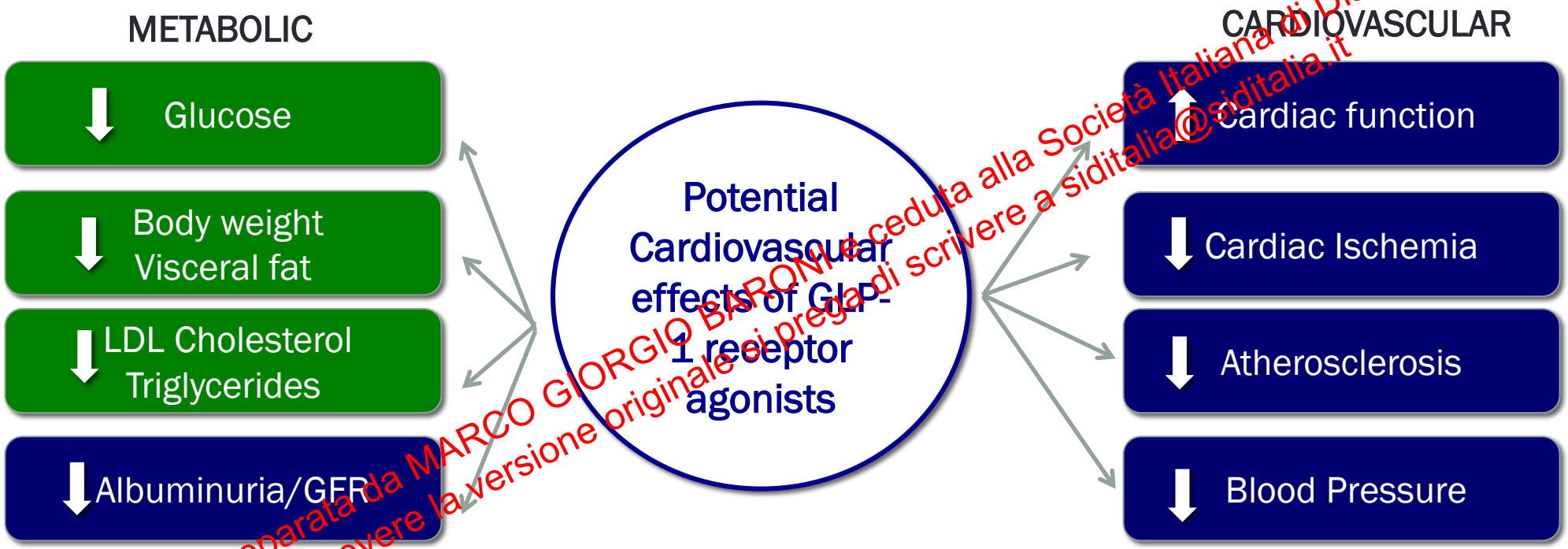

Quali sono gli effetti degli analoghi del GLP-1 sull'assetto lipidico?

1. Modesta riduzione di colesterolo e trigliceridi
2. Riduzione significativa del colesterolo
3. Riduzione significativa dei trigliceridi
4. Riduzione HDL

GLP-1 receptor agonists: impact on blood lipids

- Network meta analysis of 35 trials with Liraglutide, Exenatide, Taspoglutide

- Effects:
  - HDL = -2.32 to -5.02 mg/dl (NS)
  - LDL = -3.09 to -6.18 mg/dl (NS)
  - TC = -6.18 to -10.44 mg/dl (NS)
  - TG = -26.57 to -43.40 mg/dl (NS)

Clinical Therapeutics/Volume 37, Number 1, 2015

GLP-1 receptor agonists

Impact on blood lipids

Liraglutide	Semaglutide	Exenatide	Albiglutide
			
Small decrease TC, LDL-C and TGs **Small increase** HDL-C	**Small decrease** TC, LDL-C and TGs **Small increase** HDL-C	**Small decrease** LDL-C and TGs HDL-C **No information**	**Not measured**

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al *N Engl J Med 2017; 1228*
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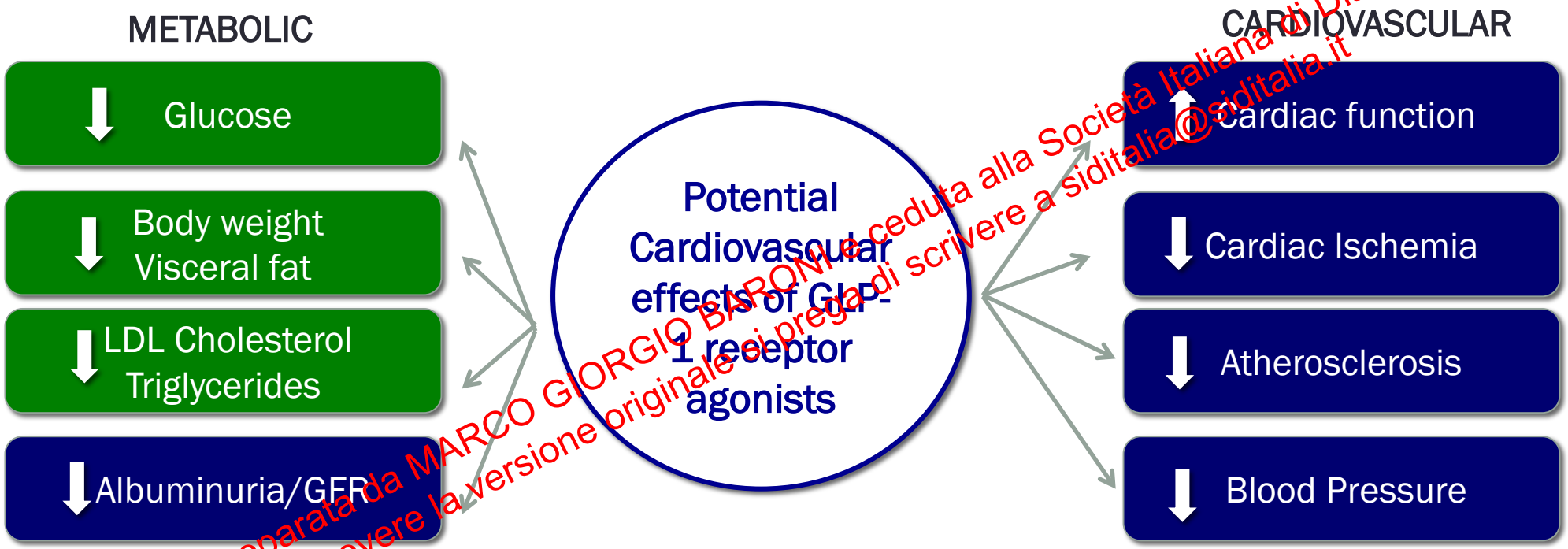
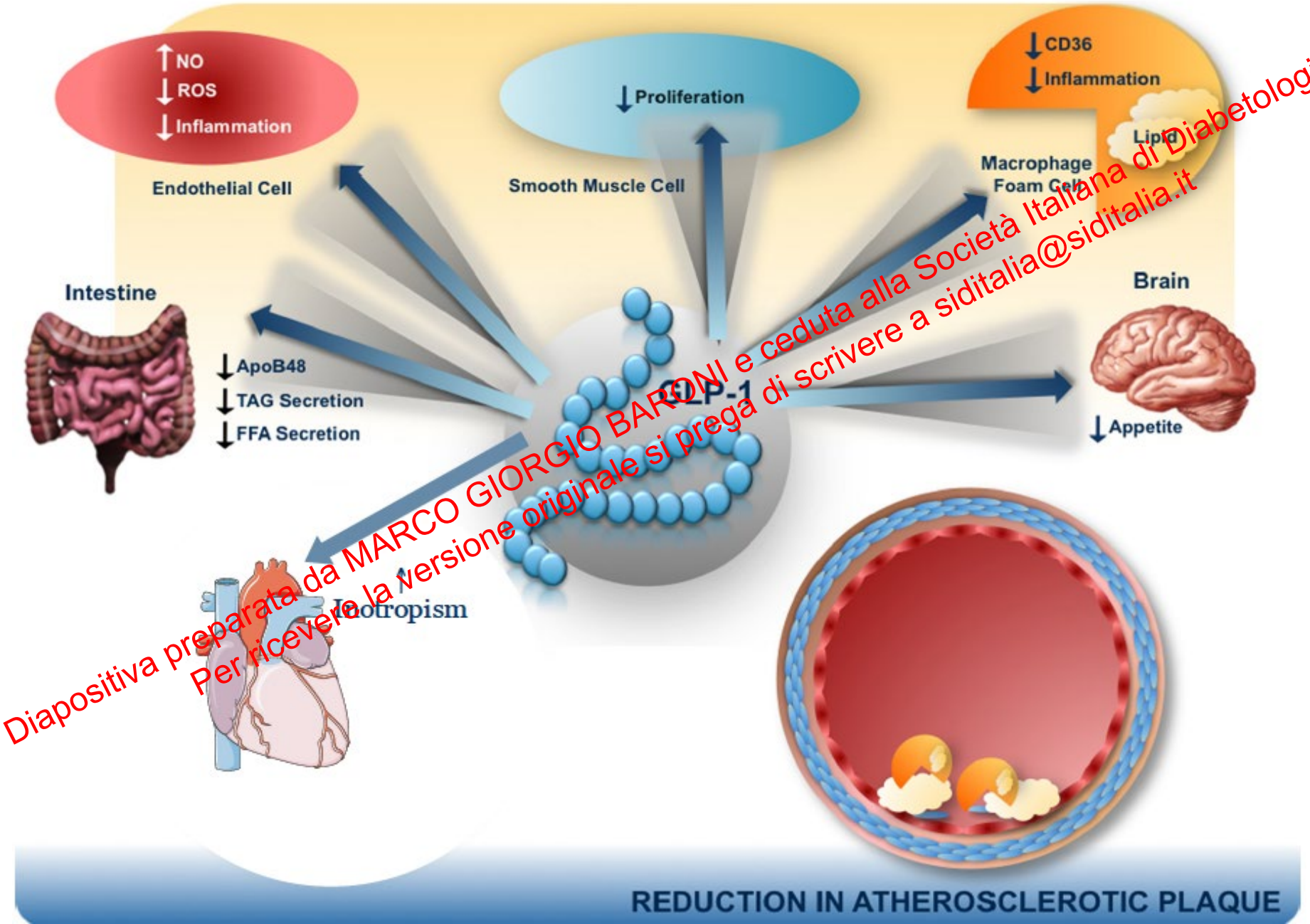
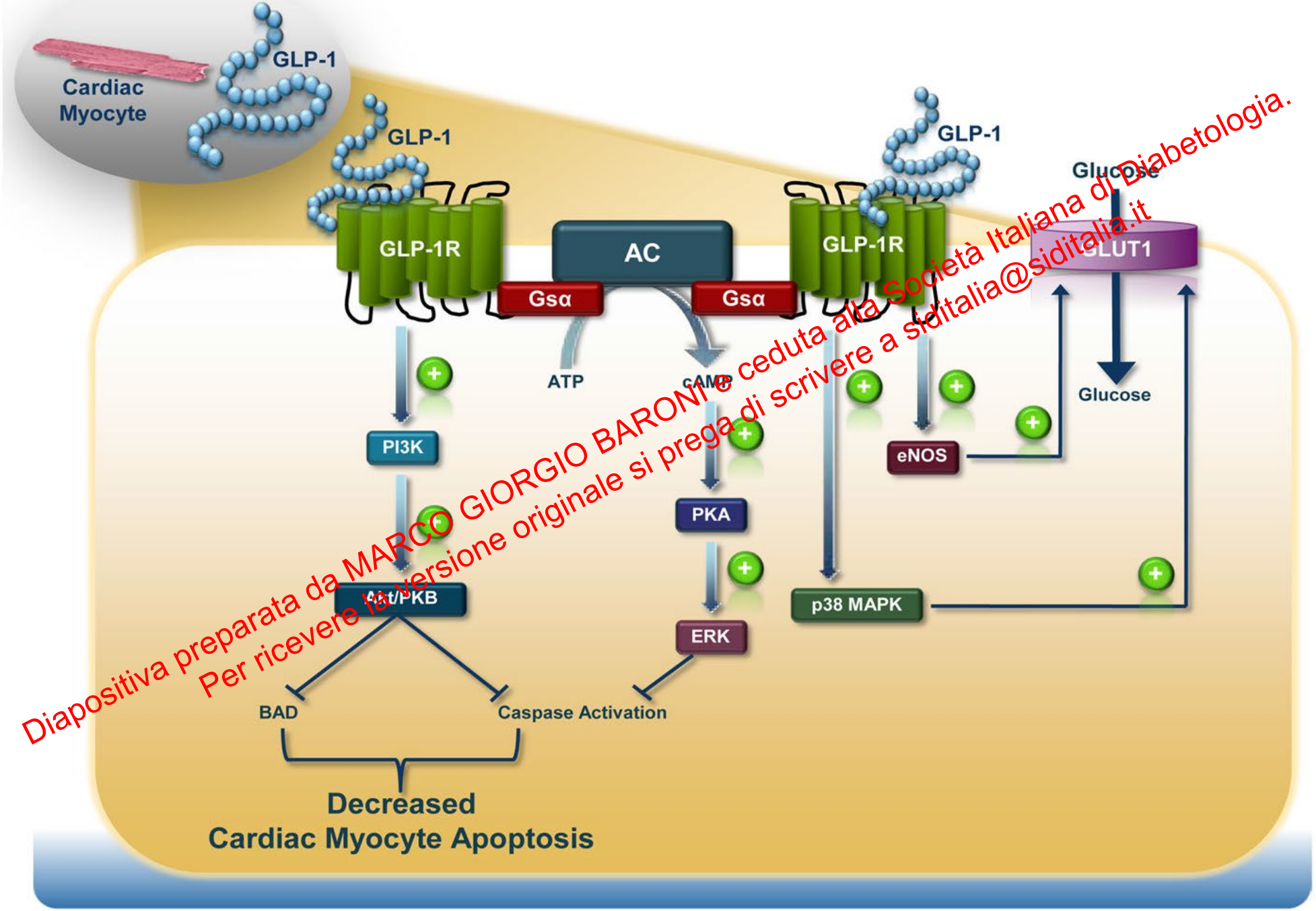


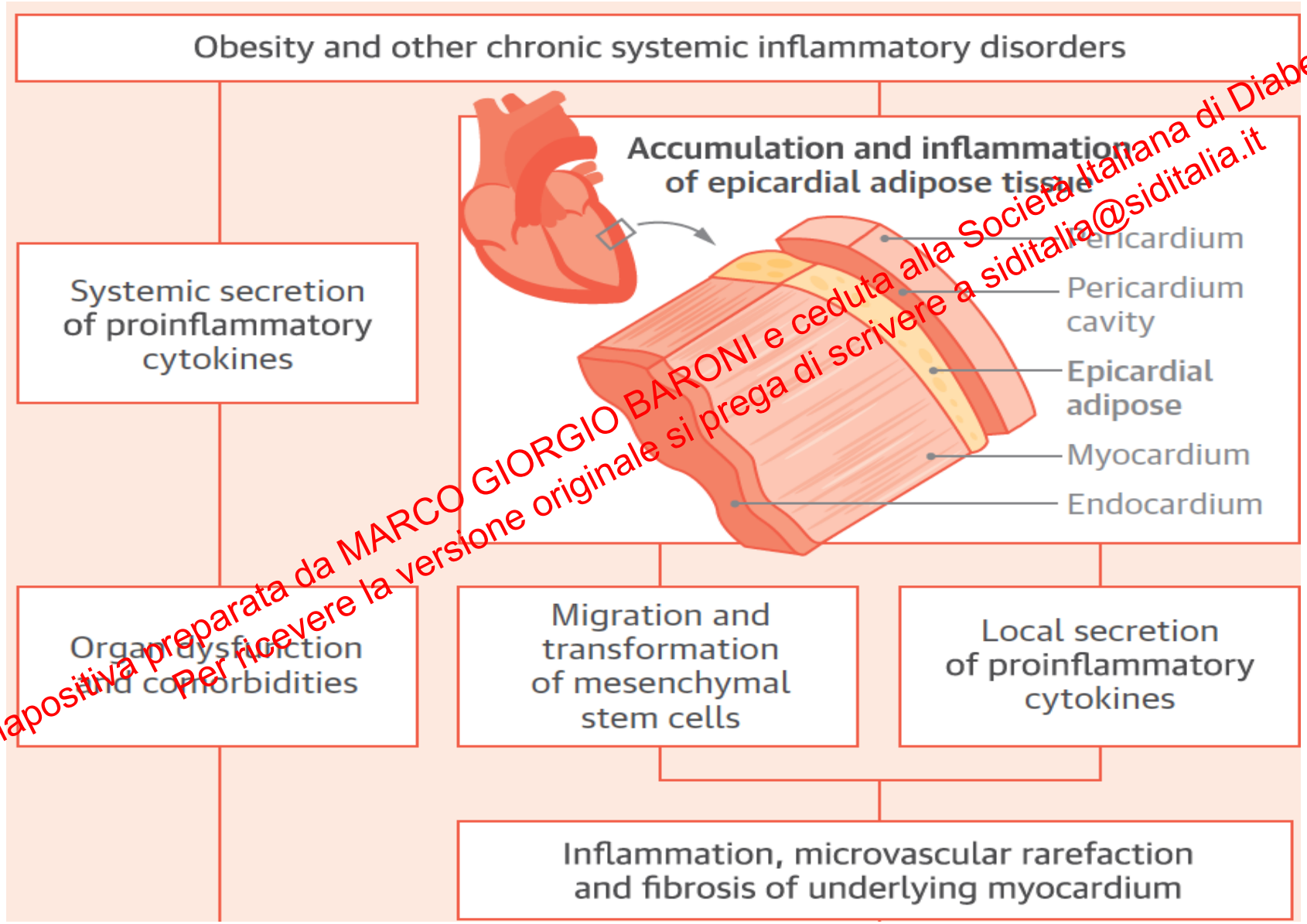
Anti-Atherosclerotic potential of GLP-1 action



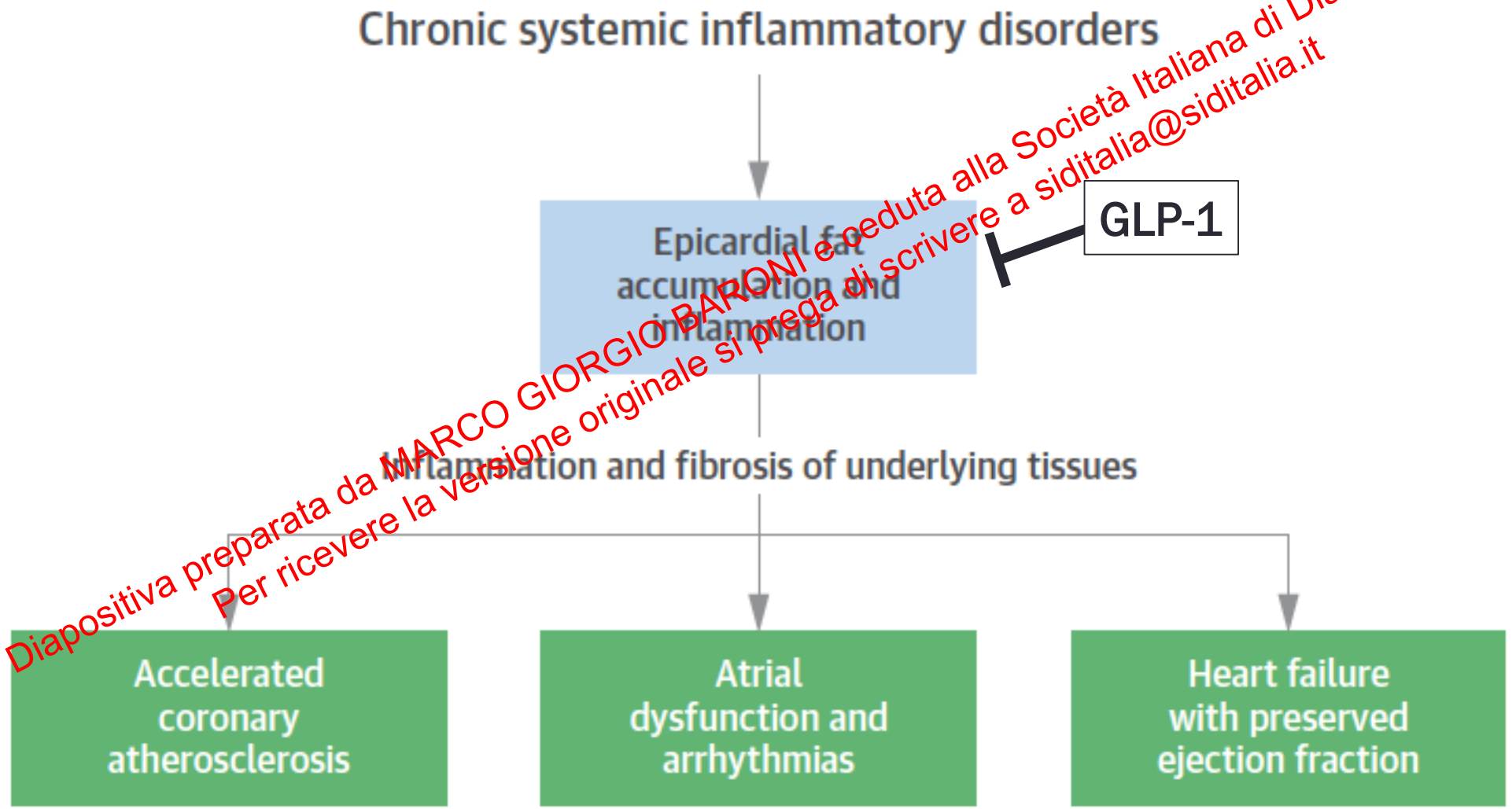
GLP-1R–Dependent Intracellular Signal Pathways in the Cardiomyocyte



Potential Role of Epicardial Adipose Tissue in the Heart

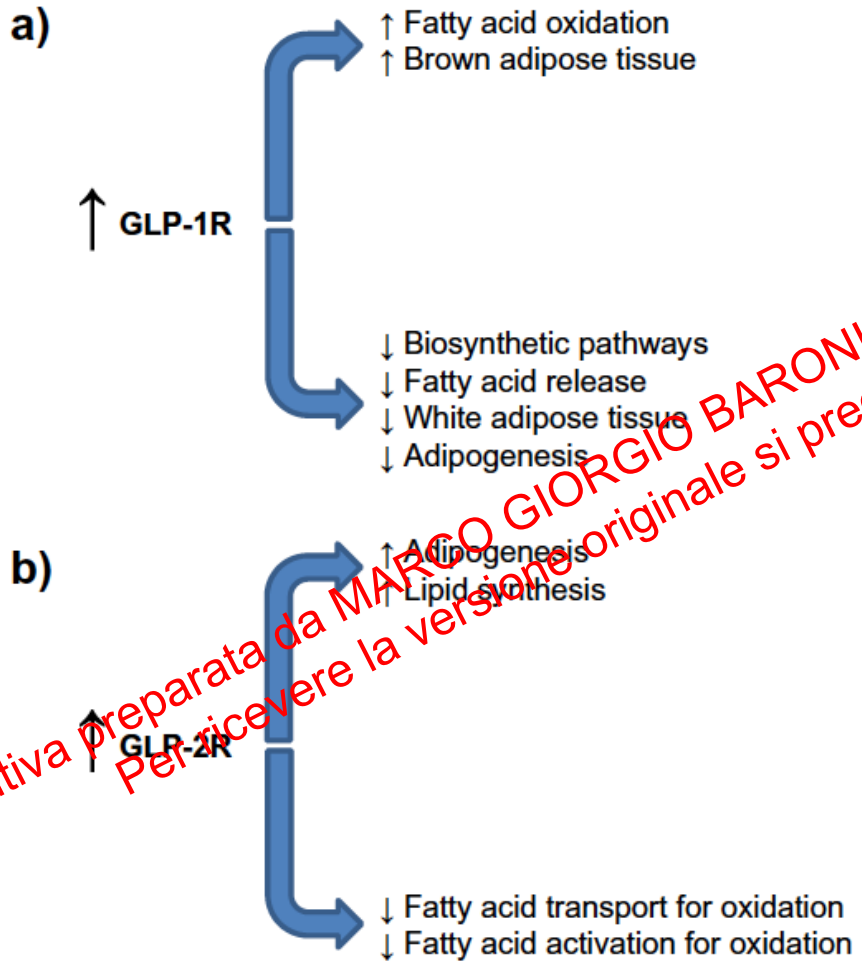


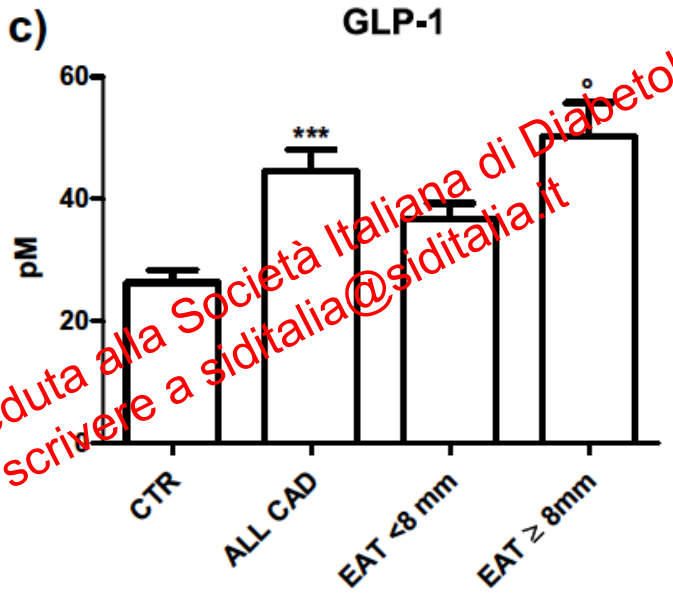
Epicardial Adipose Tissue Mediates the Effect of Chronic Systemic Inflammatory Disorders to Cause Coronary Atherosclerosis, Atrial Arrhythmias, and Heart Failure With Preserved Ejection Fraction

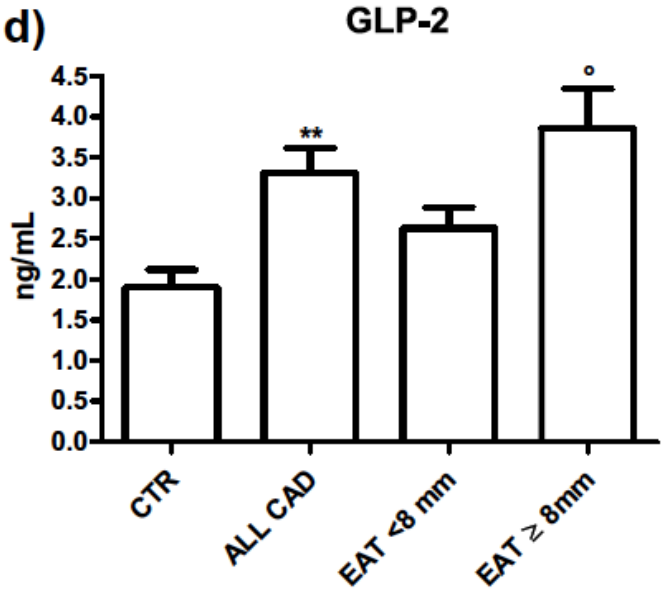


Packer M JACC 2018

Metabolic pathways associated to GLP-1R and GLP-2R levels in EAT from CAD patients

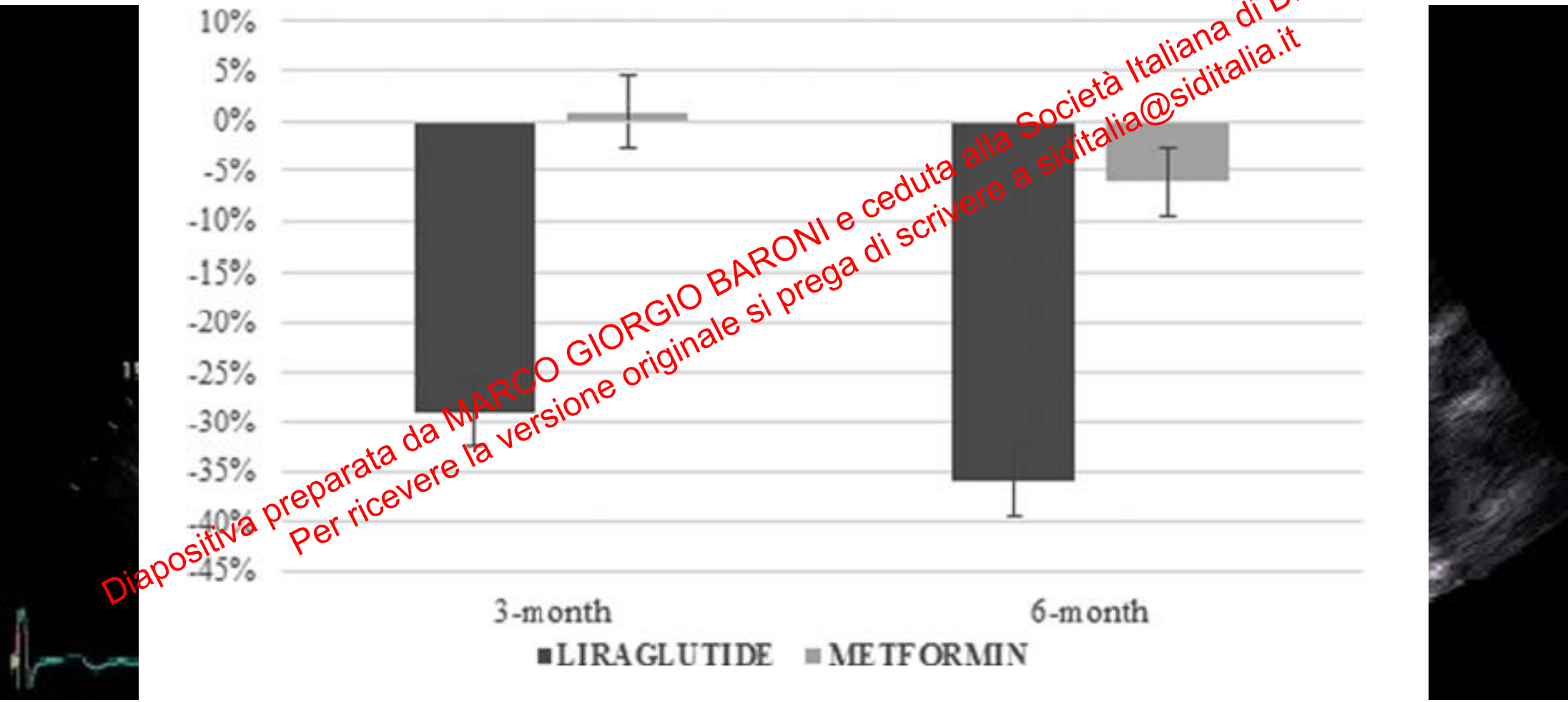




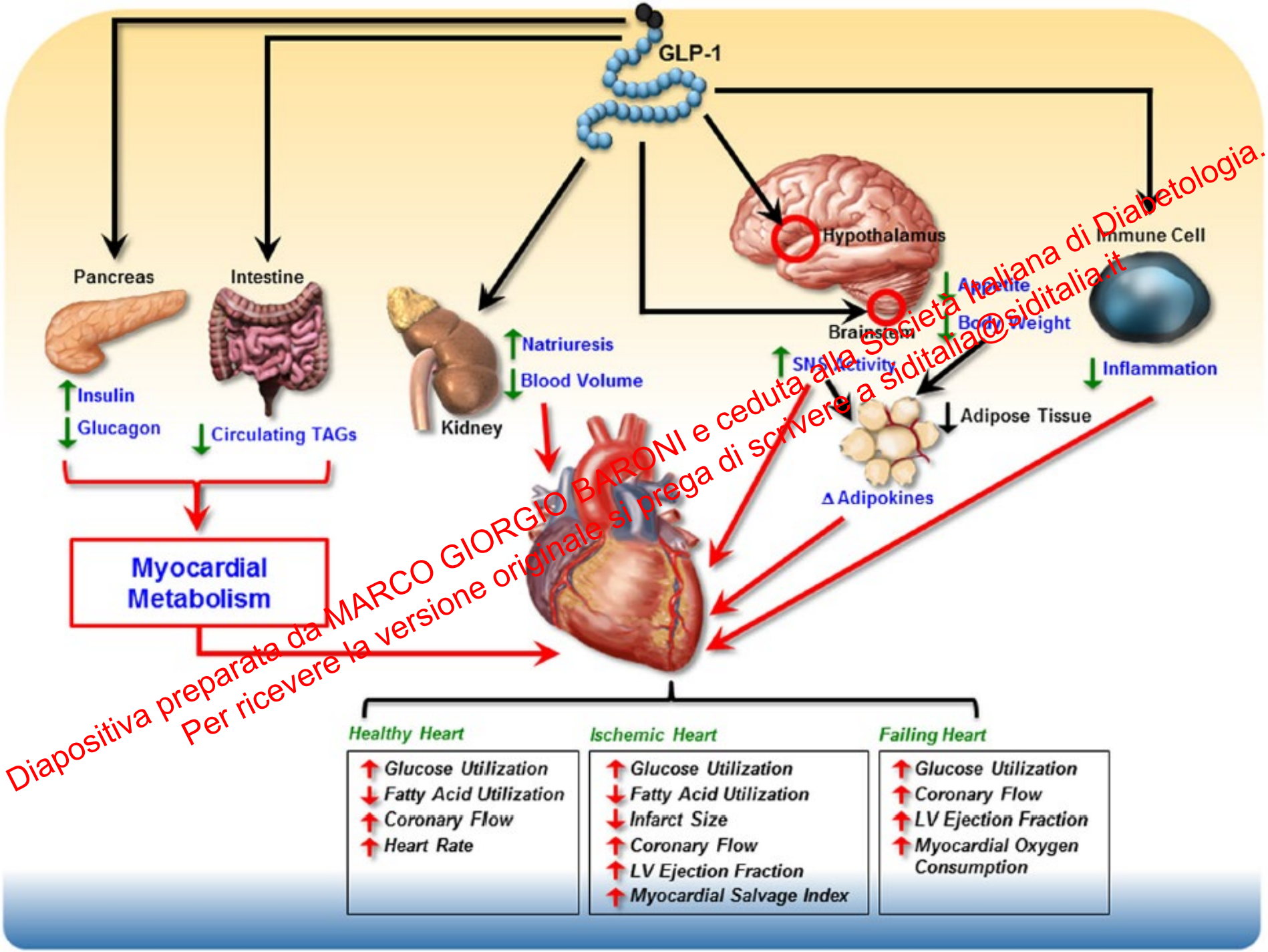


Dozio E Int J Cardiol 2019

Epicardial fat thickness (yellow filling between the white arrows) before (on the left) and after 3 months of liraglutide combined with metformin treatment (on the right) in the same patient



Iacobellis G Obesity 2017



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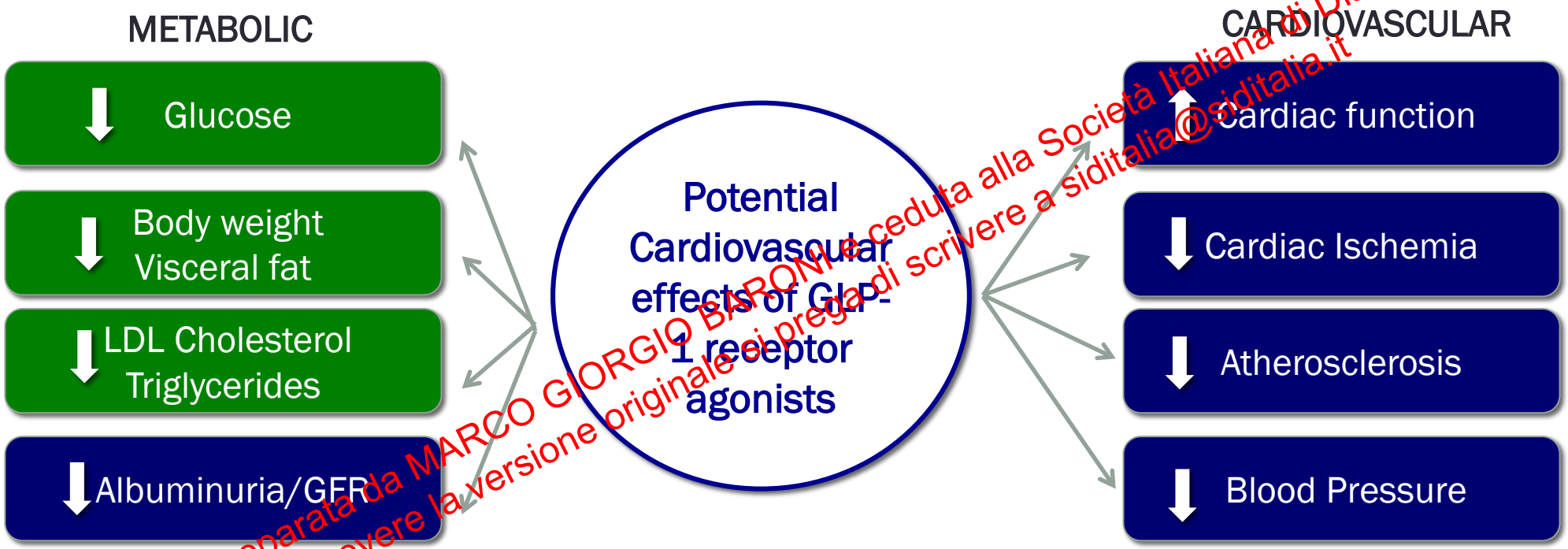
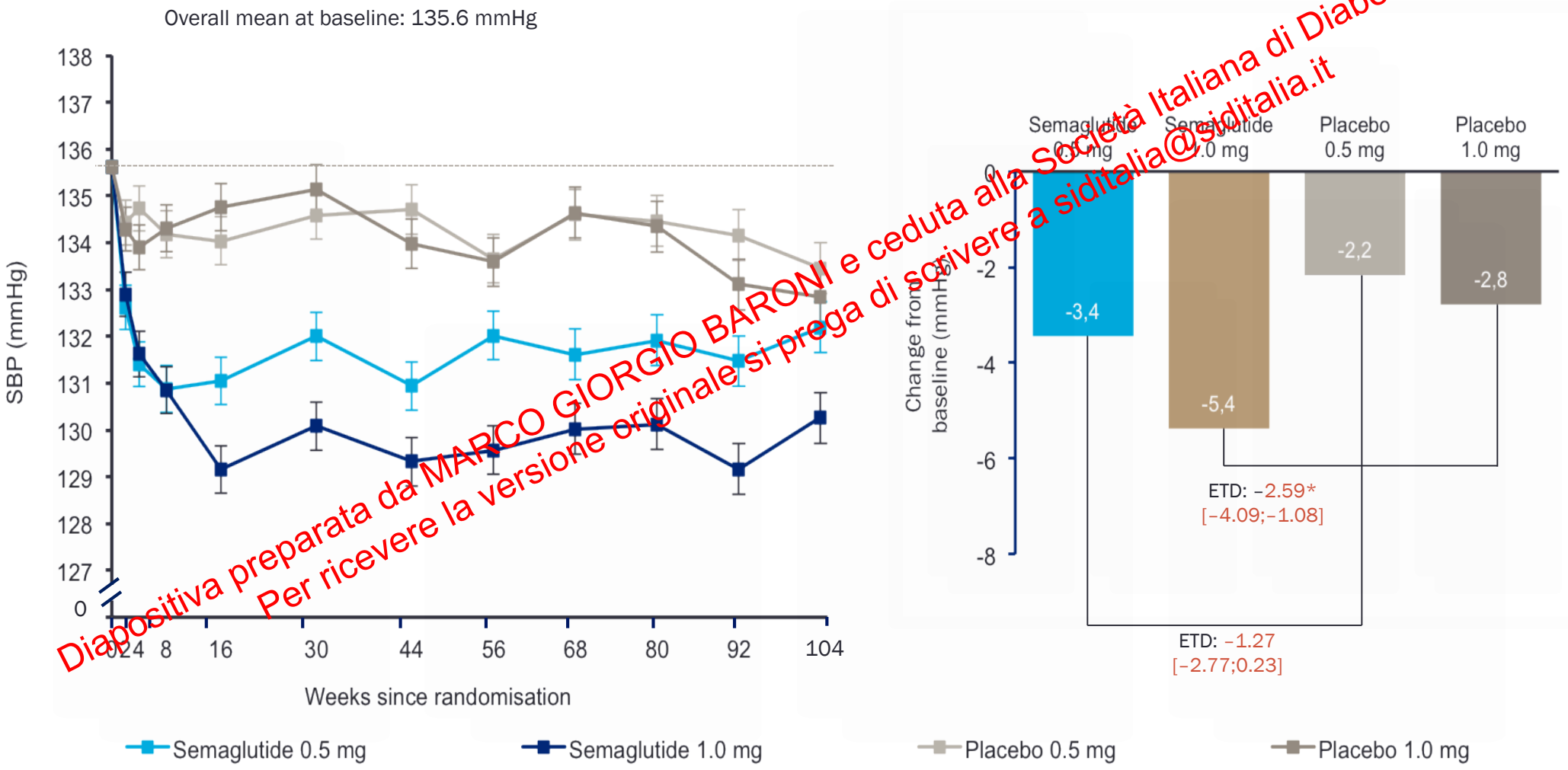


Quali sono gli effetti degli analoghi del GLP-1 sulla pressione arteriosa sistolica?

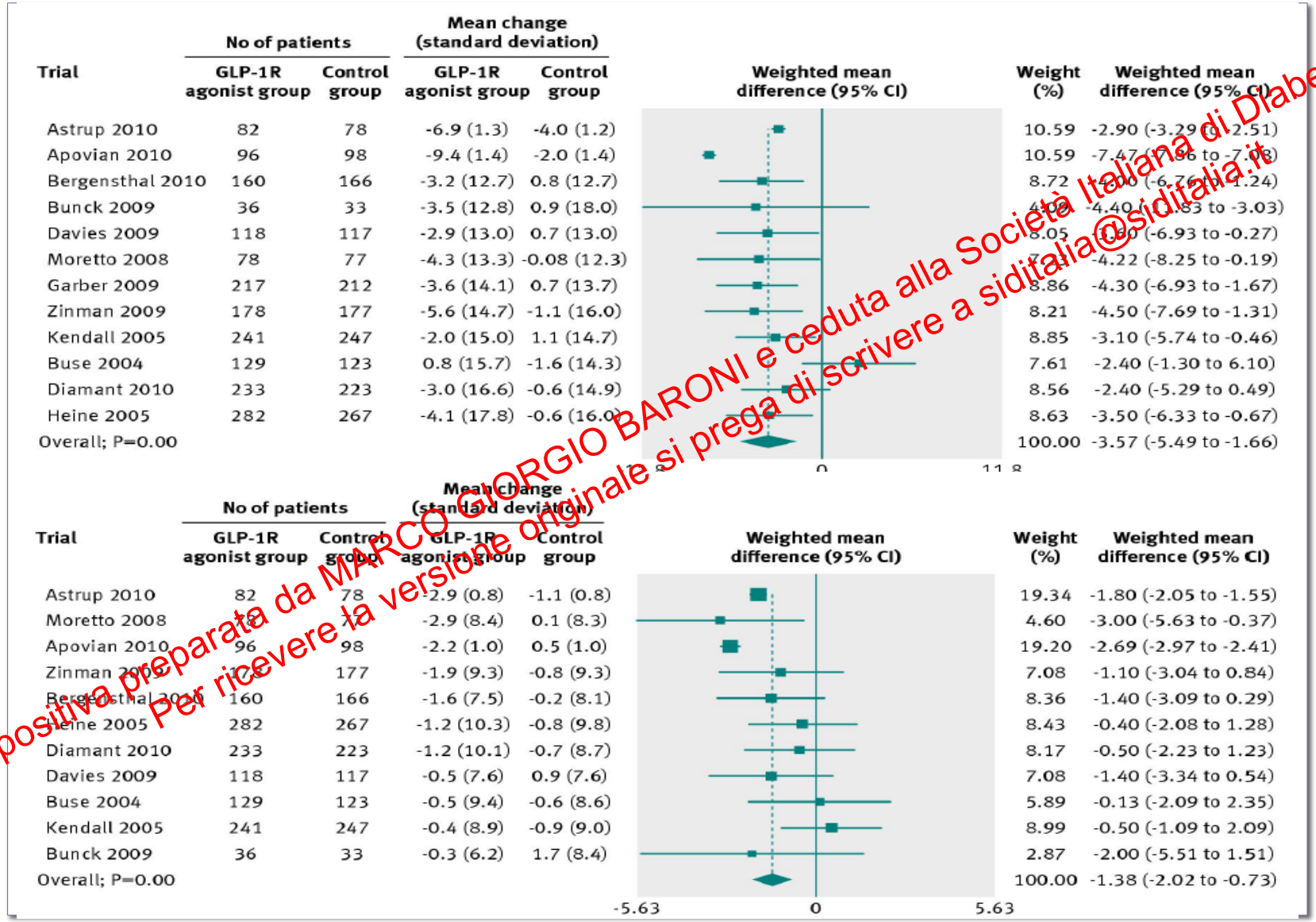
1. Nessun effetto
2. Riduzione di 3-4 mmHg
3. Riduzione 7-8 mmHg
4. Aumento di 1-2 mmHg

SUSTAIN-6 - Systolic Blood Pressure



Marso SP et al *N Engl J Med*. 2016;375:1834-1844.

Meta-analysis of Change in Systolic (top) and Diastolic Blood Pressure (mmHg) in T2DM Patients Treated with GLP1-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	Weighted mean difference (95% CI)	Weight (%)	Weighted mean difference (95% CI)
Astrup 2010	82	78	-6.9 (1.3)	-4.0 (1.2)		10.59	-2.90 (-3.29 to -2.51)
Apovian 2010	96	98	-9.4 (1.4)	-2.0 (1.4)		10.59	-7.47 (-7.86 to -7.08)
Bergensthal 2010	160	166	-3.2 (12.7)	0.8 (12.7)		8.72	-4.00 (-6.76 to -1.24)
Bunck 2009	36	33	-3.5 (12.8)	0.9 (18.0)		4.08	-4.40 (-5.83 to -3.03)
Davies 2009	118	117	-2.9 (13.0)	0.7 (13.0)		8.05	-3.60 (-6.93 to -0.27)
Moretto 2008	78	77	-4.3 (13.3)	-0.08 (12.3)		7.33	-4.22 (-8.25 to -0.19)
Garber 2009	217	212	-3.6 (14.1)	0.7 (13.7)		8.86	-4.30 (-6.93 to -1.67)
Zinman 2009	178	177	-5.6 (14.7)	-1.1 (16.0)		8.21	-4.50 (-7.69 to -1.31)
Kendall 2005	241	247	-2.0 (15.0)	1.1 (14.7)		8.85	-3.10 (-5.74 to -0.46)
Buse 2004	129	123	0.8 (15.7)	-1.6 (14.3)		7.61	-2.40 (-1.30 to 6.10)
Diamant 2010	233	223	-3.0 (16.6)	-0.6 (14.9)		8.56	-2.40 (-5.29 to 0.49)
Heine 2005	282	267	-4.1 (17.8)	-0.6 (16.0)		8.63	-3.50 (-6.33 to -0.67)
Overall; P=0.00						100.00	-3.57 (-5.49 to -1.66)

- 3.57 mmHg

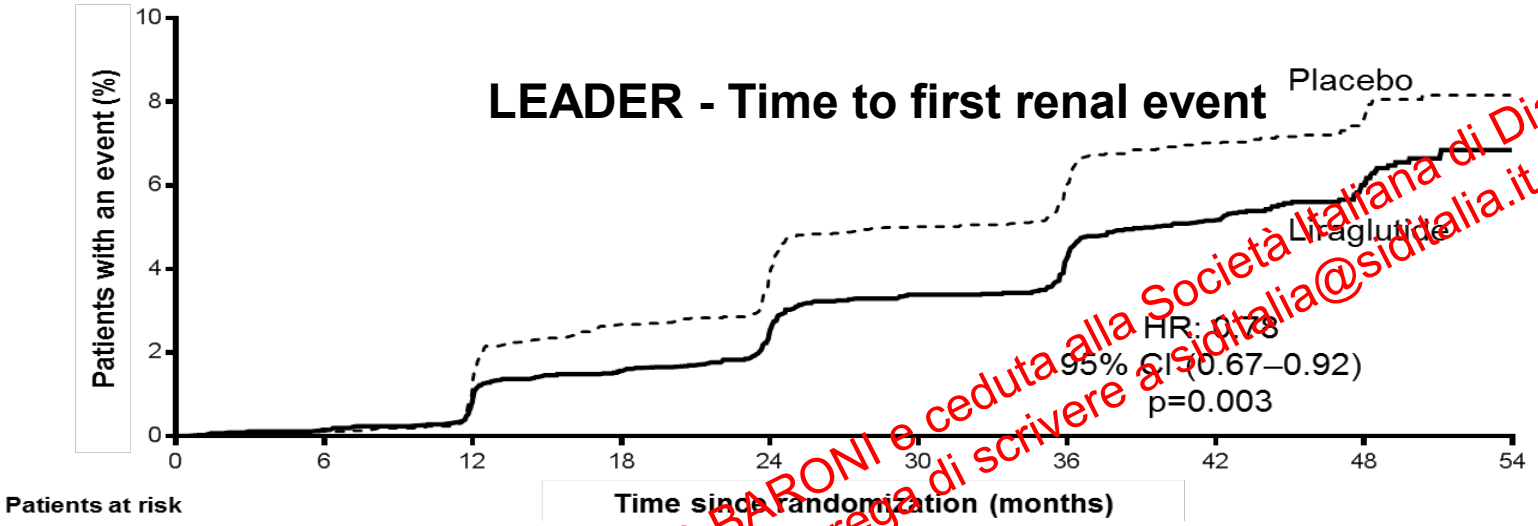
Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weighted mean difference (95% CI)	Weight (%)	Weighted mean difference (95% CI)
Astrup 2010	82	78	-2.9 (0.8)	-1.1 (0.8)		19.34	-1.80 (-2.05 to -1.55)
Moretto 2008	78	77	-2.9 (8.4)	0.1 (8.3)		4.60	-3.00 (-5.63 to -0.37)
Apovian 2010	96	98	-2.2 (1.0)	0.5 (1.0)		19.20	-2.69 (-2.97 to -2.41)
Zinman 2009	178	177	-1.9 (9.3)	-0.8 (9.3)		7.08	-1.10 (-3.04 to 0.84)
Bergensthal 2010	160	166	-1.6 (7.5)	-0.2 (8.1)		8.36	-1.40 (-3.09 to 0.29)
Heine 2005	282	267	-1.2 (10.3)	-0.8 (9.8)		8.43	-0.40 (-2.08 to 1.28)
Diamant 2010	233	223	-1.2 (10.1)	-0.7 (8.7)		8.17	-0.50 (-2.23 to 1.23)
Davies 2009	118	117	-0.5 (7.6)	0.9 (7.6)		7.08	-1.40 (-3.34 to 0.54)
Buse 2004	129	123	-0.5 (9.4)	-0.6 (8.6)		5.89	-0.13 (-2.09 to 2.35)
Kendall 2005	241	247	-0.4 (8.9)	-0.9 (9.0)		8.99	-0.50 (-1.09 to 2.09)
Bunck 2009	36	33	-0.3 (6.2)	1.7 (8.4)		2.87	-2.00 (-5.51 to 1.51)
Overall; P=0.00						100.00	-1.38 (-2.02 to -0.73)

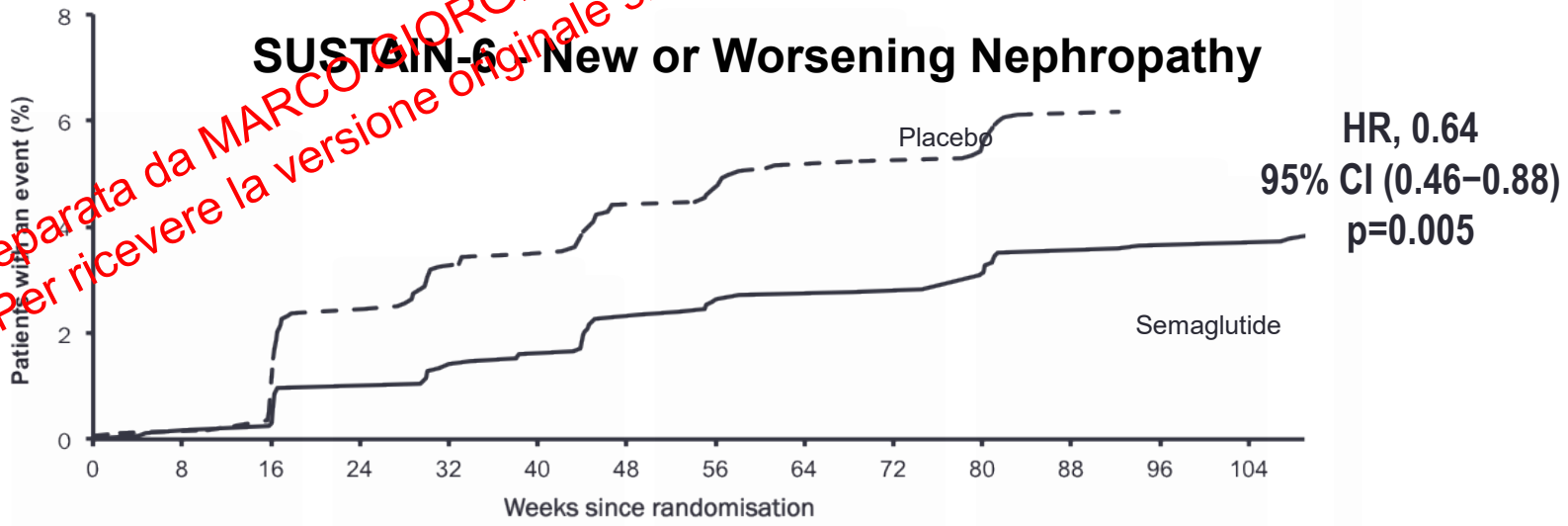
-5.63 0 5.63

- 1.38 mmHg

Visboll T et al BMJ 2012;344:d7771 doi: 10.1136/bmj.d7771

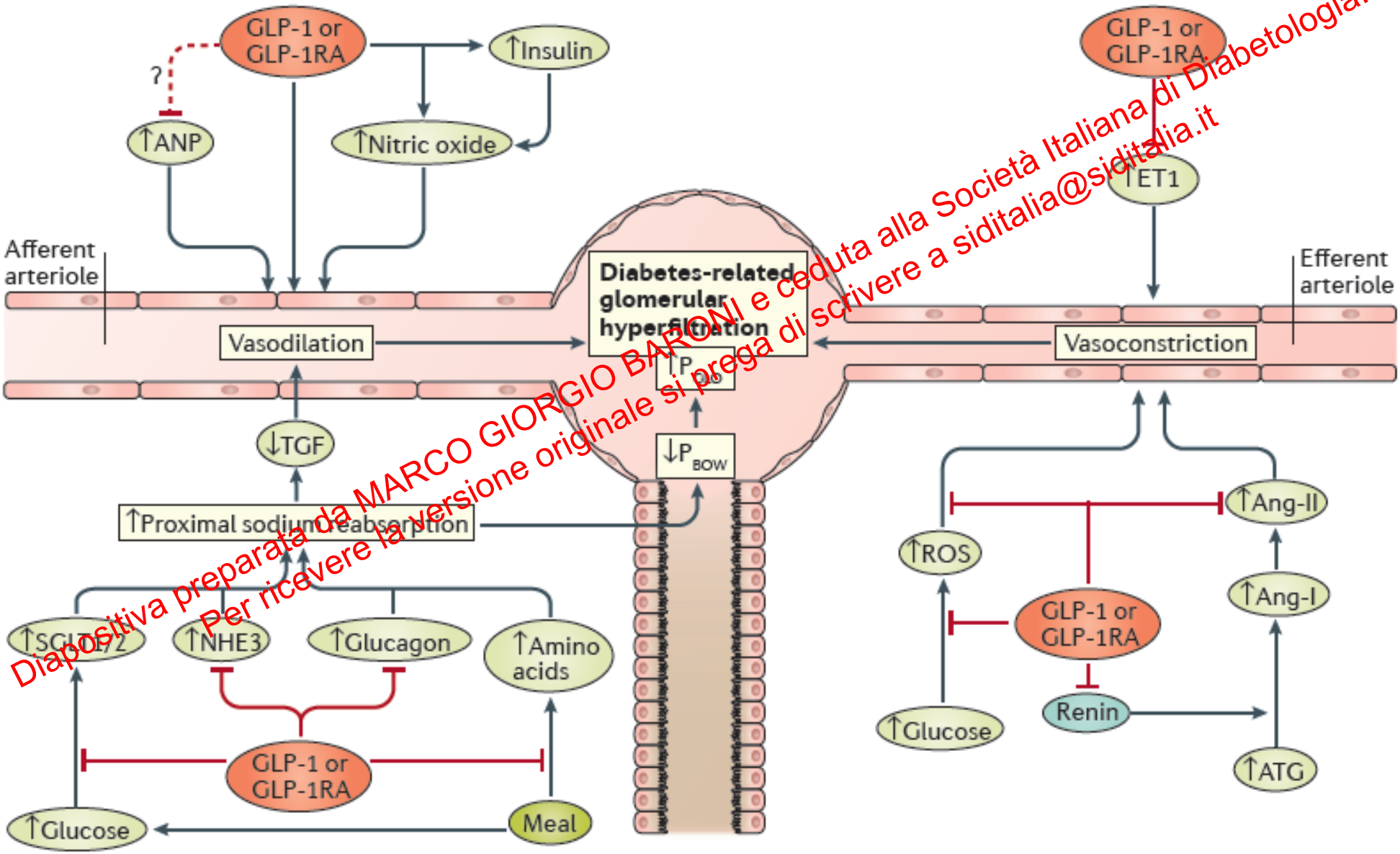
LEADER & SUSTAIN 6 – Renal Outcomes



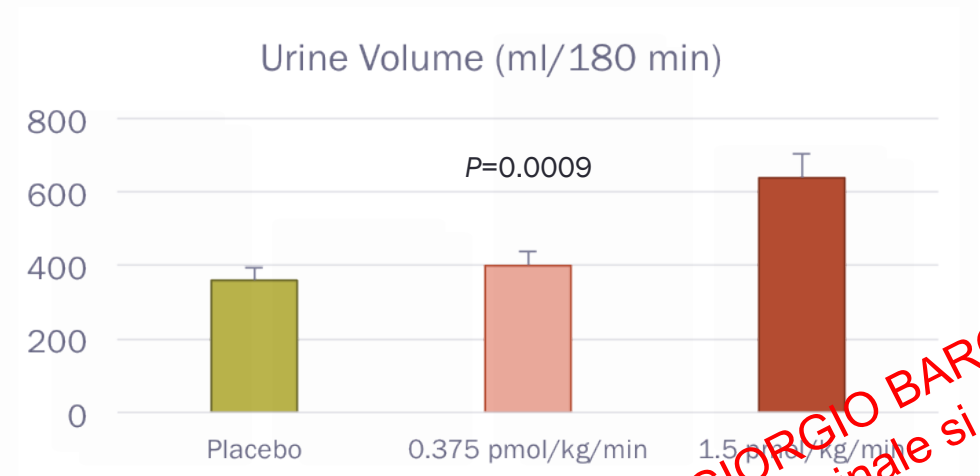


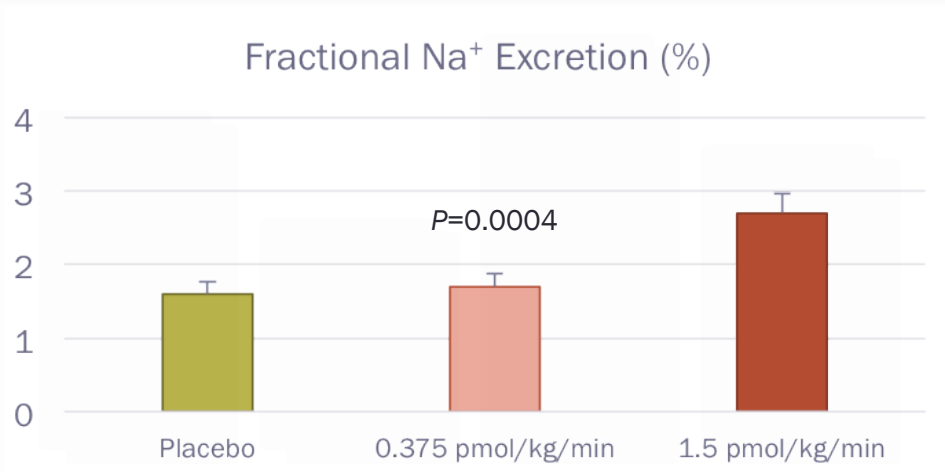
Marso SP et al ***N Engl J Med***. 2016;375:311-22; Marso SP et al ***N Engl J Med***. 2016;375:1834-1844.

Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes



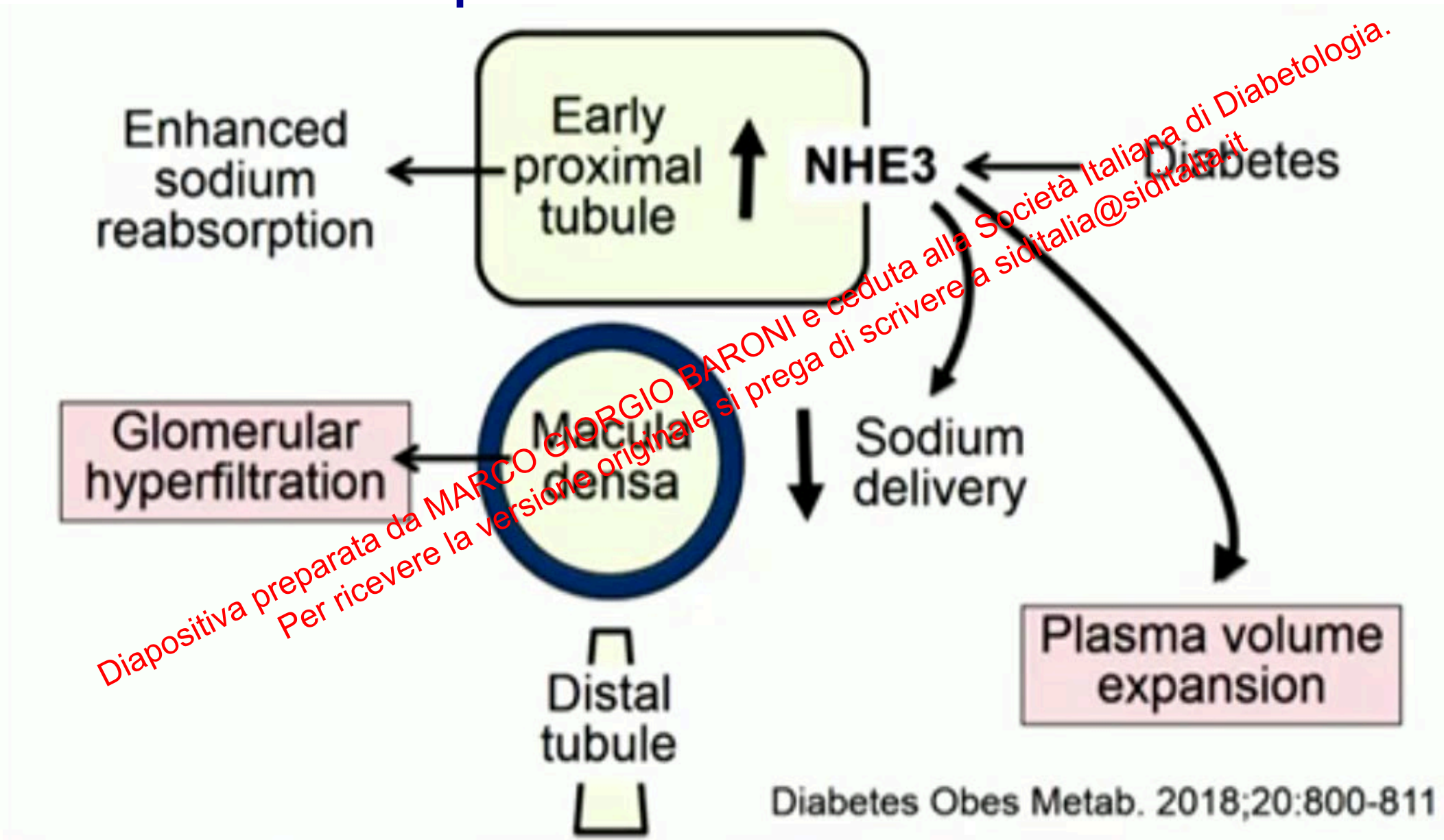
Effect of 3h GLP-1 infusion on Urine Fluid and Electrolyte Output in Healthy Subjects





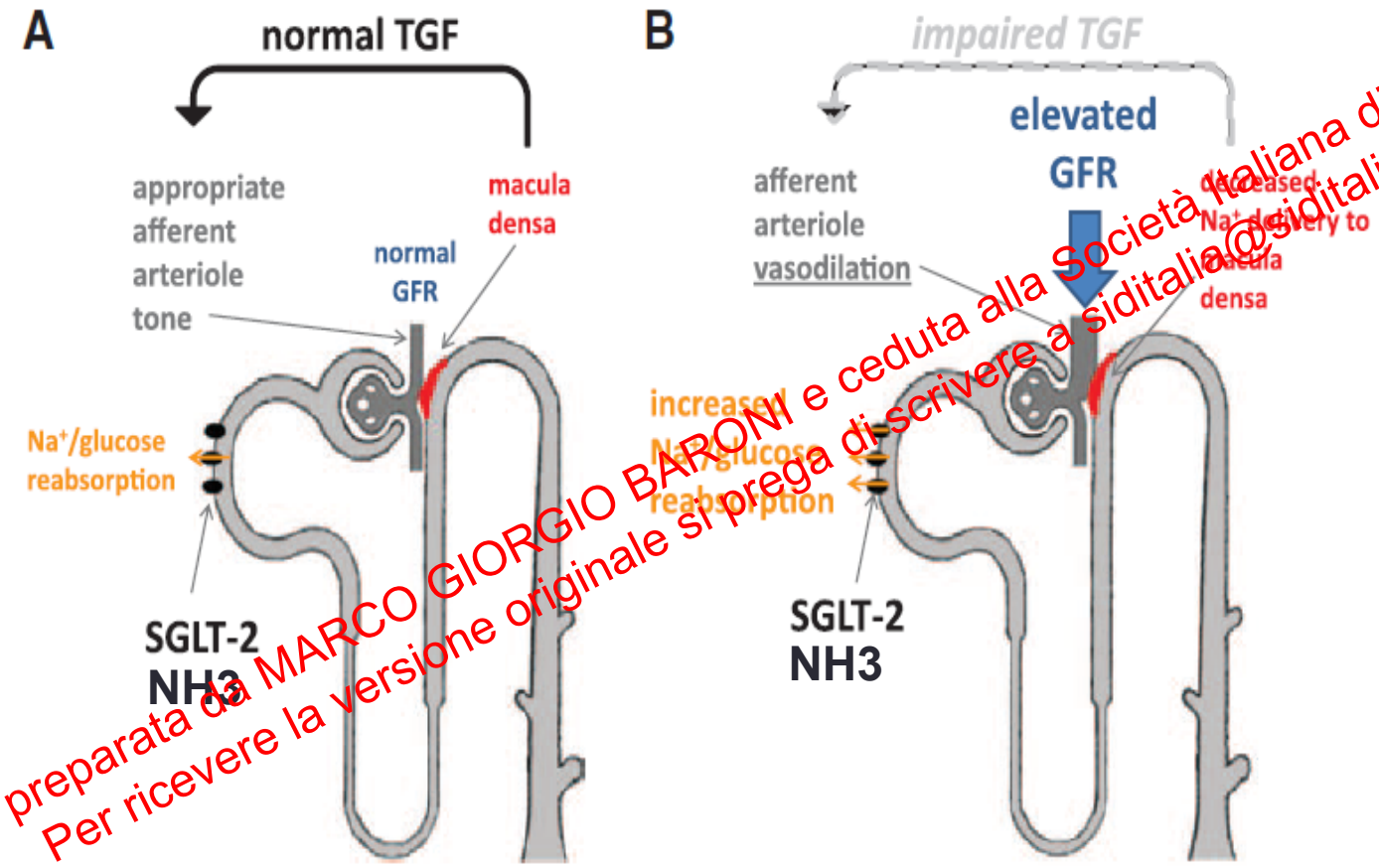
Gutzwiller J-P et al *J Clin Endocrinol Metab* 2004;89:3055-3061

Diabetes activates proximal tuble NH3 and enhances sodium reabsorption



Diabetes Obes Metab. 2018;20:800-811

Postulated tubuloglomerular feedback (TGF) mechanism

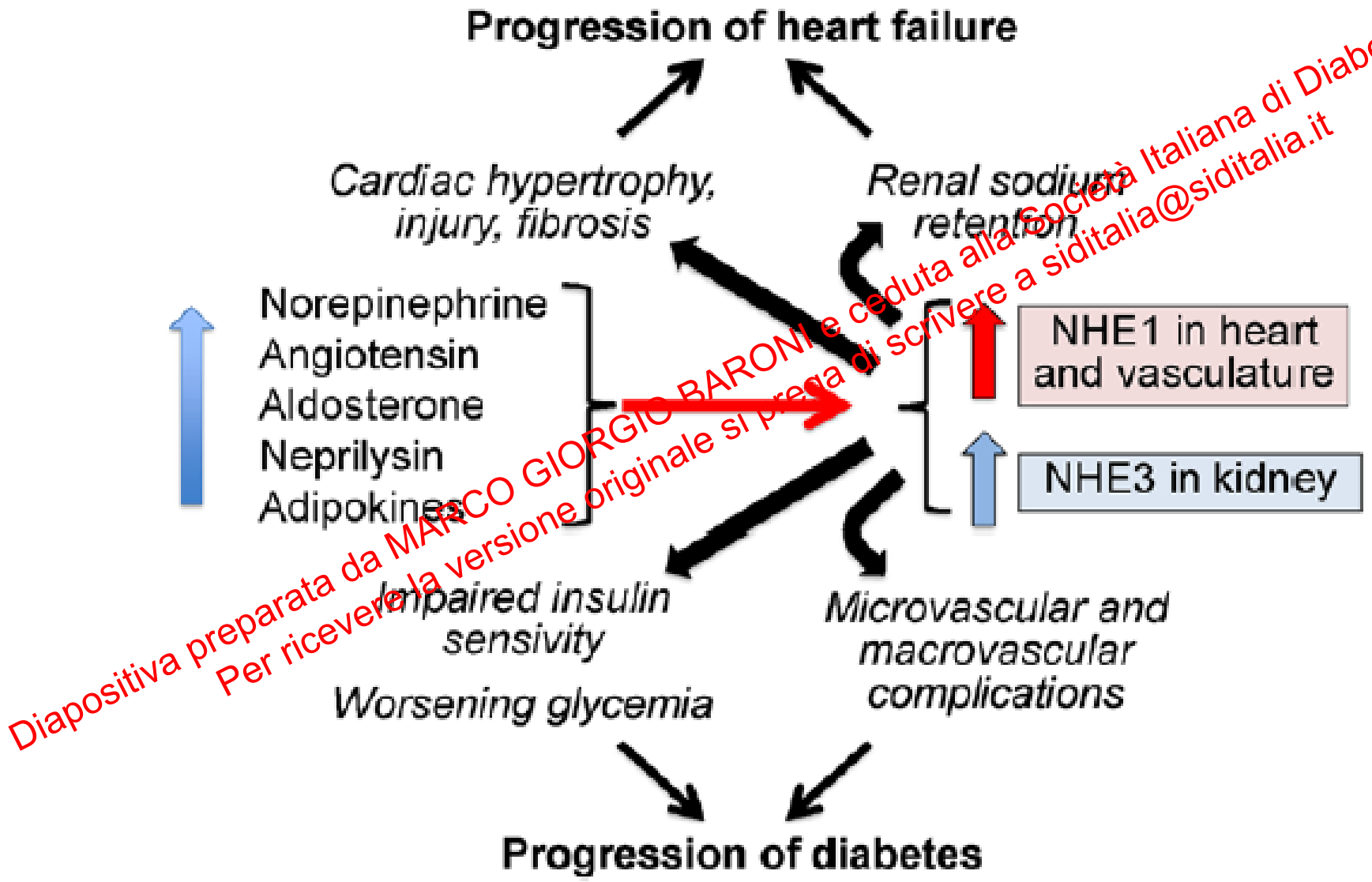


Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

Circulation. 2014;129:587-597.

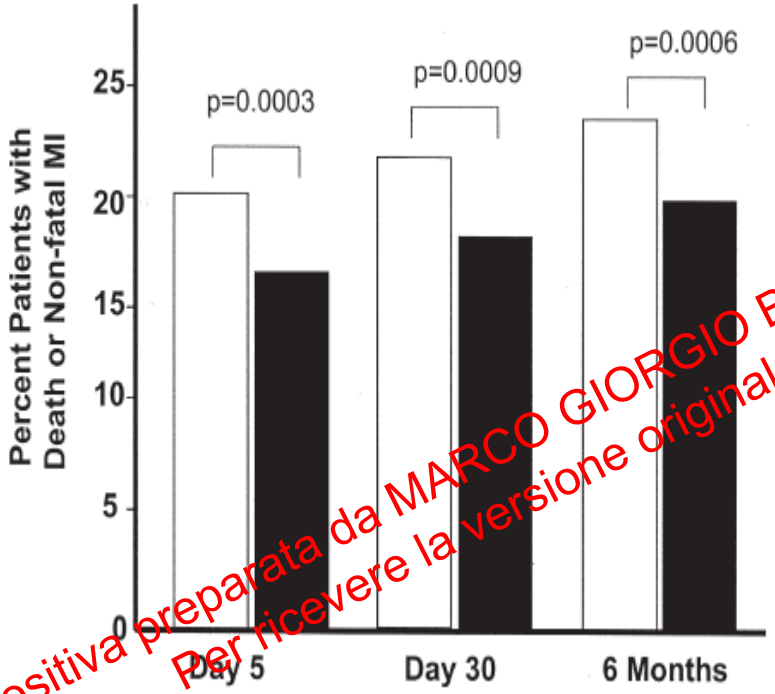
NHE-dependent pathways that may underlie the interplay of the pathogenesis of heart failure and diabetes

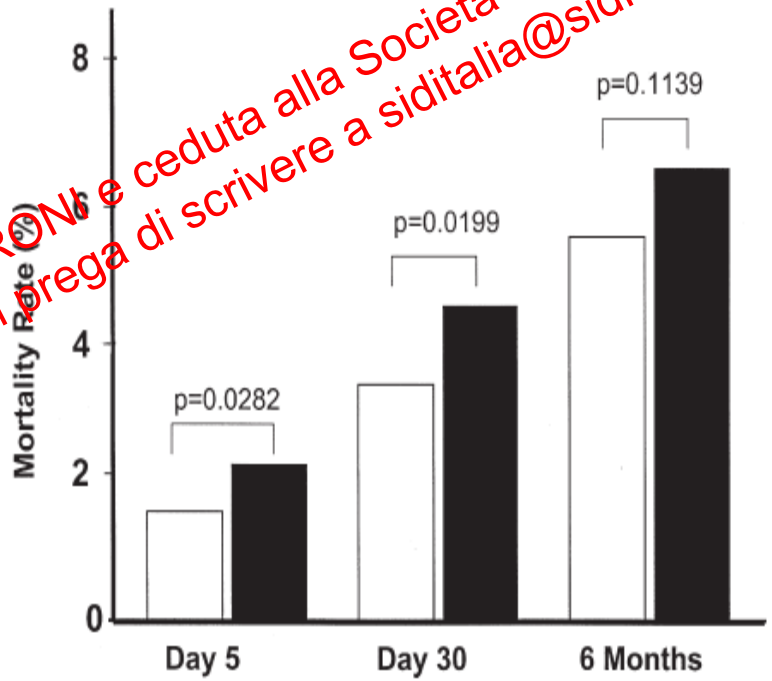


Circulation. 2017;136:1548–1559.

Sodium-Hydrogen Exchange Inhibition by Cariporide to Reduce the Risk of Ischemic Cardiac Events in Patients Undergoing Coronary Artery Bypass Grafting: Results of the EXPEDITION Study

N=5791

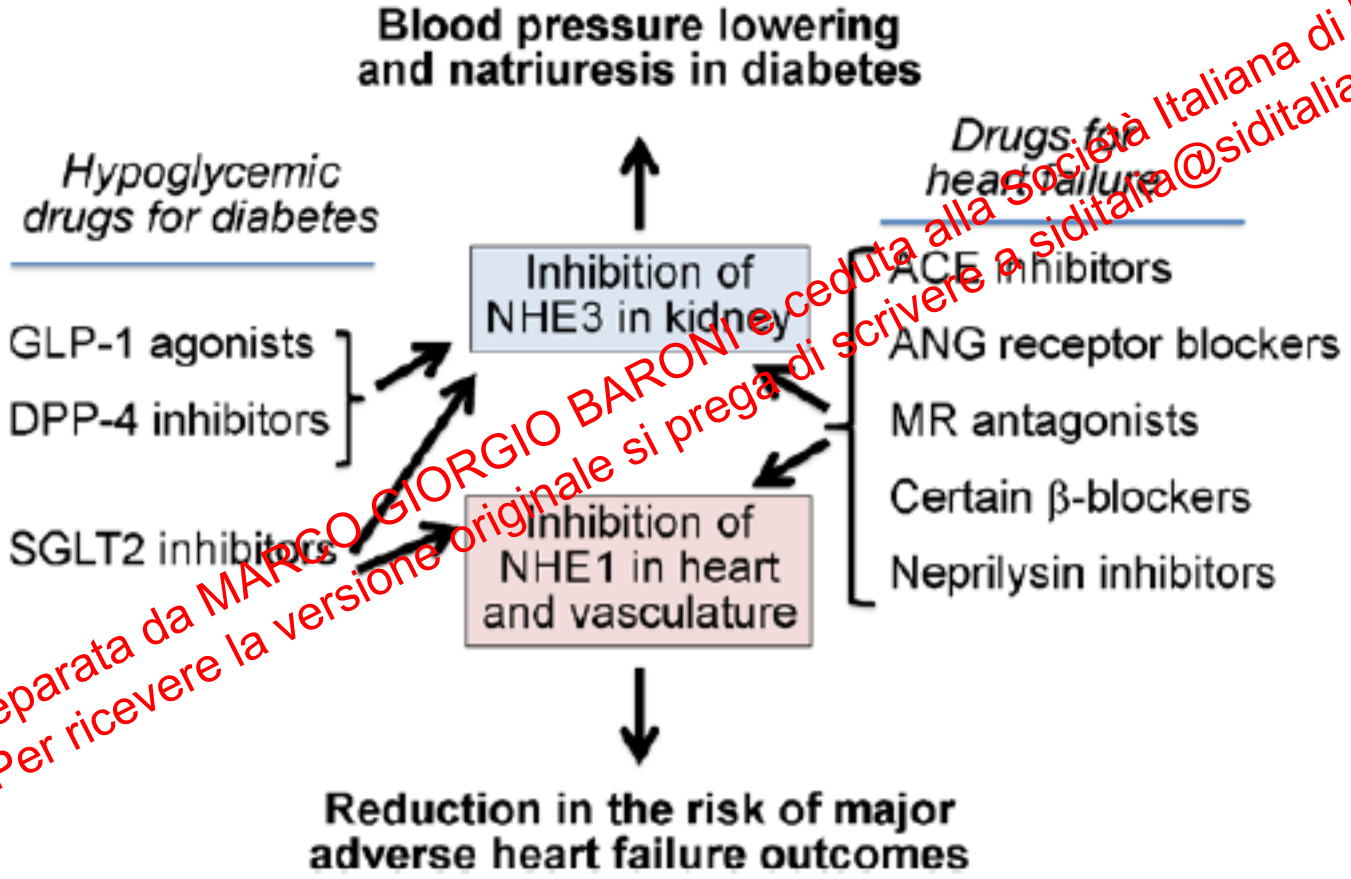




Cariporide (■) ev (180 mg in a 1-hour preoperative loading dose, then 40 mg per hour over 24 hours and 20 mg per hour over the subsequent 24 hours) vs placebo (□)

(Ann Thorac Surg 2008;85:1261–70)

Effects of diabetes treatments on NHE-dependent pathways.



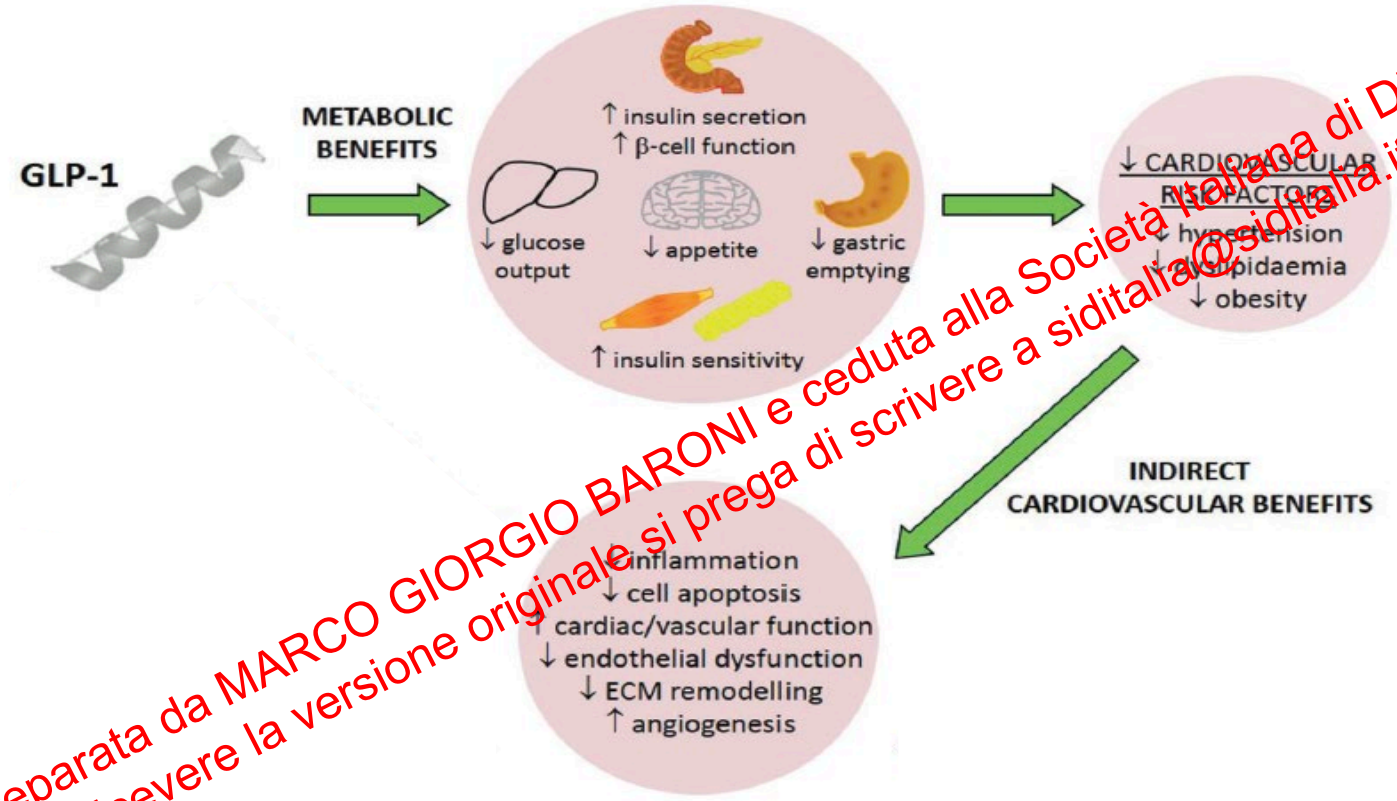
Circulation. 2017;136:1548–1559.

Possible Mechanisms Regulating Antihypertensive Effect(s) of Incretin-based Diabetes Therapies

Non-Renal Mediated Effects	Renal-Mediated Effects
Weight loss	Natriuresis
Central inhibition of salt intake	Renal Na+/H+ ion exchanger activity
Inhibition of intestinal salt absorption	Renal hemodynamics (increased urinary flow/diuresis)
Neuronally stimulated catechcolaminergic activity	
Endothelial-dependent vasodilation	

Lovshin JA, Zinman B *Can J Diabetes* 38;2014:364e371

Selective Targeting of GLP-1 Signalling as a Therapeutic Approach for CVD in Diabetes



Tate M et al *British Journal of Pharmacology* 2015;172 721–736 721

In conclusione....

- in prevenzione secondaria gli analoghi del GLP-1 si sono dimostrati efficaci nel ridurre gli eventi CV e la mortalità, e devono essere presi in considerazione nella terapia del diabete.

- I meccanismi coinvolti sembrano essere sia “glicemici” che “extra-glicemici”

- Se i meccanismi di protezione CVD sono prevalentemente extraglicemici, perché non utilizzarli anche nei non diabetici?

EASD ADA 2018

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

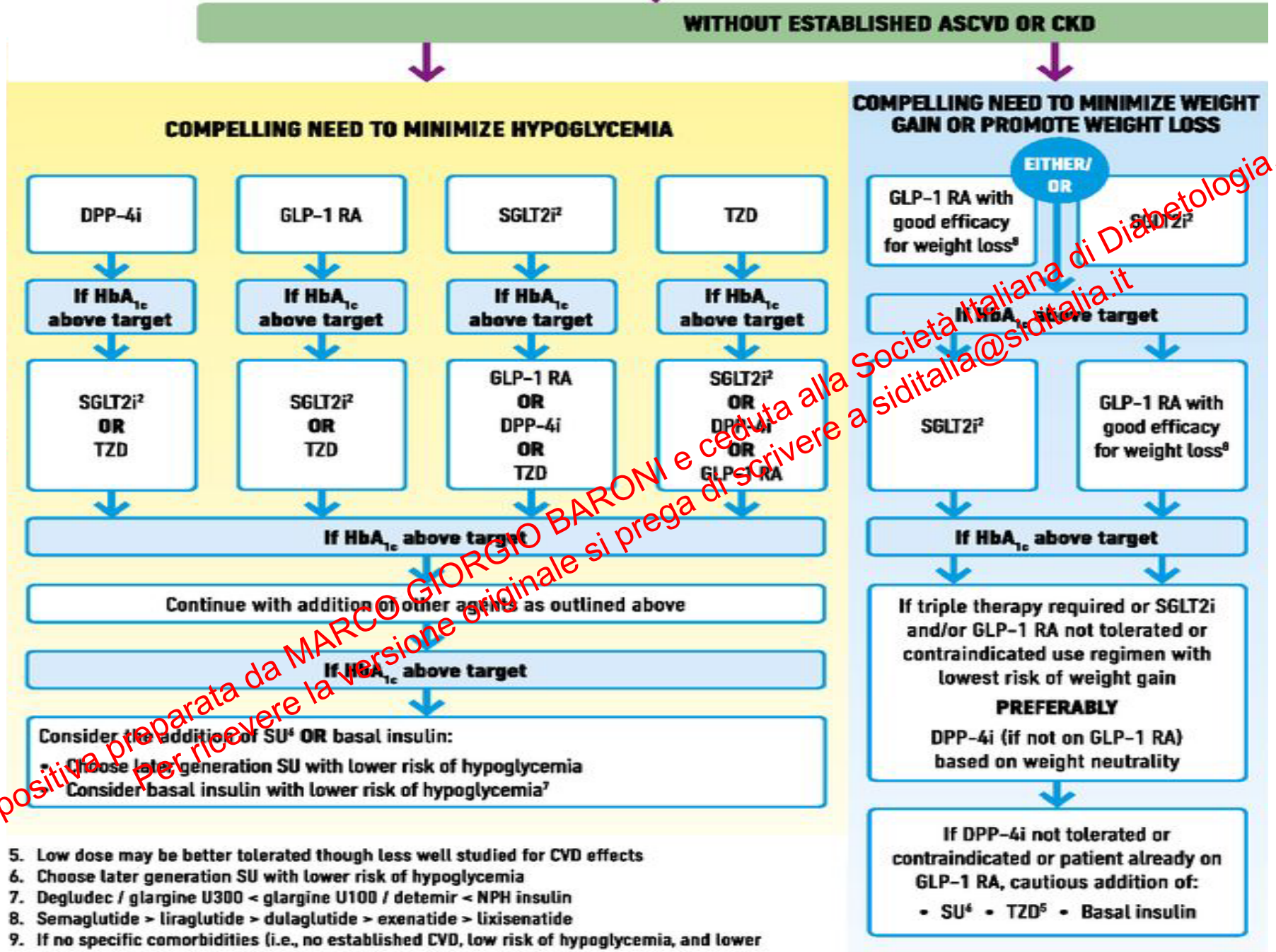
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]



5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease in patients with diabetes