Come può un farmaco per il diabete aiutare il cuore?

GLP-1 RA e Cuore

FRANCESCO GIORGINO, M.D., PH.D.
PROFESSOR OF ENDOCRINOLOGY

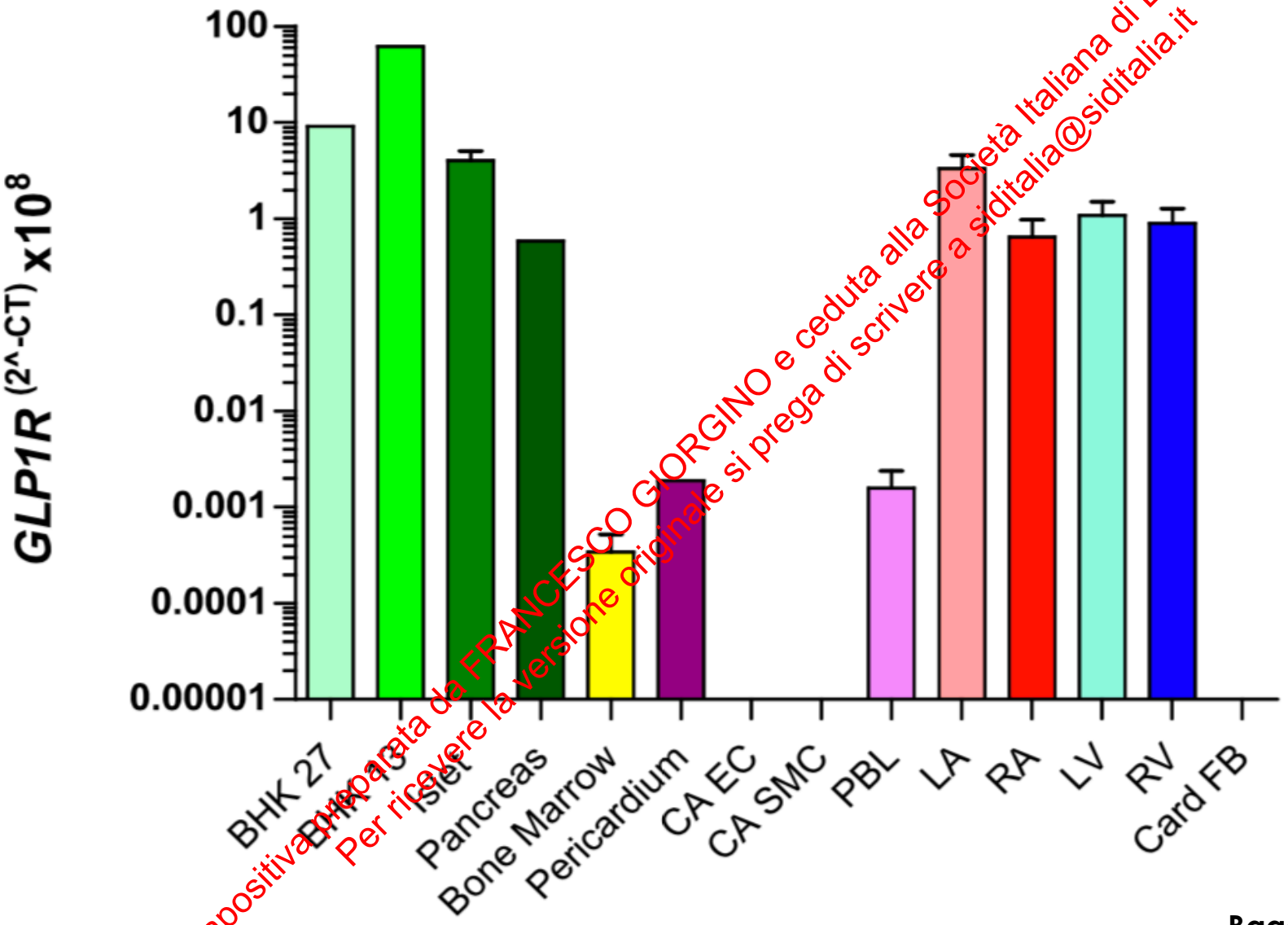
DEPARTMENT OF EMERGENCY AND ORGAN TRANSPLANTATION
SECTION OF INTERNAL MEDICINE, ENDOCRINOLOGY,
ANDROLOGY AND METABOLIC DISEASES

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Disclosures

- Advisory Boards: AstraZeneca; Eli Lilly; Novo Nordisk; Roche Diabetes Care, Sanofi
- Consultant: Boehringer Ingelheim; Lifescan; Merck Sharp & Dohme; Sanofi, AstraZeneca, Medimmune, Roche Diabetes Care, Sanofi
- Research Support: Eli Lilly, Lifescan, Takeda, Roche Diabetes Care

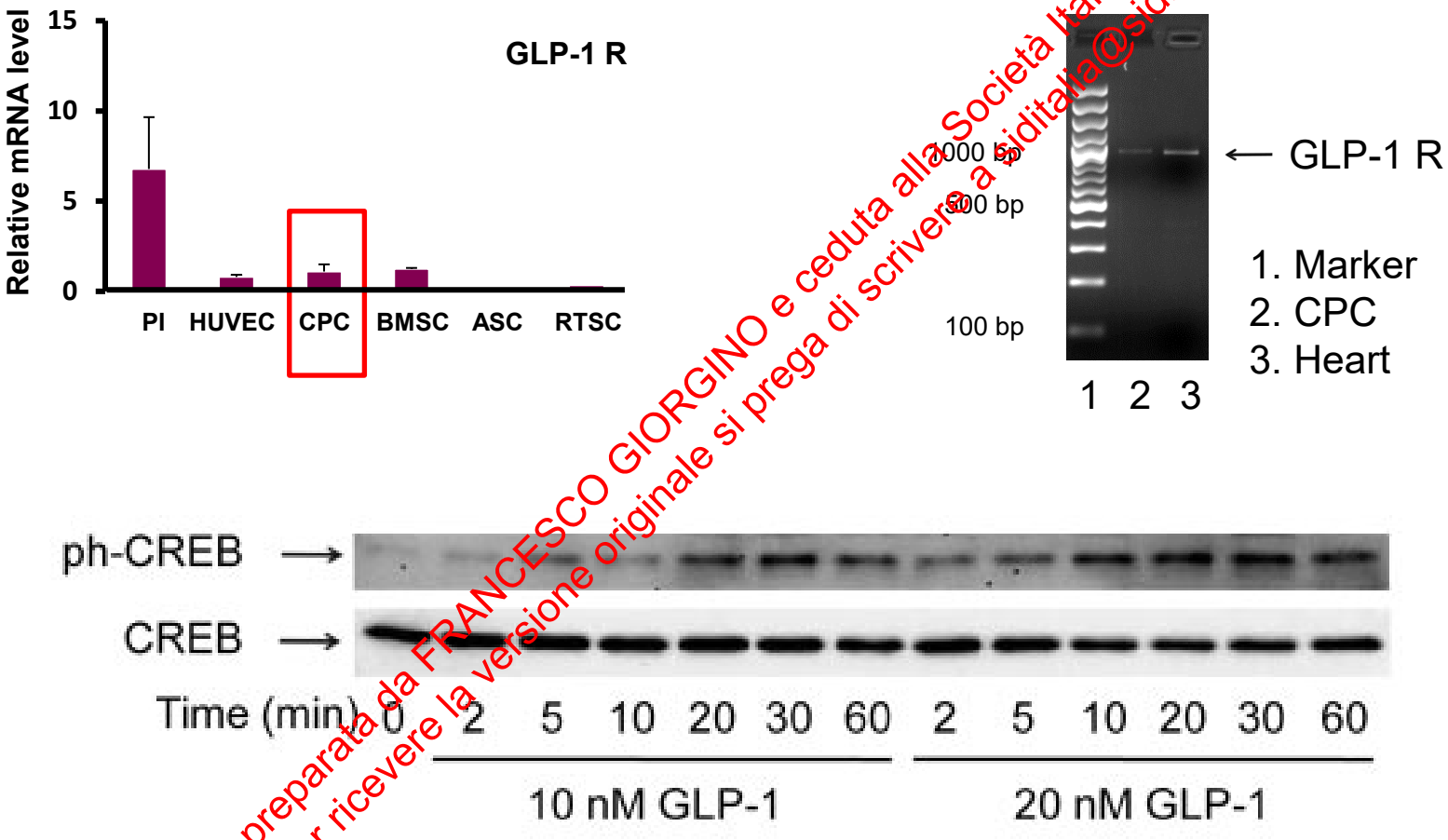
mRNA Expression of GLP-1 Receptor in Human Heart



LA, left atria; RA, right atria; LV, left ventricle; RV, right ventricle; CA EC, coronary artery endothelial cells; CA SMC, coronary artery smooth muscle cells; PBL, peripheral blood lymphocytes; Card FB, cardiac fibroblasts.

Baggio LL et al, *Endocrinology*, 2018

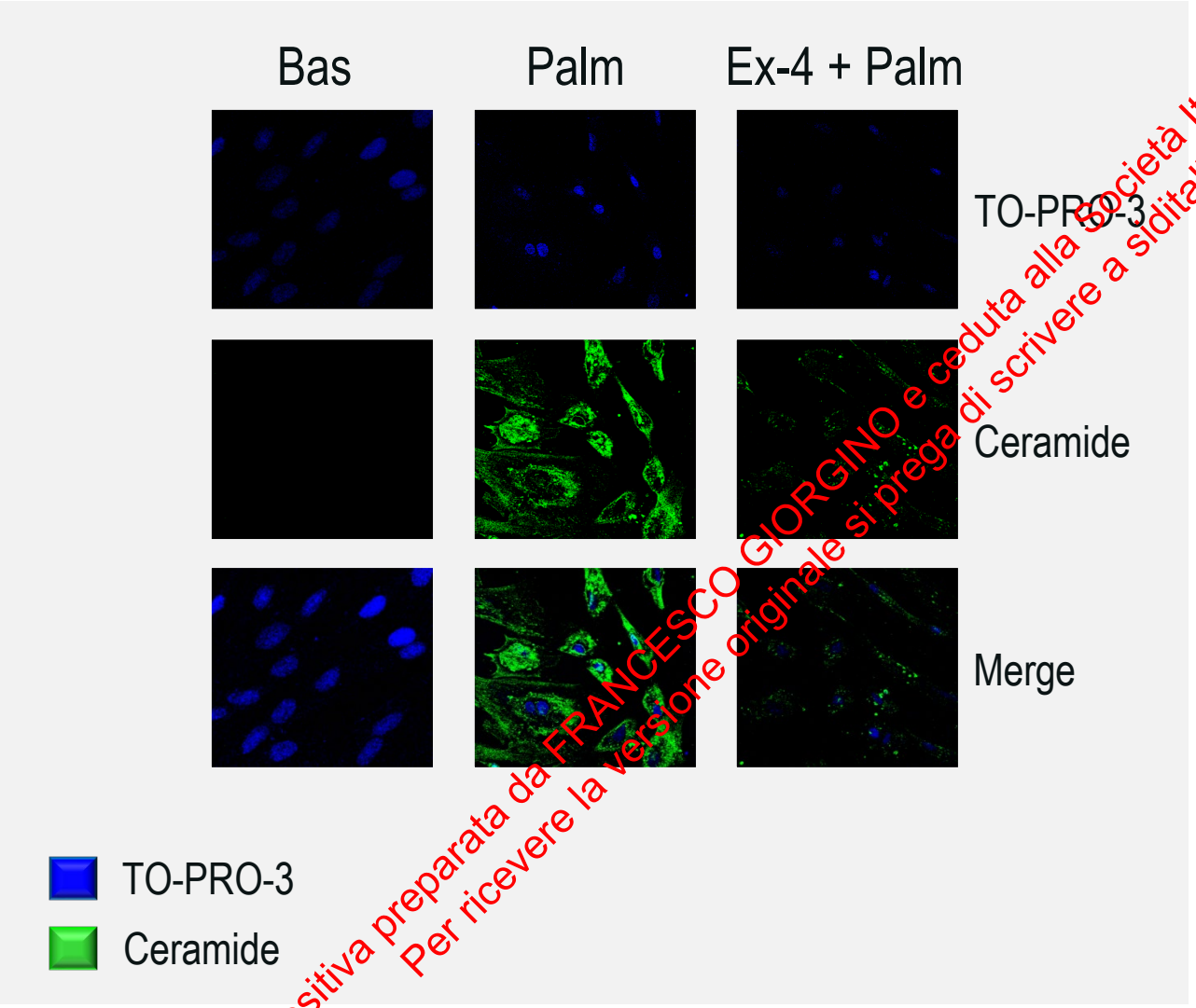
The GLP-1 Receptor in Human CPC

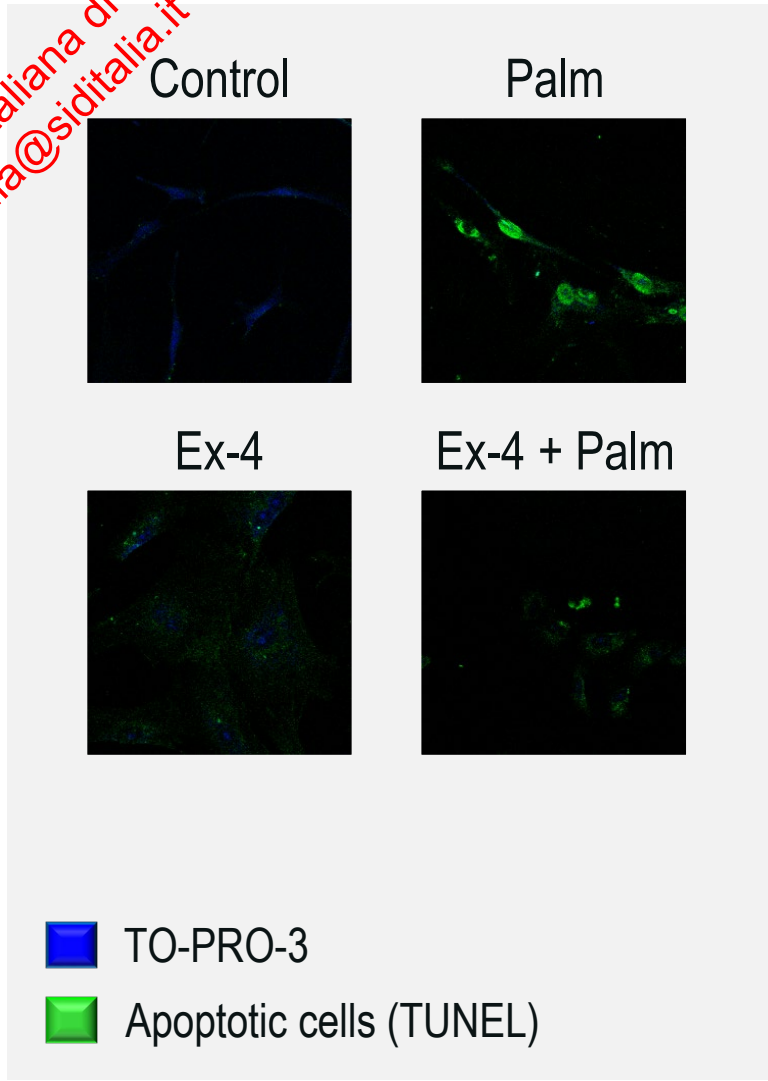


ASC, adipose tissue-derived stem cells; BMSC, human bone marrow stem cells; CPC, cardiac progenitor cells; CREB, cAMP-response-element binding protein; GLP-1, glucagon-like peptide-1; HUVEC, human umbilical vein endothelial cells; RTSC, human renal tubular stem cells

Laviola L, Leonardini A, et al. *Endocrinology* 2012;153:5770–5781

Exendin-4 Inhibits de Novo Production of Ceramide and Apoptosis in Human CPC





CPC, cardiac progenitor cells

Leonardini A, et al. *J Clin Endocrinol Metab* 2017;102:4136–47

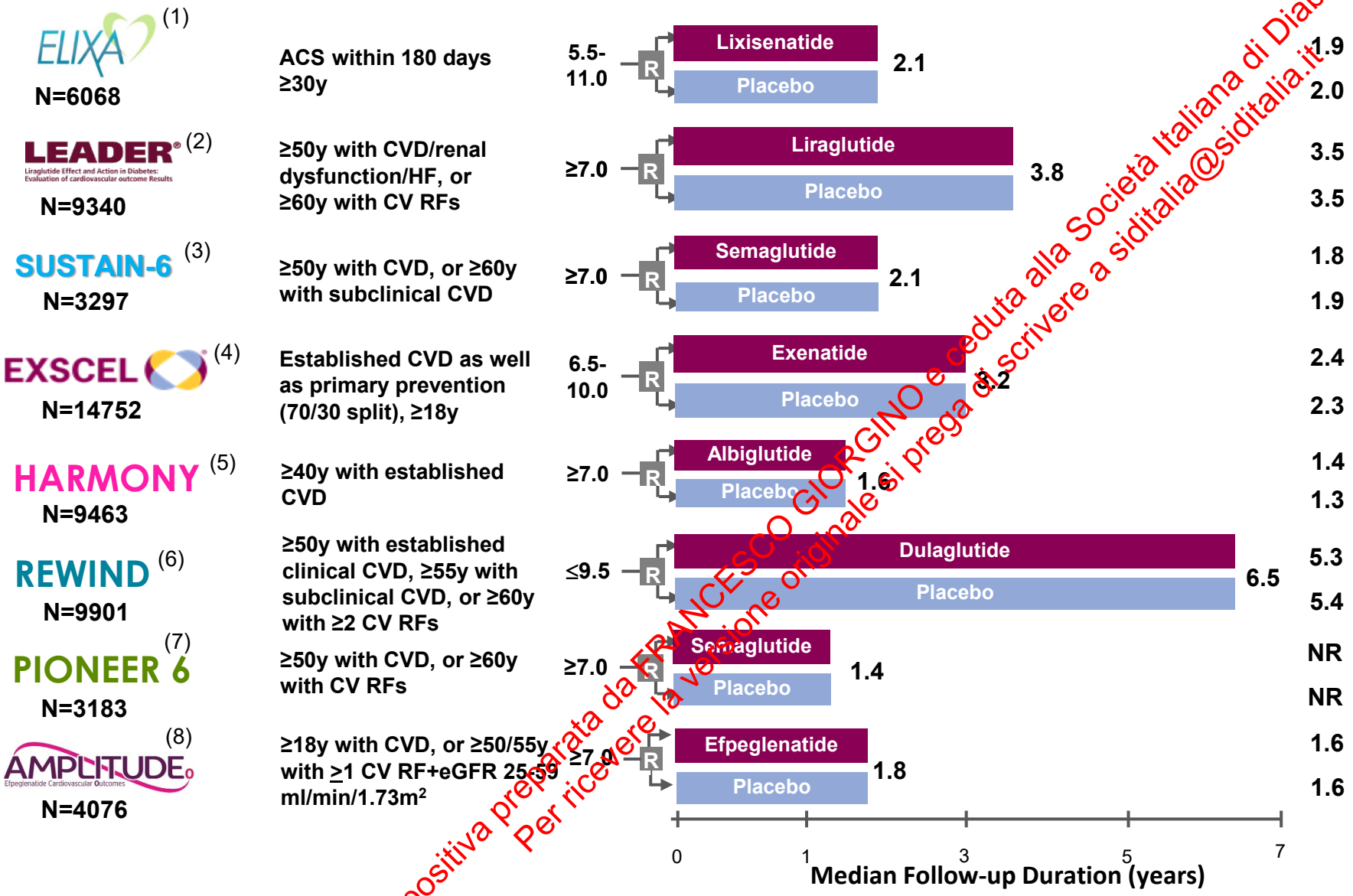
Effects of GLP-1RA on Heart Glucose Metabolism

	Glucose Uptake	Glucose Metabolism	Infarct Size	Functional Recovery
Heart				
		Experimental animals		
hypoglycemia				
euglycemia	↑[1,2,3] ↓[4]	↑ anaerobic[1] ↑ aerobic[3,5]/anaerobic[3] ↔[4]	↓[5,3]	↑[1,5,3]
hyperglycemia	n.a.[6]	n.a.[6]	↓[6]	
		Humans		
hypoglycemia	↔[7]			
euglycemia	↔[7] ↑[9]	↔[8]		↑[8]
hyperglycemia	↓[9]	↔[10]		

Experiments under ischemic conditions are presented in red

1, Zhao T et al, *J Pharmacol Exp Ther*, 2006; 2, Moberly SP et al, *Exp Biol Med*, 2012; 3, Aravindhan K et al, *PLoS One*, 2015; 4, Nguyen TD et al, *Int J Cardiol*, 2013; 5, Bao W et al, *PLoS One*, 2011; 6, Hausenloy DJ, *Cardiovasc Diabetol*, 2013; 7,Gejl M et al, *PLoS One*, 2014;8, McCormick LM et al, *JACC Cardiovasc Interv*, 2015; 9, Moberly SP et al, *Basic Res Cardiol*, 2013 ;10, Gejl M, *J Clin Endocrinol Metab*, 2012.

Completed GLP-1 RA CVOTs



ACS, acute coronary syndrome; CV, cardiovascular; CVD, CV disease; CVOTs, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; MACE, major adverse CV events; NR, not reported; R, randomisation; RFs, risk factors; y, years.

[1]Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
[2]Marso SP, et al. *N Engl J Med* 2016;375:311–322
[3]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844
[4]Holman RR, et al., *N Engl J Med* 2017;377:1228–1239
[5]Hernandez AF, et al. *Lancet* 2018;392(10157):1519–1529
[6]Gerstein HC, et al. *Lancet* 2019;294(10193):121-130
[7]Husain M, et al *N Eng J Med* 2019;381(9):841-851
[8]Gerstein HC, et al *N Eng J Med* 2021;385(10):896-907

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	AMPLITUDE-O	
Diabetes duration (years)	9.3	12.8	13.9	12	14.1	10	14.9	15.4	Baseline Risk Level
Baseline HbA1c (%)	7.6	8.7	8.7	8.0	8.7	7.3	8.2	8.9	
Baseline BMI (kg/m²)	30.1	32.5	32.8	31.7	32.3	32.3	32.3	32.7	
History of CVD (%)	100	81.3	83	73.1	100	31.4	84.6	89.6	
Hypertension (%)	76.3	90	92.8	90.3	86.4	93.2	95.3	91.3	
eGFR <60 (%)	23.2	21.7	28.5	21.7	22.6	22.2	27	31.6	
Mortality rate (events/100 patient-yr)	3.1; 3.3	2.1; 2.5	1.8; 1.7	2.0; 2.3	2.4; 2.5	2.1; 2.3	1.1; 2.2	2.2;2.8	
MACE rate (events/100 patient-yr)	6.4; 6.3	3.4; 3.9	3.2; 4.4	3.7; 4.0	4.6; 5.9	2.4; 2.7	2.9; 3.7	3.9;5.3	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11] p=0.17	**0.73 [95% CI 0.58-0.92] p=0.007**	Main Outcomes
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74 –1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	0.78 [95%CI 0.58-1.06]	

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ration; MACE, major adverse cardiovascular event; yr, year.

Adapted from **Caruso I, et al. *Trends Endocrinol. Metab.* 2019;30(9):578-89**

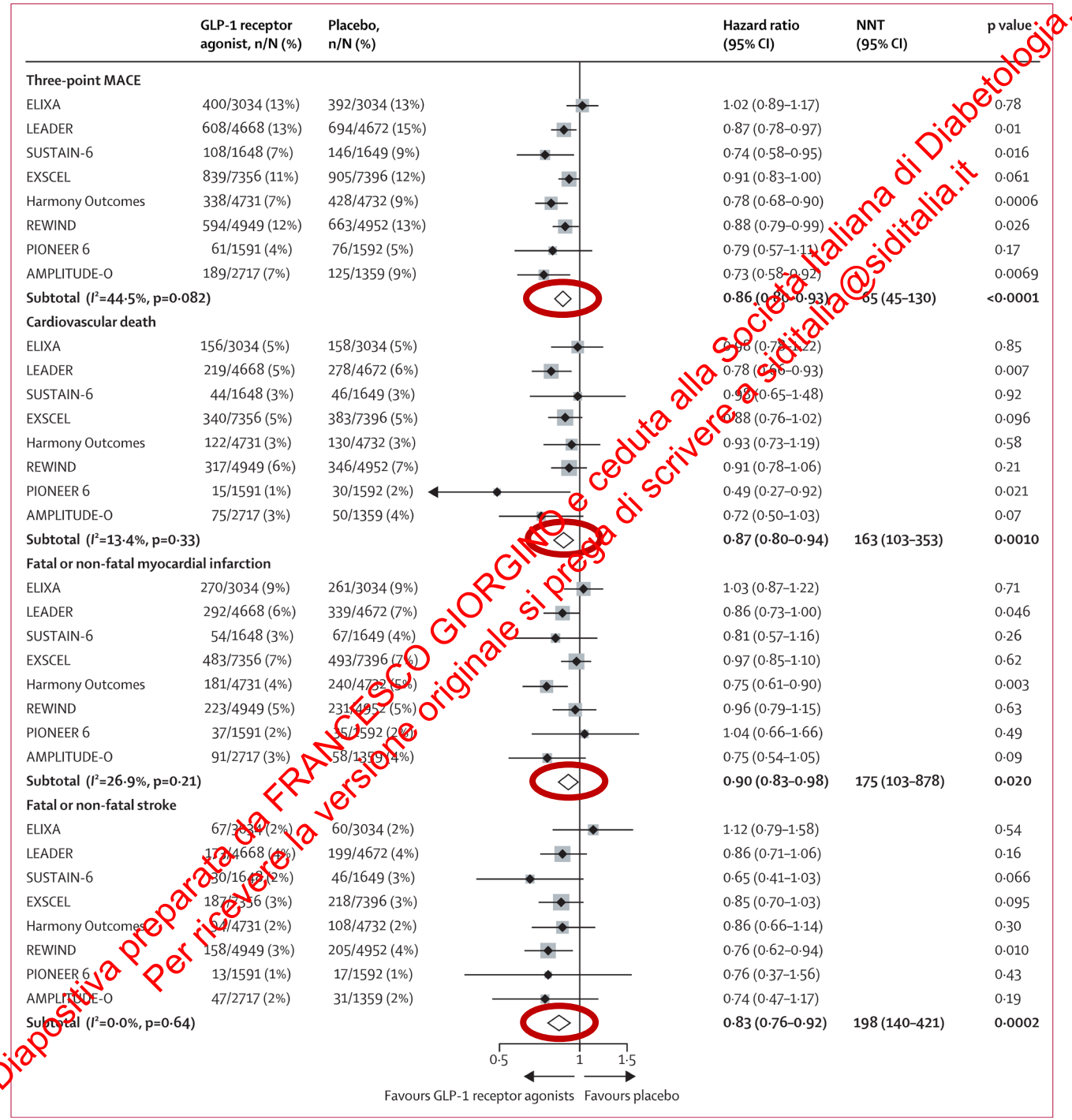
Individual Components of the Primary Endpoint in GLP-1RA CVOTs

3-P MACE

CV death

Fatal or non-fatal MI

Fatal or non-fatal stroke



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
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
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·79–1·22)		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
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
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
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	174/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	104/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

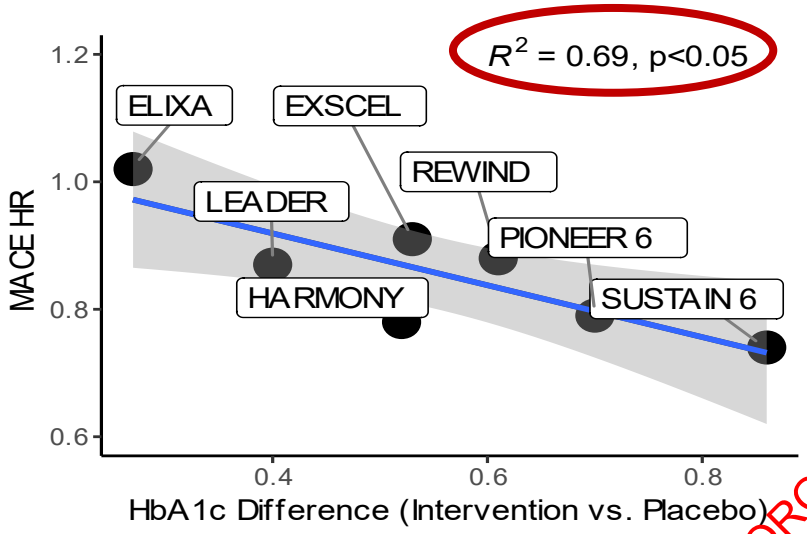
0·5 1 1·5

Favours GLP-1 receptor agonists Favours placebo

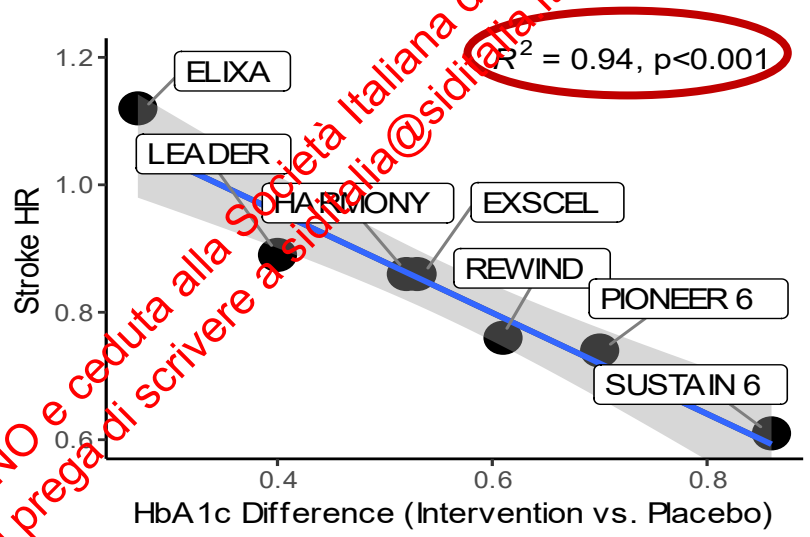
Sattar N, et al, *Lancet Diabetes Endocrinol* 2021

Association of Mean Between-arm HbA1c Difference in GLP-1 RA CVOT and MACE HR

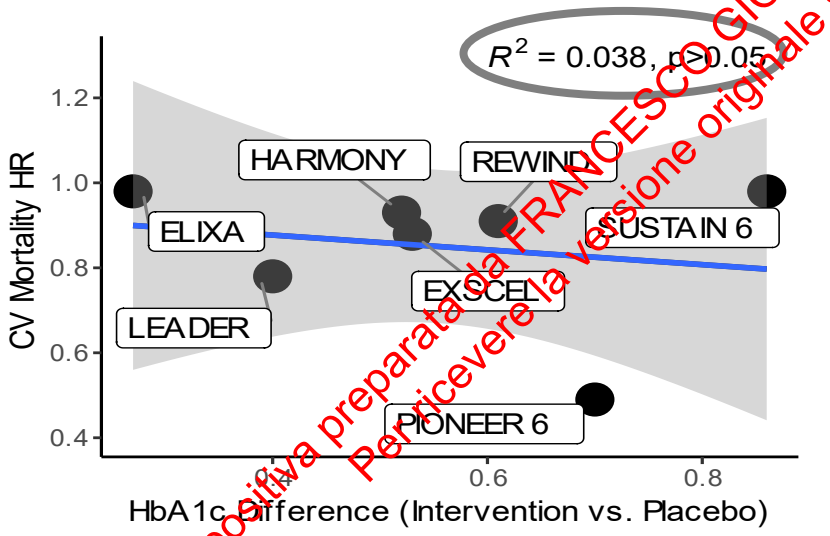
MACE



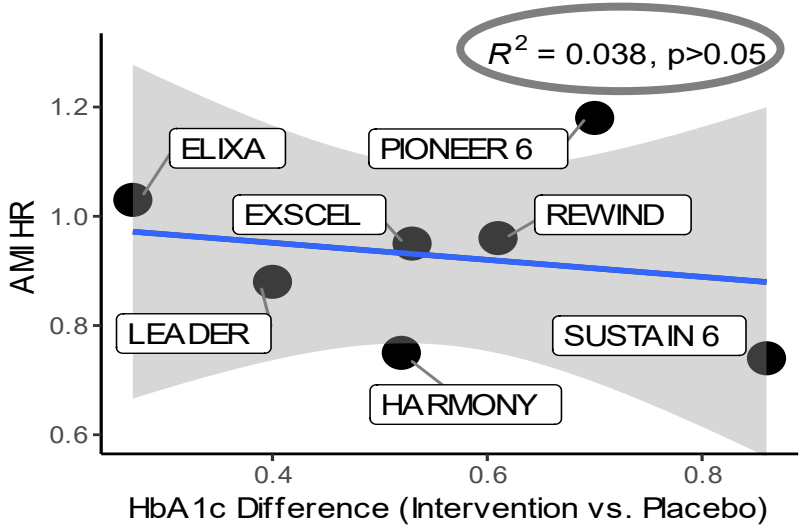
Stroke



CV death



AMI



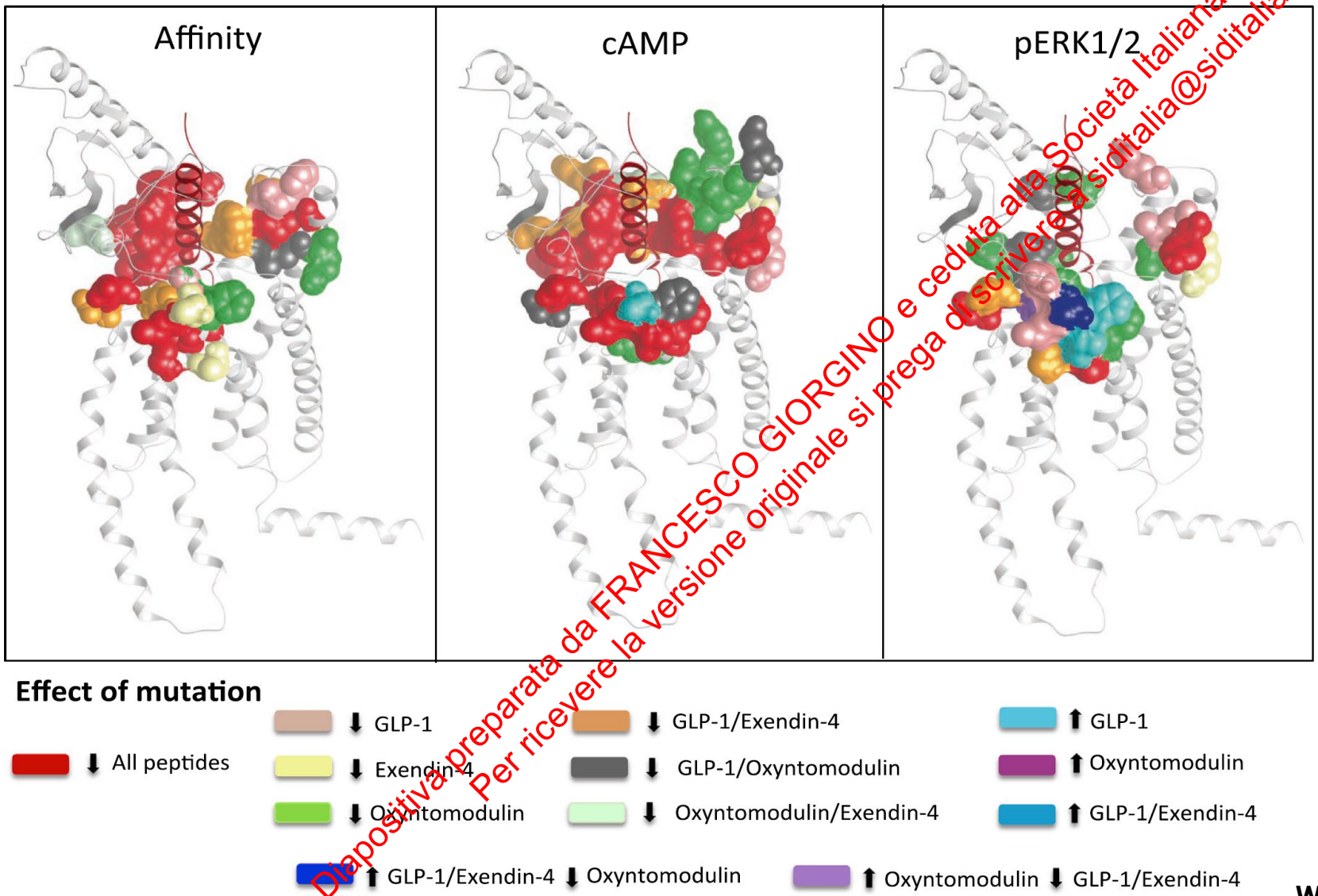
Caruso I, et al., Glucose control: Not just a bystander in GLP-1RA-mediated cardiovascular protection. Metabolism. 2020 Aug;109:154272.

AMI, Acute myocardial infarction; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

Gli effetti cardioprotettivi dei GLP-1RA sono più evidenti con gli analoghi basati sulla struttura chimica del GLP-1 umano rispetto a quelli basati su Exendin-4?

- SI
- NO
- NON VI SONO SUFFICIENTI EVIDENZE

Amino Acid Residues in the GLP-1 Receptor That Are Important for GLP-1, Exendin-4 and Oxyntomodulin Binding and Signaling



Residues highlighted **in red reduce function of all three peptides**, those **in pink selectively reduce GLP-1 only**, those in **yellow selectively reduce exendin-4 only**, and those in green selectively reduce oxyntomodulin only.

A large number of residues are important for both GLP-1 and exendin but not oxyntomodulin, and these are highlighted in orange.

Other colors represent either enhanced function or existence of opposite effects when mutated on oxyntomodulin compared to GLP-1 and exendin-4.

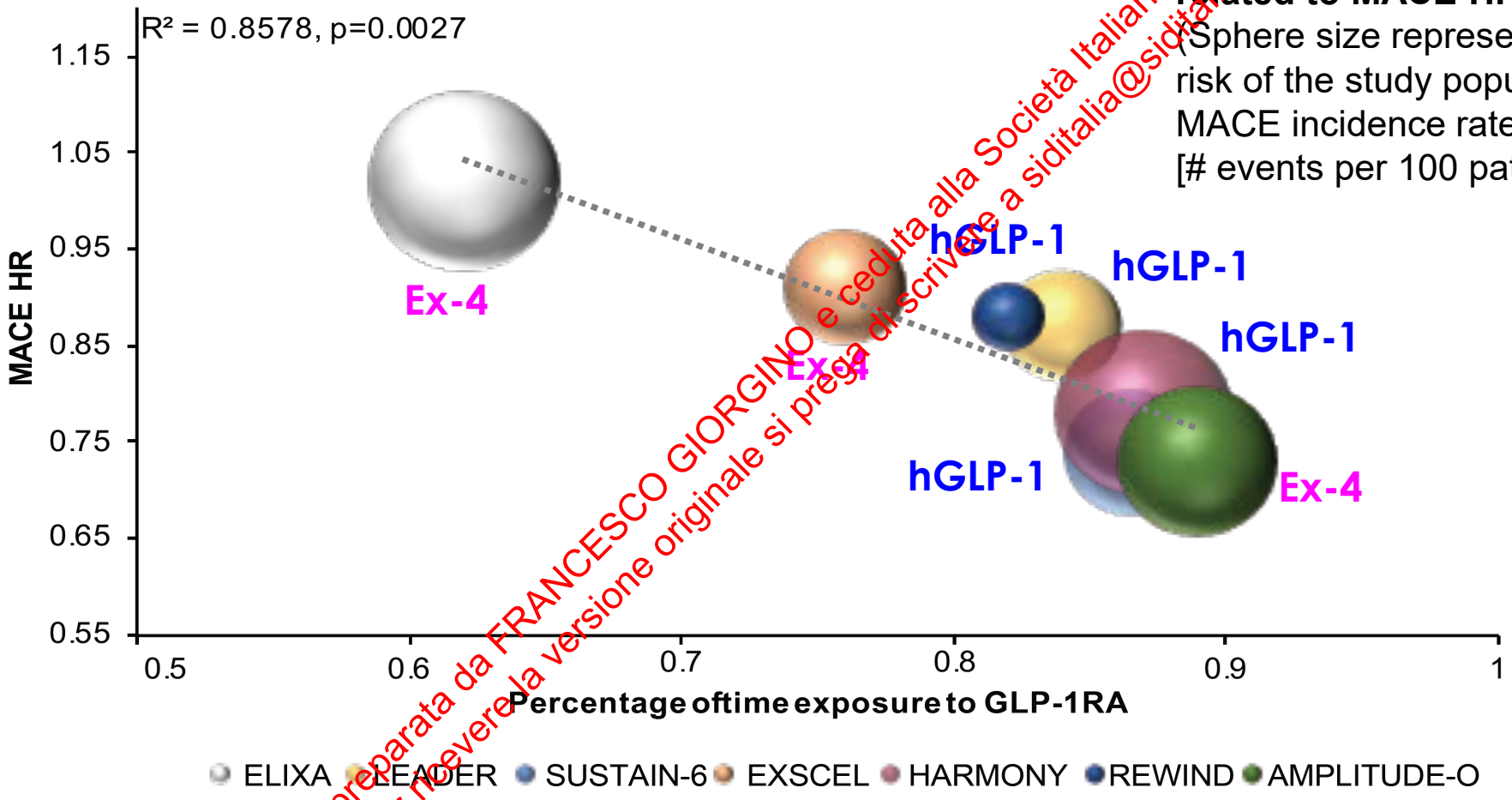
GLP-1, glucagon-like peptide-1

Wootten et al. *Cell.* 2016;165:1632–1643

Correlation between Percentage of Time Exposure to GLP-1 RA and MACE HR

- **Baseline CV risk level not apparently related to MACE HR.**

(Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])



The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes, REWIND and AMPLITUDE-O, and as mean in LEADER, SUSTAIN–6 and EXSCEL, . Actual exposure to lixisenatide in ELIXA is estimated to be approximately 56%.

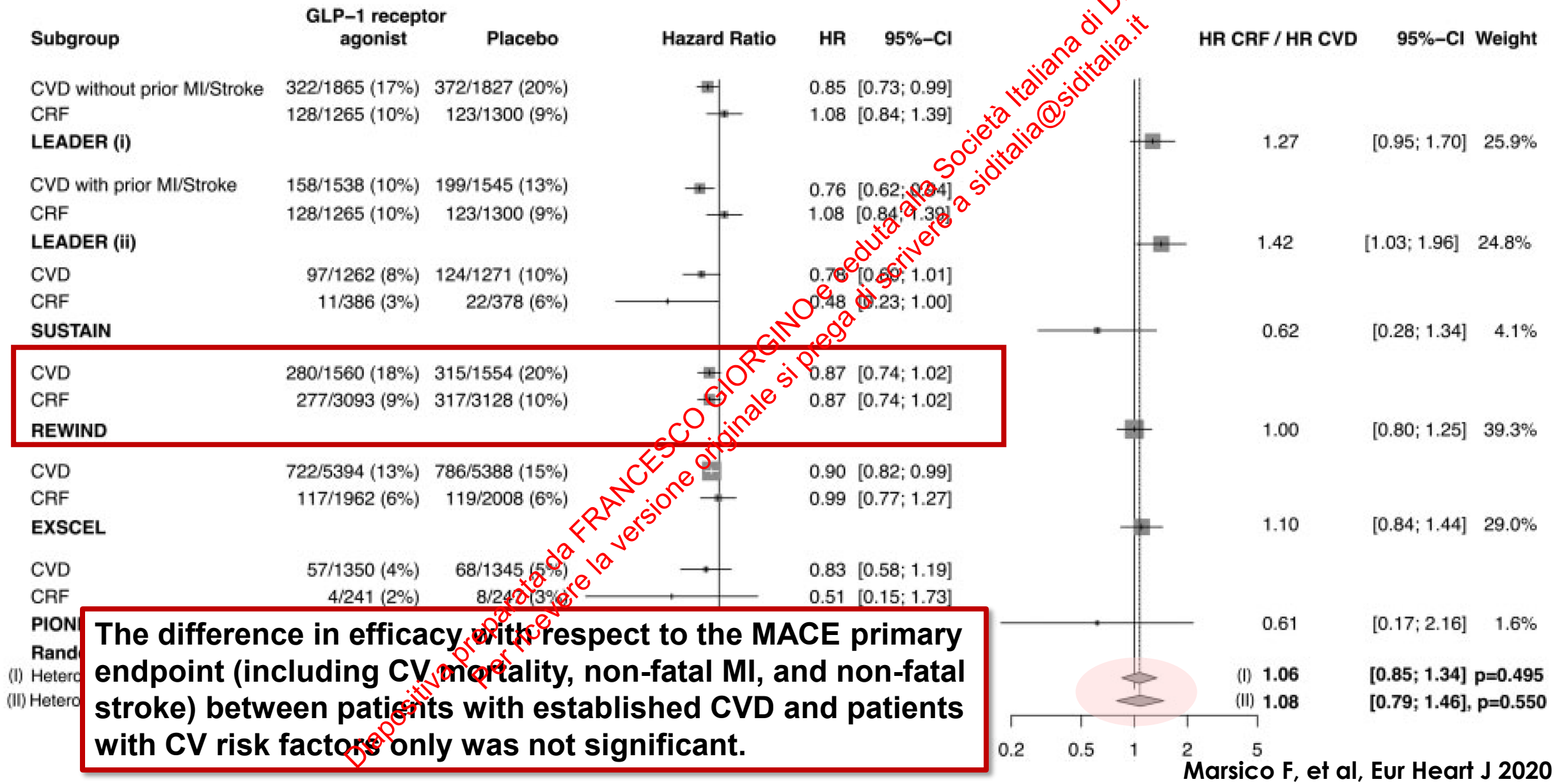
Ex-4, exendin-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; hGLP-1, human GLP-1; HR, hazard ratio; MACE, major adverse cardiovascular event.

Adapted from **Caruso I et al., *Diabetes Care*, 2022**

Gli effetti cardioprotettivi dei GLP-1RA sono evidenti anche in pazienti con diabete di tipo 2 senza malattia cardiovascolare?

- SI
- NO
- NON VI SONO SUFFICIENTI EVIDENZE

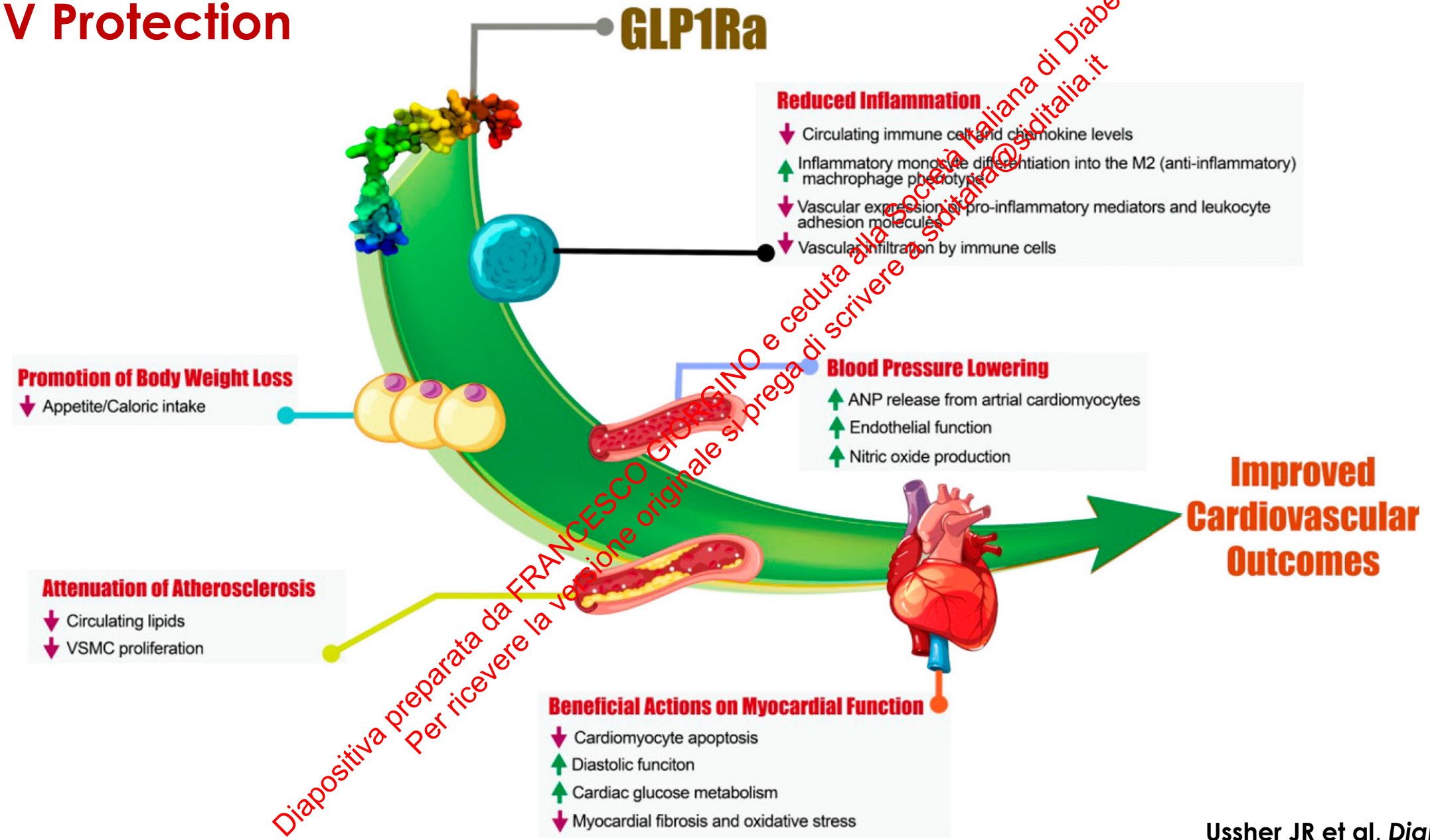
Interaction Analysis for the 3P-MACE between Previous CVD (41,996) and CV Risk Factors Only (14,008) Subgroups



The difference in efficacy with respect to the MACE primary endpoint (including CV mortality, non-fatal MI, and non-fatal stroke) between patients with established CVD and patients with CV risk factors only was not significant.

Marsico F, et al, Eur Heart J 2020

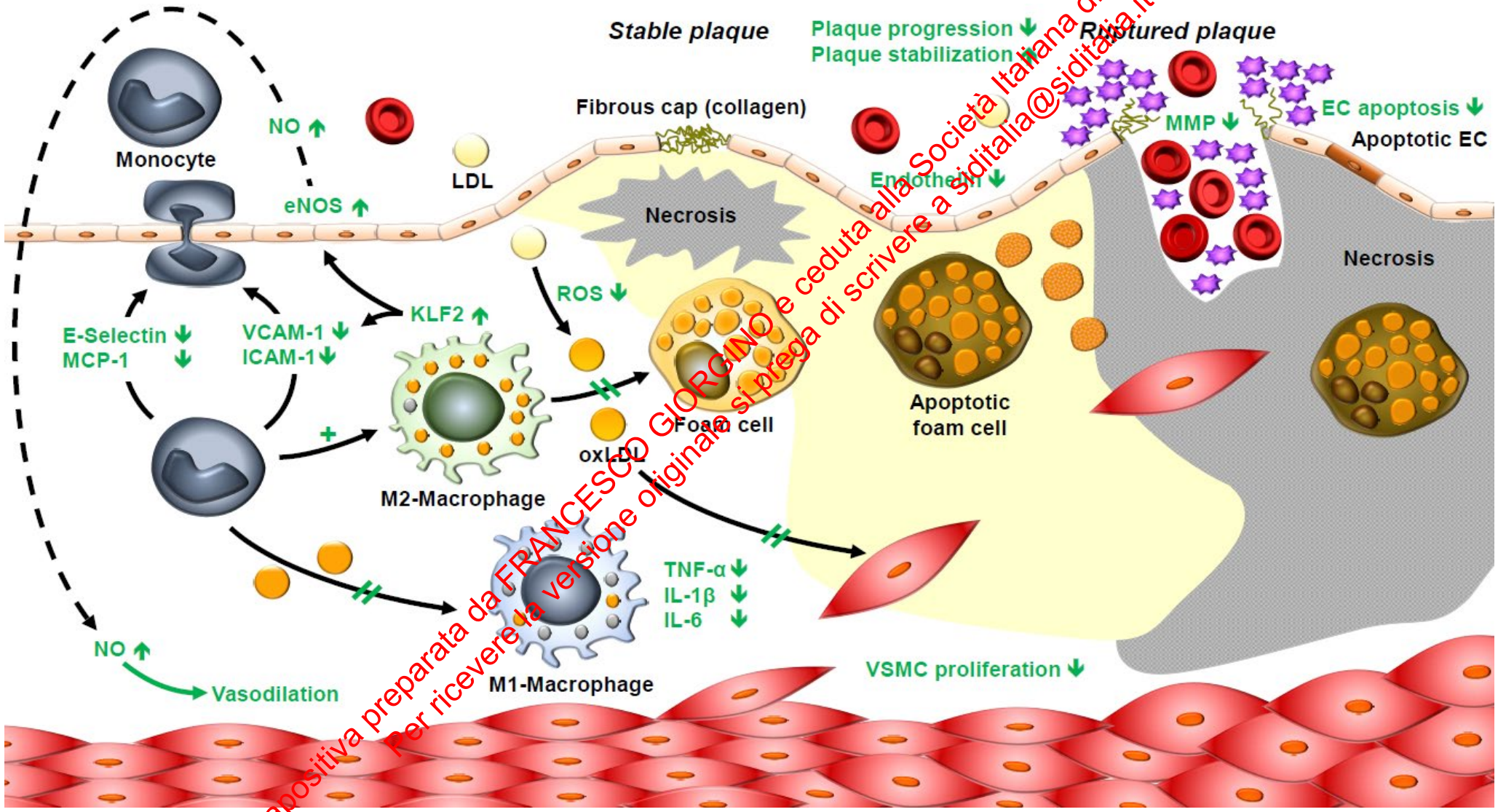
Potential Mechanisms Contributing to GLP-1RA-mediated CV Protection



ANP, atrial natriuretic peptide; CV, cardiovascular; VSMC, vascular smooth muscle cells

Ussher JR et al, *Diabetes* 2022

Effects of GLP-1 RAs on the Progression of Atherogenesis and Plaque Evolution



Nauck M, et al, *Mol Metab*, 2020

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ORIGINAL ARTICLE

WILEY

Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

Marta Baviera PharmD[1] | Stefano Genovese MD[2] | Vito Lepore MD[3,4] | Pierluca Colacioppo MSc[1] | Fabio Robusto MD[3] | Mauro Tettamanti MSc[5] | Antonio D'Ettorre MSc[3] | Fausto Avanzini MD[1] | Ida Fortino MSc[6] | Antonio Nicolucci MD[3] | Maria C. Roncaglioni MSc[1] | Francesco Giorgino MD[7]

Baseline Characteristics of Matched Populations According to GLP-1RA Treatment in Lombardy and Apulia

Lombardy

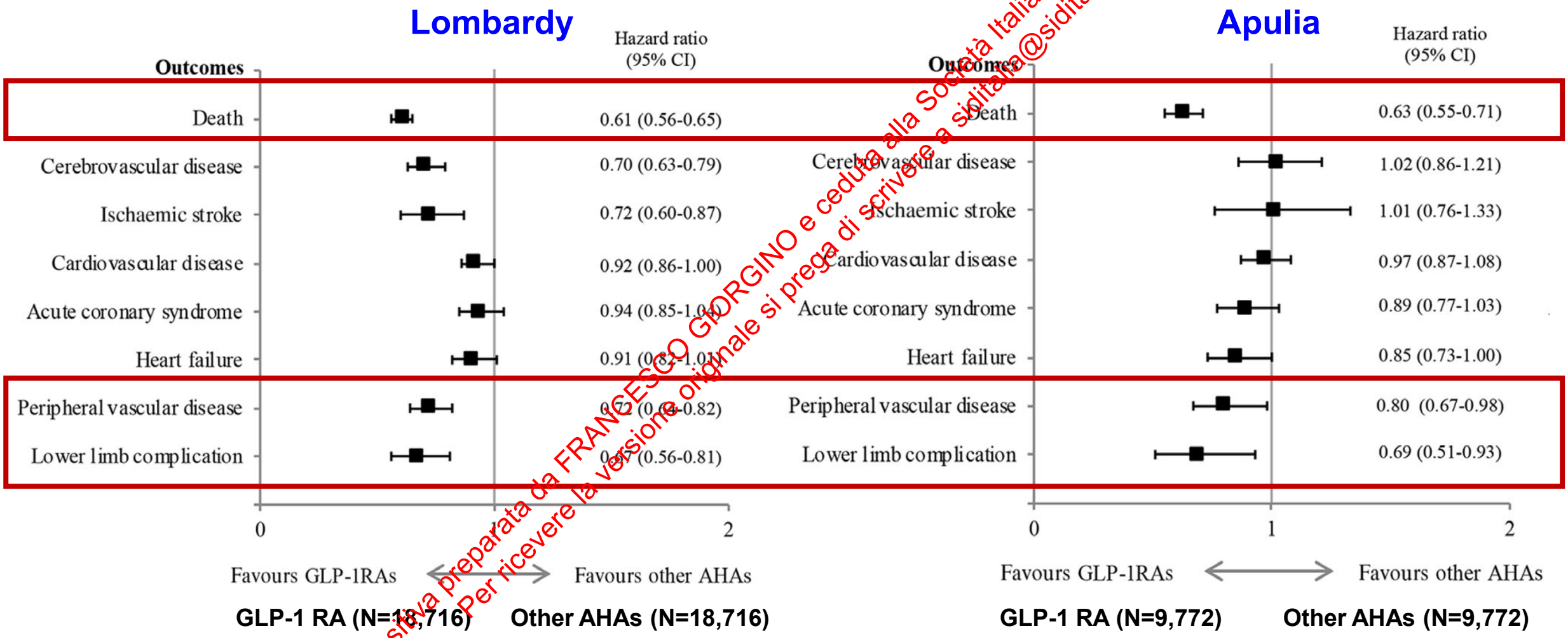
Variables	Matched population		
	GLP-1RA[a] (N = 18 716)	Other AHAs (N = 18 716)	Standardized differences
Mean (±SD) age, years	65.4 ± 8.0	65.5 ± 8.0	−0.01
Women, n (%)	8355 (44.6)	8248 (44.1)	0.01
Comorbidities of interest, n (%)			
Cerebrovascular disease	695 (3.7)	935 (5.0)	−0.06
CV disease	2201 (11.8)	2273 (12.1)	−0.01
HF	670 (3.6)	816 (4.4)	−0.03
Peripheral vascular disease	627 (3.4)	757 (4.0)	−0.03
Lower limb complication	154 (0.8)	260 (1.4)	−0.05
Renal disease	318 (1.7)	613 (3.3)	−0.10
Neuropathy	415 (2.2)	383 (2.0)	0.01
Diabetic retinopathy	19 (0.1)	29 (0.2)	−0.01
Chronic obstructive pulmonary disease	661 (3.5)	808 (4.3)	−0.04
Cancer	1244 (6.6)	1558 (8.3)	−0.06

Apulia

Variables	Matched population		
	GLP-1RA[a] (N = 9772)	Other AHAs (N = 9772)	Standardized differences
Mean (±SD) age, years	64.6 ± 7.7	64.3 ± 7.9	0.03
Women, n (%)	4892 (50.1)	4876 (49.9)	0.00
Comorbidities of interest, n (%)			
Cerebrovascular disease	523 (5.3)	679 (6.9)	−0.06
CV disease	1167 (11.9)	1257 (12.9)	−0.02
HF	408 (4.2)	541 (5.5)	−0.06
Peripheral vascular disease	594 (6.1)	548 (5.6)	0.02
Lower limb complication	73 (0.7)	106 (1.1)	−0.03
Renal disease	315 (3.2)	418 (4.3)	−0.05
Neuropathy	279 (2.9)	298 (3.0)	−0.01
Diabetic retinopathy	24 (0.2)	20 (0.2)	0.00
Chronic obstructive pulmonary disease	553 (5.7)	611 (6.2)	−0.02
Cancer	817 (8.4)	972 (9.9)	−0.05

Baviera M, et al., *DOM*, 2021

Risk of Death and Clinical Events in Matched Populations According to GLP-1RA Treatment in Lombardy and Apulia from 2010 to 2018

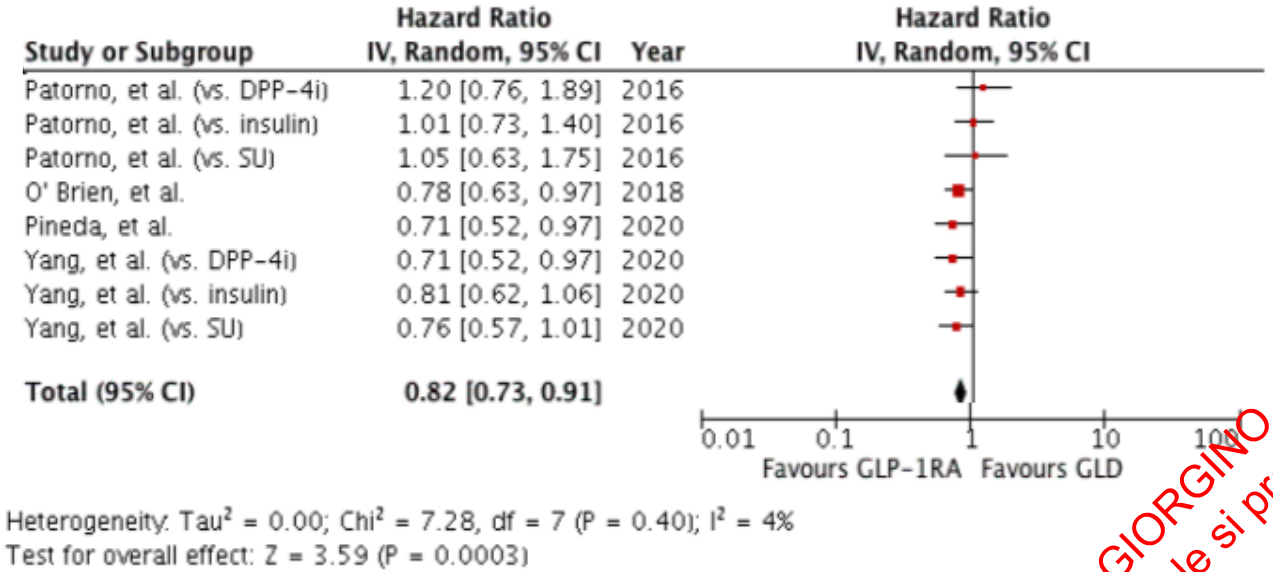


AHAs, anti-hyperglycemic agents; GLP-1RA, Glucagon-like peptide-1 receptor agonists

Baviera M, et al., *DOM*, 2021

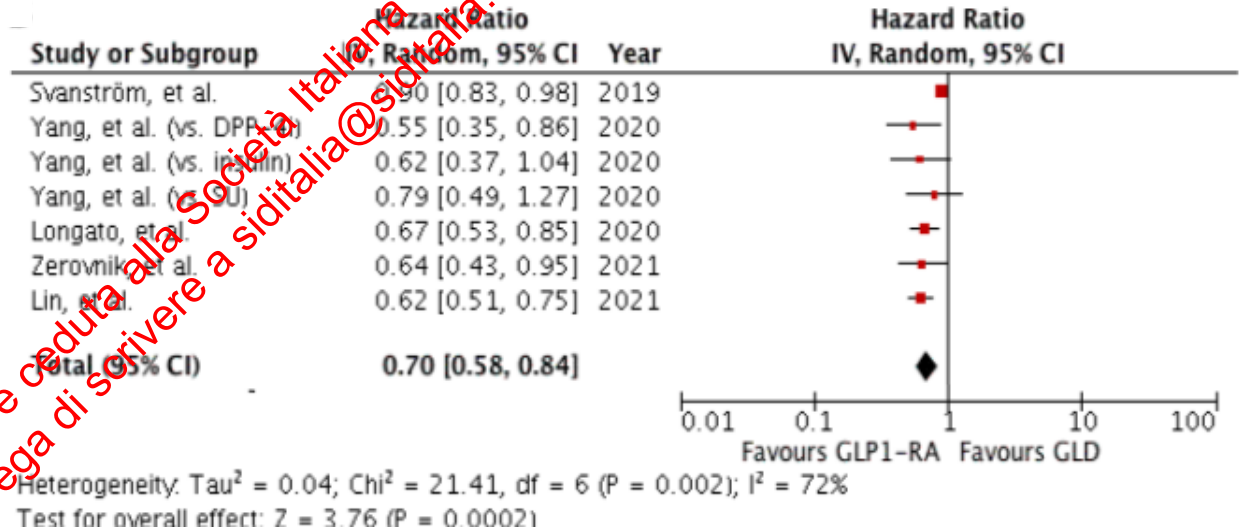
Effects of GLP-1RA vs. Other GLD on CV Outcomes in RWS

Composite CV Outcome



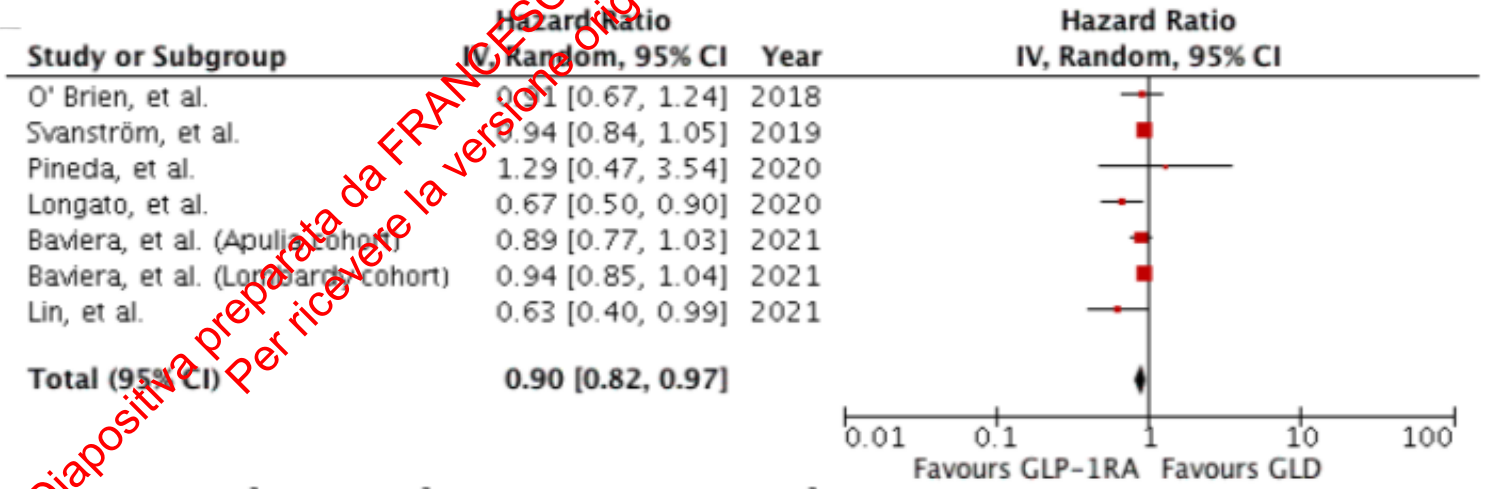
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.28$, df = 7 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 3.59 (P = 0.0003)

MACE



Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 21.41$, df = 6 (P = 0.002); $I^2 = 72\%$
Test for overall effect: Z = 3.76 (P = 0.0002)

MI



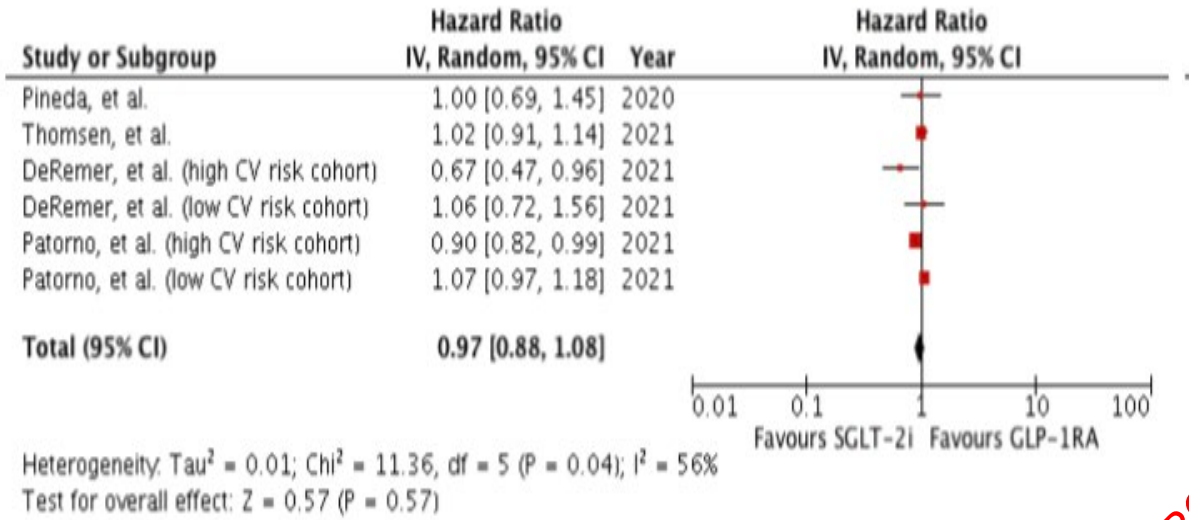
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.99$, df = 6 (P = 0.24); $I^2 = 25\%$
Test for overall effect: Z = 2.61 (P = 0.009)

CV, cardiovascular; GLD, glucose-lowering drugs; MACE, major adverse cardiovascular outcomes (non-fatal MI, non-fatal stroke, CV death); MI, myocardial infarction; RWS, real-world studies

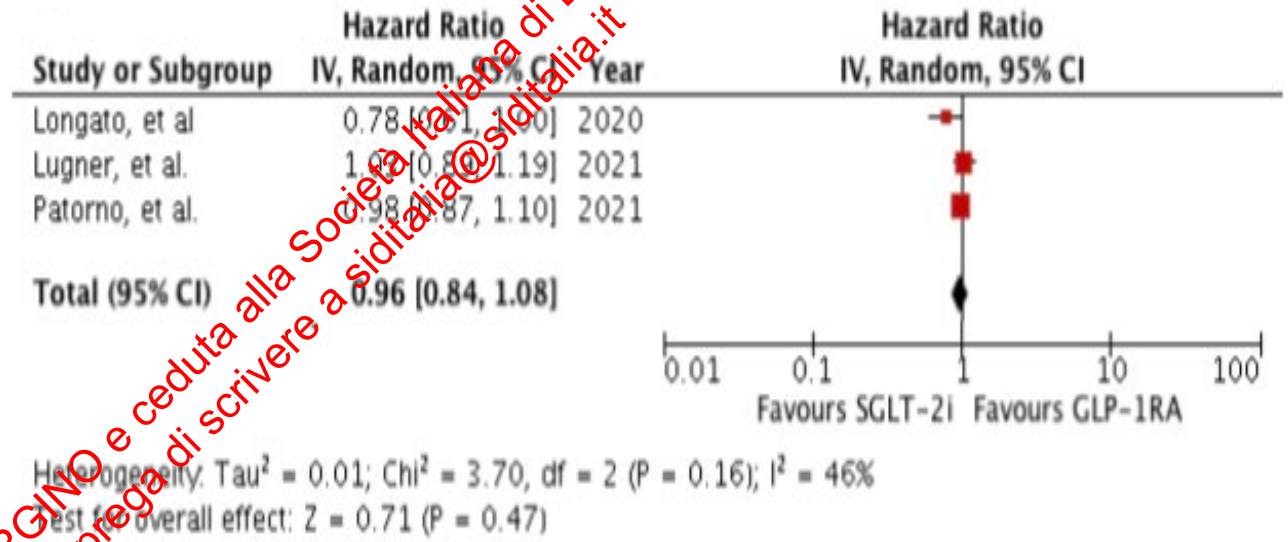
Caruso I et al, *Metabolites*, 2022

Effects of GLP-1RA vs. SGLT-2i on CV Outcomes in RWS

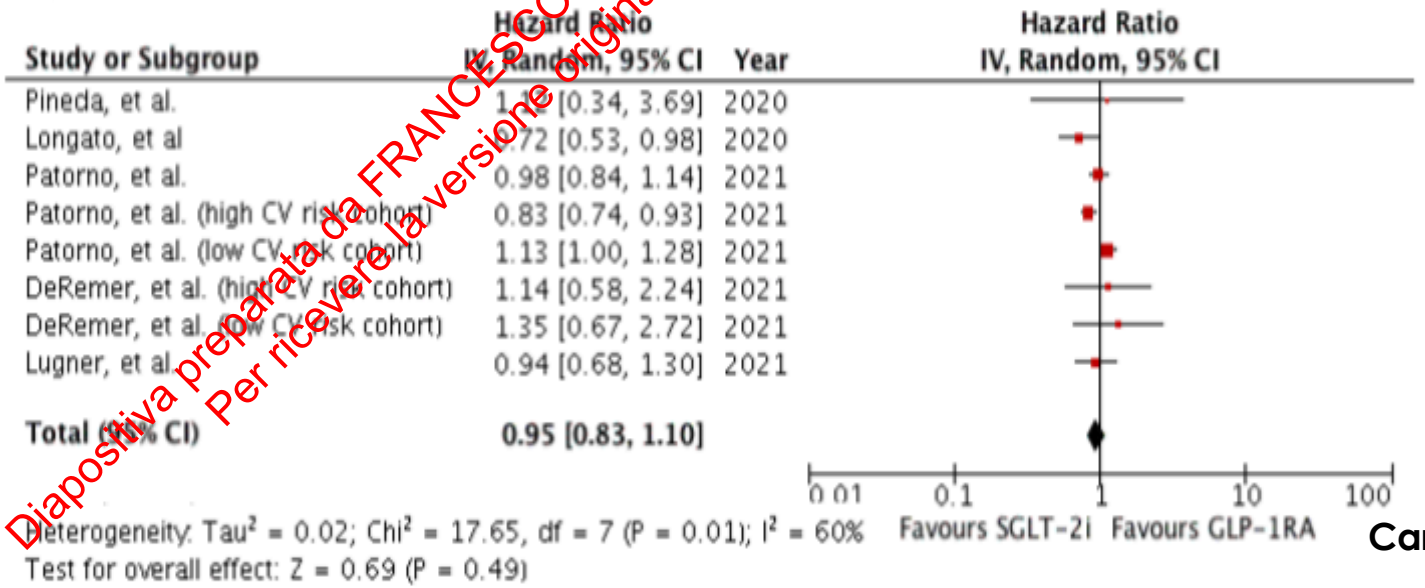
Composite CV Outcome



MACE



MI



CV, cardiovascular; MACE, major adverse cardiovascular outcomes (non-fatal MI, non-fatal stroke, CV death); MI, myocardial infarction; RWS, real-world studies

Caruso I et al, *Metabolites*, 2022

I GLP-1RA hanno effetti favorevoli sullo scompenso cardiaco?

- SI
- NO
- NON VI SONO SUFFICIENTI EVIDENZE

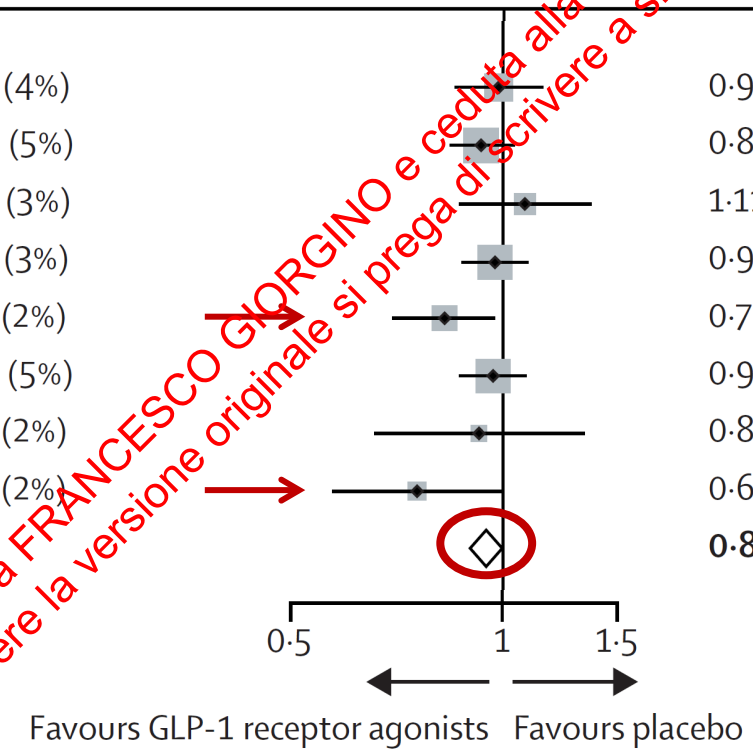
Effects of GLP-1RA on LV function and structure in RCT conducted in T2D patients

Study	Design	Exposure, duration	Outcome, method	Population, n	Baseline	Change (%)	*p*
Systolic parameters							
[23]	Prospective vs. placebo	Liraglutide 1.8 µg/die for 26 weeks	LVEF, CMRI	NoHF, 23 vs. 26	55%	− 1%	0.002
[28]	Prospective vs. placebo	Albiglutide various dosage, 12 weeks	LVEF, US	HFrEF, 29 vs. 30	32%	− 2%	ns
[22]	Single arm, prospective	Liraglutide 0.9 µg/die for 26 weeks	LVEF, US	HFpEF, 31	NA	NA	ns
[24]	Prospective vs. aCTRL	Liraglutide 1.8 µg/die vs. metformin 2 g for 6 months	GLS', US	NoHF, 30 vs. 30	15%	+ 1.2	0.043
[25]	Prospective vs. aCTRL	Liraglutide 1.8 mg, or glimepiride 4 mg for 18 weeks	LVEF, US	NoHF with subclinical dysf, 33 vs. 29	53%	− 2.1	ns
			GLS, US		15%	0	ns
[26]	Prospective vs. aCTRL	Liraglutide 1.8 mg, or glimepiride 4 mg for 25 weeks	LVEF, US	HFrEF, 146 vs. 156	25	+ 1.1	ns
[27]	Prospective vs. placebo	Liraglutide 1.8 mg for 24 weeks	LVEF, US	HFrEF, 122 vs. 119	33%	− 0.7	ns
			GLS, US		11%	0.6	ns
Diastolic parameters							
[23]	Prospective vs. placebo	Liraglutide 1.8 µg/die for 26 weeks	E/e', CMRI	NoHF, 23 vs. 26	7.3	− 0.9	0.001
[22]	Single arm, prospective	Liraglutide 0.9 µg/die for 26 weeks	E/e', US	HFpEF, 31	12.7	− 2.7	0.0371
[24]	Prospective vs. aCTRL	Liraglutide 1.8 µg/die vs. metformin 2 g for 6 months	E/A, US	NoHF, 30 vs. 30	0.92	+ 0.6	ns
[25]	Prospective vs. aCTRL	Liraglutide 1.8 mg, or glimepiride 4 mg for 18 weeks	E/e', US	NoHF, 33 vs. 29	12.5	− 0.5	ns
[27]	Prospective vs. placebo	Liraglutide 1.8 mg for 24 weeks	LVEF, US	HFrEF, 122 vs. 119	12.6	− 0.6	0.03
Remodeling							
[28]	Prospective vs. placebo	Albiglutide various dosage, 12 weeks	LVDV, US	HFrEF, 29 vs. 30	196	− 0.2%	ns
			LVMi, US				
[23]	Prospective vs. placebo	Liraglutide 1.8 µg/die for 26 weeks	LVEDV, CMRI	NoHF, 23 vs. 26	147	− 11	0.002
			LVMi, CMRI		49	− 1.5	ns
[26]	Prospective vs. aCTRL	Liraglutide 1.8 mg, or placebo 4 mg for 25 weeks	LVEFVi, US	HFrEF, 146 vs. 156	140	+ 6.7	ns
[27]	Prospective vs. placebo	Liraglutide 1.8 mg for 24 weeks	LVEDV, US	HFrEF, 122 vs. 119	163	− 4	ns

Natali A et al, *Cardiovasc Diabetol*, 2021

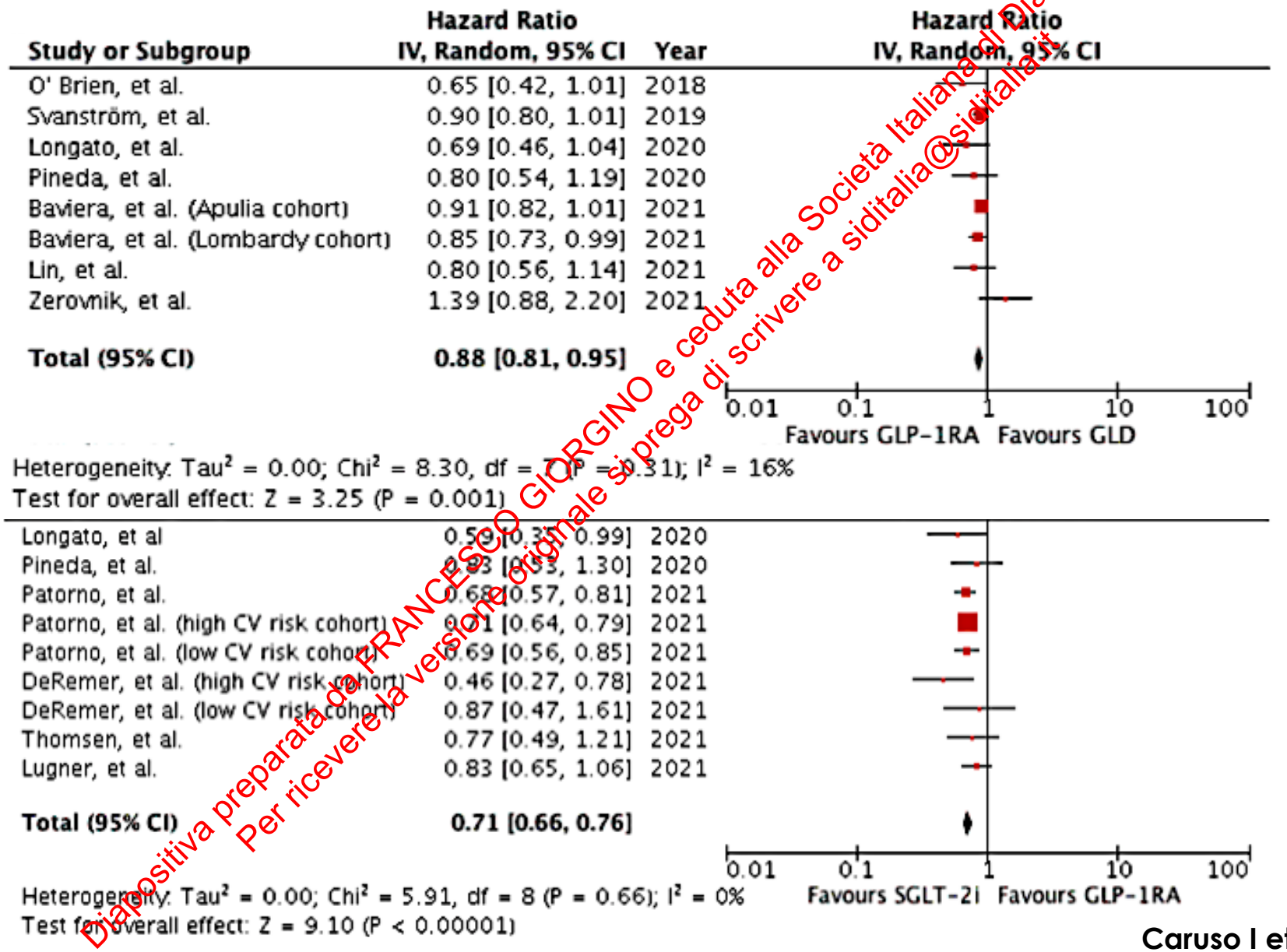
GLP-1RA Reduced the Incidence of HF-Related Outcomes in CVOT

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**



Sattar N, et al, *Lancet Diabetes Endocrinol* 2021

Effects of GLP-1RA on HF-Related Outcomes in RWS



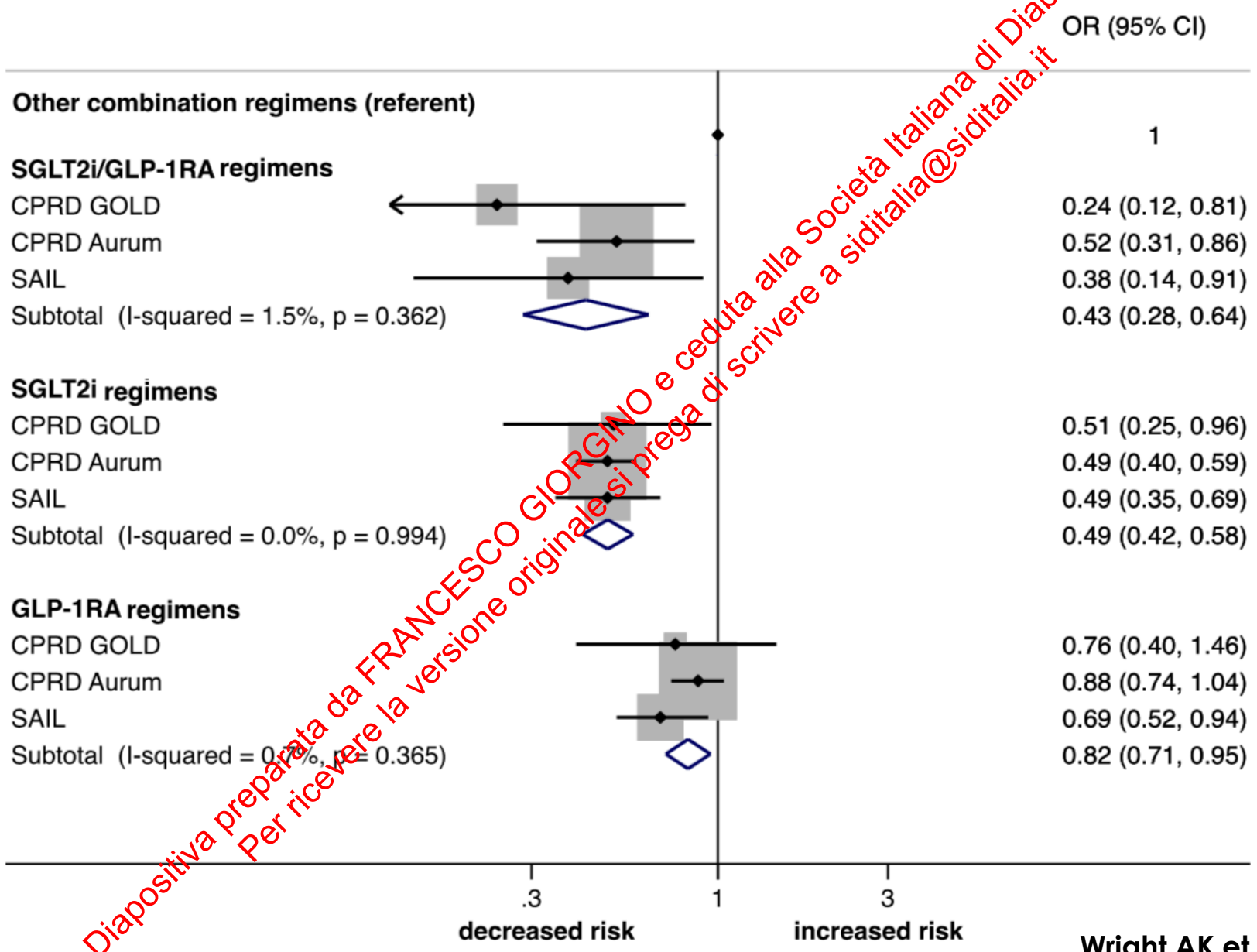
Caruso I et al, *Metabolites*, 2022

GLD, other glucose lowering drugs; HF, heart failure; RWS, real-world studies

Role of GLP-1RA in Primary Prevention of HF in T2D Patients

3 nested case-control studies in England and Wales (primary care data)

17,451 (4.2%) experienced a HF event in a cohort of 411,206 with T2D without HF



Wright AK et al, *Diabetes Care*, 2022

HF, heart failure; GLP-1RA, GLP-1 receptor agonists, SGLT2i, sodium-glucose transporter 2 inhibitors, T2D, type 2 diabetes

Summary

- GLP-1 RA **reduce CV outcomes** (CV death, non-fatal myocardial infarction, non-fatal stroke).
- GLP-1RA-mediated cardioprotection results from **multiple contributing factors**, including **reduced inflammation and body weight**, **improved myocardial and vascular functions**, **decreased blood pressure**, **attenuation of atherosclerosis**.
- The **effect of glucose lowering** may play an important role in the ability of GLP-1 RA to **reduce stroke**.
- **Persistence to treatment** contributes to the CV benefit of GLP-1 RA – chemical structure of GLP-1RA seems irrelevant.
- GLP-1 RA may prevent CV events **throughout the CV risk continuum** (reduction of CV events in relatively lower-risk as well as higher-risk T2D subjects) – see **evidence from both CVOT and real-world studies**.
- GLP-1RA **reduce HF-related outcomes** vs. placebo in CVOT and vs. other glucose-lowering drugs (except SGLT-2i) in RWS, but improvement of LV function in human models of chronic heart failure is inconclusive.

CV, cardiovascular; CVOT, cardiovascular outcome studies; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; LV, left ventricular; RWS, real-world studies; SGLT-2i, sodium glucose cotransporter-2 inhibitors; T2D, type 2 diabetes.