Gestione del rischio globale del

diabetico di tipo 2:

un ruolo per i DPP4?

23 novembre 2019

Roma

Hotel Royal Santina

Sicurezza Cardiovascolare e Renale degli inibitori di DPP IV: popolazioni e risultati dei trials

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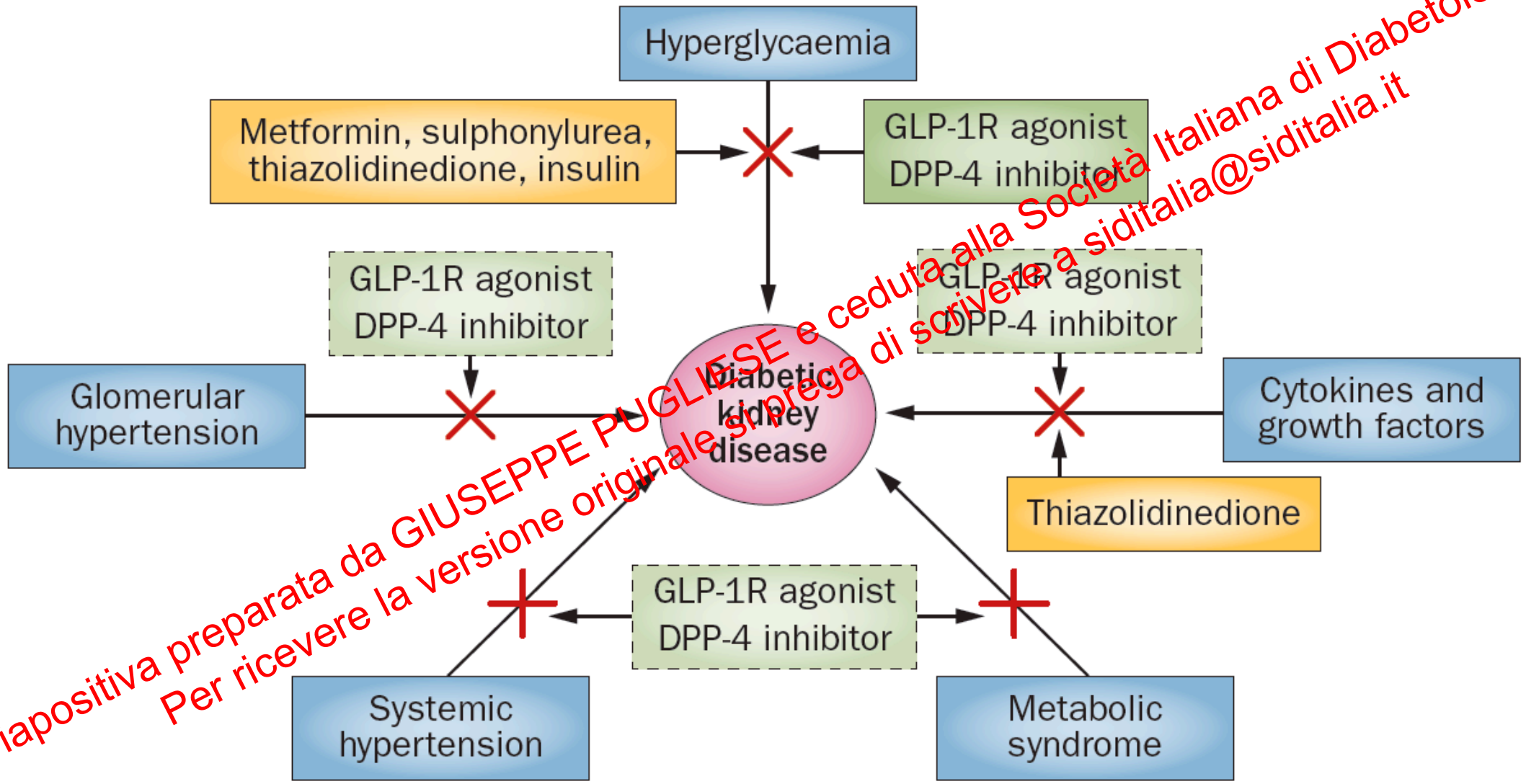
In fede

Giuseppe Pugliese

Agenda

- Proposed mechanisms for cardiorenal protection by DPP-4 inhibitors
- Cardiovascular outcomes with DPP-4 inhibitors
- Renal outcomes with DPP-4 inhibitors
- Treatment with DPP-4 inhibitors in patients with impaired renal function

Mechanisms of cardiorenal protection by incretins



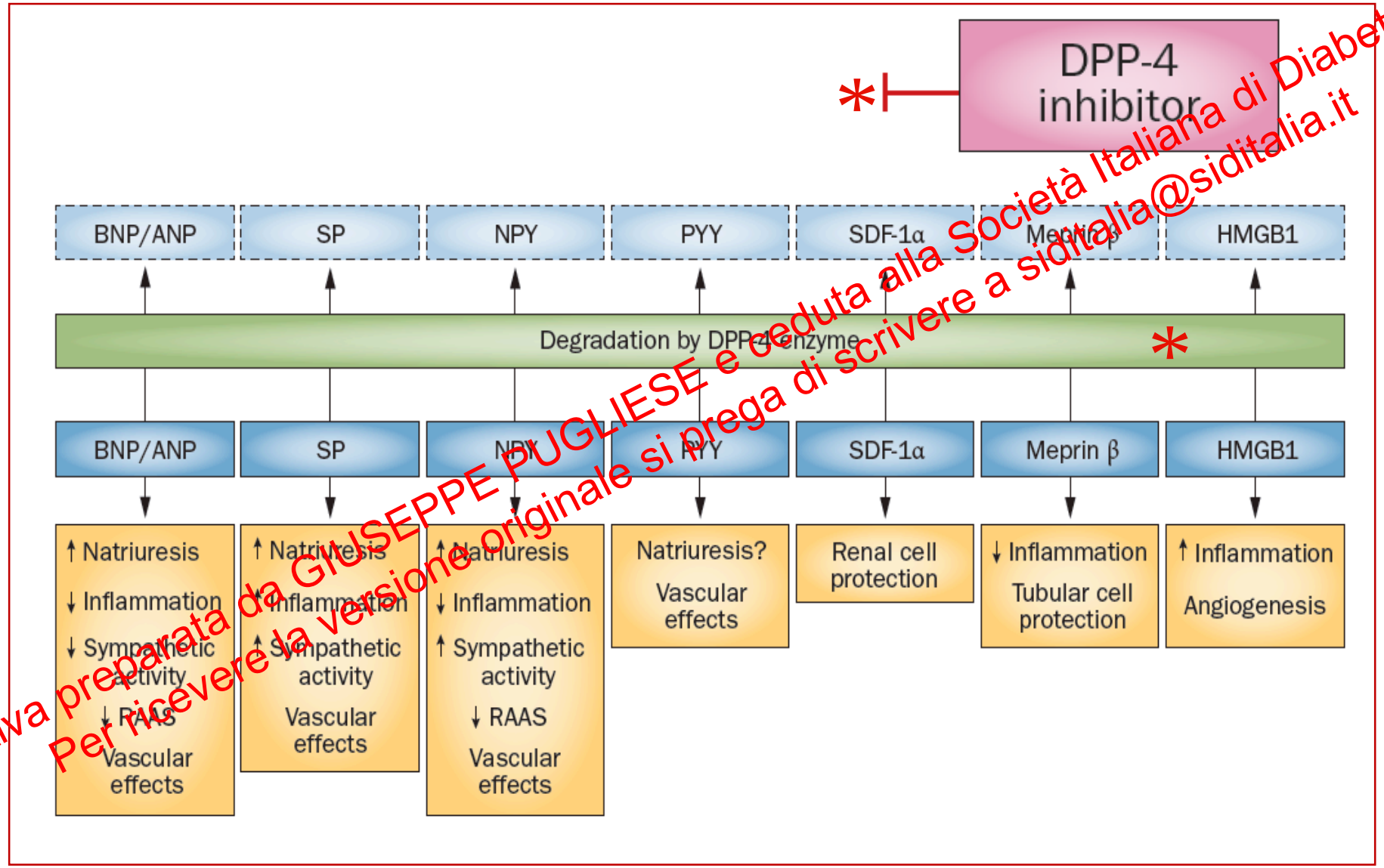
Muskiet MHA et al. Nat Rev Nephrol. 2014;10:88–103

Mechanisms of cardiorenal protection by incretins

Renal risk factor	GLP-1RA	DPP-4 inhibitor	Putative GLP-1-mediated mechanisms	Putative GLP-1-independent mechanisms of DPP-4 inhibitors
Obesity	Decrease	Neutral effect	↓Appetite (direct effect on CNS or via vagal afferents, ↓GEE* and ↑nausea) ↑Energy expenditure[35]? ↑Natriuresis and/or diuresis?	Effect possibly counteracted by ↑PYY (1–36) and ↓PYY (3–36)[257,258‡]
Blood pressure	Decrease	Decrease or neutral effect	↓Body weight ↑Endothelial independent vasodilation[259,260]? ↑Natriuresis[261§] ↓Intestinal sodium reabsorption[98]? ↓Sodium intake (direct effect on CNS)? ↓RAAS activity[87,127]? ↑ANP[130]?	↑Natriuresis (↑SDF1α[119], ↓DPP-4–NHE3 complex[262]?, ↑BNP[263]) ↑Vasodilation (↑BNP[263], ↑bradykinin) Effects possibly counteracted by ↑substance P (↑SNS activity) and ↑NPY (potentiates SNS activity) during concomitant ACE inhibition[127‖]
Dyslipidaemia	Decrease	Neutral effect	↓Body weight ↓Intestinal lipid uptake (partly by ↓GEE*) ↓Hepatic lipoprotein synthesis and secretion ↑Insulin sensitivity (partly by ↓body weight) ↑Insulin and ↓glucagon ↑Triglyceride uptake in white adipose tissue ↑Brown adipose tissue activation[169]	Effects possibly counteracted by factors related to steroid metabolism[264]
Inflammation and fibrosis	Decrease	Decrease	↓Renal ROS production (cAMP and PKA)[102,179] ↓AGE–RAGE-mediated renal ROS production (cAMP)[181,265,266] ↓Angiotensin II-induced renal ROS production (PKC)[182,183] ↑Adiponectin (reduces podocyte inflammation; PKA in adipocytes)[267]	↑SDF1α[119,268,269] ↓Profibrotic endothelial-to-mesenchymal transition[105,186¶]
Glomerular hyperfiltration	Decrease or neutral effect	Neutral effect	↑Tubuloglomerular feedback (by ↓NHE3 activity) ↓Postprandial glucagon (particularly short-acting GLP-1RA)[70,71,90]? ↓Body weight[90]? ↓GEE* (postprandial hyperfiltration)[90]? ↓RAAS activity[87,127]?	↑SDF1α[119]?

Muskiet MHA et al. Nat Rev Nephrol. 2017; 13:605–628

Mechanisms of cardiorenal protection by DPP-4 inhibitors



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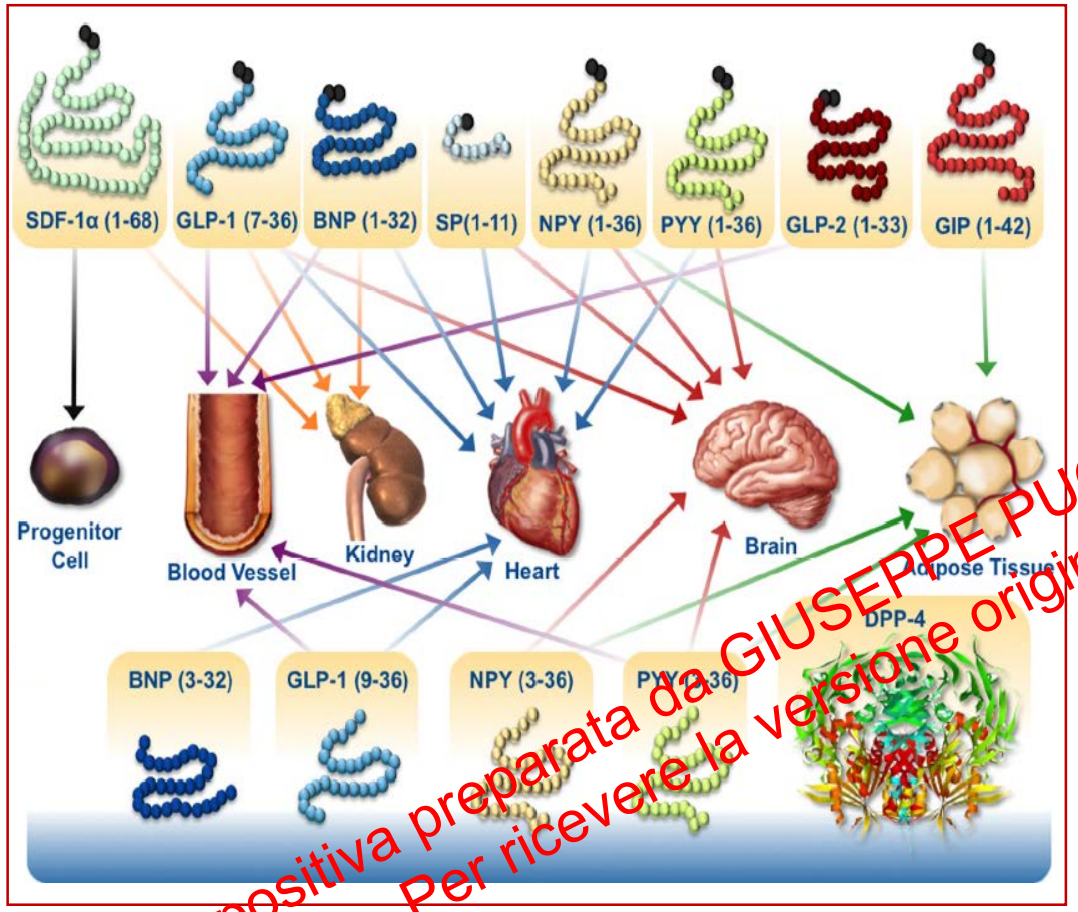
Mechanisms of cardiorenal protection by DPP-4 inhibitors



Peptide	Target tissue	Effect
GLP-1 (7-36)	Heart	Increased cardiac function, glucose uptake, decreased contractility, apoptosis
	Blood vessel	Increased NO production, decreased inflammation
	Brain	Decreased appetite
GLP-1 (9-36)	Heart	Increased cardiac function, glucose uptake, decreased apoptosis
	Blood vessel	Increased vasodilation
GIP (1-42)	Adipose tissue	Increased lipogenesis and adipogenesis
GLP-2 (1-33)	Blood vessel	Increased blood flow, HR, and BP
SDF-1 (1-68)	Progenitor cell	Increased homing of progenitor cells to ischemic myocardium, increased angiogenesis
BNP (1-32)	Heart	Decreased LV remodeling
	Blood vessel	Increased vasodilation
	Kidney	Increased natriuresis
BNP (3-32)	Kidney	Increased natriuresis
SP(1-11)	Heart	Decreased chronotropy and inotropy
	Brain	Altered cardiac adrenergic tone
NPY (1-36)	Heart	Increased $[Ca^{2+}]_i$ current
	Brain	Increased appetite
	Adipose tissue	Increased adipocyte differentiation, decreased lipolysis
NPY (3-36)	Adipose tissue	Increased lipogenesis
	Blood vessel	Increased angiogenesis
PYY (1-36)	Blood vessel	Increased collateral blood flow
	Adipose tissue	Decreased lipolysis

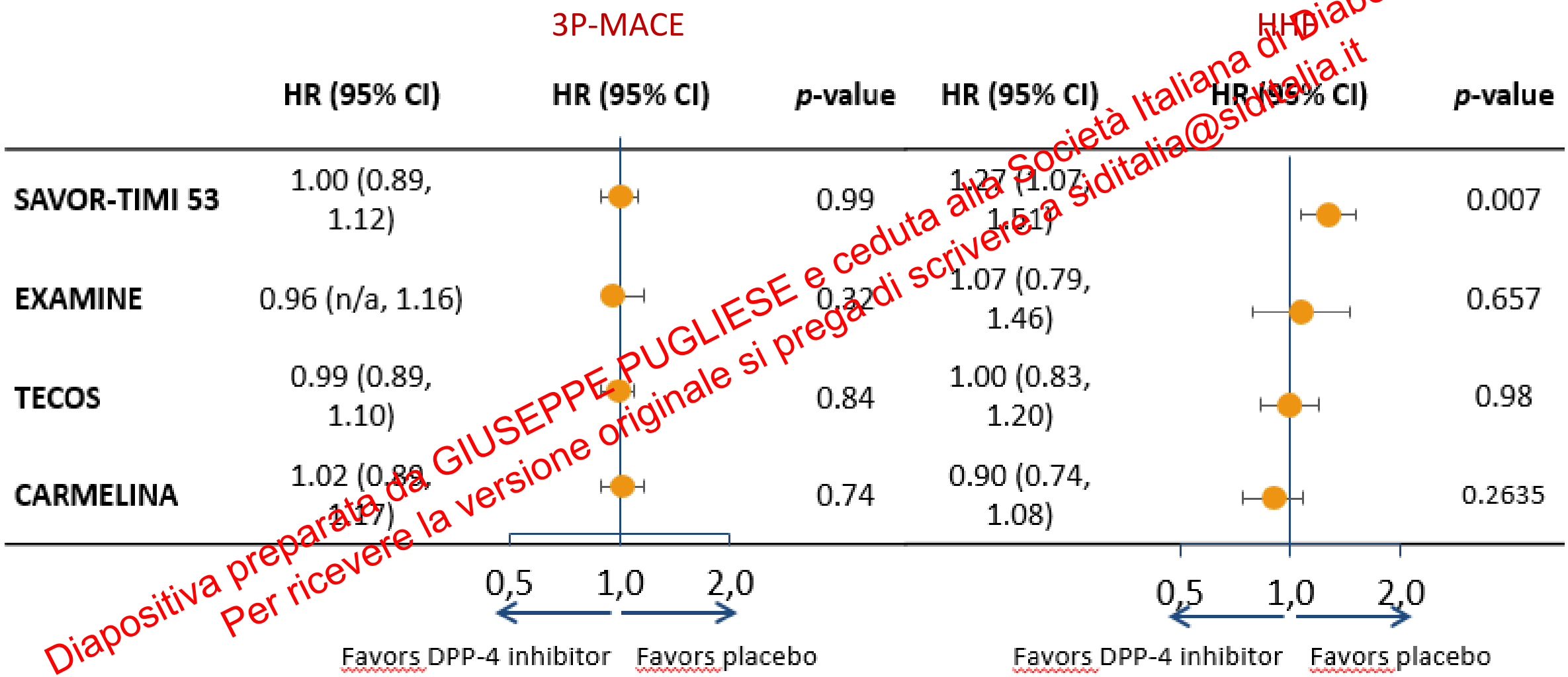
Ussher JR, Drucker DJ. Endocr Rev. 2012;33:187–215

Cardiovascular outcome trials (CVOTs) with DPP-4 inhibitors

	SAVOR-TIMI[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]
N	16,492	5,380	14,671	6,979
Inclusion criteria	High CV risk or prior CV event	ACS within 15-90 days before recruitment	High CV risk or prior CV event	High CV and renal risk
Intervention	saxagliptin vs. placebo	alogliptin vs. placebo	sitagliptin vs. placebo	linagliptin vs. placebo
Age (years)	65	61	65	66
Diabetes durat (yearbs)	10	7	12	15
History of CVD (%)	78	100	74	90
HbA_{1c} (%)	8.0	8.0	7.2	8.0
BMI (kg/m^2)	31.0	28.7	30.2	31.3
History of HF (%)	12.8	28.0	18.0	26.4
Follow-up (years)	2.1	1.8	3.0	2.2
Primary endpoint	3-point MACE	3-point MACE	4-point MACE	3-point MACE

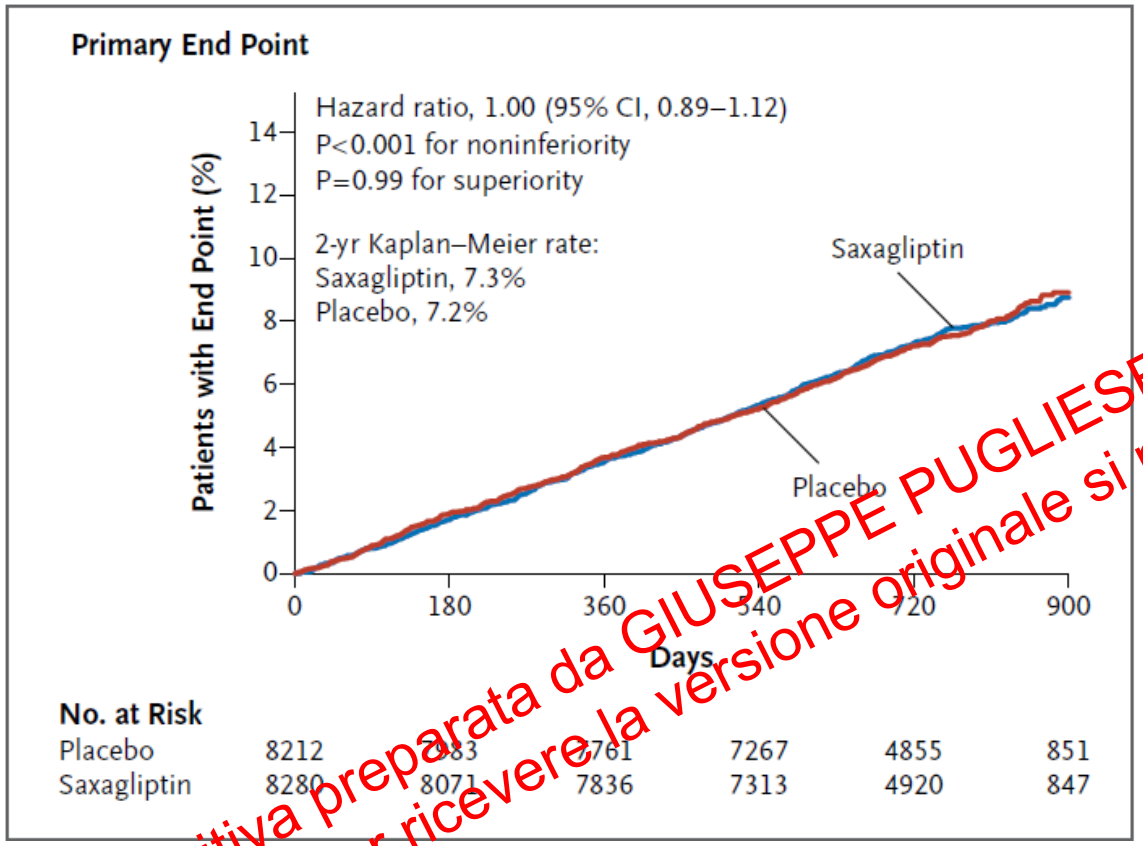
1. Scirica BM et al. N Engl J Med. 2013;369:1317–1326
2. White WB et al. N Engl J Med. 2013;369:1327–1335
3. Green JB et al. N Engl J Med. 2015;373:232–242
4. Rosenstock J et al. JAMA. 2019;321:69–79

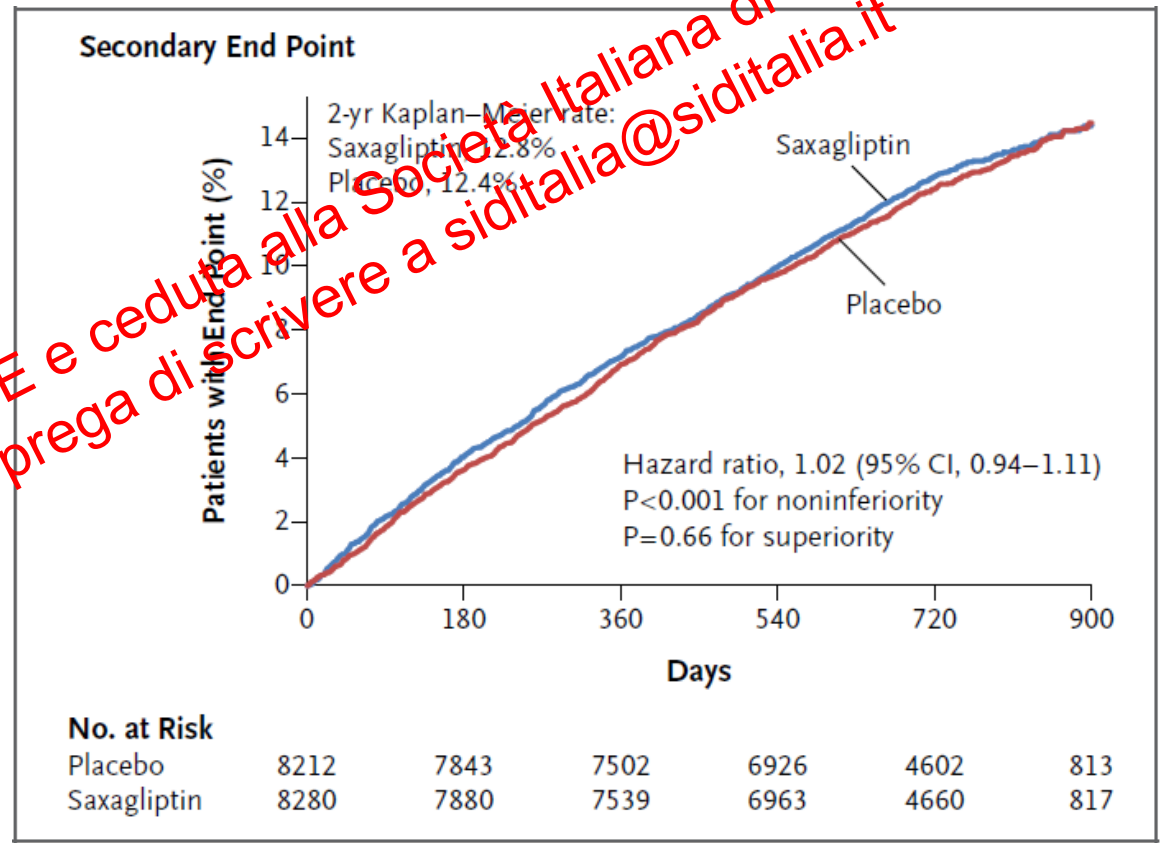
Cardiovascular outcome trials (CVOTs) with DPP-4 inhibitors



Cardiovascular outcomes with saxagliptin

The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study





Primary end point: composite of CV death, non-fatal myocardial infarction and non-fatal (ischemic) stroke

Secondary end point: composite of CV, non-fatal myocardial infarction non-fatal (ischemic) stroke, hospitalization for unstable angina, coronary revascularization, or heart failure

Scirica BM et al. N Engl J Med. 2013;369:1317–1326

Cardiovascular outcomes with saxagliptin

The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

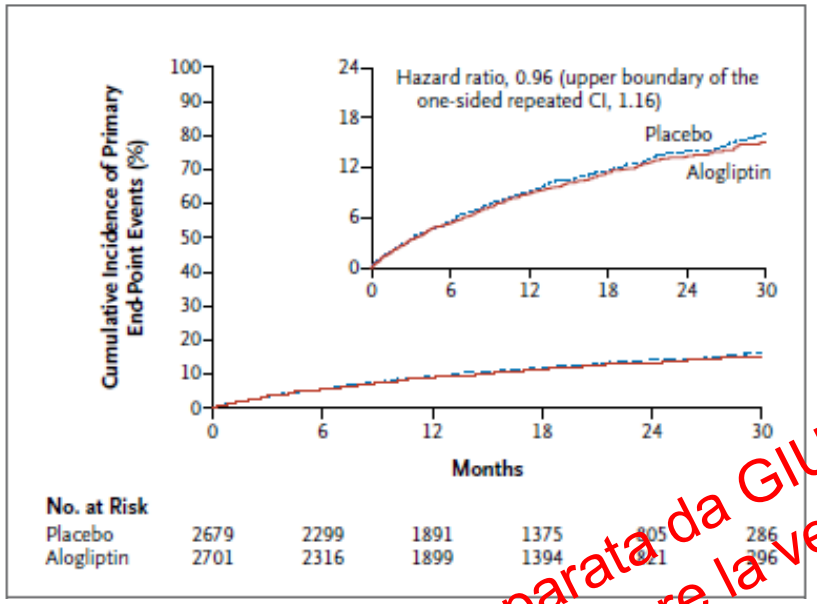
* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica BM et al. N Engl J Med. 2013;369:1317–1326

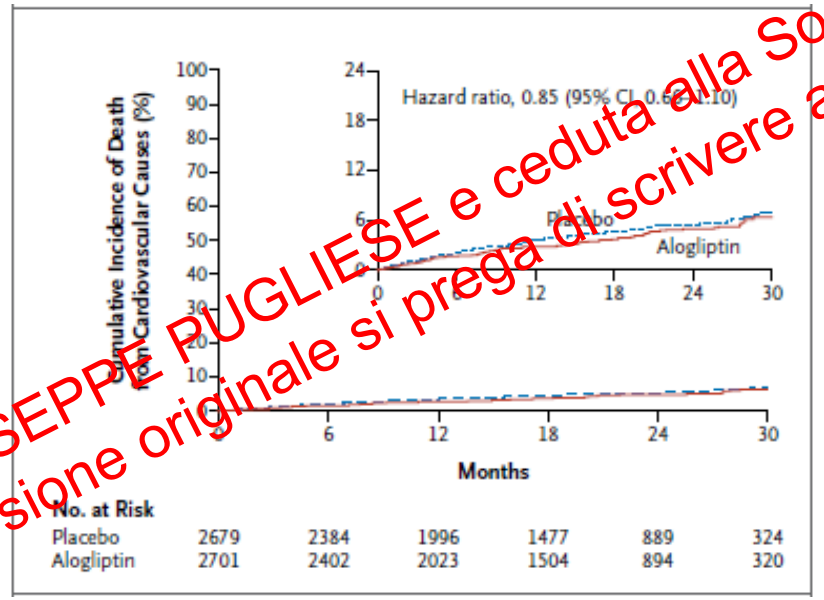
Cardiovascular outcomes with alogliptin

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study

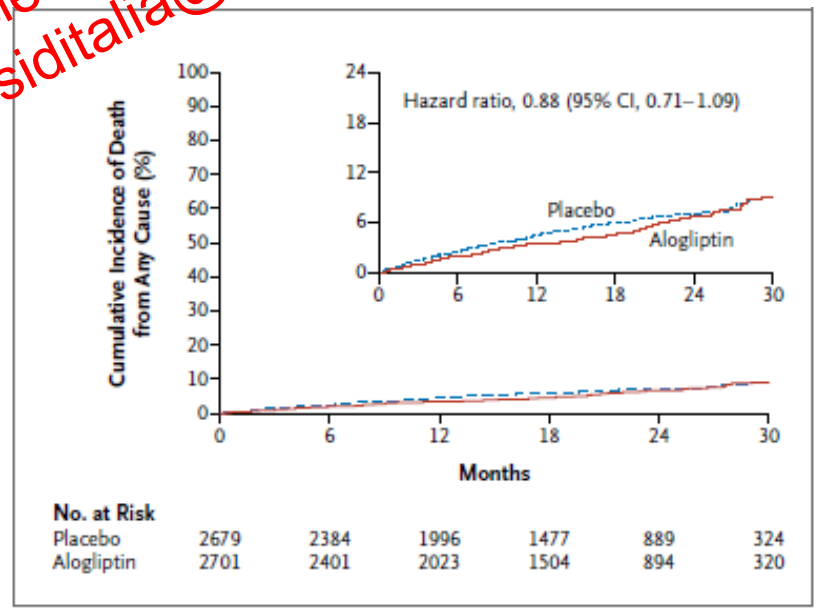
Primary end point*



Cardiovascular mortality



All-cause mortality



* composite of CV death, non-fatal myocardial infarction and non-fatal (ischemic) stroke

White WB et al. N Engl J Med. 2013;369:1327–1335

Cardiovascular outcomes with alogliptin

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

* P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
† The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI at an alpha level of 0.01.
§ The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end point events and deaths that occurred after a nonfatal primary end-point event.

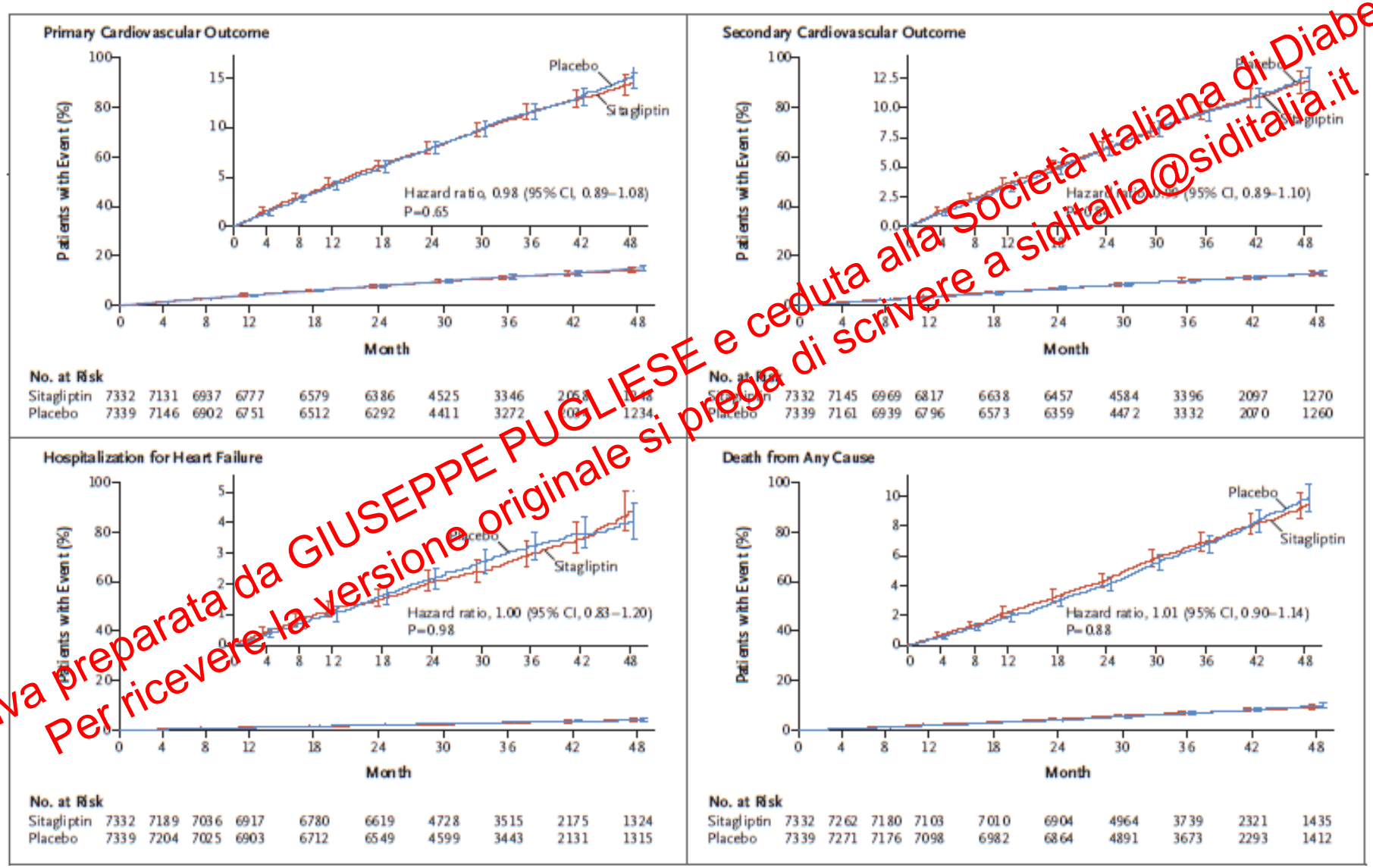
	Alogliptin (n=2701)	Placebo (n=2679)	Hazard ratio (95% CI)	p value
Composite	433 (16·0%)	441 (16·5%)	0·98 (0·86–1·12)	0·728
All-cause mortality	106 (3·9%)	131 (4·9%)	0·80 (0·62–1·03)	0·081
Non-fatal myocardial infarction	171 (6·3%)	155 (5·8%)	1·10 (0·88–1·37)	0·393
Non-fatal stroke	28 (1·0%)	29 (1·1%)	0·97 (0·58–1·62)	0·898
Urgent revascularisation due to unstable angina	43 (1·6%)	47 (1·8%)	0·90 (0·60–1·37)	0·632
Hospital admission for heart failure	85 (3·1%)	79 (2·9%)	1·07 (0·79–1·46)	0·657

White WB et al. N Engl J Med. 2013;369:1327–1335

Cardiovascular outcomes with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

composite of:
- CV death
- non-fatal myocardial infarction
- non-fatal stroke
- hospitalization for unstable angina



composite of:
- CV death
- non-fatal myocardial infarction
- non-fatal stroke

Green JB et al. N Engl J Med. 2015;373:232–242

Cardiovascular outcomes with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

Outcome	Sitagliptin		Placebo		Hazard Ratio (95% CI)	P Value
	no. (%)	*no. per 100 person-yr*	*no. (%)*	*no. per 100 person-yr*		
Per-protocol analysis						
No. of patients in analysis	7257		7266			
Cardiovascular outcome						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: primary composite outcome	695 (9.6)	3.73	699 (9.6)	3.82	0.98 (0.88–1.09)	<0.001*
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke: secondary composite outcome	609 (8.4)	3.24	602 (8.3)	3.28	0.99 (0.89–1.11)	<0.001*
Noncardiovascular outcome						
Acute pancreatitis	20 (0.3)	0.10	11 (0.2)	0.06	1.80 (0.86–3.76)	0.12
Charter-defined cancer	248 (3.4)	1.30	260 (3.6)	1.40	0.93 (0.78–1.10)	0.38
Pancreatic cancer	9 (0.1)	0.05	10 (0.1)	0.05	0.91 (0.37–2.25)	0.85
Severe hypoglycemia	144 (2.0)	0.77	125 (1.7)	0.68	1.13 (0.89–1.44)	0.31

* The P value is for the noninferiority of sitagliptin, as compared with placebo, which was calculated by determining whether the upper boundary of the two-sided 95% confidence interval of the hazard ratio exceeded 1.30. All other listed P values are based on the Wald statistic from a Cox model stratified according to region with a test of differences in hazard ratios.

† The analyses of hospitalization for heart failure were adjusted for a history of heart failure at baseline.

Green JB et al. N Engl J Med. 2015;373:232–242

Cardiovascular outcomes with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

Outcome	Sitagliptin		Placebo		Hazard Ratio (95% CI)	P Value
	no. (%)	no. per 100 person-yr	no. (%)	no. per 100 person-yr		
Intention-to-treat analysis						
No. of patients in analysis	7332		7339			
Cardiovascular outcome						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: primary composite outcome	839 (11.4)	4.06	851 (11.6)	4.17	0.98 (0.89–1.08)	0.65
Cardiovascular death	311 (4.2)		291 (4.0)			
Nonfatal myocardial infarction	275 (3.8)		286 (3.9)			
Nonfatal stroke	145 (2.0)		157 (2.1)			
Hospitalization for unstable angina	108 (1.5)		117 (1.6)			
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke: secondary composite outcome	745 (10.2)	3.58	746 (10.2)	3.62	0.99 (0.89–1.10)	0.84
Cardiovascular death	313 (4.3)		293 (4.0)			
Nonfatal myocardial infarction	285 (3.9)		294 (4.0)			
Nonfatal stroke	147 (2.0)		159 (2.2)			

Outcome	Sitagliptin		Placebo		Hazard Ratio (95% CI)	P Value
	no. (%)	no. per 100 person-yr	no. (%)	no. per 100 person-yr		
Secondary outcome						
Cardiovascular death	382 (5.2)	1.72	366 (5.0)	1.67	1.03 (0.89–1.19)	0.71
Hospitalization for unstable angina	116 (1.6)	0.54	129 (1.8)	0.61	0.90 (0.70–1.16)	0.42
Fatal or nonfatal myocardial infarction	300 (4.1)	1.42	316 (4.3)	1.51	0.95 (0.81–1.11)	0.49
Fatal or nonfatal stroke	178 (2.4)	0.83	183 (2.5)	0.87	0.97 (0.79–1.19)	0.76
Death from any cause	547 (7.5)	2.48	537 (7.3)	2.45	1.01 (0.90–1.14)	0.88
Hospitalization for heart failure†	228 (3.1)	1.07	229 (3.1)	1.09	1.00 (0.83–1.20)	0.98
Hospitalization for heart failure or cardiovascular death†	538 (7.3)	2.54	525 (7.2)	2.50	1.02 (0.90–1.15)	0.74
Noncardiovascular outcome						
Acute pancreatitis	23 (0.3)	0.11	12 (0.2)	0.06	1.93 (0.96–3.88)	0.07
Charter-defined cancer	268 (3.7)	1.25	290 (4.0)	1.37	0.91 (0.77–1.08)	0.27
Pancreatic cancer	9 (0.1)	0.04	14 (0.2)	0.07	0.66 (0.28–1.51)	0.32
Severe hypoglycemia	160 (2.2)	0.78	143 (1.9)	0.70	1.12 (0.89–1.40)	0.33

* The P value is for the noninferiority of sitagliptin, as compared with placebo, which was calculated by determining whether the upper boundary of the two-sided 95% confidence interval of the hazard ratio exceeded 1.30. All other listed P values are based on the Wald statistic from a Cox model stratified according to region with a test of differences in hazard ratios.

† The analyses of hospitalization for heart failure were adjusted for a history of heart failure at baseline.

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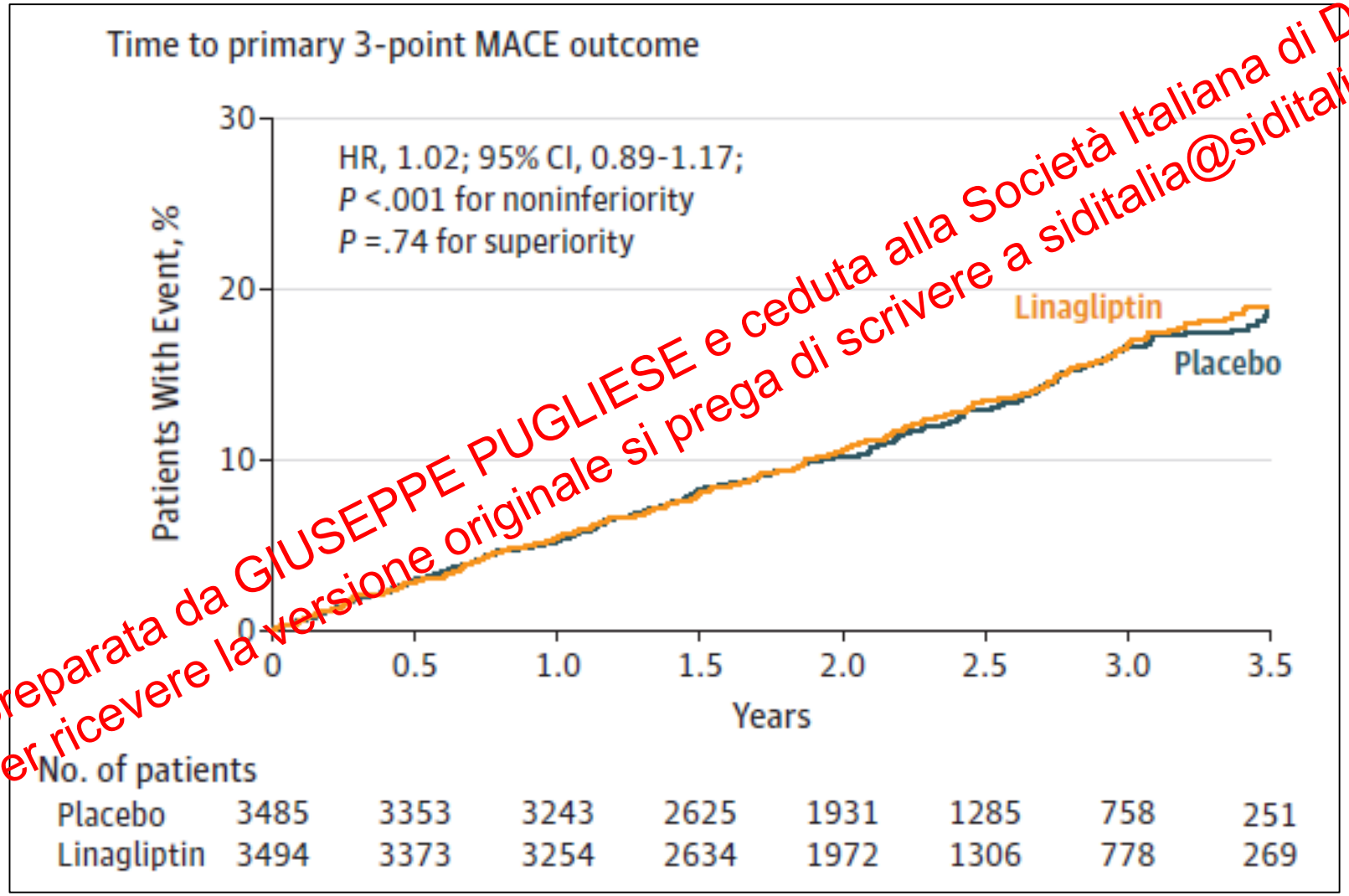
Cardiovascular outcomes with linagliptin

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) study



Rosenstock J et al. JAMA. 2019;321:69–79

Cardiovascular outcomes with linagliptin

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) study

Outcomes	Linagliptin (n = 3494)[a] No. (%)	Linagliptin (n = 3494)[a] Rate per 100 Patient-Years	Placebo (n = 3485)[a] No. (%)	Placebo (n = 3485)[a] Rate per 100 Patient-Years	Incidence Rate Difference, Linagliptin – Placebo (95% CI)	Hazard Ratio (95% CI)[b]	*P* Value
Primary Outcome (3-Point MACE)							
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	434 (12.4)	5.77	420 (12.1)	5.63	0.13 (−0.63 to 0.90)	1.02 (0.89-1.17)	<.001[c];.74[d]
Cardiovascular death[e]	221 (6.3)		225 (6.5)				
Nonfatal myocardial infarction[e]	154 (4.4)		132 (3.8)				
Nonfatal stroke[e]	59 (1.7)		63 (1.8)				
Exploratory Cardiovascular and Death Outcomes							
All-cause death	367 (10.5)	4.69	373 (10.7)	4.80	−0.11 (−0.79 to 0.58)	0.98 (0.84-1.13)	.74
Cardiovascular death	255 (7.3)	3.26	264 (7.6)	3.40	−0.14 (−0.71 to 0.44)	0.96 (0.81-1.13)	.63
Noncardiovascular death	112 (3.2)	1.43	109 (3.1)	1.40	0.03 (−0.34 to 0.40)	1.02 (0.78-1.33)	.89
Fatal myocardial infarction	11 (0.3)	0.14	14 (0.4)	0.18	−0.04 (−0.17 to 0.09)	0.78 (0.36-1.72)	.54
Nonfatal myocardial infarction	156 (4.5)	2.06	135 (3.9)	1.80	0.27 (−0.18 to 0.71)	1.15 (0.91-1.45)	.23
Fatal or nonfatal myocardial infarction	165 (4.7)	2.18	146 (4.2)	1.94	0.24 (−0.22 to 0.70)	1.12 (0.90-1.40)	.30
Fatal stroke	17 (0.5)	0.22	16 (0.5)	0.21	0.01 (−0.13 to 0.16)	1.05 (0.53-2.09)	.88
Nonfatal stroke	65 (1.9)	0.85	73 (2.1)	0.96	−0.12 (−0.42 to 0.19)	0.88 (0.63-1.23)	.45
Fatal or nonfatal stroke	81 (2.3)	1.06	88 (2.5)	1.16	−0.11 (−0.44 to 0.23)	0.91 (0.67-1.23)	.53
4-point MACE (3-point MACE plus hospitalization for unstable angina)	463 (13.3)	6.20	459 (13.2)	6.21	−0.02 (−0.82 to 0.79)	1.00 (0.88-1.13)	.96
Hospitalization for unstable angina	42 (1.2)	0.55	48 (1.4)	0.63	−0.09 (−0.33 to 0.16)	0.87 (0.57-1.31)	.50
Coronary revascularization procedure	160 (4.6)	2.12	149 (4.3)	1.99	0.13 (−0.33 to 0.59)	1.07 (0.85-1.33)	.57
Hospitalization for heart failure	209 (6.0)	2.77	226 (6.5)	3.04	−0.27 (−0.82 to 0.28)	0.90 (0.74-1.08)	.26

[a] The mean observation time and cumulative time in study, respectively, were 2.2 years and 7829.1 person-years for linagliptin and 2.2 years and 7781.6 patient years for placebo.

[b] Hazard ratio based on Cox regression analyses in patients treated with at least 1 dose of study drug.

[c] *P* value for noninferiority.

[d] *P* value for superiority.

[e] Events for individual components of composite outcomes were counted only when they were the first event in the composite.

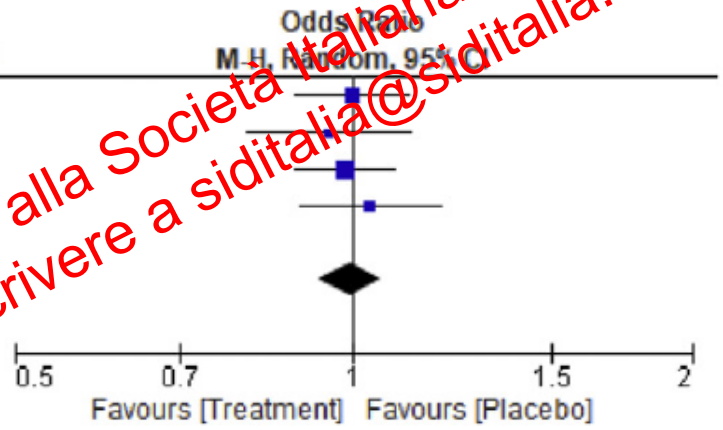
Rosenstock J et al. JAMA. 2019;321:69–79

Meta-analysis of CVOTs with DPP-4 inhibitors

Major adverse cardiovascular events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	613	8280	609	8212	28.8%	1.00 [0.89, 1.12]	2013
EXAMINE 2015	305	2701	316	2679	14.0%	0.95 [0.81, 1.13]	2015
TECOS 2015	839	7332	851	7339	38.1%	0.99 [0.89, 1.09]	2015
CARMELINA 2018	434	3494	420	3485	19.1%	1.04 [0.90, 1.19]	2018
Total (95% CI)		**21807**		**21715**	**100.0%**	**0.99 [0.93, 1.06]**	
Total events	2191		2196				

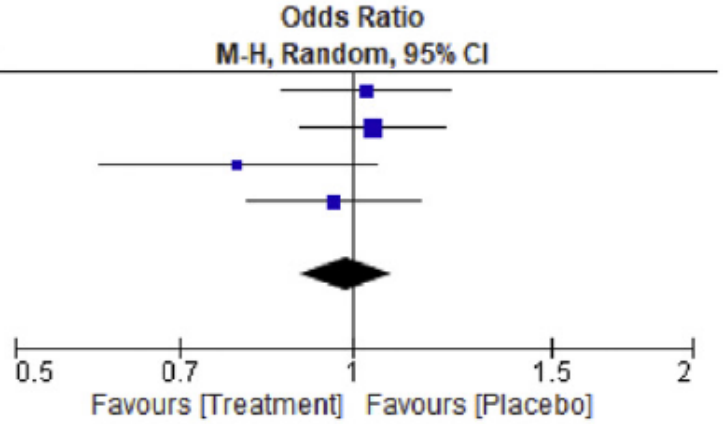
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)



Cardiovascular death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	269	8280	260	8212	27.2%	1.03 [0.86, 1.22]	2013
TECOS 2015	380	7332	366	7339	36.6%	1.04 [0.90, 1.21]	2015
EXAMINE 2015	89	2701	111	2679	10.6%	0.79 [0.59, 1.05]	2015
CARMELINA 2018	255	3494	264	3485	25.6%	0.96 [0.80, 1.15]	2018
Total (95% CI)		**21807**		**21715**	**100.0%**	**0.99 [0.90, 1.08]**	
Total events	993		1001				

Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 3 (P = 0.36); I² = 6%
Test for overall effect: Z = 0.28 (P = 0.78)



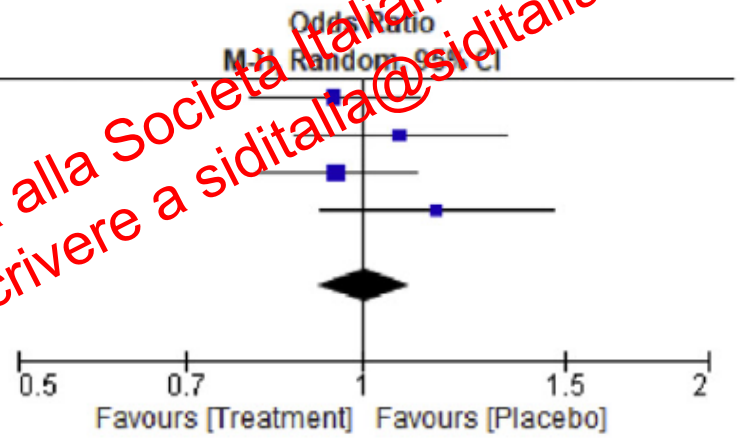
Alfayez OM et al. Can J Diabetes. 2019;43;538–545

Meta-analysis of CVOTs with DPP-4 inhibitors

Myocardial infarction

Study or Subgroup	Treatment Events	Treatment Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	265	8280	278	8212	30.4%	0.94 [0.80, 1.12]	2013
EXAMINE 2015	187	2701	173	2679	19.4%	1.08 [0.87, 1.33]	2015
TECOS 2015	300	7332	316	7339	34.1%	0.95 [0.81, 1.11]	2015
CARMELINA 2018	156	3494	135	3485	16.1%	1.16 [0.92, 1.47]	2018
Total (95% CI)		**21807**		**21715**	**100.0%**	**1.00 [0.91, 1.10]**	
Total events	908		902				

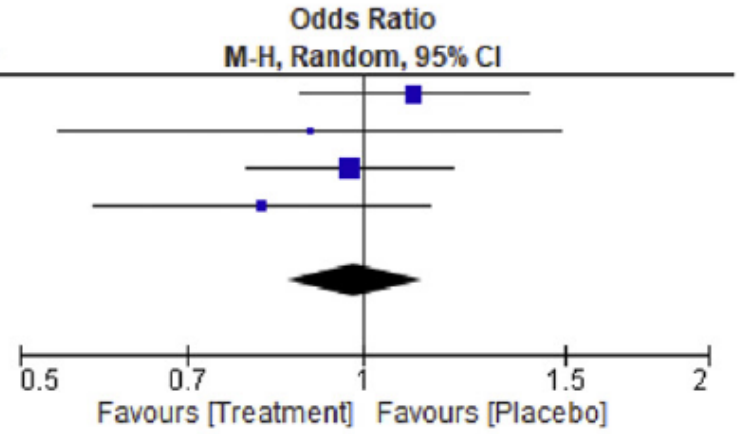
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



Stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	157	8280	141	8212	34.8%	1.11 [0.88, 1.39]	2013
EXAMINE 2015	39	2701	32	2679	7.2%	0.90 [0.54, 1.49]	2015
TECOS 2015	178	7332	183	7339	42.0%	0.97 [0.79, 1.20]	2015
CARMELINA 2018	55	3794	73	3485	16.1%	0.81 [0.58, 1.14]	2018
Total (95% CI)		**22107**		**21715**	**100.0%**	**0.98 [0.86, 1.13]**	
Total events	429		429				

Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



Alfayez OM et al. Can J Diabetes. 2019;43;538–545

Cardiovascular outcomes with DPP-4 inhibitors

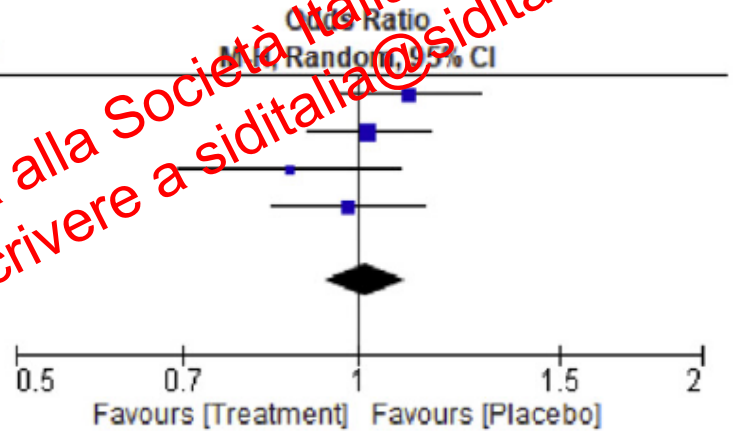
Meta-analysis of CVOTs with DPP-4 inhibitors

Death from any cause

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	420	8280	378	8212	27.8%	1.11 [0.96, 1.28]	2013
TECOS 2015	547	7332	537	7339	35.1%	1.02 [0.90, 1.16]	2015
EXAMINE 2015	153	2701	173	2679	12.4%	0.87 [0.69, 1.09]	2015
CARMELINA 2018	367	3494	373	3485	24.8%	0.98 [0.84, 1.14]	2018
Total (95% CI)		**21807**		**21715**	**100.0%**	**1.01 [0.93, 1.10]**	
Total events	1487		1461				

Heterogeneity: Tau² = 0.00; Chi² = 3.48, df = 3 (P = 0.32); I² = 14%

Test for overall effect: Z = 0.32 (P = 0.75)

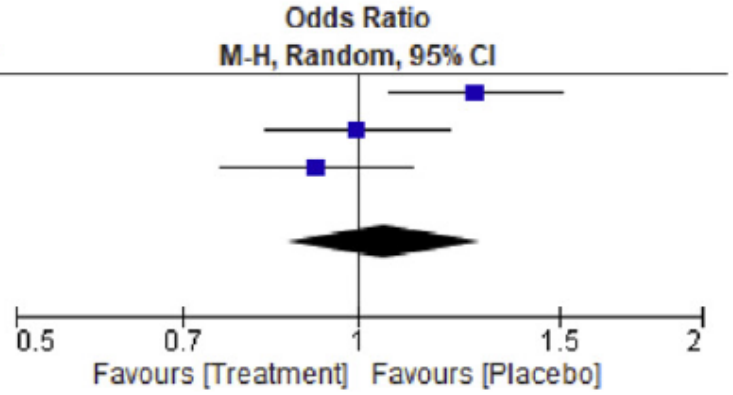


Hospitalization for heart failure

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
SAVOR-TIMI 53 2013	269	8280	228	8212	34.4%	1.27 [1.06, 1.51]	2013
TECOS 2015	228	7332	229	7339	33.3%	1.00 [0.83, 1.20]	2015
CARMELINA 2018	229	3494	226	3485	32.4%	0.92 [0.76, 1.11]	2018
Total (95% CI)		**19106**		**19036**	**100.0%**	**1.05 [0.87, 1.28]**	
Total events	726		683				

Heterogeneity: Tau² = 0.02; Chi² = 6.46, df = 2 (P = 0.04); I² = 69%

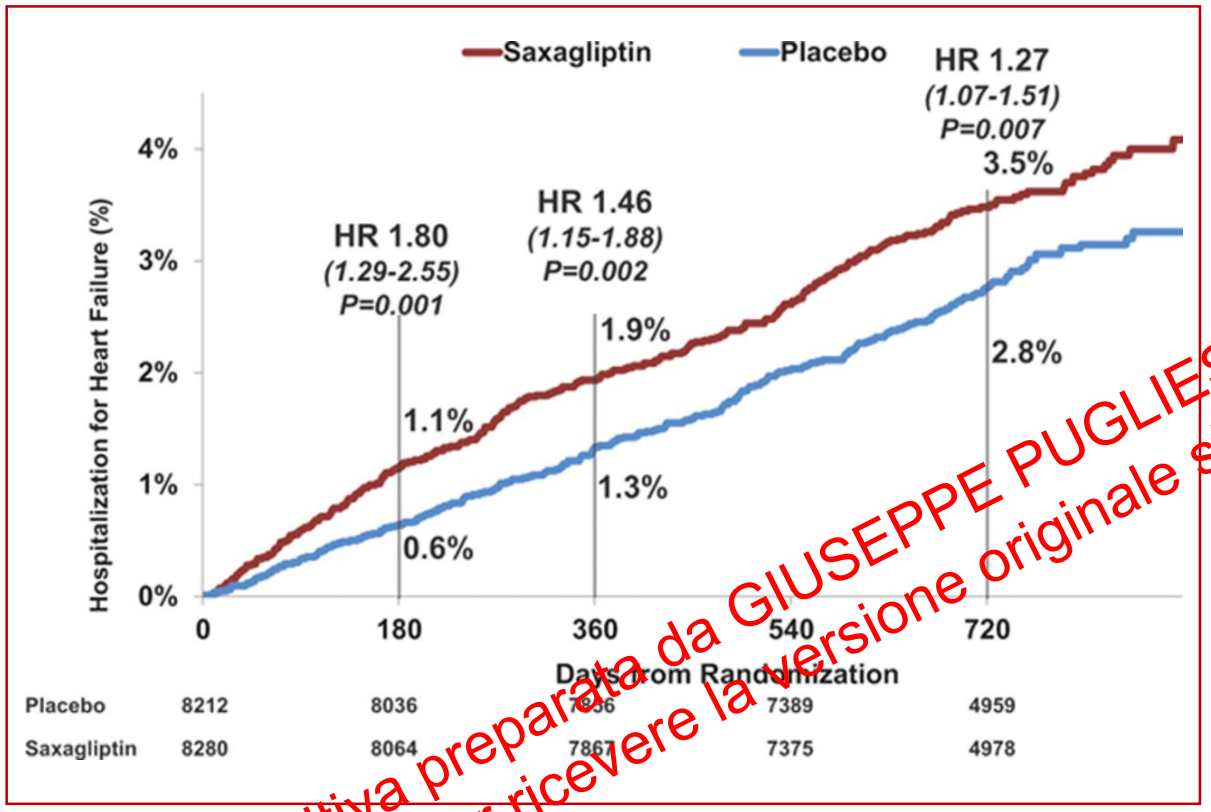
Test for overall effect: Z = 0.53 (P = 0.60)

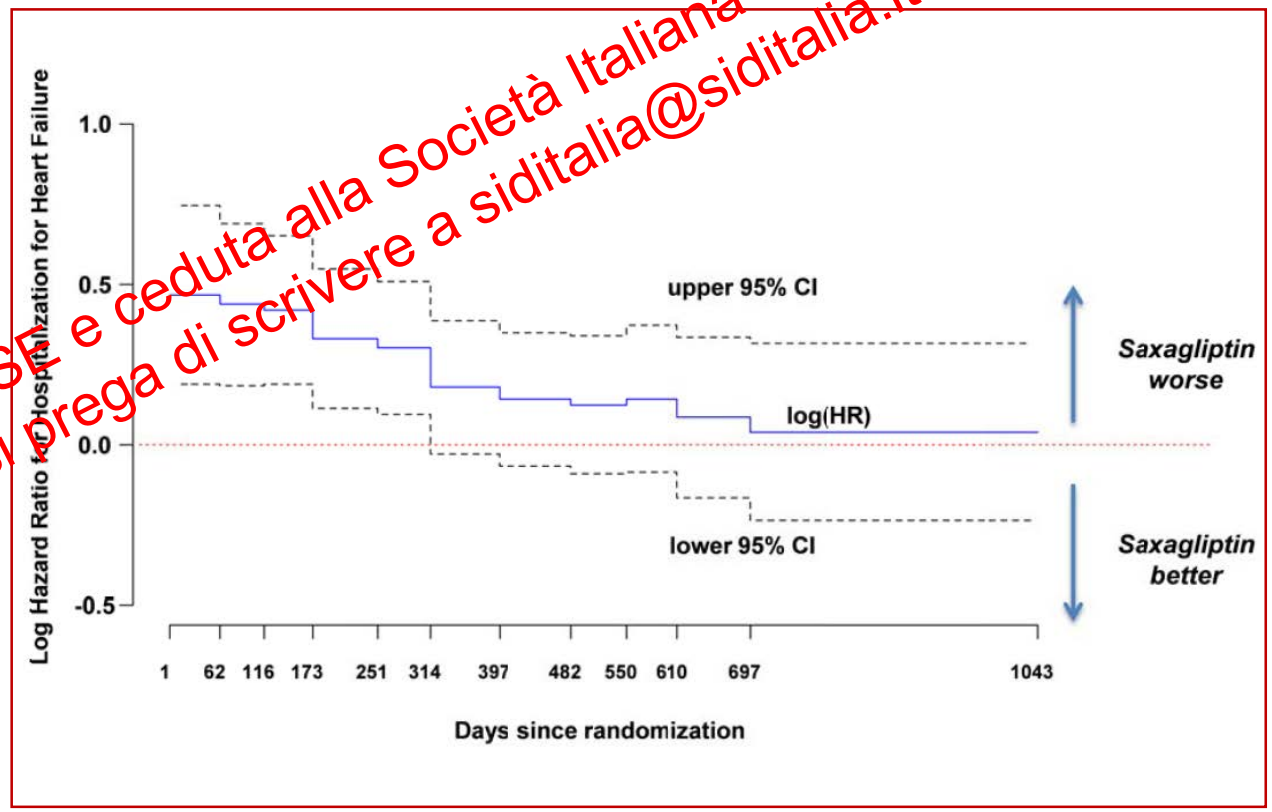


Alfayez OM et al. Can J Diabetes. 2019;43;538–545

Risk of heart failure with saxagliptin

The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study





Scirica BM et al. Circulation. 2014;130:1579–1588

Risk of heart failure with saxagliptin

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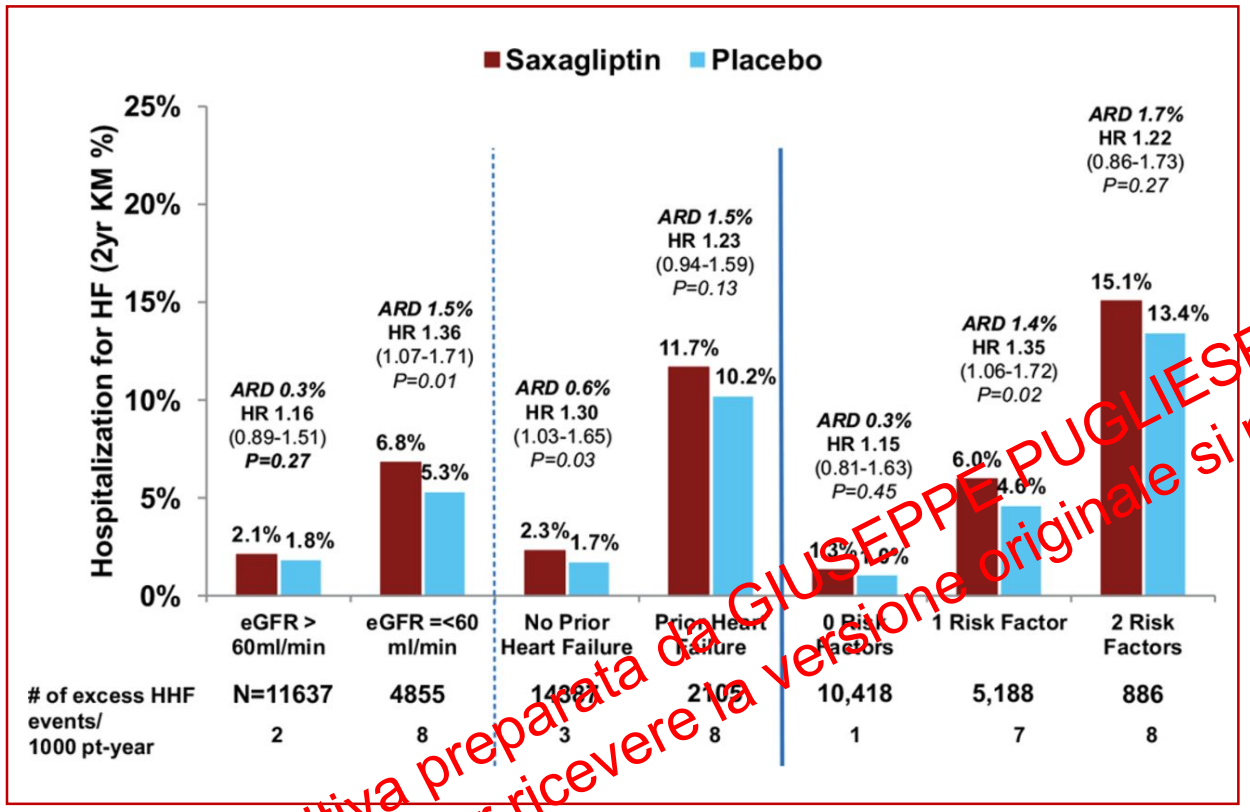
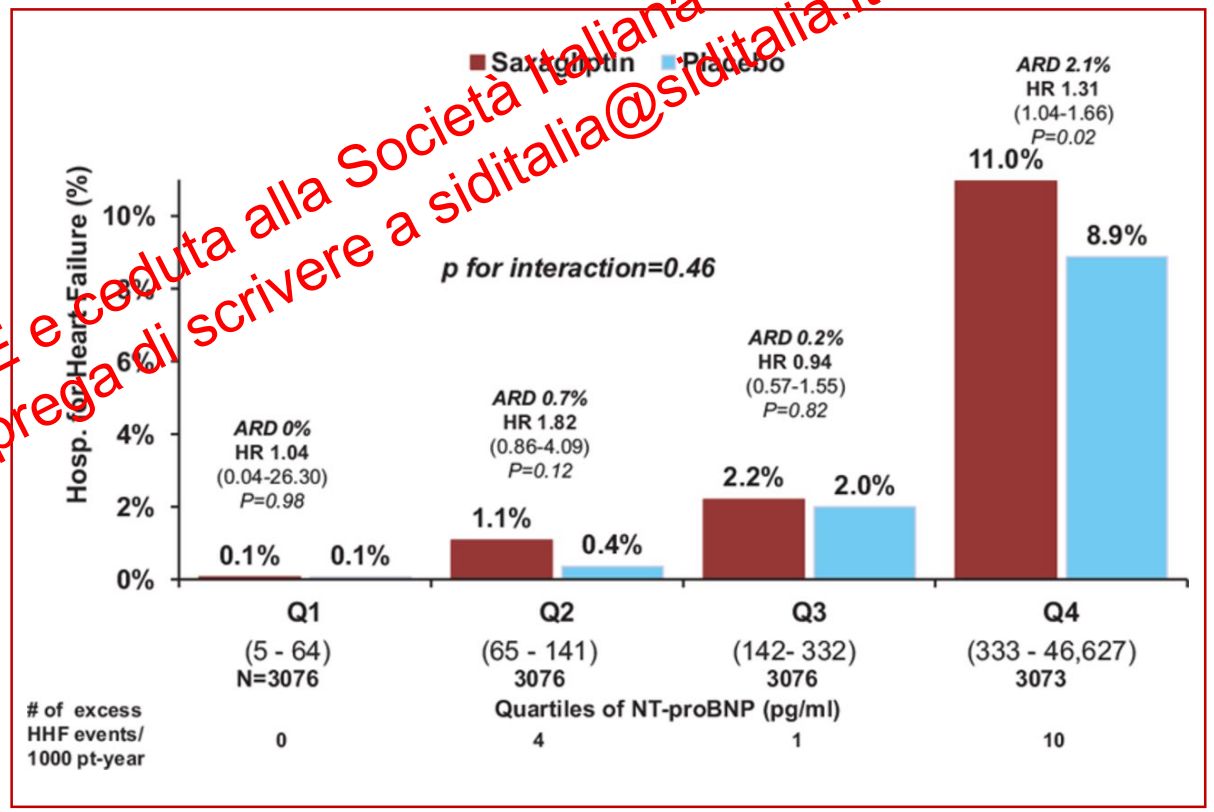




Scirica BM et al. Circulation. 2014;130:1579–1588

Risk of heart failure with alogliptin

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study

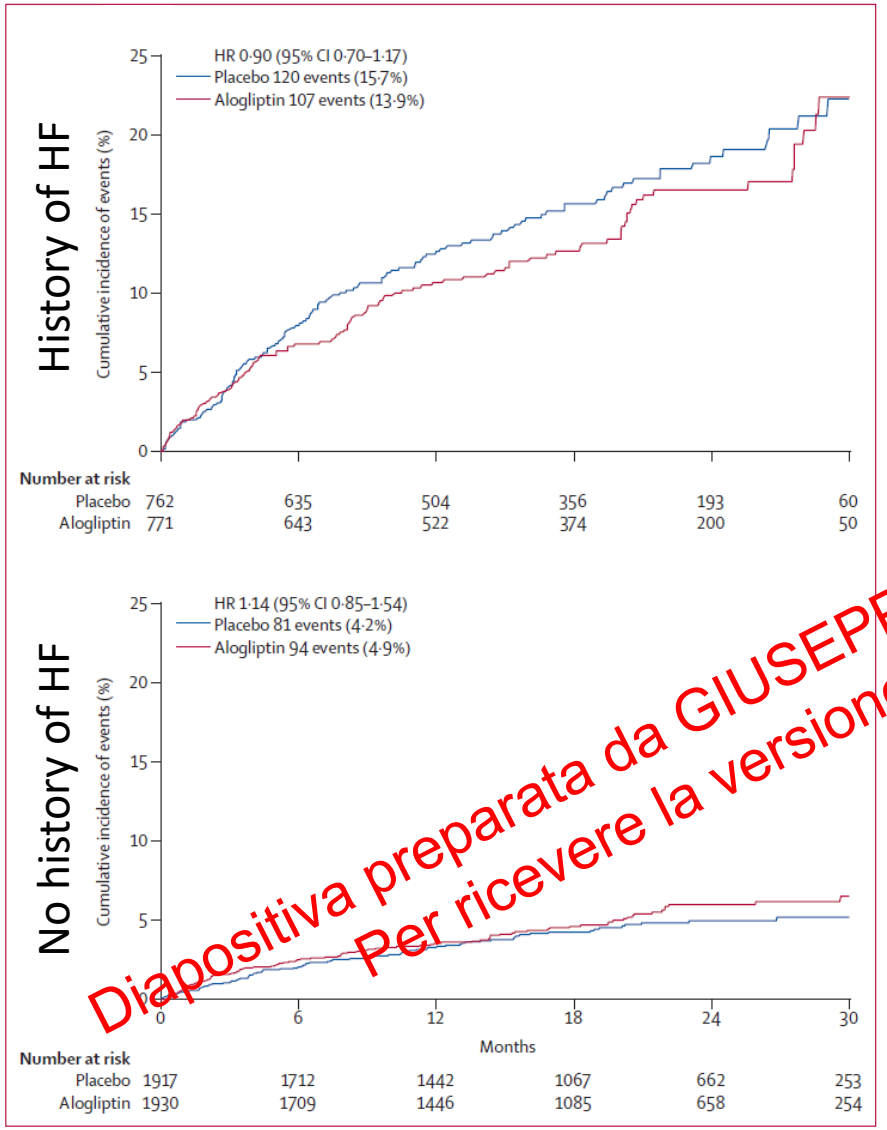
	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Primary MACE endpoint						
Composite	305 (11·3%)	316 (11·8%)	123 (16·0%)	131 (17·2%)	182 (9·4%)	185 (9·7%)
Cardiovascular death	89 (3·3%)	111 (4·1%)	43 (5·6%)	59 (7·7%)	46 (2·4%)	52 (2·7%)
Non-fatal myocardial infarction	187 (6·9%)	173 (6·5%)	69 (8·9%)	66 (8·7%)	118 (6·1%)	107 (5·6%)
Non-fatal stroke	29 (1·1%)	32 (1·2%)	11 (1·4%)	6 (0·8%)	18 (0·9%)	26 (1·4%)
Hazard ratio (95% CI)	0·96 (≤1·16)†		0·94 (0·74–1·20)		0·97 (0·79–1·19)	
p value	0·315		0·622		0·772	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·874	..	..	..
Secondary MACE endpoint						
Composite	344 (12·7%)	359 (13·4%)	127 (16·5%)	141 (18·5%)	217 (11·2%)	218 (11·4%)
Cardiovascular death	89 (3·3%)	111 (4·1%)	42 (5·4%)	59 (7·7%)	45 (2·3%)	52 (2·7%)
Non-fatal myocardial infarction	185 (6·8%)	169 (6·3%)	69 (8·9%)	65 (8·5%)	116 (6·0%)	104 (5·4%)
Non-fatal stroke	29 (1·1%)	32 (1·2%)	11 (1·4%)	6 (0·8%)	18 (0·9%)	26 (1·4%)
Urgent revascularisation due to unstable angina	43 (1·6%)	47 (1·8%)	5 (0·6%)	11 (1·4%)	38 (2·0%)	36 (1·9%)
Hazard ratio (95% CI)	0·95 (≤1·14)†		0·89 (0·70–1·14)		0·98 (0·81–1·18)	
p value	0·258		0·358		0·832	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·581	..	..	..

MACE=major adverse cardiovascular endpoint. *Before or after index acute coronary syndrome event. †Upper bound of the one-sided 95% CI, α=0·01.

Zannad F et al. Lancet 2015;385:2067–2076

Risk of heart failure with alogliptin

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study



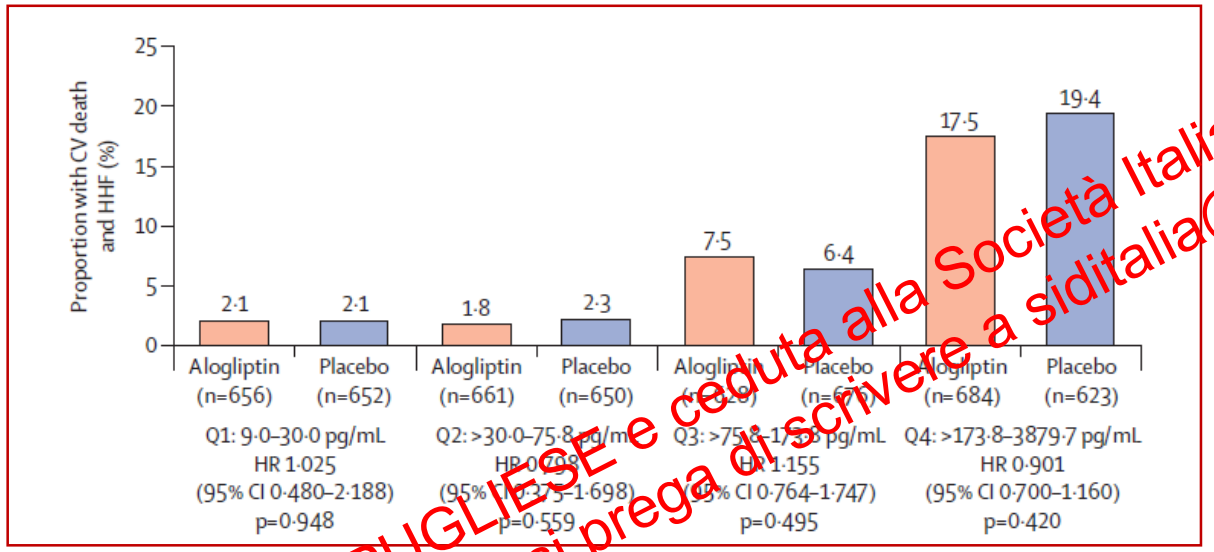
	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7·4)	201 (7·5)	107 (13·9)	120 (15·7)	94 (4·9)	81 (4·2)
Hazard ratio (95% CI)	1·00 (0·82–1·21)		0·90 (0·70–1·17)		1·14 (0·85–1·54)	
p value	0·976		0·446		0·337	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·221	..	..	..
Cardiovascular death*	112 (4·1)	130 (4·9)	55 (7·1)	69 (9·1)	57 (3·0)	61 (3·2)
Hazard ratio (95% CI)	0·85 (0·66–1·10)		0·77 (0·54–1·09)		0·92 (0·64–1·32)	
p value	0·212		0·141		0·643	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·508	..	..	..
Hospital admission for heart failure	106 (3·9)	89 (3·3)	63 (8·2)	65 (8·5)	43 (2·2)	24 (1·3)
Hazard ratio (95% CI)	1·19 (0·90–1·58)		1·00 (0·71–1·42)		1·76 (1·07–2·90)	
p value	0·220		0·996		0·026	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·068	..	..	..

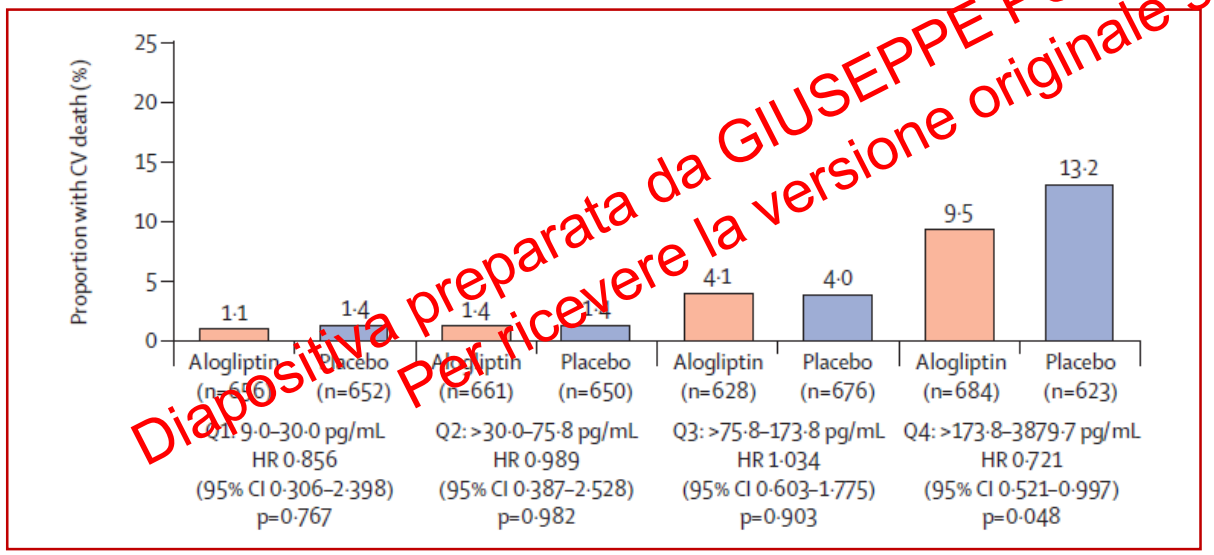
*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

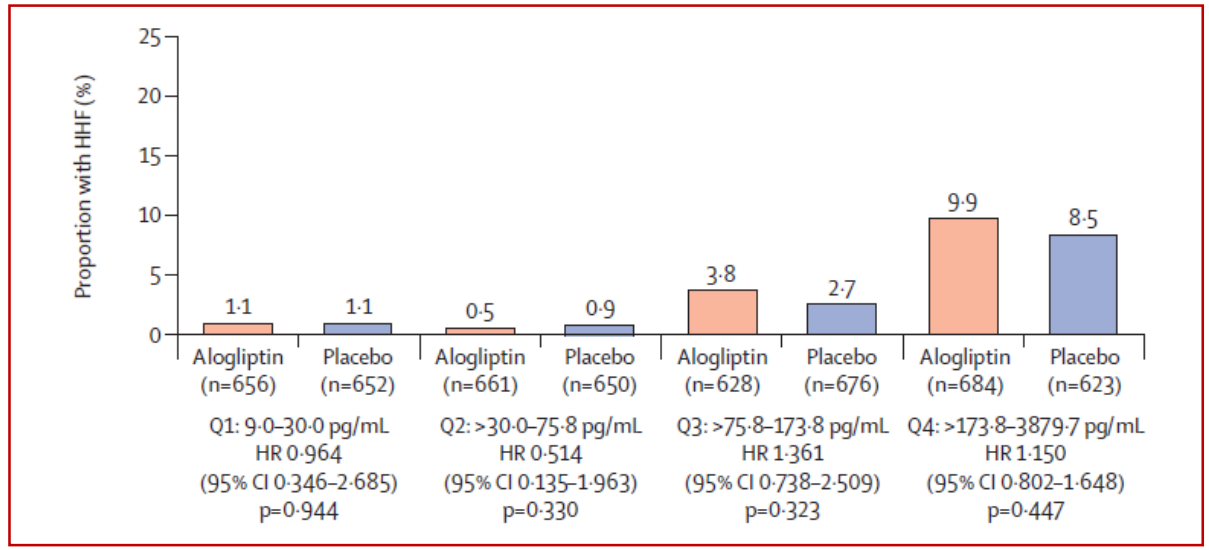
Zannad F et al. Lancet 2015;385:2067–2076

Risk of heart failure with alogliptin

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study



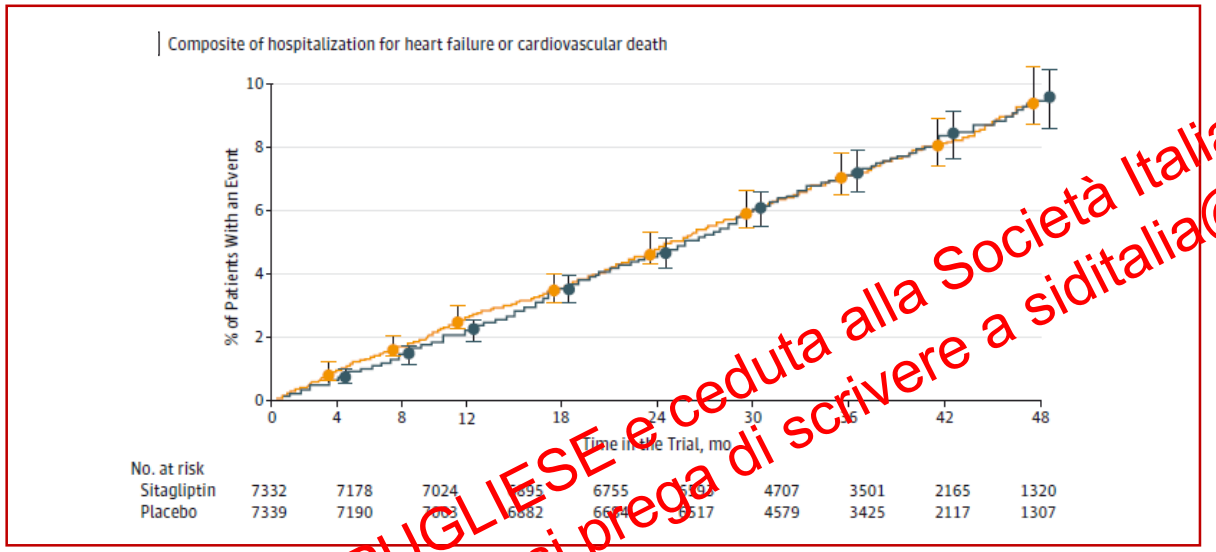


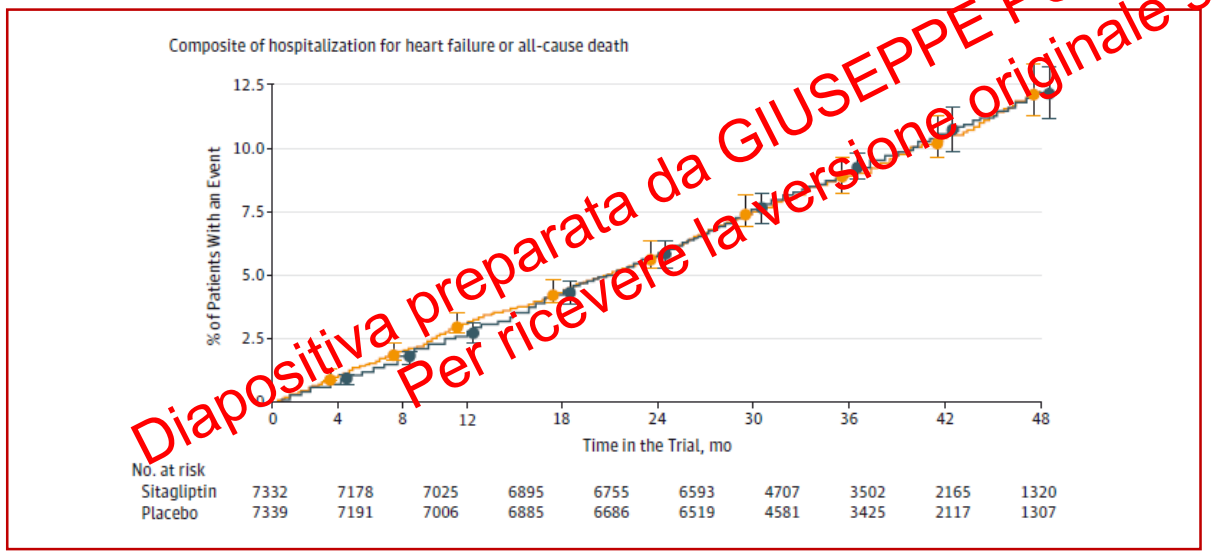


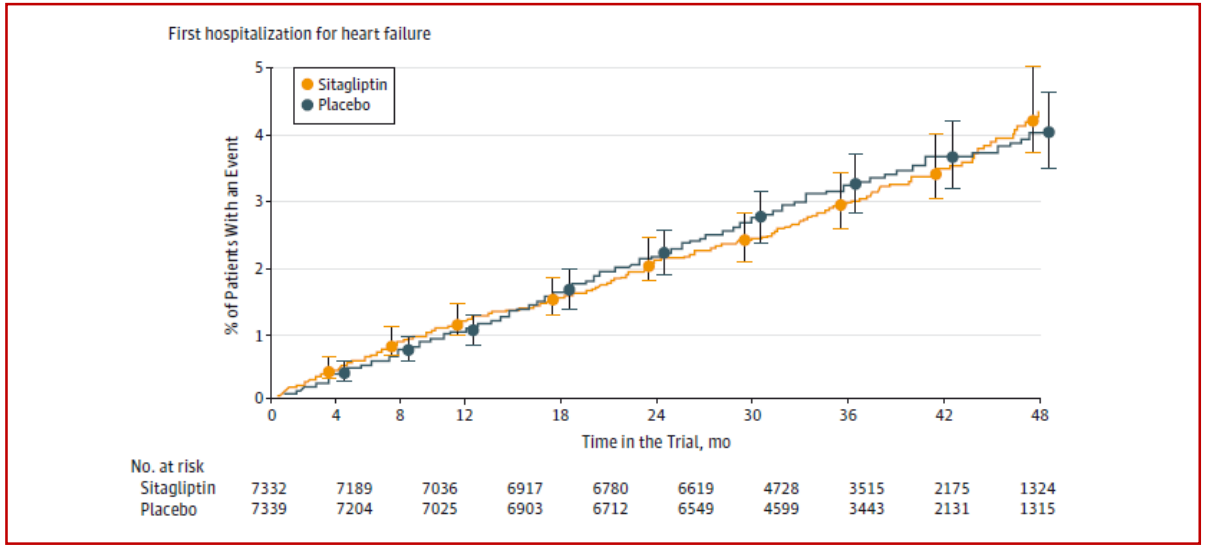
Zannad F et al. Lancet 2015;385:2067–2076

Risk of heart failure with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)







McGuire DK et al. JAMA Cardiol. 2016;1:126–135

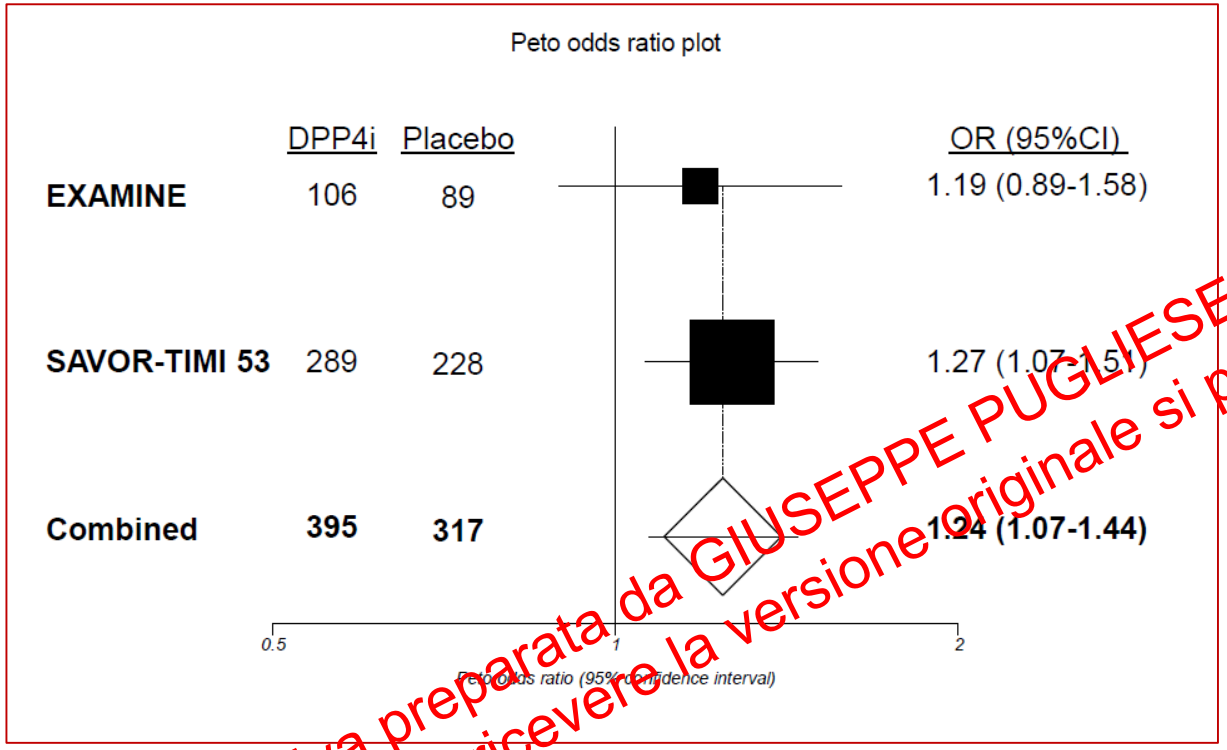
Risk of heart failure with sitagliptin

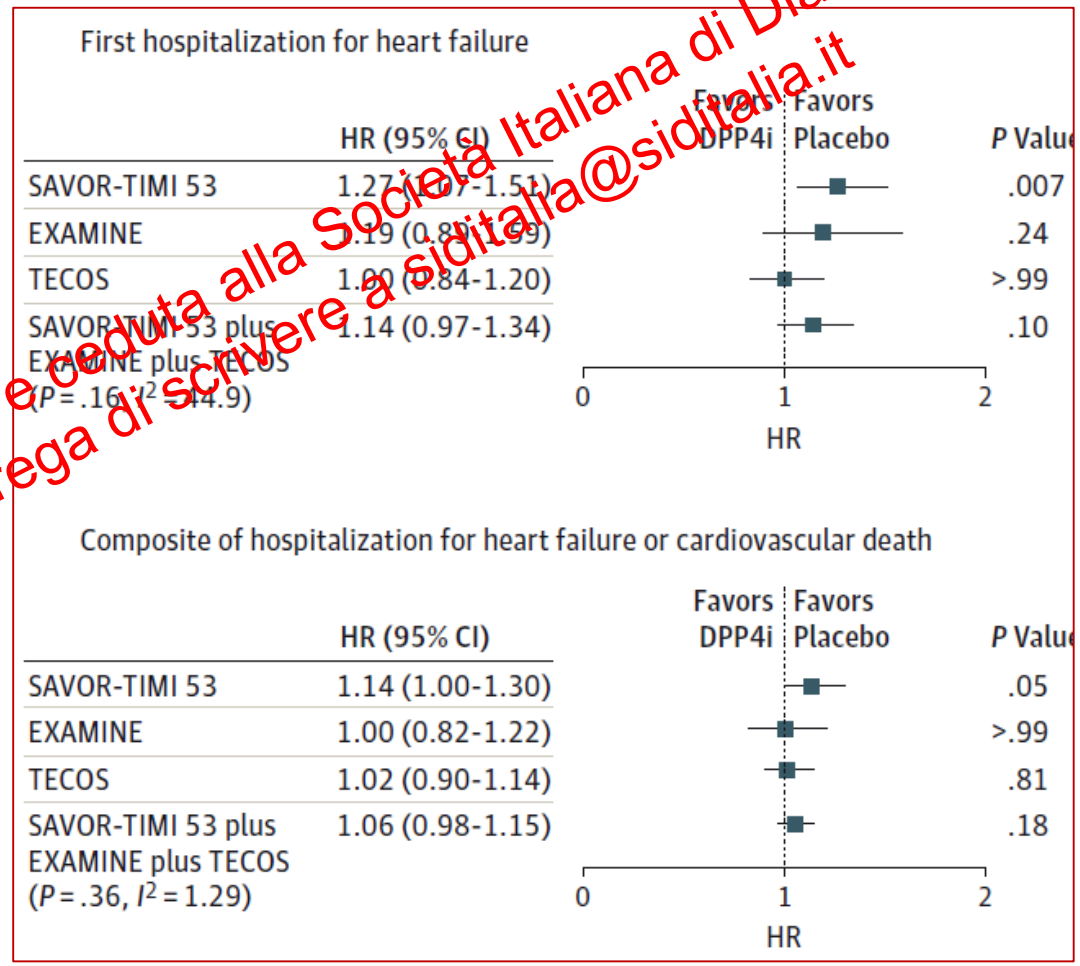
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

Variable	No./Total No. (%)		HR (95% CI)	*P* Value
	Sitagliptin (n = 7332)	Placebo (n = 7339)		
Overall Intent-to-Treat Population				
First hospitalization for heart failure (unadjusted)	228 (3.1)	229 (3.1)	1.00 (0.83-1.19)	.98
Adjusted for region and prior heart failure at baseline	NA	NA	1.00 (0.83-1.20)	.98
Multivariable adjusted[a]	NA	NA	1.02 (0.83-1.25)	.82
Composite of hospitalization for heart failure or cardiovascular death (unadjusted)	538 (7.3)	525 (7.2)	1.02 (0.90-1.14)	.81
Adjusted for region and prior heart failure at baseline	NA	NA	1.02 (0.90-1.15)	.74
Composite of hospitalization for heart failure or all-cause death (unadjusted)	685 (9.3)	682 (9.3)	1.00 (0.90-1.11)	.93
Total hospitalization for heart failure events (first plus recurrent) (unadjusted)[b]	345	347	1.00 (0.80-1.25)	>.99
Patients with 2 events	37	44	NA	NA
Patients with ≥3 events	26	25	NA	NA
Death during or after first hospitalization for heart failure (unadjusted)				
Cardiovascular death	51/228 (22.4)	53/229 (23.1)	NA	NA
All-cause death	68/228 (29.8)	66/229 (28.8)	NA	NA
Subset of Patients With Prior Heart Failure at Baseline				
First hospitalization for heart failure (unadjusted)	97/1303 (7.4)	94/1340 (7.0)	1.03 (0.77-1.36)	.86
Cardiovascular death (unadjusted)	120/1303 (9.2)	133/1340 (9.9)	0.91 (0.71-1.17)	.46
Composite of hospitalization for heart failure or cardiovascular death (unadjusted)	183/1303 (14.0)	191/1340 (14.3)	0.96 (0.79-1.18)	.71
All-cause death	166/1303 (12.7)	182/1340 (13.6)	0.92 (0.75-1.14)	.46

McGuire DK et al. JAMA Cardiol. 2016;1:126–135

Risk of heart failure with DPP-4 inhibitors





Scirica BM et al. Circulation. 2014;130:1579–1588

McGuire DK et al. JAMA Cardiol. 2016;1:126–135

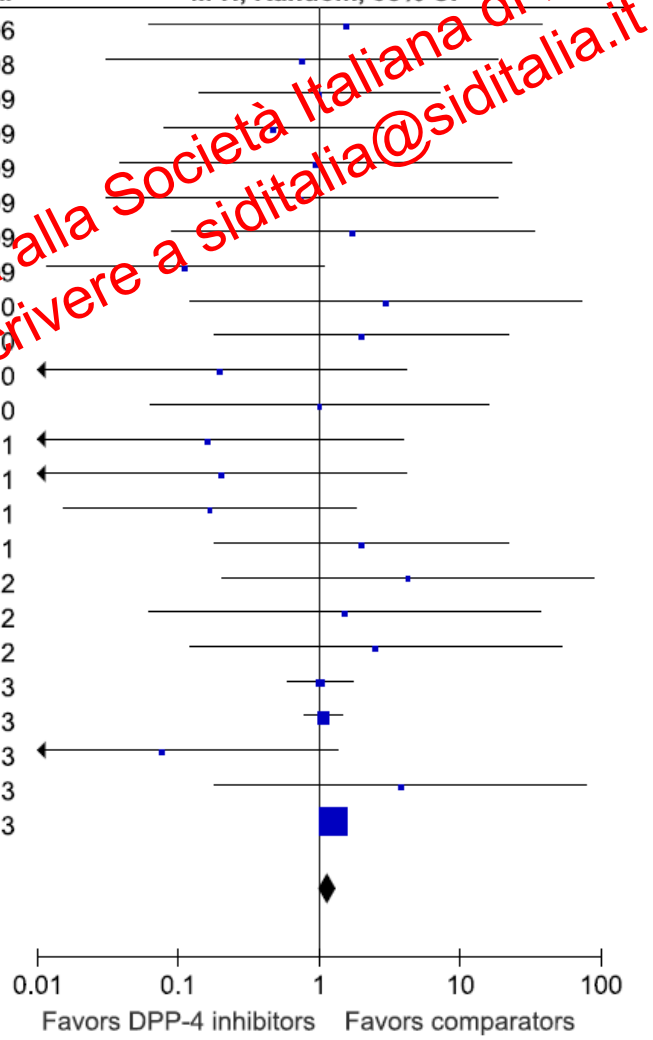
Risk of heart failure with DPP-4 inhibitors vs comparators

Meta-analysis of Randomized Clinical Trials with DPP-4 inhibitors

Study or subgroup	DPP-4 inhibitors Events	Total	All comparators Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Charbonnel et al. 2006	1	464	0	237	0.2%	1.54 [0.06, 37.55]	2006
Nauck et al. 2009	1	420	0	104	0.2%	0.75 [0.03, 18.24]	2008
Ferrannini et al. 2009	2	1396	2	1393	0.5%	1.00 [0.14, 7.07]	2009
DeFronzo et al. 2009	3	564	2	179	0.6%	0.48 [0.08, 2.83]	2009
Rosenstock (1) 2009	1	306	0	95	0.2%	0.94 [0.04, 22.84]	2009
Pratley et al. (2) 2009	1	401	0	99	0.2%	0.75 [0.03, 18.18]	2009
Pratley et al. (1) 2009	3	396	0	97	0.2%	1.73 [0.09, 33.18]	2009
Jadzinsky et al. 2009	1	978	3	328	0.4%	0.11 [0.01, 1.07]	2009
Williams-Herman 2010	1	551	0	540	0.2%	2.94 [0.12, 72.03]	2010
Seck et al. 2010	2	588	1	584	0.3%	1.99 [0.18, 21.85]	2010
Vilsboll et al. 2010	0	322	2	319	0.2%	0.20 [0.01, 4.11]	2010
Goke et al. 2010	1	428	1	430	0.3%	1.00 [0.06, 16.01]	2010
Hollander et al. 2011	0	381	1	184	0.2%	0.16 [0.01, 3.94]	2011
Nowicki et al. 2011	0	85	2	85	0.2%	0.20 [0.01, 4.10]	2011
Pfutzner et al. 2011	1	978	2	328	0.3%	0.17 [0.02, 1.84]	2011
Bosi et al. 2011	2	404	1	399	0.3%	1.98 [0.18, 21.70]	2011
Haak et al. 2012	2	428	0	383	0.2%	4.24 [0.20, 88.08]	2012
Kawamori et al. 2012	1	319	0	162	0.2%	1.53 [0.06, 37.30]	2012
Barnett et al. (2) 2012	2	304	0	151	0.2%	2.49 [0.12, 51.58]	2012
McMurray et al. 2013	23	128	22	125	6.9%	1.02 [0.60, 1.73]	2013
White et al. 2013	85	2701	79	2679	21.3%	1.07 [0.79, 1.44]	2013
NCT00509262	0	211	6	212	0.2%	0.08 [0.00, 1.36]	2013
NCT00722371	2	922	0	693	0.2%	3.76 [0.18, 78.18]	2013
Scirica et al. 2013	289	8280	228	8212	66.2%	1.26 [1.06, 1.49]	2013
Total (95% CI)		**21,955**		**17,998**	**100.0%**	**1.16 [1.01, 1.33]**	
Total events	424		352				

Heterogeneity: Tau² = 0.00; Chi² = 19.02, df = 23 (P = 0.70); I² = 0%

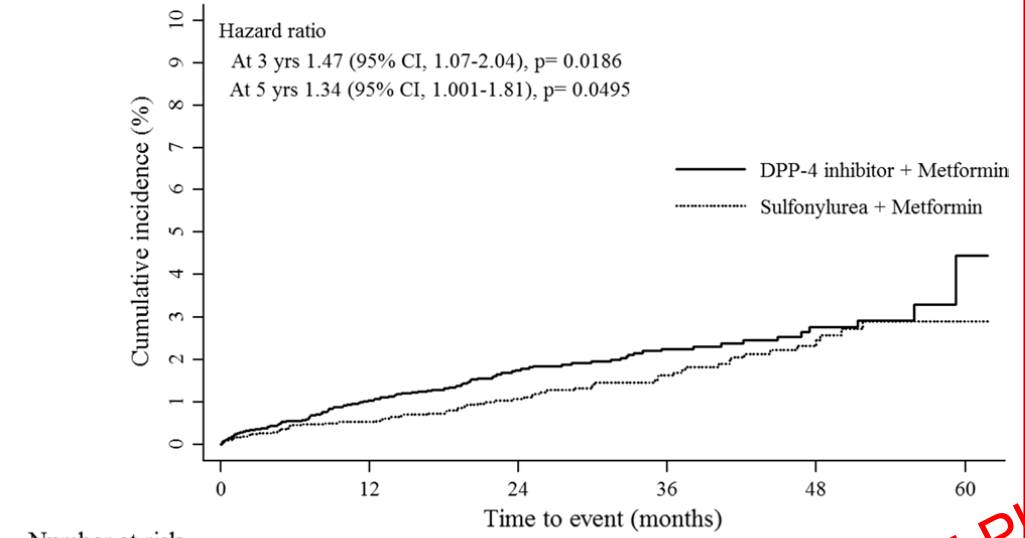
Test for overall effect: Z = 2.08 (P = 0.04)



Wu S et al. Cardiovasc Ther. 2014;32:147–158

Risk of heart failure with DPP-4 inhibitors vs sulphonyureas (+ metformin)

Retrospective study from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS)



23,674 patients with type 2 diabetes

Study outcomes	Total			History of baseline HF			No history of baseline HF		
	SU + MET (*n* = 4674)	DPP4i + MET (*n* = 9348)	*P*-value	SU + MET (*n* = 412)	DPP4i + MET (*n* = 824)	*P*-value	SU + MET (*n* = 4262)	DPP4i + MET (*n* = 8524)	*P*-value
HHF									
N. of events	70	131		44	73		26	58	
Cumulative incidence at 3 years (%)[a]	1.70 (1.30–2.23)	2.20 (1.82–2.66)		11.08 (8.00–15.26)	13.40 (10.53–16.97)		0.73 (0.47–1.15)	1.09 (0.81–1.47)	
HR (95% CI) at 3 years[b]	1.00	1.39 (1.02–1.90)	0.0369	1.00	1.29 (0.86–1.95)	0.2250	1.00	1.61 (0.97–2.67)	0.0634
Cumulative incidence at 5 years (%)[a]	2.89 (2.25–3.91)	3.30 (2.46–4.44)		19.96 (14.24–27.58)	19.44 (12.38–29.79)		1.21 (0.77–1.91)	1.68 (1.15–2.45)	
HR (95% CI) at 5 years[b]	1.00	1.26 (0.95–1.67)	0.1132	1.00	1.12 (0.77–1.64)	0.5574	1.00	1.51 (0.96–2.39)	0.0765

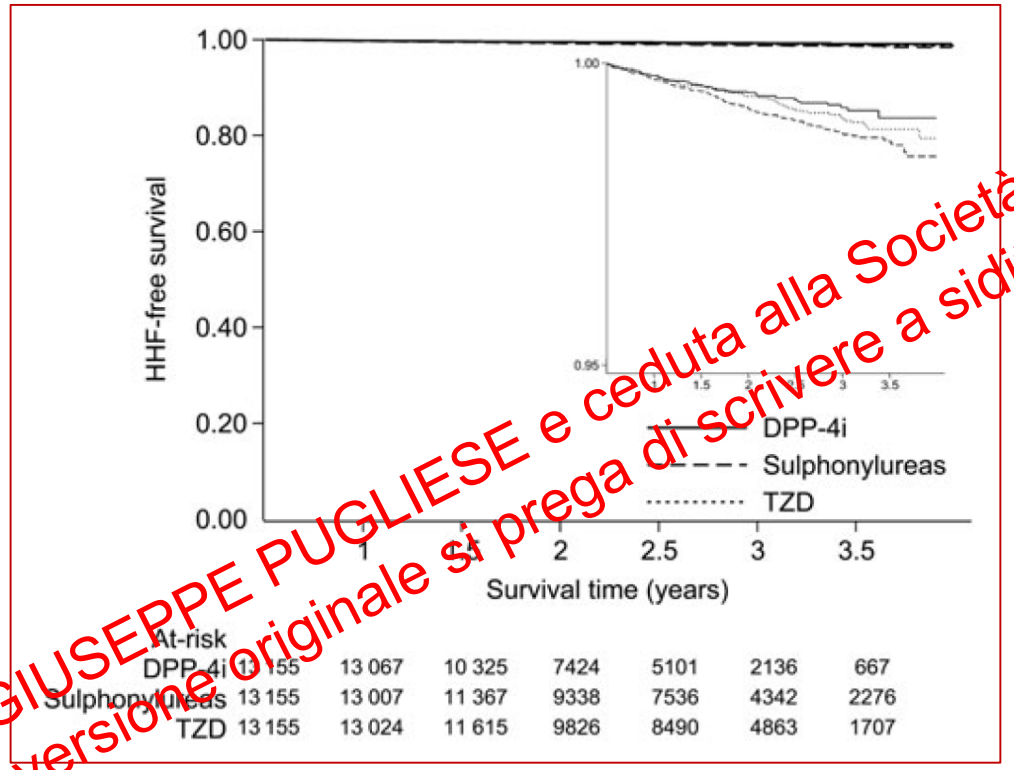
Study outcomes	Total			History of baseline CVD			No history of baseline CVD		
	SU + MET (*n* = 4684)	DPP4i + MET (*n* = 9368)	*P*-value	SU + MET (*n* = 2025)	DPP4i + MET (*n* = 4050)	*P*-value	SU + MET (*n* = 2659)	DPP4i + MET (*n* = 5318)	*P*-value
HHF									
N. of events	65	128		56	103		9	25	
Cumulative incidence at 3 years (%)[b]	1.63 (1.23–2.17)	2.26 (1.85–2.74)		3.34 (2.48–4.48)	3.98 (3.20–4.93)		0.28 (0.12–0.68)	0.95 (0.62–1.47)	
HR (95% CI) at 3 years[c]	1.00	1.47 (1.07–2.04)	0.0186	1.00	1.30 (0.92–1.84)	0.1425	1.00	3.32 (1.28–8.62)	0.0139
Cumulative incidence at 5 years (%)[b]	2.90 (2.16–3.89)	4.43 (2.55–7.66)		5.29 (3.87–7.21)	8.63 (4.74–15.43)		0.94 (0.44–1.99)	0.95 (0.62–1.47)	
HR (95% CI) at 5 years[c]	1.00	1.34 (1.00–1.81)	0.0495	1.00	1.26 (0.91–1.74)	0.1717	1.00	1.91 (0.93–3.93)	0.0777

Kim KJ et al. Cardiovasc Diabetol. 2019;18:28

Risk of heart failure with DPP-4 inhibitors vs sulphonyureas or thiazolidinediones

Retrospective study from the Nationwide OsMed Health-DB Database

127,555 patients
with type 2 diabetes



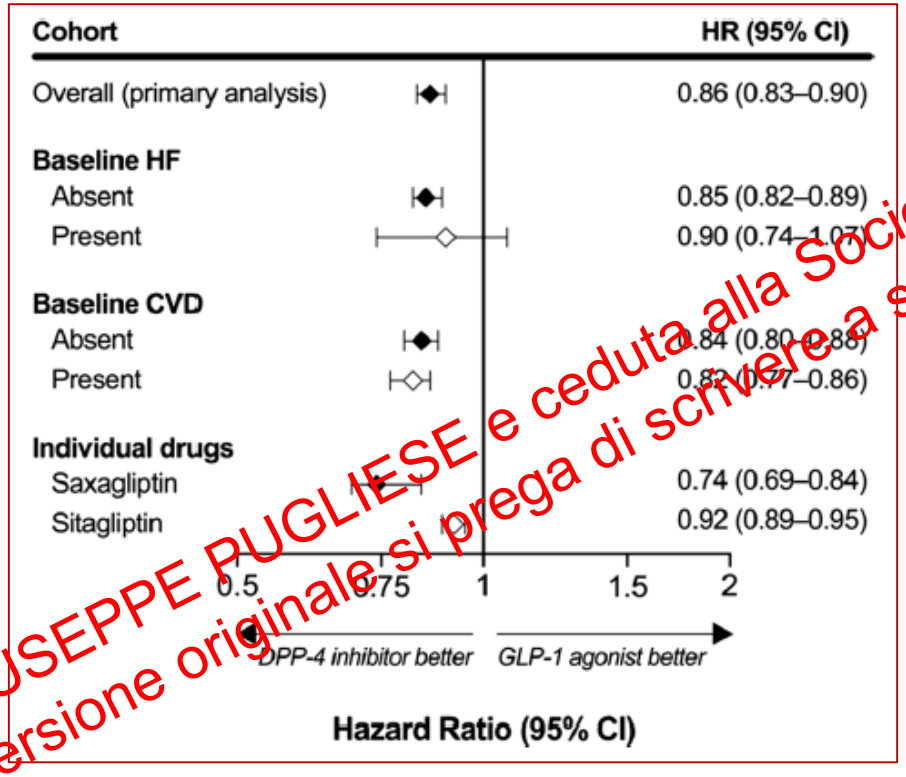
Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

Fadini GP et al. Eur Heart J. 2015;36:2454–2462

Risk of heart failure with DPP-4 inhibitors vs GLP-1 receptor agonists

Retrospective cohort study of patients with type 2 diabetes newly initiated on DPP-4 inhibitors or GLP-1 agonists

321,606 patients
with type 2 diabetes



Study population	Medications	Person-years	No. of HF events	Crude incidence (per 1000 person-years)	Adjusted HR of HF (95% CI)
Primary diagnosis only	DPP-4 inhibitors	77,070	3107	40	0.84 (0.80, 0.89)
	GLP-1 agonists	70,706	3424	48	Reference
Extend follow-up to 45 days	DPP-4 inhibitors	94,201	5714	61	0.89 (0.85, 0.92)
	GLP-1 agonists	89,315	6098	68	Reference

CI confidence interval, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *HF* heart failure, *HR* hazard ratio

Dawwas GK et al. Cardiovasc Diabetol. 2018;17:102

Serious hypoglycemic events and cardiovascular risk

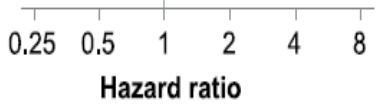
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

Previous SHEs increase the subsequent risk of CV events

Event	ADJUSTED HR (95% CI)	*P* value
4-point MACE	1.55 (1.06, 2.28)	0.025
3-point MACE	1.68 (1.14, 2.48)	0.009
All-cause death	1.83 (1.22, 2.75)	0.004
Cardiovascular death	1.72 (1.02, 2.87)	0.040
MI (fatal + nonfatal)	1.59 (0.85, 2.99)	0.148
Hospitalization for UA	1.20 (0.38, 3.76)	0.757
Stroke (fatal + nonfatal)	1.91 (0.90, 4.06)	0.093
Hospitalization for HF	1.17 (0.52, 2.62)	0.709

Previous CV events increase the subsequent risk of SHEs

Preceding event	ADJUSTED HR (95% CI)	*P* value
Nonfatal CV event or hUA	2.48 (1.65, 3.75)	<0.001
Nonfatal CV event	2.86 (1.85, 4.41)	<0.001
Nonfatal MI	3.02 (1.83, 4.96)	<0.001
Hospitalization for UA	1.35 (0.50, 3.65)	0.555
Nonfatal stroke	2.77 (1.36, 5.63)	0.005
Hospitalization for HF	3.68 (2.13, 6.36)	<0.001

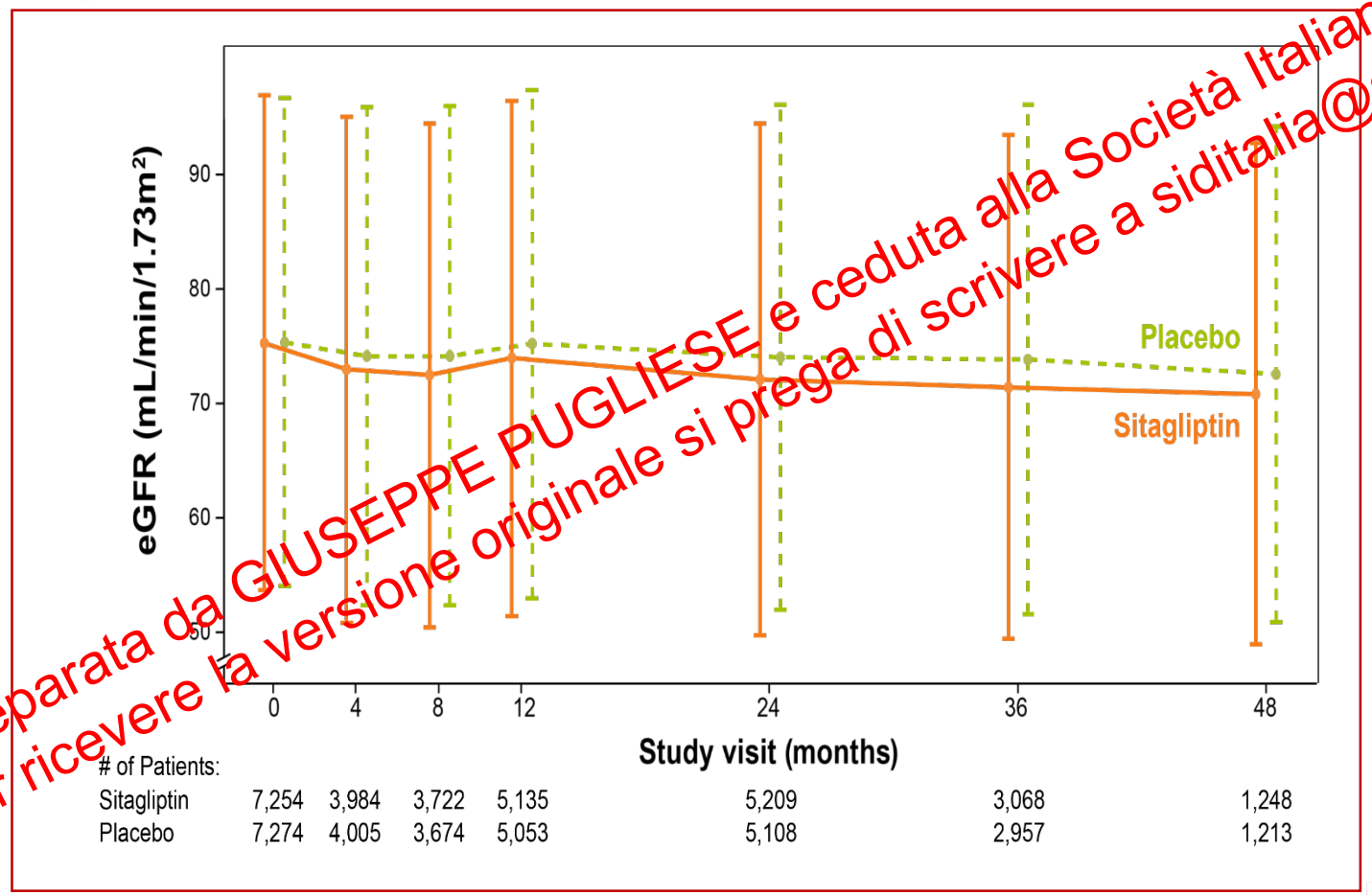


Standl E, Diabetes Care 2018

Standl E et al. Diabetes Care. 2018;41:596–603

Renal outcomes with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

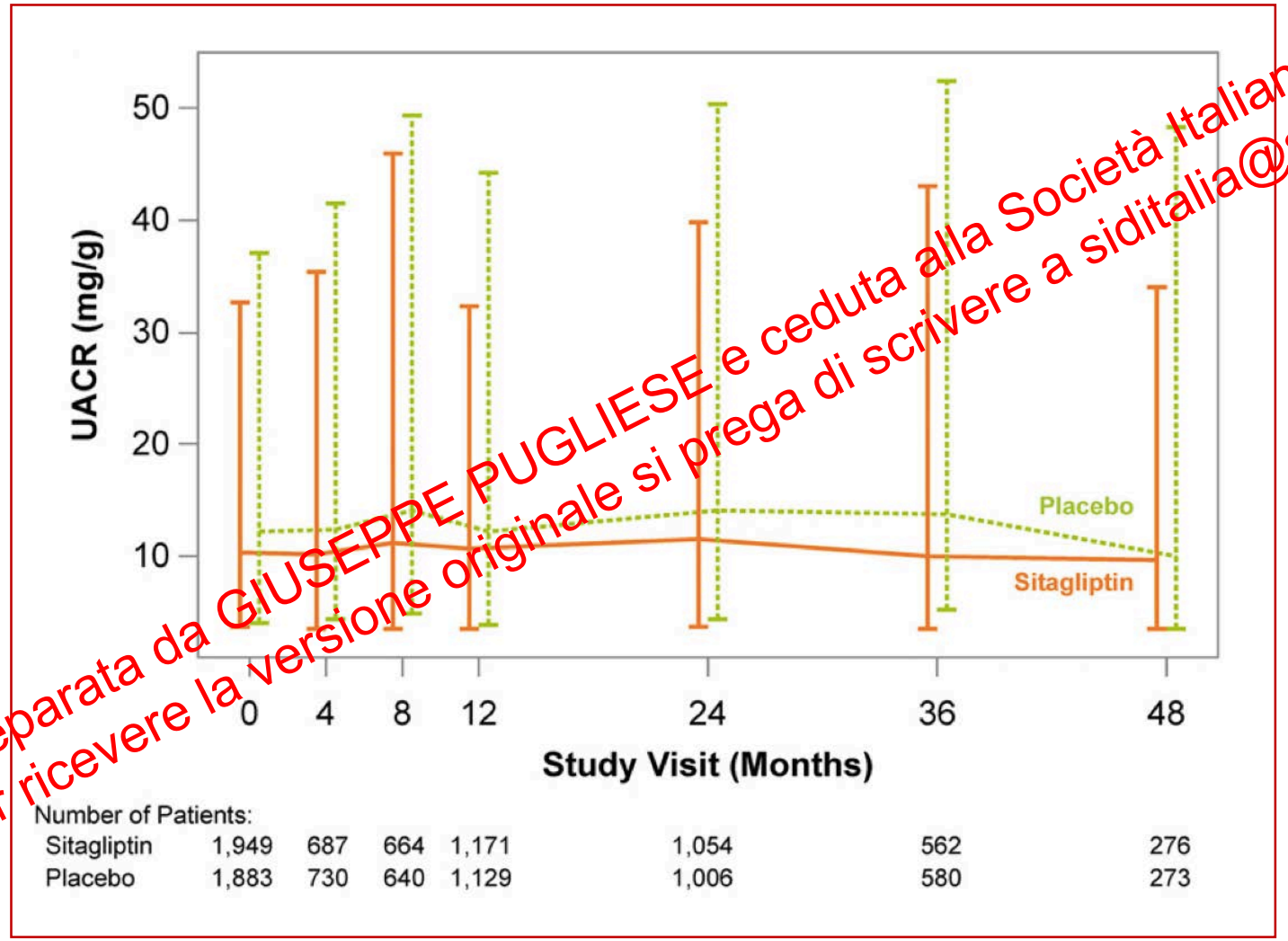


Estimated overall mean difference: -1.34 ml/min/1.73m² (95%CI -1.76, -0.91), p<0.001

Cornel JH et al. Diabetes Care. 2016;39:2304–2310

Renal outcomes with sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

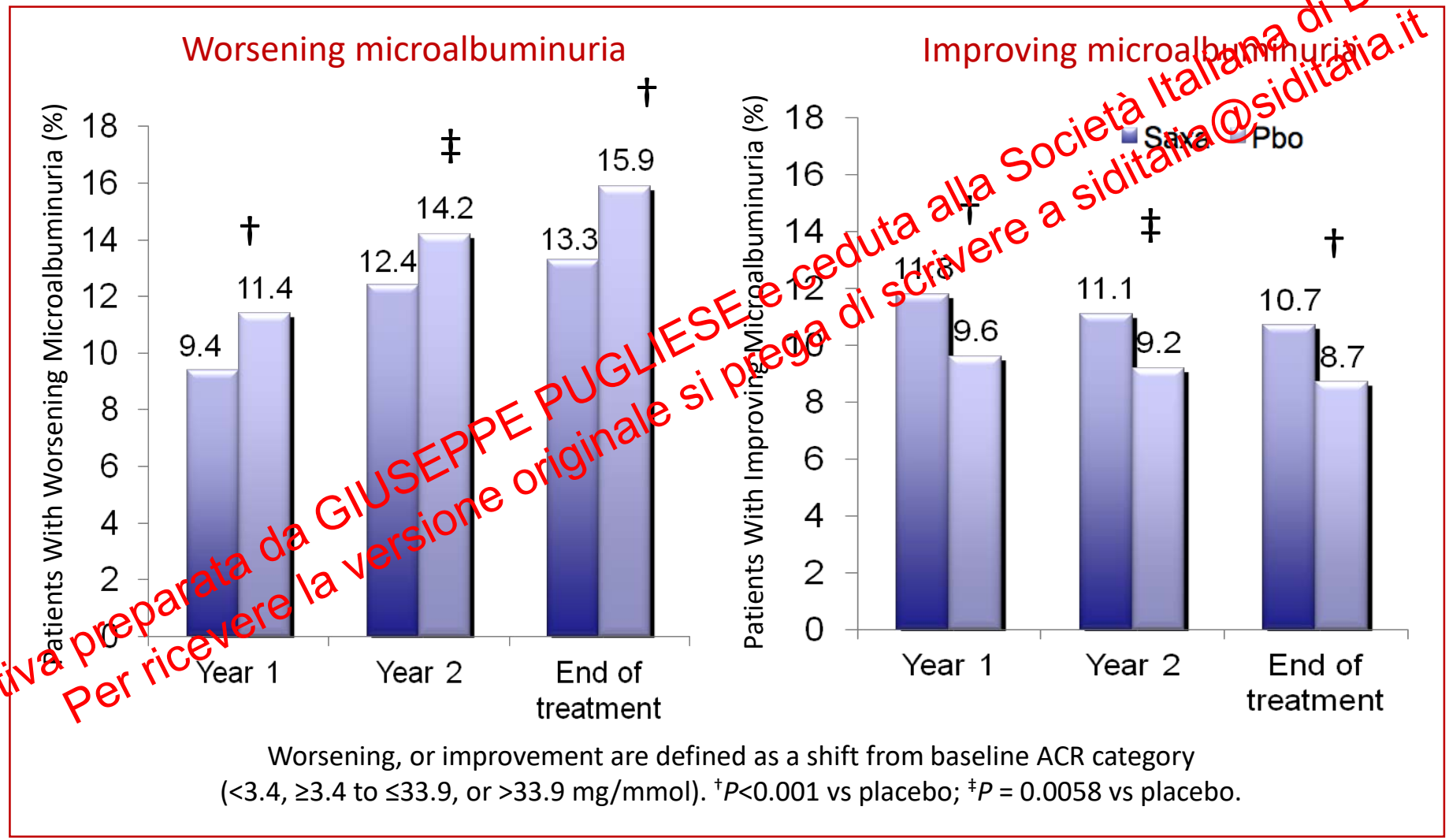


Estimated overall mean difference: -0.18 mg/g (95%CI -0.35, -0.02), p<0.031

Cornel JH et al. Diabetes Care. 2016;39:2304–2310

Renal outcomes with saxagliptin

The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study

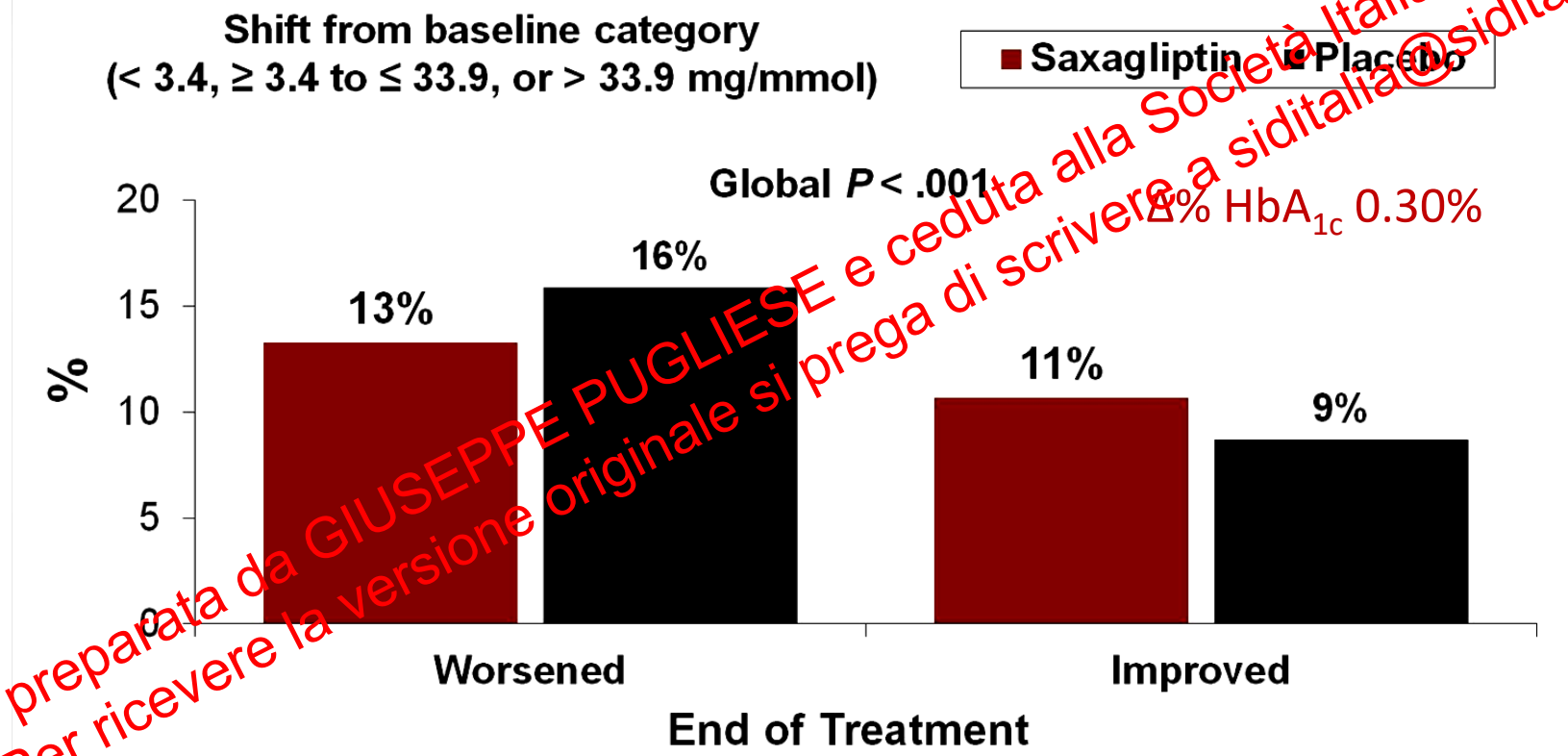


Worsening, or improvement are defined as a shift from baseline ACR category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol). †*P*<0.001 vs placebo; ‡*P* = 0.0058 vs placebo.

Scirica BM et al. N Engl J Med. 2013;369:1317–1326

Renal outcomes with saxagliptin

The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study

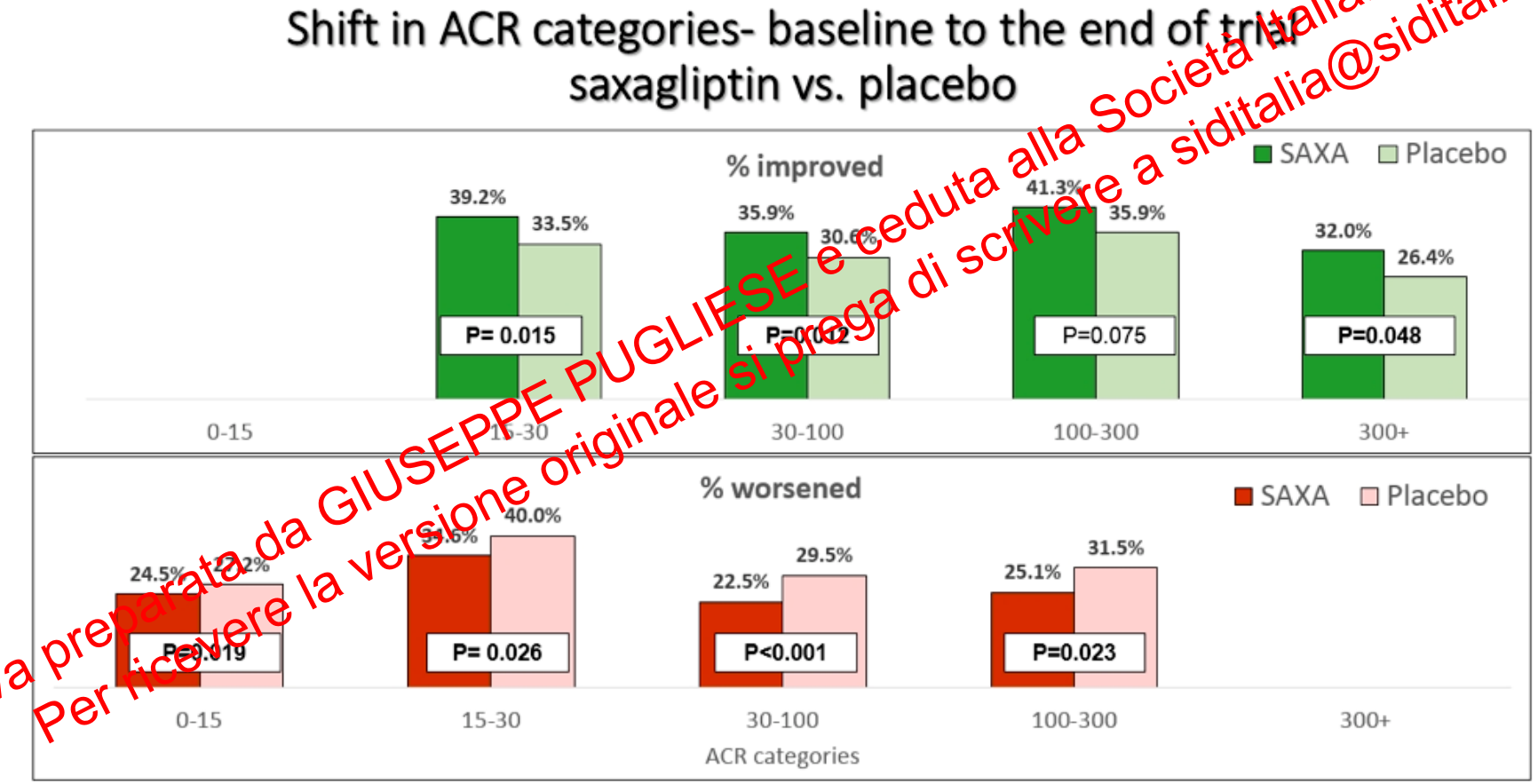


Treatment difference in the number and proportion of patients with albumin/creatinine ratios that worsened, did not change, or improved is defined as a shift from baseline category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol).
†*P*<0.001 vs placebo; ‡*P* = 0.0058 vs placebo.

Scirica BM et al. N Engl J Med. 2013;369:1317–1326

Renal outcomes with saxagliptin

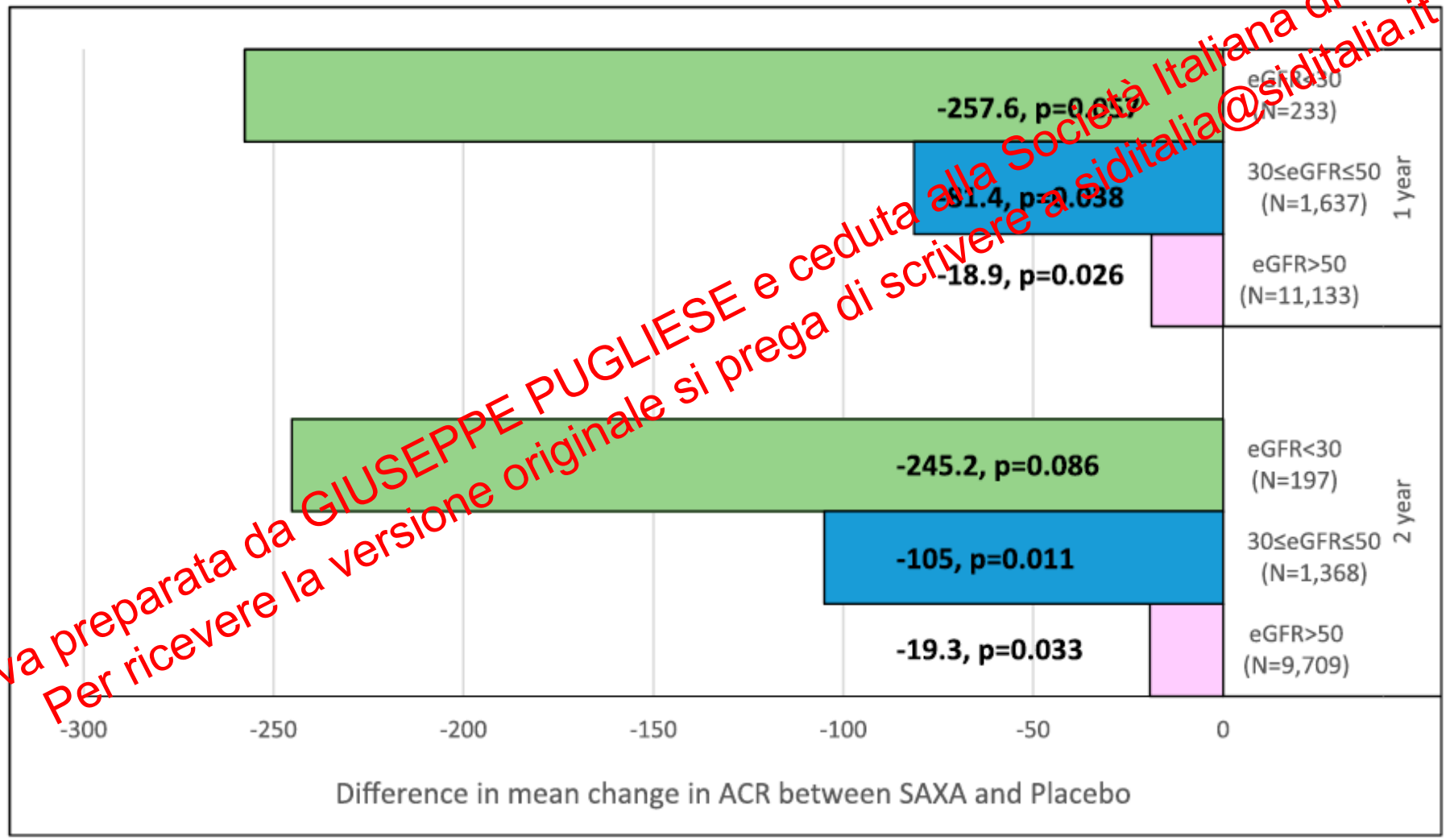
The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study



Mosenzon O et al. Diabetes Care. 2017;40:69–76

Renal outcomes with saxagliptin

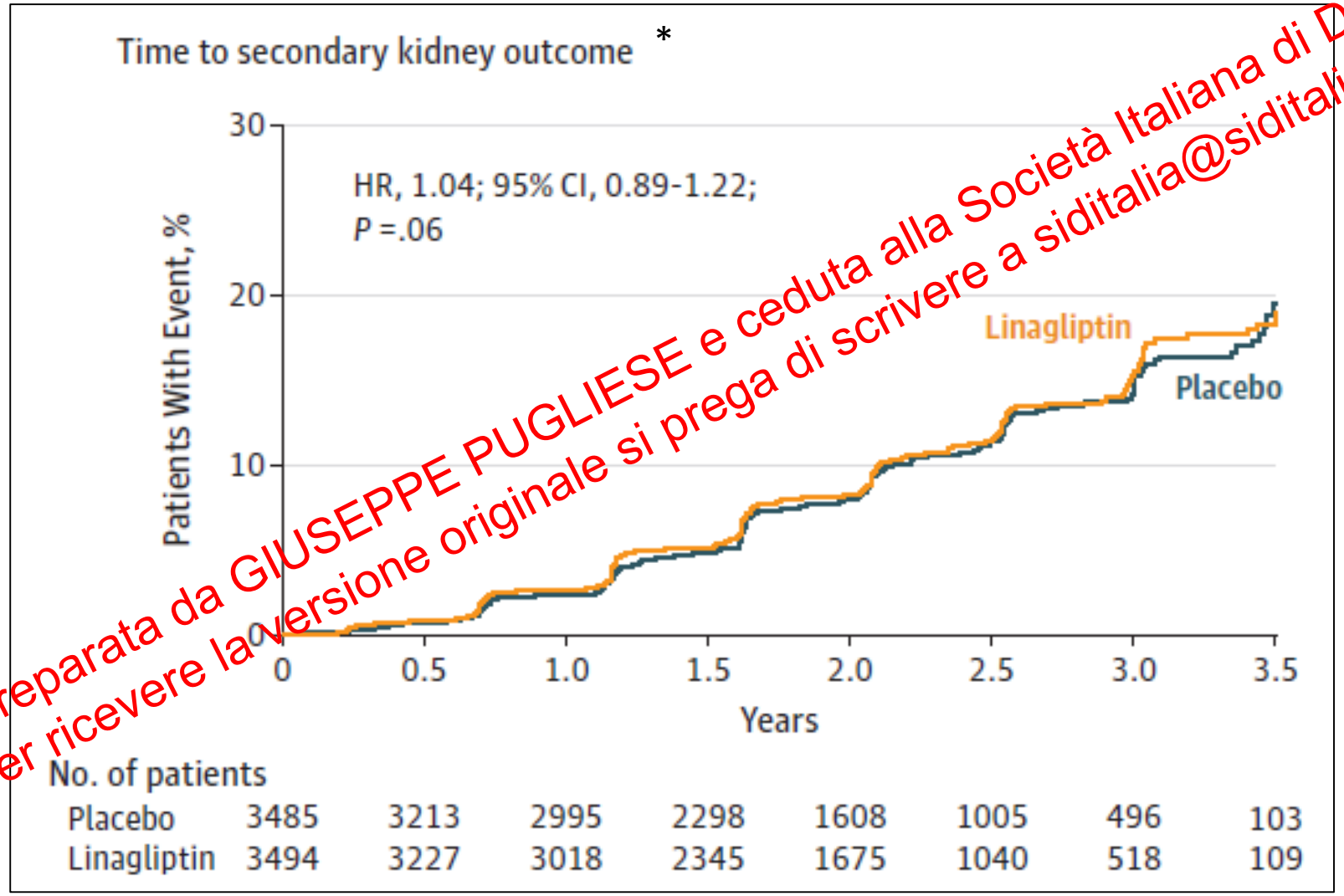
The Trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 study



Mosenzon O et al. Diabetes Care. 2017;40:69–76

Renal outcomes with linagliptin

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) study



* Composite of:
- sustained ESRD
- renal death
- sustained eGFR decline from baseline ≥40%

Rosenstock J et al. JAMA. 2019;321:69–79

Renal outcomes with linagliptin

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) study

Outcomes	Linagliptin (n = 3494)[a] No. (%)	Linagliptin (n = 3494)[a] Rate per 100 Patient-Years	Placebo (n = 3485)[a] No. (%)	Placebo (n = 3485)[a] Rate per 100 Patient-Years	Incidence Rate Difference, Linagliptin – Placebo (95% CI)	Hazard Ratio (95% CI)[b]	P Value
Secondary Kidney Composite Outcome							
Sustained ESRD, death due to kidney failure, or sustained decrease of ≥40% in eGFR from baseline	327 (9.4)	4.89	306 (8.8)	4.66	0.22 (−0.52 to 0.97)	1.04 (0.89-1.22)	.62
ESRD[e]	63 (1.8)		64 (1.8)				
Death due to renal failure[e]	1 (0.03)		1 (0.03)				
Sustained decrease of ≥40% in eGFR[e]	263 (7.5)		241 (6.9)				
Exploratory Kidney and Microvascular Outcomes							
Sustained ESRD, death due to kidney failure, or sustained decrease of ≥50% in eGFR from baseline	230 (6.6)	3.39	227 (6.5)	3.42	−0.03 (−0.65 to 0.60)	0.98 (0.82-1.18)	.87
Death due to renal failure or sustained ESRD	136 (3.9)	1.98	154 (4.4)	2.04	−0.26 (−0.70 to 0.18)	0.87 (0.69-1.10)	.24
Albuminuria progression	763 (35.1)	21.36	819 (38.5)	24.54	−3.18 (−5.44 to −0.92)	0.86 (0.78-0.95)	.003
Composite microvascular end point[f]	785 (36.3)	22.14	843 (39.6)	25.42	−3.28 (−5.59 to −0.97)	0.86 (0.78-0.95)	.003
Composite ocular end point[g]	36 (1.0)	0.47	49 (1.4)	0.65	−0.18 (−0.41 to 0.01)	0.73 (0.47-1.12)	.15

Microvascular end point: composite of:

- ESRD
- renal death
- sustained eGFR decline from baseline ≥50%
- albuminuria progression
- retinal photocoagulation
- anti–vascular endothelial growth factor injection therapy
- vitreous hemorrhage
- diabetes-related blindness

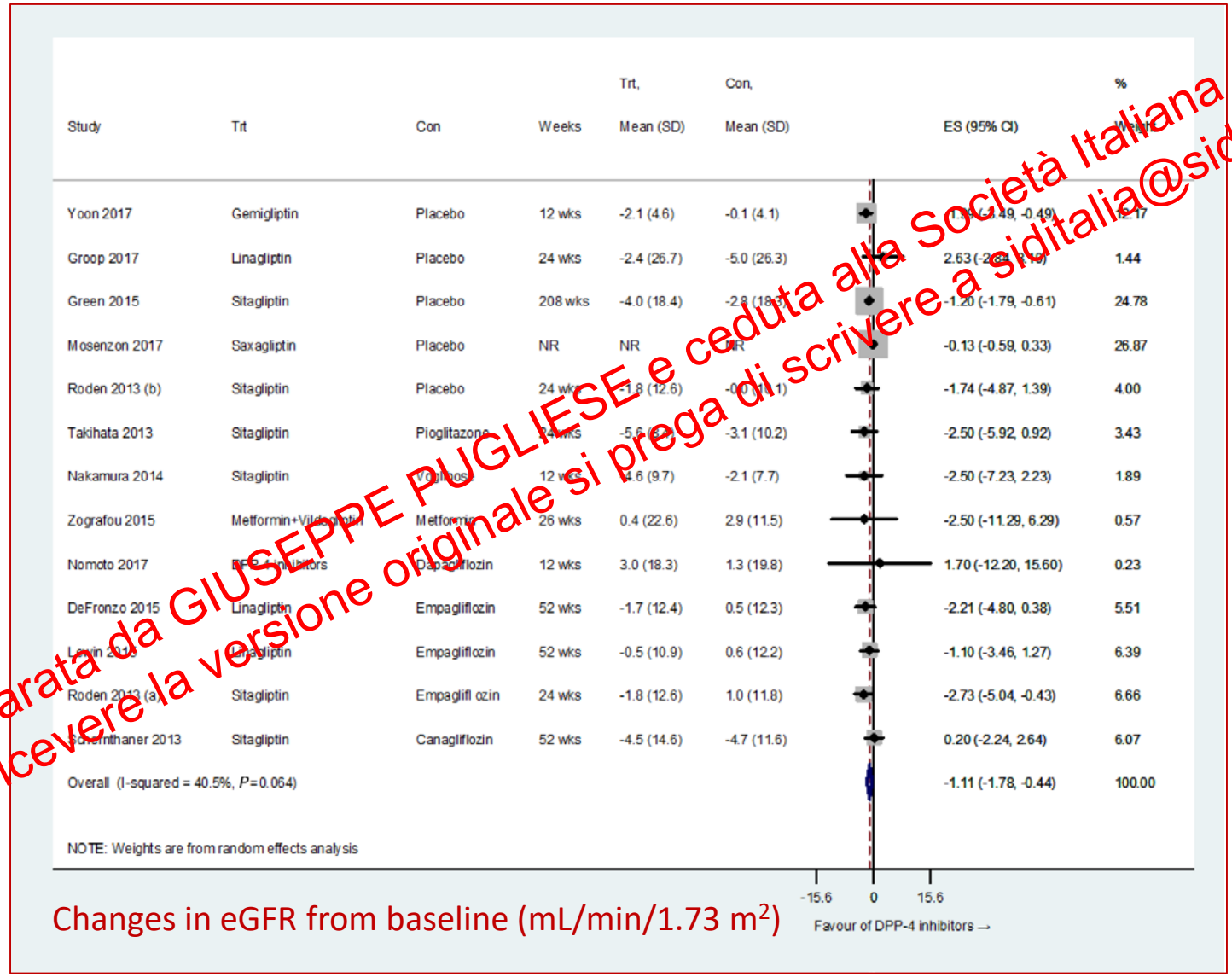
Ocular end point: composite of:

- retinal photocoagulation
- anti–vascular endothelial growth factor injection therapy
- vitreous hemorrhage
- diabetes-related blindness

Rosenstock J et al. JAMA. 2019;321:69–79

Renal outcomes with DPP-4 inhibitors

Meta-analysis of Randomized Clinical Trials with DPP-4 inhibitors

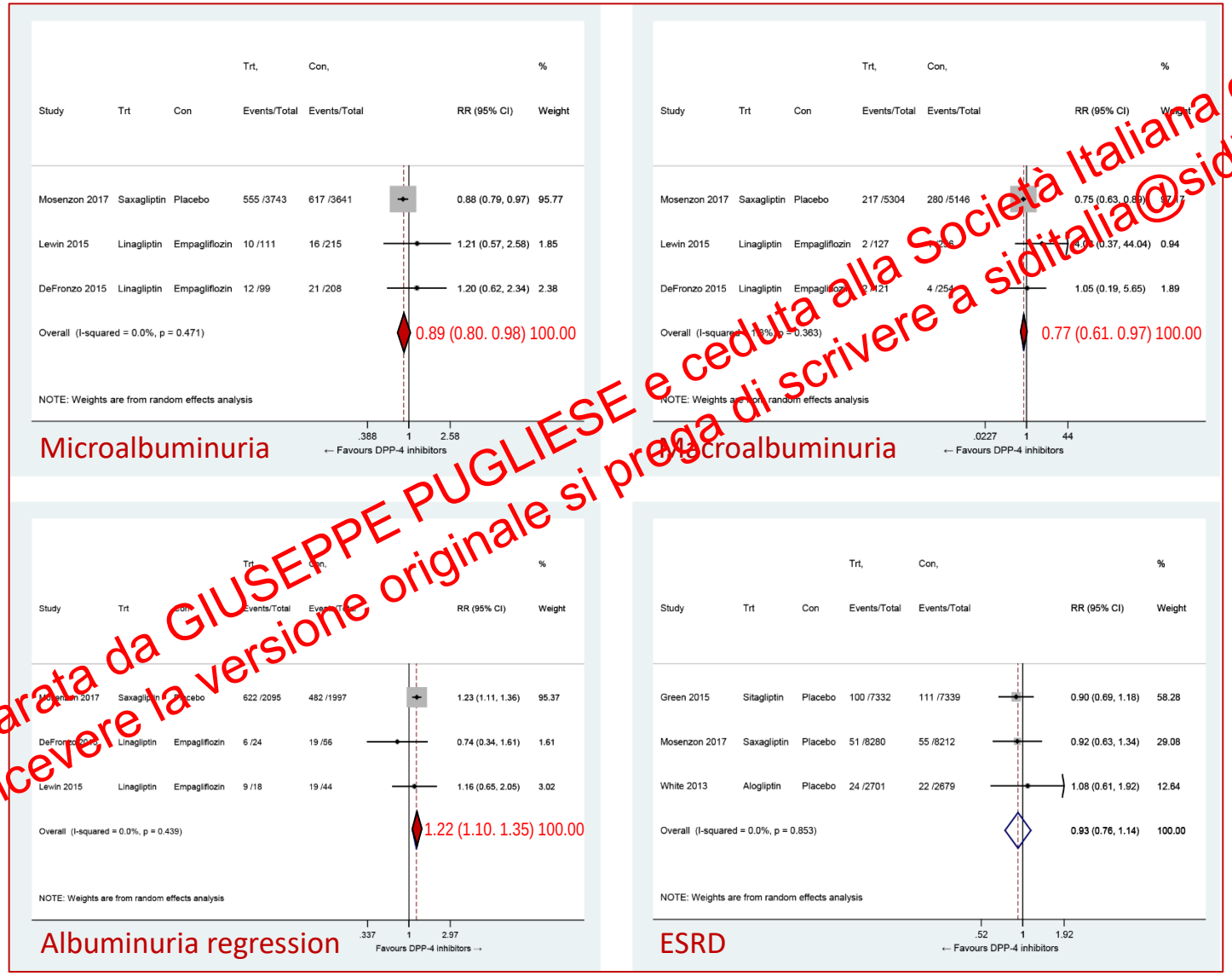


Changes in eGFR from baseline (mL/min/1.73 m^2)

Bae JH et al. Endocrinol Metab. 2019;34:80–92

Renal outcomes with DPP-4 inhibitors

Meta-analysis of Randomized Clinical Trials with DPP-4 inhibitors

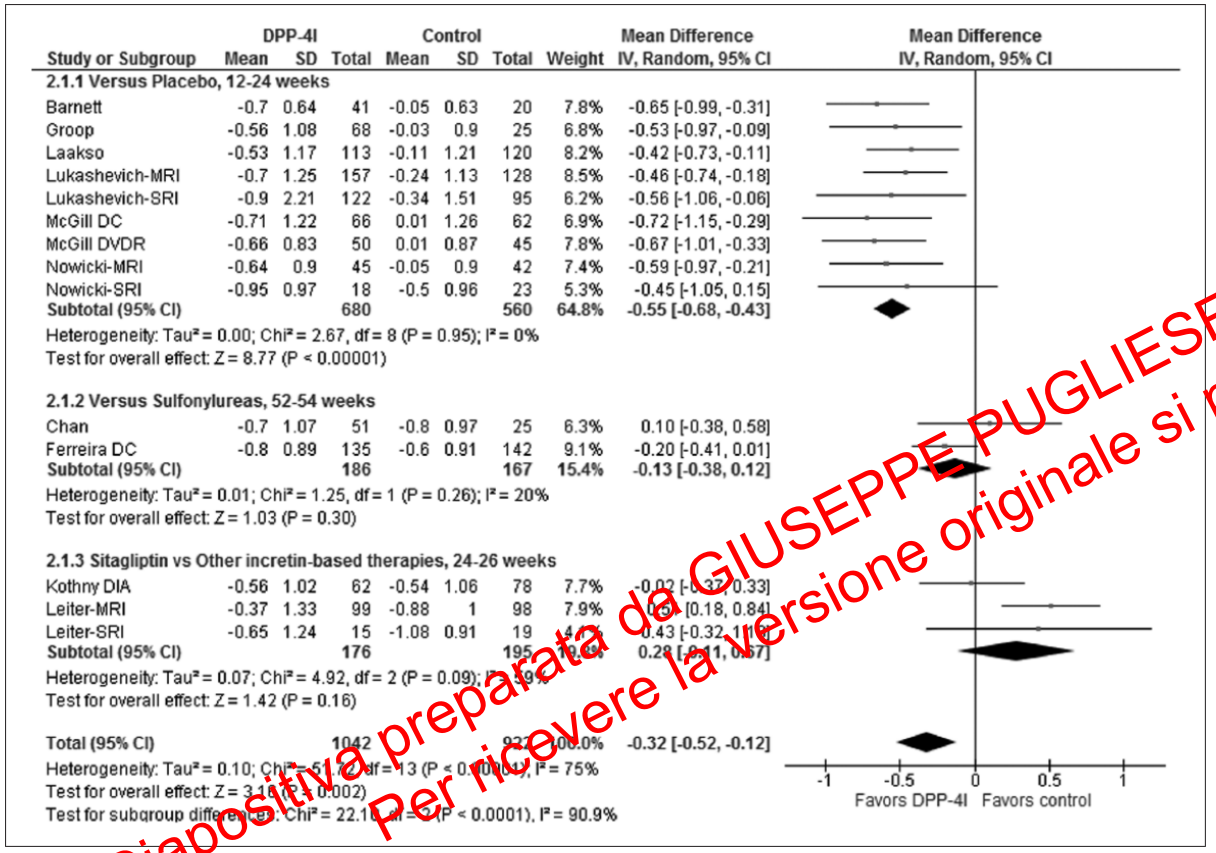


Bae JH et al. Endocrinol Metab. 2019;34:80–92

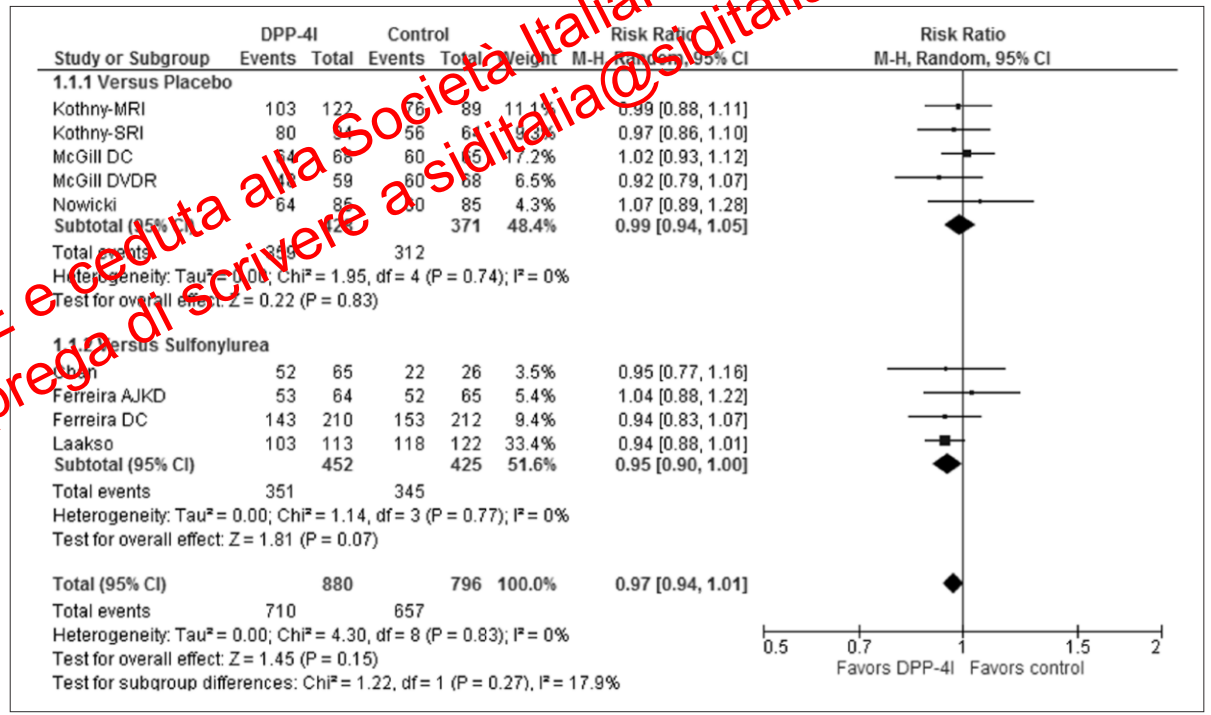
Treatment with DPP-4 inhibitors in CKD

Meta-analysis of studies with DPP-4 inhibitors in patients with type 2 diabetes with moderate to severe CKD

Change in HbA_{1c}



Adverse events



Singh-Franco D et al. SAGE Open Med. 2016;4:2050312116659090

Treatment with DPP-4 inhibitors in ESRD

Retrospective study reviewed in patients with type 2 diabetes on renal replacement therapy

Hemodialysis

	Sitagliptin (n = 31)			Vildagliptin (n = 37)			Linagliptin (n = 47)		
Parameter	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***
FPG, mg/dL	175.6 ± 75.1	143.2 ± 59.8	0.021	169.3 ± 77.4	158.2 ± 78.5	0.464	143.7 ± 62.6	136.3 ± 50.7	0.304
Δ FPG	−32.4 ± 72.7			−11.1 ± 90.3			−7.4 ± 48.2		0.261
HbA1c, %	7.38 ± 1.50	6.98 ± 1.31	0.220	7.36 ± 1.84	7.04 ± 1.42	0.340	6.99 ± 1.40	6.87 ± 1.25	0.621
Δ HbA1c	−0.40 ± 1.65			−0.31 ± 1.82			−0.12 ± 1.54		0.773
TC, mg/dL	146.5 ± 30.6	140.6 ± 36.4	0.411	161.4 ± 62.8	148.9 ± 32.8	0.105	145.2 ± 51.4	145.3 ± 38.9	0.987
Δ TC	−5.9 ± 38.0			−16.4 ± 59.3			0.1 ± 43.7		0.300

Data are presented as mean ± standard deviation. Paired *t*-test (white box) and 1-way ANOVA (gray shades) were performed.
Δ = change between the level of baseline and the level of 12 weeks for the given parameter, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, TC = total cholesterol.

Peritoneal dialysis

	Sitagliptin (n = 13)			Vildagliptin (n = 35)			Linagliptin (n = 37)		
Parameter	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***
FPG, mg/dL	169.6 ± 51.8	146.8 ± 44.8	0.235	180.6 ± 79.3	154.3 ± 53. 7	0.040	163.0 ± 65.0	144.1 ± 65.4	0.003
Δ FPG	−22.8 ± 62.7			−26.3 ± 71.5			−18.9 ± 35.9		0.861
HbA1c, %	6.41 ± 1.46	6.89 ± 0.99	<0.001	7.07 ± 1.48	6.61 ± 1.25	0.011	7.20 ± 1.38	7.16 ± 1.39	0.852
Δ HbA1c	−1.58 ± 0.95			−0.46 ± 0.98			−0.04 ± 1.22		0.001
TC, mg/dL	165.6 ± 28.9	165.0 ± 48.6	0.459	137.6 ± 36.3	145.1 ± 51.3	0.280	171.7 ± 62.1	158.0 ± 41.3	0.103
Δ TC	9.5 ± 40.7			7.5 ± 39.8			−13.7 ± 49.1		0.097

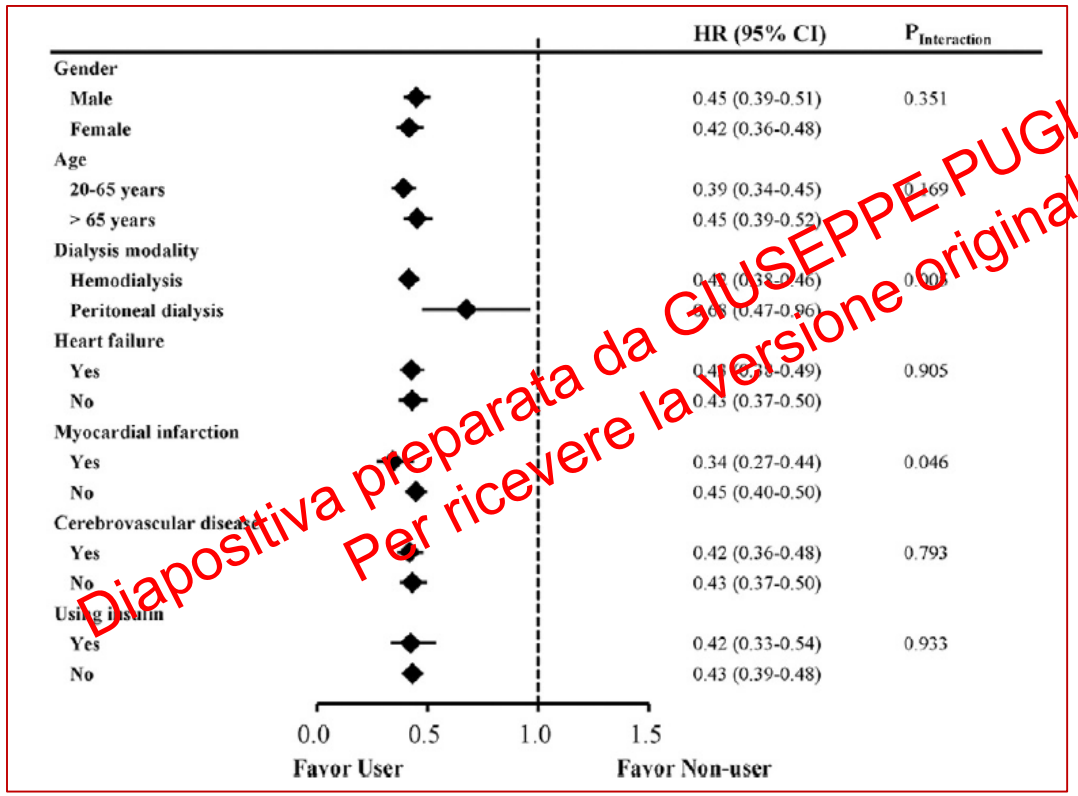
Data are presented as mean ± standard deviation. Paired *t* test (white box) and 1-way ANOVA (gray shades) were performed.
Δ = change between the level of baseline and the level of 12 weeks for the given parameter, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, TC = total cholesterol.

Park SH et al. Medicine. 2016;95:32(e4543)

Treatment with DPP-4 inhibitors in ESRD

Nationwide observational study in patients with type 2 diabetes on renal replacement therapy

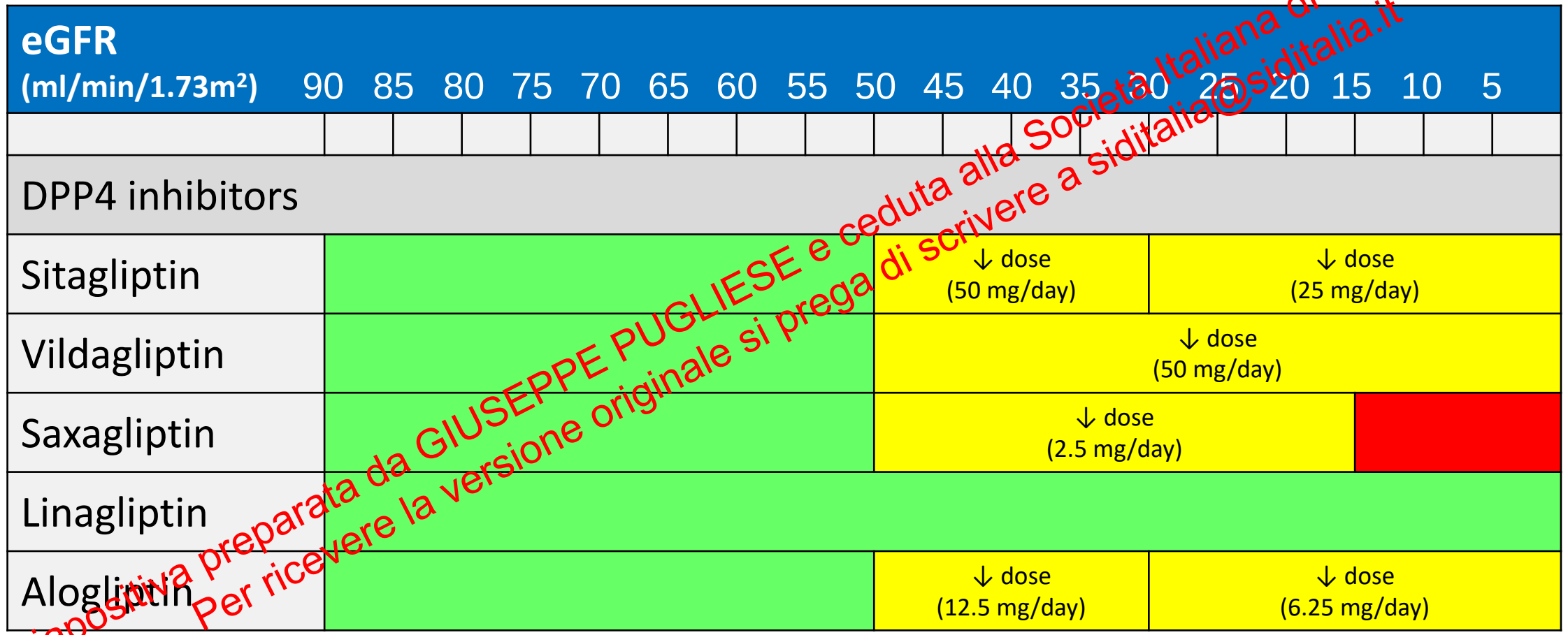
	DPP-4 inhibitor user			DPP-4 inhibitor non-user			Crude	
	No. of events	Person-Years	Incidence rate*	No. of events	Person-Years	Incidence rate*	Hazard ratio (95% CI)	*P*
All-cause mortality	629	6228	100.99	1110	4501	246.60	0.43 (0.39–0.47)	<0.001
MACEs †	298	5980	49.83	291	4335	67.12	0.76 (0.65–0.90)	0.001
Myocardial infarction	167	6094	27.40	155	4416	35.10	0.81 (0.65–1.01)	0.059
Ischemic stroke	149	6103	24.41	143	4419	32.36	0.77 (0.61–0.97)	0.024
Heart failure	110	5987	18.37	72	4343	16.58	1.14 (0.85–1.54)	0.389
Hypoglycemia	200	5991	33.39	163	4373	37.28	0.95 (0.77–1.17)	0.617



Chan SY et al. Int J Cardiol. 2016;218:170–175

Therapeutic algorithm for adults with type 2 diabetes and impaired GFR

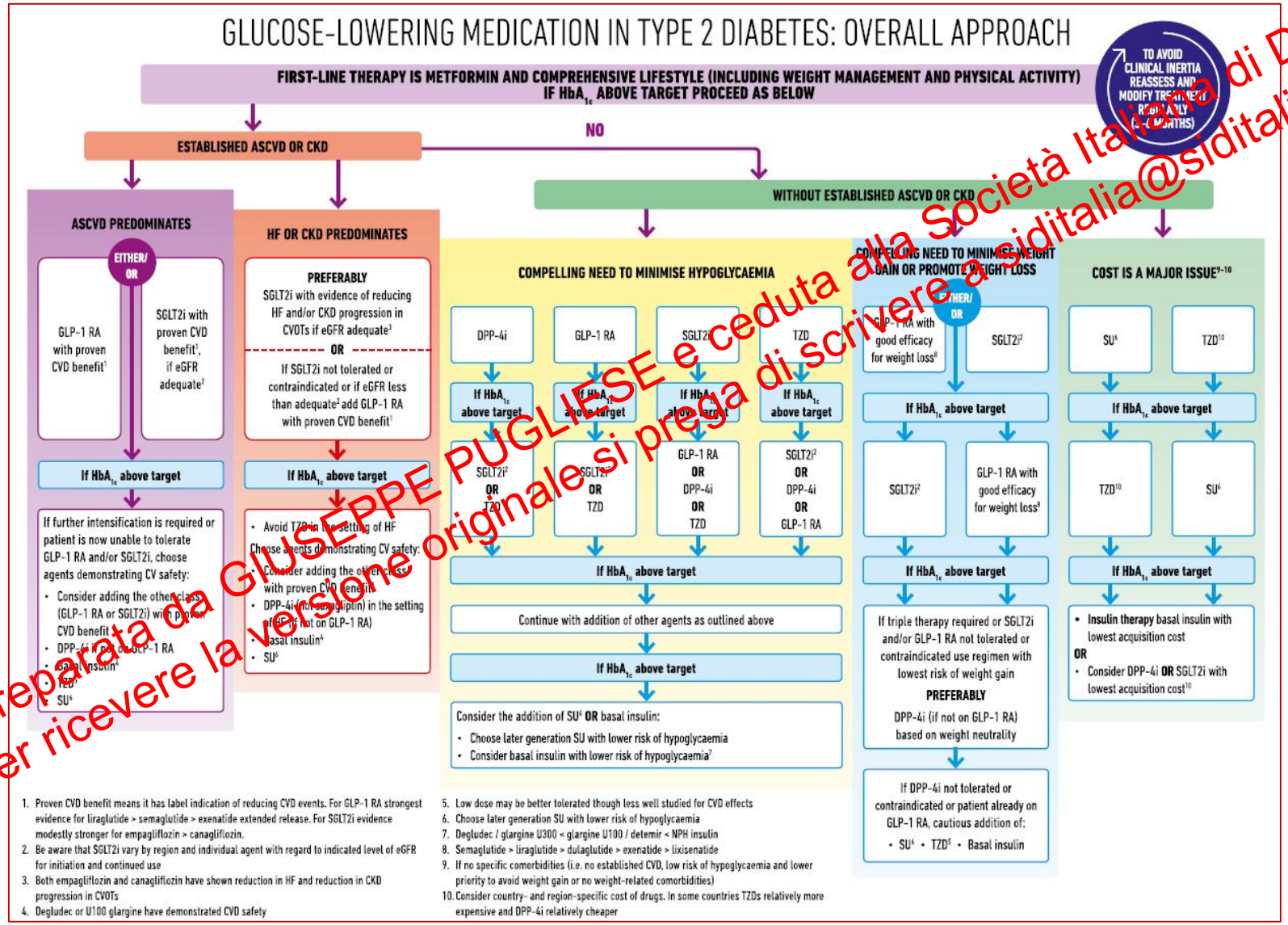
Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology



Pugliese G et al. Nutr Metab Cardiovasc Dis. 2019; 29:1127–1150

Therapeutic algorithm for adults with type 2 diabetes

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



Davies MJ et al. Diabetologia. 2018;61:2461–2498

Conclusions

Cardiovascular safety
(↑ risk for heart failure with saxagliptin)

DPP-4 inhibitors

Renal safety
(↓ albuminuria, whole eGFR range)

No hypoglycemia
Weight neutral
Safe risk profile