SID Società Italiana di Diabetologia

ROMA | 29 OTTOBRE 2019

Terapia con analoghi del GLP-1: quando e perché

Possiamo puntare ancora di più sulla protezione renale?

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Disclosures

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

- ✓ Partecipazioni a Congressi: Astra-Zeneca, Laboratori Guidotti, Sanofi-Aventis, Takeda;
- ✓ Relazioni/moderazioni/partecipazioni a board retribuite: Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, MundiPharma, Novartis, Novo Nordisk, Sigma-Tau, Takeda.

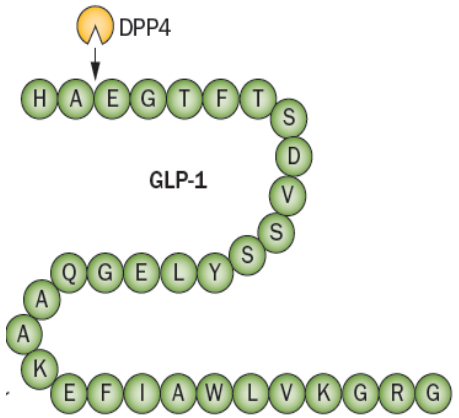
Dichiaro altresì il mio impegno ad astenermi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

In fede

Giuseppe Pugliese

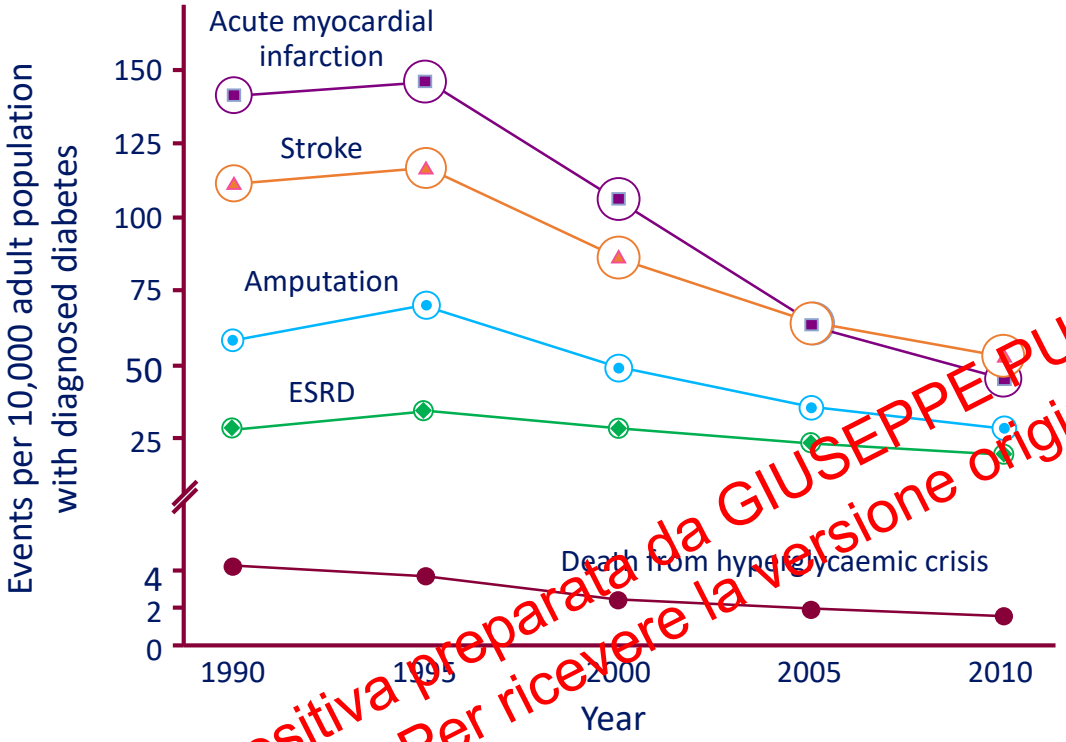
Agenda

- Unmet needs in diabetic kidney disease (DKD)
- Glucagon-like peptide 1 receptor agonists (GLP-1 RAs)
- Renal protection with GLP-1 RAs
- Renal protection with GLP-1 RAs vs SGLT2-Is



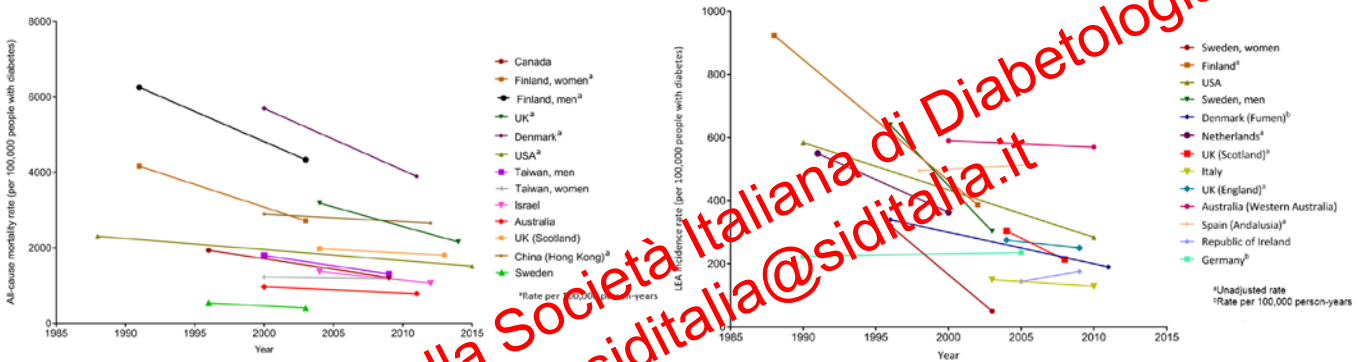
Trends in diabetic complications in type 2 diabetes

The National Health Interview Survey, National Hospital Discharge Survey, U.S. Renal Data System, and U.S. National Vital Statistics System

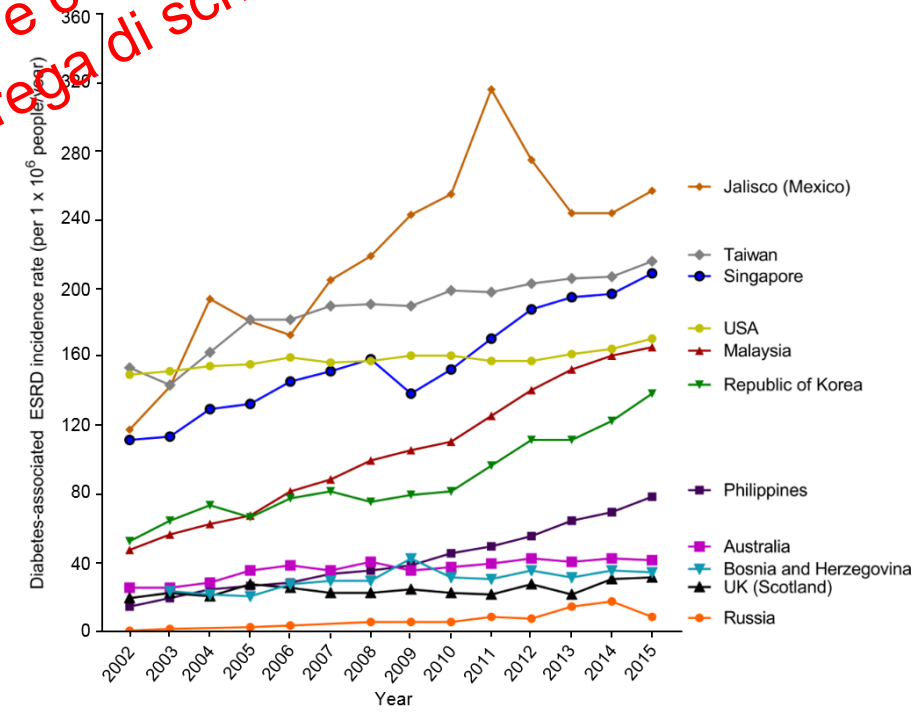


Trends in age-standardized rates of diabetes-related complications among US adults with diagnosed diabetes, 1990–2010

Gregg EW et al. N Engl J Med. 2014;370:1514-1523



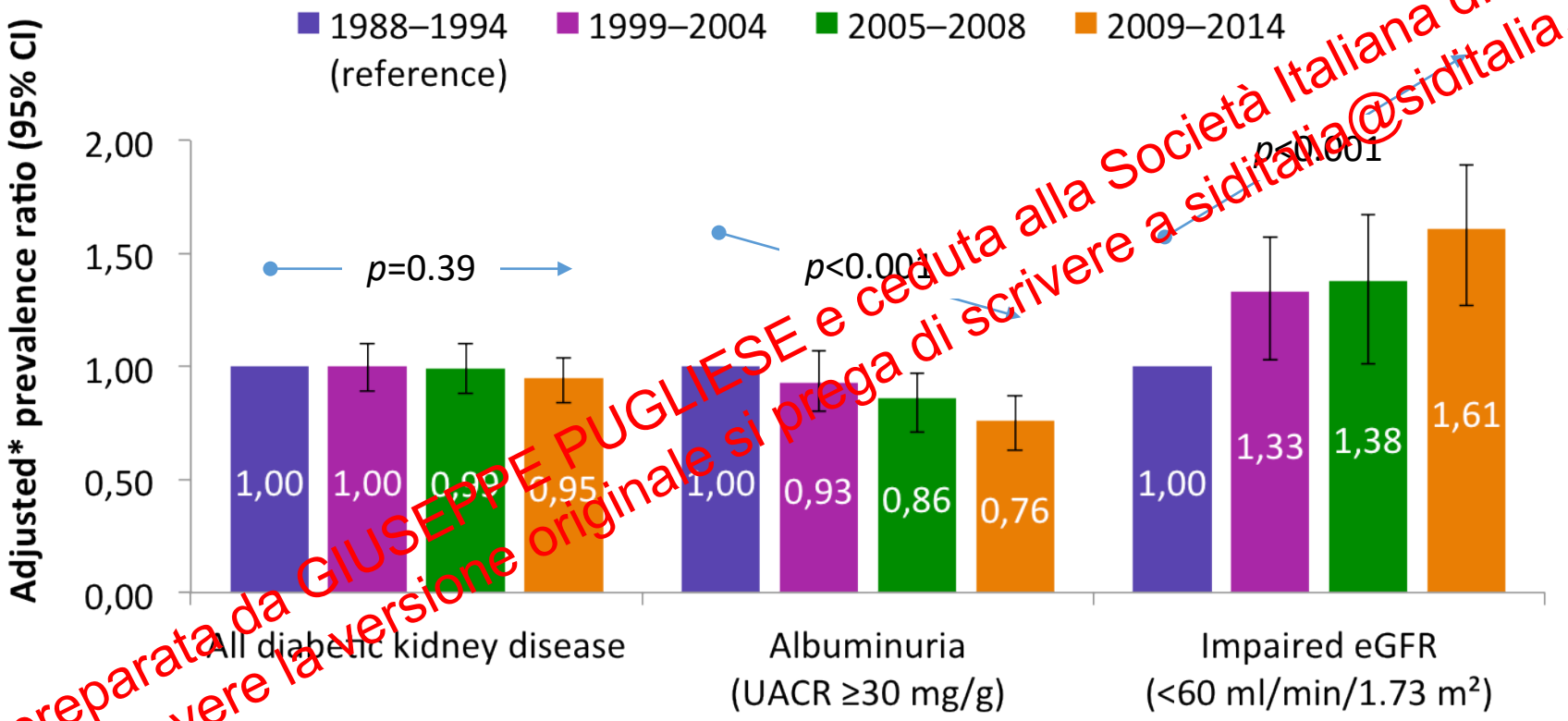
The United States Renal Data System (USRDS)



Harding JL et al. Diabetologia. 2019;62:3–16

Trends in DKD in type 2 diabetes

The National Health and Nutrition Examination Survey (NHANES) 1988-2014



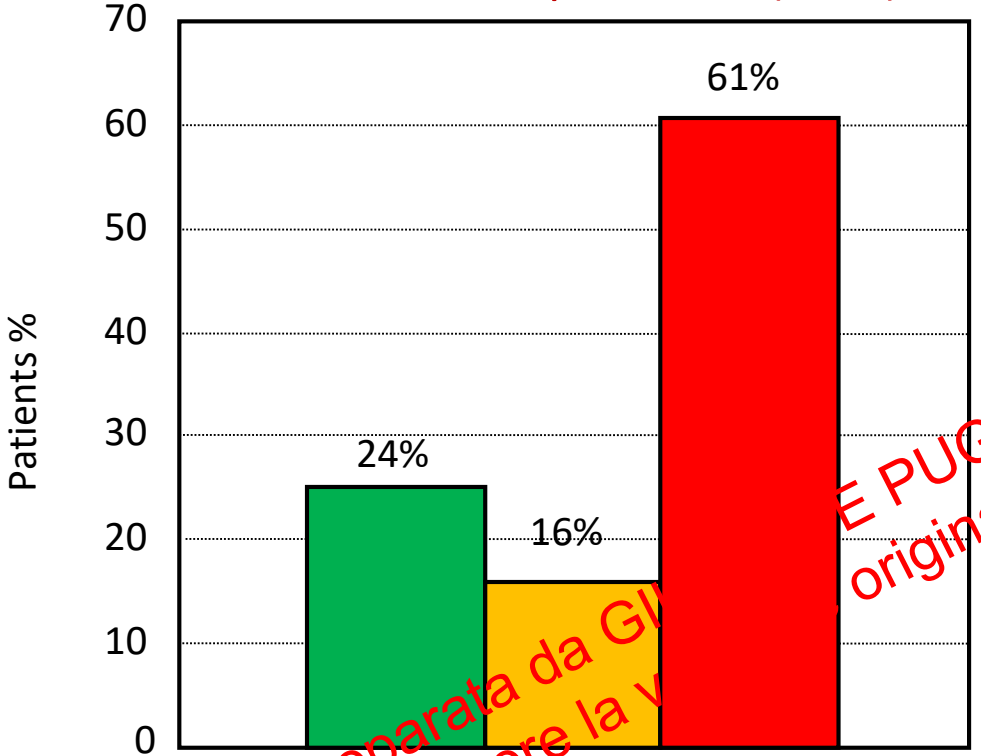
*Adjusted for age, sex, and race/ethnicity. p-values are for trend

Prevalent cases of CKD in the US accounting for persistence

Afkarian M et al. JAMA. 2016;316:602-610

Nonalbuminuric renal impairment

The Diabetes Control and Complications Trial (DCCT) / Epidemiology of Diabetes Interventions and Complications (EDIC)

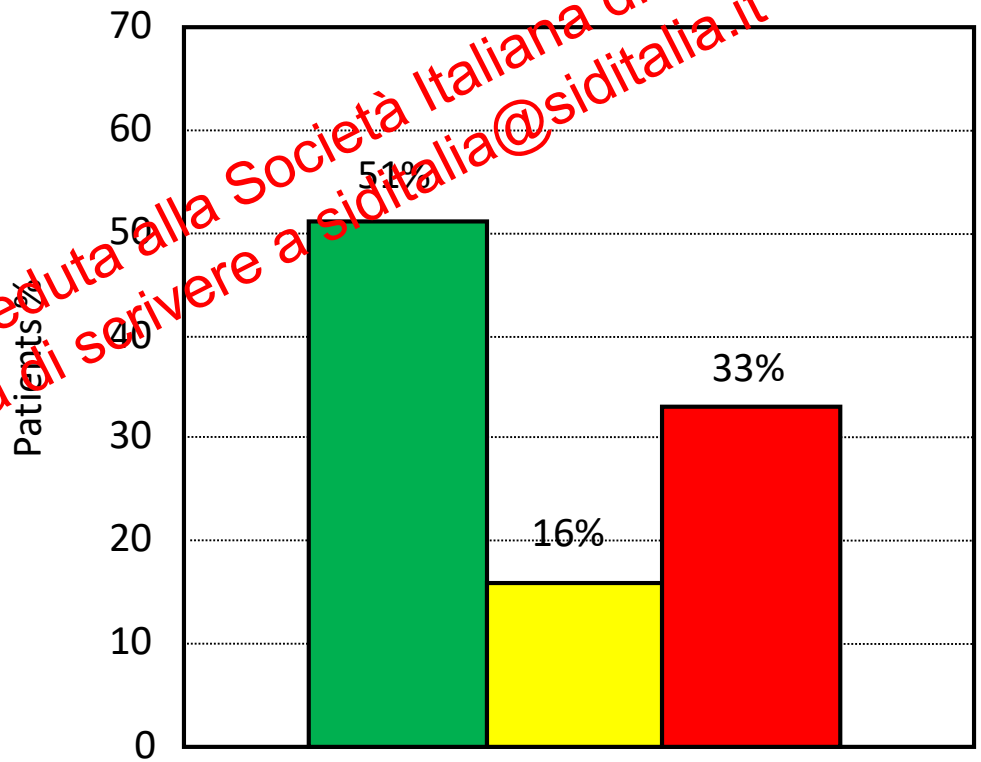


1,439 patients with T1DM, median follow-up 19 years
89 (6.2%) with an eGFR <60 ml/min/1.73 m^2

- Normalbuminuria
- Microalbuminuria
- Macroalbuminuria

Molitch ME et al. Diabetes Care. 2010;33:1536-1543

The United Kingdom Prospective Diabetes Study (UKPDS)



4,006 patients with T2DM, median follow-up 15 years
1,132 (28%) with an eGFR <60 ml/min/1.73 m^2

- No albuminuria
- Albuminuria after eGFR reduction
- Albuminuria before eGFR reduction

Retnakaran R et al. Diabetes. 2006;55:1832-1839

Progressive renal decline

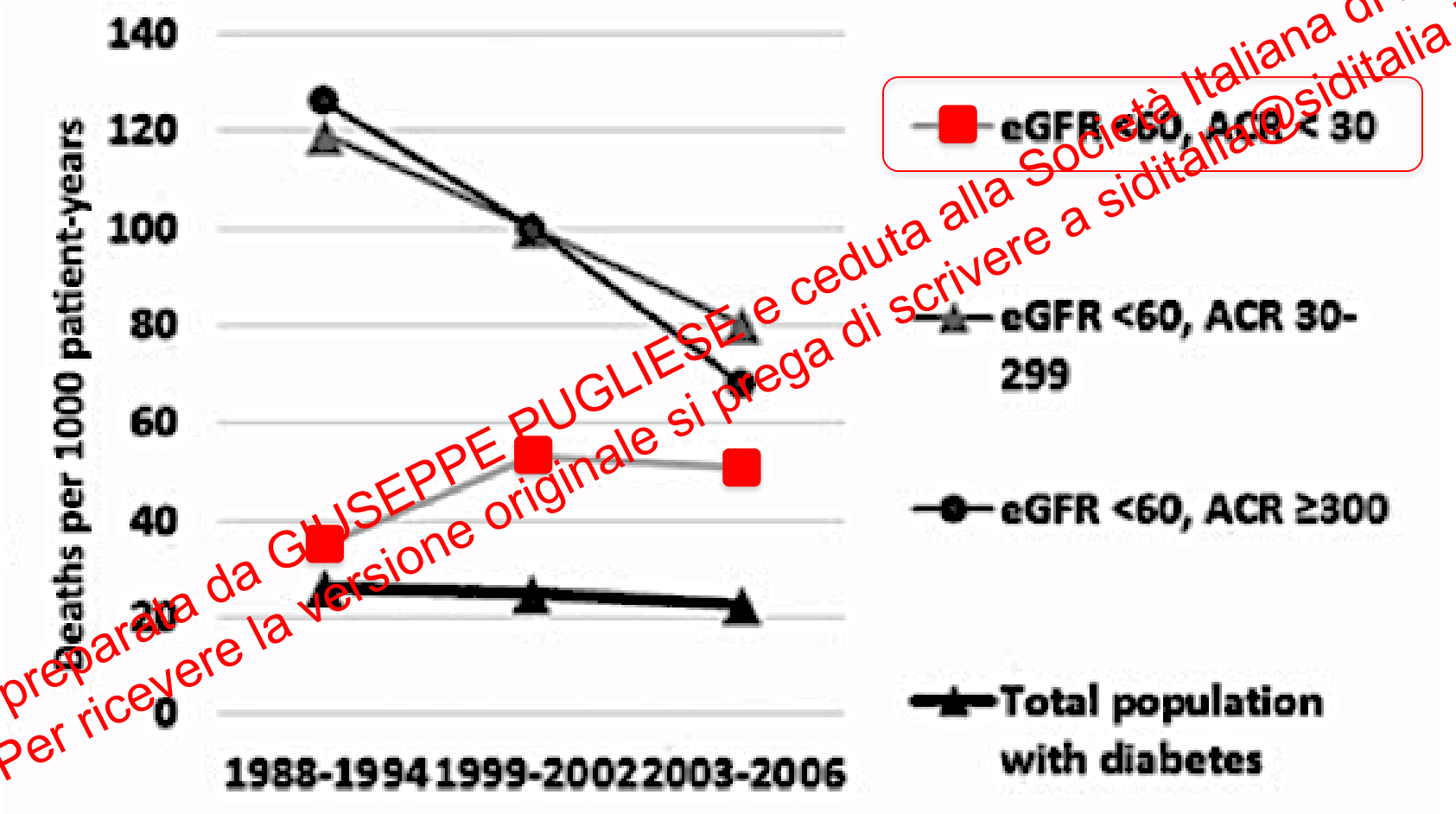
The Joslin Diabetes Study

eGFR decline ml/min/year	Normoalbuminuria % (n)	Microalbuminuria % (n)	Macroalbuminuria % (n)	Total % (n)
T1D				
<2.9	91	78	49	81
3-4.9	6	11	16	8
5-9.9	2	7	19	7
≥10	1	4	16	4
Total	100 (933)	100 (525)	100 (275)	100 (1,732)
T2D				
<2.9	80	67	32	72
3-4.9	13	18	17	15
5-9.9	6	12	30	10
≥10	1	3	21	3
Total	100 (681)	100 (418)	100 (82)	100 (1,181)

Krolewski AS et al. Kidney Int. 2017;91:1300–1311

Trends in mortality by DKD phenotype in type 2 diabetes

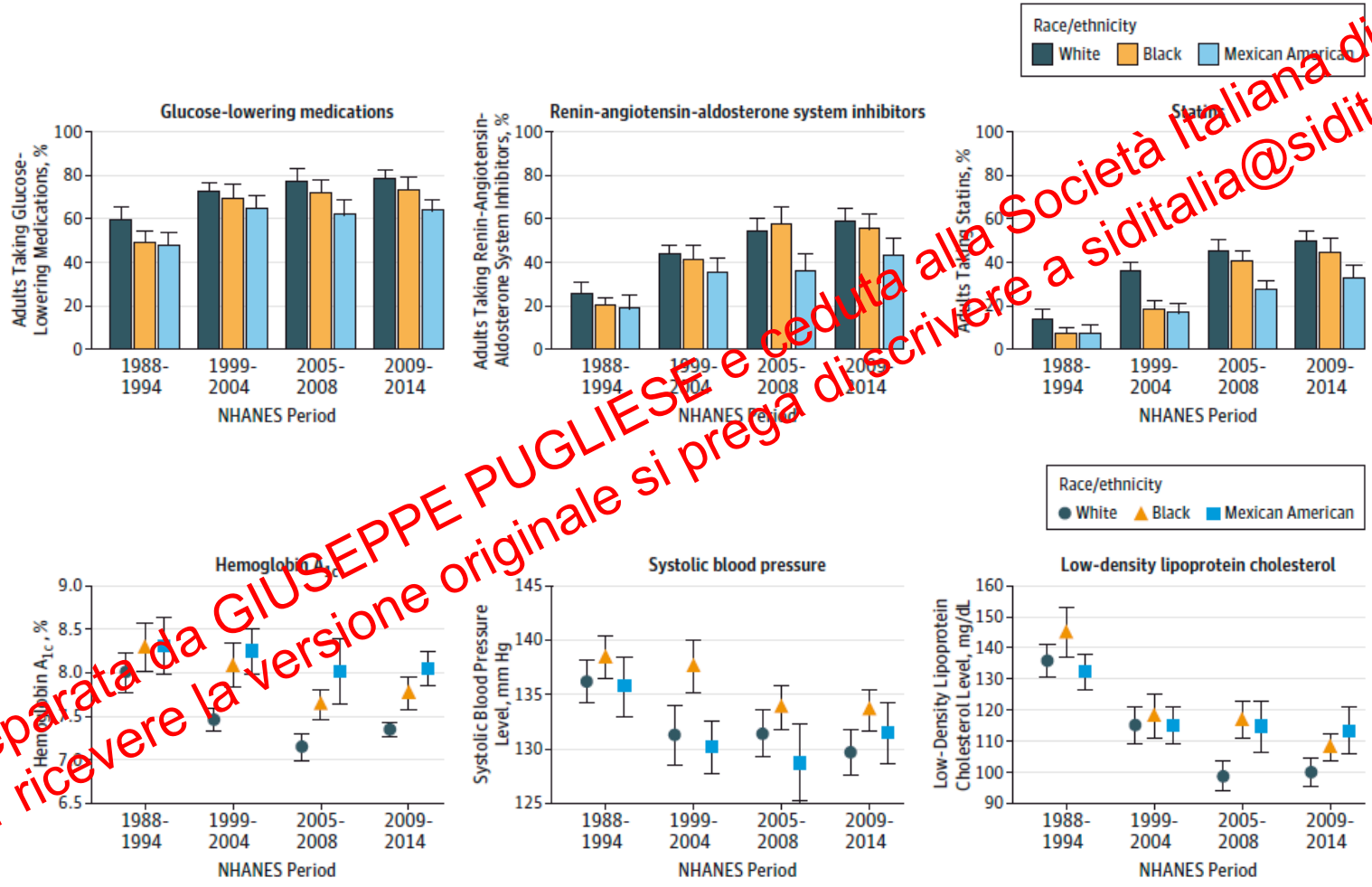
The National Health and Nutrition Examination Survey (NHANES) 1988-2006



Kramer H et al. Diabetes Care. 2018;41:775-781

Trends in the management of type 2 diabetes

The National Health and Nutrition Examination Survey (NHANES) 1988-2014

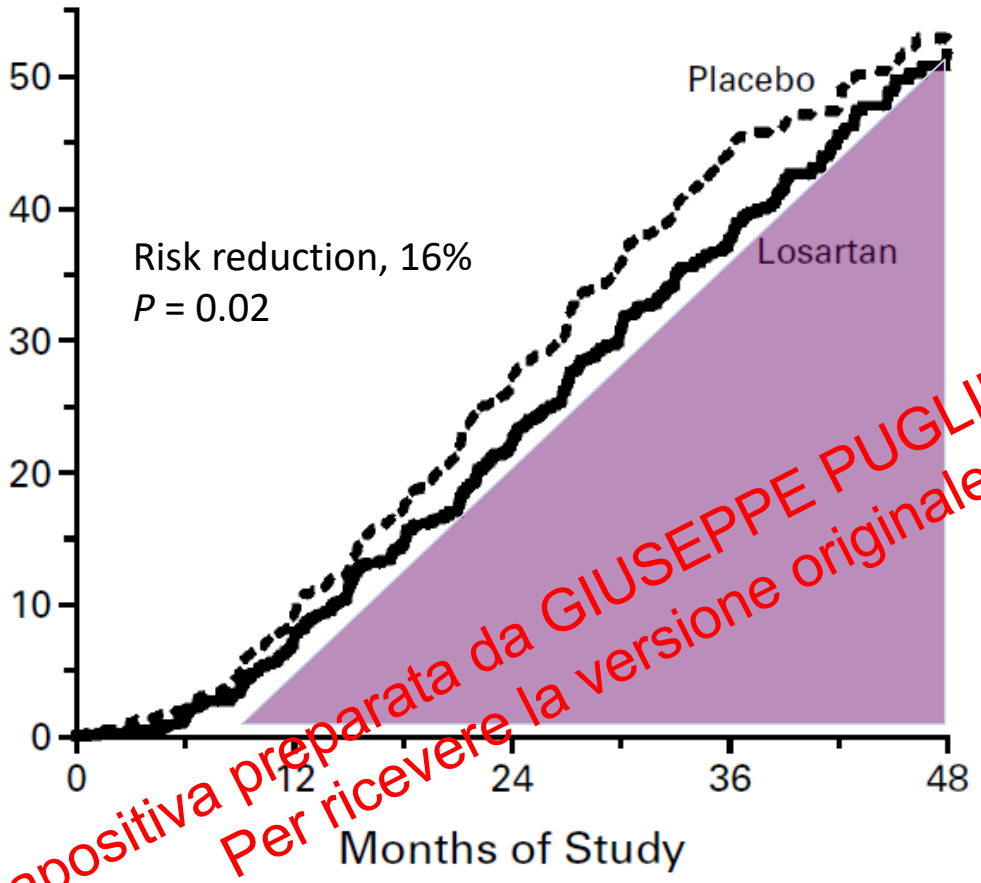


Medication use and clinical targets

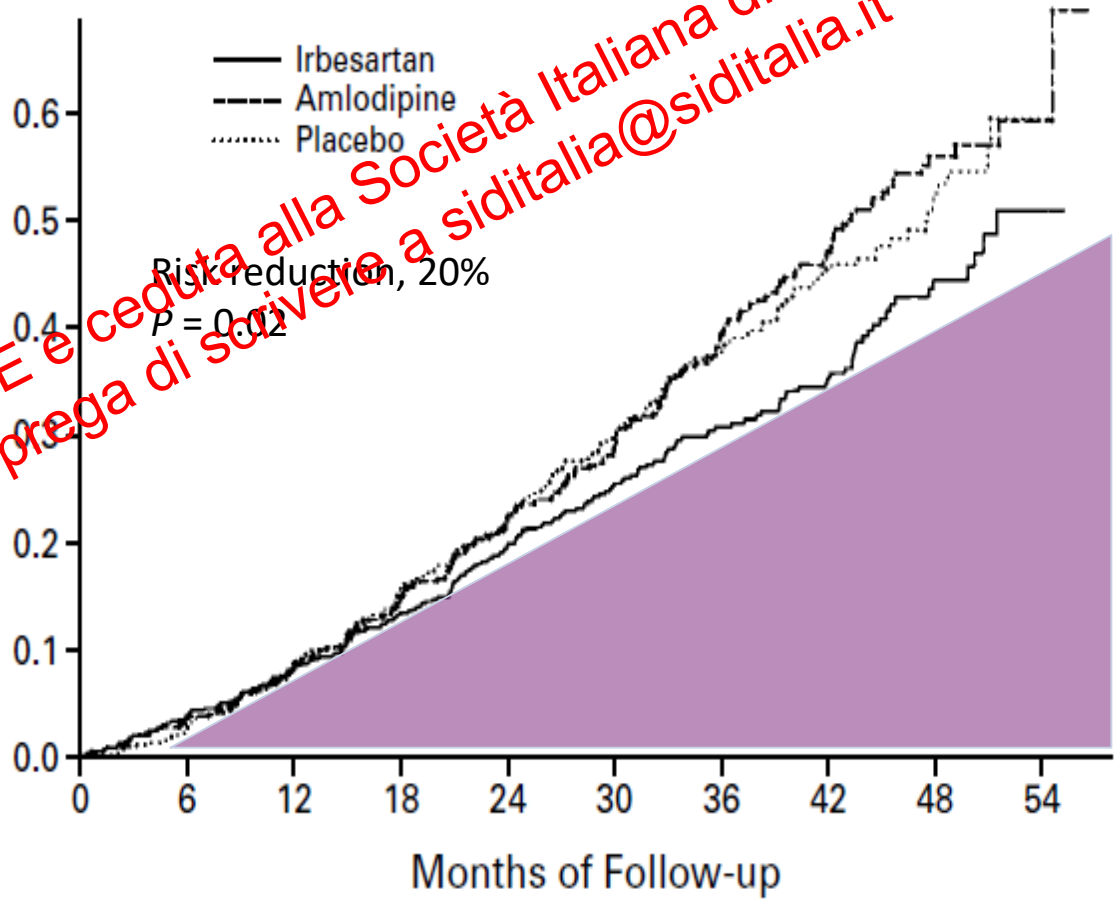
Afkarian M et al. JAMA. 2016;316:602-610

Renal protection with RAS blockers

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study



The Irbesartan Diabetic Nephropathy Trial (IDNT)



Renal composite
(doubling of serum
creatinine, ESKD, or death)

Brenner B et al. N Engl J Med. 2001;345:861-869

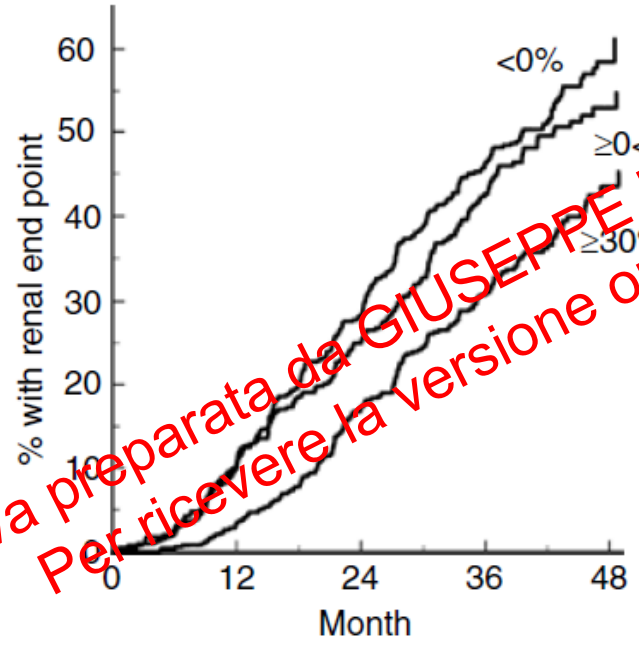
Lewis EJ et al. N Eng J Med. 2001;345:851-860

Renal protection with RAS blockers

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study

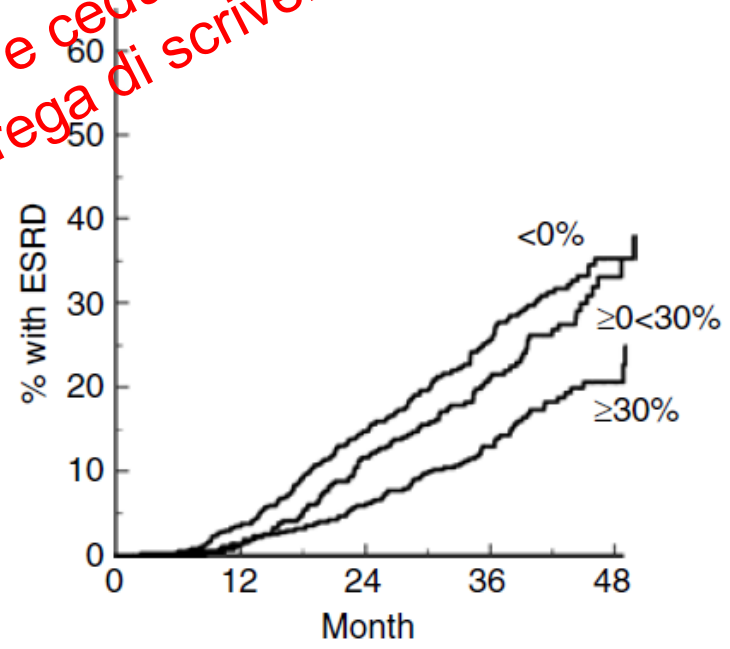
Renal end point

	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.88	0.1570	0.76	0.0028
Δ Alb: ≥30 vs. <0%	0.60	<.0001	0.46	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.68	0.0003	0.61	<.0001



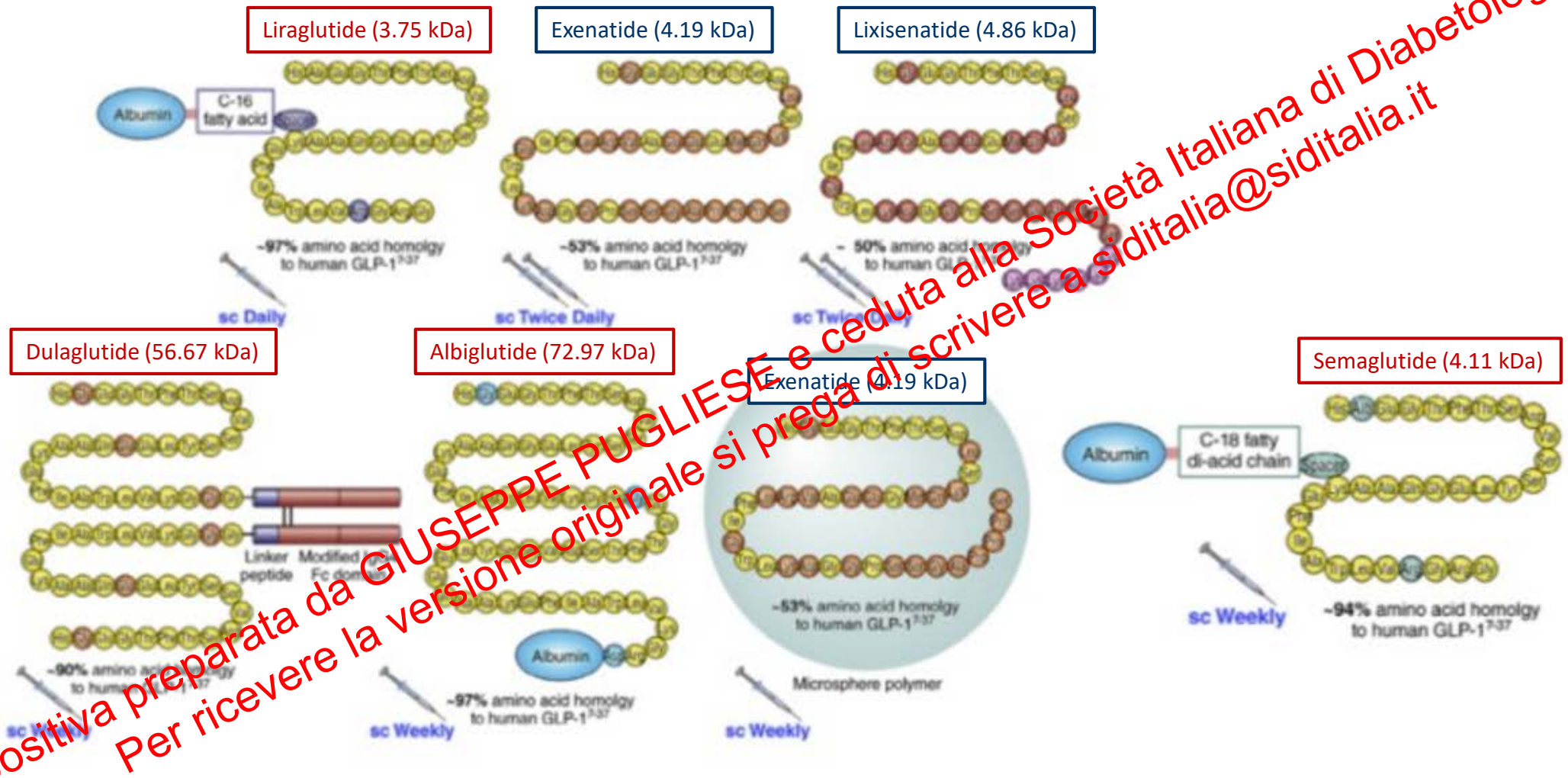
ESRD

	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.82	0.1242	0.62	<.0003
Δ Alb: ≥30 vs. <0%	0.5	<.0001	0.37	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.62	0.0019	0.60	0.0010



De Zeeuw D et al. Kidney Int. 2004;65:2309–2320

Currently available GLP-1 RAs



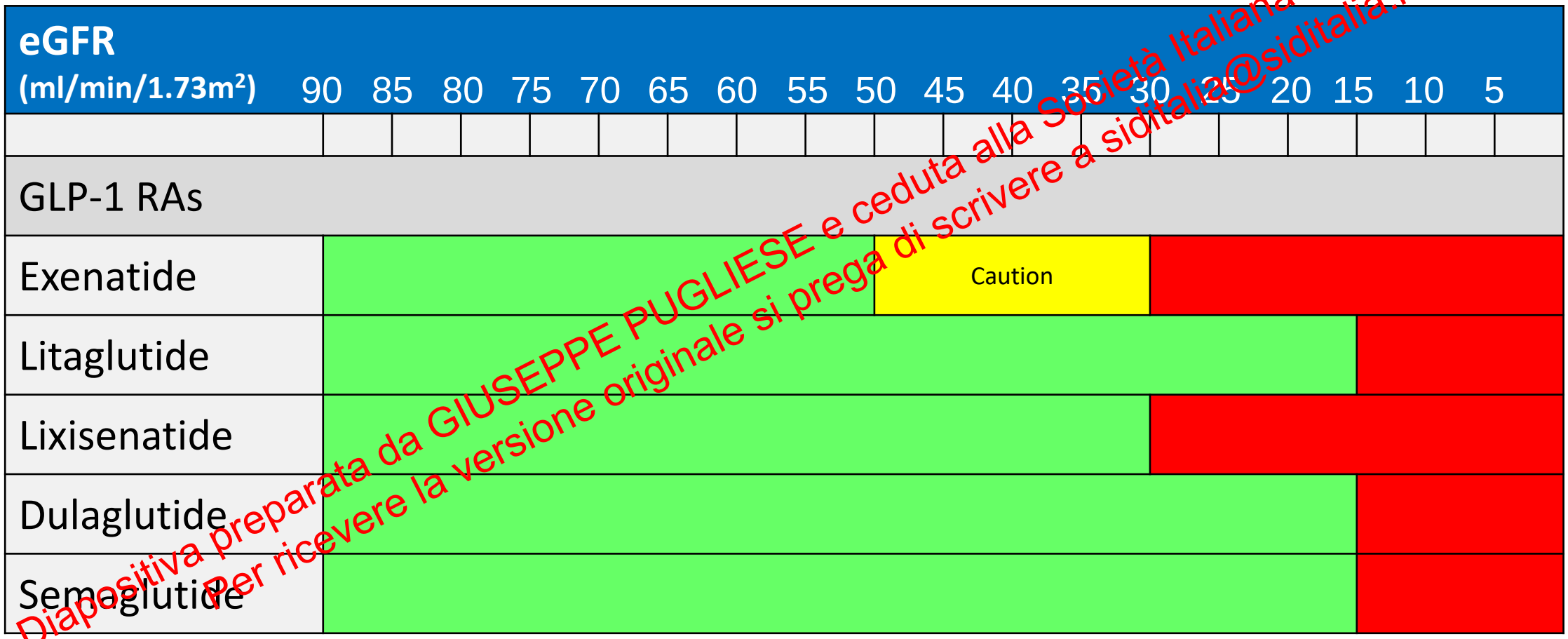
Human GLP-1 backbone

Exendin-4 backbone

Feingold KR. Endotext. 2019 July 8

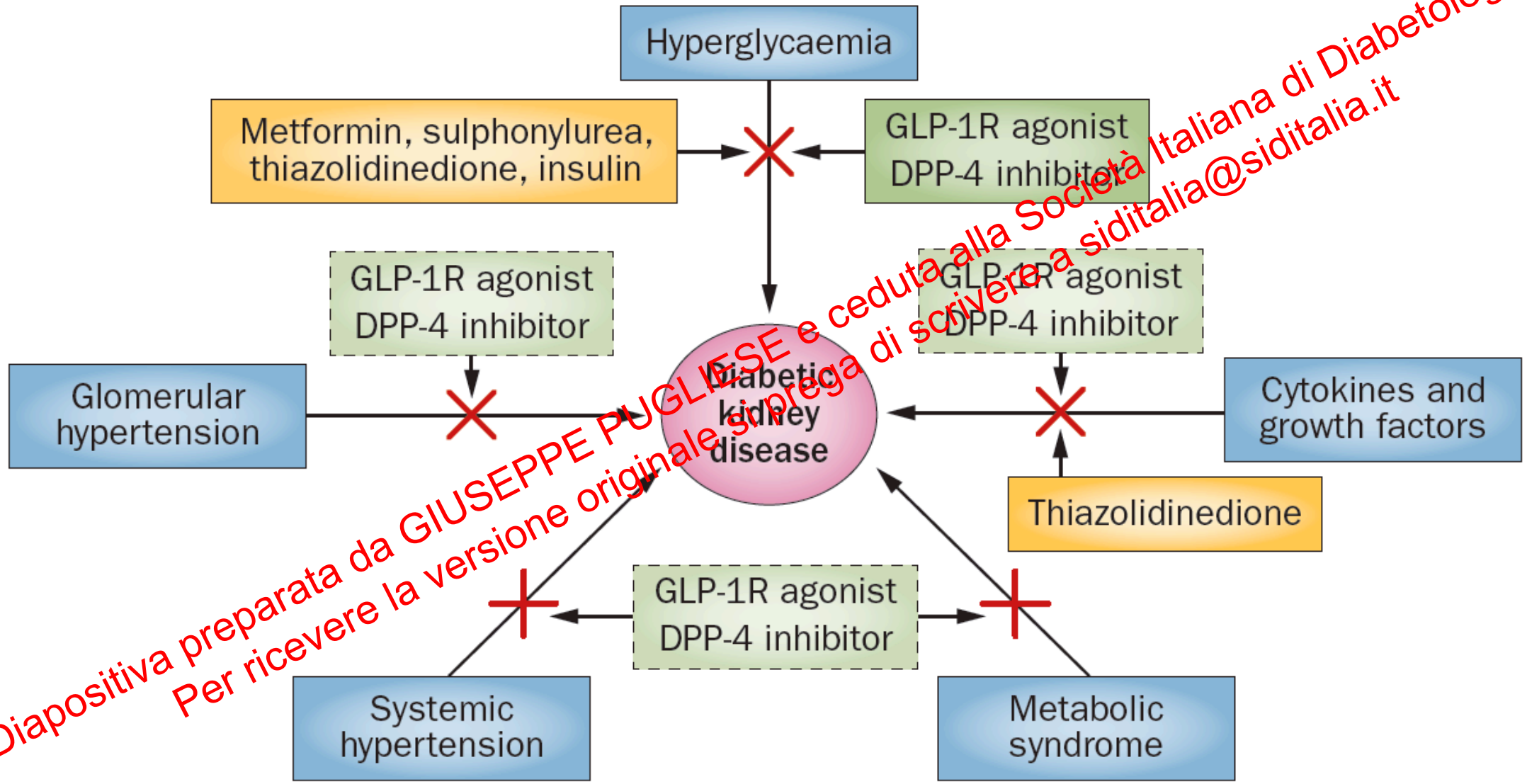
Treatment with GLP-1 RAs according to renal function

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



Pugliese G et al. Nutr Metab Cardiovasc Dis. 2019 Sep 25

Mechanisms of renal protection with GLP-1 RAs



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

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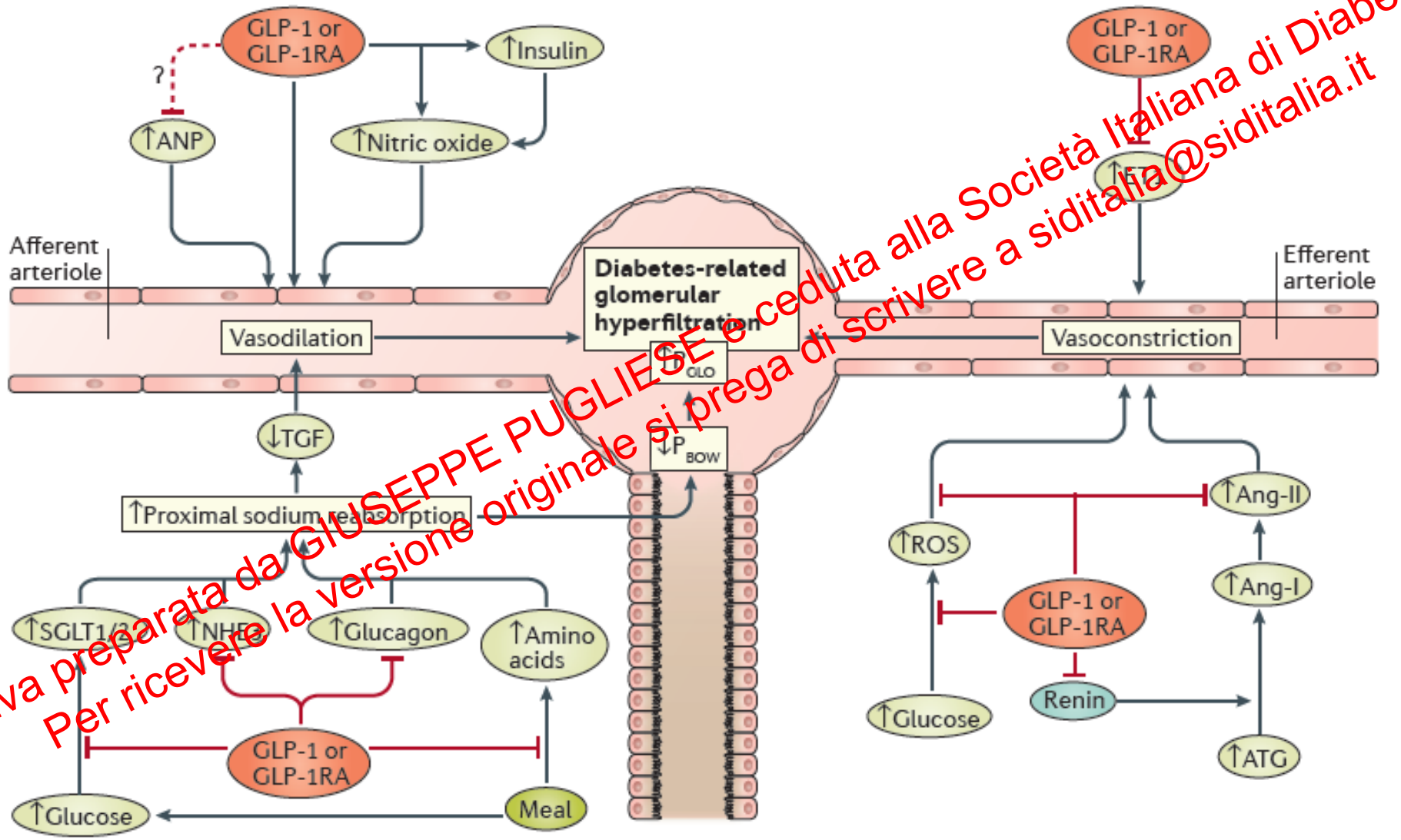

Muskiet MHA et al. Nat Rev Nephrol. 2017;13:605-628

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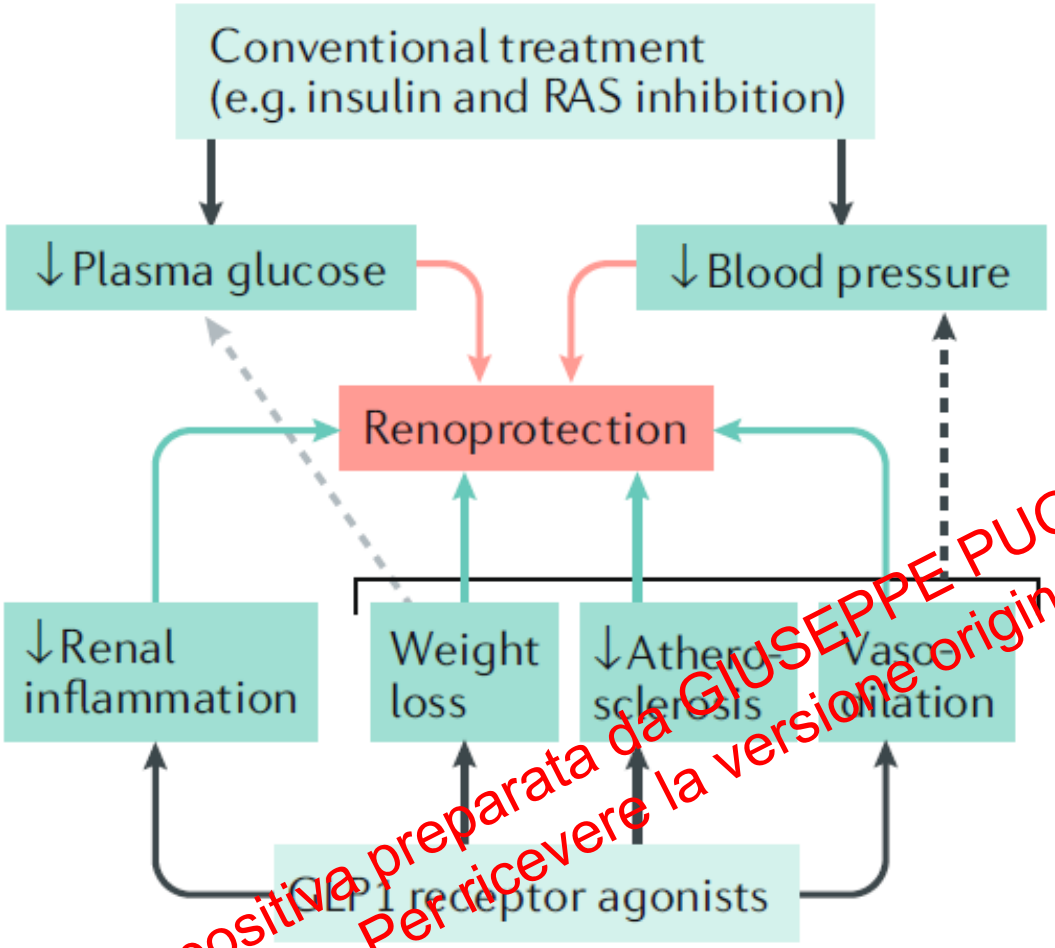
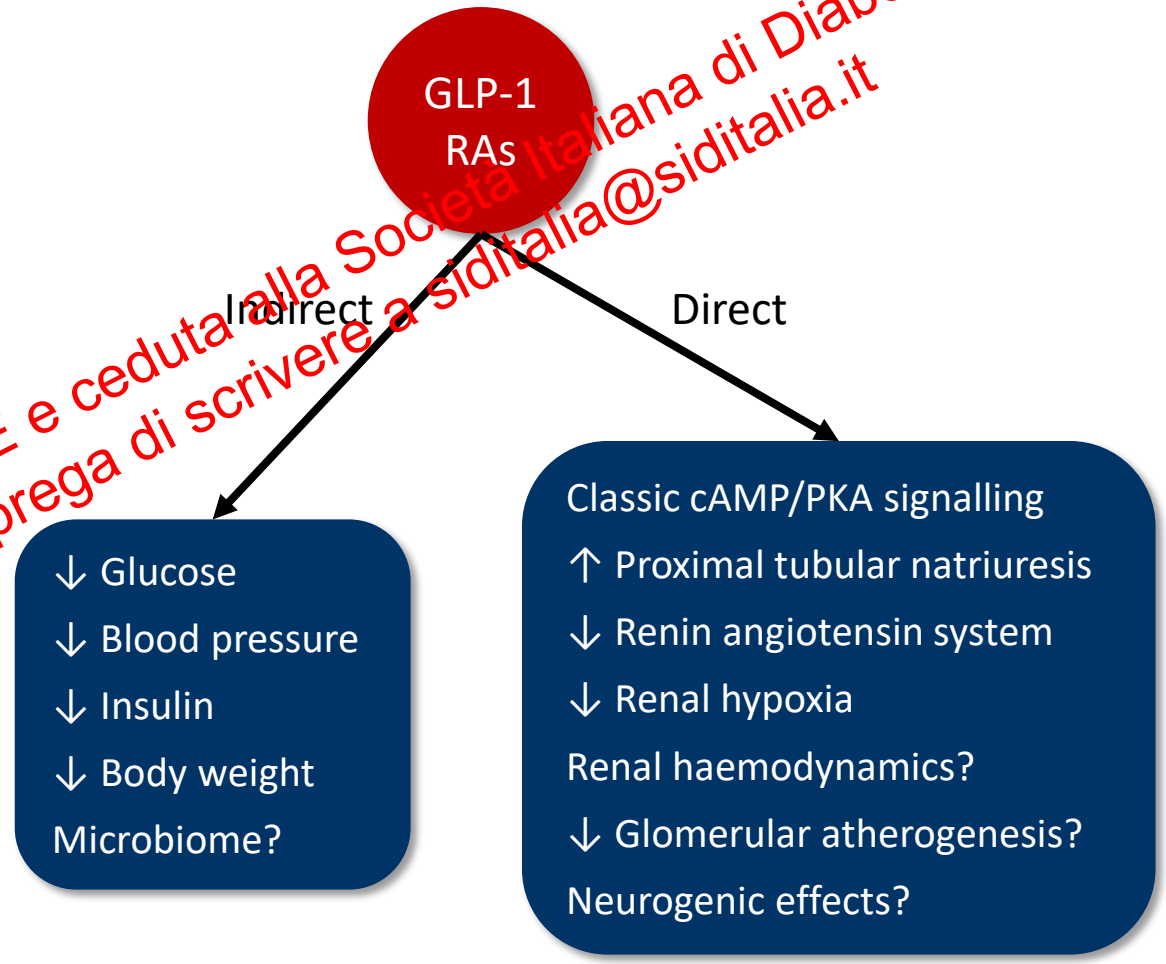


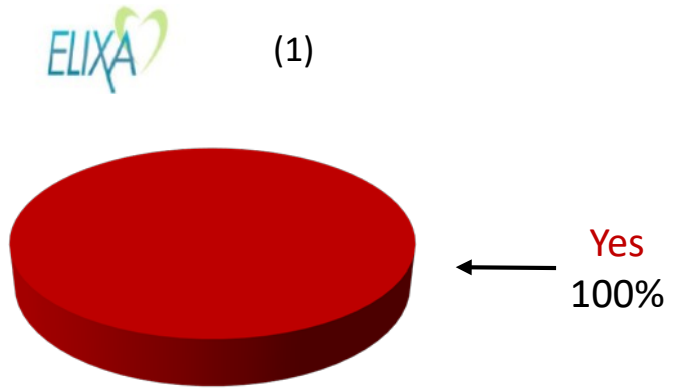


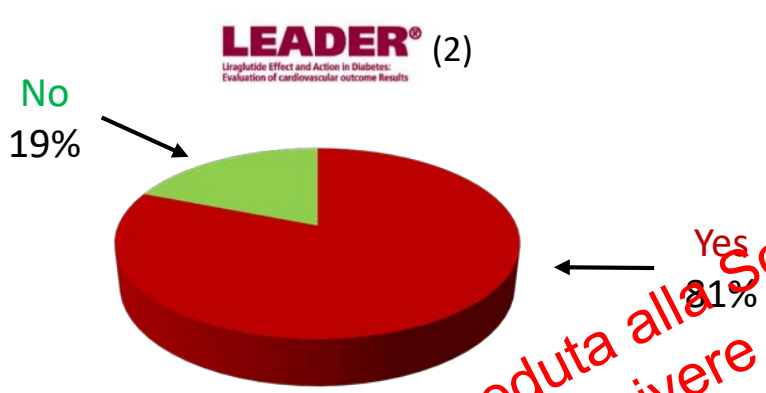
Sorensen CM & Holst JJ. Nat Rev Nephrol. 2018;14:659-660

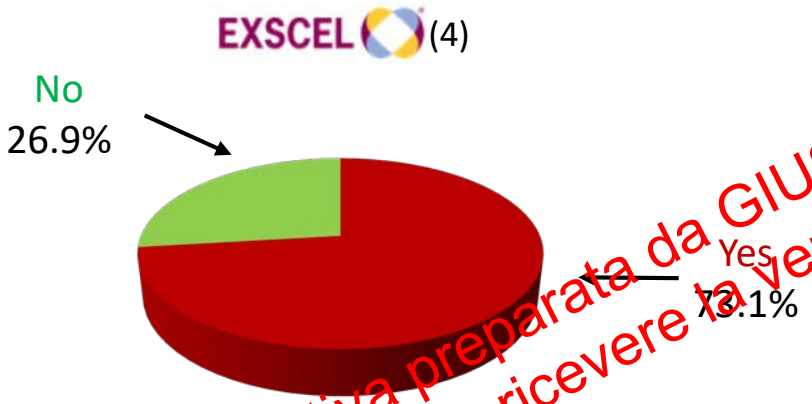
Thomas M. Diabetes Metab. 2017;43:2S20-2S27

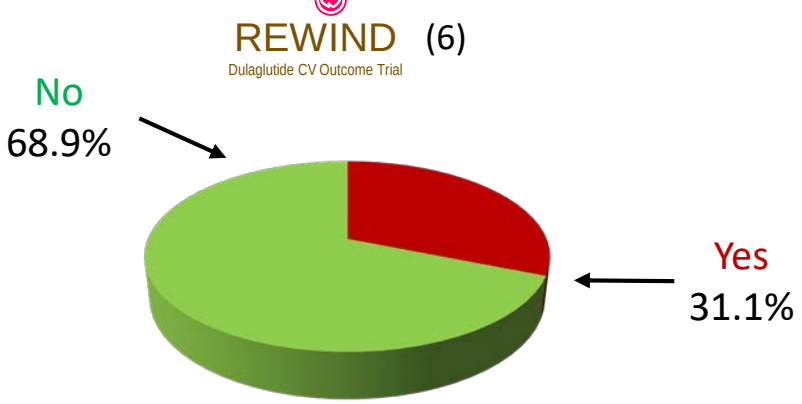
DOMANDA 1

Baseline CVD in CVOTs with GLP-1 RAs





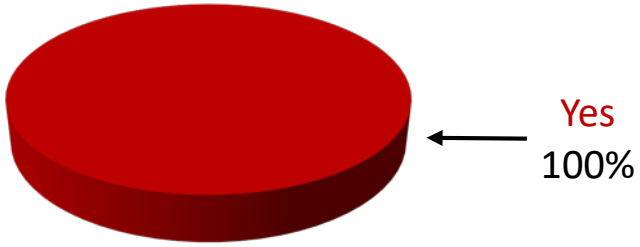




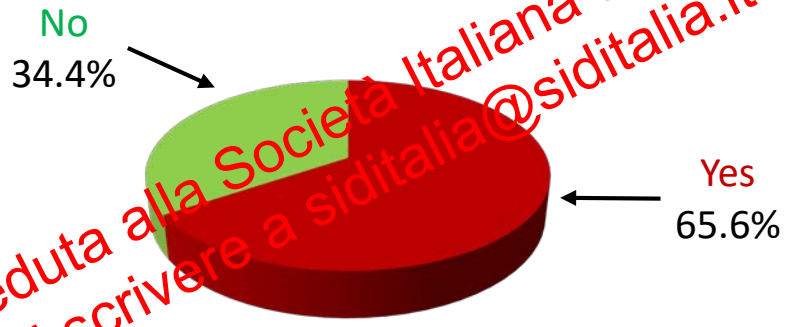
1. Pfeffer MA et al. N Engl J Med. 2015;373;2247-2257; 2. Marso SP et al. N Engl J Med. 2016;375;311-322;
3. Marso SP et al. N Engl J Med. 2016;375;1834-1844; 4. Holman RR et al. N Engl J Med. 2017;377;1228-1239;
5. Hernandez HF et al. Lancet. 2018;392:1519–1529; 6. Gerstein H et al. Lancet. 2019;394:121-130

Baseline CVD in CVOTs with GLP-1 RAs

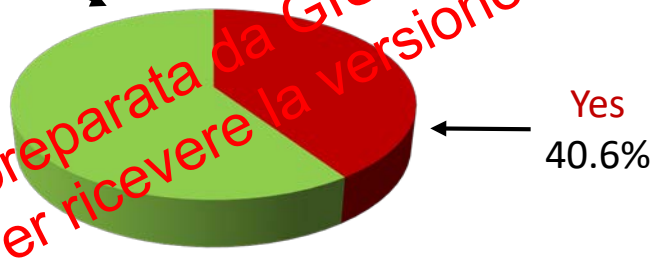
EMPA-REG OUTCOME® (1)



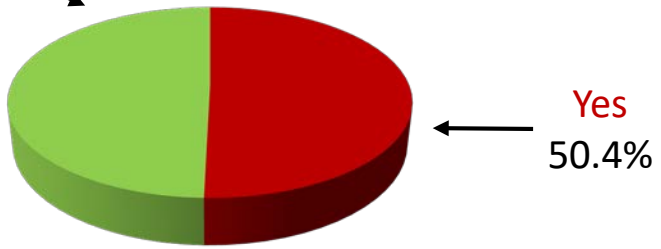
CANVAS Program (2)



DECLARE TIMI-58 (3)

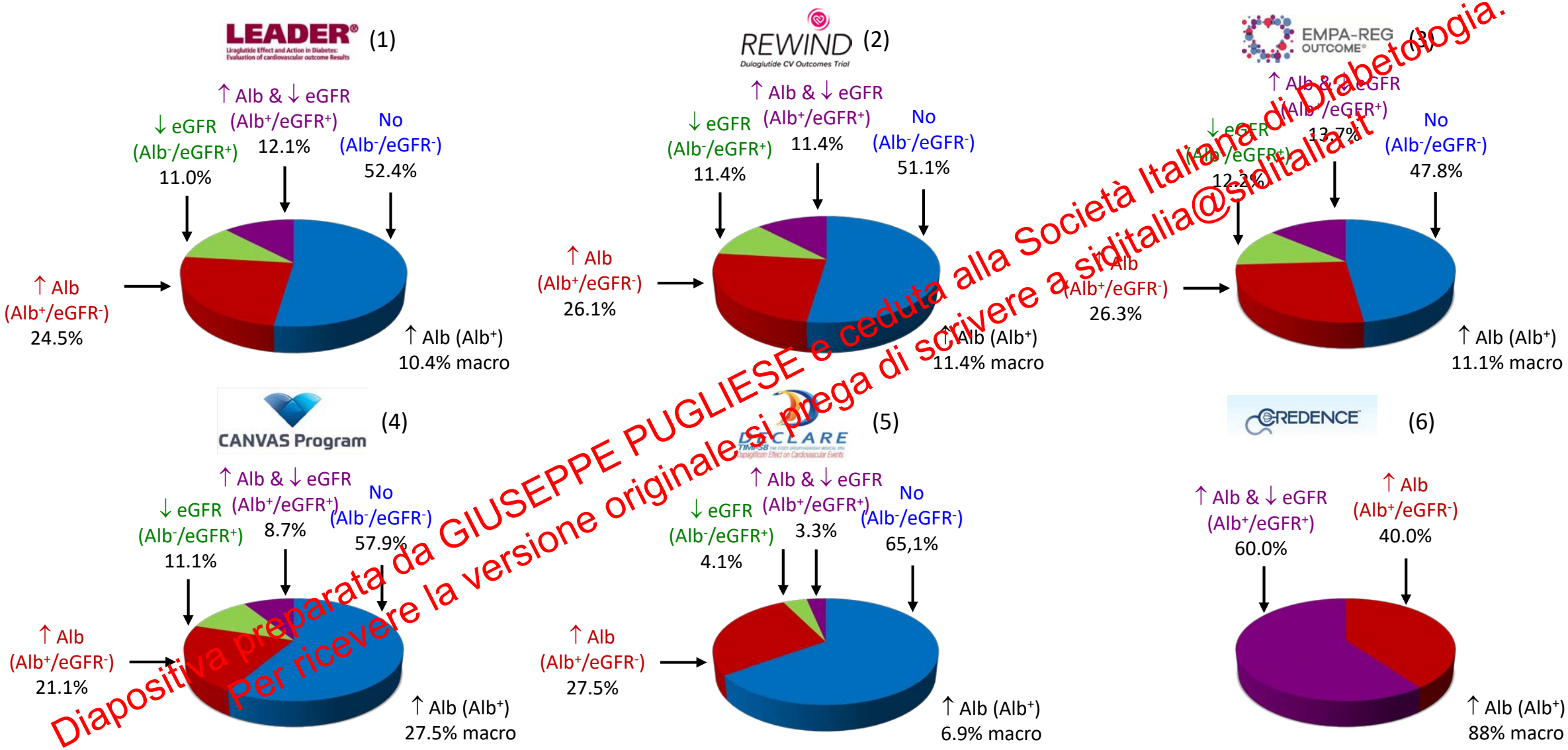


CREDENCE (4)



1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128; 2. Neal B et al. N Engl J Med. 2017;377:644-657;
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357; 4. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

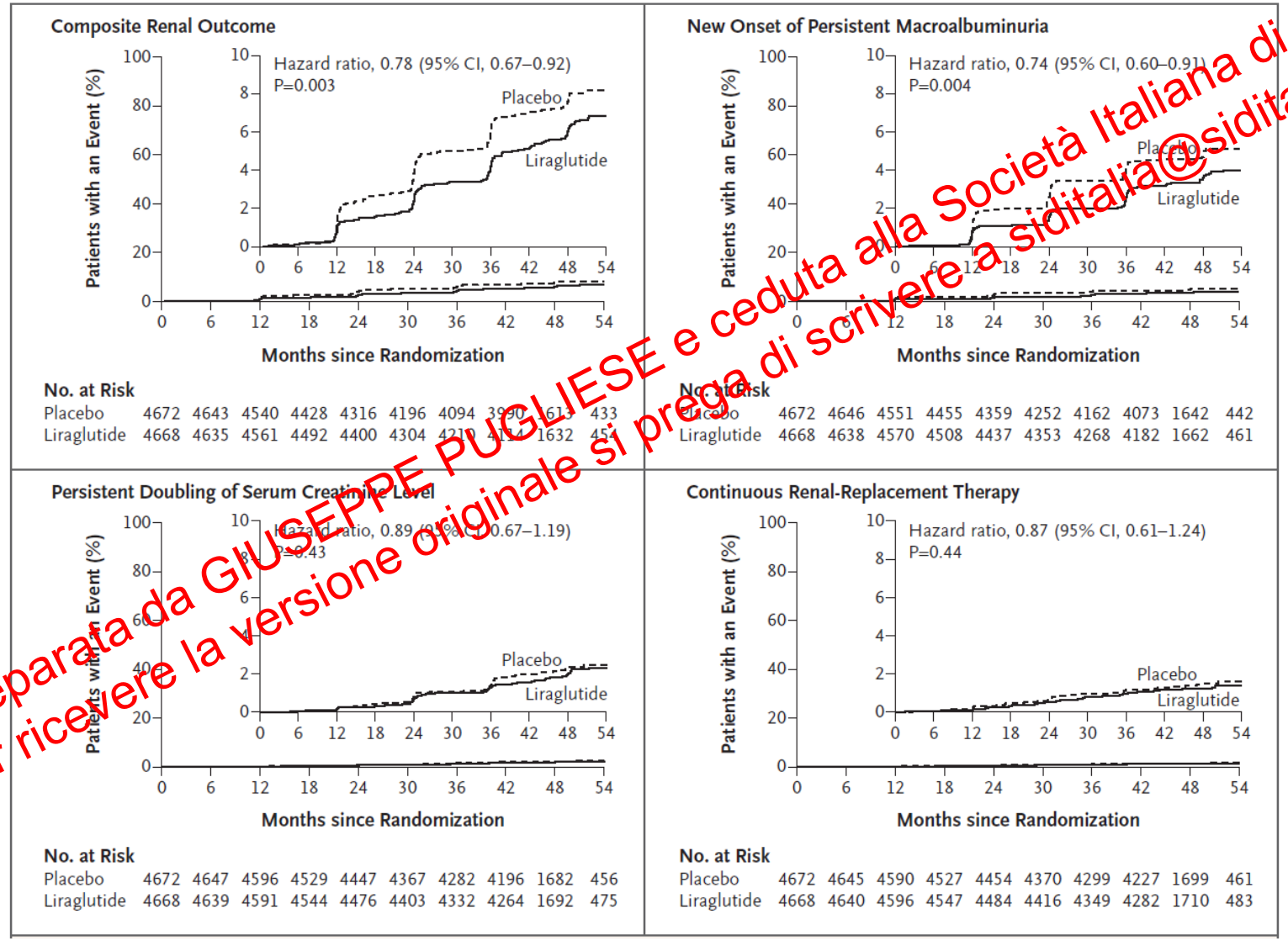
Baseline renal function in CVOTs with GLP-1 RAs



1. Marso SP et al. N Engl J Med. 2016;375;311-322; 2. Gerstein HC et al. Lancet. 2019;394:131-138;
3. Wanner C et al. N Engl J Med. 2016;375:323-334; 4. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704;
5. Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:606-617; 6. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

Renal protection with liraglutide

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) Trial



Mann JFE et al. N Engl J Med. 2017;377:839-848

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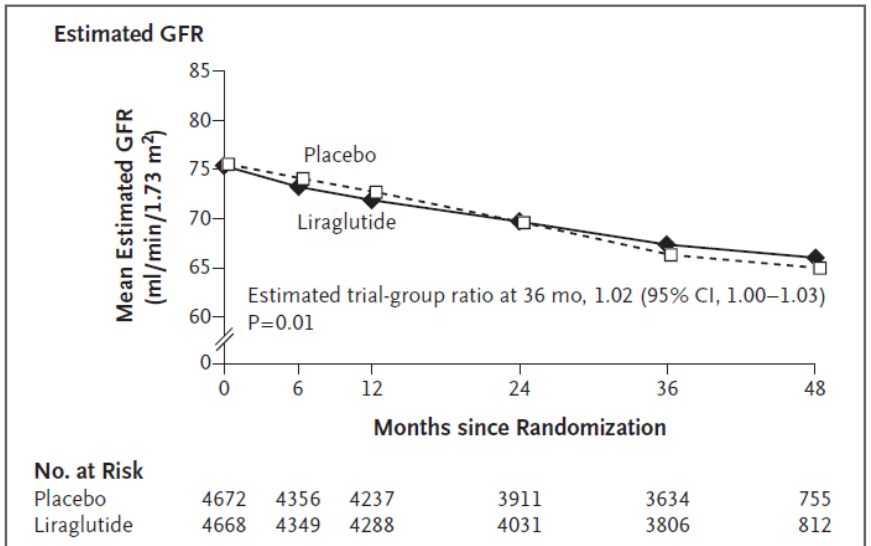

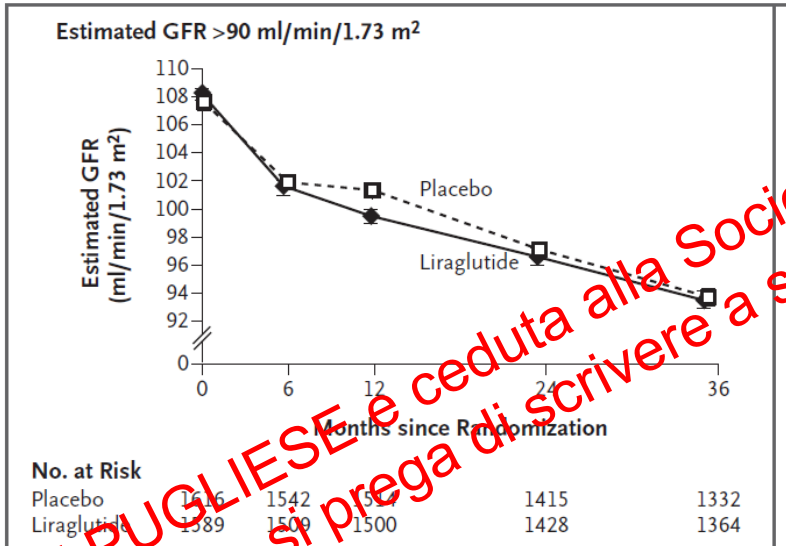

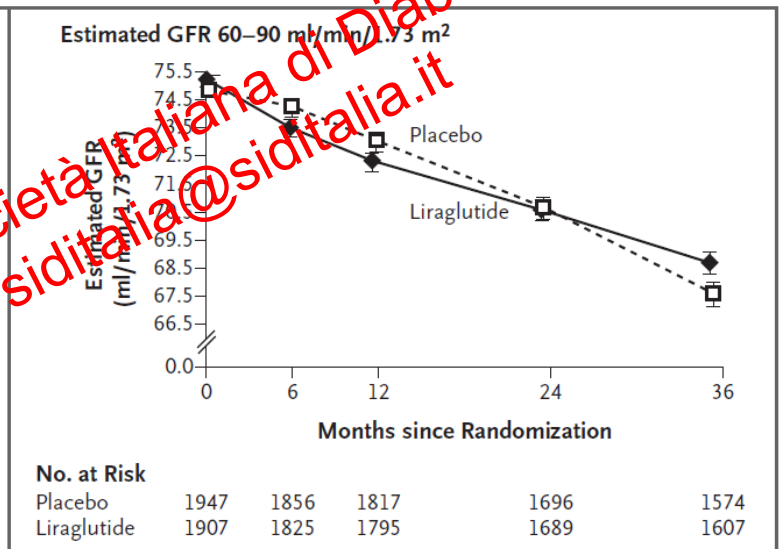

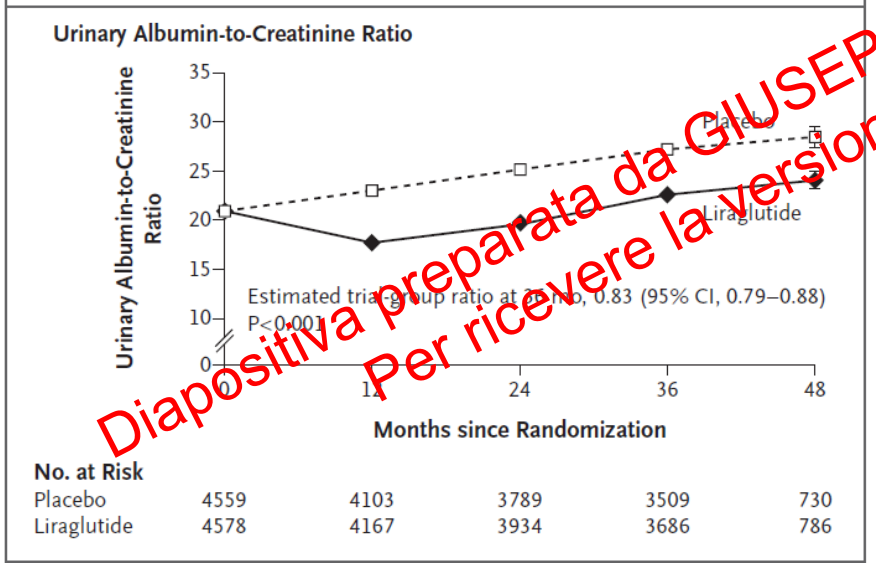

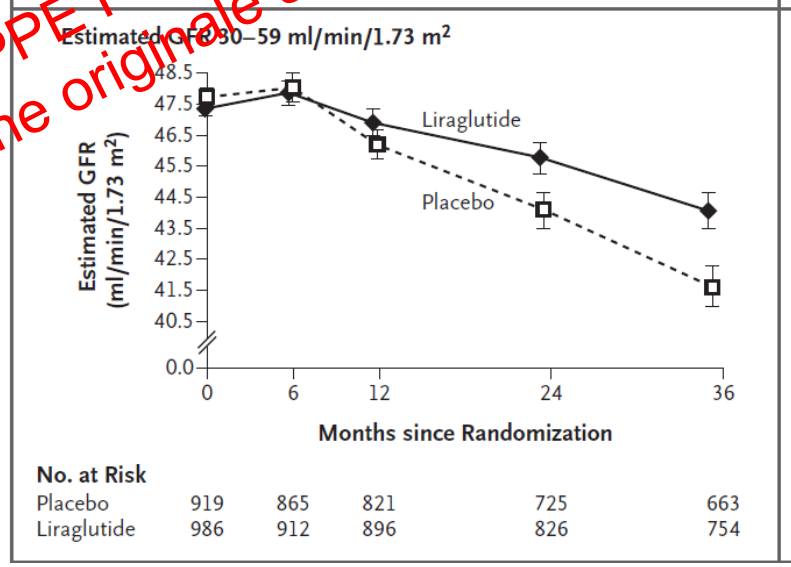

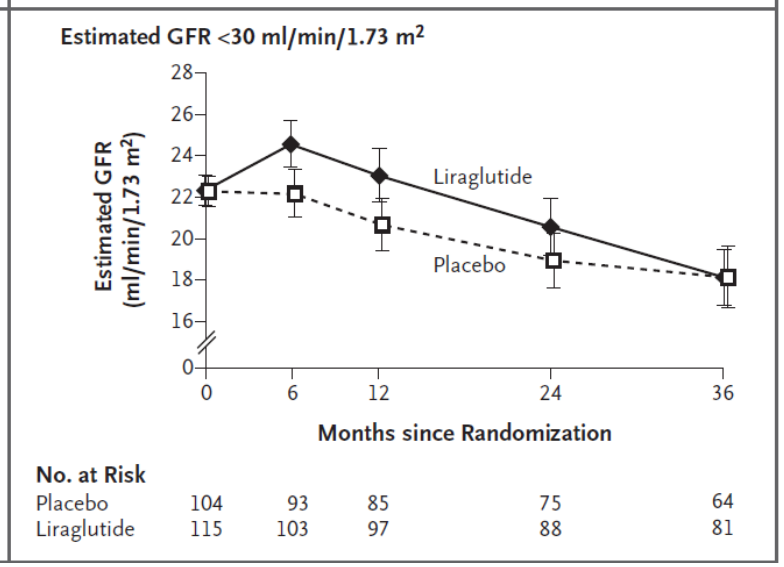

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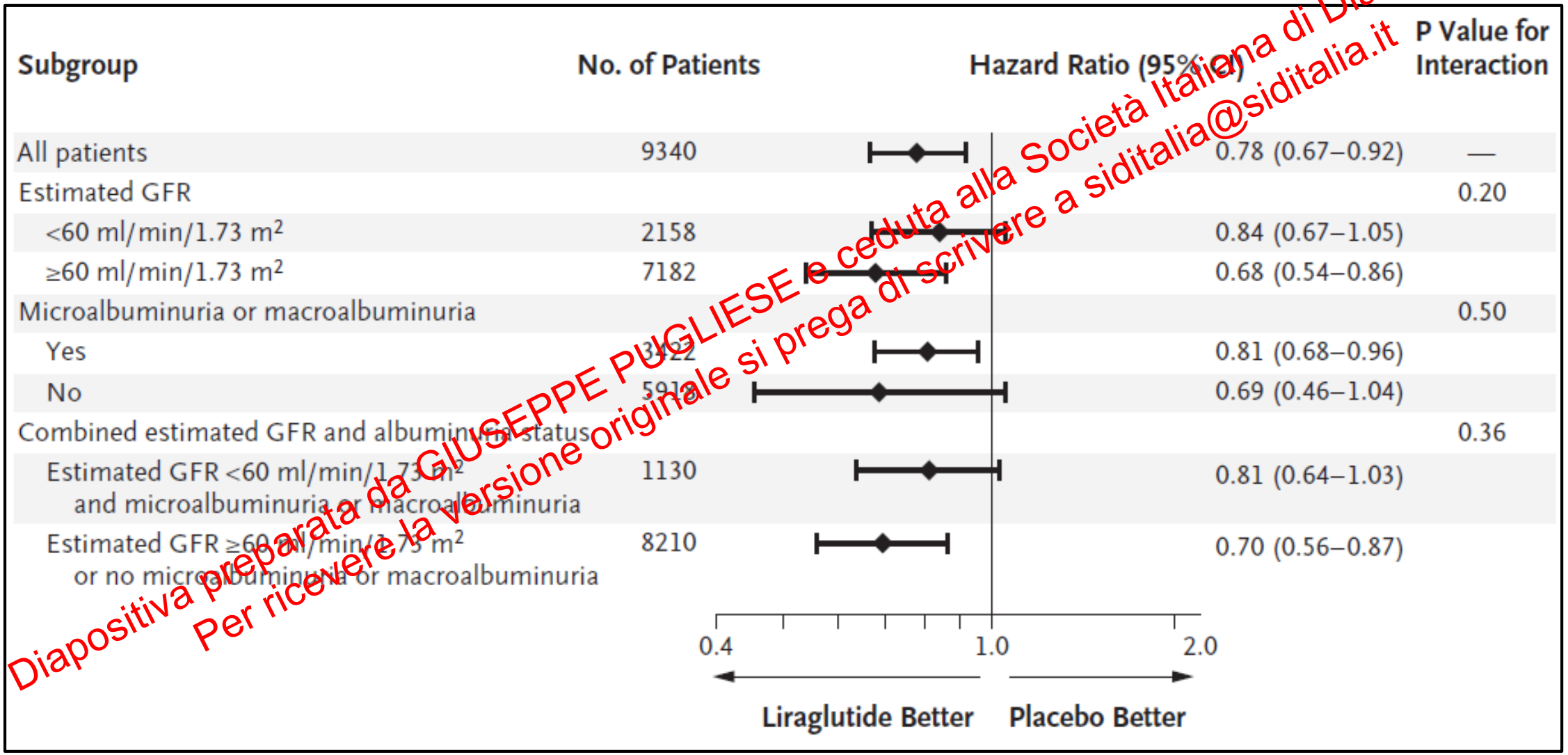


Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
All patients	9340	0.78 (0.67–0.92)	—
Estimated GFR			0.20
<60 ml/min/1.73 m²	2158	0.84 (0.67–1.05)	
≥60 ml/min/1.73 m²	7182	0.68 (0.54–0.86)	
Microalbuminuria or macroalbuminuria			0.50
Yes	3422	0.81 (0.68–0.96)	
No	5918	0.69 (0.46–1.04)	
Combined estimated GFR and albuminuria status			0.36
Estimated GFR <60 ml/min/1.73 m² and microalbuminuria or macroalbuminuria	1130	0.81 (0.64–1.03)	
Estimated GFR ≥60 ml/min/1.73 m² or no microalbuminuria or macroalbuminuria	8210	0.70 (0.56–0.87)	

Mann JFE et al. N Engl J Med. 2017;377:839-848

Renal protection with semaglutide

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)

SUSTAIN™ SEMAGLUTIDE UNABATED SUSTAINED IN TREATMENT OF TYPE 2

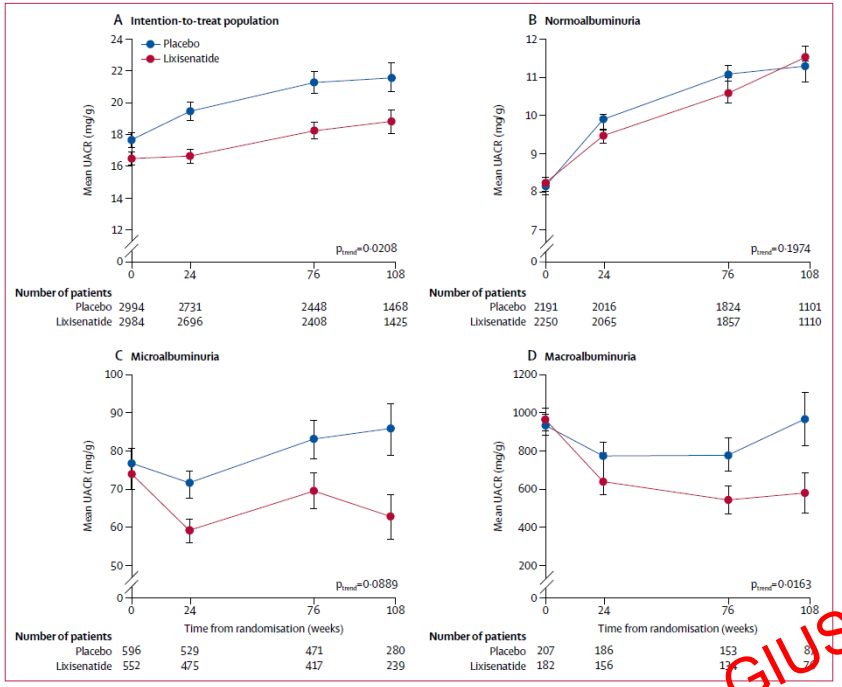
Primary and Secondary Cardiovascular and Microvascular Outcomes.

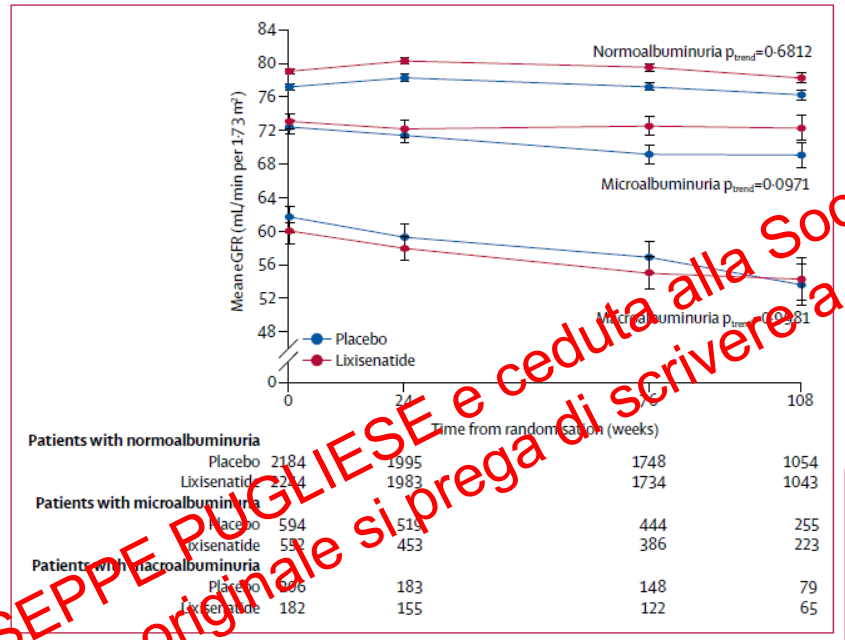
Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.65	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

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

Renal protection with lixisenatide

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) Trial

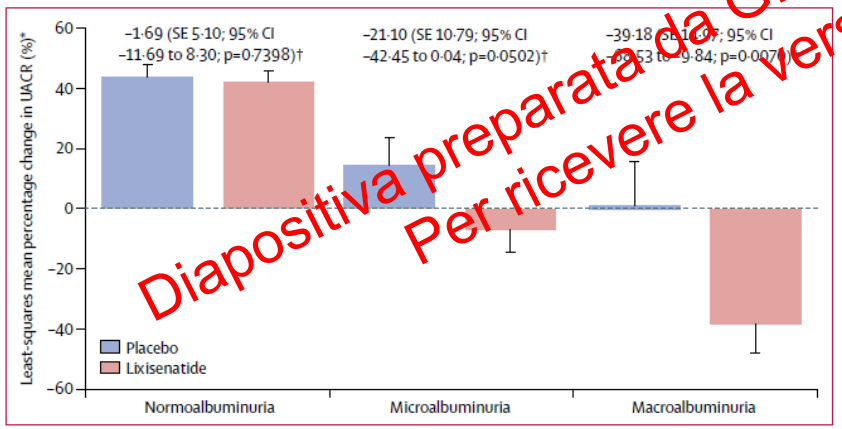


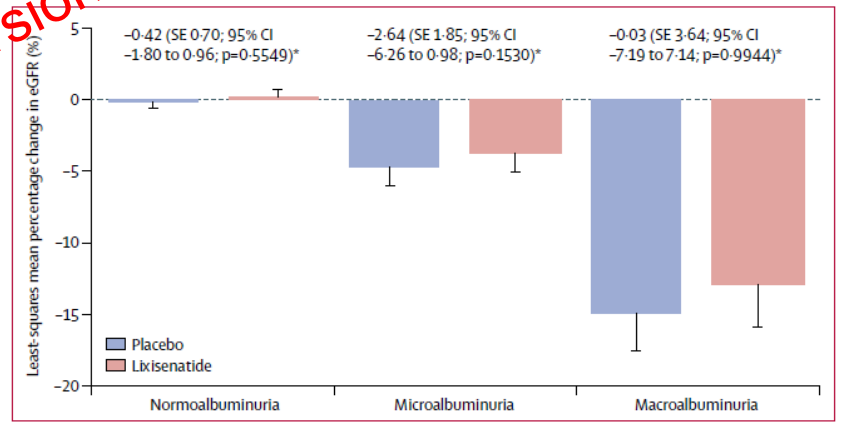


Macroalbuminuria

Adjustments	HR (95% CI)	p value
Unadjusted	0·835 (0·682–1·023)	0·0825
Age and baseline eGFR	0·861 (0·703–1·056)	0·1501
Baseline HbA_{1C}	0·808 (0·660–0·991)	0·0404
Baseline HbA_{1C}, on-trial HbA_{1C}	0·815 (0·665–0·999)	0·0491
Baseline HbA_{1C}, on-trial HbA_{1C}, baseline systolic blood pressure, baseline weight	0·823 (0·671–1·009)	0·0610
Parsimonious model	0·850 (0·691–1·046)	0·1252

0·5 1·0 2·0
Favours lixisenatide
Favours placebo





Muskiet MHA et al. Lancet Diabetes Endocrinol. 2018;6:859–869

Renal protection with exenatide

The Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)

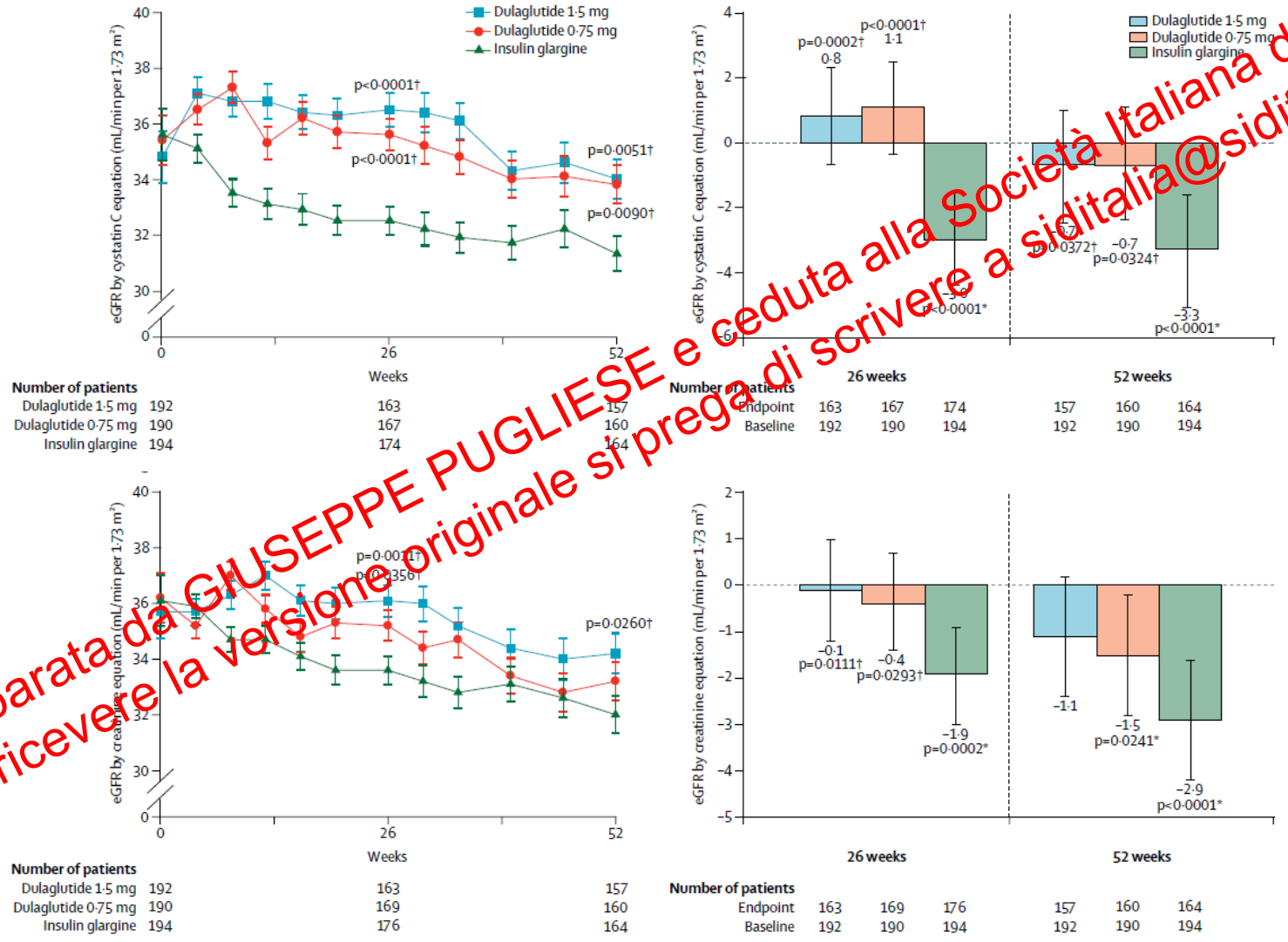
	Exenatide		Placebo			
	# with event, n/N (%)	Incidence/ 100 pyr	# with event, n/N (%)	Incidence/ 100 pyr	HR (95% CI)	p
Renal composite 1	246/6456 (3.8%)	1.2	273/6458 (4.2%)	1.4	0.88 (0.74, 1.05)	0.164
*Adjusted HR**					0.87 (0.73, 1.04)	0.128
40% eGFR decline	239		266			
Renal replacement	7		7			
Renal death	0		0			
Renal composite 2	366/6256 (5.8%)	1.9	407/6222 (6.5%)	2.2	0.88 (0.76, 1.01)	0.065
*Adjusted HR**					0.85 (0.73, 0.98)	0.027
40% eGFR decline	216		228			
Renal replacement	7		6			
Renal death	0		0			
New macroalbuminuria	143		173			

*Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and BMI.

Bethel MA et al. Diabetes. 2018;67:522P

Renal protection with dulaglutide

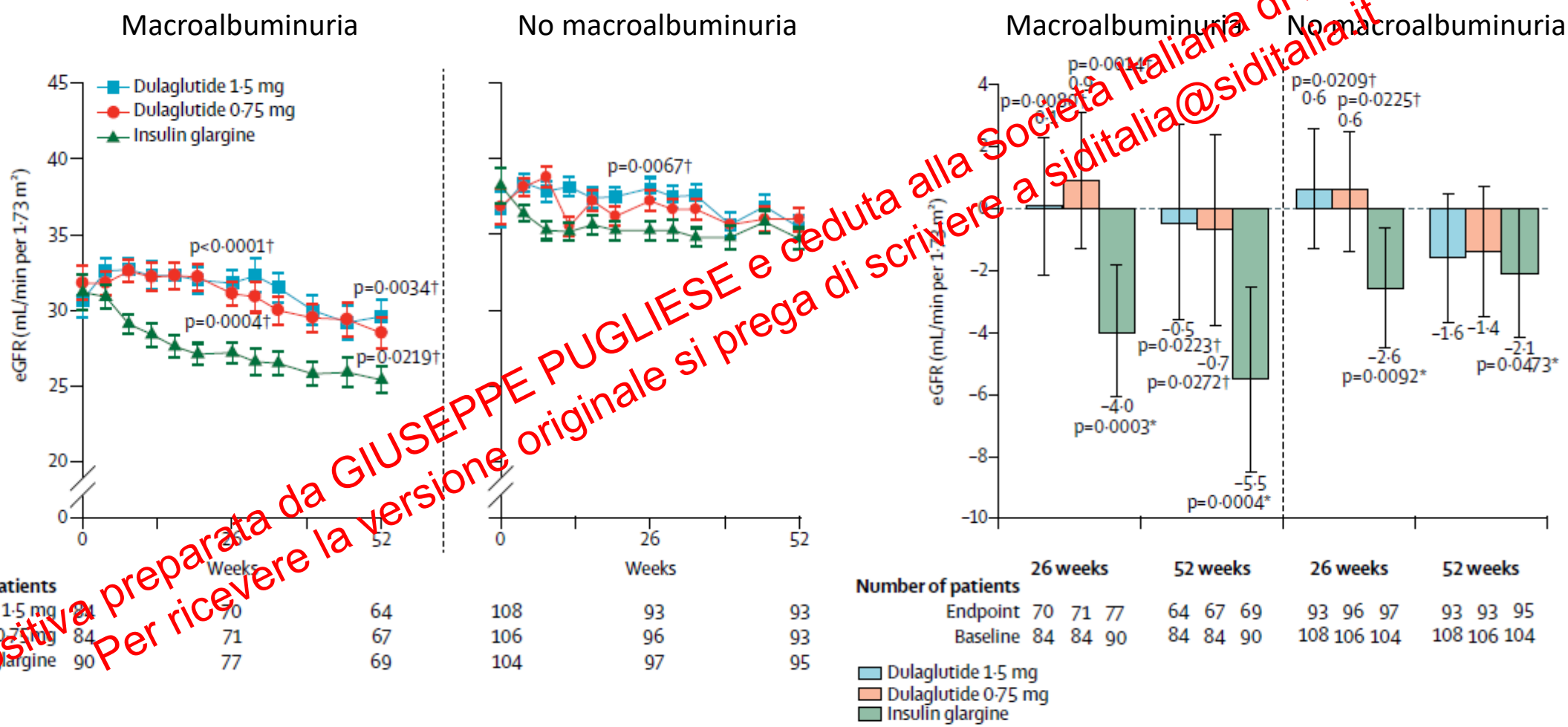
Assessment of Weekly AdministRation of LY2189265 in Diabetes- (AWARD)-7



Tuttle KR et al. Lancet Diabetes Endocrinol. 2018;6:605-617

Renal protection with dulaglutide

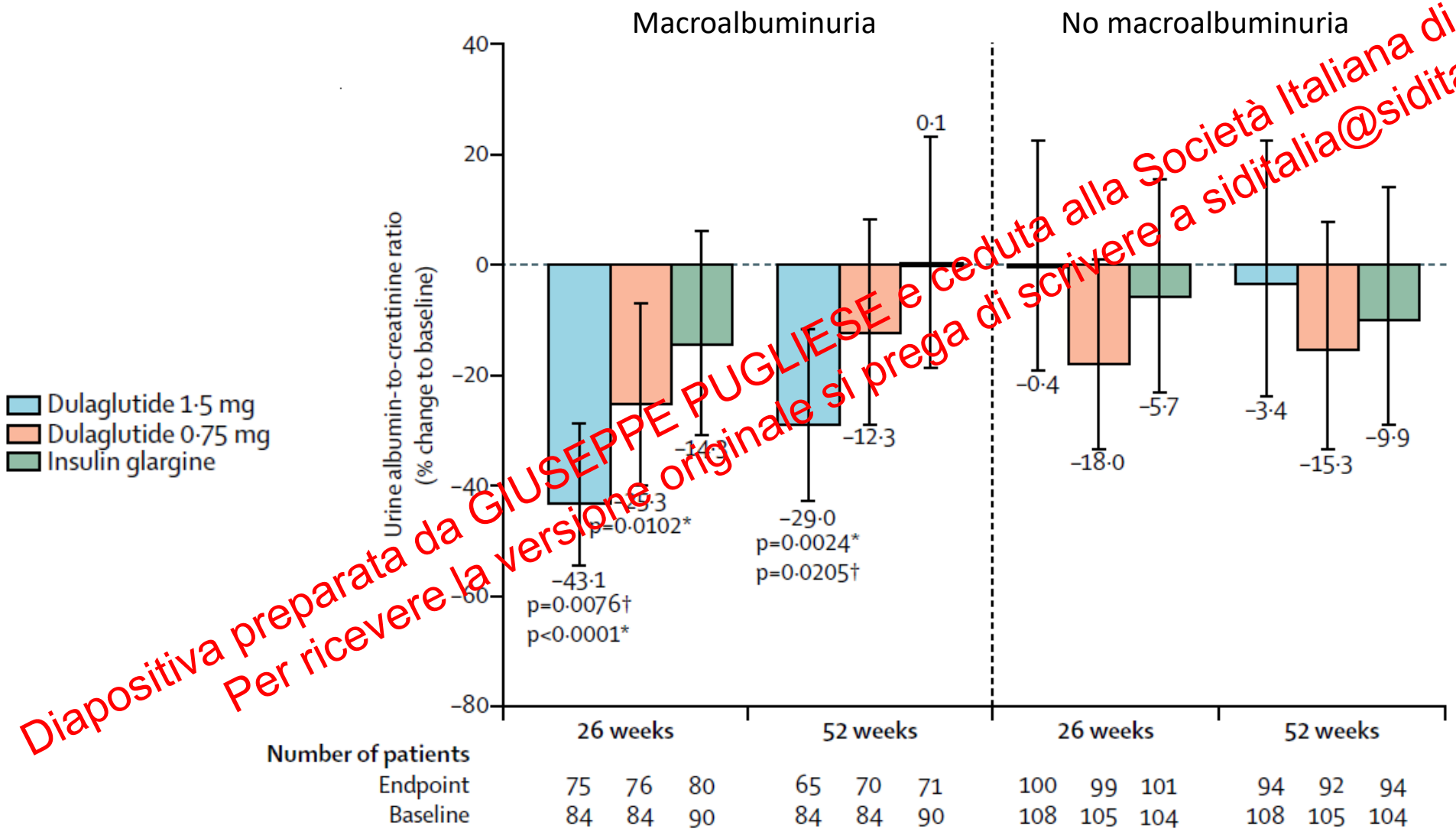
Assessment of Weekly AdministRation of LY2189265 in Diabetes- (AWARD)-7



Tuttle KR et al. Lancet Diabetes Endocrinol. 2018;6:605-617

Renal protection with dulaglutide

Assessment of Weekly AdministRation of LY2189265 in Diabetes- (AWARD)-7



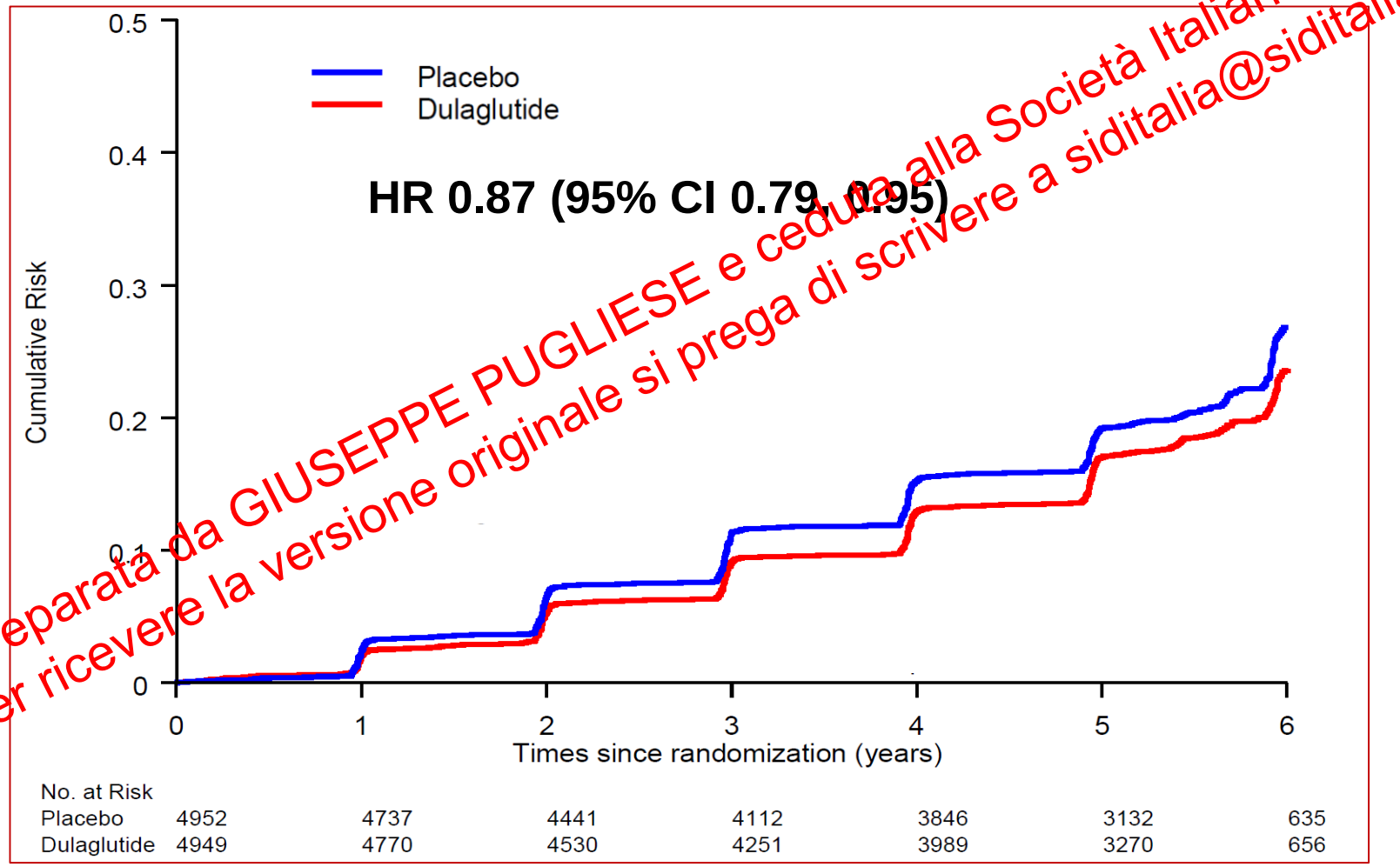
Tuttle KR et al. Lancet Diabetes Endocrinol. 2018;6:605-617

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial

Microvascular composite*



* Microvascular composite
Eye: laser, anti VEGF, vitrectomy
or
Kidney: new macroalbuminuria, or 30% fall in eGFR, or renal replacement therapy

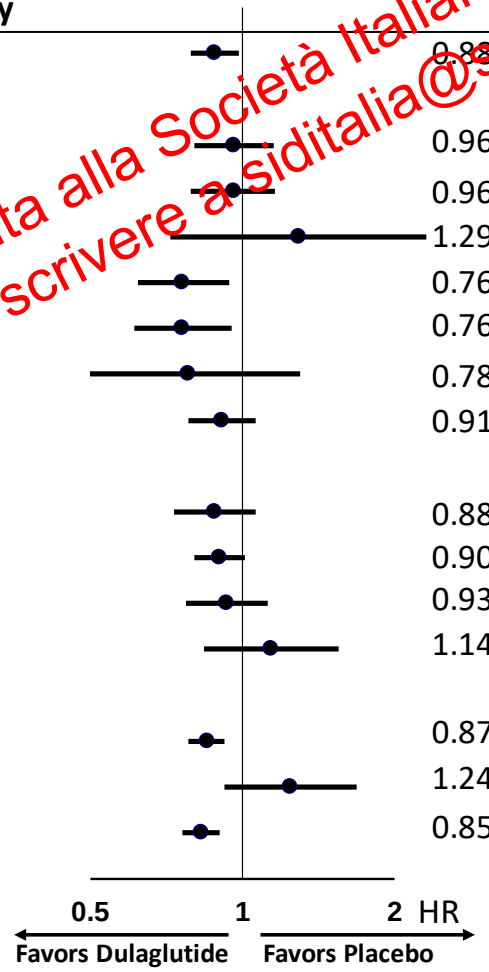
Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial

	Dulaglutide (N=4949) N (%)	Dulaglutide (N=4949) N/100 py	Placebo (N=4952) N (%)	Placebo (N=4952) N/100 py	HR (95%CI)
Primary Composite	594 (12.0)	2.35	663 (13.4)	2.66	0.88 (0.79, 0.99)
MI	223 (4.5)	0.87	231 (4.7)	0.91	0.96 (0.79, 1.15)
Nonfatal MI	205 (4.1)	0.80	212 (4.3)	0.84	0.96 (0.79, 1.16)
Fatal MI	26 (0.5)	0.10	20 (0.4)	0.08	1.29 (0.72, 2.30)
Stroke	158 (3.2)	0.61	205 (4.1)	0.81	0.76 (0.62, 0.94)
Nonfatal Stroke	135 (2.7)	0.52	175 (3.5)	0.69	0.76 (0.61, 0.95)
Fatal Stroke	26 (0.5)	0.10	33 (0.7)	0.13	0.78 (0.47, 1.30)
CV Death	317 (6.4)	1.22	346 (7.0)	1.34	0.91 (0.78, 1.06)
Non-CV Death	219 (4.4)	0.84	246 (5.0)	0.95	0.88 (0.73, 1.06)
All Death	536 (10.8)	2.06	592 (12.0)	2.29	0.90 (0.80, 1.01)
Heart Failure	213 (4.3)	0.83	226 (4.6)	0.89	0.93 (0.77, 1.12)
Unstable Angina	88 (1.8)	0.34	77 (1.6)	0.30	1.14 (0.84, 1.54)
Composite Microvascular	910 (18.4)	3.76	1019 (20.6)	4.31	0.87 (0.79, 0.95)
Eye Outcome	95 (1.9)	0.40	76 (1.5)	0.30	1.24 (0.92, 1.68)
Renal Outcome	848 (17.1)	3.47	970 (19.6)	4.07	0.85 (0.77, 0.93)



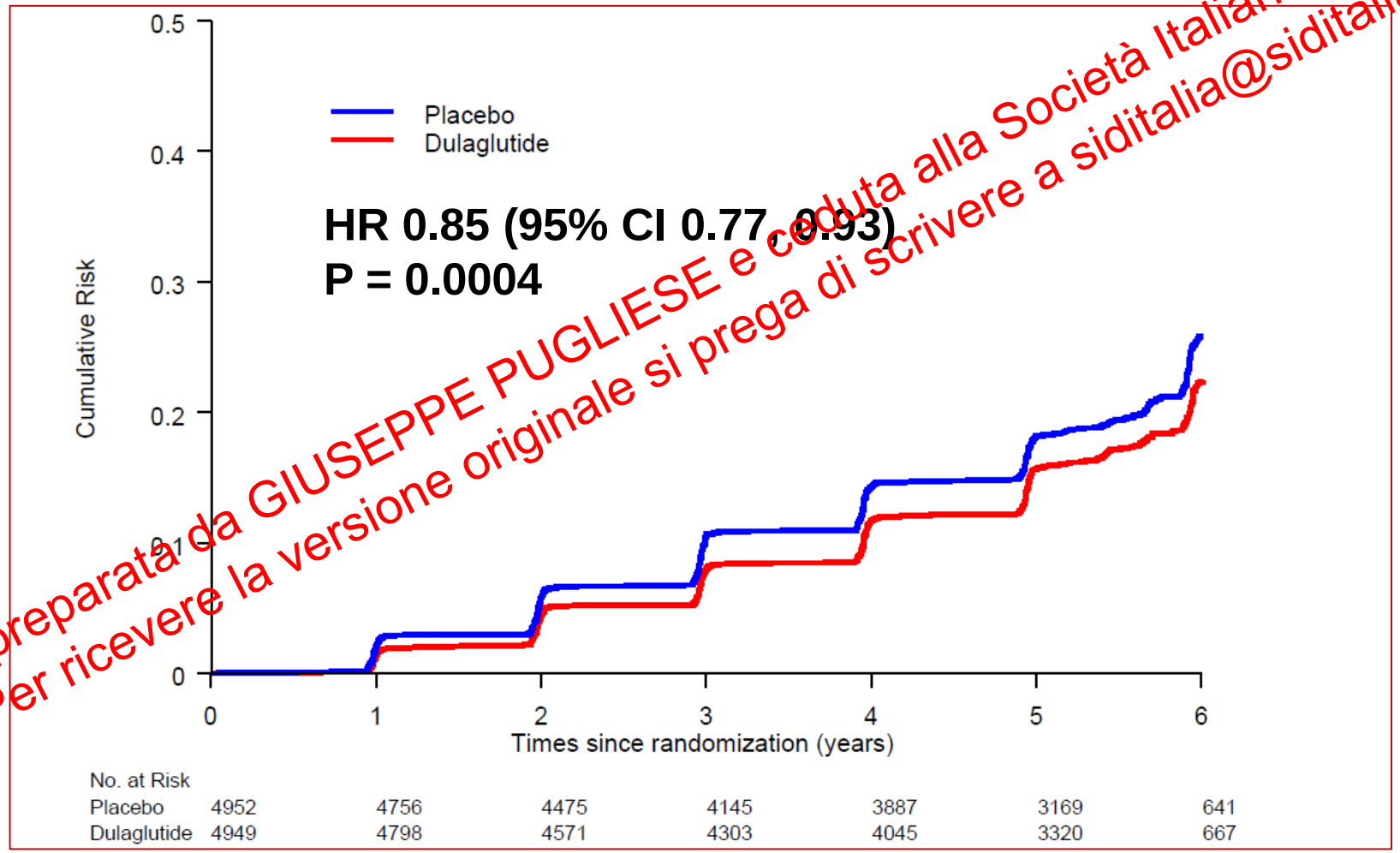
Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial

Renal composite*

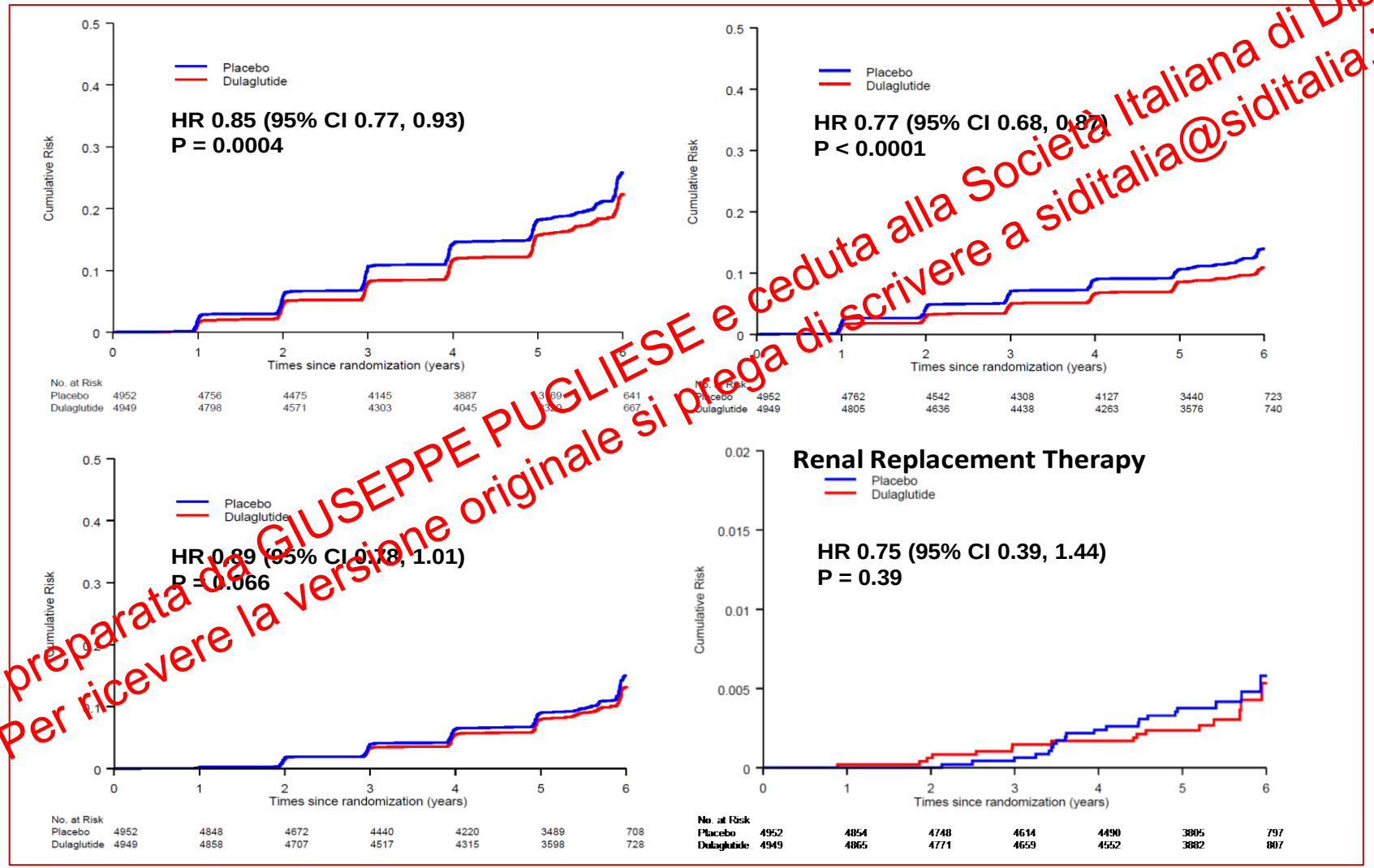


* Renal composite
New macroalbuminuria
or
30% fall in eGFR
or
renal replacement therapy

Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)



Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Effect of treatment allocation on renal outcomes

Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial

	Composite renal outcome				Sustained decline in eGFR of ≥30%				New macroalbuminuria*			
	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$†	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$†	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$†
Overall effect	848/4949 (17·1%)	970/4952 (19·6%)	0·85 (0·78–0·93)	..	453/4949 (9·2%)	500/4952 (10·1%)	0·89 (0·78–1·01)	..	441/4949 (8·9%)	561/4952 (11·3%)	0·77 (0·68–0·87)	..
eGFR (mL/min per 1·73 m²)	..	..	..	0·65	..	..	..	0·47	..	..	..	0·046
<60	219/1081 (20·3%)	251/1118 (22·5%)	0·88 (0·73–1·05)	..	81/1081 (7·5%)	102/1118 (9·1%)	0·81 (0·60–1·08)	..	154/1081 (14·2%)	171/1118 (15·3%)	0·91 (0·73–1·13)	..
≥60	610/3734 (16·3%)	701/3707 (18·9%)	0·83 (0·75–0·93)	..	372/3734 (10·0%)	398/3707 (10·7%)	0·91 (0·79–1·04)	..	268/3734 (7·2%)	372/3707 (10·0%)	0·70 (0·59–0·81)	..
Baseline albuminuria status	..	..	..	0·66	..	..	..	0·64	..	..	..	0·84
Normoalbuminuria	330/2917 (11·3%)	365/2863 (12·7%)	0·87 (0·75–1·01)	..	241/2917 (7·3%)	237/2863 (8·3%)	0·87 (0·73–1·05)	..	123/2917 (4·2%)	154/2863 (5·4%)	0·78 (0·61–0·99)	..
Microalbuminuria or macroalbuminuria	468/1707 (27·4%)	543/1760 (30·9%)	0·84 (0·74–0·95)	..	224/1707 (13·1%)	240/1760 (13·6%)	0·93 (0·78–1·12)	..	279/1707 (16·3%)	360/1760 (20·5%)	0·76 (0·65–0·89)	..
ACE inhibitor or ARB use	..	..	..	0·23	..	..	..	0·45	..	..	..	0·55
No	146/940 (15·5%)	141/893 (15·8%)	0·97 (0·77–1·22)	..	79/940 (8·4%)	74/893 (8·3%)	1·00 (0·73–1·37)	..	70/940 (7·4%)	77/893 (8·6%)	0·84 (0·61–1·16)	..
Yes	702/4009 (17·5%)	829/4059 (20·4%)	0·83 (0·75–0·92)	..	374/4009 (9·3%)	426/4059 (10·5%)	0·87 (0·76–1·00)	..	371/4009 (9·3%)	484/4059 (11·9%)	0·76 (0·66–0·87)	..

Data are n/N (%) unless otherwise stated. eGFR=estimated glomerular filtration rate. HR=hazard ratio. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *The 791 people with macroalbuminuria at baseline were not eligible to develop the new macroalbuminuria component of the outcome after randomisation. †p value for the interaction of subgroup with allocation.

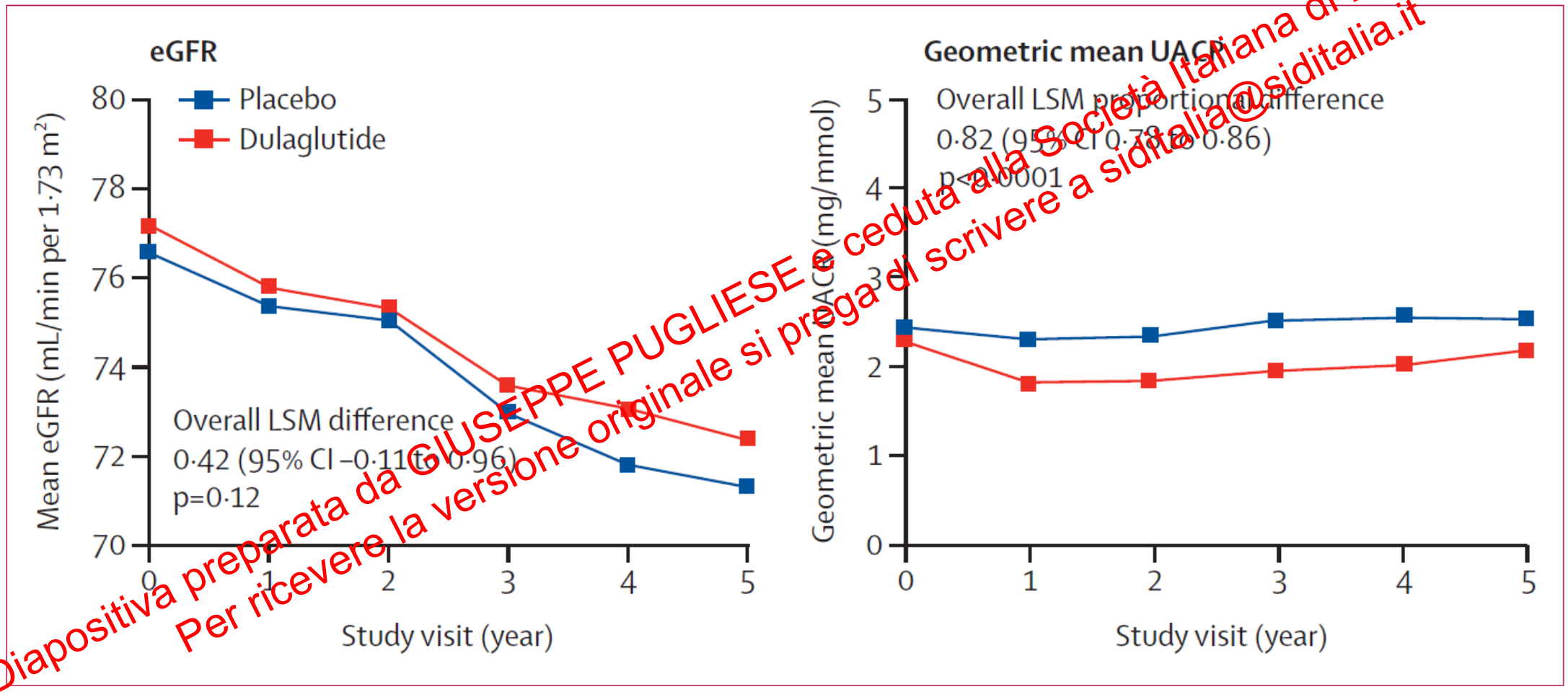
Effect of dulaglutide on renal outcomes in exploratory subgroups

Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with dulaglutide

Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND)

REWIND Dulaglutide CV Outcomes Trial



Gerstein HC et al. Lancet. 2019;394:131-138

Renal protection with GLP-1 RAs

Systematic review and meta-analysis of GLP1-RA CVOTs

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (6%)	0·84 (0·68–1·03)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·66–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		0·0004
Overall (I^2=0·0%, p=0·413)	**1716/20160 (9%)**	**2017/20142 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·0001**
Worsening of kidney function *					
ELIXA	35/3032 (1%)	41/3034 (1%)	1·16 (0·74–1·83)		0·51
LEADER	87/4668 (2%)	107/4672 (2%)	0·89 (0·67–1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64–2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74–1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57–0·85)		0·0004
Overall (I^2=42·7%, p=0·137)	**555/20753 (3%)**	**662/20762 (3%)**	**0·87 (0·73–1·03)**	**245 (118 to –1064†)**	**0·098**

* Worsening of kidney function: either doubling of serum creatinine or ≥40% decline in eGFR

Kristensen S et al. Lancet Diabetes Endocrinol. 2019;7:776–785

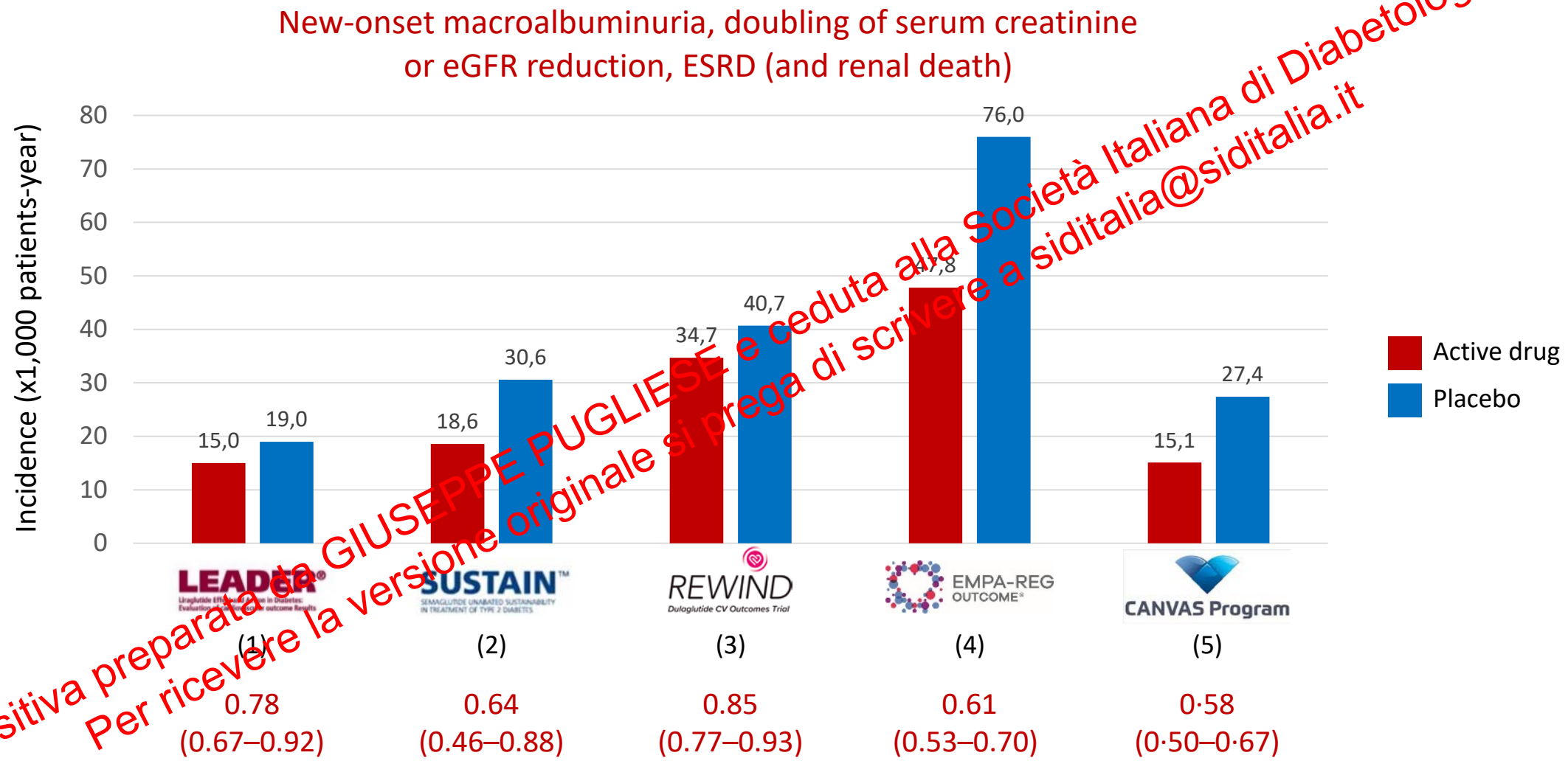
DOMANDA 2

Renal protection with GLP-1 RAs and SGLT2-Is

	LEADER® (1)	REWIND (2)	EMPA-REG OUTCOME® (3)	CANVAS Program (4)	DECLARE (5)	CREDENCE (6)
Drug	Liraglutide	Dulaglutide	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
N	9,340	9,901	7,020	10,142	17,160	4,401
Follow-up (years)	3.8	5.4	3.1	2.4	4.2	2.6
Prevalence of any DKD	47.6	48.9	52.2	42.1	34.4	100
Prevalence of ↓ eGFR	23.1	22.8	25.9	19.8	7.4	60
Prevention of macroalb	0.74 (0.60–0.91)	0.77 (0.68–0.87)	0.95 (0.87–1.04)	0.80 (0.73-0.87)	0.77 (0.68–0.87)	NA
Progression of alb	NA	NA	0.62 (0.54-0.72)	0.58 (0.50-0.68)	0.73 (0.67–0.79)	NA
Regression of alb	NA	NA	1.61 (1.34-1.94)	1.70 (1.51-1.91)	1.41 (1.27–1.56)	NA
Doubling of sCreat	0.89 (0.67–1.19)	NA	0.56 (0.39–0.79)	0.50 (0.30–0.84)	NA	0.60 (0.48–0.76)
40% eGFR reduction	NA	0.70 (0.57–0.85)	NA	0·60 (0·47–0·78)	0.54 (0.43–0.67)	NA
ESRD/RRT	0.82 (0.61–1.24)	0.75 (0.39–1.44)	0.45 (0.21–0.97)	0.77 (0.30–1.97)	0.31 (0.13–0.79)	0.68 (0.54–0.86)
Renal death	1.59 (0.52–4.87)	NA	NA	NA	0.60 (0.22–1.65)	NA

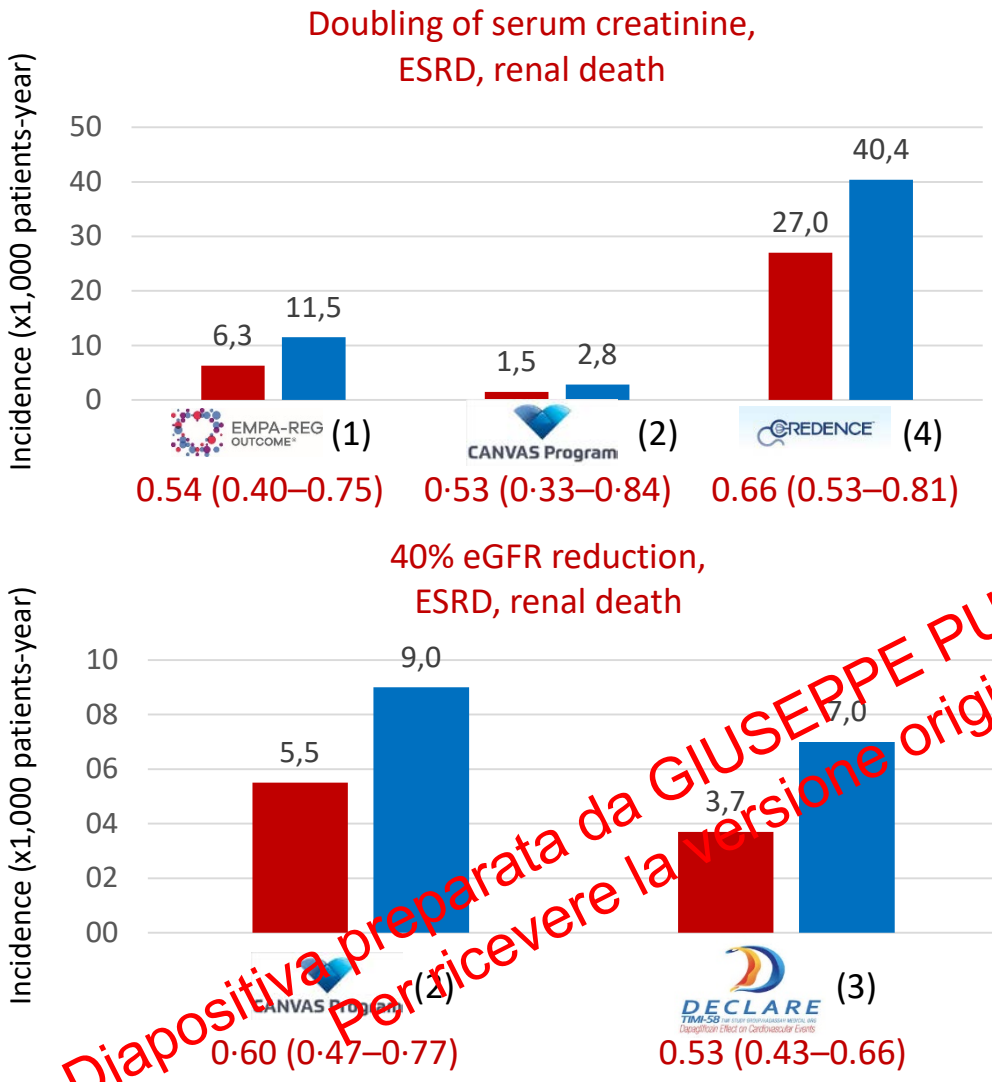
1. Marso SP et al. N Engl J Med. 2016;375;311-322; 2. Gerstein HC et al. Lancet. 2019;394:131-138;
3. Wanner C et al. N Engl J Med. 2016;375:323-334; 4. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704;
5. Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:606-617; 6. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

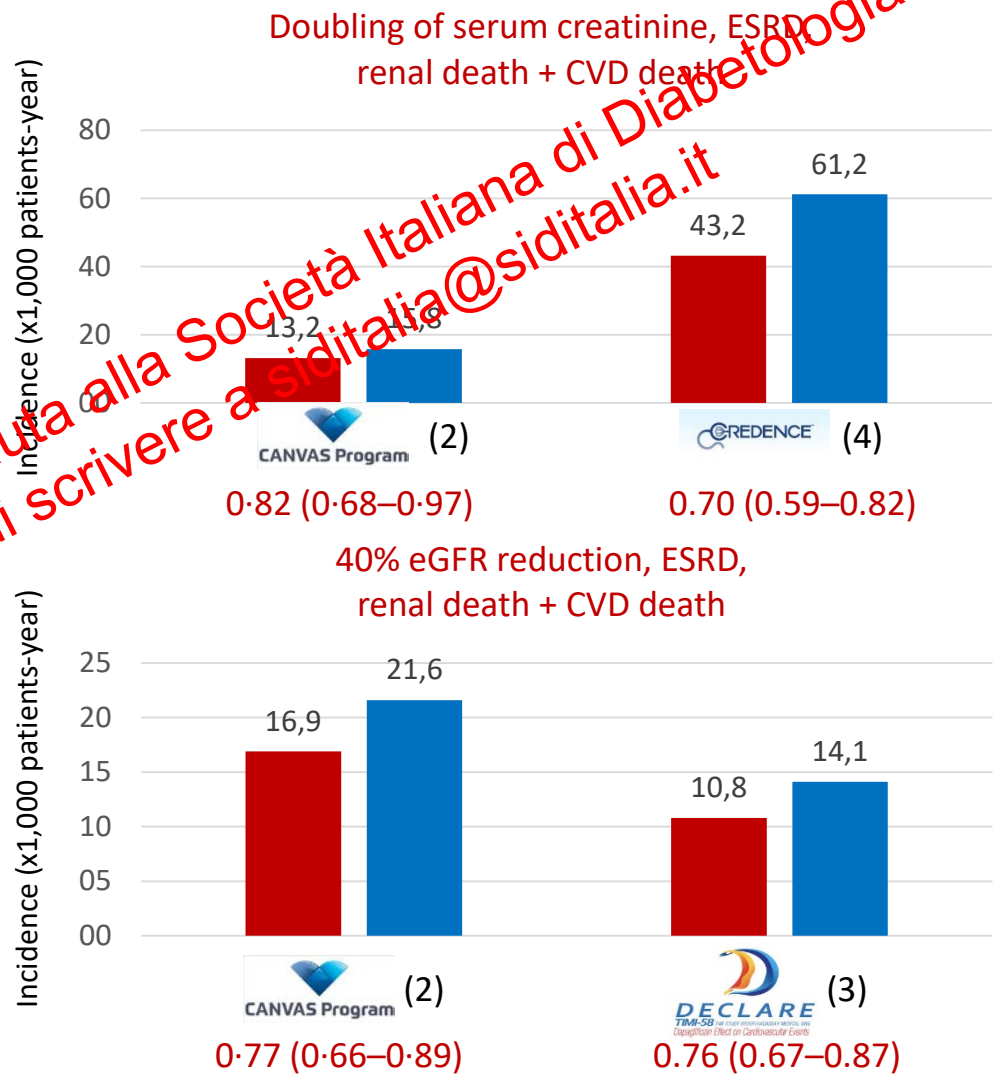
Renal protection with GLP-1 RAs and SGLT2-Is



1. Marso SP et al. N Engl J Med. 2016;375;311-322
2. Marso SP et al. N Engl J Med. 2016;375:1834–1844
3. Gerstein HC et al. Lancet. 2019;394:131-138
4. Wanner C et al. N Engl J Med. 2016;375:323-334
5. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704

Renal protection with SGLT2-Is





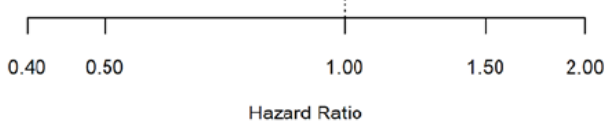
1. Wanner C et al. N Engl J Med. 2016;375:323-334
2. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357
4. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

Renal protection with GLP-1 RAs and SGLT2-Is

Systematic review and trial-level meta-analysis of GLP1-RA and SGLT2i CVOTs

Composite renal outcome with macroalbuminuria (new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or renal death)

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 [0.68, 1.02]
LEADER	9340	605	268/4668	337/4672	32.2	0.78 [0.67, 0.92]
SUSTAIN-6	3297	162	62/1648	100/1649	7.7	0.64 [0.46, 0.88]
EXSCEL	14752	773	366/6256	407/8222	40.1	0.88 [0.76, 1.01]
Fixed Effects for GLP1-RA (P-value<0.001)						0.82 [0.75, 0.89]
SGLT2i						
EMPA-REG OUTCOME	6186	913	525/4124	388/2061	24.9	0.61 [0.53, 0.70]
CANVAS Program	10142	847	NA	NA	25.0	0.57 [0.50, 0.66]
DECLARE-TIMI 58	17160	1675	678/8582	997/8578	50.1	0.66 [0.60, 0.73]
Fixed Effects for SGLT2i (P-value<0.001)						0.62 [0.58, 0.67]

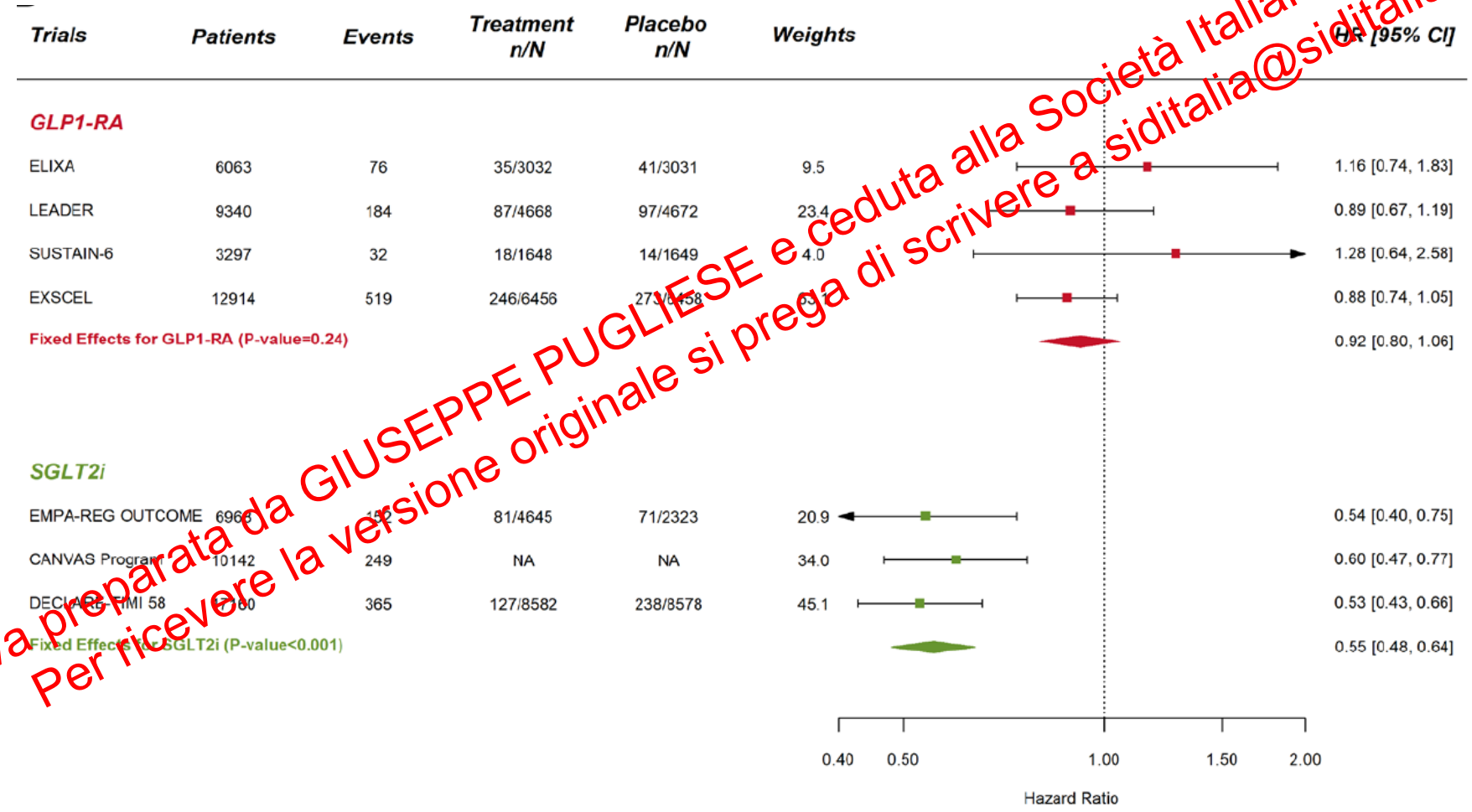


Zelniker TA et al. Circulation. 2019;139:2022–2031

Renal protection with GLP-1 RAs and SGLT2-Is

Systematic review and trial-level meta-analysis of GLP1-RA and SGLT2i CVOTs

Composite renal outcome without macroalbuminuria (sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or renal death



Zelniker TA et al. Circulation. 2019;139:2022–2031

Conclusions

- Unmet needs: renoprotective drugs for reduction of albuminuria and eGFR decline
- GLP-1 RAs: use allowed up to G4 stage, renal protection by multiple mechanisms
- Renal protection with GLP-1 RAs: driven by macroalbuminuria reduction
- Renal protection with GLP-1 RAs vs SGLT2-Is: equally effective on albuminuria, less effective on eGFR decline (?)