Il dr. *ROBERTO TREVISAN* dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- NOVO
- SANOFI
- LILLY
- NOVARTIS
- ASTRA ZENECA
- MEDTRONIC
- MERCK
- TAKEDA
- BOEHRINGER

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

SID

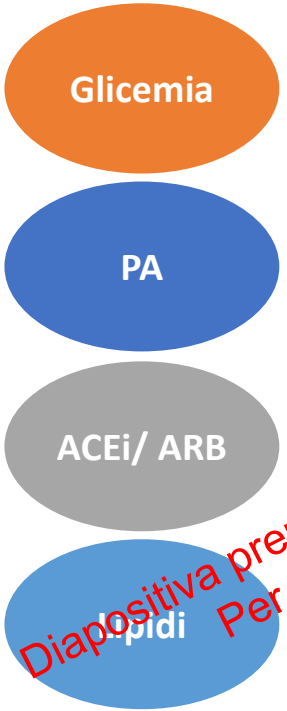
BOLOGNA | 19 NOVEMBRE 2019

Terapia con analoghi del GLP-1: quando e perché

Possiamo puntare ancora di più sulla protezione renale?

Roberto Trevisan
U.O.C. Malattie Endocrine 1 – Diabetologia
ASST Papa Giovanni XXIII Bergamo
Dipartimento Di Medicina e Chirurgia
School of Medicine and Surgery
Università degli Studi di Milano Bicocca

Una strategia multifattoriale aggressiva è raccomandata nel diabetico con malattia renale cronica proteinurica



HbA1c <58 mmol/mol cercando di ridurre al massimo il rischio di ipoglicemie severe

Obiettivo <130/80 mmHg

Utilizzare ACEi and/or ARBs per ridurre la proteinuria

Terapia con farmaci ipolipemizzanti è raccomandata per ridurre il rischio cardiovascolare

1. National Kidney Foundation. *Am J Kidney Dis* 2012;60:850; 2. NICE. Clinical guideline: Type 2 diabetes (CG87), May 2009

Cochrane Library

Cochrane Database of Systematic Reviews

2017, Issue 6. Art. No.: CD010137

Glucose targets for preventing diabetic kidney disease and its progression (Review)

Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, Cignarelli M, Fioretto P, Vecchio M, Craig JC, Strippoli GFM

Analysis 1.10. Comparison 1 Tight versus non-tight glycaemic control, Outcome 10 Onset microalbuminuria.

Review: Glucose targets for preventing diabetic kidney disease and its progression

Comparison: 1 Tight versus non-tight glycaemic control

Outcome: 10 Onset microalbuminuria

Onset microalbuminuria

Study or subgroup	Tight n/N	Non-tight n/N	Risk Ratio IVRandom,95% CI	Weight	Risk Ratio IVRandom,95% CI
VADT Study 2003	43/442	61/463		6.8 %	0.74 [0.51, 1.07]
DCCT 1986	110/671	166/694		16.6 %	0.69 [0.55, 0.85]
ACCORD Study 2007	720/3250	828/3273		36.4 %	0.88 [0.80, 0.96]
ADVANCE Study 2001	1318/5571	1434/5569		41.1 %	0.92 [0.86, 0.98]
Total (95% CI)	**9934**	**9999**		**100.0 %**	**0.85 [0.77, 0.94]**

Total events: 2191 (Tight), 2489 (Non-tight)

Heterogeneity: Tau² = 0.01; Chi² = 7.62, df = 3 (P = 0.05); I² = 61%

Test for overall effect: Z = 3.08 (P = 0.002)

Test for subgroup differences: Not applicable

HR – 15%

0.85 (0.77-0.94)

0.5 0.7 1 1.5 2

Less with tight | Less with non-tight

Analysis 1.11. Comparison 1 Tight versus non-tight glycaemic control, Outcome 11 Progression of microalbuminuria.

Review: Glucose targets for preventing diabetic kidney disease and its progression

Comparison: 1 Tight versus non-tight glycaemic control

Outcome: 11 Progression of microalbuminuria

Progression of microalbuminuria

Study or subgroup	Tight n/N	Non-tight n/N	Risk Ratio IVRandom,95% CI	Weight	Risk Ratio IVRandom,95% CI
Feldt-Rasmussen 1986	0/18	5/18		2.4 %	0.09 [0.01, 1.53]
STENO-2 Study 1999	13/80	31/80		21.5 %	0.42 [0.24, 0.74]
DCCT 1986	18/710	42/659		21.9 %	0.50 [0.29, 0.87]
VADT Study 2003	14/442	29/240		21.9 %	0.63 [0.36, 1.09]
ADVANCE Study 2001	257/5571	411/5569		32.4 %	0.92 [0.86, 0.98]
Total (95% CI)	**6636**	**6636**		**100.0 %**	**0.59 [0.38, 0.93]**

Total events: 302 (Tight), 1512 (Non-tight)

Heterogeneity: Tau² = 0.16; Chi² = 16.46, df = 4 (P = 0.003); I² =75%

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

HR – 41%

0.59 (0.38-0.93)

0.005 0.1 1 10 200

Less with tight | Less with non-tight

Analysis 1.2. Comparison 1 Tight versus non-tight glycaemic control, Outcome 2 Development ESKD.

Review: Glucose targets for preventing diabetic kidney disease and its progression

Comparison: 1 Tight versus non-tight glycaemic control

Outcome: 2 Development ESKD

Development ESKD

Study or subgroup	Tight n/N	Non-tight n/N	Risk Ratio IVRandom,95% CI	Weight	Risk Ratio IVRandom,95% CI
STENO-2 Study 1999	0/80	3/80		3.8 %	0.14 [0.01, 2.72]
VADT Study 2003	7/899	11/899		22.6 %	0.64 [0.25, 1.63]
ADVANCE Study 2001	7/5571	20/5569		25.0 %	0.35 [0.15, 0.83]
ACCORD Study 2007	138/5119	151/5115		48.5 %	0.91 [0.73, 1.15]
Total (95% CI)	**11669**	**11663**		**100.0 %**	**0.62 [0.34, 1.12]**

Total events: 152 (Tight), 185 (Non-tight)

Heterogeneity: Tau² = 0.18; Chi² = 6.22, df = 3 (P = 0.10); I² =52%

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

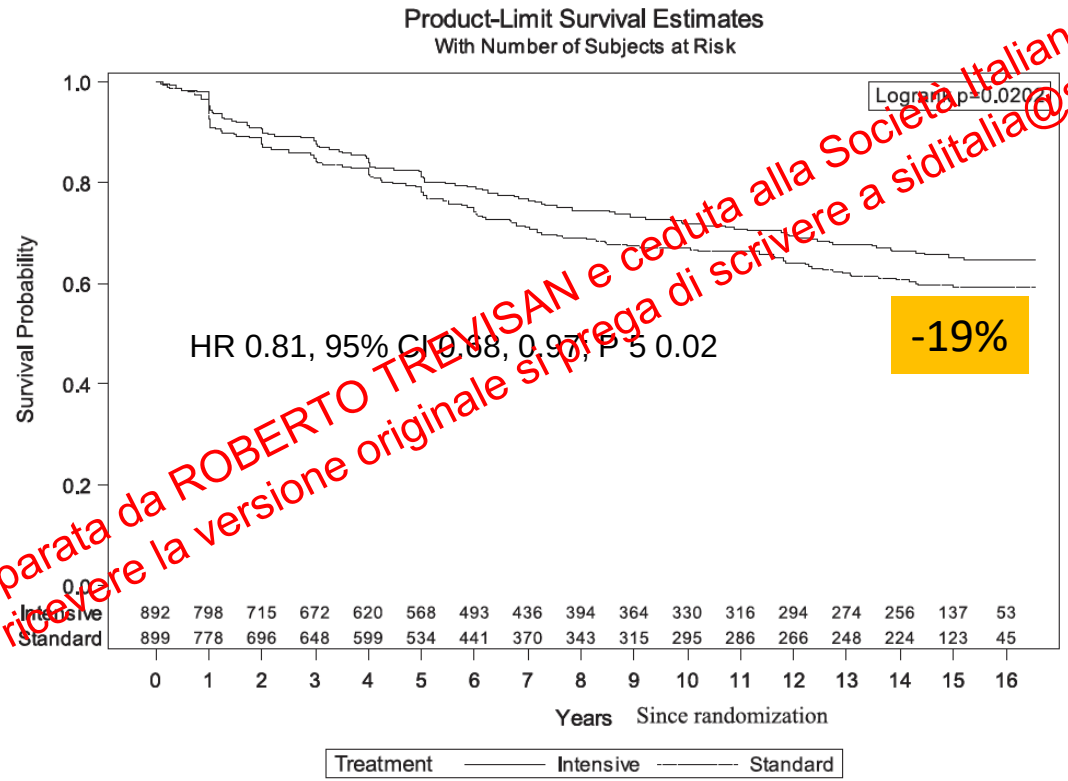
HR – 38%

0.62 (0.34-1.12)

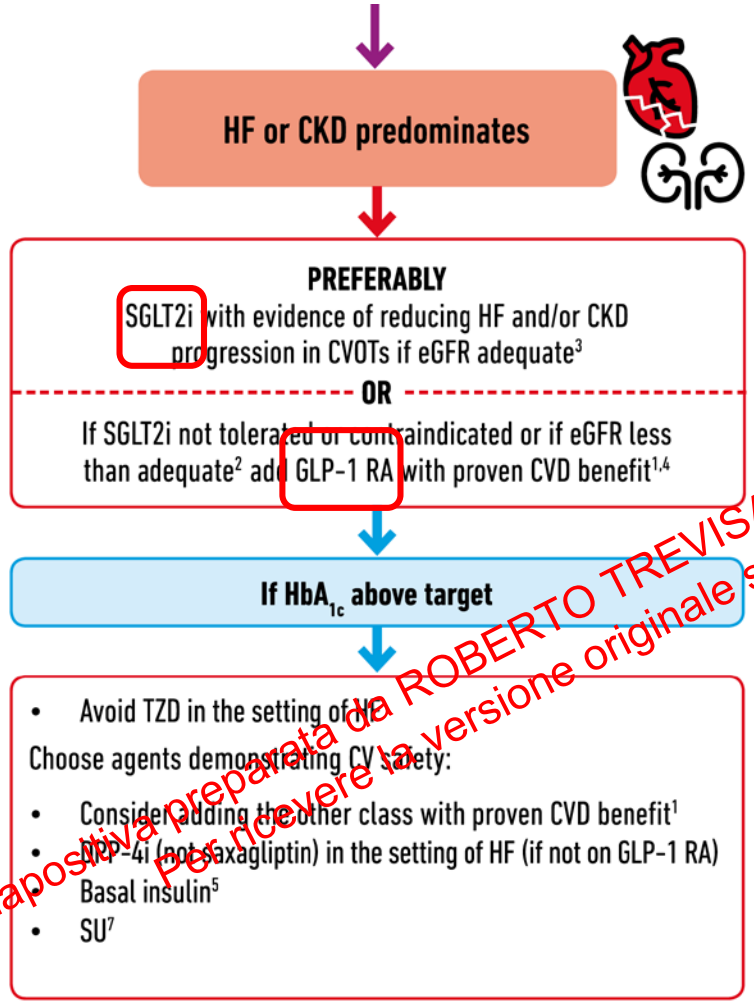
0.005 0.1 1 10 200

Less with tight | Less with non-tight

Intensive Glycemic Control Improves Long-term Renal Outcomes in Type 2 Diabetes in the Veterans Affairs Diabetes Trial (VADT)



Diabetes Care 2019



Diabetes Care

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

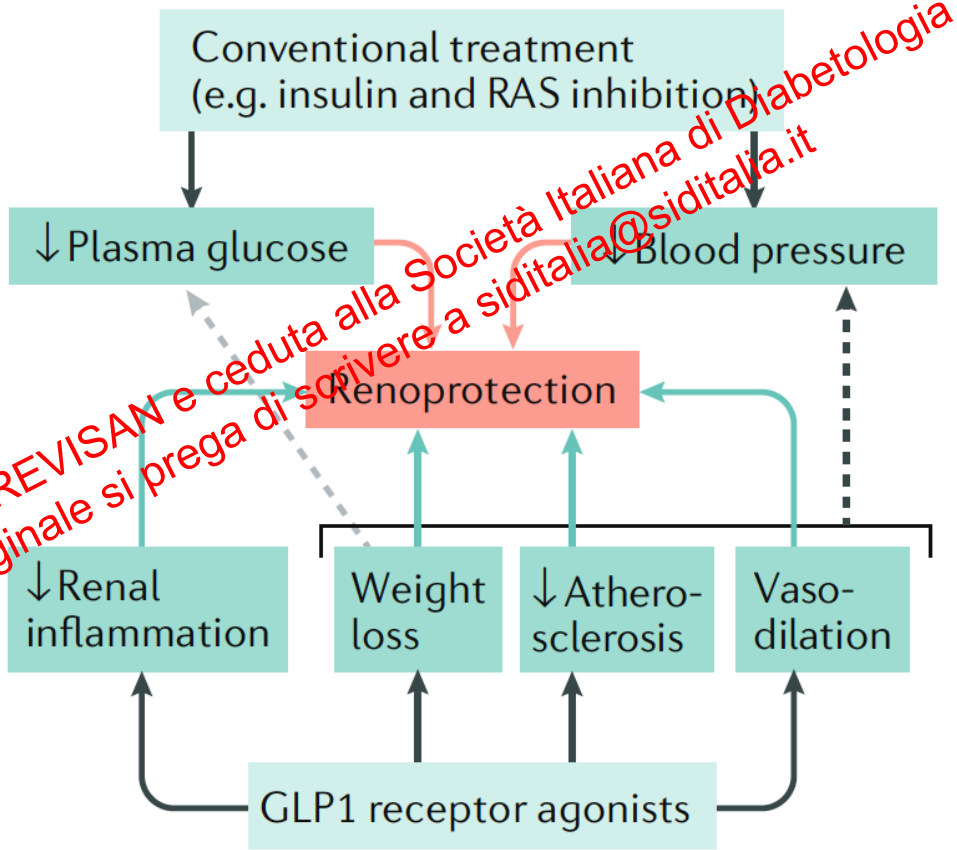
Melanie J. Davies,[1,2] David A. D'Alessio,[3] John Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs

4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycemia

Ma perché le *Linee Guida* consigliano anche in questi pazienti i GLP-1 RA?

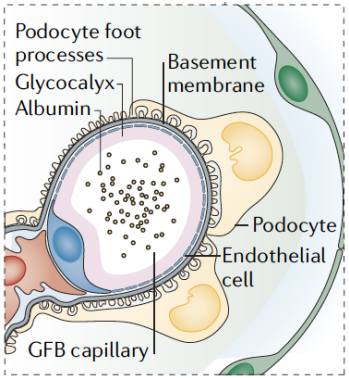
Potential renoprotective effects of GLP1 receptor agonists



nature Reviews | NePhroLoGy, Nov 2018

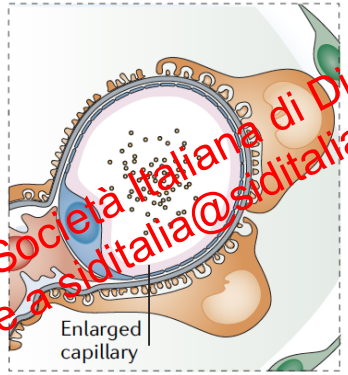
Total GFR and SNGFR ~120 ml/min

Normal



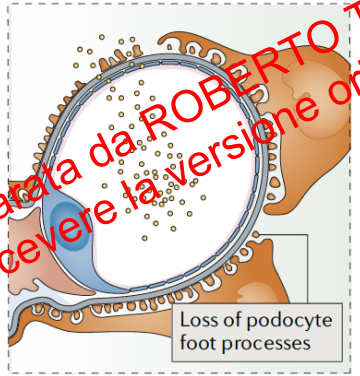
↑SNGFR →↑ total GFR
Glomerular hypertrophy

DM



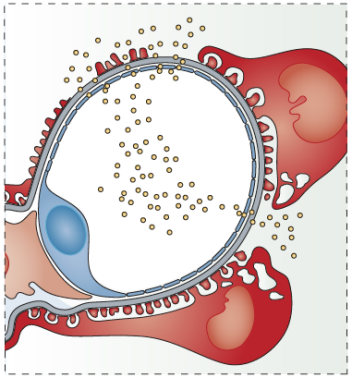
↑ ↑ SNGFR →↑ total GFR
Glomerular hypertrophy

DM
Early CKD



↑ ↑ ↑ SNGFR →↓ total GFR
Massive Glomerular hypertrophy

DM
Advanced
CKD



Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Josef Coresh, Hiddo J L Heerspink, Yingying Sang, Kunihiro Matsushita, Johan Arnlov, Brad C Astor, Corri Black, Nigel J Brunskill, Juan-Jesus Carrero, Harold I Feldman, Caroline S Fox, Lesley A Inker, Areef Ishani, Sadayoshi Ito, Simerjot Jassal, Tsuneo Konta, Kevan Polkinghorne, Solfrid Romundstad, Marit D Solbu, Nikita Stempniewicz, Benedicte Stengel, Marcello Tonelli, Mitsumasa Umesawa, Sushrut S Waikar, Chi-Pang Wen, Jack F M Wetzels, Mark Woodward, Morgan E Grams, Csaba P Kovesdy, Andrew S Levey, Ron T Gansevoort, for the Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration*

Summary

Background Change in albuminuria as a surrogate endpoint for progression of chronic kidney disease is strongly supported by biological plausibility, but empirical evidence to support its validity in epidemiological studies is lacking. We aimed to assess the consistency of the association between change in albuminuria and risk of end-stage kidney disease in a large individual participant-level meta-analysis of observational studies.

Methods In this meta-analysis, we collected individual-level data from eligible cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) with data on serum creatinine and change in albuminuria and more than 50 events on outcomes of interest. Cohort data were eligible if participants were aged 18 years or older, they had a repeated measure of albuminuria during an elapsed period of 8 months to 4 years, subsequent end-stage kidney disease or mortality follow-up data, and the cohort was active during this consortium phase. We extracted participant-level data and quantified percentage change in albuminuria, measured as change in urine albumin-to-creatinine ratio (ACR) or urine protein-to-creatinine ratio (PCR), during baseline periods of 1, 2, and 3 years. Our primary outcome of interest was development of end-stage kidney disease after a baseline period of 2 years. We defined an end-stage kidney disease event as initiation of kidney replacement therapy. We quantified associations of percentage change in albuminuria with subsequent end-stage kidney disease using Cox regression in each cohort, followed by random-effects meta-analysis. We further adjusted for regression dilution to account for imprecision in the estimation of albuminuria at the participant level. We did multiple subgroup analyses, and also repeated our analyses using participant-level data from 14 clinical trials, including nine clinical trials not in CKD-PC.

Findings Between July, 2015, and June, 2018, we transferred and analysed data from 28 cohorts in the CKD-PC, which included 693 816 individuals (557 583 [80%] with diabetes). Data for 675 904 individuals and 7461 end-stage kidney disease events were available for our primary outcome analysis. Change in ACR was consistently associated with subsequent risk of end-stage kidney disease. The adjusted hazard ratio (HR) for end-stage kidney disease after a 30% decrease in ACR during a baseline period of 2 years was 0·83 (95% CI 0·74–0·94), decreasing to 0·78 (0·66–0·92) after further adjustment for regression dilution. Adjusted HRs were fairly consistent across cohorts and subgroups (ie, estimated glomerular filtration rate, diabetes, and sex), but the association was somewhat stronger among participants with higher baseline ACR than among those with lower baseline ACR ($p_{interaction}<0·0001$). In individuals with baseline ACR of 300 mg/g or higher, a 30% decrease in ACR over 2 years was estimated to confer a more than 1% absolute reduction in 10-year risk of end-stage kidney disease, even at early stages of chronic kidney disease. Results were generally similar when we used change in PCR and when study populations from clinical trials were assessed.

Interpretation Change in albuminuria was consistently associated with subsequent risk of end-stage kidney disease across a range of cohorts, lending support to the use of change in albuminuria as a surrogate endpoint for end-stage kidney disease in clinical trials of progression of chronic kidney disease in the setting of increased albuminuria.

Funding US National Kidney Foundation and US National Institute of Diabetes and Digestive and Kidney Diseases.

Lancet Diabetes Endocrinol 2019

Published Online January 8, 2019 http://dx.doi.org/10.1016/S2213-8587(18)30313-9

See Online/Comment http://dx.doi.org/10.1016/S2213-8587(18)30352-8

*Members listed at the end of the Article

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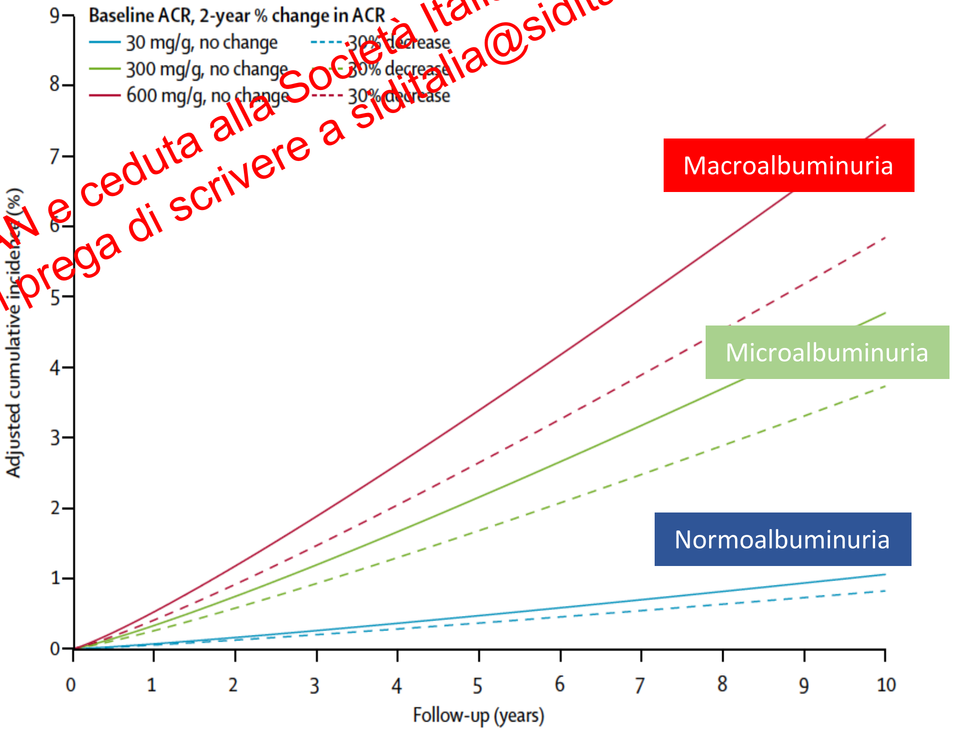
Introduction

On March 15–16, 2018, a scientific workshop sponsored by the US National Kidney Foundation (NKF), in collaboration with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), investigated candidate surrogate endpoints for clinical trials of drugs designed to slow the progression of kidney disease, particularly among patients in the early stages of chronic kidney disease. For decades, change in albuminuria has been used in some clinical trials for the development of

Adjusted cumulative incidence of ESRD by years of follow-up for three levels of baseline albuminuria and a 30% decline in albuminuria for each level, measured by ACR



Putative renal distribution of GLP-1R

Location	Species	mRNA or protein	Detection method
GLP-1R			
Preglomerular* vascular smooth muscle cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1 agonist) and exendin 9–39 (GLP-1R antagonist)
Hilar and intralobular arteries	Human	Protein	Autoradiography of ^{125}I-labelled GLP-1
Glomerular capillary and vascular walls	Mouse	mRNA	*In situ* hybridization; RT-PCR
Glomerular endothelial cells and macrophages	Rat	Protein	Immunofluorescence
Glomerulus (not specified)	Rat	mRNA	RT-PCR
Juxtaglomerular cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Immunohistochemistry
Proximal tubule	Rat	mRNA	RT-PCR
	Pig; human	mRNA, protein	RT-PCR, immunocytochemistry, immunohistochemistry, Western blotting
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1R agonist) and exendin 9–39 (GLP-1R antagonist)

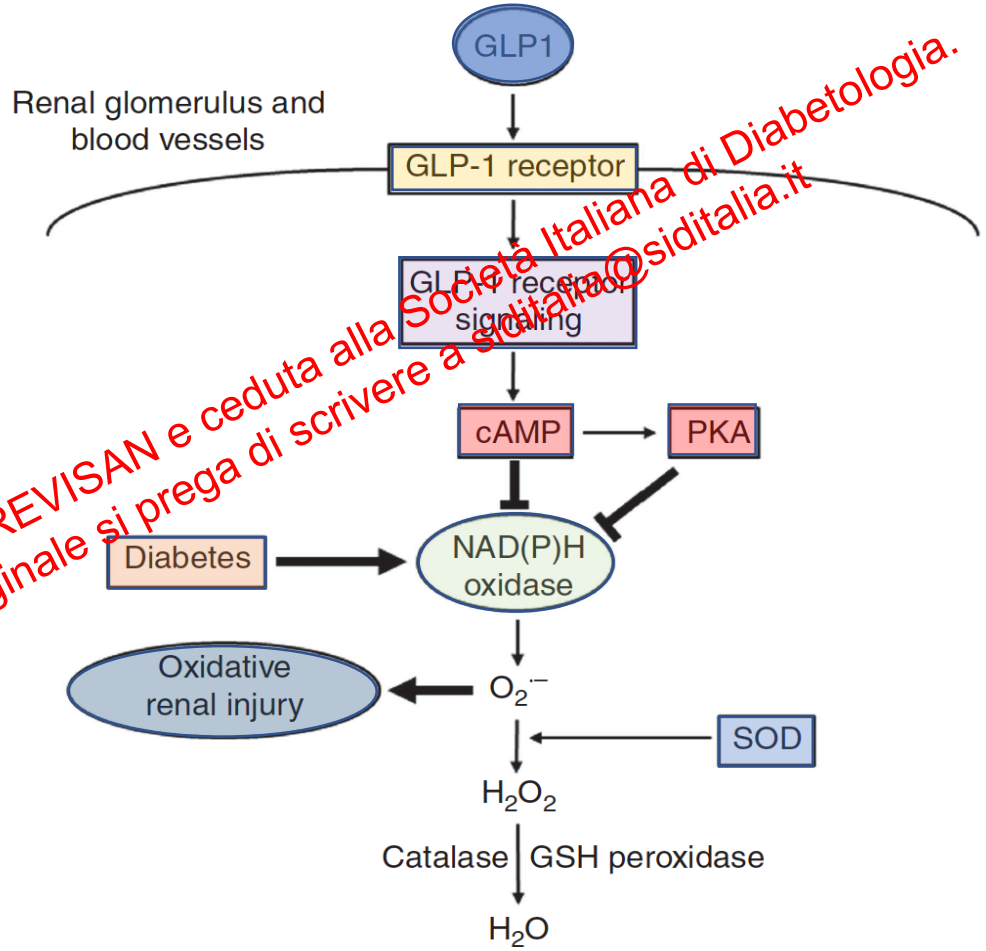
Muskiet, M. H. A. *et al.* (2017) GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes
Nat. Rev. Nephrol. doi:10.1038/nrneph.2017.123

Glucose-independent effects of GLP-1 RA on renal risk factors in type 2 diabetes mellitus

Glomerular hyperfiltration	↓ NHE3 activity⇢ ↑Tubuloglomerular Feedback ⇢ ↑ Natriuresis
	↓ Post Prandial Glucagon
	↓ Body Weight and Plasma Glucose
	↓RAAS activity ↓AII concentration

Modified from Muskiet, M. H. A. *et al.* (2017) *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2017.123

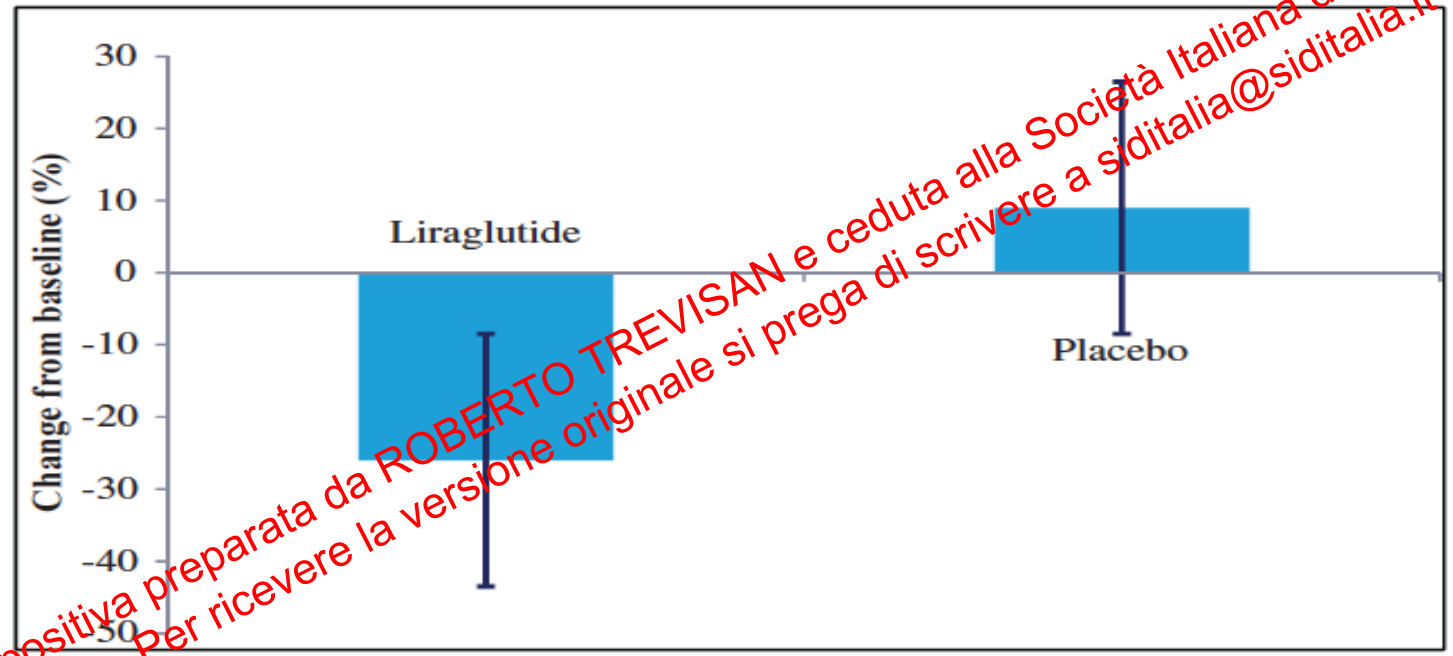
The protective role of GLP-1 receptor–dependent signal-transduction pathway in the kidney



Kidney International (2014) 85, 579–589;

The effect of liraglutide on renal function: A randomized clinical trial

Changes in urinary albumin excretion rate



UAER was reduced by **26** (95% CI: 5; 43)% during liraglutide treatment and increased by 9 (95% CI: −6; 22)% during placebo treatment.

Diabetes Obes Metab 2017; **19(2):**239–247

The effect of liraglutide on renal function: A randomized clinical trial

Parametri clinici

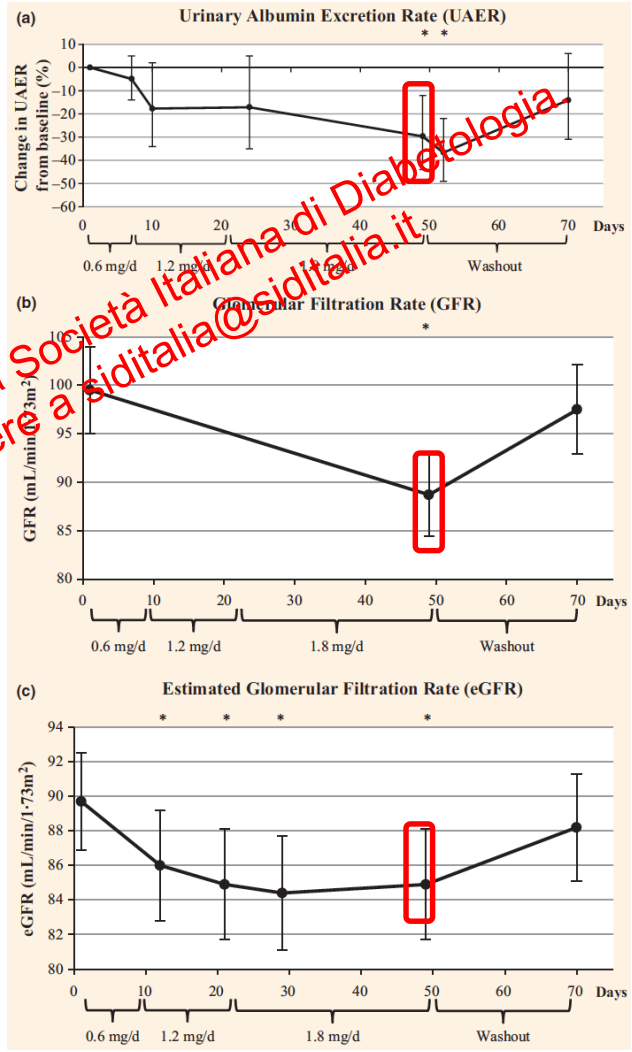
- A1c – 0.7%
- Body Weight – 1.8 kg
- Measured GFR: – 5 ml/min/1.73m²

Parametri ormonali

- P Renin Con – 35%
- P AII conc – 43%
- TNF alpha conc – 12%
- MR- ProANP – 13%

Diabetes Obes Metab 2017; **19(2):**239–247

Effect of liraglutide treatment on kidney measurements in 31 Type 2 diabetic patients with hypertension



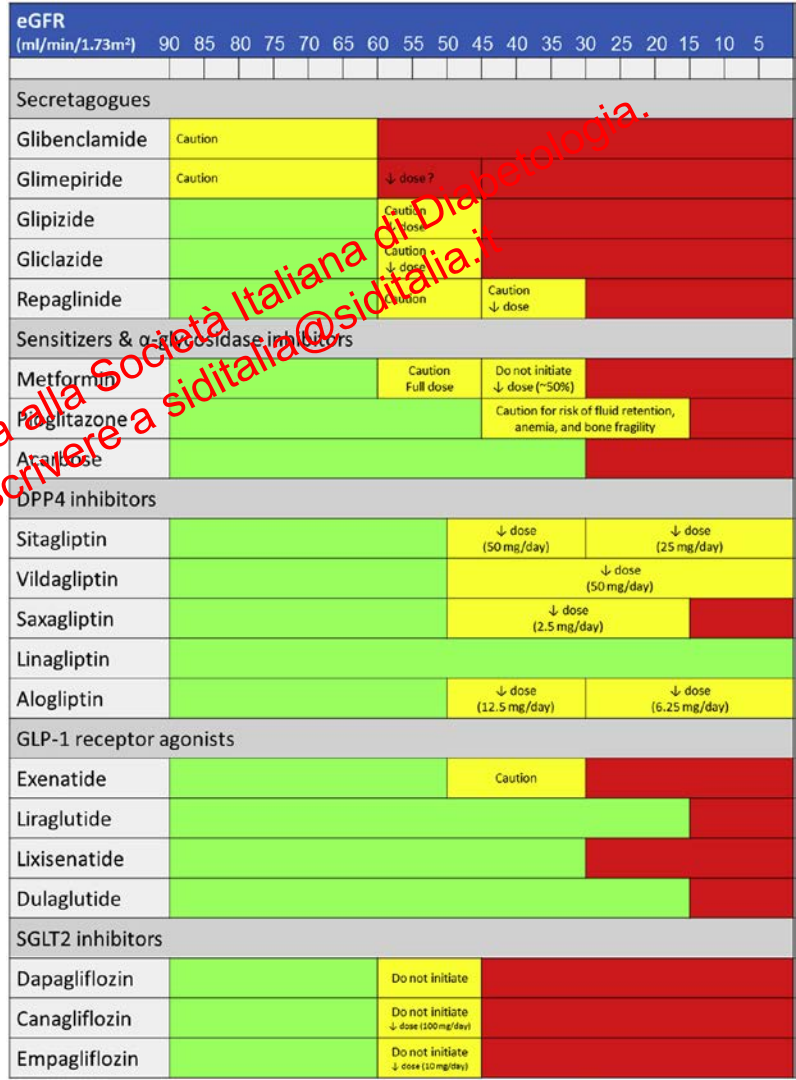
Diabet. Med. 32, 343–352 (2015)

DIABETIC KIDNEY DISEASE

The role of GLP1 - RA

- LIRAGLUTIDE, DULAGLUTIDE e SEMAGLUTIDE possono essere usati in sicurezza fino a 15 ml/min/1.73m².
- La loro efficacia sul controllo glicemico non si riduce con la riduzione della funzione renale.

Nutrition, Metabolism & Cardiovascular Diseases 2019



Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

Lancet Diabetes Endocrinol 2019

Development of macroalbuminuria, doubling of serum creatinine or 40% or greater decline in eGFR, development of ESRD, or death due to kidney disease

Composite kidney outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (6%)		0·84 (0·69–1·02)	0·083
LEADER	268/4668 (6%)	337/4672 (7%)		0·78 (0·67–0·92)	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 (I²=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%)	41/3031 (1%)		1·16 (0·74–1·83)		0·51
LEADER	87/4668 (2%)	97/4672 (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	246/6246 (4%)	273/6458 (4%)		0·88 (0·74–1·05)		0·16
REWIND	206/4949 (2%)	237/4952 (5%)		0·70 (0·57–0·85)		0·0004
Overall (I²=42·7%, p=0·137)	**592/20753 (3%)**	**662/20762 (3%)**		**0·87 (0·73–1·03)**	**245 (118 to –1064†)**	**0·098**

-36%

-22%

-15%

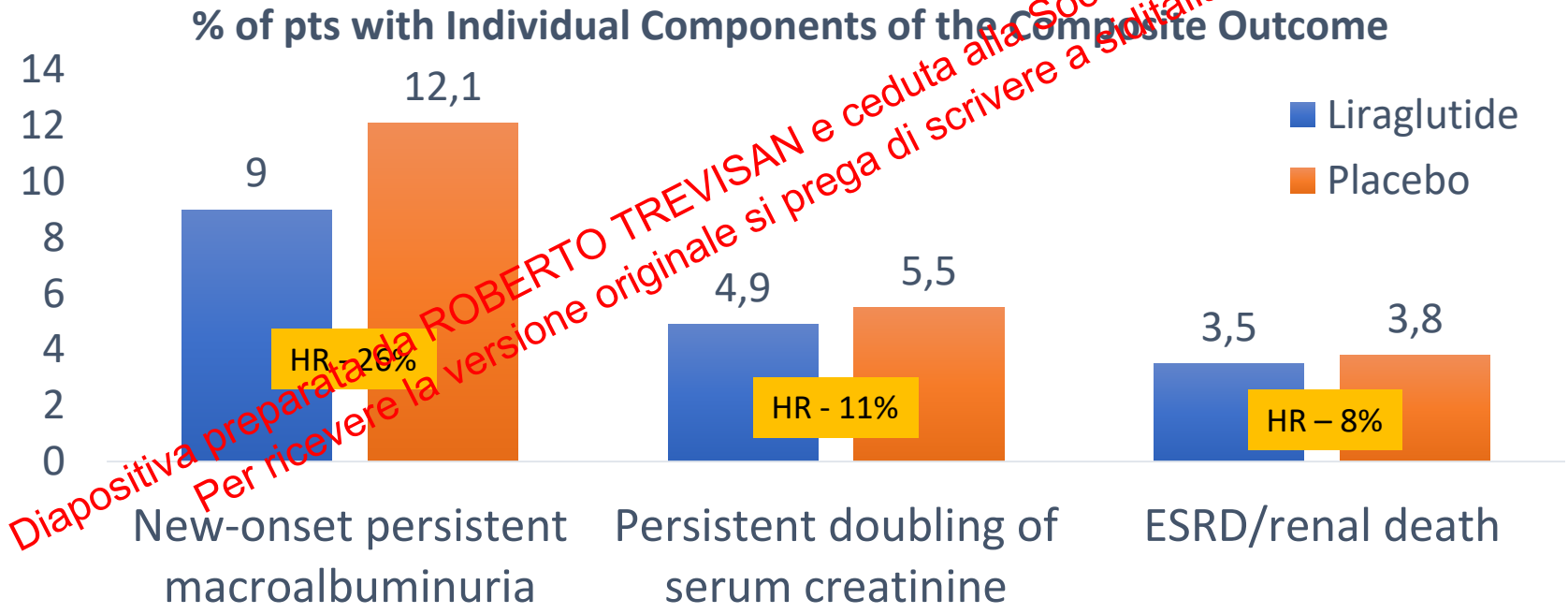
Doubling of serum creatinine or 40% or greater decline in eGFR

0·5 1 1·5

Favours GLP-1 receptor agonist

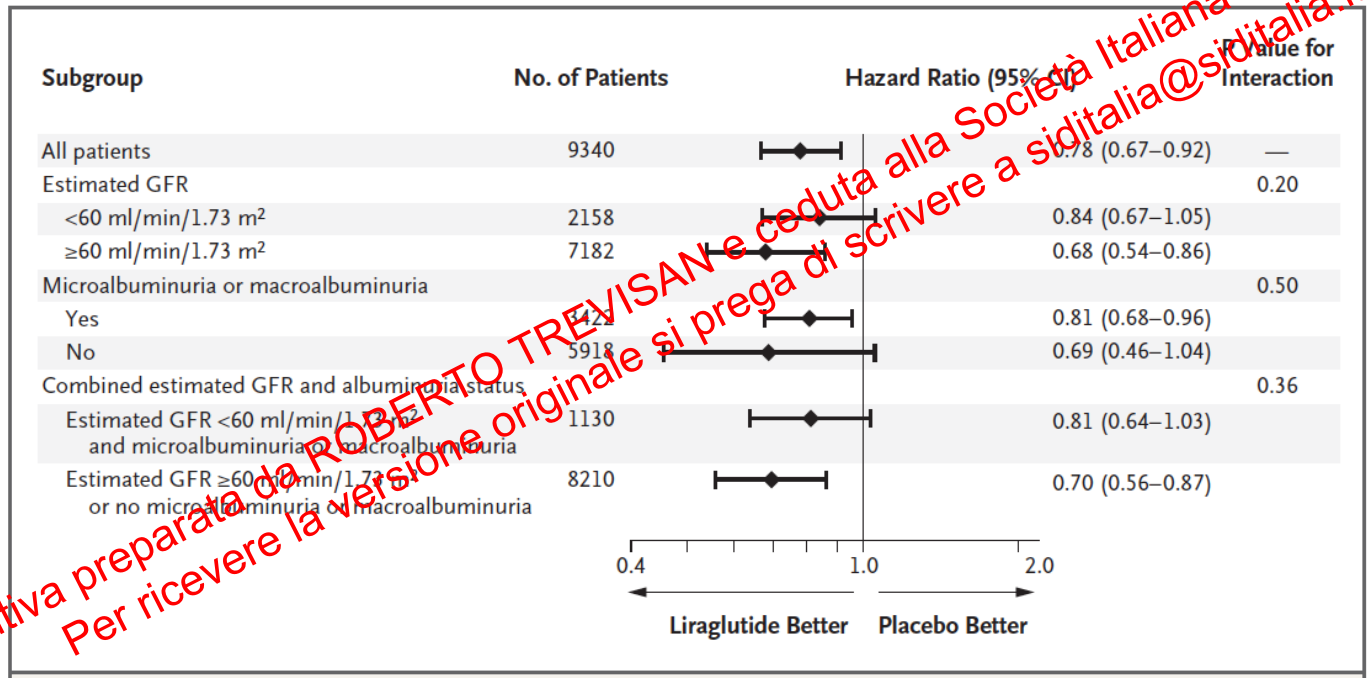
Favours placebo

LEADER:
Individual Components of the Composite Renal Outcome



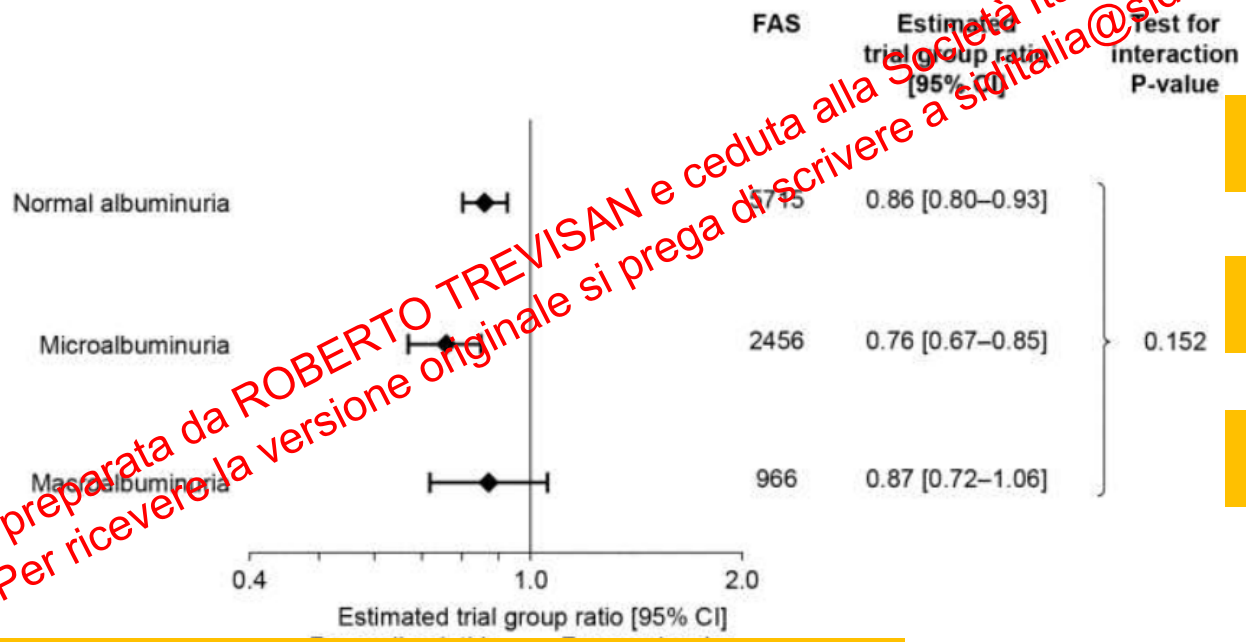
LEADER:

Composite Renal Outcome, According to Baseline Renal Risk



N Engl J Med 2017;377:839-48.

LEADER: Urinary albumin-to-creatinine: ratio to baseline at 3-year visit in subgroups according to albuminuria at baseline



HR - 14%

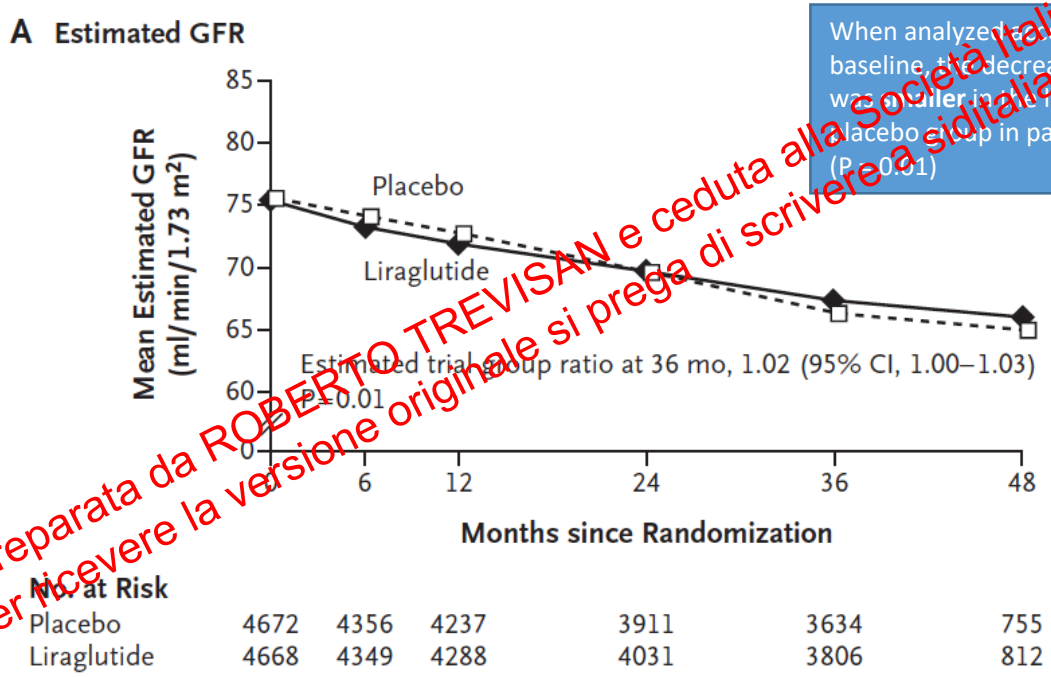
HR - 24%

HR - 13%

Risk of new onset microalbuminuria - 13%

N Engl J Med 2017;377:839-48.

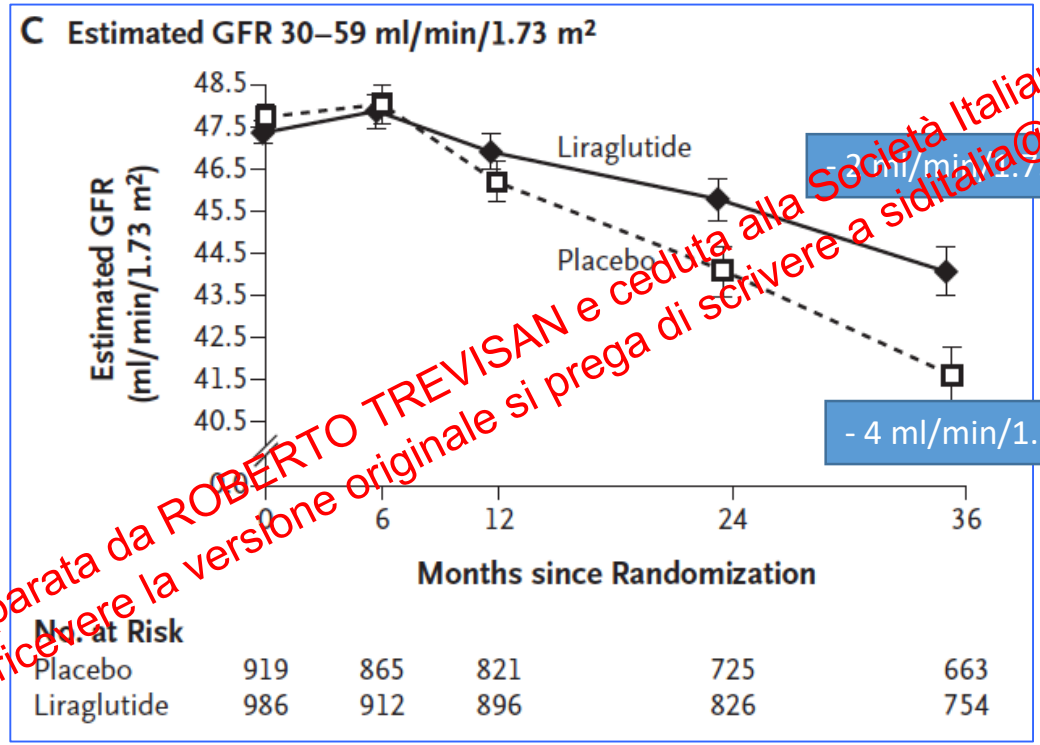
LEADER: Changes in the Estimated eGFR



When analyzed according to albuminuria at baseline, the decrease in the estimated GFR was smaller in the liraglutide group than in the placebo group in patients with macroalbuminuria (P=0.01)

N Engl J Med 2017;377:839-48.

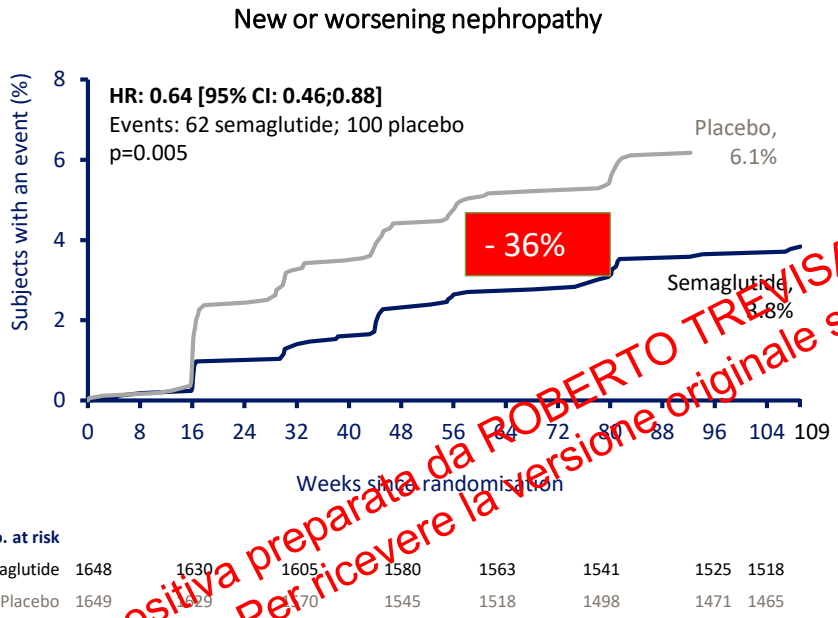
LEADER: Mean Estimated GFR during the Trial in Subgroup with Estimated GFR at Baseline between 30-59 ml/min/1.73m^2



N Engl J Med 2017;377:839-48.

SUSTAIN 6

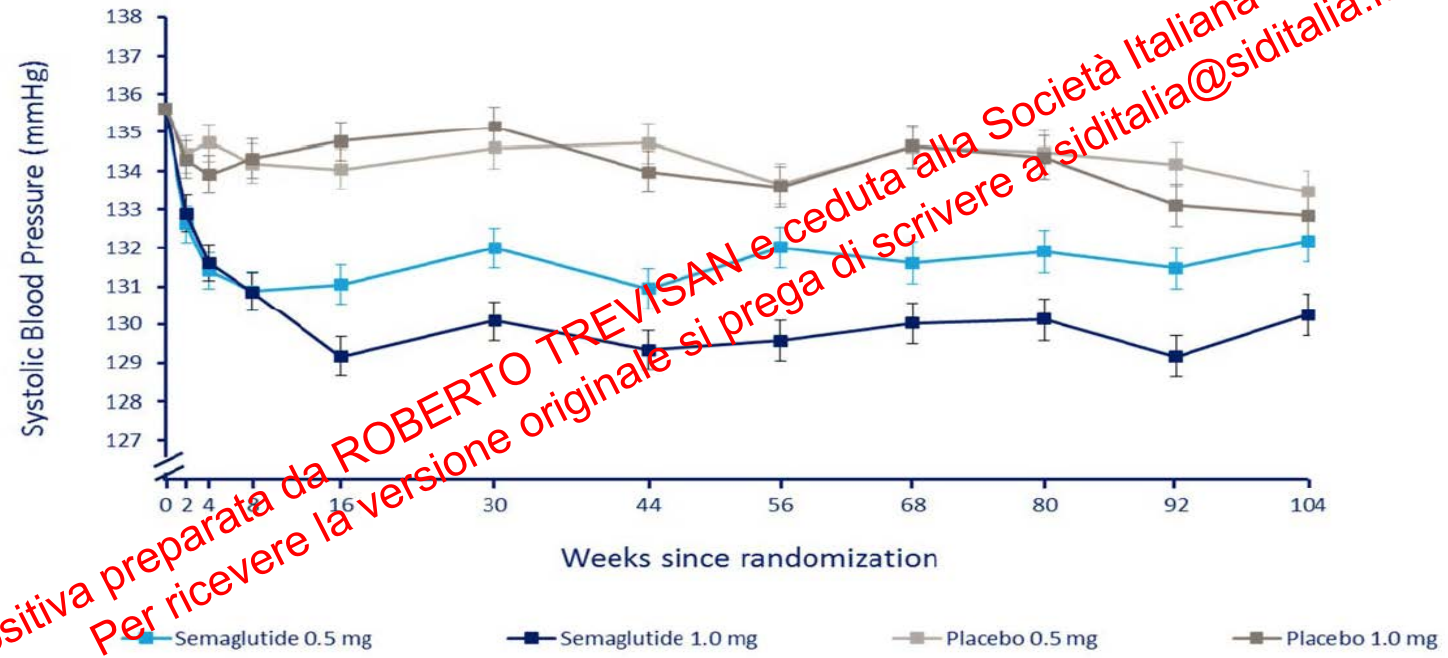
Nephropathy outcomes



Nephropathy outcomes	Semaglutide N (%)	Semaglutide Incidence rate per 100 PYR	Placebo N (%)	Placebo Incidence rate per 100 PYR	HR (95% CI)	P value
New or worsening nephropathy	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46; 0.88)	0.005
Persistent macroalbuminuria	44 (2.7)	1.31	81 (4.9)	2.47	0.54 (0.37; 0.77)	0.001
Persistent doubling of serum Cr level and CrCl per MDRD <45 ml/min/1.73 m^2	18 (1.1)	0.53	14 (0.8)	0.41	1.28 (0.64; 2.58)	0.48
Need for continuous renal-replacement therapy	11 (0.7)	0.32	12 (0.7)	0.35	0.91 (0.40; 2.07)	0.83

- Kaplan–Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy (A) or EAC-confirmed diabetic retinopathy complication (B) using 'in-trial' data from subjects in the full analysis set. HR is from a proportional hazard model. CI, confidence interval; Cr, creatinine; CrCl, creatinine clearance; EAC, (external) event adjudication committee; HR, hazard ratio; MDRD, modification of diet in renal disease.
- Marso SP et al. *N Engl J Med* 2016;375:1834–44.

SUSTAIN 6
Systolic Blood Pressure



Supplement to: N Engl J Med 2016;375:1834-44.

L'effetto è significativo sulla comparsa di NUOVA MACROALBUMINURIA

LEADER

Nephropathy outcomes	Liraglutide N	Liraglutide Incidence rate per 100 PYR	Placebo N	Placebo Incidence rate per 100 PYR	HR (95% CI)	P value
New or worsening nephropathy	268	1.50	337	1.90	0.78 (0.67; 0.92)	0.003
Persistent macroalbuminuria	**161**	**0.9**	**215**	**1.21**	**0.74 (0.60; 0.91)**	**0.004**
Persistent doubling of serum Cr level and CrCl per MDRD <45 ml/min/1.73 m^2	87	0.48	97	0.55	0.89 (0.67; 1.198)	0.43
Need for continuous renal-replacement therapy	56	0.31	64	0.36	0.87 (0.61; 1.24)	0.44

N Engl J Med 2016; 375: 311-22.

SUSTAIN 6

Nephropathy outcomes	Semaglutide N	Semaglutide Incidence rate per 100 PYR	Placebo N	Placebo Incidence rate per 100 PYR	HR (95% CI)	P value
New or worsening nephropathy	62	1.88	100	3.06	0.64 (0.46; 0.88)	0.005
Persistent macroalbuminuria	**44**	**1.31**	**81**	**2.47**	**0.54 (0.37; 0.77)**	**0.001**
Persistent doubling of serum Cr level and CrCl per MDRD <45 ml/min/1.73 m^2	18	0.53	14	0.41	1.28 (0.64; 2.58)	0.48
Need for continuous renal-replacement therapy	11	0.32	12	0.35	0.91 (0.40; 2.07)	0.83

N Engl J Med. 2016 Nov 10;375(19):1834-1844.

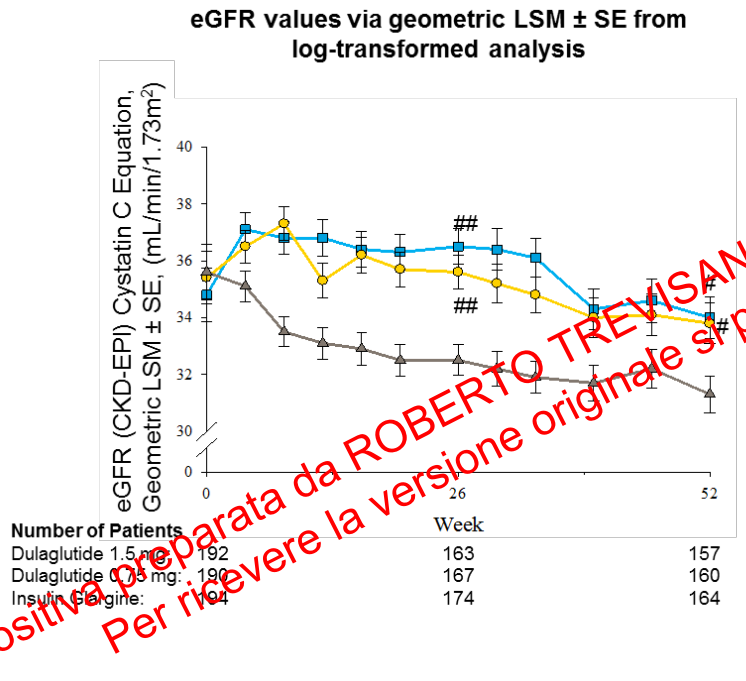
Lancet Diabetes Endocrinol 2018 ,Published Online, June 14, 2018

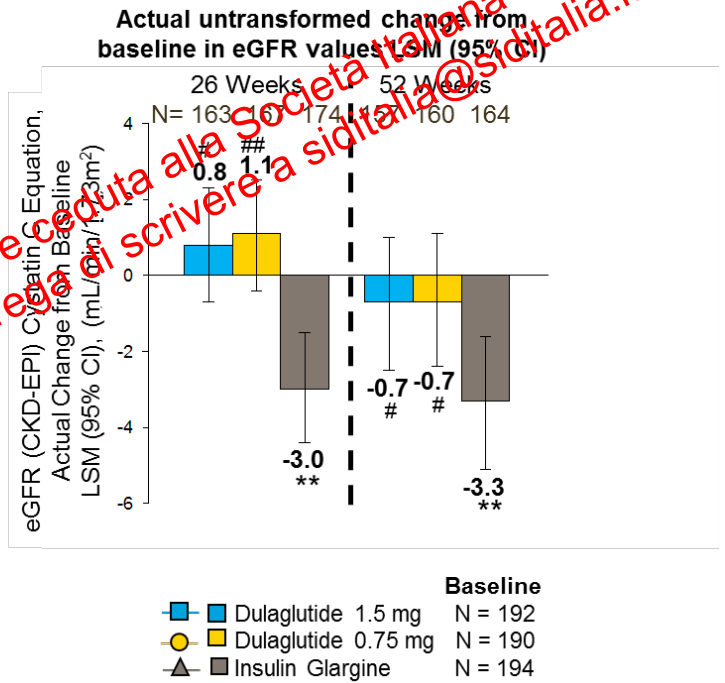
Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fadia E Botros

- Multicentre, open-label trial done in nine countries.
- Adults with type 2 diabetes and moderate-to-severe CKD (stages 3–4), with an A1c of 7·5–10·5%, and who were being treated with insulin or insulin plus an oral antihyperglycaemic drug and were taking a maximum tolerated dose of ACEi or an ARB.
- Participants randomly assigned (1:1:1) to once-weekly injectable dulaglutide 1·5 mg, once-weekly dulaglutide 0·75 mg, or daily insulin glargine as basal therapy, all in combination with insulin lispro, for 52 weeks.
- **Primary outcome A1c at 26 weeks.**
- **Secondary outcomes: eGFR and UACR.**

Change from Baseline eGFR (CKD-EPI) Cystatin C Equation

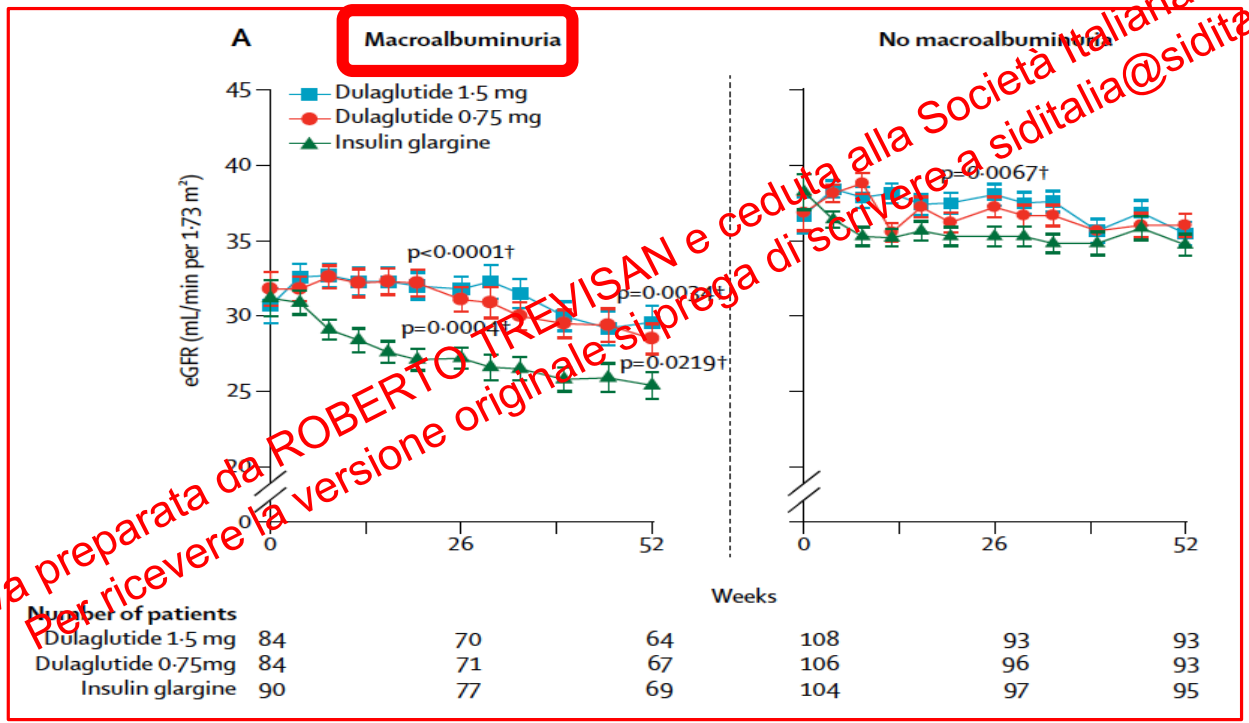




Data presented for safety population, MMRM analysis. P-values are reported for statistical significance at the 26- and 52-week pre-specified analyses points; **p<.0001 versus baseline; #p<.05 and ##p<.0001 versus insulin glargine.

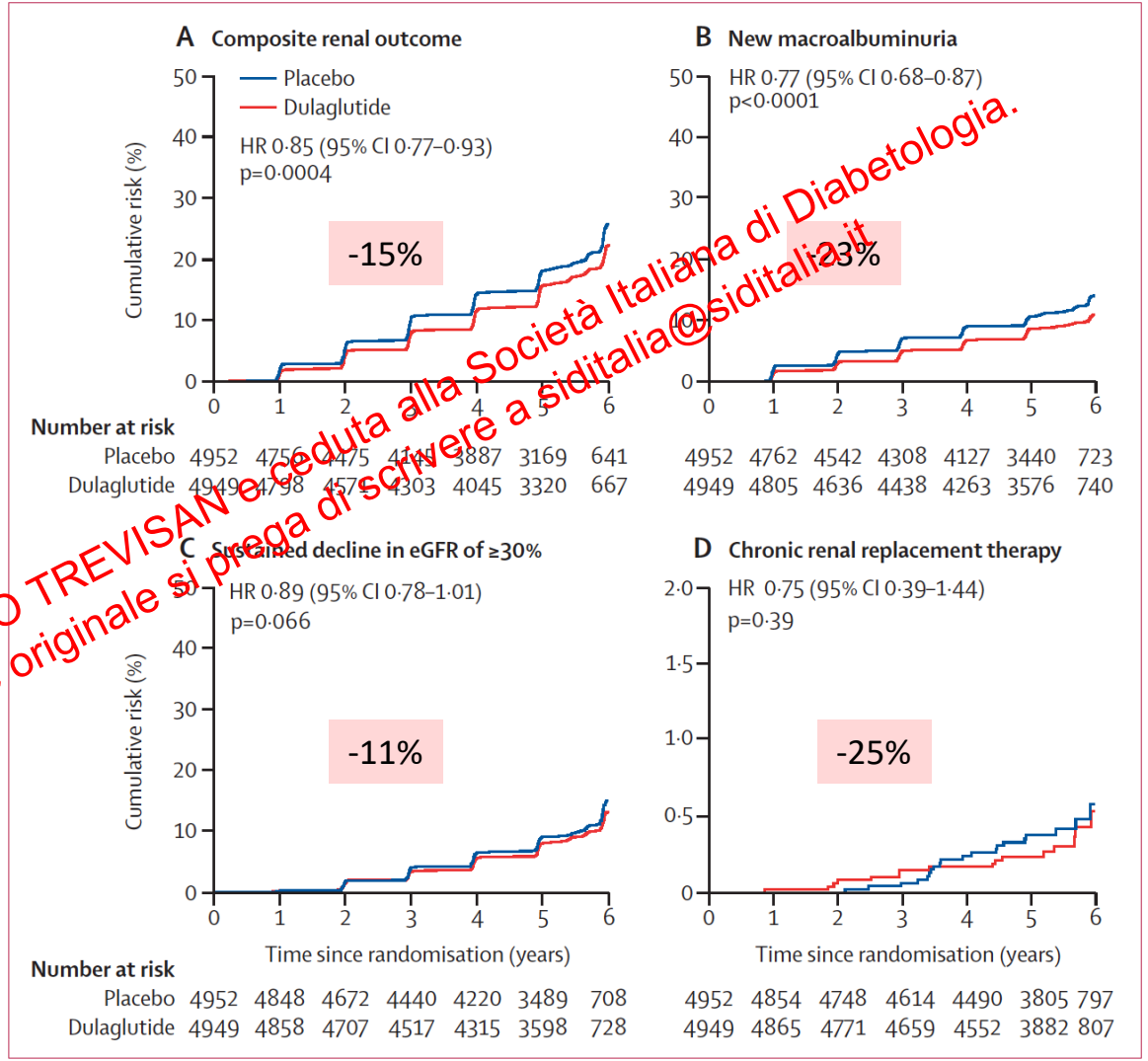
AWARD-7 (Dulaglutide)

Changes in estimated glomerular filtration rate by macroalbuminuria status at baseline



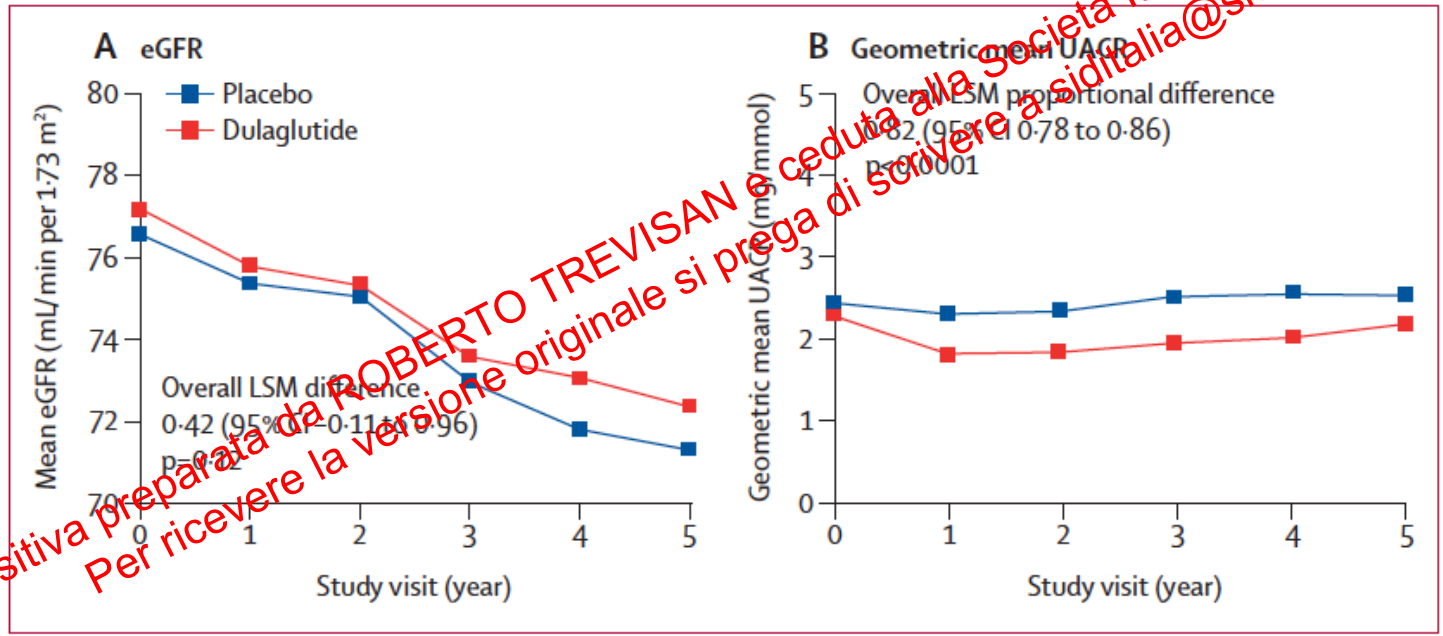
Lancet Diabetes Endocrinol 2018

REWIND
Cumulative incidence of renal outcomes



Lancet Diabetes and Endocrinology 2019

REWIND:
changes in eGFR and UACR during the study



Lancet Diabetes and Endocrinology 2019

REWIND

Effect of treatment allocation on renal outcomes

	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)			
Sensitivity analyses of renal effect							
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	-30%	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	387 (11·9%)	2·36	751 (15·2%)	3·10		0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥40%	61 (1·2%)	0·24	108 (2·2%)	0·42	-44%	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

Lancet Diabetes and Endocrinology 2019

CONCLUSIONI

- I GLP1 – RA sono i farmaci più potenti (dopo insulina) nel ridurre l'emoglobina glicata e, oltre a ridurre peso e pressione arteriosa, sono sicuri nei pazienti diabetici di tipo 2 con malattia renale anche con IRC medio severa (fino a eGFR = 15 ml/min).
- I GLP1-RA sono efficaci non solo nel ridurre CVD, ma rappresentano una nuova opzione terapeutica per la prevenzione della progressione della nefropatia diabetica: riducono albuminuria e il declino del GFR.
- La riduzione di peso e glicemia non sembrano sufficienti a spiegare la rapida comparsa del beneficio renale dopo l'assunzione dei GLP1 – RA.
- Azioni dirette a livello renale (inibizione del NHE3, riduzione dell'AII e dell'infiammazione cronica) potrebbero giocare un ruolo nella nefroprotezione.

Grazie per la vostra attenzione