Controllo glicemico nel paziente con insufficienza renale

Paola Fioretto

Dipartimento di Medicina

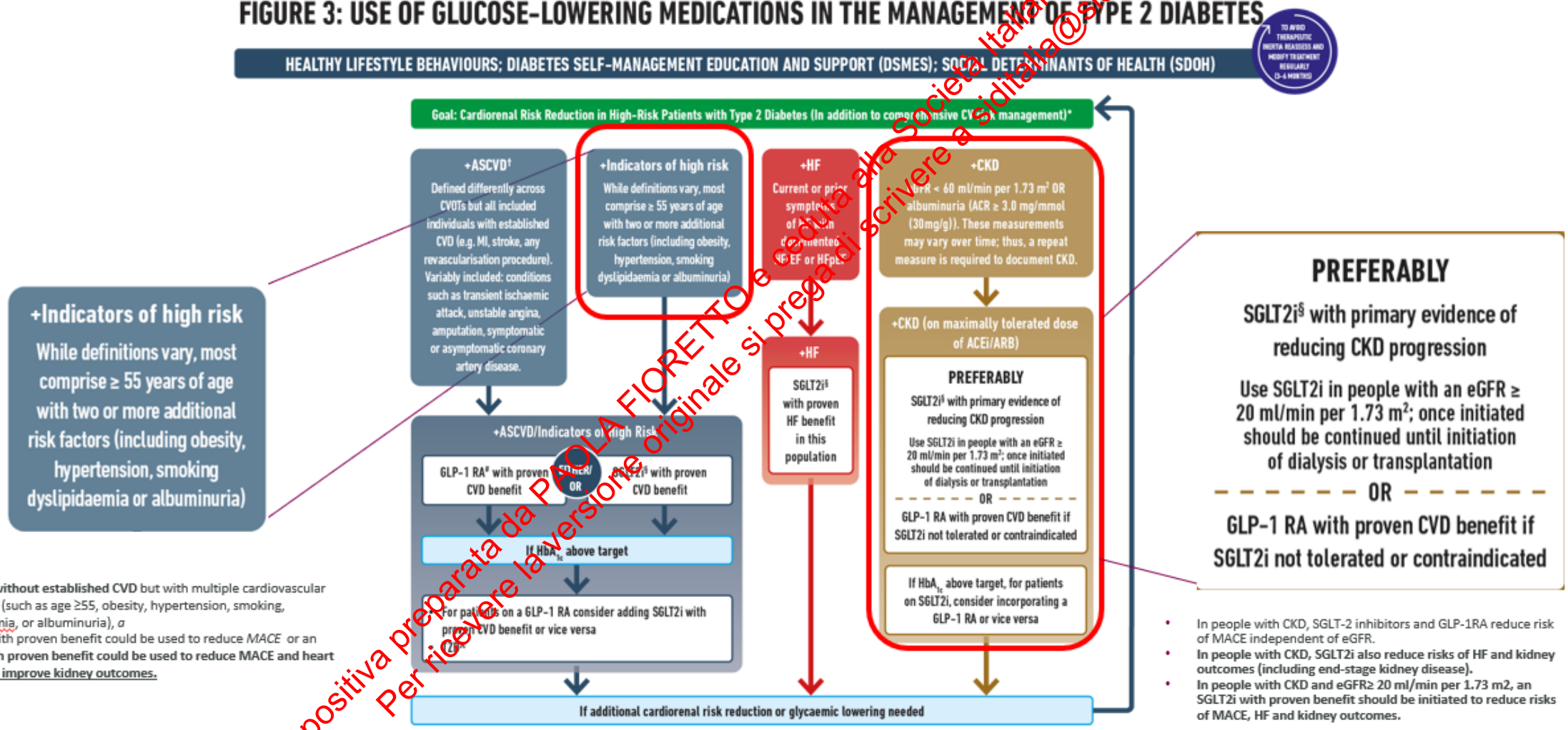
Università di Padova

Controllo glicemico nel paziente con insufficienza renale

- Quali farmaci ipoglicemizzanti nel paziente con insufficienza renale

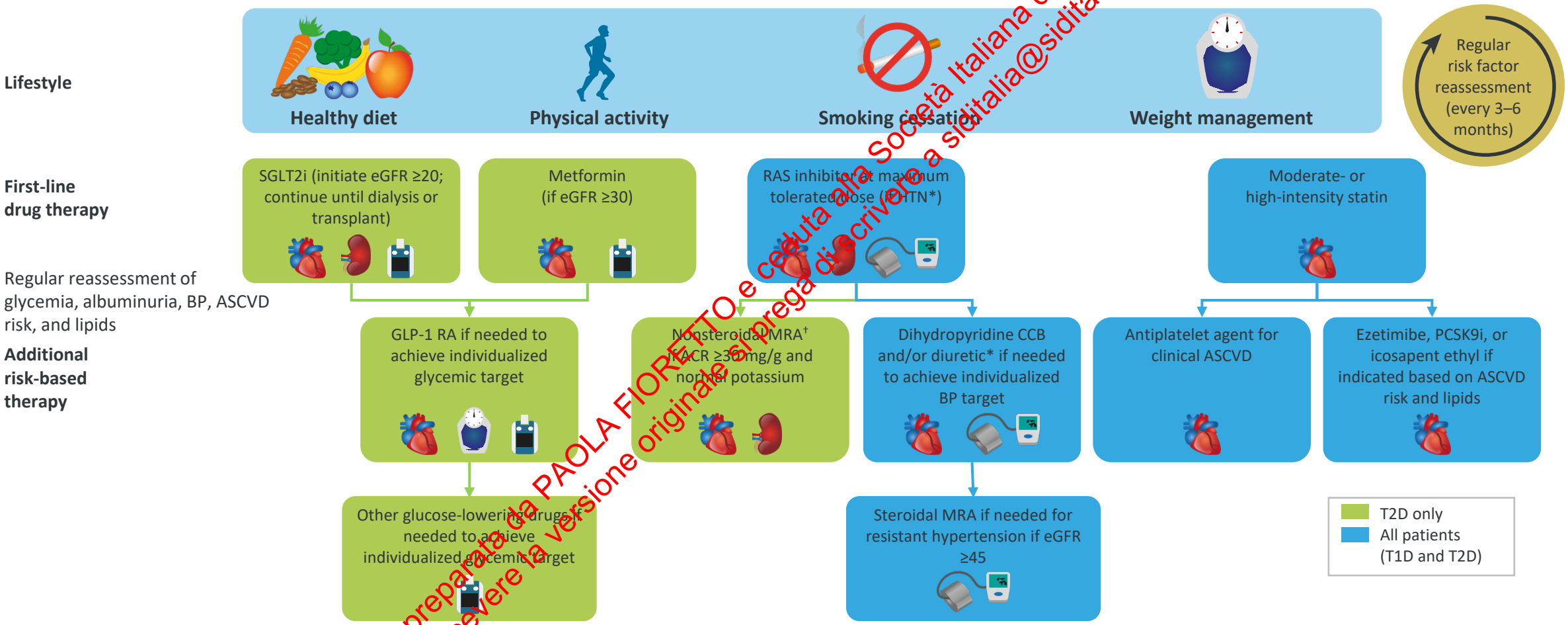
- Efficacia nefroprotettiva dei farmaci ipoglicemizzanti

CONSENSUS EASD-ADA 2022



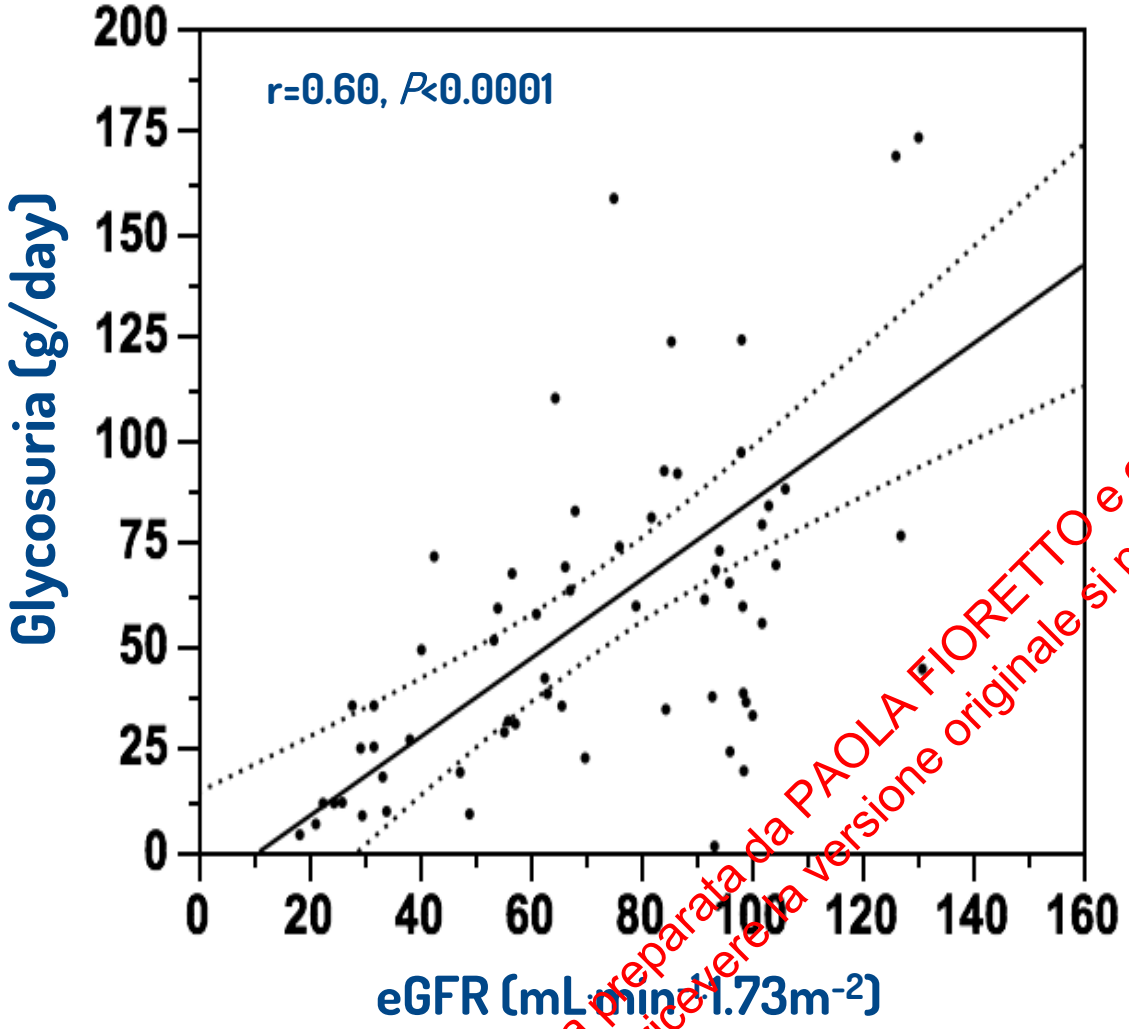
Davies MJ, et al. Diabetes Care 2022; Diabetologia 2022

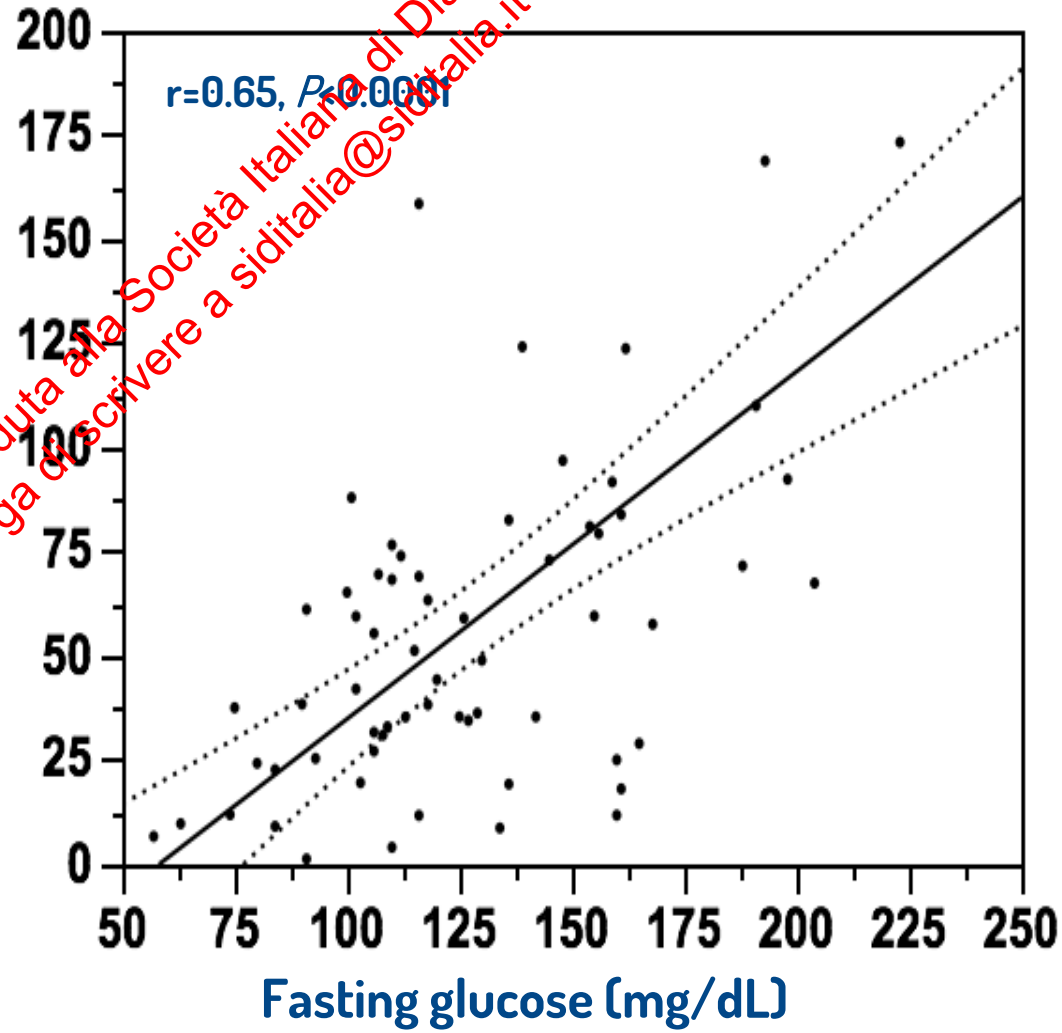
Comprehensive care for Diabetes & CKD



de Boer IH et al, Kidney Int, 3 oct 2022

Glycosuria Depends on GFR and Glycemia

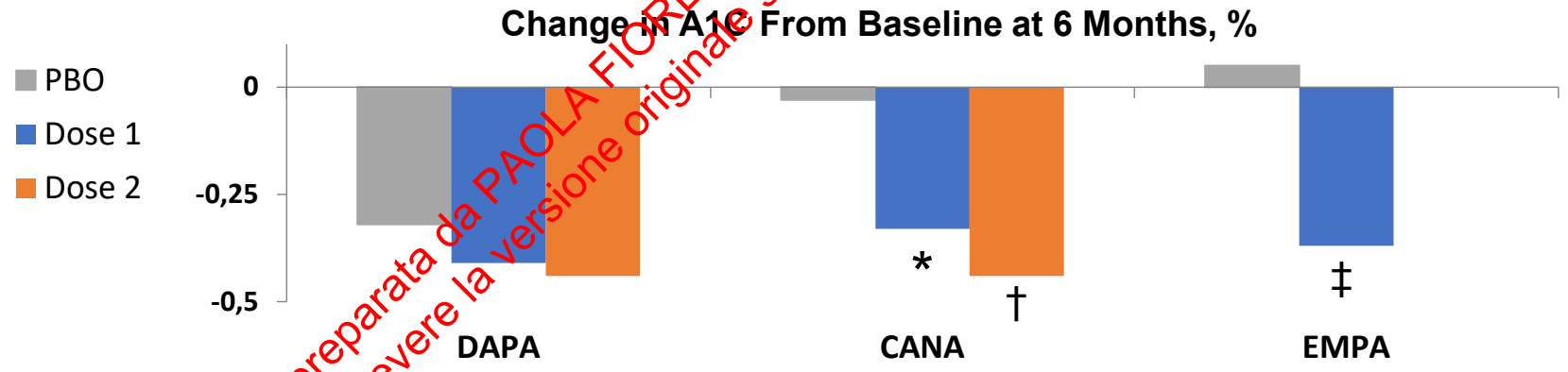




Ferrannini E, et al. Diabetes Care 2013;36:1260-1265.

Efficacy of SGLT-2 Inhibitors in Patients With Stage 3 CKD

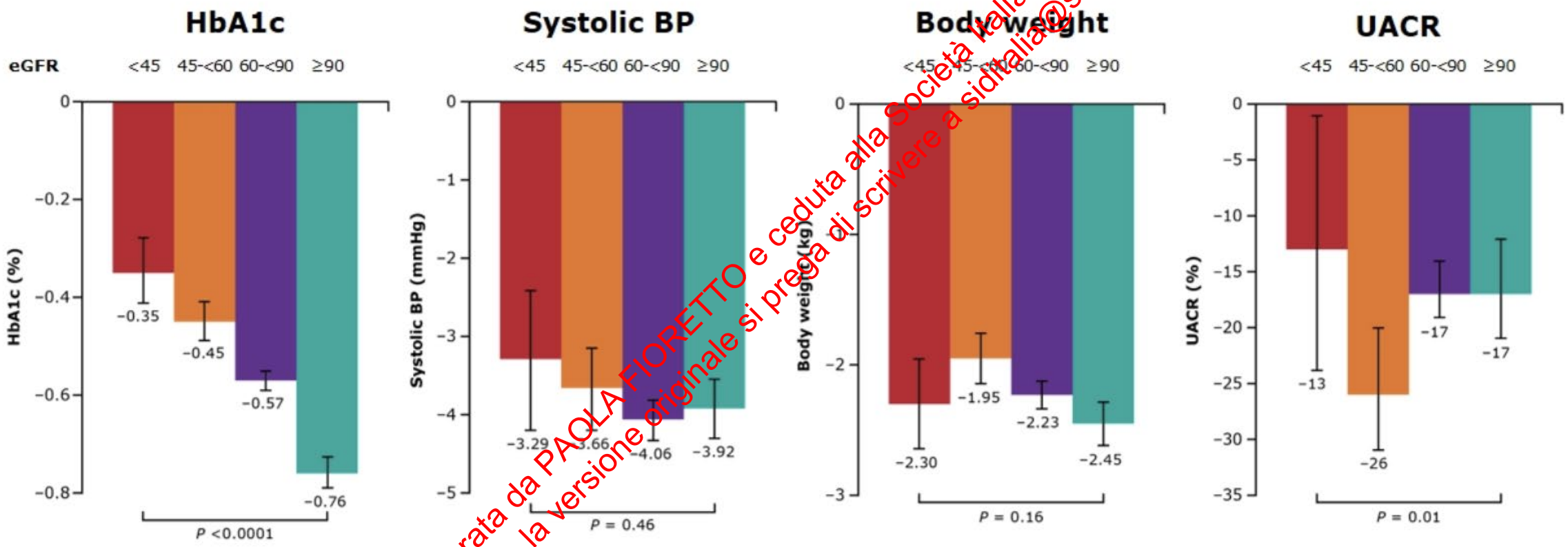
	DAPA			CANA			EMPA	
	PBO	5 mg	10 mg	PBO	100 mg	300 mg	PBO	25 mg
n	82	83	82	90	90	89	187	187
Baseline A1C	8.53%	8.30%	8.22%	8.0%	7.9%	8.0%	8.0%	8.0%
Change at 6 months	-0.32%	-0.41%	-0.44%	-0.03%	-0.33%	-0.44%	0.05%	-0.37%
Difference vs PBO		-0.08%	-0.11%		-0.30%*	-0.40%†		-0.42%‡



.

1. Kohan DE et al. *Kidney Int.* 2014;85:962-971.
2. Yale JF et al. *Diabetes Obes Metab.* 2013;15:463-473.
3. Barnett AH et al. *Lancet Diabetes Endocrinol.* 2014;doi:10.1016/S2213-8587(13)70208-0.

Effects on HbA1c, Systolic BP, Body Weight and UACR



Data are placebo-subtracted differences in each subgroup.

Neuen B, et al. *Circulation*. 2018;doi: 10.1161/CIRCULATIONAHA.118.035901.

CANVAS Program

SGLT2 INHIBITORS IN PATIENTS WITH DKD

SGLT2 Inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Canagliflozin	100–300 mg once daily	CANVAS: eGFR ≥30 ml/min per 1.73 m² CREDENCE: eGFR 30–90 ml/min per 1.73 m²	No dose adjustment if eGFR >60 ml/min per 1.73 m² 100 mg daily if eGFR 30–59 ml/min per 1.73 m² Avoid initiation with eGFR <30 ml/min per 1.73 m², discontinue when initiating dialysis
Dapagliflozin	5–10 mg once daily	DECLARE-TIMI 58: CrCl ≥60 ml/min DAPA-HF: eGFR ≥30 ml/min per 1.73 m² DAPA-CKD: eGFR 25–75 ml/min per 1.73 m²	No dose adjustment if eGFR ≥45 ml/min per 1.73 m² Not recommended with eGFR <45 ml/min per 1.73 m² Contraindicated with eGFR <30 ml/min per 1.73 m²
Empagliflozin	10–25 mg once daily	EMPA-REG: eGFR ≥30 ml/min per 1.73 m² EMPA-KIDNEY: eGFR 20–90 ml/min per 1.73 m² EMPEROR-Reduced: eGFR ≥20 ml/min per 1.73 m²	No dose adjustment if eGFR ≥45 ml/min per 1.73 m² Avoid use, discontinue with eGFR persistently <45 ml/min per 1.73 m²

KDIGO clinical practice guideline on diabetes management in chronic kidney disease. Kidney Int, 2020

SGLT2 inhibitors are recommended for patients with T2D,CKD and eGFR ≥20 mL/min/1.73 m2

Lifestyle changes

Physical activity, nutrition, weight loss

First line drug therapy

SGLT2i*

- eGFR ≥ 20 mL/min/1.73 m^2
- eGFR < 20 mL/min/1.73 m^2: do not initiate
- Dialysis: discontinue

+

Metformin

- eGFR ≥ 30 mL/min/1.73 m^2: adjust dose in line with eGFR
- eGFR < 30 mL/min/1.73 m^2: discontinue
- Dialysis: discontinue

Additional drug therapy as needed for glycaemic control, guided by patient preferences, comorbidities, eGFR and cost

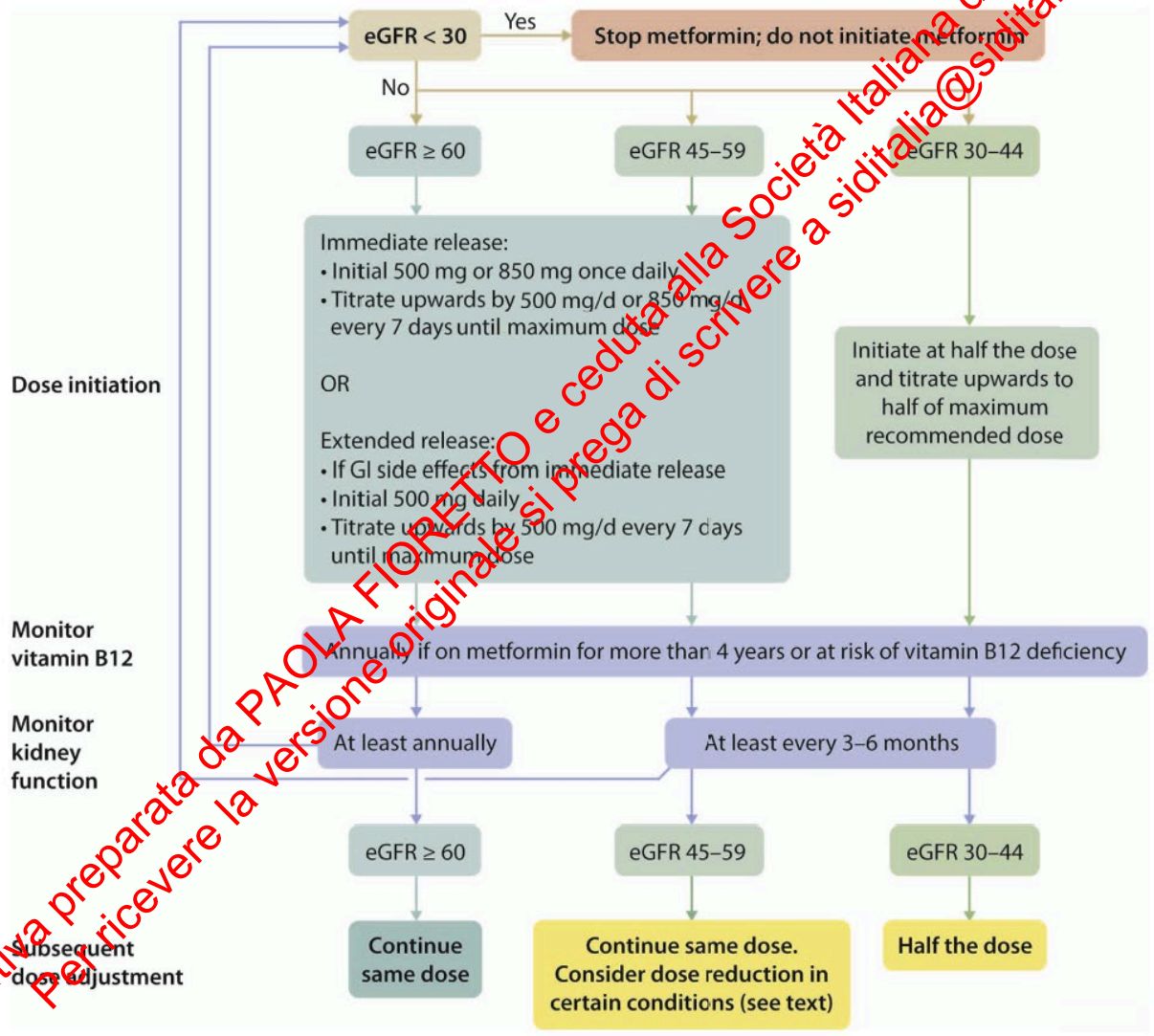
GLP1RA (preferred)

Insulin | DPP4i

SU | TZDs

Alpha-glucosidase inhibitors

METFORMIN IN PATIENTS WITH DKD



KDIGO clinical practice guideline on diabetes management in chronic kidney disease. Kidney Int, 2020

Review

Metformin in Patients With Type 2 Diabetes and Kidney Disease
A Systematic Review

Silvio E. Inzucchi, MD; Kasia J. Lipska, MD, MHS; Helen Mayo, MLS; Clifford J. Bailey, PhD; Darren K. McGuire, MD, MHSc

JAMA. 2014;312(24):2668-2675. doi:10.1001/jama.2014.15298

Cause di instabilità della funzione renale:

Disidratazione
Febbre/infezioni
Eccesso di diuretici
Diarrea
Eccessiva sudorazione
Grave ipotensione (da farmaci)

Table 2. Possible Approach to Metformin Prescribing in the Setting of

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dosing	Other Recommend
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

Effectiveness and safety of metformin in 51,675 patients with T2DM and different levels of renal function: a cohort study from the Swedish National Diabetes Register

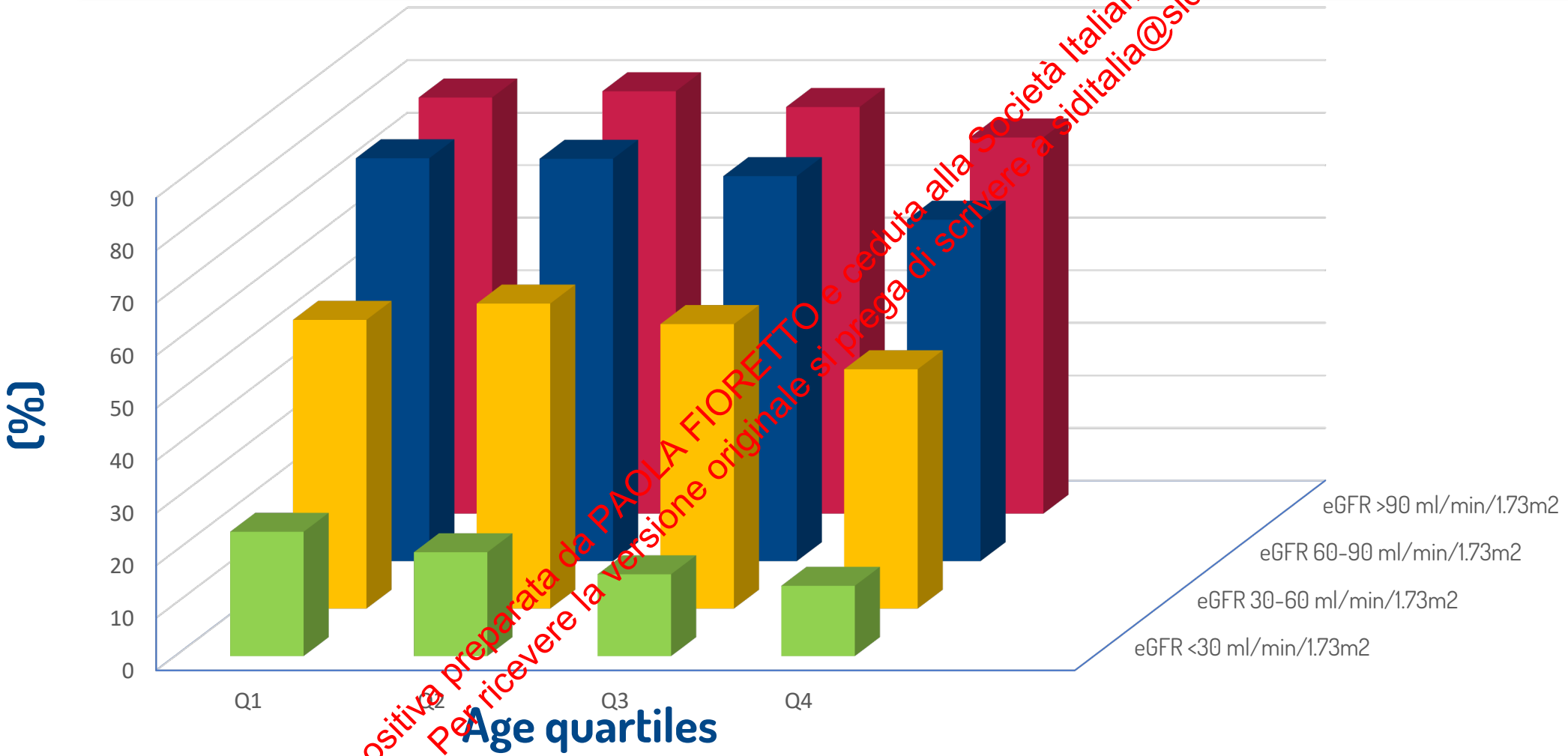
Adjusted HRs for any CVD, any acidosis/infection and all-cause mortality

	30≤ eGFR <45	45≤ eGFR <60	eGFR ≥60
Any CVD			
Metformin	1.00 (0.83-1.19)	0.94 (0.84-1.05)	0.98 (0.92-1.05)
Insulin	1.30 (1.02-1.64)	1.24 (1.09-1.42)	1.19 (1.11-1.27)
Other OHA	1.03 (0.85-1.26)	1.05 (0.93-1.18)	1.03 (0.97-1.09)
Any acidosis/infection			
Metformin	0.98 (0.79-1.21)	0.85 (0.74-0.97)	0.91 (0.84-0.98)
Insulin	1.34 (1.02-1.76)	1.07 (0.91-1.26)	1.22 (1.12-1.32)
Other OHA	--	0.87 (0.75-1.00)	1.02 (0.95-1.09)
All-cause mortality			
Metformin	1.02 (0.84-1.24)	0.87 (0.77-0.99)	0.87 (0.81-0.94)
Insulin	1.16 (0.91-1.47)	1.12 (0.95-1.31)	1.29 (1.19-1.41)
Other OHA	0.97 (0.79-1.19)	0.97 (0.84-1.11)	1.10 (1.02-1.19)

HR associated with the examined agent in any combination is given with any other glucose-lowering treatment as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-high-density lipoprotein-cholesterol, BMI, smoking, eGFR, multidose dispensation,history of CVD and HF. Microalbuminuria, and treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides.

Ekstrom N,BMJ 2012

Proportion of T2DM patients taking metformin according to age and eGFR levels



S. Gentile & S. De Cosmo. Oncotaregt, 2017

GLP1 RA IN PATIENTS WITH DKD

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with CrCl >30 ml/min
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

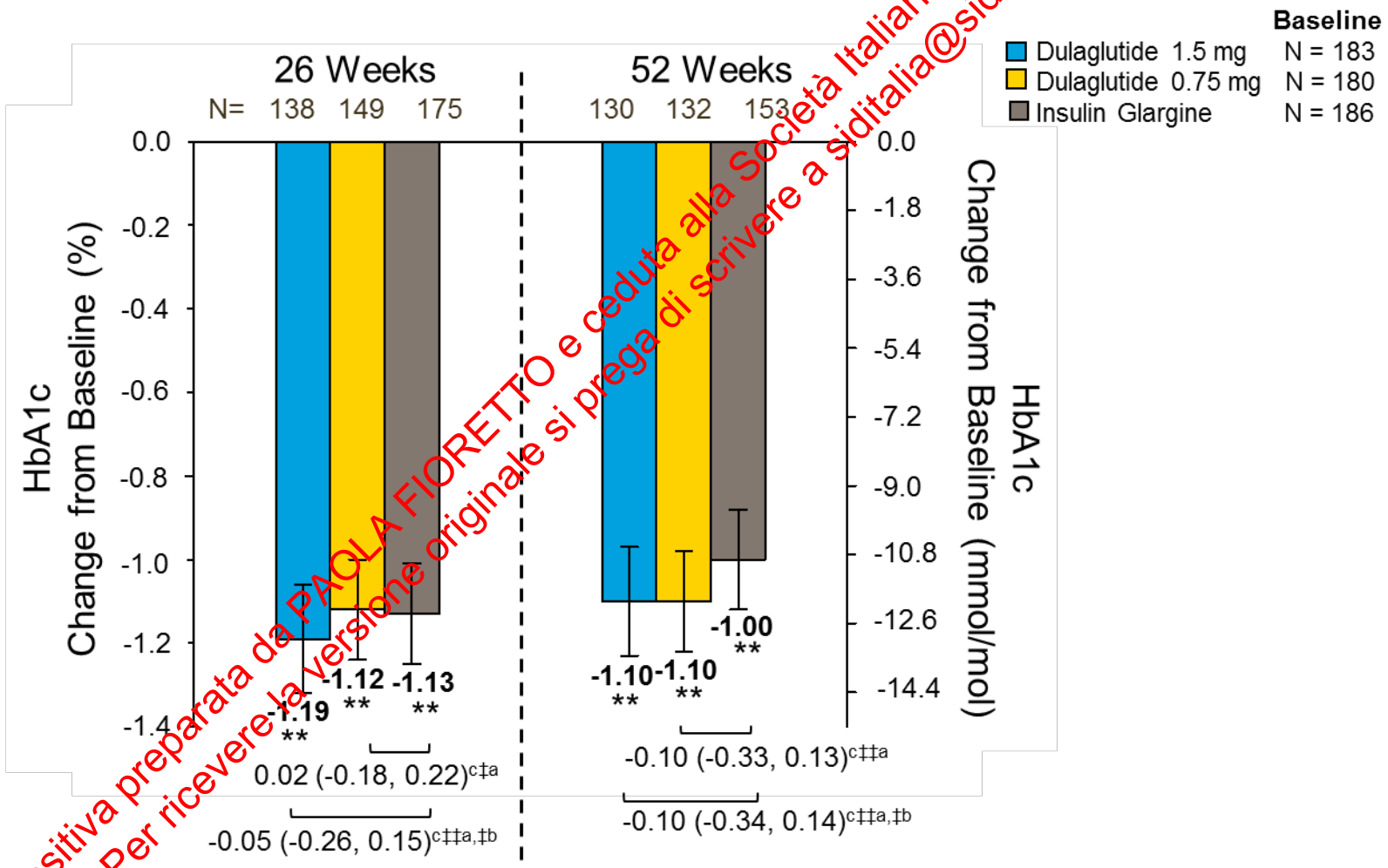
KDIGO clinical practice guideline on diabetes management in chronic kidney disease. Kidney Int, 2020

AWARD 7: Clinical Characteristics

Clinical Characteristics	Dulaglutide 1.5 mg (N = 192)	Dulaglutide 0.75 mg (N = 190)	Insulin Glargine (N = 194)
Duration of CKD,[a] years	4.2 ± 5.6	4.0 ± 4.9	3.5 ± 4.0
eGFR (creatinine), mL/min/1.73m², mean ± SD	38.1 ± 13.2	38.3 ± 12.3	38.5 ± 13.0
eGFR (creatinine), mL/min/1.73m², geometric mean ± SE	35.7 ± 1.0	36.2 ± 0.9	36.1 ± 0.9
Baseline eGFR ≥60 to <90	9 (5)	7 (4)	14 (7)
Baseline eGFR ≥45 to <60	53 (28)	53 (28)	51 (26)
Baseline eGFR ≥30 to <45	73 (38)	75 (39)	67 (35)
Baseline eGFR ≥15 to <30	55 (29)	55 (29)	61 (31)
Baseline eGFR <15	2 (1)	0 (0)	1 (1)
eGFR (cystatin C), mL/min/1.73m², mean ± SE	37.3 ± 14.2	37.7 ± 13.7	38.3 ± 14.8
eGFR (cystatin C), mL/min/1.73m², geometric mean ± SE	34.8 ± 1.0	35.4 ± 0.9	35.6 ± 1.0
UACR, mg/g, median (interquartile range)	213.7 (45.8 - 868.0)	233·6 (36.7 - 946.5)	195.6 (30.1 - 1015.1)
Normal albuminuria (UACR <30)	34 (18)	44 (23)	48 (25)
Microalbuminuria (UACR 30-300)	74 (39)	61 (32)	56 (29)
Macroalbuminuria (UACR >300)	84 (44)	84 (44)	90 (46)
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use (miTT population)[b]	165 (90)	170 (94)	174 (94)

Tuttle et al. *Lancet Diabetes Endocrinology* 2018

Change in HbA1c from Baseline



Tuttle et al. *Lancet Diabetes Endocrinology* 2018

Glycaemic & Bodyweight efficacy in kidney impairment

PIONEER 5 : Oral semaglutide was superior to placebo in decreasing HbA_{1c} and Bodyweight in people with kidney function impairment

Trial Information

Randomised, double-blind, placebo-controlled, parallel group, multicentre, phase 3a trial

Key inclusion criteria

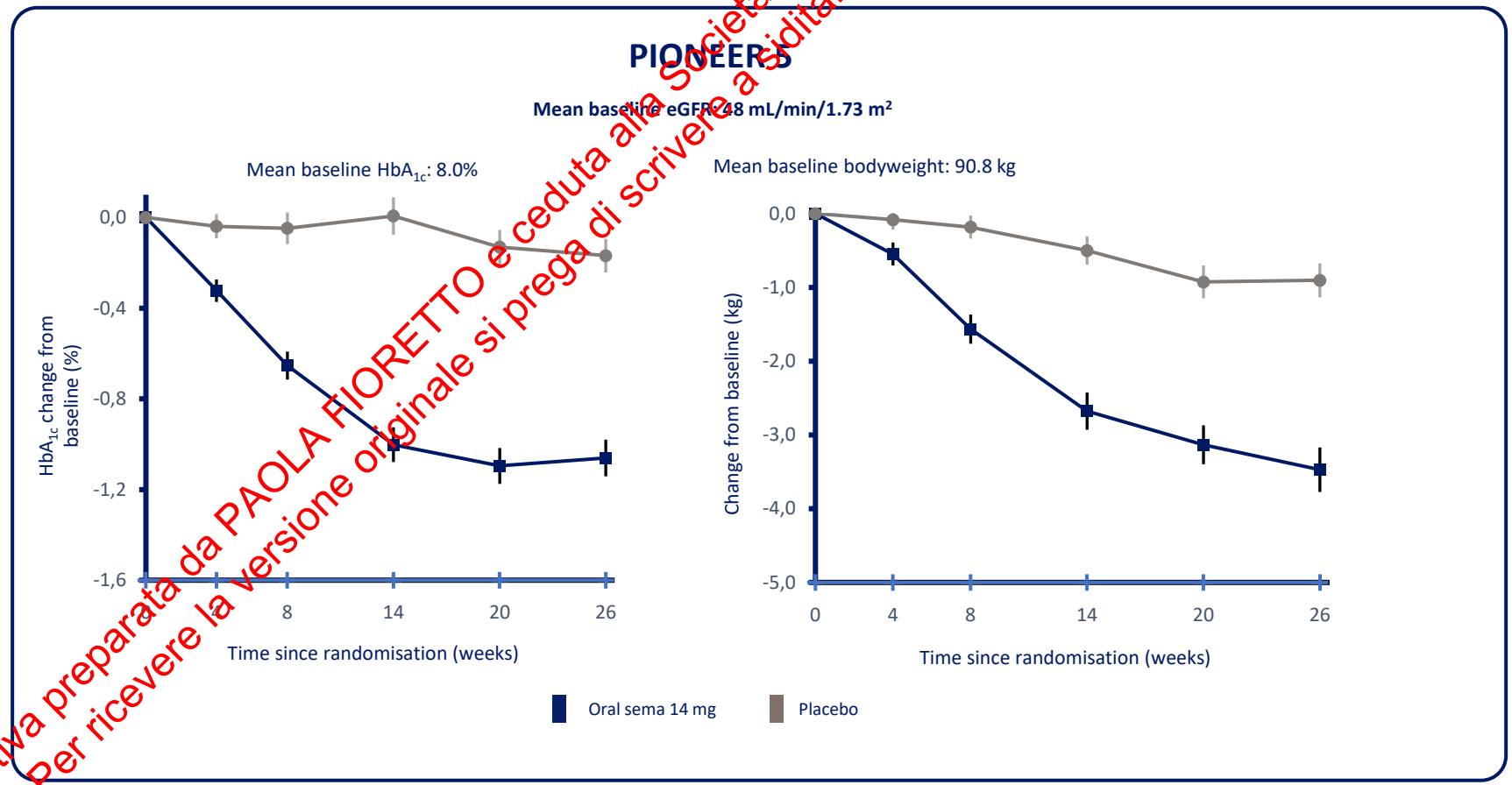
- HbA_{1c} 7.0–9.5% (53–80 mmol/mol)
- eGFR 30–59 mL/min/1.73 m^2
- Stable doses of 1–2 OADs (metformin, SU) and/or basal insulin for ≥90 days

Primary Endpoint

- Change from baseline at week 26 in HbA_{1c}

Key Secondary Endpoints

- Change from baseline at week 26 in body weight*



*Confirmatory secondary endpoint. Treatment policy estimand. Line graph: values are observed means ± standard error of the mean. Bar graph: estimated mean changes from baseline to week 26. *p<0.05 in favour of oral semaglutide. Sema, semaglutide. eGFR, estimated glomerular filtration rate; OAD, oral anti-diabetes drug; SU, sulphonylurea.*

Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515–27.

Glycaemic efficacy in kidney impairment

Post hoc analysis of SUSTAIN and PIONEER programs showed HbA_{1c} reduction with GLP-1 RA semaglutide is independent of baseline eGFR

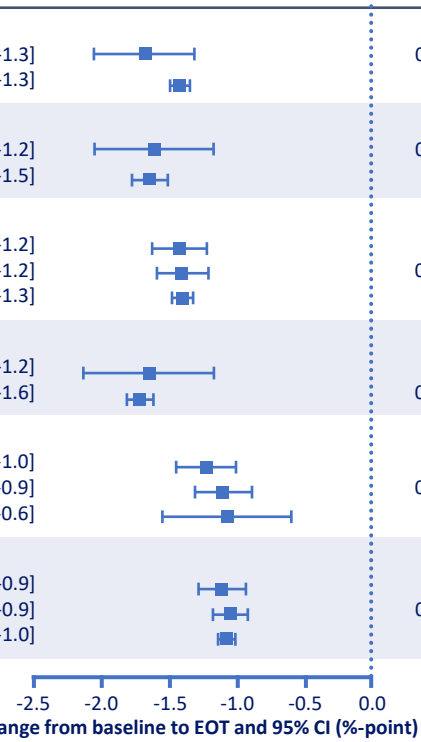
This post hoc analysis considered SUSTAIN (1–10) and PIONEER (1–10) trials where sufficient subjects had eGFR <60 ml/min/1.73m^2

Results:

- Mean HbA_{1c} at baseline ranged from 7.9% to 8.7% across the trials.
- Semaglutide consistently reduced HbA_{1c} at across eGFR subgroups in all trials:
  - Mean reduction of 1.0–1.7% from baseline to EOT
  - P-interactions >0.148

Trial and eGFR subgroup, (mL/min/1.73 m^2)	Trial duration (Weeks)	Mean (SD) baseline eGFR (mL/min/1.73 m^2)	Mean (SD) baseline HbA_{1c} (%)	n/N	Mean change in HbA_{1c} from baseline to EOT (%-point)	[95% CI]	P-value
SUSTAIN 4	30						
<60		52.7 (6.5)	8.4 (1.0)	22/29	-1.7	[-2.1; -1.3]	0.15
≥60		97.9 (15.7)	8.2 (0.9)	549/693	-1.4	[-1.5; -1.3]	
SUSTAIN 5	30						
<60		50.6 (7.6)	8.4 (0.9)	18/20	-1.6	[-2.0; -1.2]	0.94
≥60		93.4 (15.3)	8.4 (0.8)	201/243	-1.6	[-1.8; -1.5]	
SUSTAIN 6	104						
<45		34.1 (8.2)	8.6 (1.4)	137/193	-1.4	[-1.6; -1.2]	
45 to <60		52.6 (4.2)	8.6 (1.4)	155/223	-1.4	[-1.6; -1.2]	0.49
≥60		86.8 (13.7)	8.7 (1.5)	900/1,215	-1.4	[-1.5; -1.3]	
SUSTAIN 10	30						
<60		43.4 (6.9)	8.1 (0.9)	8/14	-1.7	[-2.1; -1.2]	
≥60		94.6 (14.5)	8.2 (1.0)	233/276	-1.7	[-1.8; -1.6]	0.95
PIONEER 5	≤26						
<45		37.8 (4.8)	8.0 (0.8)	54/65	-1.2	[-1.5; -1.0]	
45 to <60		51.3 (3.9)	8.0 (0.7)	60/83	-1.1	[-1.3; -0.9]	0.71
≥60		65.5 (5.8)	7.9 (0.7)	12/15	-1.1	[-1.5; -0.6]	
PIONEER 6	≤83						
<45		37.4 (5.8)	8.0 (1.5)	121/167	-1.1	[-1.3; -0.9]	
45 to <60		52.3 (4.4)	8.1 (1.6)	217/267	-1.0	[-1.2; -0.9]	0.28
≥60		84.5 (13.6)	8.2 (1.6)	952/1,150	-1.0	[-1.1; -1.0]	

Semaglutide by eGFR groups



CI, confidence interval; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated hemoglobin; SD, standard deviation

Cherney D et al. Kidney International Reports (2022) , DOI: https://doi.org/10.1016/j.ekir.2022.07.167

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

DPP4 inhibitors in patients with renal impairment

Agent	Dose	Approval (year)		Half-life (h)	DPP-4 inhibition (24 h post-dose*)	Elimination	Use in patients with renal insufficiency		
		EMA	FDA				Mild (CrCl 50/60–89 ml/min)	Moderate (CrCl 30–50/60 ml/min)	Severe or ESRD (CrCl <30 ml/min)
DPP-4 inhibitors (oral)									
Sitagliptin	100 mg QD	2007	2006	~12.4	>80%	Renal ~87%; faeces ~13%	No adjustment	Dose reduction (50 mg QD)	Dose reduction (25 mg QD)
Vildagliptin	50 mg BID or 50 mg QD plus SU	2007	2007	~2.0	<40% (~80% after 12 h)	Renal ~85%; faeces ~15%	No adjustment	Dose reduction (50 mg QD)	Dose reduction (50 mg QD)
Saxagliptin	5 mg QD	2009	2009	~2.5 (metabolite ~3.1)	~70%	Renal 12–29% (metabolite 21–52%); faeces 22%	No adjustment	Dose reduction (2.5 mg QD)	Dose reduction (2.5 mg QD)
Alogliptin	25 mg QD	2013	2013	~21.0	~75%	Renal ~76%; faeces ~13%	No adjustment	Dose reduction (12.5 mg QD)	Dose reduction (6.25 mg QD)
Linagliptin	5 mg QD	2011	2011	~12.0	>80%	Renal ~5%; faeces ~80%	No adjustment	No adjustment	No adjustment

Muskiet MH et al. Nat Rew Nephrol 2017

Risk of hypoglycemia with DPP-IV inhibitors in patients with moderate to severe CKD

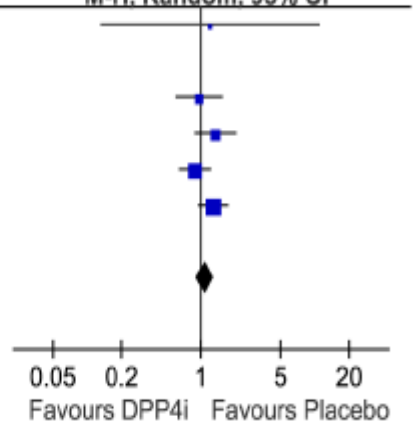
10 studies, 1915 participants

vs placebo

Study or Subgroup	DPP4i Events	DPP4i Total	Placebo or No Treatment Events	Placebo or No Treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Chan 2008	3	65	1	26	0.7%	1.20 [0.13, 11.02]	2008	
Ito 2011	0	30	0	21		Not estimable	2011	
Nowicki 2011b	24	85	25	85	14.8%	0.96 [0.60, 1.54]	2011	
Kothny 2012	49	216	26	153	18.0%	1.33 [0.87, 2.05]	2012	
Laakso 2013	41	113	50	122	31.4%	0.89 [0.64, 1.22]	2013	
McGill 2013	43	68	32	65	35.2%	1.28 [0.95, 1.74]	2013	
Total (95% CI)		**577**		**472**	**100.0%**	**1.10 [0.92, 1.32]**		
Total events	160		134					

Heterogeneity: Tau² = 0.00; Chi² = 3.82, df = 4 (P = 0.43); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.30)

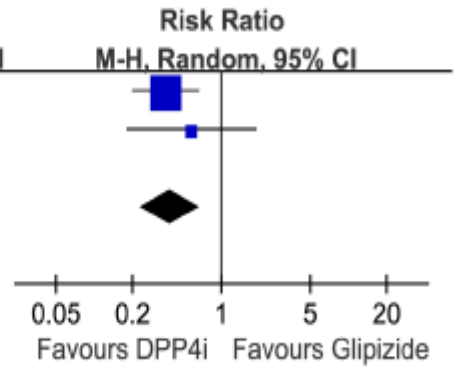


vs glipizide

Study or Subgroup	DPP4i Events	DPP4i Total	Glipizide Events	Glipizide Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arjona Ferreira 2013a	13	210	36	212	79.2%	0.36 [0.20, 0.67]	
Arjona Ferreira 2013b	4	64	7	65	20.8%	0.58 [0.18, 1.89]	
Total (95% CI)		**274**		**277**	**100.0%**	**0.40 [0.23, 0.69]**	
Total events	17		43				

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%

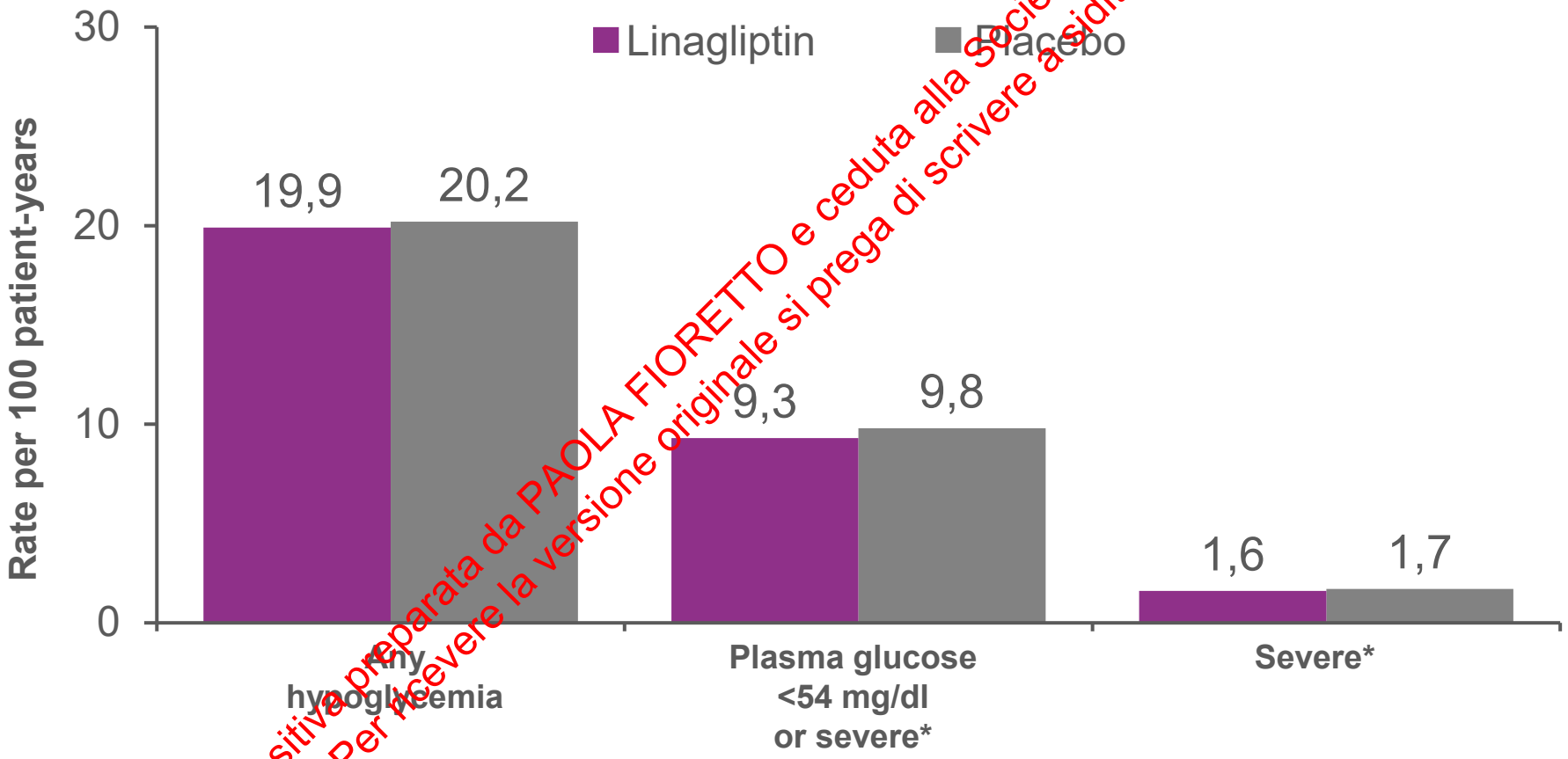
Test for overall effect: Z = 3.32 (P = 0.0009)



Cheng D, PLoS One 2014

Overall linagliptin did not increase the risk of hypoglycemia

Hypoglycemia: rates per 100 patient-years overall



Treated set. MedDRA version used for reporting: 20.1. AEs occurring between first study drug intake until 7 days after last permanent study drug stop
*Requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
Boehringer Ingelheim. Data on file. 2018

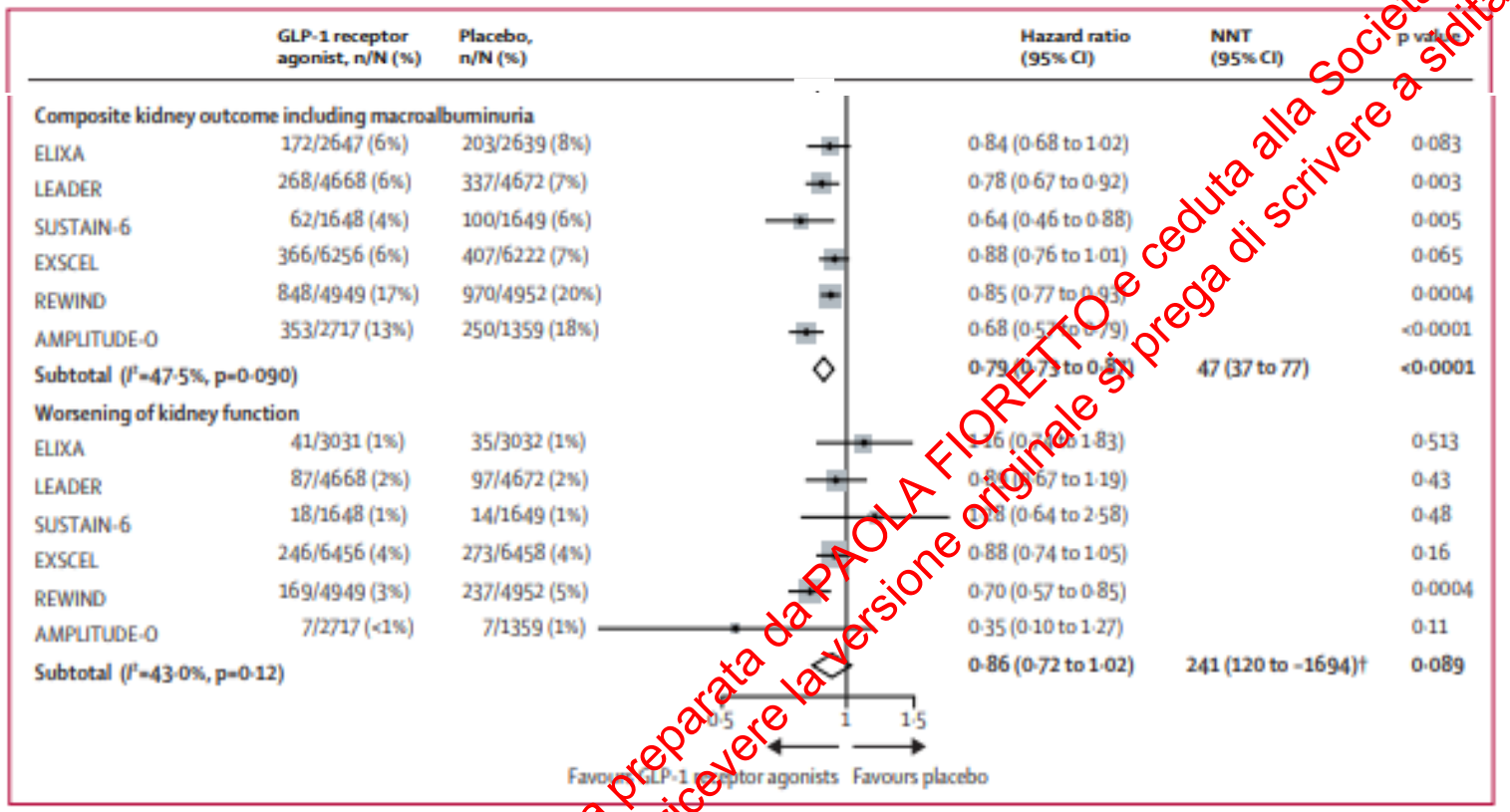
CARMELINA

Controllo glicemico nel paziente con insufficienza renale

- Quali farmaci ipoglicemizzanti nel paziente con insufficienza renale

- Efficacia nefroprotettiva dei farmaci ipoglicemizzanti

Kidney outcomes in CVOTs with GLP-1 RA in patients with type 2 diabetes: a systematic review and meta-analysis of randomized trials



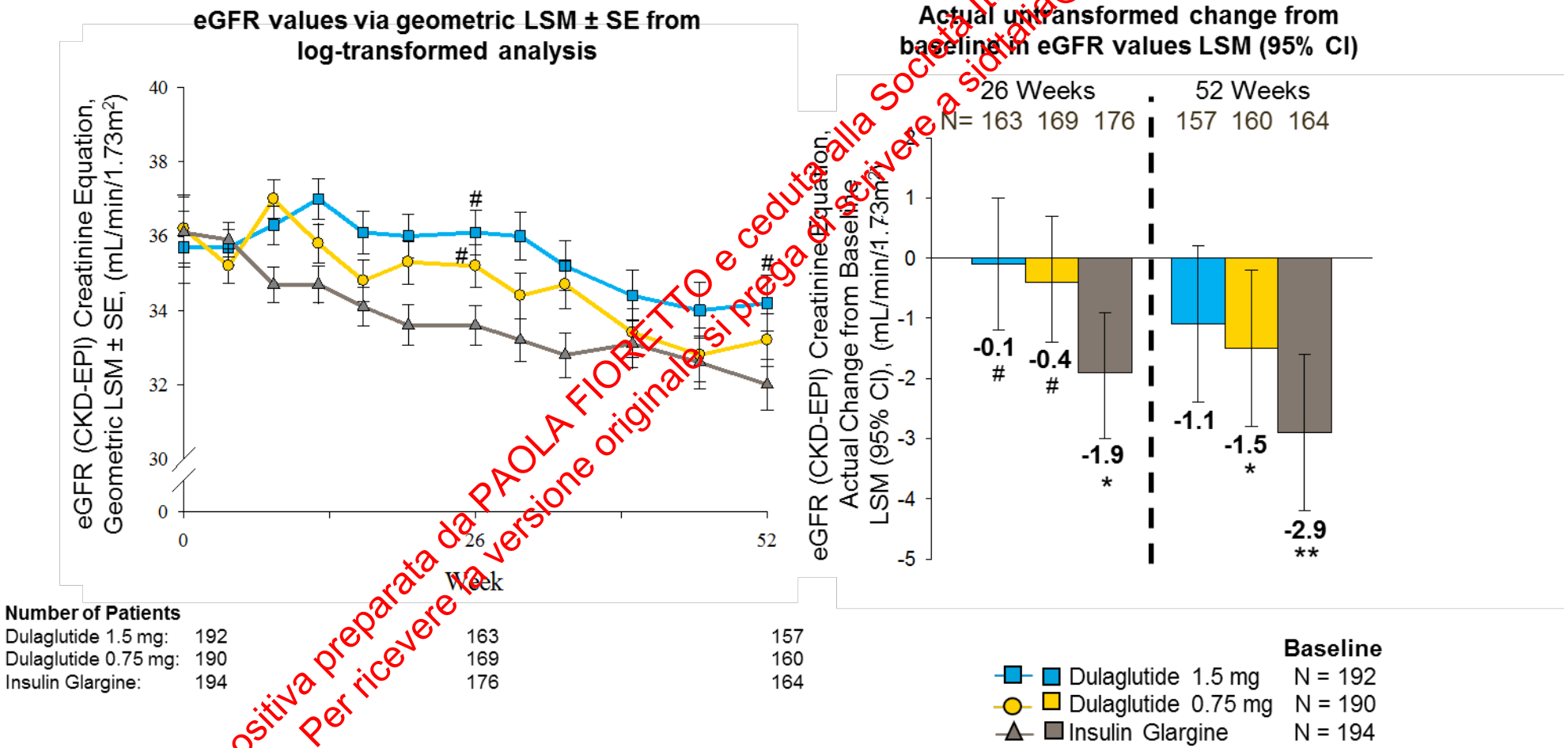
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73 to 0·85)**	**47 (37 to 77)**	**<0·0001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·76 to 1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·88 (0·67 to 1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64 to 2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74 to 1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57 to 0·85)		0·0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10 to 1·27)		0·11
Subtotal (I^2=43·0%, p=0·12)			**0·86 (0·72 to 1·02)**	**241 (120 to −1694)†**	**0·089**

Kidney outcome ↓ RR 21%

Worsening of kidney function ↓ RR 14%

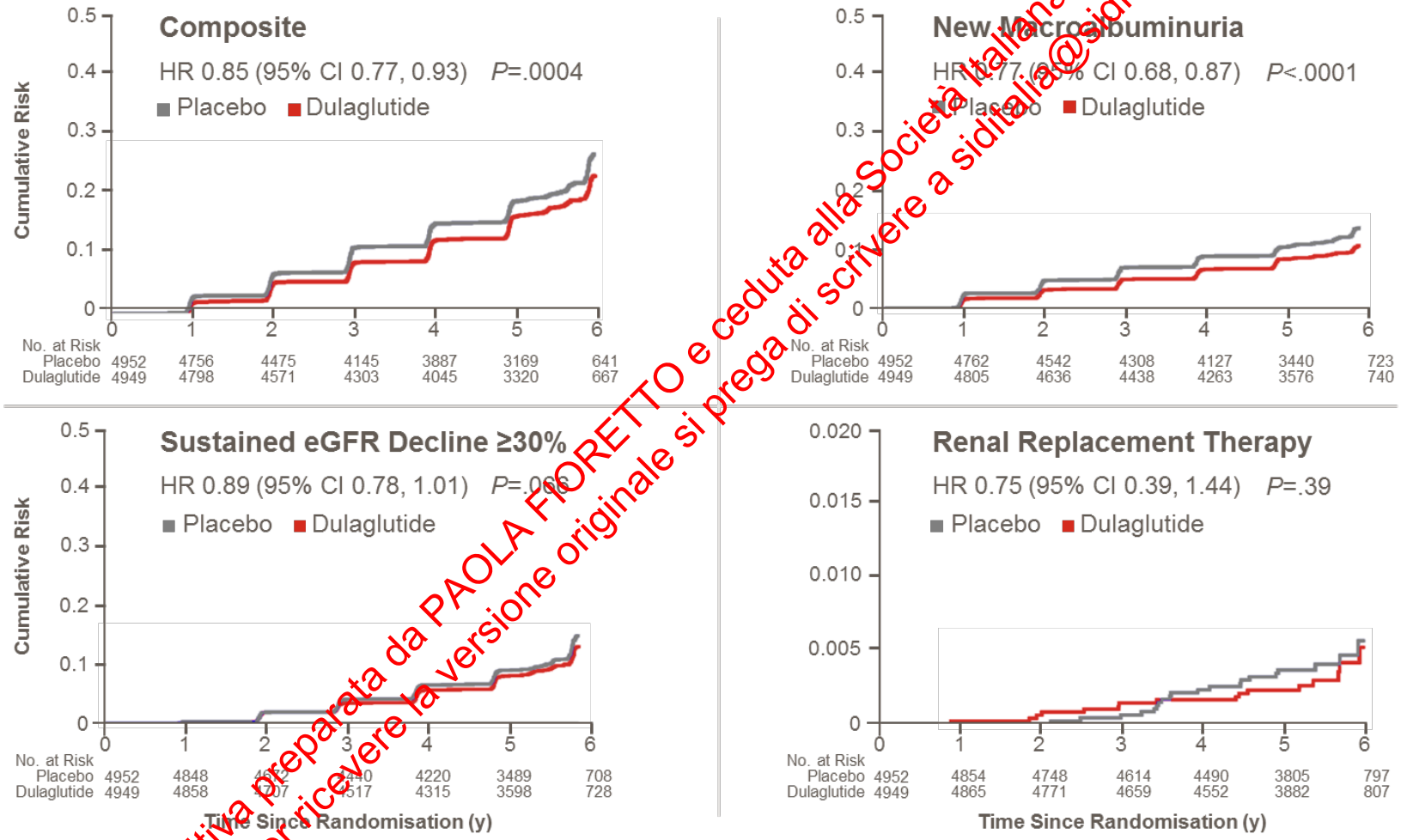
Sattar N et al. Lancet Diabetes Endocrinol 2021

Change from Baseline in eGFR (CKD-EPI) Creatinine Equation



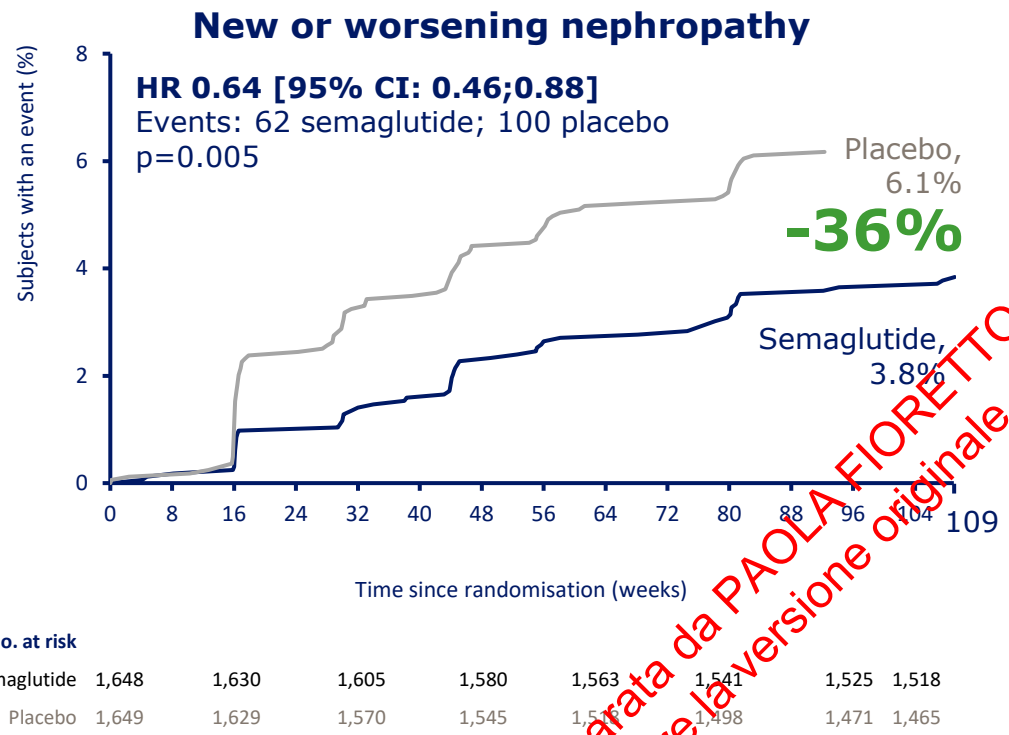
Tuttle et al. *Lancet Diabetes Endocrinology* 2018

REWIND: Renal Outcomes



Gerstein HC et al, Lancet, 2019

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

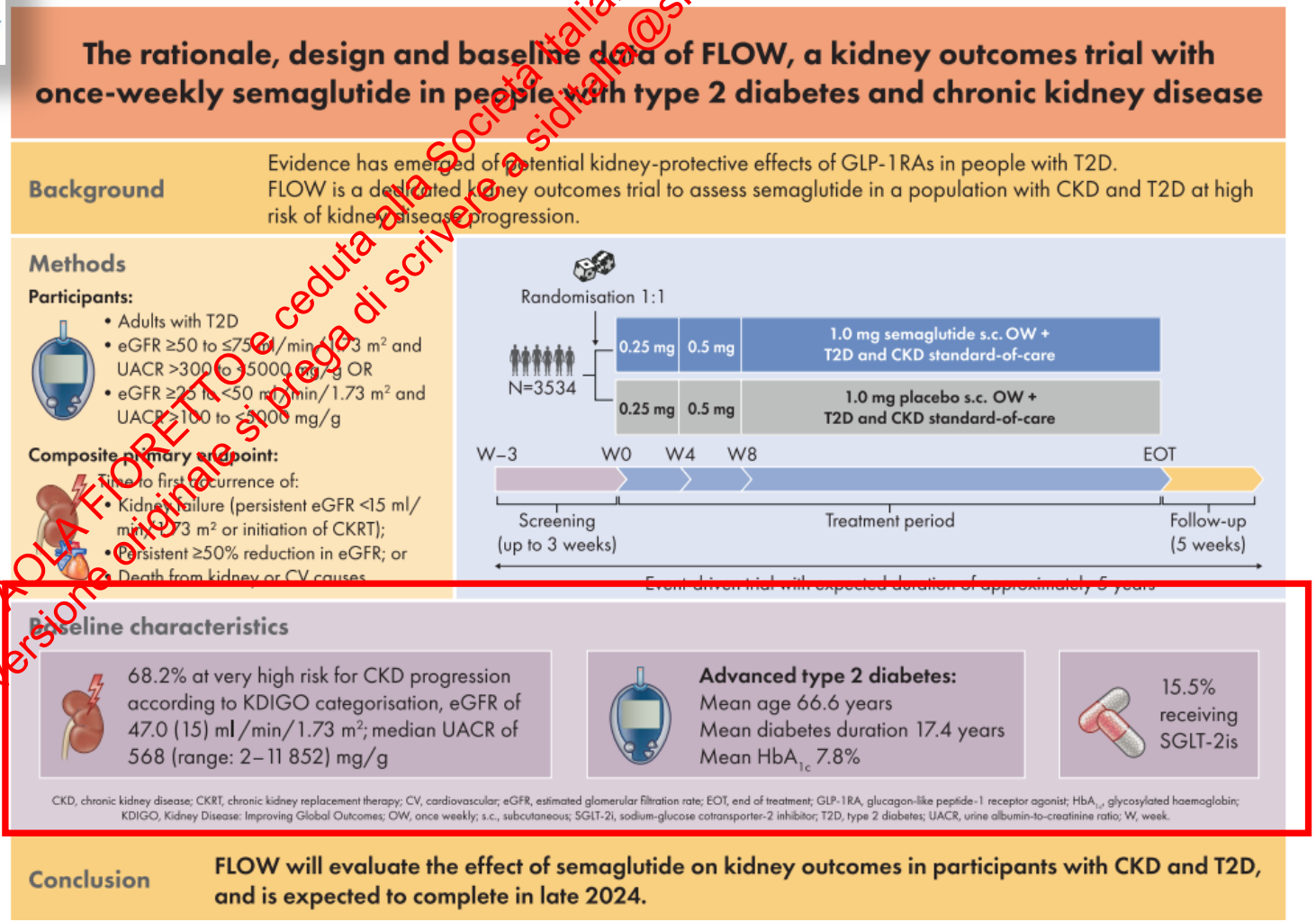
Marso SP et al. *N Engl J Med* 2016;375:1834–44.

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Peter Rossing[1,2], Florian M.M. Baeres[3], George Bakris[4], Heidrun Bosch-Traberg[3], Mette Gislum[3], Stephen C.L. Gough[3], Thomas Idorn[3], Jack Lawson[3], Kenneth W. Mahaffey[5], Johannes F.E. Mann[6], Henriette Mersebach[3], Vlado Perkovic[7], Katherine Tuttle[8], Richard Pratley[9], and on behalf of the FLOW Steering Committee and FLOW Trial Investigators

Enrolled participants (N = 3534) had a baseline mean age of 66.6 years, haemoglobin A1c of 7.8%, diabetes duration of 17.4 years, eGFR of 47.0 ml/min/1.73 m2 and median UACR of 568 mg/g (range 2–11 852). According to Kidney Disease: Improving Global Outcomes guidelines categorisation, 68.2% were at very high risk for CKD progression

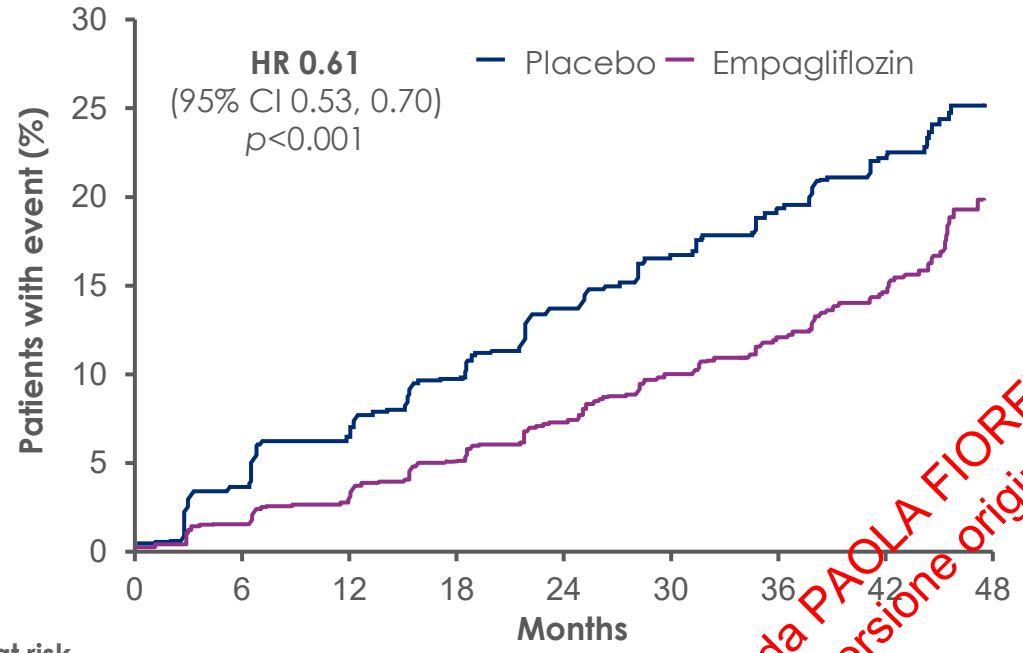
P. Rossing et al., 2023



Renal data from EMPA-REG OUTCOME

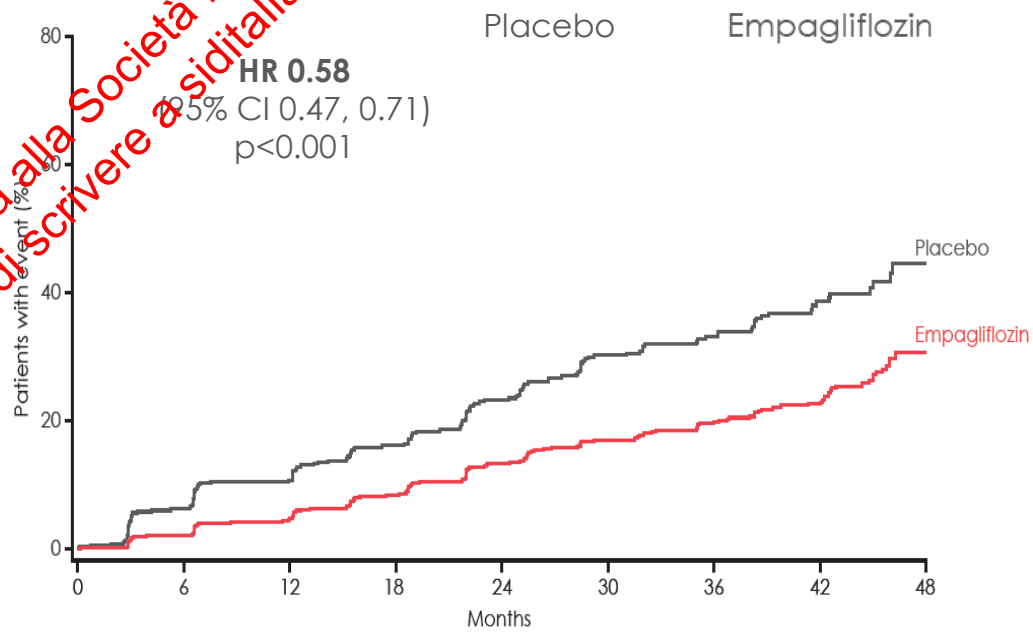
Incident or worsening nephropathy in the overall population or in patients with prevalent kidney disease*

Overall population



No. at risk									
Placebo	2061	1946	1836	1703	1433	1016	833	521	106
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290

Prevalent kidney disease



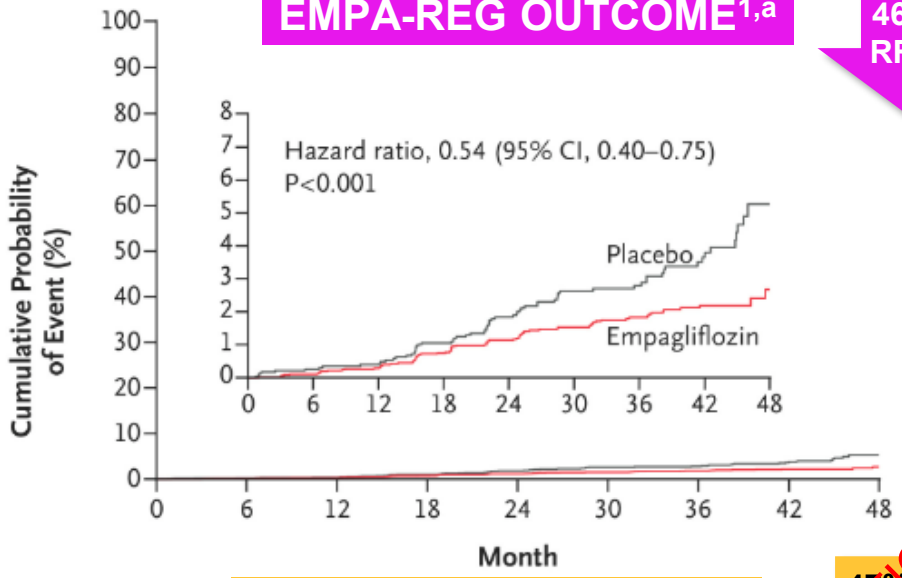
No. at risk									
Placebo	507	462	425	377	302	206	172	102	23
Empagliflozin	998	952	895	836	694	516	420	273	69

Wanner C et al. *N Engl J Med* 2016;375:323

SGLT2 inhibitors in CVOTs reduced the risk of kidney composite endpoints compared with placebo

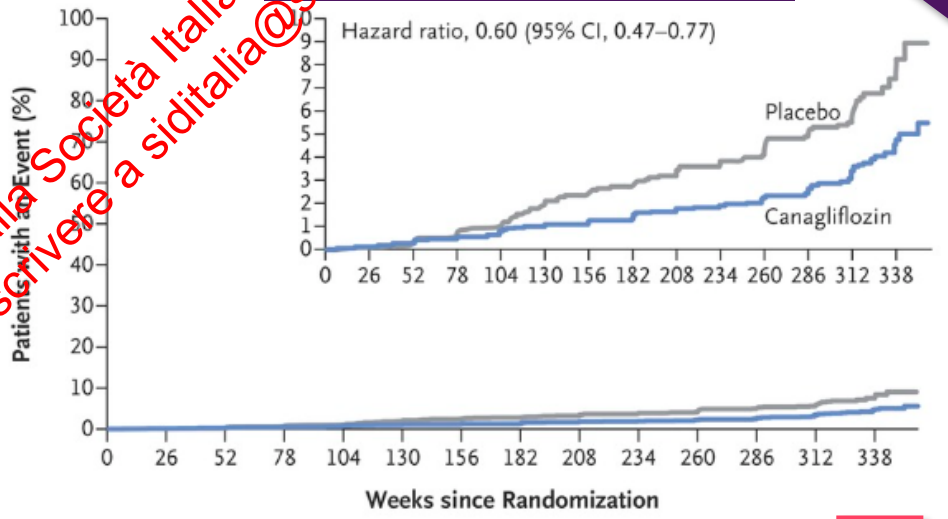
EMPA-REG OUTCOME[1,a]

46% RRR



CANVAS Program[2,b]

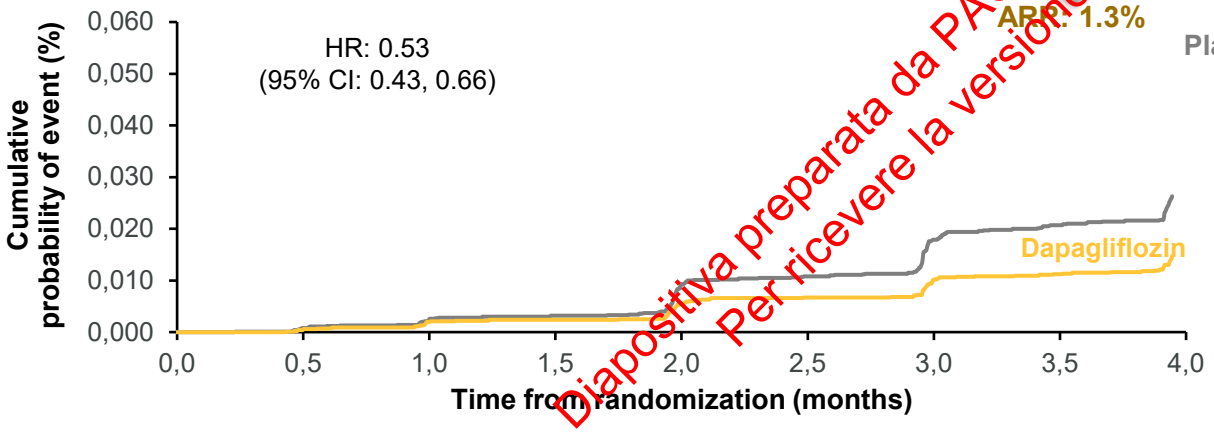
40% RRR



DECLARE-TIMI 58[3,c]

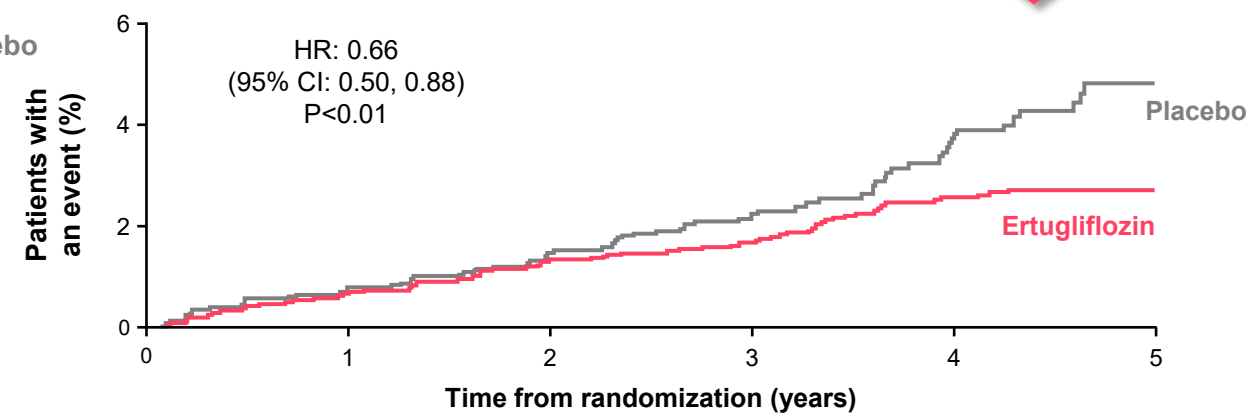
47% RRR

ARR: 1.3%



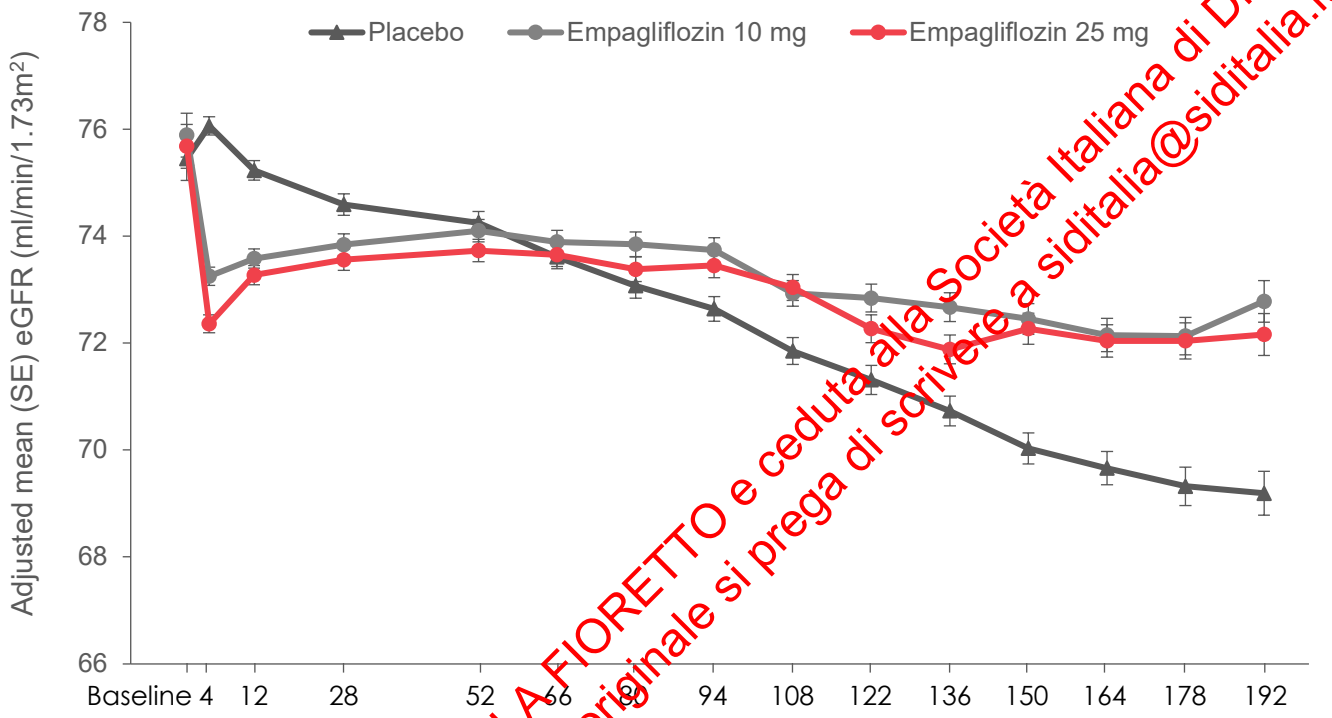
VERTIS CV[4,d]

34% RRR



1. Wanner C, et al. N Engl J Med 2016;375:323–334; 2. Neal B, et al. N Engl J Med 2017;377:644–657; 3. Mosenzon O, et al. Lancet Diabetes Endocrinol 2019;7:606–617; 4. Cherney DZI, et al. Diabetologia 2021;64:1256–1267
No es una comparativa entre CVOTs, solo se presentan los resultados

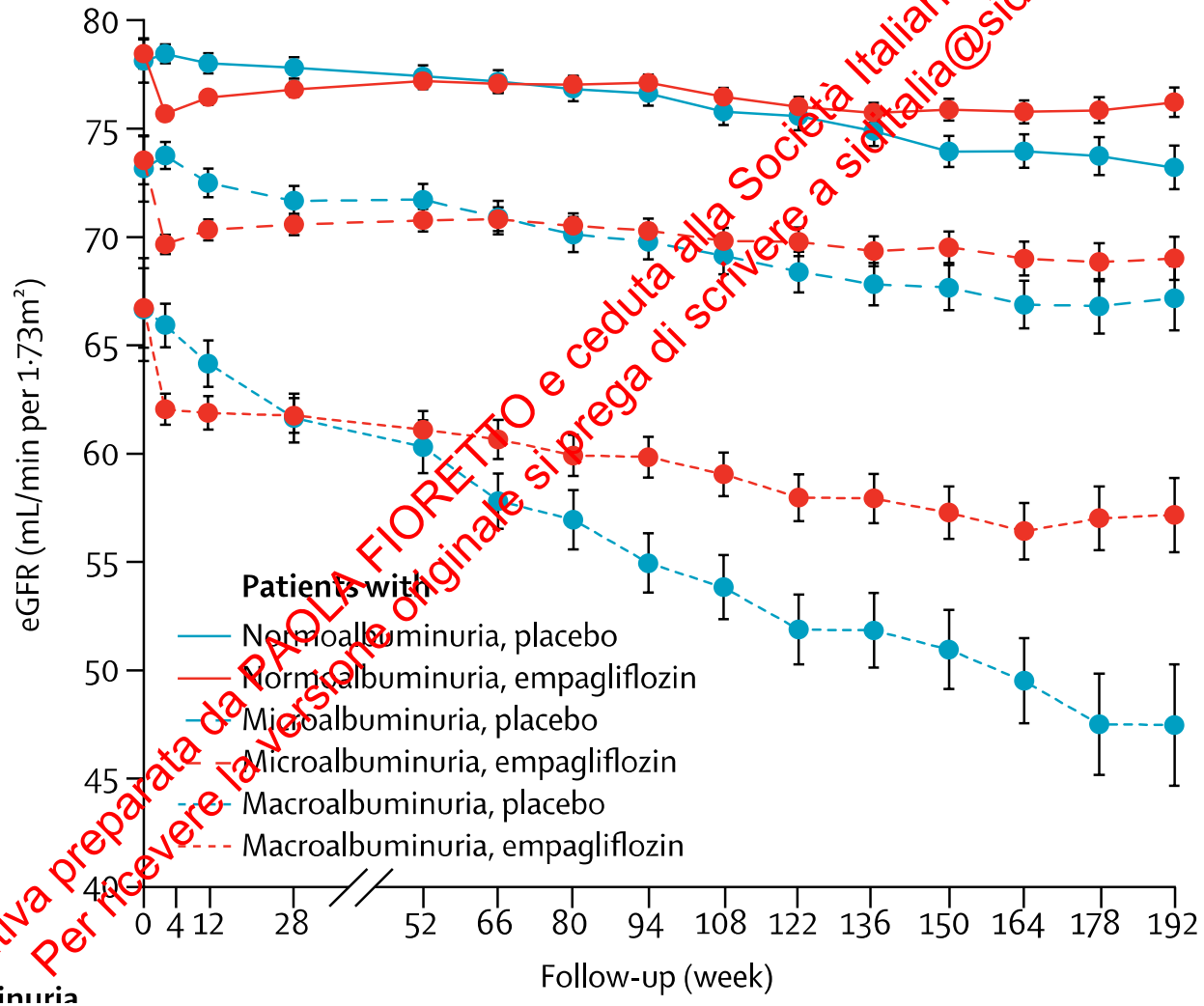
eGFR (CKD-EPI) over 192 weeks



No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6995	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Wanner C et al. *N Engl J Med* 2016;375:323

Effects of empagliflozin on eGFR: an exploratory analysis from the EMPA-REG OUTCOME trial

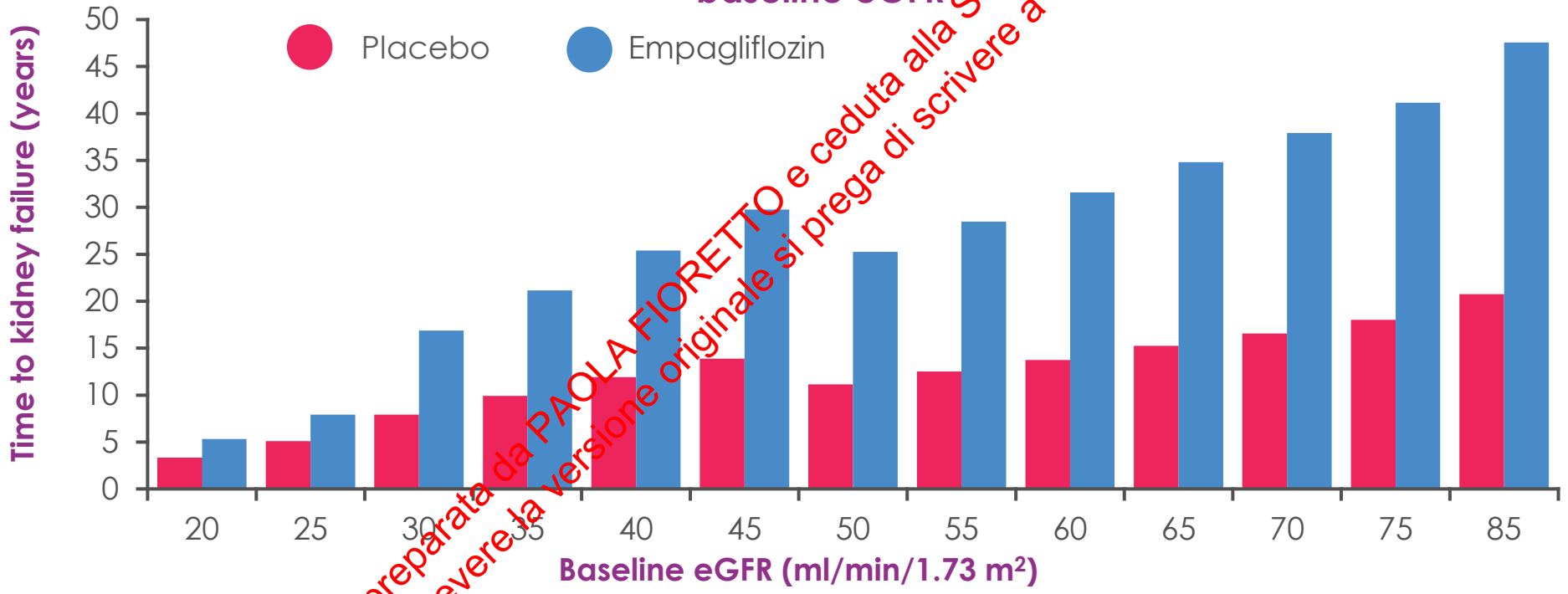


Cherney DZI et al. *Lancet Diabetes Endocrinol*. 2017;5(8):610-621

EMPA-KIDNEY: time to kidney failure by baseline eGFR

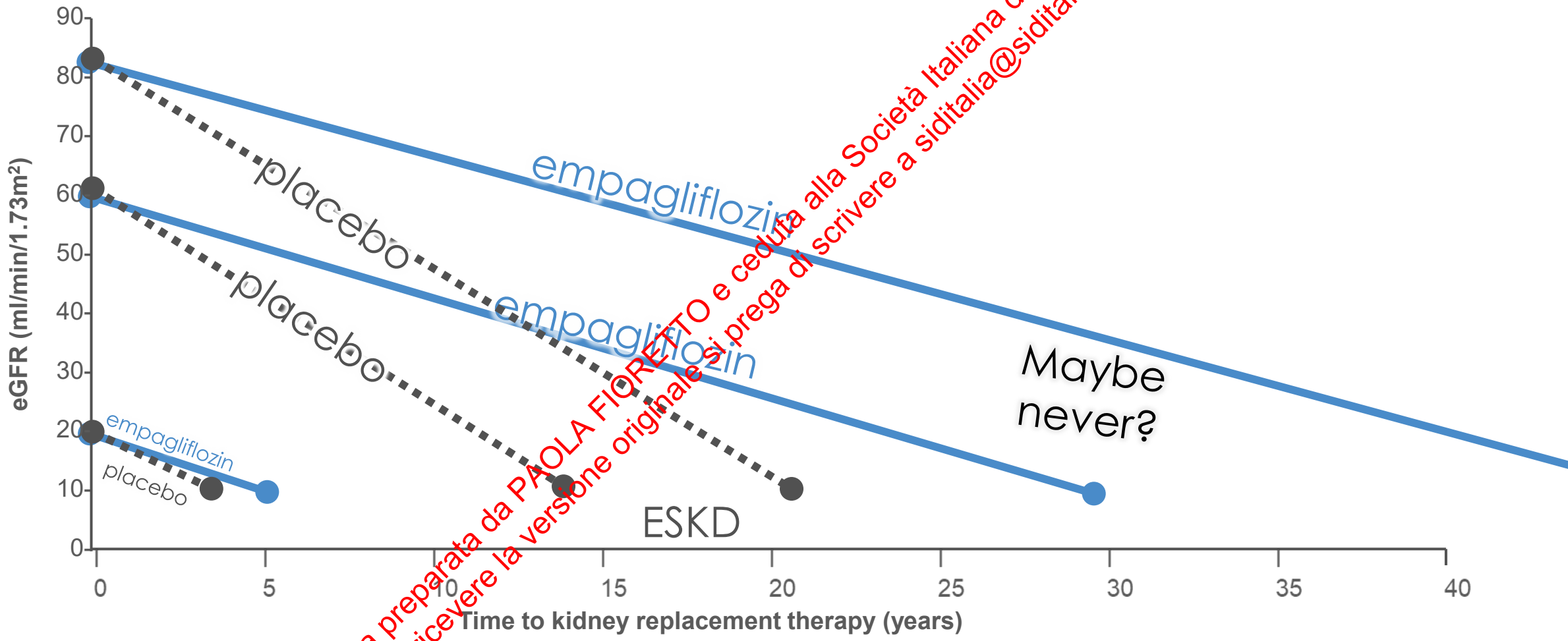
Hypothetical transformation of chronic eGFR slopes into time to kidney failure
Fernández-Fernandez B *et al*. Editorial comment

Time to kidney failure in years for empagliflozin compared with placebo by baseline eGFR*



Fernández-Fernandez B *et al. Clin Kidney J* 2023;0:1

What would happen if we began with an SGLT2 inhibitor as a foundational treatment in CKD?

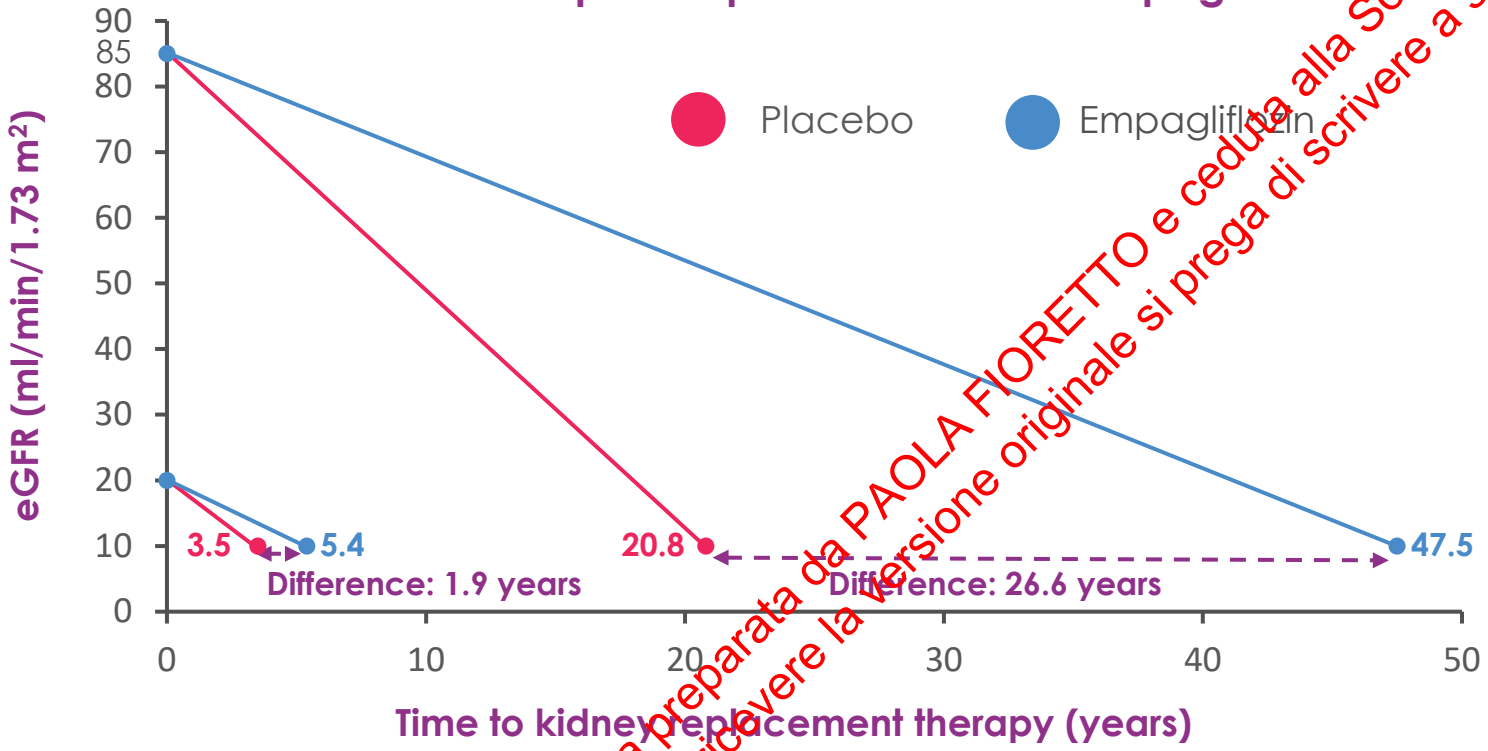


Fernández-Fernandez B *et al. Clin Kidney J* 2023;0:1

EMPA-KIDNEY: time to kidney replacement therapy

Hypothetical transformation of chronic eGFR slopes into time to kidney replacement therapy
Fernández-Fernandez B *et al.* Editorial comment

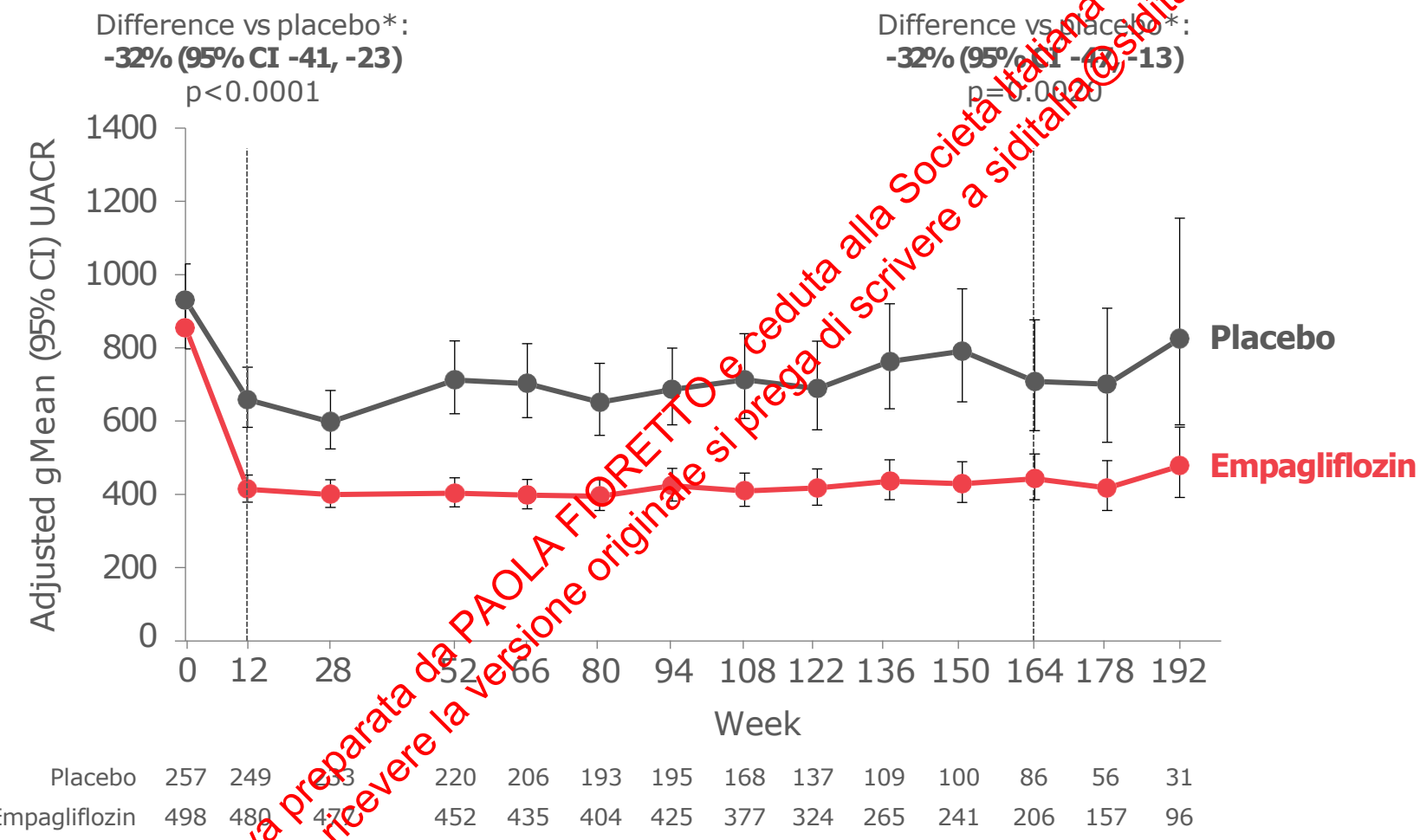
Potential impact on time to kidney replacement therapy of the different eGFR slopes on placebo and on empagliflozin*



- Hypothetical lines have been traced starting from extremes of the baseline eGFR inclusion criteria values (20 and 85 ml/min/1.73 m²) to eGFR 10 ml/min/1.73 m², corresponding to chronic eGFR slopes of participants on placebo and on empagliflozin within each baseline eGFR subgroup

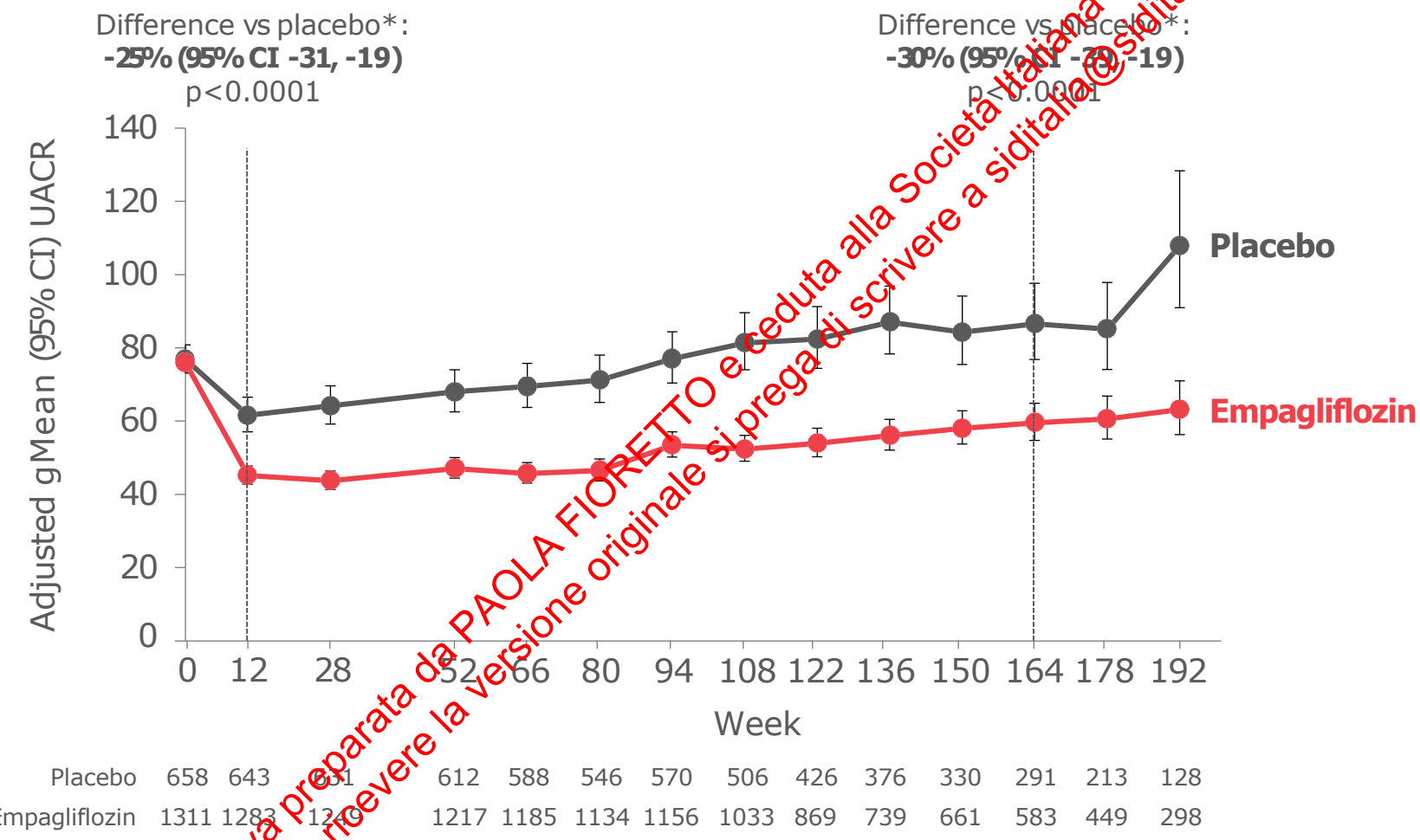
Fernández-Fernandez B *et al. Clin Kidney J* 2023;0:1

UACR over 192 weeks: Patients with macroalbuminuria at baseline



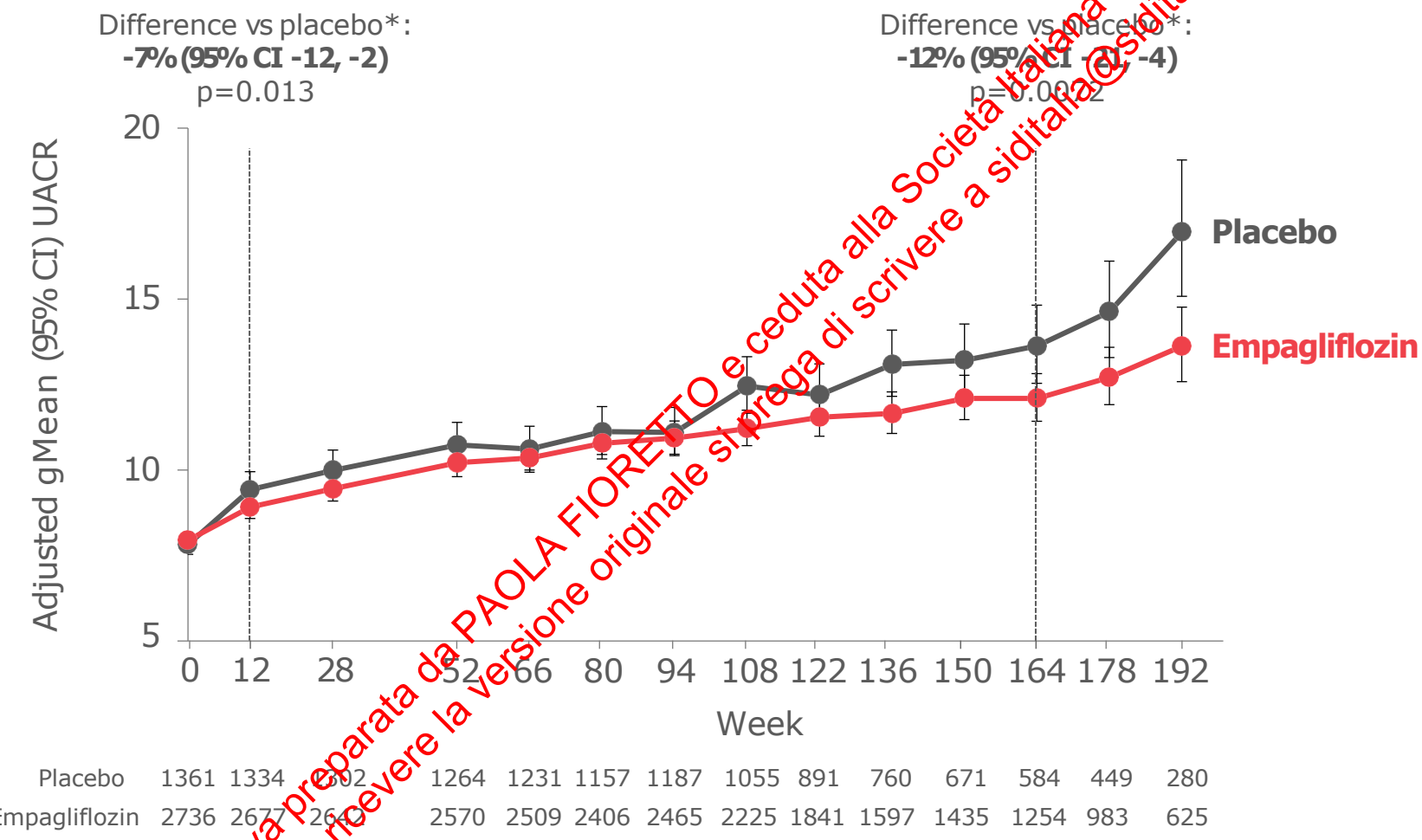
Cherney DZ let al. *Lancet Diabetes Endocrinol*. 2017;5(8):610-621.

UACR over 192 weeks: Patients with microalbuminuria at baseline



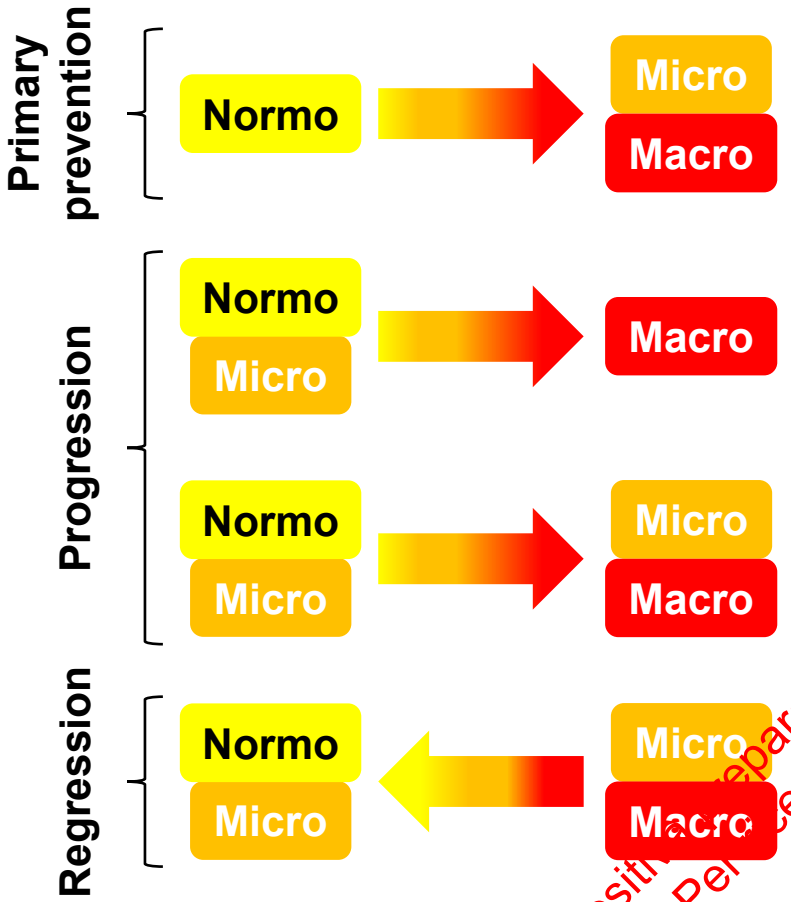
Cherney DZIet al. *Lancet Diabetes Endocrinol*. 2017;5(8):610-621.

UACR over 192 weeks: Patients with normoalbuminuria at baseline



Cherney DZI et al. *Lancet Diabetes Endocrinol*. 2017;5(8):610-621.

SGLT2 inhibitors consistently reduce albuminuria progression and increase albuminuria regression in T2D



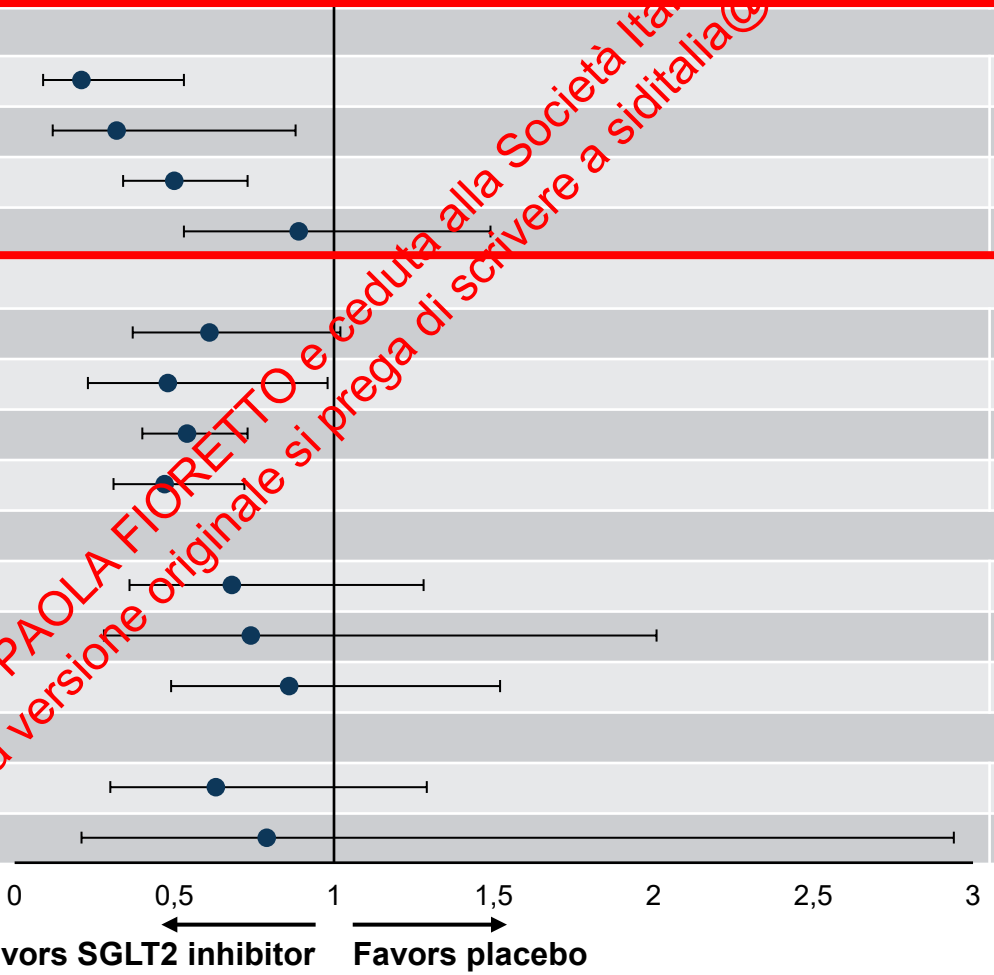
	DECLARE-TIMI 58[1]	CANVAS program[2]	EMPA-REG OUTCOME[2]
Primary prevention: Normo → Micro/Macro	↓ 21% 0.79 (0.72, 0.87)[a]	↓ 20% 0.80 (0.73, 0.88)[b]	↓ 16% 0.84 (0.74, 0.95)[b]
Progression: Normo/Micro → Macro	↓ 46% 0.54 (0.45, 0.65)[a]	↓ 42% 0.58 (0.50, 0.68)[b]	↓ 38% 0.62 (0.54, 0.72)[c]
Progression: Normo/Micro → Micro/Macro	↓ 27% 0.73 (0.67, 0.79)[a]	↓ 27% 0.73 (0.67, 0.79)[b]	↓ 33% 0.67 (0.59, 0.77)[d]
Regression: Normo/Micro ← Micro/Macro	↑ 54% 1.54 (1.40, 1.69)[a]	↑ 70% 1.70 (1.51, 1.91)[b]	↑ 61% 1.61 (1.34, 1.94)[d]

1. Raz I, et al. Presented at 79th Scientific Sessions of the American Diabetes Association; June 7th–11th, 2019; San Francisco, CA, USA; 244-OR; 2. Barutta F, et al. *Diabetes Metab Res Rev* 2019;35:e3171

The kidney benefits of SGLT2 inhibitors were consistent over a wide range of eGFR

Effect of SGLT2 inhibitors on composite kidney composite endpoints, stratified by eGFR

	Events	Patients	RR (95% CI)
eGFR ≥90 mL/min/1.73 m²			
EMPA-REG OUTCOME	22	1529	0.21 (0.09, 0.53)
CANVAS Program	17	2476	0.32 (0.12, 0.88)
DECLARE-TIMI 58	120	8162	0.50 (0.34, 0.73)
VERTIS CV[a]	61	2048	0.89 (0.53, 1.49)
eGFR 60–<90 mL/min/1.73 m²			
EMPA-REG OUTCOME	61	3638	0.61 (0.37, 1.02)
CANVAS Program	30	5625	0.48 (0.23, 0.98)
DECLARE-TIMI 58	186	7732	0.54 (0.40, 0.73)
VERTIS CV[a]	86	4390	0.47 (0.31, 0.72)
eGFR 45–<60 mL/min/1.73 m²			
EMPA-REG OUTCOME	39	1238	0.68 (0.36, 1.28)
CANVAS Program	16	1485	0.74 (0.28, 2.01)
VERTIS CV[a]	51	1807	0.86 (0.49, 1.52)
eGFR <45 mL/min/1.73 m²			
EMPA-REG OUTCOME	30	563	0.63 (0.30, 1.29)
CANVAS Program	10	554	0.79 (0.21, 2.94)

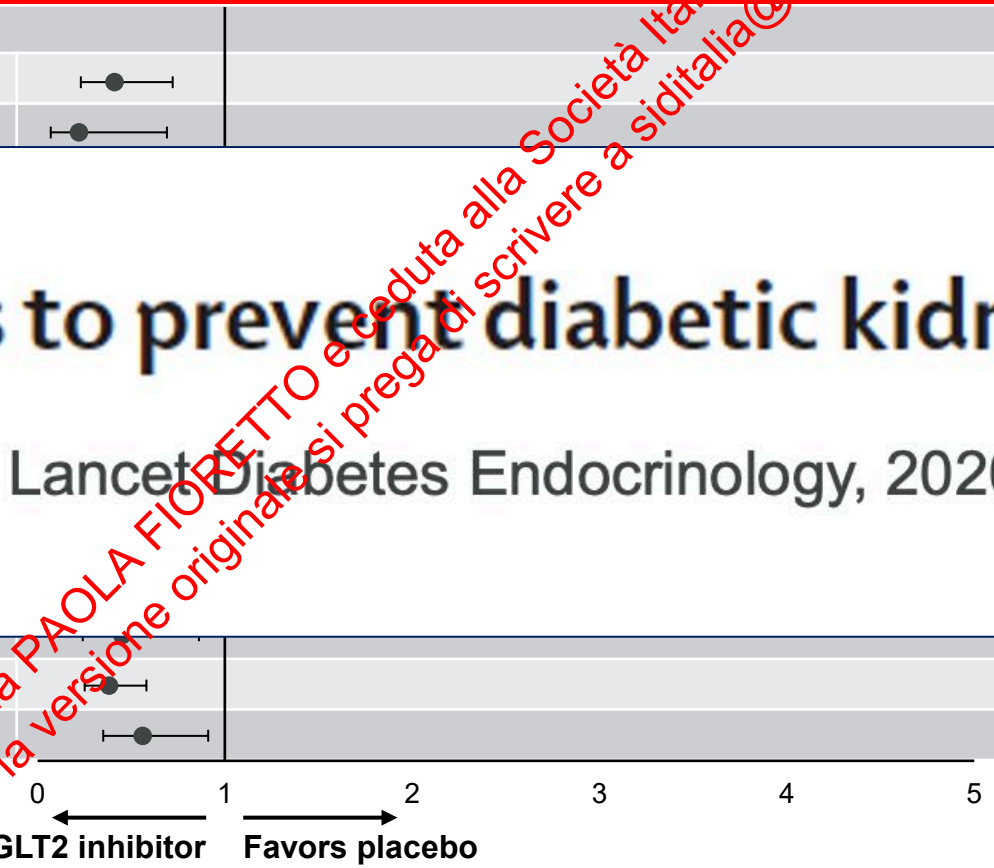


1. Neuen BL, et al. Lancet Diabetes Endocrinol 2019; 2. Cherney DZI, et al. Diabetologia 2021

…as well as over a range of UACR

Effect of SGLT2 inhibitors on composite kidney composite endpoints, stratified by UACR

	Events	Patients	RR (95% CI)
UACR <30 mg/g			
EMPA-REG OUTCOME	48	4142	0.41 (0.23, 0.72)
CANVAS Program	15	7007	0.22 (0.07, 0.69)
DECLARE-TIMI 58	106	1169	0.38 (0.25, 0.58)
VERTIS CV	66	755	0.56 (0.35, 0.91)



1. Neuen BL, et al. Lancet Diabetes Endocrinol 2019; 2. Cherney DZI, et al/ Diabetalogica 2021