Incretine e nefroprotezione nel paziente con diabete mellito tipo 2

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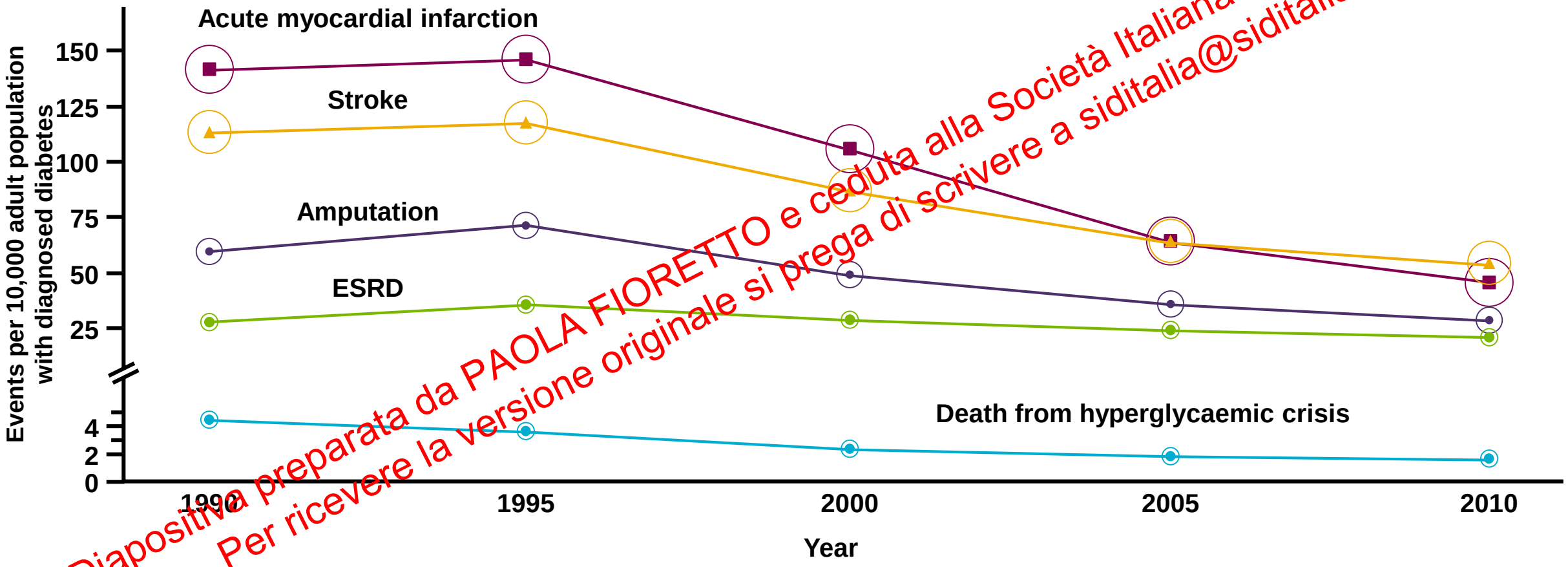
La dr. Fioretto dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche:

Astra Zeneca, Boehringer Ingelheim, Lilly, MSD, Novartis

Trends in diabetes-related complications among U.S. adults with diagnosed diabetes 1990–2010



Gregg EW, et al. *New Engl J Med* 2014;370:1514–1523

Treatment of DKD in patients with Type 2 diabetes

1. Blockade of the RAAS
2. Blood pressure control
3. Glucose control
4. Lipid control

What about individual antidiabetes agents?

- GLP-1 receptor agonists

- DD4 inhibitors

- SGLT2 inhibitors

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

GLP1 RA 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)
Short-acting GLP-1 receptor agonists (subcutaneous injection)									
Exenatide	5–10 µg BID	2005	2005	2.4	NA	Mainly renal	No adjustment	Conservative dose escalation	Not recommended
Lixisenatide	10–20 µg QD	2013	2016	3.0	NA	Mainly renal	No adjustment	No adjustment	Not recommended
Long-acting GLP-1 receptor agonists (subcutaneous injection)									
Exenatide	2 mg QW	2011	2012	NS‡	NA	Mainly renal (~10 weeks to fully clear)	No adjustment	Not recommended	Not recommended
Liraglutide	0.6 mg, 1.2 mg or 1.8 mg QD	2009	2010	12.6–13.0	NA	Peptidases and renal 6%; faeces 5%	No adjustment	No adjustment	Not recommended
Albuglutide	30–50 mg QW	2014	2014	~120.0	NA	Peptidases and renal	No adjustment	No adjustment	Not recommended
Dulaglutide	0.75–1.5 mg QW	2014	2014	~112.8	NA	Peptidases and renal	No adjustment	No adjustment	Not recommended
Semaglutide	0.5–1.0 mg QW	Pending	Pending	165.0–184.0	NA	Peptidases and renal	Unknown	Unknown	Unknown

Muskiet MH et al. Nat Rew Nephrol 2017

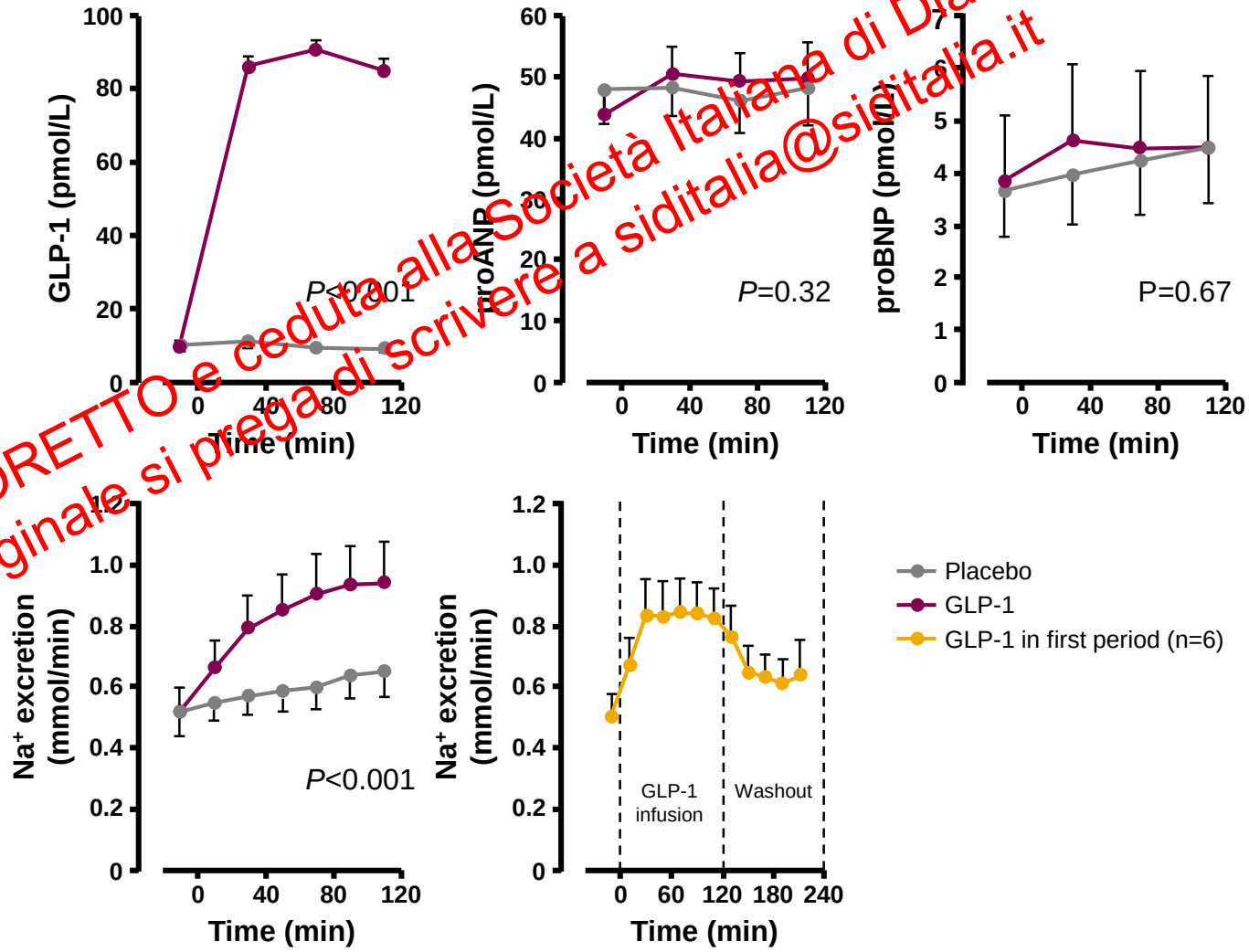
GLP-1 and the kidney

Potential mechanisms

- Blood glucose reduction
- Blood pressure reduction
- Increased sodium excretion
- Renin-angiotensin pathway
- Reduced glucose-induced oxidative stress
- Reduced inflammation

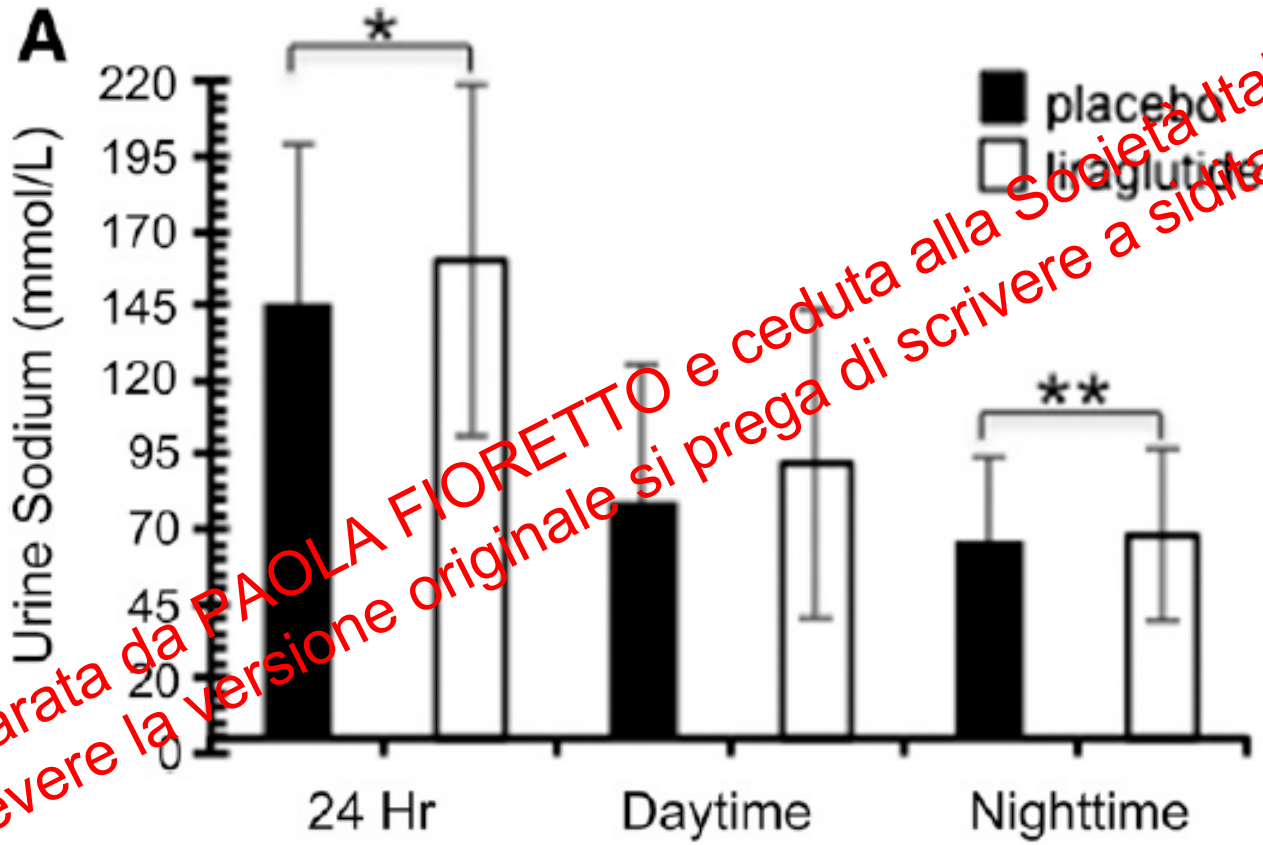
Effects of GLP-1 in healthy subjects

- Healthy young males (N=12) were evaluated in a RCT to evaluate the effects of a 2-hour native GLP-1 infusion on atrial natriuretic peptide
- GLP-1 infusion increased plasma GLP-1 concentration, but had **no significant effect on proANB or proBNP, despite increases in urinary sodium excretion**



Skov J, et al. Endocrin Conn 2014

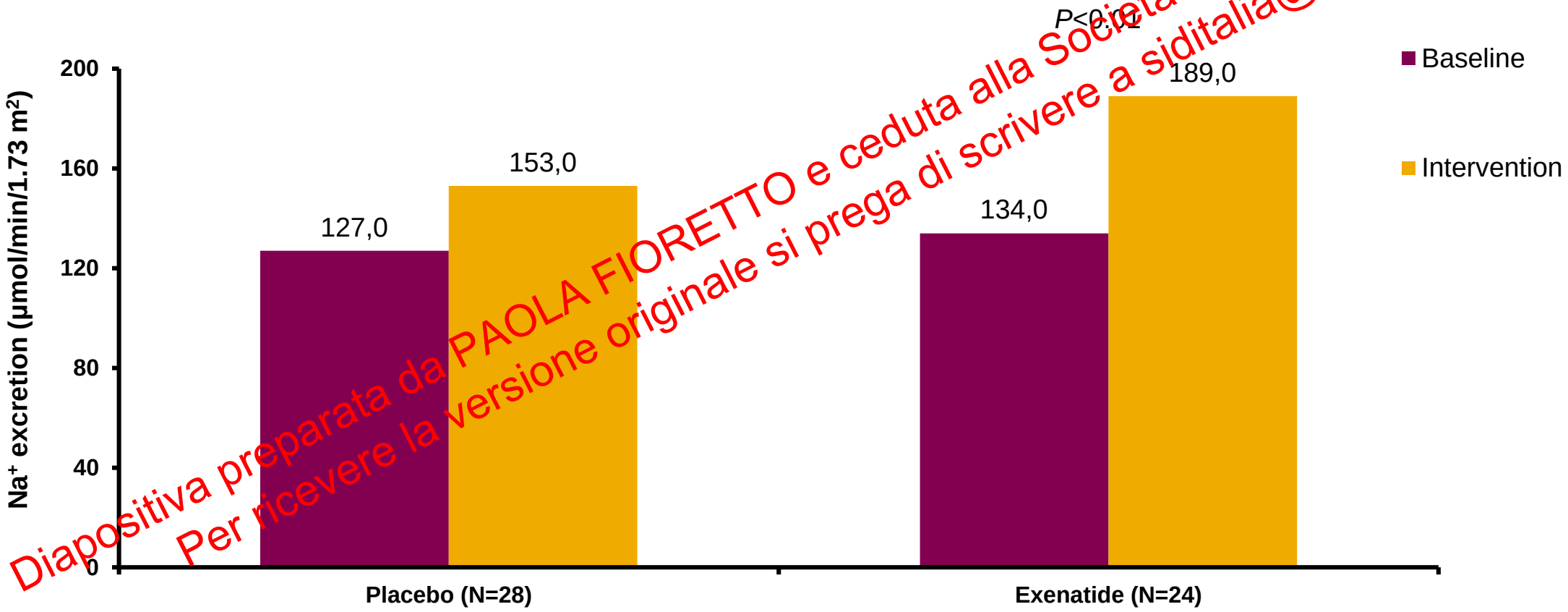
Liraglutide inreases urinary sodium excretion in T2DM (n=18, 21 d)



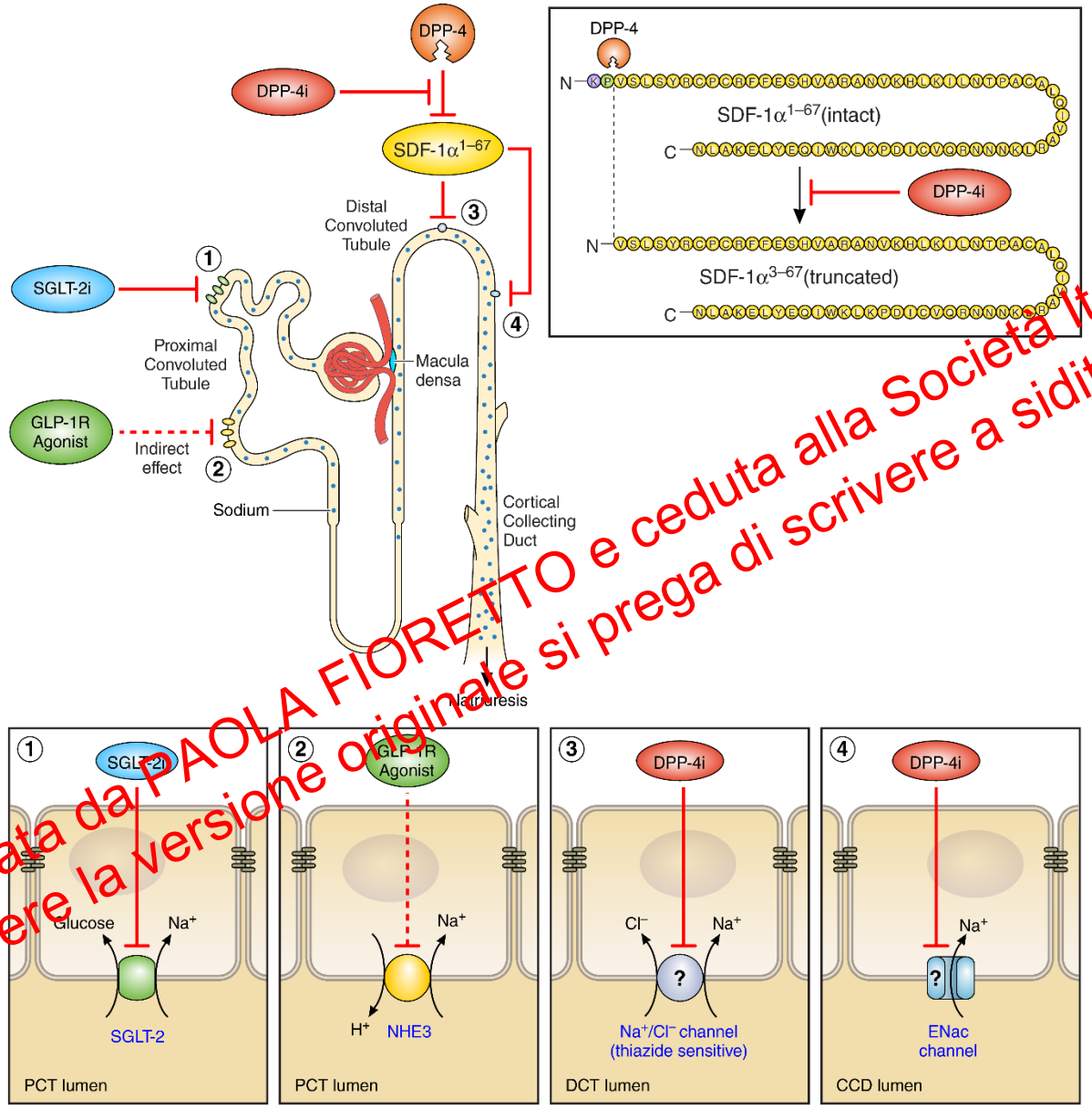
Lovshin JA et al Diabetes Care 2015

Acute exenatide administration was shown to increase proximal sodium excretion in overweight patients with Type 2 diabetes

- Study included overweight men (BMI 25–40 kg/m^2) and postmenopausal women aged 35–75 years with Type 2 diabetes (HbA_{1c} 6.5–9.0%) and estimated GFR ≥60 mL/min/1.73 m^2



Tonnejick L, et al. Diabetologia 2016



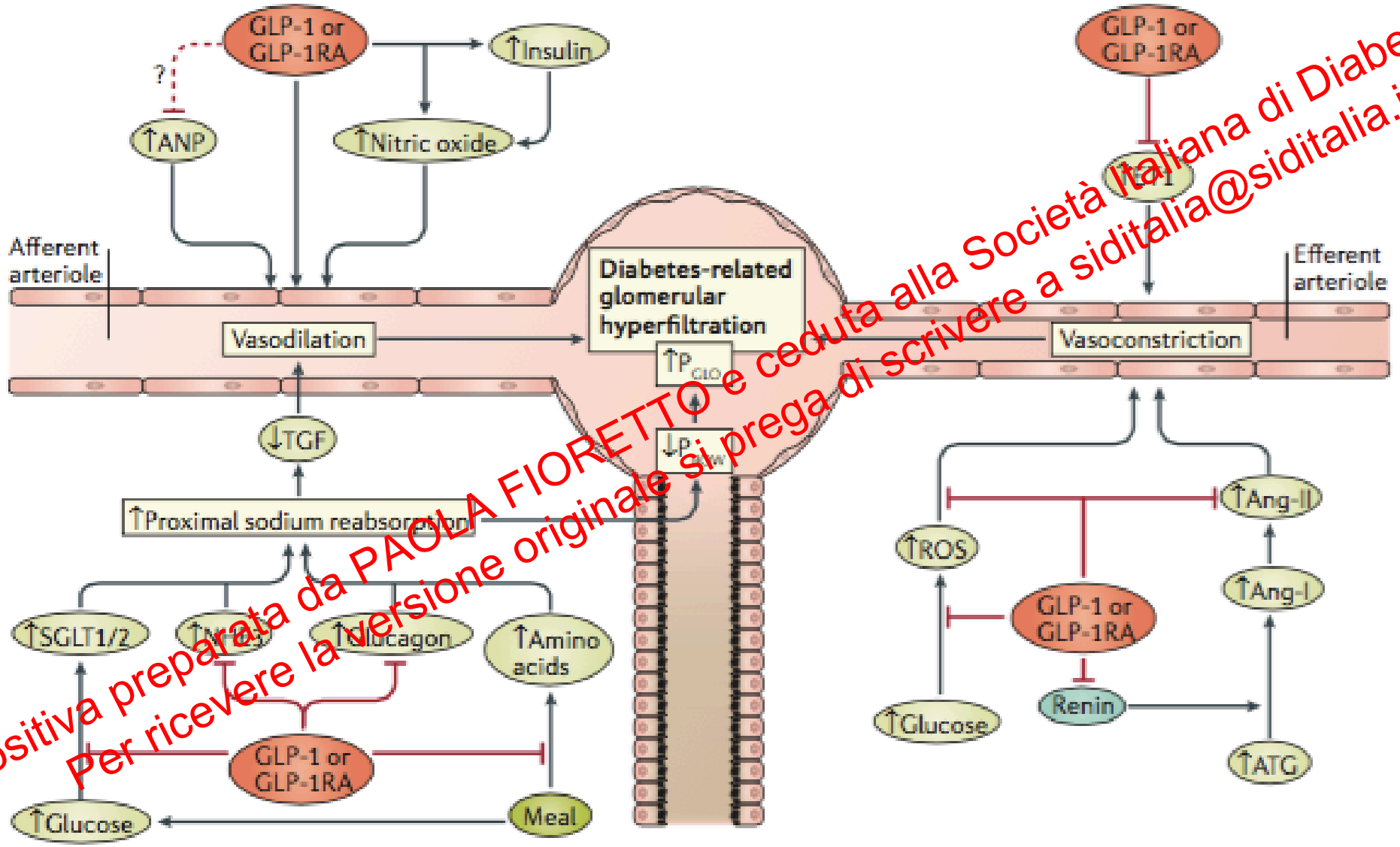
Lovshin JA et al, Diabetes Care, 2017

RAAS hormones in patients with Type 2 diabetes before and after 12 weeks' treatment with liraglutide

	Before liraglutide	After liraglutide	Change for liraglutide group (95% CI)	Before placebo	After placebo	Change for placebo group (95% CI)	*P* value for comparison between therapies (end vs end)
p-Renin concentration, mU/L	83.7 [34.5, 322.0]	52.4 [14.0, 204.1]	–37% (–58, –5) *P*=0.030	81.9 [30.0, 241.0]	60.1 [15.9, 242.3]	–27% (–56, 18) *P*=0.22	0.57
p-Renin activity, mIU/L	67.7 [24.5, 252.5]	44.0 [11.0, 146.5]	–35% (–59, 2) *P*=0.060	65.8 [20.0, 181.8]	46.9 [13.0, 153.1]	–29% (–59, 19) *P*=0.21	0.80
p-Angiotensin II, pmol/L	9.7 [3.2, 50.5]	5.5 [1.1, 29.4]	–43% (–64, –9) *P*=0.022	9.0 [4.0, 39.0]	6.4 [1.6, 33.9]	–28% (–57, 17) *P*=0.20	0.53
p-Aldosterone, ng/L	214.9 [161.8, 292.2]	213.6 [158.0, 319.9]	–1 (–19, 18) *P*=0.95	225.0 [182.0, 299.0]	206.4 [157.8, 293.5]	–6 (–20, 13) *P*=0.45	0.53

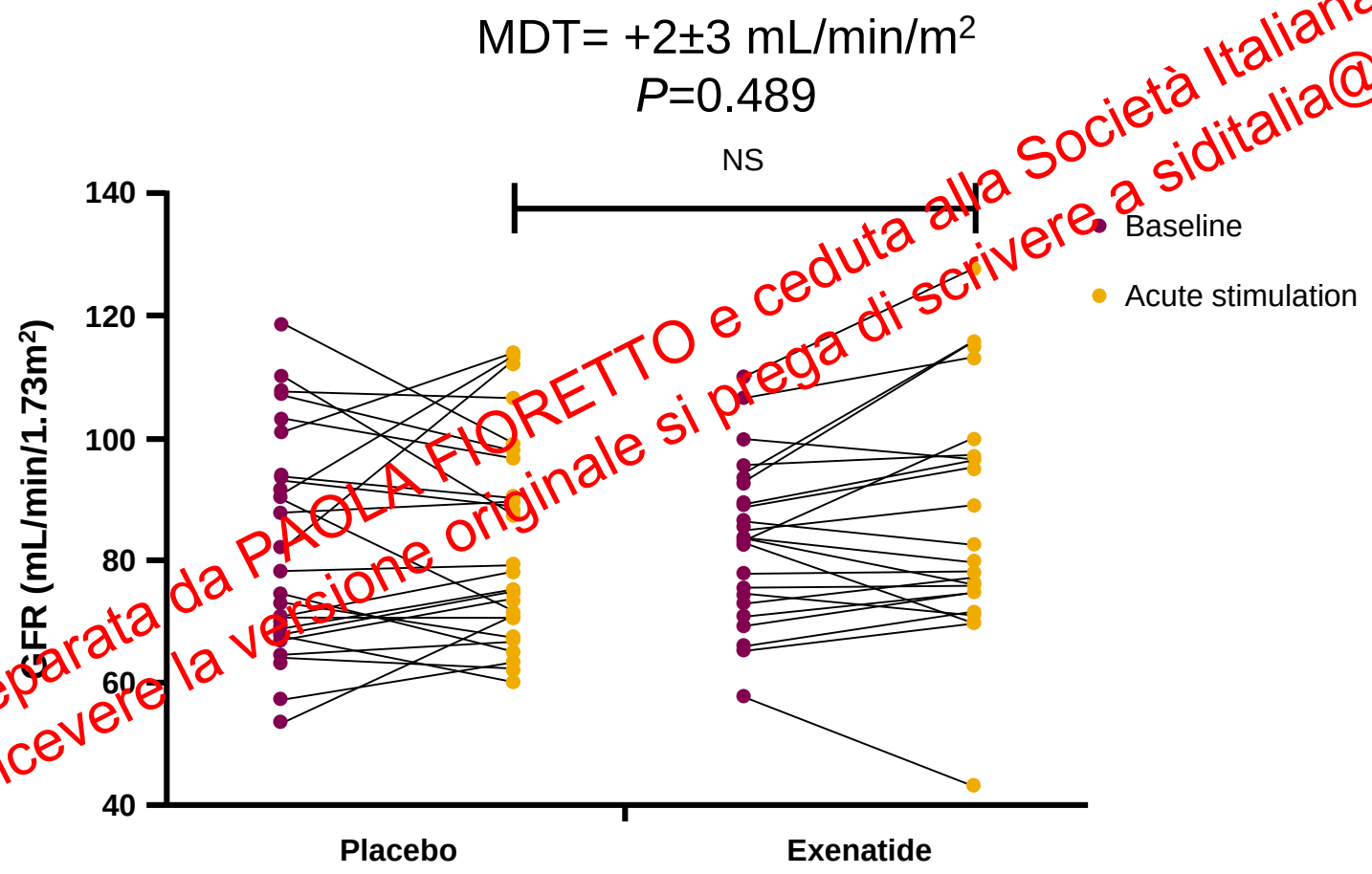
Von Scholten BJ, et al. *Diabetes Obes Metab* 2017

Effects of GLP1 RA on renal hemodynamics



Muskiet MH et al. Nat Rew Nephrol 2017

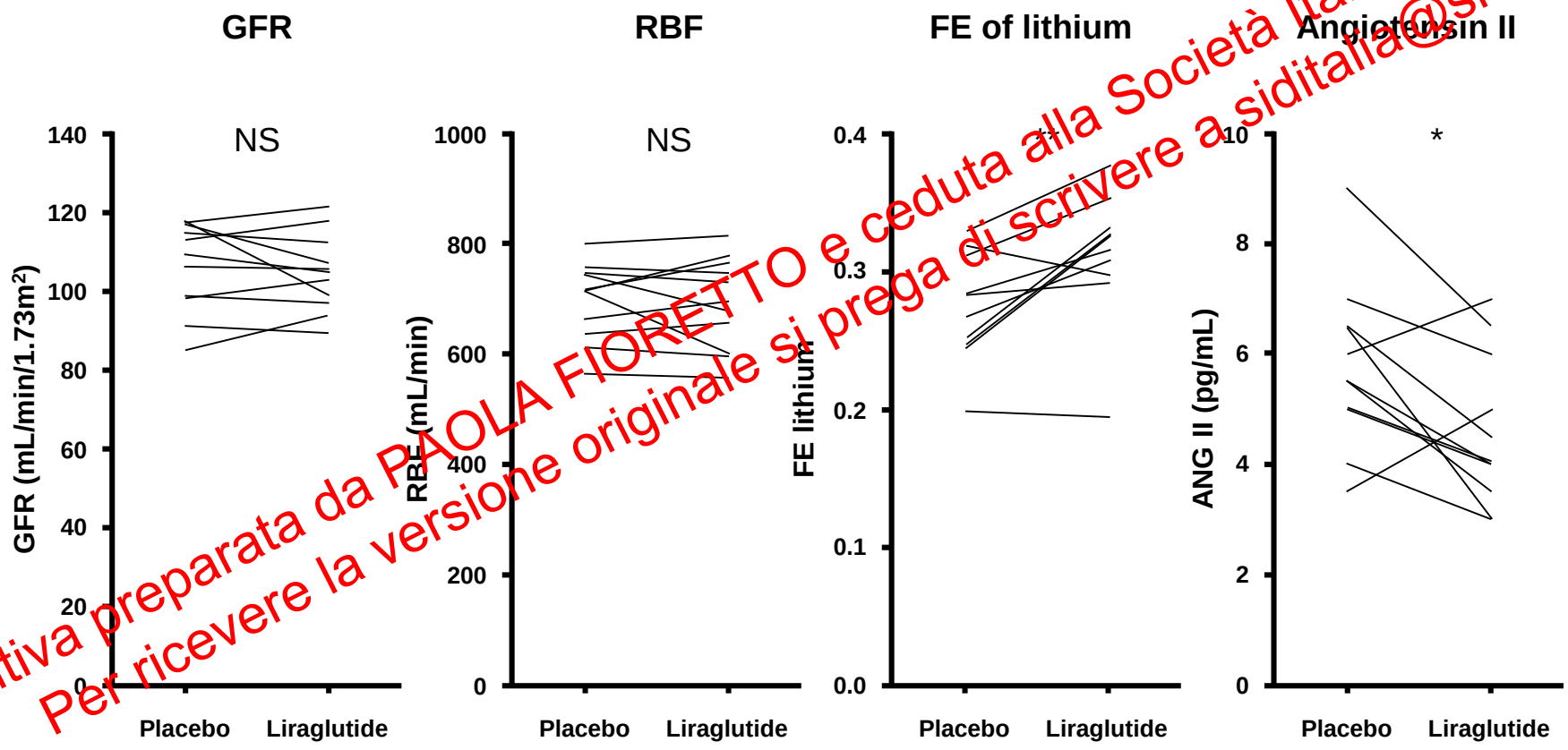
Acute exenatide administration does not affect eGFR in overweight patients with Type 2 diabetes, compared with placebo



Tonnejick L, et al. Diabetologia 2016

Acute renal effects of liraglutide in patients with Type 2 diabetes

In patients with Type 2 diabetes (N=11), a single dose of liraglutide 1.2 mg had no effect on renal haemodynamics but decreased the proximal tubular sodium reabsorption



Skov J, et al. Diabetes Obes Metab 2016

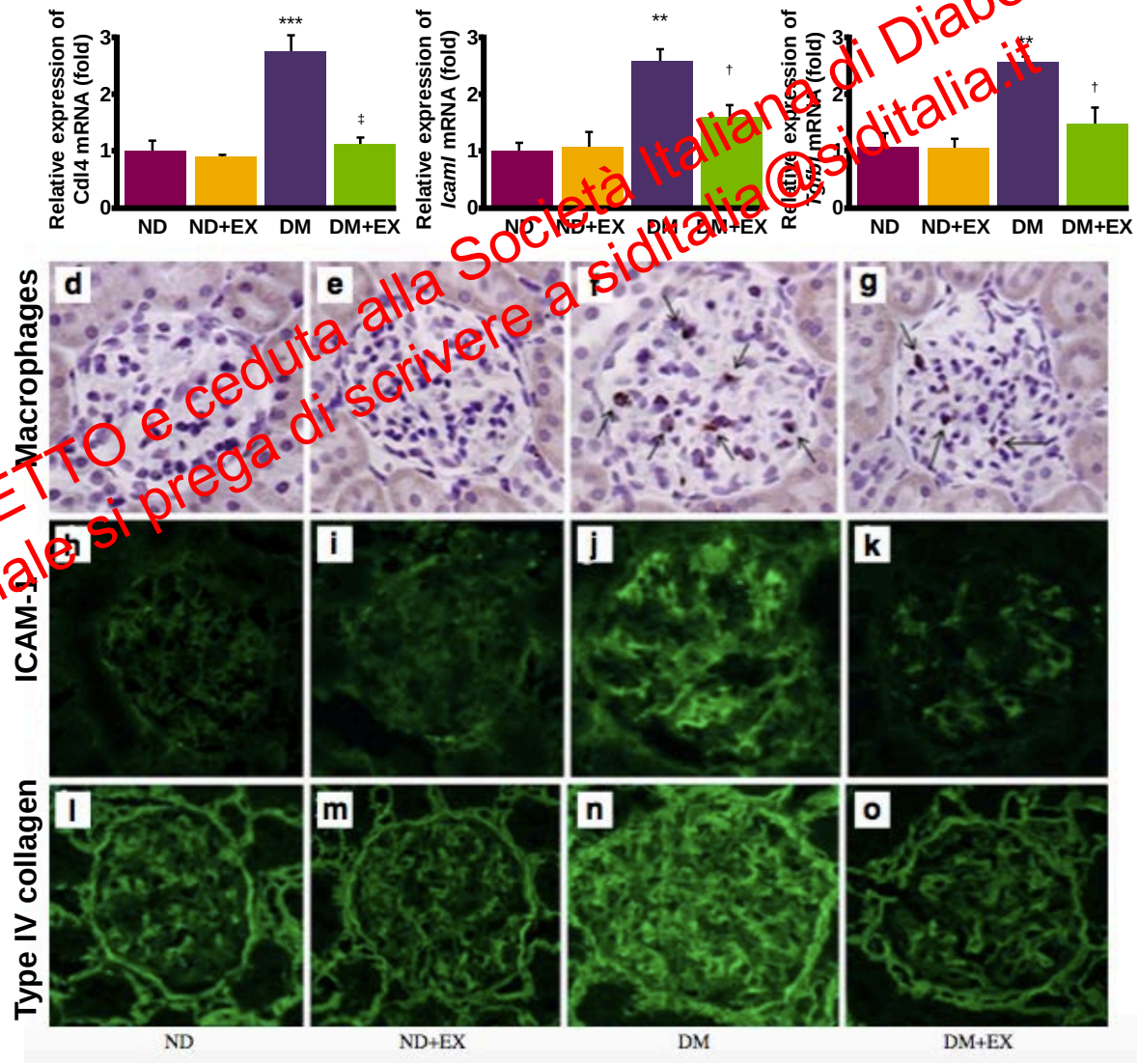
GLP-1 and the kidney

Potential mechanisms

- Blood glucose reduction
- Blood pressure reduction
- Increased sodium excretion
- Renin–angiotensin pathway
- Reduced glucose-induced oxidative stress
- Reduced inflammation

Exendin-4 suppressed the inflammatory axis in the kidney

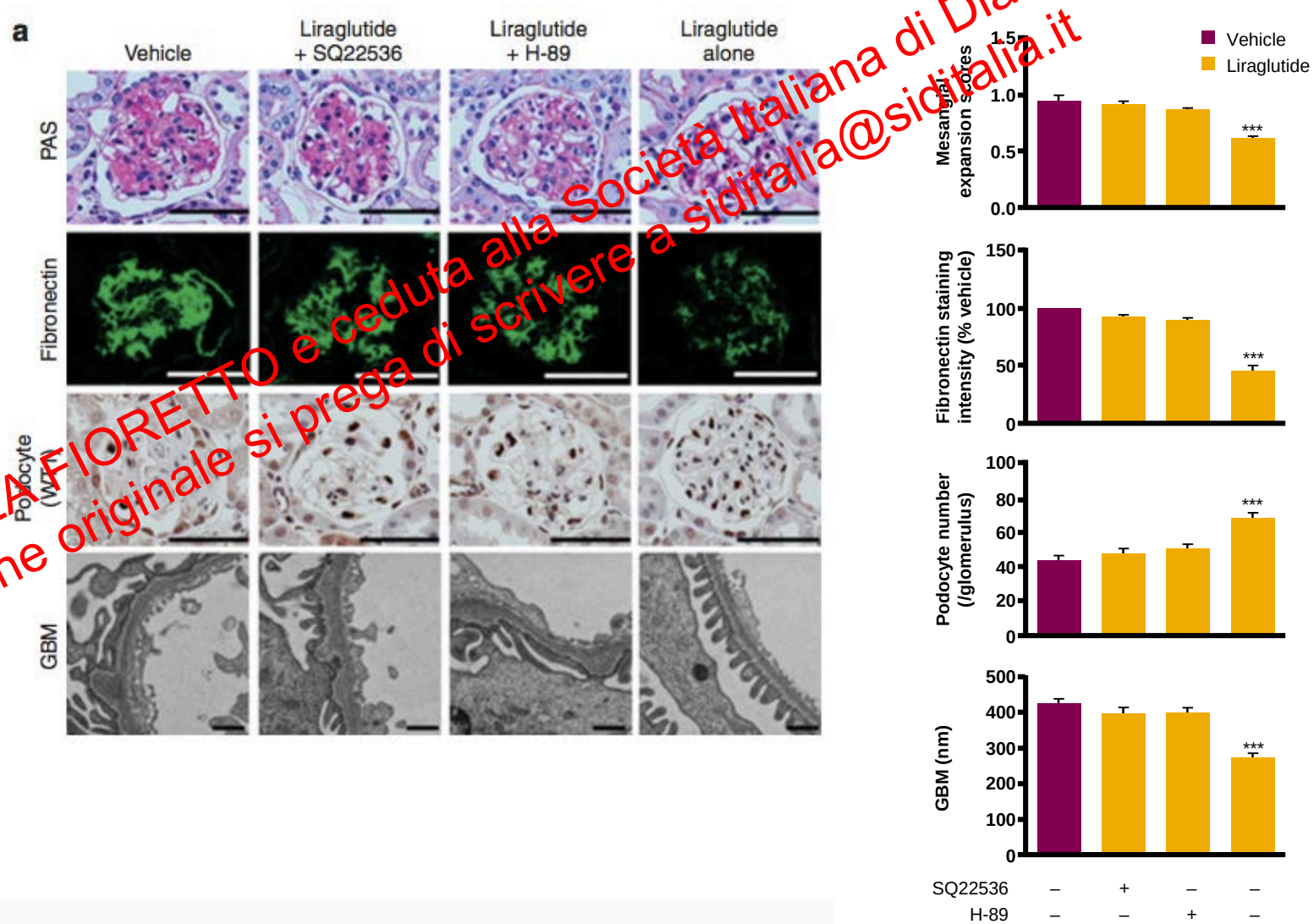
- Exendin-4 was administered at 10 μg/kg daily for 8 weeks to a STZ-induced rat model of Type 1 diabetes
- Markers of inflammation were significantly up-regulated in the diabetes group and significantly downregulated by exendin-4 treatment



Kodera R, et al. Diabetologia 2011

GLP-1 receptor agonists and oxidative stress

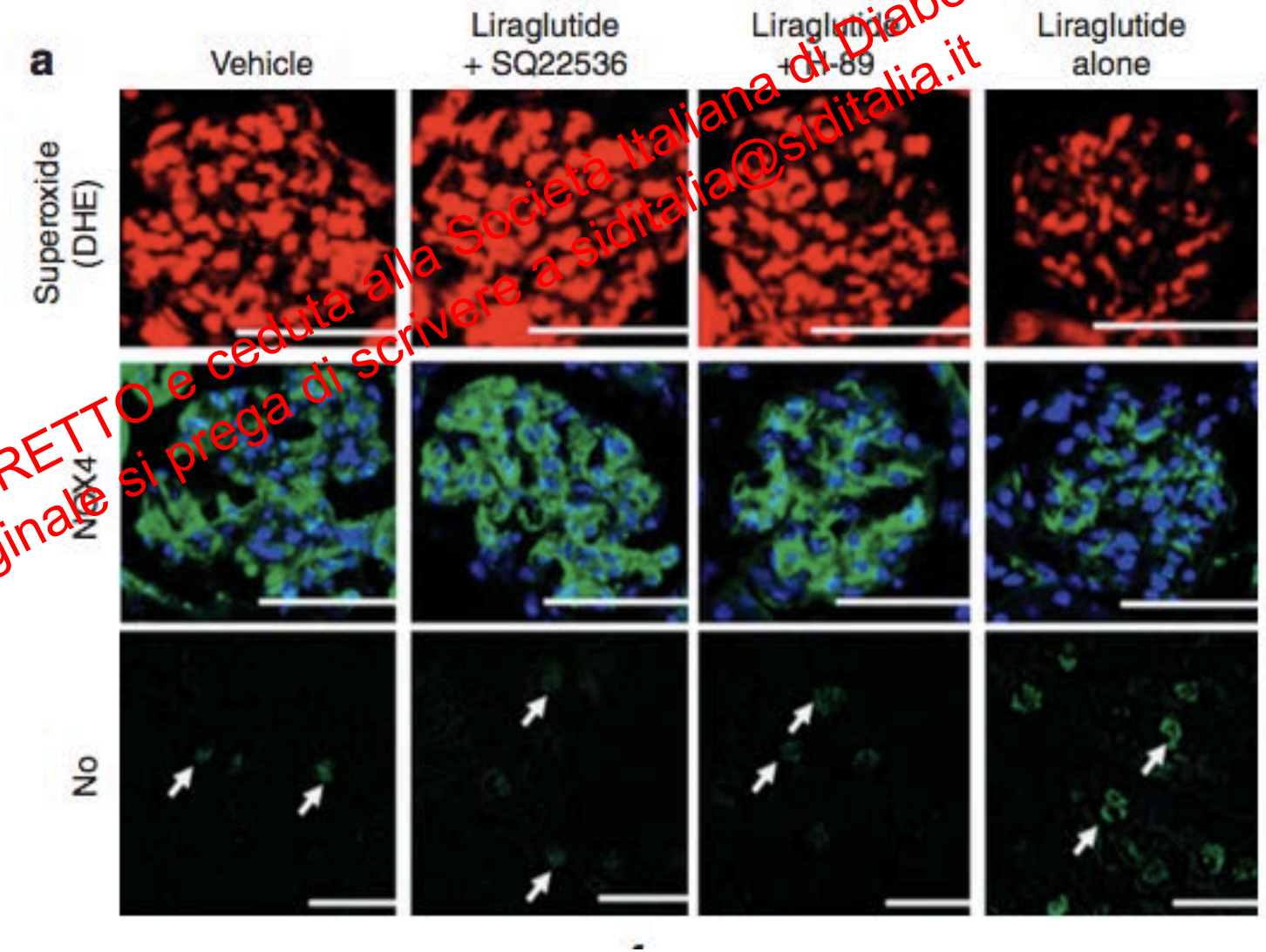
- Treatment with liraglutide in Akita mice reduced albuminuria and mesangial expansion
- These effects were abolished by cAMP inhibitor SW22536 and PKA inhibitor H-89



Fujita H, et al. Kidney Int 2014

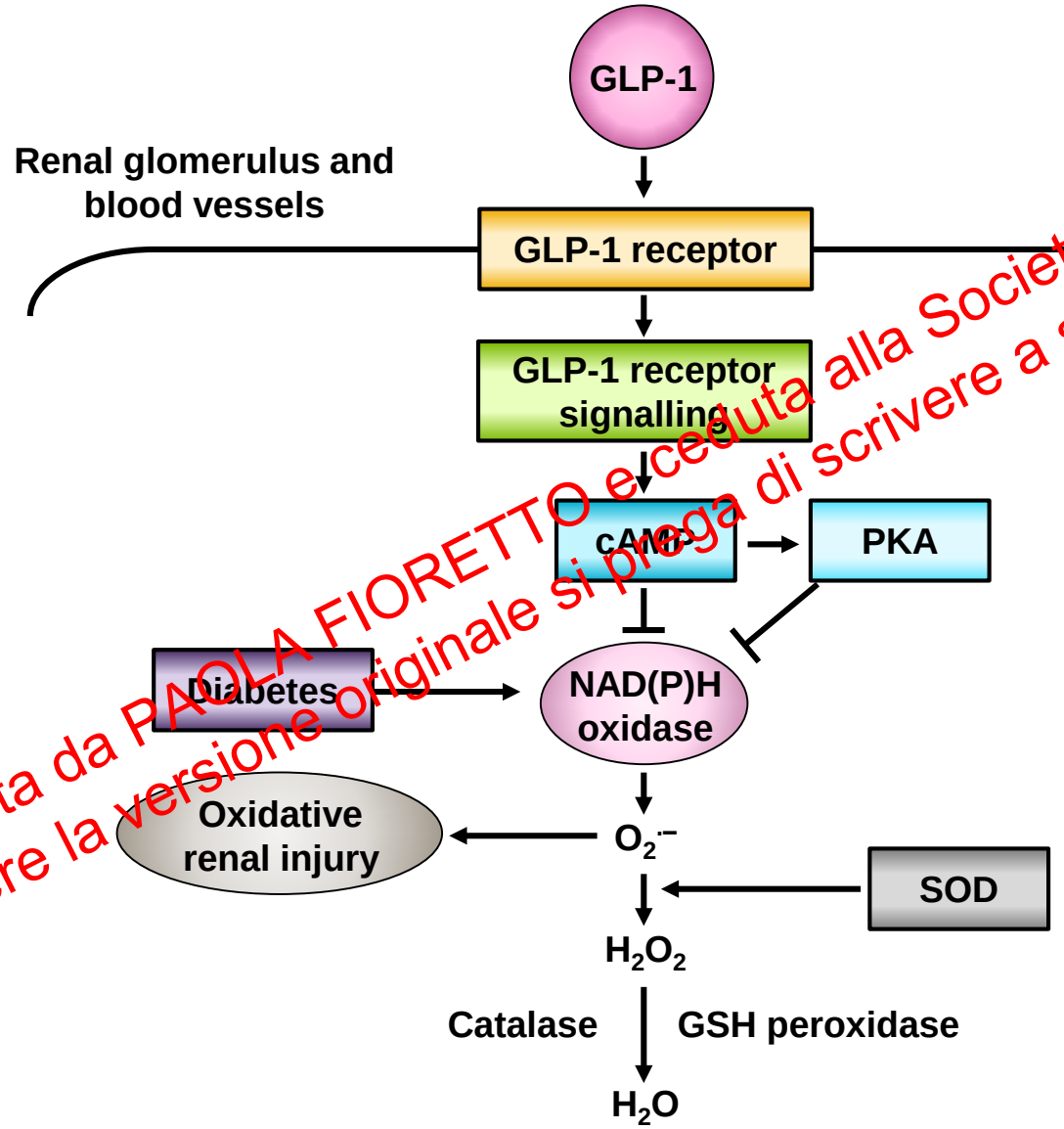
GLP-1 receptor agonists and oxidative stress

- Treatment with liraglutide in Akita mice decreased levels of superoxide and renal NAD(P)H oxidase and elevated renal cAMP and PKA activity
- These effects were abolished by cAMP inhibitor SW22536 and PKA inhibitor H-89



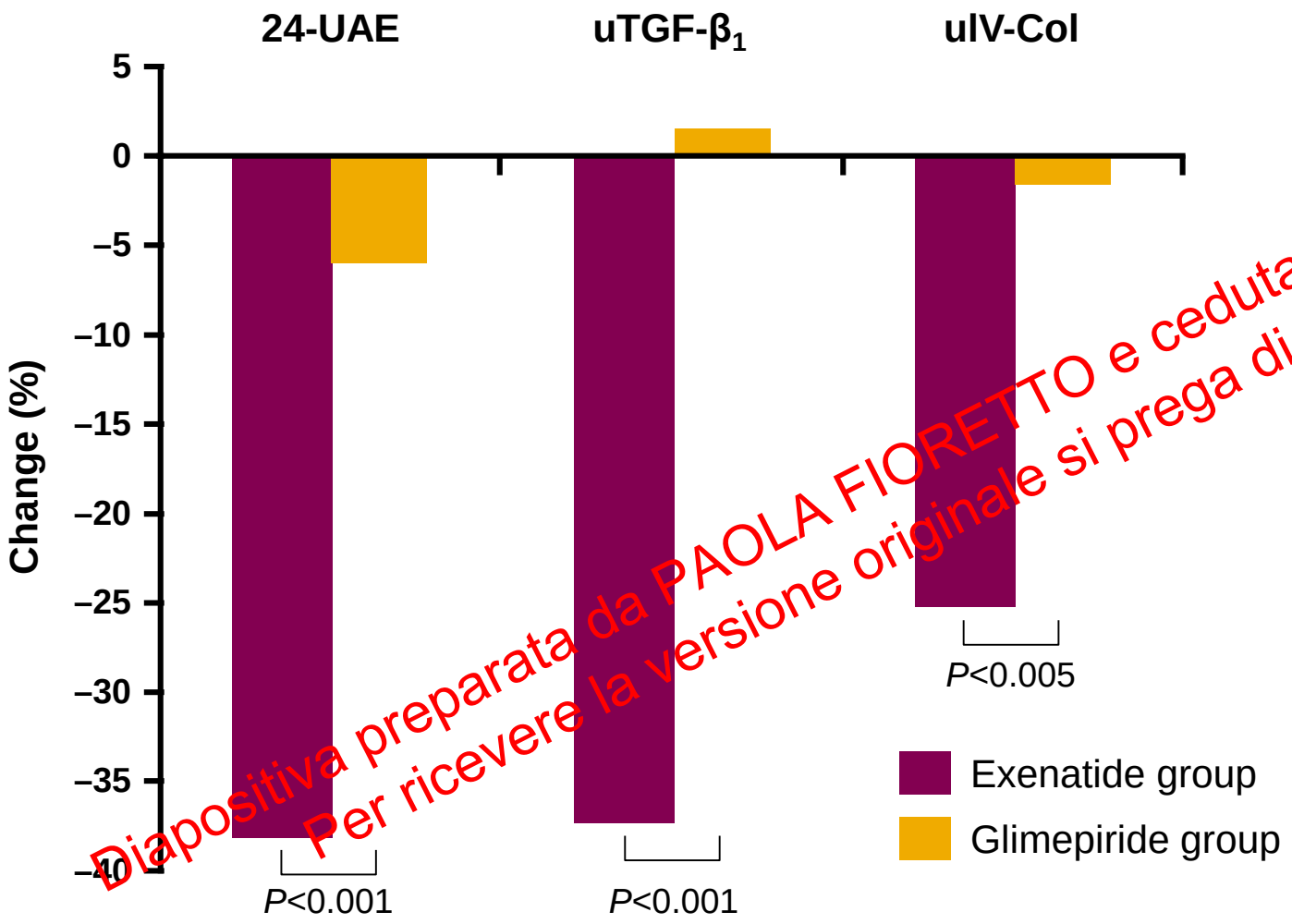
Fujita H, et al. Kidney Int 2014

The protective roles of GLP-1 R signaling in diabetic nephropathy



Fujita H, et al. Kidney Int 2014

Exenatide reduced 24-hour UAE, TGF-β1 and type IV collagen excretion in patients with Type 2 diabetes and microalbuminuria



- The levels of 24-hour urinary albumin in the exenatide group dropped significantly by 37.97% from 107 to 65 mg/L after 16 weeks of treatment ($P<0.01$)
- The levels of urinary TGF-β_1 were significantly reduced following treatment with exenatide ($P<0.01$)
- A significant reduction was also observed for urinary type IV collagen in the exenatide group ($P<0.01$)

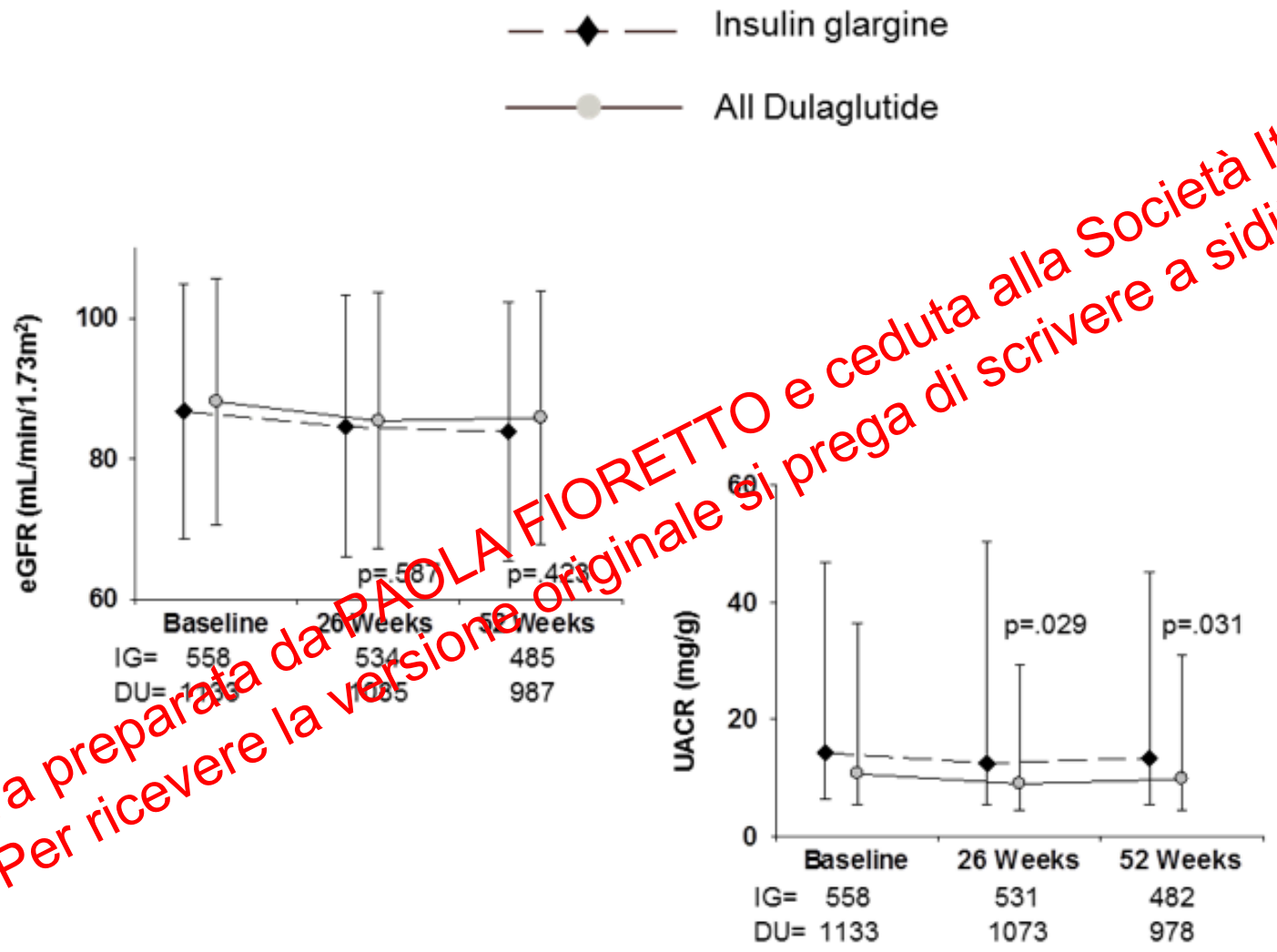
Zhang H, et al. Kidney Blood Press Res 2012

DURATION-2: switch from sitagliptin and pioglitazone to exenatide QW

	Exenatide QW → exenatide QW (N=103)	Sitagliptin → exenatide QW (N=116)	Pioglitazone → exenatide QW (N=100)
ACR (baseline)	15.31±2.37	11.46±1.27	13.23±1.92
Δ weeks 26–52	–19% (–31, –5)*	–14% (–26, 0)	–12% (–25, 4)
Δ weeks 0–52	–34% (–45, –20)*	–18% (–31, –3)*	–23% (–36, –7)*
BNP (baseline, pg/mL)	9.66±1.00	11.69±1.03	9.60±0.84
Δ weeks 26–52	–10% (–23, 6)	–16% (–27, –3)*	–26% (–37, –14)*
Δ weeks 0–52	–18% (–31, –3)*	–15% (–28, –1)*	–13% (–26, 3)
hsCRP (baseline, mg/L)	2.50±0.24	2.35±0.18	2.33±0.24
Δ weeks 26–52	–2% (–15, 12)	–8% (–20, 5)	37% (19, 58)*
Δ weeks 0–52	–25% (–35, –13)*	–17% (–27, –4)*	–5% (–18, 11)
PAI-1 (baseline, ng/mL)	39.14±2.29	32.97±1.71	36.18±1.95
Δ weeks 26–52	16% (4, 30)*	–3% (–12, 8)	27% (14, 42)*
Δ weeks 0–52	4% (–8, 16)	–8% (–18, 2)	12% (0, 25)

Wysham C, et al. Diabetic Med 2017

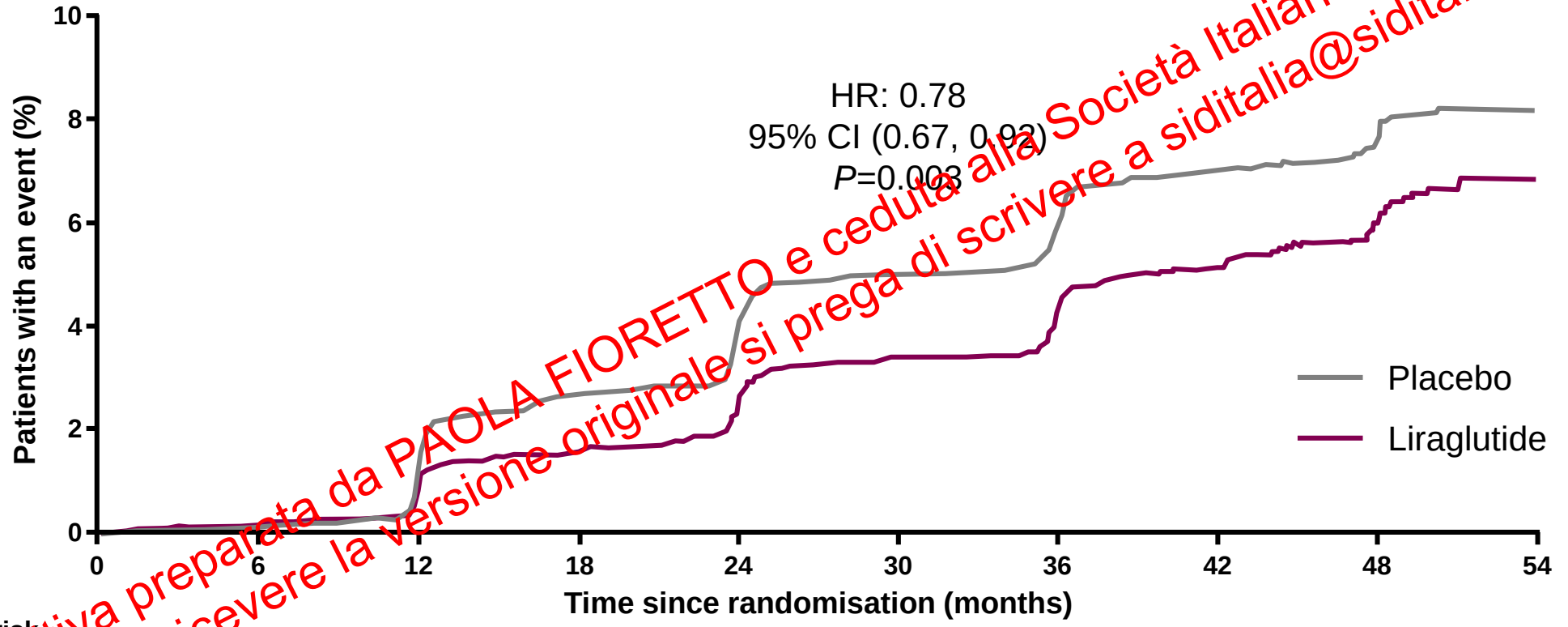
Effects of Dulaglutide on eGFR and ACR Compared to Insulin Glargine (pooled analisys)



Tuttle K et al, DOM 2016

LEADER: renal endpoint

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



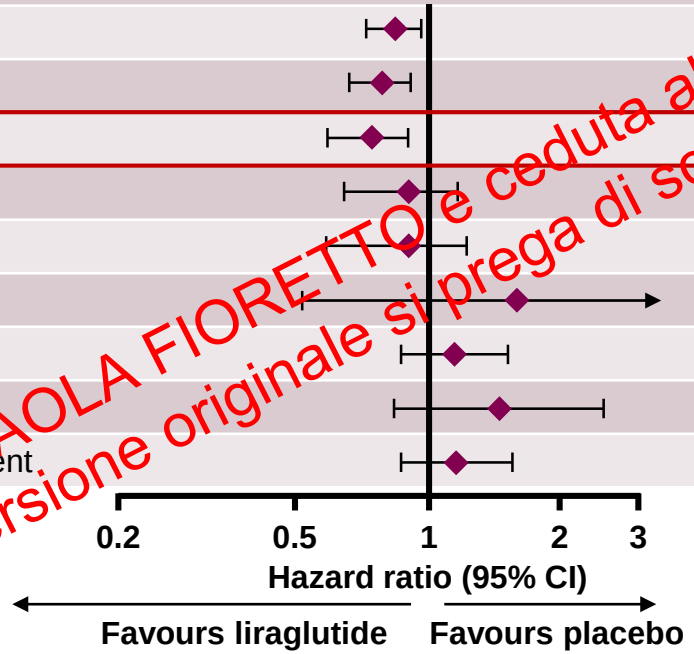
Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

Buse JB et al, N Eng J Med 2016

LEADER: Time to first microvascular endpoints

	Hazard ratio (95% CI)	Liraglutide		Placebo	
		N	%	N	%
Number of patients		**4668**	**100**	**4672**	**100**
Microvascular endpoint	**0.84 (0.73, 0.97)**	**355**	**7.6**	**416**	**8.9**
Renal event	**0.78 (0.67, 0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria[a]	0.74 (0.60, 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine[b]	0.88 (0.66, 1.18)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61, 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52, 4.87)	8	0.2	5	0.1
Eye event	**1.15 (0.87, 1.52)**	**106**	**2.3**	**92**	**2.0**
Vitreous haemorrhage	1.45 (0.84, 2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87, 1.55)	100	2.1	86	1.8



Buse JB et al, N Eng J Med 2016

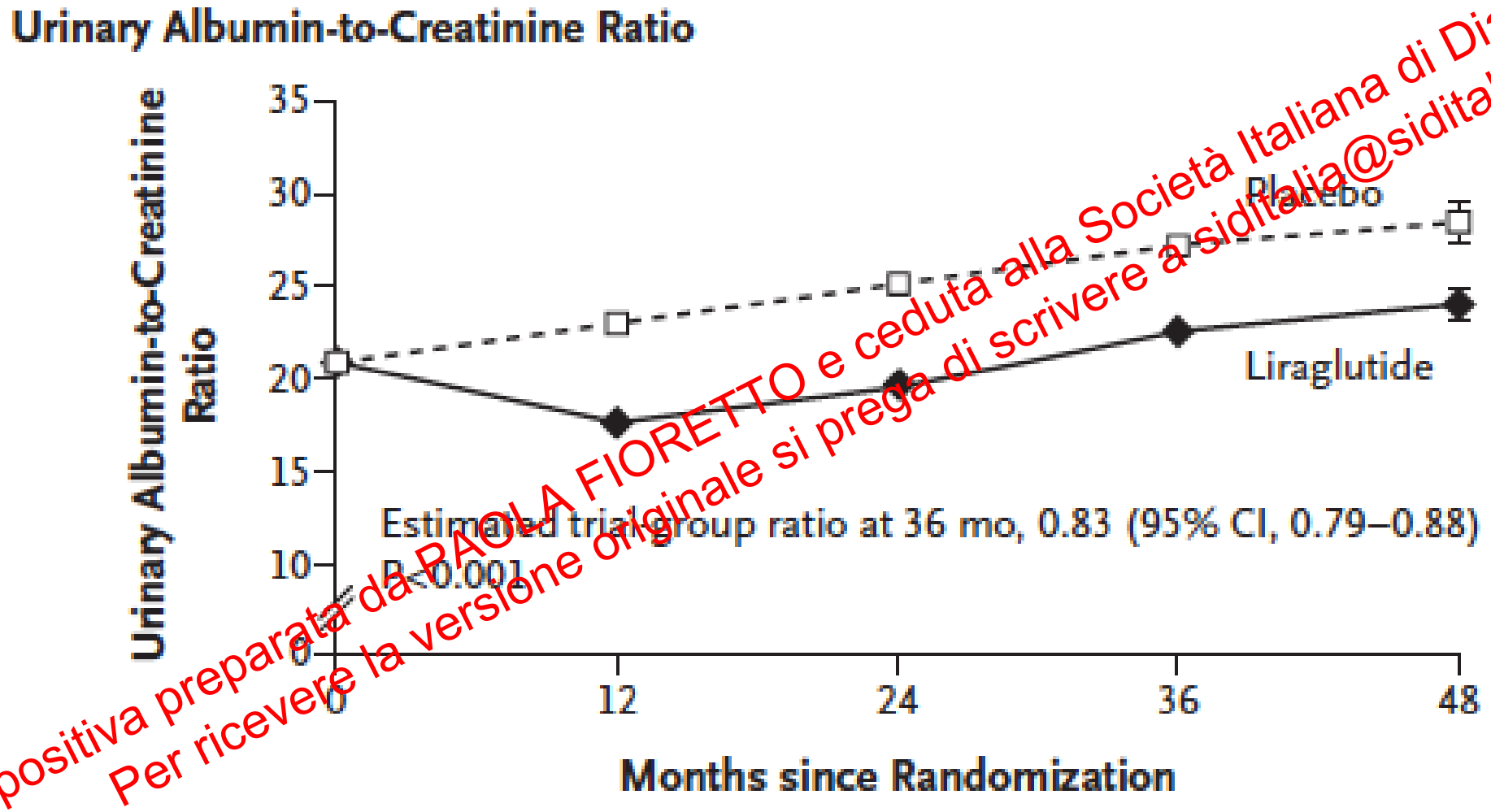
Baseline characteristics

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic regi		
Europe		(35.5)
North America		(31.0)
Asia		1 (7.5)
Rest of the wo		(26.1)
HbA_{1c}, %		± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

	Liraglutide	Placebo
Microalbuminuria	26.4%	26.6%
Macroalbuminuria	10.9%	11.0%
eGFR <60 mL/min/1.73 m^2	23.9%	22.3%

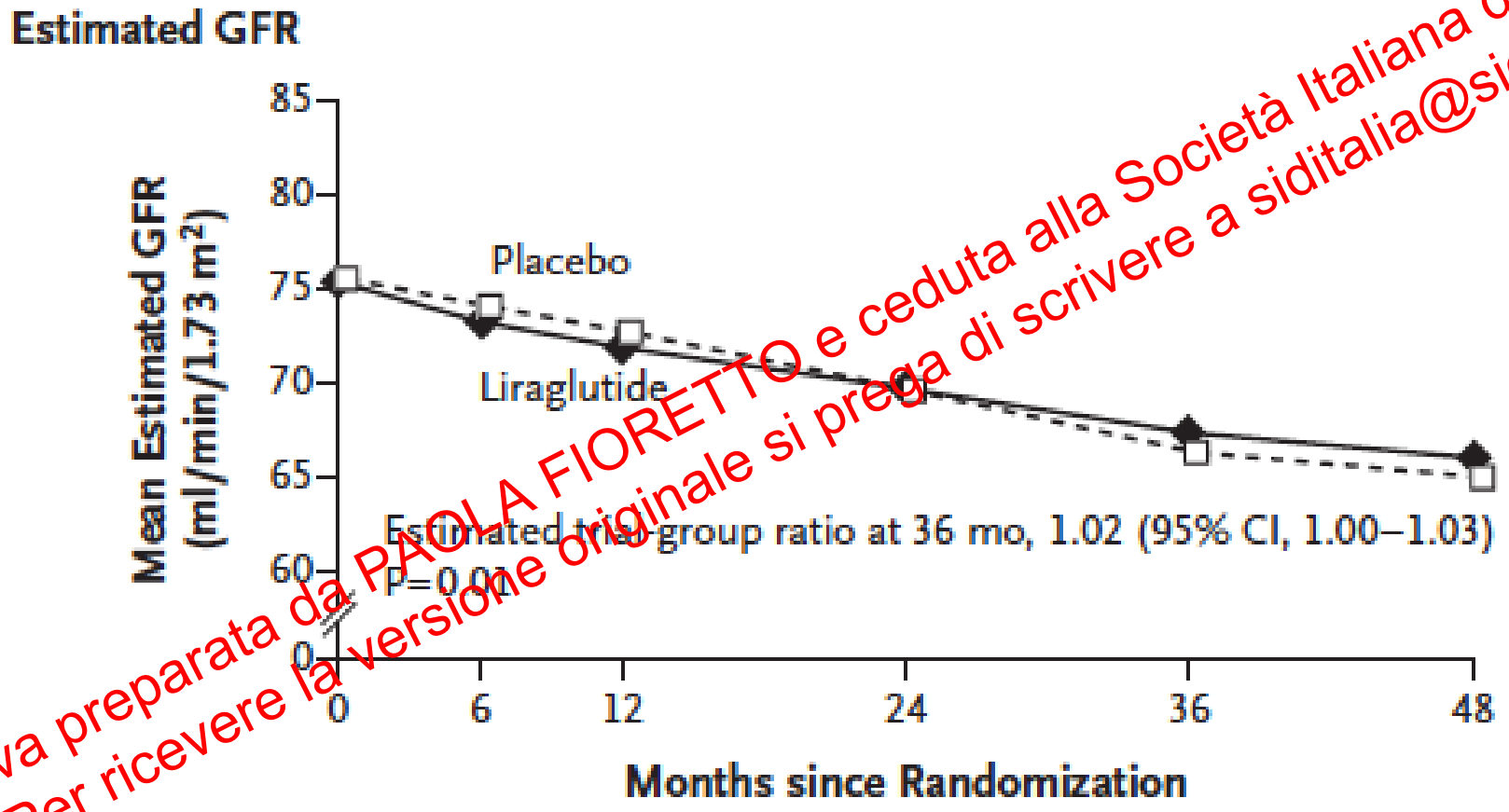
Mann J et al, NEJM 2017

LEADER: Urinary Albumin/Creatinine



Mann J et al, NEJM 2017

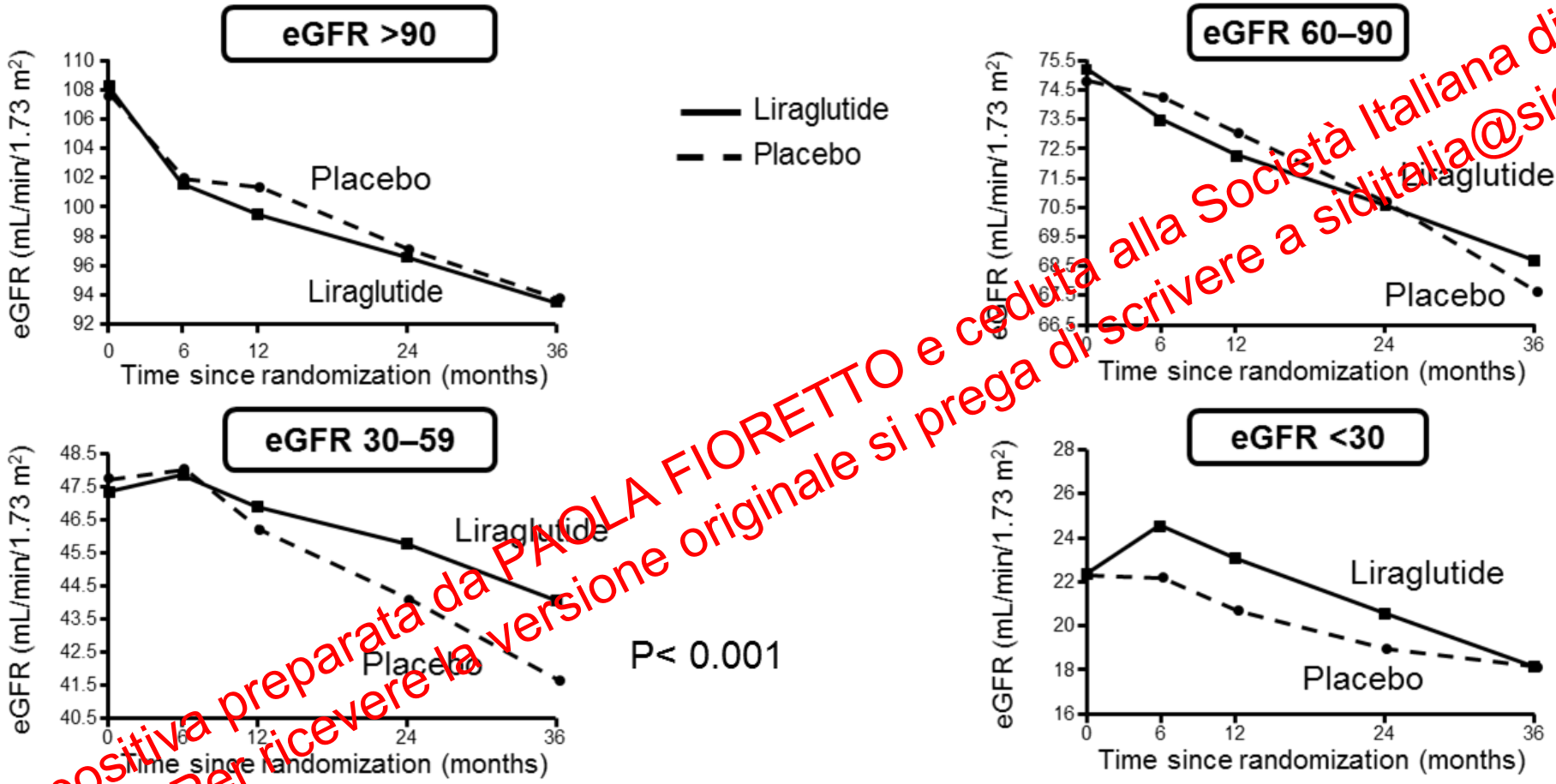
LEADER: eGFR



Mann J et al, NEJM 2017

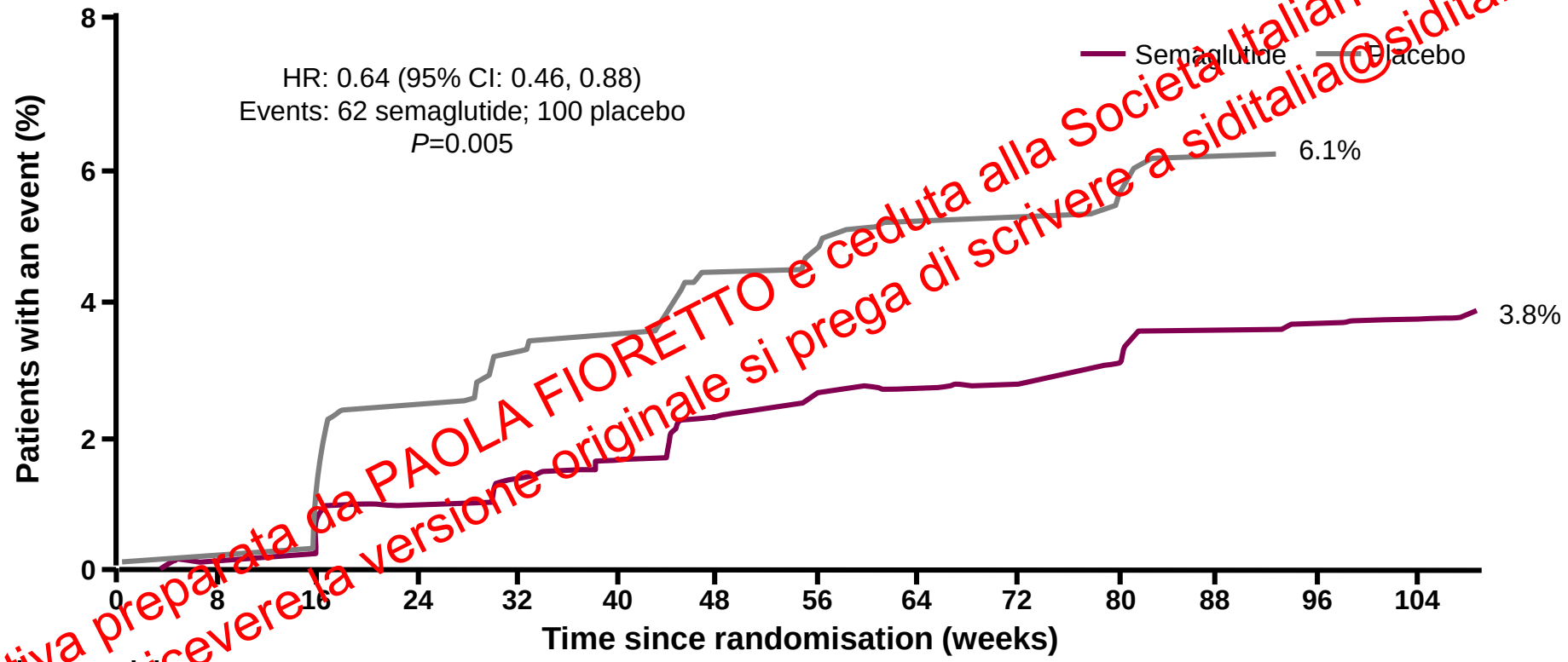
Change in eGFR (MDRD)

Pre-defined subgroups



Mann J et al, NEJM 2017

SUSTAIN-6: Semaglutide reduced the risk of new or worsening nephropathy compared with placebo

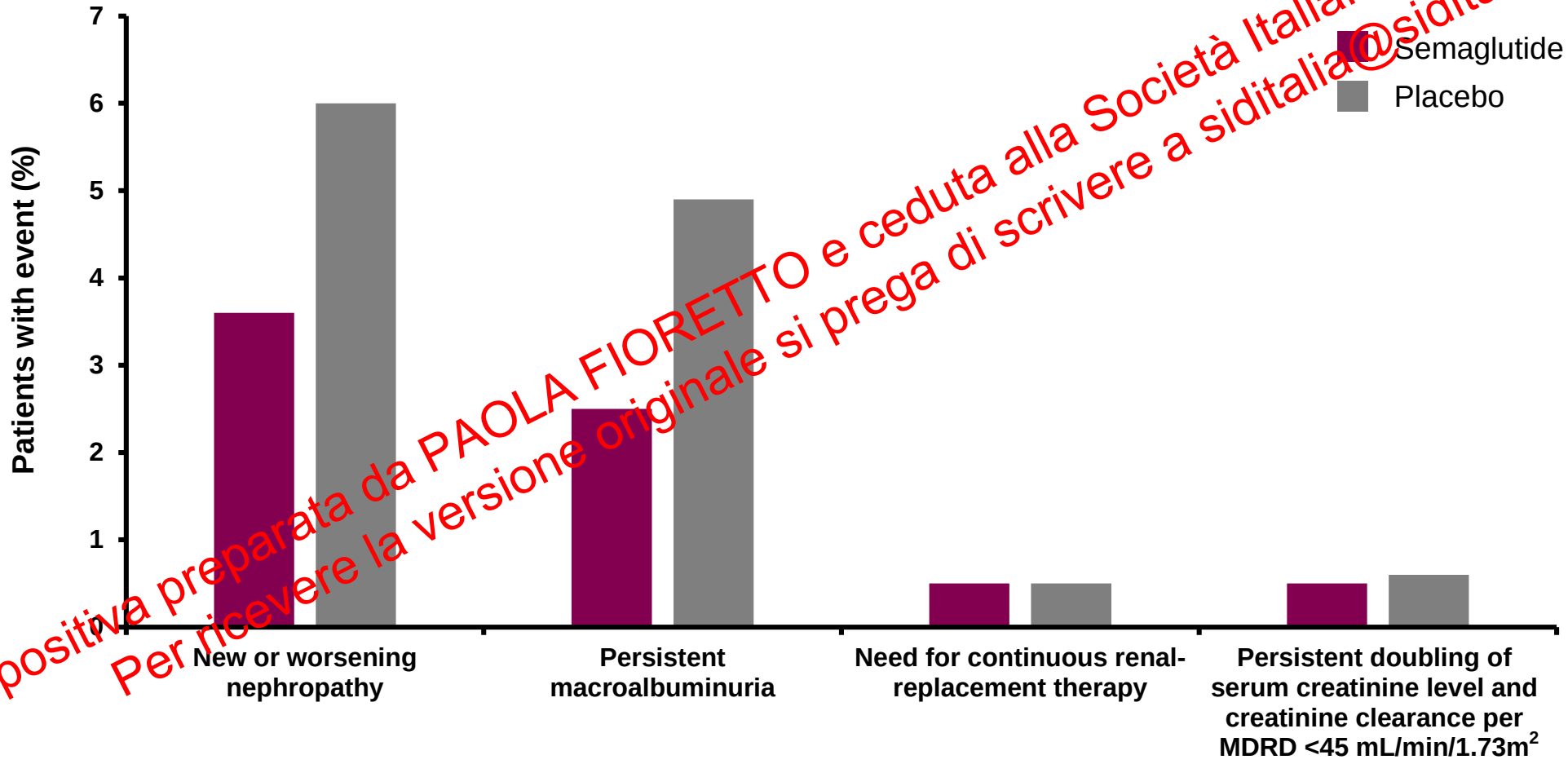


No. of patients at risk

Semaglutide	1648	1630	1605	1580	1563	1541	1525	1518
Placebo	1649	1629	1570	1545	1518	1498	1471	1465

Marso SP et al, N Eng J Med 2016

SUSTAIN-6: New or worsening nephropathy: Benefit driven by reduction in persistent macroalbuminuria



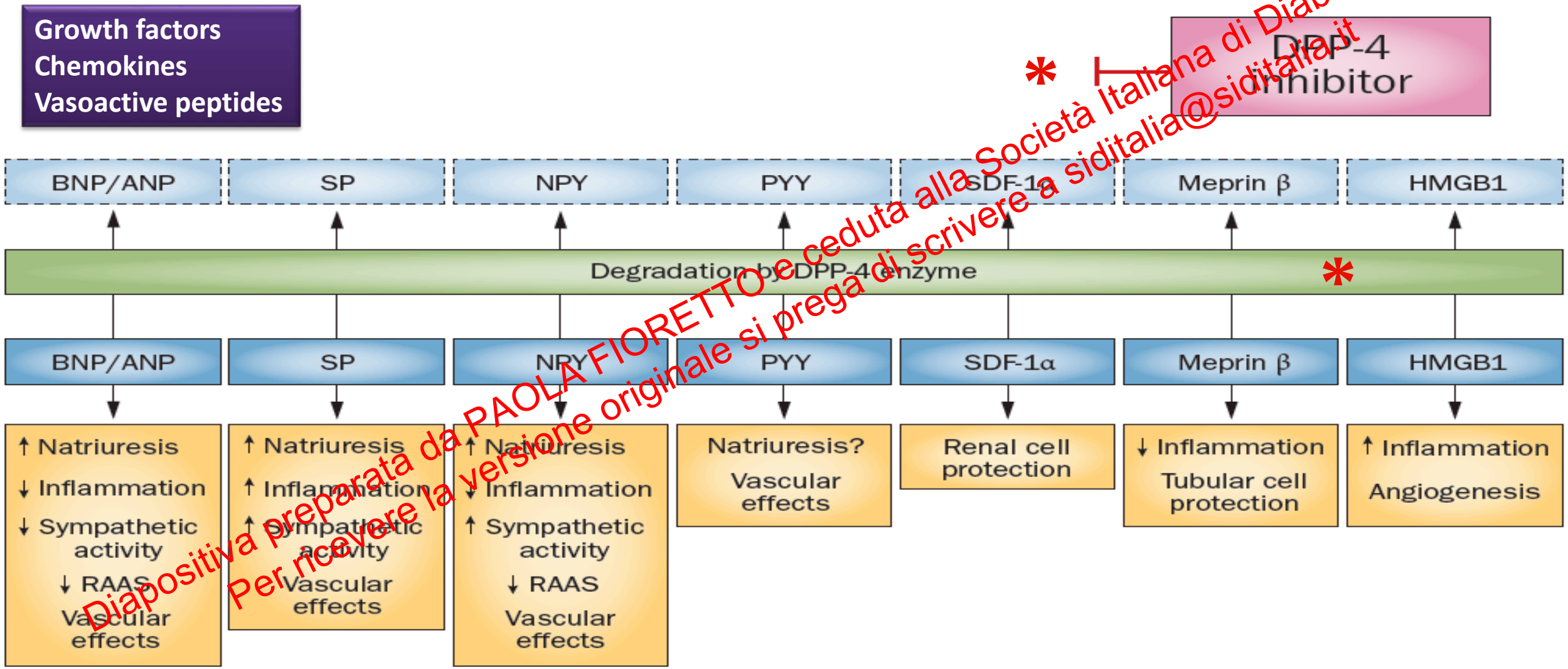
MDRD, Modification of Diet in Renal Disease

Vilsboll T. Presented 16th September at the 52nd EASD Annual Meeting 2016, Munich, Germany; OP S35.3

What about individual antidiabetes agents?

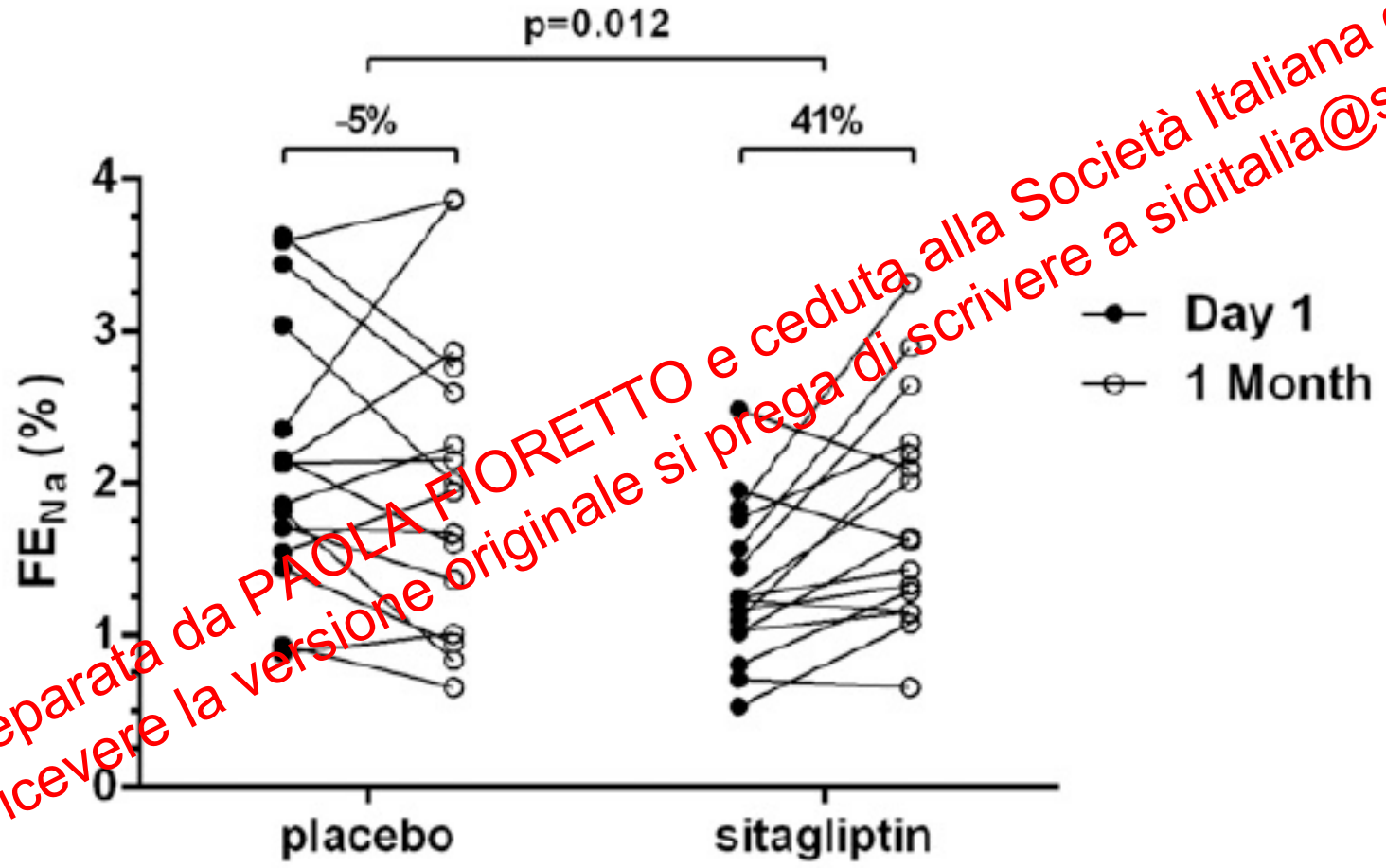
– DPP4 inhibitors

Potential GLP-1-independent effects of DPP-4 inhibitors on renal outcomes



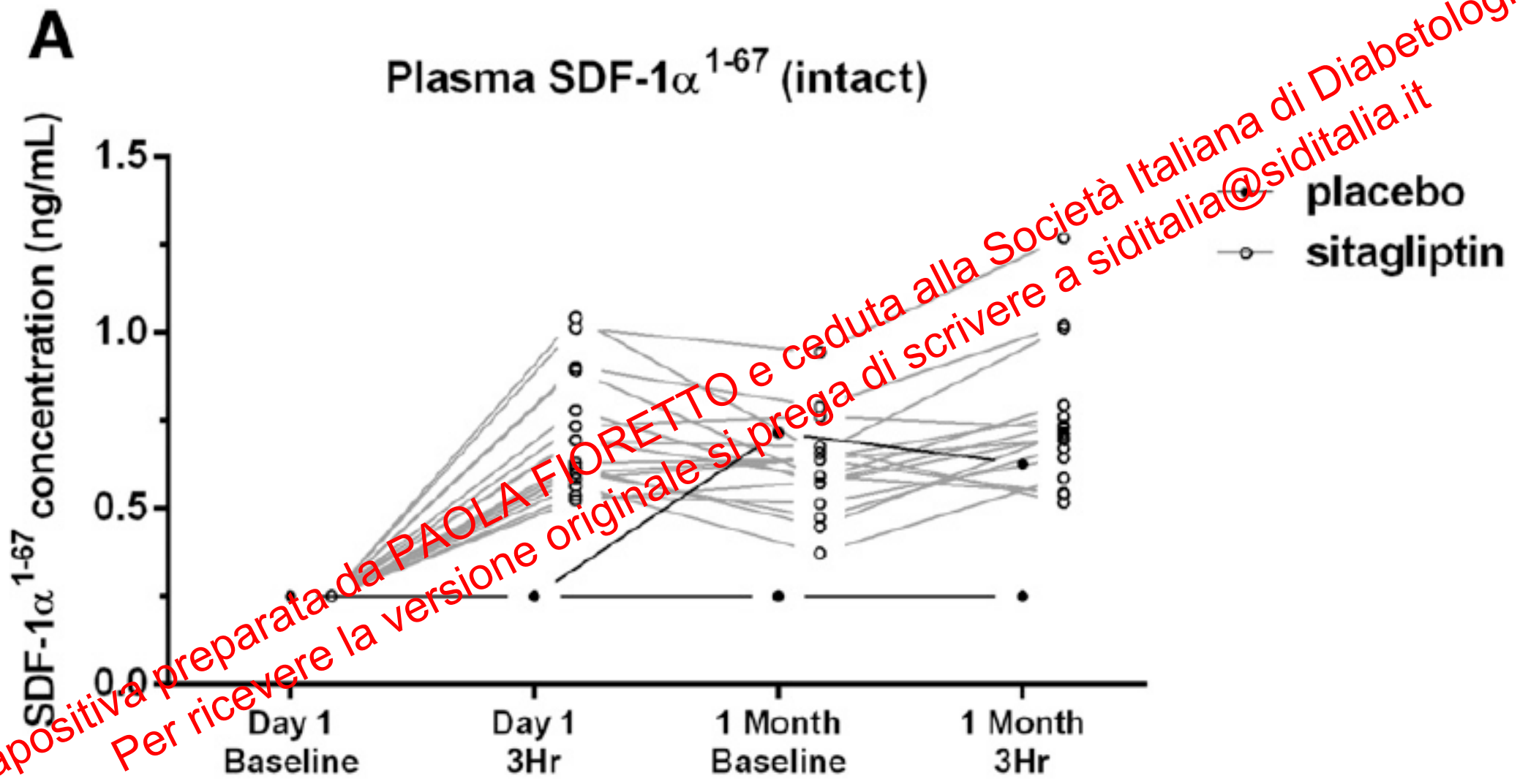
Muskiet MH, et al. Nat Rev Neprhol 2014;10:88–103

Effects of sitagliptin on fractional excretion of sodium

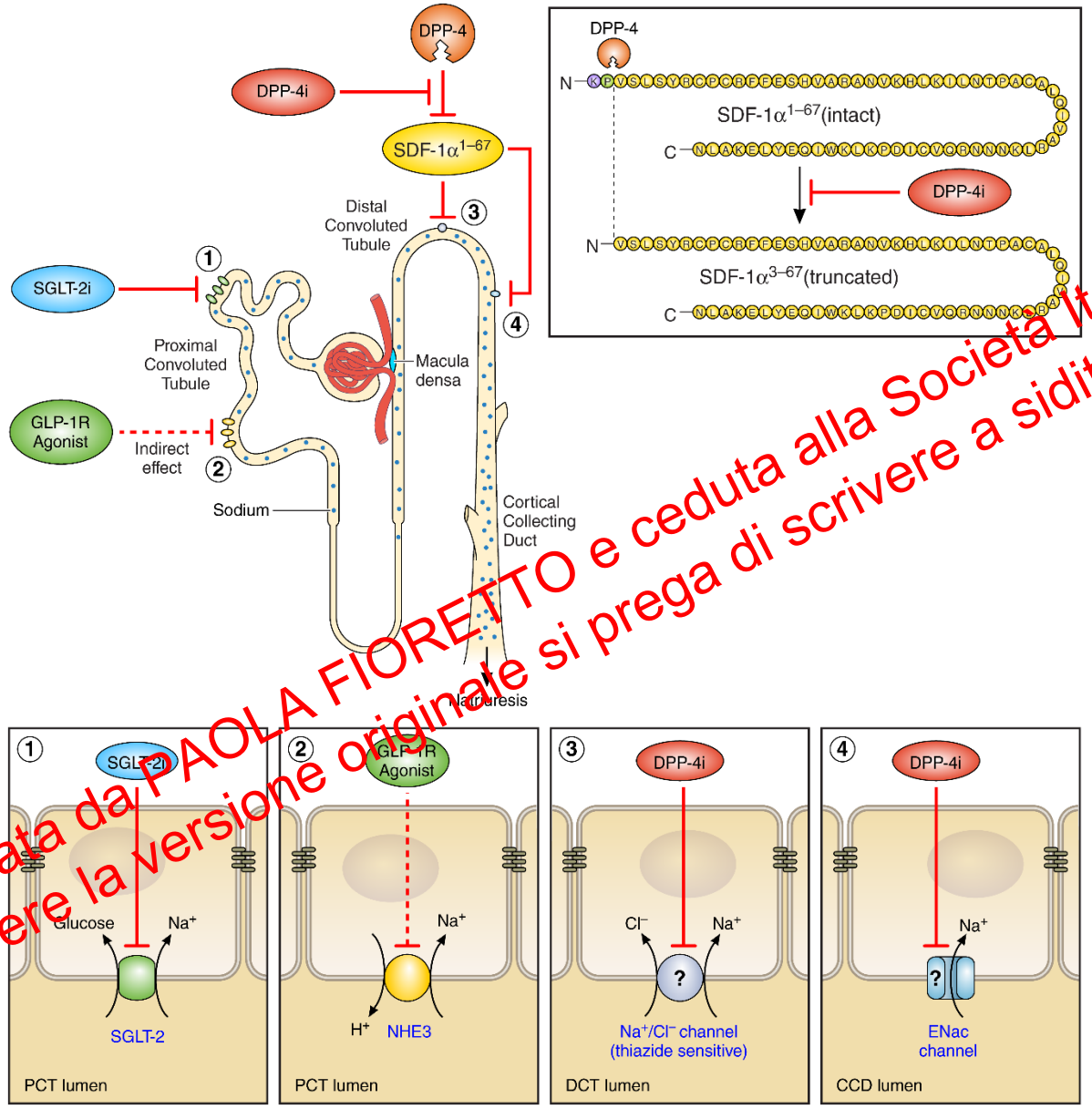


Lovshin JA et al, Diabetes Care, 2017

Effects of sitagliptin on intact plasma SDF-1a



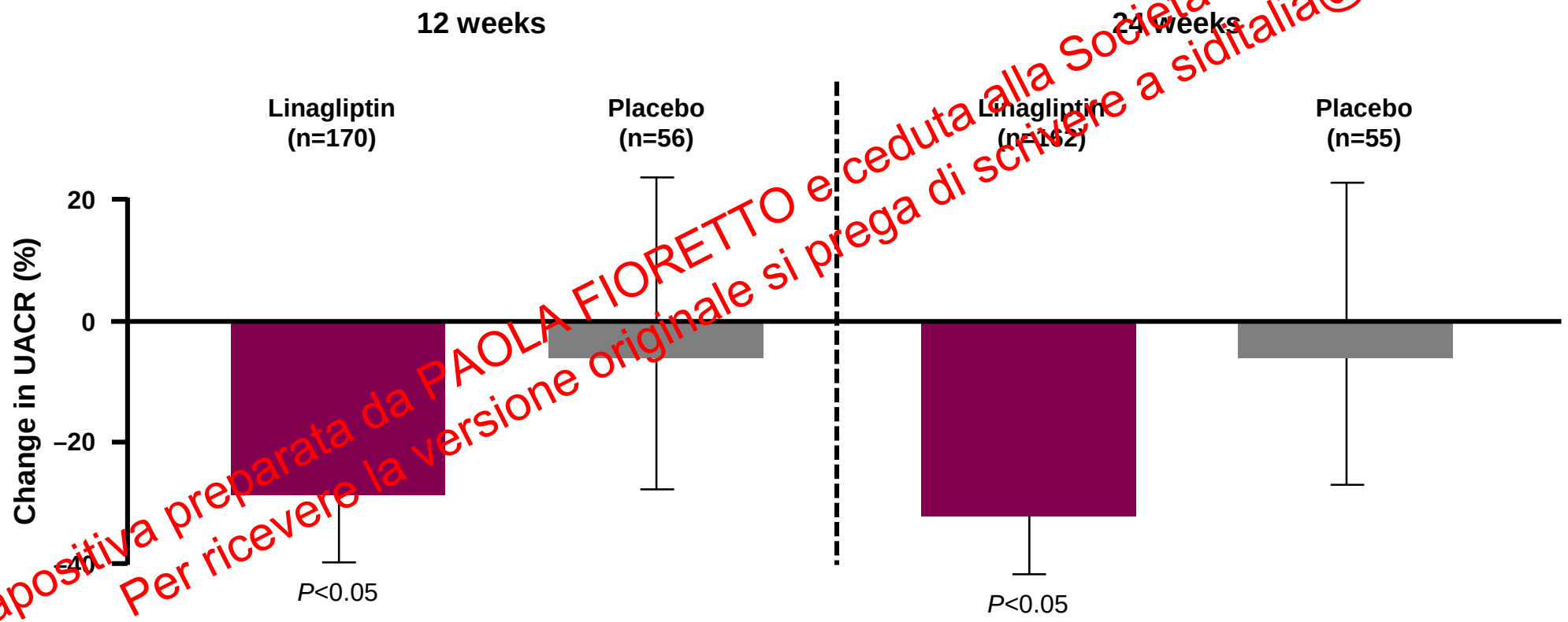
LovshinJA et al, Diabetes Care, 2017



Lovshin JA et al, Diabetes Care, 2017

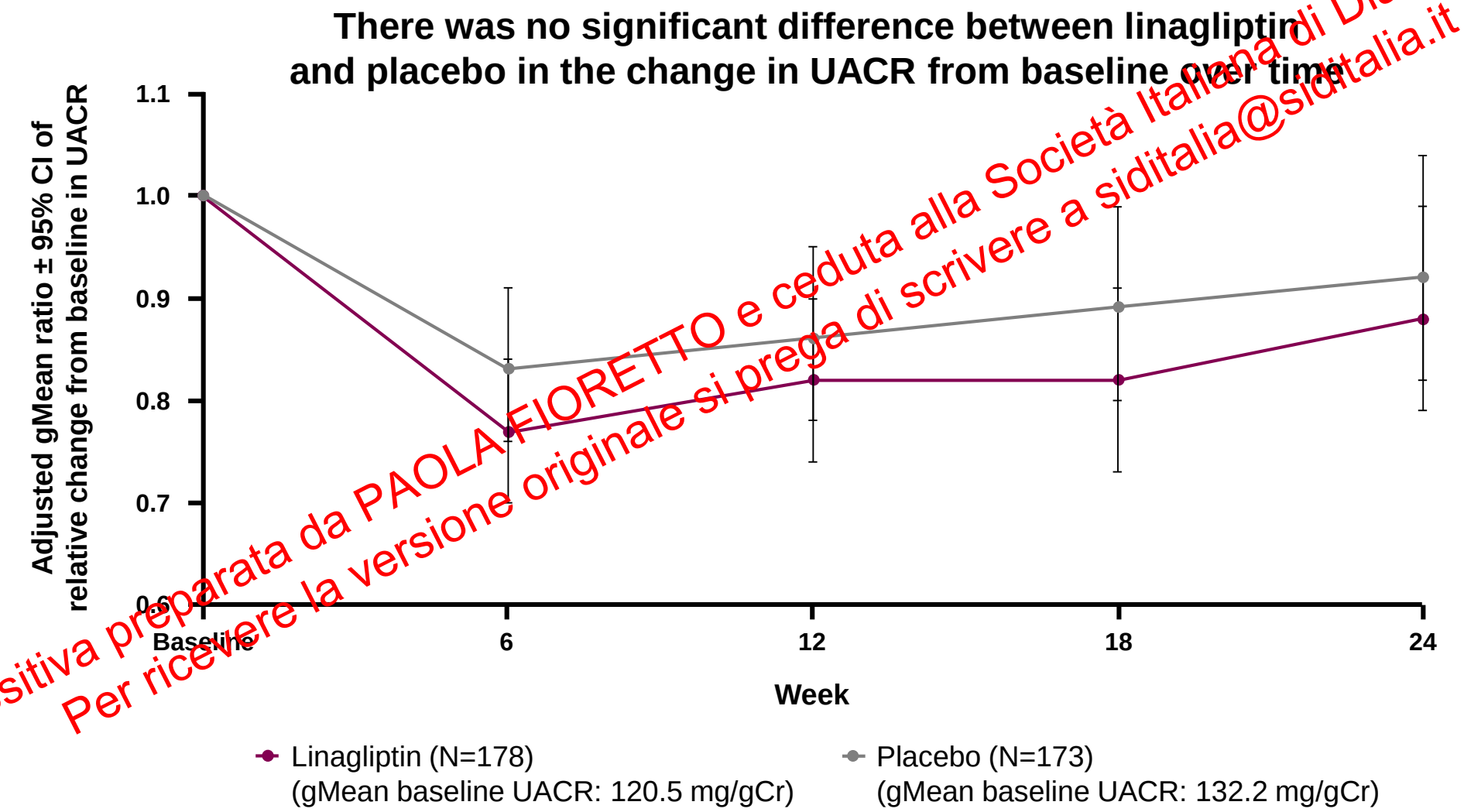
DPP-4 inhibitors are associated with a reduction in albuminuria

- Retrospective data showed a significant decrease in albuminuria in patients who had Type 2 diabetes and were treated with linagliptin compared with those on placebo



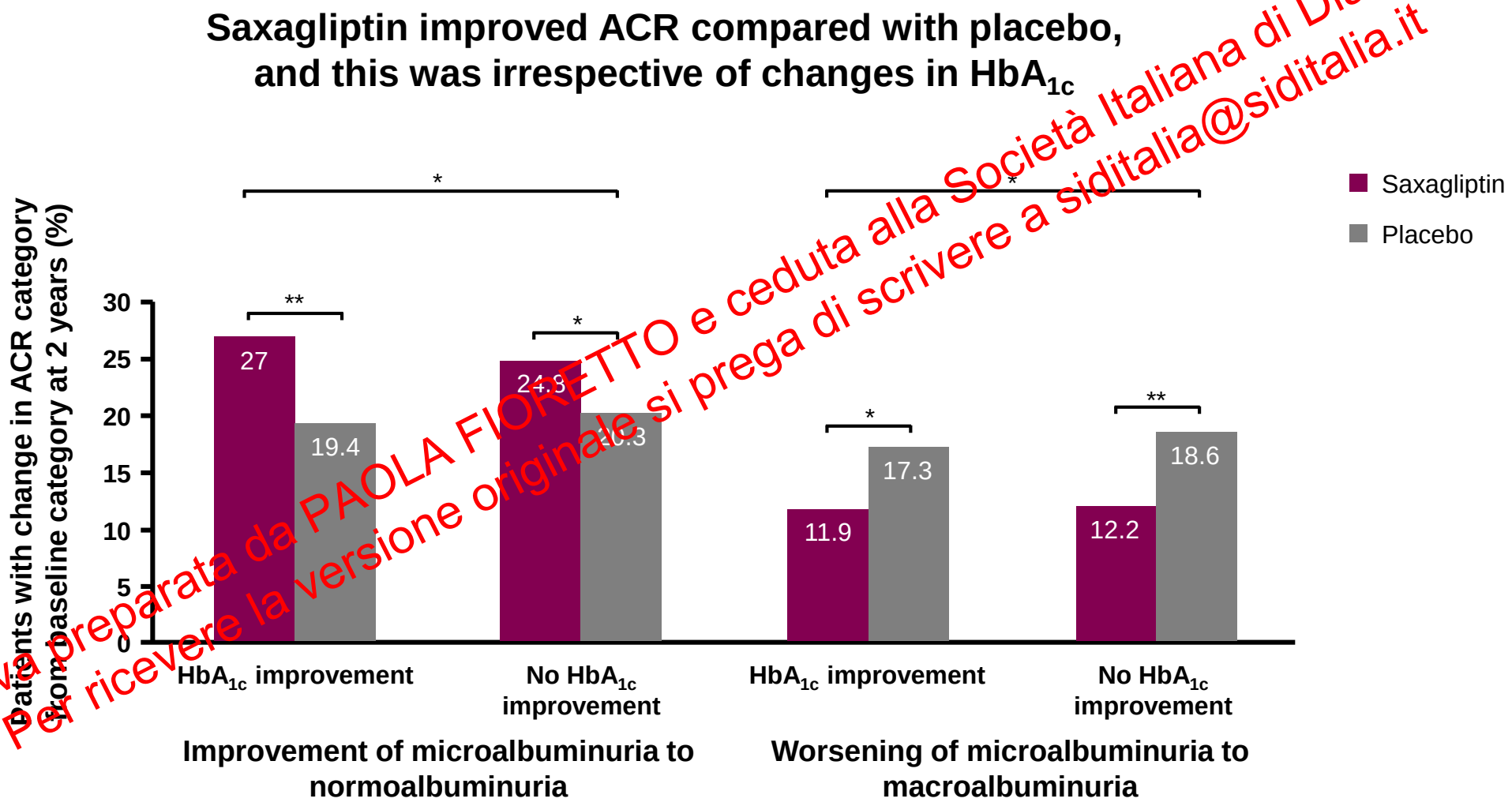
Groop P-H, et al. Diabetes Care 2013;36:3460–3468

Effects of linagliptin on UACR in the Marlina study



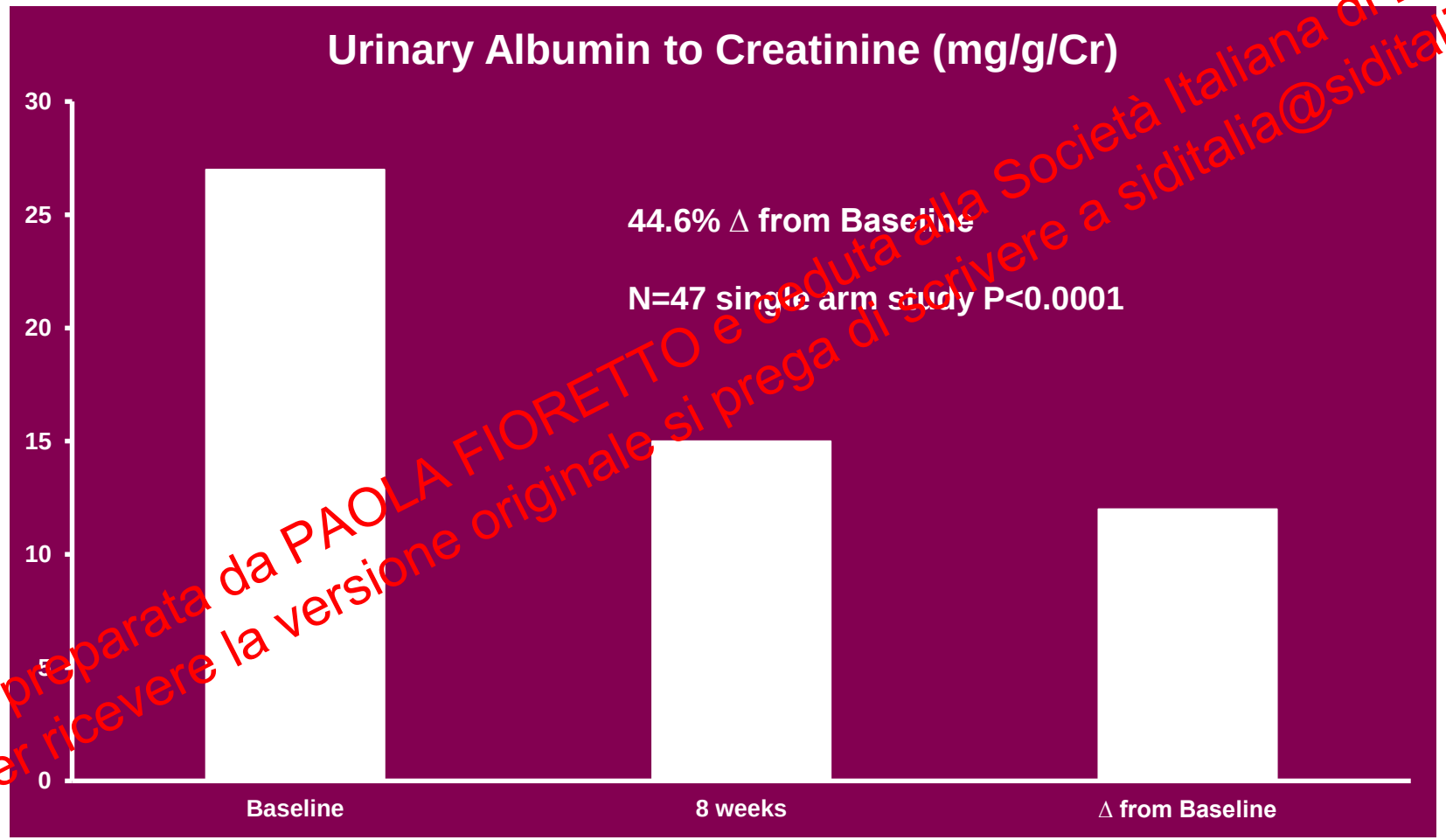
Groop PH, et al Diab Obesity Metab 2017

Effects of saxagliptin on ACR at 2 years in the SAVOR study



Mosenzon O, et al. Diabetes Care 2017

Effects of Vildagliptin on ACR (8 weeks)



Tami et al, Am J Cardiovasc Drugs, 2013

Summary

- Intensive glycaemic control is associated with improved CKD outcomes.
- Newer anthyperglycaemic classes have been demonstrated to have nephroprotective effects:
- Animal models indicate that GLP-1 RA and DPP4 inhibitors decelerate the progression of diabetic nephropathy by inhibiting inflammation and oxidative stress
- DPP4 inhibitors and GLP 1 RA, in addition to HbA1c, lower BP and weight, increase natriuresis and influences RAAS
- DPP4 inhibitors and GLP 1 RA lower albuminuria progression
- These agents represent a useful treatment paradigm in patients with T2DM and kidney disease