SID
Società Italiana di Diabetologia
fondata nel 1964

CORSO ECM

SHARE THE EXPERIENCE

# NEFROPROTEZIONE NEL PAZIENTE DIABETICO



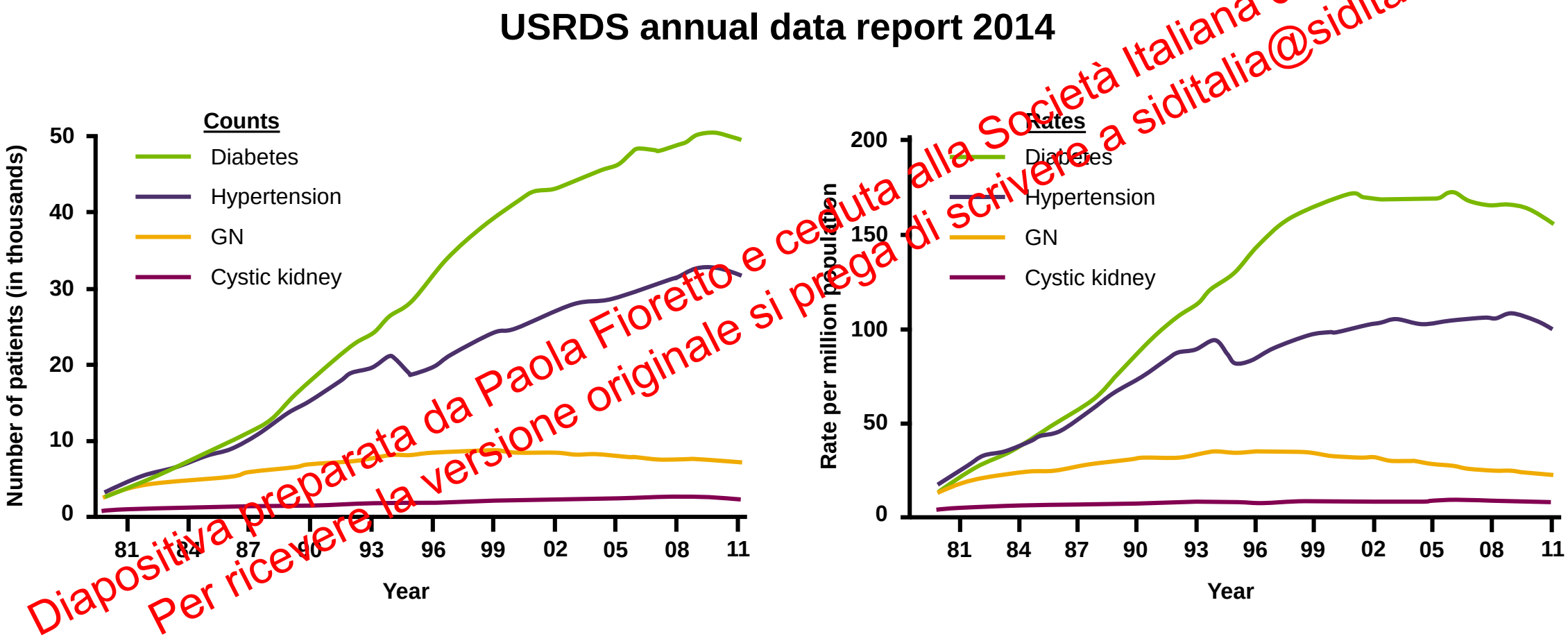
BOLOGNA,
16/17 GIUGNO 2017

Paola Fioretto
Dipartimento di Medicina
Università di Padova

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

- ASTRA ZENECA
- JANSSEN
- BOEHRINGER INGHELEIM
- LILLY

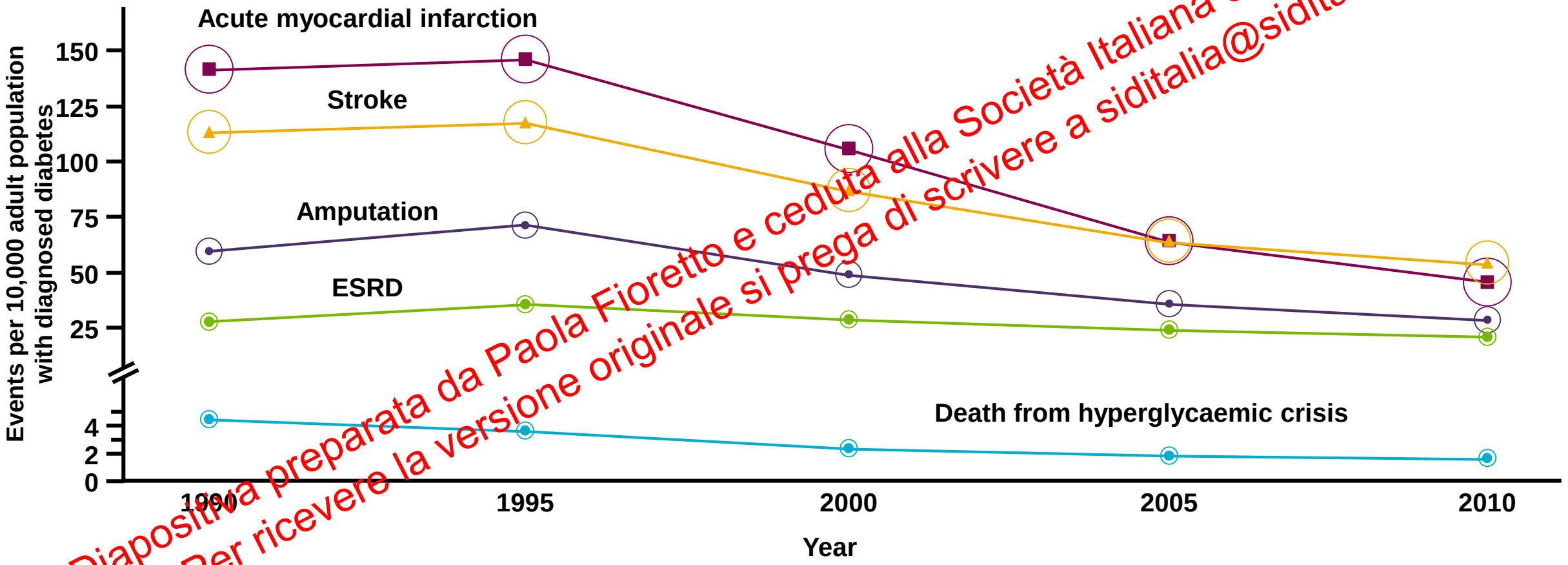
# Incident counts and adjusted rates of ESRD, by primary diagnosis






United States Renal Data System. 2014 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014. Available at: https://www.usrds.org/2014/download/V2_Ch_01_ESRD_Incidence_Prevalence_14.pdf. Accessed March 2017

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



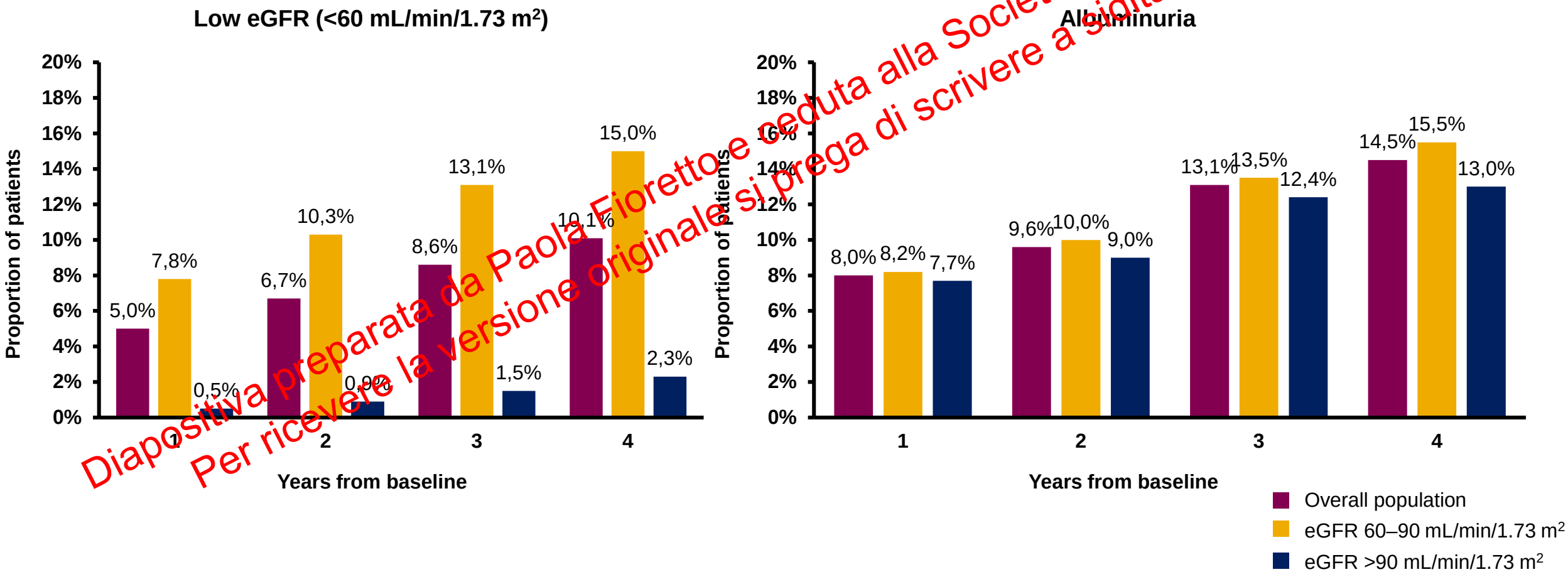



ESRD, end-stage renal disease

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

# The incidence of low eGFR and albuminuria increased during follow up of patients with Type 2 diabetes in an Italian network

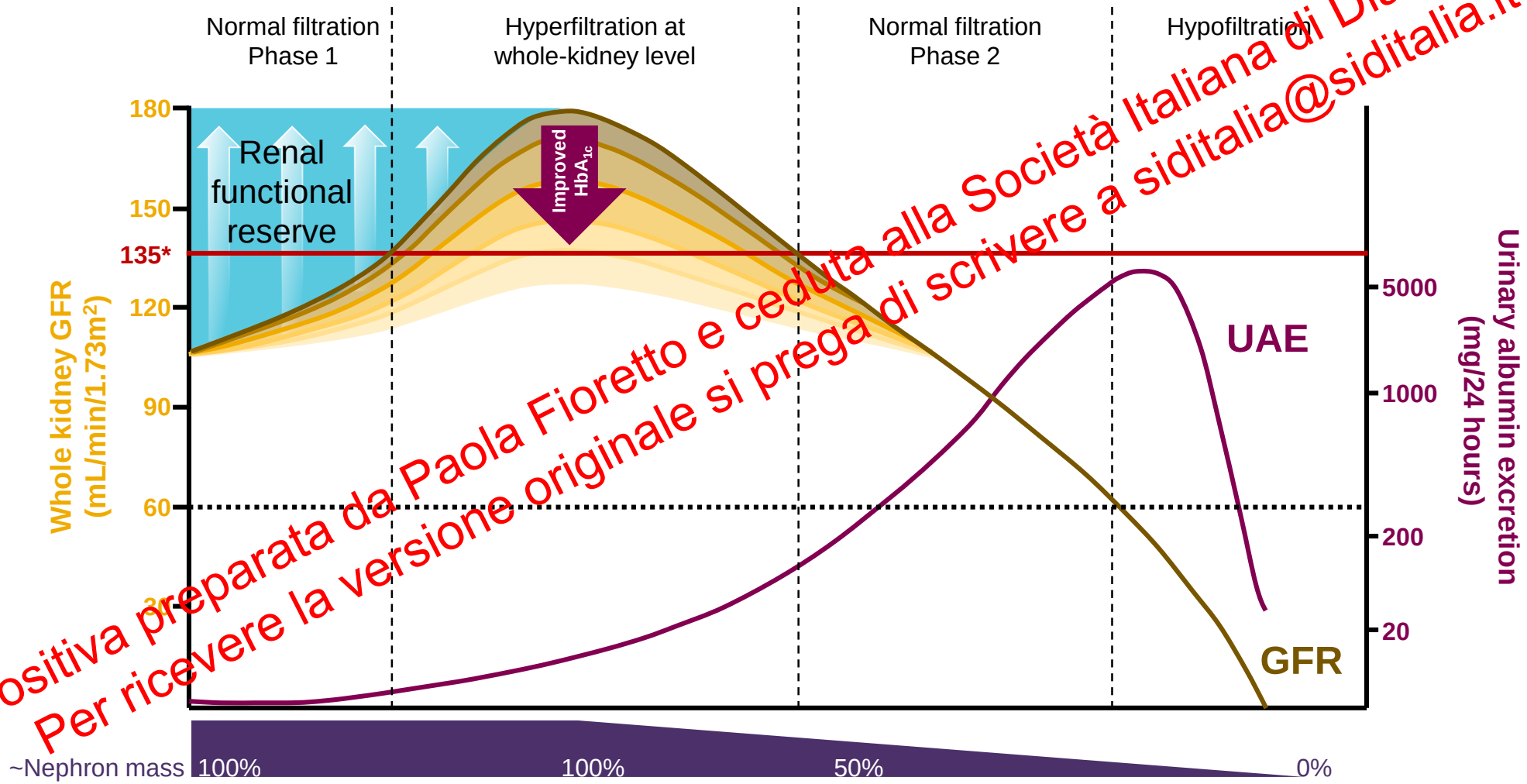
The incidence of low eGFR and albuminuria was assessed in patients with Type 2 diabetes in the Italian Association of Clinical Diabetologists network






De Cosmo S, et al. *Medicine* 2016;95:e4007

# Natural history of diabetic nephropathy

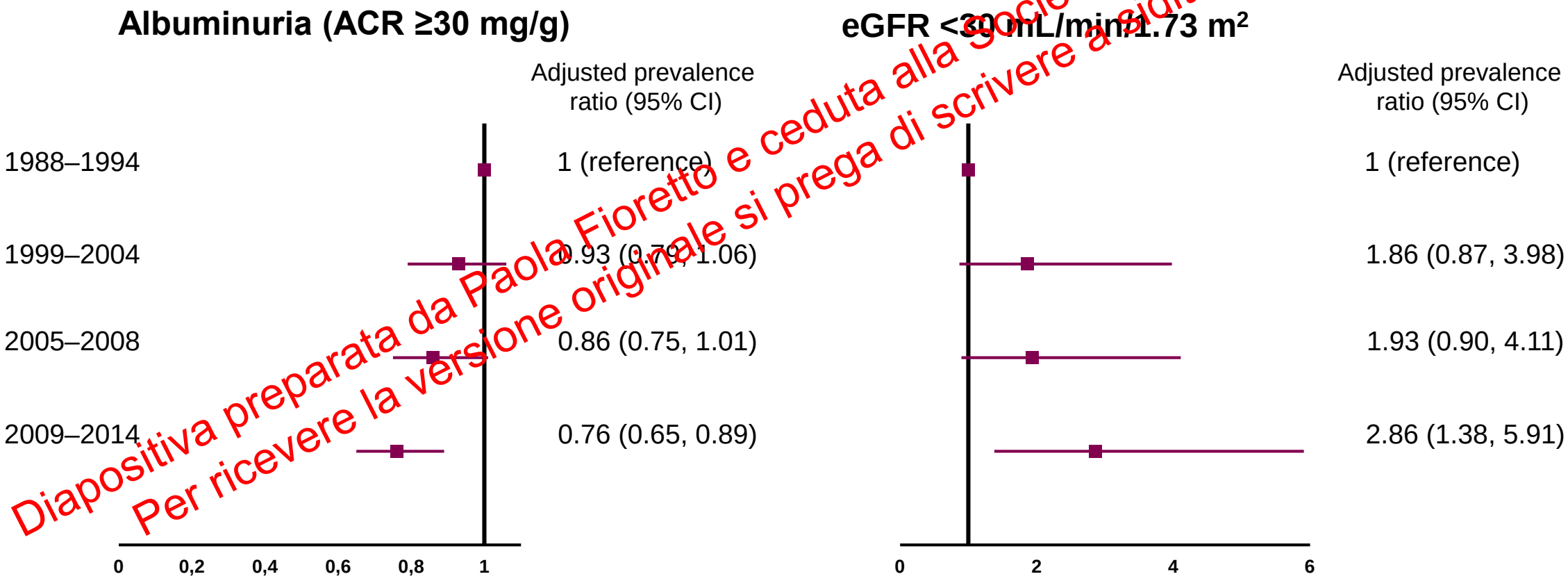





*Whole-kidney hyperfiltration is generally defined as a GFR that exceeds approximately 135 mL/min, and is indicated with the red line
GFR, glomerular filtration rate; UAE, urinary albumin excretion
Tonneijck L, et al. *J Am Soc Nephrol* 2017;28:1023–1039

# Clinical manifestations of kidney disease in patients with Type 2 diabetes

- Among US adults with diabetes from 1988–2014, the overall prevalence of DKD did not change significantly, whereas the prevalence of **albuminuria declined** and the prevalence of **reduced eGFR increased**



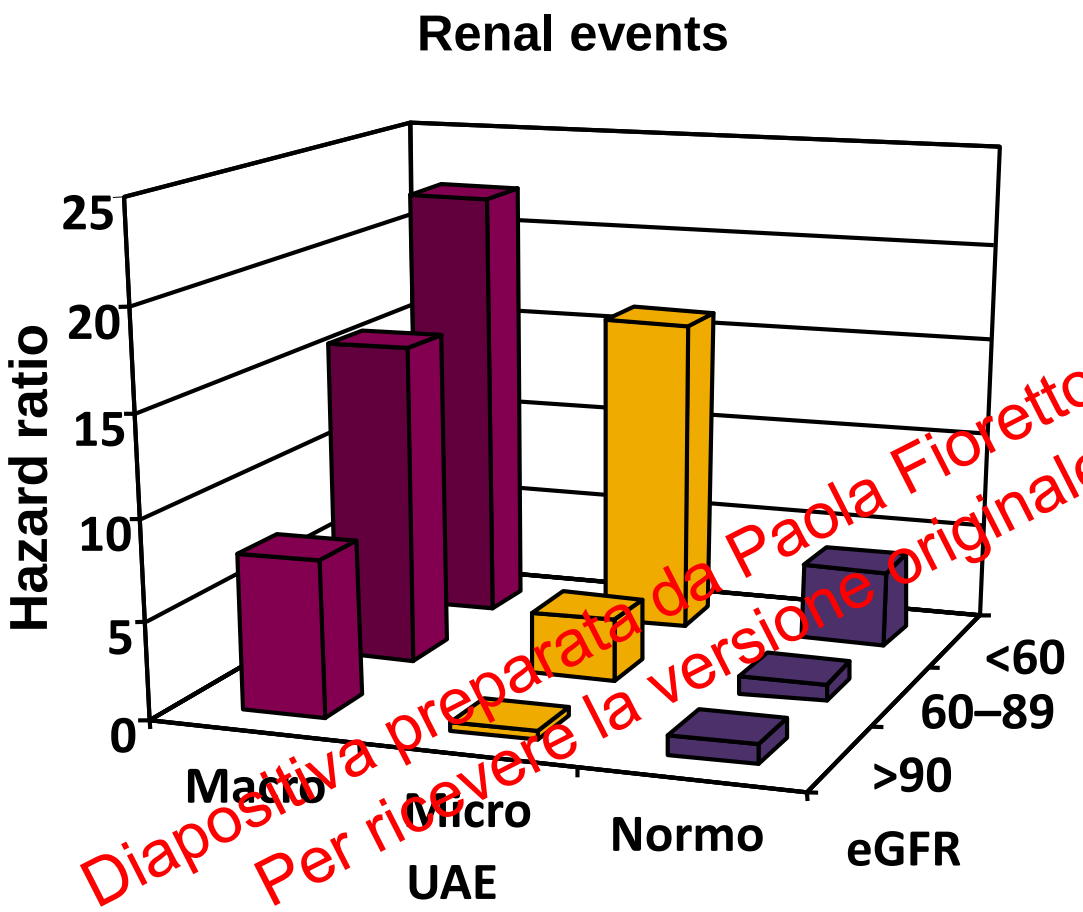


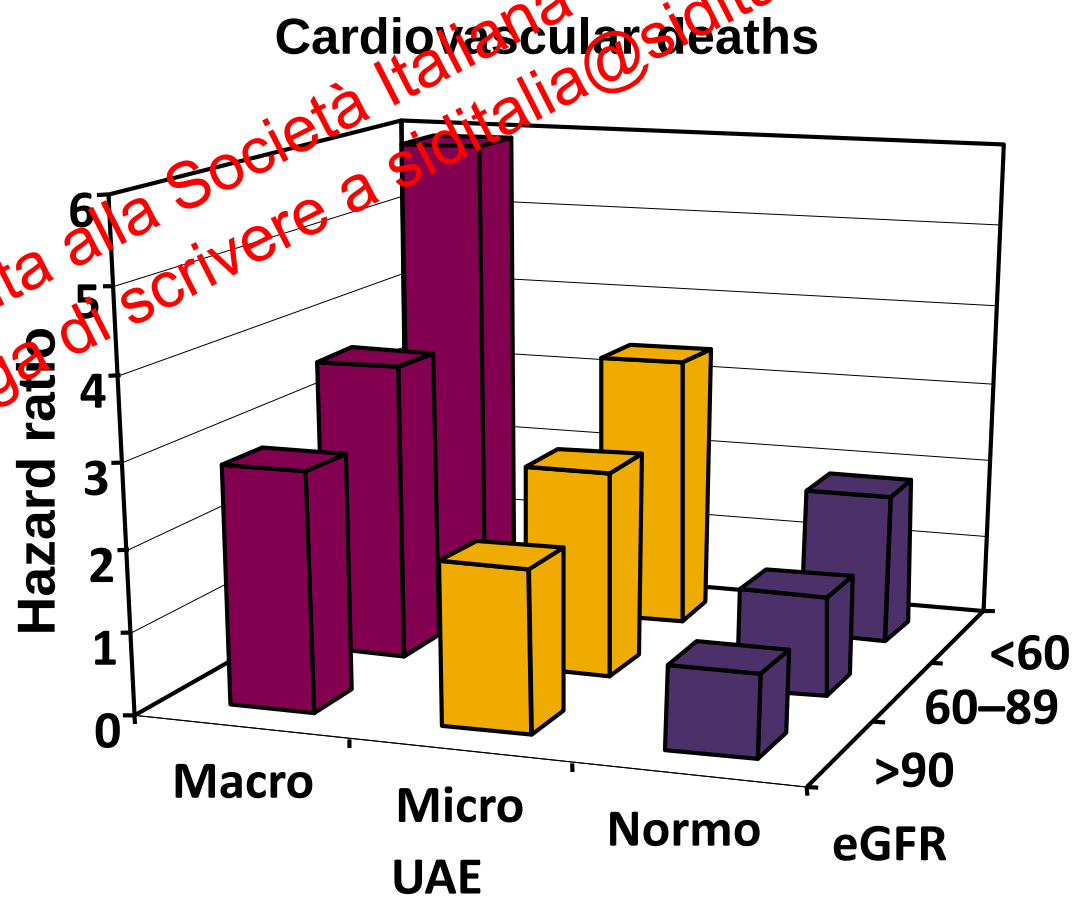

ACR, albumin:creatinine ratio; CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate

Afkarian M, et al. *JAMA* 2016;316:602–610

# CVD and renal outcomes by eGFR and albuminuria

## The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) Study



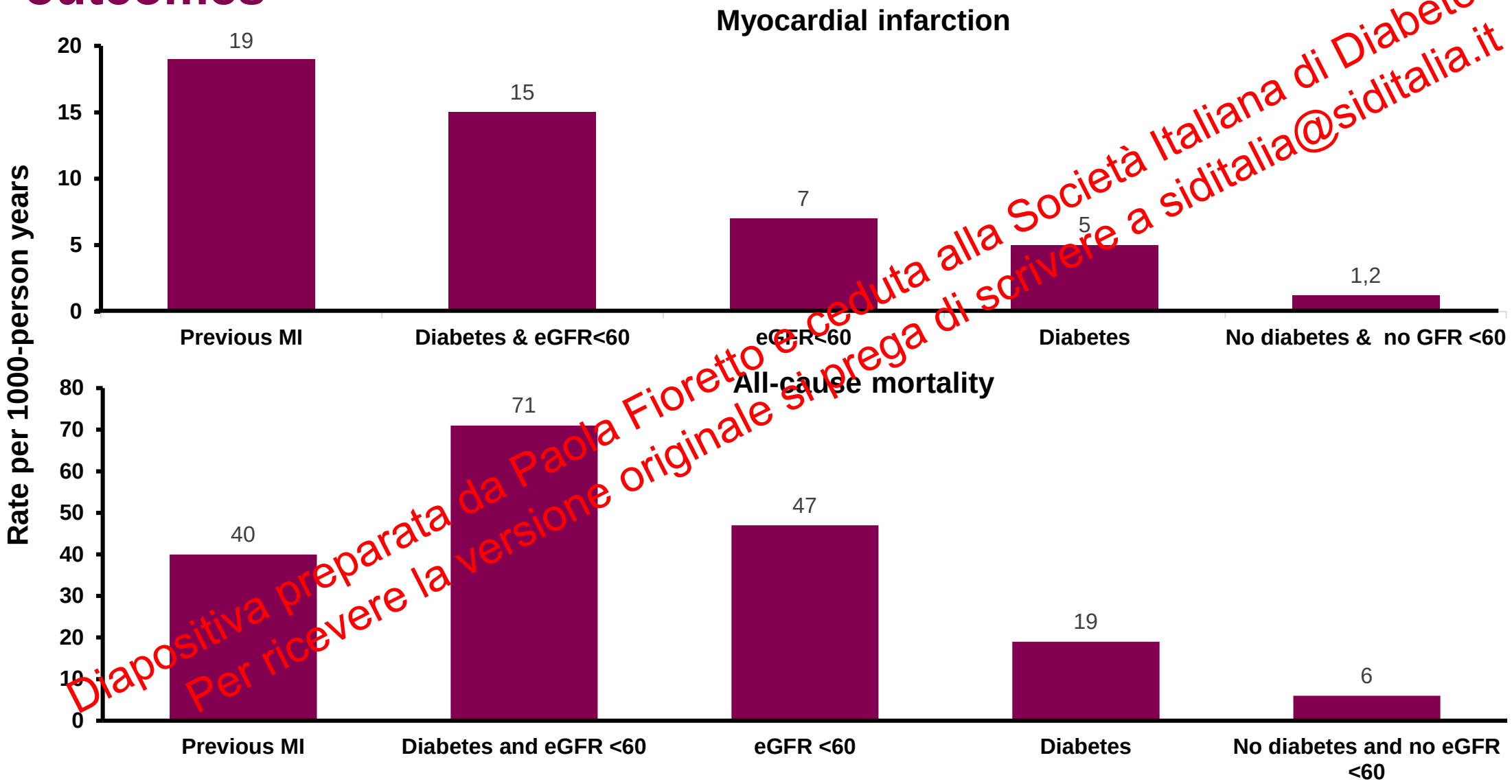



- 10,640 patients with Type 2 diabetes, median follow-up of 4.3 years

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion

Ninomiya T, et al. *J Am Soc Nephrol* 2009;20:1813–1821

# Presence and severity of CKD are associated with adverse outcomes






CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction

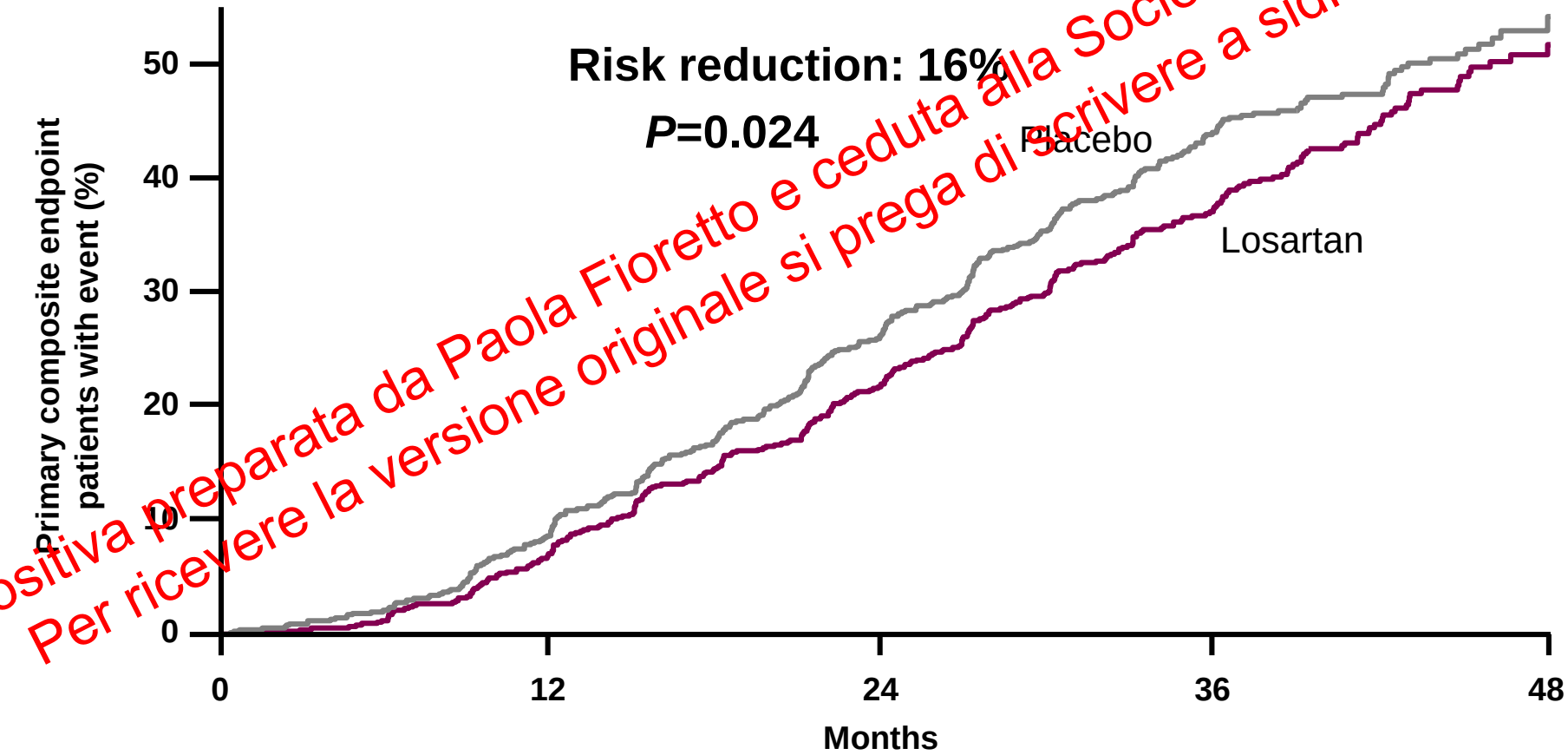
Tonelli M, et al. *Lancet* 2012;380:807–814

# Treatment of DKD in patients with Type 2 diabetes

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

# RENAAL study: Losartan conferred significant renal benefits in patients with Type 2 diabetes and nephropathy

- Mean treatment duration 3.4 years; N=1513
- Primary composite endpoint was doubling of serum creatinine, ESRD or death



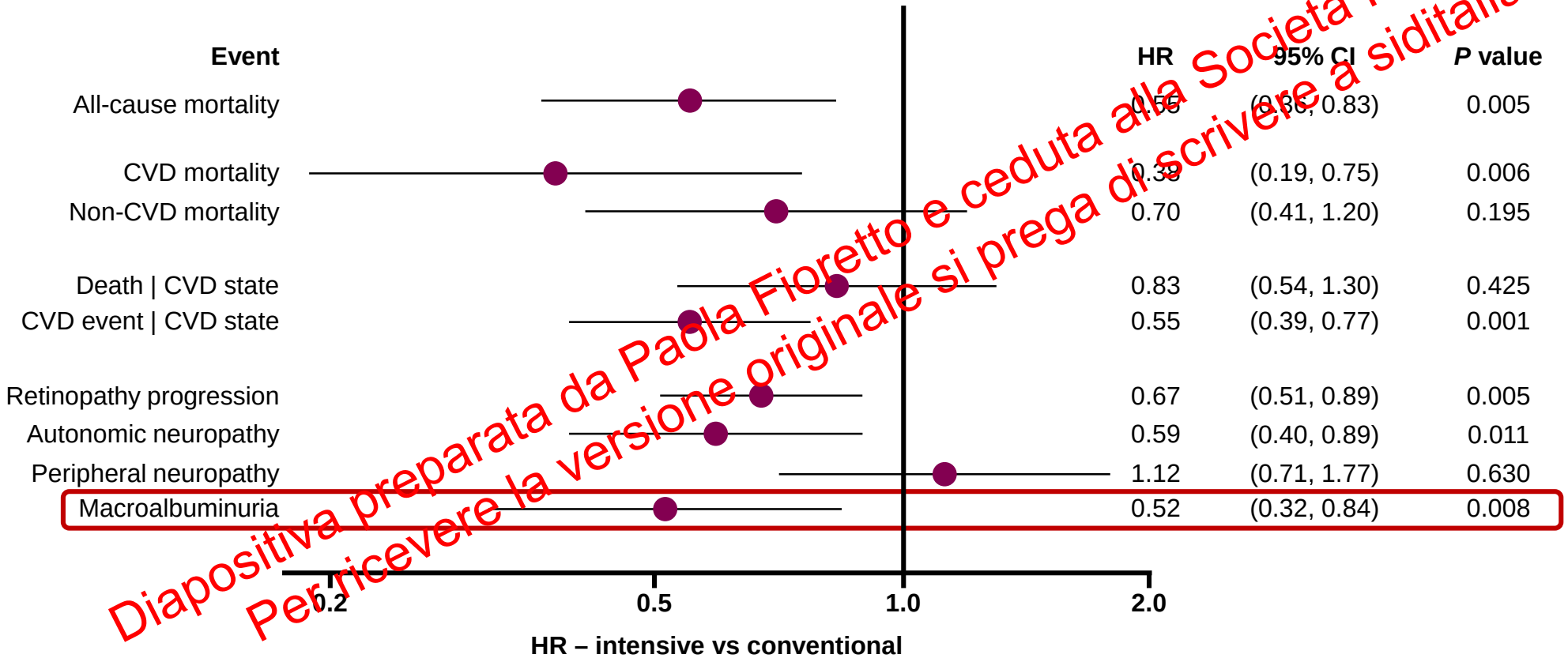



ESRD, end-stage renal disease; NIDDM, non-insulin-dependent diabetes mellitus

Brenner BM. *N Engl J Med* 2001;345:861–869

# STENO-2: 21-year follow-up demonstrated intensive intervention reduces CKD progression in patients with Type 2 diabetes

- The original intervention (mean treatment duration 7.8 years) involved 160 patients with Type 2 diabetes and microalbuminuria randomly assigned to receive either conventional therapy or intensified, multifactorial treatment




- Progression to diabetic nephropathy was reduced by 48% in the intensive therapy group
- Ten patients in the conventional therapy groups versus five patients in the intensive therapy group progressed to ESRD (*P*=0.061)



CI, confidence interval; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio

Gæde P, et al. *Diabetologia* 2016;59:2298–2307

# The legacy effect: Strict glycaemic control can result in sustained reductions in renal complications

- Long-term follow-ups from several trials have shown that intensive glycaemic control can result in **sustained reductions in diabetic renal complications that last for many years**

| Trial | Diabetes type | Initial treatment period (years) | Follow-up period (years) | Sustained beneficial renal function observations |
|---|---|---|---|---|
| DCCT-EDIC[1] | Type 1 | 6.5 | 22 (median) | Risk for impaired GFR reduced by 50% in the intensive-treatment group compared with the control group |
| UKPDS[2] | Type 2 | 10 | 10 | 25% risk reduction for microvascular outcomes observed in the intensive-treatment group<br>33% reduction in microalbuminuria or proteinuria at 12 years[4] |
| ADVANCE-ON[3] | Type 2 | 5 | 6 | Intensive treatment was associated with a significant cumulative benefit with respect to ESRD, but had no effect on the rate of death from renal disease |

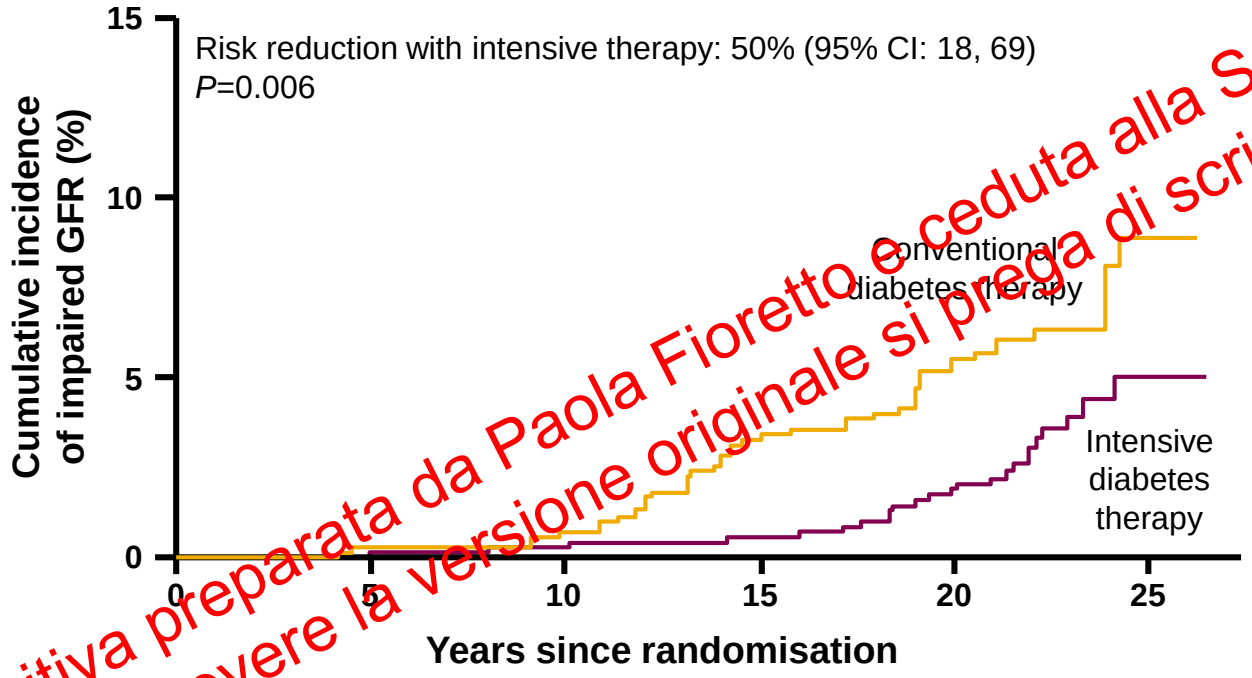


ESRD, end-stage renal disease; GFR, glomerular filtration rate

1. The DCCT/EDIC Research Group. *New Engl J Med* 2011;365:2366–2376; 2. Holman RR, et al. *New Engl J Med* 2008;359;1577–1589;
3. Zoungas S, et al. *New Engl J Med* 2014;371:1392–1403; 4. Bilous R. *Diabet Med* 2008;25(Suppl) 2:25–29

# DCCT/EDIC: Early intensive glycaemic control reduces long-term risk of impaired eGFR in patients with Type 1 diabetes

**Median follow-up period 22 years; impairment of GFR developed in 24 patients assigned to intensive therapy and in 46 assigned to conventional therapy**




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Intensive therapy | 711 | 704 | 684 | 672 | 619 | 108 |
| Conventional therapy | 730 | 719 | 697 | 657 | 594 | 90 |

Intensive diabetes therapy reduced the risk of an impaired eGFR[a] by 50% in patients with Type 1 diabetes



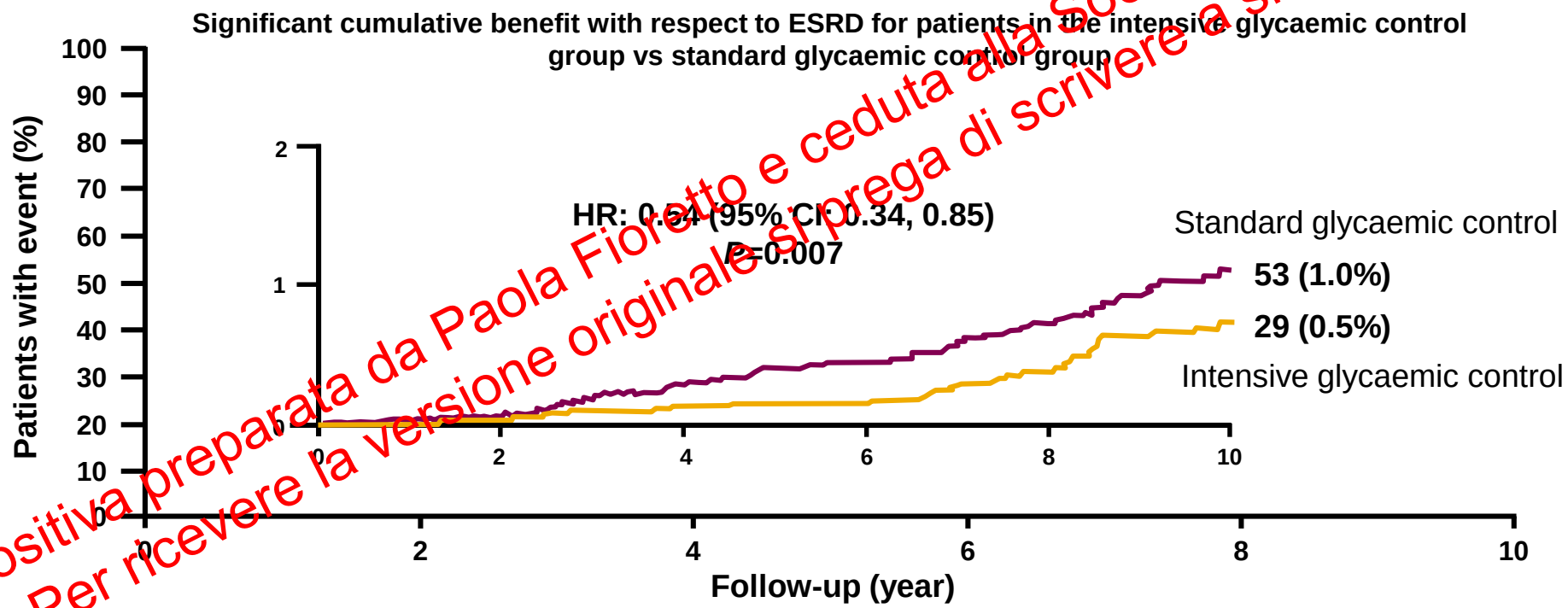
[a]Impaired eGFR was defined as a sustained estimated GFR <60 mL/min/1.73m$^2$ of body surface area

CI, confidence interval; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate

DCCT/EDIC Research Group. *N Engl J Med* 2011;365:2366–2376

# Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE): 6-year follow-up

**Median post-trial follow-up was 5.4 years for the glycaemic control comparison (N=8494)**




| Patients | | | | | | |
|---|---|---|---|---|---|---|
| Intensive | 5571 | 5402 | 5186 | 4124 | 3764 | 2811 |
| Standard | 5569 | 5400 | 5173 | 4041 | 3681 | 2683 |

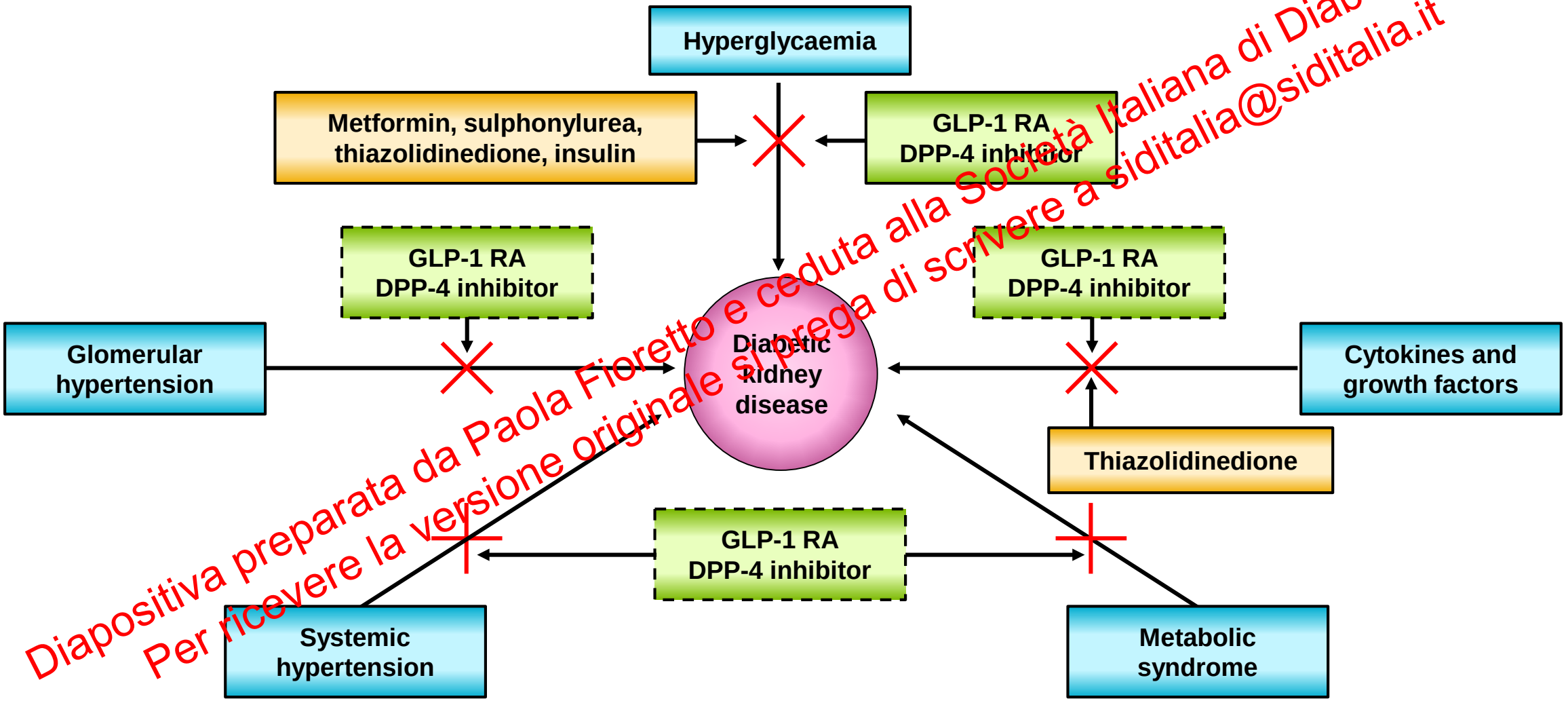
CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio

Zoungas, et al. *N Engl J Med* 2014;371:1392–1406

# What about individual antidiabetes agents?

## – GLP-1 receptor agonists

# Effects of incretin-based therapies on renal risk factors






DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist

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

# GLP-1 and the kidney

## Potential mechanisms

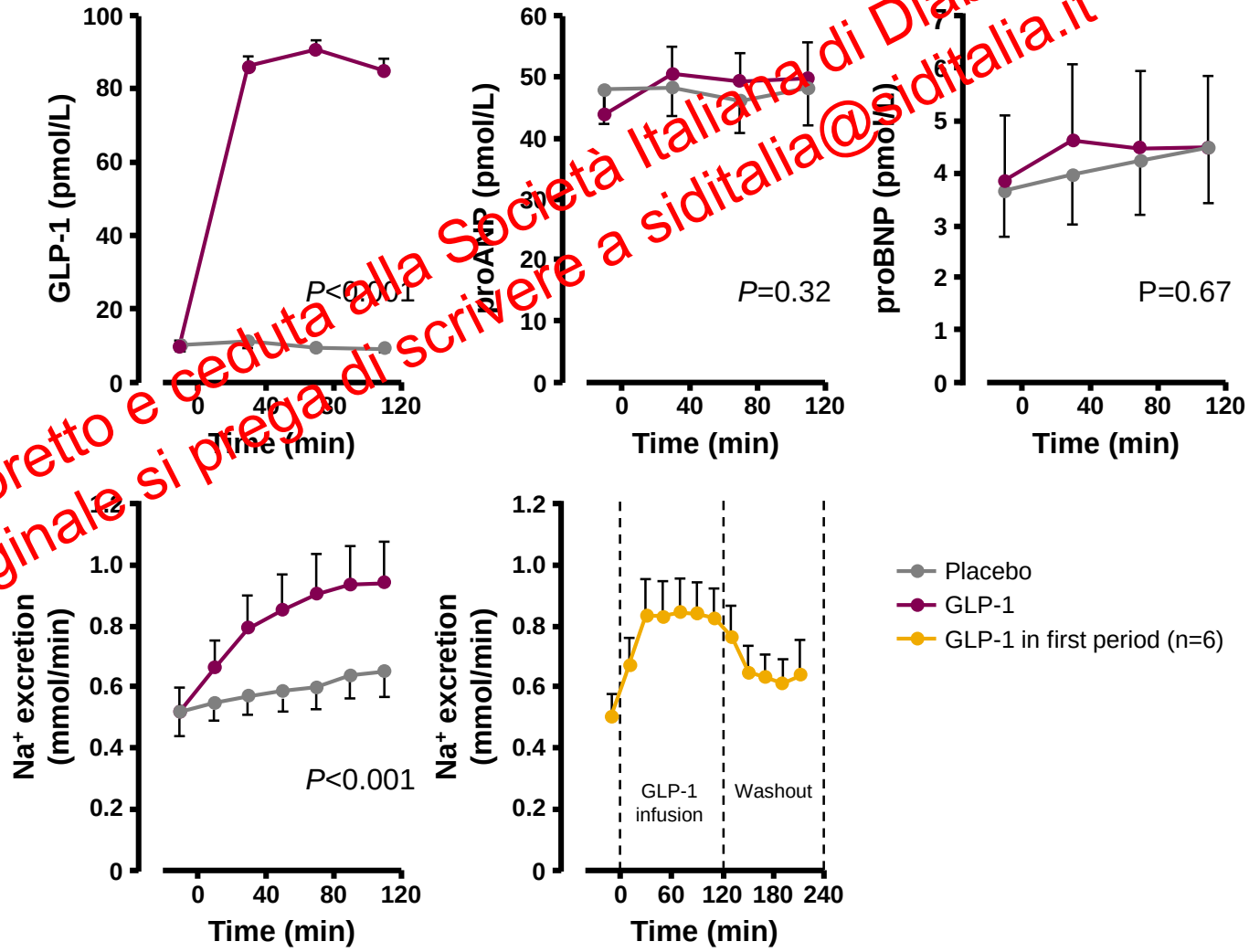
- Blood glucose reduction
- Blood pressure reduction
- Increased sodium excretion
- Renin-angiotensin pathway
- Reduced glucose-induced oxidative stress
- Reduced inflammation



GLP-1, glucagon-like peptide-1

# 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**

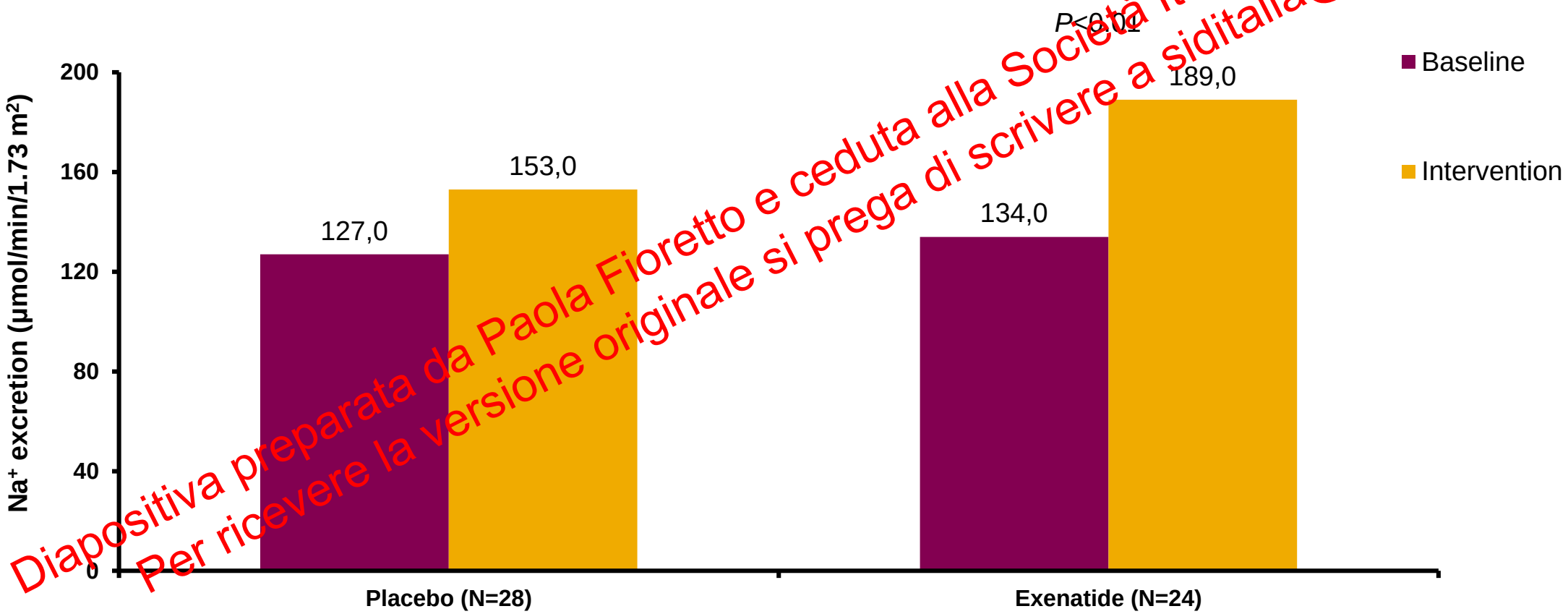





GLP-1, glucagon-like peptide-1; proANB, pro-atrial natriuretic peptide; proBNP, pro B-type natriuretic peptide
Skov J, et al. *Endocrin Conn* 2014;3:11–16

# 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$^2$






BMI, body mass index; GFR, glomerular filtration rate; $HbA_{1c}$, glycated haemoglobin

Tonnejick L, et al. *Diabetologia* 2016;59:1412–1421

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

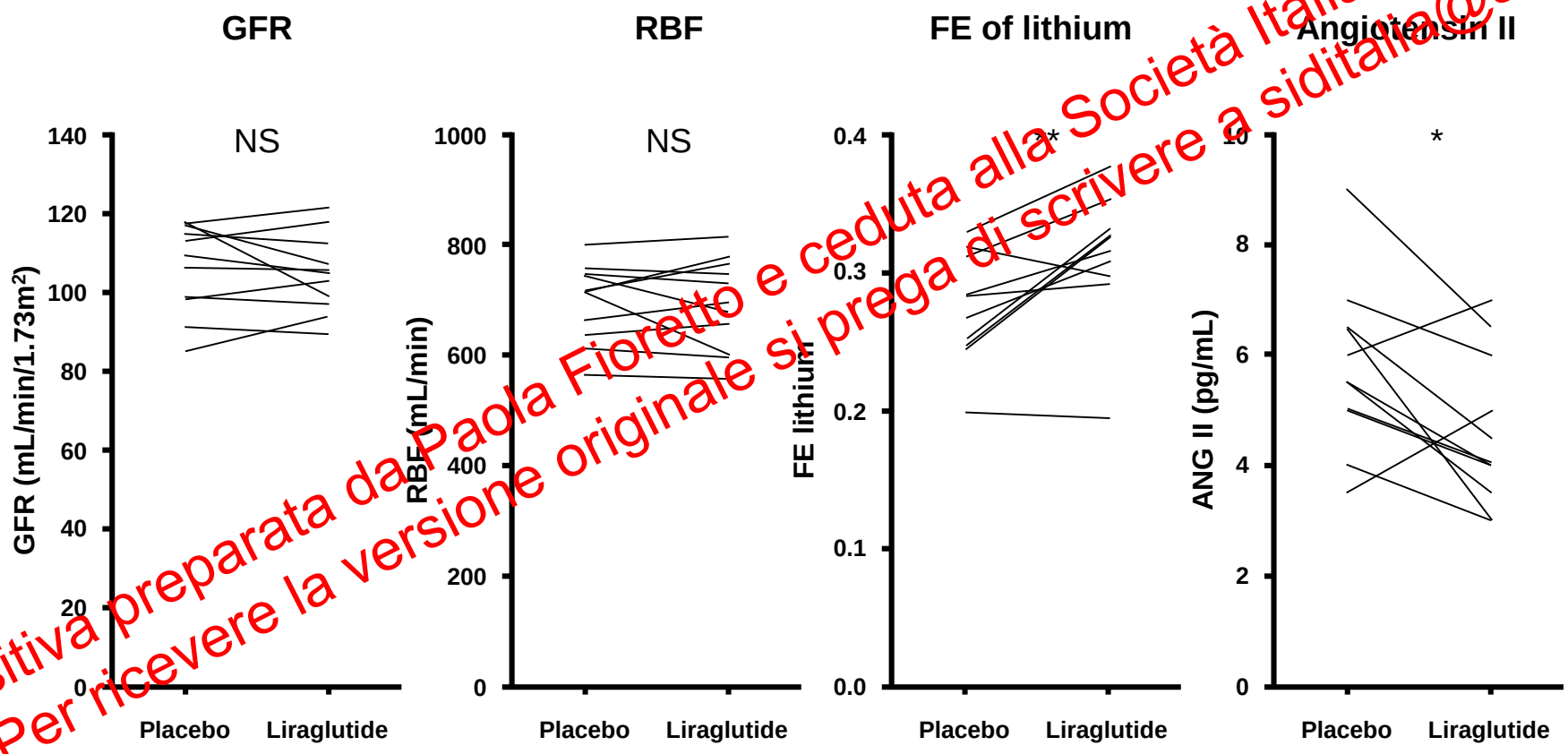
| | Before liraglutide | After liraglutide | Change for liraglutide group (95% CI) | Before placebo | After placebo | Change for placebo group (95% CI) | *P* value for comparison between therapies (end vs end) |
|---|---|---|---|---|---|---|---|
| p-Renin concentration, mU/L | 83.7 [34.5, 322.0] | 52.4 [14.0, 204.1] | –37% (–59, –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 [3.0, 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 |



Data are presented as geometric mean [interquartile range] or mean (95% CI)
CI, confidence interval; RAAS, renin-angiotensin-alterosterone system
Von Scholten BJ, et al. *Diabetes Obes Metab* 2017;19:239–247

# Acute renal effects of liraglutide in patients with Type 2 diabetes

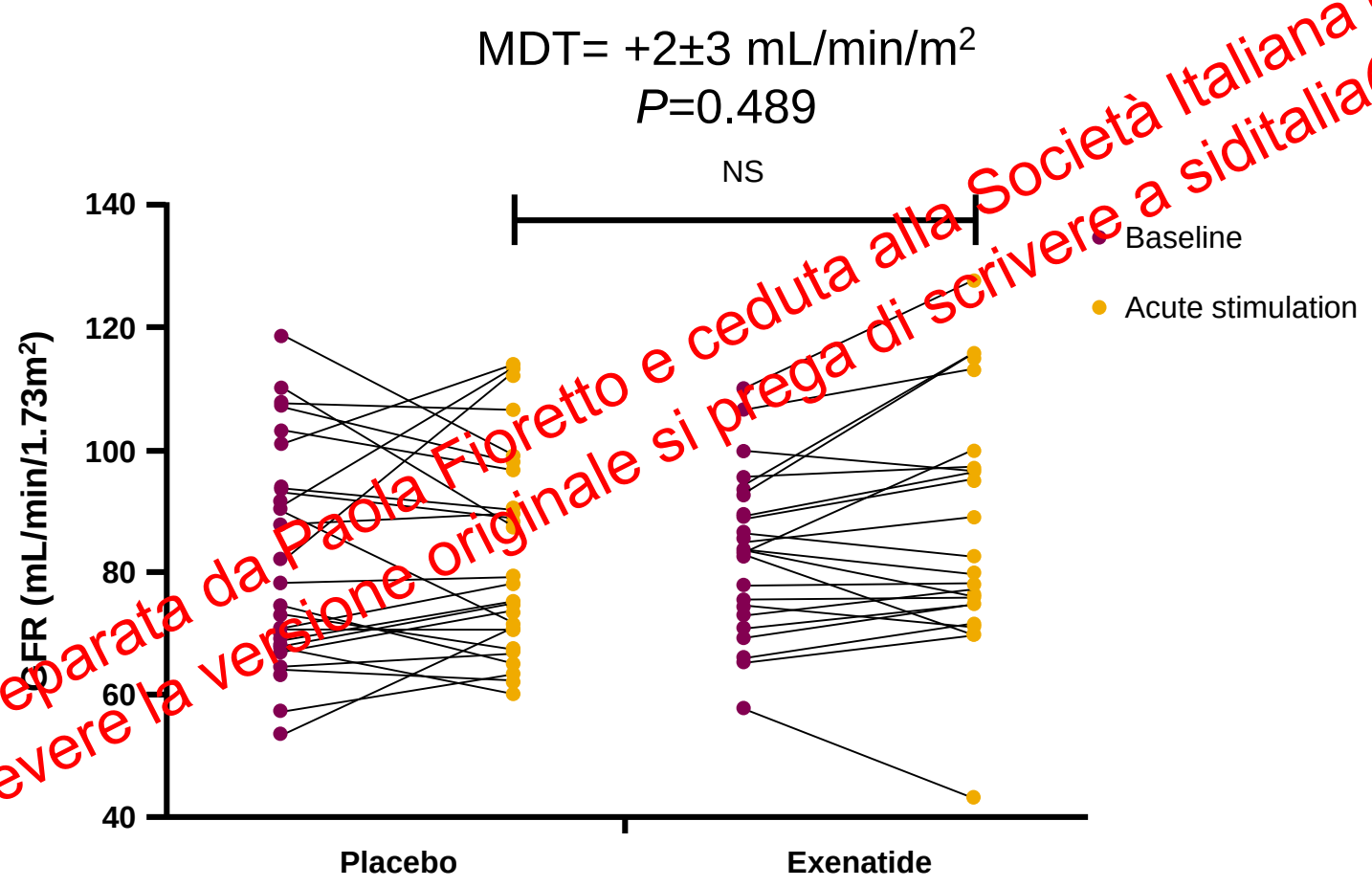
In patients with Type 2 diabetes (N=11), a single dose of liraglutide 1.2 mg had no effect on renal haemodynamics but increased the proximal tubular sodium reabsorption






*$P$<0.05; **$P$<0.01
FE, fractional excretion; GFR, glomerular filtration rate; NS, not significant; RBF, renal blood flow
Skov J, et al. *Diabetes Obes Metab* 2016;18:581–589

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






eGFR, estimated glomerular filtration rate; $HbA_{1c}$, glycated haemoglobin; MTD, mean treatment difference
Tonnejick L, et al. *Diabetologia* 2016;59:1412–1421

# GLP-1 and the kidney

## Potential mechanisms

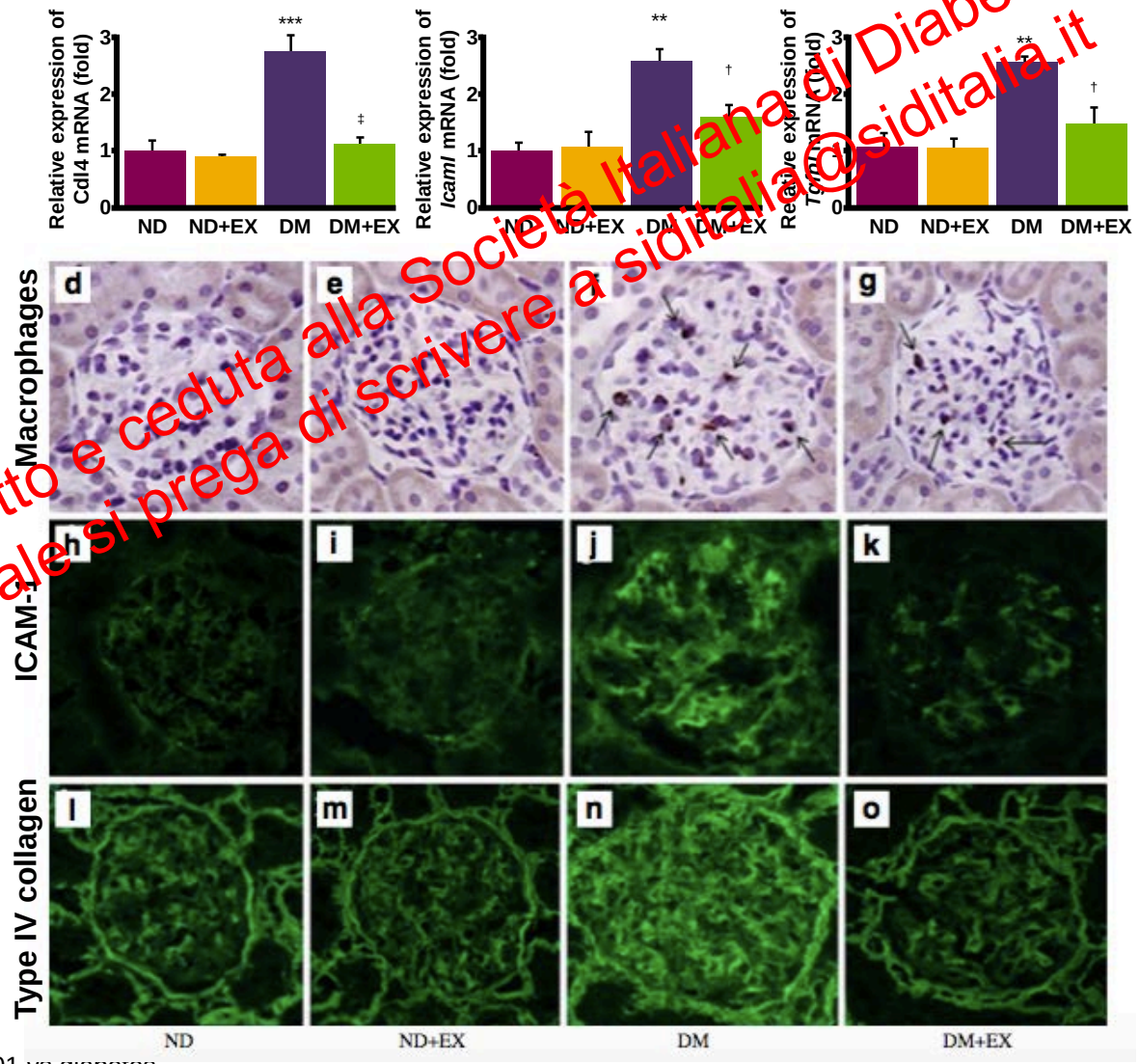
- Blood glucose reduction
- Blood pressure reduction
- Increased sodium excretion
- Renin–angiotensin pathway
- Reduced glucose-induced oxidative stress
- Reduced inflammation



GLP-1, glucagon-like peptide-1

# Exendin-4 suppressed the inflammatory axis in the kidney

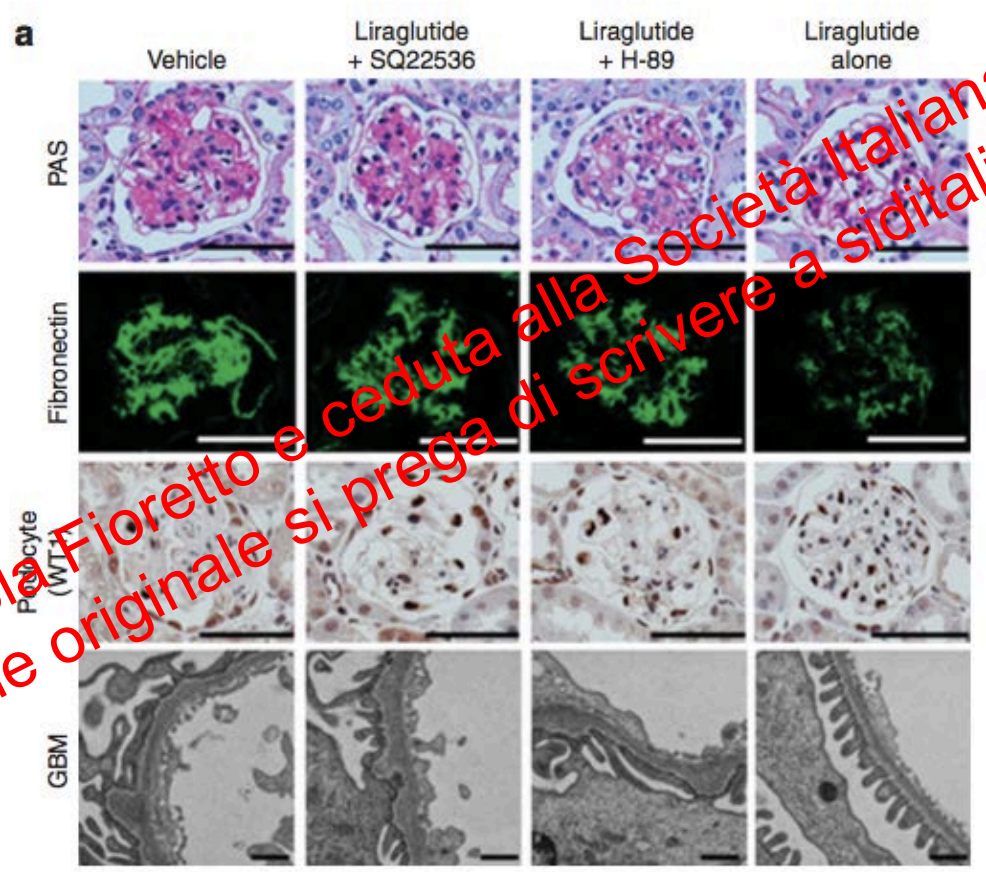
- Exendin-4 was administered at 10 µg/kg daily for 8 weeks to a STZ-induced rat model of Type 1 diabetes
- Markers of inflammation were significantly up-regulated in the diabetes group and significantly downregulated by exendin-4 treatment

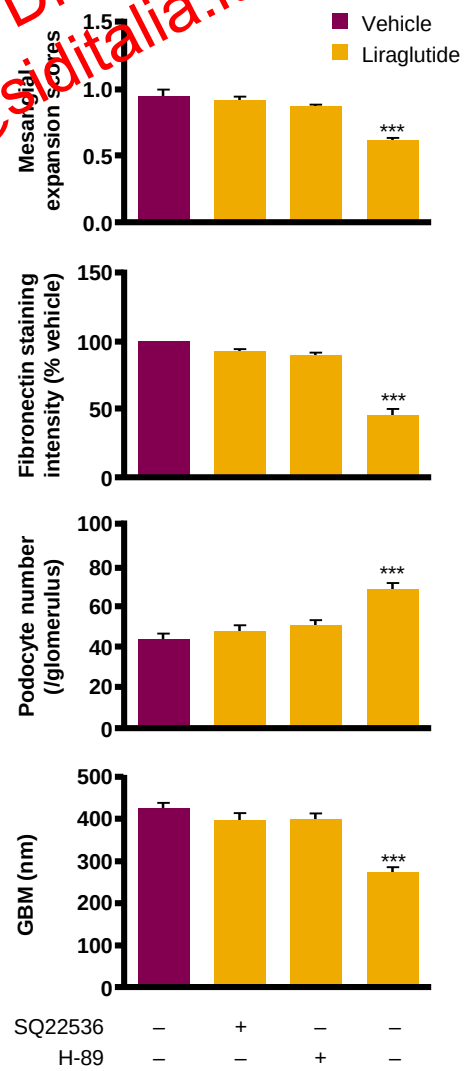



**P<0.01 and ***P<0.001 vs non-diabetes and non-diabetes + exendin-4; †*P*<0.05 and ‡*P*<0.001 vs diabetes
ICAM, intercellular adhesion molecule-1; STZ, streptozotocin
Kodera R, et al. *Diabetologia* 2011;54:965–978

# 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



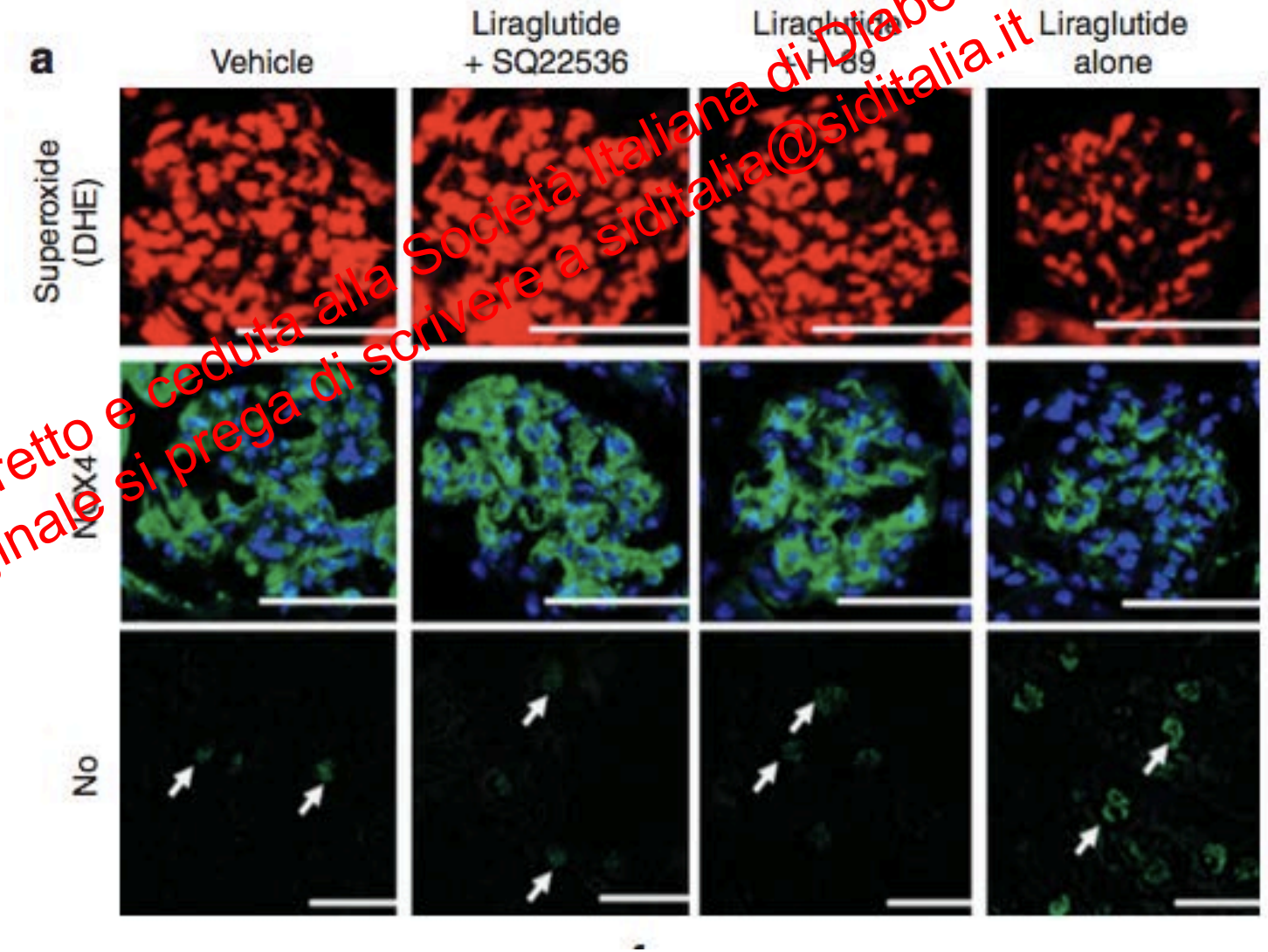






***$P$<0.001 vs vehicle
cAMP, cyclic adensosine monophosphate; GLP-1, glucagon-like peptide-1
Fujita H, et al. *Kidney Int* 2014;85:579–589

# 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

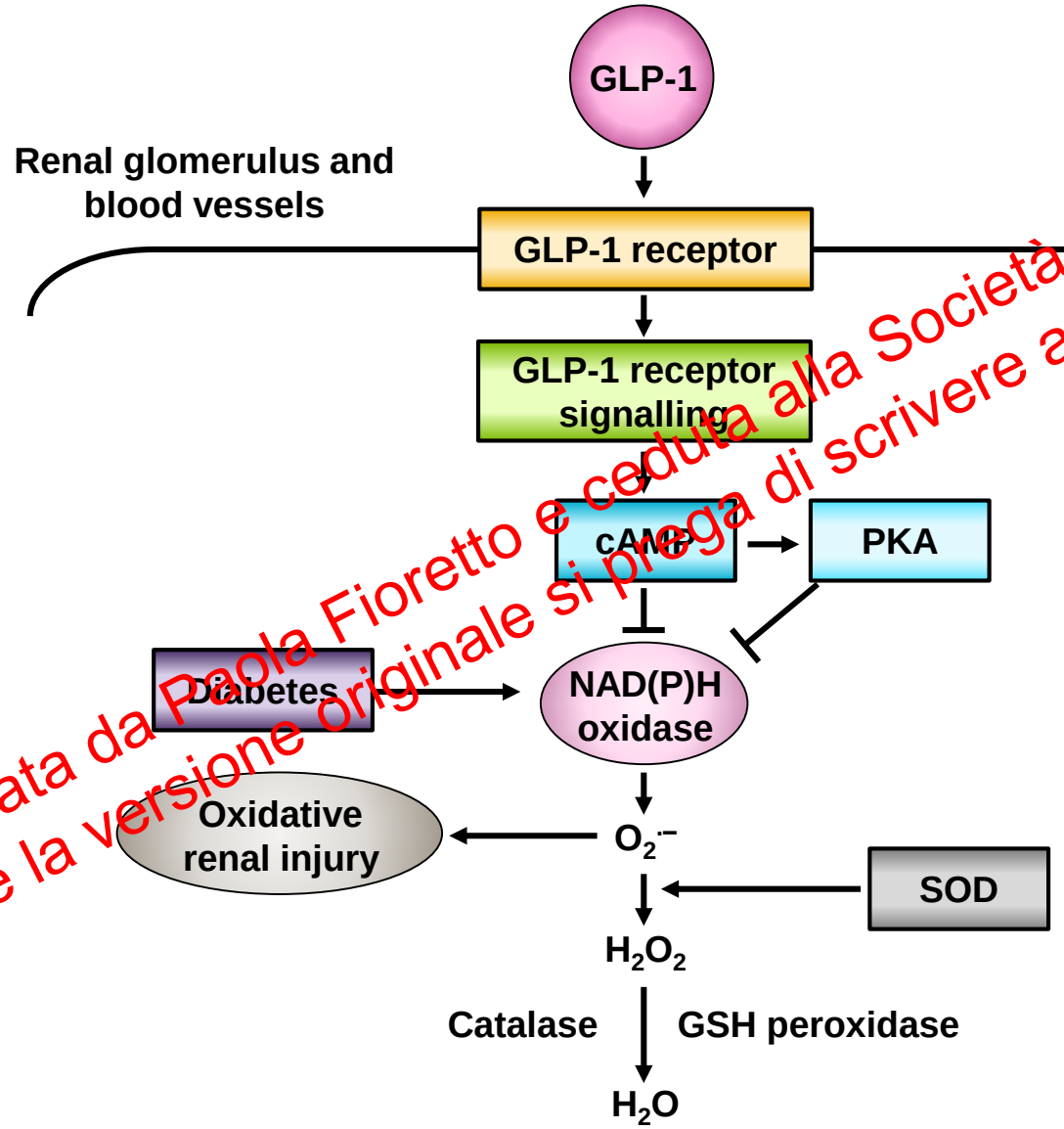





cAMP, cyclic adenosine monophosphate; NADPH, nicotinamde adenine dinucleotide phosphate; PKA, protein kinase A

Fujita H, et al. *Kidney Int* 2014;85:579–589

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

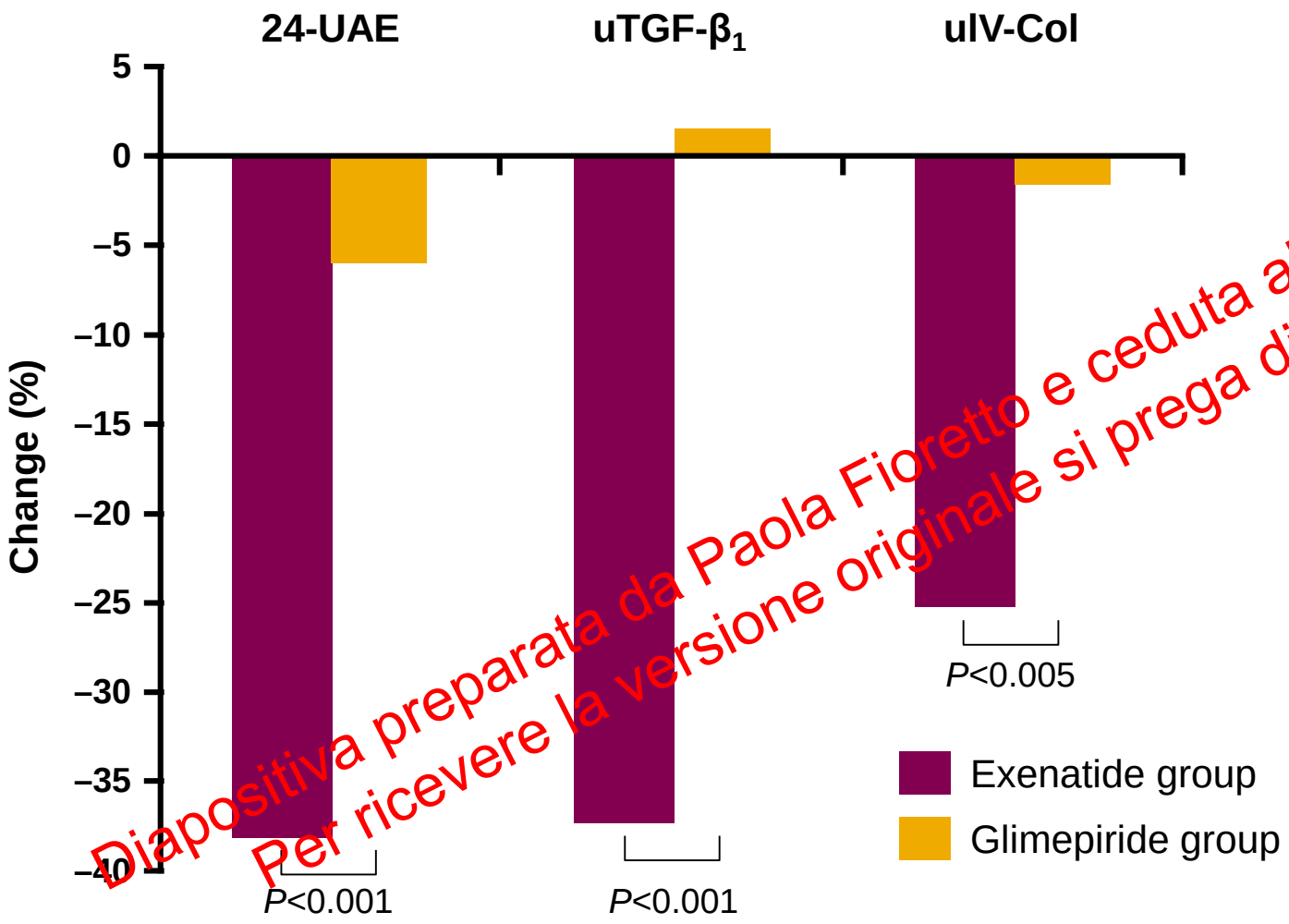





cAMP, cyclic adenosine monophosphate; NADPH, nicotinamde adenine dinucleotide phosphate; PKA, protein kinase A; SOD, superoxide dismutase

Fujita H, et al. *Kidney Int* 2014;85:579–589

# 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-$\beta_1$ 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)



Col, collagen; TGF, transforming growth factor; UAE, urinary albumin excretion

Zhang H, et al. *Kidney Blood Press Res* 2012;35:483–488

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

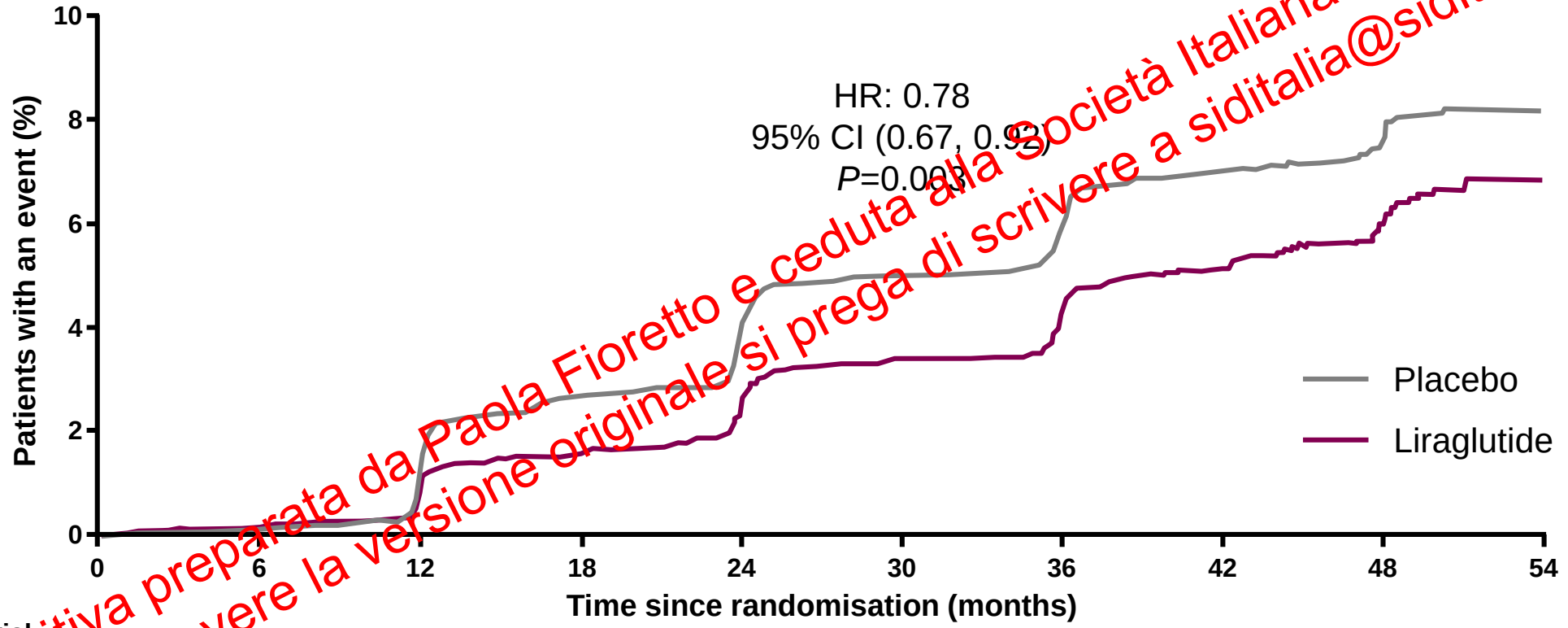
| | Exenatide QW → exenatide QW (N=103) | Sitagliptin → exenatide QW (N=116) | Pioglitazone → exenatide QW (N=100) |
|---|---|---|---|
| ACR (baseline) | 15.31±2.37 | 11.46±1.27 | 13.23±1.92 |
| Δ weeks 26–52 | –19% (–31, –5)* | –14% (–26, 0) | –12% (–25, 4) |
| Δ weeks 0–52 | –34% (–45, –20)* | –18% (–31, –3)* | –23% (–36, –7)* |
| BNP (baseline, pg/mL) | 9.66±1.00 | 12.69±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) |



*$P$<0.05
Data are presented as mean±standard error, or geometric least square mean % change (95% confidence interval)
ACR, uinary abumin:creatinine ratio; BNP, B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; PAI-1, plasminogen activator inhibitor 1; QW, once weekly
Wysham C, et al. *Diabetic Med* 2017

# 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 |



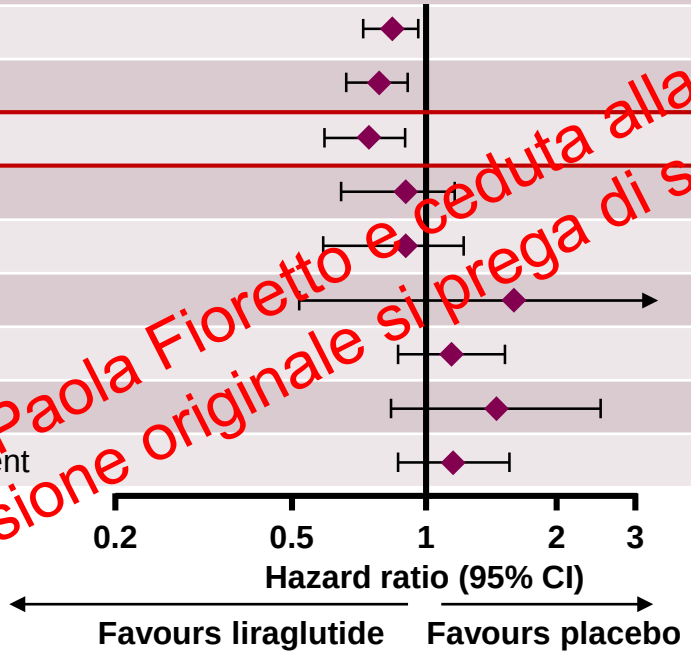
The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model; the data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio

Marso SP, et al. *N Eng J Med* 2016;375:311–322

# 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 |



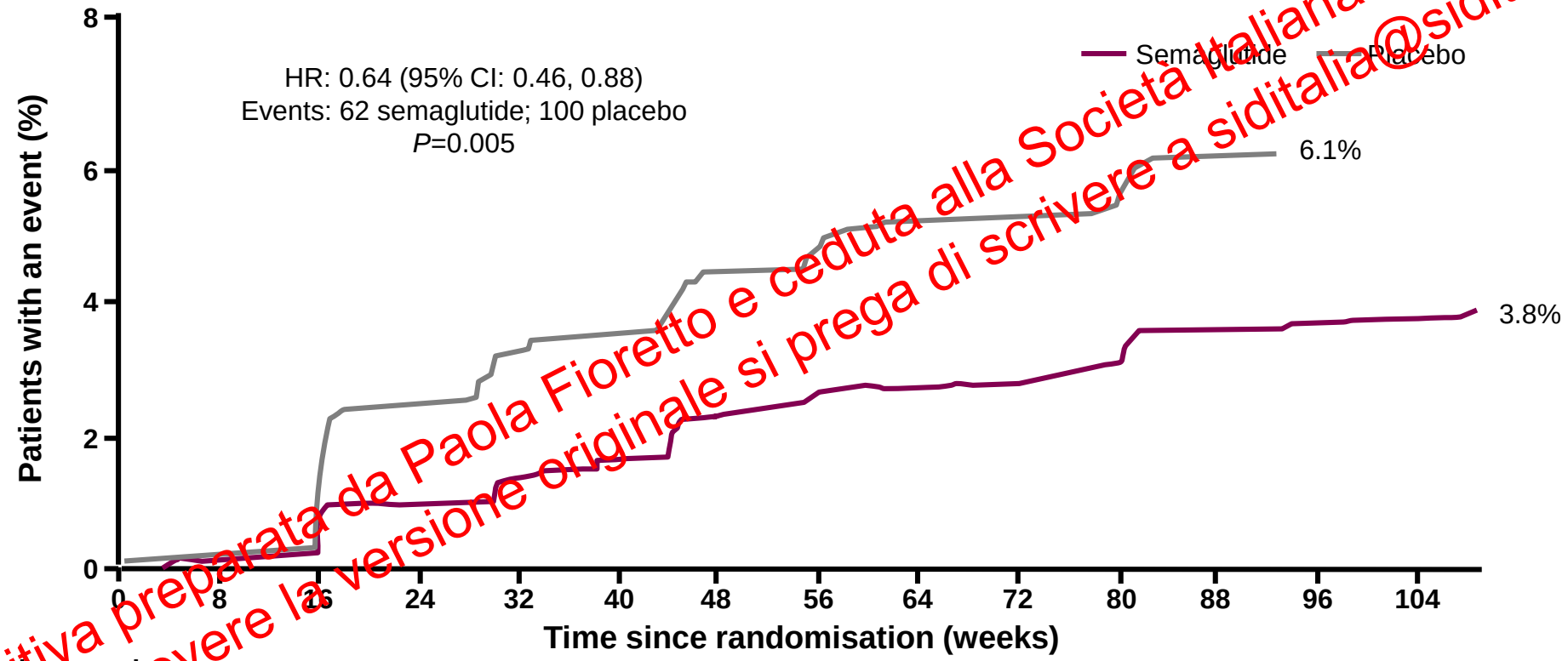



Full analysis set. EAC-confirmed microvascular events including events with onset between date of randomisation and date of follow-up; Cox proportional hazard model adjusted for treatment; development of diabetes-related blindness was not analysed as an individual component because only one event was observed; [a]New onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine; [b]Persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 $m^2$ per MDRD

CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease

Marso SP, et al. *N Eng J Med* 2016;375:311–322

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



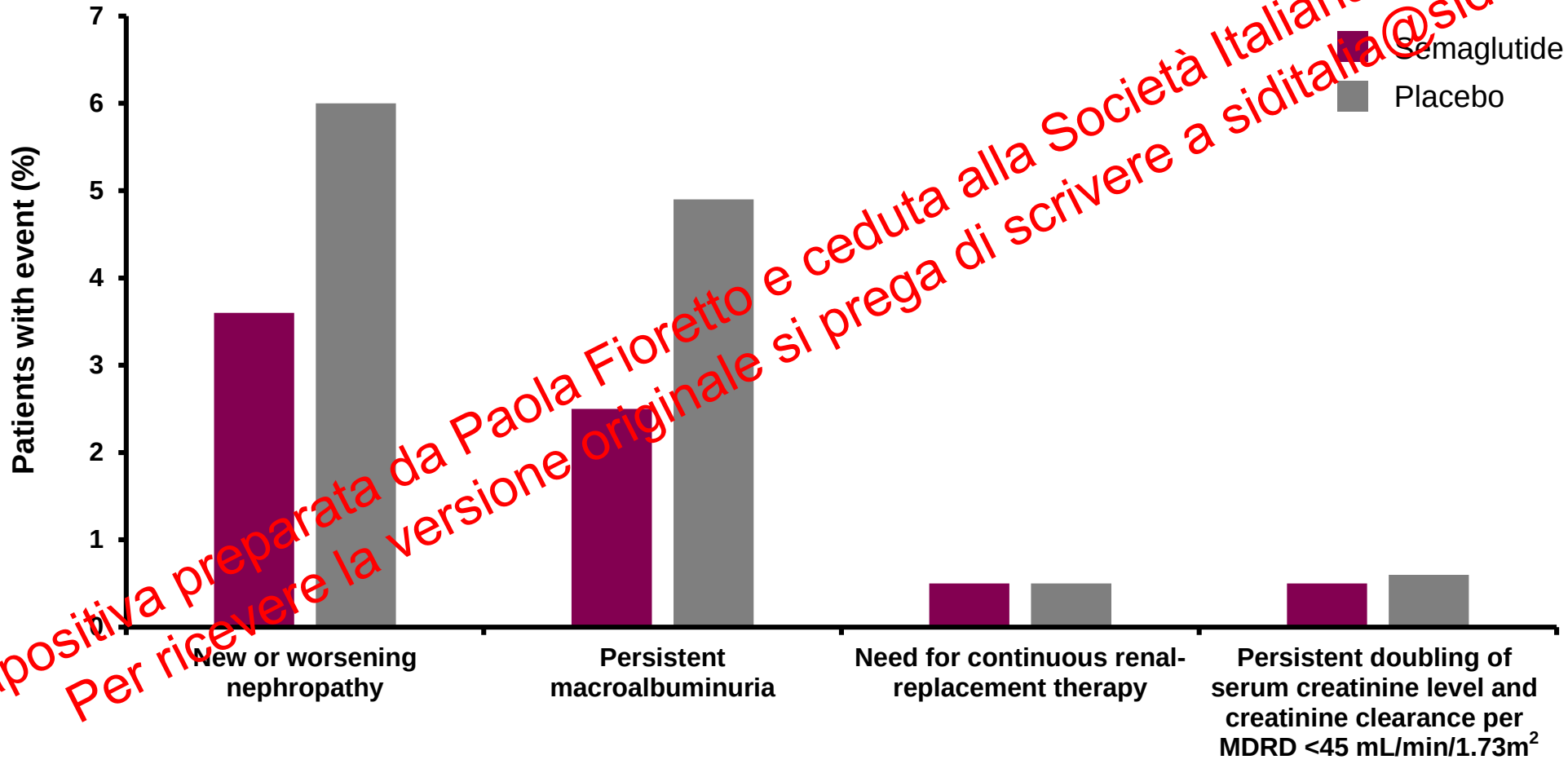

**No. of patients at risk**

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



Kaplan–Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy using 'in-trial' data from subjects in the full analysis set; HR is from a proportional hazard model
CI, confidence interval; EAC, (external) event adjudication committee; HR, hazard ratio
Vilsbøll T. Presented at the 52nd EASD Annual Meeting 2016. Munich, Germany; 16th September 2016; OP S35.3

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





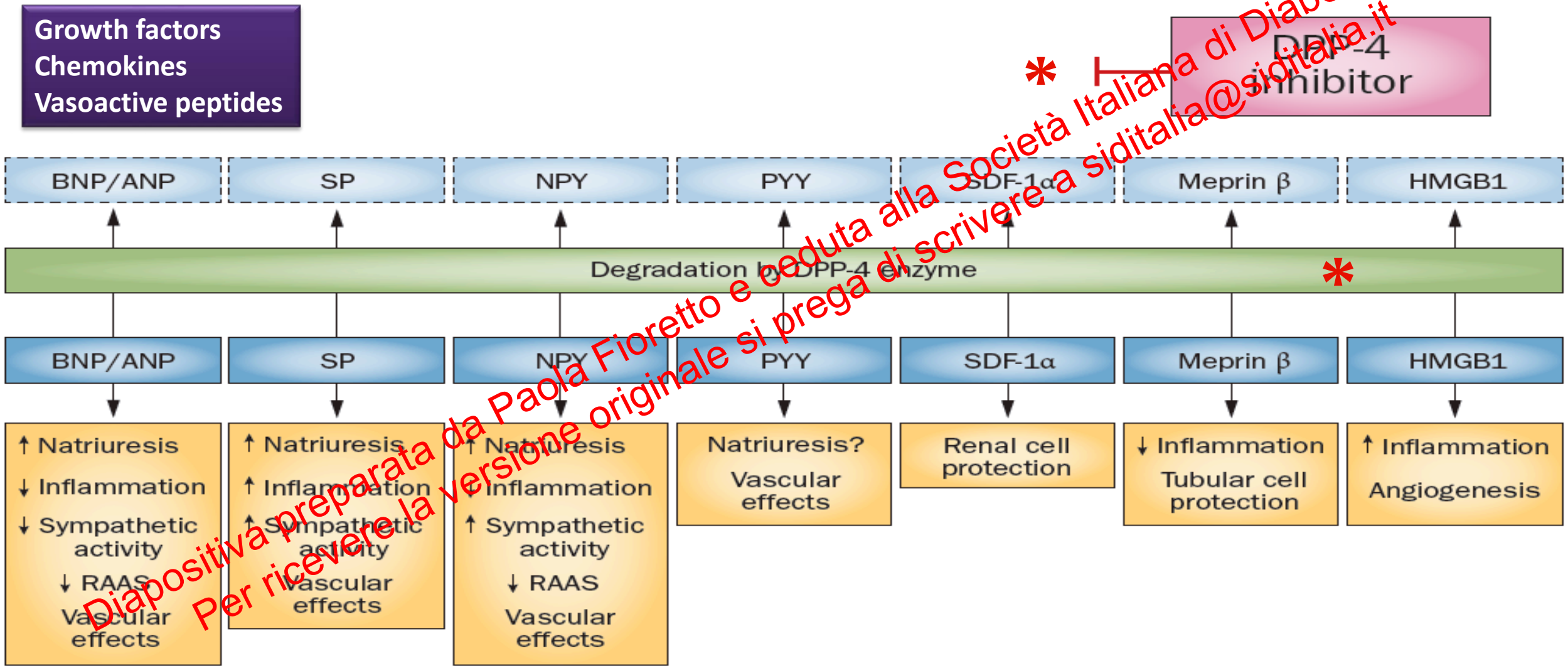

MDRD, Modification of Diet in Renal Disease

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

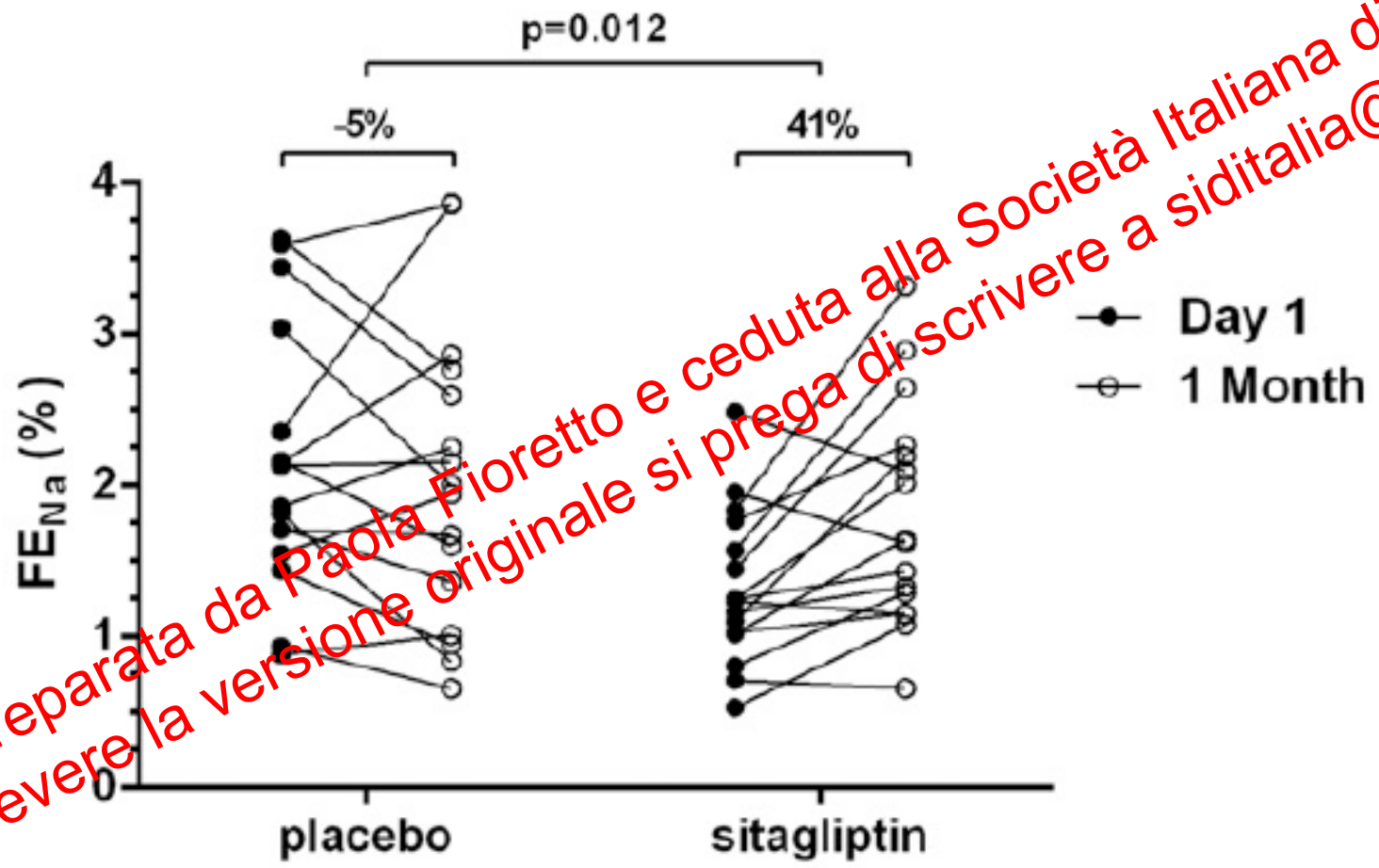





ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; DPP-4, dipeptidyl peptidase-4; GIP, gastric inhibitory polypeptide; GLP-1, glucagon0like peptide 1; HMGB1, high-mobility group protein B1; NPY, neuropeptide Y; PYY, peptide YY; RAAS, renin-angiotensin-aldosterone system; SDF-1α, stromal cell-derived factor 1$^{\alpha}$; SP, substance P

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

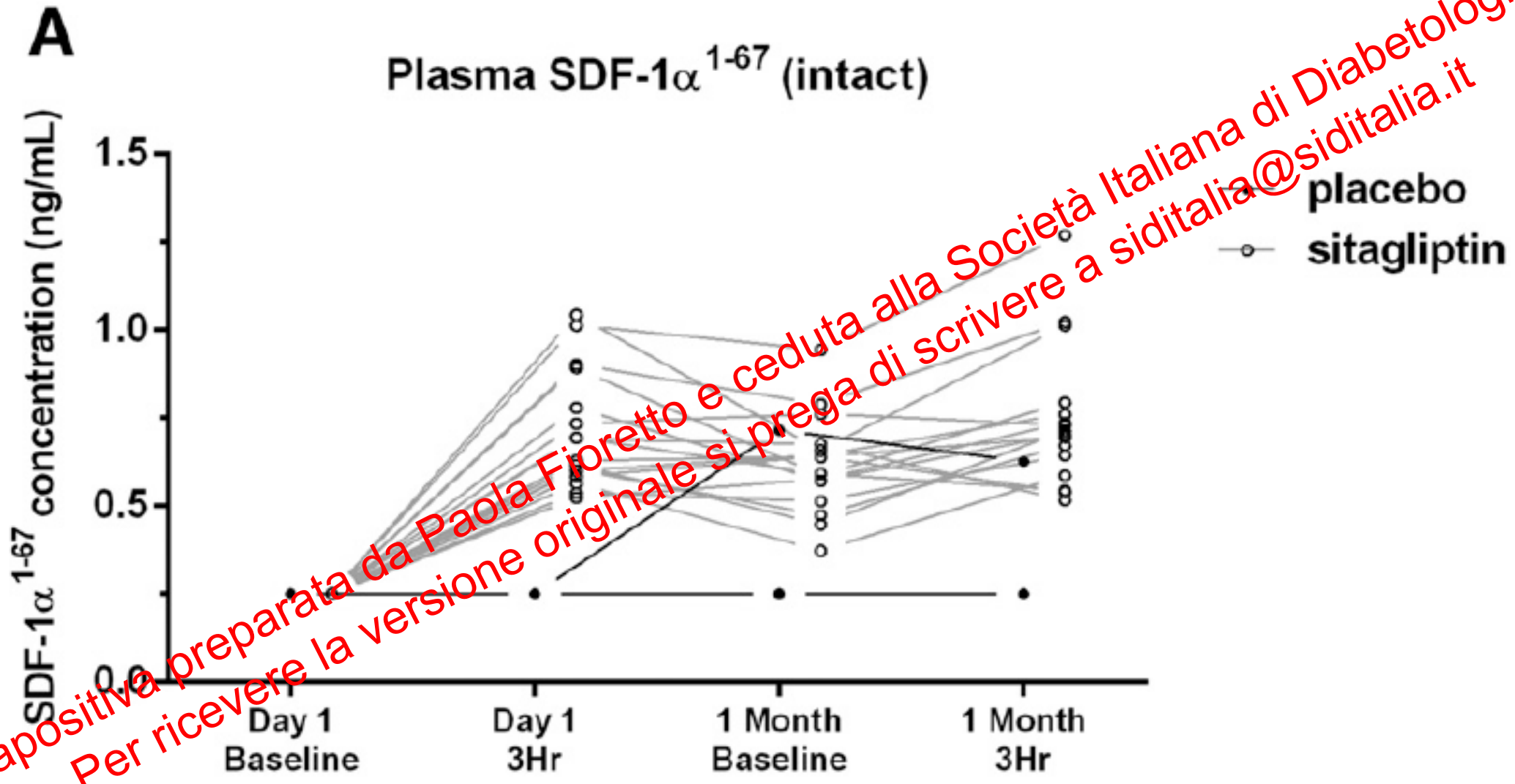
# Effects of sitagliptin on fractional excretion of sodium





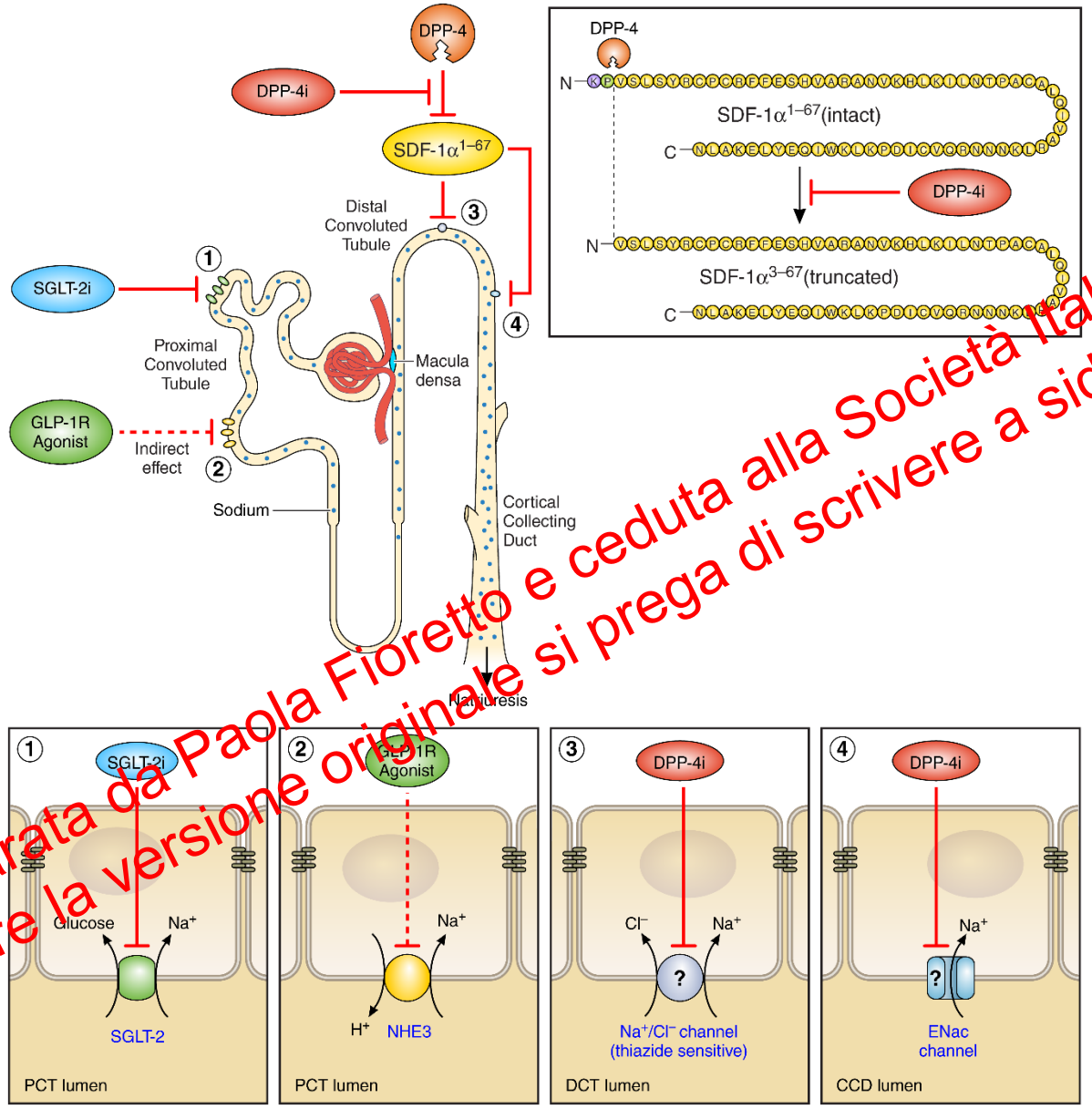

LovshinJA et al, Diabetes Care, 2017

# Effects of sitagliptin on intact plasma SDF-1a






LovshinJA et al, Diabetes Care, 2017

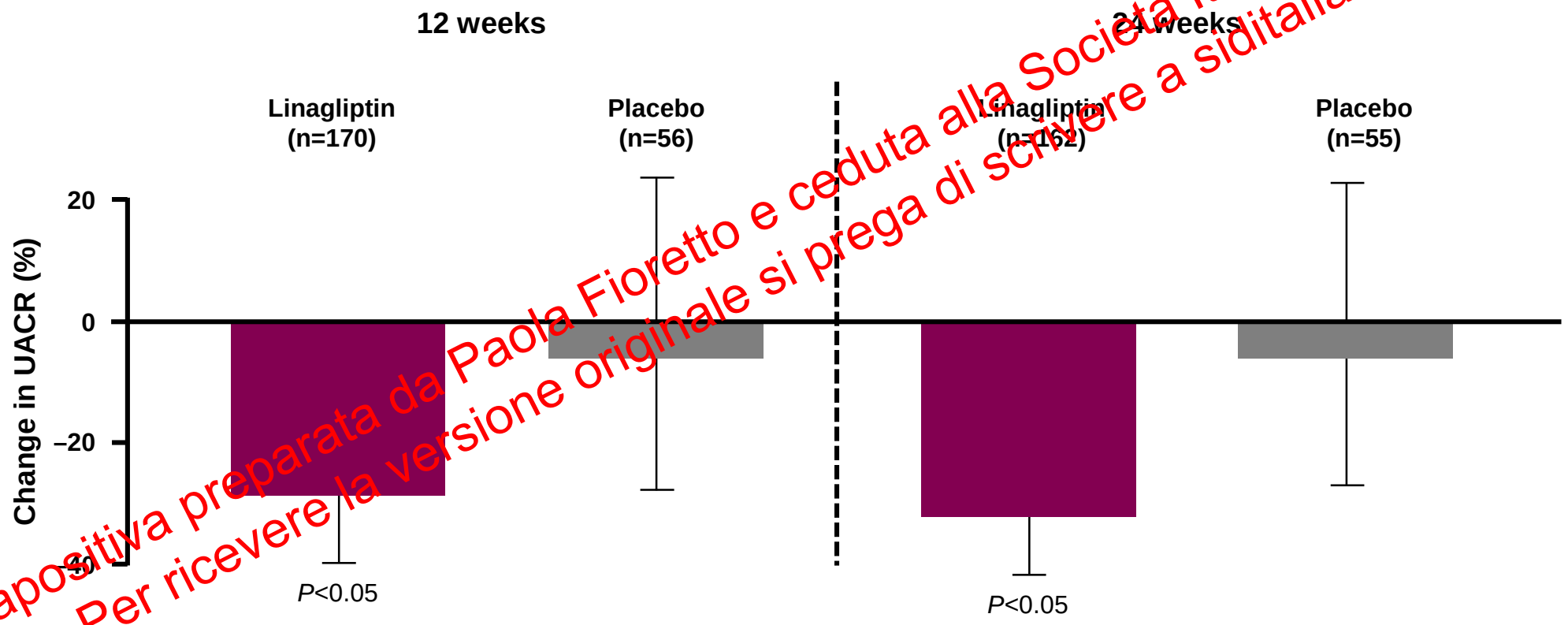





LovshinJA et al, Diabetes Care, 2017

# 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



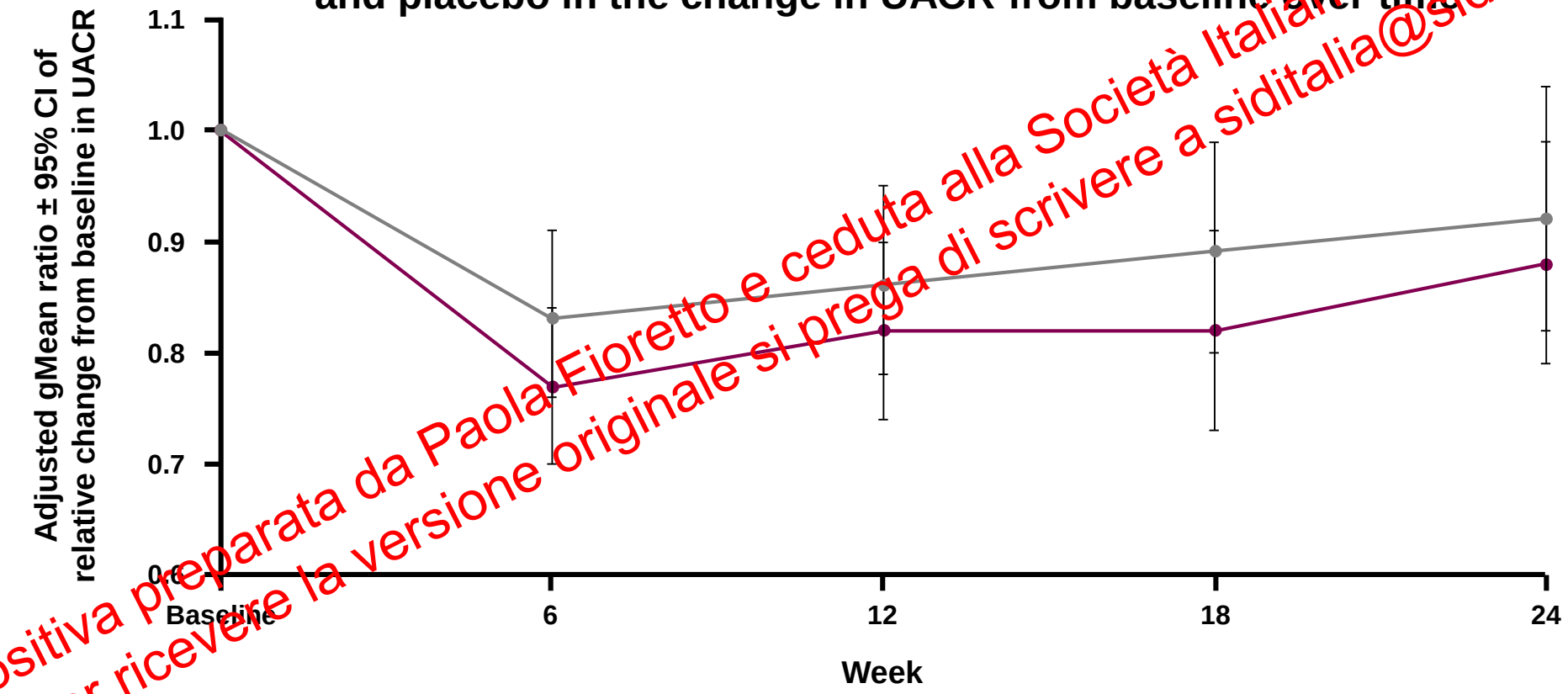



DPP-4, dipeptidyl peptidase-4; UACR, urinary albumin:creatinine ratio

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

# Effects of linagliptin on UACR in the Marlina study

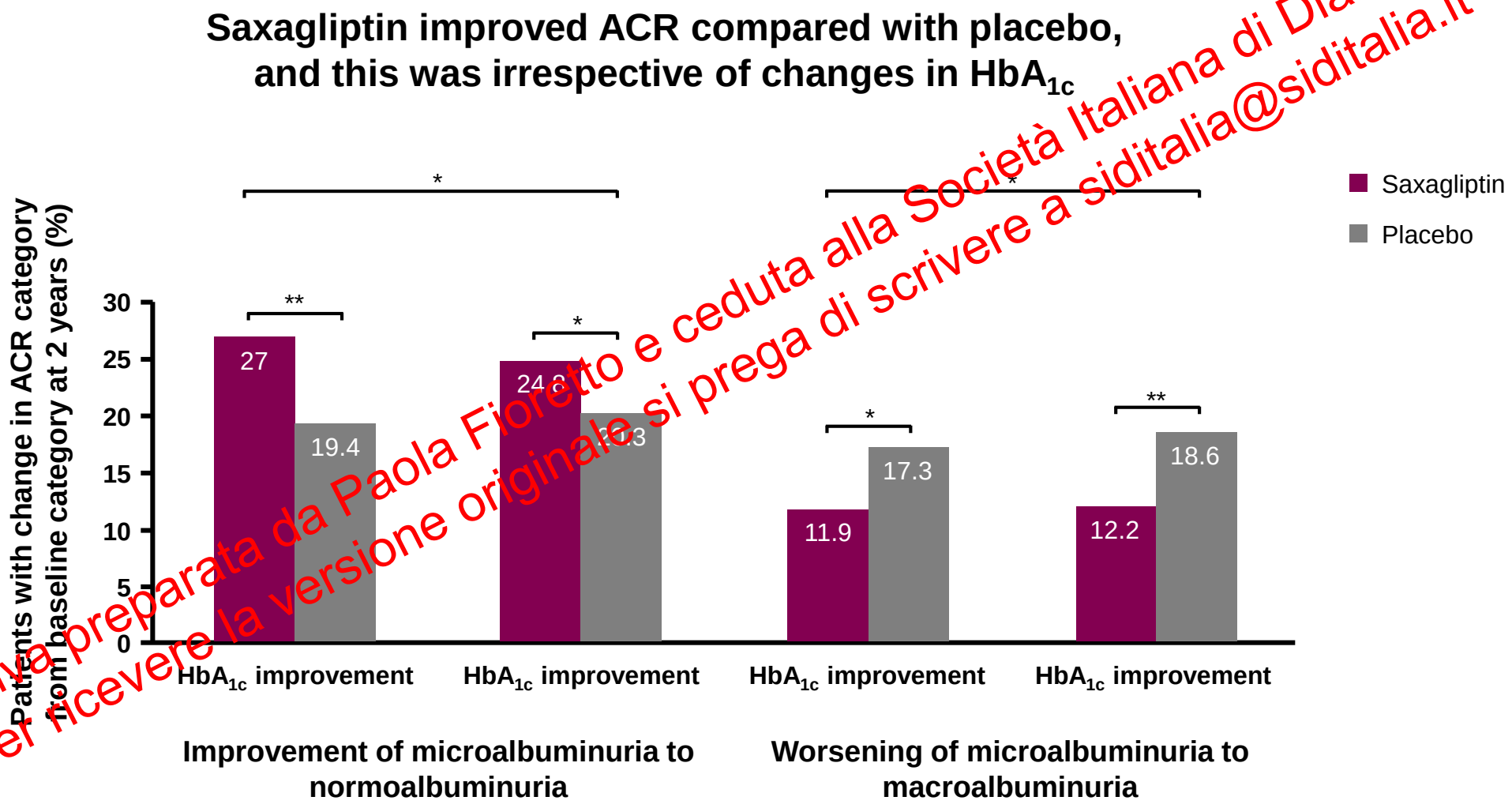
**There was no significant difference between linagliptin and placebo in the change in UACR from baseline over time**






CI, confidence interval; UACR, urinary albumin:creatinine ratio
Groop PH, et al. ADA 2016, Poster 17-LB

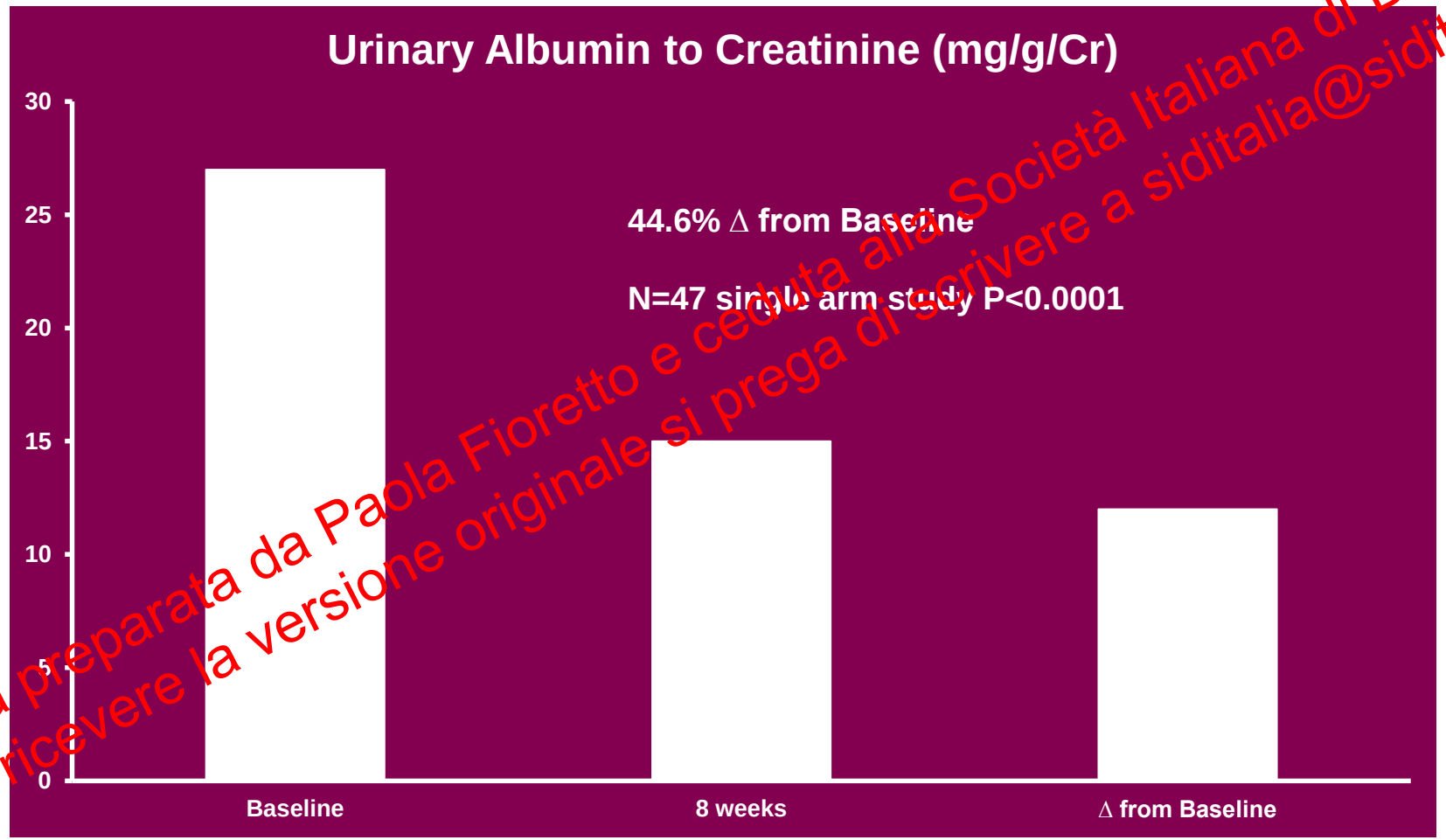
# Effects of saxagliptin on ACR at 2 years in the SAVOR study






*$P$<0.05; **$P$<0.01
ACR, albumin:creatinine ratio; $HbA_{1c}$, glycated haemoglobin
Mosenzon O, et al. *Diabetes Care* 2017;40:69–70

# Effects of Vildagliptin on ACR (8 weeks)






Tami et al, Am J Cardiovasc Drugs, 2013

# What about individual antidiabetes agents?

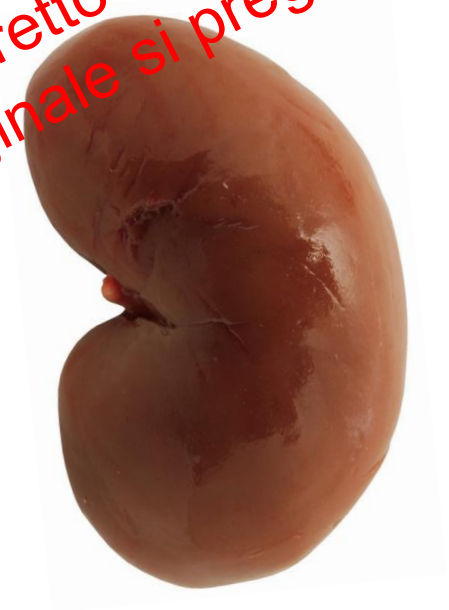
## – SGLT2 inhibitors

# SGLT2 inhibition and potential renal protection

SGLT2 inhibition

**Indirect benefits for the kidney**

- Improved glycaemic control
- Reduced insulin levels
- Increased insulin sensitivity
- Reduced blood pressure
- Reduced body weight/fat
- Reduced plasma uric acid



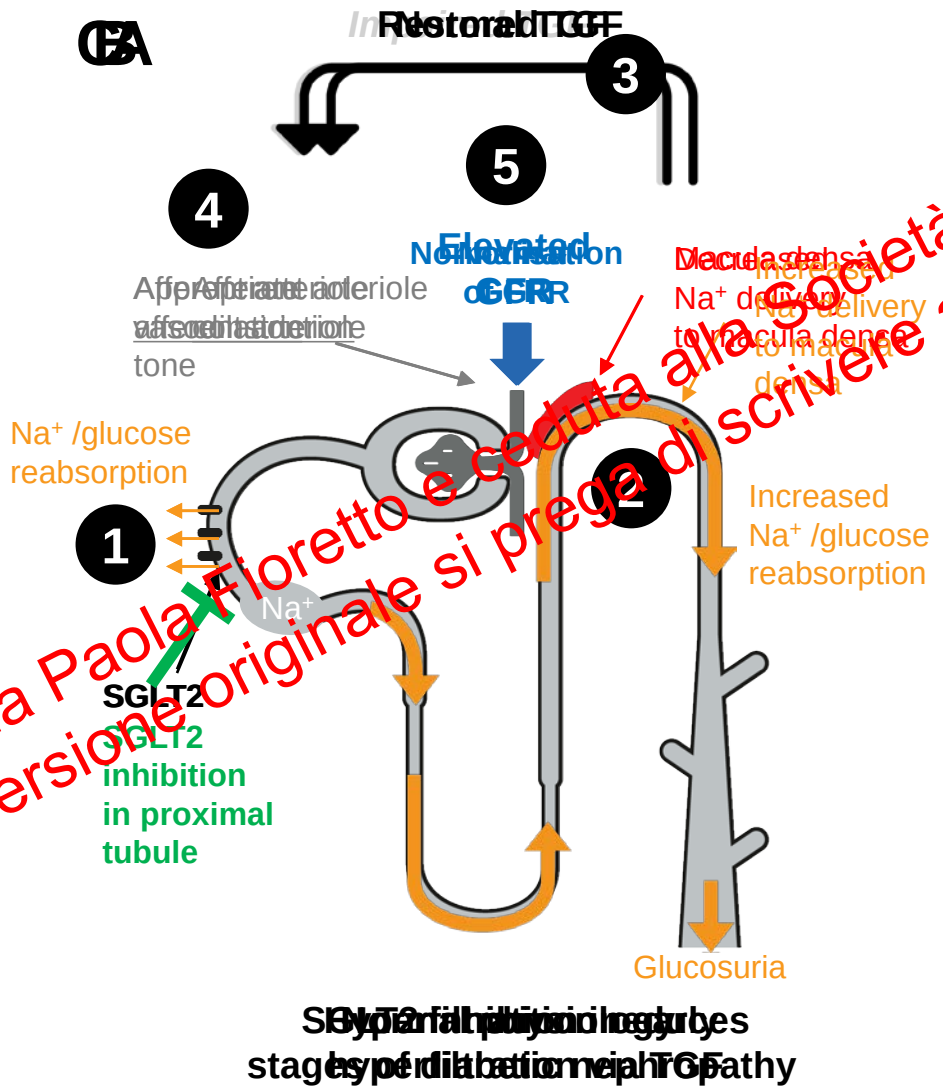
**Potential direct benefits**

- Reduction in hyperfiltration
- Inhibition of intra-renal RAS?
- Attenuation of renal hypertrophy
- Reduction in tubulotoxicity of glucose



RAS, renin-angiotensin system; SGLT2, sodium–glucose co-transporter 2

# Tubuloglomerular feedback and SGLT2 inhibition



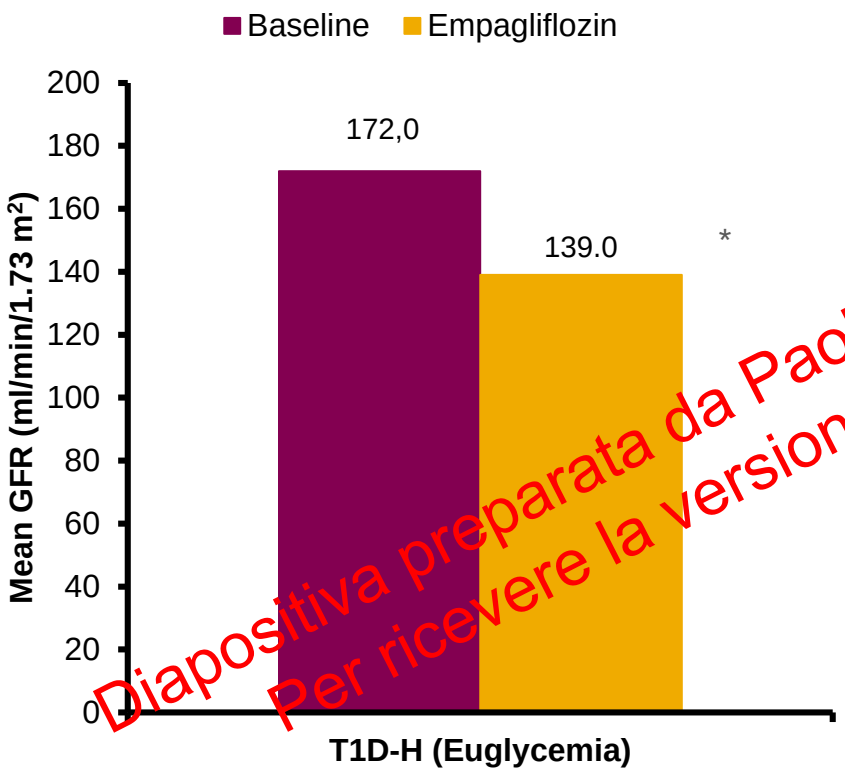



GFR, glomerular filtration rate; SGLT, sodium–glucose co-transporter; TGF, tubuloglomerular feedback
Cherney D, et al. *Circulation* 2014;129:587–597

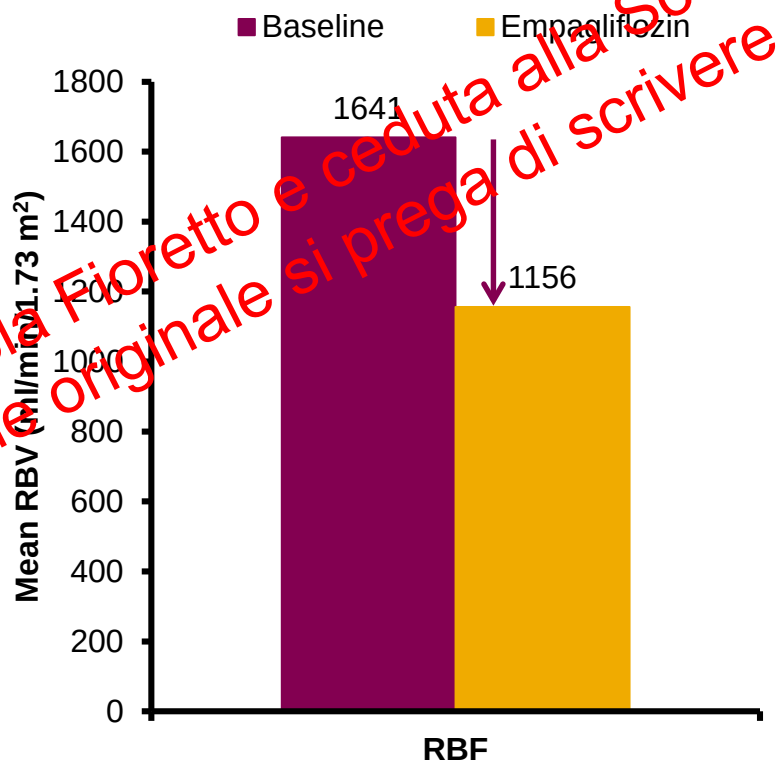
# Type 1 diabetes – Reduced hyperfiltration was mediated by effects on renal blood flow and vascular resistance

- Reduced **renal blood flow** (RBF) & increased **renal vascular resistance** (RVR) after empagliflozin treatment are consistent with **afferent arteriole vasoconstriction**

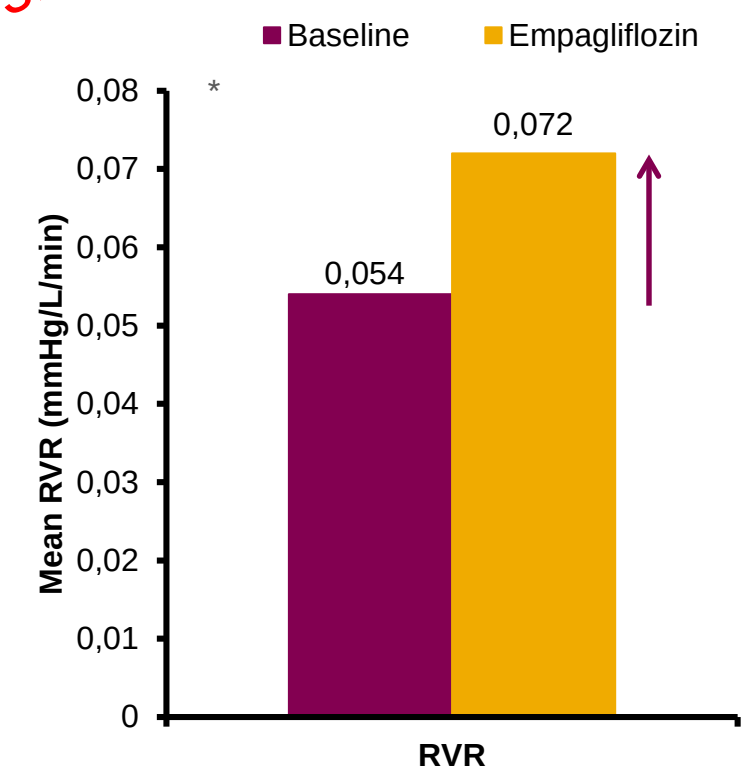
## Glomerular filtration rate




## Renal blood flow




## Renal vascular resistance





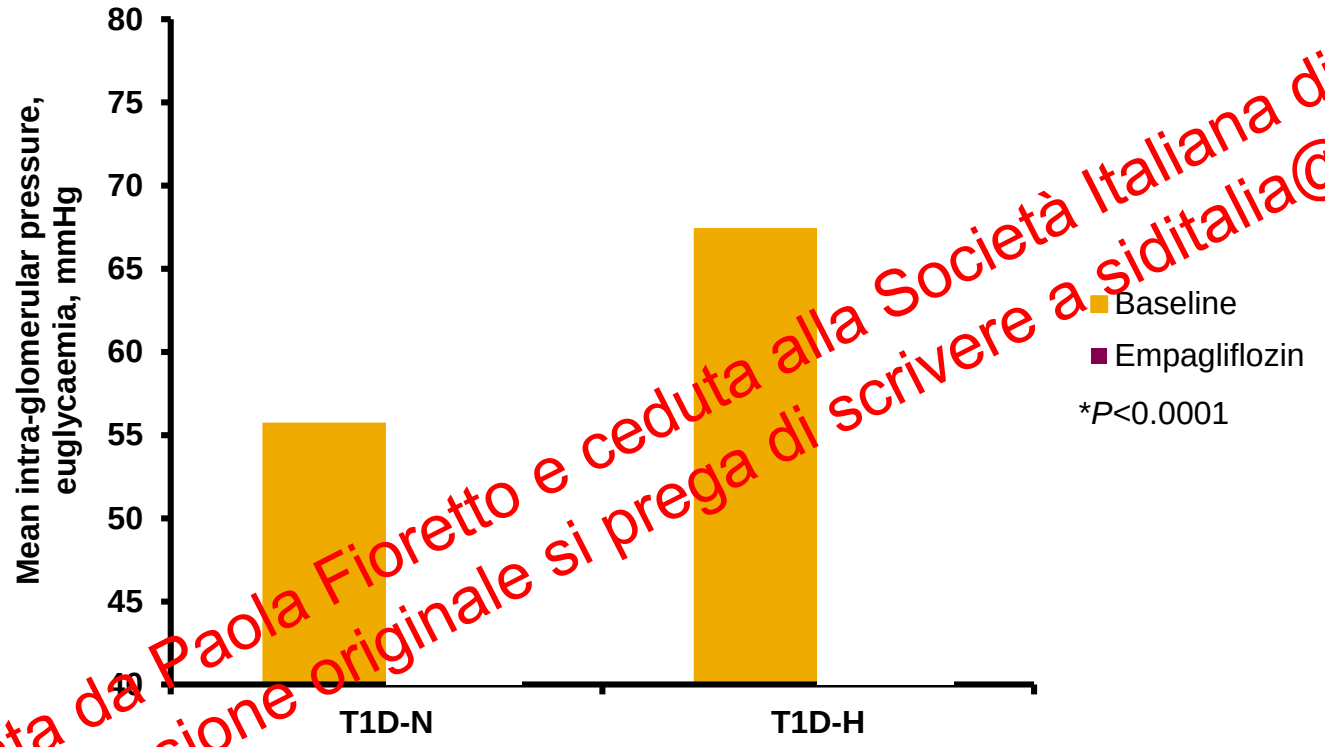

* $p<0.01$

Patients with type 1 diabetes and hyperfiltration at baseline. RBV and RVR recorded in euglycaemic state.

RBF, renal blood flow; RVR, renal vascular resistance

Cherney D, et al. *Circulation* 2014;129:587–597

# Empagliflozin reduces intraglomerular pressure



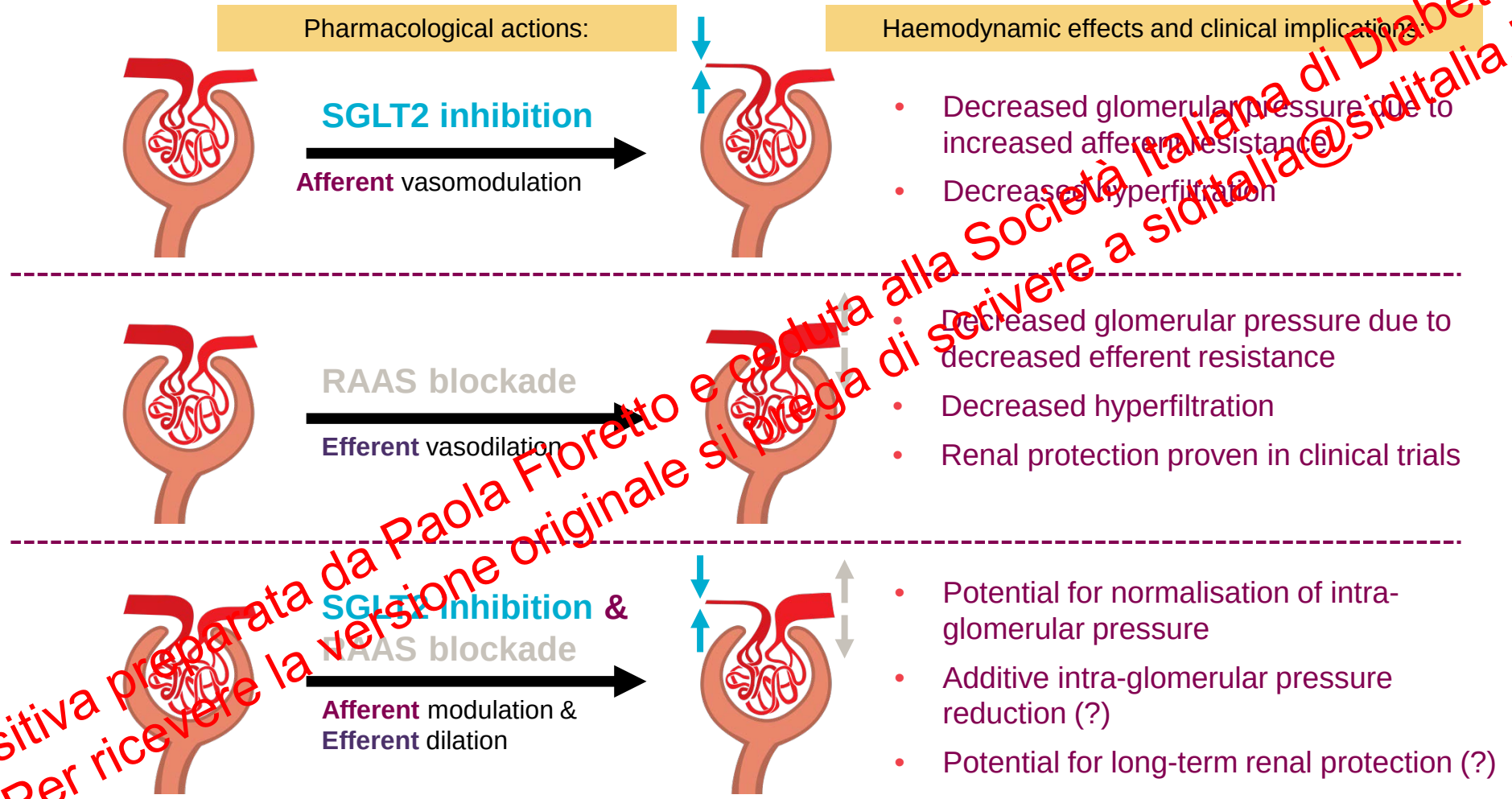

**Intraglomerular pressure recorded at baseline and after 8 weeks treatment with empagliflozin**

| Glomerular pressure T1D-H (mmHg) | Baseline | EMPA | *P* value | Change from baseline |
|---|---|---|---|---|
| Euglycaemia (mmHg) | 67.4 ± 5.4 | 61.0 ± 5.2 | <0.0001 | 9.5% |
| Hyperglycaemia (mmHg) | 69.3 ± 6.5 | 61.6 ± 6.3 | <0.0001 | 11.1% |

**►~6–8 mmHG ↓**

T1D-H, Type 1 diabetes and renal normofiltration; T1D-H, Type 1 diabetes and renal hyperfiltration
Skrtic M, et al. *Diabetologia* 2014;57:2599–2602

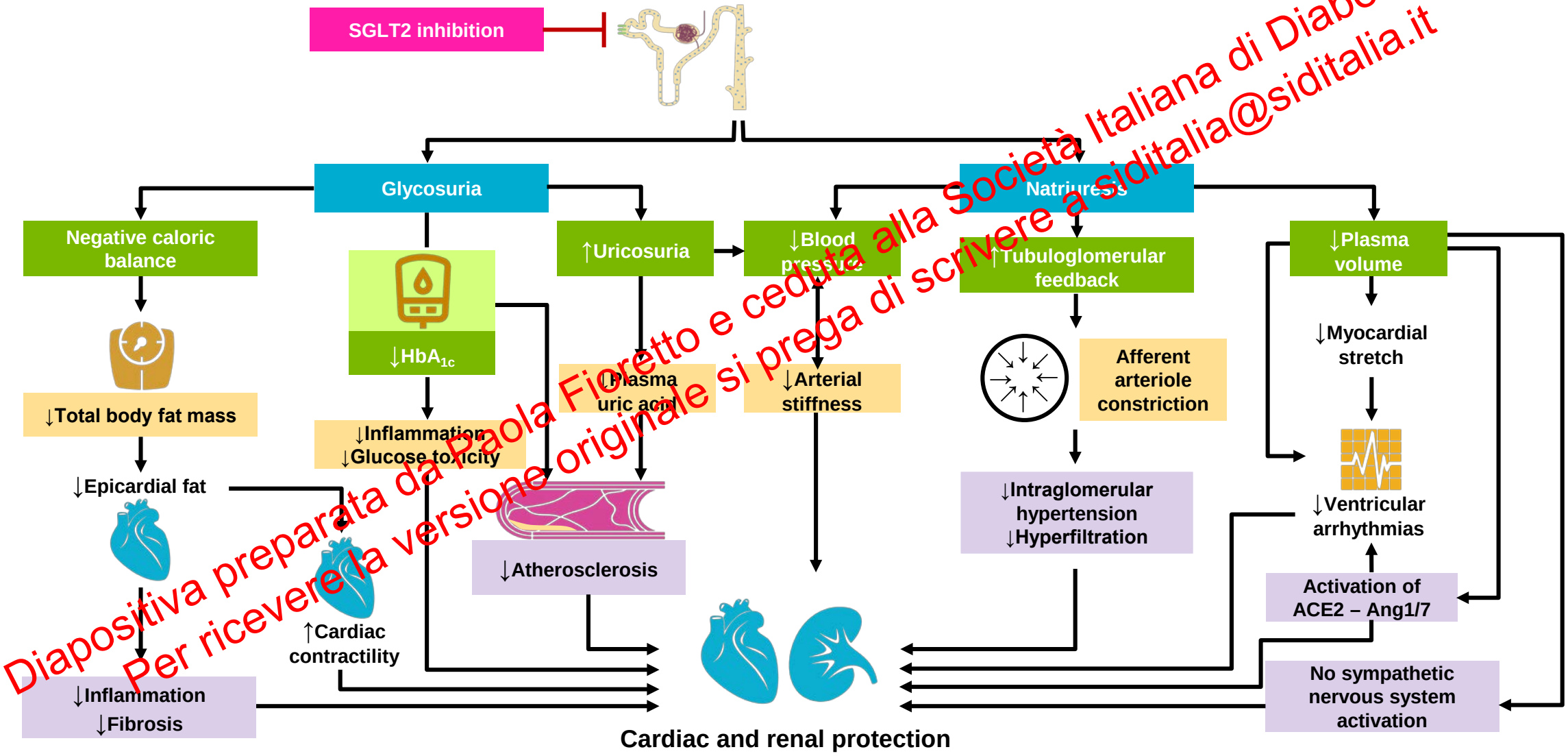
# SGLT2 and RAAS inhibition






RAAS, renin-angiotensin-aldosterone inhibitor; SGLT2, sodium–glucose co-transporter 2
Adapted from: Cherney D *et al. Circulation* 2014;129:587

# Possible mechanisms responsible for cardiovascular and renal protection with SGLT2 inhibition

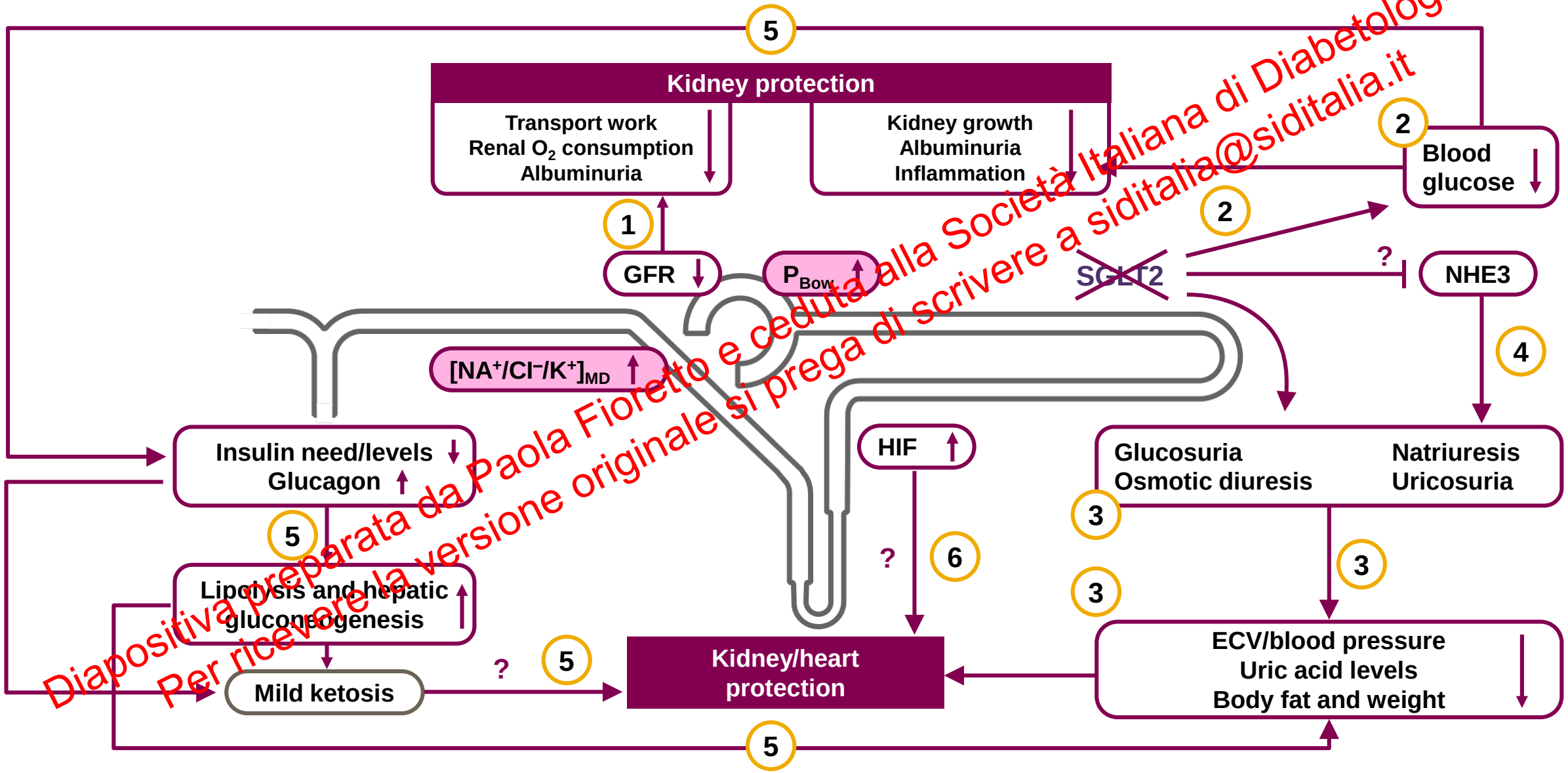





ACE, angiotensin-converting enzyme; $HbA_{1c}$, glycated haemoglobin; SGLT2, sodium–glucose co-transporter 2

Heerpsink HJ, et al. *Circulation* 2016;134:752–772

# Additional mechanisms of SGLT2i-mediated organ protection

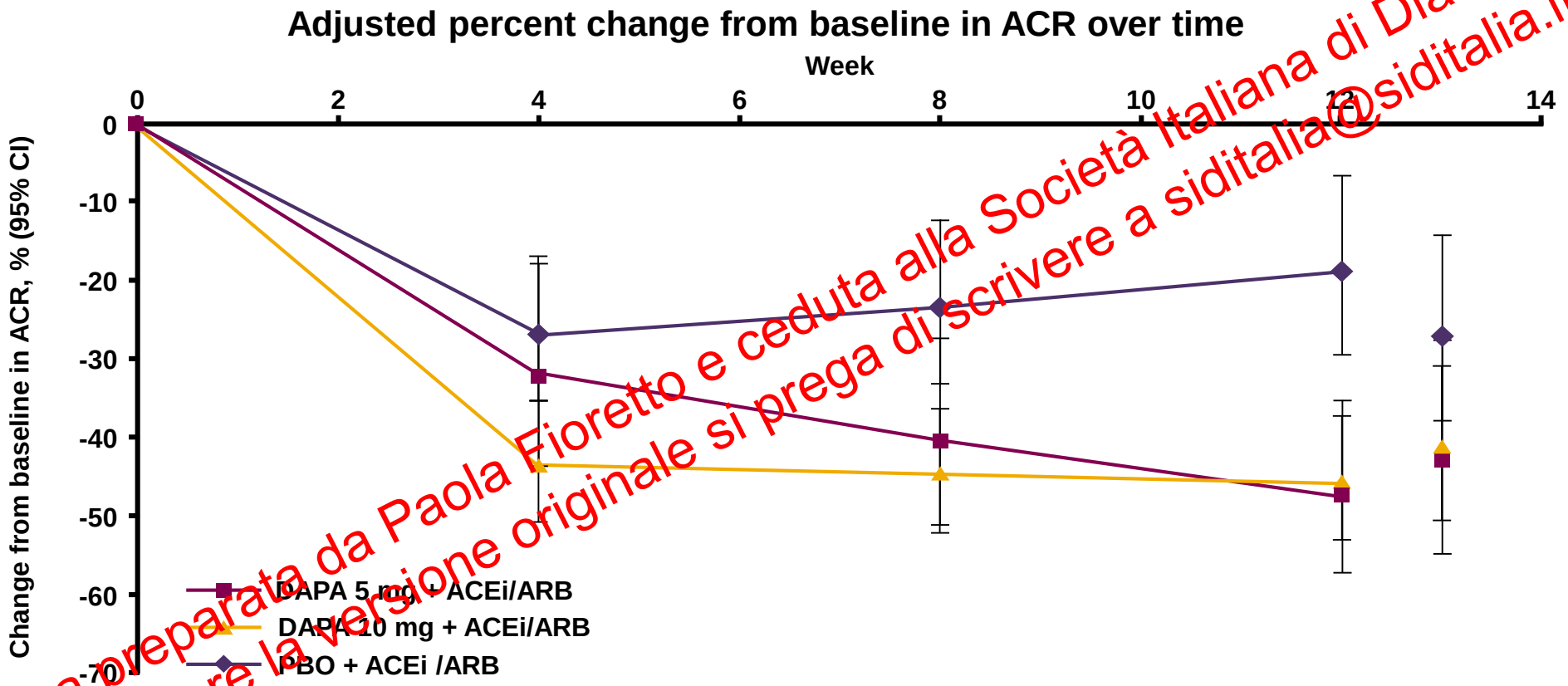





ECV, extracellular volume; GFR, glomerular filtration rate; HIF, hypoxia-inducible factor; MD, macula densa; NHE, sodium-hydrogen exchanger; $P_{Bow}$, hydrostatic pressure in Bowman's capsule

Vallon V, et al. *Diabetologia* 2017;60:215–225

# SGLT2 inhibitors lowered albuminuria in patients with Type 2 diabetes and hypertension



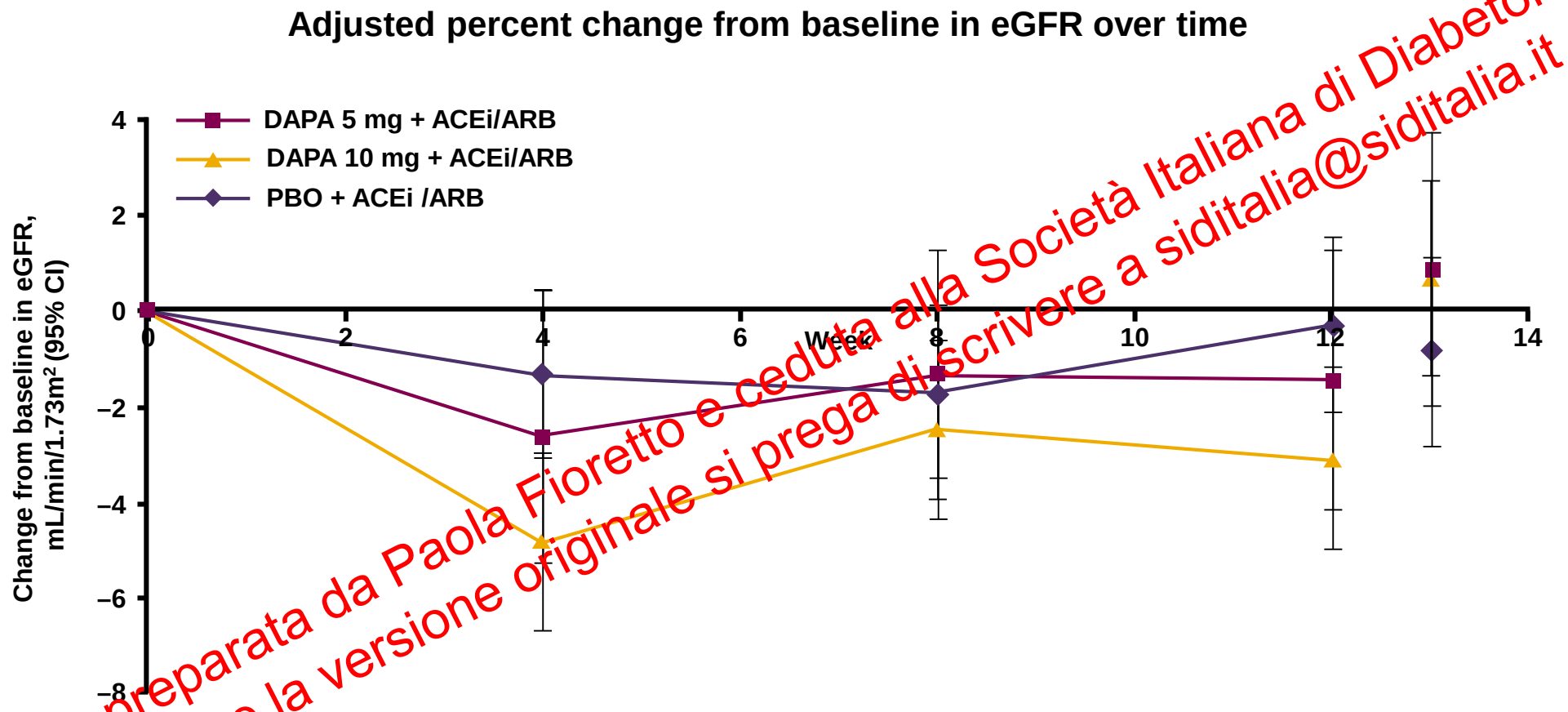

| n | Baseline | Week 4 | Week 8 | Week 12 | Follow-up (Week 13) |
|---|---|---|---|---|---|
| DAPA 5 mg + ACEi/ARB | 85 | 81 | 79 | 73 | 74 |
| DAPA 10 mg + ACEi/ARB | 165 | 160 | 124 | 153 | 144 |
| PBO + ACEi /ARB | 185 | 182 | 172 | 163 | 158 |



ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin:creatinine ratio; ARB, angiotensin II receptor blocker; DAPA, dapagliflozin; PBO, placebo; SGLT2, sodium–glucose co-transporter 2

Lambers Heerspink Y, et al. *Diabetes Obes Metab* 2016;18:590–597

# SGLT2 inhibitors are associated with an initial reduction in eGFR




| n | Baseline | Week 8 | Week 12 | Follow-up (Week 13) |
|---|---|---|---|---|
| DAPA 5 mg + ACEi/ARB | 85 | 79 | 74 | 74 |
| DAPA 10 mg + ACEi/ARB | 165 | 154 | 153 | 147 |
| PBO + ACEi /ARB | 186 | 172 | 163 | 157 |

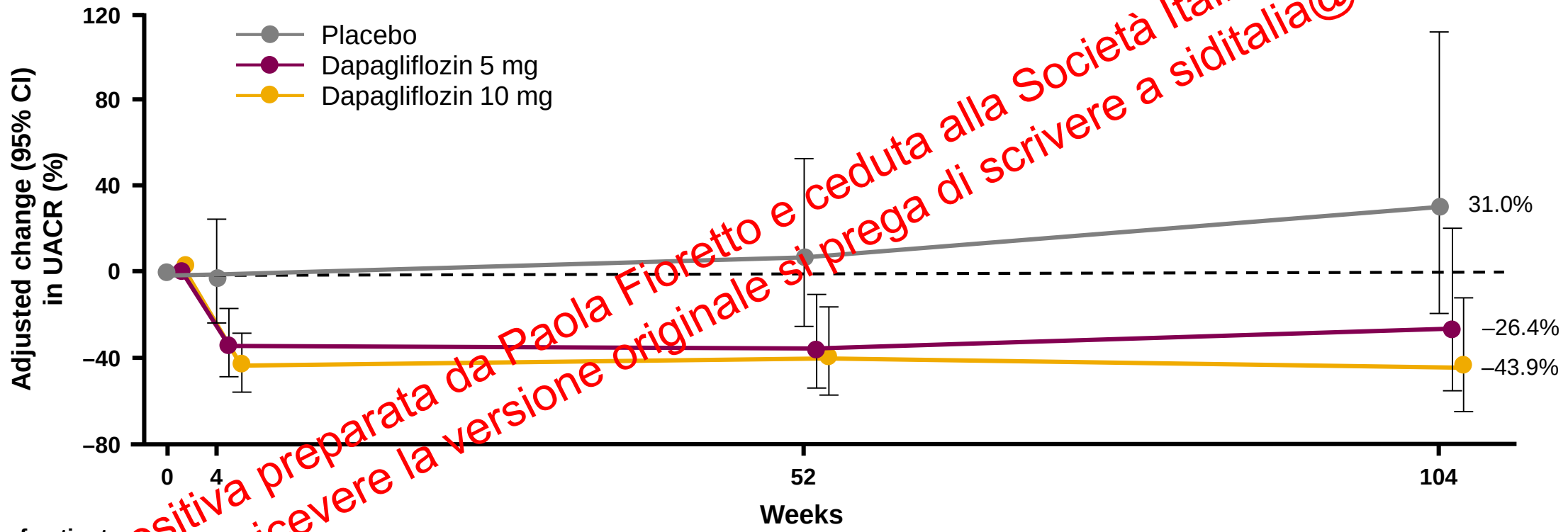


ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter 2

Lambers Heerspink Y, et al. *Diabetes Obes Metab* 2016;18:590–597

# Effects of dapagliflozin on UACR in patients with CKD stage 3

- This post-hoc analysis included 166 patients with CKD stage 3 and increased albuminuria (≥3.4 mg/mmol)



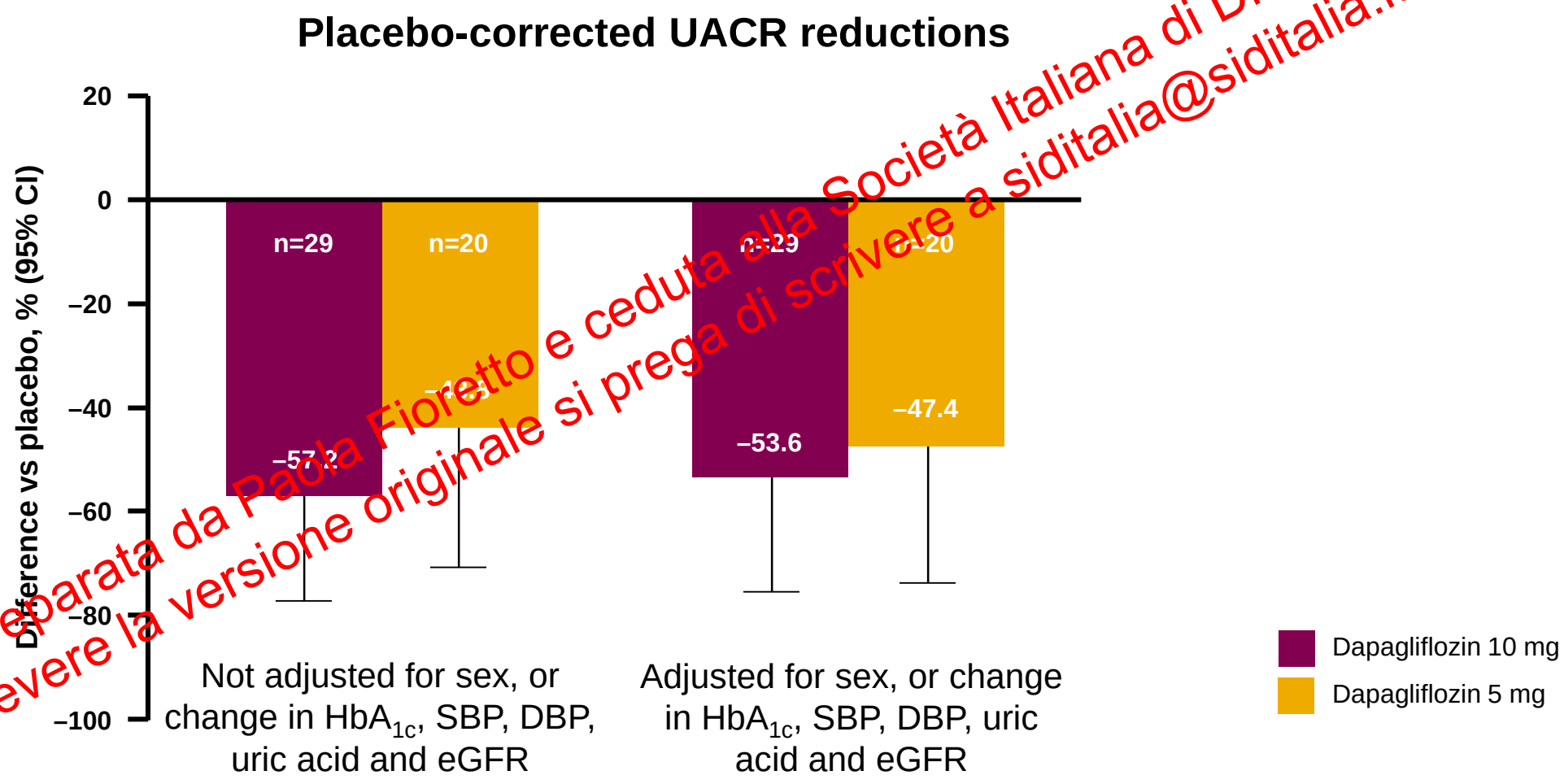

| No. of patients | | | | |
|---|---|---|---|---|
| Placebo | 56 | 49 | 31 | 25 |
| DAPA 5 mg | 53 | 50 | 39 | 20 |
| DAPA 10 mg | 56 | 52 | 40 | 29 |



CI, confidence interval; CKD, chronic kidney disease; DAPA, dapagliflozin; PBO, placebo; UACR, urine albumin:creatinine ratio

Fioretto P, et al. *Diabetologia* 2016;59:2036–2039

# Effects of dapagliflozin on UACR in patients with CKD stage 3

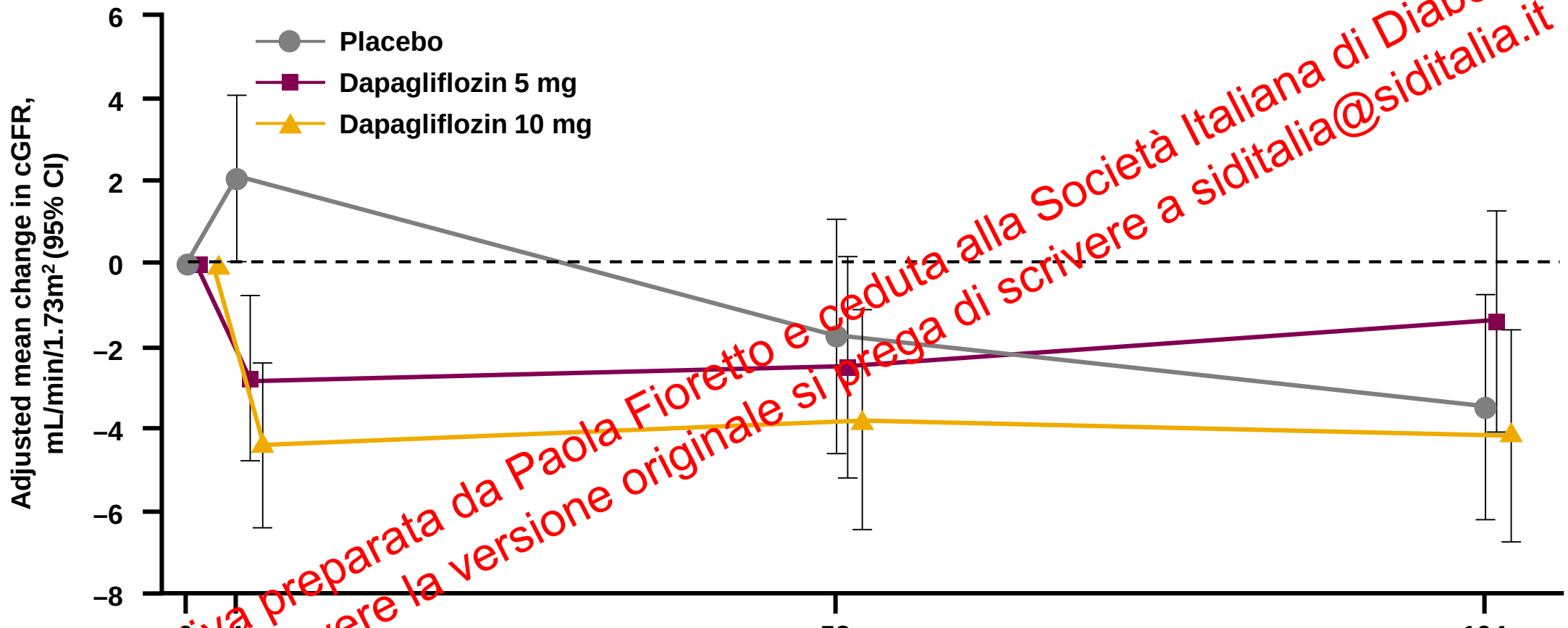





CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; DBP, diastolic blood pressure; $HbA_{1c}$, glycated haemoglobin; UACR, urinary albumin:creatinine ratio

Fioretto P, et al. *Diabetologia* 2016;59:2036–2039

# Effects of dapagliflozin on eGFR in patients with CKD stage 3



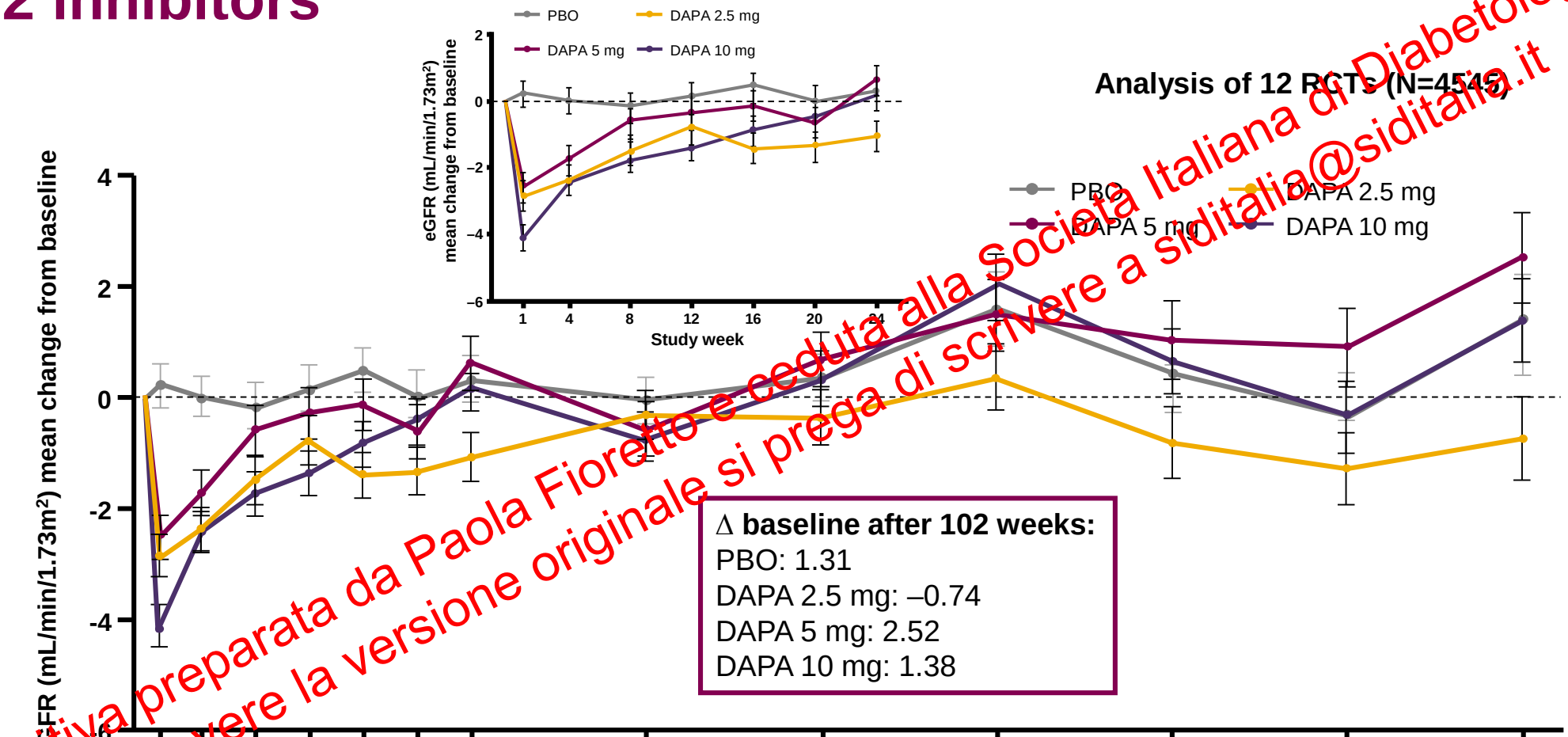

| No. of patients | | | | | BL eGFR, mL/min/1.73 m² |
|---|---|---|---|---|---|
| Placebo | 56 | 50 | 31 | 25 | 45.1 |
| DAPA 5 mg | 53 | 52 | 39 | 20 | 43.9 |
| DAPA 10 mg | 56 | 52 | 41 | 30 | 44.1 |



BL, baseline; CI, confidence interval; CKD, chronic kidney disease; DAPA, dapaglilfozin; eGFR, estimated glomerular filtration rate

Fioretto P, et al. *Diabetologia* 2016;59:2036–2039

# There was a temporary initial reduction in eGFR with SGLT2 inhibitors





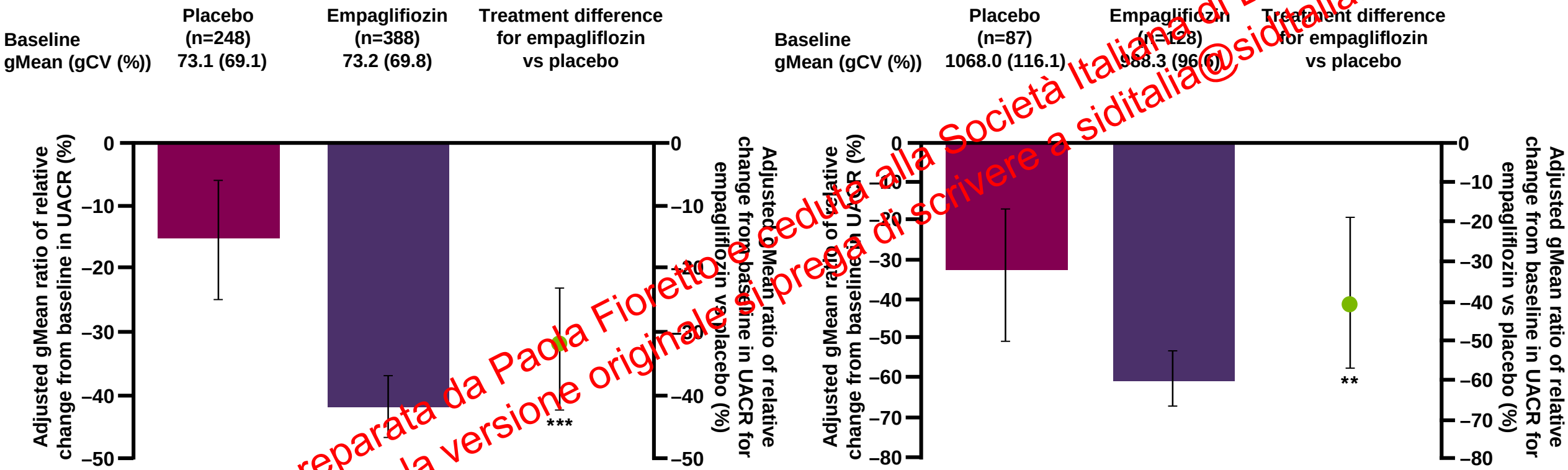

| No. of patients | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PBO | 683 | 666 | 649 | 626 | 616 | 598 | 598 | 578 | 546 | 266 | 219 | 148 | 107 |
| DAPA 2.5 mg | 623 | 611 | 593 | 583 | 574 | 561 | 555 | 548 | 525 | 349 | 284 | 199 | 136 |
| DAPA 5 mg | 748 | 740 | 714 | 705 | 696 | 681 | 669 | 659 | 628 | 354 | 288 | 208 | 159 |
| DAPA 10 mg | 744 | 740 | 728 | 717 | 706 | 681 | 676 | 670 | 646 | 367 | 310 | 220 | 166 |

DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; PBO, placebo; RCT, randomised controlled trial; SGLT2, sodium–glucose co-transporter 2

Kohan D, et al. *J Nephrol* 2016;29:391–400

# Effects of Empagliflozin on Albuminuria

## Mean ratio of relative change from baseline in UACR

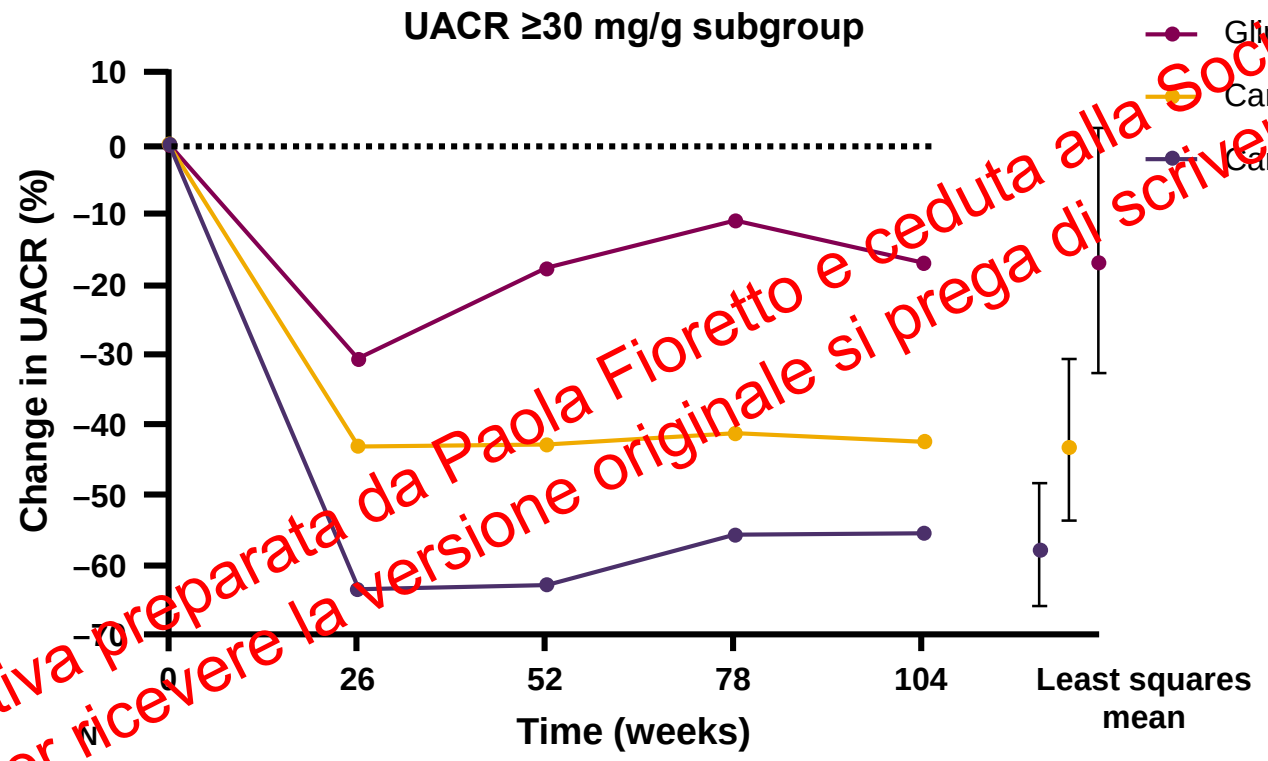





***P*<0.01; ****P*<0.001
CV, cardiovascular; gCV, geometric coefficient of variation; gMean, geometric mean; UACR, urine albumin:creatinine ratio
Cherney D, et al. *Diabetologia* 2016;59:1860–1870

# Effect of canagliflozin vs glimepiride on UACR

- Patients with Type 2 diabetes (N=1450) treated with metformin were given either glimepiride or canagliflozin




| N | | | | | |
|---|---|---|---|---|---|
| Glimepiride | 65 | 65 | 57 | 52 | 45 |
| Canagliflozin 100 mg | 68 | 68 | 64 | 56 | 52 |
| Canagliflozin 300 mg | 66 | 66 | 63 | 52 | 45 |

**Changes in UACR relative to glimepiride**

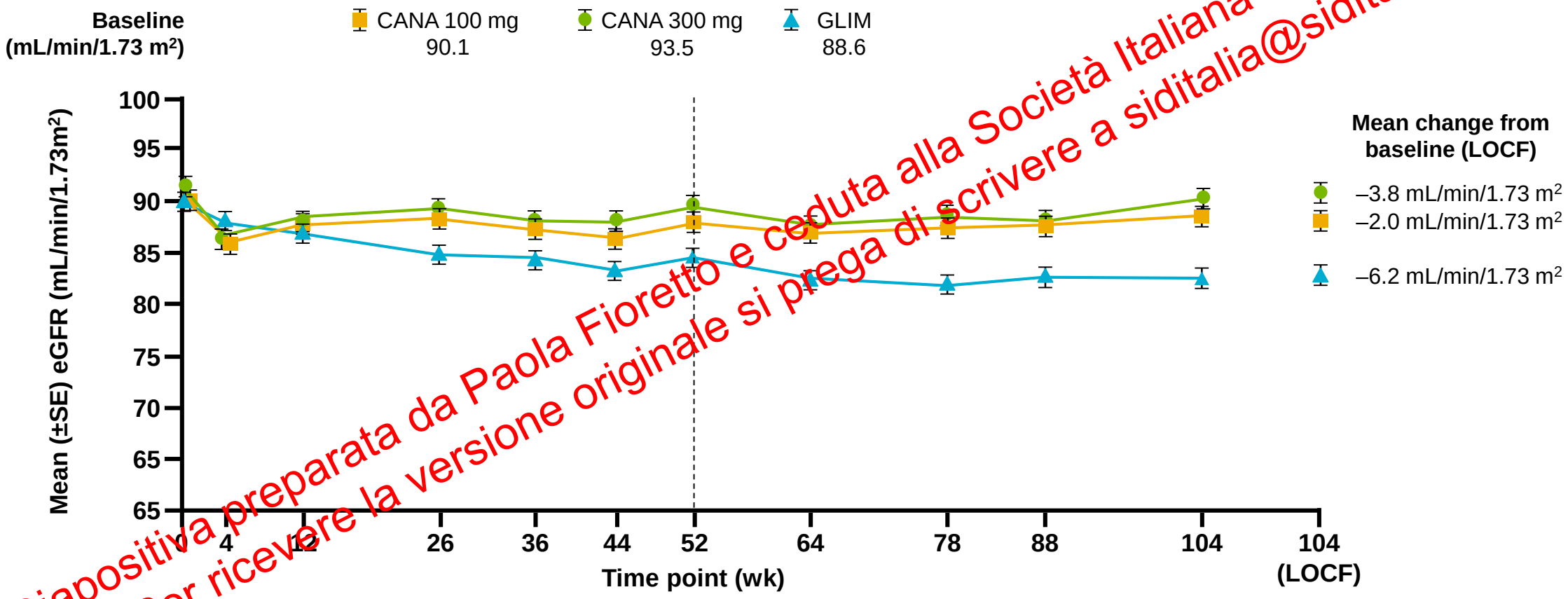
| | % change (95% CI) | *P* value |
|---|---|---|
| CANA 100 mg vs glimepiride | –37.7% (8.6, 48.9) | 0.01 |
| CANA 300 mg vs glimepiride | –49.3 (31.9, 62.2) | <0.001 |

BL, baseline; $HbA_{1c}$, glycated haemoglobin; UACR, urine albumin:creatinine ratio

Heerspink HJ, et al. *J Am Soc Nephrol* 2016;28:368–375

# Mean eGFR in Patients with T2DM Treated with Canagliflozin

**Patients with T2DM were treated with canagliflozin (100 or 300 mg) or glimepiride (N=1,450)**



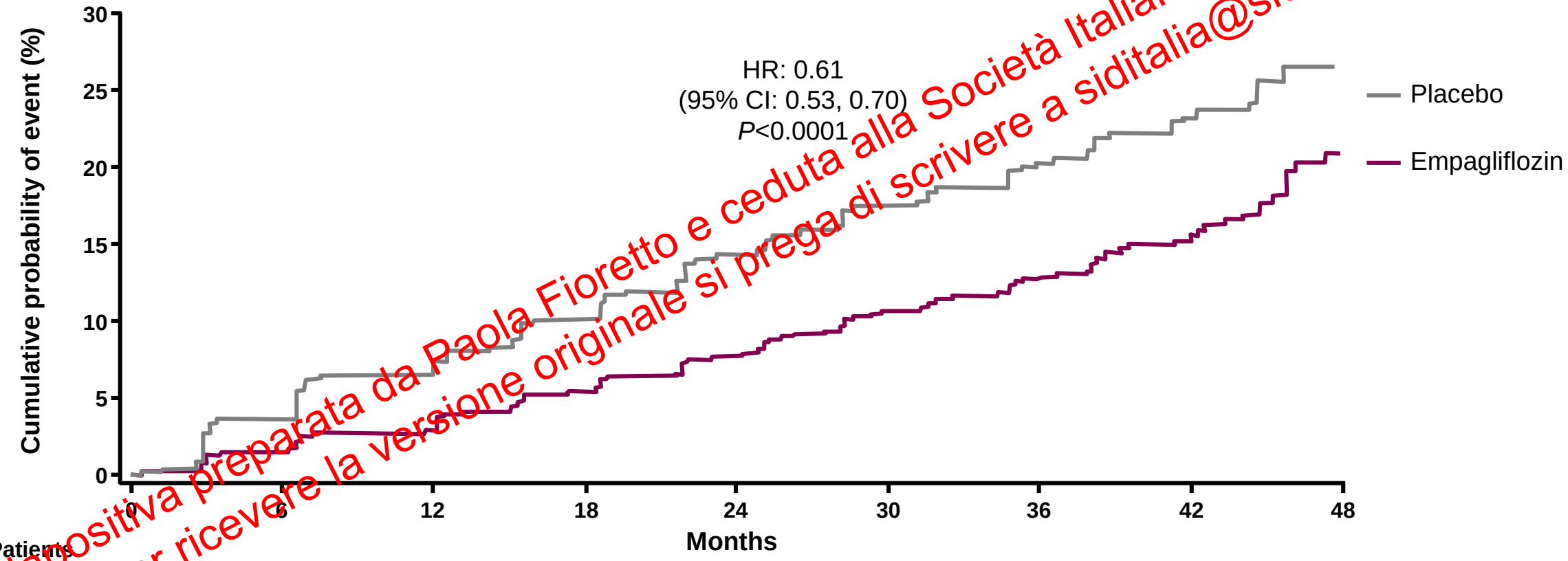



CANA, canagliflozin; eGFR, estimated glomerular filtration rate; GLIM, glimepiride; LOCF, last observation carried forward; SE, standard error; T2DM, type 2 diabetes mellitus; wk, week

Leiter LA, et al. *Diabetes Care* 2015;38:355–364

# EMPA-REG: New-onset or worsening of nephropathy

- Incident or worsening nephropathy occurred in 12.7% and 18.8% of patients in the empagliflozin and placebo groups, respectively; a significant relative risk reduction of 39%



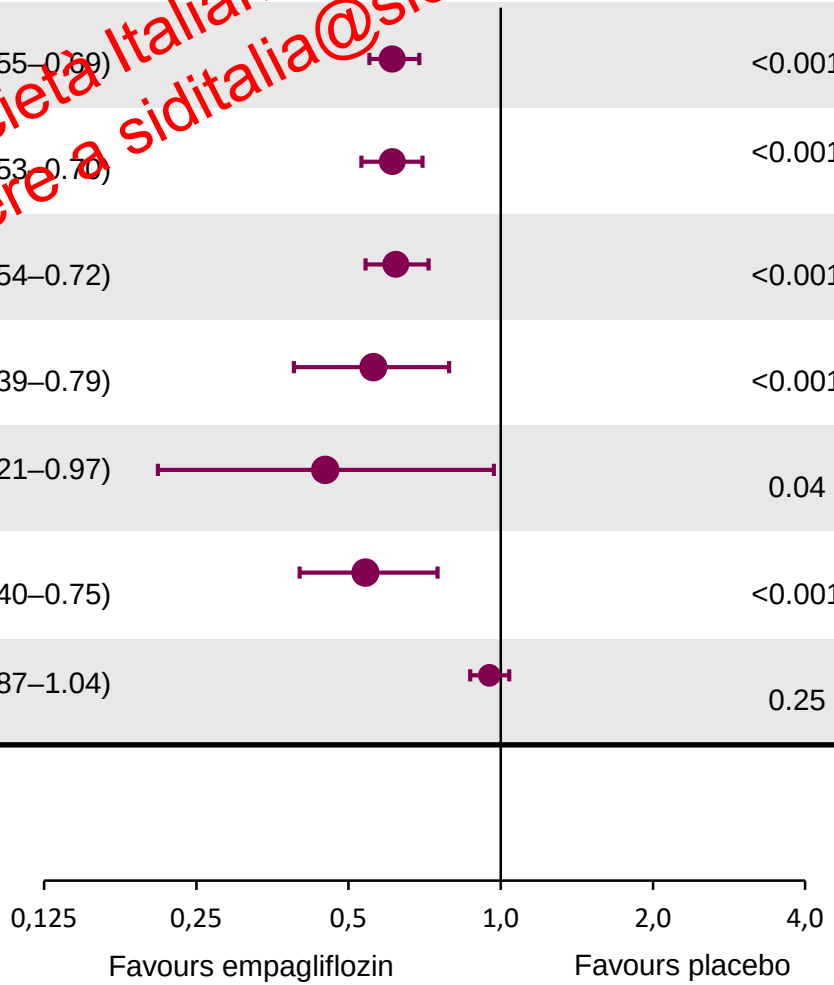

| Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4124 | 3994 | 3848 | 3669 | 3171 | 2279 | 1887 | 1219 | 290 |
| Placebo | 2061 | 1946 | 1836 | 1703 | 1433 | 1016 | 833 | 521 | 106 |



CI, confidence interval; HR, hazard ratio
Wanner C, et al. *N Engl J Med* 2016;375:323–334

# EMPA-REG: Renal outcomes

| | Empagliflozin | | Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | no. with event/ analysed (%) | rate/1000 pt-yr | no. with event/ analysed (%) | rate/1000 pt-yr | HR (95% CI) | HR (95% CI) | *P* value |
| Incident or worsening nephropathy or CV death | 675/4170 (16.2) | 60.7 | 497/2102 (23.6) | 95.9 | 0.61 (0.55–0.69) | | <0.001 |
| Incident or worsening nephropathy | 525/4124 (12.7) | 47.8 | 388/2061 (18.8) | 76.0 | 0.61 (0.53–0.70) | | <0.001 |
| Progression to macroalbuminuria | 459/4091 (11.2) | 41.8 | 330/2033 (16.2) | 64.9 | 0.62 (0.54–0.72) | | <0.001 |
| Doubling of serum creatinine | 70/4645 (1.5) | 5.5 | 60/2323 (2.6) | 9.7 | 0.56 (0.39–0.79) | | <0.001 |
| Initiation of renal replacement therapy | 13/4687 (0.3) | 1.0 | 14/2333 (0.6) | 2.1 | 0.45 (0.21–0.97) | | 0.04 |
| Doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease | 81/4645 (1.7) | 6.3 | 71/2323 (3.1) | 11.5 | 0.54 (0.40–0.75) | | <0.001 |
| Incident albuminuria in patients with normoalbuminuria at baseline | 1430/2779 (51.5) | 252.5 | 703/1374 (51.2) | 266.0 | 0.95 (0.87–1.04) | | 0.25 |



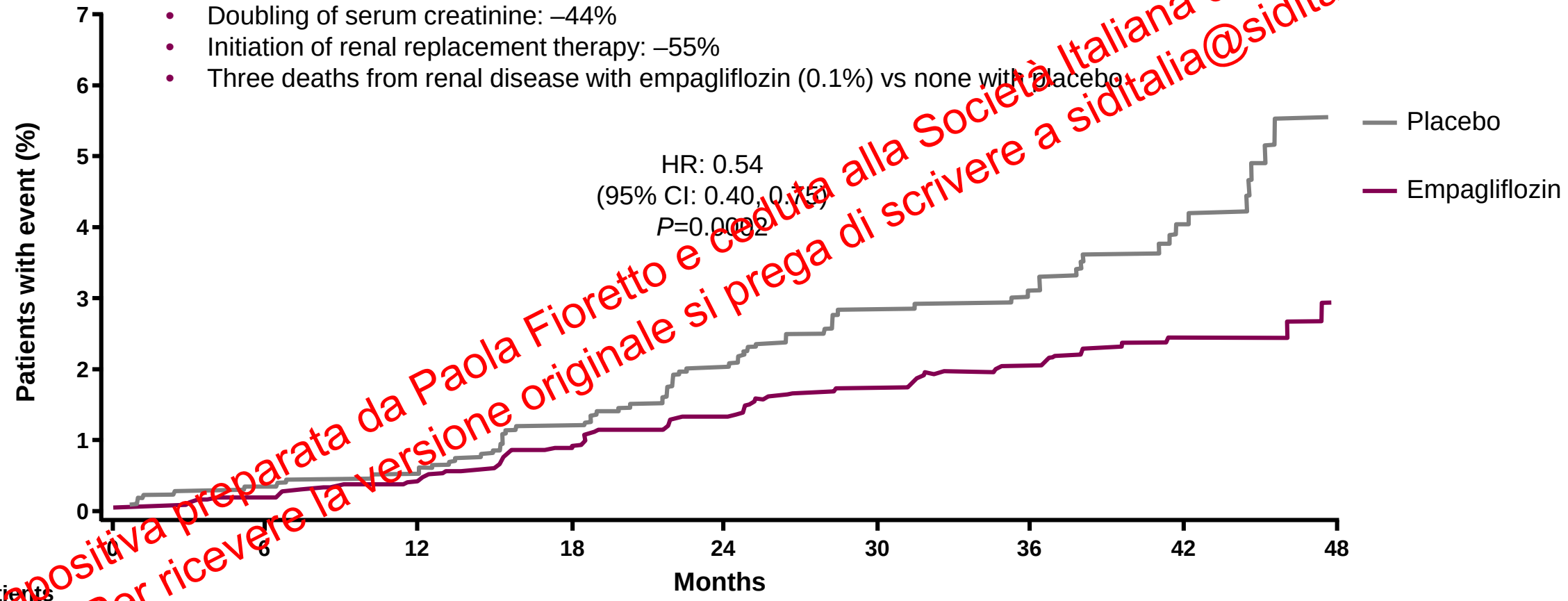



CI, confidence interval; CV, cardiovascular; HR, hazard ratio
Wanner C, et al. N Engl J Med 2016;375:323–334

# EMPA-REG: Composite of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease

**Individual relative risk reductions for empagliflozin vs placebo:**

- Doubling of serum creatinine: –44%
- Initiation of renal replacement therapy: –55%
- Three deaths from renal disease with empagliflozin (0.1%) vs none with placebo




| No. of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4645 | 4500 | 4377 | 4241 | 3729 | 2715 | 2280 | 1496 | 360 |
| Placebo | 2323 | 2229 | 2146 | 2047 | 1771 | 1289 | 1079 | 680 | 144 |

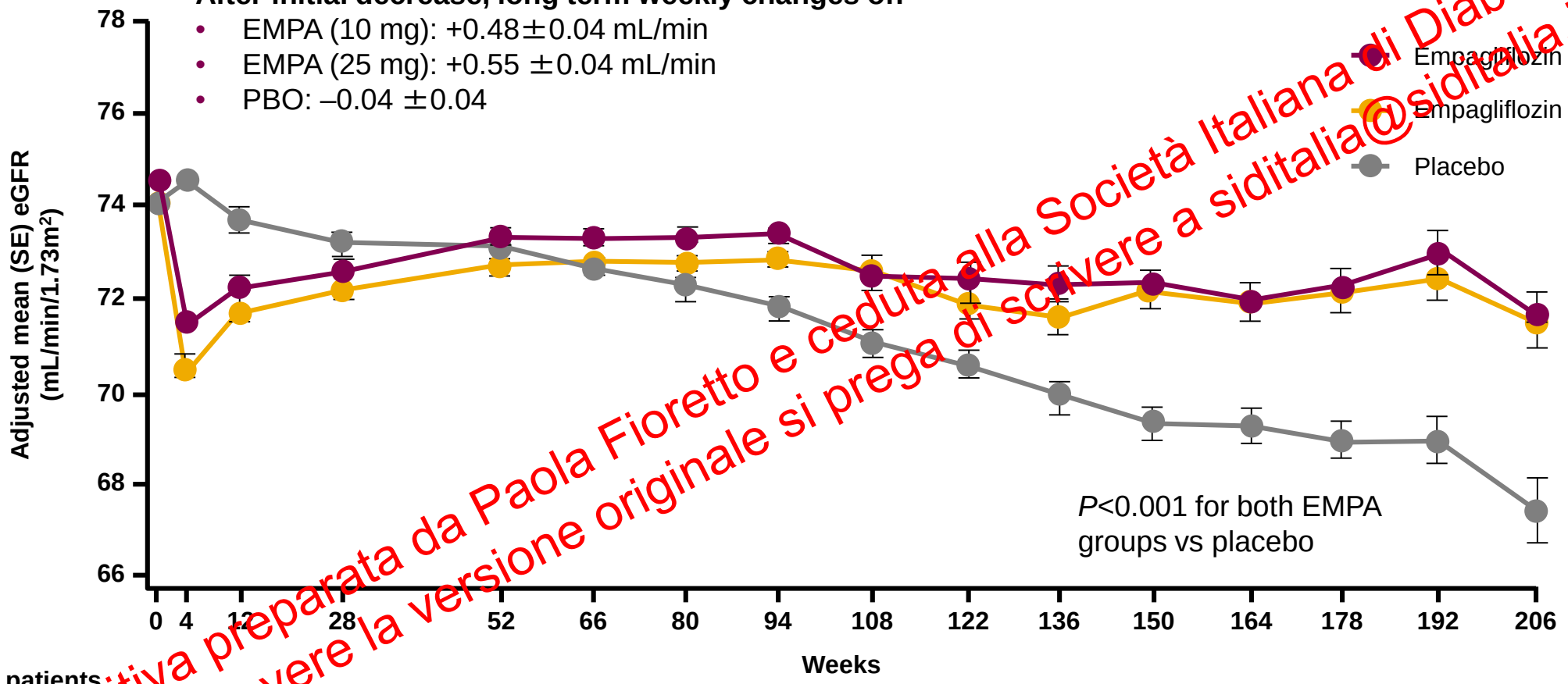
CI, confidence interval; HR, hazard ratio

Wanner C, et al. *N Engl J Med* 2016;375:323–334

# EMPA-REG: Change in eGFR over time

**After initial decrease, long term weekly changes of:**

- EMPA (10 mg): +0.48±0.04 mL/min
- EMPA (25 mg): +0.55 ±0.04 mL/min
- PBO: –0.04 ±0.04




**No. of patients**

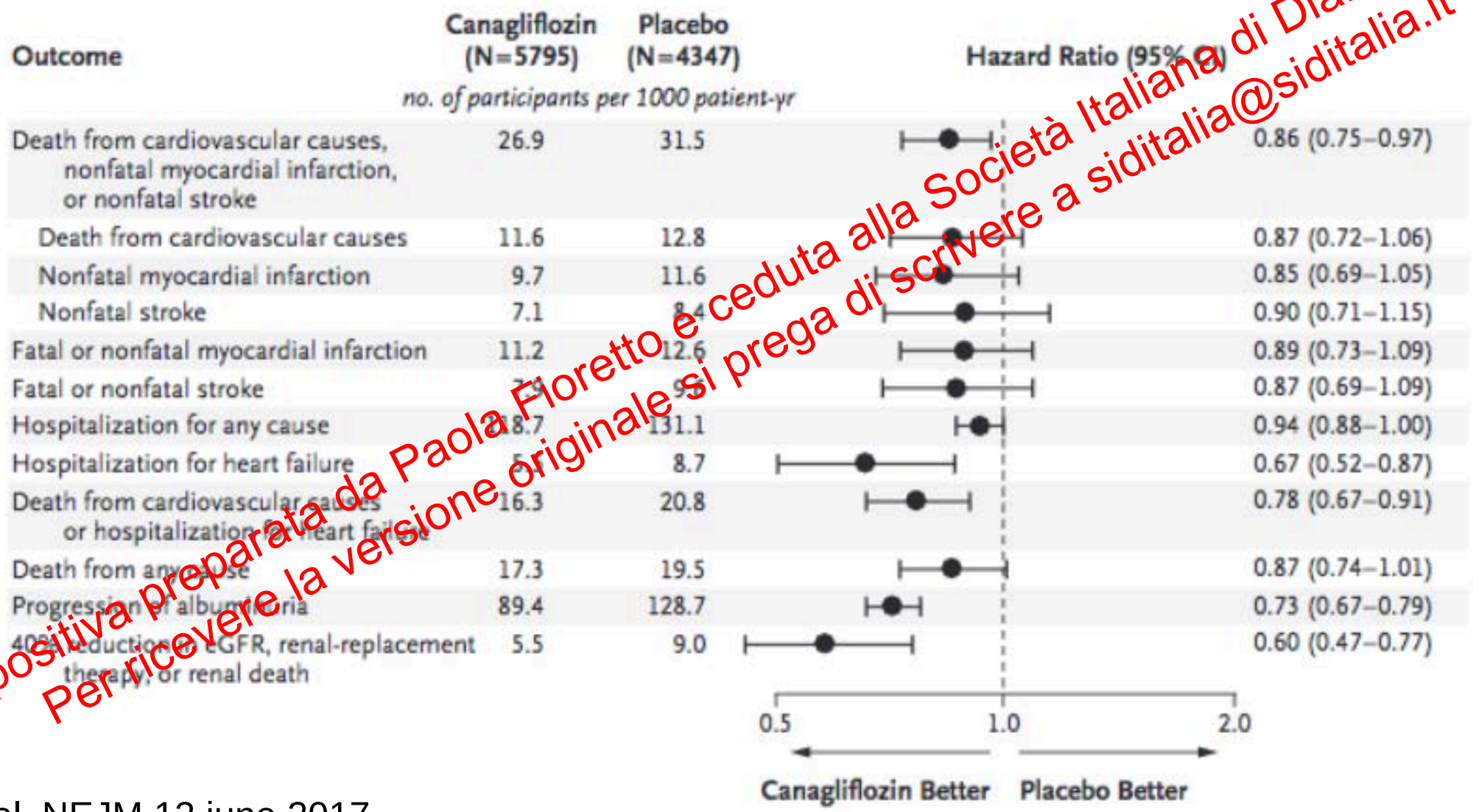
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2323 | 2295 | 2267 | 2205 | 2121 | 2064 | 1927 | 1981 | 1763 | 1479 | 1262 | 1123 | 977 | 731 | 448 | 171 |
| EMPA 10 mg | 2322 | 2290 | 2264 | 2235 | 2161 | 2114 | 2012 | 2064 | 1839 | 1540 | 1314 | 1180 | 1024 | 785 | 513 | 193 |
| EMPA 25 mg | 2322 | 2288 | 2269 | 2216 | 2156 | 2111 | 2006 | 2067 | 1871 | 1563 | 1340 | 1207 | 1063 | 838 | 524 | 216 |



eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; PBO, placebo; SE, standard error

Wanner C, et al. *N Engl J Med* 2016;375:323–334

# CANVAS: cardiovascular and renal endpoints



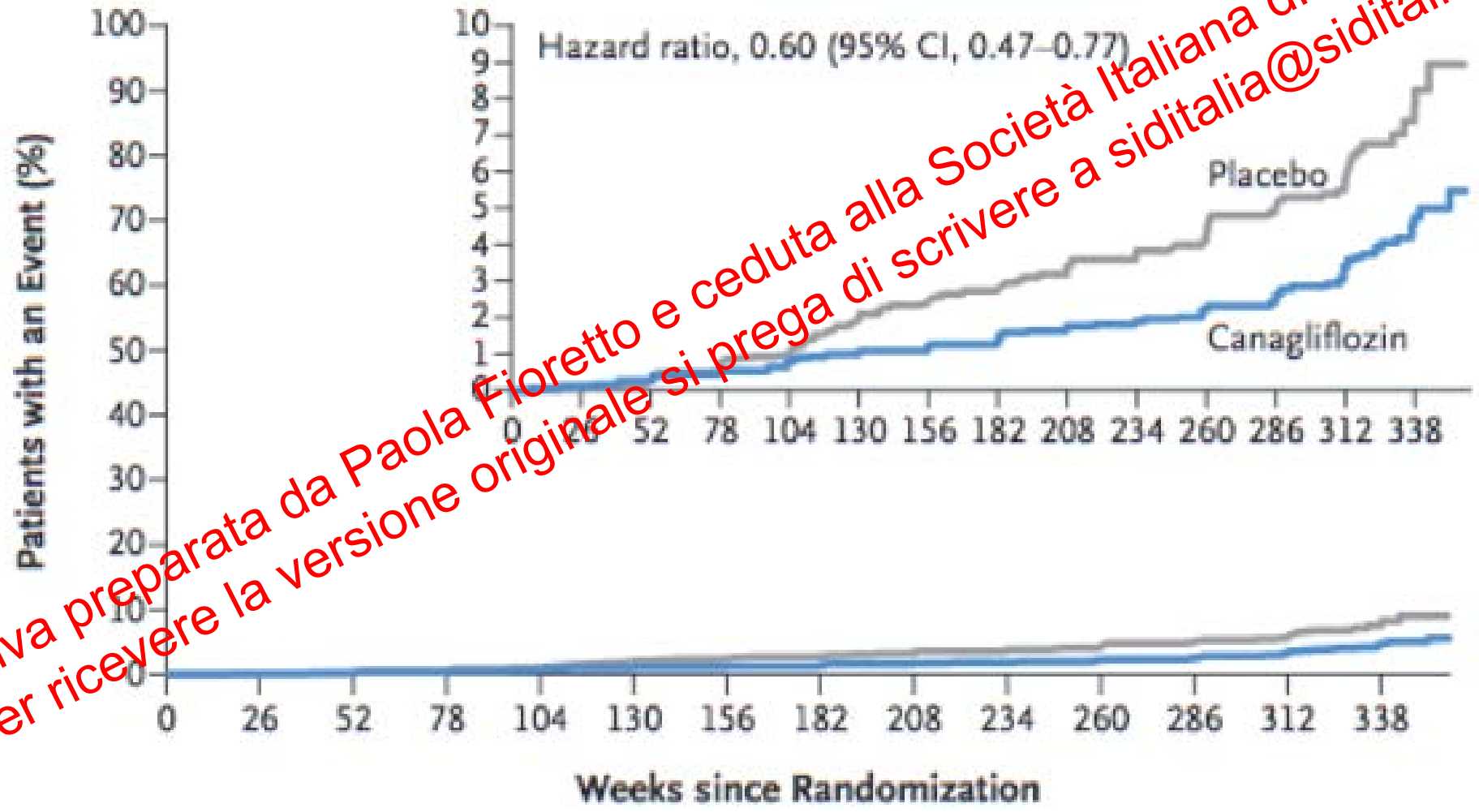
| Outcome | Canagliflozin (N=5795) | Placebo (N=4347) | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of participants per 1000 patient-yr* | | |
| Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | 26.9 | 31.5 | 0.86 (0.75–0.97) |
| Death from cardiovascular causes | 11.6 | 12.8 | 0.87 (0.72–1.06) |
| Nonfatal myocardial infarction | 9.7 | 11.6 | 0.85 (0.69–1.05) |
| Nonfatal stroke | 7.1 | 8.4 | 0.90 (0.71–1.15) |
| Fatal or nonfatal myocardial infarction | 11.2 | 12.6 | 0.89 (0.73–1.09) |
| Fatal or nonfatal stroke | 7.9 | 9.5 | 0.87 (0.69–1.09) |
| Hospitalization for any cause | 118.7 | 131.1 | 0.94 (0.88–1.00) |
| Hospitalization for heart failure | 5.5 | 8.7 | 0.67 (0.52–0.87) |
| Death from cardiovascular causes or hospitalization for heart failure | 16.3 | 20.8 | 0.78 (0.67–0.91) |
| Death from any cause | 17.3 | 19.5 | 0.87 (0.74–1.01) |
| Progression of albuminuria | 89.4 | 128.7 | 0.73 (0.67–0.79) |
| 40% reduction in eGFR, renal-replacement therapy, or renal death | 5.5 | 9.0 | 0.60 (0.47–0.77) |





Neal B et al, NEJM 12 june 2017

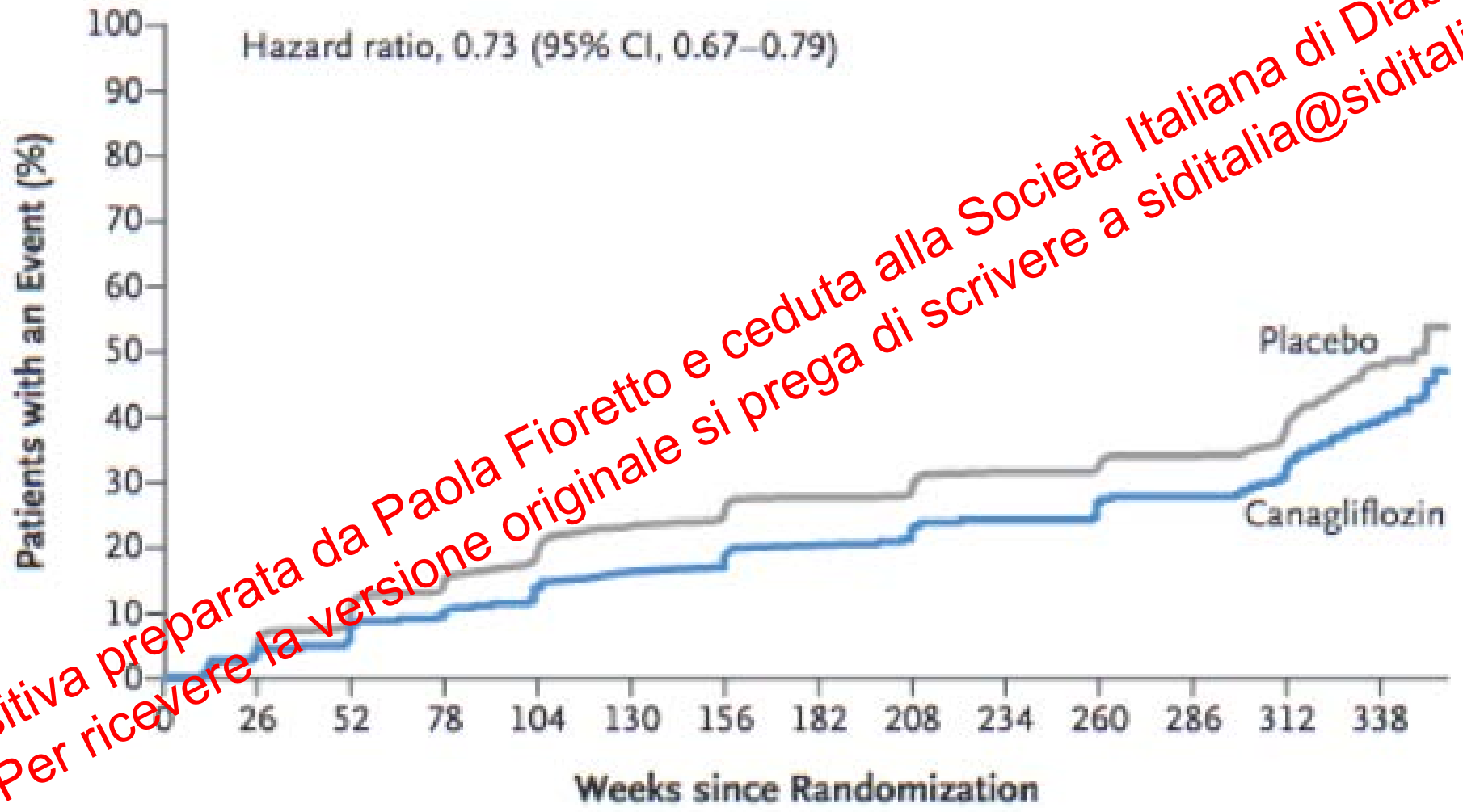
# CANVAS: composite of 40% reduction in eGFR, ESRD, death from renal causes






Neal B et al, NEJM 12 june 2017

# CANVAS: progression of albuminuria






Neal B et al, NEJM 12 june 2017

# Cardiovascular outcome trials with SGLT2 Inhibitors that will generate data on renal endpoints

| Trial | Patient cohorts | N | Endpoints |
|---|---|---|---|
| CANVAS-R[1] | Canagliflozin / placebo 1:1 | 5813 | Primary: Progression of albuminuria<br>Secondary: Regression of albuminuria, eGFR, UACR |
| CANVAS[2] | Canagliflozin / placebo 2:1 | 4331 | Primary: MACE (CV death, non-fatal MI or non-fatal stroke)<br>Secondary: Fasting insulin secretion, progression of albuminuria, blood glucose reduction |
| DECLARE[3] | Dapagliflozin / placebo 1:1 | 17,150 | Primary: MACE non-inferiority and then superiority of co-primary endpoints of MACE and hospitalisation for heart failure or CV death<br>Secondary: all-cause mortality, renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m$^2$ and/or ESRD and/or renal or CV death) |
| CREDENCE[4] | Canagliflozin / placebo 1:1 | 4200 | Primary: Composite renal and CV endpoint (ESRD, doubling of serum creatinine, renal or CV death)<br>Secondary: 5P-MACE (CV death, non-fatal MI or non-fatal stroke, hospitalisation for CHF, hospitalisation for unstable angina), renal composite endpoint (ESRD, doubling of serum creatinine, renal death), all-cause mortality |




CHF, congestive heart failure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio

1. NCT01989754. Available at https://clinicaltrials.gov/ct2/show/NCT01989754; 2. NCT01032629. Available at https://clinicaltrials.gov/ct2/show/NCT01032629; 3. NCT01730534. Available at https://clinicaltrials.gov/ct2/show/NCT01730534; 4. NCT02065791. Available at https://clinicaltrials.gov/ct2/show/NCT02065791

# Summary

- Intensive glycaemic control is associated with improved CKD outcomes; however, multifactorial intervention is necessary to prevent its progression
- Newer anthyperglycaemic classes have been demonstrated to nephroprotective effects:
- SGLT2i: ↓ intraglomerular hypertension
  - Reduce eGFR loss and albuminuria in Type 2 diabetes
- Incretin therapies – no apparent TGFB effect
  - Reduce albuminuria in Type 2 diabetes
- Results of several cardiovascular outcomes and dedicated renal endpoint studies to further investigate the potential of newer agents in diabetes and CKD are eagerly anticipated