



Nefropatia diabetica: misure d'intervento e nuovi farmaci

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DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

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Ai sensi dell'art. 76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 02 febbraio 2017 in materia di ECM

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

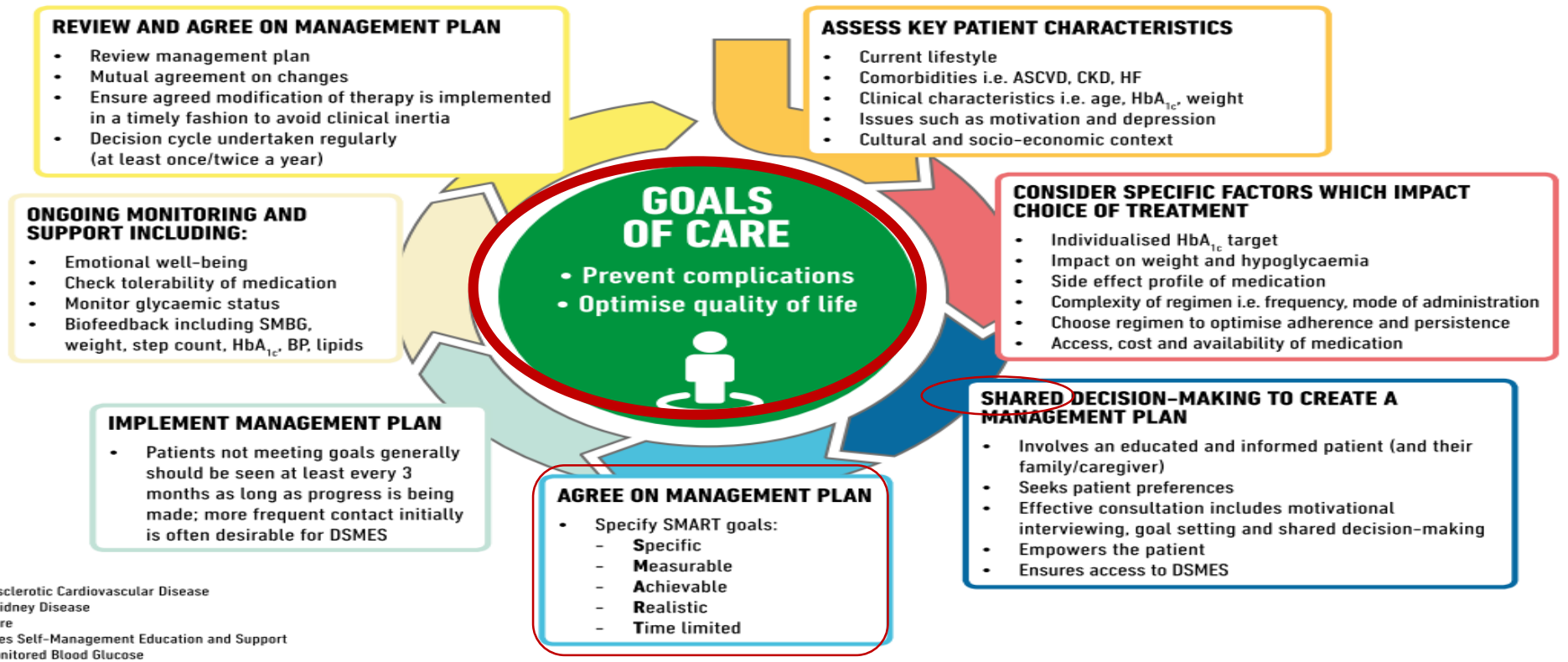
CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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

Sono cambiati gli obiettivi di cura del diabete di tipo 2…

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

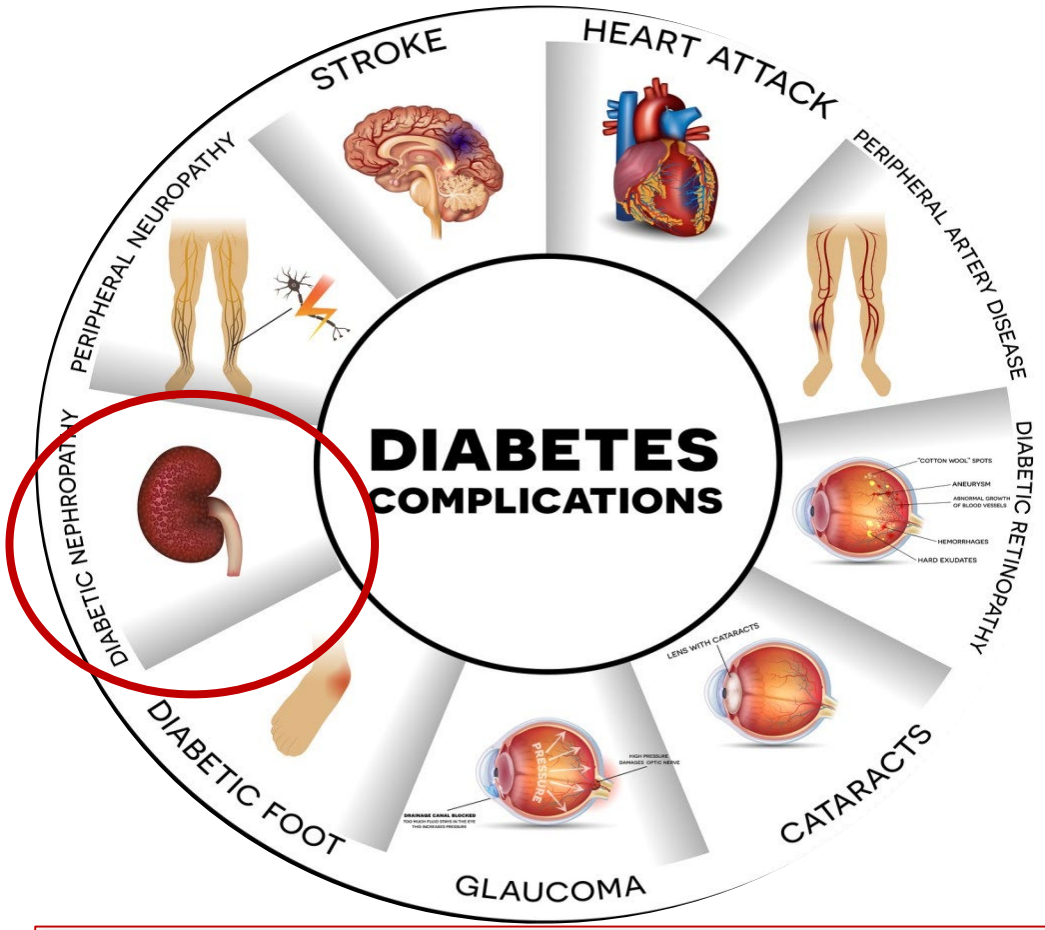


ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes

Diabetologia

✓ Diabetes is expected to double within the next 20 years, with a significant increase in cardiovascular disease and in all the diabetes-related complications that are a major cause of disability, reduced quality of life and premature death



La nefropatia diabetica è tra le più gravi complicanze del diabete per il rischio di progressione verso l'uremia terminale e l'elevata mortalità.

Diabetic kidney disease (DKD), Diabetic Neuropathy (DN) and diabetic retinopathy (DR) are the most common microvascular complications of diabetes

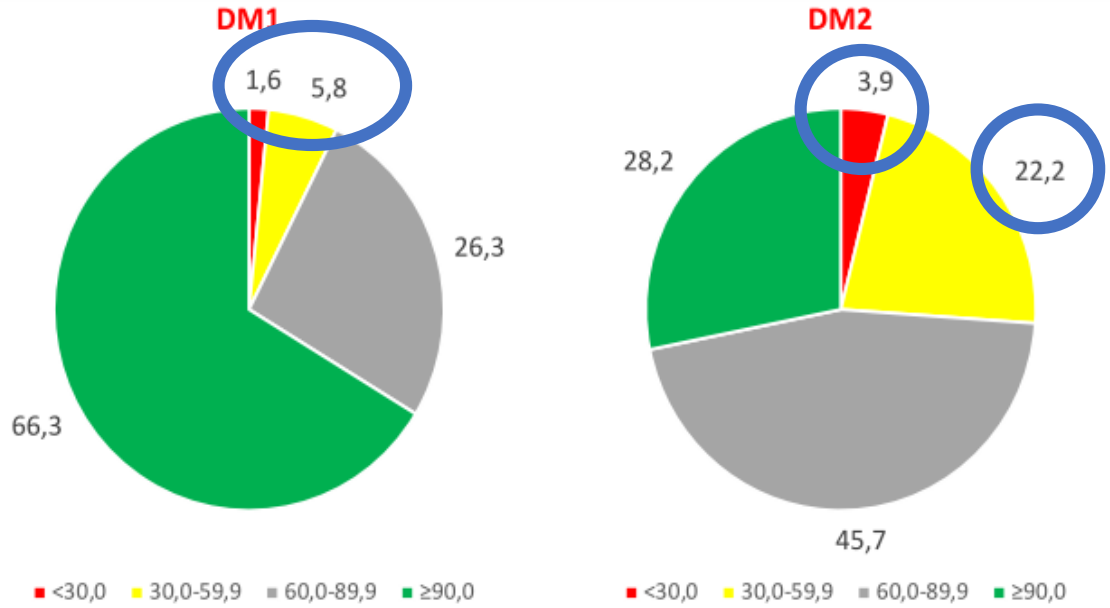
Health Related Quality of Life

Complication	Mean
Mild stroke	0.70
Diabetic neuropathy	0.66
Angina	0.64
DIABETIC NEPHROPATHY	0.64
Amputation	0.55
Diabetic retinopathy	0.53
Blindness	0.38
End-stage renal disease	0.35
Major stroke	0.31

0 = death, 1 = life in perfect health

Huang S et al. Diabetes Care 2007

ANDAMENTO PER CLASSI DI GFR (%)



La quota di pazienti con riduzione del filtrato glomerulare è pari al 7.4% nel DM1 e al 26.1% nel DM2. Piccola ma degna di attenzione la quota di soggetti con netta riduzione del filtrato in entrambi i tipi di diabete.

PREVALENZA DELLA NEFROPATIA DIABETICA NEL DM1 E NEL DM2 IN ITALIA



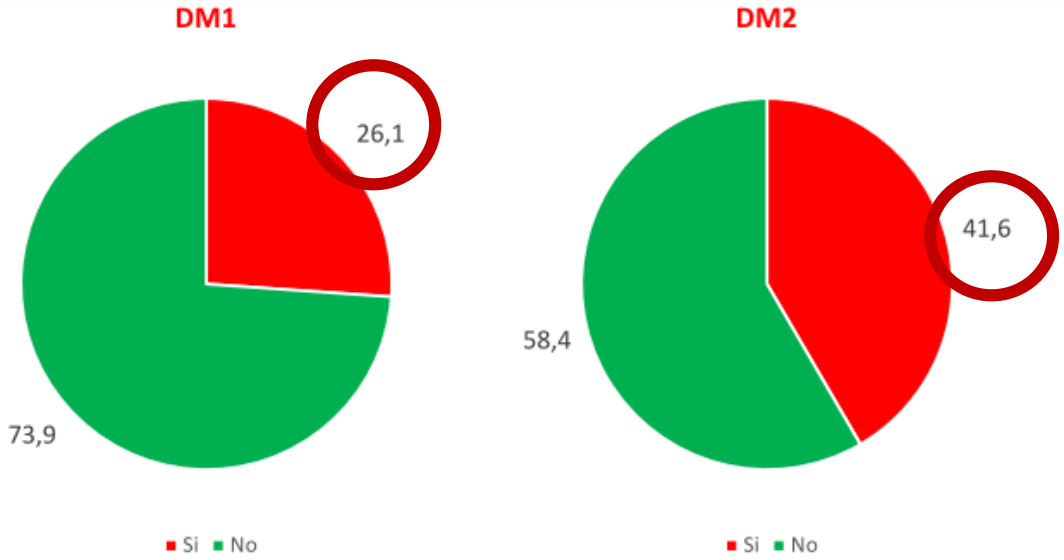
Nel DM2: **26.1%** con GFR<60

Nel DM1: **7,4%** con GFR<60

Nel DM2: **41,6 %** con MAU

Nel DM1: **26,1% %** con MAU

SOGGETTI CON MAU (%)



La micro/macroalbuminuria è risultata avere una prevalenza piuttosto elevata, in quanto riscontrata nel 26.1% dei pazienti monitorati con DM1 e nel 41.6% con DM2.

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

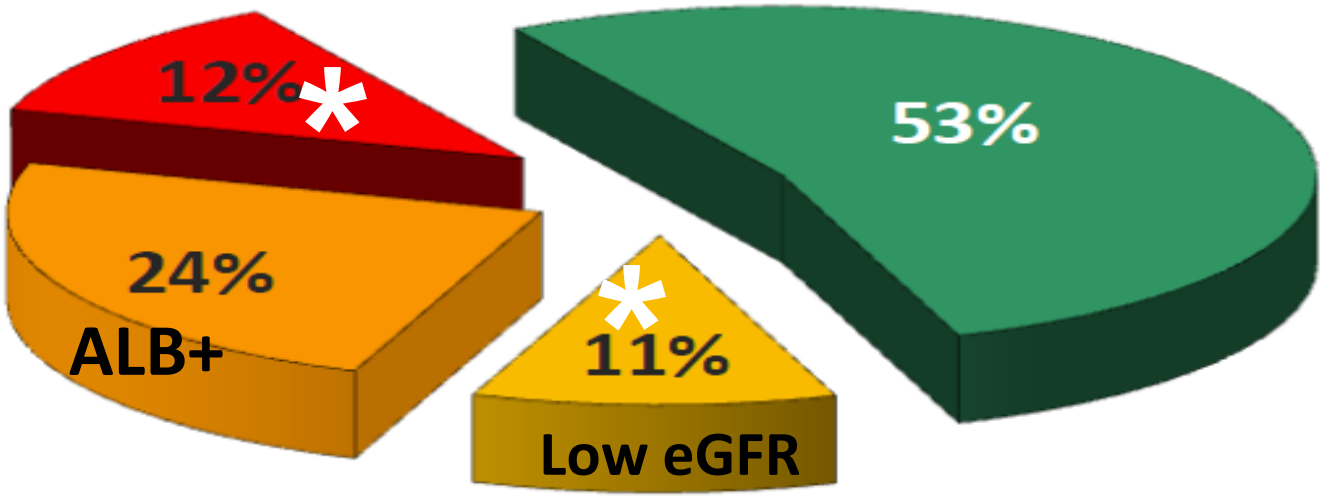
Large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009

Alb– and low eGFR– | Alb– and low eGFR+

Alb+ and low eGFR– | Alb+ and low eGFR+

Nel DM2: **23%** con **GFR<60**

Nel DM2:**36 %** con **MAU**



S. De Cosmo, Russo GT et al. for AMD-Annals Study Group, *NDT* 2014

Low GFR without albuminuria: *a distinct entity or a DKD variant*?

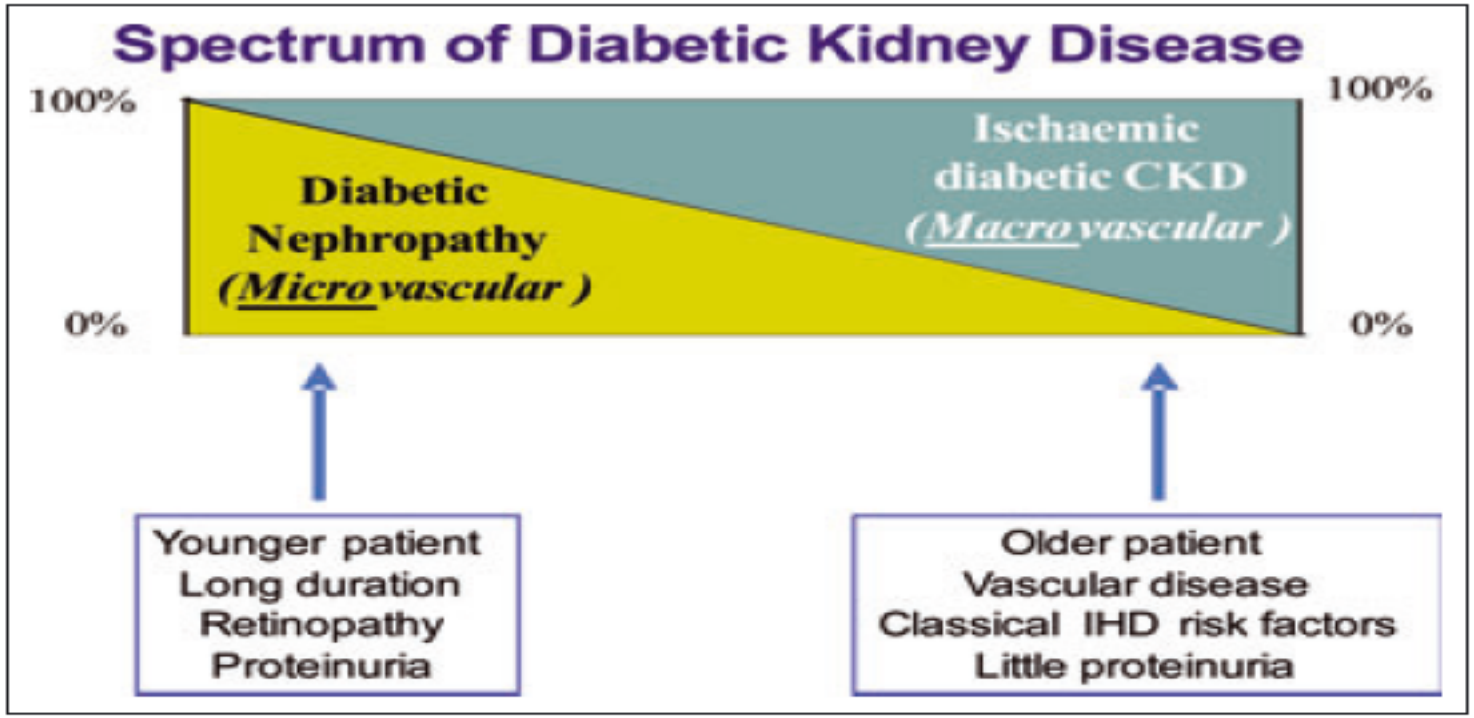
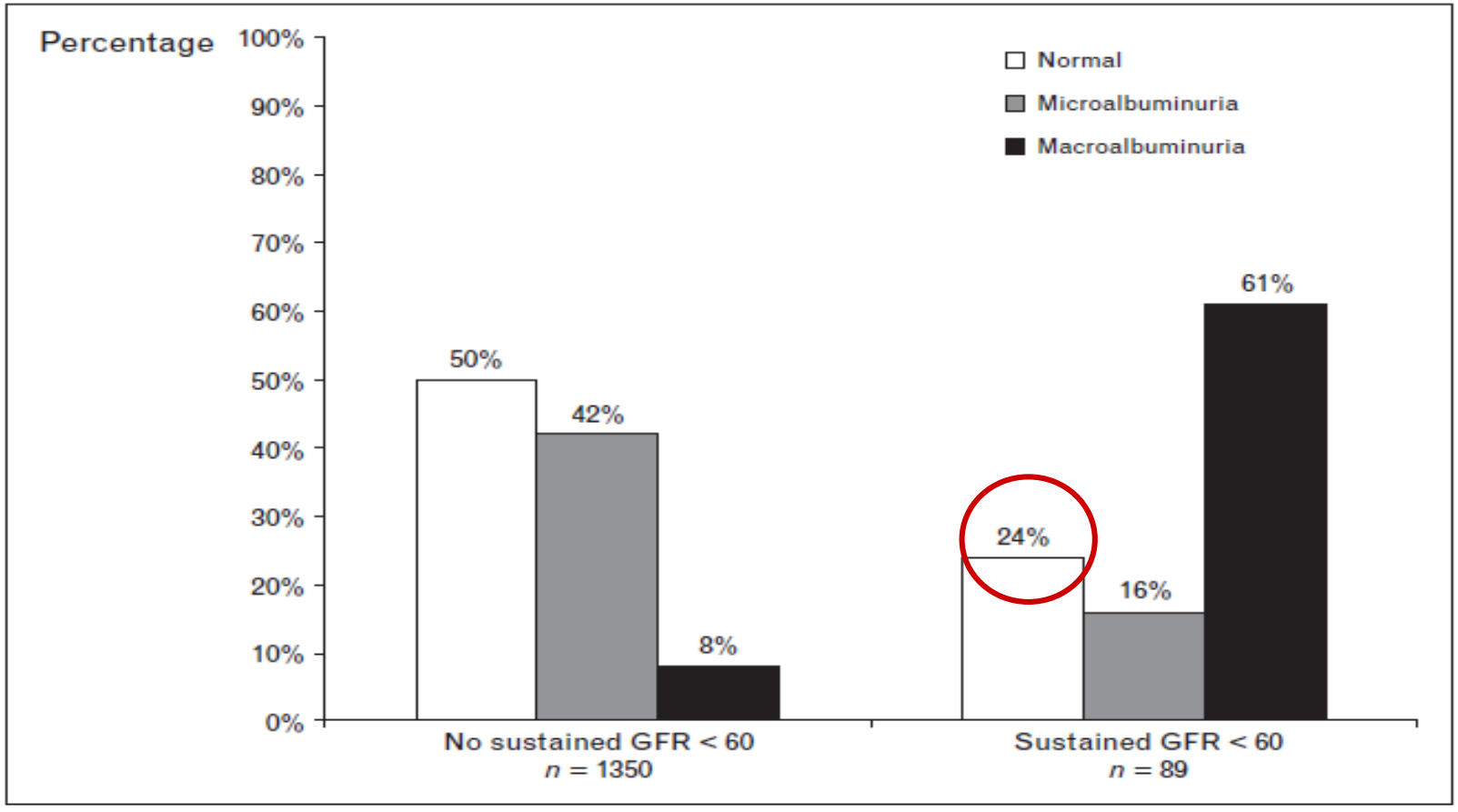


Figure 1. Spectrum of diabetic kidney disease with classical diabetic nephropathy as exemplified with proteinuria and other micro-vascular complications on the left and a macro-vascular CKD variant on the right.

Hill, Fogarty. J Renal Care 2012

Prevalenza di Low GFR senza MAU nel DCCT/EDIC

Figure 4 The proportion of patients with type 1 diabetes with normalbuminuria, microalbuminuria or macroalbuminuria and a sustained eGFR less than 60 ml/min/1.73 m^2 in the DCCT and EDIC study



DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate. Reproduced with permission from [37••].

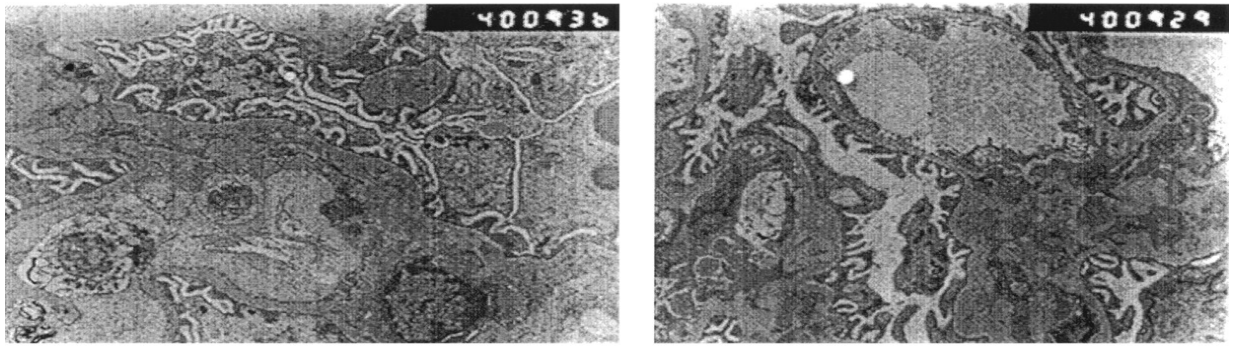
Molitch ME, Steffes M, Sun W, *et al.* Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care 2010; 33: 1536–1543.

Current Opinion in Nephrology and Hypertension 2011, 20:246–257

Nonproteinuric Diabetes-Associated Nephropathy in the Cohen Rat Model of Type 2 Diabetes

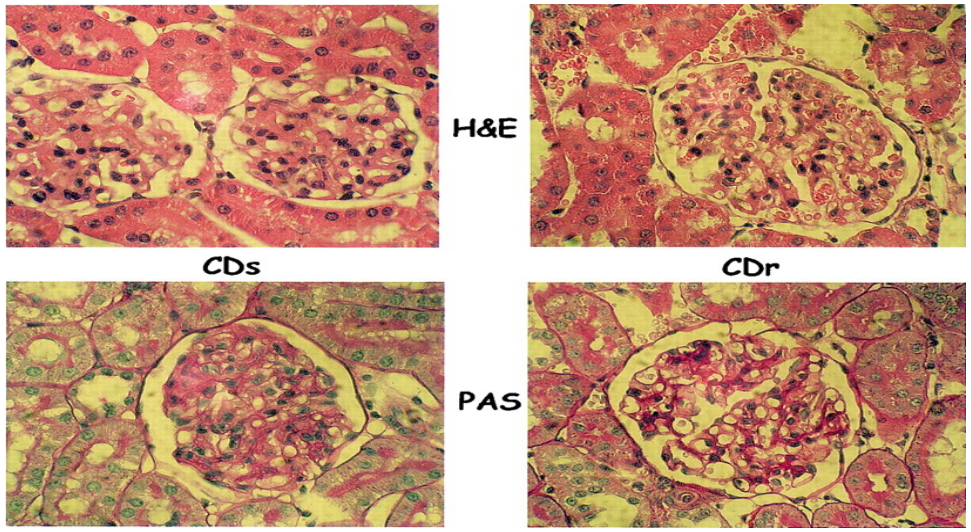
Chana Yagil,[1] Adiel Barak,[2] David Ben-Dor,[3] Eliezer Rosenmann,[1] Joel Bernheim,[4] Mordechai Rosner,[5] Yael Segev,[6] Sarah Weksler-Zangen,[7] Itamar Raz,[8] and Yoram Yagil[1]

The Cohen diabetic rat is known to develop progressive impairment in renal function with morphological changes that are typical of diabetic glomerulosclerosis but without proteinuria.

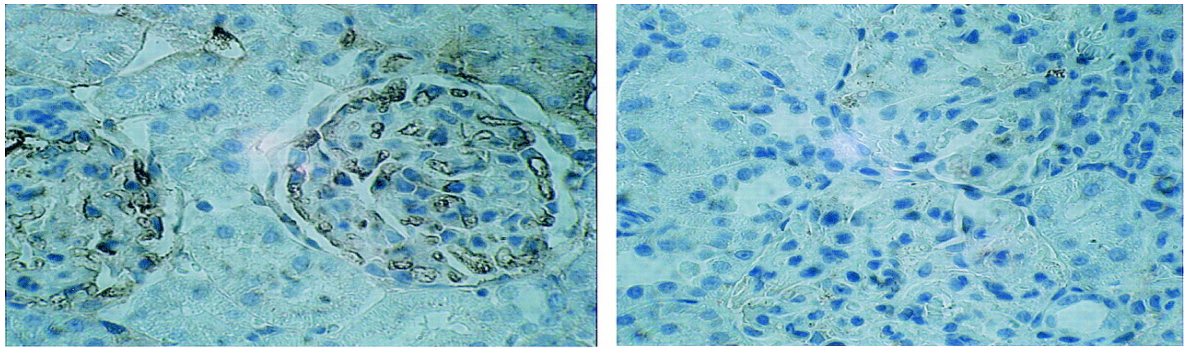


CDs CDr

Electron micrographs (×4,000) of representative kidney sections of CDs and CDr fed diabetogenic diet for 3 months.



Hematoxylin and eosin (H&E) and PAS stains of 2- to 3-μm sections of kidneys (×400) from CDs and CDr fed diabetogenic diet for 3 months.



CDs CDr

Immunocytochemical staining for type IV collagen (in brown) in sections of kidneys of CDs and CDr fed diabetogenic diet for 3 months.

Diabetes 2005;54:1487–1496

Acta Diabetologica (2018) 55:1093–1104
https://doi.org/10.1007/s00592-018-1193-0

REVIEW ARTICLE

Advances in understanding the genetic basis of diabetic kidney disease

Man Li[1,2] · Marcus G. Pezzolesi[1,3,4]

Diverse varianti genetiche associate con DKD, tuttavia isolated low eGFR poco studiato

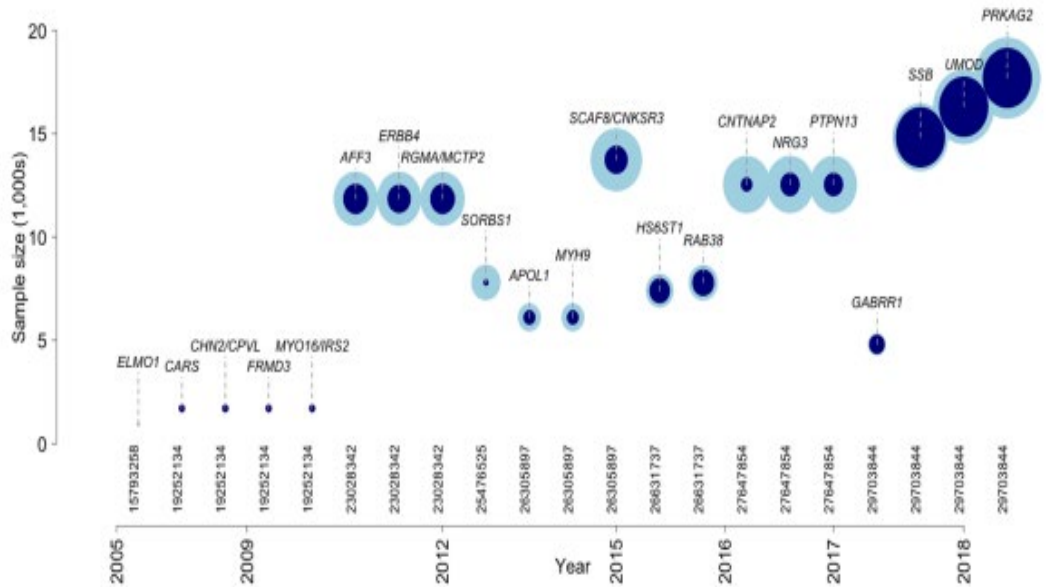
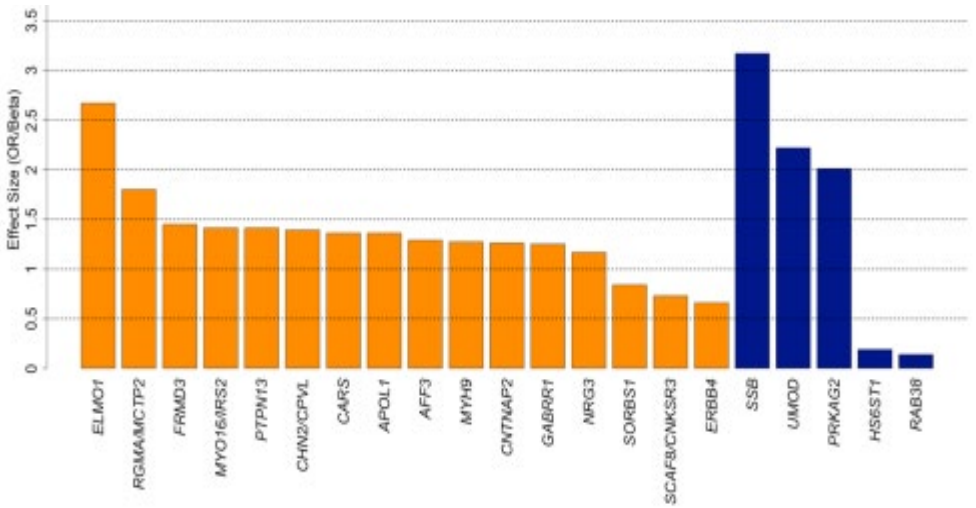


Fig. 3 Effect sizes for DKD loci identified through GWAS. Odds ratios (OR) and beta estimates for dichotomous (orange) and quantitative DKD traits (blue), respectively, are presented for all DKD GWAS loci with p value $< 1.0 \times 10^{-5}$. Of note, the effect sizes for the *SSB*, *UMOD*, and *PRKAG2* loci are from associations with eGFR while those for *HS6ST1* and *RAB38* are from associations with uACR



Overall, small Effect size

CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease

Hans-Joachim Anders[1], Tobias B. Huber[2], Berend Isermann[3] and Mario Schiffer[4]*

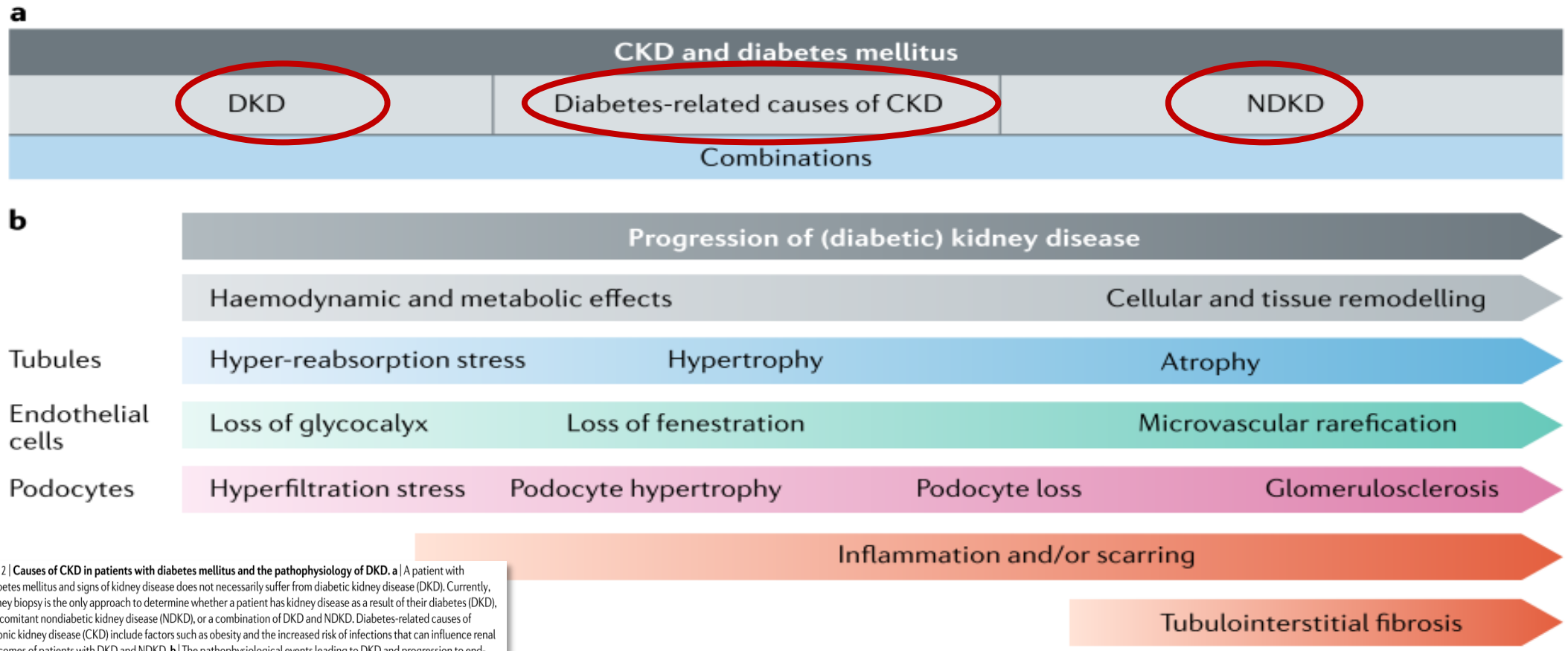


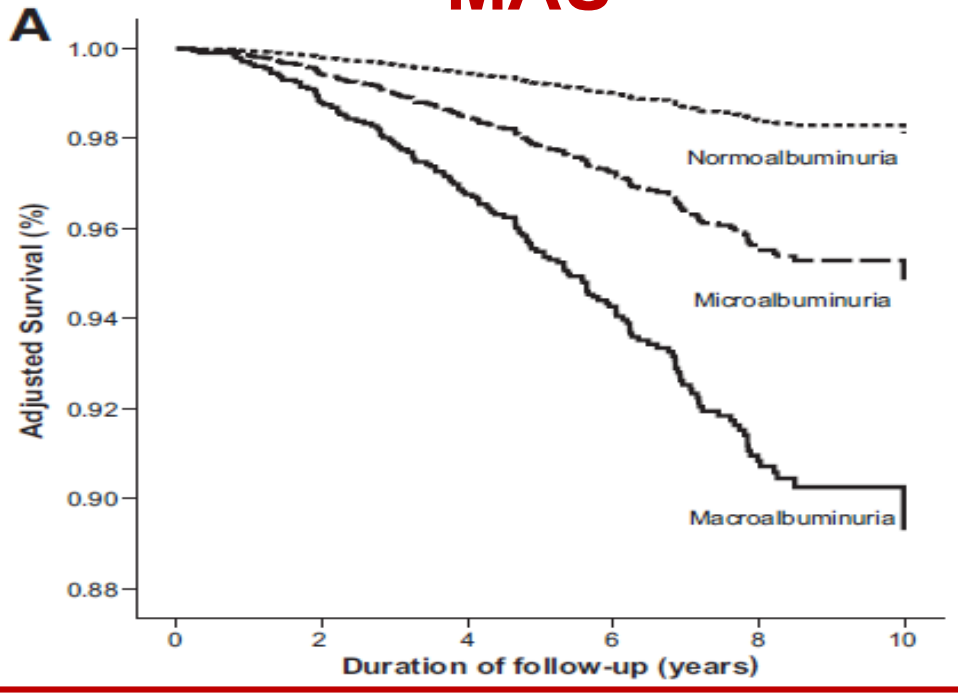
Fig. 2 | **Causes of CKD in patients with diabetes mellitus and the pathophysiology of DKD. a** | A patient with diabetes mellitus and signs of kidney disease does not necessarily suffer from diabetic kidney disease (DKD). Currently, kidney biopsy is the only approach to determine whether a patient has kidney disease as a result of their diabetes (DKD), concomitant nondiabetic kidney disease (NDKD), or a combination of DKD and NDKD. Diabetes-related causes of chronic kidney disease (CKD) include factors such as obesity and the increased risk of infections that can influence renal outcomes of patients with DKD and NDKD. **b** | The pathophysiological events leading to DKD and progression to end-stage renal disease can be separated into early (haemodynamic and metabolic) and late (cellular and tissue remodelling) events. In the early phase, massive glucose filtration and glomerular hyperfiltration induce tubular hyper-reabsorption of glucose and sodium, leading to glomerular and tubular hypertrophy and, eventually, to glomerulosclerosis and tubule atrophy. In endothelial cells, early loss of glycocalyx and fenestration leads first to proteinuria and later to microvascular rarefication, promoting atrophy and scaring. Sterile inflammation (that is, the local induction of cytokines, chemokines, and immune cell recruitment) accompanies and promotes tissue remodelling, contributing to atrophy and scarring.

ORIGINAL ARTICLE

The Presence and Severity of Chronic Kidney Disease Predicts All-Cause Mortality in Type 1 Diabetes

Per-Henrik Groop,[1,2] Merlin C. Thomas,[3] John L. Moran,[4] Johan Wadèn,[1,2] Lena M. Thorn,[1,2] Ville-Petteri Mäkinen,[1,2] Milla Rosengård-Bärlund,[1,2] Markku Saraheimo,[1,2] Kustaa Hietala,[1,2,5] Outi Heikkilä,[1,2] and Carol Forsblom[1,2] on behalf of the FinnDiane Study Group

MAU



CONCLUSIONS—An independent graded association was observed between the presence and severity of kidney disease and mortality in a large contemporary cohort of individuals with type 1 diabetes. These findings highlight the clinical and public health importance of chronic kidney disease and its prevention in the management of type 1 diabetes. *Diabetes* 58:1651–1658, 2009

eGFR

FinnDiane Study
4,201 DM1 adults

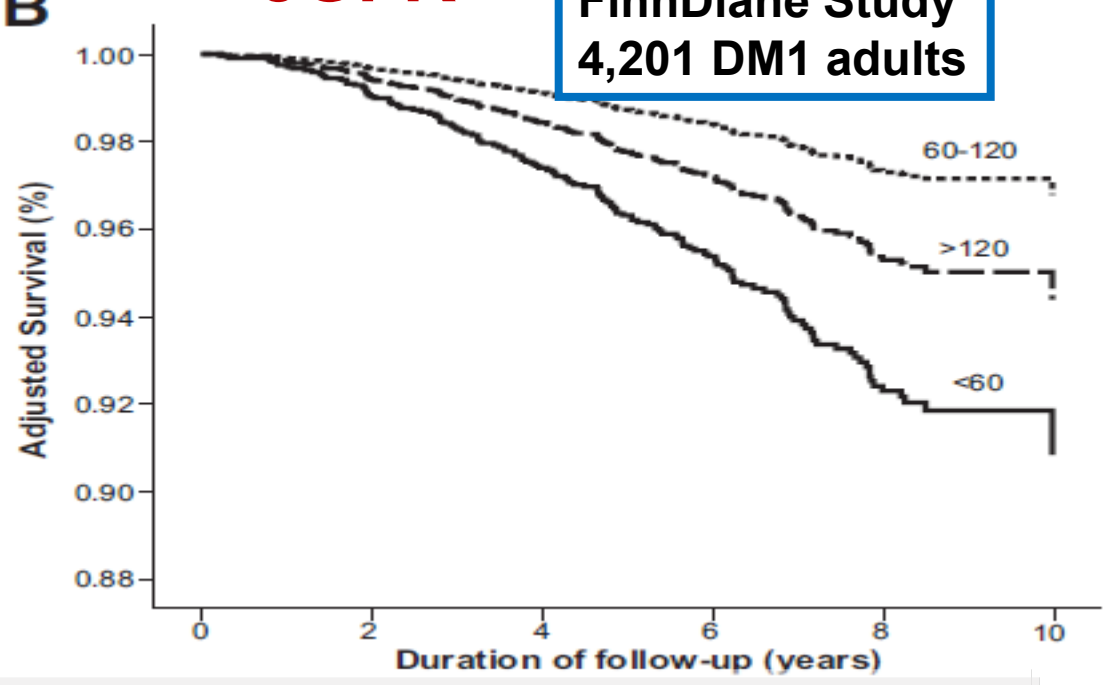


FIG. 1. Survival plots showing Cox-adjusted survival of individuals with type 1 diabetes from the FinnDiane study, stratified for the presence and severity of albuminuria (*A*), estimated GFR (*B*), and the presence and severity of retinopathy (*C*) at baseline. All figures are adjusted for age; sex; duration of diabetes; body habitus; the presence and extent of macro- and microvascular complications; glycemic, lipid, and blood pressure control; and drug management. The latter figure (*C*) is not adjusted for the presence and severity of nephropathy, as discussed in the text.

Diverging Association of Reduced Glomerular Filtration Rate and Albuminuria With Coronary and Noncoronary Events in Patients With Type 2 Diabetes

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

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ENZO BONORA, MD[3]
CECILIA FONDELLI, MD[4]
EMANUELA ORSI, MD[5]
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FRANCESCO ANDREOZZI, MD[10]
ANTONIO NICOLUCCI, MD[11]
GIUSEPPE PUGLIESE, MD[12]
FOR THE RENAL INSUFFICIENCY AND CARDIOVASCULAR EVENTS (RIACE) STUDY GROUP*

- Coronary events, *N* = 2,405,
- Cerebrovascular, *N* = 1,298,
- Peripheral, *N* = 894

Table 3—*Logistic regression analysis of coronary (N = 2,405), cerebrovascular (N = 1,298), or peripheral (N = 894) events with CKD phenotypes as covariates*

Variable	Coronary events	Cerebrovascular events	Peripheral events
Age (1 year)	1.020 (1.014–1.026)	1.030 (1.022–1.038)	1.013 (1.004–1.021)
Male sex	2.129 (1.906–2.379)	1.16 (1.02–1.33)	1.23 (1.04–1.45)
CKD phenotype			
No CKD	1.0	1.0	1.0
Stages 1–2 CKD	0.901 (0.794–1.022)	1.41 (1.20–1.65)	1.51 (1.25–1.82)
Nonalbuminuric stage ≥3 CKD	1.514 (1.304–1.757)	1.22 (1.01–1.48)	1.40 (1.11–1.76)
Albuminuric stage ≥3 CKD	1.270 (1.083–1.490)	1.69 (1.40–2.00)	1.88 (1.52–2.34)
Cerebrovascular events	2.472 (2.156–2.834)	2.51 (2.19–2.87)	2.77 (2.37–3.23)
Peripheral events	2.702 (2.306–3.167)	3.75 (3.17–4.44)	3.81 (3.21–4.51)

Results are presented as OR (95% CI). Variables excluded: HbA_{1c}, BMI. OHA, oral hypoglycemic agent.

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Low eGFR e MAU differente *set* di fattori di rischio

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[2], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

Table 3. Results of multivariate logistic regression analysis (backward models) showing the relationship between traits of DKD and traditional diabetic and cardiovascular risk factors. Reference category for all were patients with normoalbuminuria and eGFR ≥ 60 mL/min/1.73 m².

	Dependent variables					
	Low eGFR normal albuminuria		Albuminuria normal eGFR		Low eGFR and albuminuria	
Independent variables	OR	95%CI	OR	95% CI	OR	95% CI
Age (by 1 year)	1.12	1.11–1.12	1.01	1.01–1.0		
DBP (by 5 mmHg)	0.97	0.95–0.99	1.04	1.03–1.0		
SBP (by 5 mmHg)	0.98	0.97–0.99	1.03	1.02–1.0		
Total cholesterol (by 10 mg/dL)	1.04	1.02–1.07	1.05	1.04–1.0		
HDL-C (by 5 mg/dL)	0.93	0.92–0.95	0.95	0.94–0.96	0.88	0.86–0.89
LDL-C (by 10 mg/dL)	0.96	0.93–0.98	0.95	0.94–0.96	0.94	0.91–0.96
Triglycerides (by 10 mg/dL)	1.02	1.02–1.03	NS	NS	1.03	1.02–1.03
BMI (by 1 kg/m²)	1.03	1.02–1.03	1.03	1.02–1.03	1.05	1.04–1.05
Duration of diabetes (by 1 year)	1.01	1.00–1.01	1.01	1.01–1.01	1.02	1.01–1.02
HbA1c (by 1%)	0.96	0.93–0.98	1.07	1.05–1.09	0.97	0.95–1.00
Males versus females	0.69	0.64–0.73	1.89	1.81–1.98	1.52	1.42–1.63
Smokers (yes versus no)	0.84	0.76–0.93	1.55	1.47–1.64	1.22	1.11–1.34
Oral agents versus diet	0.88	0.78–0.99	1.47	1.34–1.62	1.14	0.98–1.32
Oral agents + insulin versus diet	1.09	0.93–1.26	2.12	1.90–2.37	2.01	1.70–2.39
Insulin versus diet	2.06	1.78–2.38	1.96	1.75–2.20	5.59	4.74–6.59
Use of antihypertensive drugs	1.60	1.42–1.80	1.36	1.26–1.48	2.67	2.34–3.05
Use of ACE inhibitors and/or ARBs	1.24	1.13–1.37	1.33	1.23–1.42	1.24	1.12–1.36
Use of statins	1.10	1.03–1.17	NS	NS	1.17	1.09–1.25
Retinopathy	NS	NS	1.41	1.33–1.49	1.64	1.52–1.77

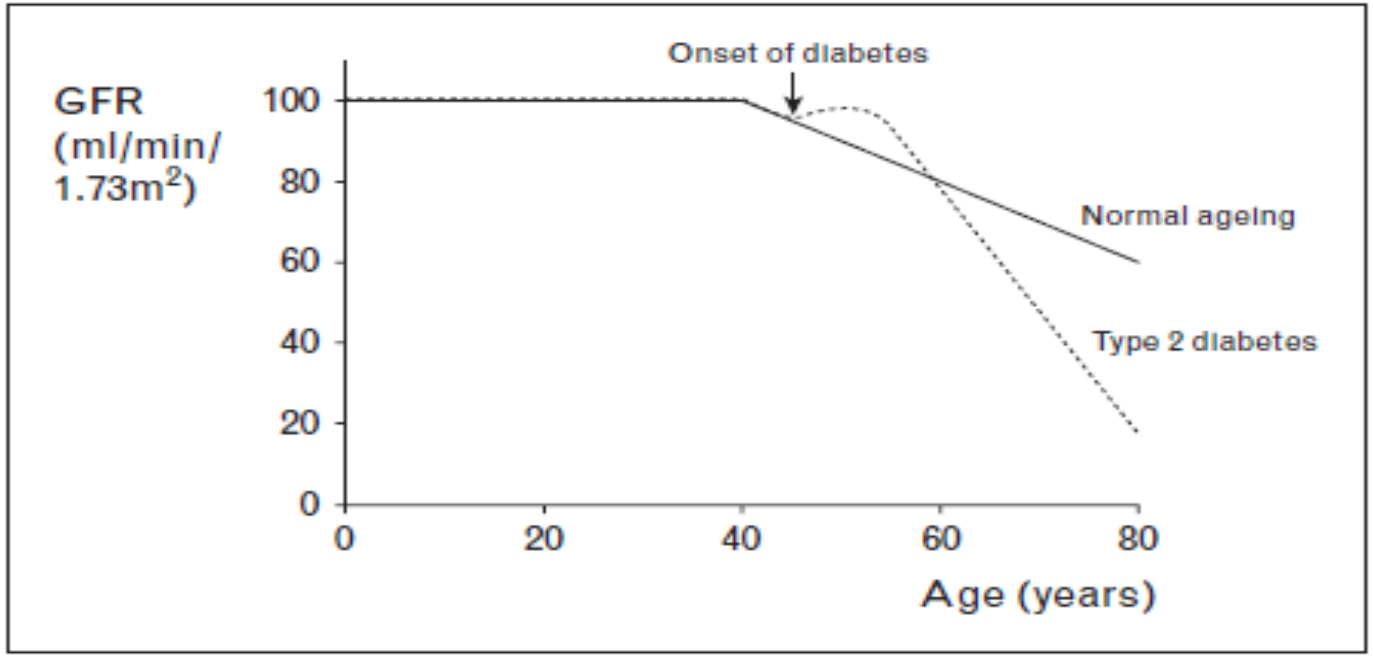
Nephrol Dial Transplant (2014) 29: 657–662
doi: 10.1093/ndt/gft506
Advance Access publication 6 January 2014

OR, odds ratio; 95% CI, 95% confidence of intervals; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

De Cosmo, Russo, et al, Nephrol Dial Transplant 2014

Il declino del GFR nel DM2 non è *solo* legato all'età….

Figure 6 Schematic representation of the expected decline in GFR with age and a proposed accelerated decline in GFR that is not accompanied by a significant increase in AER that occurs after the onset of type 2 diabetes over and above that expected with age alone



AER, albumin excretion rate; GFR, glomerular filtration rate.



Current Opinion in Nephrology and Hypertension 2011, 20:246–257

Russo et al. BMC Geriatrics (2018) 18:38
DOI 10.1186/s12877-018-0732-4

BMC Geriatrics

RESEARCH ARTICLE Open Access

Diabetic kidney disease in the elderly: prevalence and clinical correlates

Giuseppina T. Russo[1,9*], Salvatore De Cosmo[2], Francesca Viazzi[3], Antonio Mirijello[2], Antonio Ceriello[4,5], Pietro Guida[6], Carlo Giorda[7], Domenico Cucinotta[1], Roberto Pontremoli[3], Paola Fioretto[8] and the AMD-Annals Study Group

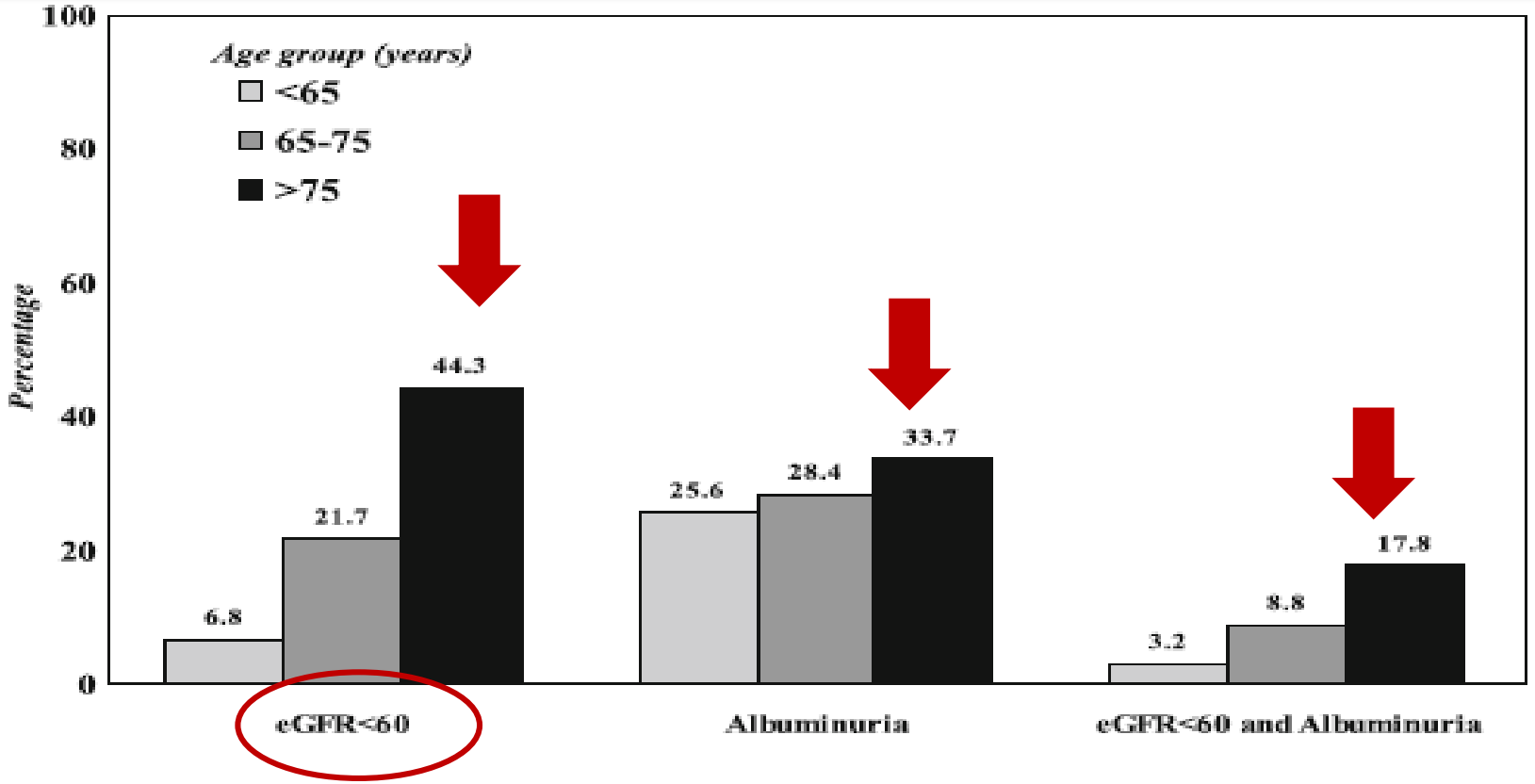
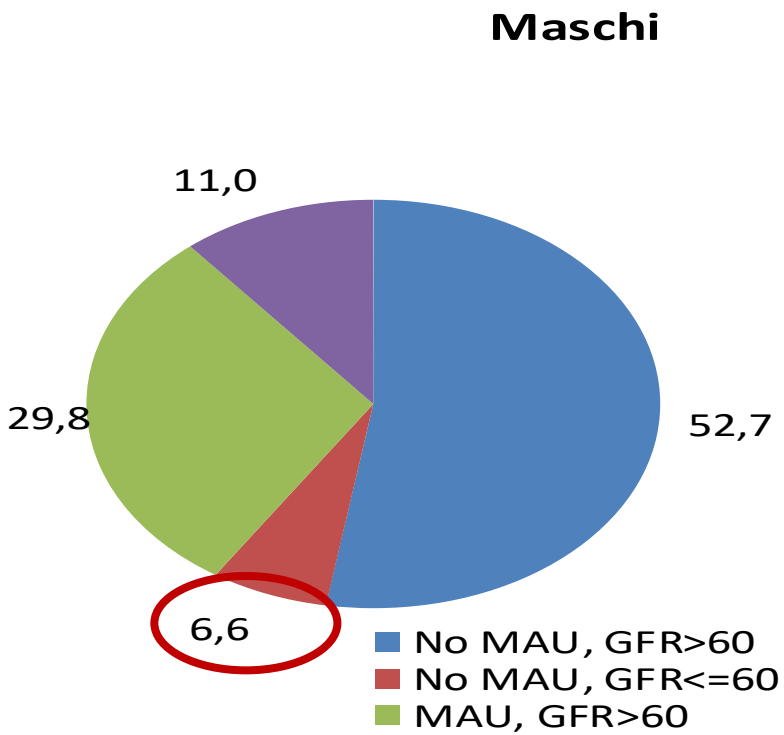
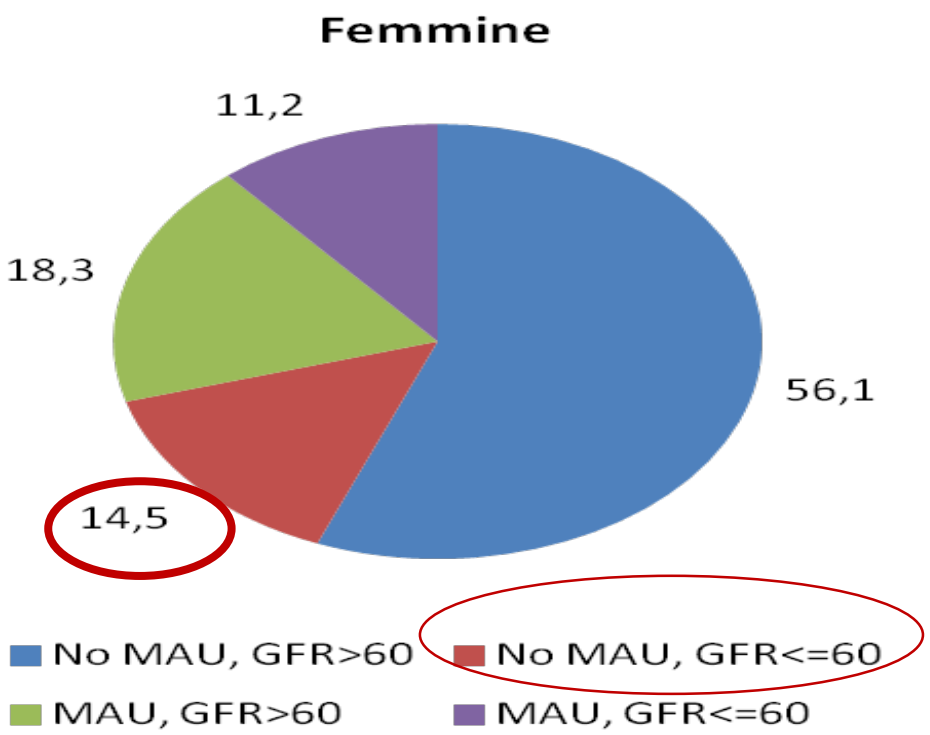




Fig. 1 Proportion of patients with eGFR< 60 mL/min/1.73 m2 or albuminuria, by age groups

Distribuzione della popolazione divisa per *sesso* in relazione alla presenza di MAU e di riduzione del GFR (%)





Nephrol Dial Transplant (2014) 29: 657–662
doi: 10.1093/ndt/gft506
Advance Access publication 6 January 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[2], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.

Clin J Am Soc Nephrol 10: 1921–1929, November, 2015

Article

Serum Uric Acid and Risk of CKD in Type 2 Diabetes

Salvatore De Cosmo, Francesca Viazzi, Antonio Pacilli, Carlo Giorda, Antonio Ceriello, Sandro Gentile, Giuseppina Russo, Maria C. Rossi, Antonio Nicolucci, Pietro Guida, Daniel Feig, Richard J. Johnson, Roberto Pontremoli, and the AMD-Annals Study Group

ORs for developing DKD by quintiles of sex-specific uric acid levels

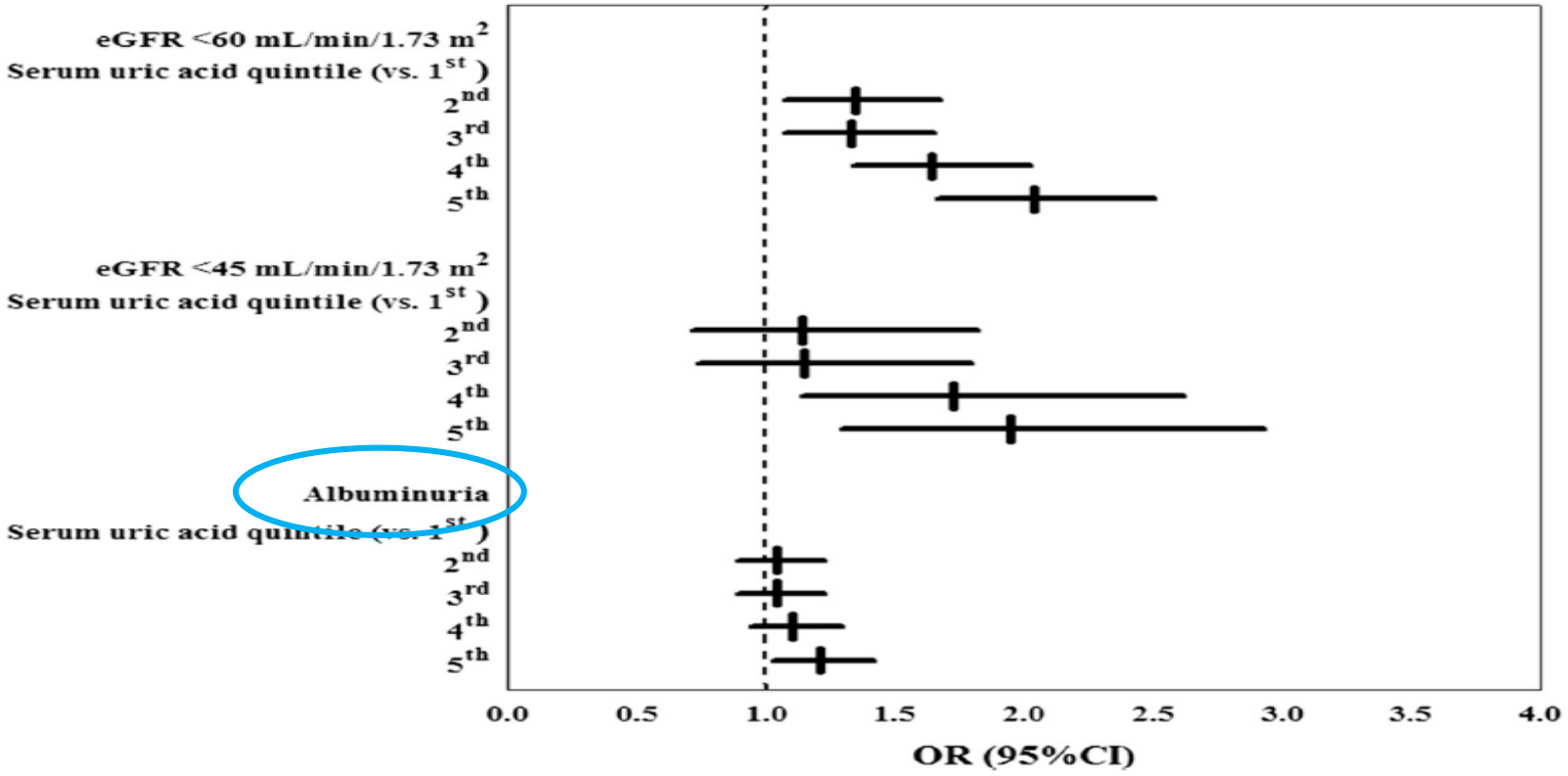


Figure 1. | The graded relationship of serum uric acid (SUA) with the development of incident low eGFR and albuminuria in type 2 diabetes. Odds ratios (ORs) with their 95% confidence intervals (95% CIs) for eGFR <60 or <45 ml/min per 1.73 m^2 and albuminuria onset by sex-specific quintile of serum uric acid adjusted for baseline eGFR. The first serum uric acid quintile was considered as reference category.

De Cosmo, Russo,et al, CJASN 2015

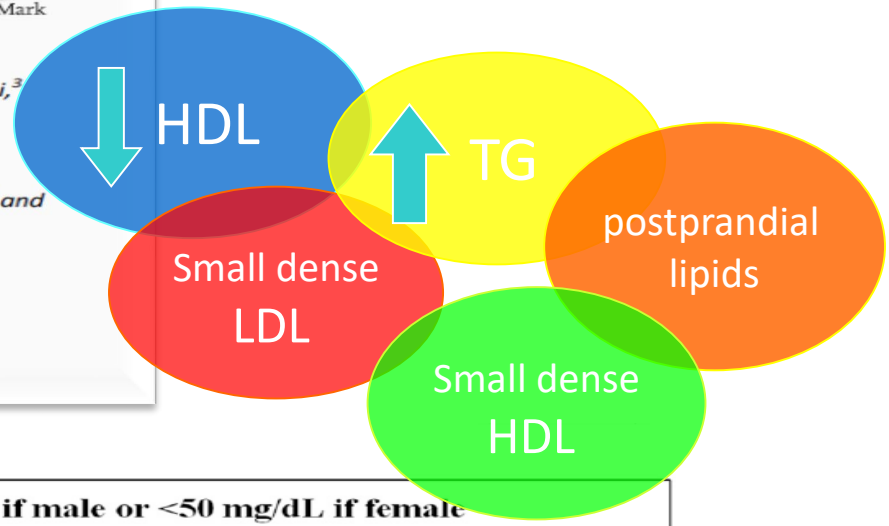
Diabetes Care Volume 39, December 2016 1

Plasma Triglycerides and HDL-C Levels Predict the Development of Diabetic Kidney Disease in Subjects With Type 2 Diabetes: The AMD Annals Initiative

Giuseppina T. Russo,[1] Salvatore De Cosmo,[2] Francesca Viazzi,[3] Antonio Pacilli,[2] Antonio Ceriello,[4,5] Stefano Genovese,[5] Pietro Guida,[6] Carlo Giorda,[7] Domenico Cucinotta,[1] Roberto Pontremoli,[3] Paola Fioretto,[8] and the AMD-Annals Study Group

Diabetes Care 2016;39:1–10 | DOI: 10.2337/dc16-1246

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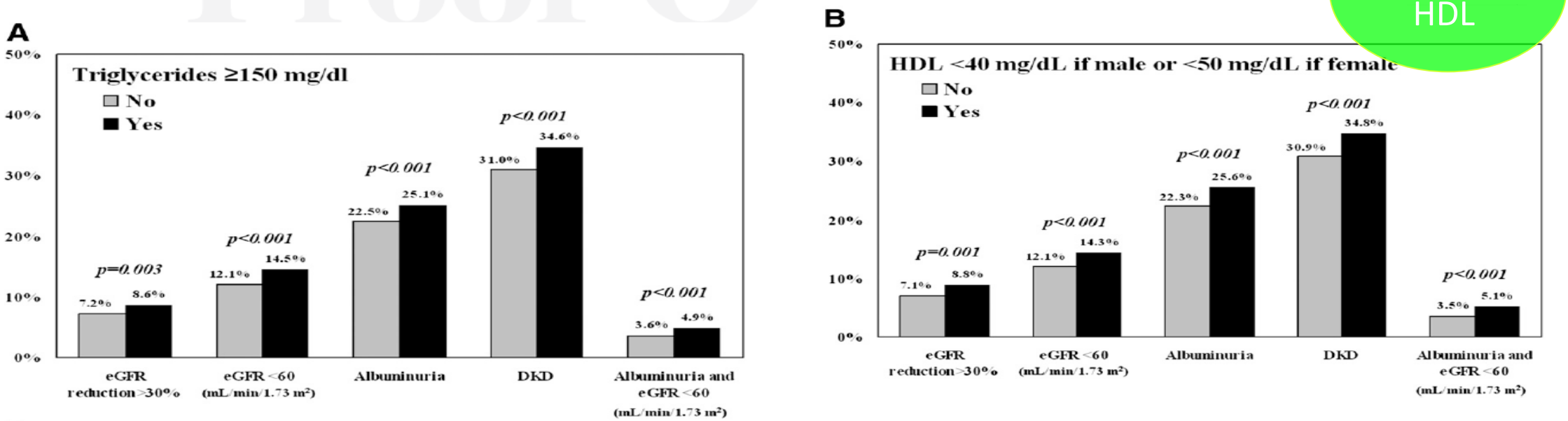


Figure 1—*A*: DKD incidence according to baseline TG ≥150 mg/dL. *B*: DKD incidence according to baseline HDL-C (<40 mg/dL in men; <50 mg/dL in women).

Russo GT, Cucinotta D et al, *Diabetes Care 2016*

RESEARCH ARTICLE

Hypertriglyceridemia Is Independently Associated with Renal, but Not Retinal Complications in Subjects with Type 2 Diabetes: A Cross-Sectional Analysis of the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

Giuseppe Penno[1], Anna Solini[1], Giacomo Zoppini[2], Cecilia Fondelli[3], Roberto Trevisan[4], Monica Vedovato[5], Gabriella Gruden[6], Olga Lamacchia[7], Antonio E. Pontiroli[8], Maura Arosio[9], Emanuela Orsi[10], Giuseppe Pugliese[11]*, for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group[¶]

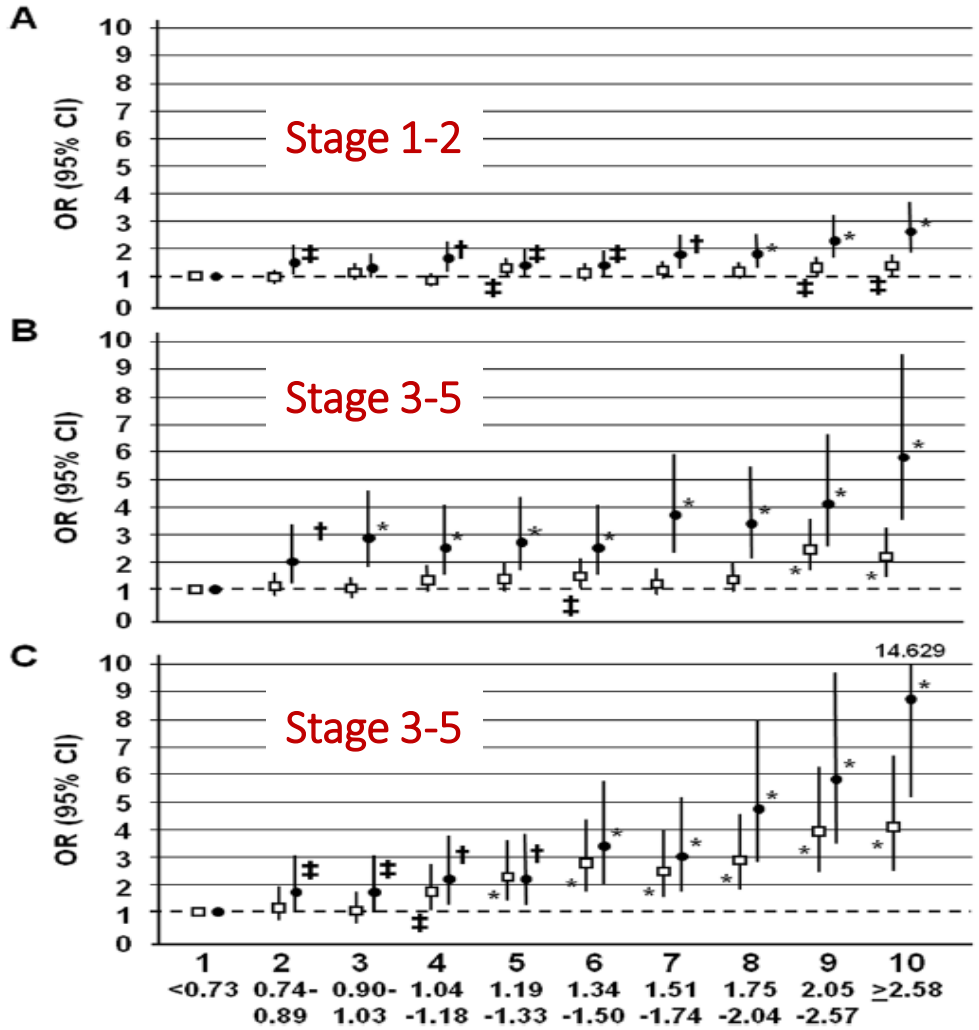


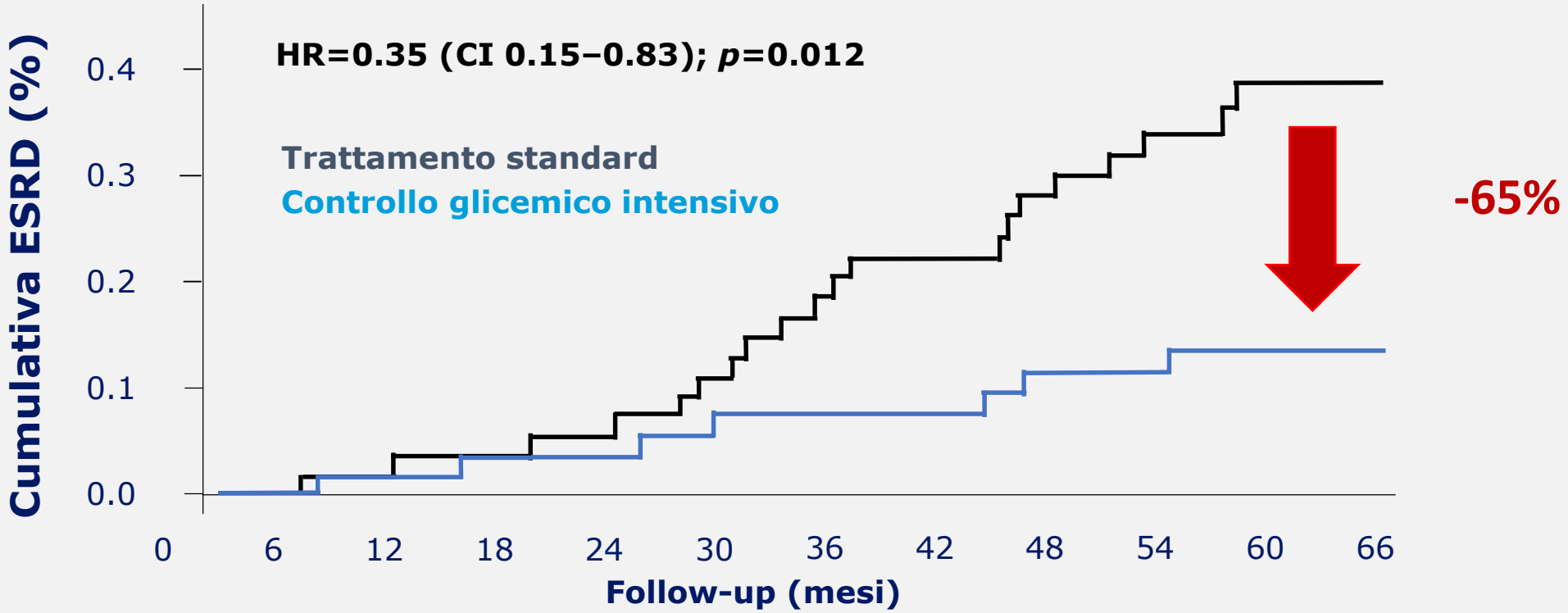
Fig 1. Adjusted risk of CKD Stages 1–2 (Panel A), CKD Stages 3–5 nonalbuminuric (Panel B) and CKD Stages 3–5 albuminuric (Panel C) (OR [95% CI]) according to deciles of triglyceride levels in subjects without (□) and with (•) statin treatment. ORs are adjusted for age, male gender, smoking status, diabetes duration, HbA_{1c}, BMI, HDL and LDL cholesterol, hypertension, and blockade of the renin-angiotensin system. Significant at * *P*<0.0001, † *P* at least <0.01, ‡ *P* at least <0.05.

doi:10.1371/journal.pone.0125512.g001

DKD : Ruolo dell'iperglicemia

RIDUZIONE DEL RISCHIO DI MALATTIA RENALE TERMINALE

Un controllo glicemico intensivo riduce il rischio *di malattia renale terminale* nei pazienti diabetici



Perkovic V et al. *Kidney Int* 2013;83:517–523

CI: intervallo di confidenza; ESRD: malattia renale allo stadio terminale; HR: hazard ratio.

Diabetologia (2017) 60:2129–2138
DOI 10.1007/s00125-017-4360-x

REVIEW

Vascular complications in diabetes: old messages, new thoughts

Josephine M. Forbes[1,2,3] · Amelia K. Fotheringham[1,4]

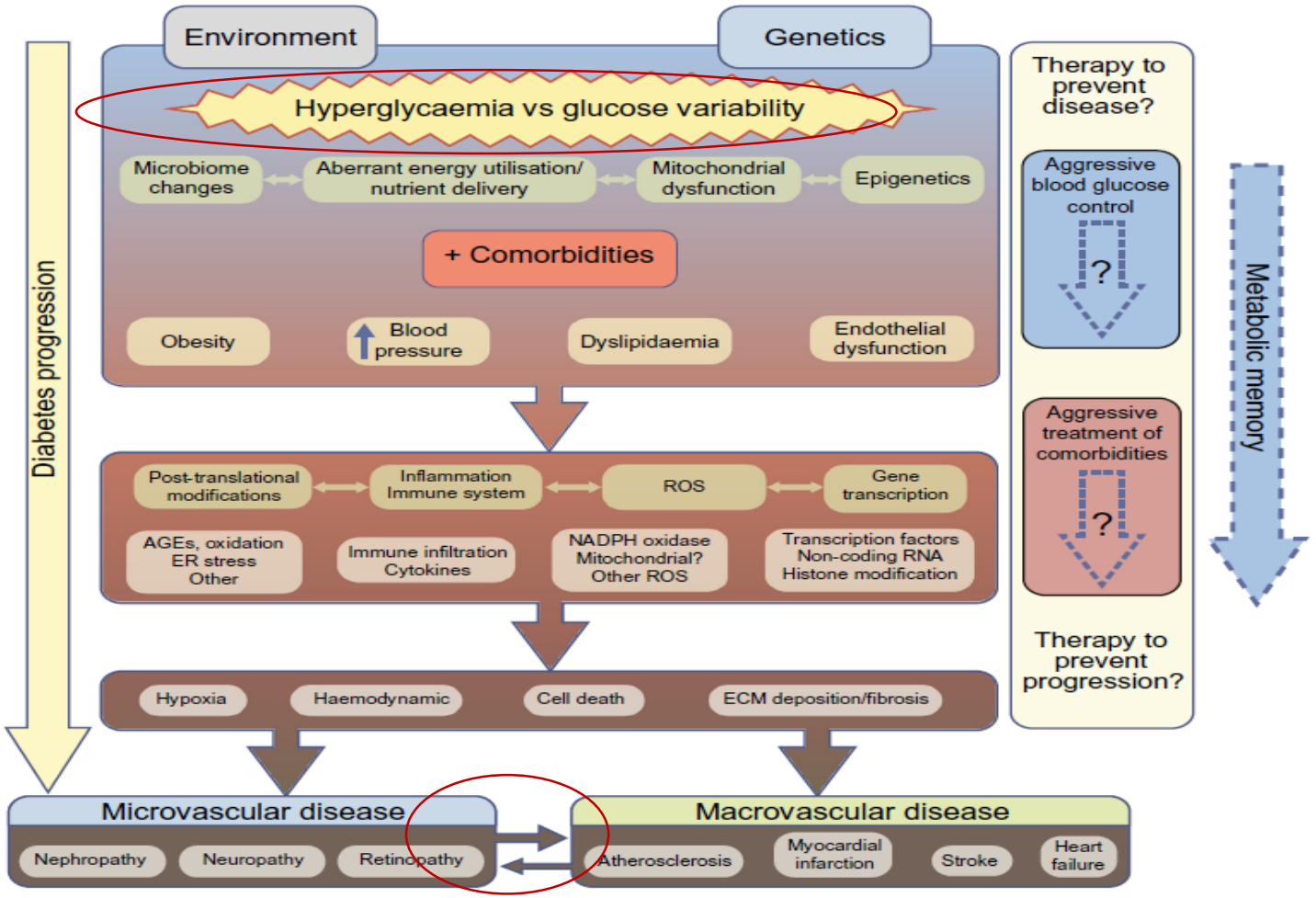
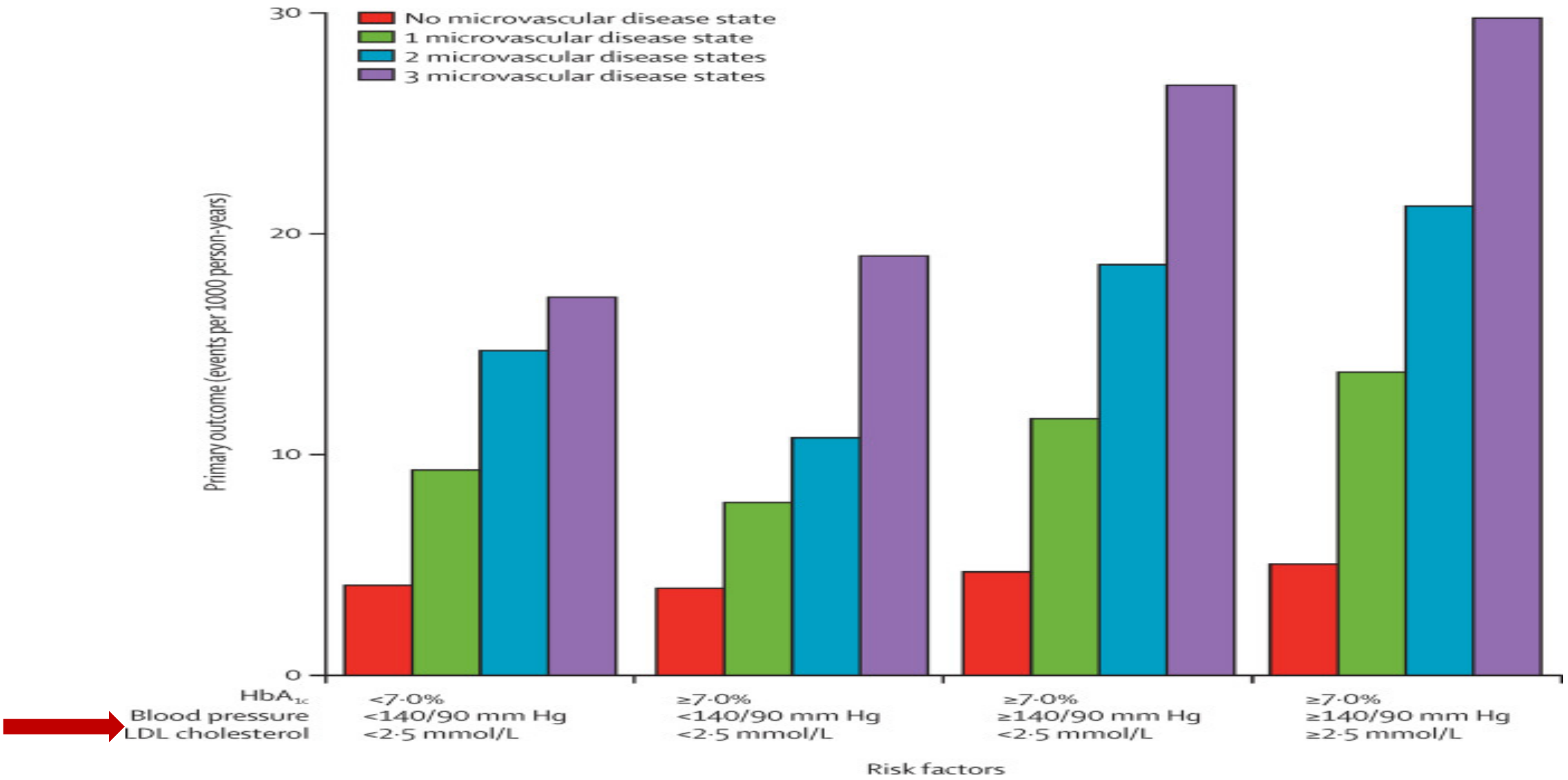


Fig. 1 Schematic representation of the pathways to diabetes complications discussed in this review and how they fit into current paradigms. Susceptibility to diabetes complications is driven by a combination of environmental factors (e.g. diet, lifestyle, microbiota, pathogen exposure) and genetic programming. With diabetes onset, many changes occur that are thought to be pathological, including involvement of pathways that have been explored recently and are highlighted in this review. These include the following: changes to the microbiome, potentially affecting substrate delivery and utilisation, gastrointestinal inflammation and permeability, release of intestinal toxins, neuroendocrine signalling and the immune system; aberrant energy utilisation, substrate delivery and nutrient flux, which can alter the metabolic pathways utilised by tissues affected by complications; mitochondrial dysfunction in the form of mitochondrial fission and fusion, decreased biogenesis, aberrant energy utilisation and delivery and, potentially, ROS generation; epigenetic changes, which alter the regulation of genes associated with pathological pathways. All these factors are likely to be exacerbated by the presence of comorbidities (obesity, raised blood pressure, dyslipidaemia, endothelial dysfunction), initiating a downstream cascade of interacting pathways ultimately resulting in microvascular and macrovascular complications. These pathways include post-translational modifications (AGE formation, oxidation of proteins and lipids and ER stress), inflammation and immune dysregulation (increases in inflammatory cytokines, chemoattractant molecules and ultimately immune cell infiltration), ROS production, and gene expression and transcription. Current therapeutic strategies include intensive blood glucose control and treatment of comorbidities, with the former appearing to be more effective early in disease development. The paucity of therapies that actually prevent or reverse complications once they are established remains one of the major challenges posed by the global diabetes pandemic. ECM, extracellular matrix; ER, endoplasmic reticulum

Adjusted event rates for the primary outcome by cumulative burden of microvascular disease and established risk factor goals



The Lancet Diabetes & Endocrinology, Volume 4, Issue 7, 2016, 588–597

AJKD

Special Report

Diabetic Kidney Disease: A Report From an ADA Consensus Conference

Katherine R. Tuttle, MD,[1] George L. Bakris, MD,[2] Rudolf W. Bilous, MD,[3] Jane L. Chiang, MD,[4] Ian H. de Boer, MD,[5] Jordi Goldstein-Fuchs, DSc, APRN, RD,[6] Irl B. Hirsch, MD,[7] Kamyar Kalantar-Zadeh, MD, MPH, PhD,[8] Andrew S. Narva, MD,[9] Sankar D. Navaneethan, MD, MPH,[10] Joshua J. Neumiller, PharmD,[11] Uptal D. Patel, MD,[12] Robert E. Ratner, MD,[4] Adam T. Whaley-Connell, DO, MSPH,[13] and Mark E. Molitch, MD[14]

Box 2. Other Cause(s) of CKD Should Be Considered in the Presence of Any of the Following Circumstances

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

Reproduced with permission of NKF from KDOQI diabetes and CKD guideline.[4]

Am J Kidney Dis. 2014;64(4):510-533



Gli Stadi della Nefropatia Diabetica

Tabella V.B2 Stadi della malattia renale cronica

Stadio	Descrizione	GFR (ml/min per 1,73 m²)
1	Danno renale* con GFR normale o aumentato	≥90
2	Danno renale* con GFR lievemente ridotto	60-89
3a	Riduzione del GFR lieve-moderata	45-59
3b	Riduzione del GFR moderata-severa	30-45
4	Severa riduzione del GFR	15-29
5	Insufficienza renale terminale	<15 o dialisi

* Il danno renale è definito dalla presenza di albuminuria, anormalità del sedimento urinario, ematochimiche, anatomopatologiche o degli esami strumentali.

(MacIsaac RJ 2004; Retnakaran R 2006; Penno G 2011). La creatinina sierica da sola non dovrebbe mai essere usata come indicatore della funzionalità renale. Qualora non riportato nel referto di laboratorio, il GFR può essere calcolato con la formula di Cockroft-Gault, l'equazione MDRD o con la equazione Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), che utilizza gli stessi parametri della formula semplificata dello studio MDRD, ma è più precisa di quest'ultima e più accurata nel definire il rischio cardiovascolare in relazione alla malattia renale cronica sia nella popolazione non diabetica sia in quella con diabete tipo 2 (Earley A 2012; Hsu CY 2012).

La stima del GFR può essere facilmente calcolata andando all'indirizzo web **https://www.kidney.org/professionals/kdoqi/gfr**.



B. SCREENING E TRATTAMENTO DELLA NEFROPATIA DIABETICA

Raccomandazioni generali

Tutti gli individui con nefropatia diabetica devono essere considerati ad elevato rischio di eventi cardiovascolari e dovrebbero essere trattati per ridurre tale rischio attraverso un intervento mirato a correggere tutti i fattori di rischio. *I A*

Ottimizzare il compenso glicemico per ridurre il rischio e/o rallentare la progressione della nefropatia. *I A*

Ottimizzare il controllo pressorio per ridurre il rischio e/o rallentare la progressione della nefropatia. *I A*

Ottimizzare il controllo degli altri fattori di rischio (lipidi, fumo) per rallentare la progressione della nefropatia. *I B*

Nei pazienti con nefropatia conclamata l'apporto proteico con la dieta dovrebbe essere pari a 0,8 g/kg/die. Un'ulteriore riduzione (0,6-0,8 g/kg/die) può essere utile nel rallentare il declino del filtrato glomerulare (GFR) in pazienti che mostrano una tendenza alla progressione del danno nonostante l'ottimizzazione del controllo glicemico e pressorio e l'uso di ACE-inibitori e/o ARB. *III B*

Nei pazienti in terapia dialitica deve essere considerato un apporto proteico superiore. *I A*

Screening e stadiazione

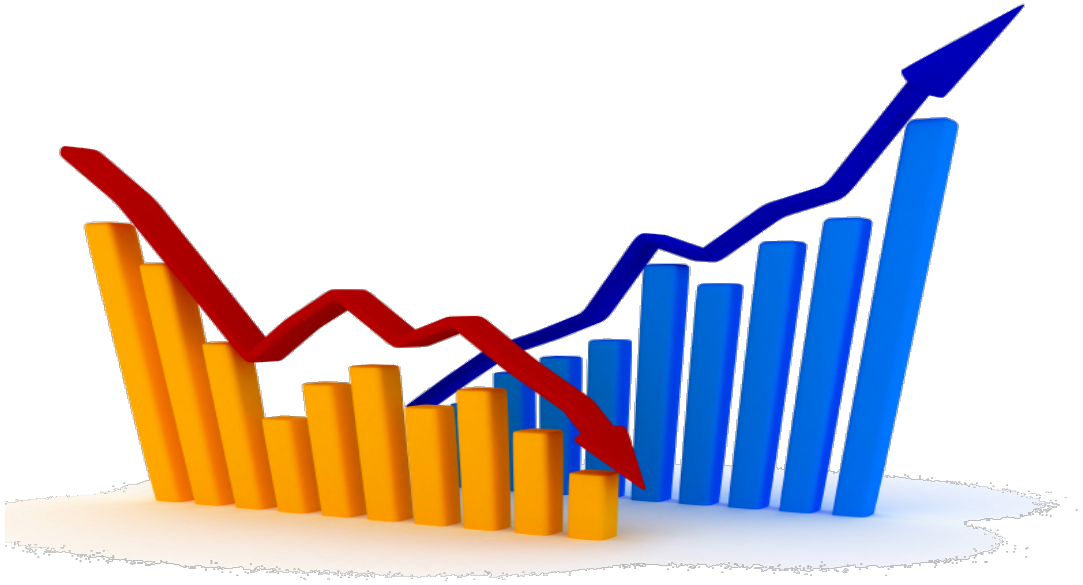
Eseguire annualmente un test per valutare l'escrezione renale di albumina ed escludere la presenza di microalbuminuria: nei soggetti con diabete tipo 1 con durata maggiore di 5 anni, in tutti i casi di diabete tipo 2 iniziando alla diagnosi di diabete e nelle donne con diabete in gravidanza. *VI B*

La creatinina sierica dovrebbe essere misurata annualmente in tutti gli adulti con diabete indipendentemente dal grado d'escrezione urinaria di albumina. La creatinina sierica da sola non dovrebbe essere usata come misura della funzionalità renale, ma piuttosto essere utilizzata per stimare la velocità di filtrazione glomerulare per eseguire una stadiazione della malattia. *VI B*

La valutazione della velocità di filtrazione glomerulare va eseguita almeno una volta l'anno nei pazienti normoalbuminurici, più spesso nei pazienti microalbuminurici o portatori di nefropatia conclamata. *VI B*

Dosaggio della albuminuria e stima del filtrato glomerulare dovrebbero essere integrati nello screening, diagnosi e monitoraggio dei soggetti con nefropatia diabetica; questo perché una quota rilevante di pazienti con diabete tipo 2 va incontro a malattia renale cronica pur rimanendo normoalbuminurico. *IV A*

Uso di *farmaci* nella DKD :*da limitazione d'uso…*



La funzione renale condiziona le nostre scelte terapeutiche

AMD-SID - Standard italiani per la cura del diabete mellito 2016

Tabella 16. Terapia non insulinica nel diabete tipo 2 con insufficienza renale cronica

Stadio IRC	LIEVE	MODERATA	GRAVE	DIALISI
eGFR	>60 ml/min	30-60 ml/min	15-30 ml/min	<15 ml/min
Metformina	≥2 g/die	Non indicato (utilizzabile)	NO	NO
Acarbosio	Da titolare	Da titolare	NO	NO
Gliptine				
Sitagliptin	100 mg/die	50 mg/die	25 mg/die	25 mg/die
Vildagliptin	100 mg/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2,5 mg/die	2,5 mg/die	NO
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12,5 mg/die[a]	6,25 mg/die	6,25 mg/die
GLP-1 agonisti				
Exenatide	20 µg/die	Cautela[b]	NO	NO
Exenatide LAR	2 mg/die	NO[c]	NO	NO
Liraglutide	Dosi usuali	Dosi usuali	NO	NO
Lixisenatide	Dosi usuali	Cautela[b]	NO	NO
Sulfoniluree	Da titolare	Da titolare[d]	NO	NO
Repaglinide	Da titolare	Non indicato (utilizzato)	NO	NO
Pioglitazone	Dosi usuali	Dosi usuali	Dosi usuali	NO[e]
Gliflozine				
Dapagliflozin	Dosi usuali	NO	NO	NO
Empagliflozin	Dosi usuali	NO	NO	NO
Canagliflozin	Dosi usuali	NO	NO	NO

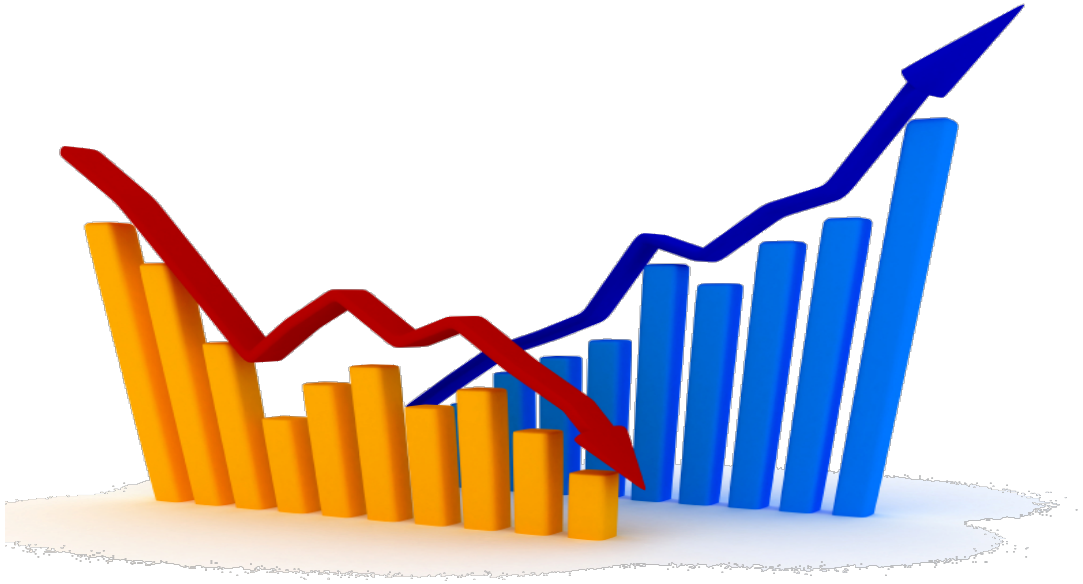


Tabella 4.H1. Terapia non insulinica nel diabete di tipo 2 con insufficienza renale cronica.

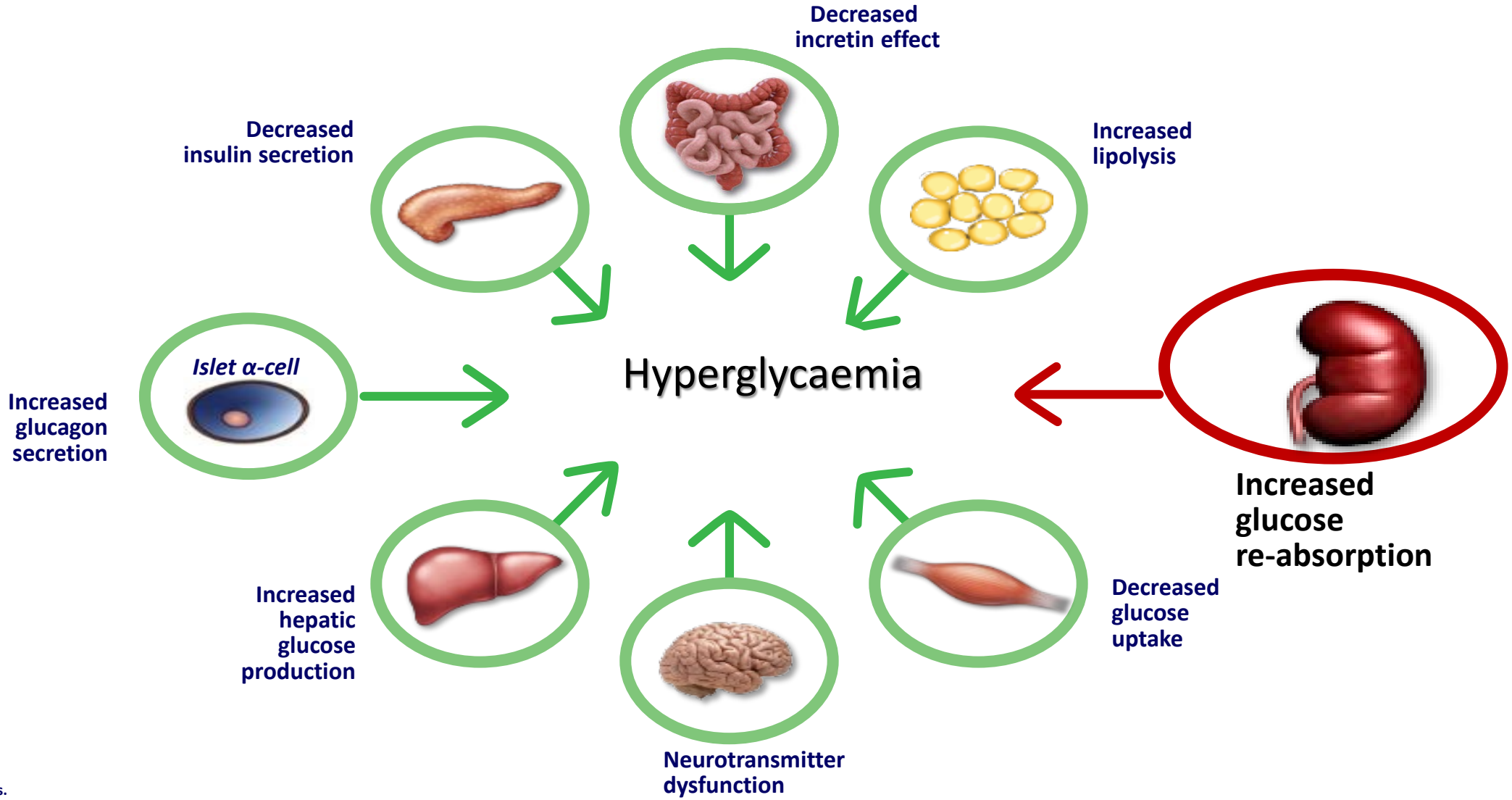
eGFR fino a (ml/min*1.73 m²)	90	80	70	60	50	40	30	20	15	Dialisi
Metformina										
Acarbosio[a]										
Gliptine										
Sitagliptin										
Vildagliptin										
Saxagliptin[b]										
Linagliptin										
Alogliptin										
GLP1 agonisti										
Exenatide										
Exenatide LAR										
Liraglutide[b]										
Lixisenatide										
Dulaglutide[b]										
Sulfoniluree										
Glibenclamide										
Gliclazide										
Glimepiride										
Repaglinide										
Pioglitazone										
Gliflozine										
Dapagliflozin										
Empagliflozin[c]										
Canagliflozin[c]										

Verde: utilizzabile senza aggiustamenti di dose. Giallo: utilizzabile con cautela e/o aggiustando le dosi. Rosso: controindicato.
[a] Utilizzabile per eGFR fino a 25 ml/min*1.73 m²; [b] Utilizzabile per eGFR fino a 15 ml/min*1.73 m²
[c] Iniziare la terapia, senza necessità di aggiustamenti di dosi, se eGFR supera 60 ml/min*1.73 m²; se, durante la terapia, eGFR scende sotto 45 ml/min*1.73 m², sospendere il farmaco

Uso di *farmaci* nella DKD :*a nuove possibilità…*



Il Rene occupa un posto importante nella fisiopatologia del diabete di tipo 2



- T2D, Type 2 Diabetes.
- Adapted from: DeFronzo RA. *Diabetes.* 2009;58:773–795; 2.
- Adapted from: Tahrani AA, et al. *Lancet*. 2011;378:182–197.

Vecchi farmaci e rene

TABLE 1 Renoprotective effects of antidiabetic drugs

Antidiabetic agents	Reno-protective effects
Insulin	Re-stores podocytes function, normalized blood glucose, and suppresses subsequent inflammation and oxidative stress, keeps GFB integrity
SGLT2i	Reduces albuminuria secondary to lower blood glucose and subsequent oxidative stress
Biguanides	Suppresses oxidative damage and inflammatory responses, suppresses PDs apoptosis, improves endothelial dysfunction, metabolic control, blood pressure, lipid profile, and insulin sensitivity
Thiazolidinediones	Suppresses the loss of anionic charges of GFB, inhibits of hyperinsulinemia, hyperglycemia, high blood pressure, endothelial dysfunction, renal cells proliferation, and renal inflammation
Sulfonylureas	No evidence of a renoprotective effect
DPP-4 inhibitors	Reduces albuminuria via lowering blood glucose and blood pressure, suppresses endothelial-to-mesenchymal transition; oxidative stress and lipotoxicity and inhibit lipotoxicity-mediated inflammation, fibrosis, and apoptosis
GLP-1 receptor agonists	Same effect to DPP-4 inhibitors, declines albuminuria dependent to hypoglycemic effects and lowering blood pressure, also suppresses oxidative stress and lipotoxicity, and inhibit lipotoxicity-mediated inflammation, fibrosis, and apoptosis

Note. DPP-4: dipeptidyl peptidase-4; GFB: glomerular filtration barrier; GLP-1: glucagon-like peptide-1; PDs: podocytes.

Diabetologia (2017) 60:1586–1593
DOI 10.1007/s00125-017-4336-x

REVIEW

Metformin: clinical use in type 2 diabetes

Elizabeth Sanchez-Rangel[1] · **Silvio E. Inzucchi**[1]

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Abstract Metformin is one of the most popular oral glucose-lowering medications, widely considered to be the optimal initial therapy for patients with type 2 diabetes mellitus. Interestingly, there still remains controversy regarding the drug's precise mechanism of action, which is thought to involve a reduction in hepatic glucose production. It is now recommended as first-line treatment in various guidelines, including that of the EASD and ADA. Its favoured status lies in its efficacy, low cost, weight neutrality and good safety profile. Other benefits have also been described, including improvements in certain lipids, inflammatory markers, and a reduction in cardiovascular events, apparently independent from the drug's glucose-lowering effect. Data have emerged questioning the previous reluctance to use this agent in those with mild to moderate chronic kidney disease. Regulations guiding its use in patients with stable, modest renal dysfunction have, as a result, become more lenient in recent years. With no long-term studies comparing it against newer glucose-lowering drugs, some of which have more robust evidence for cardioprotection, metformin's established role as 'foundation therapy' in type 2 diabetes may justifiably be challenged.

Keywords Biguanides · Glucose-lowering therapy · Metformin · Review · Type 2 diabetes mellitus

Electronic supplementary material The online version of this article (doi:10.1007/s00125-017-4336-x) contains a slideset of the figures for download, which is available to authorised users.

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Abbreviations

DPP-4	Dipeptidyl peptidase-4
DPPOS	Diabetes Prevention Program Outcomes Study
eGFR	Estimated GFR
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
MALA	Metformin-associated lactic acidosis
Metformin XR	Extended-release metformin
SGLT2	Sodium–glucose cotransporter 2
UKPDS	UK Prospective Diabetes Study

Introduction

Metformin hydrochloride, a biguanide, is the most popular oral glucose-lowering medication in most countries, widely viewed as 'foundation therapy' for individuals with newly diagnosed type 2 diabetes mellitus. This reputation has resulted from its effective glucose-lowering abilities, low cost, weight neutrality, overall good safety profile (especially the lack of hypoglycaemia as an adverse effect), and modest evidence for cardioprotection [1]. A derivative of guanidine, which was initially extracted from the plant *Galega officinalis* or French lilac, metformin was first synthesised in 1922 and introduced as a medication in humans in 1957, after the studies of Jean Sterne [2]. Its popularity increased after eventual approval in the USA in 1994, although it was used extensively in Europe and other regions of the world prior to that [3]. The drug's efficacy has been demonstrated in monotherapy as well as in combination with other glucose-lowering medications for type 2 diabetes mellitus. Based on these important characteristics, there continues to be extensive interest in this compound, even now, many years after its



Is It Time to Change the Type 2 Diabetes Treatment Paradigm? No! Metformin Should Remain the Foundation Therapy for Type 2 Diabetes

Silvio E. Inzucchi

Diabetes Care 2017;40:1128–1132 | https://doi.org/10.2337/dc16-2372

Table 2—Randomized clinical trials involving metformin and CVD outcomes

Trial/year	Comparison	Study population	*N*	Main CVD outcome(s)	HR (95% CI)	*P*
UKPDS 34 (4) (1998)	Metformin vs. diet Metformin vs. SU/insulin	Overweight, newly diagnosed T2D patients	1,704	All-cause mortality Myocardial infarction	0.64 (0.45, 0.91) 0.61 (0.41, 0.89)	NR 0.010
HOME (6) (2009)	Metformin vs. placebo	T2D patients on insulin	390	Expanded MACE*	0.61 (0.40, 0.94)	0.02
SPREAD-DIMCAD (7) (2013)	Metformin vs. glipizide	T2D patients with CAD	304	Expanded MACE†	0.54 (0.30, 0.90)	0.026

CAD, coronary artery disease; MACE, major adverse cardiovascular events; NR, not reported; SU, sulfonylurea. *Myocardial infarction, acute coronary syndrome, coronary or peripheral revascularization, electrocardiogram changes, heart failure, stroke/transient ischemic attack. †Cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization.

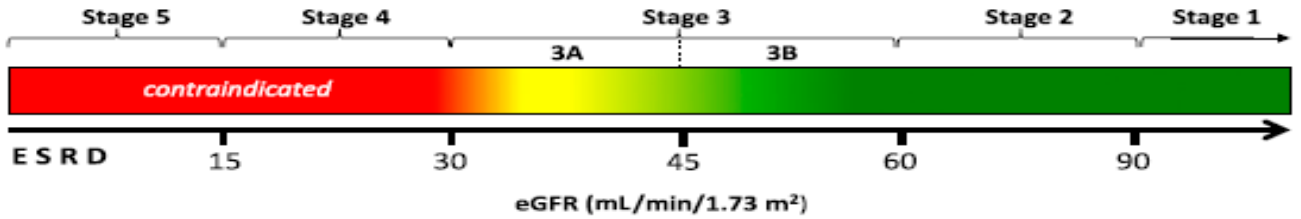


Figure 2—Recently updated U.S. Food and Drug Administration guidelines for the use of metformin in CKD. Metformin may now be used in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 but is contraindicated in those with an eGFR <30 mL/min/1.73 m^2. If eGFR falls <45 mL/min/1.73 m^2, the benefits and risks of continuing treatment should be assessed. Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. ESRD, end-stage renal disease.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2012, Article ID 210821, 9 pages
doi:10.1155/2012/210821

MET

Research Article

Renal Podocyte Injury in a Rat Model of Type 2 Diabetes is Prevented by Metformin

Measures of Podocyte loss

Junghyun Kim, Eunjin Shon, Chan-Sik Kim, and Jin Sook Kim

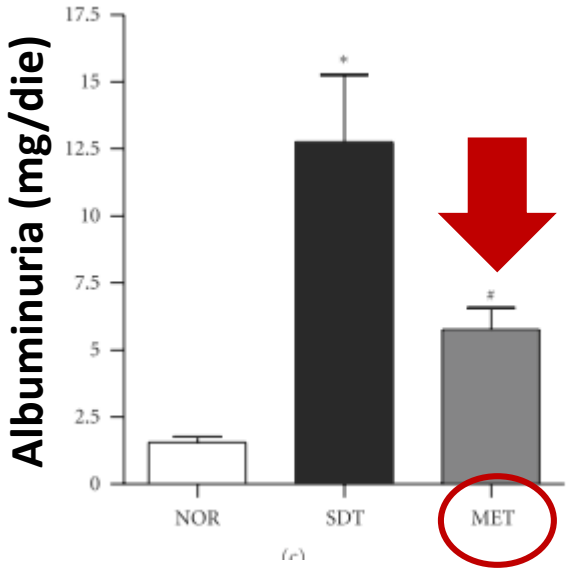


Figure 1: Renal histopathology and function(a). Periodic acid-Schiff staining of glomeruli, ×400 magnification (b). Masson's trichrome stained renal sections, ×400 magnification (c). Albuminuria in normal rat (NOR), spontaneously diabetic Torii rat (SDT) and SDT rat treated with 350 mg/kg metformin (MET). All data are expressed as mean ± SE ($n = 8$). $^{*}P < 0.01$ versus NOR group, $^{\sharp}P < 0.01$ versus SDT group.

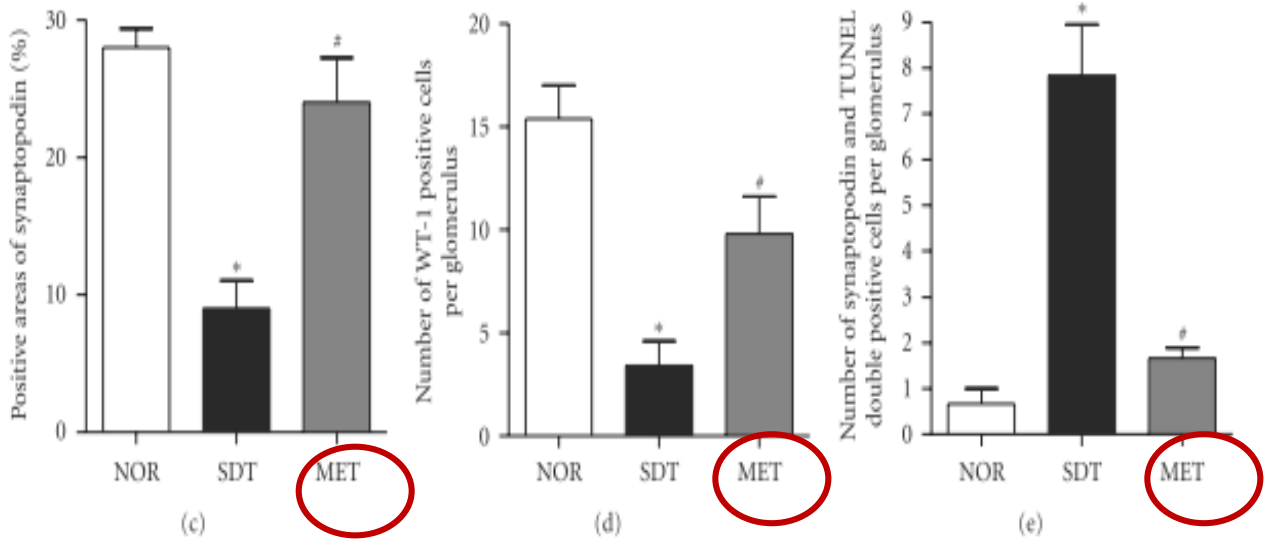


Figure 3: Podocyte loss. A representative photomicrograph of (a) dual labelling for TUNEL (black) and synaptopodin (red) and (b) WT-1 (black). ×400 magnification. Double-positive cells (magnified inset) indicates the colocalization of the podocyte marker and apoptosis. Quantitative analyses of (c) positive areas of synaptopodin, (d) positive cells of WT-1 and (e) TUNEL and synaptopodin-double-positive cells. All data are expressed as mean ± SE ($n = 8$). $^{*}P < 0.01$ versus NOR group, $^{\sharp}P < 0.01$, versus SDT group.

ELSEVIER

MET

Archives of Medical Research

Archives of Medical Research 31 (2000) 571–575

ORIGINAL ARTICLE

The Short-Term Effect of a Switch from Glybenclamide to Metformin on Blood Pressure and Microalbuminuria in Patients with Type 2 Diabetes Mellitus

Norma Amador-Licona,* Juan-Manuel Guízar-Mendoza,** Enrique Vargas,*** Guillermo Sánchez-Camargo**** and Lilia Zamora-Mata*

Background. Renal hyperfiltration and albuminuria have a deleterious effect on kidney function. Therefore, we studied the effect of metformin on blood pressure, renal hemodynamics, and microalbuminuria in type 2 diabetic patients.

Methods. A clinical trial was designed in type 2 diabetic patients with incipient nephropathy. All patients were below the age of 65, normotensive, and without evidence of malignant, hepatic, or cardiovascular disorders. They were randomly allocated to receive glybenclamide or metformin. At baseline and 12 weeks thereafter we measured body mass index (BMI), serum insulin, blood glucose, lipid profile, glycosylated hemoglobin, blood pressure, glomerular filtration rate, renal plasma flow, and urine albumin.

Results. We studied 23 patients in the glybenclamide group and 28 in the metformin group. There was no difference in baseline variables between the groups. Metabolic control was obtained in both groups. In the metformin group, all the following variables decreased: microalbuminuria was reduced by a mean of 24.2 mg/day ($p = 0.008$); systolic and diastolic blood pressure by a mean of 5.3 mmHg ($p = 0.002$) and 3.93 mmHg ($p = 0.009$), respectively; insulin levels by an average of 11.8 μIU/mL ($p = 0.001$), and total cholesterol levels and triglycerides by an average of 0.45 and 0.18 mmol/L, respectively. Insulin resistance measured by the homeostasis model decreased more in the metformin group than in the glybenclamide group. Patients treated with glybenclamide had an increase in HDL cholesterol of 0.082 mmol/L ($p = 0.01$).

Conclusions. Metformin significantly decreased the urine albumin excretion rate with none of the expected changes in renal hemodynamics, probably due to its favorable effects on blood pressure, lipid profile, metabolic control, and insulin resistance. © 2001 IMSS. Published by Elsevier Science Inc.

Table 2. Metabolic and hemodynamic measurements before and 12 weeks after the administration of glybenclamide or metformin in patients with incipient diabetic nephropathy

	Glybenclamide ($n = 23$)			Metformin ($n = 28$)		
	Baseline	Final	*p* value	Baseline	Final	*p* value
Weight (kg)	73.2 ± 11.8	74.1 ± 12.6	0.1	70.7 ± 14.8	69.6 ± 14.3	0.07
Glycated hemoglobin (%)	8.4 ± 1.4	7.6 ± 0.8	0.009	8.5 ± 1.5	7.6 ± 0.8	0.003
Total cholesterol (mmol/L)	4.8 ± 1	4.9 ± 1.1	0.47	5.1 ± 0.85	4.6 ± 0.9	0.002
HDL cholesterol (mmol/L)	0.94 ± 0.18	1.0 ± 0.28	0.01	0.82 ± 0.23	0.91 ± 0.23	0.0001
Triglycerides (mmol/L)	1.96 ± 0.92	1.87 ± 1.1	0.67	2.2 ± 0.92	2.0 ± 0.74	0.04
Insulin (mIU/mL)	19.2 (8.5–69.4)	18.3 (3.7–48.4)	0.62	22.4 (5.94–86)	11.9 (6.89–41.3)	0.001
HOMA IR	6.5 (2.9–29.6)	5.7 (.62–16.1)	0.013	7.2 (1.8–30.7)	3.8 (1.1–10.4)	0.0001
Systolic blood pressure (mmHg)	120 (100–140)	130 (100–140)	0.18	120 (100–140)	115 (100–140)	0.002
Diastolic blood pressure (mmHg)	70 (70–85)	80 (60–90)	0.16	75 (60–85)	70 (60–80)	0.009
Microalbuminuria (mg/d)	83 (32–198)	102 (16.3–255)	0.09	74 (33–200)	49 (0–244)	0.008
Renal plasma flow (mL/min)	607 ± 79	593 ± 100	0.4	586 ± 92	566 ± 100	0.37
Glomerular filtration rate (mL/min)	136 ± 29	151 ± 39	0.04	138 ± 28	134 ± 24	0.46

Current Diabetes Reports (2018) 18: 97
https://doi.org/10.1007/s11892-018-1064-7

MICROVASCULAR COMPLICATIONS—NEPHROPATHY (M AFKARIAN AND B ROSHANRAVAN, SECTION EDITORS)

Metabolic Abnormalities in Diabetes and Kidney Disease: Role of Uremic Toxins

Laetitia Koppe[1,2] · Denis Fouque[1,2] · Christophe O. Soulage[2]

The Gut- Kidney Axis in diabetes

Fattori di rischio

Terapia

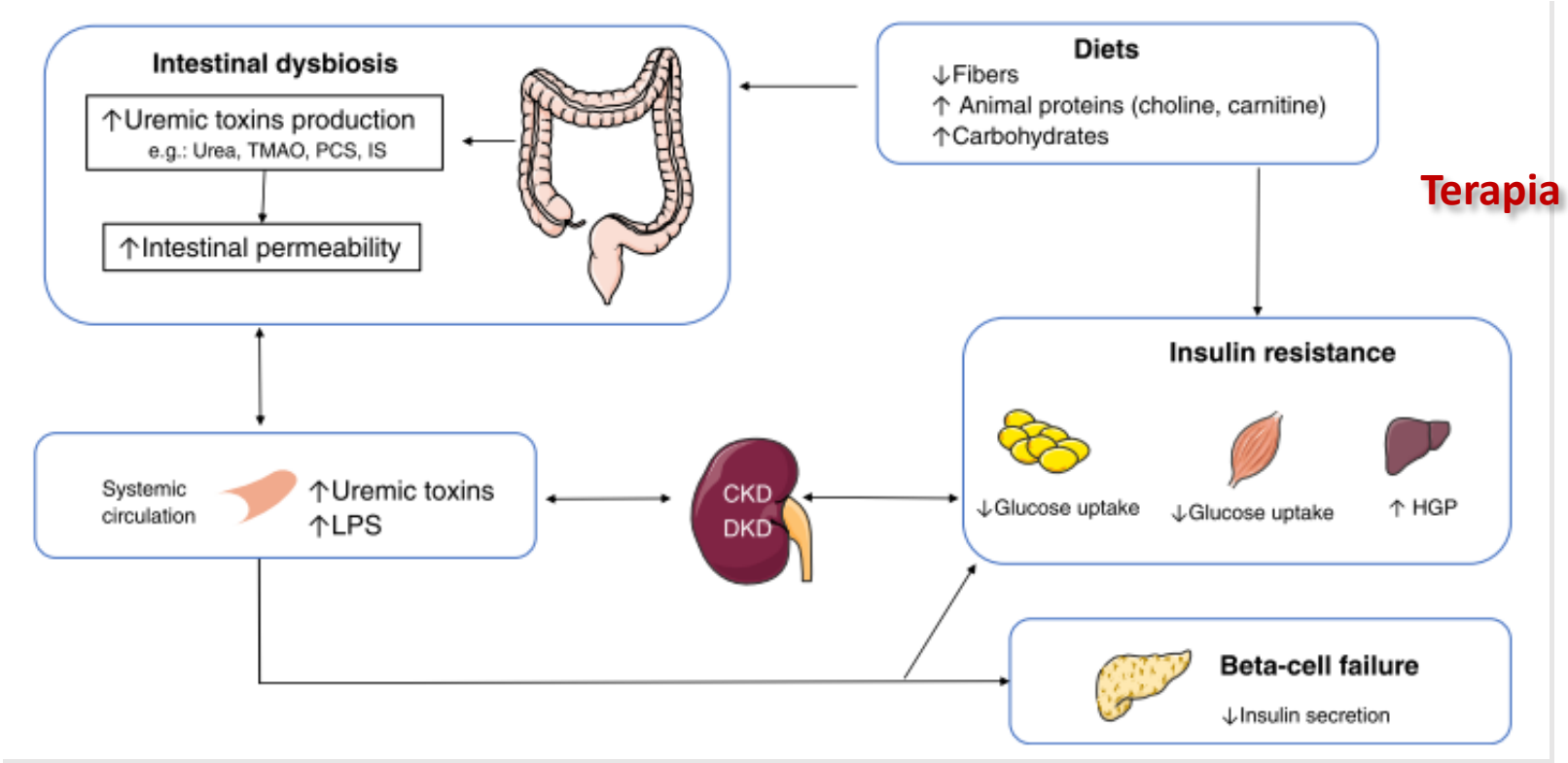
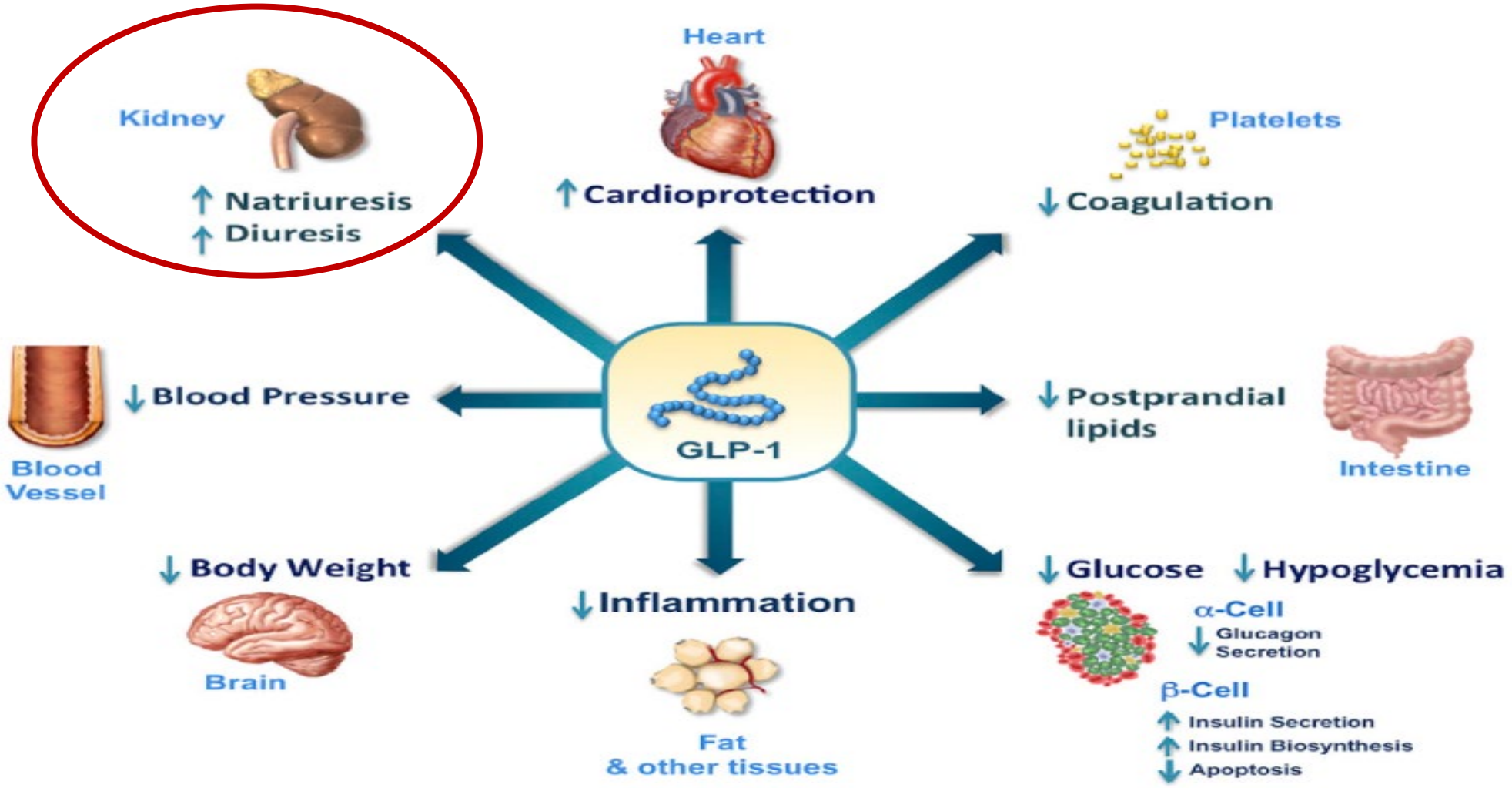


Fig. 1 The role of gut–kidney axis in diabetes and metabolic complications of CKD. Dysbiosis induced by an imbalanced or/and excess of nutrients leads to overproduction and accumulation of URS (e.g., PCS, IS, urea, TMAO) in the intestine. This accumulation disrupts the gut barrier and increases gut permeability. Consequently, influx of LPS and URS into the kidney via the circulation contributes to renal failure, insulin resistance, and β cell failure. These pathological events in the gut and kidney substantially contribute to the development of metabolic complications and CKD. HGP: hepatic glucose production; LPS: lipopolysaccharides; TMAO: trimethylamine N-oxide; IS: indoxyl sulfate; PCS: p-cresyl sulfate; DKD: diabetic kidney disease; CKD: chronic kidney disease

GLP-1: Beyond glycaemic control



CV, cardiovascular; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor;
Drucker DJ. *Cell Metab* 2016;24:15–30.

Putative renal distribution of GLP-1 and membrane-bound DPP-4

Box 1 | **Putative renal distribution of GLP-1 and membrane-bound DPP-4**

GLP-1

The majority of glucagon-like peptide 1 (GLP-1) actions *in vivo* are transduced by the GLP-1 receptor (GLP-1R). This G-protein-coupled receptor was originally identified in islet β-cells, but its expression has now been reported in numerous extrapancreatic tissues, including the lung, brain, enteric and peripheral nervous systems, lymphocytes, heart and blood vessels and various locations in the kidney. Most of the commercially available antisera that are used to detect GLP-1R expression (by immunohistochemistry or western blot analysis) are neither sensitive nor specific, and important control experiments are frequently absent. Furthermore, interspecies differences might hamper exact mapping of the distribution of a functional GLP-1R. A study that used the most extensively validated monoclonal antibody to date showed that in primate kidneys, GLP-1R is exclusively expressed in preglomerular vascular smooth muscle cells and juxtaglomerular cells[106].

Membrane-bound DPP-4

Dipeptidyl peptidase 4 (DPP-4) is highly active and abundantly expressed in the kidney. The highest level of expression of DPP-4 is at the brush border of the S1–S3 segment of the proximal tubule (where it is functionally coupled to intestinal sodium–hydrogen exchanger isoform 3). Lower expression levels are present at other sites in the nephron and tubulointerstitium. The results of studies that analysed the renal distribution of GLP-1R and/or DPP-4 in the kidneys of various organisms are summarized below.

Location	Species	mRNA or protein	Detection method	Refs
GLP-1R				
Preglomerular* vascular smooth muscle cells	Monkey; human	Protein	Immunohistochemistry	106
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1 agonist) and exendin 9–39 (GLP-1R antagonist)	103
Hilar and intralobular arteries	Human	Protein	Autoradiography of ^{125}I-labelled GLP-1	105
Glomerular capillary and vascular walls	Mouse	mRNA	*In situ* hybridization; RT-PCR	102
Glomerular endothelial cells and macrophages	Rat	Protein	Immunofluorescence	104
Glomerulus (not specified)	Rat	mRNA	RT-PCR	101
Juxtaglomerular cells	Monkey; human	Protein	Immunohistochemistry	106
	Rat	Protein	Immunohistochemistry	103
Proximal tubule	Rat	mRNA	RT-PCR	101
	Pig; human	mRNA, protein	RT-PCR, immunocytochemistry, immunohistochemistry, Western blotting	107
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1R agonist) and exendin 9–39 (GLP-1R antagonist)	103
Membrane-bound DPP-4				
Preglomerular vascular smooth muscle cells	Rat	mRNA, protein	RT-PCR, Western blotting	252
Mesangial cells	Rat	mRNA, protein	RT-PCR, Western blotting	252
Podocytes	Rat	Protein	Immunohistochemistry	253
Proximal tubule	Pig; human	mRNA	RT-PCR, immunocytochemistry	107
	Rat	Protein	Immunohistochemistry	253
Loop of Henle, distal convoluted tubule, connecting tubule, cortical collecting duct	Rat	mRNAs	Deep sequencing of RNA species	254

*Afferent arterioles, interlobular arteries and arcuate arteries.

Keizo Kanasaki,[1] Sen Shi,[1] Megumi Kanasaki,[1] Jianhua He,[1] Takako Nagai,[1] Yuka Nakamura,[2] Yasuhito Ishigaki,[2] Munehiro Kitada,[1] Swayam Prakash Srivastava,[1] and Daisuke Koya[1]

Linagliptin-Mediated DPP-4 Inhibition Ameliorates Kidney Fibrosis in Streptozotocin-Induced Diabetic Mice by Inhibiting Endothelial-to-Mesenchymal Transition in a Therapeutic Regimen

Diabetes 2014;63:2120–2131 | DOI: 10.2337/db13-1029

DPP4 i

Kidney fibrosis is the final common pathway of all progressive chronic kidney diseases, of which diabetic nephropathy is the leading cause. Endothelial-to-mesenchymal transition (EndMT) has emerged as one of the most important origins of matrix-producing fibroblasts. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been introduced into the market as antidiabetes drugs. Here, we found that the DPP-4 inhibitor linagliptin ameliorated kidney fibrosis in diabetic mice without altering the blood glucose levels associated with the inhibition of EndMT and the restoration of microRNA 29s. Streptozotocin-induced diabetic CD-1 mice exhibited kidney fibrosis and strong immunoreactivity for DPP-4 by 24 weeks after the onset of diabetes. At 20 weeks after the onset of diabetes, mice were treated with linagliptin for 4 weeks. Linagliptin-treated diabetic mice exhibited a suppression of DPP-4 activity/protein expression and an amelioration of kidney fibrosis associated with the inhibition of EndMT. The therapeutic effects of linagliptin on diabetic kidneys were associated with the suppression of profibrotic programs, as assessed by mRNA microarray analysis. We found that the induction of DPP-4 observed in diabetic kidneys may be associated with suppressed levels of microRNA 29s in diabetic mice; linagliptin restored microRNA 29s and suppressed DPP-4 protein levels. Using cultured endothelial cells, we found that linagliptin inhibited TGF-β2–induced EndMT, and such anti-EndMT effects of linagliptin were mediated through microRNA 29 induction. These results indicate the possible novel pleiotropic action of linagliptin to restore normal kidney function in diabetic patients with renal impairment.

Diabetic nephropathy is a leading cause of kidney disease, which progresses into end-stage renal disease, requiring kidney replacement therapy (1,2). Glycemic control could be essential for therapies combating diabetic nephropathy, although normalizing the blood glucose levels in such patients with appropriate monitoring is challenging (2). Therefore, to prevent/retard diabetic nephropathy, in addition to achieving proper glycemic control, strategies that are not directly related with blood glucose normalization are required.

Fibrosis in the kidney is the final common pathway of progressive kidney diseases and results in the destruction of the kidney structure and the deterioration of the kidney filtration function (3–8). Kidney fibrosis is caused

Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 361–373

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Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

Dipeptidyl peptidase-4 inhibition in chronic kidney disease and potential for protection against diabetes-related renal injury

G. Penno*, M. Garofolo, S. Del Prato

Section of Diabetes and Metabolic Disease, Department of Clinical and Experimental Medicine, University of Pisa, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

Urinary ACR in SAVOR TIMI 53

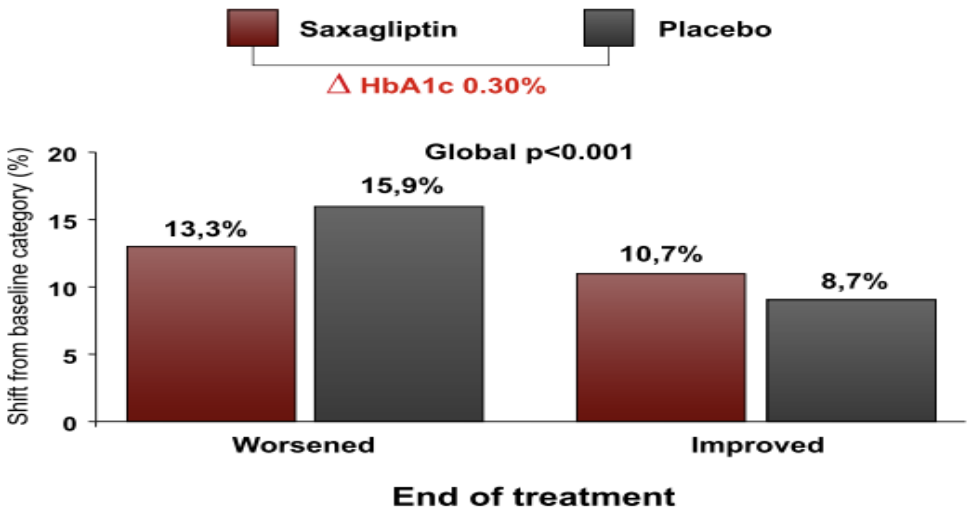
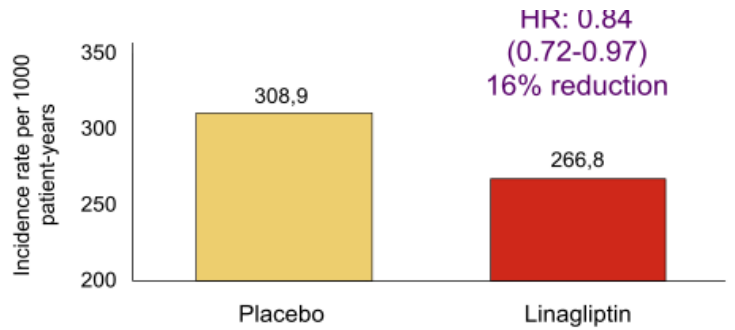


Figure 2 Treatment difference in the proportions of patients with worsening or improved urinary ACR in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) trial (SAVOR—TIMI 53). Any change is defined as a shift from the baseline category to the category achieved at the end of the study (<3.4, ≥3.4 to ≤33.9, or ≥33.9 mg/mmol). This end point was reached in 12,360 patients [48].

COMPOSITE RENAL ENDPOINT MAU + loss eGFR>50% + acute renal failure + death any cause in Linagliptin Pooled Analysis



Renal events	306	448
Time at risk, years	991	1679
Patients, n	1961	3505

Microalbuminuria, macroalbuminuria, CKD (sCR >2.8 mg/dl), worsening of CKD (loss eGFR >50% of baseline, acute renal failure, death from any cause

Figure 1 Renal outcomes with linagliptin: a meta-analysis of individual data for 5466 patients with type 2 diabetes. The primary composite renal outcome was seen in 448 (12.8%) subjects in the linagliptin group and 306 (15.6%) in the placebo group. The composite outcome is defined as microalbuminuria (first documented urinary ACR ≥ 30 mg/g), macroalbuminuria (first documented urinary ACR ≥ 300 mg/g), CKD (first documented serum creatinine ≥ 2.83 mg/dl, ≥250 μmol/l), worsening of CKD (loss in eGFR > 50% compared with baseline), acute renal failure, and death of any cause [42].

From: **Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal RiskThe CARMELINA Randomized Clinical Trial**

JAMA. Published online November 09, 2018. doi:10.1001/jama.2018.18269

COMPOSITE RENAL: first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥ 40% in eGFR from baseline

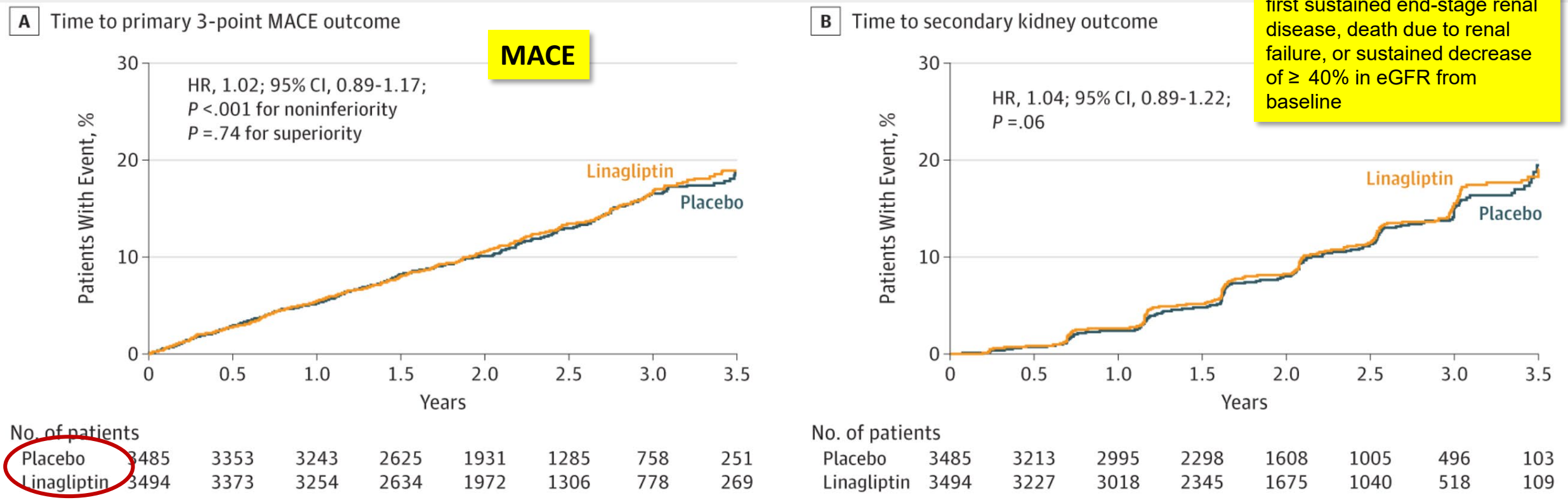


Figure Legend:

Time to Primary and Secondary OutcomesHazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo. B, **Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥ 40% in estimated glomerular filtration rate from baseline).**

Median observation time was 1.9 years (IQR, 1.2-2.6) for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

Date of download: 11/27/2018

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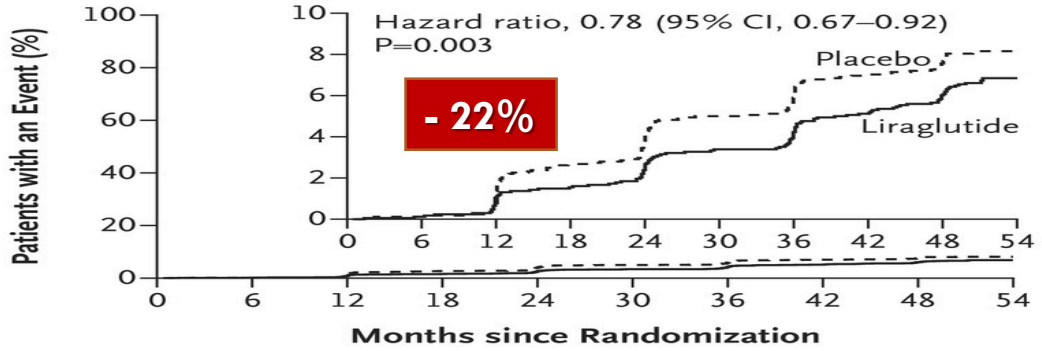
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE



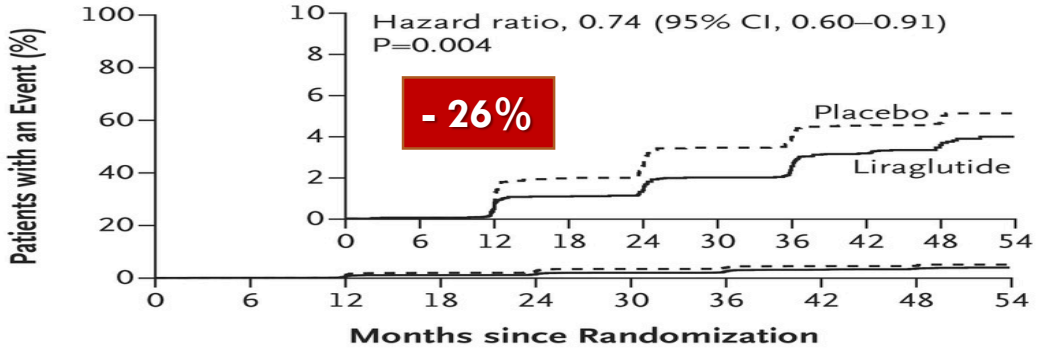
Liraglutide and Renal Outcomes in Type 2 Diabetes

A Composite Renal Outcome



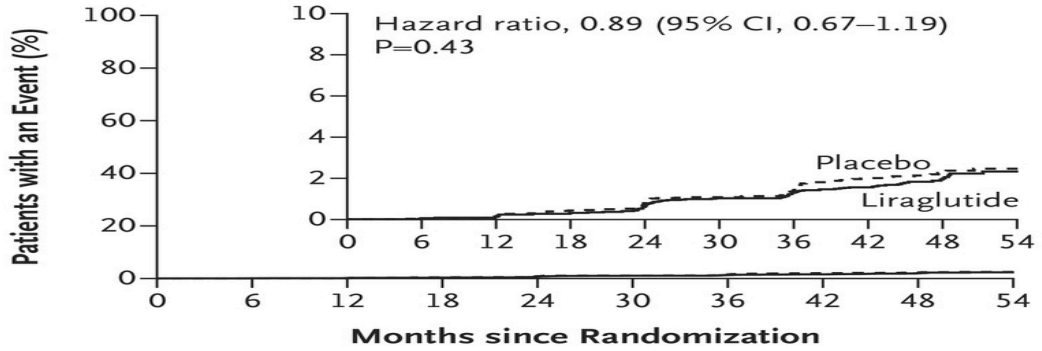
No. at Risk										
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454

B New Onset of Persistent Macroalbuminuria



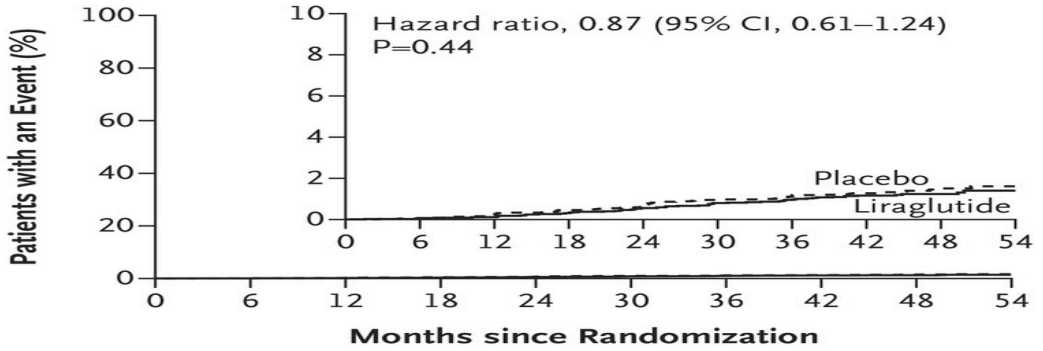
No. at Risk										
Placebo	4672	4646	4551	4455	4359	4252	4162	4073	1642	442
Liraglutide	4668	4638	4570	4508	4437	4353	4268	4182	1662	461

C Persistent Doubling of Serum Creatinine Level



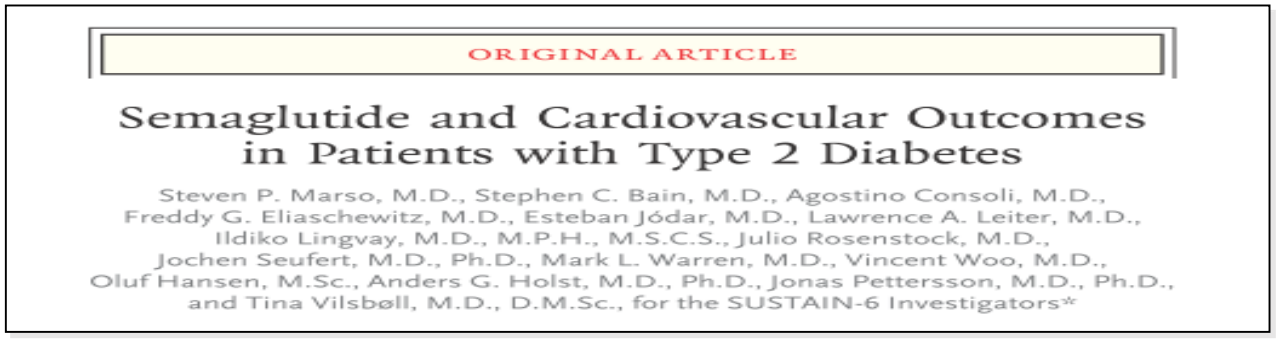
No. at Risk										
Placebo	4672	4647	4596	4529	4447	4367	4282	4196	1682	456
Liraglutide	4668	4639	4591	4544	4476	4403	4332	4264	1692	475

D Continuous Renal-Replacement Therapy



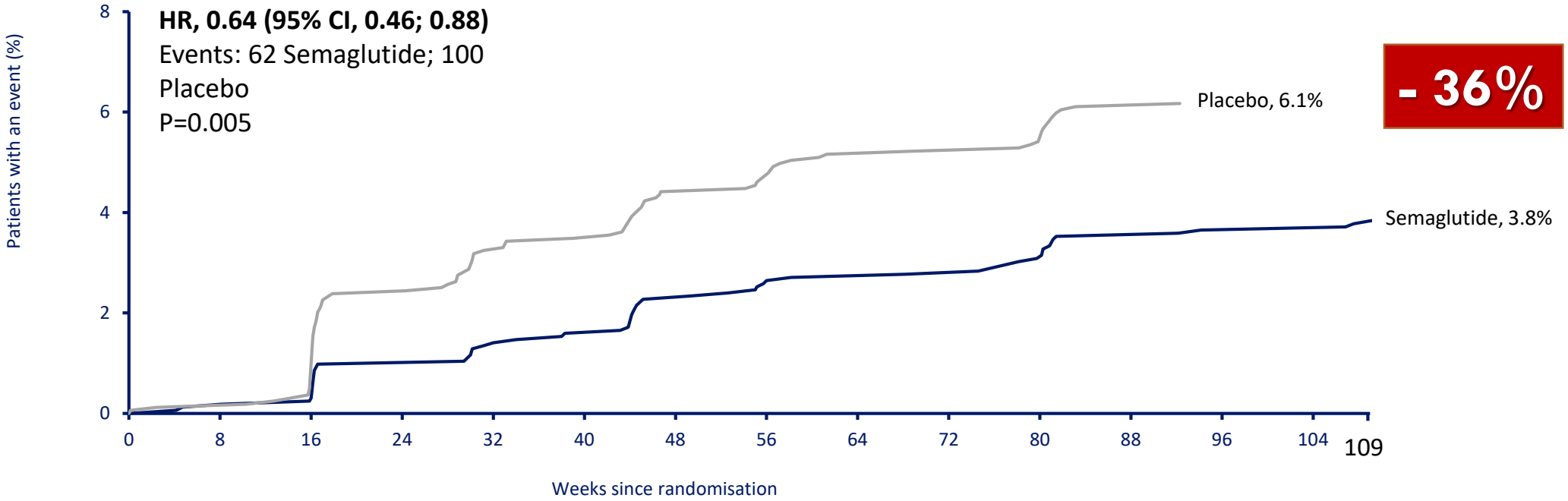
No. at Risk										
Placebo	4672	4645	4590	4527	4454	4370	4299	4227	1699	461
Liraglutide	4668	4640	4596	4547	4484	4416	4349	4282	1710	483

New or worsening nephropathy


ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

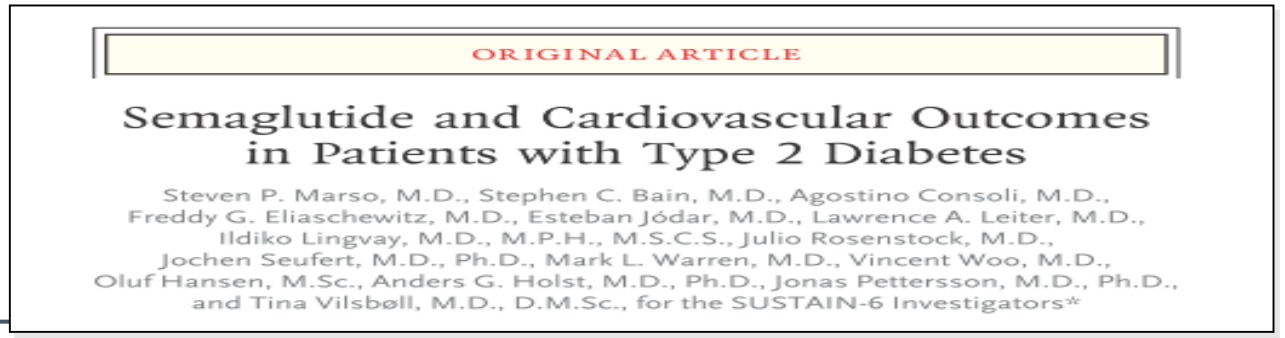


Number of patients at risk

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

Supplementary Figure 5B. 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.
Marso *et al. NEJM* [in press]

Microvascular outcomes



ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

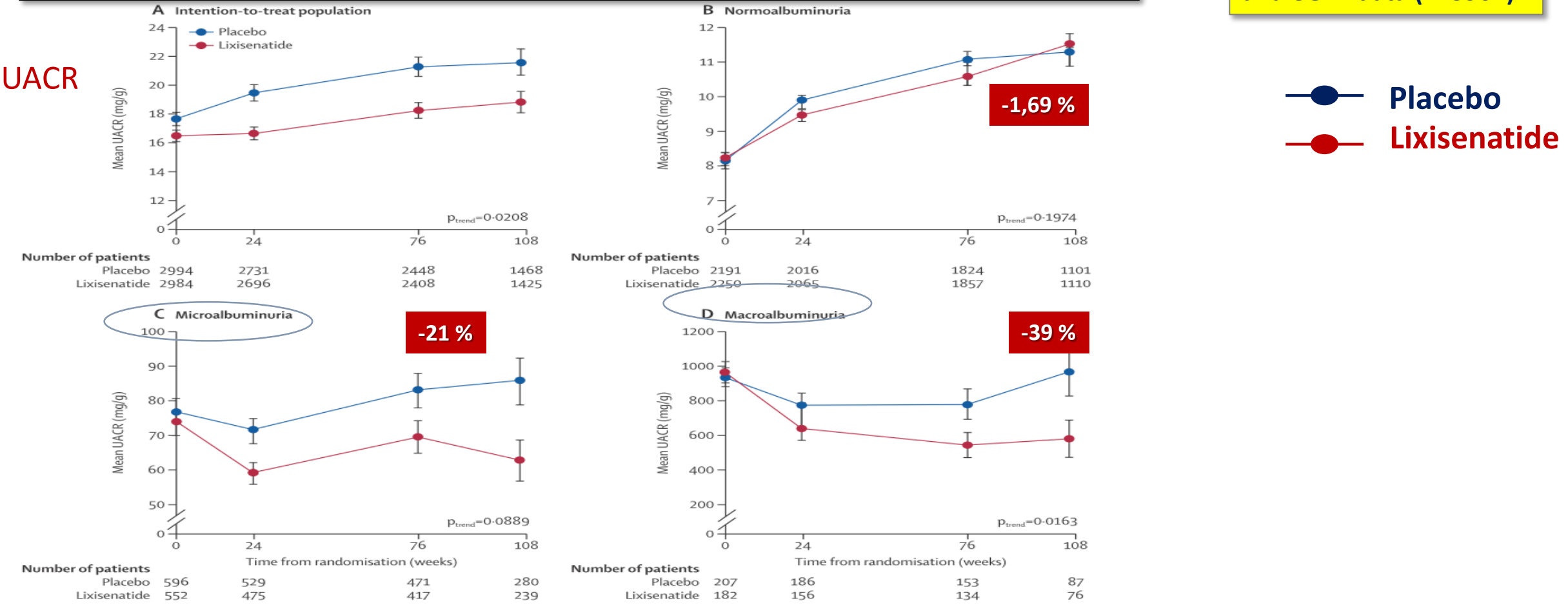
	HR (95% CI)		P value
Retinopathy complications	**1.76**	**1.11; 2.78**	**0.02**
Need for retinal photocoagulation	**1.91**	**1.11; 3.28**	**0.02**
Vitreous haemorrhage	**2.29**	**0.94; 5.57**	**0.07**
Need for treatment with intravitreal agent	**1.25**	**0.59; 2.56**	**0.58**
Onset of diabetes-related blindness	**5.01**	**0.59; 42.88**	**0.14**
New or worsening nephropathy	**0.64**	**0.46; 0.88**	**0.005**
Persistent macroalbuminuria	**0.54**	**0.37; 0.77**	**0.001**
Persistent doubling of serum creatinine level and creatinine clearance per MDRD <45 ml/min/1.73m2	**1.28**	**0.64; 2.58**	**0.48**
Need for continuous renal-replacement therapy	**0.91**	**0.40; 2.07**	**0.83**

Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial

ELIXA RENAL

in the safety population with baseline UACR and eGFR data (*n*=5962)

UACR



Placebo

Lixisenatide

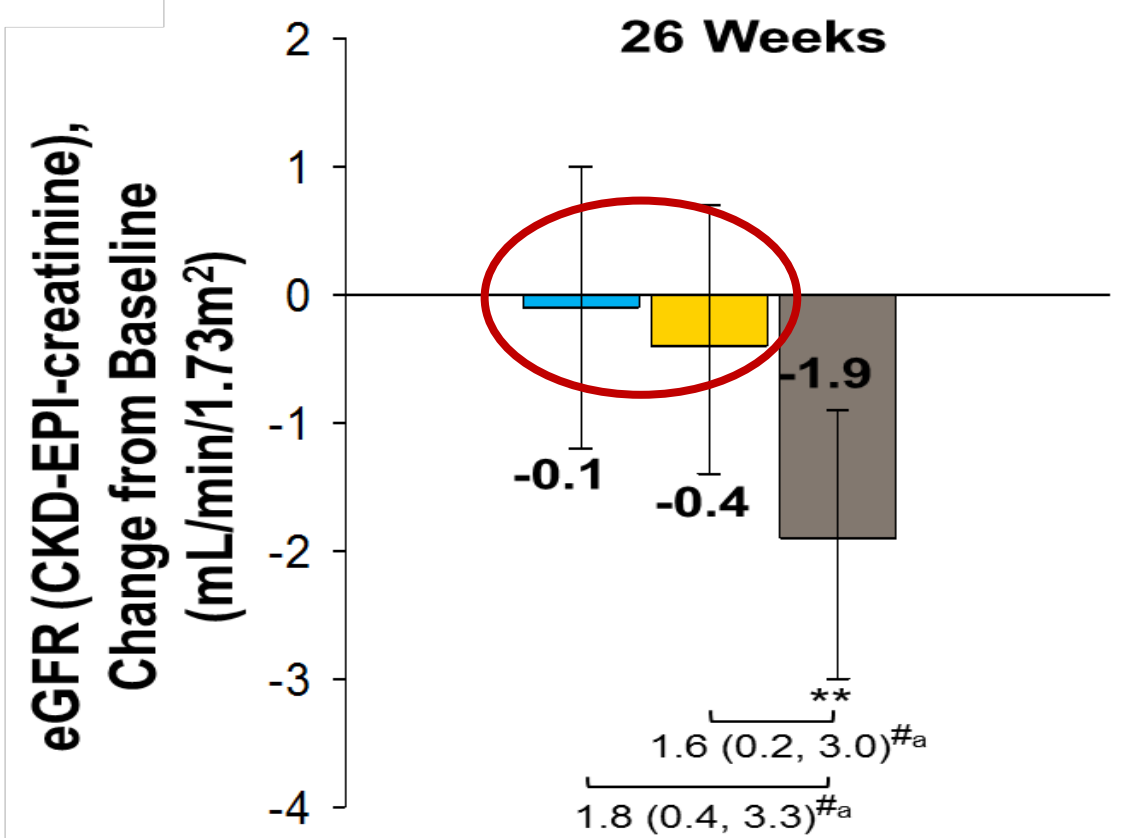
Muskiet MH, New Engl J Med 2018

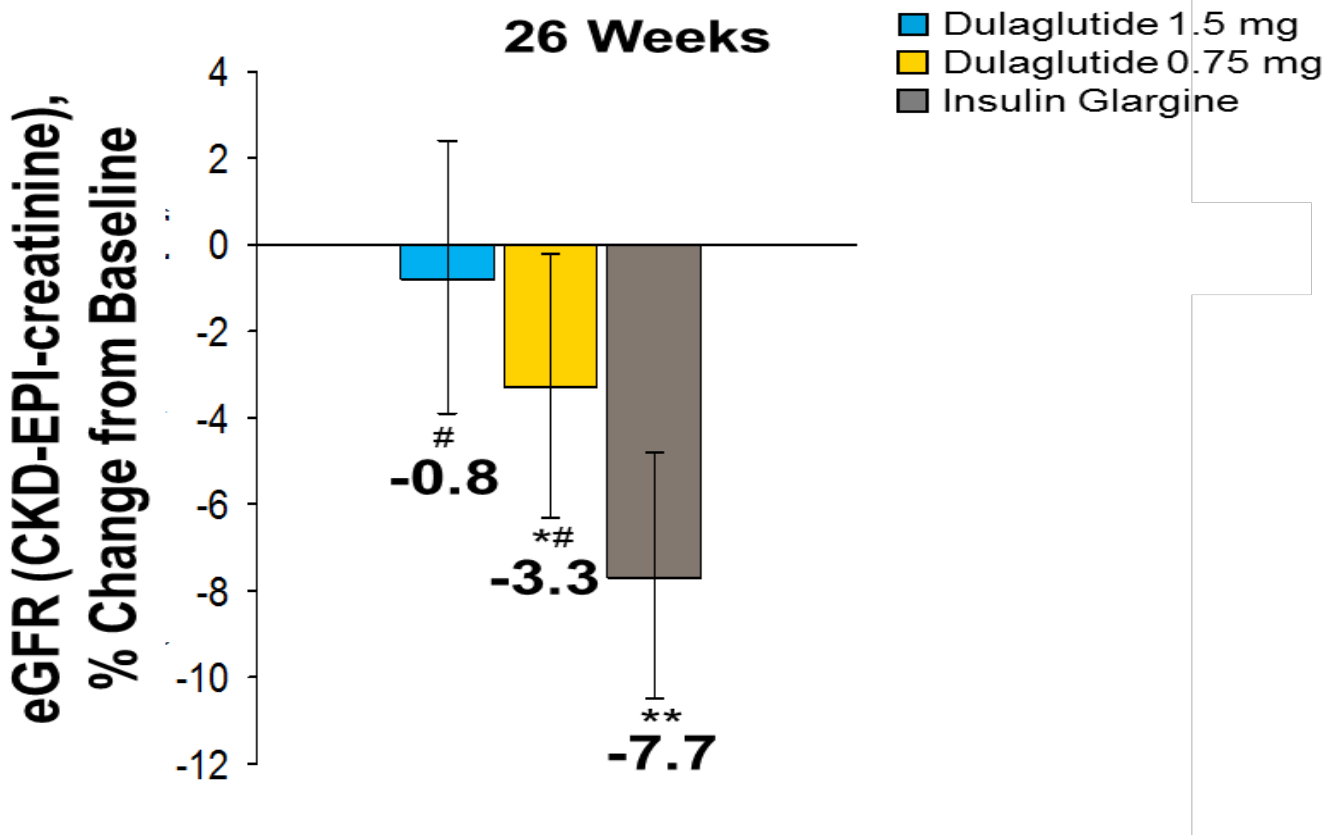
Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

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

Basal bolus *vs* Rapida + Dula

eGFR (CKD-EPI-creatinine) Change from Baseline and % Change from Baseline





Data presented as LSM (95% CI); Safety population, MMRM analysis; *,**p<0.05 or p<0.001 vs. BL; #p<0.05 vs. insulin glargine; [a]Treatment difference (nominal 95% CI), Safety population, MMRM. Abbreviations: BL=baseline; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; eGFR=estimated glomerular filtration rate; LSM=least squares mean; MMRM=mixed effect model repeat measures

Glucose-independent effects of incretin-based therapies on renal risk factors in type 2 diabetes mellitus

Table 2 | **Glucose-independent effects of incretin-based therapies on renal risk factors in type 2 diabetes mellitus**

Renal risk factor	GLP-1RA	DPP-4 inhibitor	Putative GLP-1-mediated mechanisms	Putative GLP-1-independent mechanisms of DPP-4 inhibitors
Obesity	Decrease	Neutral effect	↓Appetite (direct effect on CNS or via vagal afferents, ↓GEE* and ↑nausea) ↑Energy expenditure[35]? ↑Natriuresis and/or diuresis?	Effect possibly counteracted by ↑PYY (1–36) and ↓PYY (3–36)[257,258‡]
Blood pressure	Decrease	Decrease or neutral effect	↓Body weight ↑Endothelial independent vasodilation[259,260]? ↑Natriuresis[261§] ↓Intestinal sodium reabsorption[98]? ↓Sodium intake (direct effect on CNS)? ↓RAAS activity[87,127]? ↑ANP[130]?	↑Natriuresis (↑SDF1α[119], ↓DPP-4/NHE3 complex[262]?, ↑BNP[263]) ↑Vasodilation (↑BNP[263], ↑bradykinin) Effects possibly counteracted by ↑substance P (↑SNS activity) and ↑NPY (potentiates SNS activity) during concomitant ACE inhibition[127‖]
Dyslipidaemia	Decrease	Neutral effect	↓Body weight ↓Intestinal lipid uptake (partly by ↓GEE*) ↓Hepatic lipoprotein synthesis and secretion ↑Insulin sensitivity (partly by ↓body weight) ↑Insulin and ↓glucagon ↑Triglyceride uptake in white adipose tissue ↑Brown adipose tissue activation[169]	Effects possibly counteracted by factors related to steroid metabolism[264]
Inflammation and fibrosis	Decrease	Decrease	↓Renal ROS production (cAMP and PKA)[102,179] ↓AGE–RAGE-mediated renal ROS production (cAMP)[181,265,266] ↓Angiotensin II-induced renal ROS production (PKC)[182,183] ↑Adiponectin (reduces podocyte inflammation; PKA in adipocytes)[267]	↑SDF1α[119,268,269] ↓Profibrotic endothelial-to-mesenchymal transition[185,186¶]
Glomerular hyperfiltration	Decrease or neutral effect	Neutral effect	↑Tubuloglomerular feedback (by ↓NHE3 activity) ↓Postprandial glucagon (particularly short-acting GLP-1RA)[70,71,90]? ↓Body weight[90]? ↓GEE* (postprandial hyperfiltration)[90]? ↓RAAS activity[87,127]?	↑SDF1α[119]?

Potenziale Effetto nefroprotettivo del miglior controllo glicemico nei CVOTs

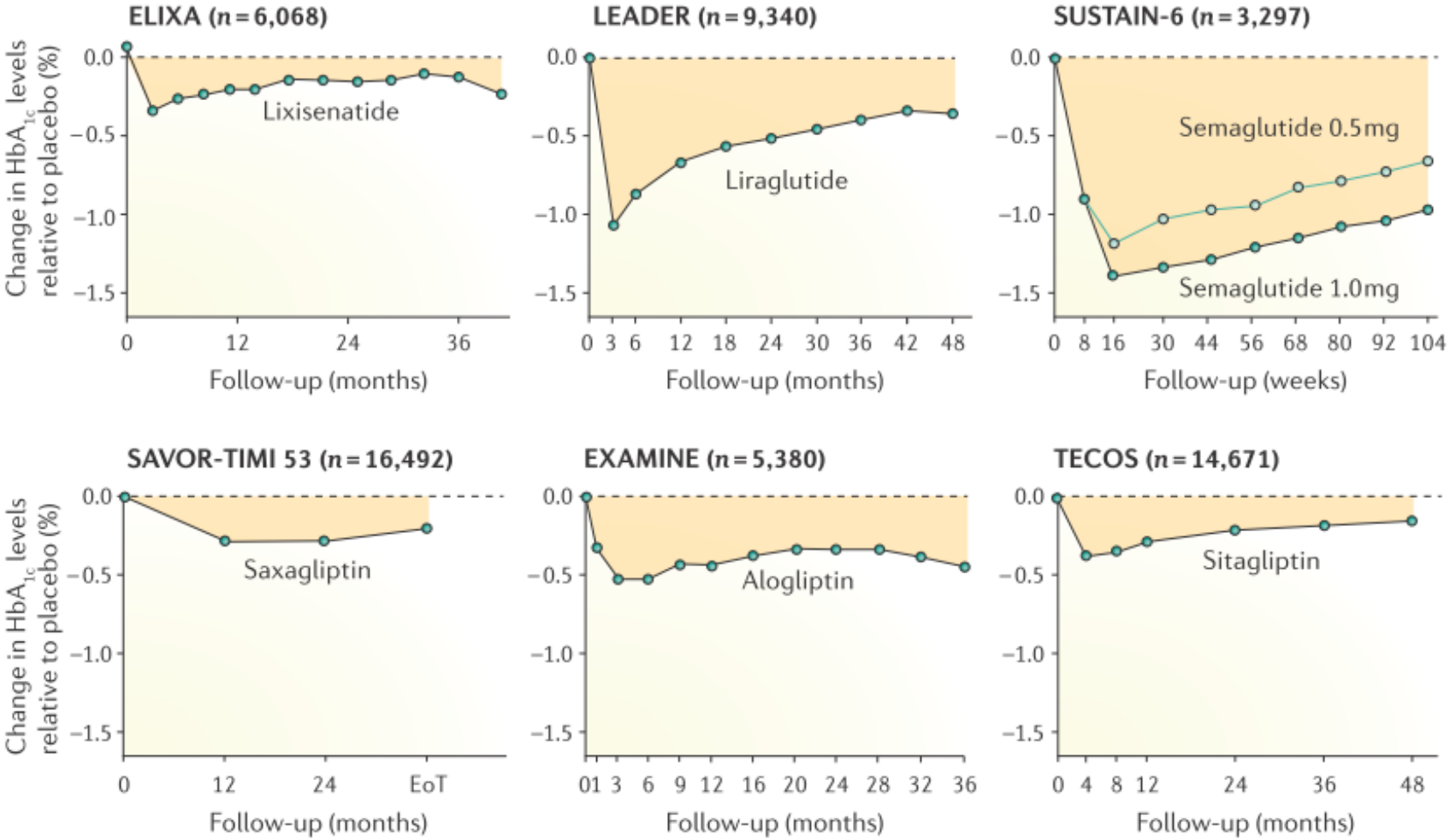
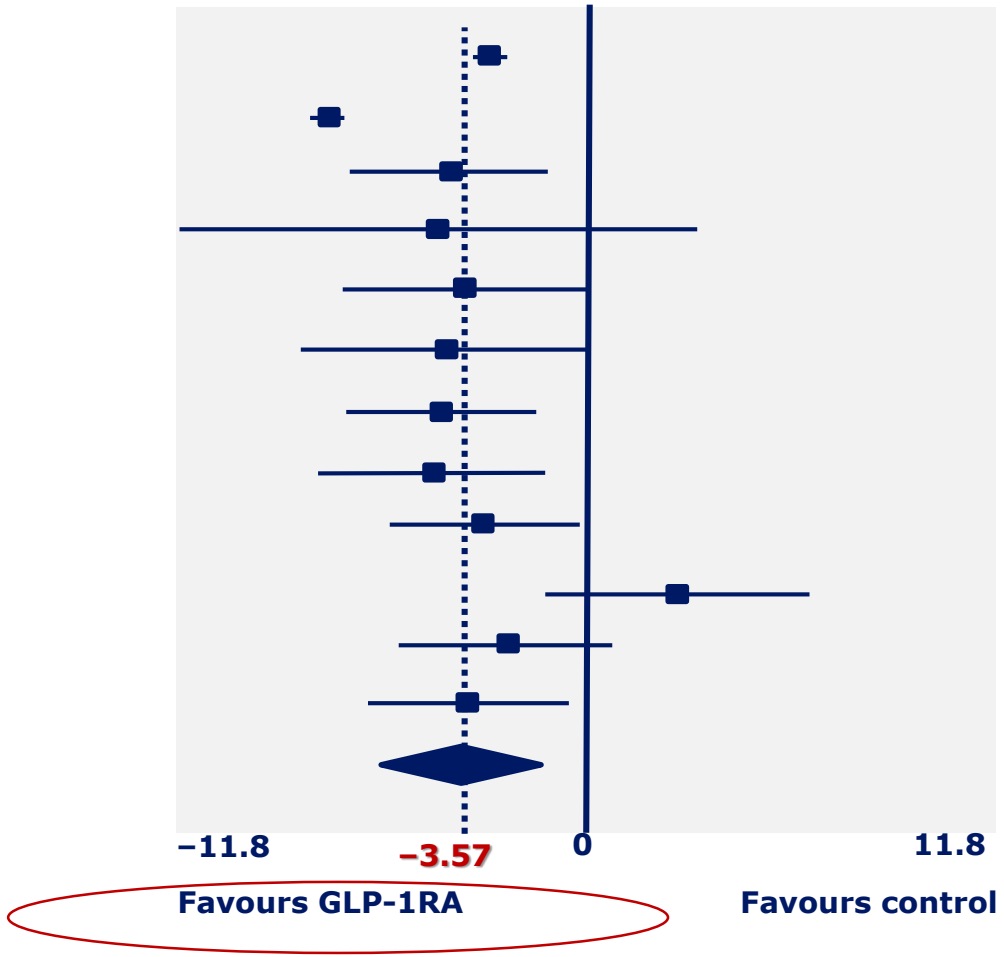


Figure 6 | **Differences in glycaemic control with the study drug versus placebo in cardiovascular outcome studies assessing the safety of incretin-based therapies in patients with type 2 diabetes mellitus at high risk of cardiac events.** Data obtained from Pfeffer *et al.* (ELIXA)[212], Marso *et al.* (LEADER)[65], Marso *et al.* (SUSTAIN-6)[213], Scirica *et al.* (SAVOR-TIMI 53)[215], White *et al.* (EXAMINE)[216] and Green *et al.* (TECOS)[217]. EoT, end of treatment.

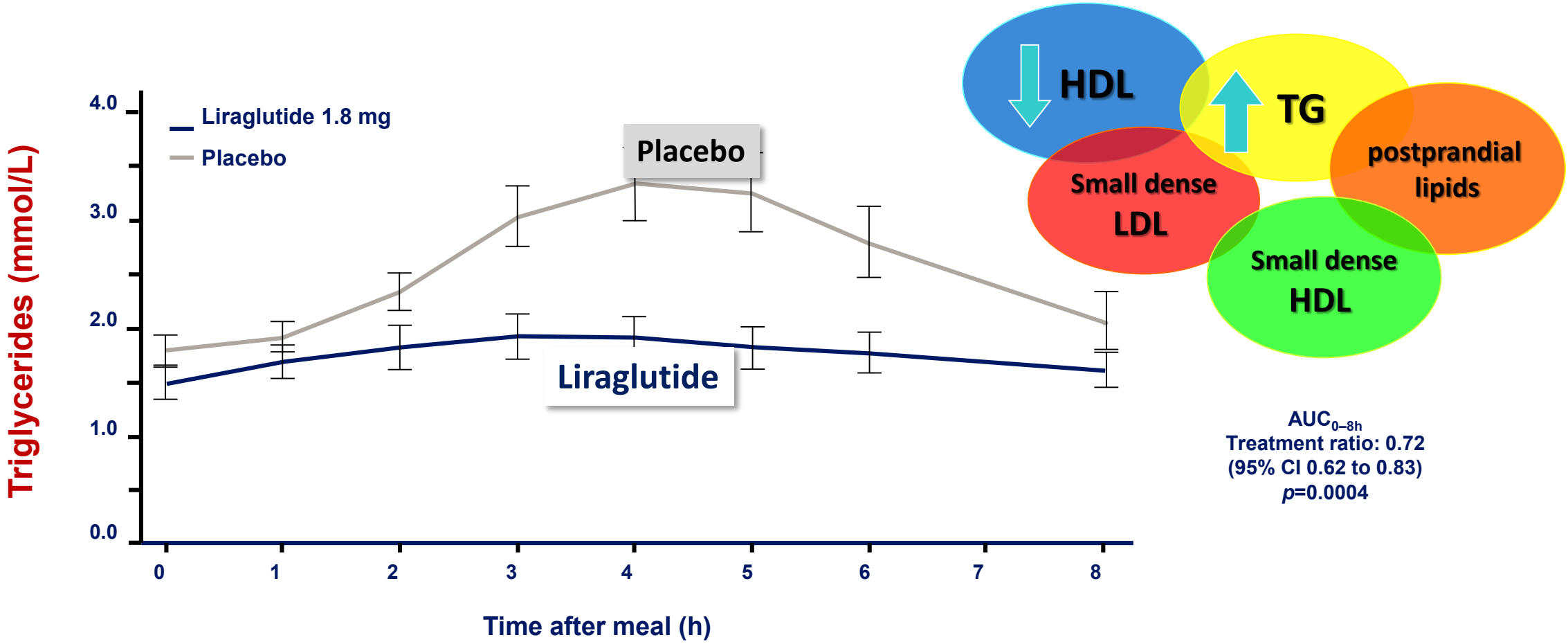
GLP-1RAs reduce *SBP* vs control

Trial	No. of patients	
	GLP-1RA	Control
Astrup 2010	82	78
Apovian 2010	96	98
Bergensthal 2010	160	166
Bunck 2009	36	33
Davies 2009	118	117
Moretto 2008	78	77
Garber 2009	217	212
Zinman 2009	178	177
Kendall 2005	241	247
Buse 2004	129	123
Diamant 2010	233	223
Heine 2005	282	267
Overall; $p<0.01$		



Change in SBP (mmHg) after at least 20 weeks' treatment
CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; SBP, systolic blood pressure.
Adapted from: Vilsbøll T et al. *Br Med J* 2012;344:d7771.

Effect of liraglutide on *postprandial lipids**



*Liraglutide treatment also significantly reduces postprandial excursions of apolipoprotein B48 in patients with type 2 diabetes (AUC_{0-8h} treatment ratio 0.65 [95% CI 0.58 to 0.73], $p<0.0001$).
Data are mean±SEM
AUC, area under the curve; CI, confidence interval; SEM, standard error of the mean; T2D, type 2 diabetes mellitus.
Hermansen K et al. *Diabetes Obes Metab* 2013;15:1040–1048.

Effetti GLP-1 RAs sui livelli circolanti dei marcatori dell'infiammazione

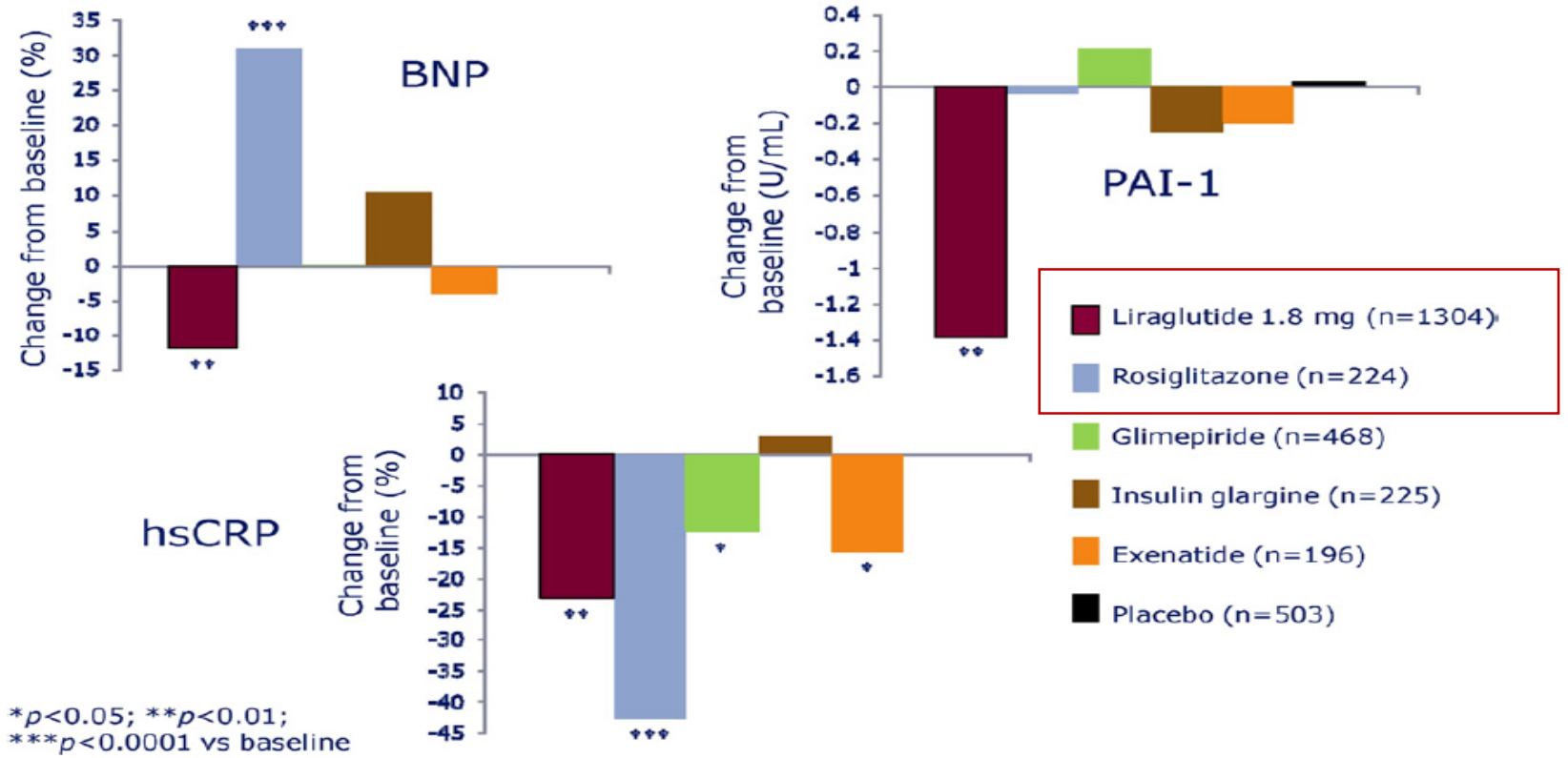


Figure 8. Meta-analysis of LEAD 1–6: improved CV biomarkers. Liraglutide use in the Liraglutide Effect and Action in Diabetes (LEAD 1-6) trials was also associated with improvements in cardiovascular (CV) biomarkers such as (high-sensitivity C-reactive protein (hs-CRP), brain natriuretic peptide (BNP), and plasminogen activator inhibitor–1 (PAI-1). (Data from *Curr Diabetes Rev*.[43])

GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes

Marcel H. A. Muskiet[1], Lennart Tonneijck[1]*, Mark M. Smits[1], Michaël J. B. van Baar[1], Mark H. H. Kramer[1], Ewout J. Hoorn[2], Jaap A. Joles[3] and Daniël H. van Raalte[1]*

GLP1 is implicated in post-prandial increment of glomerular filtration

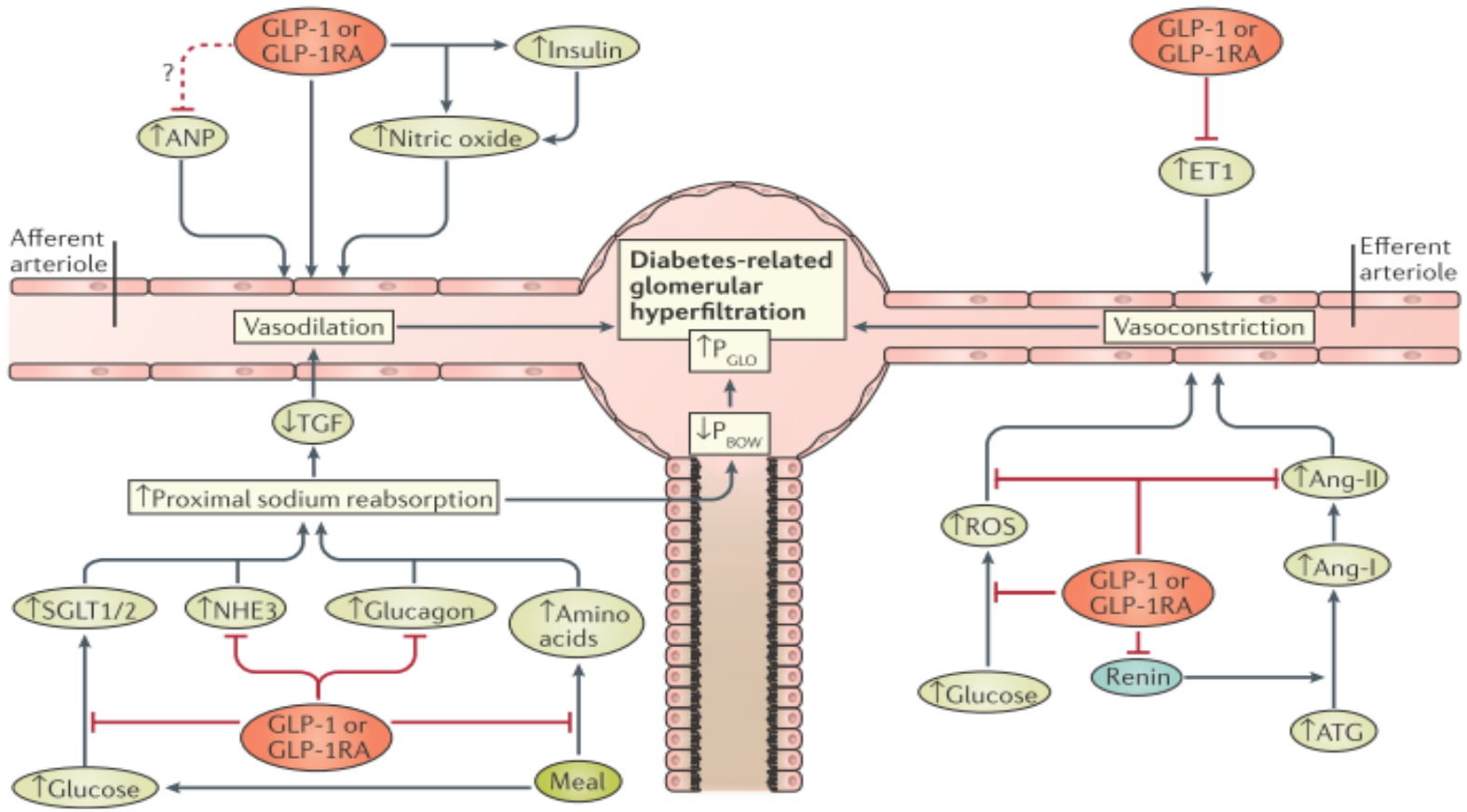


Figure 4 | **Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus.** Several vascular and tubular factors are implicated in fasting and postprandial glomerular hyperfiltration in the setting of diabetes. These factors result in a net reduction in afferent renal arteriolar resistance, a net increase in efferent renal arteriolar resistance and/or a reduction in hydraulic pressure in Bowman space (P_{BOW}), and thereby an increase in glomerular hydraulic pressure (P_{GLO}) and single nephron glomerular filtration rate. GLP-1RAs are associated with direct GLP-1R-mediated and, at least in part, nitric oxide-dependent vasodilation of the afferent renal arteriole, as well as indirect inhibition of vascular and tubular factors that are putative mediators of glomerular hyperfiltration in diabetes. The integrated effect of incretin-based therapy on renal haemodynamics seems to be the result of direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration. Theoretically, this effect is dependent on baseline phenotypic characteristics and co-medication. Ang-I, angiotensin I; Ang-II, angiotensin II; ANP, atrial natriuretic peptide; ATG, angiotensinogen; ET1, endothelin 1; NHE3, sodium–hydrogen exchanger isoform 3; ROS, reactive oxygen species; SGLT, sodium–glucose co-transporter; TGF, tubuloglomerular feedback.

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journal homepage: www.elsevier.com/locate/ejphar

Effects of incretin-based therapies on renal function

Vasilis Tsimihodimos*, Moses Elisaf

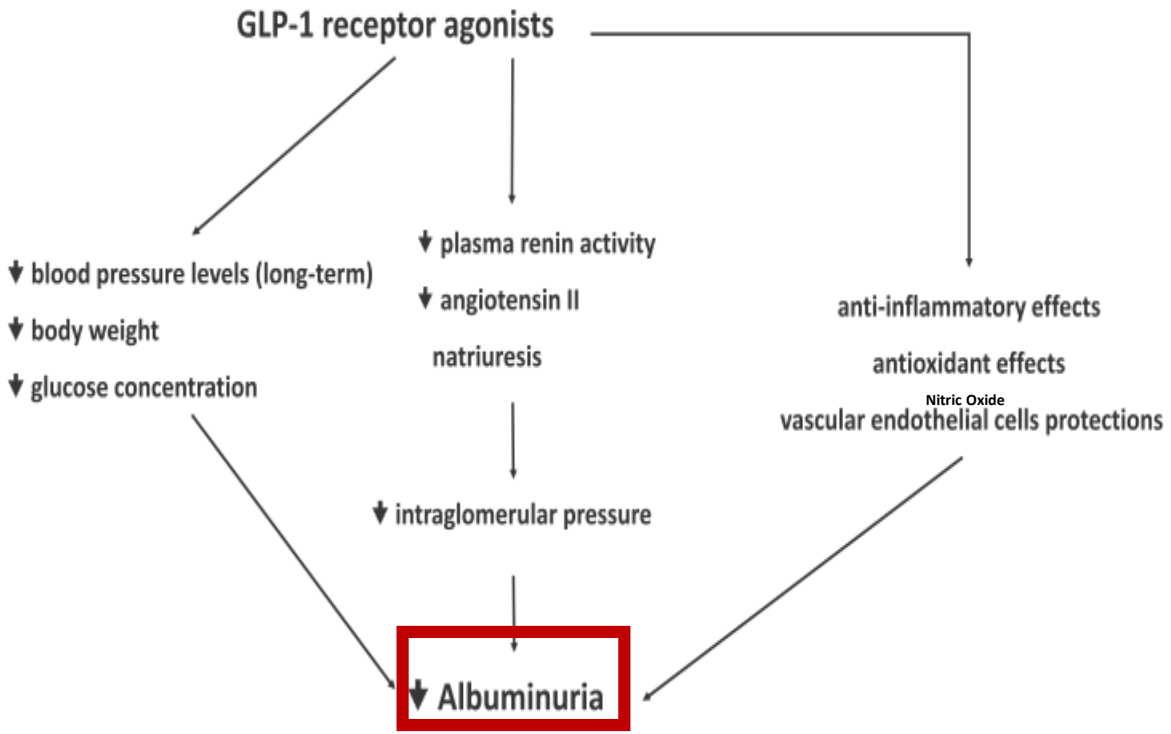


Fig. 1. Mechanisms underlying the antialbuminuric properties of glucagon like peptide1-receptor agonists. Roughly, the effect of glucagon like peptide-1 analogs can be attributed to the effect of these drugs on the conventional risk factors for diabetic nephropathy, their impact on intraglomerular pressure and their beneficial actions on the oxidative stress and the inflammation of the renal tissues. GLP-1: glucagon like peptide-1.

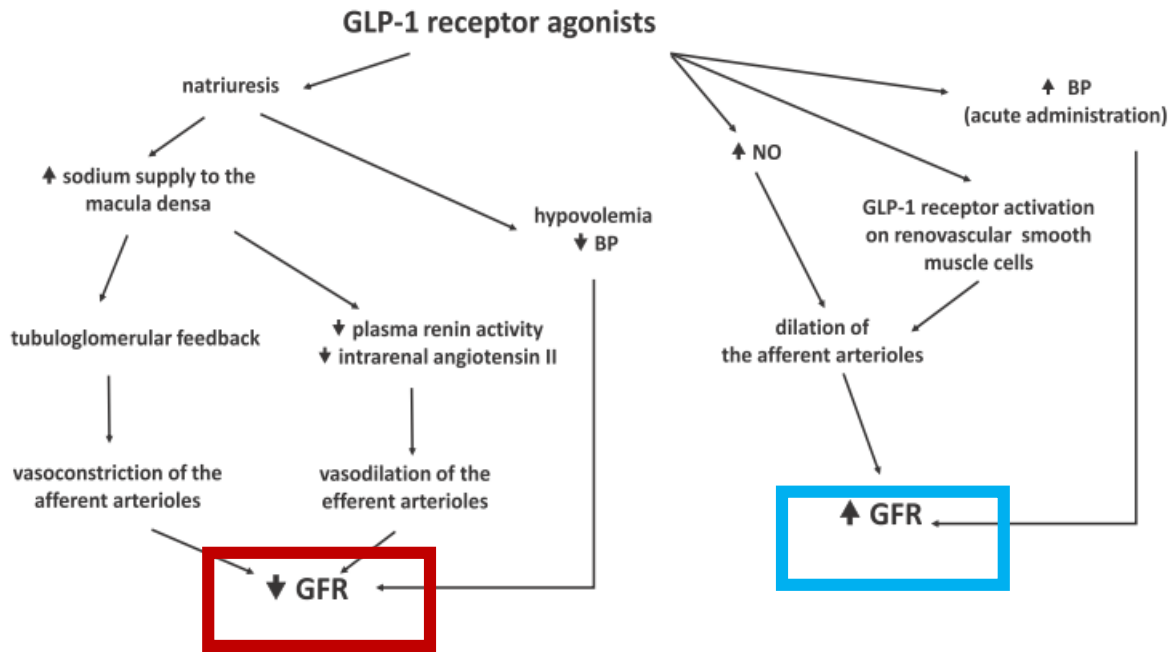


Fig. 2. Effects of glugagon like peptide-1-receptor agonists on renal hemodynamics and the glomerular filtration rate. Depending on the clinical setting (acute vs chronic administration, diabetic patients vs healthy individuals, hyperfiltration vs normal renal function at baseline) these drugs have been described to either increase or decrease the glomerular filtration rate. GLP-1: glucagon like peptide-1, GFR: glomerular filtration rate, BP: blood pressure, NO: nitric oxide.

SGLT2 inhibition and potential renal protection

SGLT2 i

INDIRECT BENEFITS FOR THE KIDNEY

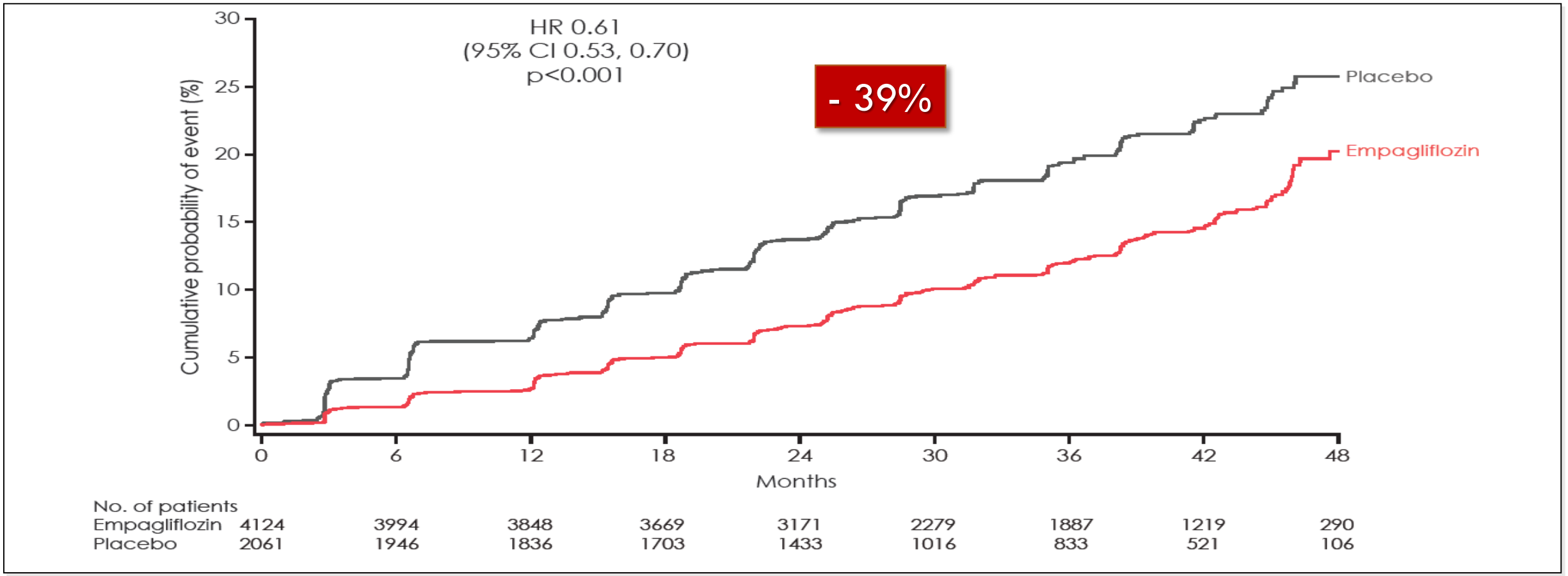
- Improved glycaemic control
- Reduced insulin levels
- Increased insulin sensitivity
- Reduced blood pressure
- Reduced body weight/fat
- Reduced plasma uric acid



POTENTIAL DIRECT BENEFITS

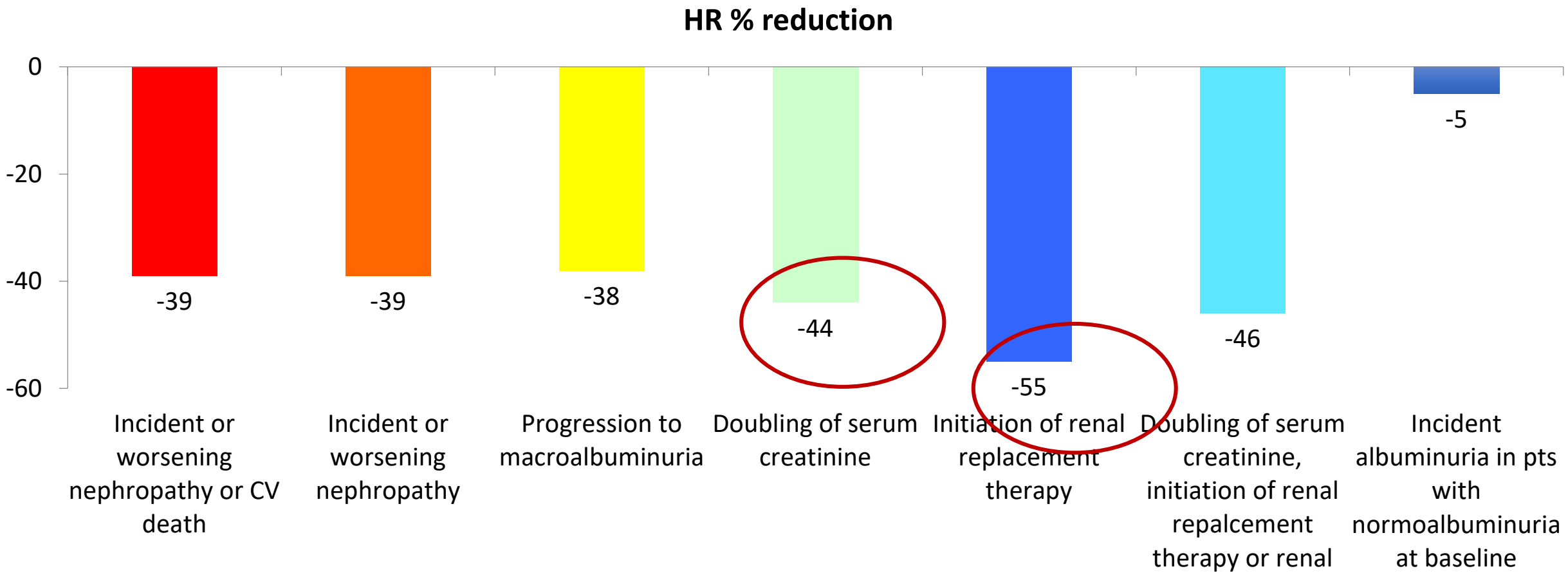
- Reduction in hyperfiltration
- Inhibition of intra-renal RAS?
- Attenuation of renal hypertrophy
- Reduction in tubulotoxicity of glucose

EMPA-REG: Incident or worsening nephropathy



N Engl J Med 2015;373:2117-28

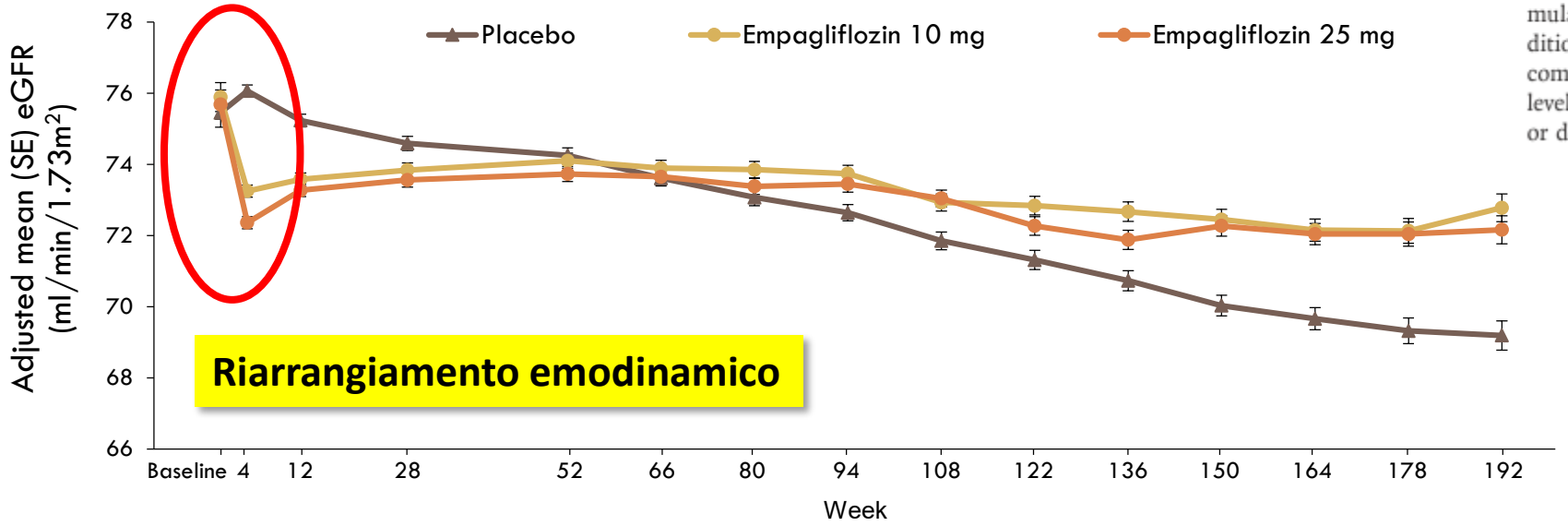
EMPAREG: Renal Outcomes



N Engl J Med 2015;373:2117-28

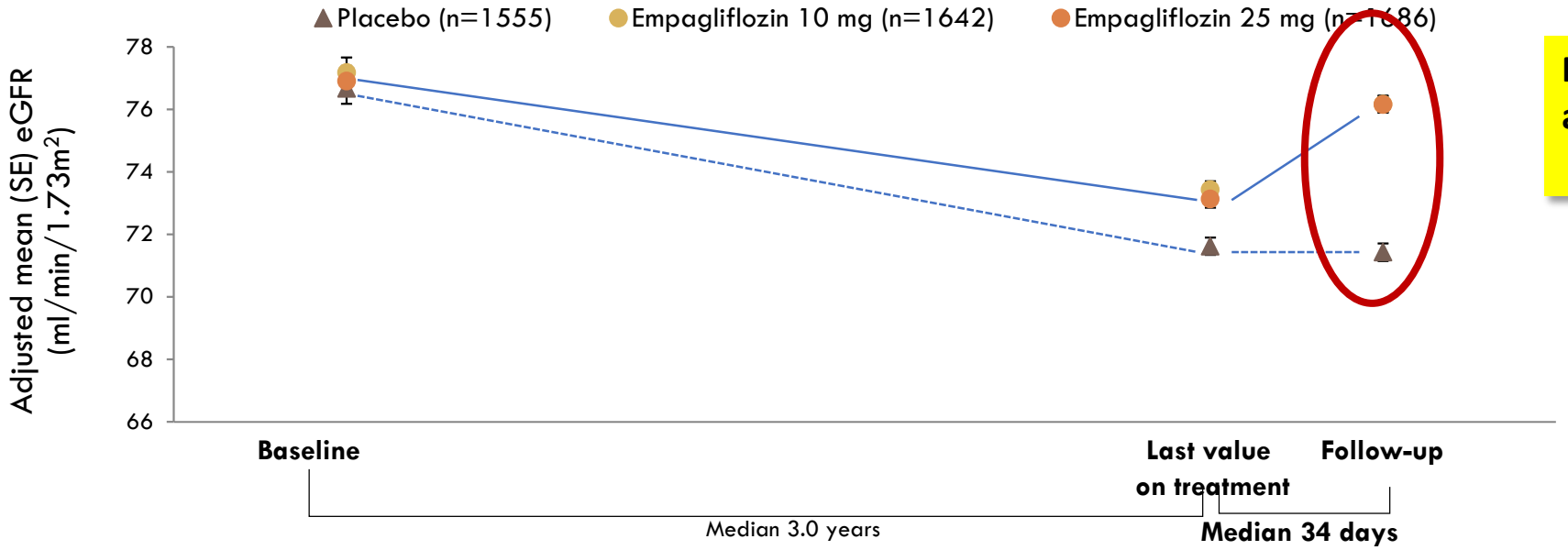
EMPAREG Study: eGFR decline during the study

We conducted post hoc analyses in a subgroup of patients with prevalent kidney disease (defined as an eGFR of 59 ml per minute per 1.73 m^2 or less, as calculated by the MDRD formula, or macroalbuminuria) at baseline. In addition, we performed post hoc analyses of a composite of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease.



- 0.2 ml/yr

- 2.1 ml/yr



Mantenuto anche nel follow-up

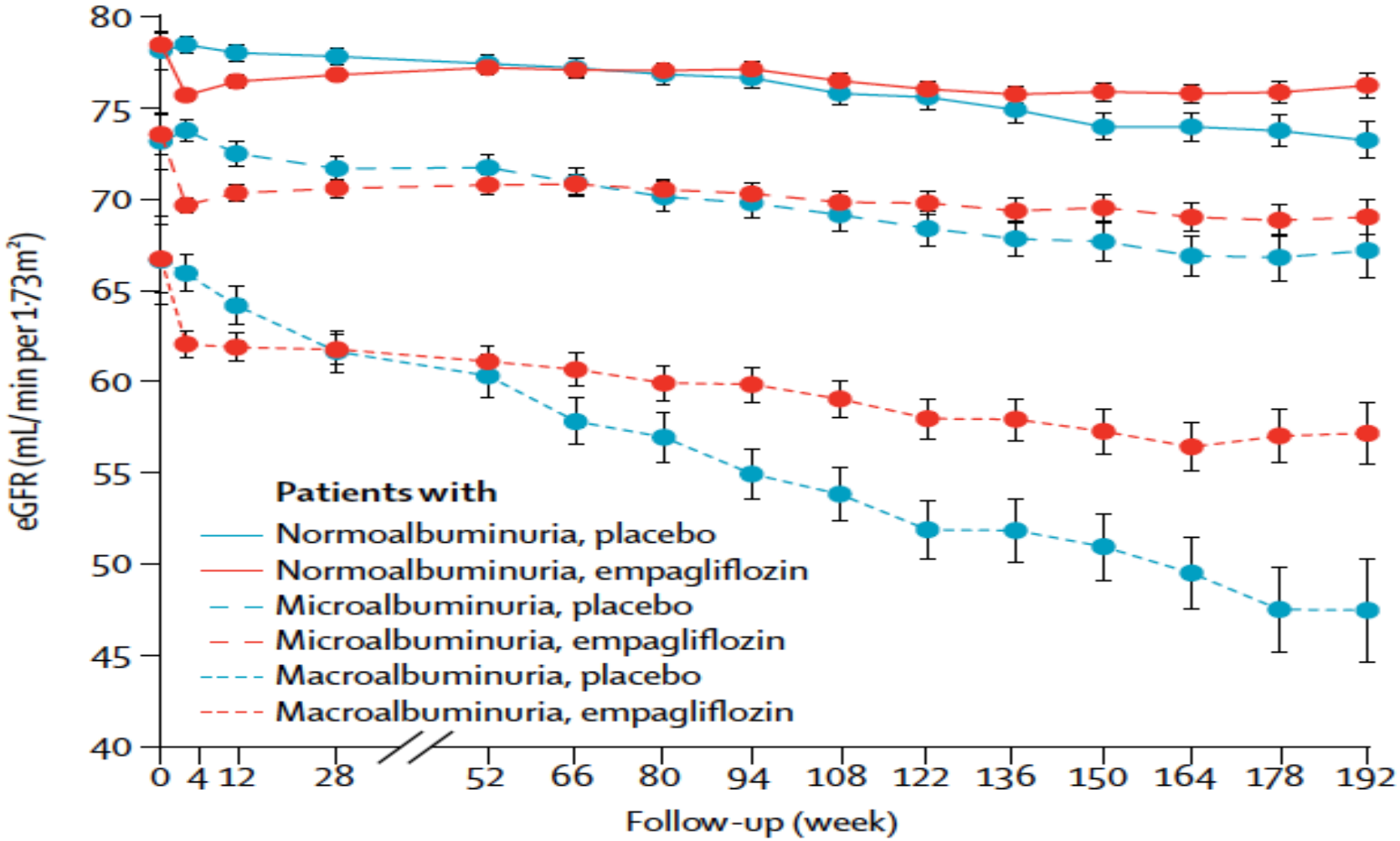
Wanner et al. NEJM 2016

Qual è la velocità di perdita del filtrato glomerulare in un paziente diabetico *con macroalbuminuria* *trattato in modo ottimale*?



- 2 ml/min/anno
- 5 ml/min/anno
- 10 ml/min/anno
- 15 ml/min/anno

EMPA-REG STUDY: Estimated glomerular filtration rate over 192 weeks



Normoalbuminuria

Microalbuminuria

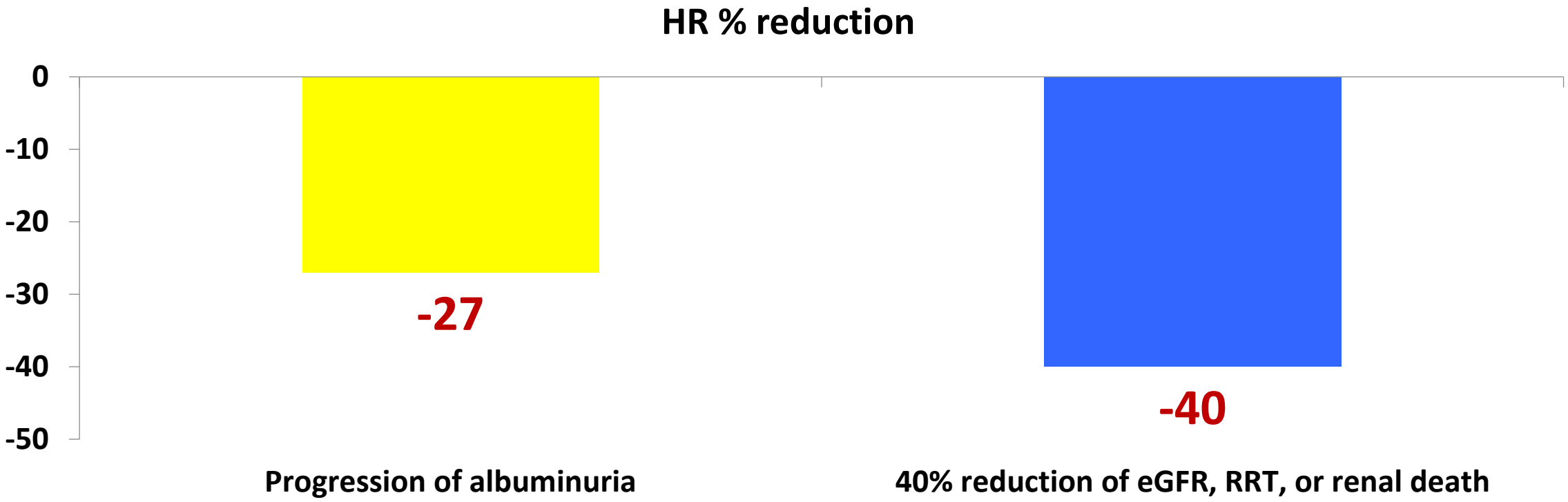
- 0.8 ml/min/yr

Macroalbuminuria

- 5.4 ml/min/yr

Lancet Diabetes Endocrinol 2017; 5: 610–21

CANVAS: Renal outcomes



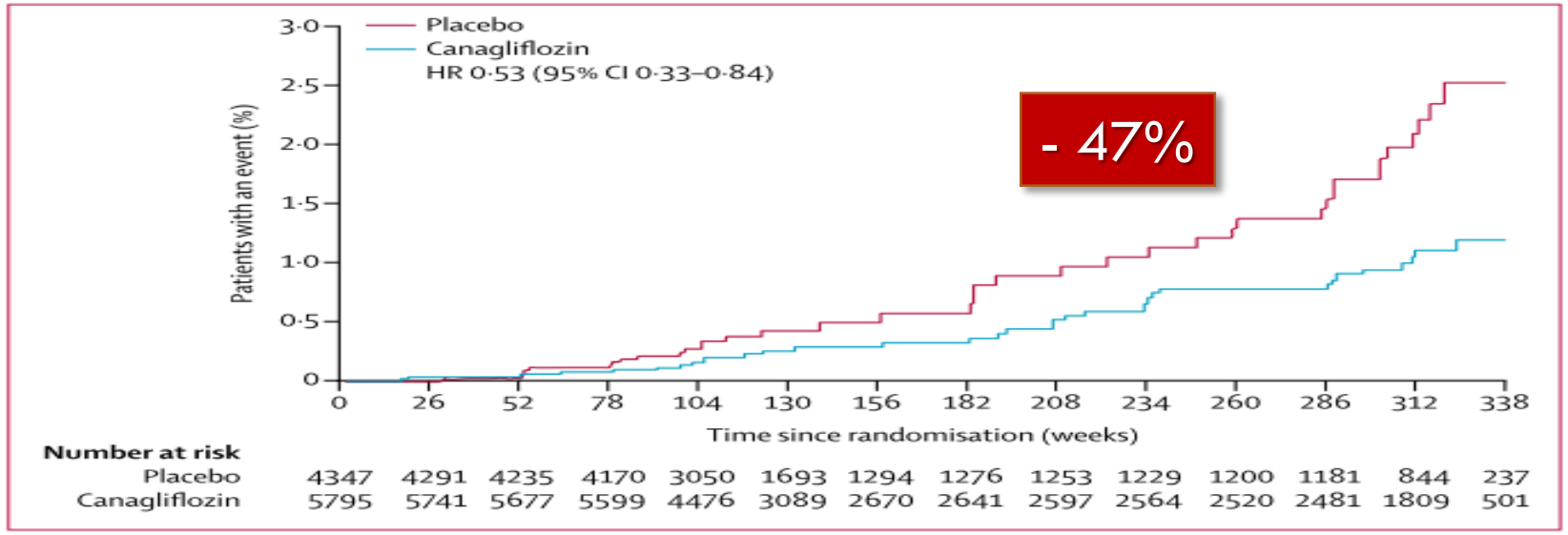
Progression was defined as more than a 30% increase in albuminuria and a change from either normo- to micro- or macroalbuminuria or from micro to macroalbuminuria.

N Engl J Med. 2017;377:644-657.

Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials

Vlado Perkovic, Dick de Zeeuw, Kenneth W Mahaffey, Greg Fulcher, Ngozi Erondu, Wayne Shaw, Terrance D Barrett, Michele Weidner-Wells, Hsiaowei Deng, David R Matthews, Bruce Neal

CANVAS+ CANVAS RENAL BASELINE DATA:
>15000 DM2
>70% prevenzione secondaria
Circa 80% RAAS
MAU 22.6 %
Baseline eGFR 76.5 mL/min



Composite of:
- ❑ 2x creatinine;
- ❑ ESRD;
- ❑ Renal death

Figure 1: **Effects of canagliflozin versus placebo on the composite outcome of doubling of serum creatinine, ESKD, or death from renal causes in the CANVAS Program**
Time to the first event was counted, with any subsequent events disregarded. Doubling of serum creatinine was required to be sustained, defined as being present on at least two consecutive measurements more than 30 days apart. End-stage kidney disease (ESKD) was defined as the composite of maintenance dialysis sustained for at least 30 days, renal transplantation, or a sustained eGFR of less than 15 mL/min per 1·73 m², and adjudicated by an expert committee. Death from renal causes was defined as death where the proximate cause was renal, as defined by the endpoint adjudication committee. HR=hazard ratio.

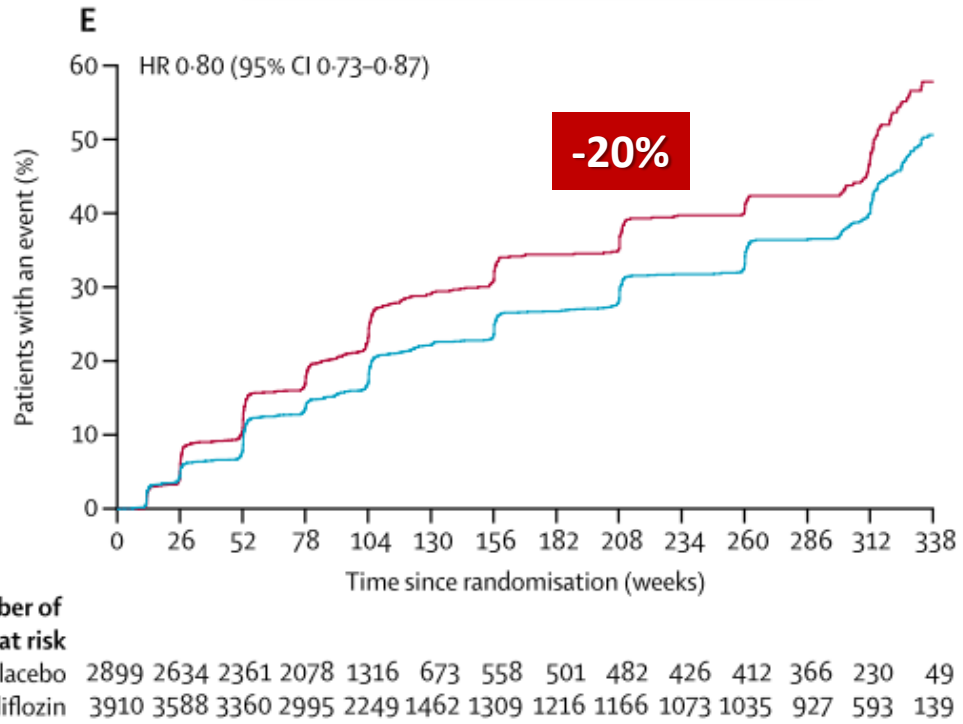
www.thelancet.com/diabetes-endocrinology **Published online June 21, 2018 http://dx.doi.org/10.1016/S2213-8587(18)30141-4**

Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials

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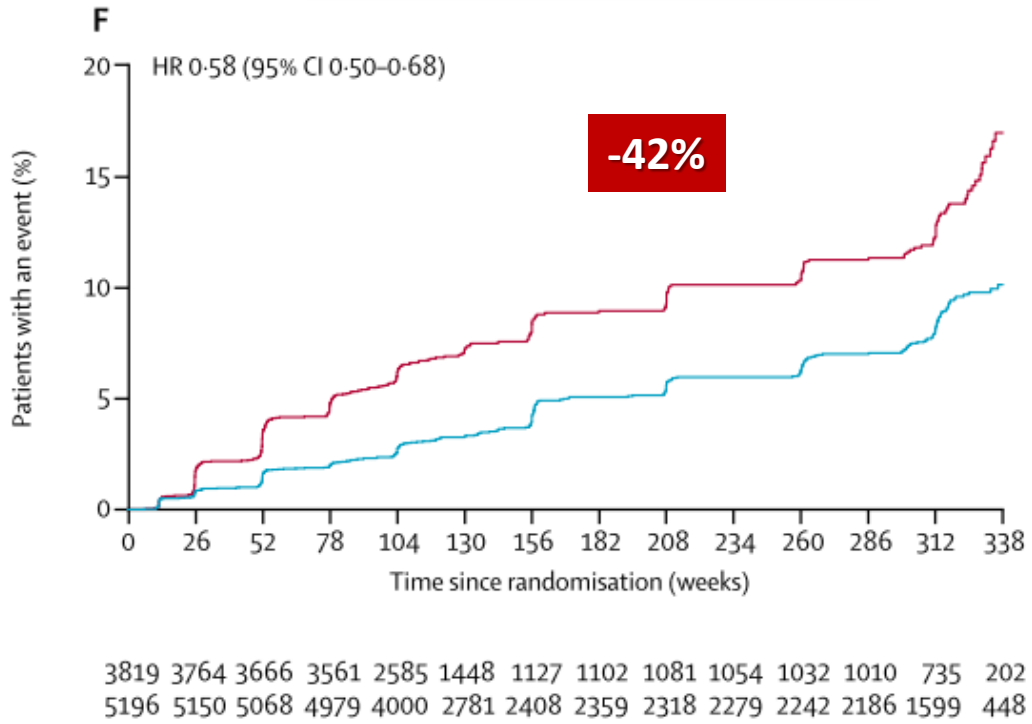
New Onset of MACROalbuminuria

Baseline Nomoalbuminuric



Number of participants at risk														
Placebo	2899	2634	2361	2078	1316	673	558	501	482	426	412	366	230	49
Canagliflozin	3910	3588	3360	2995	2249	1462	1309	1216	1166	1073	1035	927	593	139

Baseline Microalbuminuric



	3819	3764	3666	3561	2585	1448	1127	1102	1081	1054	1032	1010	735	202
	5196	5150	5068	4979	4000	2781	2408	2359	2318	2279	2242	2186	1599	448

www.thelancet.com/diabetes-endocrinology **Published online June 21, 2018 http://dx.doi.org/10.1016/S2213-8587(18)30141-4**

Diabete di tipo 2 e malattia renale cronica, alt anticipato dello studio CREDENCE su canagliflozin in virtù dei risultati positivi

PRESS RELEASE

Lo studio di Fase III in pazienti con diabete di tipo 2 e malattia renale cronica in trattamento con l'antidiabetico SGLT2-inibitore canagliflozin, è stato interrotto anticipatamente sulla base dei risultati positivi dimostrati dal farmaco.

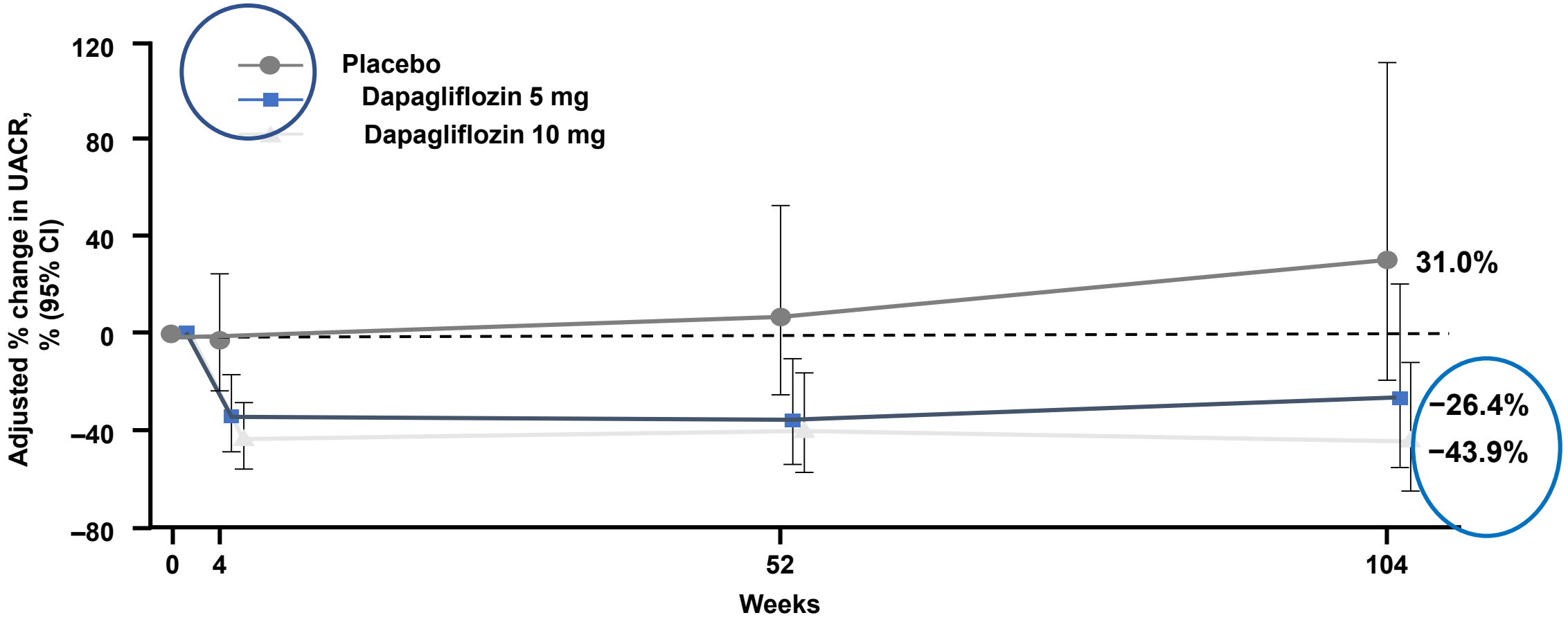
Prevenzione primaria danno renale

Il trial clinico su canagliflozin

Lo studio CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), multicentrico randomizzato, in doppio cieco, controllato con placebo, a gruppi paralleli, ha valutato l'efficacia e la sicurezza di canagliflozin rispetto al placebo in aggiunta alla terapia renale standard, nella prevenzione di esiti renali e cardiovascolari clinicamente importanti in pazienti con diabete di tipo 2 e malattia renale accertata.

Effects of Dapagliflozin on albuminuria

A post-hoc analysis of 166 patients with CKD stage 3 and increased albuminuria



Fioretto P, et al. Diabetologia 2016

DECLARE-TIMI 58

The NEW ENGLAND JOURNAL of MEDICINE

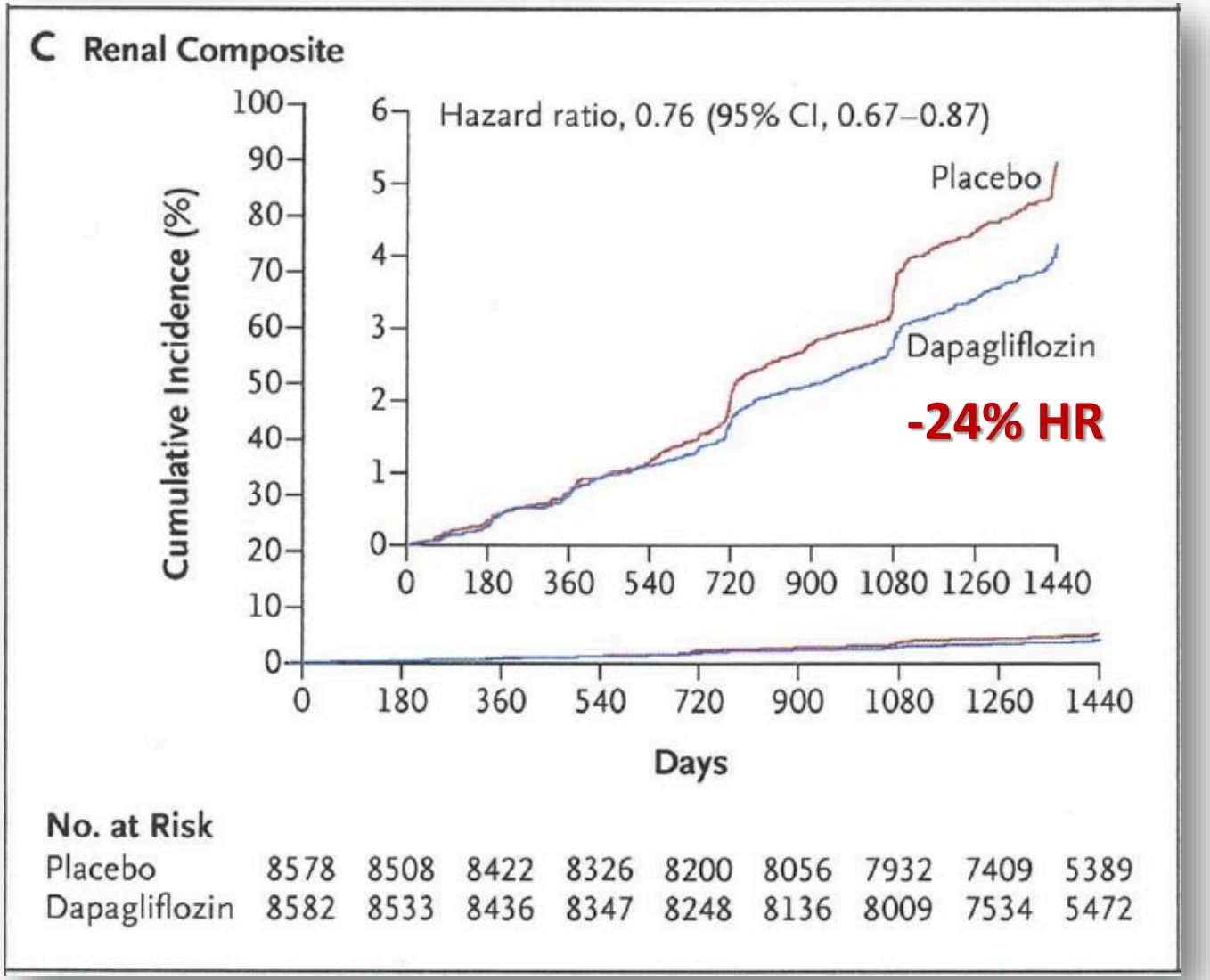
ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

60% dei pazienti in prevenzione primaria da eventi CV

Clearance creatinina > 60 ml/min; eGFR medio 85 ml/min/1,73m^2



Effetto nefro-protettivo prolungato anche con DAPAgliflozin

End-point secondario

- Declino funzione renale
- Nuova Insorgenza di dialisi
- Morte per cause renali

(≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) (Panel C)

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Renal end-points

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**

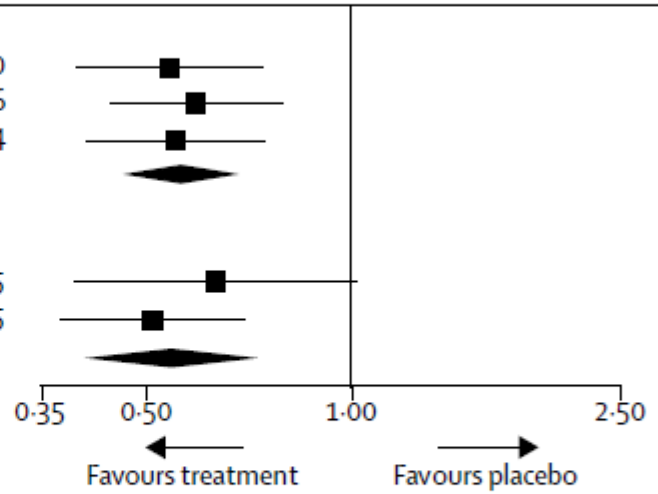


Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

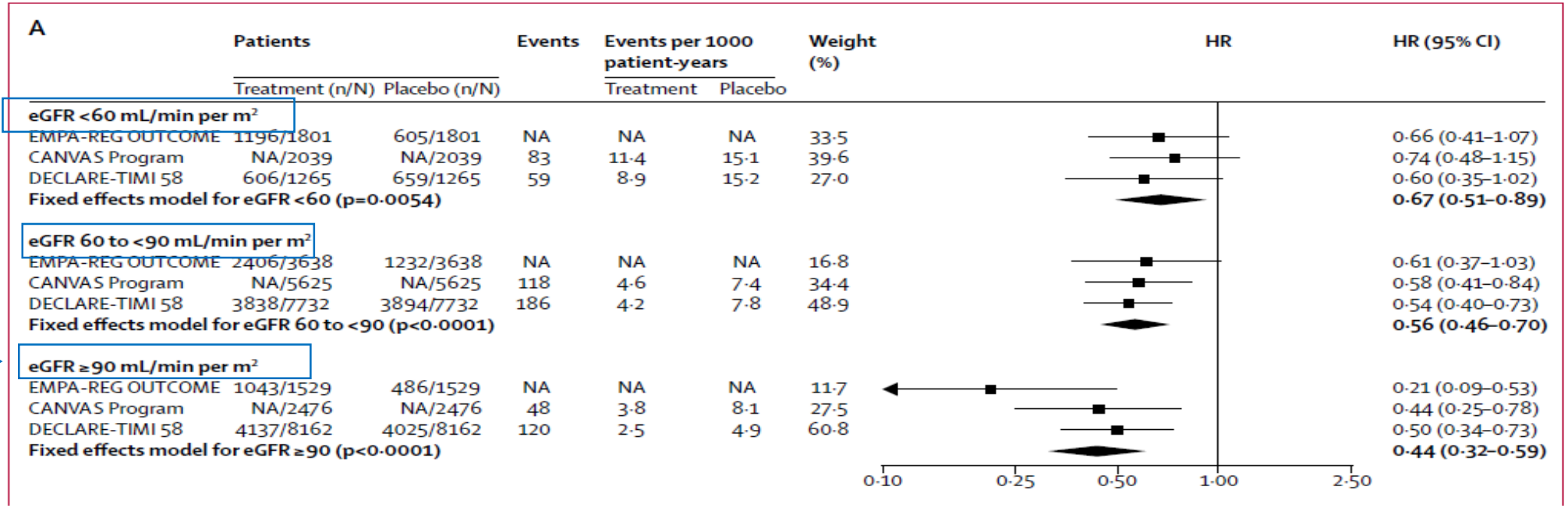
Atherosclerotic cardiovascular disease: Q statistic=0·19, p=0·91, I^2=0%; multiple risk factors: Q statistic=0·52, p=0·47, I^2=0% The p value for subgroup differences was 0·71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Lancet , Novembre 2018

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

A: *Composite of* worsening of renal function, end –stage renal disease, or renal death



A	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196/1801	605/1801	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA/2039	NA/2039	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606/1265	659/1265	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406/3638	1232/3638	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA/5625	NA/5625	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838/7732	3894/7732	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043/1529	486/1529	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA/2476	NA/2476	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137/8162	4025/8162	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**

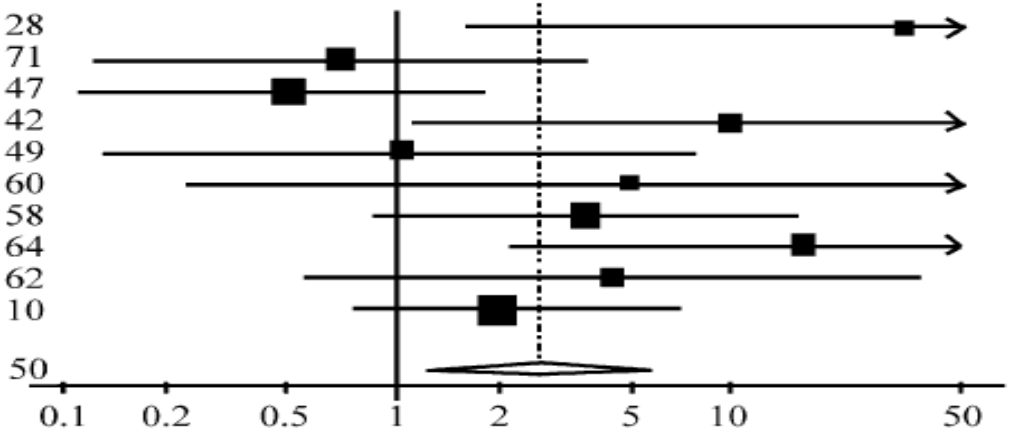
Diabetologia (2009) 52:691–697
DOI 10.1007/s00125-009-1268-0

META-ANALYSIS

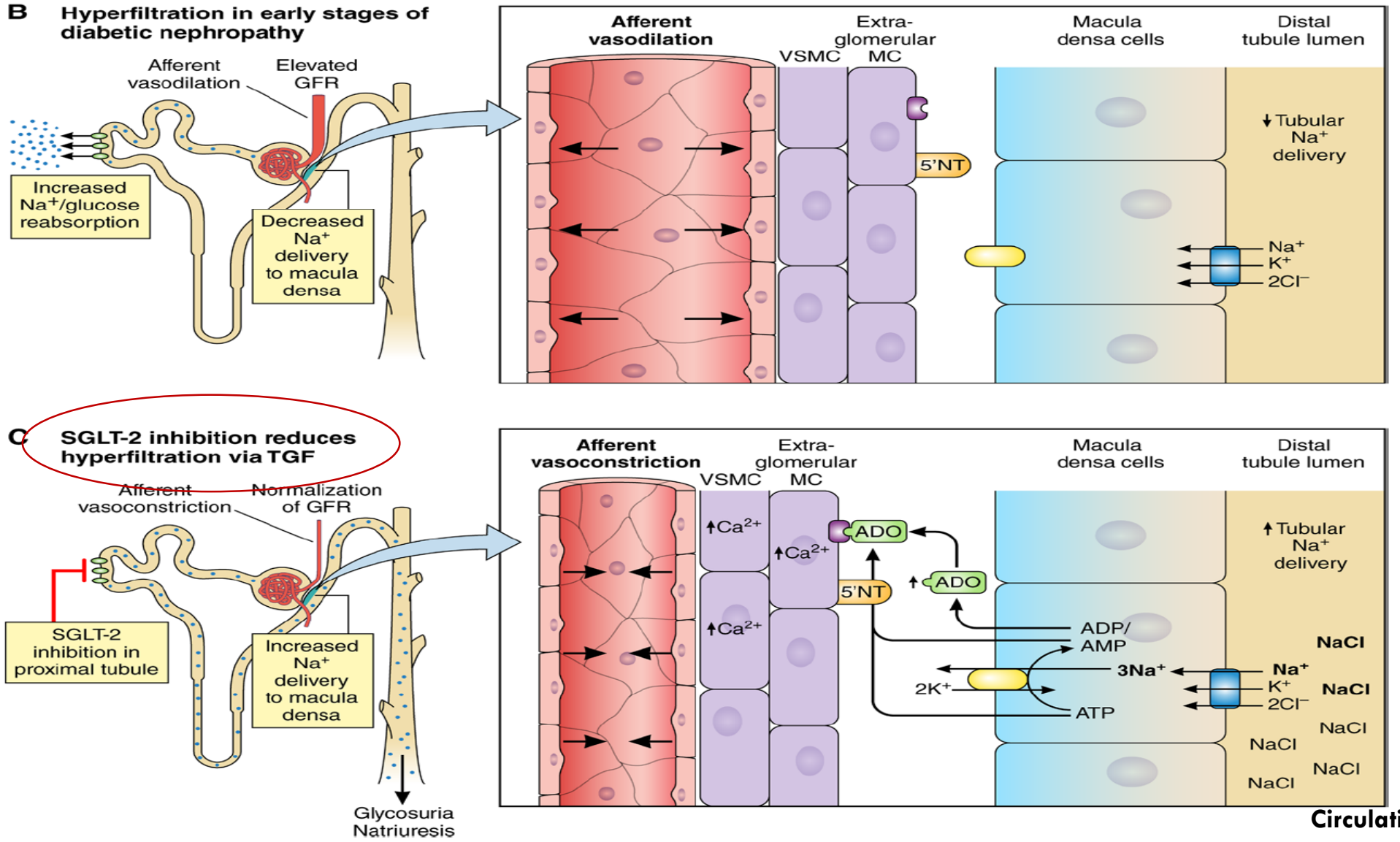
Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis

G. M. Magee · R. W. Bilous · C. R. Cardwell · S. J. Hunter · F. Kee · D. G. Fogarty

First author [reference no.]	Progression HF/Non HF (*n*)	%	No progression HF/Non HF (*n*)	%	OR (95% CI)	OR (95% CI)	Relative weight (%)
Mogensen [22]	6/0	100	5/13	28		33.12 (1.58–694.03)	5
Lervang [23]	5/3	63	15/6	71		0.67 (0.12–3.73)	11
Lervang [24]	5/12	29	8/9	47		0.45 (0.11–1.85)	13
Chiarelli [25]	7/1	88	16/22	42		9.97 (1.11–89.30)	9
Yip [26]	2/2	50	20/21	49		1.00 (0.13–7.79)	9
Caramori [27]	3/0	100	18/12	60		4.95 (0.23–104.46)	5
Dahlquist [28]	16/3	84	14/10	58		3.67 (0.84–16.06)	13
Amin [29]	29/1	97	156/87	64		16.44 (2.20–122.81)	9
Steinke [30]	7/1	88	61/38	62		4.48 (0.53–37.87)	9
Zerbini [31]	5/22	19	12/107	10		2.01 (0.64–6.29)	16
Overall[a]	85/45	65	325/325	50		2.71 (1.20–6.11)	



Putative mechanism for sodium-mediated changes in adenosine bioactivity at the afferent arteriole

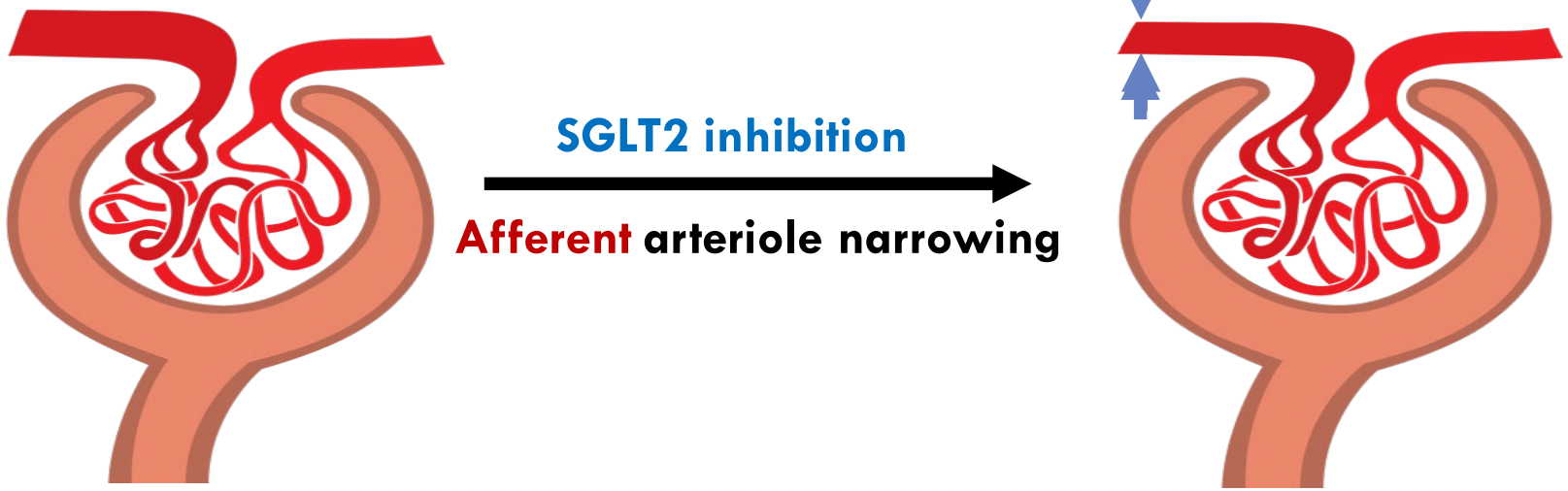


Circulation. 2016;134:752–772

SGLT2i exerts a hemodynamic effect within the kidney

By restoring the *Tubulo-Glomerular Feedback* (TGF), SGLT2i increase the afferent arteriole tone, thereby lowering glomerular hypertension

Action:



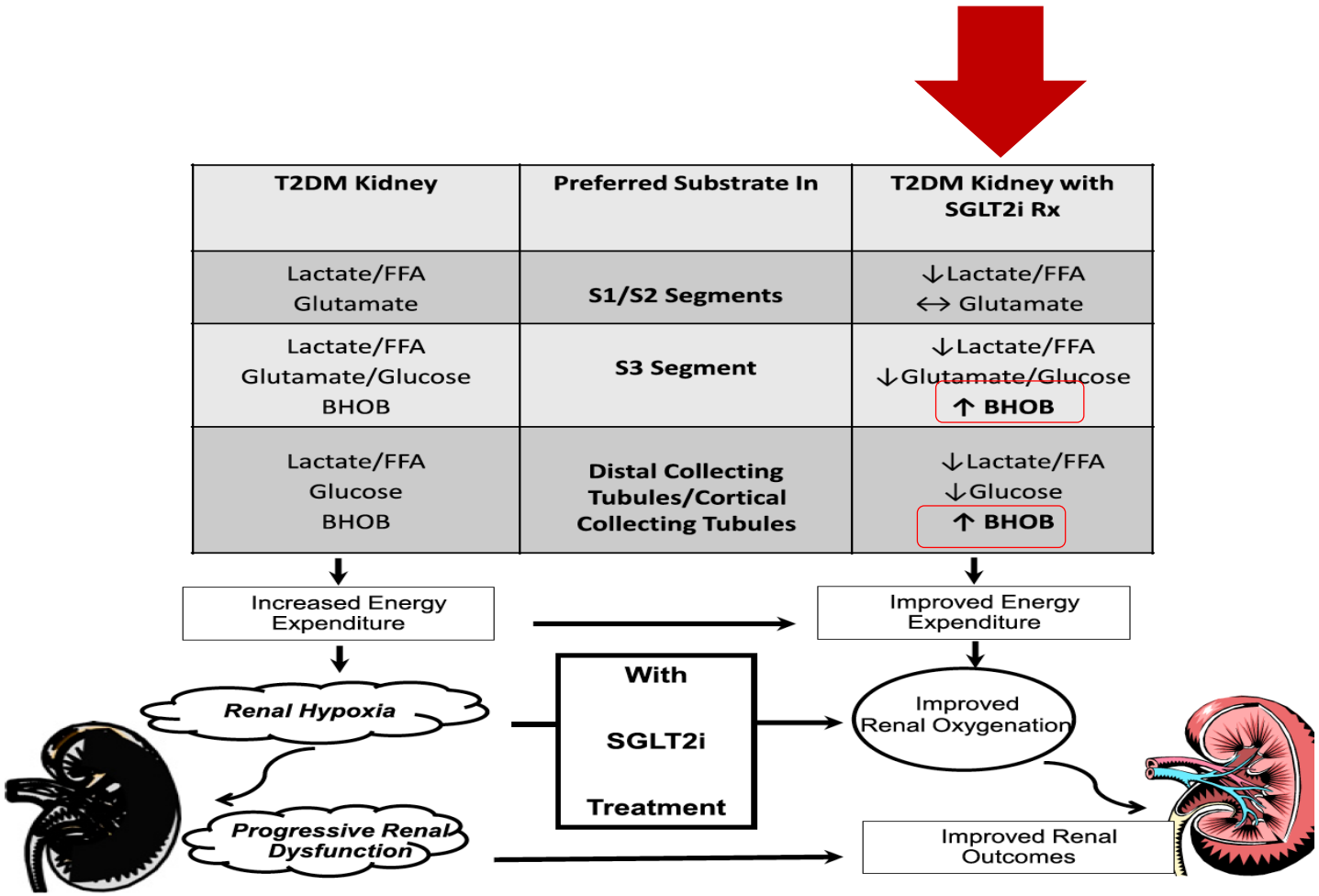
Clinical implications:

- **Glomerular pressure decreases**
- **Early clinical marker:**
  - **Initial dip in GFR**
  - **Reduction of albuminuria**

Adapted from: Cherney D *et al. Circulation* 2014;129:587
Skrtic M *et al. Diabetologia* 2014;57:2599

Postulated *changes in renal fuel metabolism* before and after SGLT2 inhibitor therapy

T2DM Kidney	Preferred Substrate In	T2DM Kidney with SGLT2i Rx
Lactate/FFA Glutamate	S1/S2 Segments	↓Lactate/FFA ↔ Glutamate
Lactate/FFA Glutamate/Glucose BHOB	S3 Segment	↓Lactate/FFA ↓Glutamate/Glucose ↑ BHOB
Lactate/FFA Glucose BHOB	Distal Collecting Tubules/Cortical Collecting Tubules	↓Lactate/FFA ↓Glucose ↑ BHOB

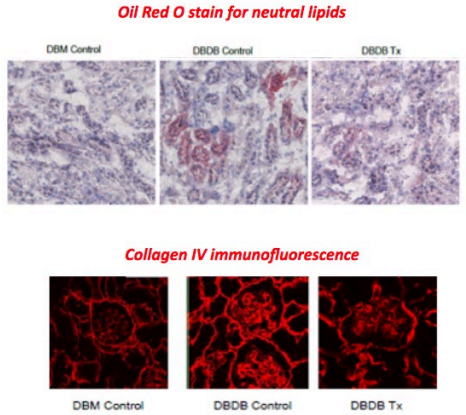


- The kidney is highly metabolically active with O_2 consumption (QO_2) per gram of tissue being second only to the heart
- Oxidative metabolism is the principal source of energy in the kidney. The renal cortex uses many metabolic substrates, including lactate, FFAs, glutamine, citrate, ketone bodies, and, to a very small extent, glucose
- SGLT2 inhibitors could improve fuel efficiency, lowering QO_2, relieving hypoxic stress, improving renal function, and preventing progression to CKD

Mudaliar S et al., Diabetes Care 2016

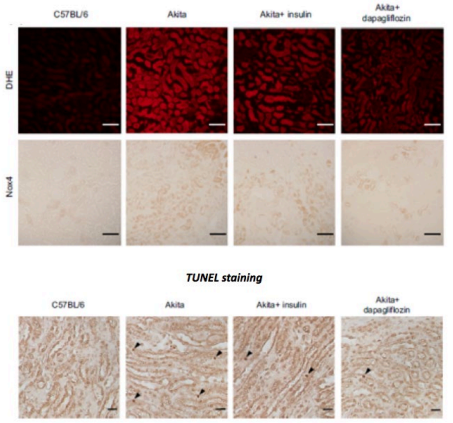
Altre EVIDENZE: *dal laboratorio alle le PROSPETTIVE FUTURE*

SGLT-2i riducono *accumulo lipidico ed infiammazione*



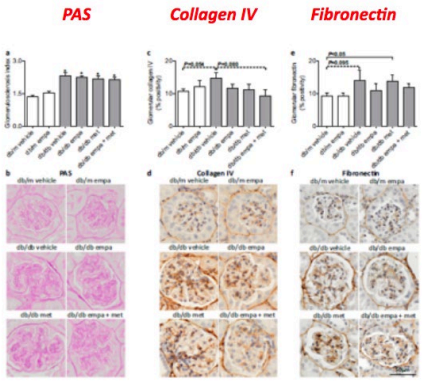
Wang XX et al JBC 2017

SGLT-2i riducono *stress ossidativo ed apoptosi*



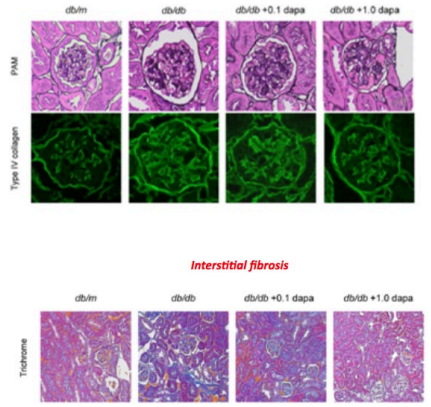
Otanaka T at al Pharmacol Res Perspect 2016

SGLT-2i riducono *glomerulosclerosi ed espansione mesangiale*



Gallo LA, Sci Rep 2016

SGLT-2i riducono *accumulo matrice mesangiale e fibrosi*



Terami N, Plos One 2014

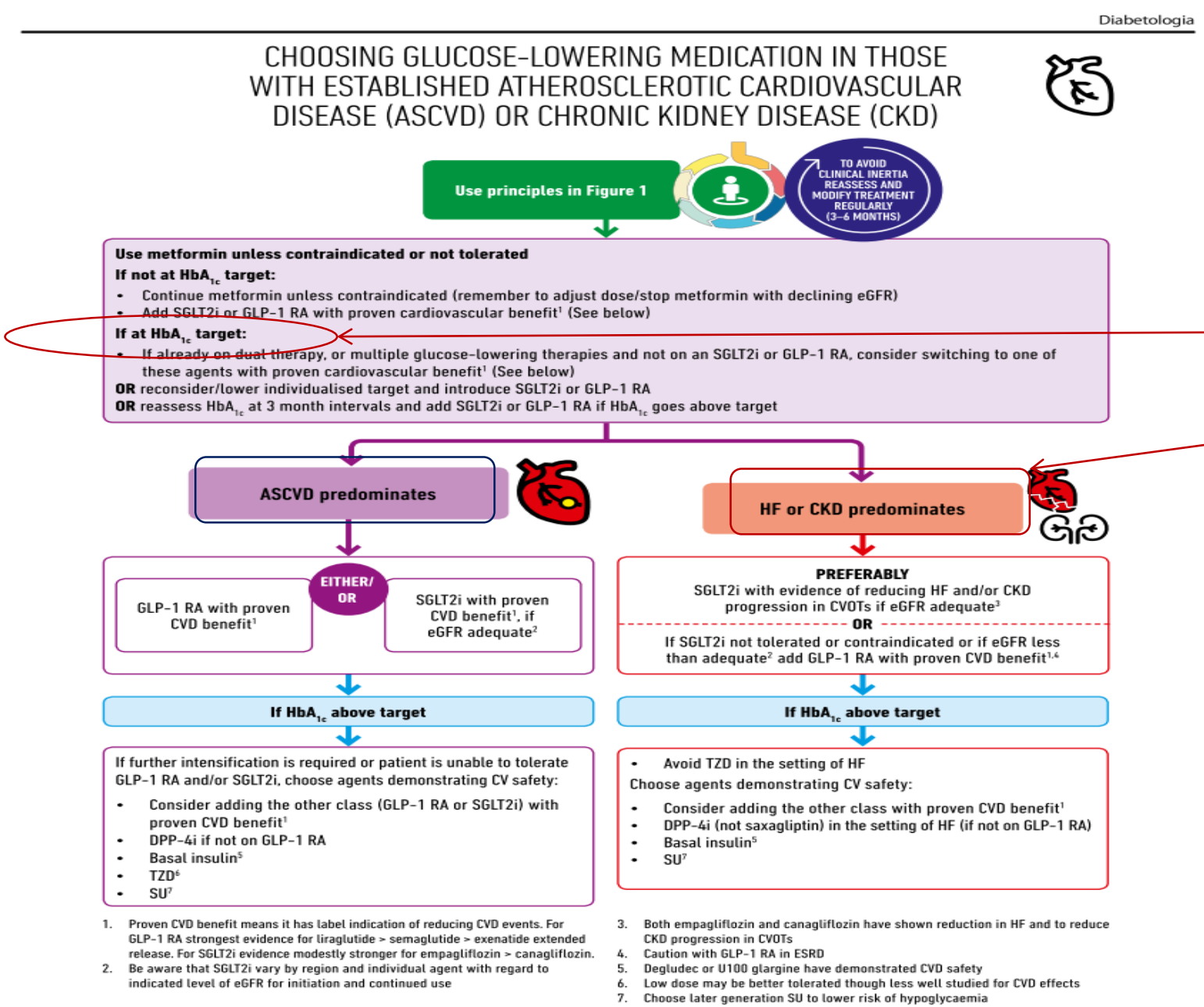
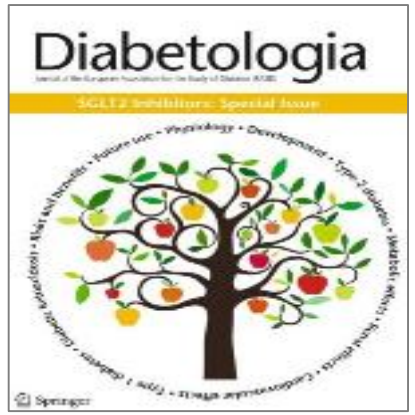


Fig. 3 Choosing glucose-lowering medication in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)

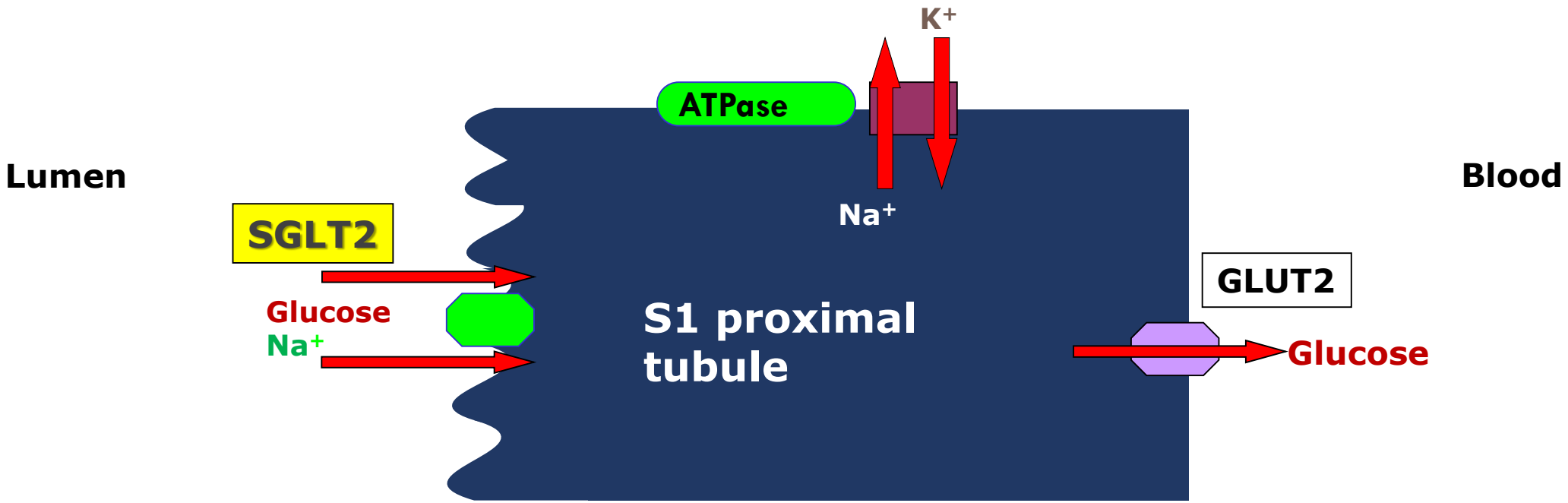
Algoritmo terapeutico del diabete tipo 2 basato sul rischio CVD e non più sulla glicemia





Grazie per l’attenzione

SGLT2 Mediates Glucose Reabsorption in the Kidney

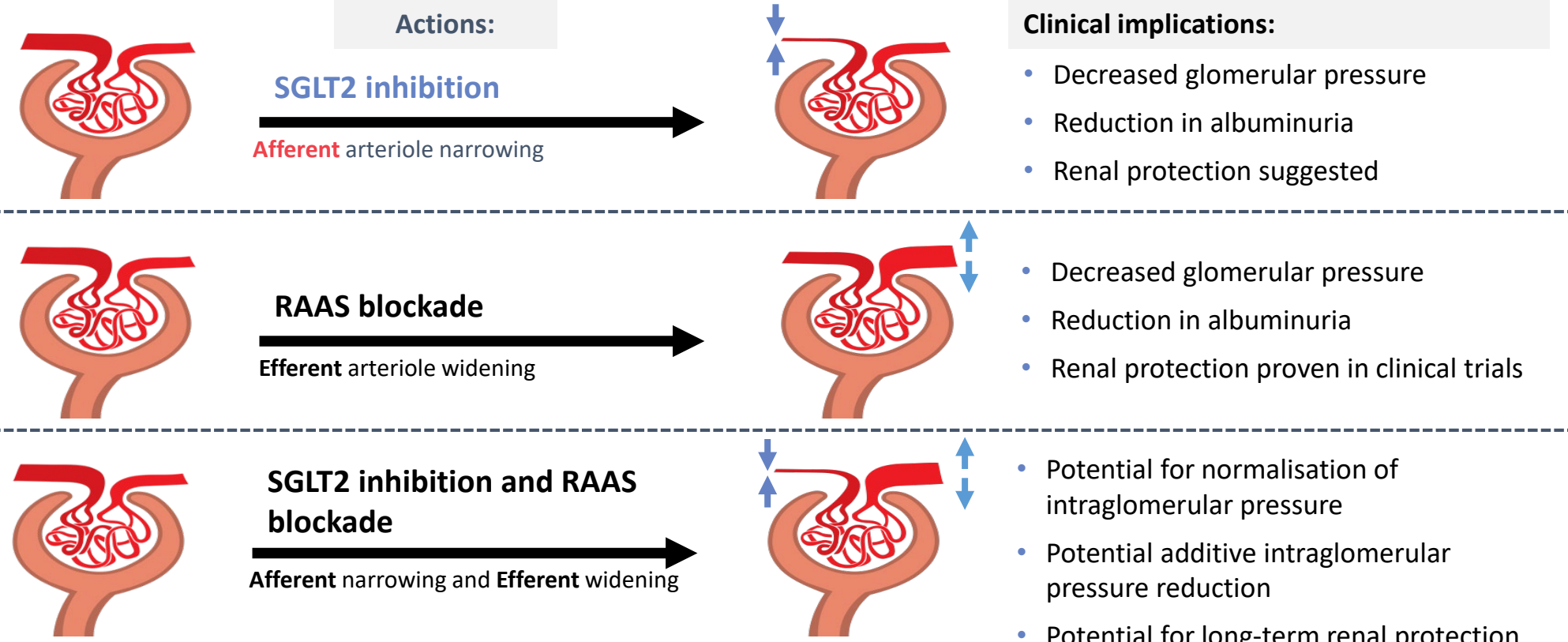


SGLT2: Major transporter of glucose in the kidney[1-3]

- **Low affinity, high capacity for glucose**
- **Co-transports Na+ and glucose at 1:1 stoichiometry**
- **Nearly exclusively expressed in the S1 portion of the proximal tubule**
- **Responsible for majority of renal glucose reabsorption in the proximal tubule**

[1]*Hediger MA, Rhoads DB. Physiol Rev 1994;74:993-1026;* [2]*Magen D, et al. Kidney Int. 2005;67:34-41;*
[3]*Kanai Y, et al. J Clin Invest 1994;93:397-404*

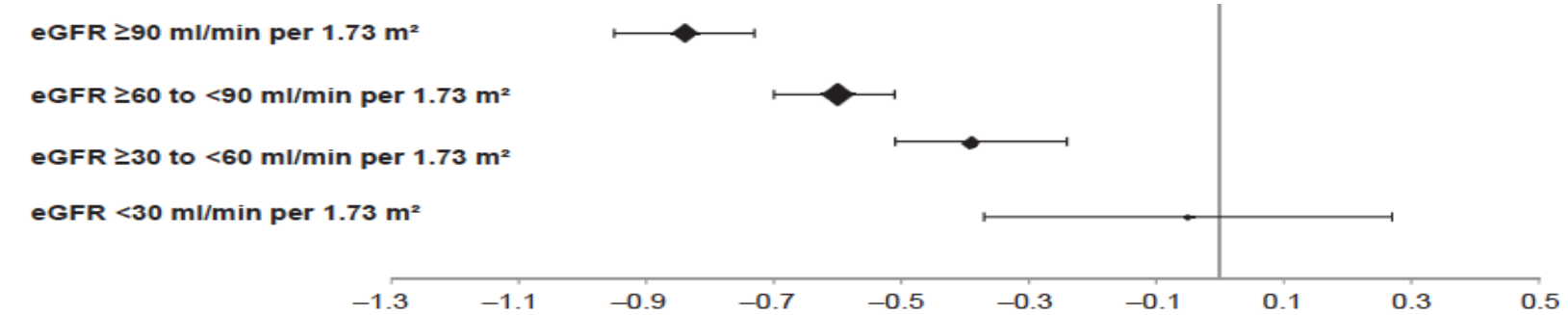
Future outlook – Dual SGLT2 and RAAS inhibition



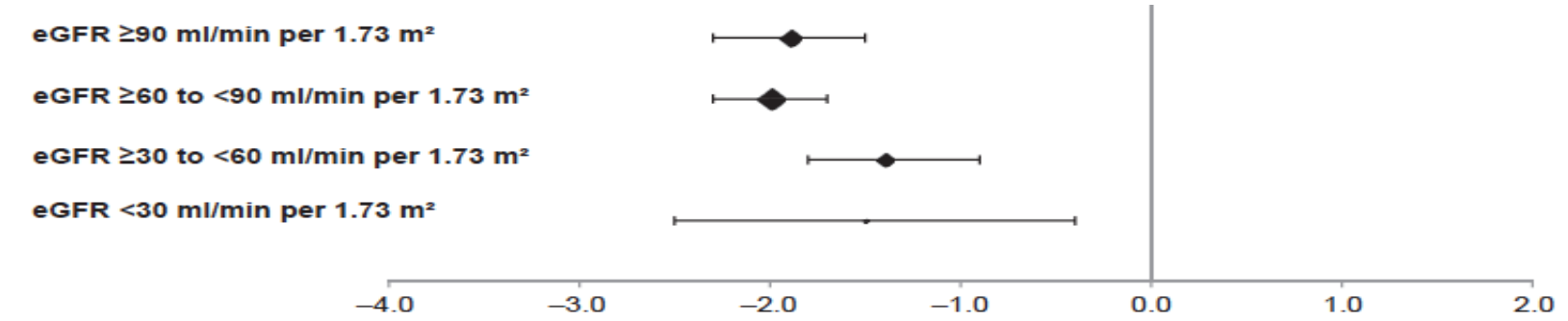
Adapted from: Cherney D *et al. Circulation* 2014;129:587-597; Lewis *et al. N Engl J Med* 2001;345:851; Kon V *et al. Kidney Int* 1993;44:545

Contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin

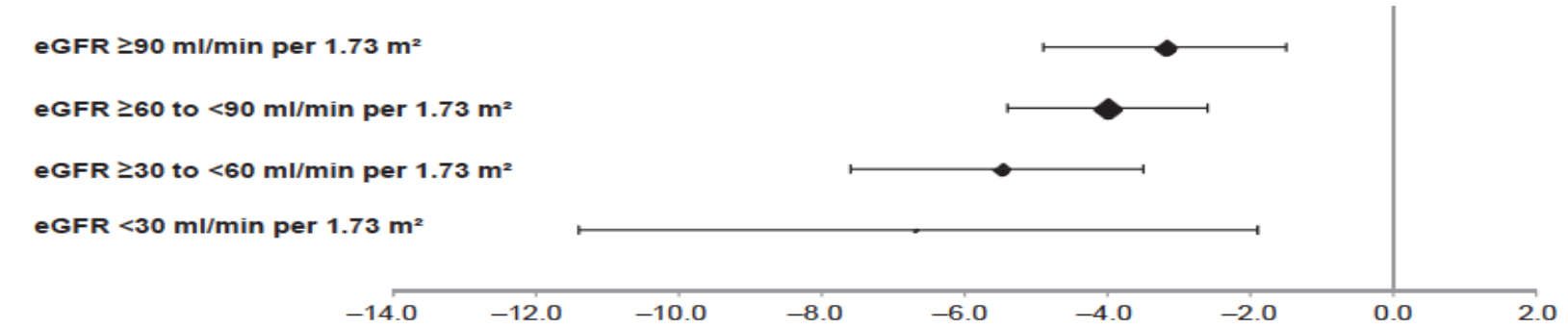
HbA1c



Weight



SBP



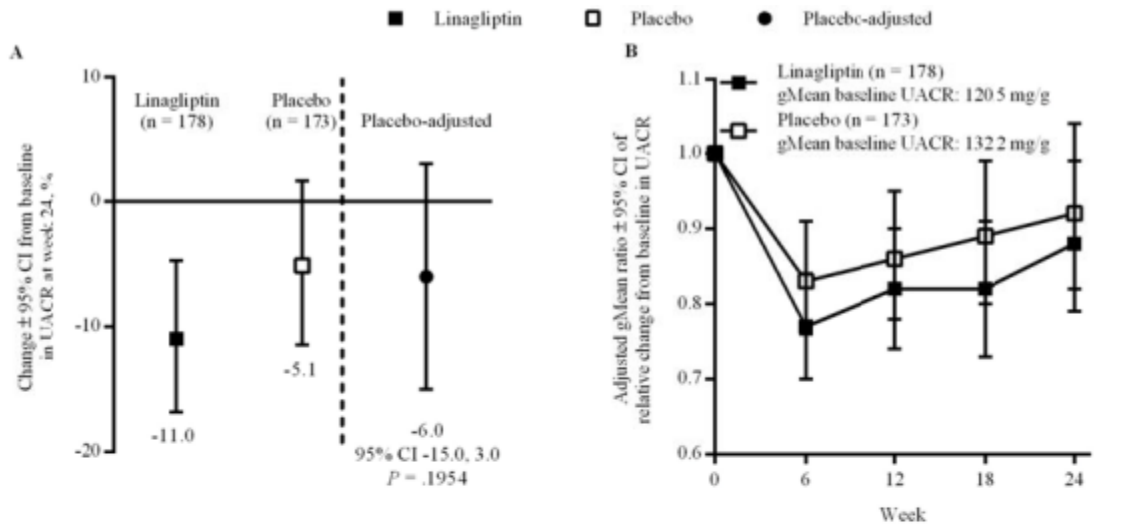
Kidney International (2018) 93, 231–244

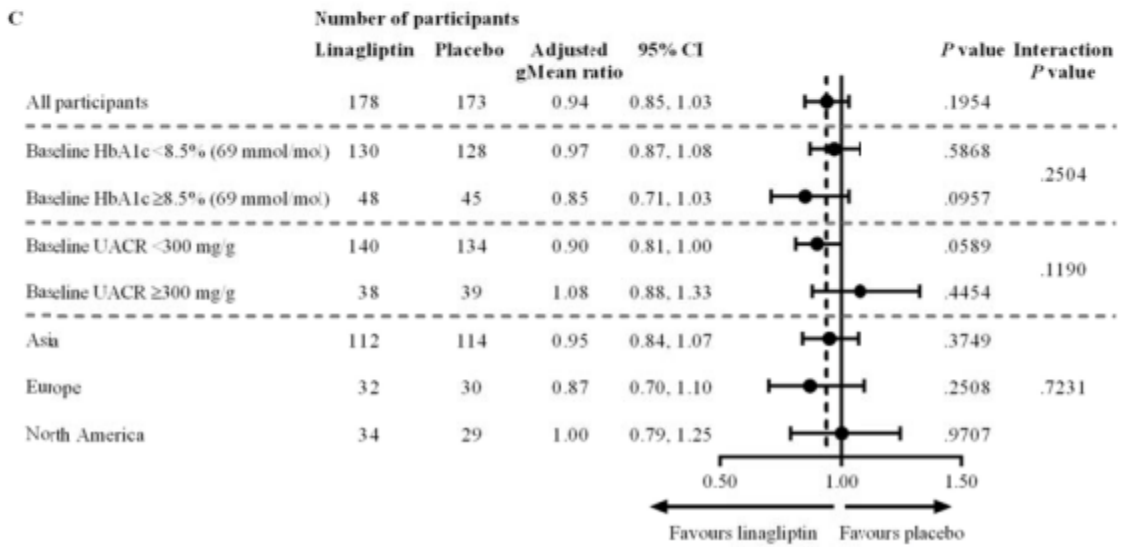
Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D™ trial

P.-H. Groop[1,2,3], M.E. Cooper[3], V. Perkovic[4], B. Hocher[5,6,7], K. Kanasaki[8,9], M. Haneda[10] Schernthaner[11], K. Sharma[12], R.C. Stanton[13], R. Toto[14], J. Cescutti[15], M. Gordat[15], T. Meinicke[16], A. Koitka-Weber[16], S. Thiemann[17] & M. von Eynatten[17]

Methods: 360 individuals with type 2 diabetes, HbA1c 6.5−10.0% (48−86 mmol/mol), estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and urinary albumin-to-cr blockade were randomized to double-blind linagliptin (n = 182) or placebo (n = 178) for 24 weeks. The primary and key secondary endpoints were change from baseline in HbA1c at week 24 and time-weighted average of percentage change from baseline in UACR over 24 weeks, respectively.

Conclusions: In individuals at early stages of diabetic kidney disease, linagliptin significantly improved glycaemic control but did not significantly lower albuminuria. There was no significant change in placebo-adjusted eGFR. Detection of clinically relevant renal effects of linagliptin may require longer treatment, as its main experimental effects in animal studies have been to reduce interstitial fibrosis rather than alter glomerular haemodynamics.





Kidney International, Vol. 63 (2003), pp. 225–232

Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64)

AMANDA I. ADLER, RICHARD J. STEVENS, SUE E. MANLEY, RUDY W. BILOUS, CAROLE A. CULL, and RURY R. HOLMAN, on behalf of the UKPDS GROUP

Annual Transition

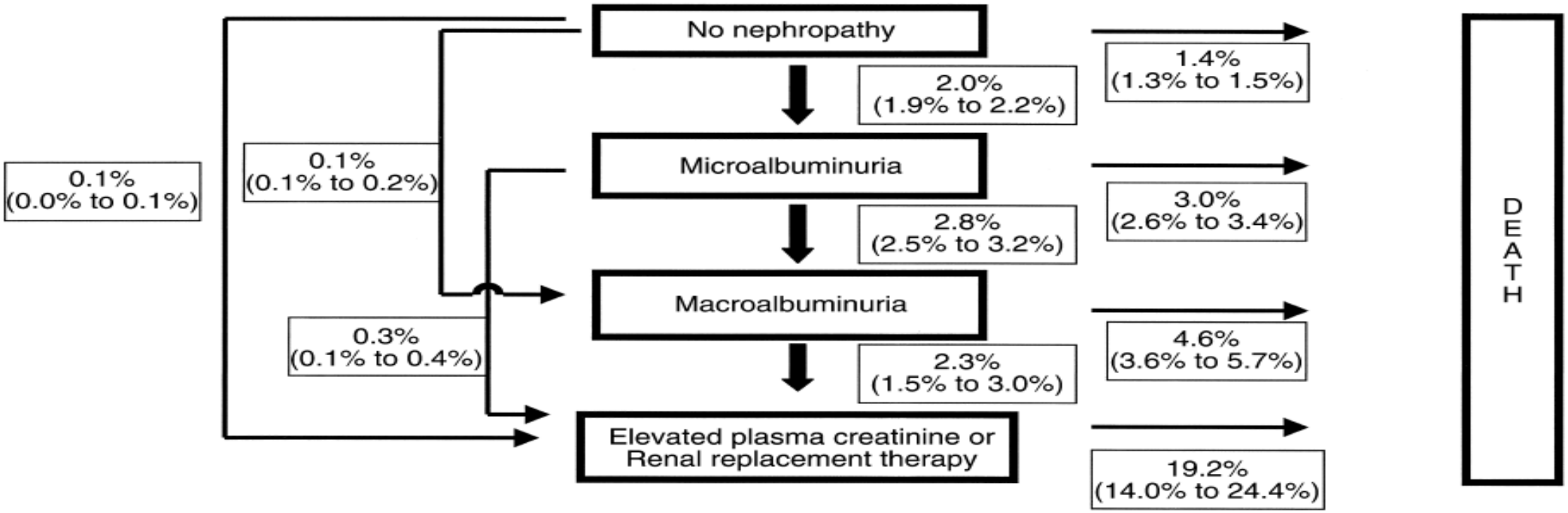
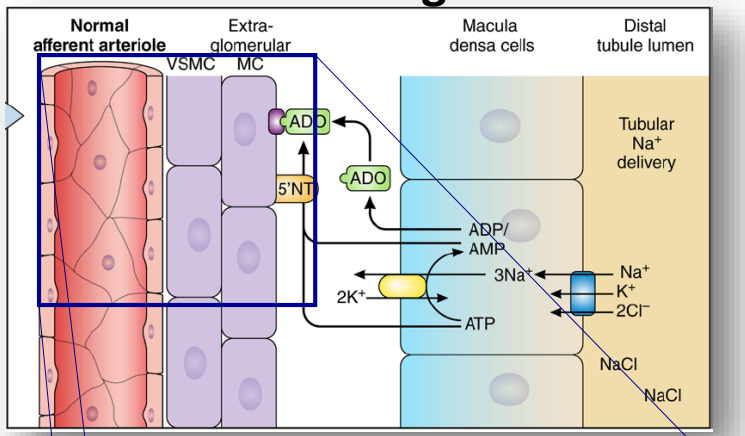


Fig. 1. Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.

Kidney Int, 2003

Feed-back tubulo-glomerulare

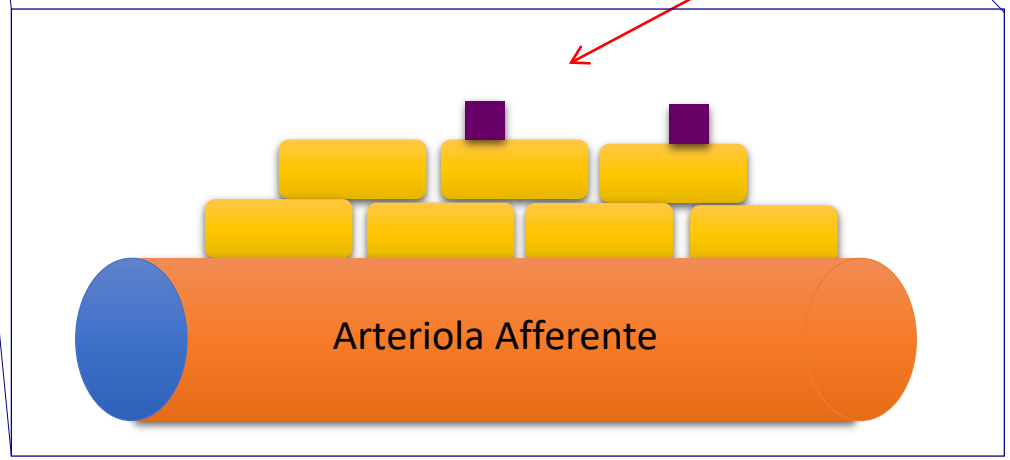


Heerspink H.J.L. et al. Circulation 2016

*

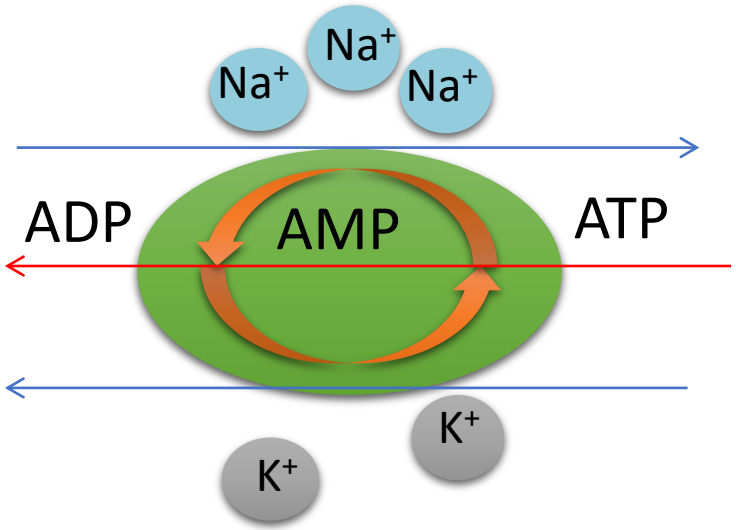
Adenosina

Potente vasocostrittore



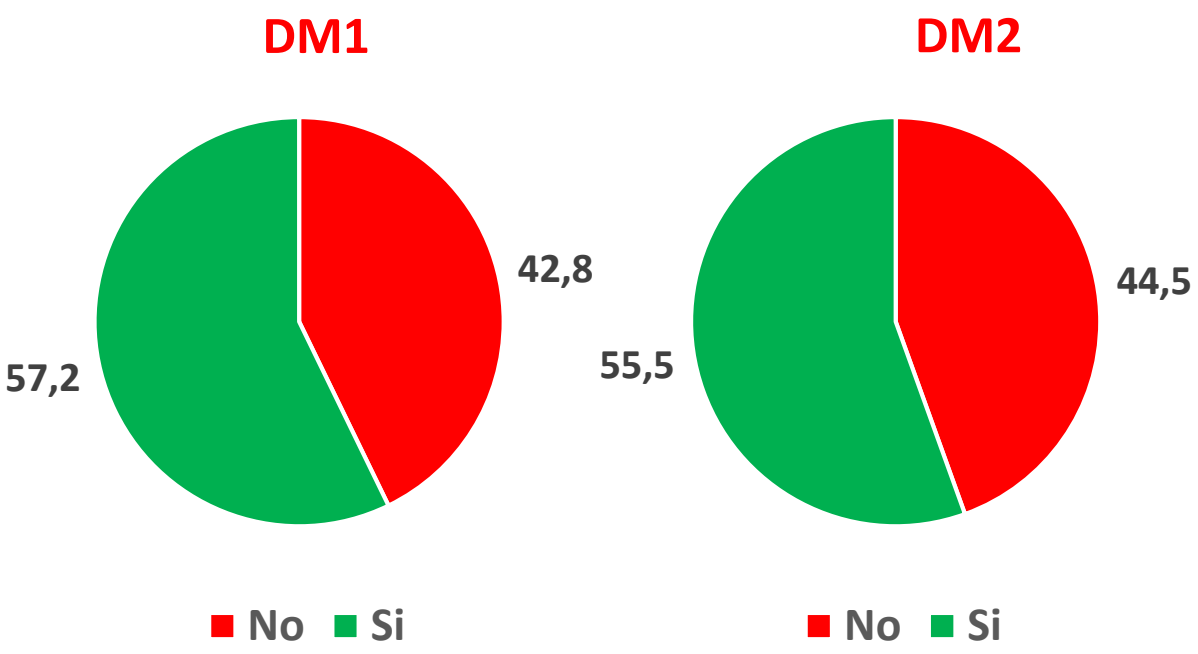
Pompa Na^+/K^+

Ingresso di 3 Na^+

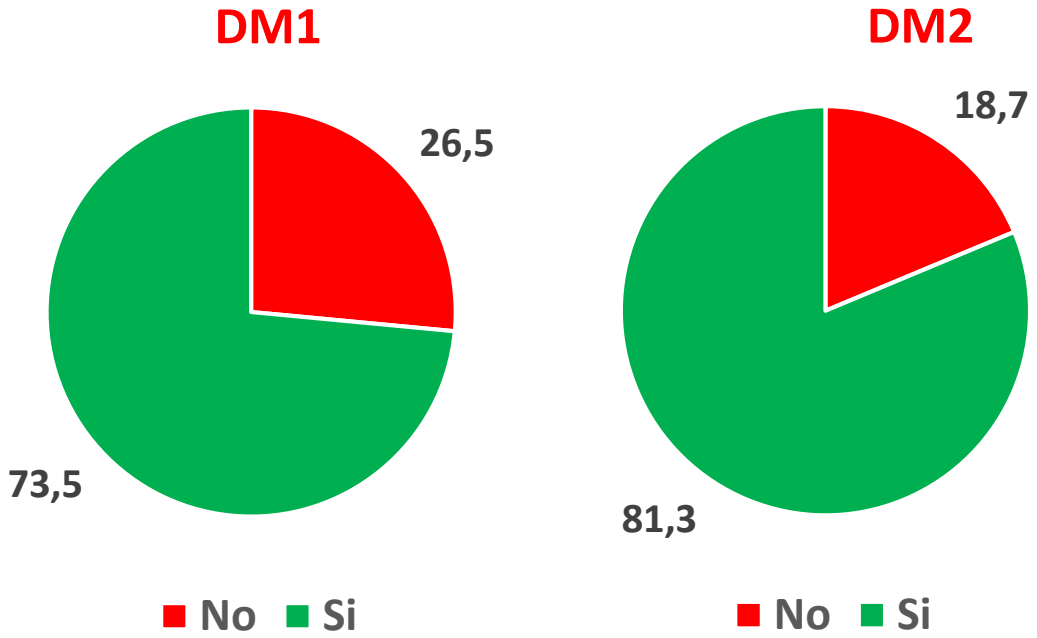


Rientro di 2 K^+

Soggetti monitorati per *albuminuria* (%)



Soggetti monitorati per *creatininemia* (%)



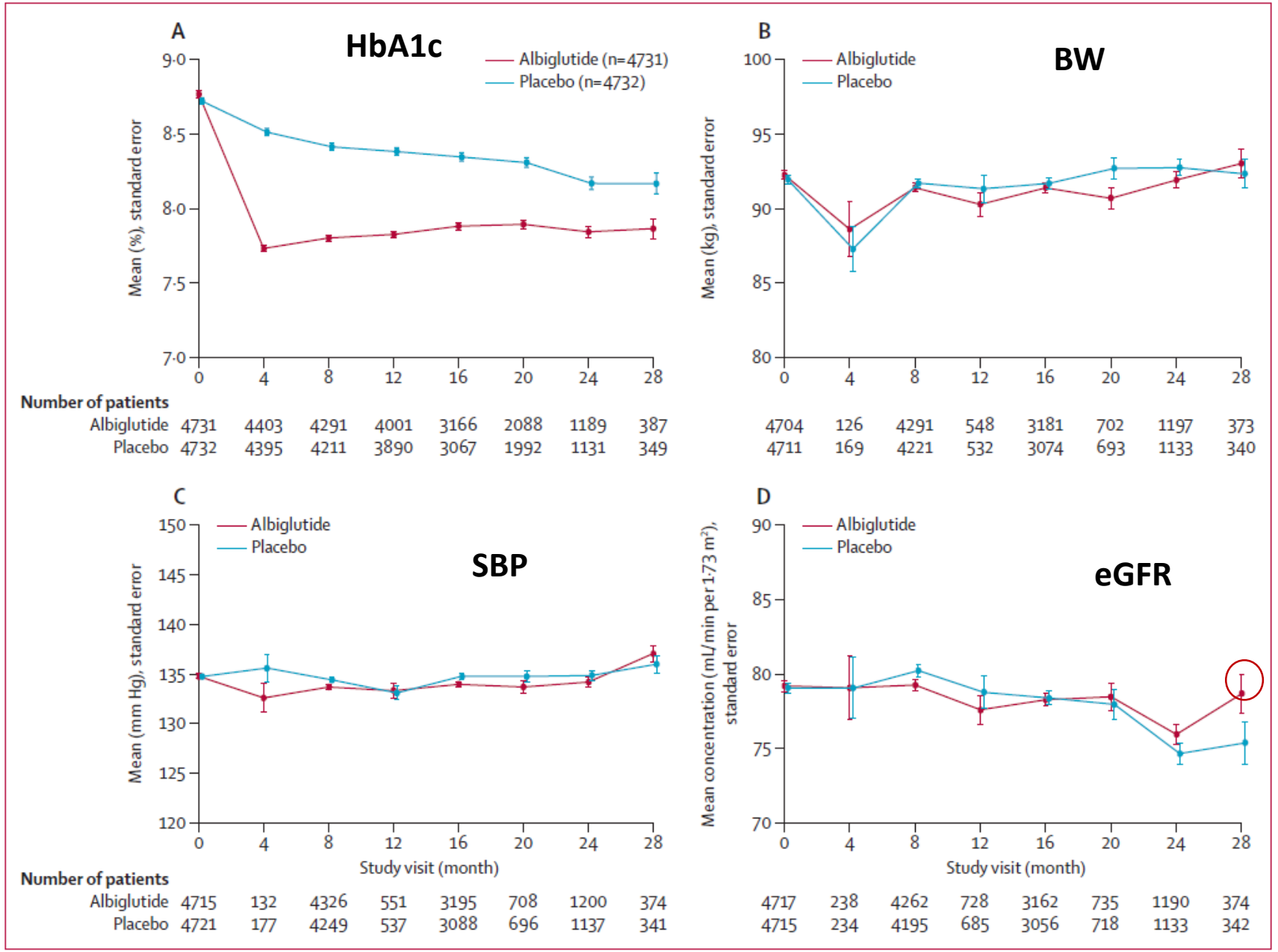
Annali AMD, 2018

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators*

HARMONY

0·9 to 1·6; 1·4 beats per min, 1·0 to 1·9; appendix 1). The difference in eGFR between patients in the albiglutide group and those in the placebo group was –1·11 mL/min per 1·73 m² (95% CI –1·84 to –0·39) at 8 months and –0·43 per 1·73 m² (–1·26 to 0·41) at 16 months. There

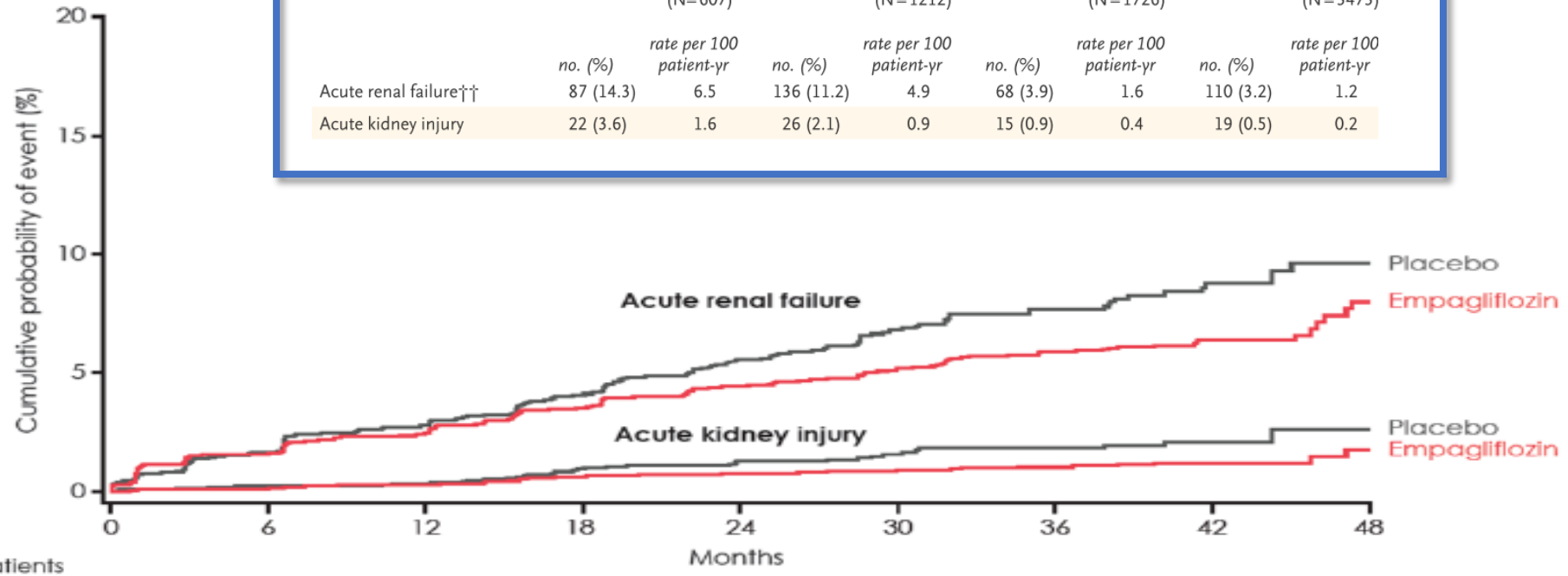


Acute renal failure and acute kidney injury

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

We conducted post hoc analyses in a subgroup of patients with prevalent kidney disease (defined as an eGFR of 59 ml per minute per 1.73 m^2 or less, as calculated by the MDRD formula, or macroalbuminuria) at baseline. In addition, we performed post hoc analyses of a composite of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease.

	Patients with Baseline eGFR of 59 ml per Minute per 1.73 m^2 or Less				Patients with Baseline eGFR of 60 ml per Minute per 1.73 m^2 or More			
	Placebo (N=607)		Empagliflozin (N=1212)		Placebo (N=1726)		Empagliflozin (N=3473)	
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*
Acute renal failure††	87 (14.3)	6.5	136 (11.2)	4.9	68 (3.9)	1.6	110 (3.2)	1.2
Acute kidney injury	22 (3.6)	1.6	26 (2.1)	0.9	15 (0.9)	0.4	19 (0.5)	0.2



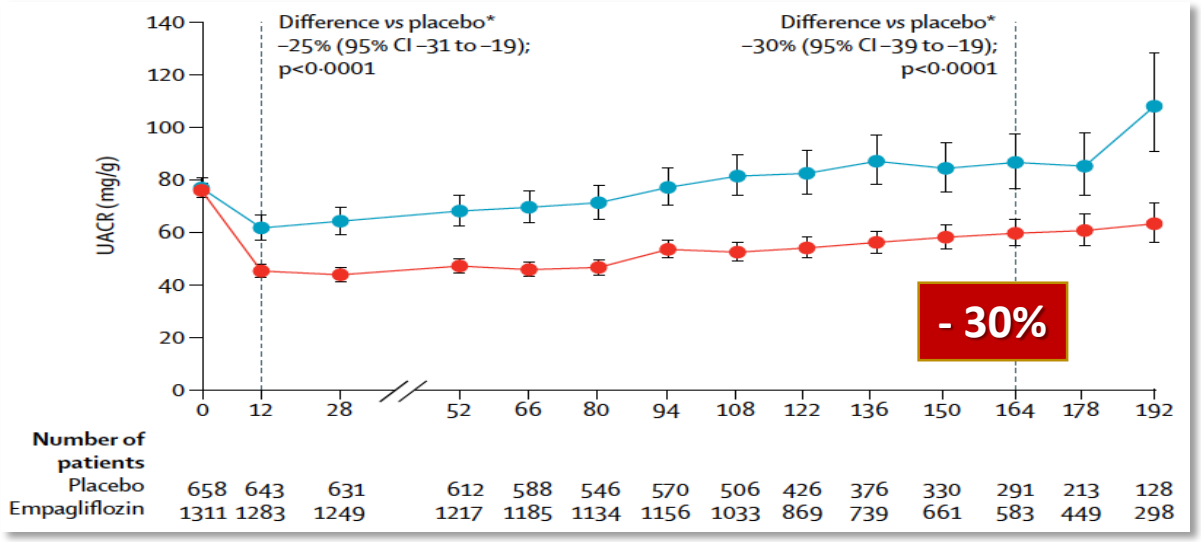
No. of patients									
Acute renal failure									
Empagliflozin	4687	4359	4159	3937	3398	2463	1897	975	268
Placebo	2333	2167	2031	1889	1588	1133	866	403	108
Acute kidney injury									
Empagliflozin	4687	4415	4238	4037	3505	2545	1965	1014	279
Placebo	2333	2194	2078	1944	1653	1178	902	427	111

- Kaplan-Meier estimates in patients treated with ≥1 dose of study drug based on events that occurred during treatment or ≤7 days after last intake of study drug. *Post-hoc* analyses. Acute renal failure: narrow standardized MedDRA query “acute renal failure”.

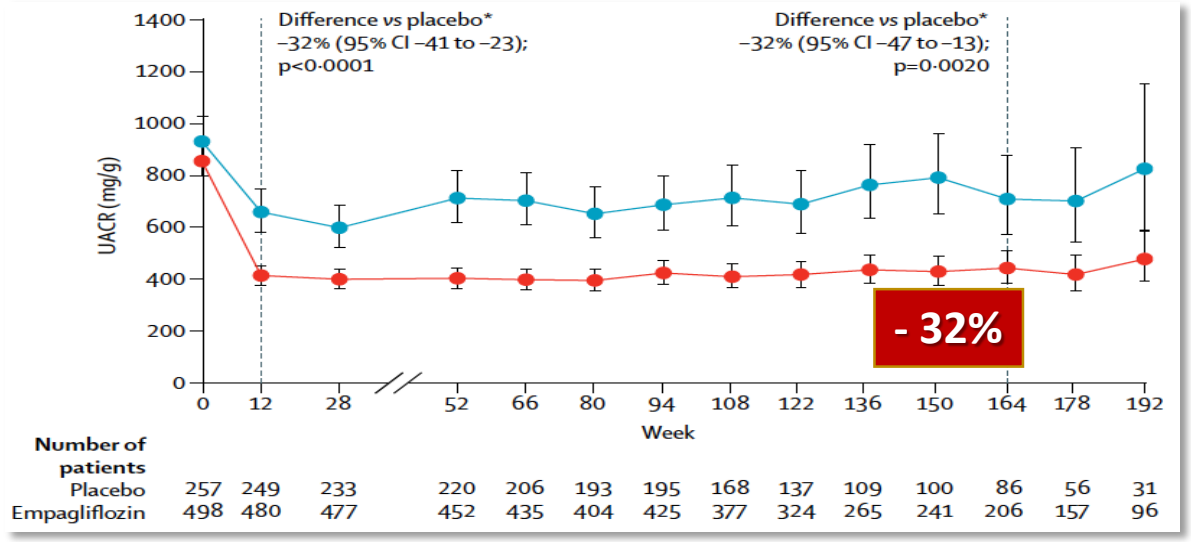
EMPAREG STUDY: Urinary albumin-to-creatinine ratio over 192 weeks

in patients with ALBUMINURIA at baseline

With Microalbuminuria



With Macroalbuminuria



On top of intensive glucose, lipid e blood pressure treatments

Lancet Diabetes Endocrinol 2017; 5: 610–21