Optimización del tratamiento antidiabético. ¿Cómo cambia mi práctica clínica como especialista?

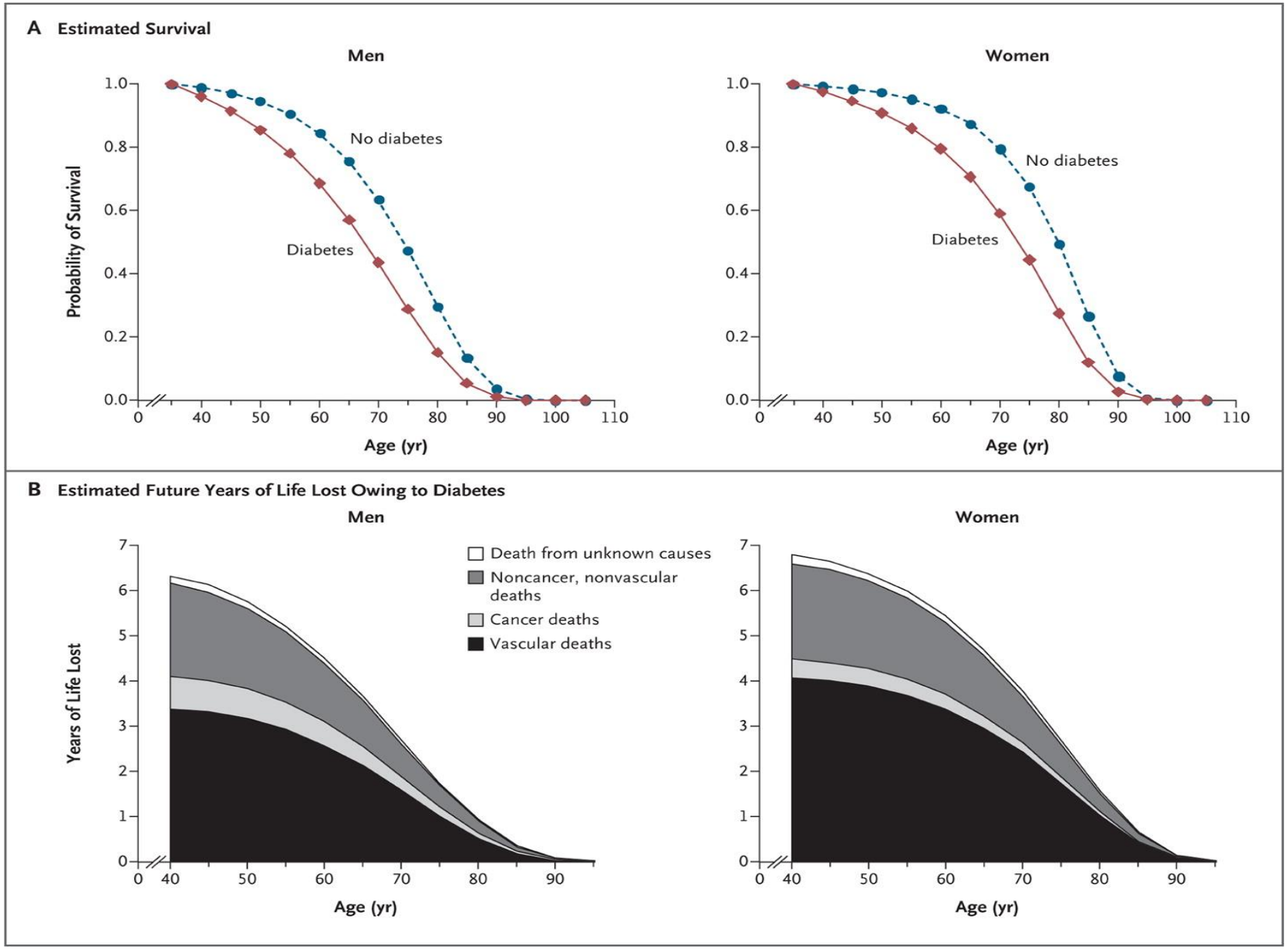
José Ignacio Cornago Delgado

Servicio de Nefrología

Hospital Galdakao – Usansolo

Santiago de Compostela

12 de Mayo de 2018



N Engl J Med 2011;364:829-41.

Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study

Gillian L Booth, Moira K Kapral, Kinwah Fung, Jack V Tu

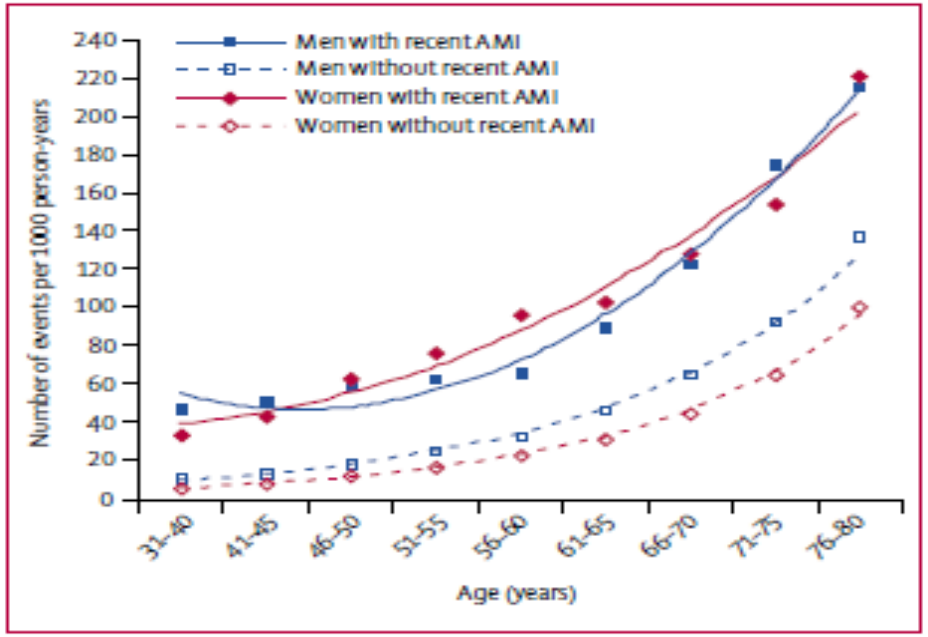
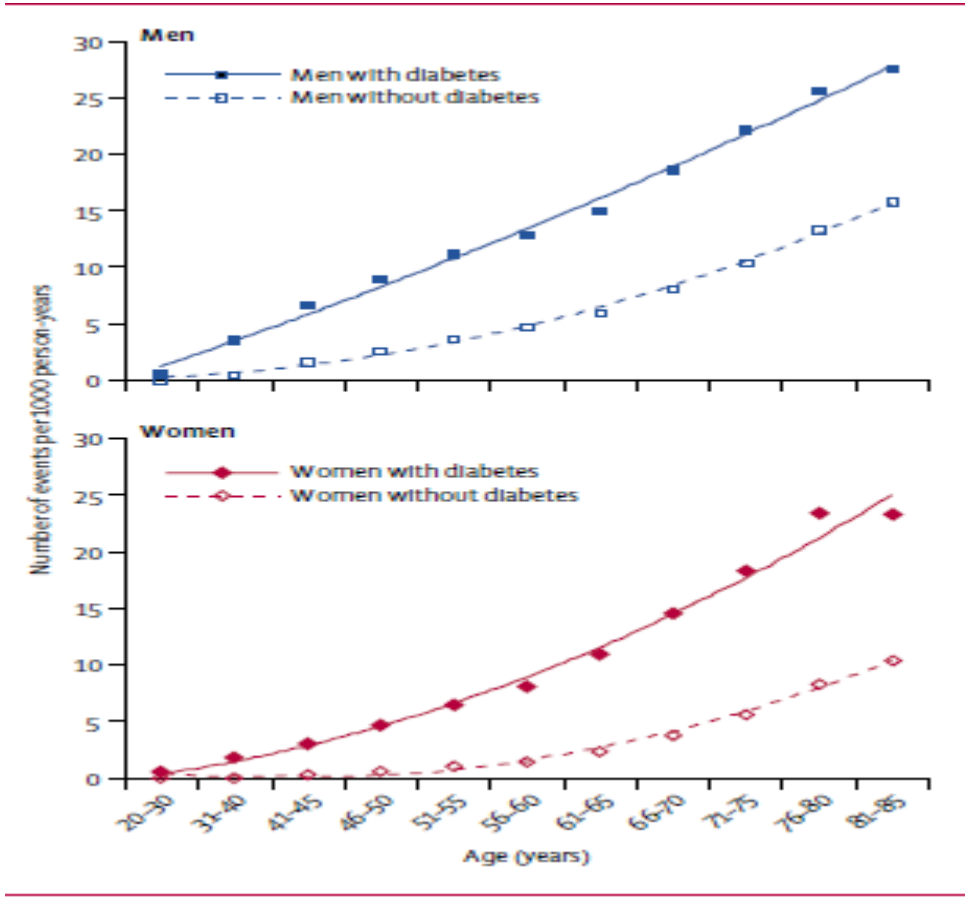


Figure 5: **Relation between age and rates of AMI or death from any cause among men and women with diabetes**
All lines fitted according to a polynomial equation. R^2>0·97 for each fitted line.

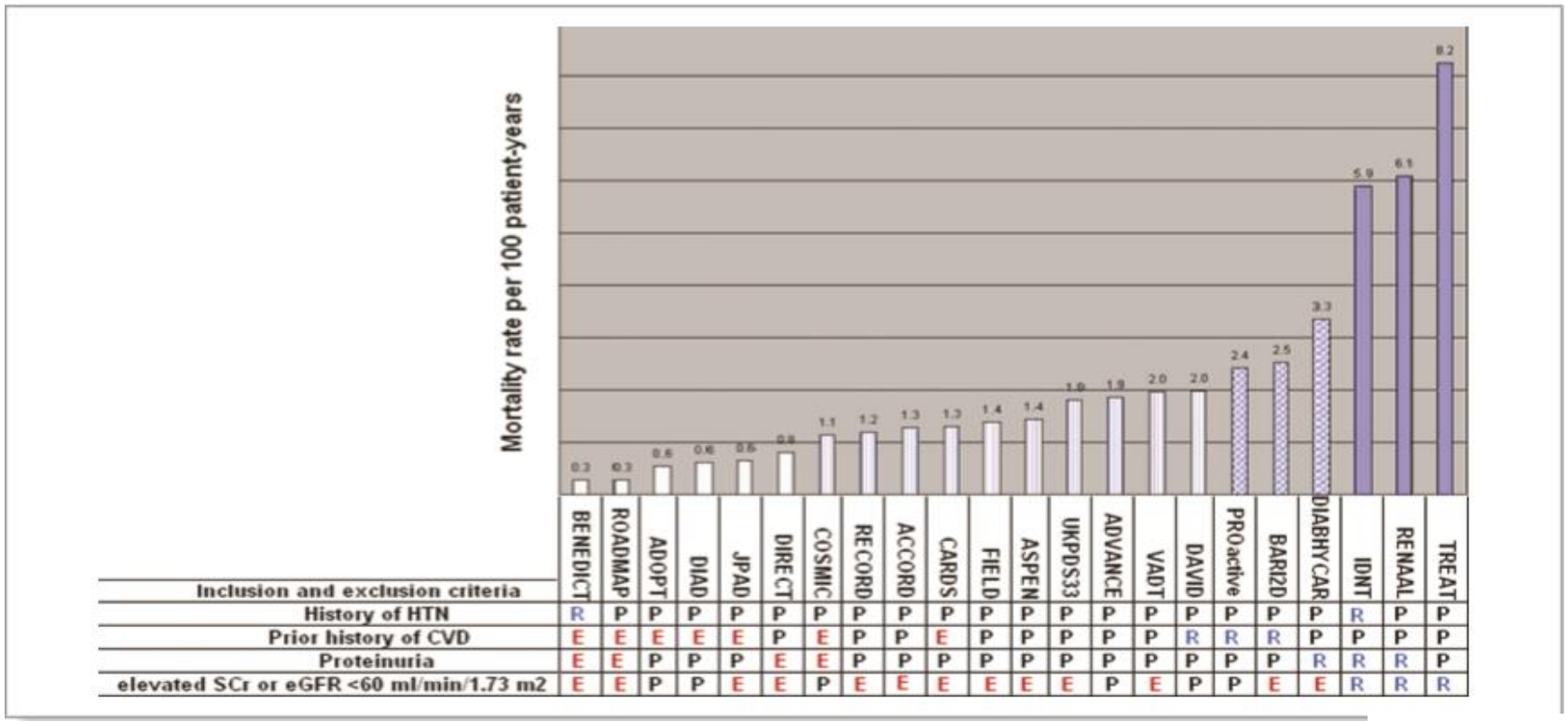


Lancet 2006; 368: 29–36

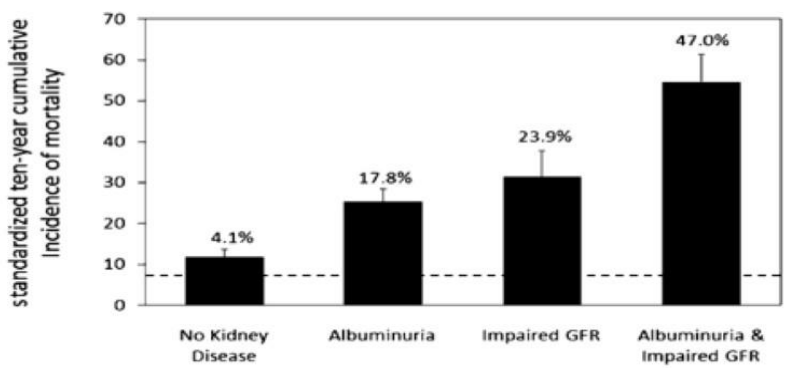
ORIGINAL RESEARCH

Mortality Rates in Trials of Subjects With Type 2 Diabetes

Ebrahim Barkoudah, MD; Hicham Skali, MD, MSc; Hajime Uno, PhD; Scott D. Solomon, MD; Marc A. Pfeffer, MD, PhD



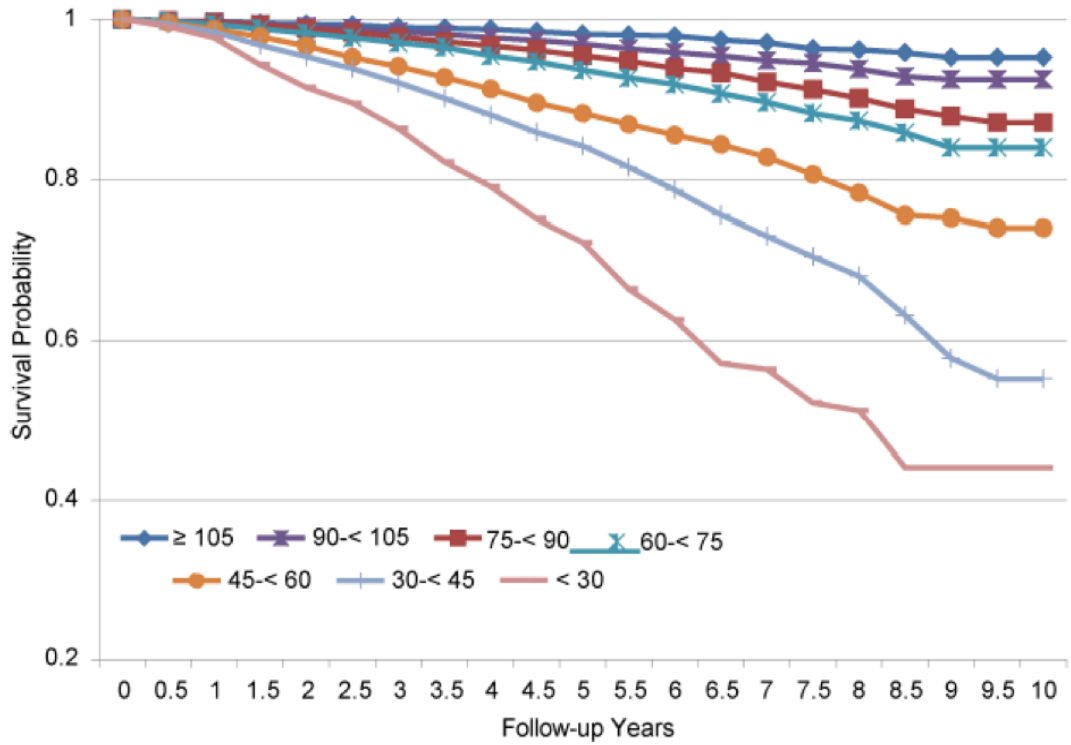
En importantes estudios epidemiológicos se ha demostrado que el incremento del riesgo cardiovascular en la población con diabetes es, sobre todo, a expensas de los pacientes que tienen deterioro de la función renal o albuminuria. Así, en pacientes con diabetes y función renal normal, el riesgo cardiovascular es semejante al de la población sin diabetes.

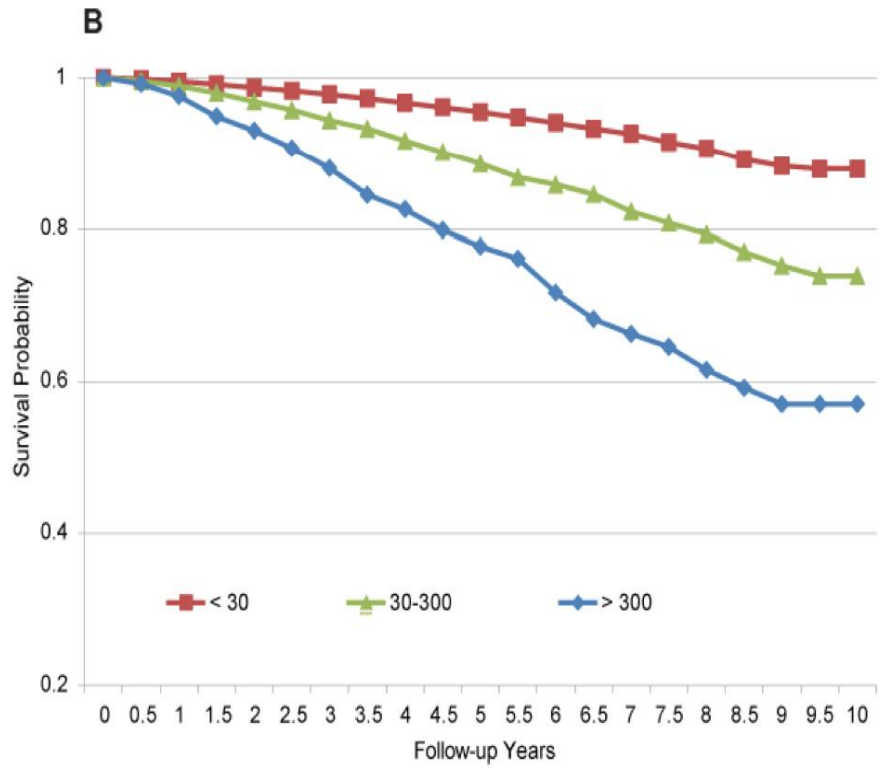


Afkarian et al. J Am Soc Nephrol. 2013; 24: 302-308.

The Synergistic Relationship between Estimated GFR and Microalbuminuria in Predicting Long-term Progression to ESRD or Death in Patients with Diabetes: Results from the Kidney Early Evaluation Program (KEEP)

Amit P. Amin, MD, MSc[1], **Adam T. Whaley-Connell, DO, MSPH**[2], **Suying Li, PhD**[3], **Shu-Cheng Chen, MS, MPH**[3], **Peter A. McCullough, MD, MPH**[4], and **Mikhail N. Kosiborod, MD**[5]
On behalf of the KEEP Investigators*





Am J Kidney Dis. 2013 April ; 61(4 0 2): S12–S23. doi:10.1053/j.ajkd.2013.01.005.

Original

Prevalencia estimada de insuficiencia renal crónica en España en pacientes con diabetes mellitus tipo 2

Pedro Luis de Pablos-Velasco [a,*], Francisco-Javier Ampudia-Blasco [b], Albert Cobos [c,d], Salvador Bergoñón [c,e], Pablo Pedrianes [a] y en representación del Grupo de Investigadores DIABIR

[a] *Unidad o Sección Hospitalaria, Hospital Universitario Dr. Negrín Las Palmas de Gran Canaria, Universidad de Las Palmas, Las Palmas de Gran Canaria, España*
[b] *Unidad de Referencia de Diabetes, Hospital Clínico Universitario de Valencia, Valencia, España*
[c] *Saalig Clinical, Barcelona, España*
[d] *Departamento de Salud Pública, Facultad de Medicina, Universidad de Barcelona, Barcelona, España*
[e] *Departamento de Farmacología, Facultad de Medicina, Universidad de Barcelona, Barcelona, España*

INFORMACIÓ

Historia del artículo
Recibido el 3 de ju
Aceptado el 22 de
On-line el 29 de di

Palabras clave:
Diabetes mellitus
Insuficiencia renal
Diagnóstico
Factores de riesgo
Control metabólico

22,9% de pacientes con DM2 tienen IR (FG <60 mL/min)

objetivo: El objetivo principal del estudio fue determinar la prevalencia actual de nal crónica (IRC) en pacientes ambulatorios con diabetes mellitus tipo 2 (DM2), en los servicios de Endocrinología a nivel nacional.

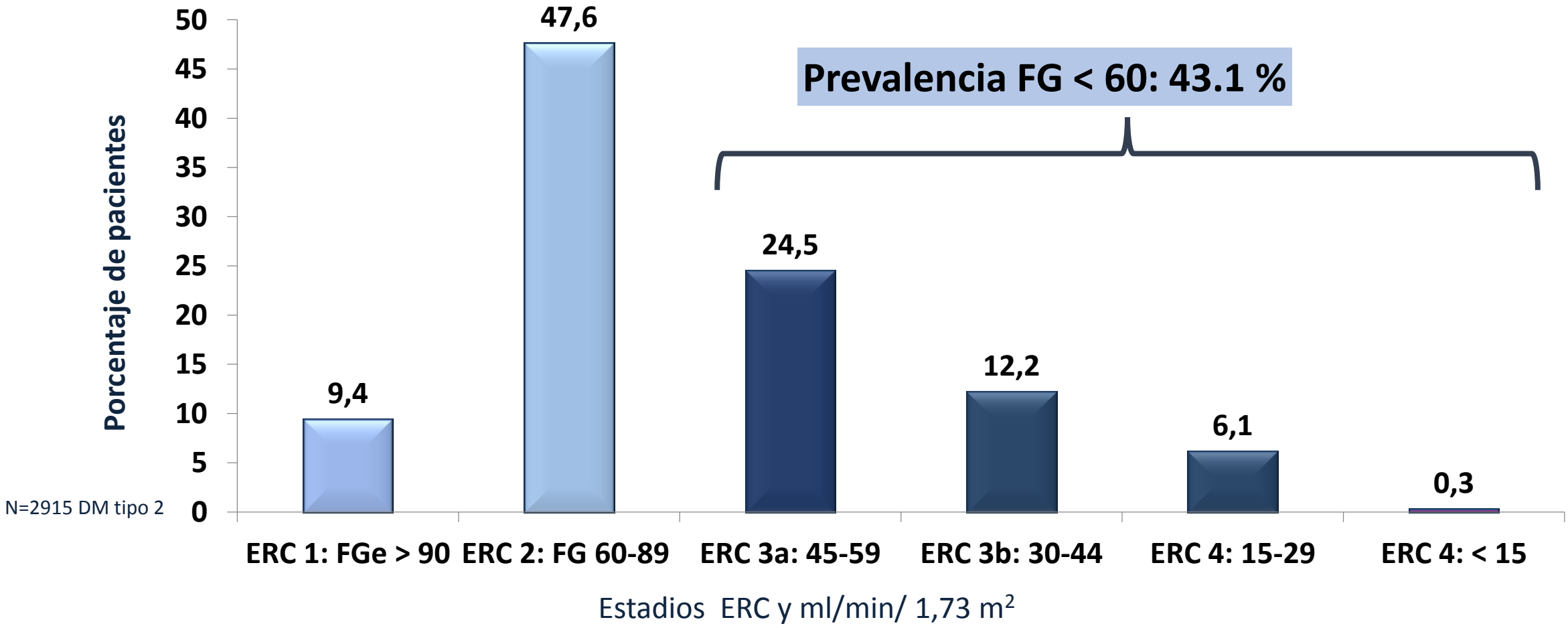
odo: Estudio con diseño observacional, transversal, multicéntrico y con recogida de datos e cada participante se registraron datos demográficos y antropométricos, de función renal, de factores de riesgo cardiovascular, comorbilidades y tratamientos. La presencia de IRC fue con un filtrado glomerular inferior a 60 ml/min/1,73 m^2, y se utilizó el método Modification in Diet isease abreviado.

Res Se incluyeron 541 pacientes con DM2 de ambos sexos (el 53% eran varones), con una edad medi de 63 años (7,9) y una hemoglobina glucosilada media del 7,6% (1,3). La prevalencia (intervalo de conf IC] del 95%) de IRC fue del 22,9% (IC del 95%: 19,4–26,7), superior a la estimada previamente, que fue de 7% (IC del 95%: 3,9–8,0) ($p < 0,0001$). Como factores de riesgo de tener IRC se identificaron la edad (*odds* [OR]: 2,07 [IC del 95%: 1,47–2,91] por cada 10 años de aumento), el sexo femenino (OR: 2,25 [IC del 95 1,36–3,71]) y la hiperuricemia (OR: 3,15 [IC del 95%: 1,56–6,37]). No hubo diferencias en el control metabólico entre los pacientes con IRC frente a sin IRC objetiva.

Conclusión: Un 22,9% de los pacientes con DM2 seguidos de manera ambulatoria por endocrinólogos presenta IRC y de esta población sólo está diagnosticada una cuarta parte. La determinación automatizada del aclaramiento de creatinina podría incrementar el porcentaje de diagnóstico y facilitar un mejor control metabólico en estos pacientes.

Med Clin (Barc). 2010; 134: 340-345.

Prevalencia de FGe < 60 ml/min/1,73 m^2 (CKD-EPI) en pacientes con diabetes mellitus tipo 2 ≥ 65 años



*Ajustado por edad poblacion en National Health Interview Survey
Estudio NHANES 1999-2012

Bailey RA. BMC Research notes 2014; 7: 415

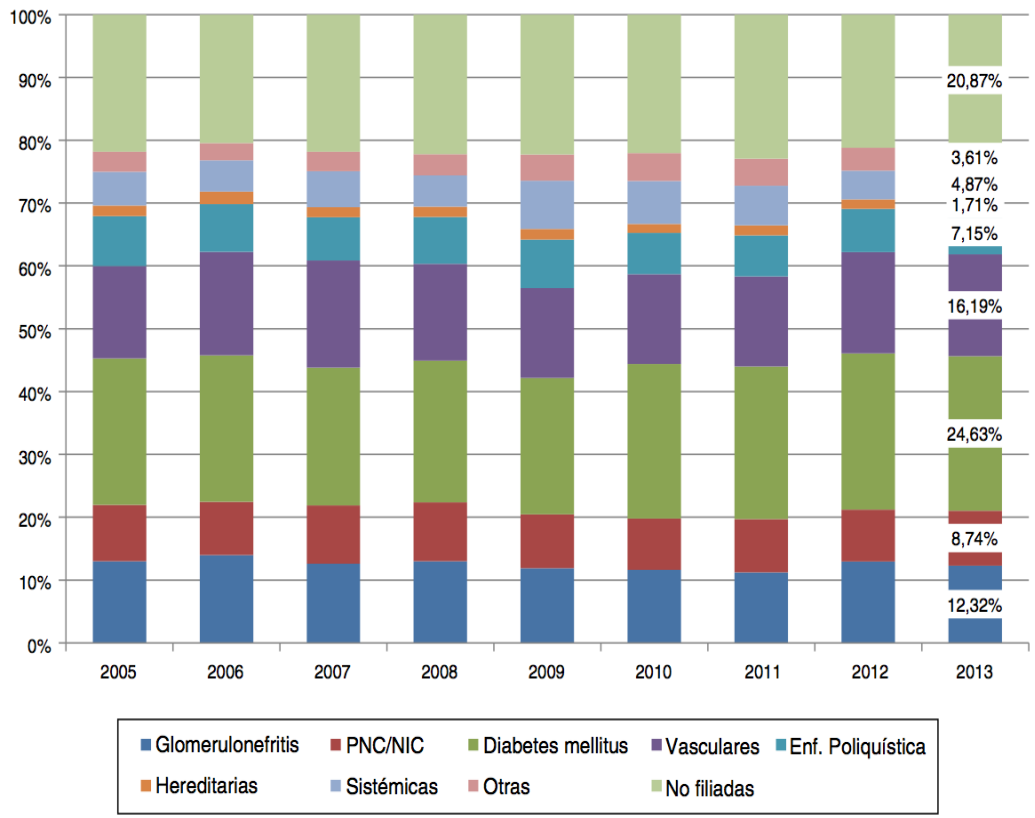
¿Qué tipo de paciente diabético se ve en Nefrología?

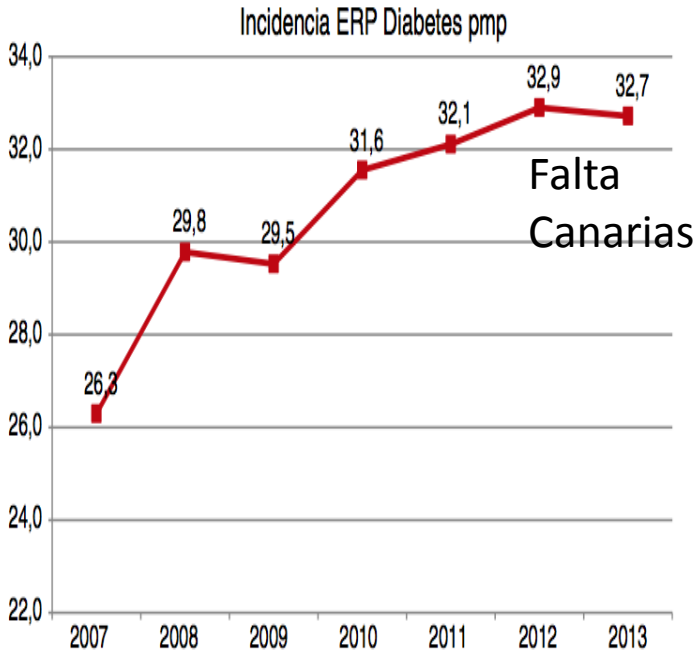
nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Artículo especial

Registro Español de Enfermos Renales. Informe 2013 y evolución 2007-2013

*Eduardo Martín Escobar (Coord.)** e *Registro Español de Enfermos Renales (REER)*◇





Características de los pacientes que se ven en Nefrología (Estudio MERENA)

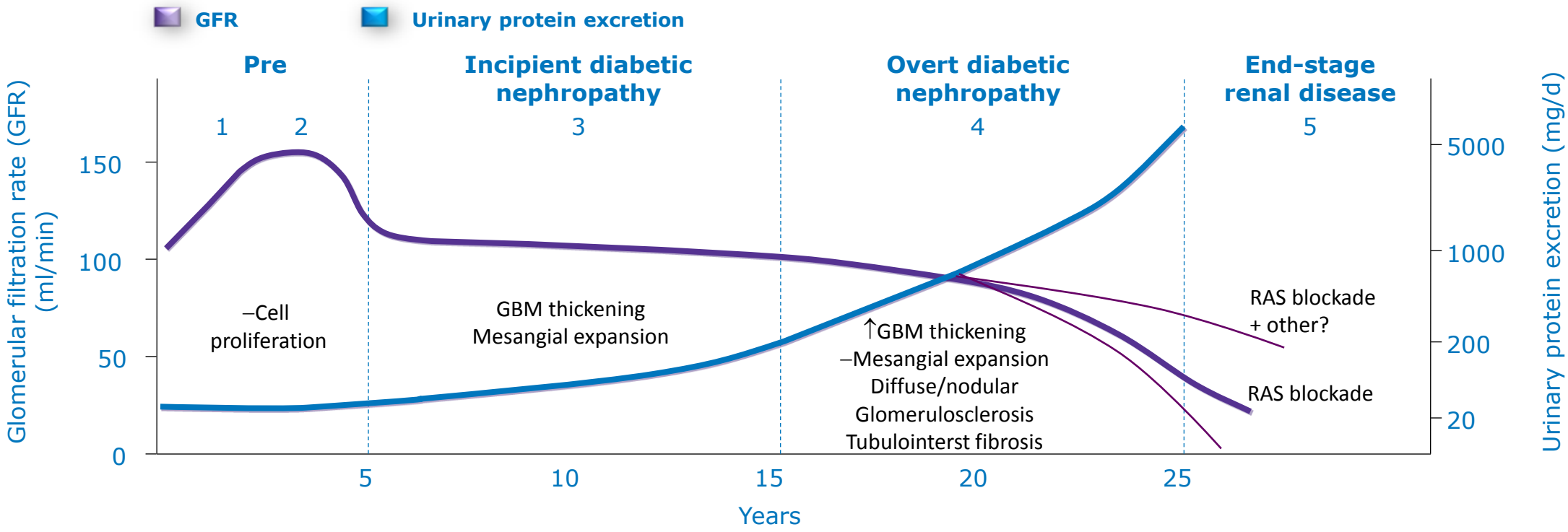
	Toda la serie (%)	No D N=668	Diab N=461	p
Sexo (% varón)	64	62,4	**66,6**	0,17
Enf. Cardiovascular*	39,1	31,9	**49,6**	**0.0001**
Enf. coronaria	21,6	18,3	**26,4**	**0,001**
Enf. Vasc. Periférica	19,7	11,5	**31,7**	**0,0001**
Enf. cerebrovascular	12,2	11,4	**13,6**	0,18
Tabaquismo	9,6	10,8	**7,9**	**0,014**
Insuf. cardiaca	17,5	13,9	**22,7**	**0,001**
Filtrado glom estimado (ml/min/1,73 m^2)	28 ± 8	27 ± 8	30 ± 9	**0,001**
Proteinuria (gr/dia)	1,2 ± 1,8	0,9 ± 1,2	1.7 ± 2,2	**0,001**

Mortalidad en DM 2 a los 5 años: ERC 3: 12.7 % , ERC 4: 24 %
El 50 % han presentado acontecimientos CV

*Enf cardiovascular: enf coronaria, ictus/AIT, enf vascular periférica

Martinez Castelao A, Gorriz JL . BMC Nephrology 2011, 12:53

Historia natural de la nefropatía diabética



Functional changes	**GFR ↑ (90-95%)**	**Microalbuminuria, hypertension**	**Proteinuria, nephrotic syndrome, GFR ↓**

Cooper ME, Gilbert RE.. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. New York: Mosby; 2000.

Nonproteinuric Diabetic Nephropathy

When Diabetics Don't Read the Textbook

Jamie P. Dwyer, MD*, Julia B. Lewis, MD

KEYWORDS

• Diabetic nephropathy • Nonproteinuric • Normoalbuminuria

KEY POINTS

- The traditional clinical paradigm of diabetic nephropathy (DN) may not apply to all patients with diabetes and decreased renal function.
- A feature of the natural history of DN that is gaining renewed investigation is the progression from normoalbuminuria to proteinuria and then to renal failure.
- A subset of patients with presumed DN have minimal proteinuria.
- Mechanisms proposed to explain this finding include use of agents which block the renin-angiotensin system, bouts of acute kidney injury, genetic predisposition, and other non-diabetic kidney diseases.

J. Clin. Med. **2015**, *4*, 1207-1216; doi:10.3390/jcm4061207

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Journal of

Clinical Medicine

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www.mdpi.com/journal/jcm

Review

The Concept and the Epidemiology of Diabetic Nephropathy Have Changed in Recent Years

Alberto Martínez-Castelao [1,*], Juan F. Navarro-González [2], José Luis Górriz [3] and Fernando de Alvaro [4]

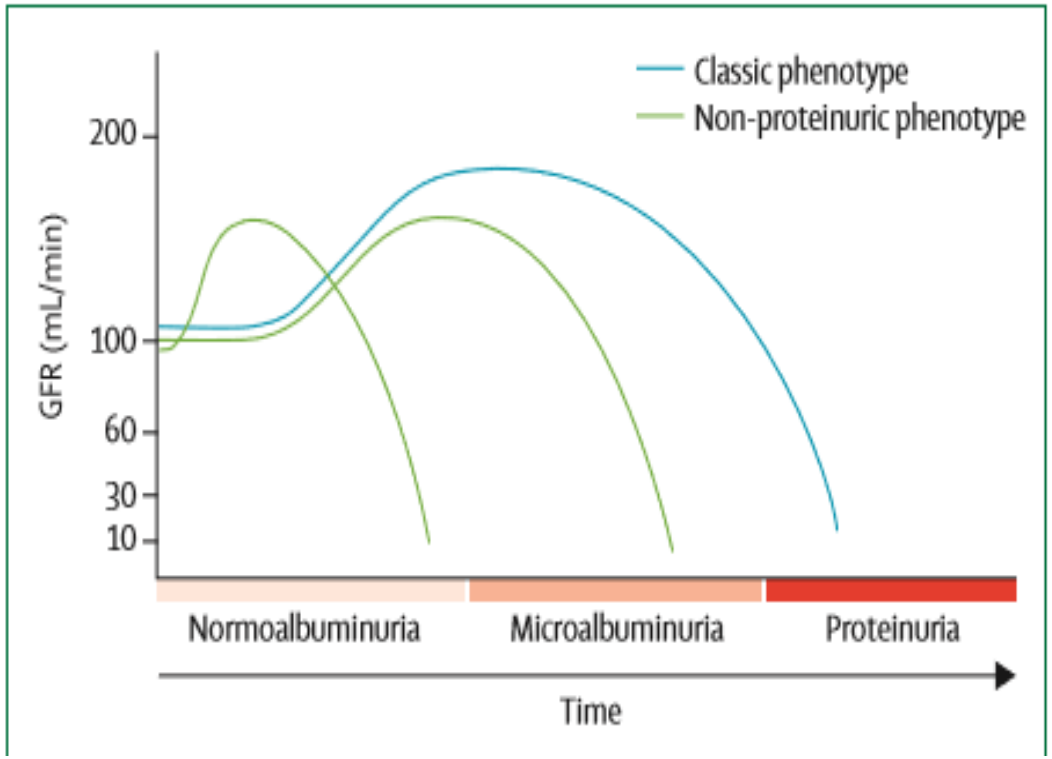
Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes

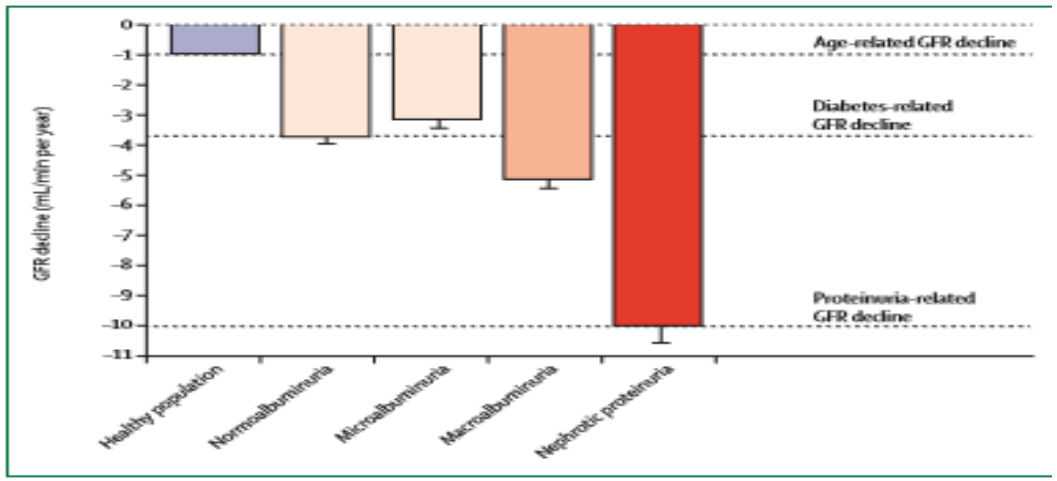
Esteban Porrini, Piero Ruggenenti, Carl Erik Mogensen, Drazenka Pongrac Barlovic, Manuel Praga, Josep M Cruzado, Radovan Hojs, Manuela Abbate, Aiko P J de Vries, for the ERA-EDTA diabesity working group.

Lancet Diabetes Endocrinol

2015; 3: 382–91

	N	Outcomes		Comments
		GFR < 60 mL/min per 1·73 m²	Albuminuria/proteinuria	
Cross-sectional studies				
Kramer et al (2003)[17] (NAHNES 1988–1994)	1197	171 (14%)	36% normoalbuminuria 45% microalbuminuria 19% macroalbuminuria or proteinuria	28% retinopathy; 30% no retinopathy plus microalbuminuria or microalbuminuria; similar results excluding users of ACE inhibitors
MacIsaac et al (2004)[24]	301	109 (36%)*	39% normoalbuminuria 35% microalbuminuria 26% macroalbuminuria or proteinuria	Chronic kidney disease, normoalbuminuria and microalbuminuria more common in women than men; 26% retinopathy in normoalbuminuria and 50% in microalbuminuria; use of ACE inhibitors >70%
So et al (2006)[19]	4421	528 (12%)	14% normoalbuminuria 26% microalbuminuria 60% macroalbuminuria or proteinuria	56% retinopathy; use of ACE inhibitors 60%
Yokoyama et al (2009)[20]	3297	506 (15%)	52% normoalbuminuria 21% microalbuminuria 27% macroalbuminuria or proteinuria	Risk factors: female sex, obesity, triglyceride concentrations, smoking, cardiovascular disease, hypertension, retinopathy.
Thomas et al (2009[21] (NEPHRON 11)	3892	920 (23%)	55% normoalbuminuria 32% microalbuminuria 13% macroalbuminuria or proteinuria	Female sex a risk factor; 14% retinopathy; use of ACE inhibtors >80%
Penno et al (2011)[22] (RIACE study)	15773	2959 (19%)	57% normoalbuminuria 31% microalbuminuria 13% macroalbuminuria or proteinuria	Risk factors: female sex, obesity, triglyceride concentrations, hypertension 32% retinopathy; 43% no retinopathy plus microalbuminuria or proteinuria; use of ACE inhibitors >70%
Dwyer et al (2012)[23] (DEMAND study)	11573	2586 (22%)	40% normoalbuminuria 47% microalbuminuria 13% macroalbuminuria or proteinuria	Risk factors: female sex, hypertension, retinopathy, dyslipidaemia, smoking, hyperglycaemia
Mottl et al (2013)[24] (NAHNES 2001-2008)	2798	575 (21%)	52% normoalbuminuria 48% microproteinuria	Chronic kidney disease, normoalbuminuria and microalbuminuria more frequent in women than in men; hypertension and hyperglycaemia were protective factors
Boronat et al (2014)[25]	..	78 (GFR <30 ml/min)	22% normoalbuminuria 20% microalbuminuria 58% proteinuria	Female sex a risk factor; hyperglycaemia and polyneuropathy were protective factors; 29% retinopathy in normoalbuminuria, 53% in microalbuminuria or proteinuria
Cohort studies				
Retnakaran et al (2006)[26] (UKPDS-74)	4006	575 (14%)	977 (24%) microalbuminuria, macroalbuminuria and proteinuria combined	557 (14%) developed chronic kidney disease and microalbuminuria or macroalbuminuria; follow-up: 15 years; risk factors: female sex, smoking, systolic BP; reduced GFR preceded microalbuminuria in 16% of cases
Bash et al (2009)[27] (ARIC study)	1871*	361 (19%)	No information	Follow-up: 11 years; 53% with retinopathy; 47% without retinopathy; 29% retinopathy plus microalbuminuria or macroalbuminuria
Afghahi et al (2011)[28] (NDR study)	3667	290 (8%)	612 (17%) microalbuminuria, macro albuminuria and proteinuria combined	117 (3%) developed chronic kidney disease and microalbuminuria or macroalbuminuria; follow-up: 5 years; risk factors: female sex, triglyceride concentrations, systolic BP





Lancet Diabetes Endocrinol
2015; 3: 382–91

Consideraciones…

Hay situaciones en las que la hiperfiltración genera deterioro de función renal sin albuminuria

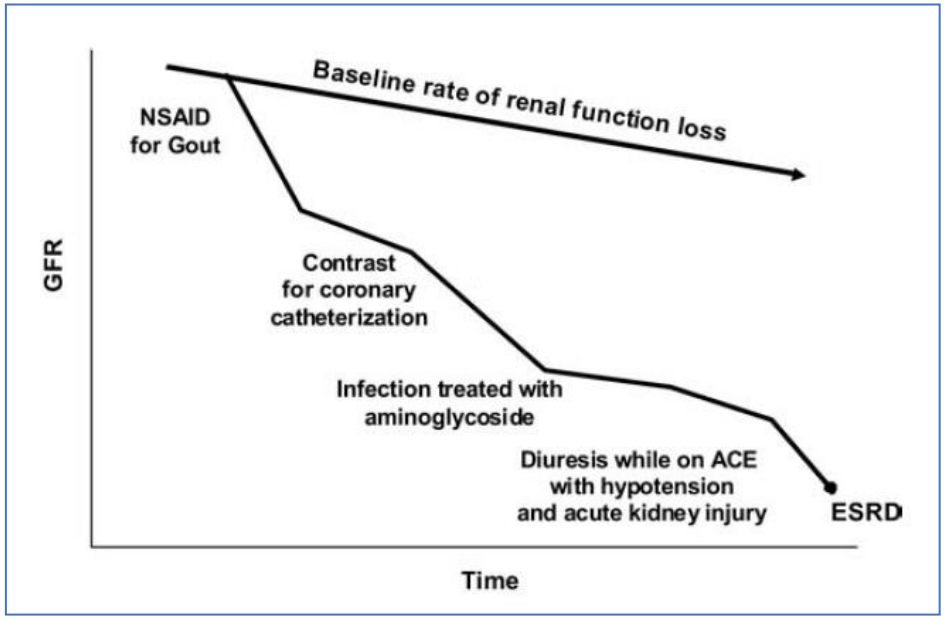
El buen control de la TA, glucemia, uso del BSRAA han cambiado la historia natural de la enfermedad

Los pocos estudios con biopsia renal de pacientes diabéticos sin proteinuria pero con ERC hacen pensar que podemos estar infraestimando otras patologías renales

El elevado riesgo cardiovascular del diabético le hace más vulnerab
Al FRA

OPTIMIZAR LA ”SEGURIDAD RENAL” DEL PACIENTE PUEDE PREVENIR LA PROGRESIÓN ACELERADA DE LA INSUFICIENCIA RENAL

EFECTOS PREVENIBLES Y ASOCIADOS A LA “SEGURIDAD RENAL” DEL PACIENTE



NARRATIVE REVIEW *Am J Kidney Dis* 53:681-688. © *2009*

CKD as an Underrecognized Threat to Patient Safety

Jeffrey C. Fink, MD,[1,2] Jeanine Brown, MS,[1] Van Doren Hsu, PharmD,[3] Stephen L. Seliger, MD,[1,2]

CKD IS A HIGH-RISK CONDITION FOR ADVERSE SAFETY EVENTS

1. Medication errors[23-26]
   a. Improper dosing
   b. Inappropriate prescription
   c. Inadequate monitoring
2. Hyperkalemia[27,28]
3. Hypoglycemia[29,30]
4. Other electrolyte intoxication
   a. Hypermagnesemia[31,32]
   b. Hyperphosphatemia[33]
5. Diagnostic testing
   a. Iodinated contrast[34,35]
   b. Gadolinium[36]
6. Cardiovascular disease
   a. Missed diagnoses[37]
   b. Improper management (hemorrhage, restenosis)[38,39]
7. Fluid, RAAS blocker, diuretic mismanagement[40-42]
   a. Hypotension
   b. Azotemia
   c. CHF exacerbation
8. Acute kidney injury[43-45]
9. Miscellaneous
   a. Hip fracture[46]
   b. Deep vein thrombosis[47]
   c. Multiresistant bacterial infection[48]

La progresión de la enfermedad renal puede verse afectada por procesos intercurrentes que pueden prevenirse, como puede ser el uso de antiinflamatorios, determinados antibióticos, u optimizar las pruebas diagnósticas de los pacientes, entre otras.

Diabetologia (2018) 61:996–1011
https://doi.org/10.1007/s00125-018-4567-5

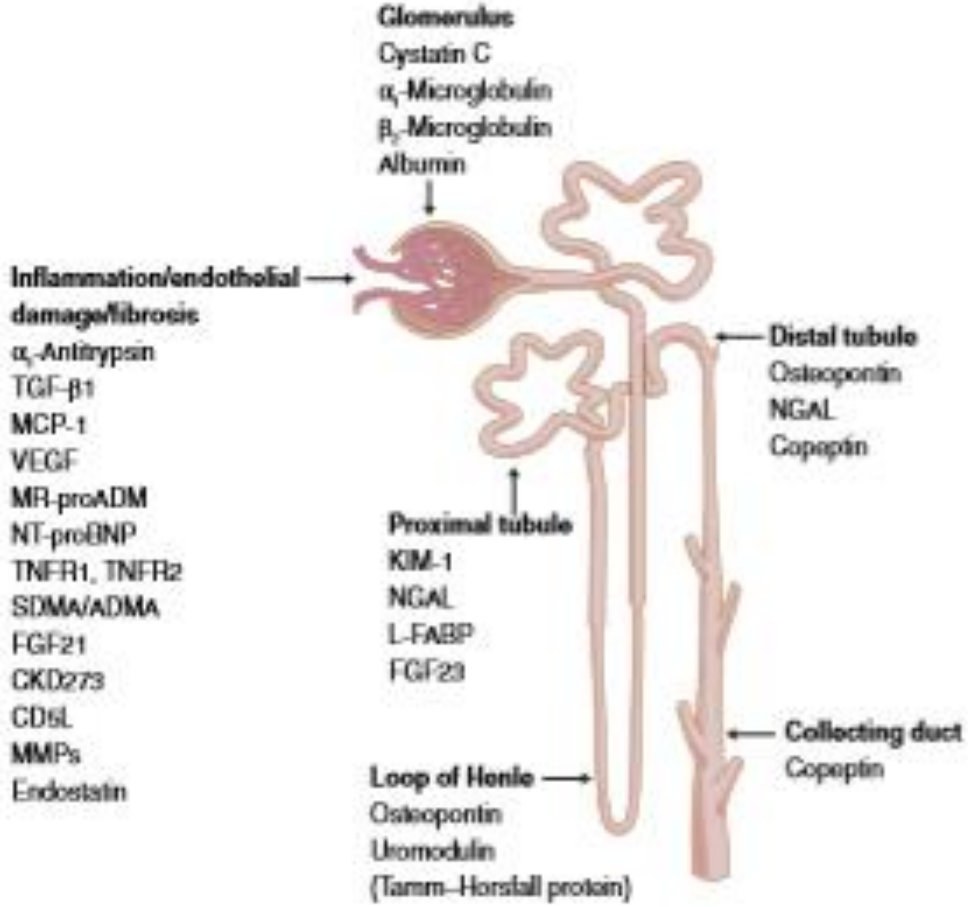
REVIEW

Biomarkers of diabetic kidney disease

Helen M. Colhoun[1] · M. Loredana Marcovecchio[2]

Received: 24 October 2017 / Accepted: 3 January 2018 / Published online: 8 March 2018

Abstract
Diabetic kidney disease (DKD) remains one of the leading causes of reduced lifespan in diabetes. The quest for both prognostic and surrogate endpoint biomarkers for advanced DKD and end-stage renal disease has received major investment and interest in recent years. However, at present no novel biomarkers are in routine use in the clinic or in trials. This review focuses on the current status of prognostic biomarkers. First, we emphasise that albuminuria and eGFR, with other routine clinical data, show at least modest prediction of future renal status if properly used. Indeed, a major limitation of many current biomarker studies is that they do not properly evaluate the marginal increase in prediction on top of these routinely available clinical data. Second, we emphasise that many of the candidate biomarkers for which there are numerous sporadic reports in the literature are tightly correlated with each other. Despite this, few studies have attempted to evaluate a wide range of biomarkers simultaneously to define the most useful among these correlated biomarkers. We also review the potential of high-dimensional panels of lipids, metabolites and proteins to advance the field, and point to some of the analytical and post-analytical challenges of taking initial studies using these and candidate approaches through to actual clinical biomarker use.



El paciente diabético con afectación renal tiene un riesgo cardiovascular muy elevado

Cada vez es más consistente el cambio de nombre hacia enfermedad renal diabética

Todavía no hay un marcador mejor ni más precoz que la albuminuria

¿ Qué han aportado desde el punto de vista renal los nuevos ADOS?

Objetivos terapéuticos en el paciente con nefropatía diabética

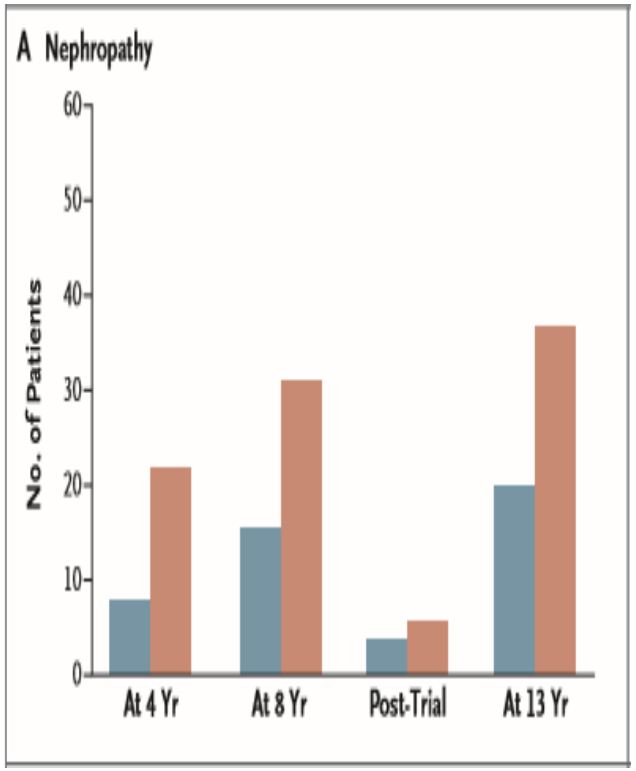
- **HbA1c< 7%** en el DM no complicado.
- Control más estricto en aquellos pacientes con DM de corta duración, expectativas de vida prolongada y sin enfermedad cardiovascular (ECV) significativa.
- Objetivos de HbA1c menos estrictos (<8%) en pacientes con antecedentes de hipoglicemias severas, escasa esperanza de vida y/o complicaciones micro y macrovasculares severas.
- Estatinas: Intensidad moderada, o alta en función de edad, ECV y factores de riesgo CV.
    - El único grupo que no recibiría estatina serían los < 40 años sin ECV ni FRV
- Aspirina 75-162 mg/día en todo DM con riesgo CV > 10% a los 10 años. (varones> 50 años y mujeres> 60 años con un factor de riesgo adicional)
- Aspirina 75-162 mg/día en todo DM con historia de ECV
- Aspirina y clopidogrel durante un año tras síndrome coronario agudo

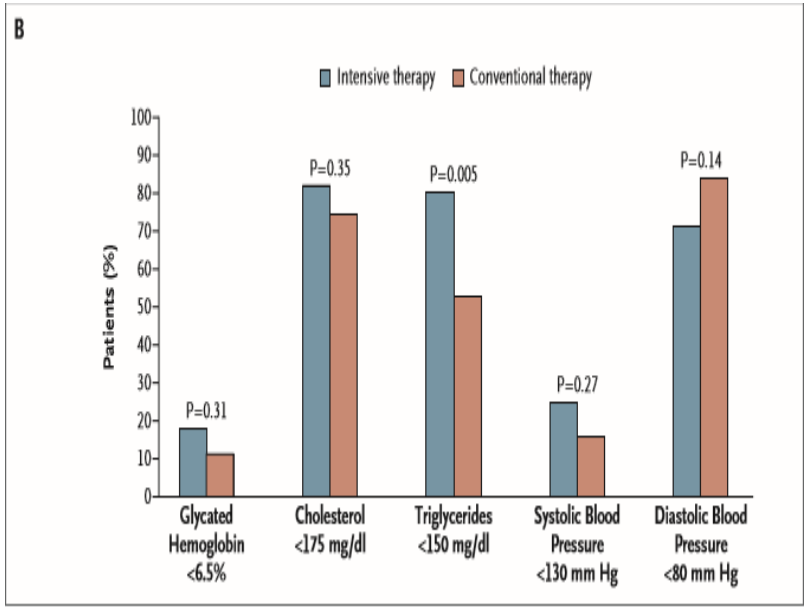
ADA – Standards of MedicalCare in Diabetes 2015 . Diabetes Care 2015; 38: S1

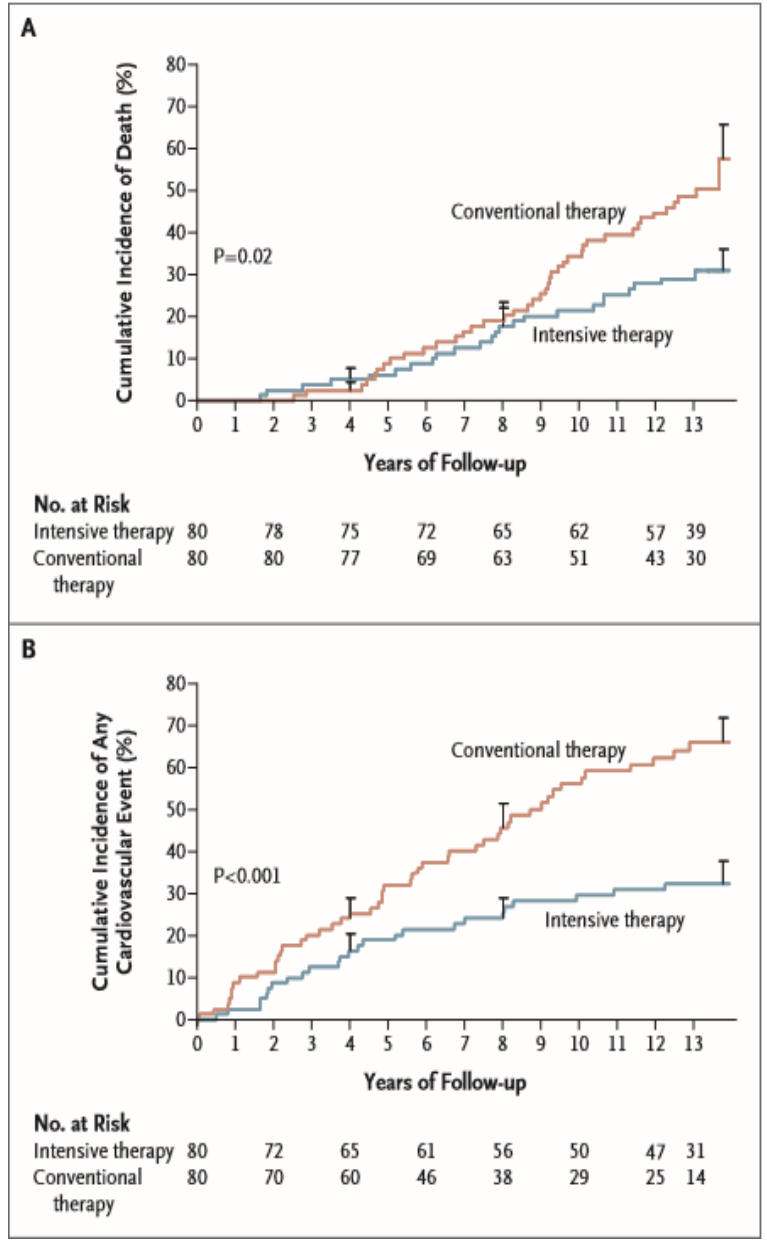
ORIGINAL ARTICLE

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.



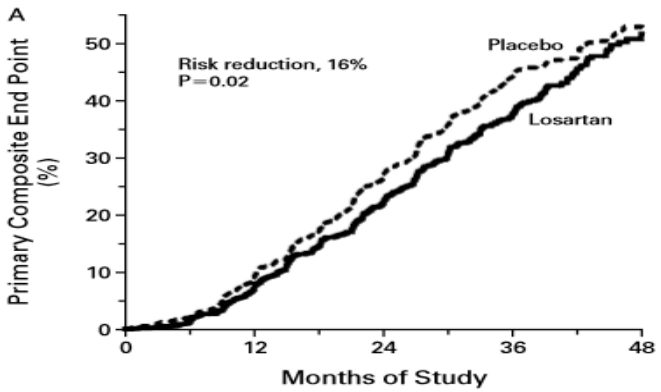


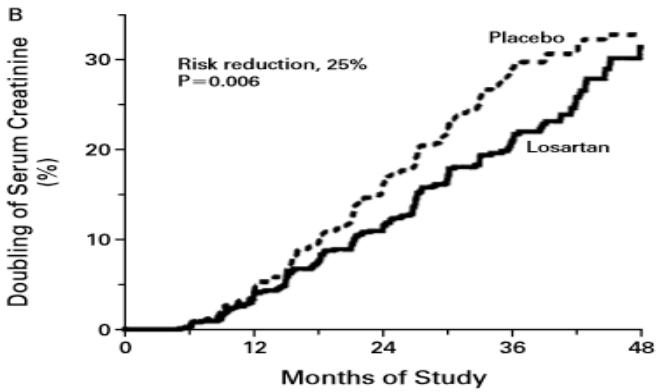


N Engl J Med 2008;358:580-91.

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

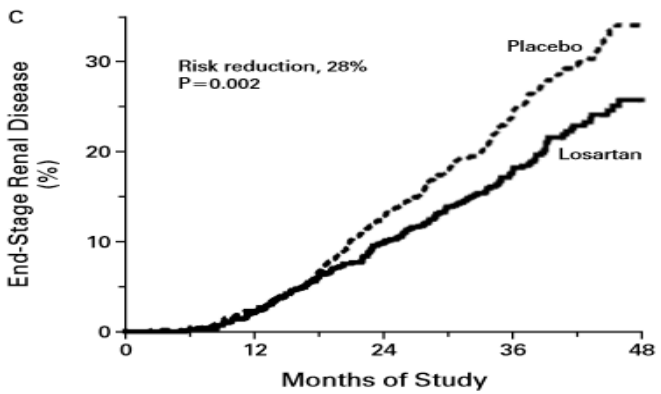
BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

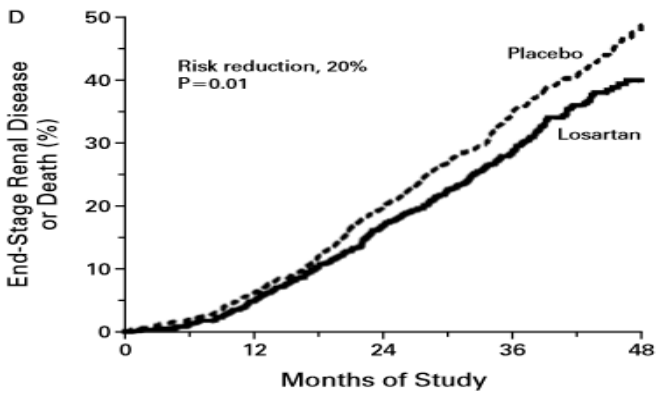


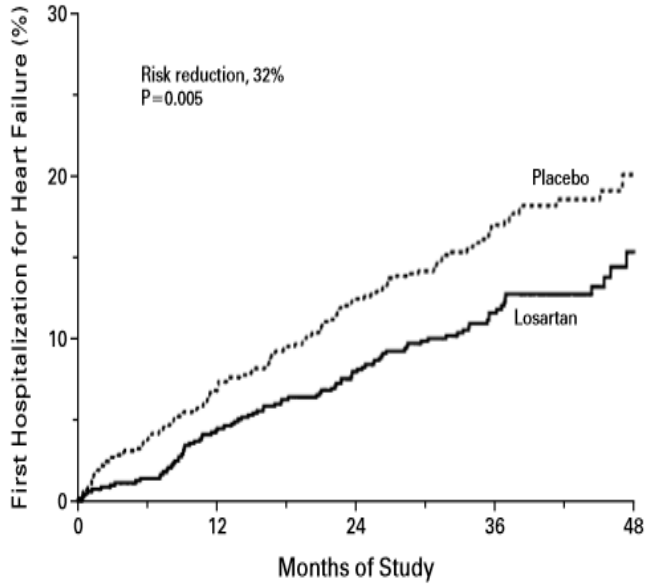


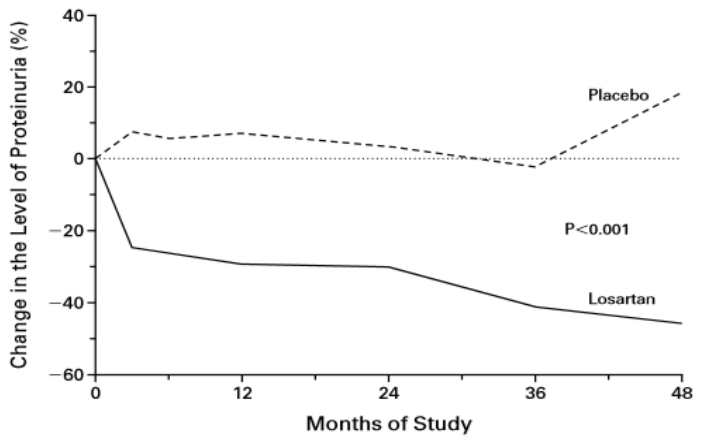
NO. AT RISK

Placebo	762	689	554	295	36
Losartan	751	692	583	329	52
	762	689	554	295	36
	751	692	583	329	52









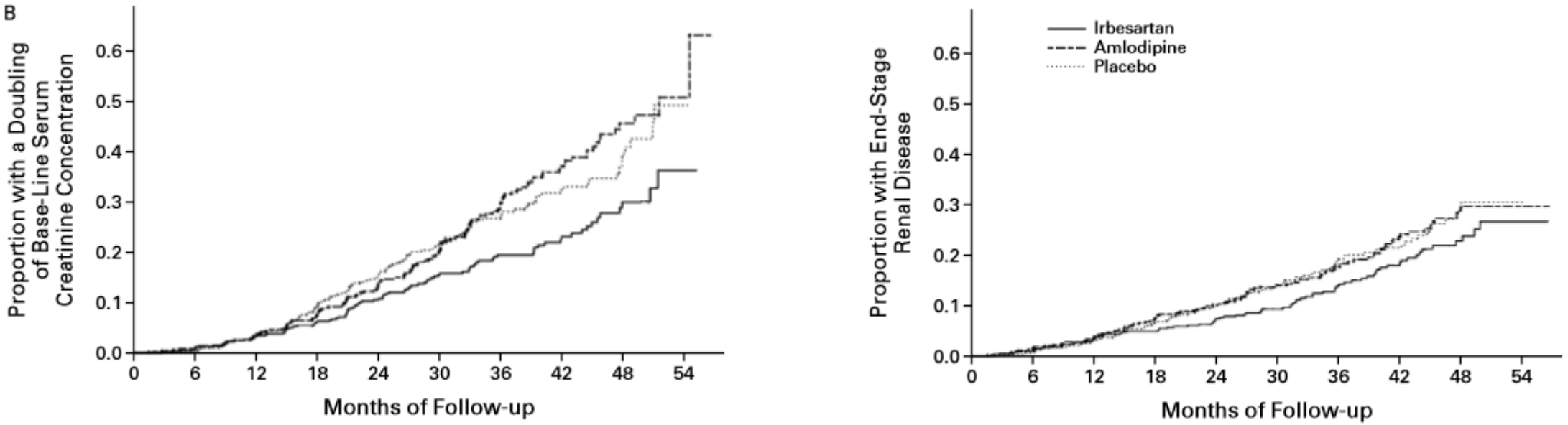
The New England
Journal of Medicine

VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*

B



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

ORIGINAL ARTICLE

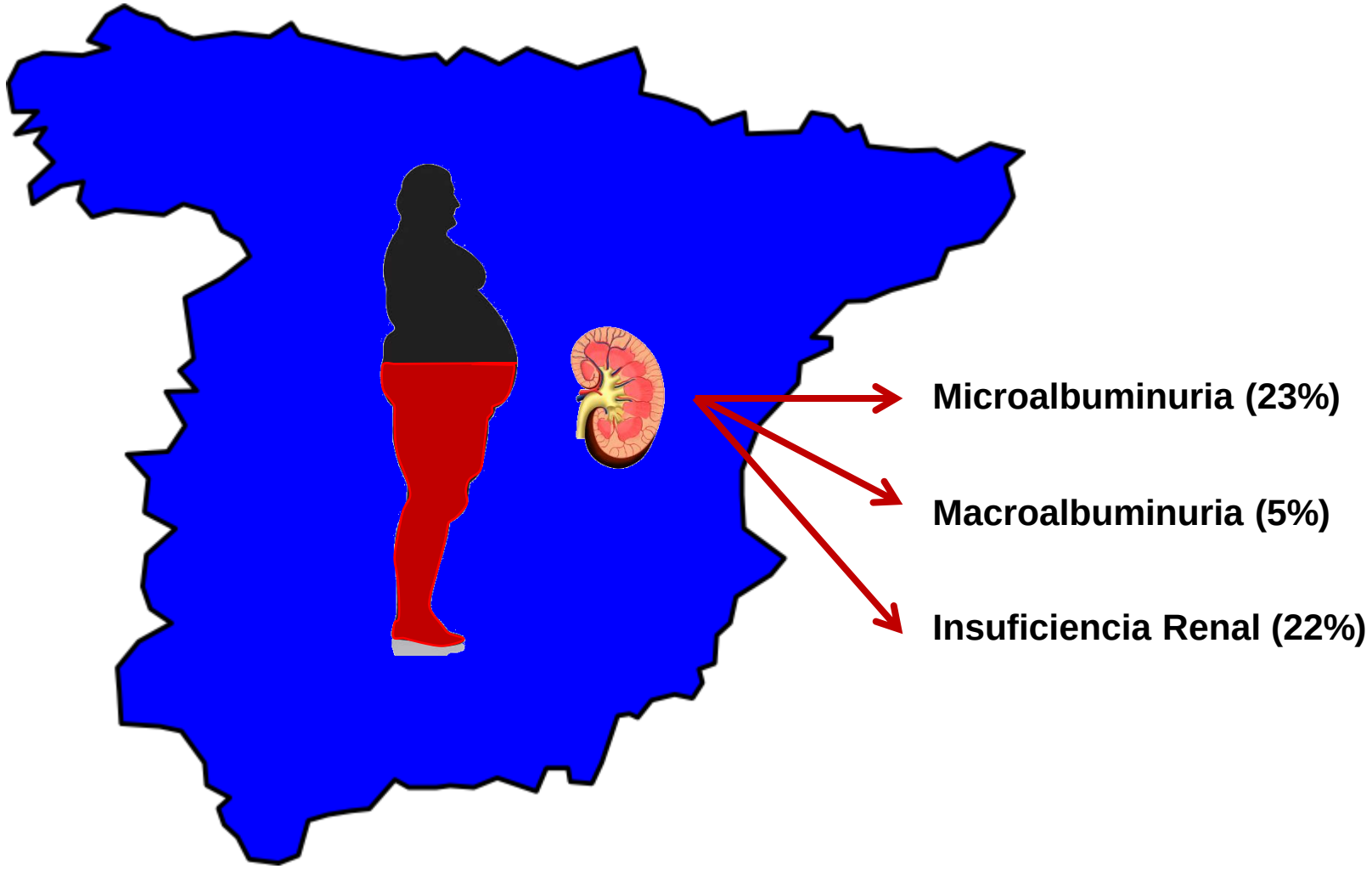
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

Articles

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

*UK Prospective Diabetes Study (UKPDS) Group**



La Diabetes es la 1ª causa de insuficiencia renal terminal en España
El 34% de pacientes que empiezan tratamiento renal sustitutivo son diabéticos

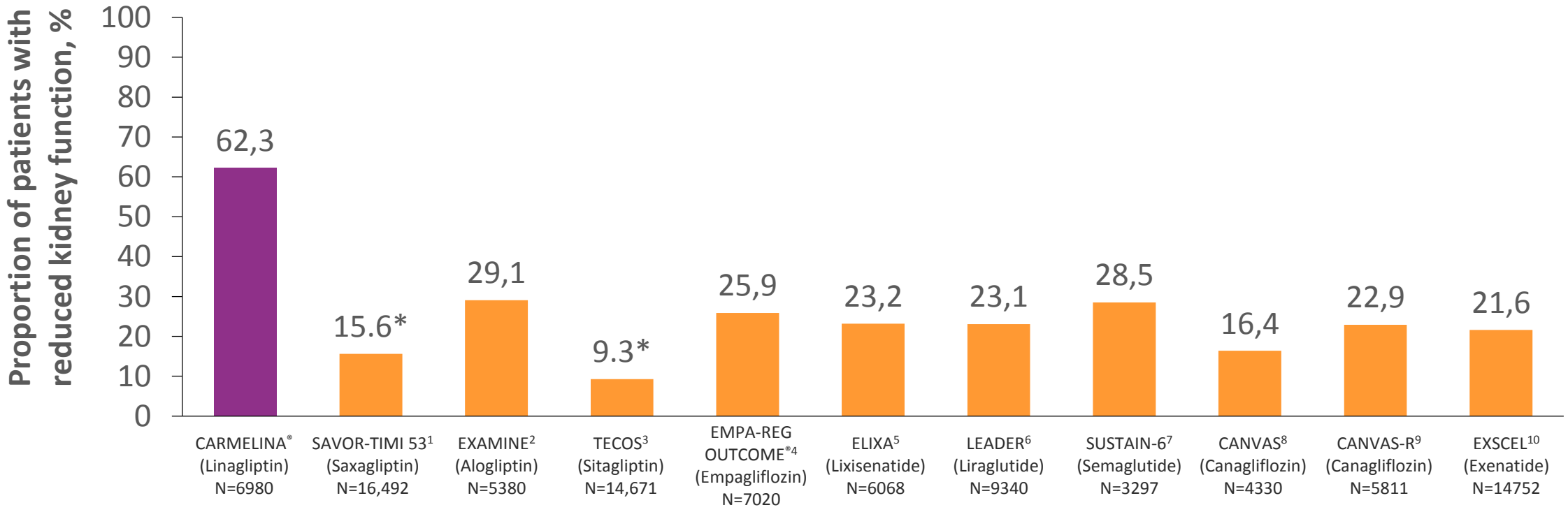
¿Existen beneficios renales mas allá del control de la glucemia en los hipoglucemiantes?

Fármaco	Beneficios mas allá de la glucemia
Insulina	No
Glinidas (repaglinida)	No
Pioglitazona	No
Algunas sulfonilureas (gliclazida, glimepirida)	No
inhib α-glucosidasa	No
Inhibidores DPP4	No
iSGLT2	Indicación según FT y Filtrado glomerular
Agonistas GLP1r	Liraglutida Semaglutida

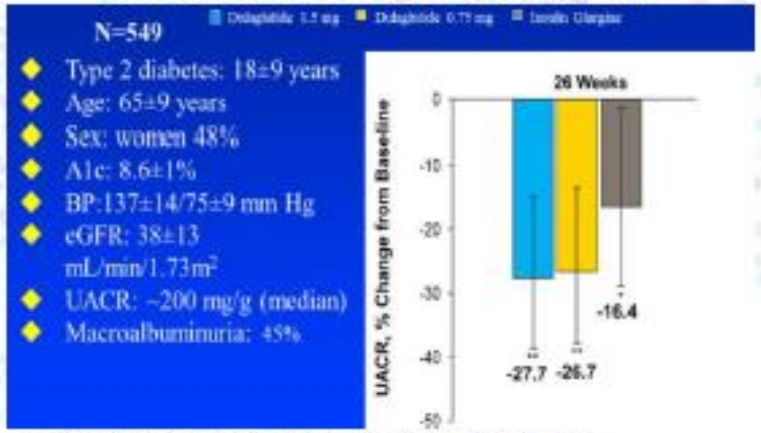
*iSGL2 no indicados en FT si FG< 45 ml/min/1.73 m2 o Dapa si FGe < 60 ml/min/1.73 m2

Arnouts P..Nephrol Dial Transplant 2015; 30: ii1–ii142; Gomez-Huelgas R,. Nefrologia 2014;34:34-45 ; Marso SP. New Engl J Med 2016; 375(4):311-22 ; Marso SP. New Eng J Med 2016; 375(19):1834-1844; Gorriz JL. J Clin Medicine 2015; 4, 1866-1889

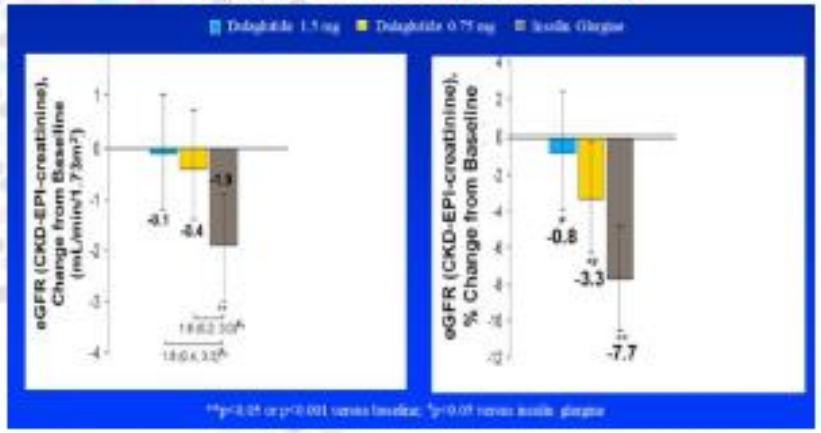
Proportion of CVOT populations with reduced kidney function at baseline (eGFR <60 ml/min/1.73 m²)

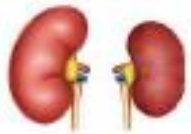


Reducción de Alb en ERC 3-4 con dulaglutida *vs.* insulina (26 w)



Menor descenso de FGe en ERC 3-4 con Dula *vs.* insulina (26 w)





Tuttle KR, et al. ADA 2017. Late-breaking clinical trials

Semaglutida y liraglutida en DM2 de alto RCV: inicio o empeoramiento de nefropatía

Semaglutida (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)	P value
no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46-0.88)	0.005

-36%

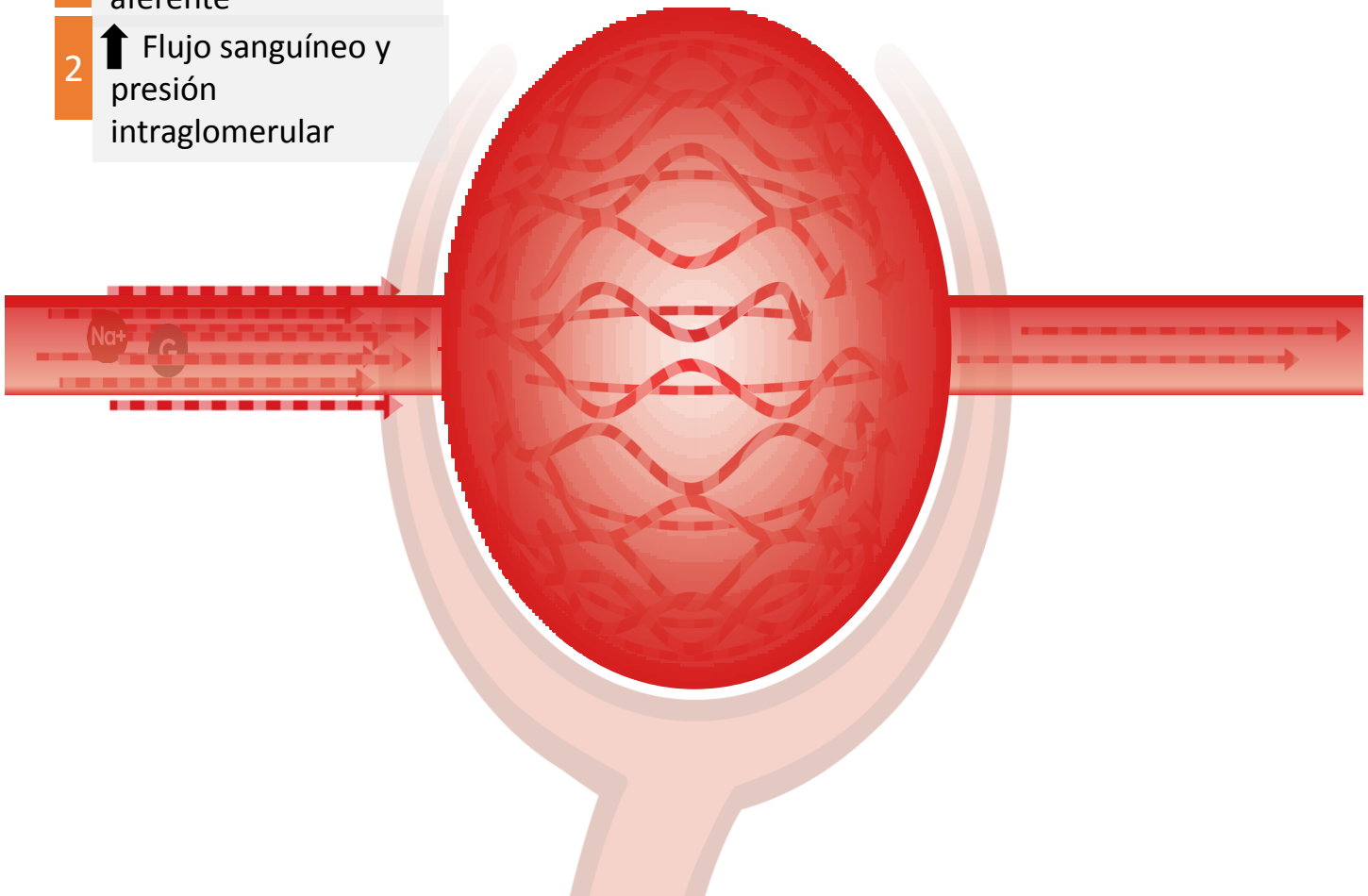
Liraglutida (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)	P value
no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67-0.92)	0.003

-22%

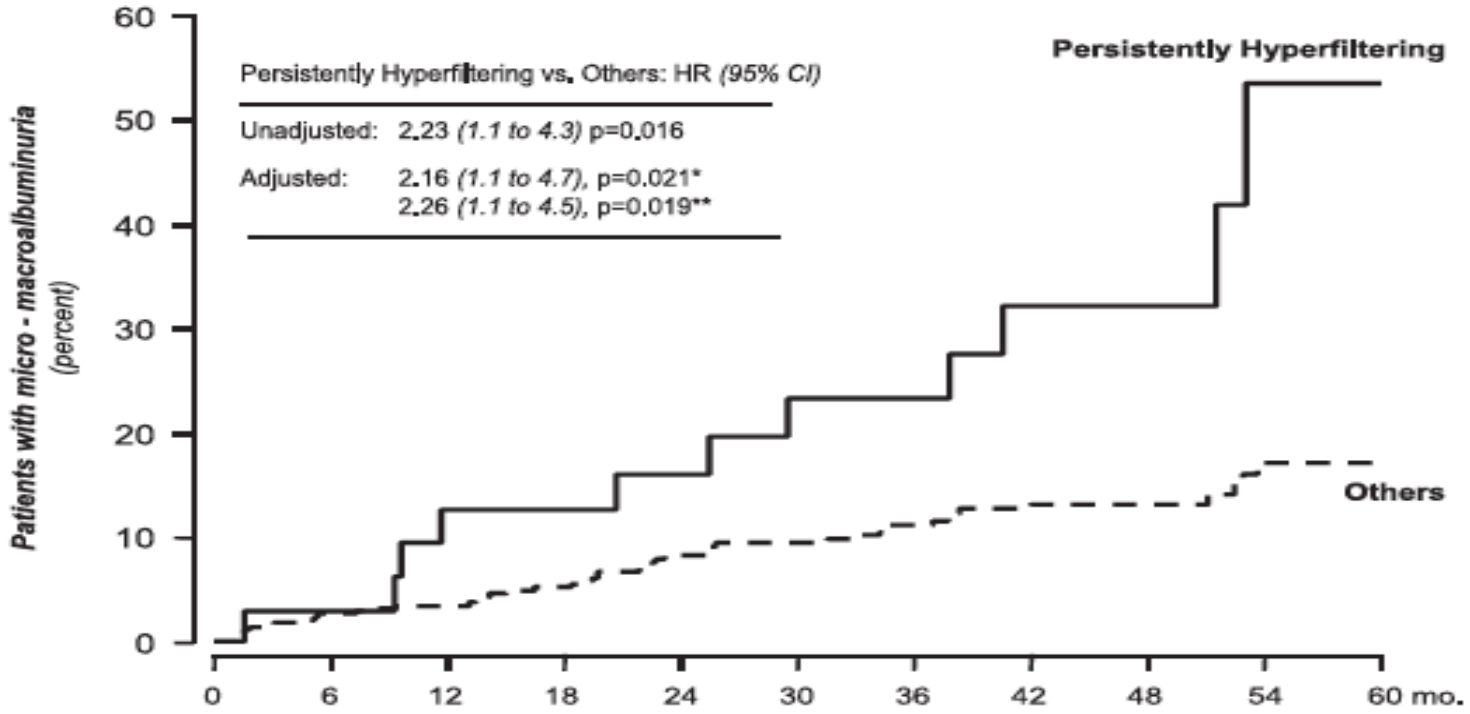
Marso SP, et al. N Engl J Med 2016;375:1834-44; Marso SP, et al. N Engl J Med 2016;375:311-22

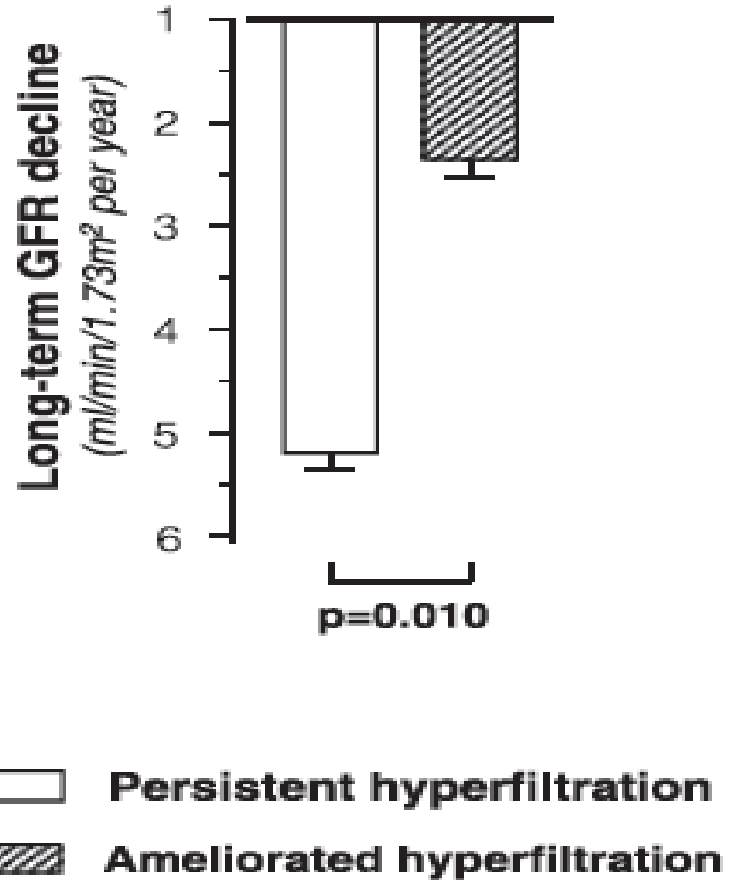
La obesidad, diabetes…

1. VD de arteriola aferente
2. ⬆ Flujo sanguíneo y presión intraglomerular



Hyperfiltration is associated with higher risk of CKD progression in the long term



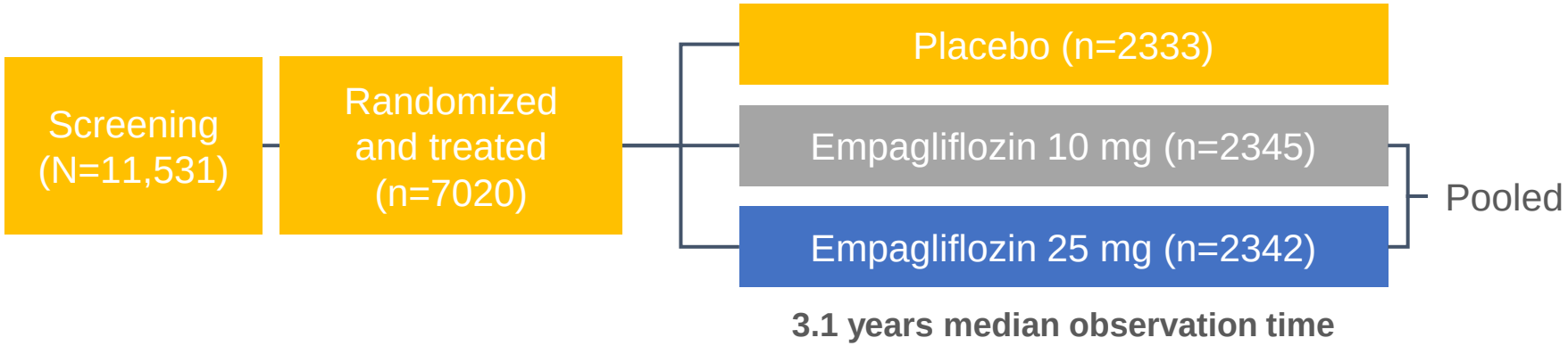


From BENEDICT-and DEMAND trials. Iohexol plasma clearance

GFR reduction > 10% at month 6 were considered as patients with ameliorated hyperfiltration.
Those with smaller reductions were categorized as " persistently hyperfiltering."

Ruggenenti P. Diab Care 2012:35:2061–2068

EMPA-REG OUTCOME® TRIAL DESIGN

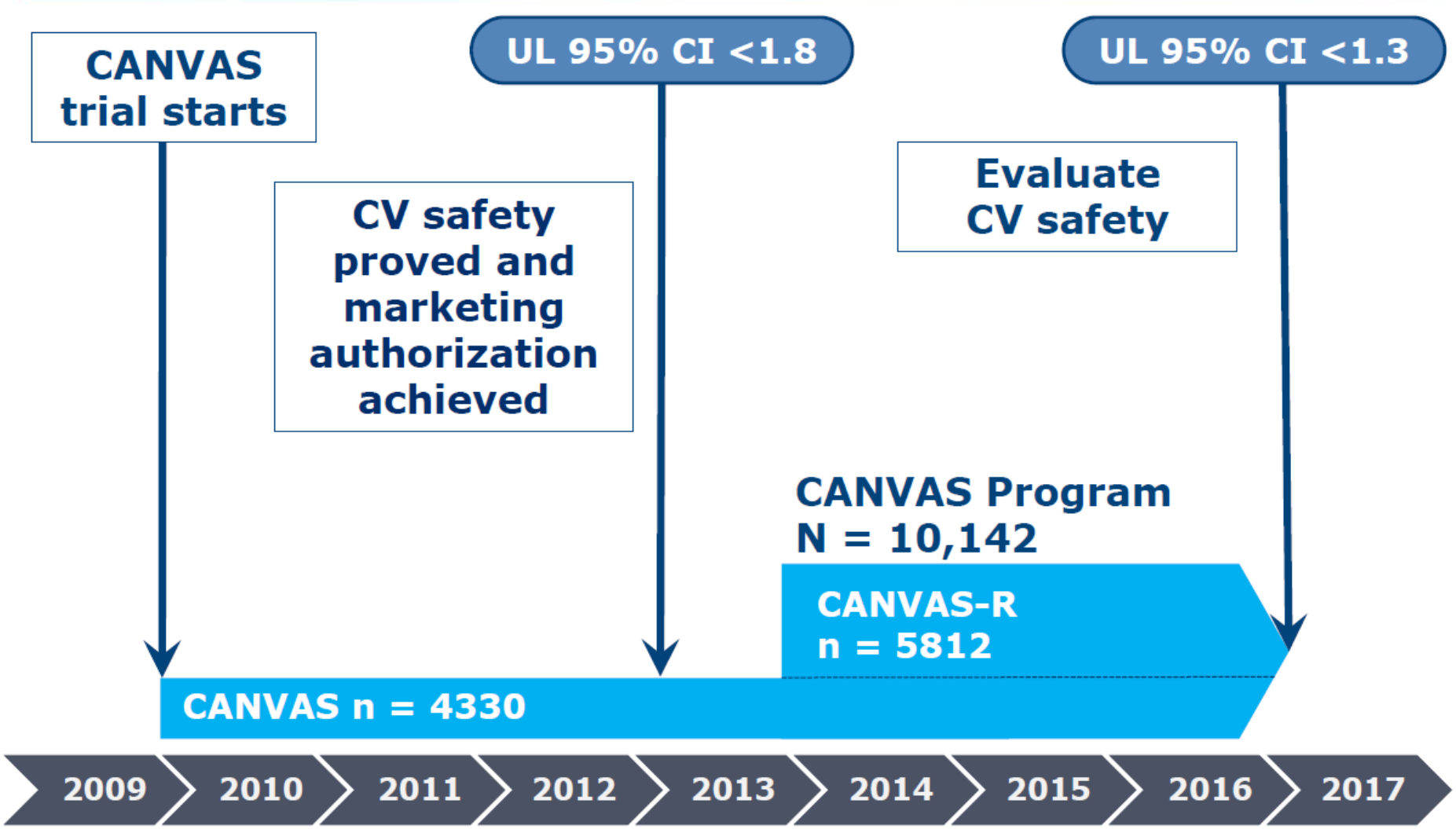


- Study medication was given on top of standard of care
  - Glucose-lowering medication was to remain unchanged for the first 12 weeks
- Key inclusion criteria
  - Adults with T2D and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; **eGFR ≥30 mL/min/1.73 m^2 (MDRD)**

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; T2D, type 2 diabetes.

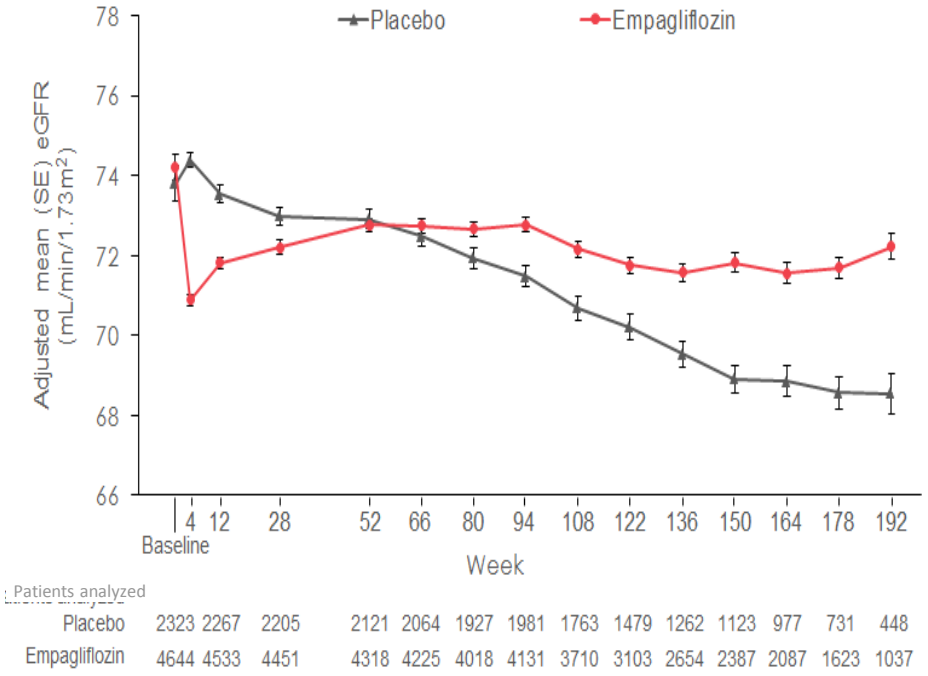
Zinman B *et al. N Engl J Med* 2015;373:2117

DISEÑO DEL PROGRAMA CANVAS

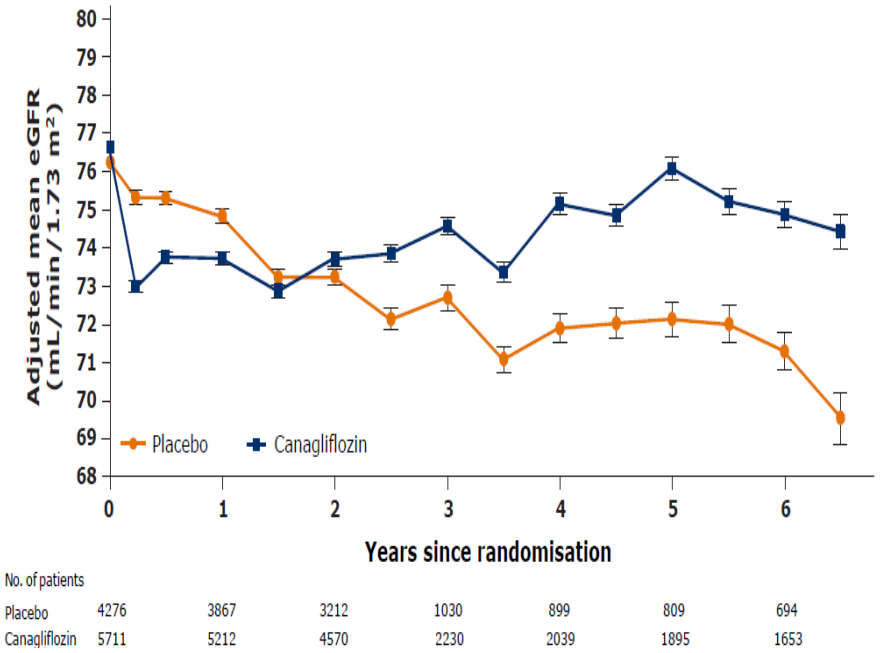


eGFR over time

EMPA-REG OUTCOME®[1]



CANVAS Program[2]



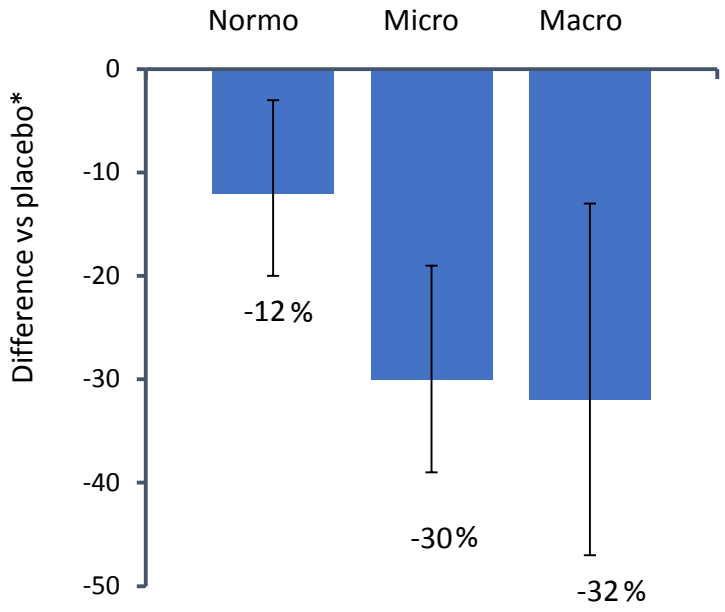
EMPA-REG OUTCOME analysis conducted using MDRD; CANVAS analysis not specified.

Wanner *et al. JASN* 2016;27:36A.

de Zeeuw D *et al*. 53rd Annual EASD Meeting; September 15, 2017; Lisbon, Portugal.

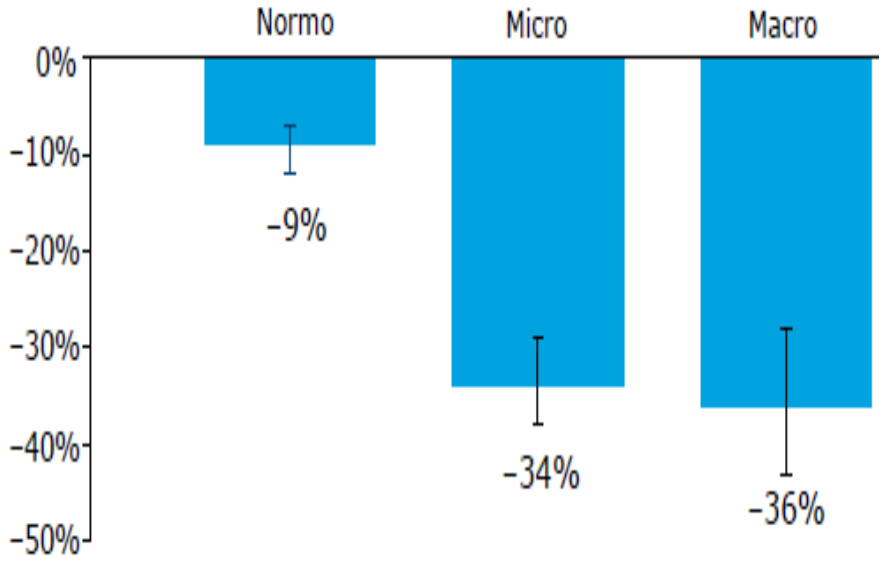
Placebo-adjusted % change in UACR by baseline albuminuria category

EMPA-REG OUTCOME®[1]
(~3 years)



*Placebo-corrected adjusted geometric mean ratio (95% CI) of relative change from baseline with empagliflozin. 164 weeks (IQR 115–186) corresponds to the median observation period.

CANVAS[2]
(~6 years)



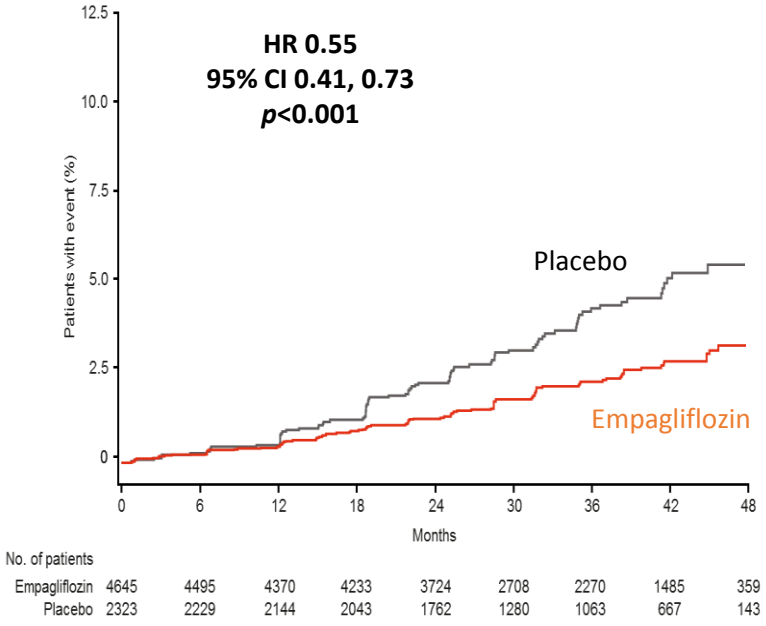
Data have only been reported in brief, and exact follow-up time was not given. Mixed model for repeated measures (MMRM) analysis excluding those below detection level.

1. Cherney DZI *et al. Lancet Diabetes Endocrinol.* 2017;5:610. 2. de Zeeuw D *et al*. Presented at the 53rd Annual Meeting of the European Association for

COMPOSITE RENAL OUTCOME

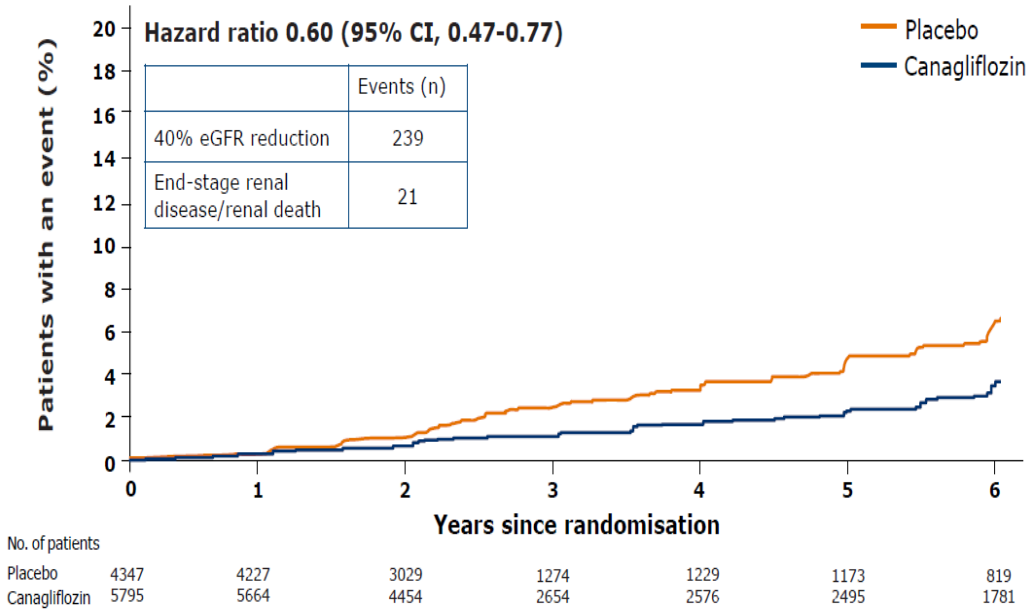
sustained 40% eGFR decline, ESRD, or renal death

EMPA-REG OUTCOME®



Kaplan-Meier estimates in patients treated with ≥1 dose of study drug.
HR and 95% CI are based on Cox regression analyses. eGFR calculated according to MDRD formula.

CANVAS Program[1]



Intention-to-treat analysis.
HR and 95% CI estimated using a Cox regression model with stratification according to trial and history of CVD for all canagliflozin groups combined vs placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization.

OVERVIEW OF STUDIES DESIGNS WITH RENAL OUTCOME

Sonesson *et al*. 2016[1]

- Meta-analysis of CV events in 21 Phase 2b/3 dapagliflozin clinical trials
- ≤ 208 weeks in duration
- Patients received dapagliflozin 2.5 or 10 mg (n=5936) or control (n=3403)

Kosiborod *et al*. 2015[2]

- Pooled data from 5 Phase 2b/3 dapagliflozin clinical trials that selected patients with a documented history of HF
- ≤ 52 weeks in duration
- Patients received dapagliflozin 10 mg (n=171) or placebo (n=149)

Lambers Heerspink *et al*. 2016[3]

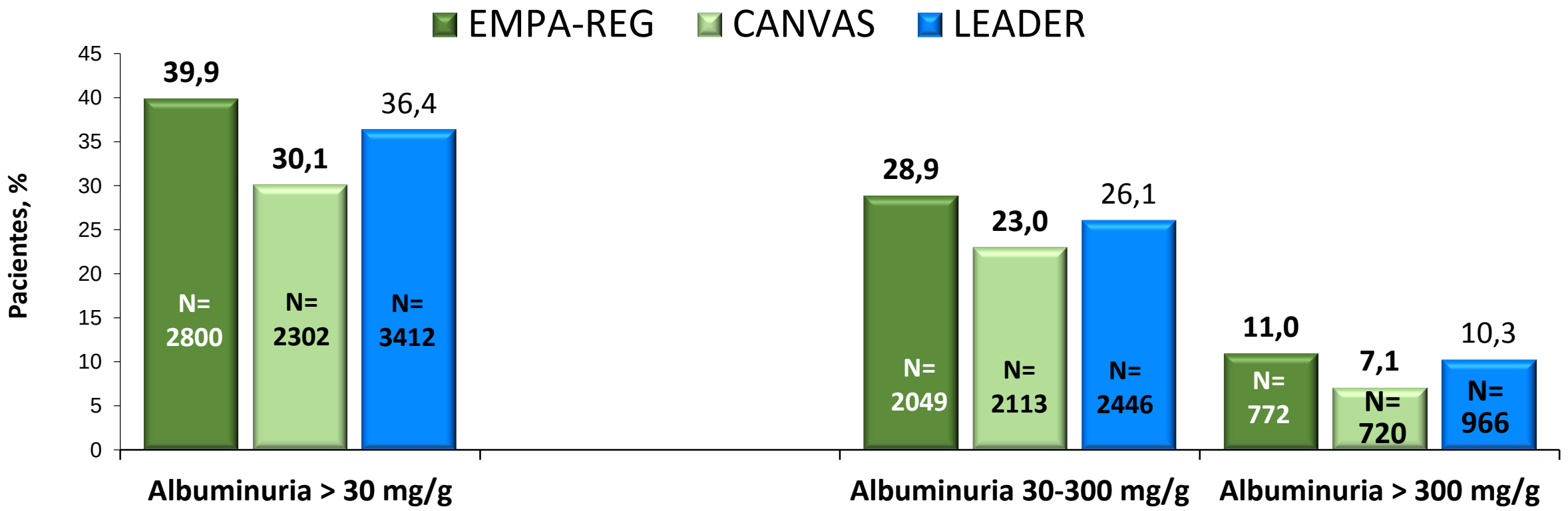
- Pooled data from Phase 2b/3 dapagliflozin clinical trials
- 12 weeks in duration
- In addition to ACEi/ARB treatment, patients randomly received dapagliflozin 5 mg (n=87), 10 mg (n=167) or placebo (n=189)

Parikh *et al*. 2015[4]

- Pooled data from 10 randomised, placebo-controlled, double-blinded clinical trials in patients with T2DM
- 24 weeks in duration
- Patients received dapagliflozin 10 mg (n=2224) or placebo (n=2153)

1. Sonesson C, *et al. Cardiovasc Diabetol.* 2016;15:37. 2. Kosiborod M, *et al.* ADA 2015 Poster 1211-P. 3. Lambers Heerspink HJ *et al. Diabetes Obes Metab*. 2016 Jun;18(6):590-7. 4. Parikh S *et al.* Oral Presentation Presented at: American Diabetes Association 75th Scientific Sessions; June 5-9 2015. Presentation #108 OR; Boston, MA. Access: http://professional.diabetes.org/search/site/parikh?retain-filters=1

Porcentaje de pacientes con ALBUMINURIA en los estudios EMPA-REG OUTCOME, CANVAS y LEADER



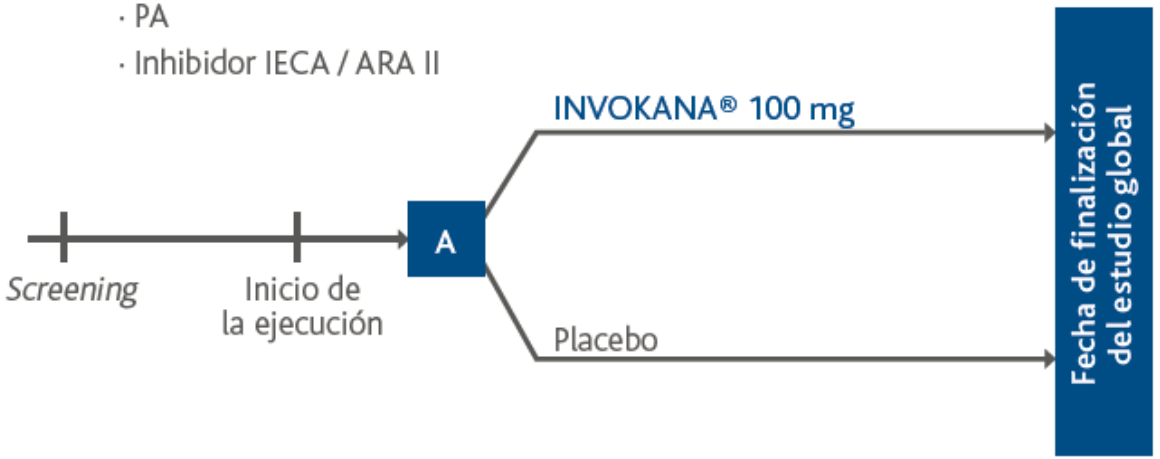
IRMA 2: 950 pacientes
RENAAL: 1513 pacientes
IDNT: 1715 pacientes

Wanner C. New Engl J Med 2016, June 14
Neal B. New Engl J Med 2017, 377(7):644-657
Perkovic V. Poster FR-PO 1058. ASN New Orleans. Novbre 2017
Mann JFE. N Engl J Med 2017;377:839-48.

Study Overview

Prescreening
· TFGe
· Albuminuria/proteinuria

Optimización del tratamiento
· AD
· Lípidos
· PA
· Inhibidor IECA / ARA II



Criterios de inclusión
· HbA_{1c} ≥ 6,5% y ≤ 12,0%
· TFGe ≥ 30 y < 90 mL/min/1,73m²
· Cociente albúmina / creatinina > 300 y ≤ 5.000 mg/g (> 33,9 y ≤ 565,6 mg/mmol)
· Dosis máxima diaria tolerada del inhibidor de la IECA o ARA II durante 4 semanas previas a la aleatorización

Las visitas presenciales se realizaron con un intervalo de 26 semanas hasta la semana 52

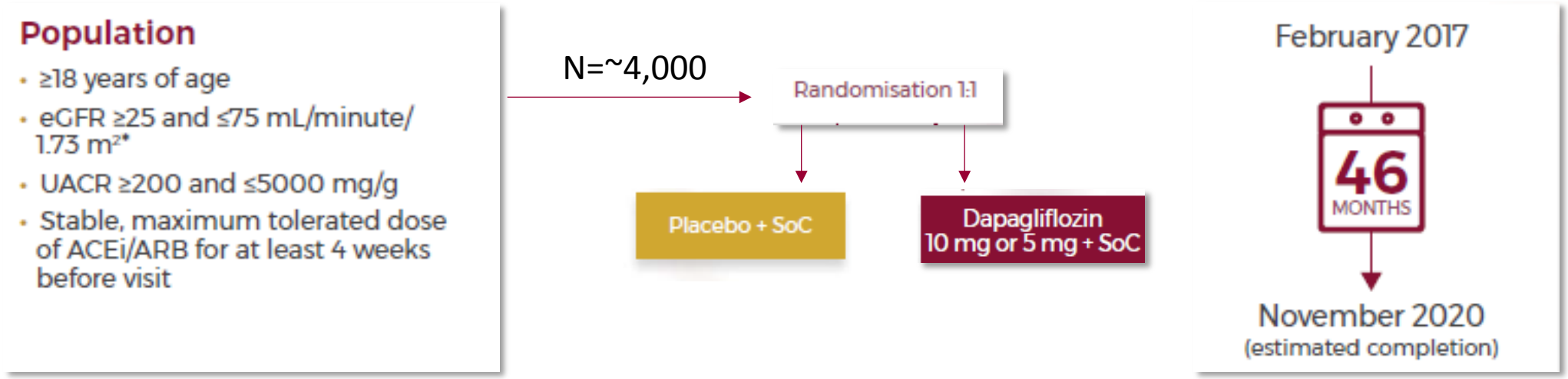
DAPACKD

~4,000 patients

Status: Currently recruiting participants

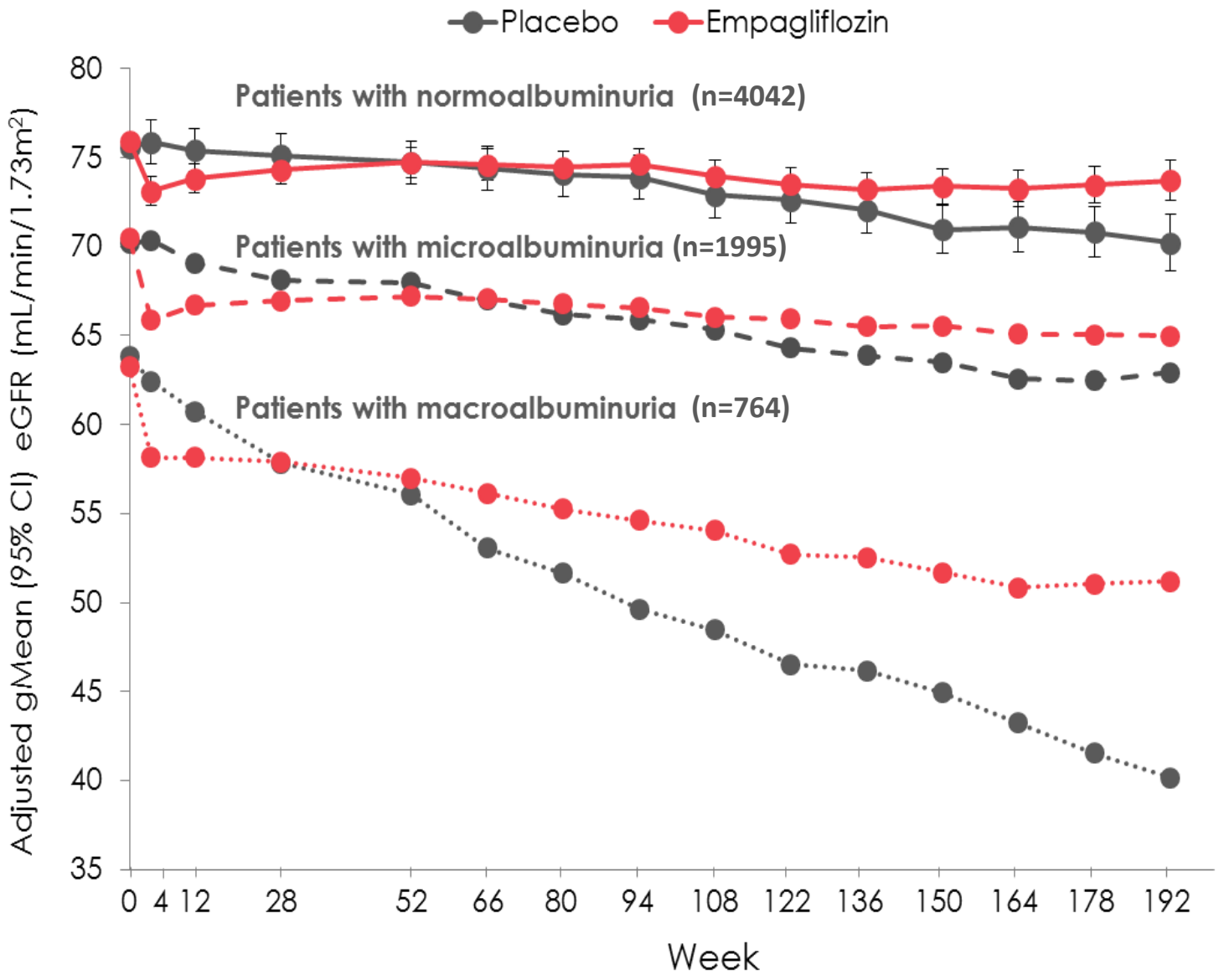
Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with CKD (Dapa-CKD)[13]

An international, multicentre, event-driven, randomised, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to SoC, to prevent the progression of CKD or CV/renal death.



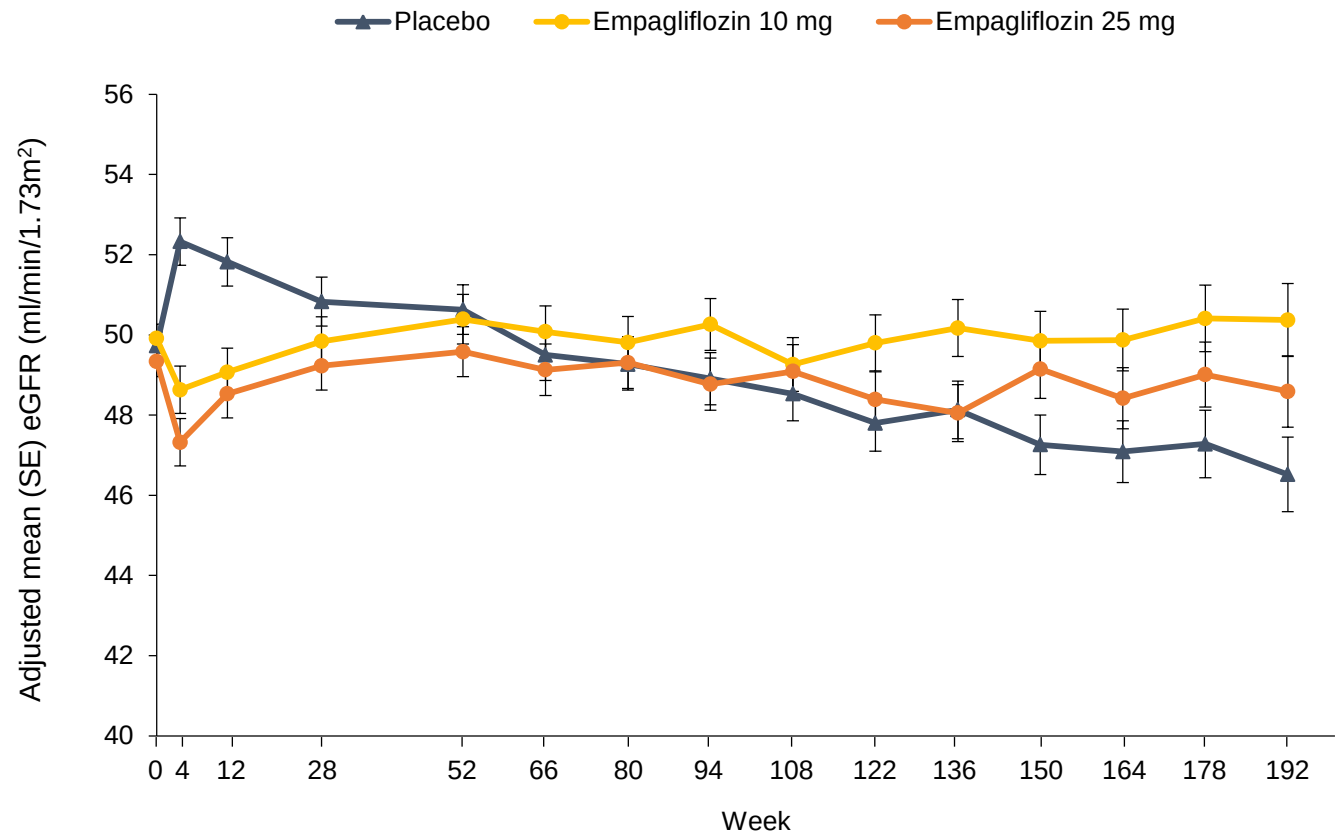
Chronic Kidney Disease

CREDENCE	eGFR 30-90 and UACR 300-5000 mg/g
DAPA-CKD	eGFR 25-75 and UACR 200-5000 mg/g
EMPA-Kidney	eGFR 20-45 or >45 mit UACR>200 mg/g



Lancet Diabetes Endocrinol 2017;5:610-621

eGFR (CKD-EPI formula) over 192 weeks in patients with eGFR <60 mL/min/1.73m² at baseline



Placebo	605	597	593	558	530	518	470	483	435	366	311	285	255	182	114
Empagliflozin 10 mg	596	590	582	566	545	524	492	503	443	390	327	295	252	196	125
Empagliflozin 25 mg	600	593	582	567	543	532	506	518	457	394	334	306	267	212	136

Post-hoc analysis. Mixed model repeated measures analysis in patients treated with ≥1 dose of study drug (OC-AD).
eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Inhibidores de SGLT-2 han demostrado un claro efecto nefroprotector. Queda pendiente dicho efecto en estudios con pacientes que presenten nefropatía diabética establecida

Análogos de GLP-1 presenta un efecto en reducción de albuminuria

¿ Qué debemos tener en cuenta a la hora de tratar con ADOS al paciente con ERC y diabetes mellitus ?

Uso de antidiabéticos en la ERC

FGe/Fármacos	45-59	30-44	15-29	< 15
Insulina	Sí	Sí	Sí (reducir dosis 25%)	Sí (reducir dosis 50%)
Metformina	Sí	Sí, valorar indicación (50% de la dosis)	No	No
Glinidas (Repaglinida)	Sí	Sí	Sí (ajustar dosis)	Sí (ajustar dosis)
Glitazonas (pioglitazona)	Sí	Sí	Sí	Sí
Sulfonilureas (gliclazida, glimepirida) evitar glibencamida	Sí	Sí (reducir dosis) Glipizida permitida Gliclacida precaución	No Glipizida permitida Gliclacida precaución	No Glipizida permitida Gliclacida precaución
Inhibidores α glucosidasa **acarbosa** **miglitol**	 Sí Sí	 Sí No	 No No	 No No
Inhibidores DPP4	Si (linagliptina no ajuste de dosis. Sitagiptina, vildagliptina, saxagliptina alogliptina requieren ajuste de dosis)			

Arnouts P.Nephrol Dial Transplant 2015; 30: ii1–ii142; Gomez-Huelgas R, Gorriz JL.; Nefrologia 2014;34(1):34-45 ; Martinez-Castelao A, Gorriz JL. Nefrologia 2014;34(2):243-62

El efecto secundario más frecuente en diabéticos con enfermedad renal crónica es la hipoglucemia

Rate of adverse drug events in ambulatory patients with CKD

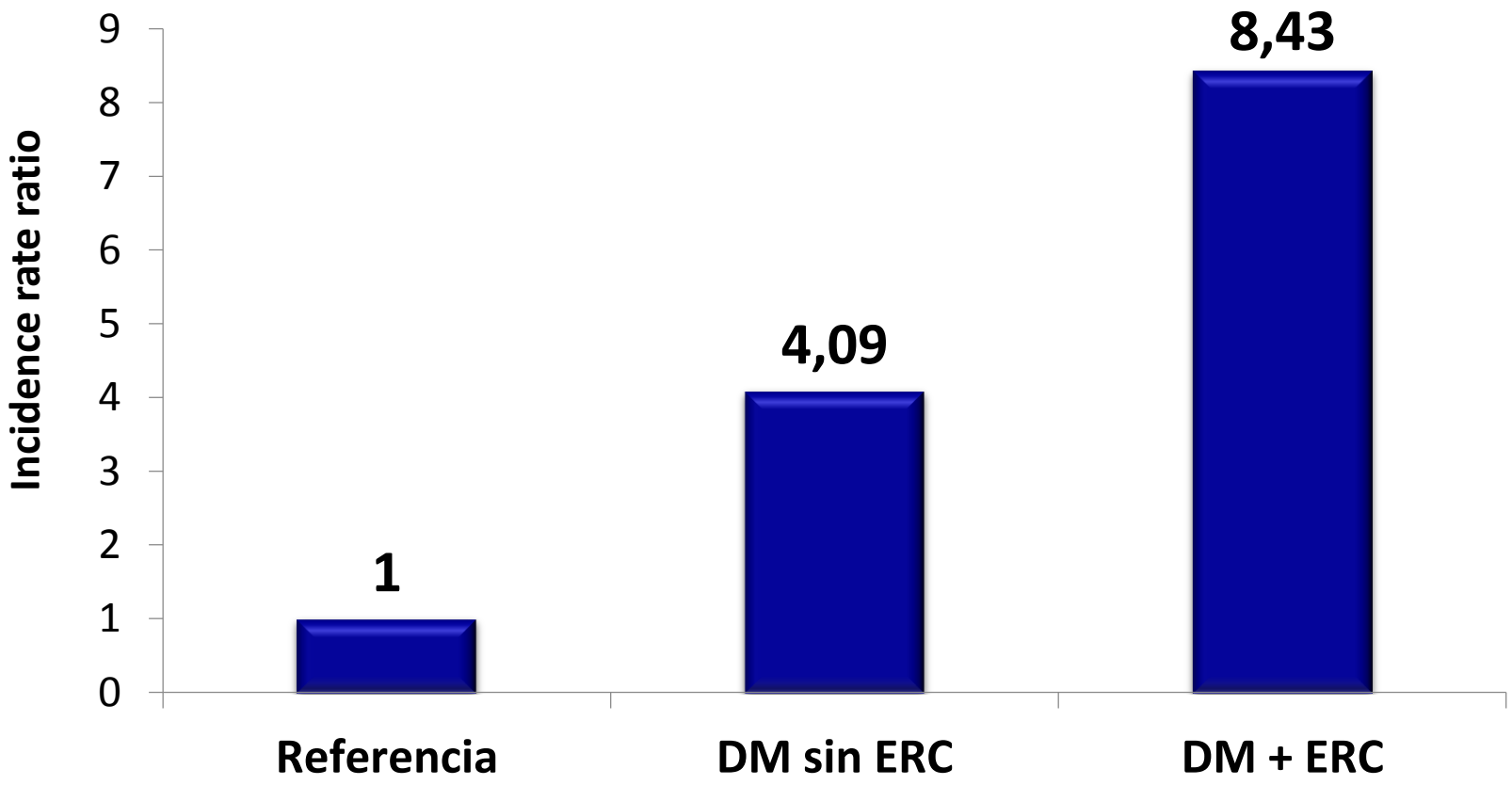
N=267	Rate (per 100 patients)*
PATIENT REPORTED	
Hypoglycemia	**57.6**
Falling/ severe dizziness	23.1
Nausea, vomiting ± diarrhea	21.1
Hyperkalemia	18.1
Confusion	16.9
DETECTED AT STUDY VISIT	
Hypoglycemia	8.3
Hyperkalemia	8.3
Bradycardia	6.4

*Adjusted for sociodemographics, comorbid conditions, GFR, and number of medications antidiabetic drugs

69.3 % reported a safety event
Diabetics 63 %

Adapted from Ginsberg JS, et al. *J Am Soc Nephrol* 2014.

Riesgo de hipoglucemia grave (< 50 mg/dl) segun presencia de ERC en DM tipo 2



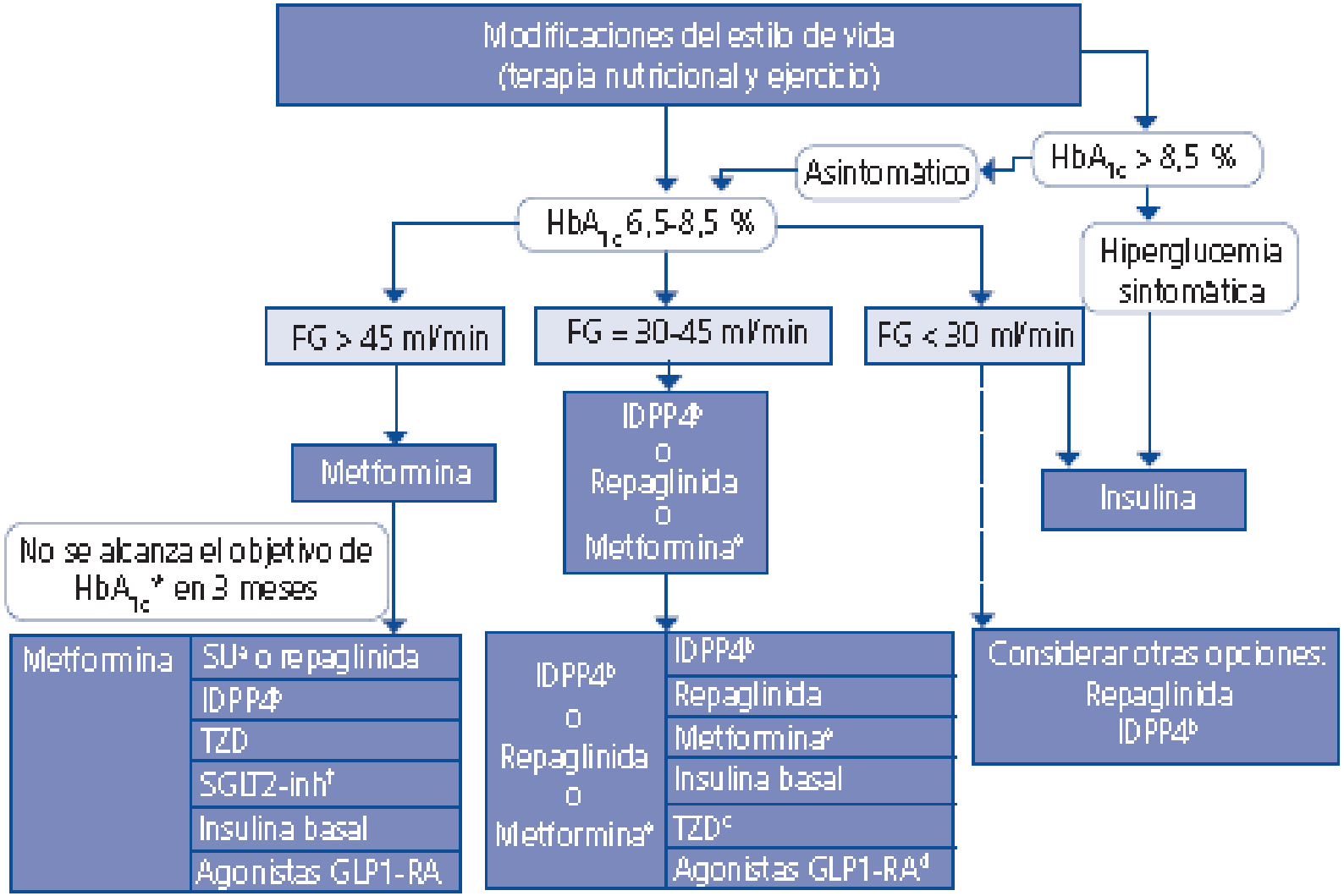
p<0.001

Ajustado por: raza, sexo, edad, índice de Charlson, cáncer, diabetes y enfermedad CV.

Estudio retrospectivo. Cohorte de 243,222 pacientes con 2,040,206 determinaciones de glucosa (Veterans Health Administration).

ERC: enfermedad renal crónica

Moen MF. Clin J Am Soc Nephrol 2009; 4: 1121–1127



Nefrologia 2014;34(1):34-45

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
α-gluc inhibitors	Acarbose	No adjustments			use lowest dose and <50mg		
	Miglitol	Limited experience available					
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

From: Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min)

Nephrol Dial Transplant. 2015;30(suppl_2):ii1-ii142. doi:10.1093/ndt/gfv100

Uso de agonistas del R- GLP-1 segun función renal

FGe/Fármacos	>60	45-59	30-44	15-29	< 15
Exenatida Lisexenatida	**No ajuste**	**No**	**No**	**No**	**No**
Exenatida Lisexenatida	**No ajuste**	**No**	**No**	**No**	**No**
Liraglutida	**No ajuste**	**No ajuste**	**No ajuste**	**No ajuste**	**No**
Albigutida	No ajuste	No ajuste	No ajuste	No	No
Dulaglutida	**No ajuste**	**No ajuste**	**No ajuste**	**No**	**No**

Indicado.

No recomendado

Fichas técnicas de Exenatida, Lisexenatida, Liraglutda, Albiglutida y Dulaglutida.
Arnouts P.Nephrol Dial Transplant 2015; 30: ii1–ii142; Gomez-Huelgas R, Gorriz JL.; Nefrologia 2014;34(1):34-45 ;
Martinez-Castelao A, Gorriz JL. Nefrologia 2014;34(2):243-62

LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

El beneficio cardiovascular global del estudio LEADER fue mas evidente en pacientes con ERC

	Reducción del riesgo	HR	IC al 95 %
Beneficio CV global	**↓ 13 %**	0,87	0,78-0,97
Beneficio en pacientes con FGe < 60 ml/min/1,73 m2	**↓ 31 %**	0,69	0,57-0,85

El nº de eventos en pacientes con ERC (FG< 60) fue el doble que en los pacientes sin ERC

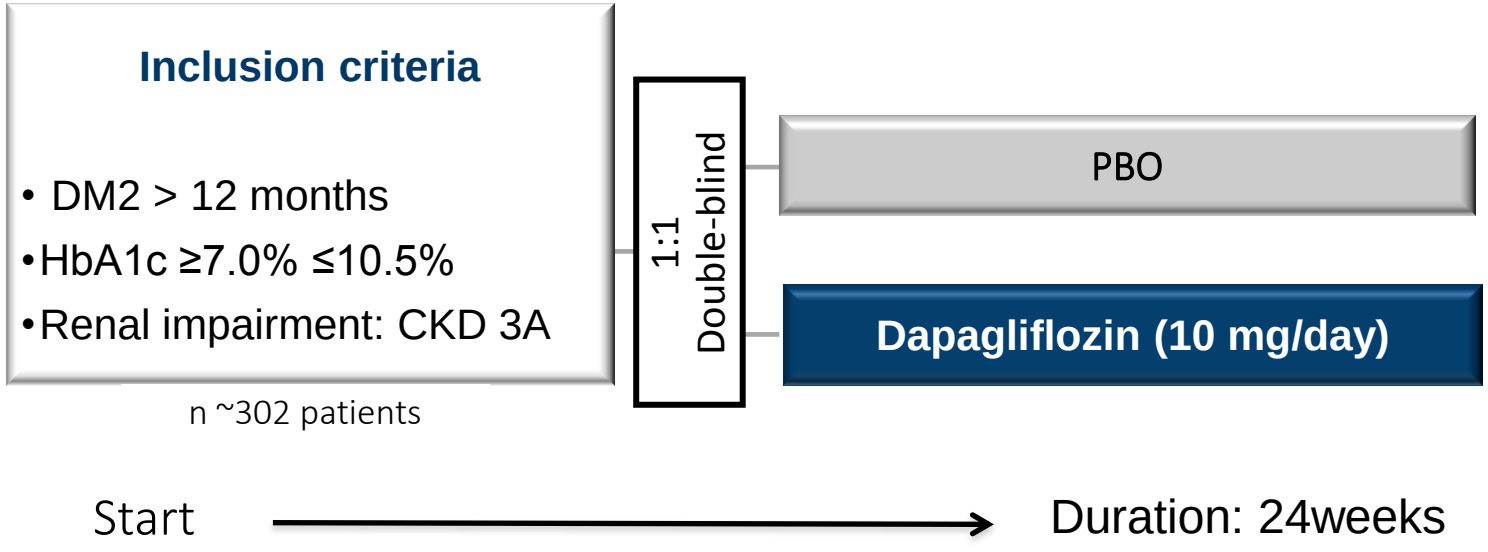
Thomas MC. Diabetes Metab. 2017 Apr;43 Suppl 1:2S20-2S27
Mann JFE. N Engl J Med 2017;377:839-48
Marso SP. N Engl J Med 2016; 375(4):311-22

Inhibidores SGLT2

FGe/Fármacos	>60	45-59	30-44	15-29	< 15
Dapagliflozina	No ajuste	Menor eficacia No recomendado	No	No	No
Empagliflozina	No ajuste	No iniciar. Si FG< 60 en tto, 10 mg/dia	No	No	No
Canagliflozina	No ajuste	No iniciar Si FG< 60 en tto, 100 mg/dia	No	No	No

The DERIVE trial is investigating the effect dapagliflozin in patients with T2DM and moderate renal impairment

Evaluation of antidiabetic effect of dapagliflozin and renal safety in patients with T2DM and moderate renal impairment CKD 3A (eGFR 45-60 mL/min)



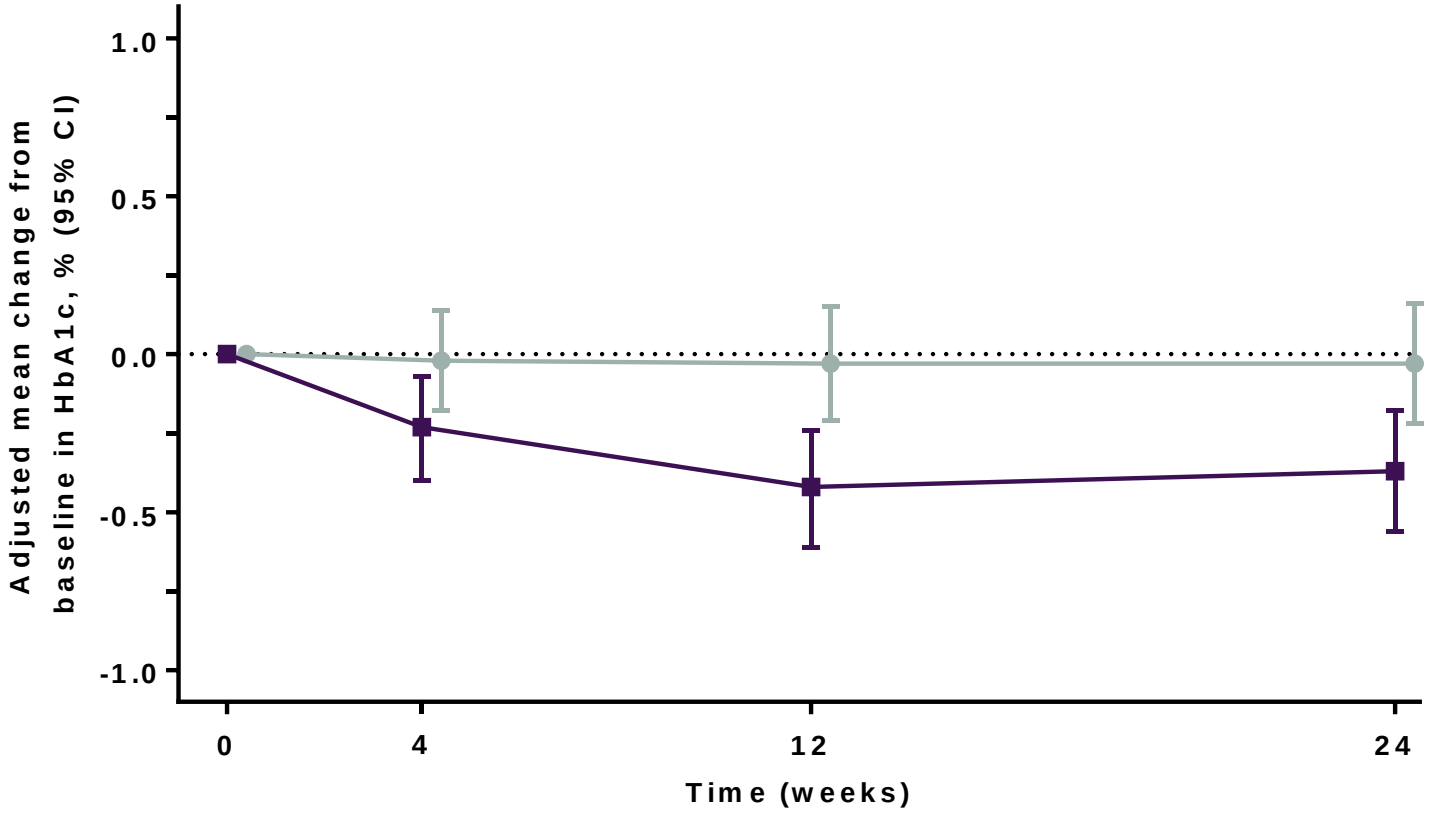
Primary endpoint: Mean change from baseline in HbA1c after 24 weeks

Secondary endpoints: Percent change from baseline in total body weight at Week 24.
Change from baseline in FPG at Week 24
Change from baseline in seated SBP at Week 24

T2DM: Type 2 diabetes mellitus; DAPA=dapagliflozin; eGFR=estimated glomerular filtration rate; PBO=placebo, CKD=Chronic kidney disease.

1. https://clinicaltrials.gov/ct2/show/NCT02413398

HbA1c – change from baseline over 24 weeks



Dapagliflozin	157	156	149	142
Placebo	159	158	147	134

Dapagliflozin 10 mg (N=159)

Mean baseline HbA1c, % (SD): 8.35 (1.06)
Adjusted mean change from baseline at Week 24 (95% CI): –0.37 (–0.56, –0.18)

Placebo (N=161)

Mean baseline HbA1c, % (SD): 8.03 (1.09)
Adjusted mean change from baseline at Week 24 (95% CI): –0.03 (–0.22, 0.16)

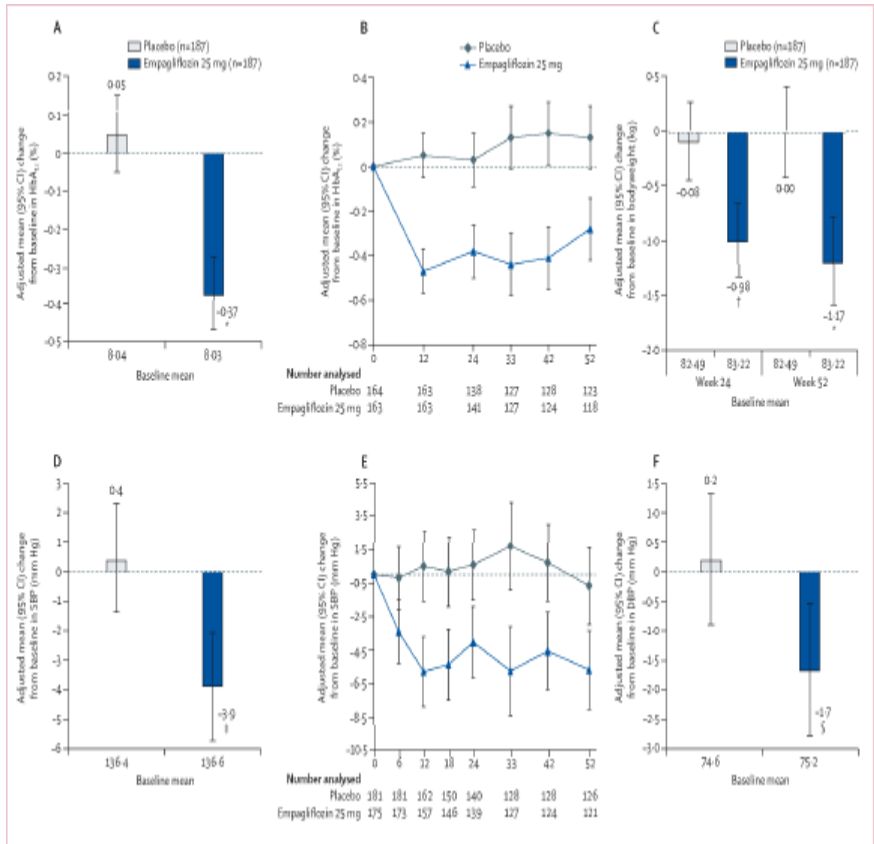
Difference vs placebo (95% CI):
–0.34 (–0.53, –0.15)
p-value: <0.001

1. Fioretto P et al. Presented at: The Endocrine Society Annual Meeting and Expo; March 17-20, 2018; Chicago, Illinois

Data are based on the full analysis set.
CI, confidence interval; HbA1c, glycated hemoglobin; SD, standard deviation

Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial

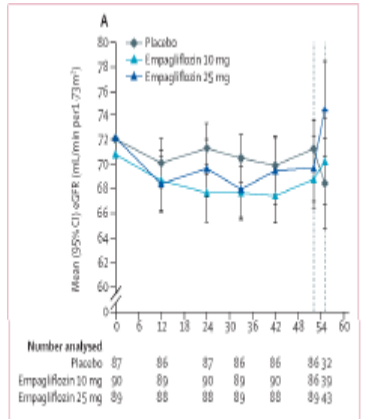
Anthony H Barnett, Ambrish Mithal, Jenny Manassie, Russell Jones, Henning Rattunde, Hans J Woerle, Uli C Broedl, on behalf of the EMPA-REG RENAL trial investigators

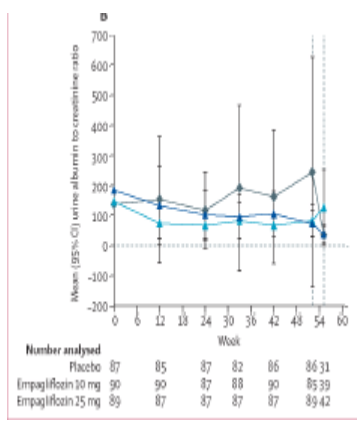


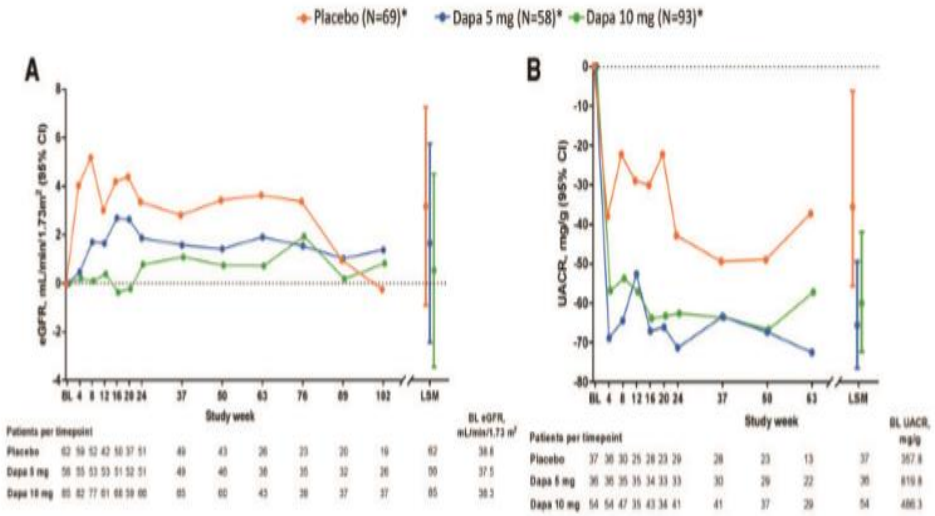
	Placebo (n=37)	Empagliflozin 25 mg (n=37)
HbA_{1c}		
HbA_{1c} at week 24, %	7·98 (1·04)	8·11 (1·73)
Change from baseline in HbA_{1c} at week 24, %	−0·18 (0·77)	0·04 (1·62)
HbA_{1c} at week 52, %	7·79 (1·04)	8·17 (1·58)
Change from baseline in HbA_{1c} at week 52, %	−0·37 (0·79)	0·11 (1·48)
Fasting plasma glucose		
Fasting plasma glucose at week 24, mmol/L	8·8 (4·5)	8·5 (5·4)
Change from baseline in fasting plasma glucose at week 24, mmol/L	0·6 (3·6)	−0·2 (6·0)
Fasting plasma glucose at week 52, mmol/L	8·6 (4·6)	8·5 (3·2)
Change from baseline in fasting plasma glucose at week 52, mmol/L	0·4 (3·9)	−0·3 (4·1)
Bodyweight		
Bodyweight at week 24, kg	84·1 (21·0)	76·5 (15·9)
Change from baseline in bodyweight at week 24, kg	−0·1 (1·9)	−1·4 (5·0)
Bodyweight at week 52, kg	84·1 (21·2)	77·0 (16·4)
Change from baseline in bodyweight at week 52, kg	0 (3·6)	−1·0 (3·3)
Systolic blood pressure		
Systolic blood pressure at week 24, mm Hg	147·4 (23·4)	137·6 (19·3)
Change from baseline in systolic blood pressure at week 24, mm Hg	1·2 (16·3)	−7·4 (16·9)
Systolic blood pressure at week 52, mm Hg	147·2 (23·8)	133·8 (16·9)
Change from baseline in systolic blood pressure at week 52, mm Hg	1·0 (17·4)	−11·2 (15·7)
Diastolic blood pressure		
Diastolic blood pressure at week 24, mm Hg	78·7 (10·0)	74·8 (9·4)
Change from baseline in diastolic blood pressure at week 24, mm Hg	0·7 (9·0)	−2·4 (8·8)
Diastolic blood pressure at week 52, mm Hg	79·3 (12·1)	72·9 (8·4)
Change from baseline in diastolic blood pressure at week 52, mm Hg	1·4 (8·7)	−4·3 (8·8)

Data are mean (SD). Descriptive statistics with last observation carried forward. CKD=chronic kidney disease.

Table 4: Efficacy results in patients with stage 4 CKD in the full analysis set

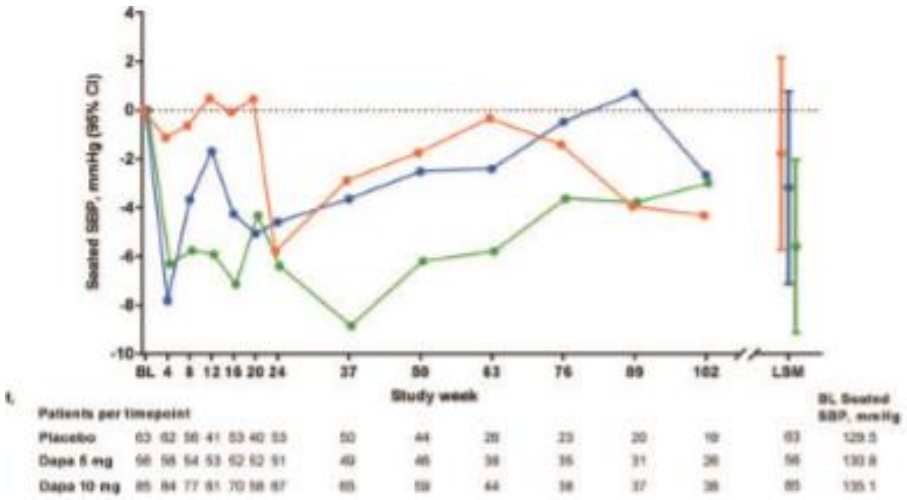


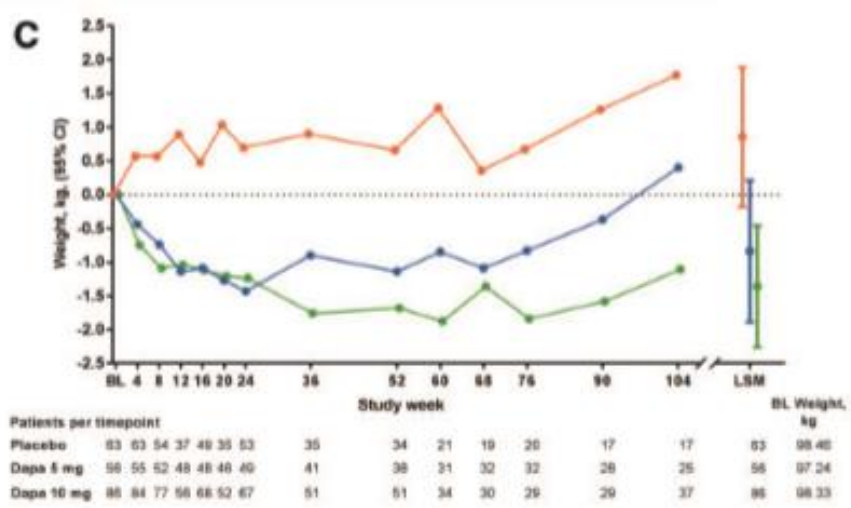




Effects of the sodium–glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b–4 chronic kidney disease

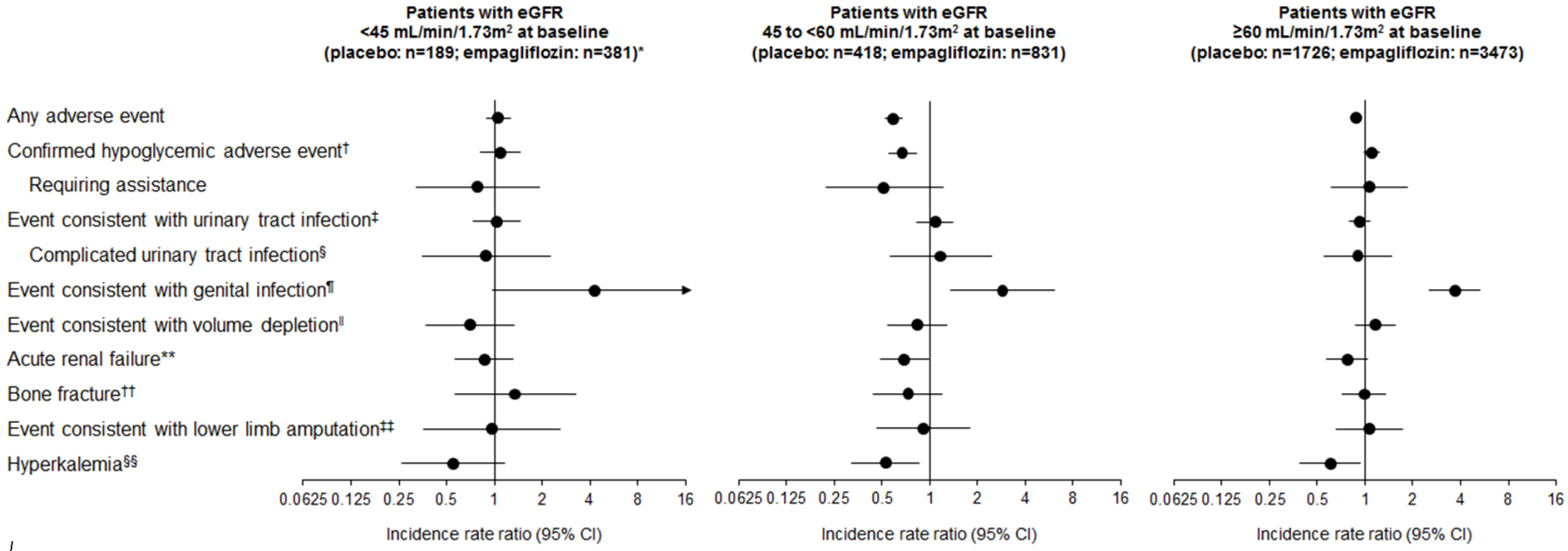
Claire C.J. Dekkers[1], David C. Wheeler[2], C. David Sjöström[3], Bergur V. Stefansson[3], Valerie Cain[4] and Hiddo J.L. Heerspink[1]





Nephrol Dial Transplant (2018) 1–7
doi: 10.1093/ndt/gfx350

Side effects of SGLT2i therapy

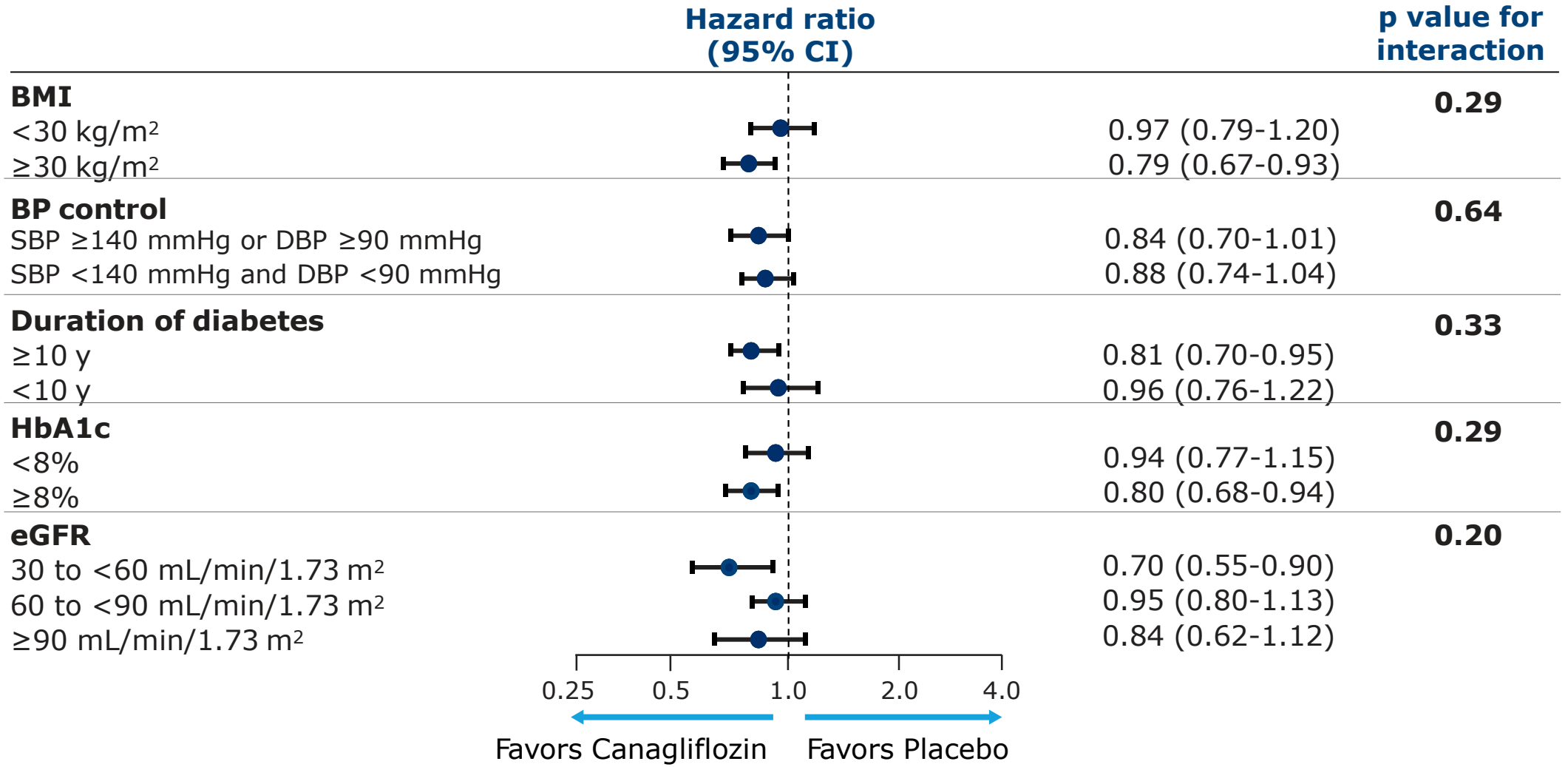


Circulation 2018;137:119-129

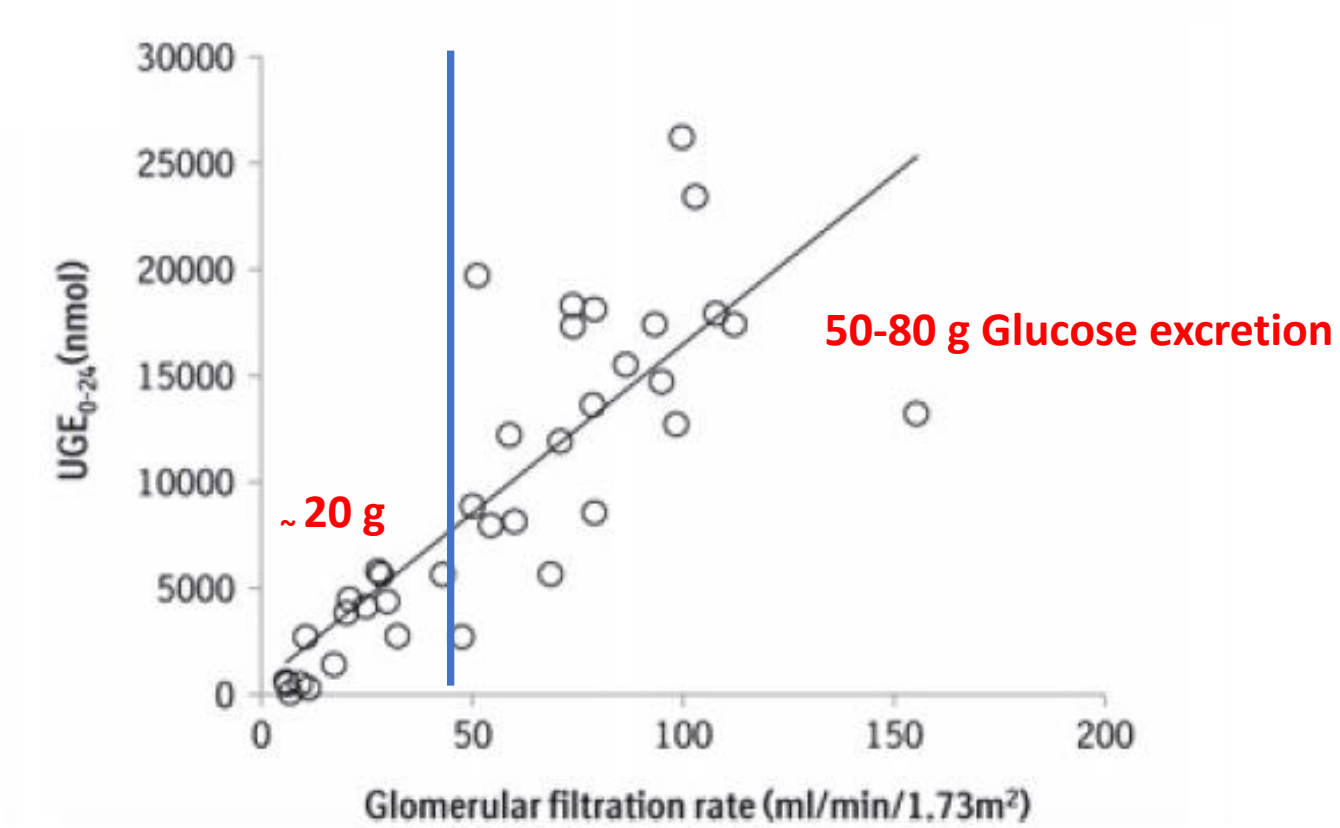
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*



24 h urinary glucose excretion declines with declining GFR



Macha S et al. Diabetes, Obesity and Metabolism 2014;16:215-222

Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
					ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin		High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs		High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors		Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

Can J Diabetes 42 (2018) S315

Contents lists available at ScienceDirect

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journal homepage:
www.canadianjournalofdiabetes.com

DIABETES CANADA

CJD

Cada vez es más factible el uso de ADOs hasta estadios más evolucionados de ERC

Probablemente podamos utilizar los inhibidores de SGLT-2 hasta filtrados más bajos dados sus efectos beneficiosos

Medication	CKD 3A (eGFR 45-59mL/min)	CKD 3B (eGFR 30-44 mL/min)	CKD 4 (eGFR 15-29 mL/min)	CKD 5 (eGFR <15 mL/min or dialysis)
Metformin‡	Dose adjustment not required	Reduce dose (500-1,000 mg/day) Do not initiate, can maintain	Use alternative agent due to risk of accumulation	
GLP-1 receptor agonists				
Dulaglutide	Dose adjustment not required			Caution as safety not established
Exenatide/ Exenatide ER	Dose adjustment not required (>50 mL/min)	Caution (30–50 mL/min)	Use alternative agent due to risk of accumulation	
Lixisenatide	Dose adjustment not required		Use alternative agent as safety not established	
Liraglutide	Dose adjustment not required			Use alternative agent as safety not established
SGLT2 inhibitors				
Canagliflozin‡	Can maintain at 100 mg daily, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	
Dapagliflozin‡	Use alternative agent due to lack of glycemic efficacy			
Empagliflozin‡	Can maintain, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	
DPP-4 Inhibitors				
Alogliptin	Lower dose 12.5 mg daily		Lower dose 6.25 mg daily	
Linagliptin	Dose adjustment not required			Caution as safety not established
Saxagliptin	Dose adjustment not required (>50 mL/min)	Lower dose 2.5 mg daily (<50 mL/min)		Use alternative agent as unproven efficacy for patients requiring hemodialysis
Sitagliptin	Dose adjustment not required (≥50 mL/min)	Lower dose 50 mg daily (30–49 mL/min)	Lower dose 25 mg daily	
Alpha-glucosidase inhibitor				
Acarbose	Dose adjustment not required		Consider alternative agent as safety not established	
Meglitinides				
Repaglinide	Consider lower doses due to risk of hypoglycemia		Consider lower doses and beware of extended duration of action due to risk of hypoglycemia	
Sulfonylureas				
Gliclazide‡	Caution due to risk of hypoglycemia		Use alternative agent due to risk of accumulation and hypoglycemia	
Glimepiride‡	Caution due to risk of hypoglycemia		Use alternative agent due to risk of accumulation and hypoglycemia	
Glyburide‡	Use alternative agent due to risk of accumulation and hypoglycemia			
Thiazolidinediones				
Rosiglitazone / Pioglitazone	Dose adjustment not required but caution as may lead to fluid retention			
Insulins	Dose adjustment not required		Consider lower doses and beware of extended duration of action due to risk of hypoglycemia	

*Limited glycemic efficacy but may be considered to reduce progression of nephropathy or for CV protection where indicated for individuals with eGFR >30mL/min (see recommendations).
‡These medications should be held during intercurrent illness – see Appendix 8. Sick Day Medication List.
Dose adjustment is not recommended for the antihyperglycemic agents listed above in CKD stages 1 and 2.
For full details on monitoring, please see product mongraphs.

Conclusiones

Resultados Cardiovasculares alcanzados en MACE iSGLT2 y arGLP1

CANVAS Program

Prevención Primaria y Secundaria

14% MACE

EMPA-REG OUTCOME®

Prevención Secundaria

14% MACE

LEADER®

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Prevención Primaria y Secundaria

13% MACE

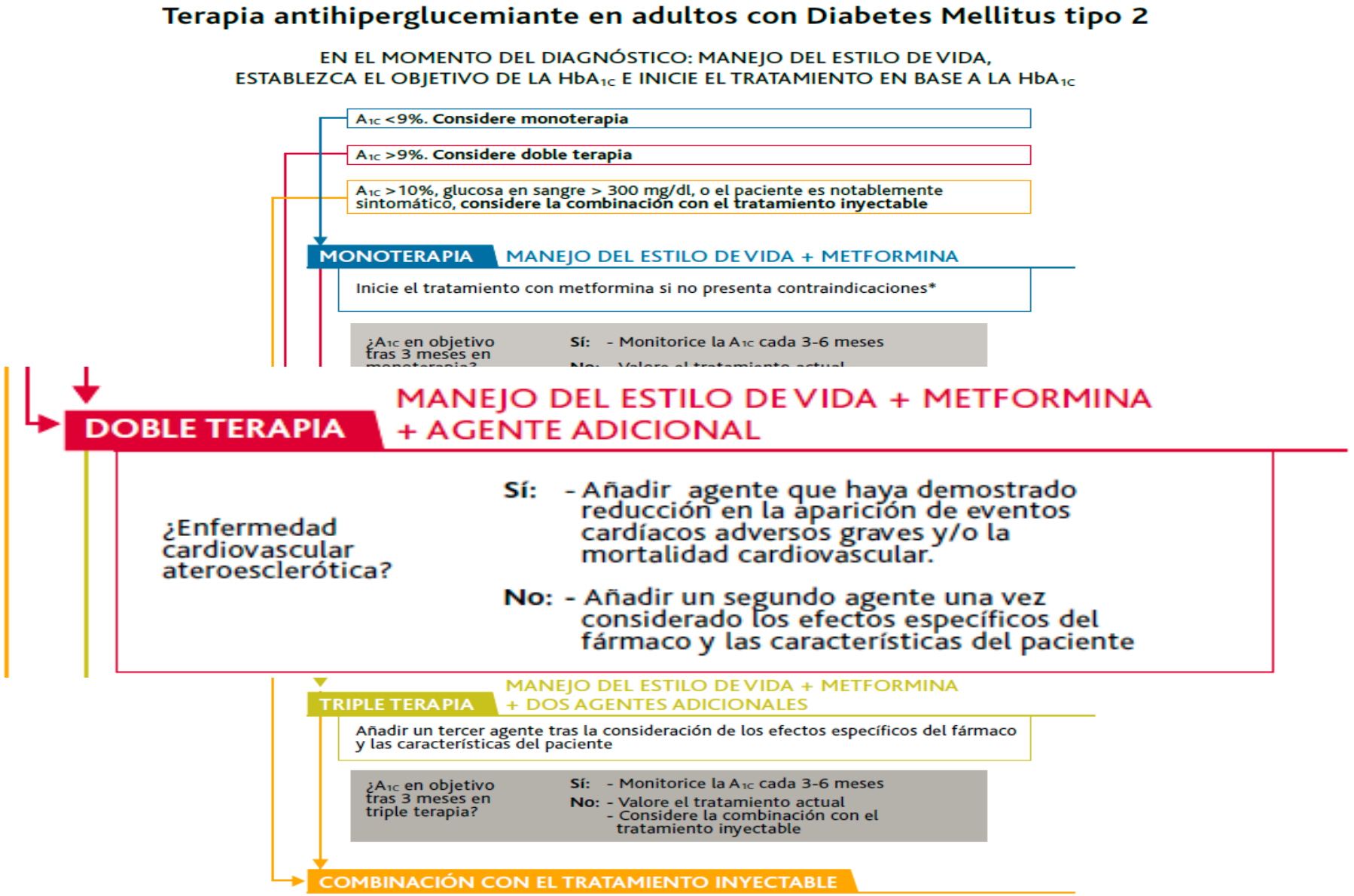
SUSTAIN

SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

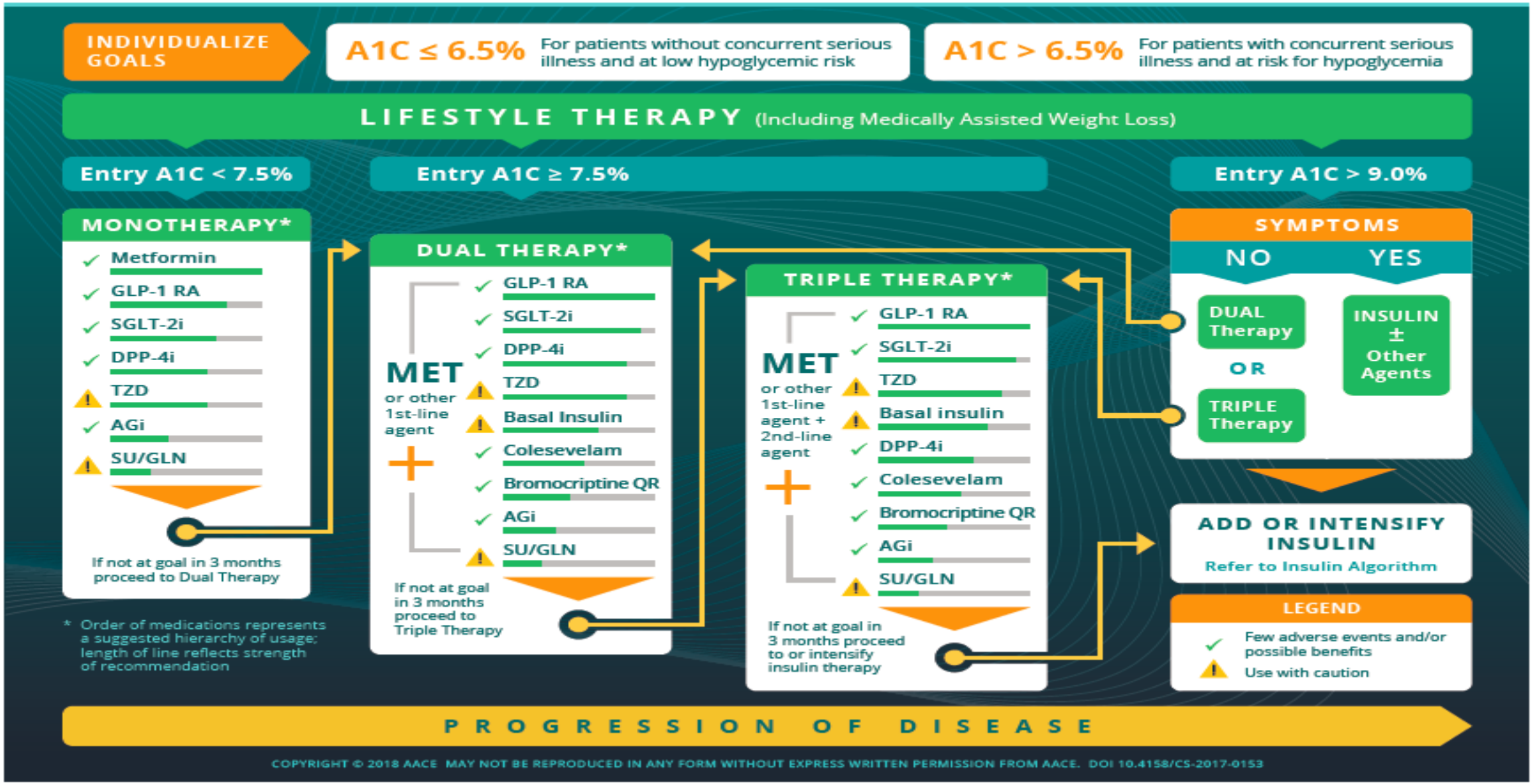
Prevención Secundaria

26% MACE

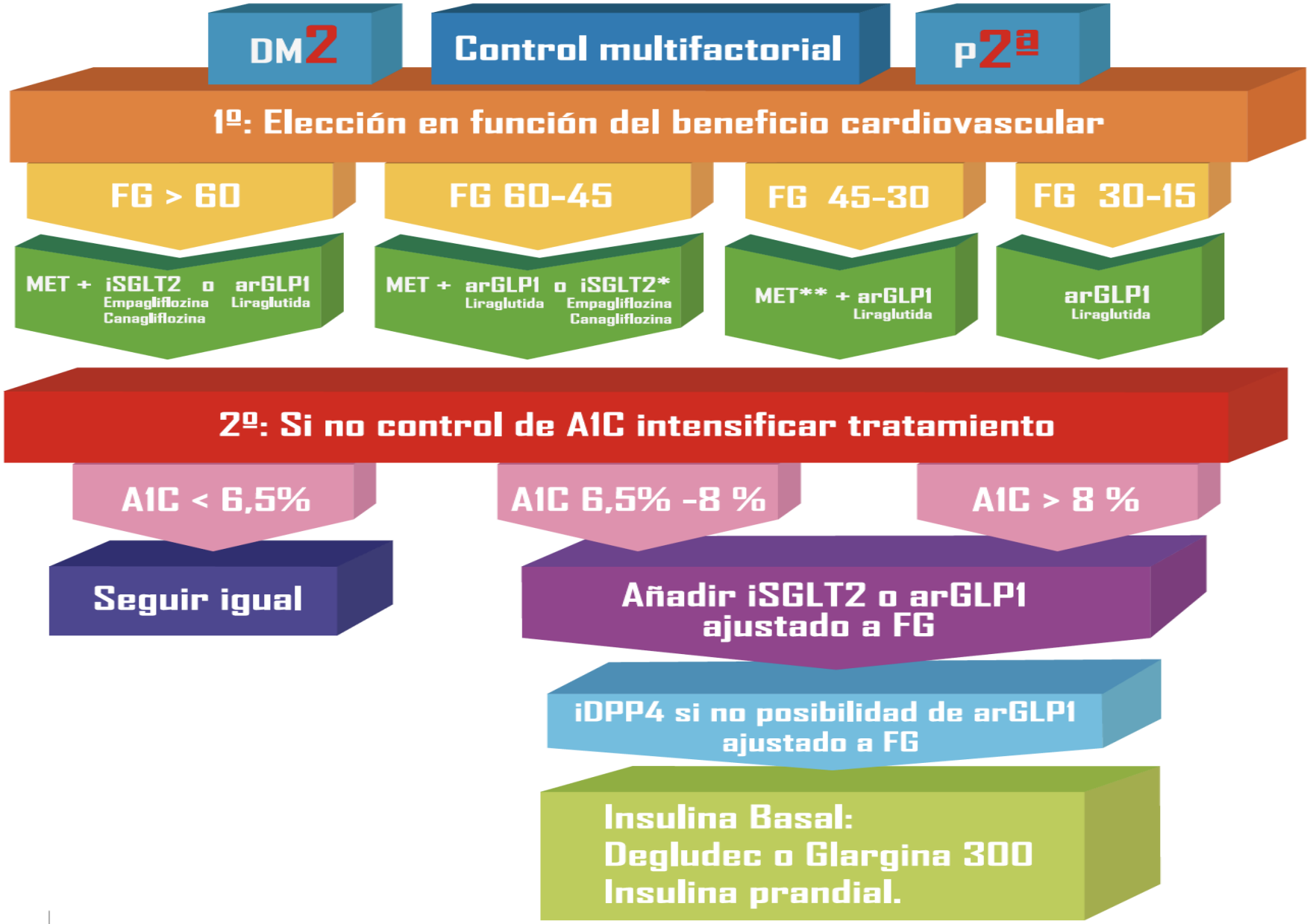
Guías Tratamiento ADA 2018



Algoritmo de Control glucémico AACE



Tratamiento de la DM2 en Prevención Secundaria



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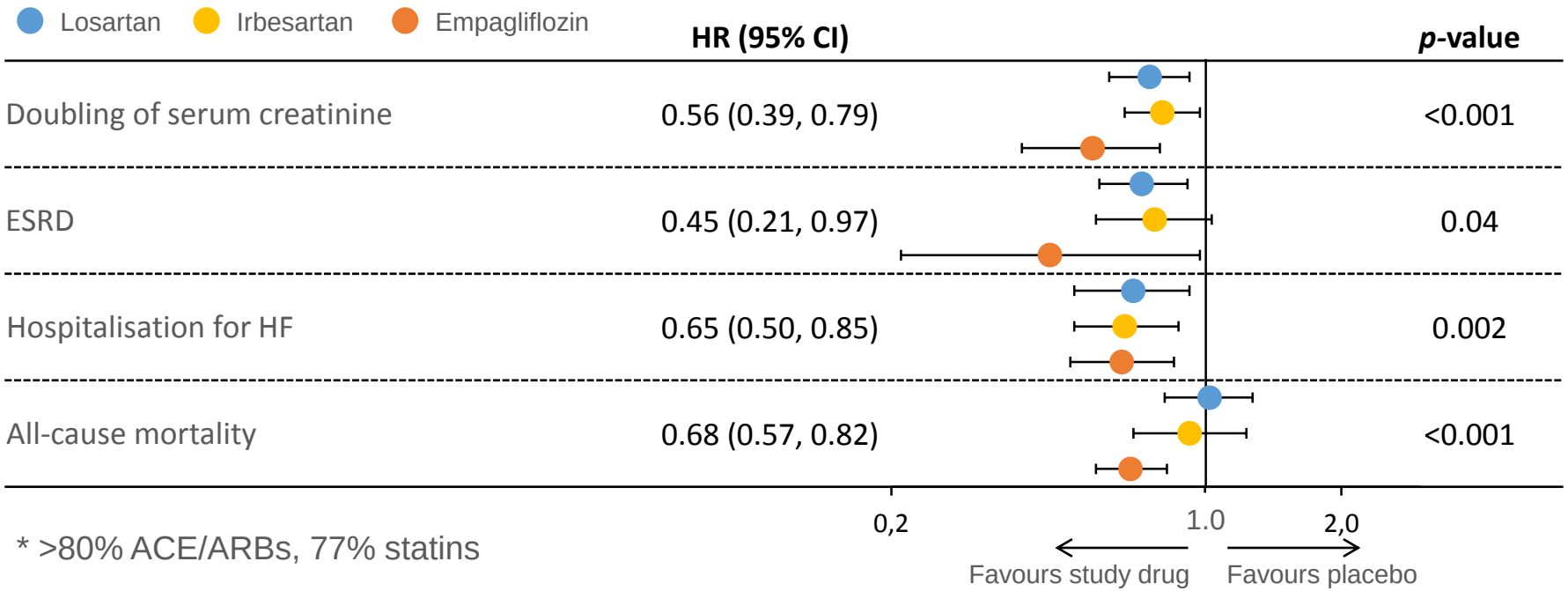
	Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

Effects of losartan, irbesartan and empagliflozin on renal and CV outcomes

Renal and CV outcomes from the RENAAL[1,2], IDNT[3,4] and EMPA-REG OUTCOME®*[5,6] trials



* >80% ACE/ARBs, 77% statins

1. Brenner B *et al. N Engl J Med* 2001;345:861;
2. Carr AA *et al. Am J Cardiol* 2005;96:1530;
3. Lewis EJ *et al. N Engl J Med* 2001;345:851;
4. de Zeeuw D *et al. Circulation* 2004;110:921;
5. Wanner C *et al. N Engl J Med* 2016;375:323;
6. Zinman B *et al. N Engl J Med* 2015;373:2117