EUSKADIKO ENDOKRINOLOGIA, DIABETES ETA NUTRIZIOKO ELKARTEA

SEDyNE

SOCIEDAD DE ENDOCRINOLOGÍA, DIABETES Y NUTRICIÓN DE EUSKADI

Tratamiento con Inhibidores de SGLT2 y protección renal

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Donosti, 15 de Octubre de 2016

VNIVERSITAT DE VALÈNCIA

ERC diabética (diabetic kidney disease)

- Principal causa de IRC terminal en el mundo (20-45 %).
- El 28 % de los diabéticos presentan algún grado de nefropatía.
  - FG estimado < 60: 12-19 %
  - Albuminuria > 30: 9-13%
  - Albuminuria >300: 2-4 %
  - FGe<60 + albuminuria>30: 28-29 %
  - FG<60 en > 65 años: 43 %
- 25 % DM 2 → albuminuria a los 10 años del Dx de la DM.
- 40 % DM 2 presentarán nefropatía durante su evolución.
- Actuar en fases precoces: prevenir progresión y mortalidad CV

ERC: enfermedad renal crónica
GF: filtrado glomerular

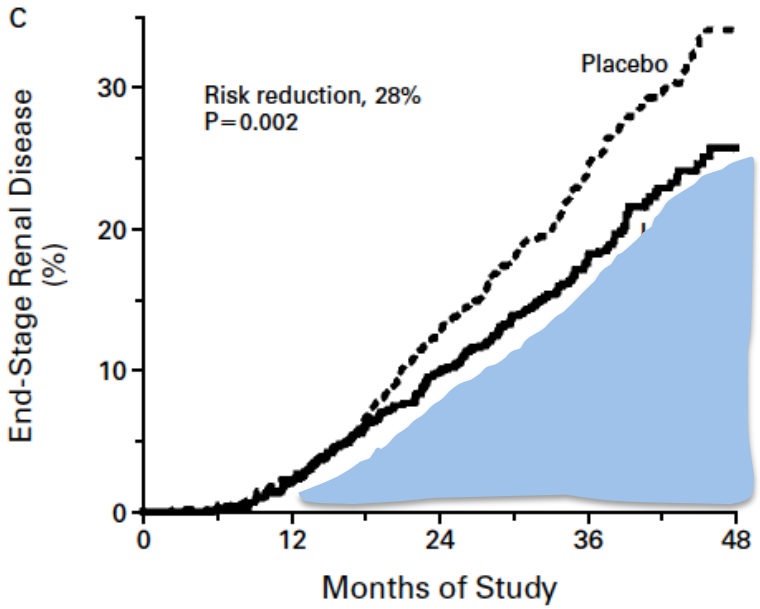
USRD 2013; NHANES III
Martinez-Castelao A, Gorriz JL, J Clin Med. 2015; 4(6): 1.207-1.216
Afkarian M. *J. Am. Soc. Nephrol. 2013;* 24, 302–308
Rodriguez-Poncelas et al. BMC Nephrology 2013, 14:46
Bailey RA. BMC Research notes 2014; 7: 415

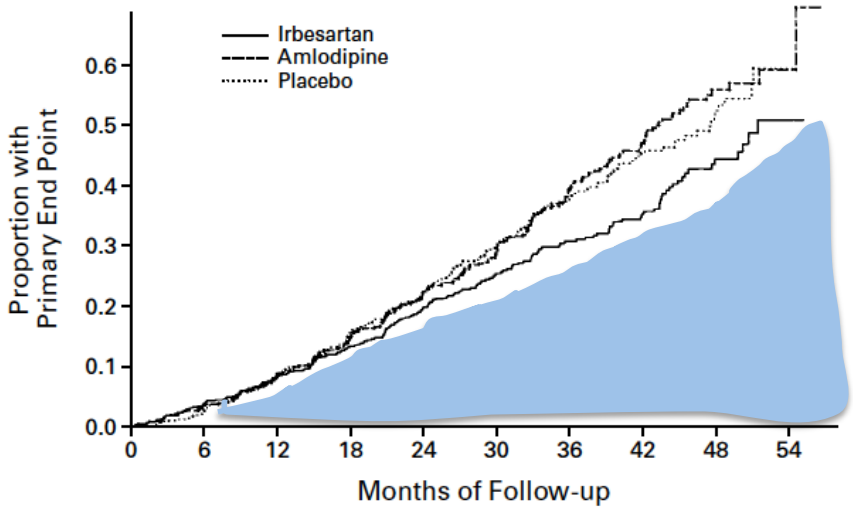
Prevención y tratamiento de la nefropatía diabética

- Control glucémico
- Control de la PA. Bloqueo SRAA. ↓ albuminuria
- Intervención multifactorial:
  - Evitar tabaquismo
  - Evitar sobrepeso
  - Restricción proteica en ERC avanzada
  - Control de la dislipemia

ADA guidelines 2014. Diab Care 2015 (Suppl 1)
Gomez Huelgas R, Martinez-Castelao A, Gorriz JL. Nefrologia 2014;34(1): 34-45
Fernandez-Fernandez B. *et al. Nat. Rev. Nephrol 2014;* 10, 325–346

Riesgo residual en ERC diabética tras inhibición del SRAA





RENAAL Study. NEJM 2001

IDNT Study. NEJM 2001

Control estricto de la glucemia y nefroprotección: Estudios controlados

	↓ Albuminuria	Prevención nefropatia diabética	Retraso inicio de diálisis-Tx
ADVANCE[1]	SI	SI	SI
ACCORD[2]	SI	NO	NO
VADT[3]	NO	NO	NO

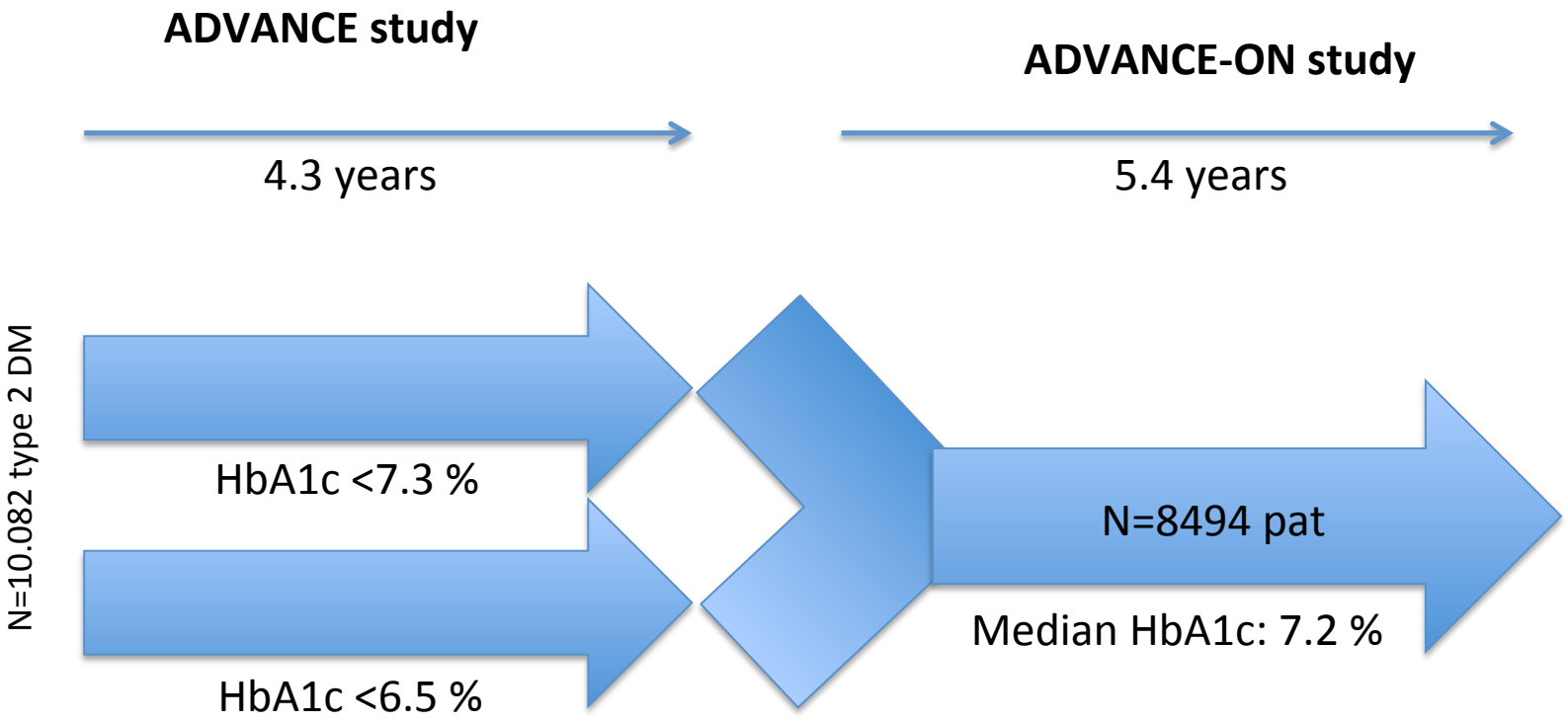
Datos contradictorios

1.- ADVANCE (Action in Diabetes and Vascular Disease). Patel A. N. Engl. J. Med. 2008, 358, 2560–2572.
2.- ACCORD (Action to Control Cardiovascular Risk in Diabetes), Cushman WC. Lancet 2010, 376, 419–430
3.- VADT (Veterans Affair Diabetic Trial). Duckworth W. N. Engl. J. Med. 2009, 360, 129–139

Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON

DOI: 10.2337/dc15-2322

Muh Geot Wong,[1] Vlado Perkovic,[1] John Chalmers,[1] Mark Woodward,[1,2,3] Qiang Li,[1] Mark E. Cooper,[4] Pavel Hamet,[5] Stephen Harrap,[6] Simon Heller,[7] Stephen MacMahon,[1,2] Giuseppe Mancia,[8] Michel Marre,[9] David Matthews,[10] Bruce Neal,[1,11] Neil Poulter,[11] Anthony Rodgers,[1] Bryan Williams,[12] and Sophia Zoungas,[1,13] for the ADVANCE-ON Collaborative Group



Wong MG. Diabetes Care. 2016 Mar 22. pii: dc152322. [Epub ahead of print]

Intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

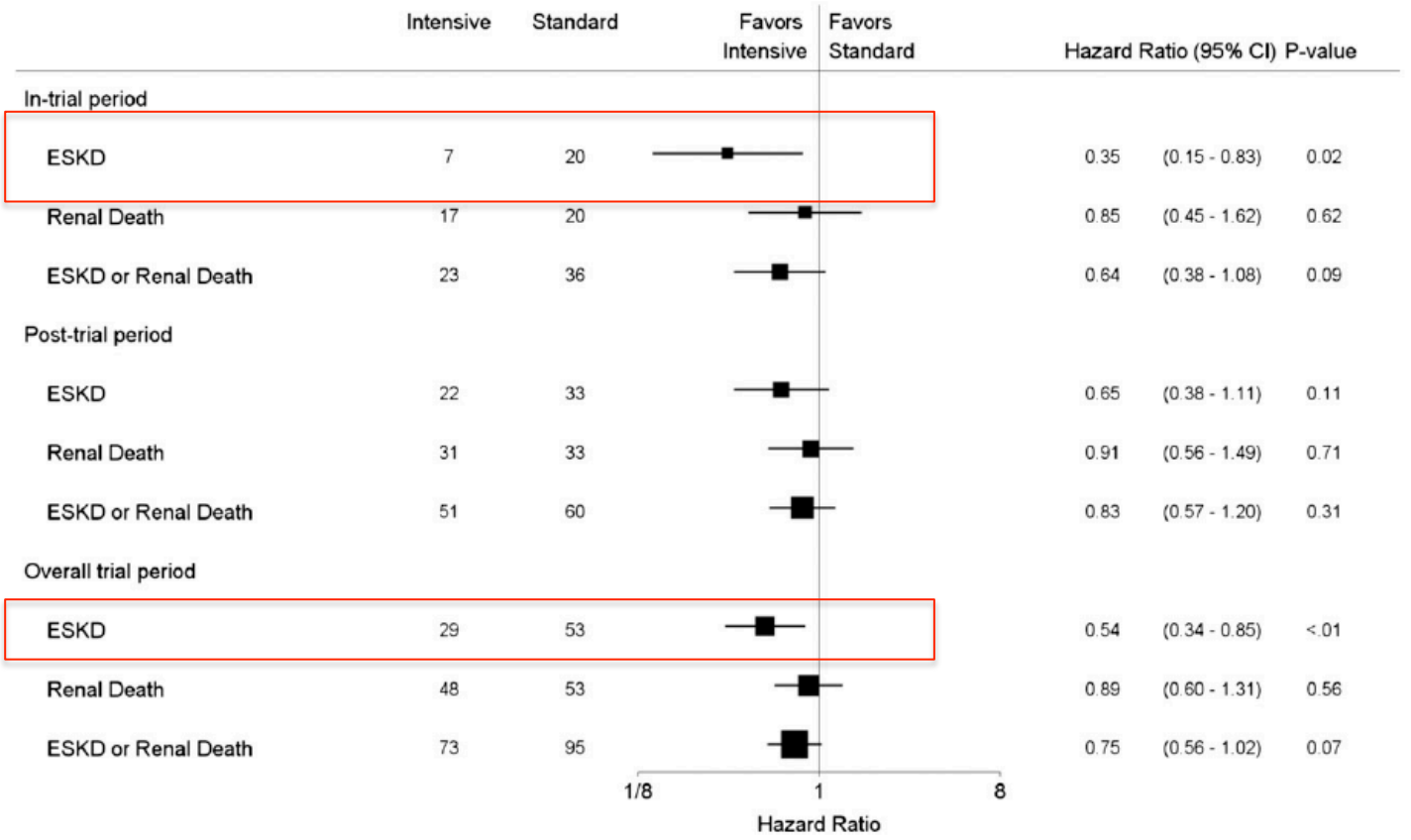
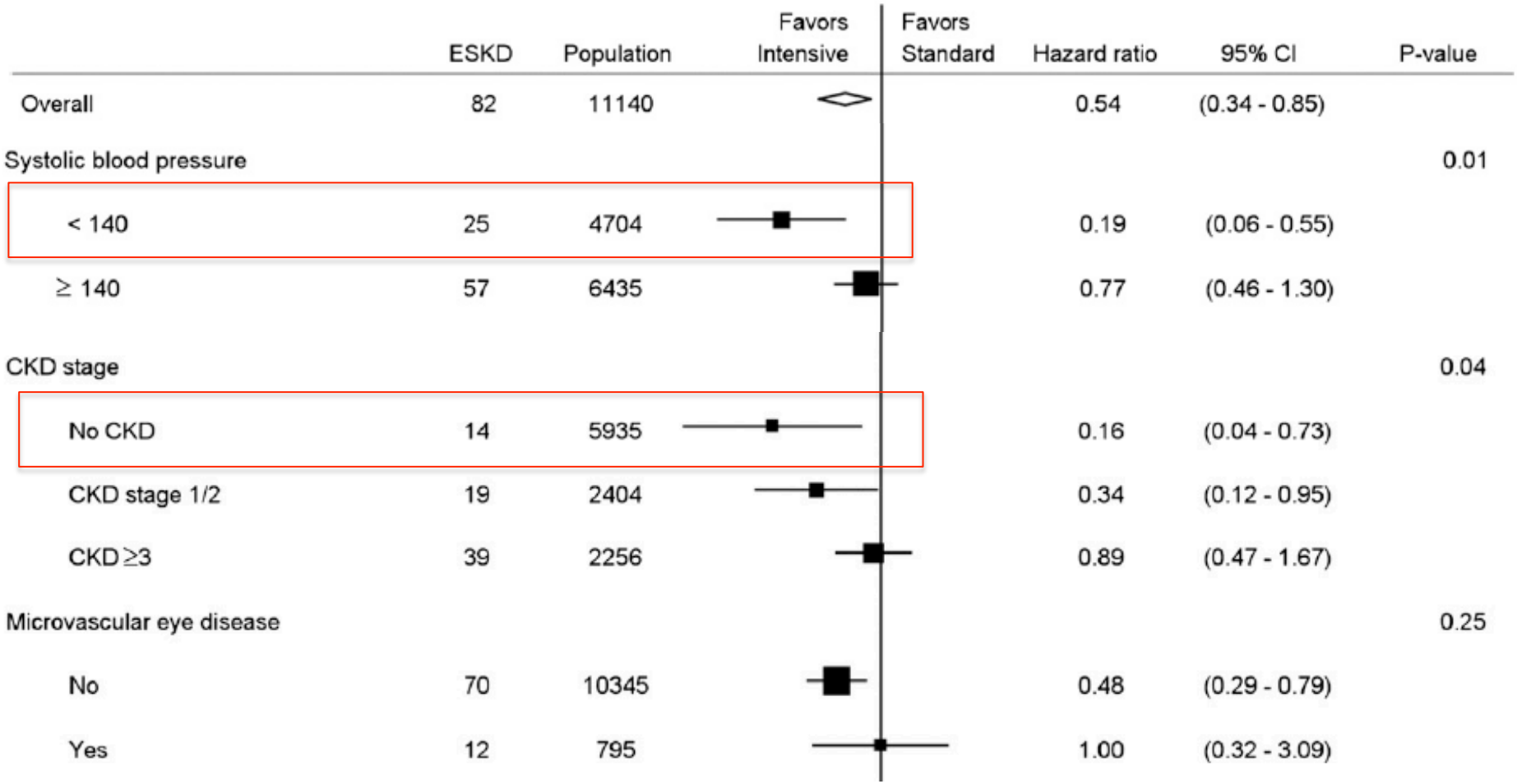


Figure 1—Summary plot showing the effects of intensive glucose lowering compared with standard glucose lowering on ESKD and/or death due to renal cause during the in-trial, post-trial, and overall study periods of follow-up. Renal death, death due to renal causes.

Wong MG. Diabetes Care. 2016 Mar 22. pii: dc152322. [Epub ahead of print]

Subgroup analyses by baseline characteristics for the outcome of ESKD



Wong MG. Diabetes Care. 2016 Mar 22. pii: dc152322. [Epub ahead of print]

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

8 Abril 2016

- Utilización de metformina en insuficiencia renal:
  - Puede utilizarse en pacientes con FG estimado > 45 ml/min/1.73 m^2
  - Entre 30-45 ml/min/1.73 m^2 evaluar ventajas y riesgos de su uso.
  - Contraindicada con FG estimado < 30 ml/min/1.73 m^2
- Utilizar el FG estimado para medición de función renal y no solo creatinina.

- Suspenderla antes de un procedimiento con contraste yodado si FGe 30-60 ml/min/1.73 m^2, o en pacientes con enfermedad hepática, insuficiencia cardiaca o si se administra el contraste yodado intraarterial. Reiniciar después si la función renal está estable.

http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm

Uso de hipoglucemiantes en la ERC (I)

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)			

Clinical Practice Guideline on management of diabetes and CKD. Nephrol Dial Transplant (2015) 30: ii1–ii142
Martinez-Castelao A, Gorriz JL, Sola E, Morillas JL, et al. Nefrologia 2012;32(4):419-26
Modificado de RedGDPS. Enfermedad renal crónica y Diabetes Mellitus Autor: Dr. Antonio Rodríguez-Poncelas

Uso de hipoglucemiantes en la ERC (II)

FGe/Fármacos	>60	45-59	30-44	15-29	< 15
Inhib SGLT2					
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	Si FG< 60 en tto, 100 mg/dia	No	No	No
Análogos r GLP1					
Exenatida Lisexenatida	No ajuste	No	No	No	No
Exenatida Lisexenatida	No ajuste	No	No	No	No
Liraglutida	No ajuste	No ajuste	No ajuste	No	No
Albigutida	No ajuste	No ajuste	No ajuste	No	No
Dulaglutida	No ajuste	No ajuste	No ajuste	No	No
Semaglutida					

Clinical Practice Guideline on management of diabetes and CKD. Nephrol Dial Transplant (2015) 30: ii1–ii142
Martinez-Castelao A, Gorriz JL, Sola E, Morillas C et al. Nefrologia 2012;32(4):419-26
Modificado de RedGDPS. Enfermedad renal crónica y Diabetes Mellitus Autor: Dr. Antonio Rodríguez-Poncelas

J. Clin. Med. **2015**, *4*, 1866-1889; doi:10.3390/jcm4101866

OPEN ACCESS

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www.mdpi.com/journal/jcm

Review

Nephroprotection by Hypoglycemic Agents: Do We Have Supporting Data?

Jose Luis Górriz [1,5,6,*], Javier Nieto [2,5], Juan F. Navarro-González [3,5,6], Pablo Molina [1], Alberto Martínez-Castelao [4,5,6] and Luis M. Pallardó [1]

Efecto de antihiperglucemiantes sobre la nefroprotección

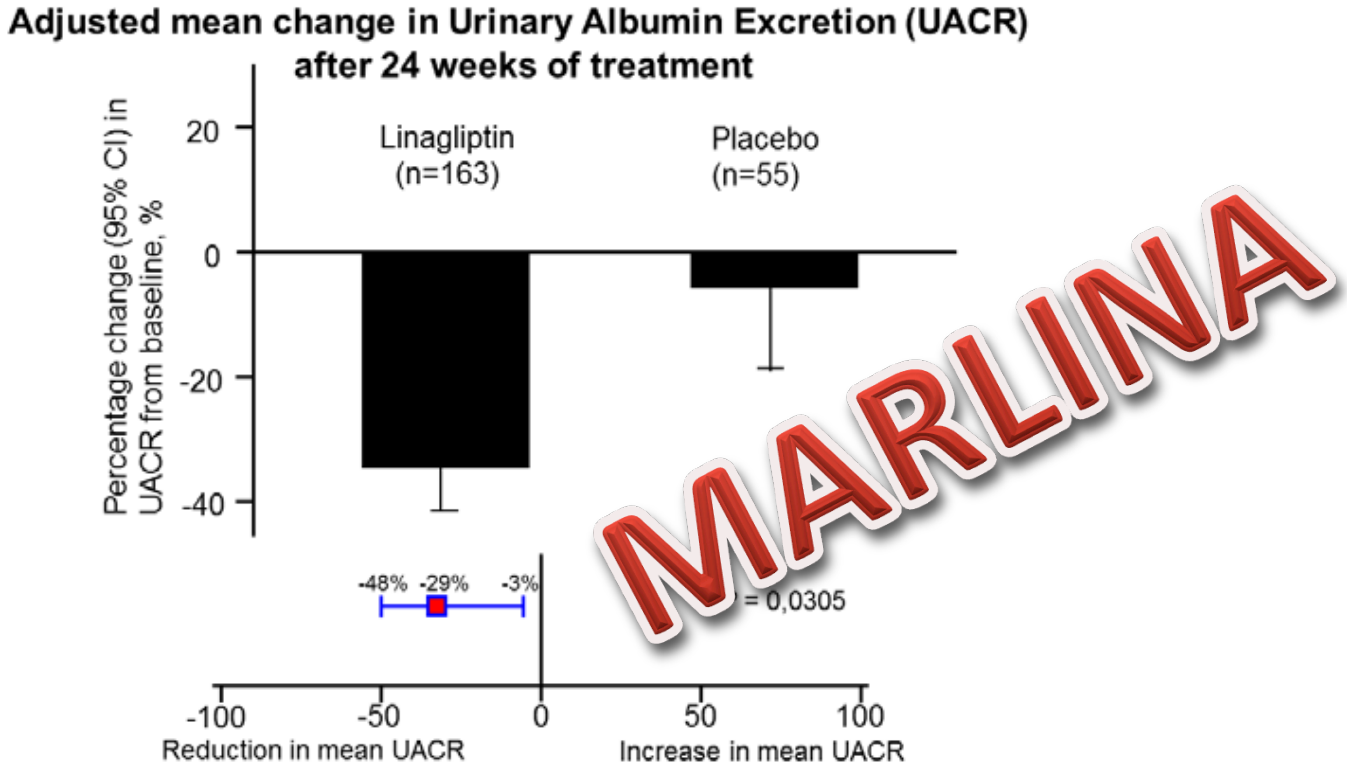
	Efecto renal directo en datos experimentales	Estudios	Ensayos clinicos	Nefropro-tección específica demostrada
Insulina	Sensib insulina	UKPDS	No	No
Metformina	↓ Disfunción vascular	No	No	No
Sulfonilureas	↓ Expresión PKC-β	No	No	No
α- glucosidasa inh	Up-regulación de GLP-1	No	No	No
Repaglinida	No	No	No	No
Tiazolidindionas	↓TNF-α ↑adipokinas	Respuesta heterogenea	+/-	Metaanálisis +

Gorriz JL. J Clin Medicine 2015; 4, 1866-1889

¿Son nefroprotectores los nuevos hipoglucemiantes?

- i-DPP4
- Anlálogos del receptor GLP1
- i-GLT2

Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction



A significative reduction in albuminuria was detected at 12th week (-29 %).

It was independent of BP levels and A1cHb.

Retrospective study of 4 clinical trials

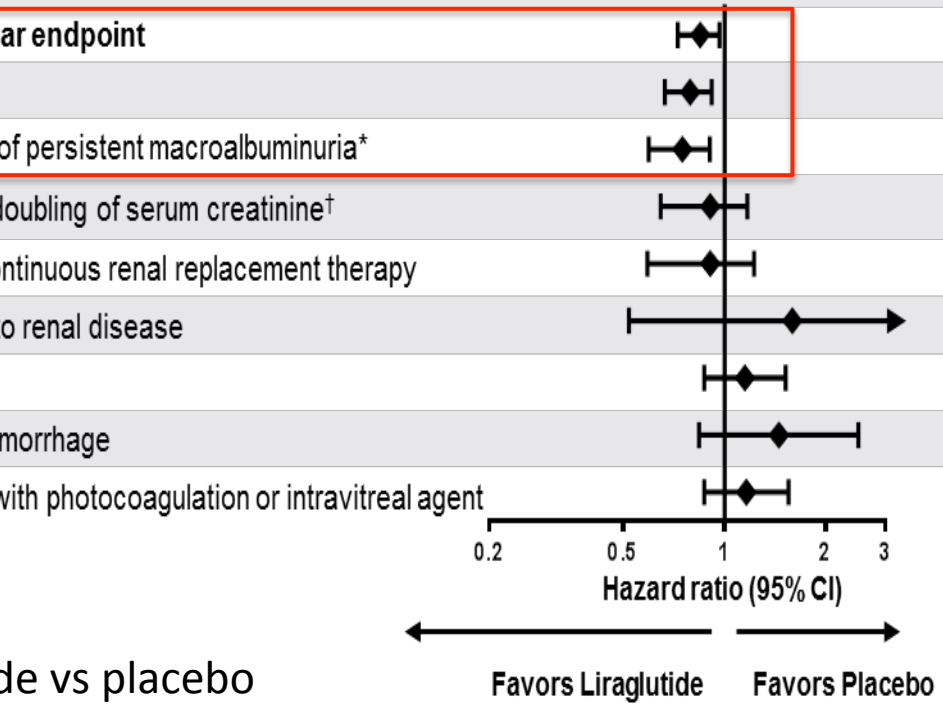
Groop PH. Diab Care 2013 Nov;36(11):3460-8

¿Son nefroprotectores los Análogos del receptor GLP1?

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

Time to first microvascular endpoints

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



Liraglutide vs placebo

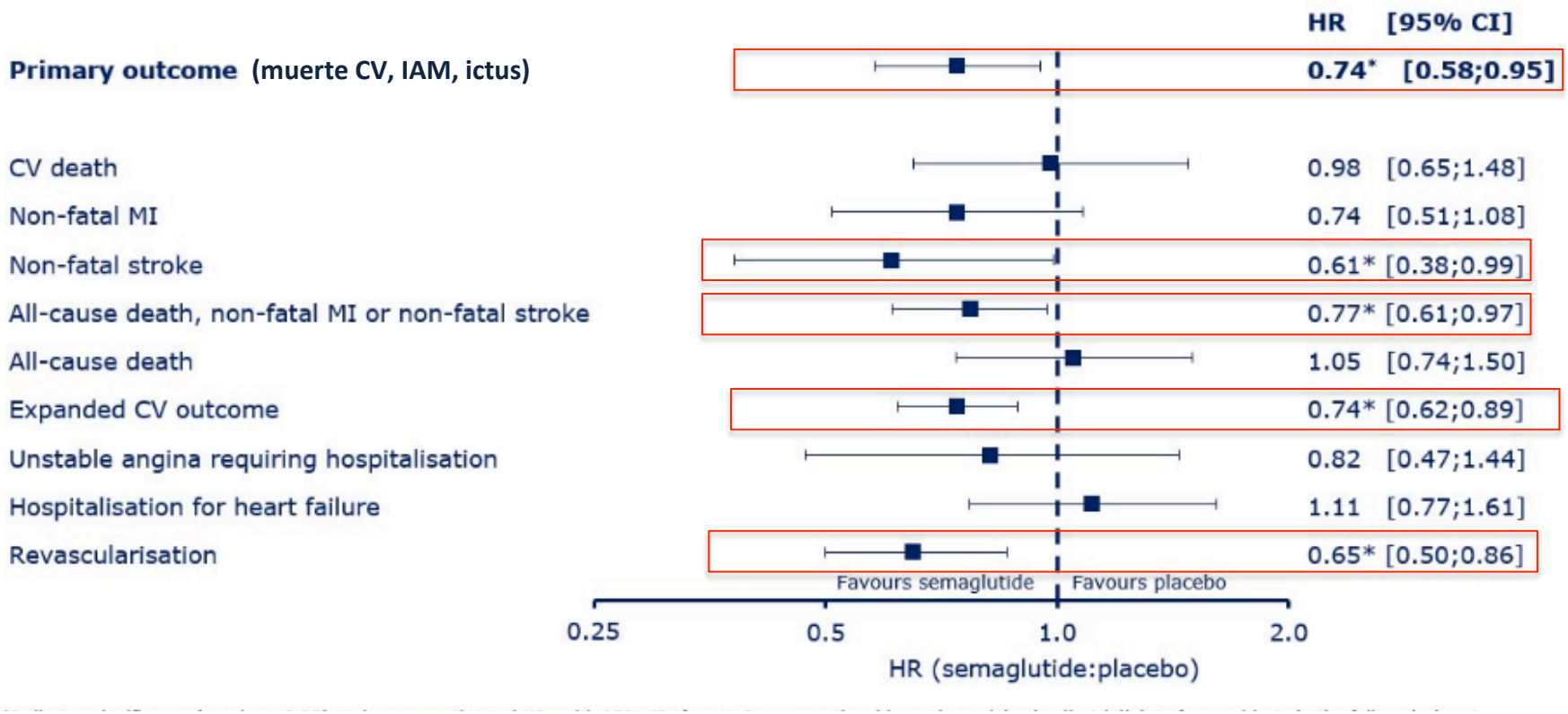
Full analysis set. EAC-confirmed microvascular events including events with onset between date of randomization and date of follow-up. Cox proportional hazard model adjusted for treatment. Development of diabetes-related blindness was not analyzed as an individual component as only one event was observed. *New onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine. †Persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 m^2 per MDRD. %: proportion of patients; CI: confidence interval; EAC: event adjudication committee; N: number of patients.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Marso SP. New Engl J Med 13 June 2016

Semaglutide vs placebo

Summary of cardiovascular outcomes

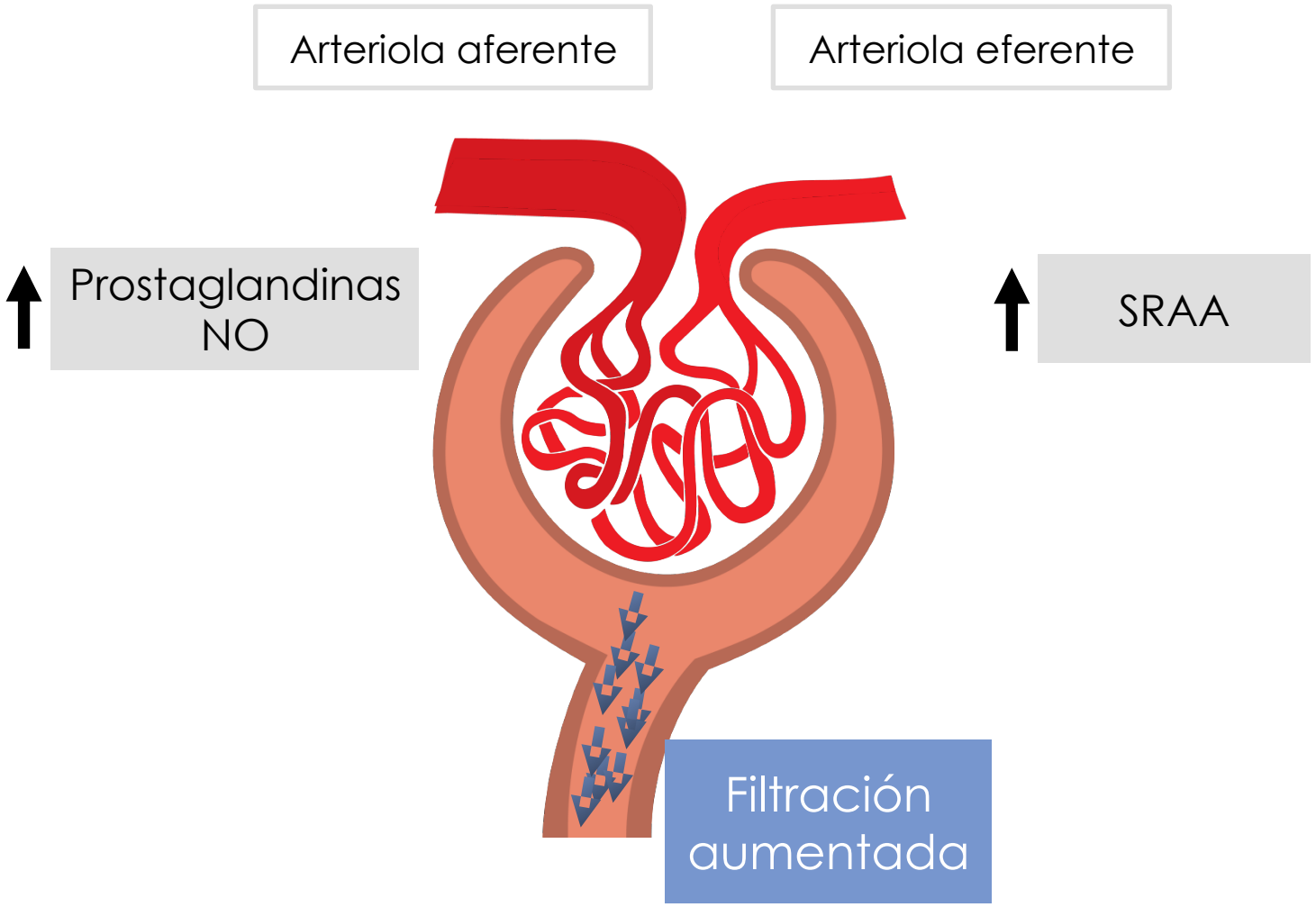


- 3297 DM2; 83 % enfermedad CV establecida, ↓HbA1c: 1.1 % (0.5 mg) y 1.3% (1 mg)

Marso SP. N Engl J Med 2016; 16 Sept. A head of print

¿Son nefroprotectores los inhibidores de SGLT2?

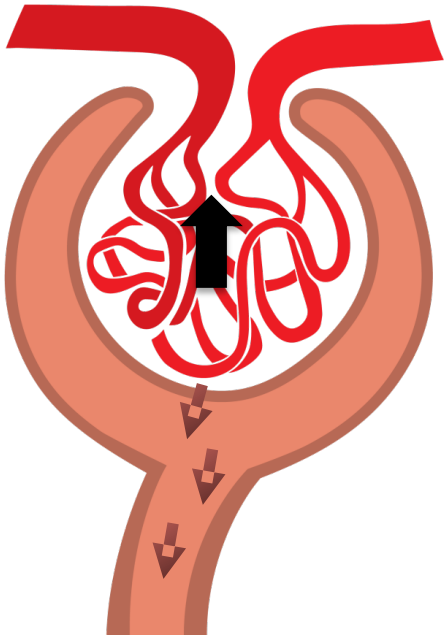
El riñon autorregula el flujo sanguíneo ajustando el tono arteriolar aferente y eferente



NO: Oxido Nítrico; SRAA: Sistema Renina-Angiotensina-Aldosterona

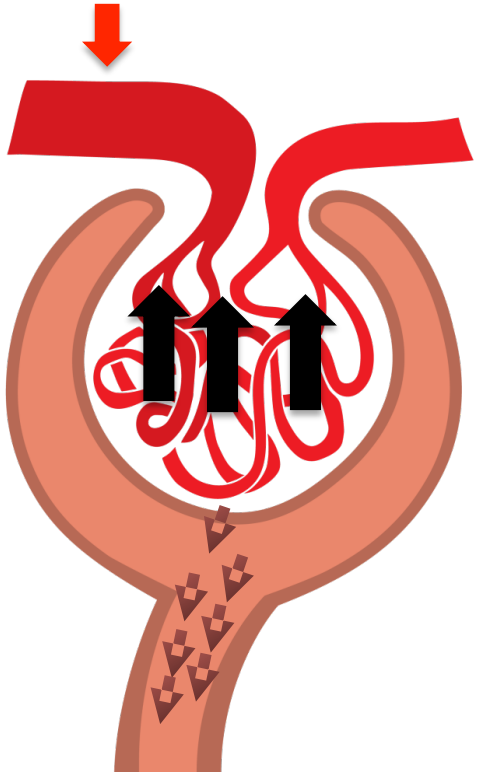
Hemodinámica glomerular

normal



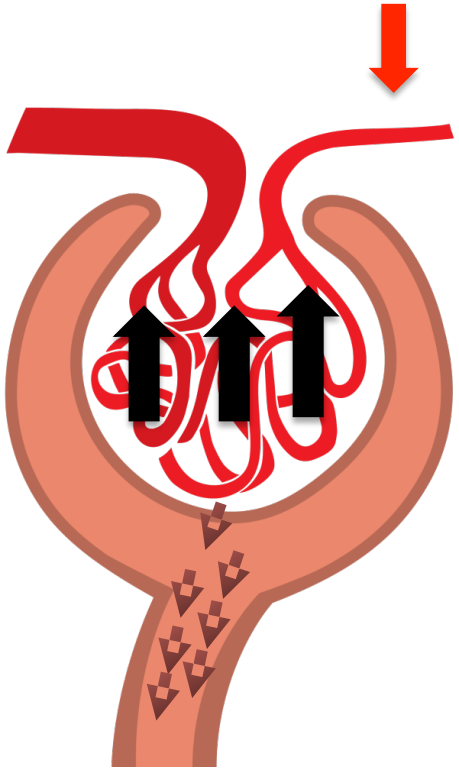
Presión glomerular normal

VD arteriola aferente



↑Presión glomerular (hiperfiltración)

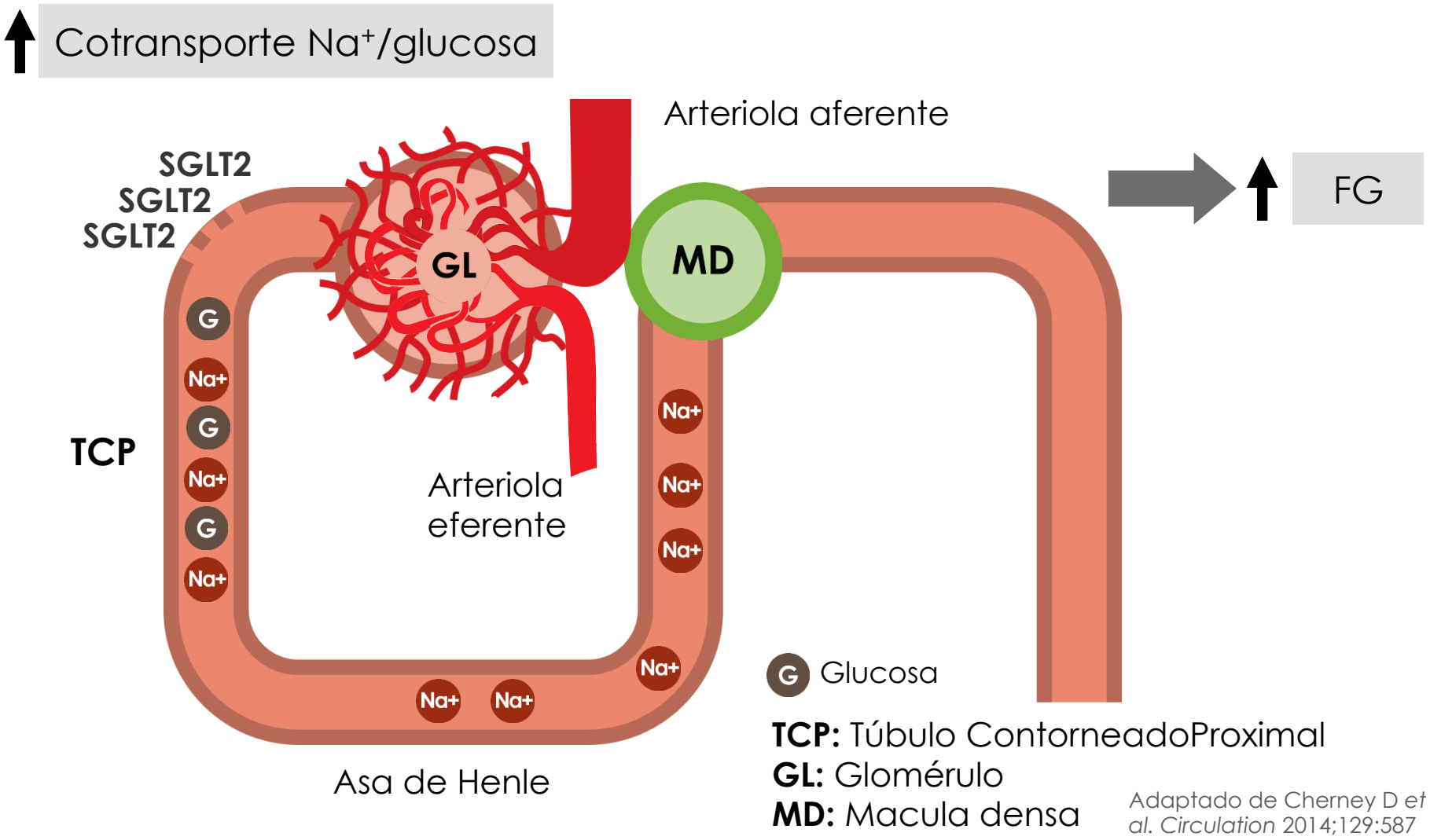
VC arteriola eferente



↑Presión glomerular (angiotensina II)

Modif JL Górriz

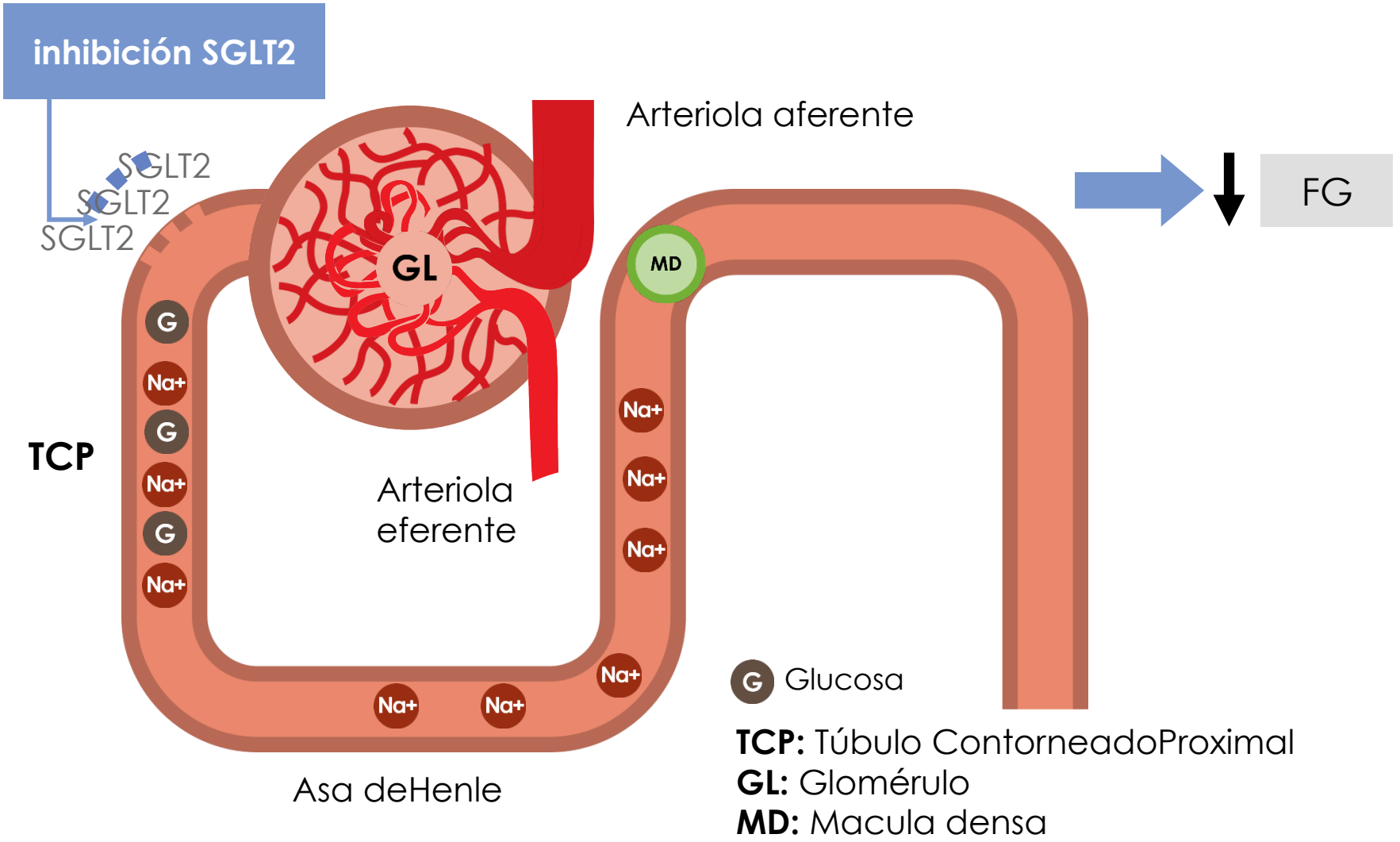
La diabetes causa hipertensión intraglomerular



Adaptado de Cherney D *et al. Circulation* 2014;129:587

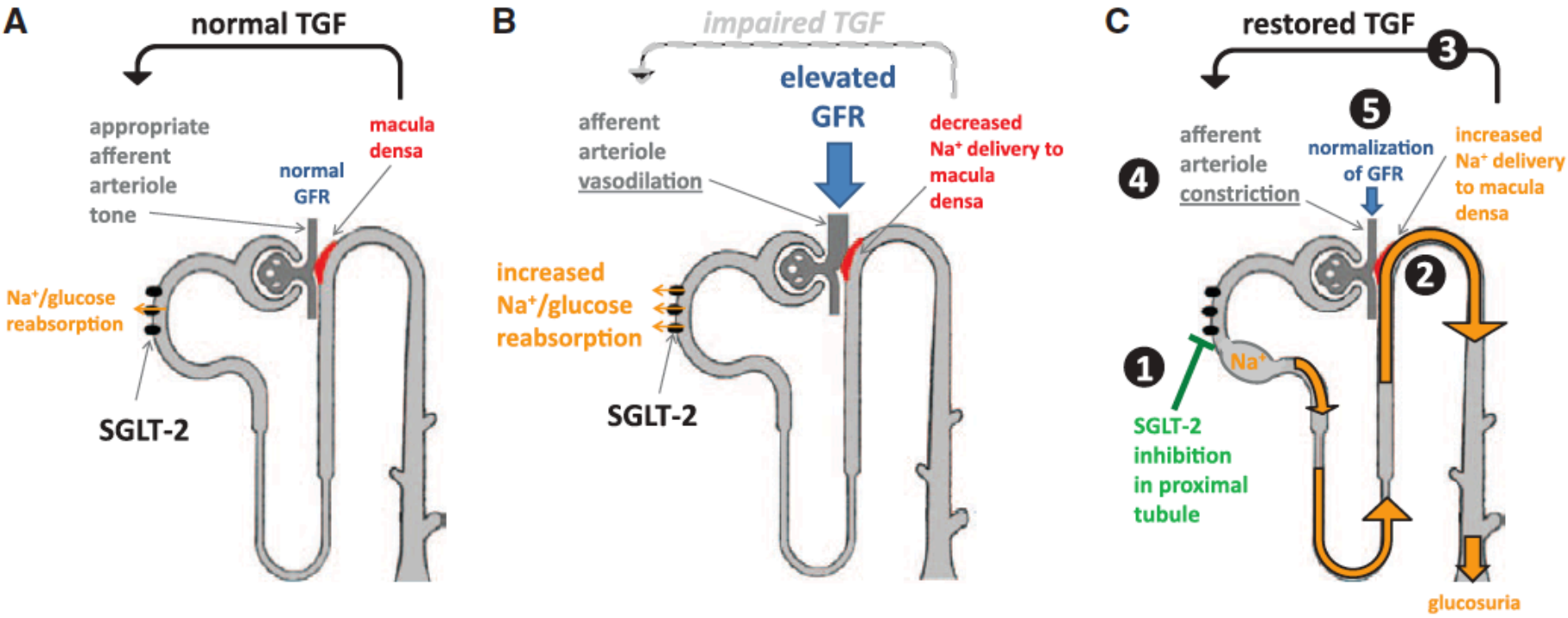
Hemodinámica renal en condiciones de hiperglucemia

Los inh SGLT2 reducen la presión intraglomerular



Hemodinámica renal con empagliflozina

Postulated tubuloglomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT) 2 inhibition.



Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

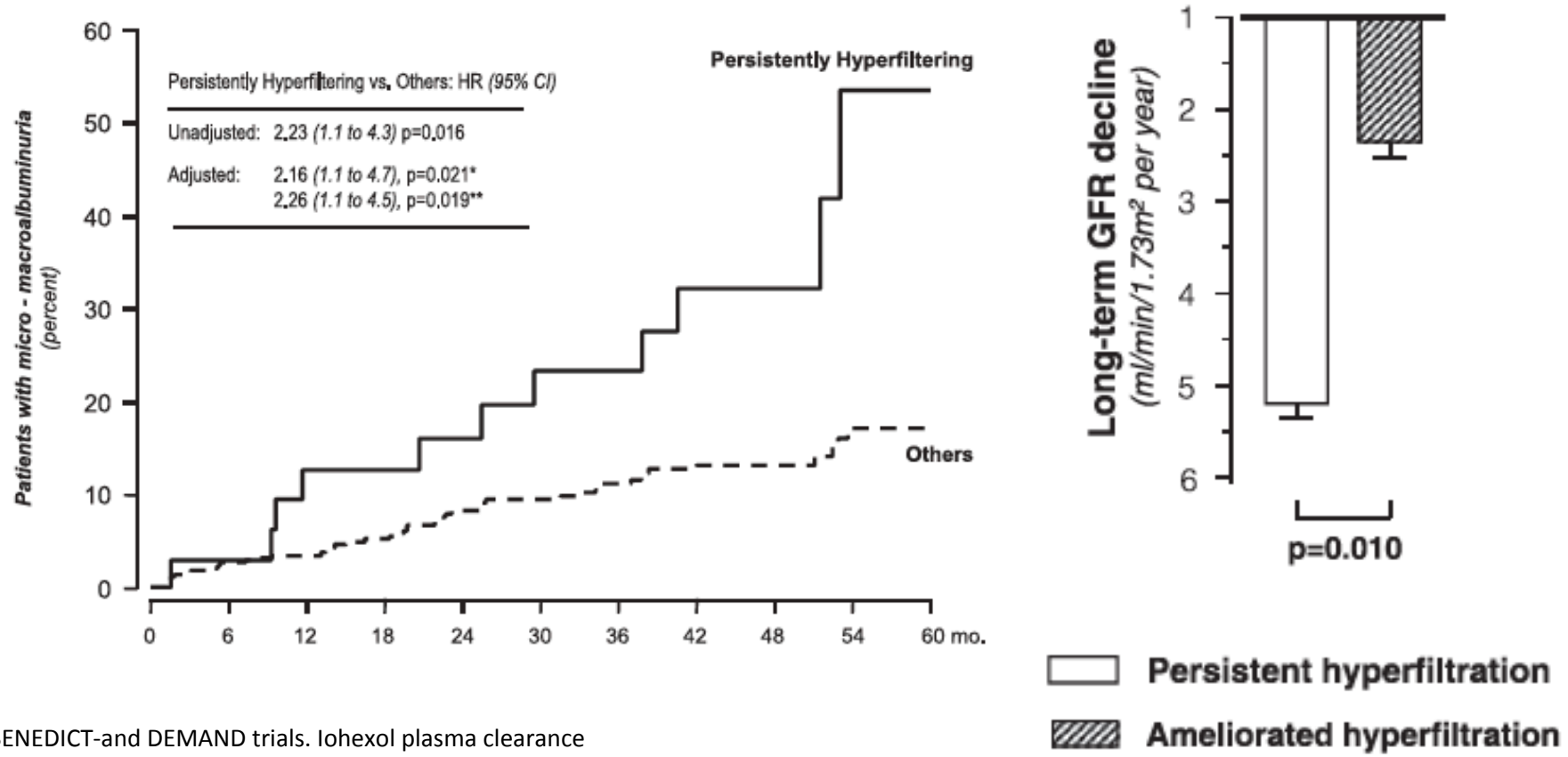
SGLT-2 inhibition reduces hyperfiltration via TGF

EMPA-REG OUTCOME®

Cherney D. Circulation. 2014;129:587-59

Importancia de la hiperfiltración en al progresión de la enfermedad renal diabética

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

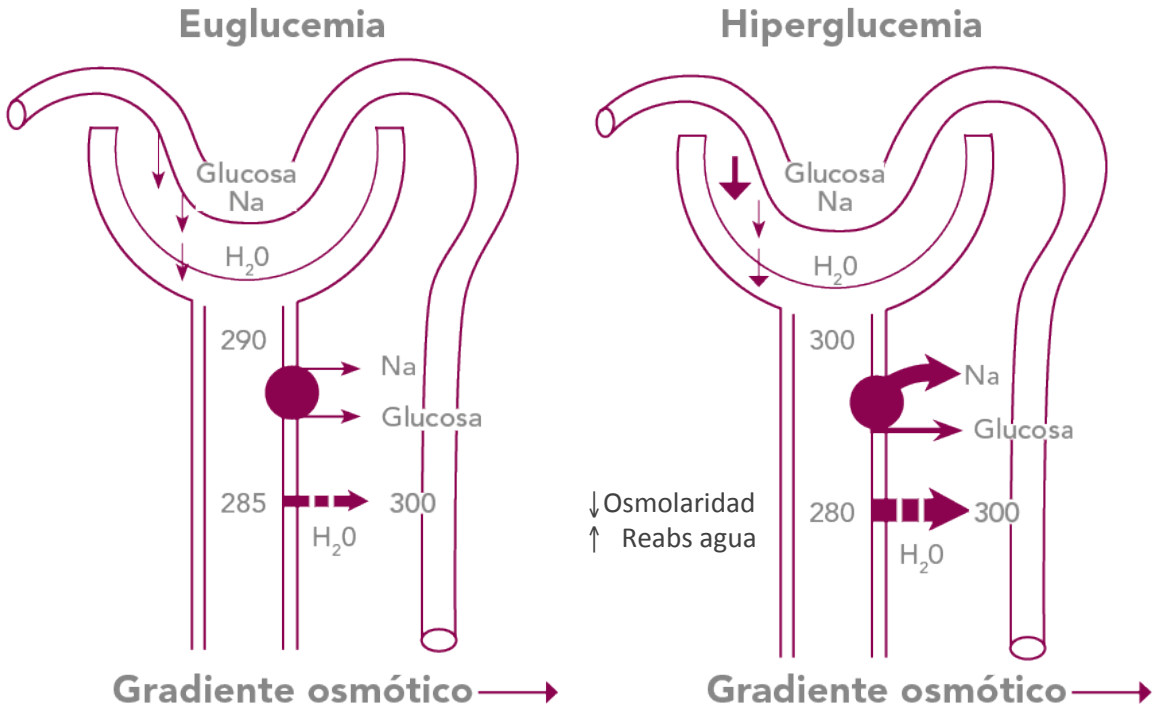


From BENEDICT-and DEMAND trials. Iohexol plasma clearance

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

Hiperglucemia e hiperfiltración



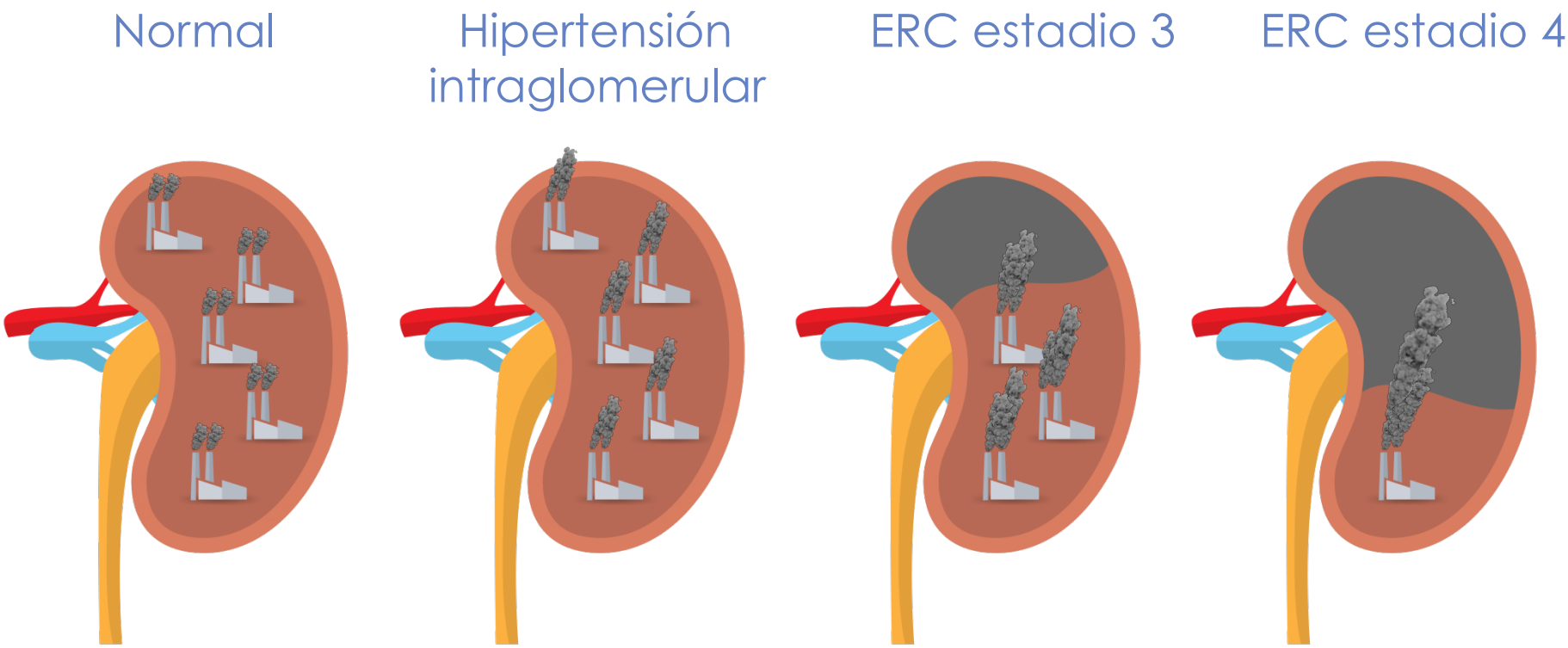
Hiperfiltración:
- ↑**Volemia**
- Activ SRAA
- Activ Simpático

Mal control glucémico: →
- ↑ Reabsorción tubular de sodio y agua
- Efecto inmediato
- Incluso en aisladas elevaciones de glucemia en pacientes con buen control

La mejoría en el control glucémico mejora la hiperfiltración

Bank N. Kidney Int 1991; 40: 792-807

La hipertensión intraglomerular y la hiperfiltración de la nefrona aislada son los causantes claves de la progresión de la nefropatía diabética



Kanzaki *et al. Hypertension Res* 2015;38:633

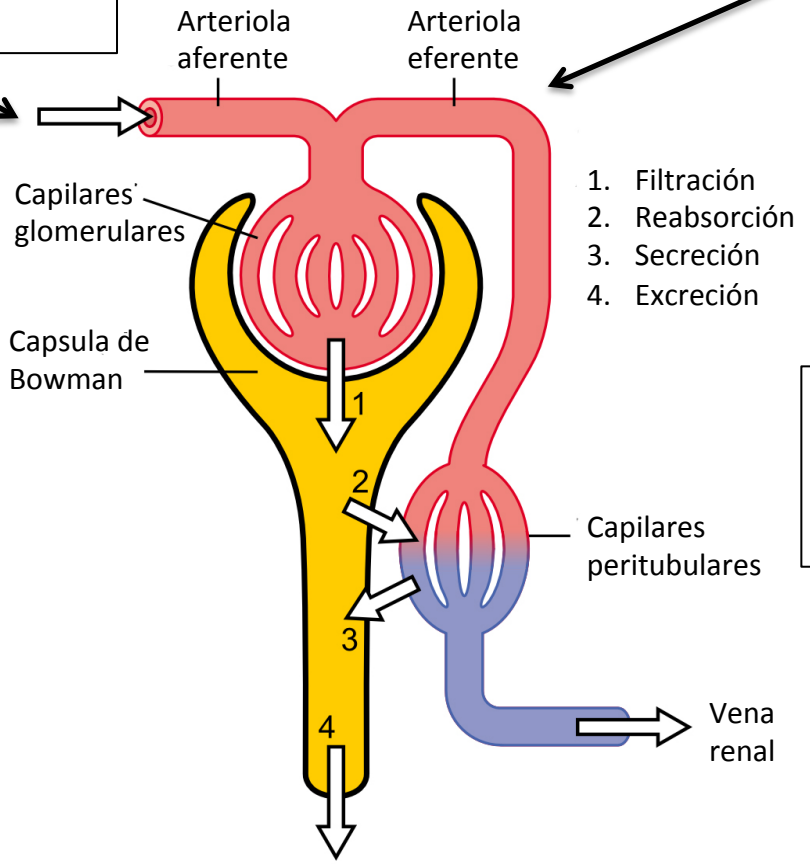
Efecto de los i-SGLT2 sobre la hemodinámica glomerular

Efectos renales de la inhibición del SGLT2. Comparación con efecto de bloqueo SRAA

iSGLT2 → ↑ feedback glomerulotubular

↑ Tono de arteriola aferente
↓ Presión intraglomerular

IECA / ARA II:
↓ tono de la arteriola eferente
↓ presión intraglomerular



1. Filtración
2. Reabsorción
3. Secreción
4. Excreción

↓ Inicial del FGe seguido de estabilización.
↓ Albuminuria

↓ Inicial del FGe seguido de estabilización.
↓ Albuminuria

¿Protección renal?

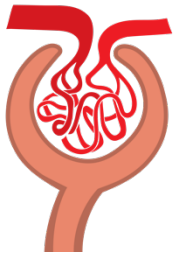
Protección renal

Excreción urinaria
Excreción= filtración–reabsorción + secreción

Mofificado de Wikipedia. User Madero 88 y Perkovic V. Curr Med Res Opin. 2015;31:2219-31. v

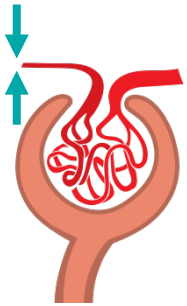
Previsiones – ¡Doble inhibición de SGLT2 y SRAA!

Acciones:



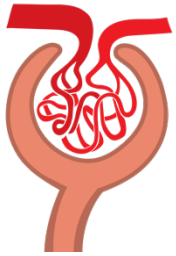
Inhibición de SGLT2

Vasomodulación **aferente**



Implicaciones clínicas:

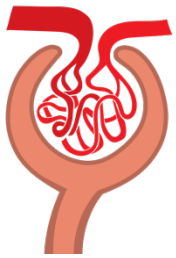
- Presión intraglomerular reducida
- Reducción de la albuminuria
- Nefroprotección sugerida



Bloqueo de SRAA

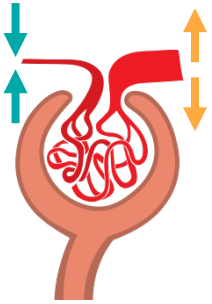
Vasodilatación **eferente**

- Presión intraglomerular reducida
- Reducción de la albuminuria
- Nefroprotección demostrada en múltiples ensayos



Inhibición de SGLT2
y Bloqueo de SRAA

Vasomodulación **aferente**
y Vasodilatación **eferente**

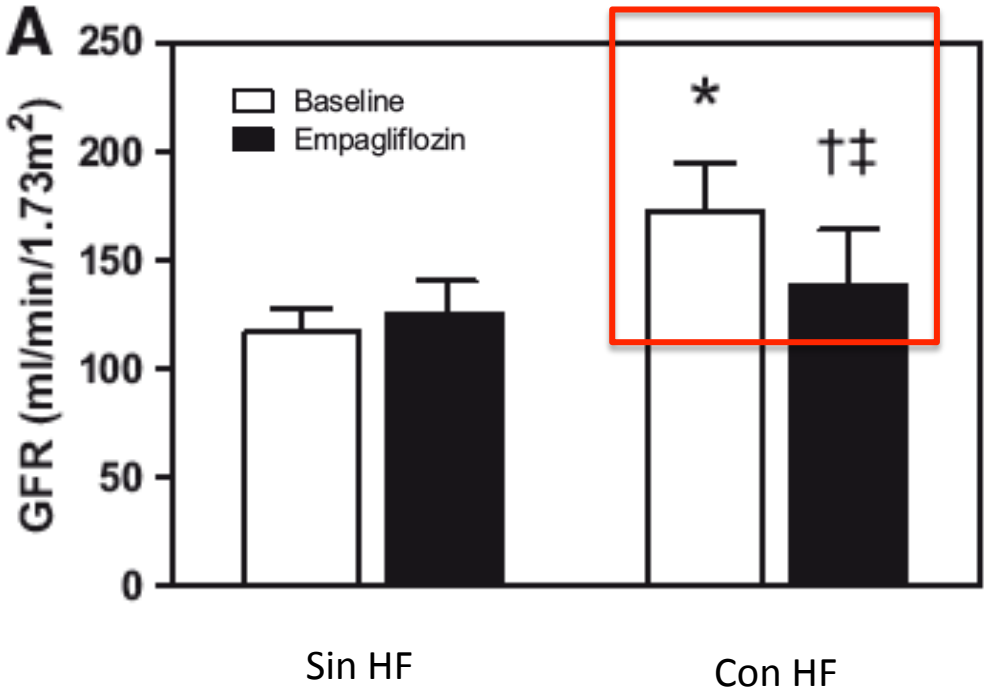


- Potencial para la normalización de la presión intraglomerular
- Reducción aditiva de la presión intraglomerular (?)
- Potencial para nefroprotección a largo plazo (?)

Adaptado de: Cherney D *et al. Circulation* 2014;129:587

Empagliflozina atenua la hiperfiltración (FG) en diabéticos con hiperfiltración sin producir cambios en pacientes sin hiperfiltración (modelo clamp euglicémico)

Cambios en filtrado glomerular
tras 8 semanas con empagliflozina



40 pacientes DM1
SGLT2 inh (empagliflozin):
↓ FG: 33 ml/min/1.73 m2
↓ Oxido nitrico
↓ Flujo plasmático renal

No se detectaron cambios en pacientes sin hiperfiltración

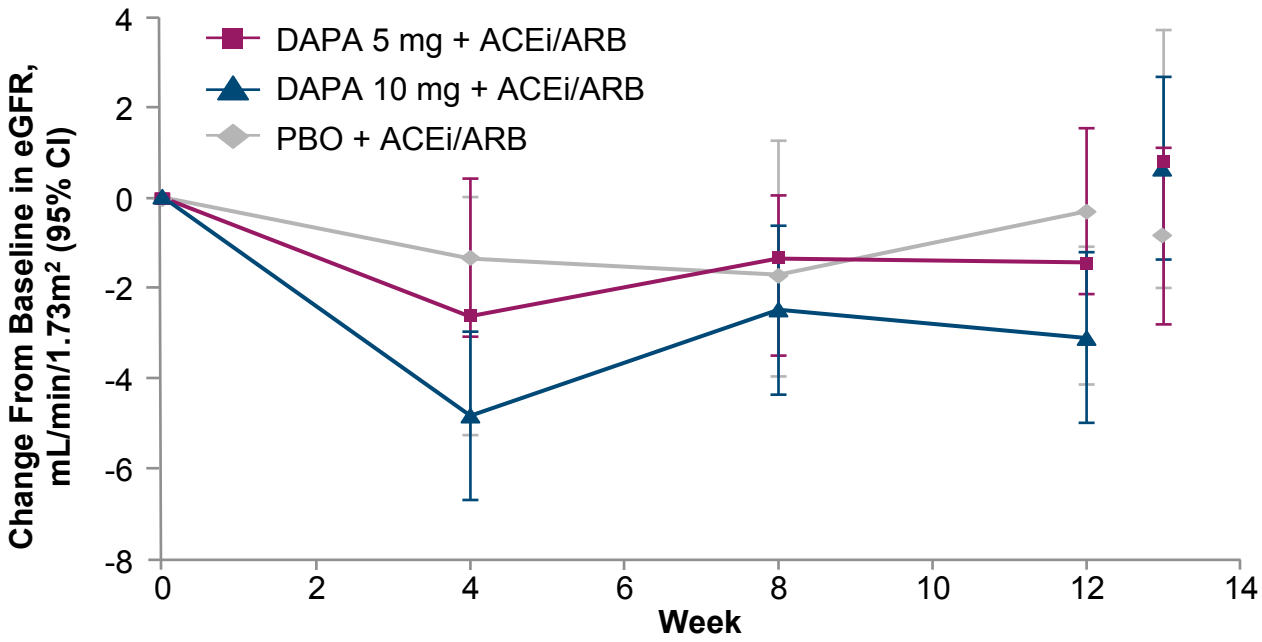
Probablemente por mec de feedback tubulo-glomerular

HF: hiperfiltración
FG: filtrado glomerular

Cherney DZI. Circulation 2014; 129: 587-597

The effect of dapagliflozin on eGFR[1]

Adjusted percentage change from baseline in eGFR over time



n	Baseline	Week 4	Week 8	Week 12	Follow-up (Week 13)
DAPA 5 mg + ACEi/ARB	85	80	79	74	74
DAPA 10 mg + ACEi/ARB	165	163	154	153	147
PBO + ACEi/ARB	186	1847	172	163	157

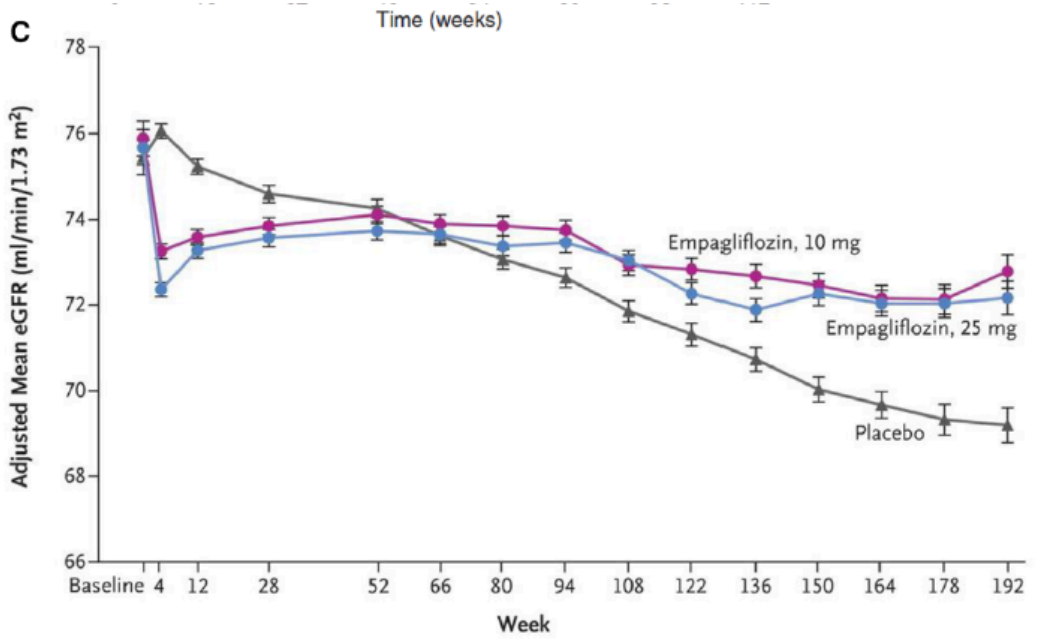
Lambers Heerspink HJ *et al*. *Diabetes Obes Metab*. 2016 Jun;18(6):590-74 .

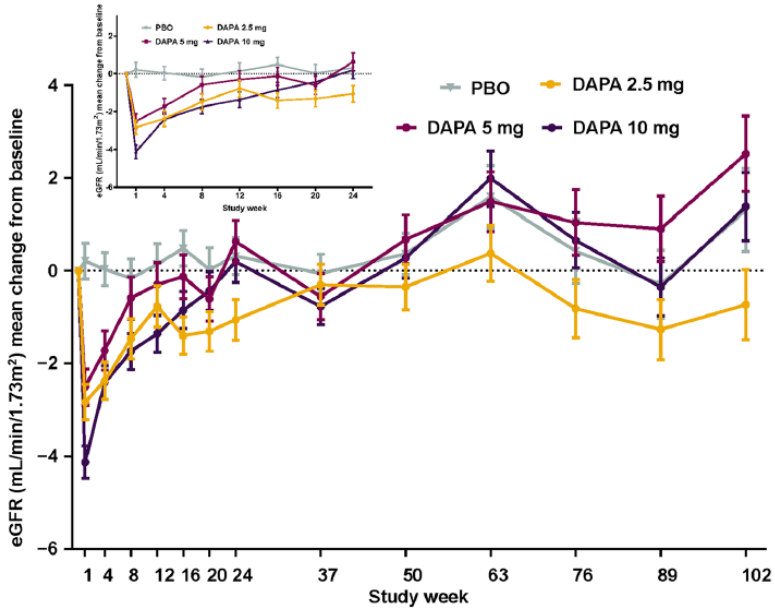
At the 1-week follow-up after discontinuation, relative to baseline, eGFR slightly increased by 0.9 percent (95% CI, -2.0 to 3.7) and 0.7 (95% CI, -1.4 to 2.7) in the dapagliflozin 5 mg and dapagliflozin 10 mg groups, respectively, and decreased by 0.9 (95% CI, -2.8 to 1.1) in the PBO group[1]

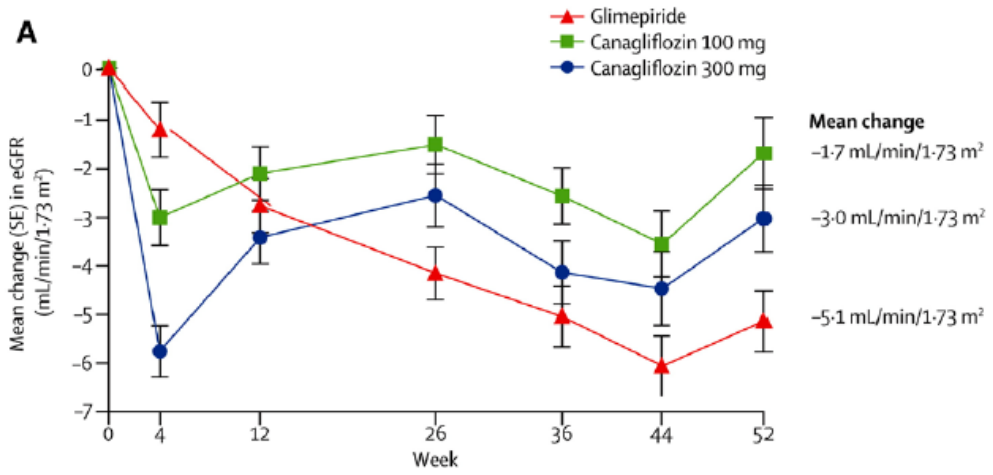
eGFR=estimated glomerular filtration rate; DAPA=dapagliflozin; ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; PBO=placebo.

1. Lambers Heerspink HJ *et al*. Poster presented at: American Diabetes Association 75th Scientific Sessions; June 5-9 2015; Boston, MA. Poster 1176-P.

Efecto de la inhibición SGLT2 sobre el filtrado glomerular estimado



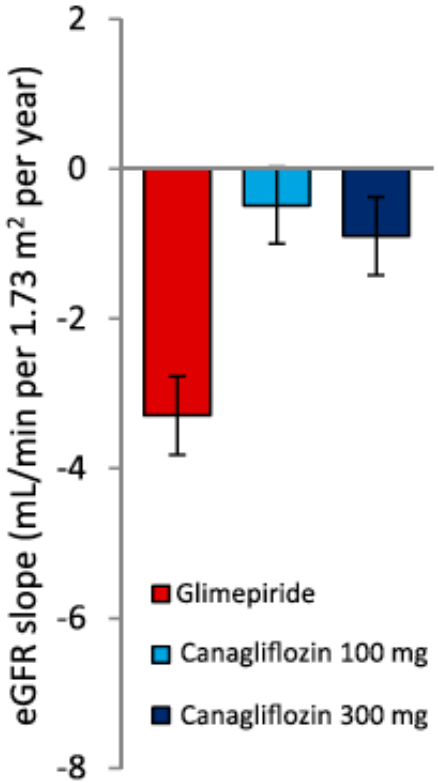




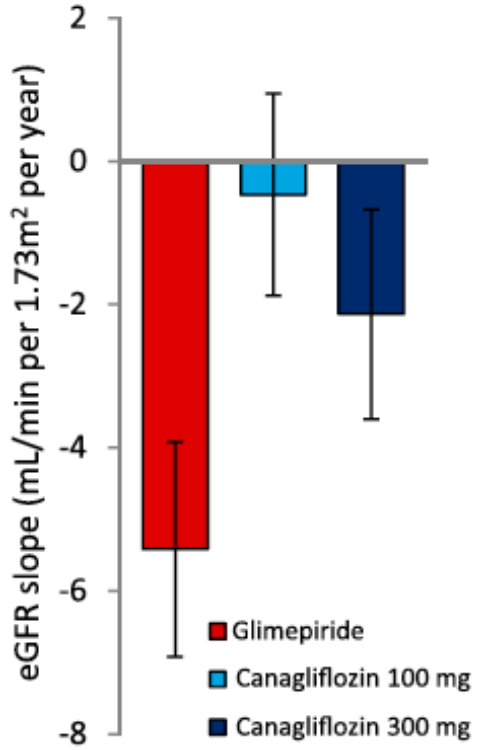
Wanner CN Engl J Med. 2016 Jul 28;375(4):323-34; Kohan DE. Kidney Int. 2014;85:962–971; Cefalu WT. Lancet. 2013;382:941–950;

Efecto de la inhibición SGLT2 (canagliflozina) sobre el filtrado glomerular

Overall population

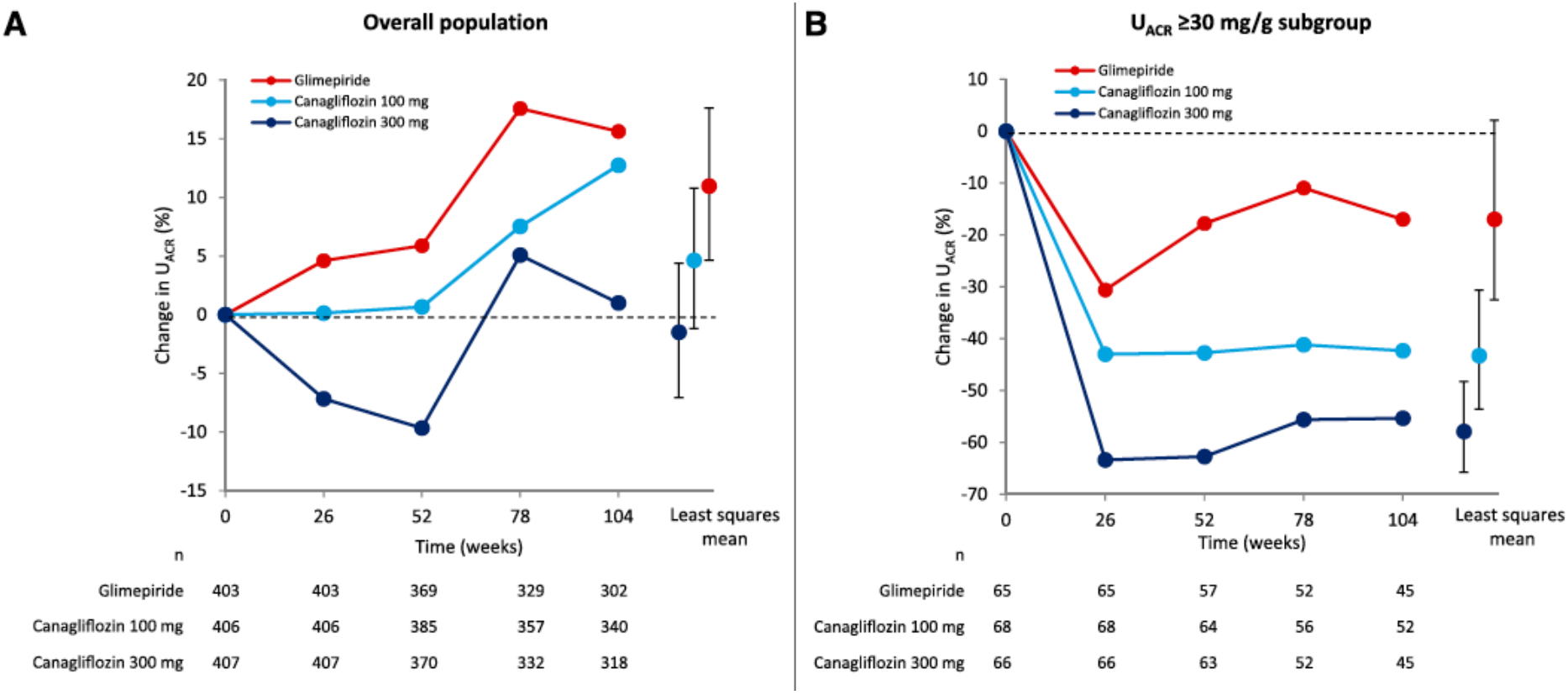


U_{ACR}≥30 mg/g subgroup



Heerspink HL. J Am Soc Nephrol. 2016 Aug 18. [Epub ahead of print]

Efecto de canagliflozina sobre la albuminuria, comparado con glimepirida

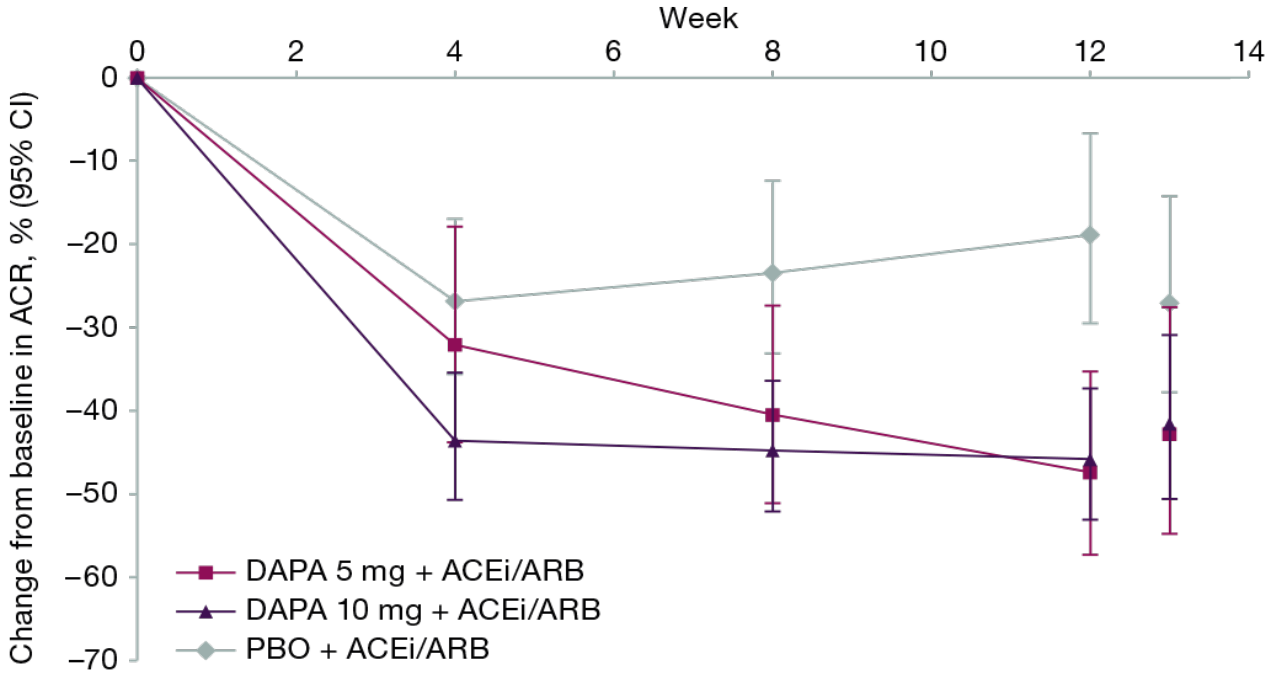


Pooling analysis, canagliflozin trials

Heerspink HL. J Am Soc Nephrol. 2016 Aug 18. [Epub ahead of print]

Efecto de dapagliflozina vs placebo sobre albuminuria en pacientes con HTA y DM2 en tratamiento con bloqueo SRA

Adjusted Percent Change from Baseline in ACR over Time



P<0.05

ACR, mg/g	n	Baseline	Week 4	Week 8	Week 12	Follow-up (Week 13)
380 ± 843	DAPA 5 mg + ACEi/ARB	85	81	79	73	74
419 ± 948	DAPA 10 mg + ACEi/ARB	165	160	124	153	144
320 ± 674	PBO + ACEi/ARB	185	182	172	163	158

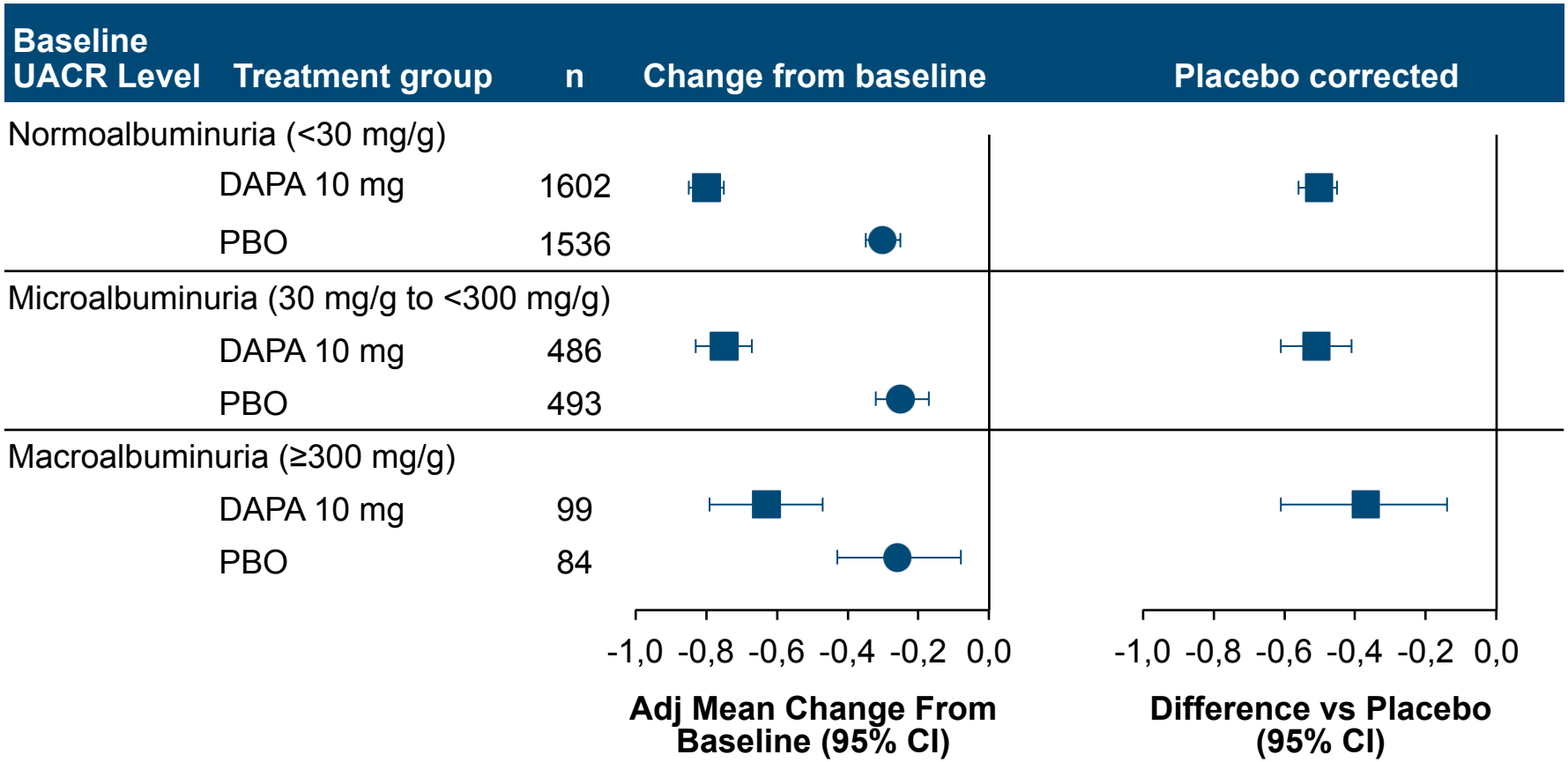
ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin:creatinine ratio; ARB, angiotensin receptor blocker; DAPA, dapagliflozin; PBO, placebc

Post hoc analysis of two phase III clinical trials with hypertensive T2DM patients

Lambers Heerspink Y, et al. Diabetes Obes Metab. 2016 Mar 3. [Epub ahead of print]

Placebo-corrected results for HbA_{1C} reductions were similar across all baseline albuminuria levels[1]

HbA_{1C} Change and Difference Versus Placebo at Week 24 by Baseline UACR Level



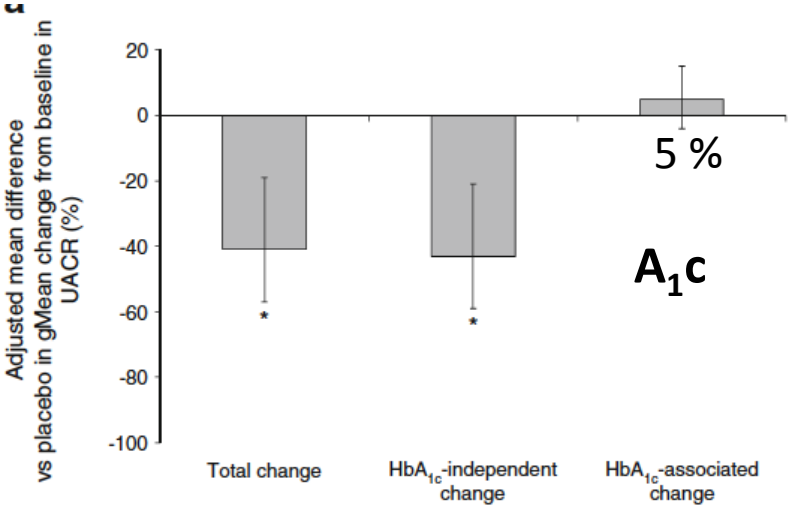
Adapted from Parikh S, *et al.* 2015.

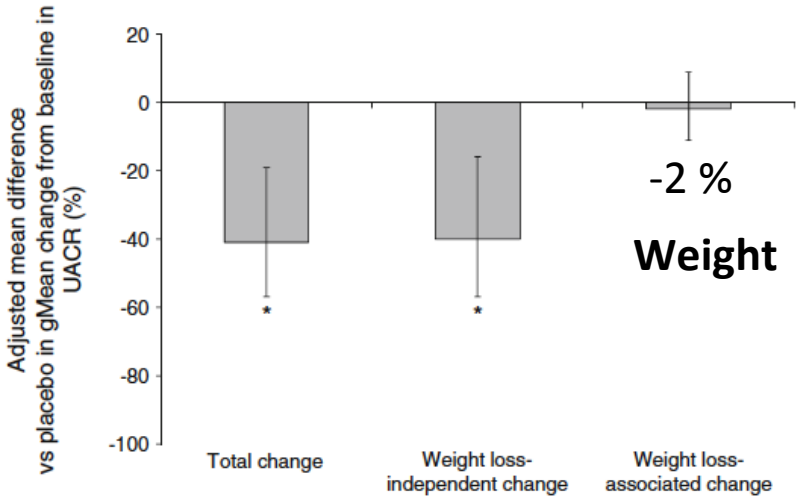
P value for treatment-by-UACR interaction was 0.5696[1]

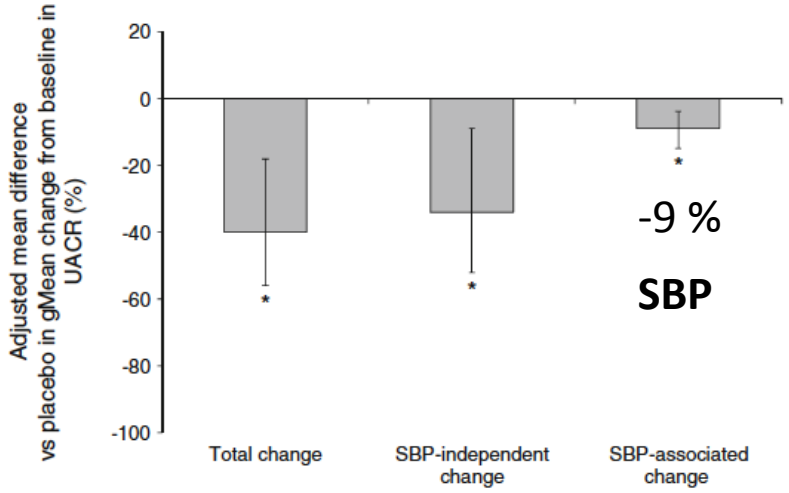
ANCOVA model, excluding data after rescue (LOCF). n is the number of subjects with nonmissing baseline and Week 24 (LOCF) values.
Adj=adjusted; HbA1c=glycated hemoglobin; UACR=urine albumin:creatinine ratio; DAPA=dapagliflozin; PBO=placebo; LOCF=last observation carried forward; CI=confidence interval.

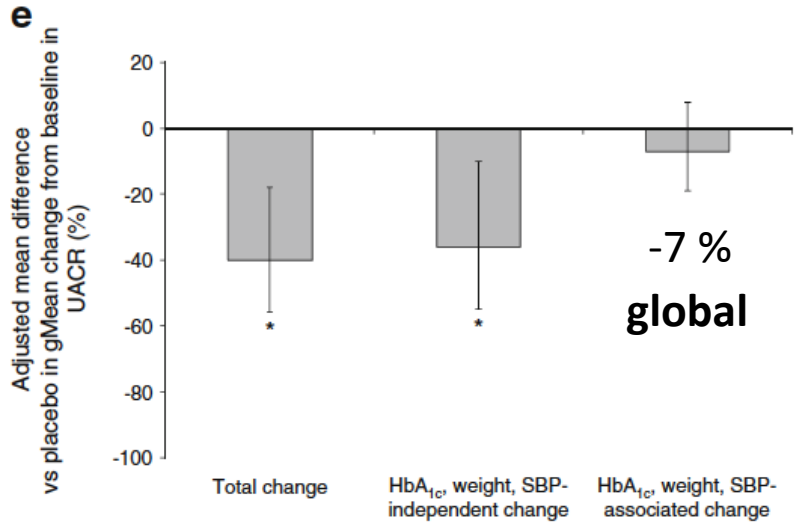
1. Parikh S *et al.* Presented at: American Diabetes Association 75th Scientific Sessions; June 5-9 2015; Boston, MA.

Contribución de los cambios de HbA1c, peso y PA sistólica a los cambios en la albuminuria (pacientes con macroalbuminuria)*









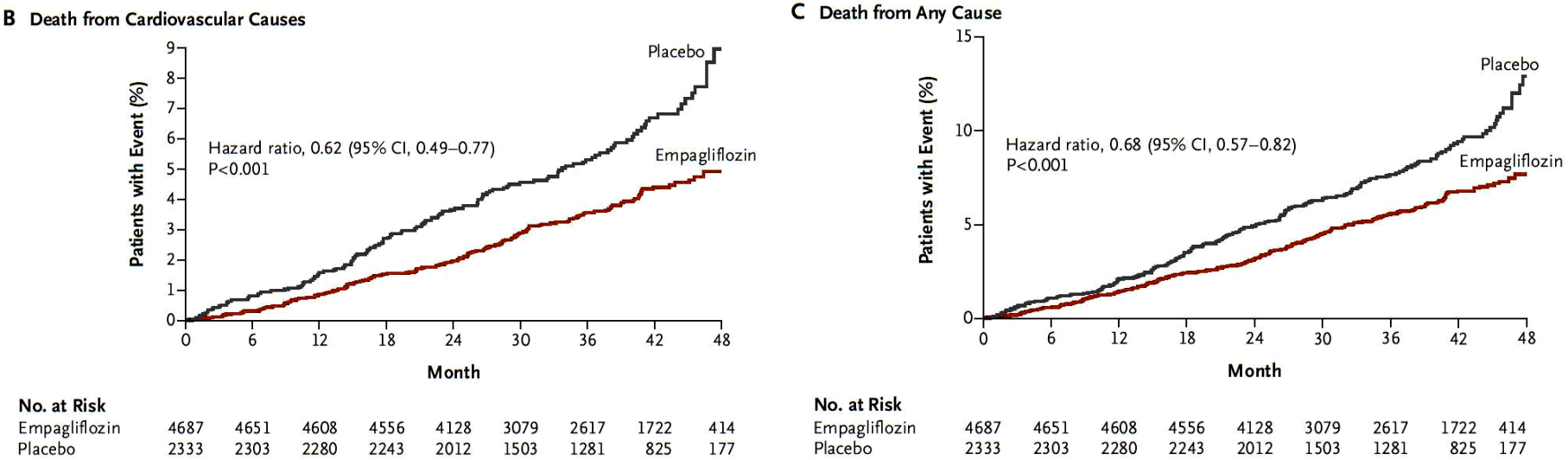
*similar in patients with albuminuria

Pooling data from 5 RCT, **empagliflozin**

Cherney D. Diabetologia. 2016 Sep;59(9):1860-70

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG OUTCOME

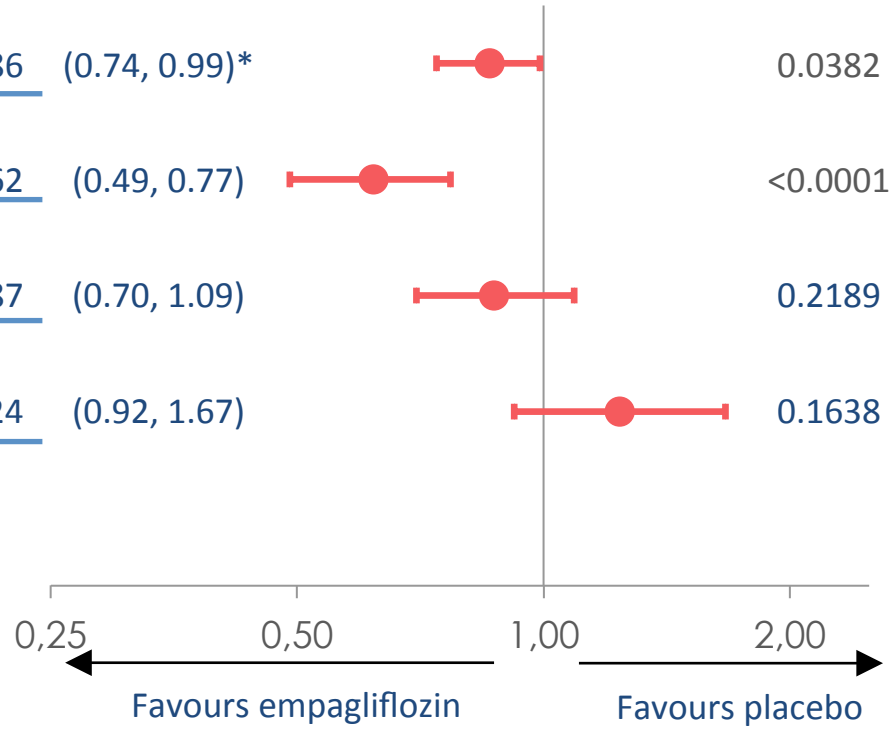


- DM tipo 2 con alto riesgo CV.
- 7020 pacientes
- Inclusión: Enf CV previa: IMA, enf coronaria, ictus, angina o en vasc periferica
- Empagliflozina 10 mg, 25 mg o placebo
- End-point 1º: muerte CV, IMA no mortal, ictus no mortal
- End-point 2º: 1º + hospitalización por angina inestable.

Zinman B. N Engl J Med. 2015 Nov 26;373(22):2117-28

EMPA REG OUTCOME: Muerte CV, IAM y ACV

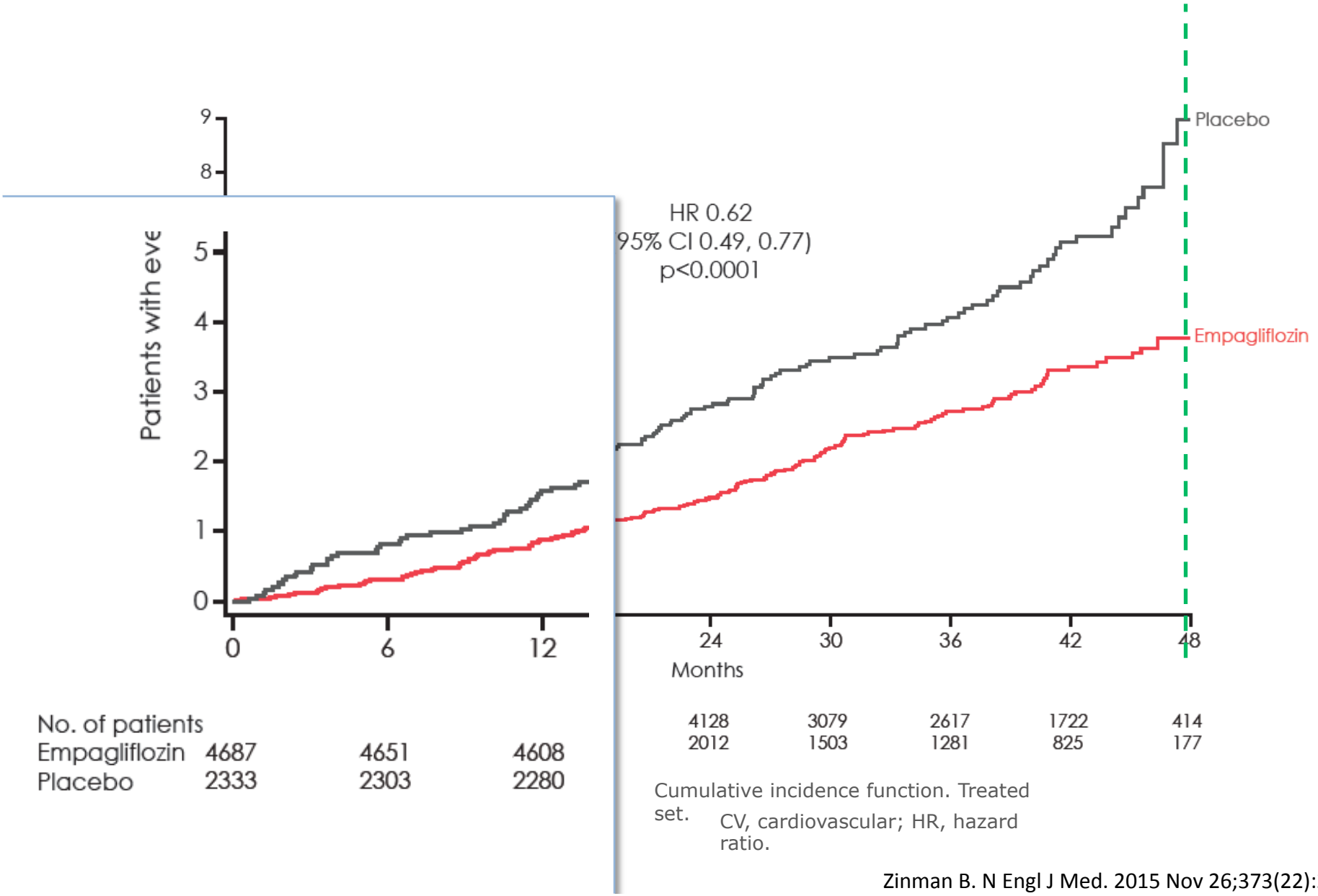
	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

Zinman B. N Engl J Med. 2015 Nov 26;373(22):2117-28

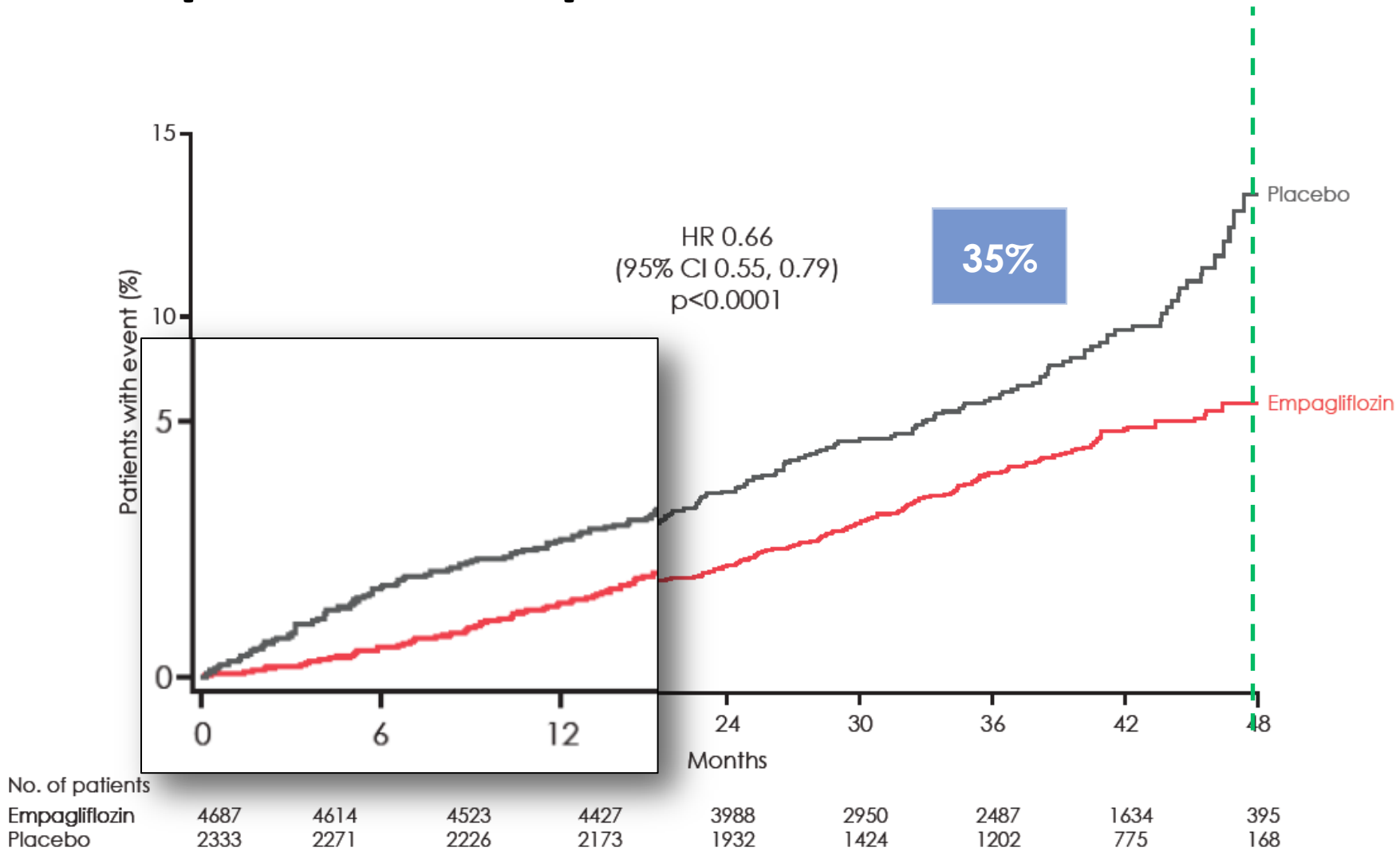
Muerte CV



Cumulative incidence function. Treated set. CV, cardiovascular; HR, hazard ratio.

Zinman B. N Engl J Med. 2015 Nov 26;373(22):2117-28

Hospitalización por insuficiencia cardiaca



Cumulative incidence function. Treated set.
CV, cardiovascular; HR, hazard ratio.

Zinman B. N Engl J Med. 2015 Nov 26;373(22):2117-28

Dapagliflozin y efectos cardiovasculares

Overview of study designs with Dapagliflozin

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 10 mg (n=5936) or control (n=3403)

Kosiborod *et al.* 2015[2]

- Pooled data from 5 Phase 2b/3 clinical trials 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)

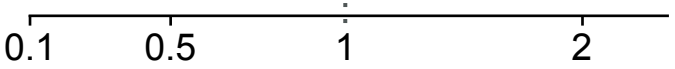
DECLARE[4-6]

- A multi-centre trial to evaluate the effect of dapagliflozin on CV events
- Estimated completion in 2019
- n=17267
- Patients randomly allocated dapagliflozin 10 mg or placebo

1. Sonesson C, *et al. Cardiovasc Diabetol.* 2016;15:37.
2. Kosiborod M, *et al.* ADA 2015 Poster 1211-P.
3. Zinman B, *et al. N Engl J Med.* 2016;374:1094
4. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed March 2016.
5. US Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM379659.pdf. Accessed March 2016.
6. TIMI Study Group. http://www.timi.org/index.php?page=declare-timi-58. Accessed March 2016

Meta-analysis shows consistent effect of dapagliflozin on CV events[1]

Event	DAPA Meta-analysis*		Favors DAPA ← • → Control	DAPA HR vs Control (95% CI)*
	DAPA N=5936	Control N=3403		
MACE plus UA	176			(0.79) (0.58, 1.1)
MACE	134			0.77 (0.54, 1.1)
CV death	20	18		0.70 (0.36, 1.36)
MI	30	33		0.57 (0.34, 0.95)
Stroke	25	18		1.00 (0.54, 1.86)
Hospitalization for heart failure	10	16		0.36 (0.16, 0.84)



21 Phase IIb/III trials, n=9339

Adapted from Sonesson C, *et al.* 2016.

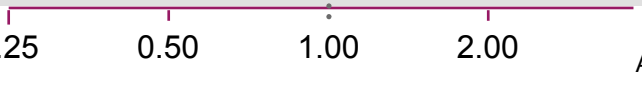
All three composite endpoints give consistent results providing comprehensive assurance of reduced risk of CV events. The results are consistent with the results of the 3 previously-conducted CV meta-analyses.[1]

*All Phase 2b and 3 Pool, ST + LT -30MU; Stratified by study; Only trials with at least one positively adjudicated event included in analysis; Cox Proportional Hazards model. †Cox regression analysis. ‡ 95.02% CI.
MACE=Major Adverse Cardiovascular Event; HR=hazard ratio; CV=cardiovascular; MI=myocardial infarction; CI=confidence interval.
1. Sonesson C, *et al. Cardiovasc Diabetol.* 2016;15:37.

Empagliflozin improves CV outcomes compared to placebo[1]

EMPA-REG OUTCOME: Key results

	Patients with event				
	Empagliflozin (n=4687)	Placebo (n=2333)	Favors EMPA ← • → Placebo	HR (95%CI)	p-value
MACE	490	282		0.86 (0.74, 0.99)*	0.0382
CV death	172	137		0.62 (0.49, 0.77)	<0.0001
Non-fatal MI	213	121		0.87 (0.70, 1.09)	0.2189
Non-fatal stroke	150	60		1.24 (0.92, 1.67)	0.1638
4-P MACE	599	333		0.89 (0.78, 1.01)*	0.0795
Hospitalization for heart failure	126	95		0.65 (0.50, 0.85)	0.0017



* 95.02% CI.

Adapted from Zinman B, *et al.* 2016.

Patients with T2DM and CVD history who received empagliflozin, as compared with placebo, had a lower rate of the primary composite CV outcome and of death from any cause when added to standard care.[1]

1. Zinman B, *et al. N Engl J Med.* 2016;374:1094.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

- Doble ciego, controlado con placebo.
- Empagliflozina 10 mg, 25 mg o placebo
- DM tipo 2 con alto riesgo CV con FGe > 30 ml/min/1.73 m2
- 7020 pacientes (placebo: 2333, Empa 10 mg: 2345, Empa 25 mg: 2342)
- 48 sem

- **End points microvasculares: retinopatía y nefropatía**

Wanner C. New Engl J Med 2016, June 14

Methods: microvascular and renal outcomes

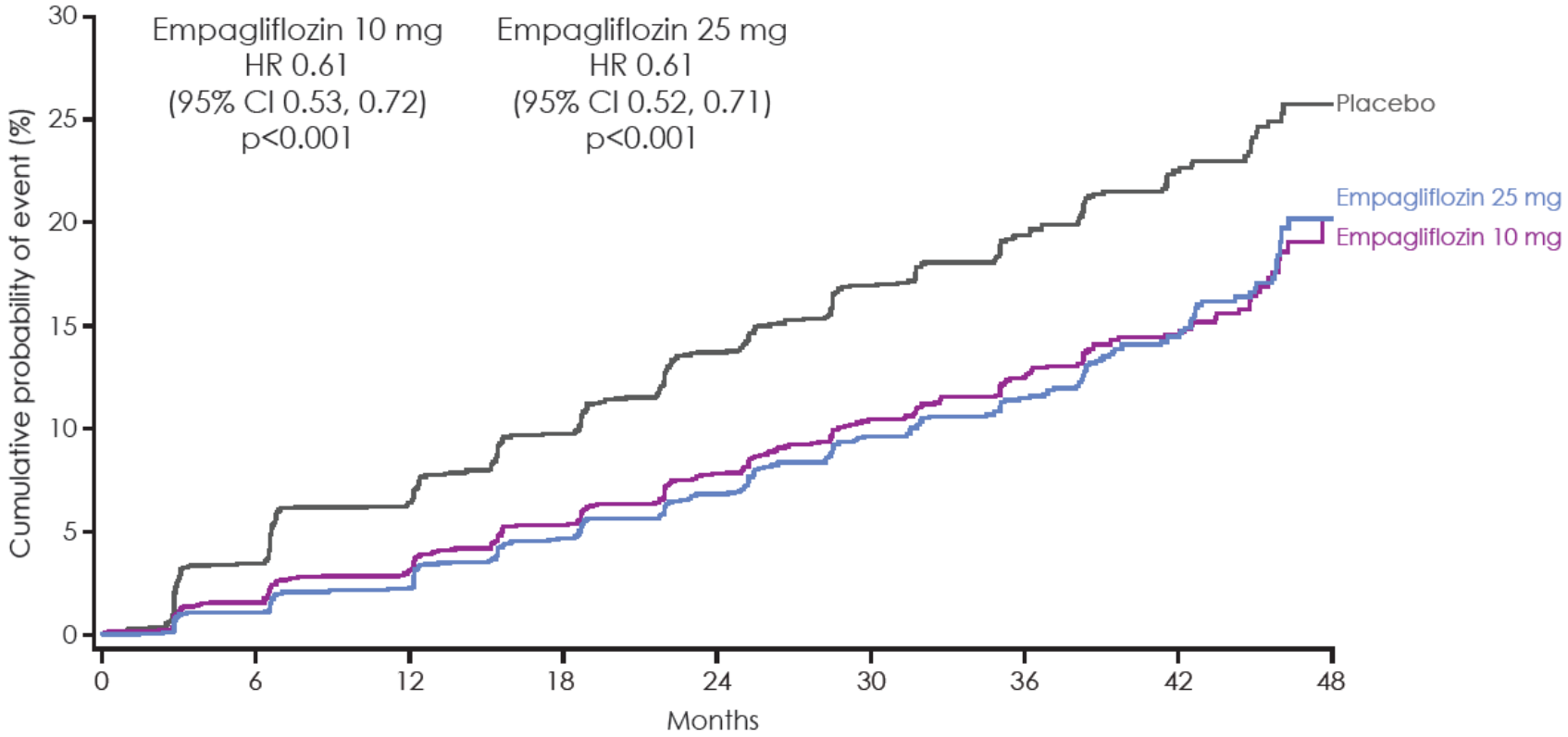
- **Composite microvascular endpoint** (a secondary outcome):
  - composite of initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or
  - incident or worsening nephropathy

  - **Incident or worsening nephropathy** was defined as:
    - Progression to macroalbuminuria (UACR >300 mg/g) or
    - Doubling of serum creatinine + eGFR ≤45 mL/min/1.73m^2 or
    - Initiation of renal replacement therapy or
    - Death due to renal disease
  - **Other microvascular outcomes**
    - Individual components / composite of incident /worsening nephropathy / death.
    - Composite of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease
    - Incident albuminuria (UACR ≥30 mg/g) in patients with normoalbuminuria at baseline
    - eGFR (CKD-EPI) over time

UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Wanner C. New Engl J Med 2016, June 14

New onset or worsening nephropathy

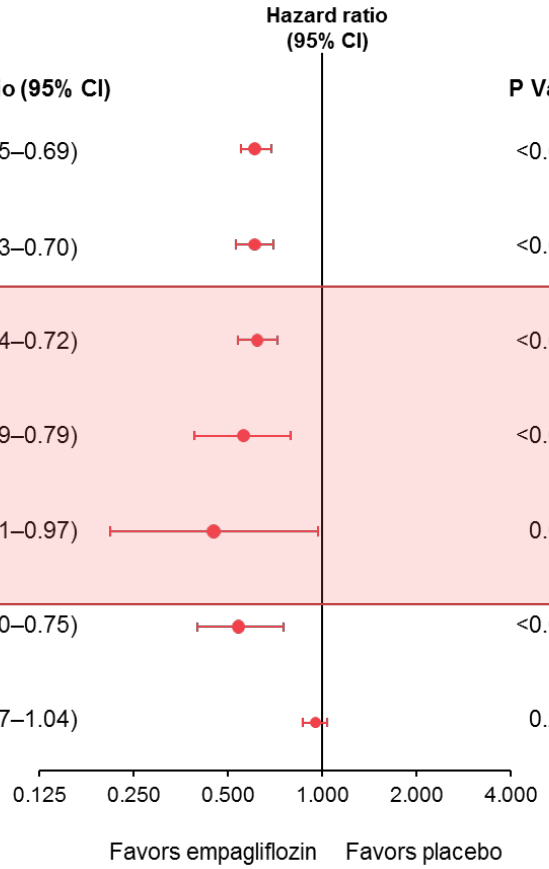


No. of patients									
Empagliflozin 10 mg	2055	1991	1912	1825	1571	1122	922	593	136
Empagliflozin 25 mg	2069	2003	1936	1844	1600	1157	965	626	154
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Kaplan-Meier estimate. Patients treated with at least one dose of study drug. Hazard ratios are based on Cox regression analyses.
HR, hazard ratio; CI, confidence interval. Pre-specified analyses.

Renal outcomes

	Empagliflozin		Placebo			
	no. with event/ analyzed (%)	*rate/1000 patient-yr*	*no. with event/ analyzed (%)*	*rate/1000 patient-yr*	**Hazard Ratio (95% CI)**	**P Value**
New or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
New or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2)	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2), initiation of renal replacement therapy or death due to renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
New onset of albuminuria in patients with normoalbuminuria at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

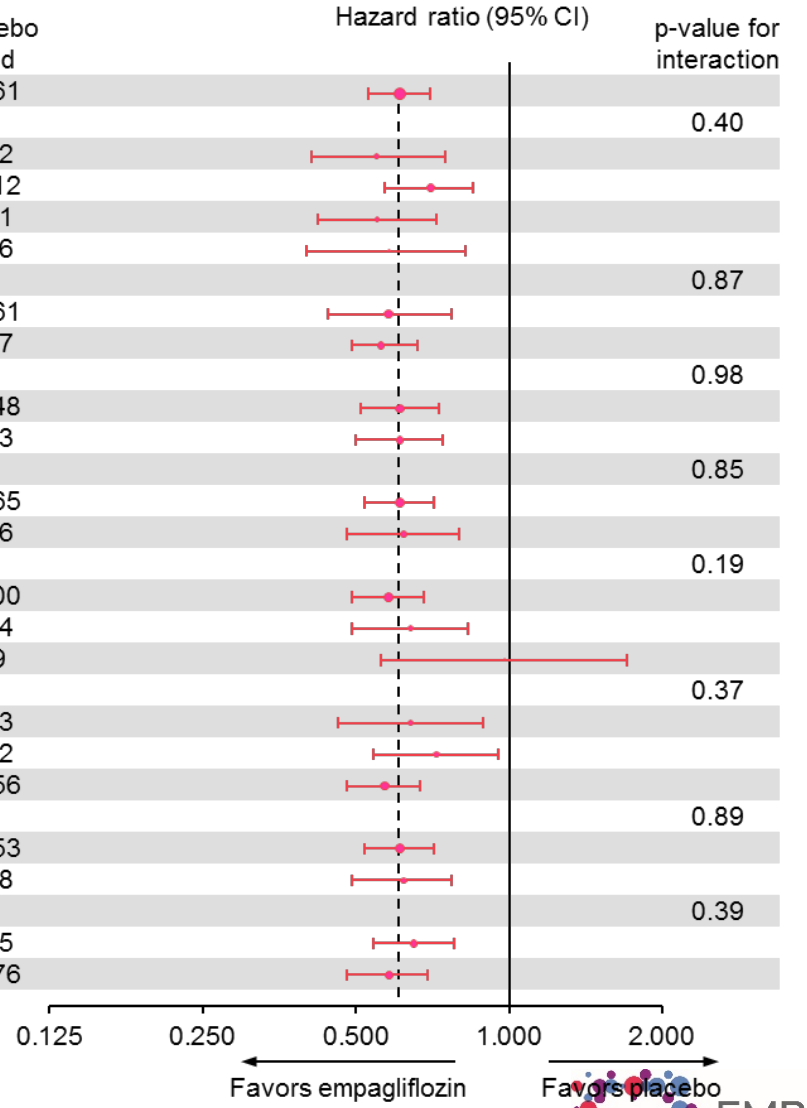


Cox regression analyses in patients treated with ≥1 dose of study drug. Analyses were pre-specified except for the composite of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease.
eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

EMPA-REG OUTCOME®

Subgroup analyses for new onset or worsening nephropathy (1/2)

	Empagliflozin	Placebo	p-value for interaction
	Patients analyzed		
All patients	4124	2061	
Estimated glomerular filtration rate			0.40
≥90 mL/min/1.73m^2	962	452	
60 to <90 mL/min/1.73m^2	2179	1112	
45 to <60 mL/min/1.73m^2	707	341	
<45 mL/min/1.73m^2	276	156	
Urine albumin-to-creatinine ratio			0.87
<30 mg/g	2737	1361	
≥30 mg/g	1344	687	
Age			0.98
<65 years	2306	1148	
≥65 years	1818	913	
Sex			0.85
Male	2924	1465	
Female	1200	596	
Race			0.19
White	3024	1500	
Asian	865	444	
Black/African-American	205	99	
Time since diagnosis of type 2 diabetes			0.37
≤5 years	771	383	
>5 to 10 years	1067	522	
> 10 years	2286	1156	
Glycated hemoglobin			0.89
<8.5%	2847	1453	
≥8.5%	1277	608	
Body mass index			0.39
<30 kg/m^2	2009	985	
≥30 kg/m^2	2115	1076	

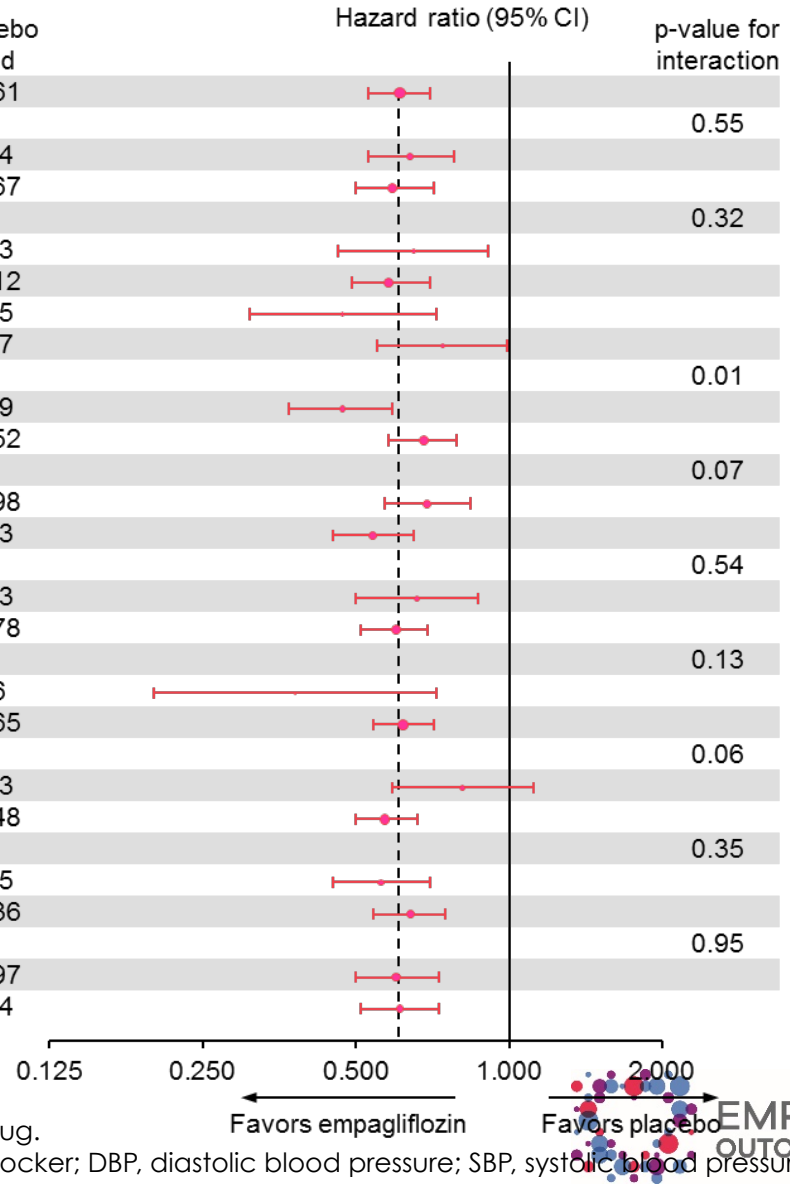


Cox regression analyses in patients treated with ≥1 dose of study drug.

EMPA-REG OUTCOME®

Subgroup analyses for new onset or worsening nephropathy (2/2)

	Empagliflozin Patients analyzed	Placebo Patients analyzed	p-value for interaction
All patients	4124	2061	
Blood pressure control			0.55
SBP ≥140 mmHg and/or DBP ≥90 mmHg	1476	794	
SBP <140 mmHg and DBP <90 mmHg	2648	1267	
Cardiovascular risk			0.32
Only cerebrovascular disease	556	283	
Only coronary artery disease	2450	1212	
Only peripheral artery disease	349	165	
2 or 3 high cardiovascular risk categories	741	377	
Metformin			0.01
No	1044	509	
Yes	3080	1552	
Insulin			0.07
No	2203	1098	
Yes	1921	963	
Statins and/or ezetimibe			0.54
No	900	483	
Yes	3224	1578	
Anti-hypertensive therapy			0.13
No	219	96	
Yes	3905	1965	
ACE inhibitor and/or ARB			0.06
No	792	413	
Yes	3332	1648	
Beta-blockers			0.35
No	1428	725	
Yes	2696	1336	
Diuretics			0.95
No	2350	1197	
Yes	1774	864	



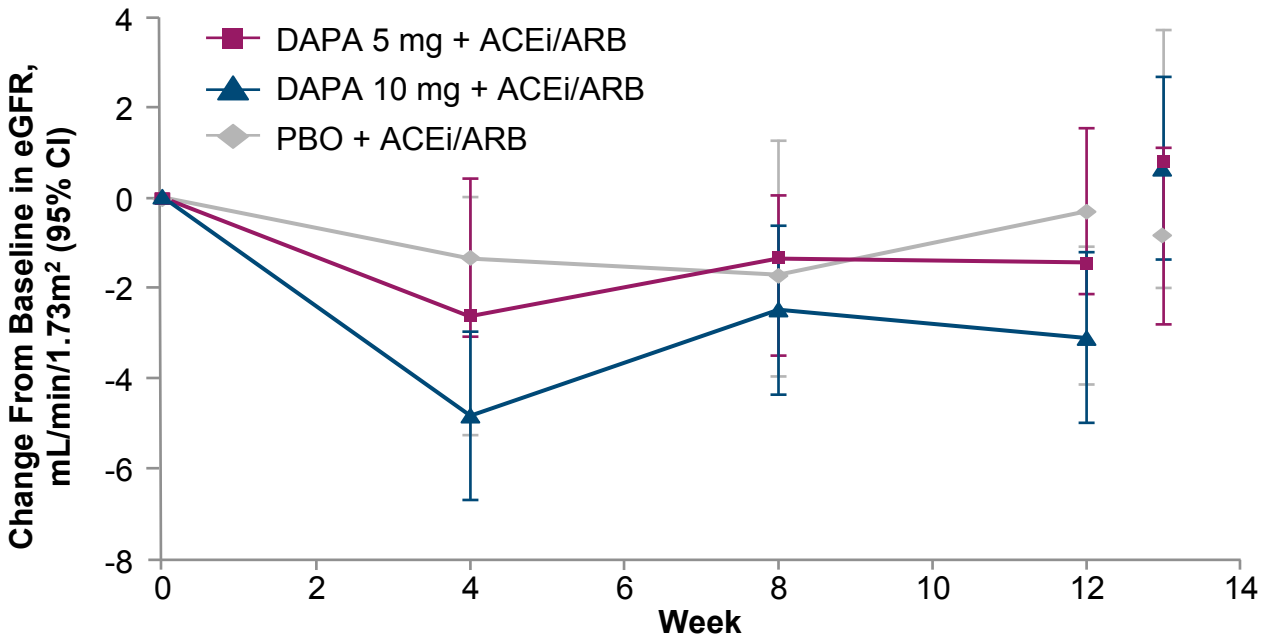
Cox regression analyses in patients treated with ≥1 dose of study drug.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

EMPA-REG OUTCOME®

The effect of dapagliflozin on eGFR[1]

VIEW STUDY DETAILS

Adjusted percentage change from baseline in eGFR over time



n	Baseline	Week 4	Week 8	Week 12	Follow-up (Week 13)
DAPA 5 mg + ACEi/ARB	85	80	79	74	74
DAPA 10 mg + ACEi/ARB	165	163	154	153	147
PBO + ACEi/ARB	186	1847	172	163	157

Lambers Heerspink HJ *et al*. *Diabetes Obes Metab*. 2016 Jun;18(6):590-74 .

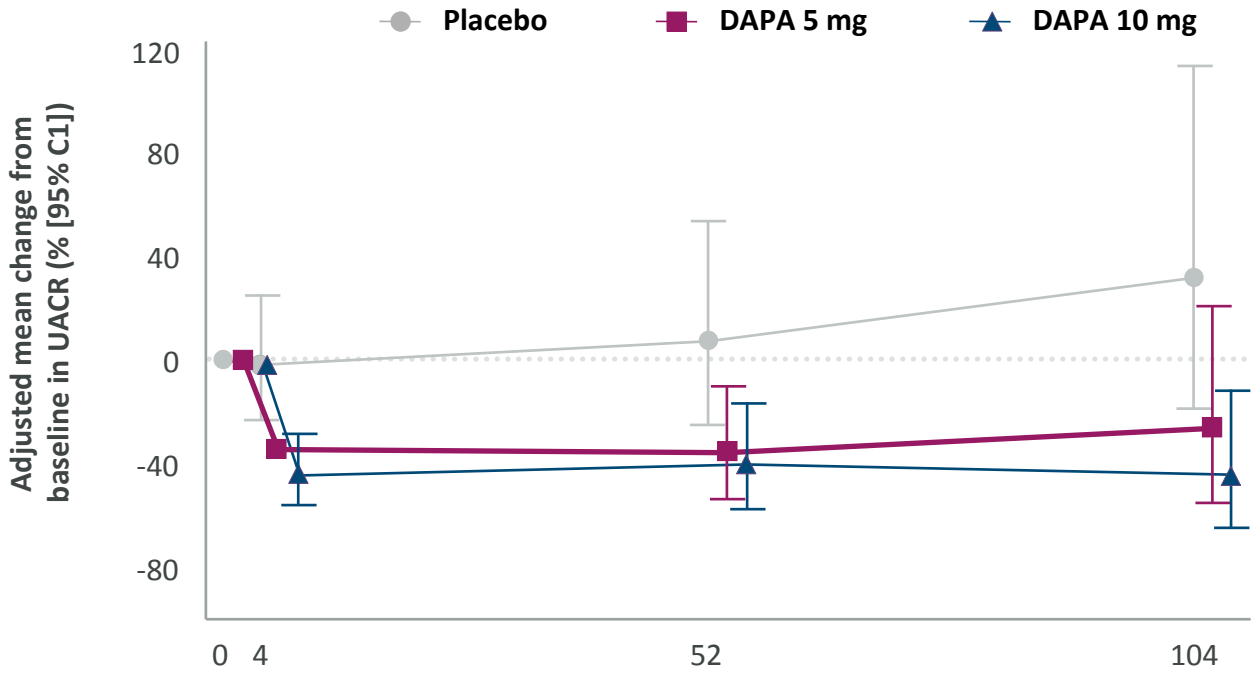
At the 1-week follow-up after discontinuation, relative to baseline, eGFR slightly increased by 0.9 percent (95% CI, -2.0 to 3.7) and 0.7 (95% CI, -1.4 to 2.7) in the dapagliflozin 5 mg and dapagliflozin 10 mg groups, respectively, and decreased by 0.9 (95% CI, -2.8 to 1.1) in the PBO group[1]

eGFR=estimated glomerular filtration rate; DAPA=dapagliflozin; ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; PBO=placebo.

1. Lambers Heerspink HJ *et al*. Poster presented at: American Diabetes Association 75th Scientific Sessions; June 5-9 2015; Boston, MA. Poster 1176-P.

The effect of dapagliflozin on albuminuria over 2 years in patients with renal impairment (CKD3) compared with placebo[1]

VIEW STUDY DETAILS



Week 104 Δ UACR

31.0 (−19.0, 111.9)

−26.4 (−55.0, 20.5)

−43.9 (−64.3, −12.0)

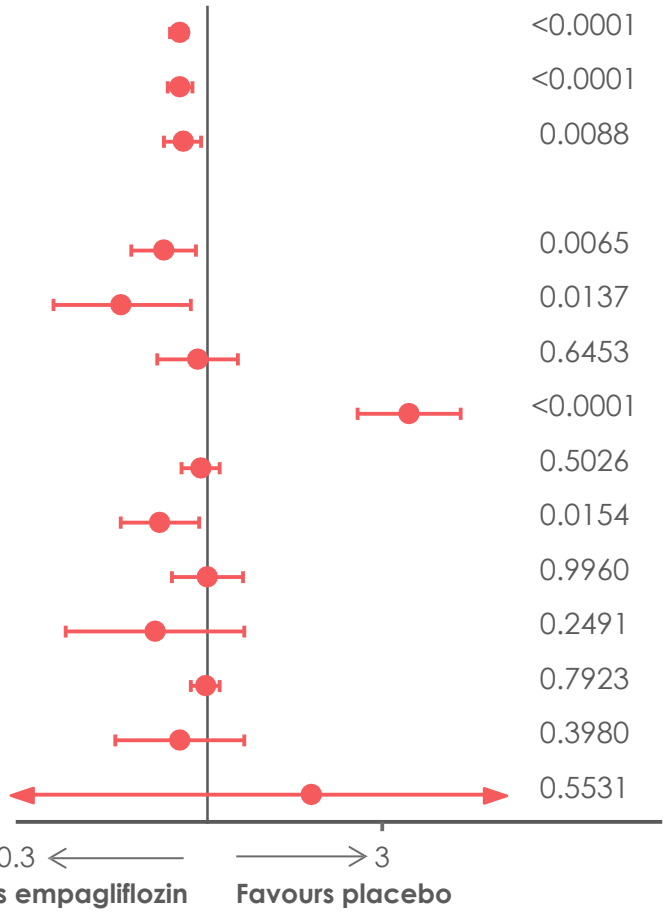
Number of Patients per Time Point					Baseline UACR
Placebo	56	49	31	25	698.0 mg/g
DAPA 5 mg	53	50	39	20	727.1 mg/g
DAPA 10 mg	56	52	40	29	604.4 mg/g

Includes data after rescue.
DAPA=dapagliflozin; UACR=urinary albumin:creatinine ratio.
1. Fioretto P *et al. Diabetologia DOI 10.1007/s00125-016-4017-1* ..

EMPA-REG OUTCOME safety summary

Event rate (per 100 patient-years)

	Empagliflozin (N=4687)	Placebo (N=2333)	IRR (95% CI)	*p*-value
Total AE	149.34	178.67	0.84 (0.79, 0.88)	<0.0001
Serious AE	18.79	22.34	0.84 (0.78, 0.91)	<0.0001
AE leading to discontinuation	7.09	8.26	0.86 (0.76, 0.96)	0.0088
Safety topic of interest				
Acute renal failure	2.09	2.77	0.76 (0.62, 0.93)	0.0065
Acute kidney injury	0.37	0.64	0.58 (0.38, 0.90)	0.0137
Bone fractures	1.52	1.61	0.94 (0.73, 1.21)	0.6453
Genital infection	2.61	0.73	3.55 (2.57, 4.91)	<0.0001
Urinary tract infection	7.88	8.21	0.96 (0.85, 1.08)	0.5026
Hepatic injury	1.42	1.91	0.74 (0.58, 0.95)	0.0154
Volume depletion	2.04	2.04	1.00 (0.80, 1.25)	0.9960
Venous embolic/thrombotic events	0.25	0.35	0.72 (0.41, 1.26)	0.2491
Confirmed hypoglycaemia	13.98	14.16	0.99 (0.90, 1.08)	0.7923
Hypoglycaemia requiring assistance	0.53	0.63	0.84 (0.56, 1.26)	0.3980
Diabetic ketoacidosis	0.03	0.02	1.92 (0.21, 17.17)	0.5531



IRR, incidence rate ratio. Patients who received ≥1 dose of study drug
Data on file. **For internal use only**

Incidence of serious renal AEs in patients with renal impairment (CKD3)[1]

VIEW STUDY DETAILS

	PBO (n=2153)			DAPA 10 mg (n=2224)		
UACR level	Normal	Microalbuminuria	Macroalbuminuria	Normal	Micro	Macro
Number of patients	1565	508	90	1636	496	103
Genital infections	10 (0.6)	3 (0.6)	0	98 (6.0)	30 (6.0)	1 (1.0)
Urinary tract infections	51 (3.3)	24 (4.7)	2 (2.2)	69 (4.2)	30 (6.0)	4 (3.9)
Hypotension/dehydration/ hypovolemia	10 (0.6)	4 (0.8)	2 (2.2)	18 (1.1)	5 (1.0)	3 (2.9)
Renal impairment/failure	26 (1.7)	13 (2.6)	3 (3.3)	44 (2.7)	19 (3.8)	12 (11.7)
Blood creatinine increased	3 (0.2)	4 (0.8)	2 (2.2)	6 (0.4)	5 (1.0)	3 (2.9)
CrCl decreased	10 (0.6)	6 (1.2)	1 (1.1)	18 (1.0)	7 (1.4)	3 (2.9)
GFR decreased	3 (0.2)	0	0	6 (0.4)	0	1 (1.0)
Renal function test abnormal	0	0	0	0	0	1 (1.0)
Cystatin-C increased	0	0	0	1 (<0.1)	1 (0.2)	0
Urine output decreased	1 (<0.1)	0	0	0	0	0
Renal failure	2 (0.1)	0	0	1 (<0.1)	22 (4.4)	3 (2.9)
Renal impairment	8 (0.5)	3 (0.6)	1 (1.1)	11 (0.7)	7 (1.4)	2 (1.9)
Renal failure, acute	0	1 (0.2)	0	2 (0.1)	0	1 (1.0)
Urine flow decreased	0	0	0	1 (<0.1)	0	0

Adapted from Parikh S, *et al.* 2015.

Renal impairment/failure occurred more frequently in patients taking dapagliflozin with baseline macroalbuminuria[1]

7 of these patients (58.3%) had a baseline eGFR level <60 mL/min/1.73m^2

PBO=placebo; DAPA=dapagliflozin; UACR=urine albumin:creatinine ratio; CrCl=creatinine clearance; GFR=glomerular filtration rate; CKD3=stage 3 chronic kidney disease.
1. Parikh S, *et al.* Presented at: American Diabetes Association 75th Scientific Sessions; June 5-9 2015; Boston, MA.

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

14 Junio 2016

- Antes de iniciar Canaglifllozina o Dapagliflozina se deben considerar los factores predisponentes a presentar deterioro renal agudo (FRA) :
  - Depleción de volumen, insuficiencia renal crónica, insuficiencia cardíaca congestiva, tratamiento con diuréticos, IECAS o ARA II, AINES.

- Estimar la función renal antes de los tratamientos con Dapagliflozina o Canagliflozina y monitorizar durante el seguimiento.
- Si se presenta FRA suspender el fármaco y tratar la causa.

- 101 casos de FRA (73 Cana y 28 Dapa). La mitad en el primer mes de tratamiento. Hospitalizacion en 96.
- Media de elevación de creatinina sérica: + 1.6 mg/dl.
- Suspensión del fármaco en 78 casos con recuperación en 56 (reversibilidad en la mayoria de los casos)

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM507426.pdf

iSGLT2 y depleción de volumen

Depleción de volumen en pacientes tratados con iSGLT2

- Relacionada con:
  - Diuresis osmótica (glucosuria)
  - Natriuresis (↓reabsorción de sodio TCP)
- Mayor riesgo en pacientes con:
  - FG <60 ml/min/1.73 m^2.
  - ≥ 75 años
  - Tratamiento con diuréticos de asa
  - Tratamiento con IECA o ARA II

Oliva RV, Bakris GL. J Am Soc Hypertens 2014; 8: 330-339
Lambers HJ. Diabetes Obes Metab. 2013; (9):853-62
Perkovic V. Curr Med Res Opin. 2015;31:2219-31.
Ficha técnica empagliflozina-Jardiance:
http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf
http://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-empagliflozina-jardiance.pdf

Efecto de diuréticos de asa en hipotensión en pacientes con dapagliflozina

	Loop Diuretic		No Loop Diuretic	
	DAPA N=179	Control N=182	DAPA N=762	Control N=753
eGFR category				
<60 mL/min/1.73 m^2	30.2	33.0	13.6	13.6
≥60 mL/min/1.73 m^2	69.3	67.0	86.4	86.4
Unknown	0.6	0	0	0
Renal impairment/failure[a]	18 (9.9)	10 (5.5)	37 (4.9)	19 (2.5)
• ↓ in creatinine clearance	7 (3.8)	3 (1.6)	13 (1.7)	11 (1.4)
• Renal impairment	6 (3.3)	4 (2.2)	11 (1.4)	5 (0.7)
• Increase blood creatinine	4 (2.2)	2 (1.1)	2 (0.3)	3 (0.4)
Volume depletion[b]	3 (1.6)	3 (1.6)	12 (1.6)	8 (1.0)
Hypotension	2 (1.1)	1 (0.5)	6 (0.8)	2 (0.3)

[a]Based on a predefined list of events

AE, adverse event; DAPA, dapagliflozin; LD, loop diuretic; SAE, serious adverse event

Cefalu WT, et al. ADA 2015 Poster 1216-P

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

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- Estimar la función renal antes de los tratamientos con Dapagliflozina o Canagliflozina y monitorizar durante el seguimiento.
- Si se presenta FRA suspender el fármaco y tratar la causa.

- 101 casos de FRA (73 Cana y 28 Dapa). Hospitalizacion en 96
- Media de elevación de creatinina sérica: + 1.6 mg/dl.
- Suspensión del fármaco en 78 casos con recuperación en 56 (reversibilidad en la mayoria de los casos)

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM507426.pdf

Depleción de volumen en pacientes tratados con iSGLT2

- Relacionada con:
  - Diuresis osmótica (glucosuria)
  - Natriuresis (↓reabsorción de sodio TCP)
- Mayor riesgo en pacientes con:
  - FG <60 ml/min/1.73 m^2.
  - ≥ 75 años
  - Tratamiento con diuréticos de asa
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Oliva RV, Bakris GL. J Am Soc Hypertens 2014; 8: 330-339
Lambers HJ. Diabetes Obes Metab. 2013; (9):853-62
Perkovic V. Curr Med Res Opin. 2015;31:2219-31.
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http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf
http://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-empagliflozina-jardiance.pdf

Inhibición SGLT2 e hipotensión arterial-FRA: precauciones

- Considerar el status volémico (hiper / normo / hipovolémico)
- Considerar la presión arterial (HTA, normo/HTA controlado /hipotenso)
- Informar acerca de la posibilidad de descenso de PA, sincope/ hipotensión ortostática
- Quizá se requiera reducción del tratamiento antihipertensivo previo o incluso suspender fármacos. Realizar ajuste de antiHTA si precisa.
- Considerar posibilidad de descenso de la PA de 3 mmHg (2-6 mmHg).
- Mayor precaución en ancianos o si toman diuréticos de asa (altas dosis).
- Disminuir dosis de diuréticos o suspender si no son necesarios.
- Aconsejar AMPA, especialmente si toman antiHTA.
- Monitorizar la presión arterial mas frecuente en las primeras semanas de tratamiento, especialmente en pacientes con HbA1c de inicio muy elevadas.

Oliva RV, Bakris GL. J Am Soc Hypertens 2014; 8: 330-339
Lambers HJ. Diabetes Obes Metab. 2013; (9):853-62
Perkovic V. Curr Med Res Opin. 2015;31:2219-31.

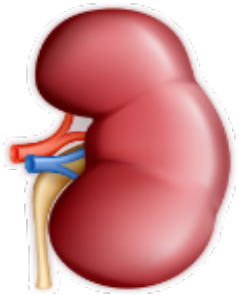
¿Por qué hay un beneficio tan precoz en los pacientes tratados con empagliflozina?

Kidney disease is associated with significant impairment of cardiac function

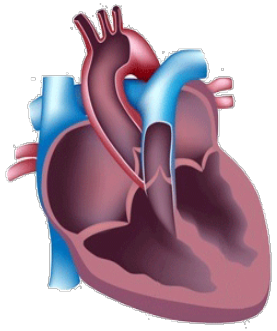
CV events

ACROSS T2D

- Renal and cardiac systems are inextricably linked; acute or chronic disorder of one can induce dysfunction in the other[1]



Organ damage/dysfunction

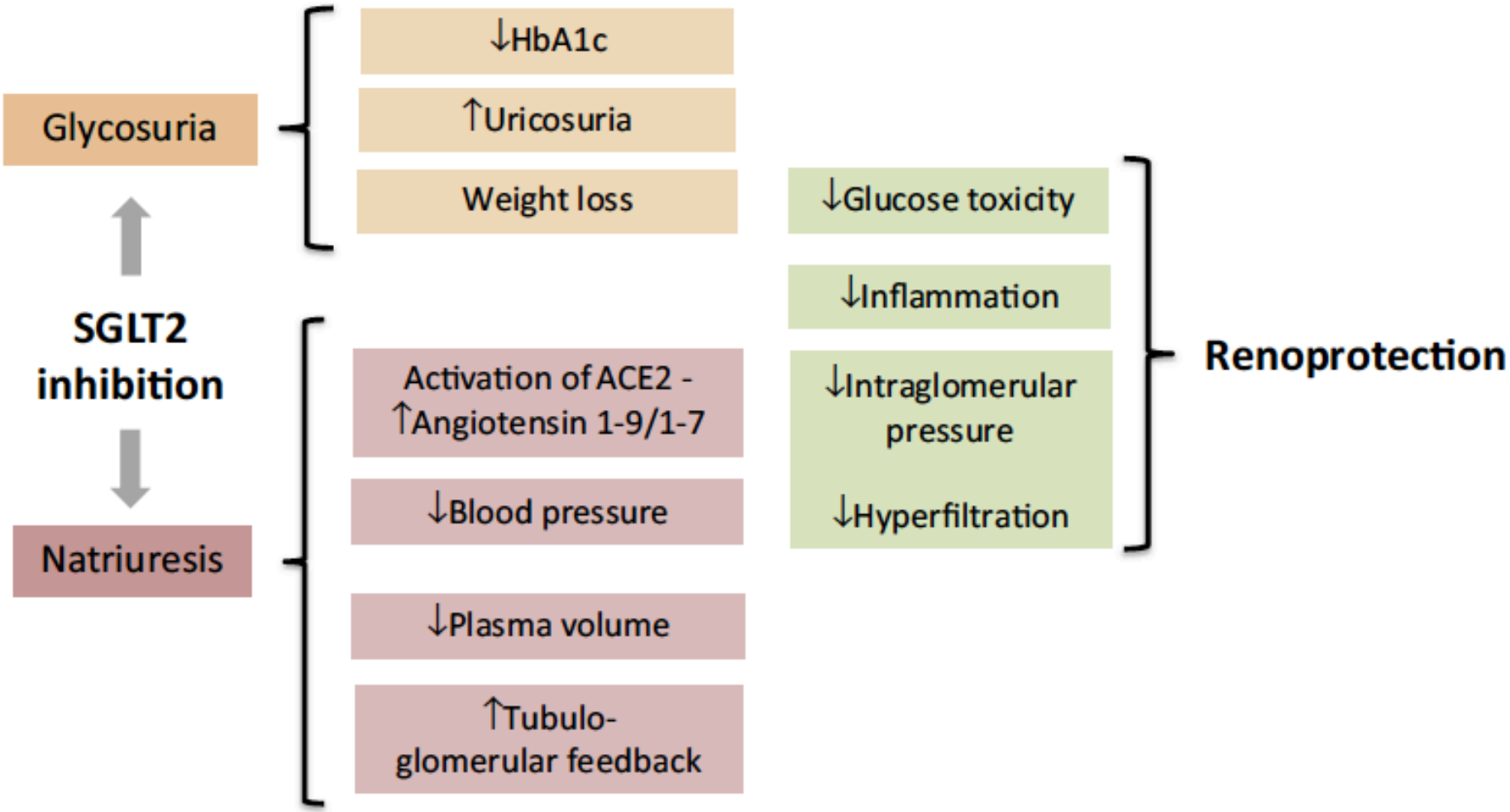


- Elderly patients with CKD are more likely to die of heart disease than advance to ESRD and dialysis[2]

Renal and cardiac systems should be considered together

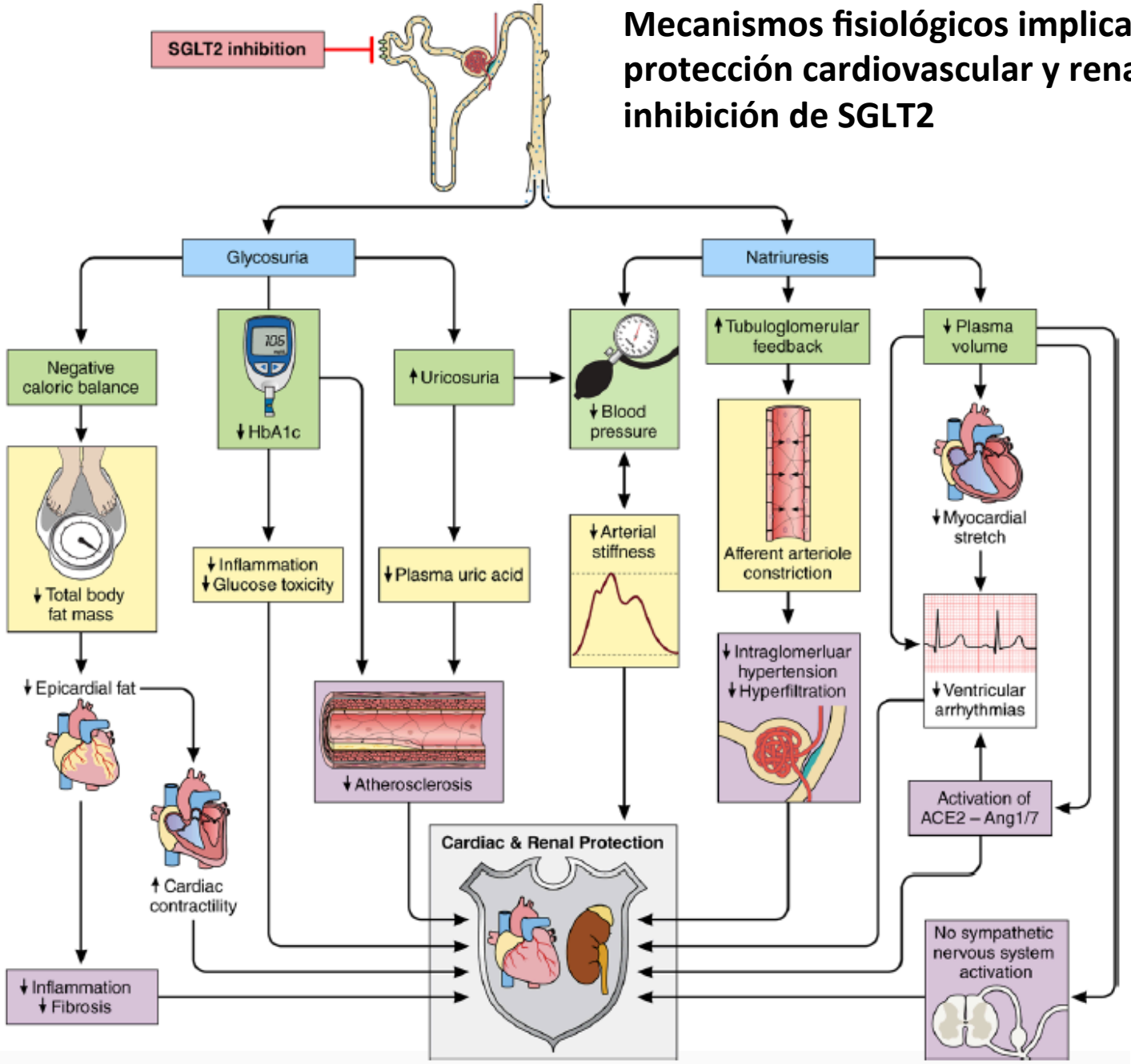
CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease
1. Ronco C *et al*. *J Am Coll Cardiol* 2008;52:1527; 2. Dalrymple L *et al*. *J Gen Intern Med* 2011;26:379

Proposed SGLT2 Inhibition-Mediated Renoprotective Mechanisms



Gnudi L. Trends Endocrinol Metab. 2016 Jul 25

Mecanismos fisiológicos implicados en la protección cardiovascular y renal tras inhibición de SGLT2



Heerspink HL. Circulation. 2016;134:752–772

Mecanismos del beneficio de iSGLT2: multiintervención

- Efecto natriurético: contracción de volumen
- Perdida de peso, glucemia y PA.
- Efectos directos sobre la hemodinámica glomerular (feedback glomerulo-tubular). Potenciación efecto IECA / ARA II.
- Efecto de iSGLT2 sobre rigidez arterial y resistencia vascular.
- Efecto en sistema renal y neurohormonal (no ↑ actividad simpática)
- ↓ ác úrico.
- Mejor de efecto sobre vias alternativas (VD) del SRAA.
- Efecto sobre glucagón.
- ↑β-OH- butirato (mejora de consumo O2 mitocondrial y eficiencia del miocardio)
- Efecto de incremento de hematocrito
- ↓Grasa epicárdica

Wanner C. New Engl J Med 2016, June 14
Muskiet MHA. Lancet Endocrinol 2015; 3: 931
Ferraninni E. J Clin Invest 2014; 124: 499–508
Ferraninni E. Diabetes Care 2016;39:1108–1114
Jordan J. Diabetes 2014;63:A265 [1030-P]. (ADA 2015)
Chilton R. Diabetes Obes Metab. 2015 Dec;17(12):1180-93

Resumen: Estrategias para la reducción de la albuminuria en la nefropatía diabética

- Optimizar el control glucémico.
- Control óptimo de la presión arterial.
- Maximizar el bloqueo del SRAA.
- Evitar sobrepeso/obesidad (dieta y ejercicio físico).
- Dieta hiposódica.
- Evitar el tabaquismo.
- Control de la dislipemia.
- Antialdosterónicos (si lo permite el K y la función renal)
- Otros (colecalciferol?, pentoxifilina? (No en F.T.)
- GLP1-análogos (Leader, Sustain)? (No en F.T.)
- iSGLT2? (No en F.T.)
- En espera de nuevos ensayos con end-points renales