sesiones bibliográficas

medicina interna
25 de octubre de 2019

Junta de Castilla y León

Sacyl

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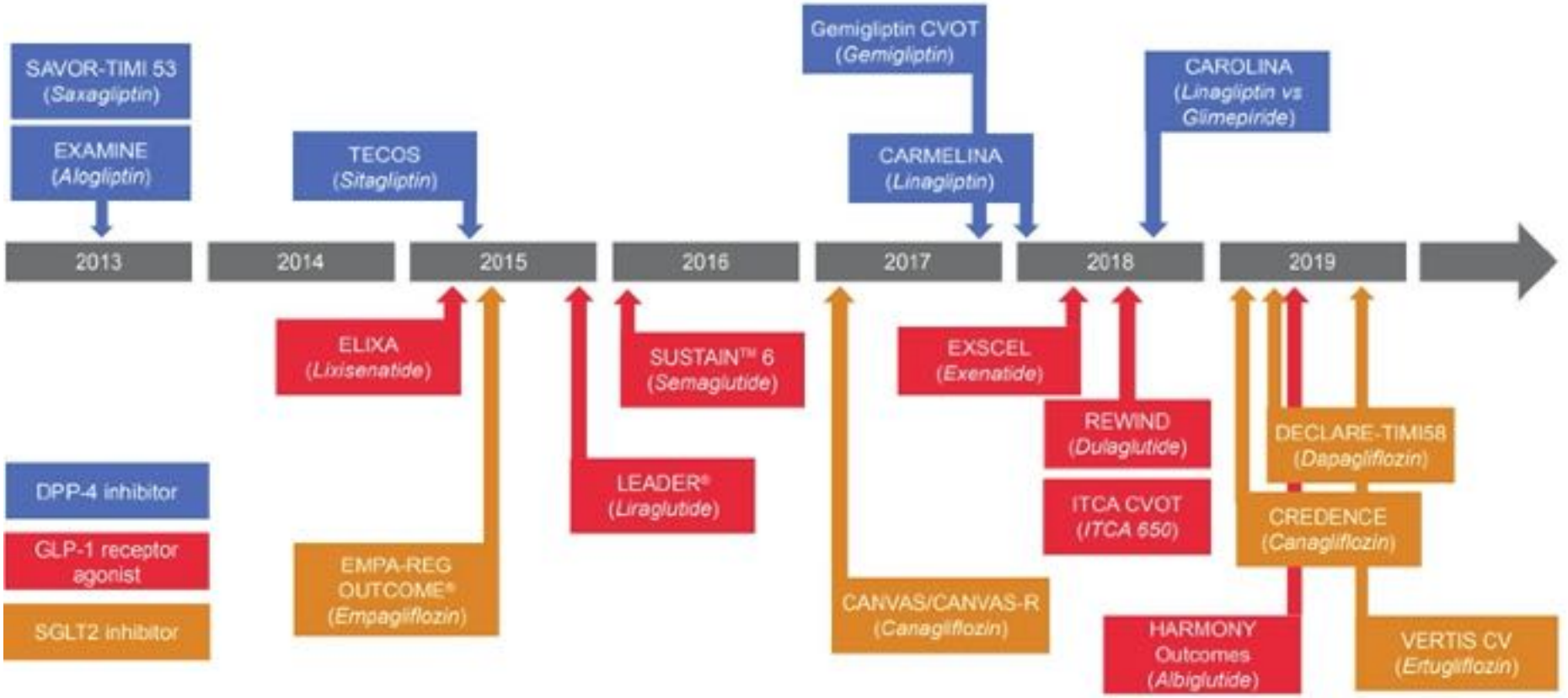
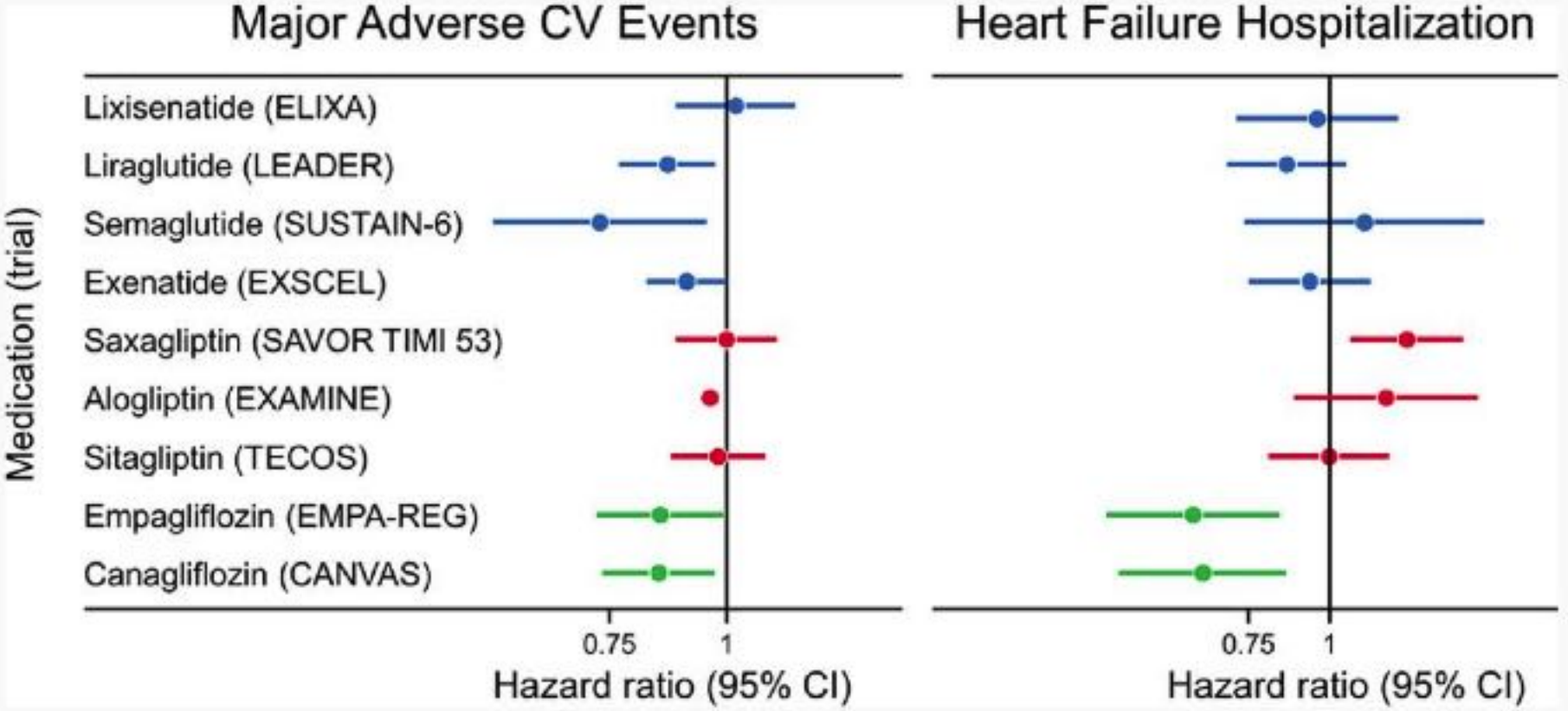

SAVOR-TIMI 53
(Saxagliptin)
EXAMINE
(Alogliptin)
TECOS
(Sitagliptin)
Gemigliptin CVOT
(Gemigliptin)
CARMELINA
(Linagliptin)
CAROLINA
(Linagliptin vs
Glimepiride)
2013
2014
2015
2016
2017
2018
2019
ELIXA
(Lixisenatide)
SUSTAIN™ 6
(Semaglutide)
EXSCEL
(Exenatide)
REWIND
(Dulaglutide)
DECLARE-TIMI58
(Dapagliflozin)
LEADER®
(Liraglutide)
ITCA CVOT
(ITCA 650)
CREDENCE
(Canagliflozin)
DPP-4 inhibitor
GLP-1 receptor
agonist
SGLT2 inhibitor
EMPA-REG
OUTCOME®
(Empagliflozin)
CANVAS/CANVAS-R
(Canagliflozin)
HARMONY
Outcomes
(Albiglutide)
VERTIS CV
(Ertugliflozin)


Major Adverse CV Events
Heart Failure Hospitalization
Medication (trial)
Lixisenatide (ELIXA)
Liraglutide (LEADER)
Semaglutide (SUSTAIN-6)
Exenatide (EXSCEL)
Saxagliptin (SAVOR TIMI 53)
Alogliptin (EXAMINE)
Sitagliptin (TECOS)
Empagliflozin (EMPA-REG)
Canagliflozin (CANVAS)
0.75
1
Hazard ratio (95% CI)
0.75
1
Hazard ratio (95% CI)

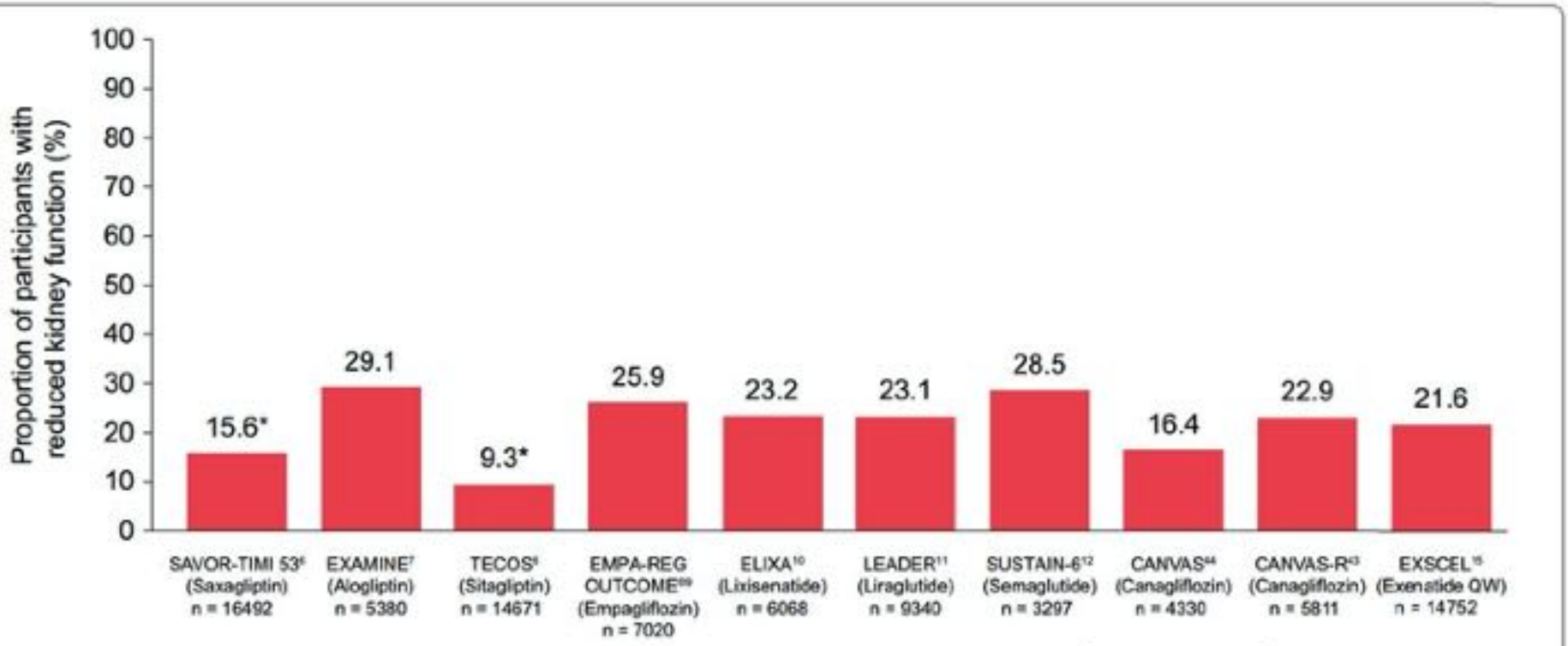
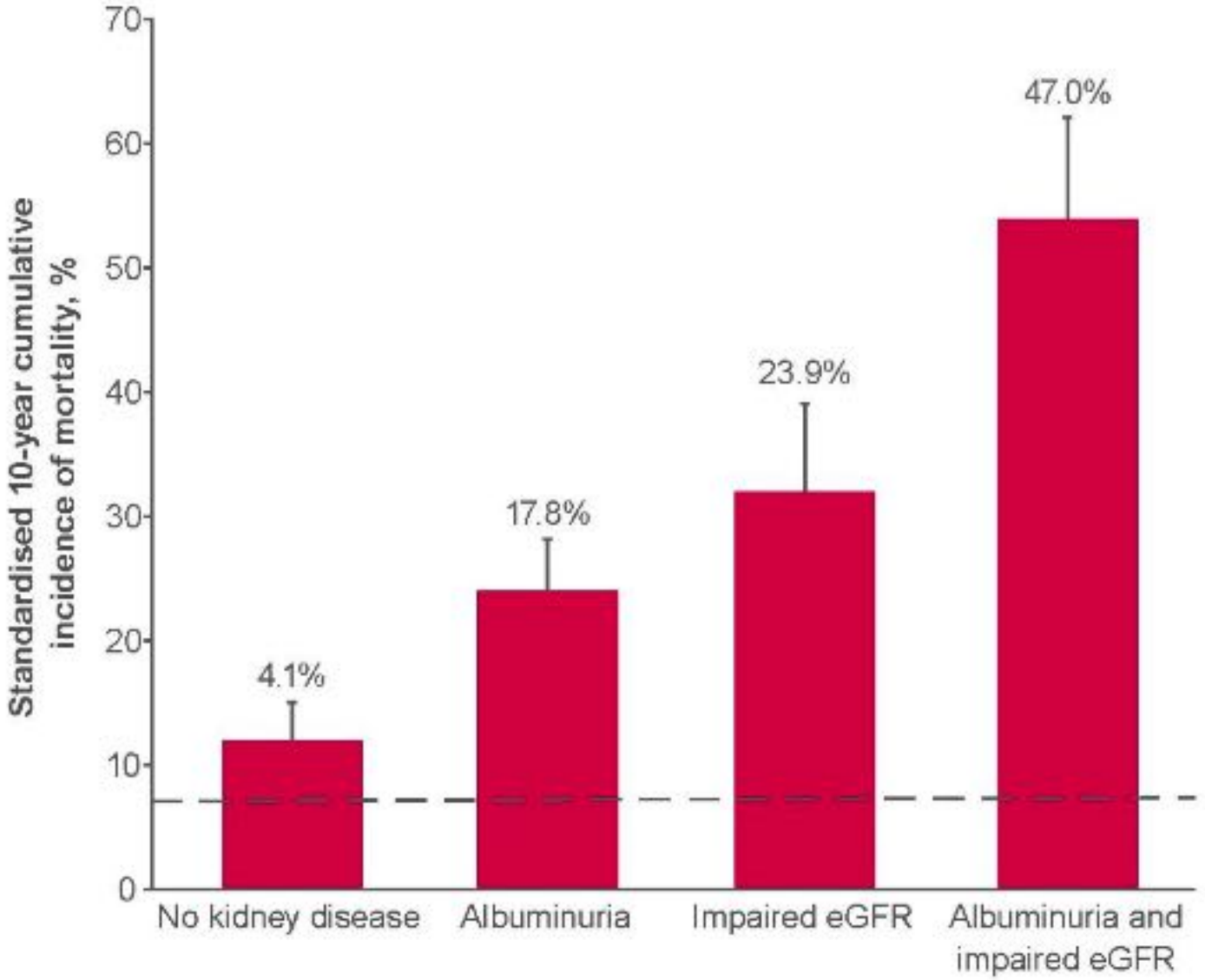


Fig. 6 Proportion of patients with reduced kidney function at baseline (eGFR < 60 mL/min/1.73 m^2) in CARMELINA® compared to previously reported CV outcome trials of non-insulin glucose-lowering drugs for T2D. *eGFR < 50 mL/min/1.73 m^2. *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *QW* once weekly, *T2D* type 2 diabetes

10-year mortality in T2DM by kidney disease manifestation in the US



¿Cómo tratamos la diabetes en los pacientes con ERC?

¿La linagliptina (Trajenta®) es la solución?

JAMA | Original Investigation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

The CARMELINA Randomized Clinical Trial

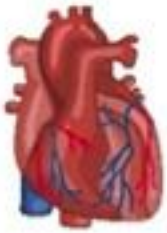
Julio Rosenstock, MD; Vlado Perkovic, MBBS, PhD; Odd Erik Johansen, MD, PhD; Mark E. Cooper, MBBS, PhD; Steven E. Kahn, MB, ChB; Nikolaus Marx, MD; John H. Alexander, MD, MHSc; Michael Pencina, PhD; Robert D. Toto, MD; Christoph Wanner, MD; Bernard Zinman, MD; Hans Juergen Woerle, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schnaidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximillian von Eynatten, MD; Darren K. McGuire, MD, MHSc; for the CARMELINA Investigators

JAMA. doi:10.1001/jama.2018.18269
Published online November 9, 2018.

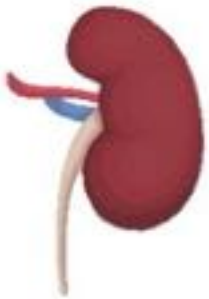
CARMELINA was a multinational, randomised, double-blind, placebo-controlled CVOT[5]

- Study medication was given on top of stable background glucose-lowering therapy and patients were treated for CV risk factors in accordance with local guidelines

Patients with documented diagnosis of T2DM at high risk of CV events defined as:



Age ≥18 years
HbA1c of ≥6.5% and ≤10.0%
BMI ≤45 kg/m²
and/or

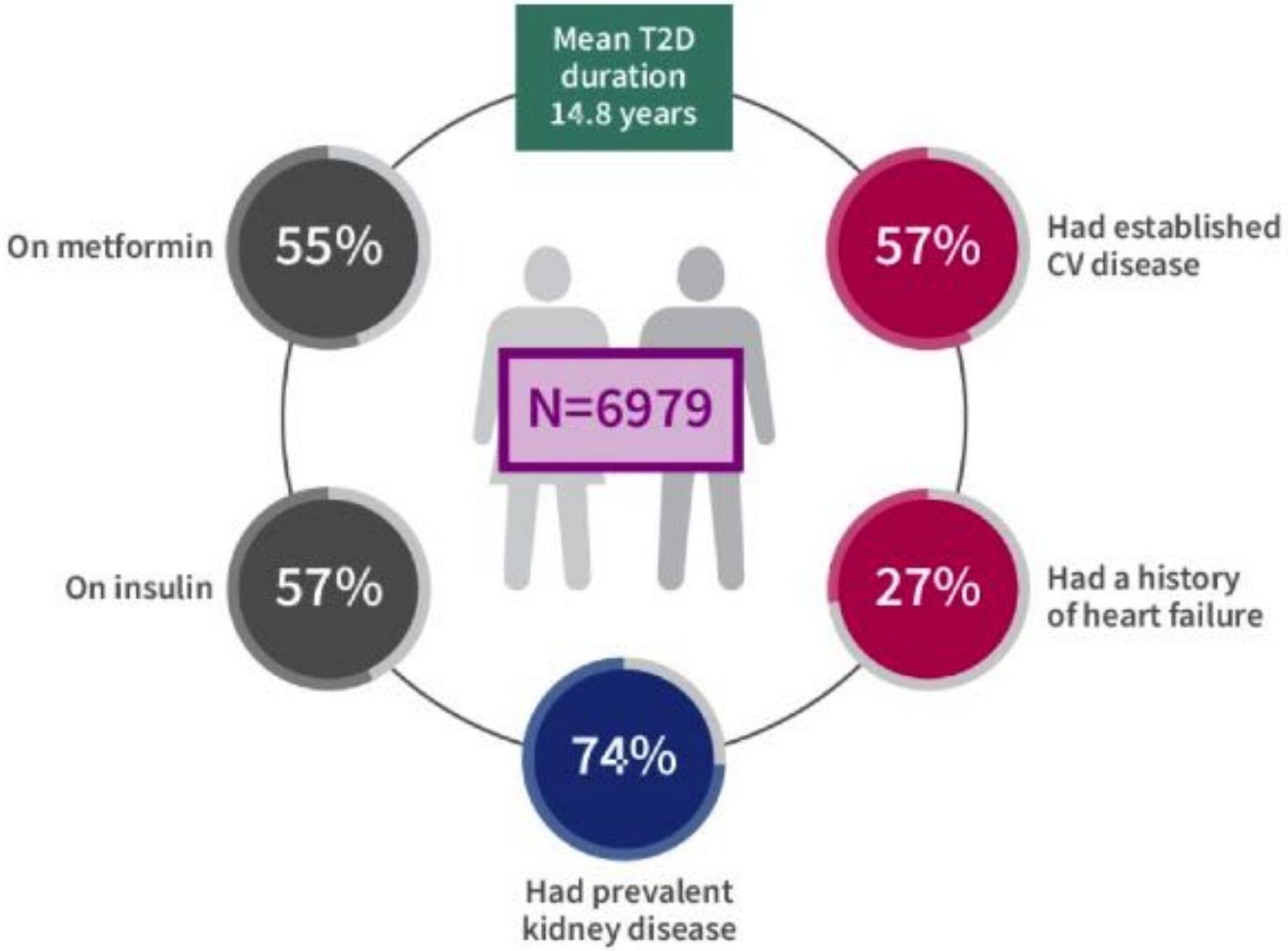


Albuminuria (urine albumin-to-creatinine ratio [UACR] >30 mg/g*) and prevalent macrovascular disease, defined as one or more of the following:

- Confirmed history of myocardial infarction (MI)
- Advanced coronary artery disease†
- High-risk single-vessel coronary artery disease
- History of ischaemic or haemorrhagic stroke
- Presence of carotid artery disease
- Presence of peripheral artery disease

Impaired kidney function with or without albuminuria

- Estimated glomerular filtration rate (eGFR):15 to <45 ml/min/1.73 m²
- eGFR ≥45 to 75 ml/min/1.73 m² with UACR >200 mg/g creatinine or >200 mg/l or >200 µg/min or >200 mg/24 h

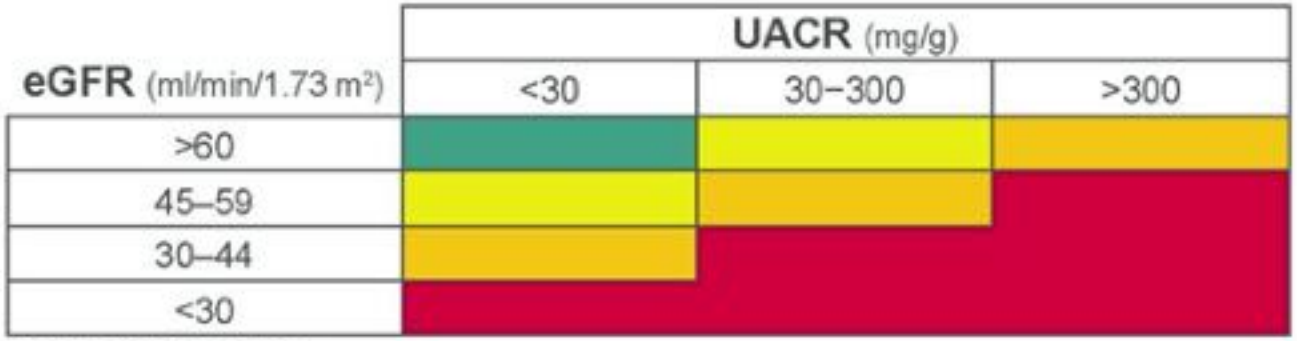

Mean T2D duration 14.8 years
On metformin
55%
57%
Had established CV disease
N=6979
On insulin
57%
27%
Had a history of heart failure
74%
Had prevalent kidney disease

Proportion of patients included in the CARMELINA® trial with established CV disease, prevalent kidney disease or both

100% (N=6980*)

- Approximately 71% of CARMELINA® participants are categorised as having a kidney prognosis of high risk (n=1902; 27.2%) or very high risk (n=3033; 43.5%) by eGFR and albuminuria categories at baseline (**Figure 6**)

Figure 6. Prognosis of CKD in CARMELINA® population by eGFR and albuminuria categories*

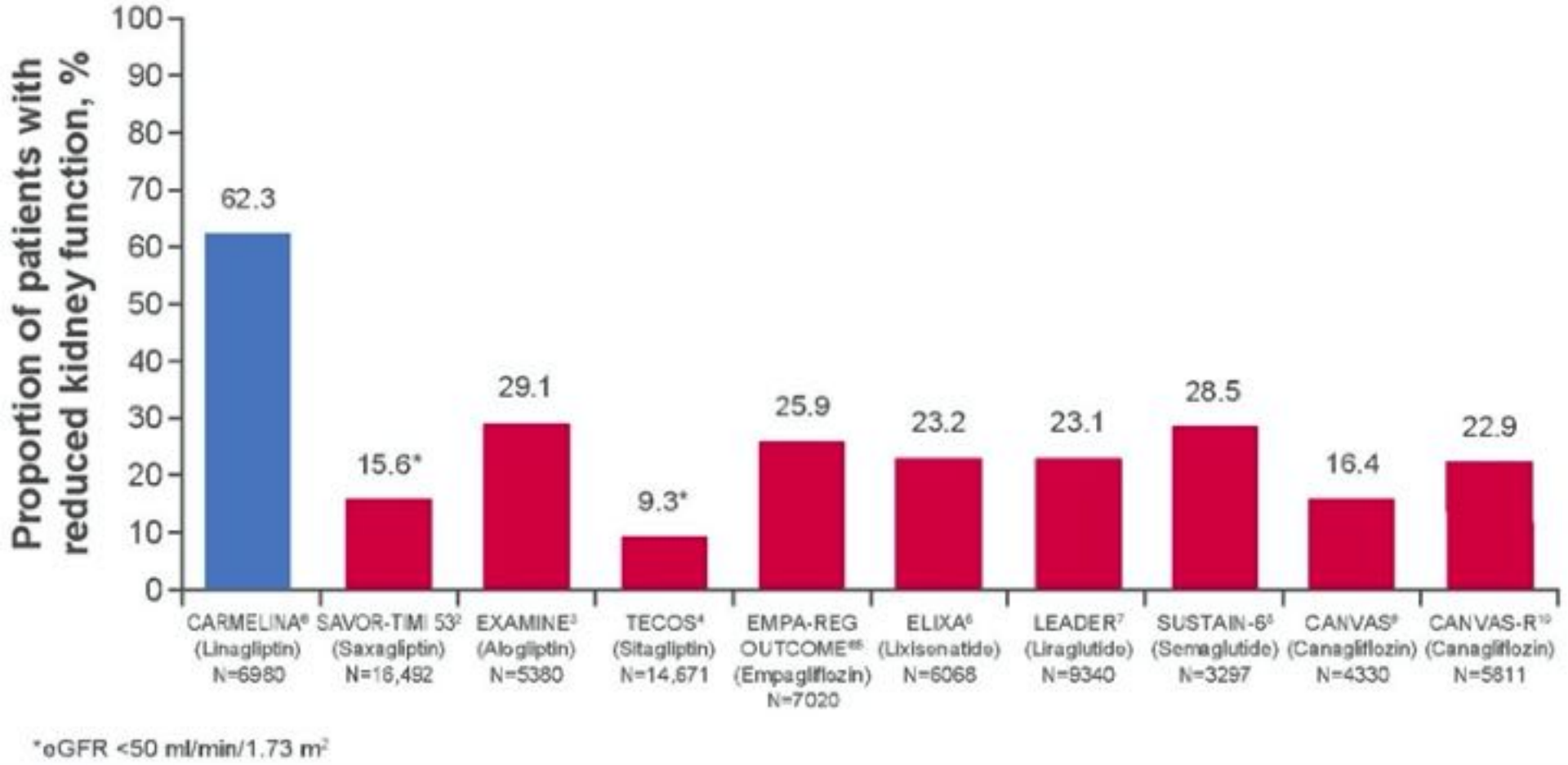


*Based on KDIGO categories.

Reprinted from Kidney Int, 80, Levey et al, The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report, 17–28, Copyright 2011, with permission from Elsevier.

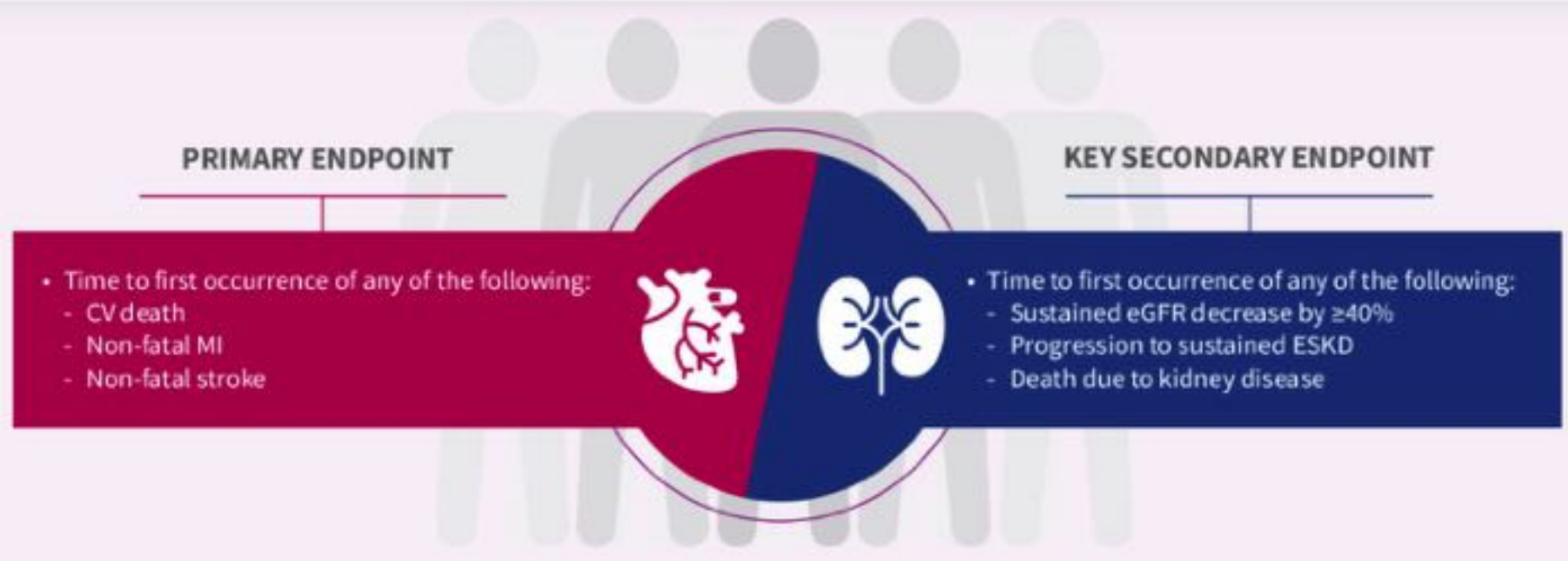
Prognosis of CKD	Low risk	Moderate risk	High risk	Very high risk
CARMELINA® population at baseline, n (%)	484 (6.9)	1561 (22.4)	1902 (27.2)	3033 (43.5)

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

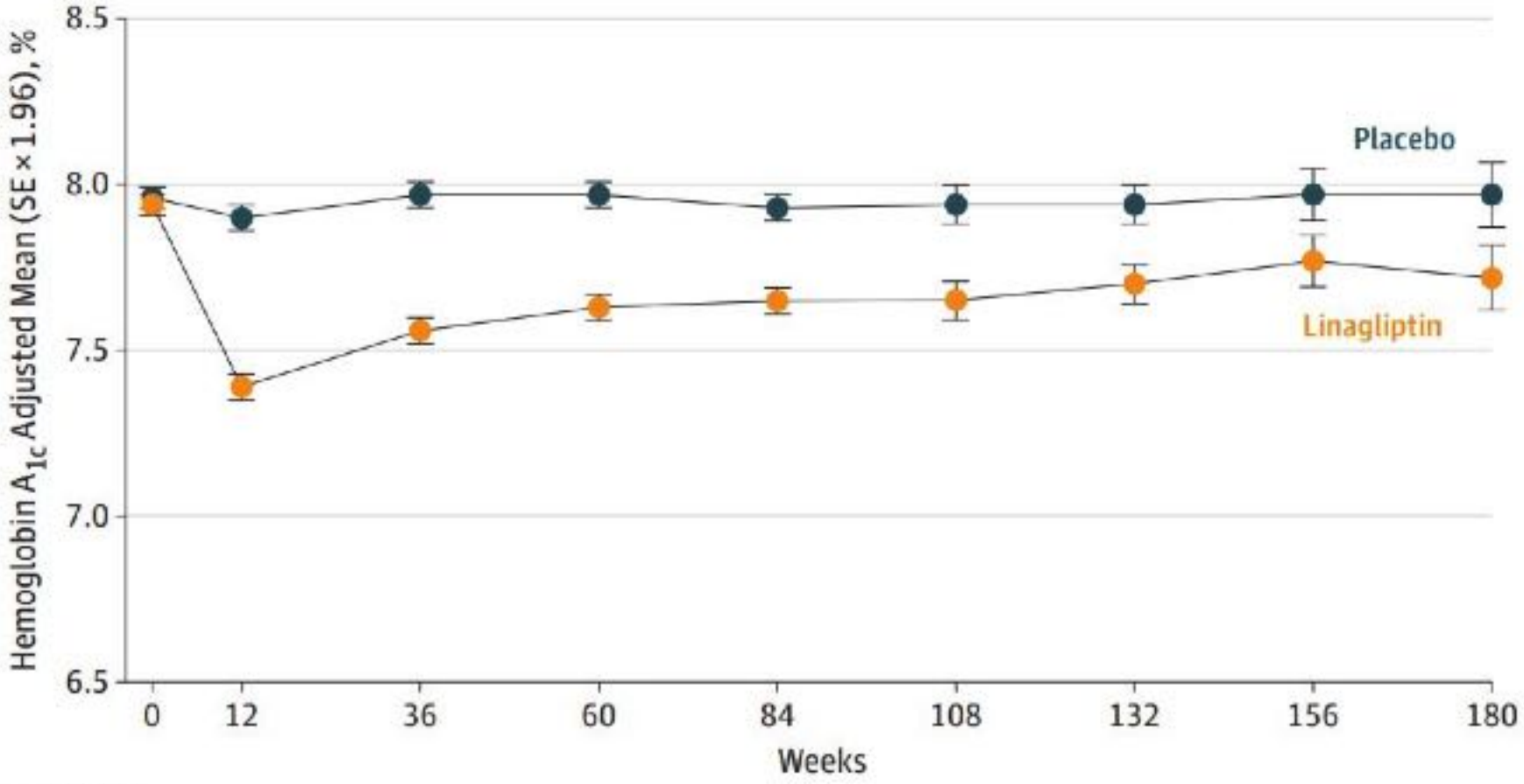


*eGFR <50 ml/min/1.73 m²

CARMELINA


PRIMARY ENDPOINT
• Time to first occurrence of any of the following:
- CV death
- Non-fatal MI
- Non-fatal stroke
KEY SECONDARY ENDPOINT
• Time to first occurrence of any of the following:
- Sustained eGFR decrease by ≥40%
- Progression to sustained ESKD
- Death due to kidney disease

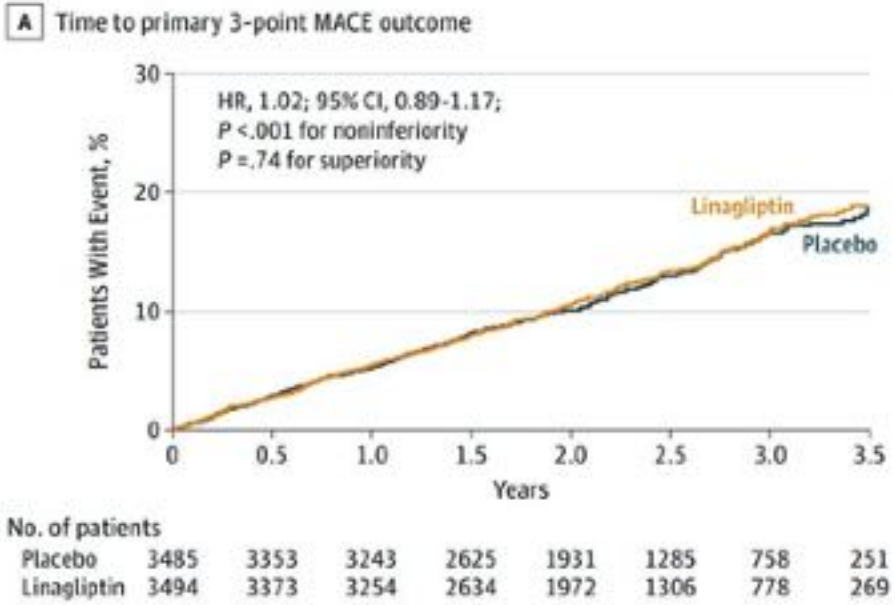
Hemoglobin A_{1c} Measurements Over Time by Treatment Group

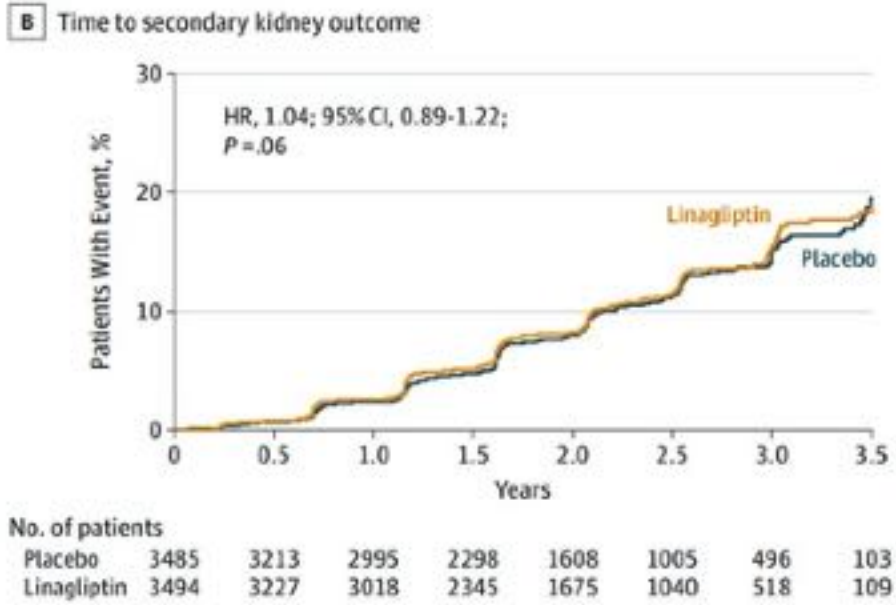


No. of patients

Placebo	3387	3331	3151	2968	2395	1725	1156	732	358
Linagliptin	3419	3373	3173	3015	2455	1811	1237	777	379

Figure 2. Time to Primary and Secondary Outcomes





Hazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo.

B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

CARMELINA

Cardiovascular

Long-term CV safety profile confirmed

El resultado primario 3P-MACE* se cumplió en 434/3494 (12.4%) and 420/3485 (12.1%) pacientes en los grupos de linagliptina y placebo respectivamente, cumpliendo el criterio de no inferioridad.
Las pruebas posteriores de superioridad no fueron estadisticamente significativas

HR 1.02 (95% CI 0.89, 1.17)
p<0.001 for non-inferiority

Hospitalisation for heart failure

No increased risk of hospitalisation for heart failure

Las tasas de hospitalización por IC no difirieron entre los grupos de tratamiento: 209/3494 (6,0%) y 226/3485 (6,5%) en los grupos de linagliptina y placebo, respectivamente.

HR 0.90 (95% CI 0.74, 1.08)
p=0.26

Kidney

Long-term kidney safety profile confirmed

El punto final secundario ocurrió en 327/3494 (9,4%) y 306/3485 (8,8%) pacientes en los grupos de linagliptina y placebo respectivamente, y no fué significativamente diferente entre los grupos.
La prueba de superioridad no alcanzó significación estadistica

HR 1.04 (95% CI 0.89, 1.22)
p=0.62

¿Mantenemos la MET como 1º línea de tratamiento AD en los enfermos renales?

¿Produce algún beneficio CV en esta situación?

JAMA | Original Investigation

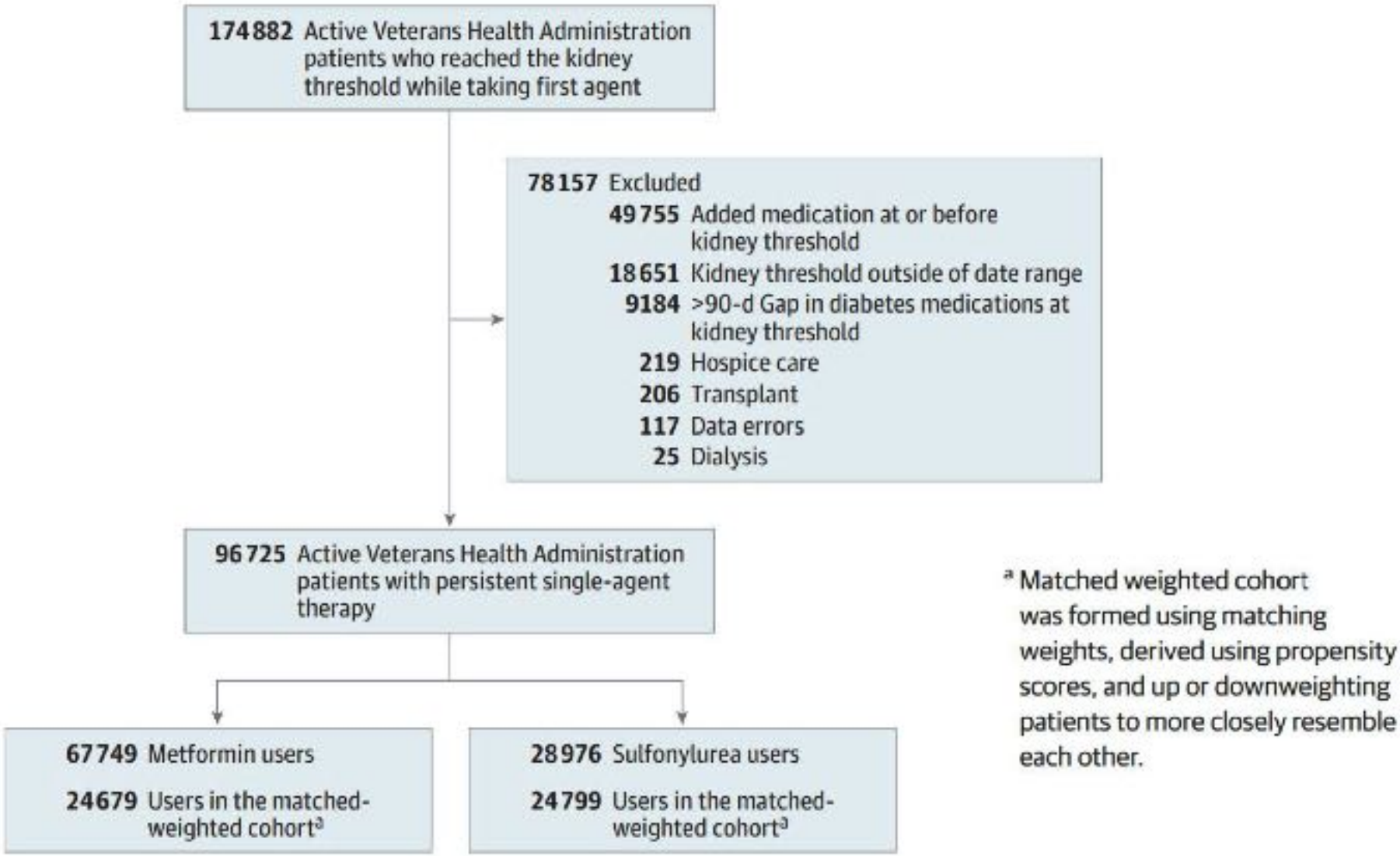
Association of Treatment With Metformin vs Sulfonylurea With Major Adverse Cardiovascular Events Among Patients With Diabetes and Reduced Kidney Function

Christianne L. Roumie, MD, MPH; Jonathan Chipman, PhD; Jea Young Min, PharmD, MPH, PhD; Amber J. Hackstadt, PhD; Adriana M. Hung, MD, MPH; Robert A. Greevy Jr, PhD; Carlos G. Grijalva, MD, MPH; Tom Elasy, MD, MPH; Marie R. Griffin, MD, MPH

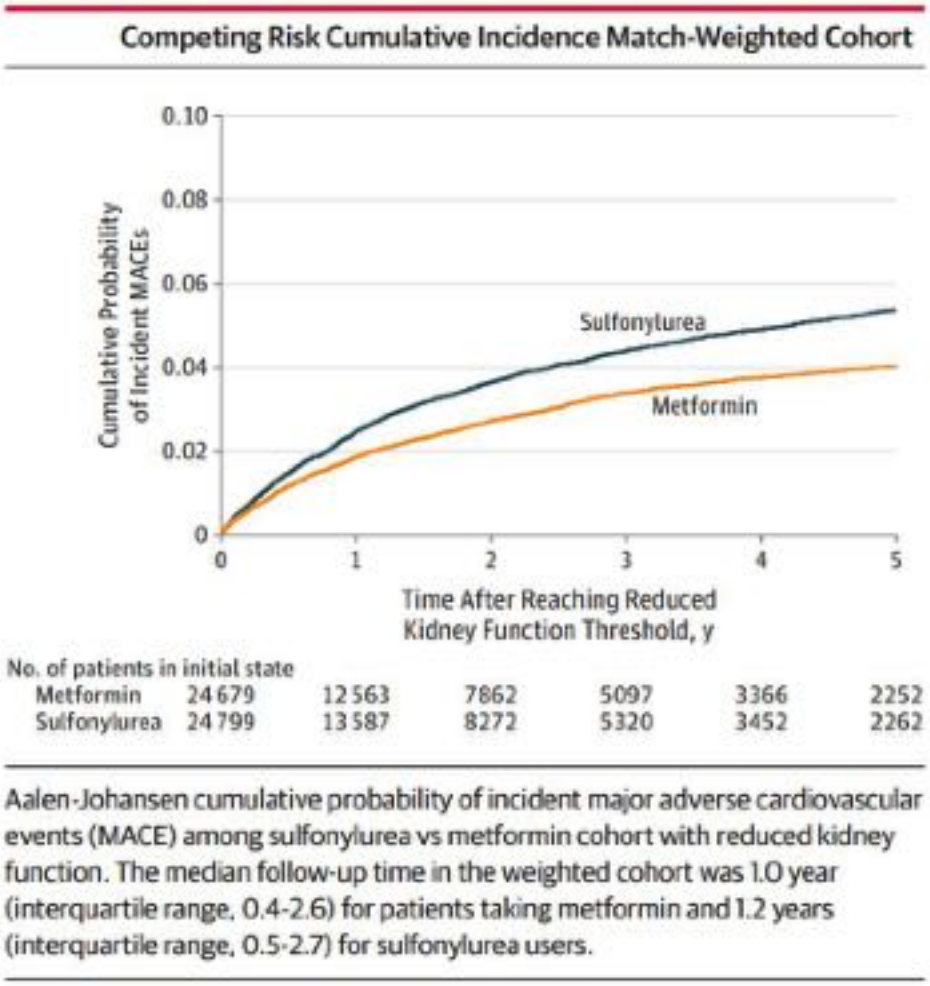
JAMA. doi:10.1001/jama.2019.13206
Published online September 19, 2019.

- **Tipo:** Estudio de cohortes retrospectivo.
- **Población seleccionada:** se comparan los eventos CV (MACE) en 2 grupos de Veteranos americanos diabéticos desde que aparece la ERC (FGE <60 ó creatinina >1,5). Cada grupo había sido tratado y continuaba siéndolo (sin interrupciones ni cambios) con la misma monoterapia a base de MET o SU desde su inicio de tratamiento. Ambos grupos se balancearon adecuadamente mediante un score de propensión.

Eligible Patients in the Veterans Health Administration



[a] Matched weighted cohort was formed using matching weights, derived using propensity scores, and up or downweighting patients to more closely resemble each other.



Aalen-Johansen cumulative probability of incident major adverse cardiovascular events (MACE) among sulfonylurea vs metformin cohort with reduced kidney function. The median follow-up time in the weighted cohort was 1.0 year (interquartile range, 0.4-2.6) for patients taking metformin and 1.2 years (interquartile range, 0.5-2.7) for sulfonylurea users.

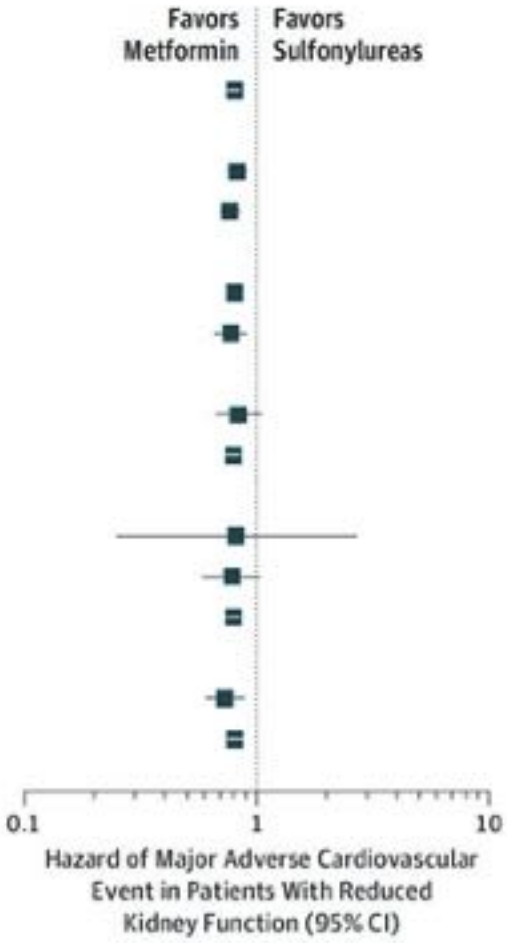
- **Resultados:** la tasa de eventos MACE fue de 23 vs 29,2 por 1000 personas-año de uso respectivo de MET y SU respectivamente, con una reducción del RR de 0.80 (95% CI, 0.75-0.86) entre grupo MET comparado con el de SU. Siendo la diferencia en la incidencia de 5,8 menos eventos por 1000 personas-año en el grupo de la metformina.
- Estos resultados fueron tb consistentes para cada uno de los componentes de eventos MACE.
- La frecuencia de lactoacidosis no aumentaba en los pacientes con MET.

Conclusiones y relevancia:

En los pacientes con DM2 y ERC, el tratamiento monoterápico con MET comparado con SU se asoció con un menor riesgo de MACE

Figure 3. Adjusted Hazard Ratios for Major Adverse Cardiovascular Events by Subgroups

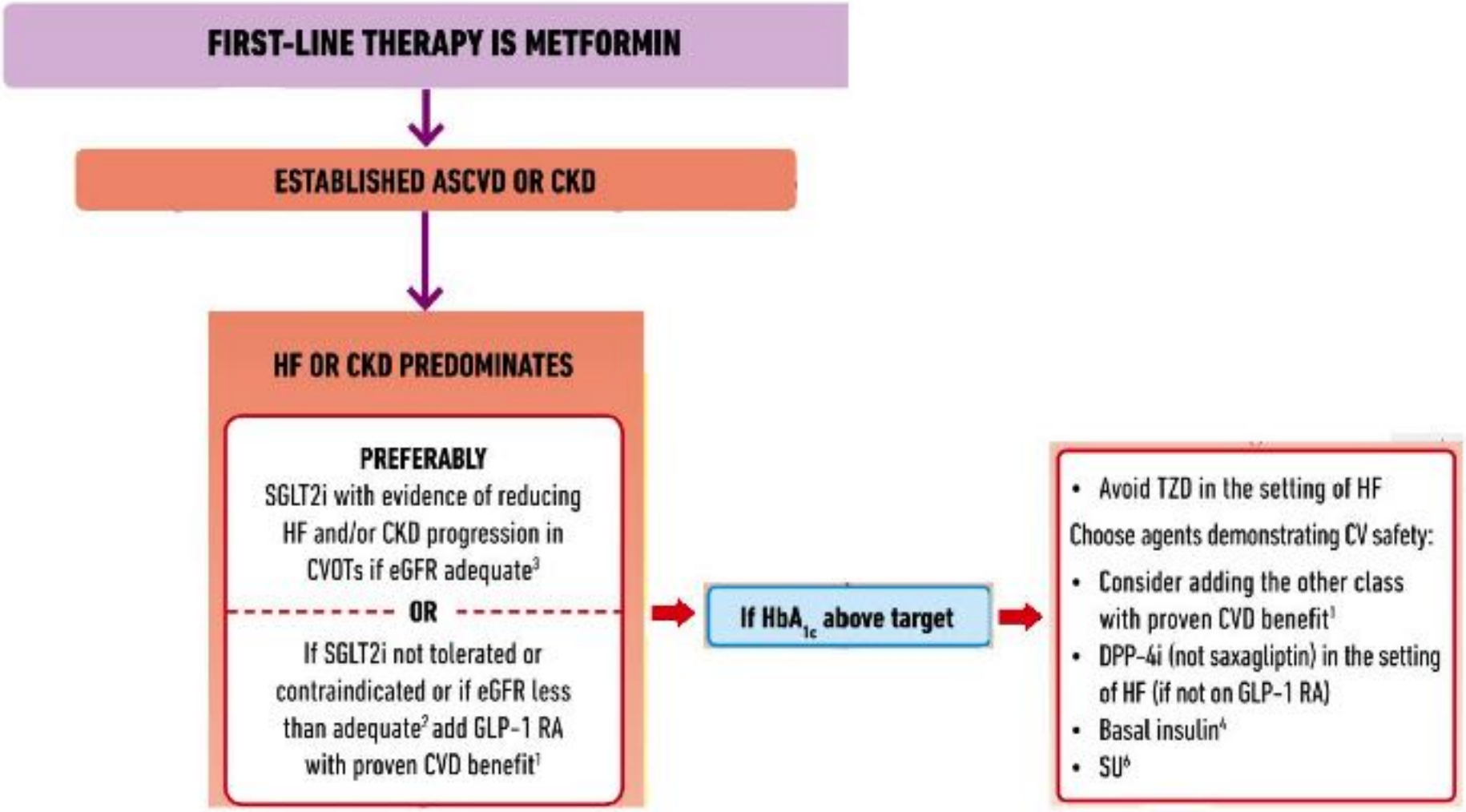
	Metformin	Sulfonylureas		
	No. of Events/ No. at Risk	No. of Events/ No. at Risk	Adjusted Hazard Ratio (95% CI)	*P* for Interaction
Full matched-weighted cohort	1048/24679	1394/24799	0.80 (0.75-0.86)	
Cardiovascular disease history				
Yes	511/7797	671/7868	0.83 (0.75-0.92)	.34
No	537/16882	723/16931	0.78 (0.70-0.86)	
Age, y				
≥65	870 /16796	136/16764	0.81 (0.75-0.88)	.53
<65	178/7883	258/8034	0.78 (0.66-0.92)	
Race				
Black	107/4035	154/4047	0.84 (0.67-1.06)	.69
Nonblack	941/20644	1240/20752	0.80 (0.74-0.86)	
Estimated glomerular filtration rate (eGFR)				
<30 mL/min/1.73 m^2	10/332	17/334	0.82 (0.25-2.72)	
30-45 mL/min/1.73 m^2	65/1903	115/1886	0.79 (0.59-1.04)	.38 and .54[a]
>45 mL/min/1.73 m^2	973/22444	1262/22578	0.80 (0.74-0.86)	
Cohort entry criteria				
Creatinine ≥ FDA threshold	125/5733	229/7779	0.74 (0.61-0.90)	.46
eGFR <60 mL/min/1.73 m^2 + creatinine <FDA threshold	923/39809	1164/39983	0.81 (0.75-0.88)	



LIMITACIONES

- Se rechazaron a demasiados pacientes por cambios, combinaciones o interrupciones de la medicación.
- El estudio incluía predominantemente personas mayores (media 70a), 82% blancos.
- Las técnicas de balanceo son siempre discutibles, y más en este estudio en el que se emplean a fondo.
- Los resultados beneficiosos de la MET vistos en este estudio no son extrapolables a los pacientes que ya tienen ERC cuando se inicia la MET.
- No se tuvo en cuenta la dosis de fármacos.
- No puede determinarse a partir de estos análisis si la MET está asociada con un riesgo reducido o las SU están asociadas con un mayor riesgo de eventos MACE.

DM2 en la ERC ¿QUE DICEN LAS GRANDES SOCIEDADES? CONSENSO 2018 ADA Y EASD



Invited Commentary

July 2018

Should Metformin Be First-line Therapy for Patients With Type 2 Diabetes and Chronic Kidney Disease?

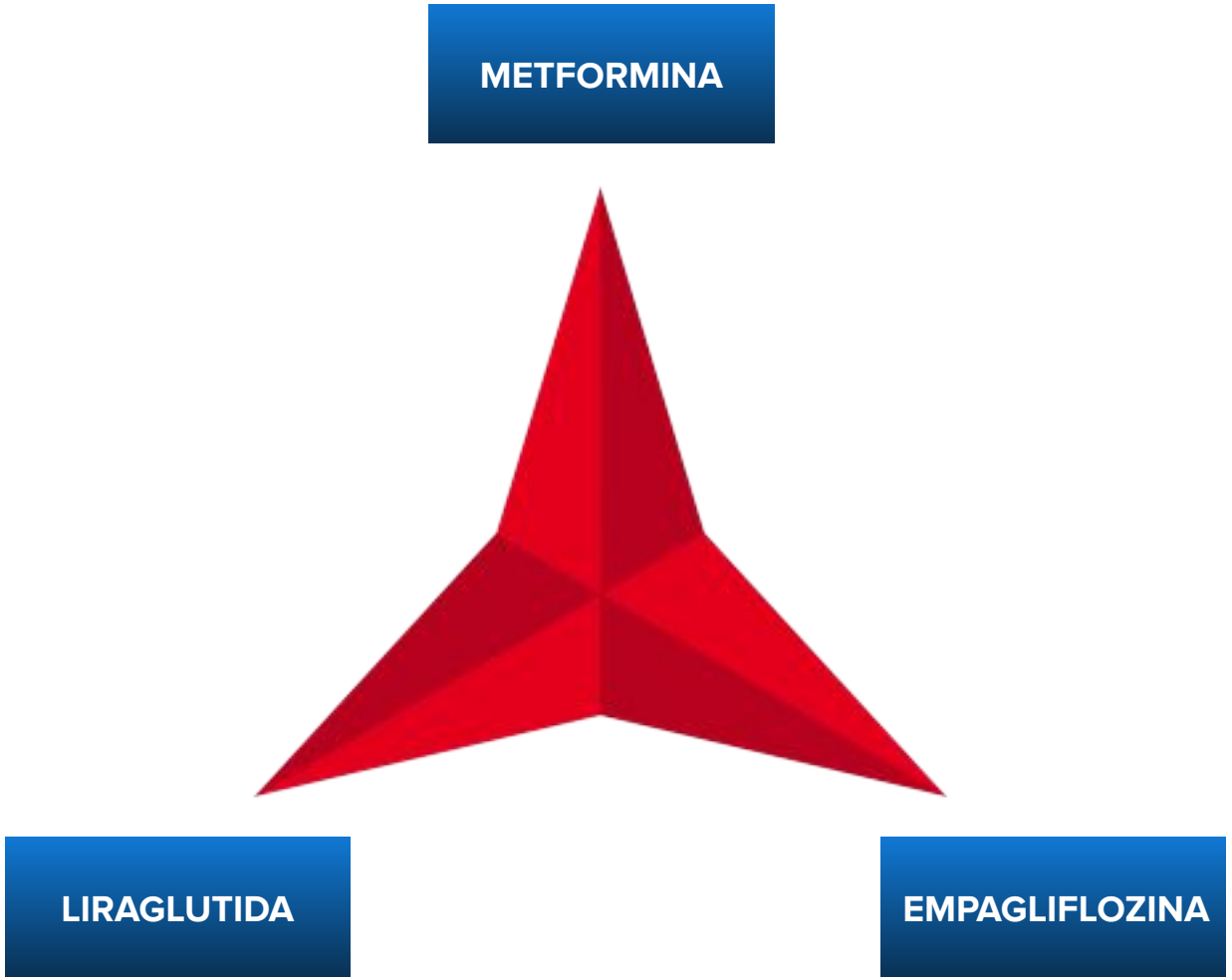
Informed Patients Should Decide

Chester B. Good, MD, MPH[1,2]; Leonard M. Pogach, MD, MBA[3]

» Author Affiliations | Article Information

JAMA Intern Med. 2018;178(7):911-912. doi:10.1001/jamainternmed.2018.0301

EDITORIAL: opinión del experto sobre tratamiento de DM2 en pacientes con ERC



EDITORIAL: opinión del experto sobre tratamiento de DM2 en pacientes con ERC

Antidiabéticos a considerar en pacientes con ERC: **MET, liraglutida y empagliflozina.**

Ojo! No se incluyen como alternativas las Insulinas ni la linagliptina

¿Cual es mas segura?

- **METFORMINA**
  - La FDA recomienda no iniciarla en sujetos con FG<45, y la contraindica en FG<30 por riesgo de lactoacidosis.
  - Según el estudio presentado no hay riesgo de lactoacidosis hasta que el FG<30, por lo que podría iniciarse a partir de dicho nivel siempre y cuando se vigile el FG especialmente en personas con más riesgo de deshidratación (ancianos frágiles, diuréticos, SGLT2).
- **LIRAGLUTIDA:**
  - Sin problemas en la ERC y sin necesidad de ajustes.
  - Descrita la insuficiencia renal en casos de deshidratación concomitante.
- **EMPAGLIFLOZINA:**
  - Sin ajuste dosis con FG >45. Contraindicada si FG <45.
  - Puede ocasionar deshidratación → empeoramiento de ERC

EDITORIAL: opinión del experto sobre tratamiento de DM2 en pacientes con ERC

¿Cual tiene mejor perfil clínico?

- ➔ **METFORMINA**
  - ◆ eL UKPDS excluyó a pacientes con creatinina >2.
  - ◆ el estudio actual demuestra un efecto CV beneficioso si se compara a SU.
- ➔ **LIRAGLUTIDA:**
  - ◆ beneficio CV demostrado en pacientes con FG entre 30-60 (estudio LEADER).
- ➔ **EMPAGLIFLOZINA:**
  - ◆ beneficio CV demostrado en pacientes con FG >60 (estudio EMPA-REG).
  - ◆ enlentece la progresión de la ERC.

EDITORIAL: opinión del experto sobre tratamiento de DM2 en pacientes con ERC

VEREDICTO FINAL:

- A falta de evidencia directa que compare los agentes más nuevos con metformina para los pacientes con DM2 y ERC, un **modelo de decisión compartida** es ideal para considerar con qué fármaco iniciar la farmacoterapia.
- Cuando se presenta una discusión equilibrada de riesgo-beneficio de los 3 agentes, muchos, si no la mayoría de los pacientes, elegirán metformina como el fármaco de primera línea en el contexto de la ERC.

¿Nos olvidamos de las sulfonilureas para siempre?

¿Cuánto hace que no ponemos una?

¿Los inhibidores de DPP-4 han desplazado a las SU?

CAROLINA

Original Investigation

September 19, 2019

Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes

The CAROLINA Randomized Clinical Trial

Julio Rosenstock, MD[1,2]; Steven E. Kahn, MB, ChB[3,4]; Odd Erik Johansen, MD, PhD[5]; et al

JAMA. 2019;322(12):1155-1166. doi:10.1001/jama.2019.13772

Junta de

Sacyl

Complejo Asistencial Universitario de León

CAROLINA

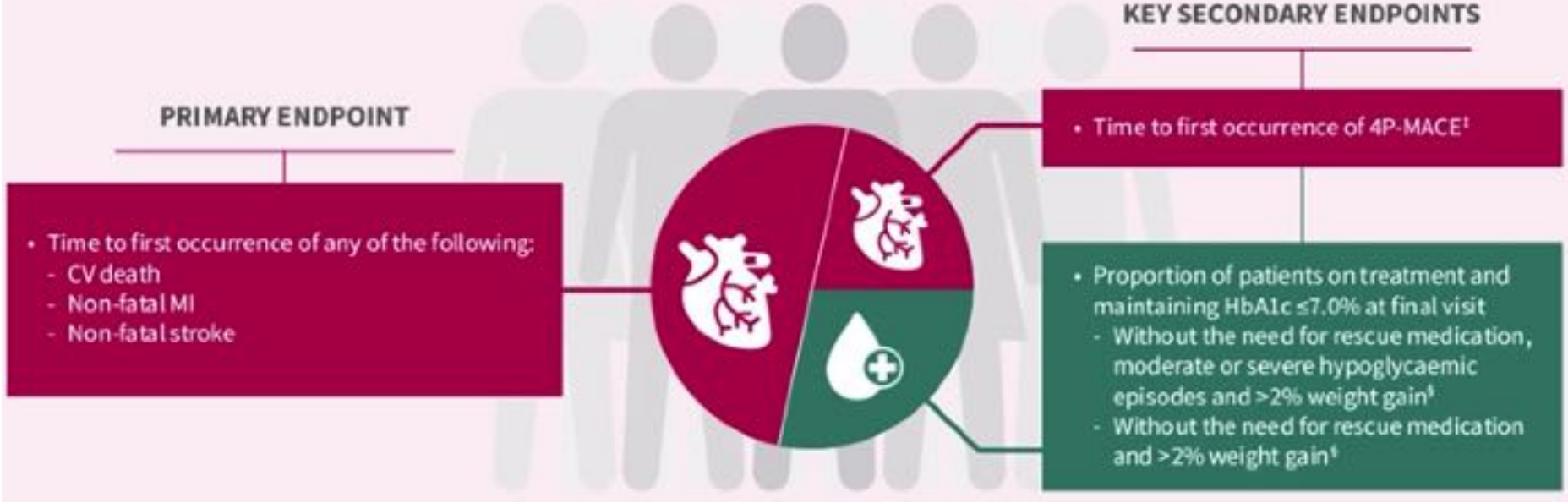

SCREENING
N=6033
1:1
RANDOMISED
LINAGLIPTIN 5 MG/DAY + STANDARD OF CARE
GLIMEPIRIDE 1–4 MG/DAY† + STANDARD OF CARE
≥631
CV EVENTS

CAROLINA

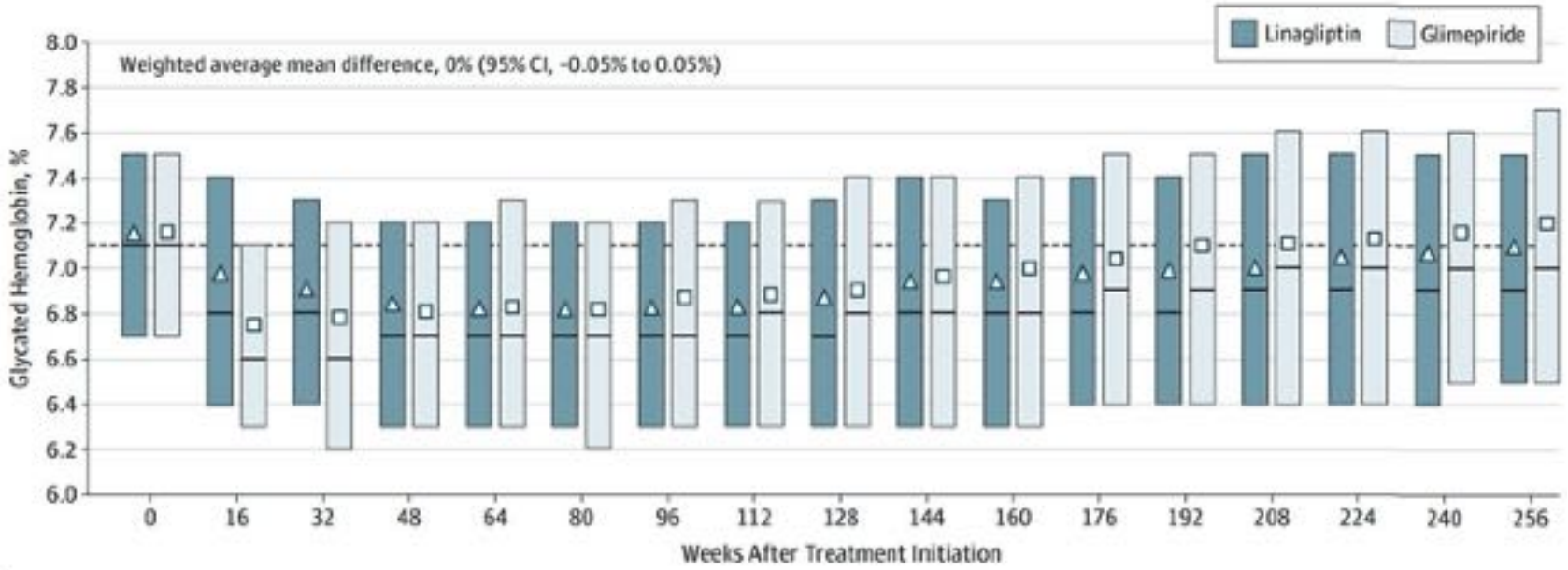

Median T2D duration 6.3 years
On metformin
83%
42%
Had established CV disease
On insulin (excluded from trial)
0%
37%
Displayed ≥2 defined CV risk factors
Treatment naïve
9%
40%
Had T2D for ≤5 years
Receiving standard of care for CV risk

CAROLINA

• The CV safety profile of linagliptin was assessed using 3P-MACE: CV death, non-fatal MI, non-fatal stroke



Glycated Hemoglobin (HbA_{1c}) Over Time by Treatment Groups



No. of participants																	
Glimepiride	3000	2920	2808	2731	2668	2600	2541	2498	2467	2401	2361	2300	2271	2223	2196	2165	2146
Linagliptin	3013	2924	2806	2719	2653	2593	2518	2467	2426	2393	2382	2333	2288	2247	2235	2190	2184
Total in follow-up analysis	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551

Figure 2. Time to Occurrence of End Points Based on Cox Regression Analyses in Patients Treated With at Least 1 Dose of the Study Drug

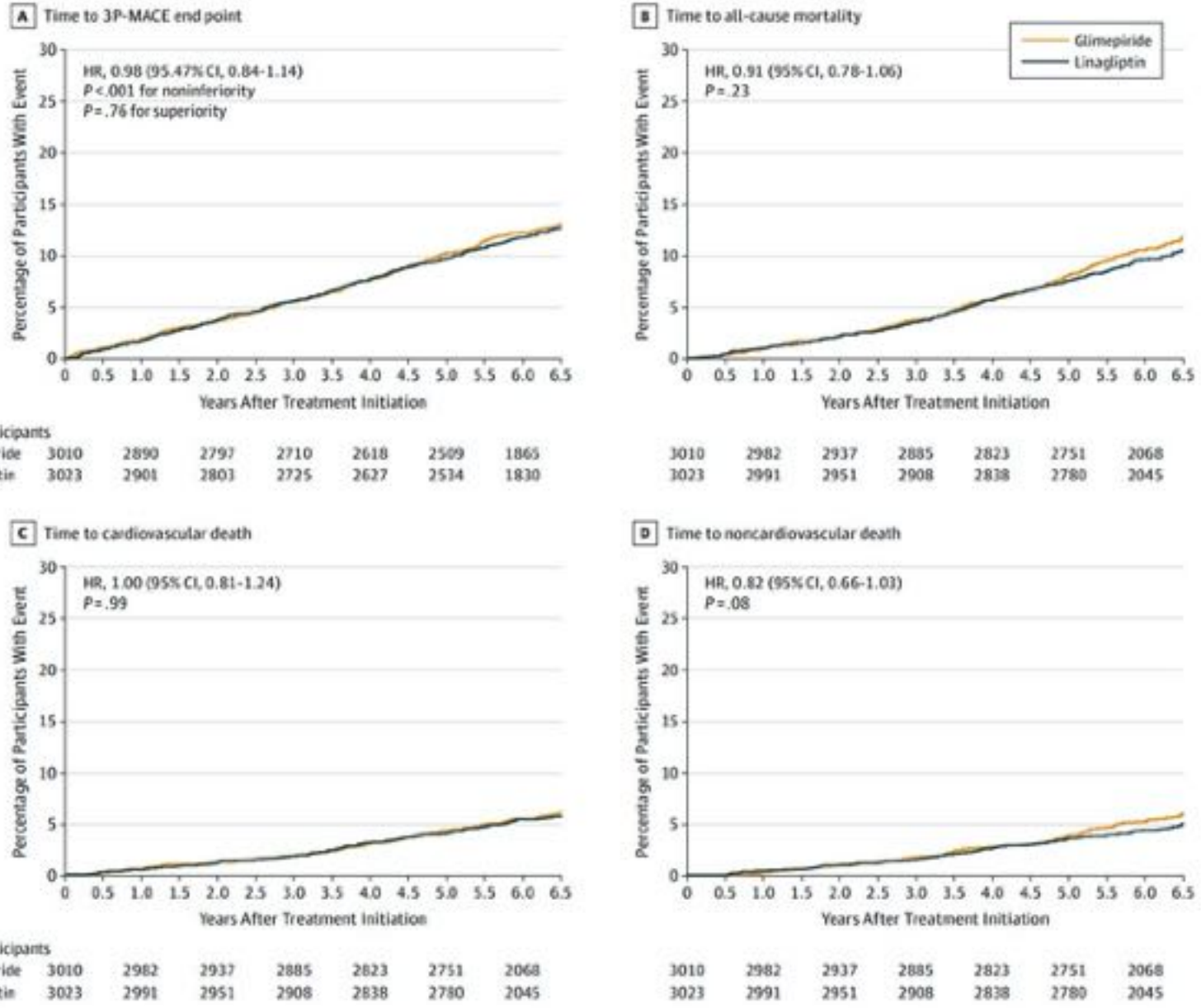
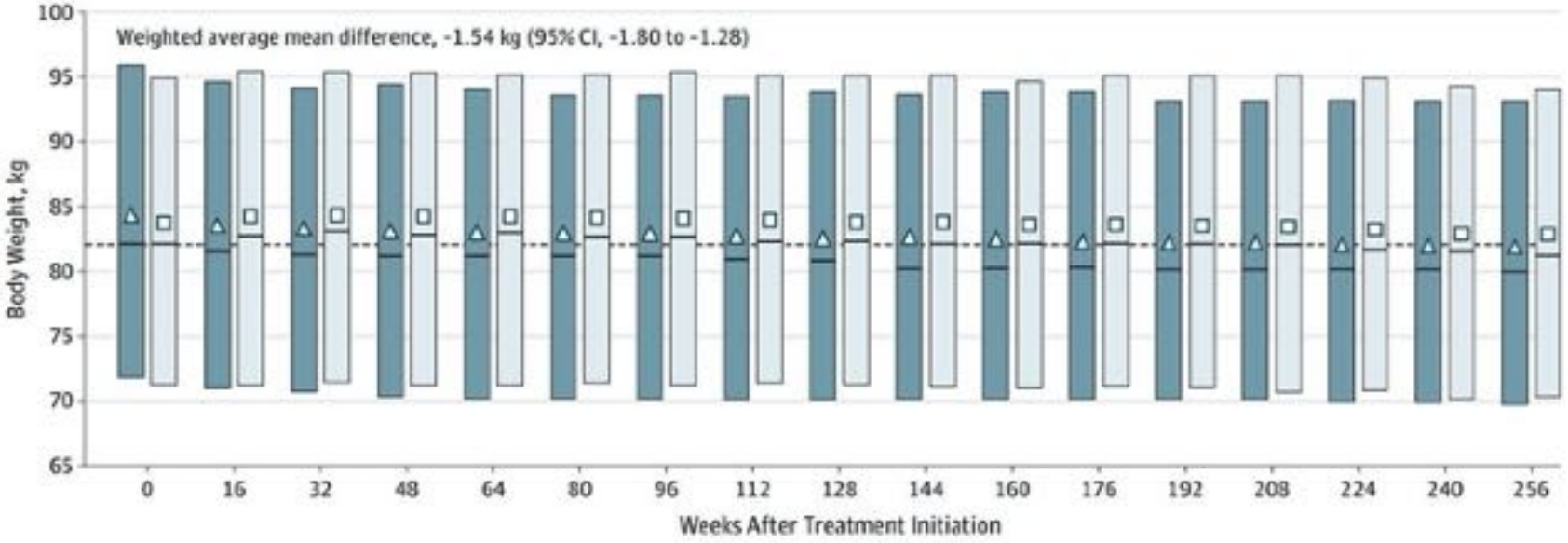


Table 2. Primary End Point, Key Secondary Outcomes, and Other Secondary or Tertiary Cardiovascular End Points in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes

Outcome	Linagliptin (n = 3023)		Glimepiride (n = 3010)		Incidence Rate/ 100 Patient-Years Difference, Linagliptin – Glimepiride (95% CI)	HR[a]/Odds Ratio[b] (95% CI)
	No. (%)	Rate/100 Patient-Years	No. (%)	Rate/100 Patient-Years		
Primary End Point						
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3P-MACE)	356 (11.8)	2.1	362 (12.0)	2.1	0.0 (−0.4 to 0.3)	0.98 (0.84 to 1.14)
Cardiovascular death[c]	129 (4.3)		125 (4.2)			
Nonfatal myocardial infarction	141 (4.7)		138 (4.6)			
Nonfatal stroke[c]	86 (2.8)		101 (3.4)			
Key Secondary End Points						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina pectoris (4P-MACE)	398 (13.2)	2.3	401 (13.3)	2.4	0.0 (−0.4 to 0.3)	0.99 (0.86 to 1.14)
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication, without any moderate/severe hypoglycemic episodes, and without >2% weight gain[c]	481 (16.0)		305 (10.2)			1.68 (1.44 to 1.96)
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication and without >2% weight gain[c]	524 (17.4)		422 (14.1)			1.29 (1.12 to 1.48)

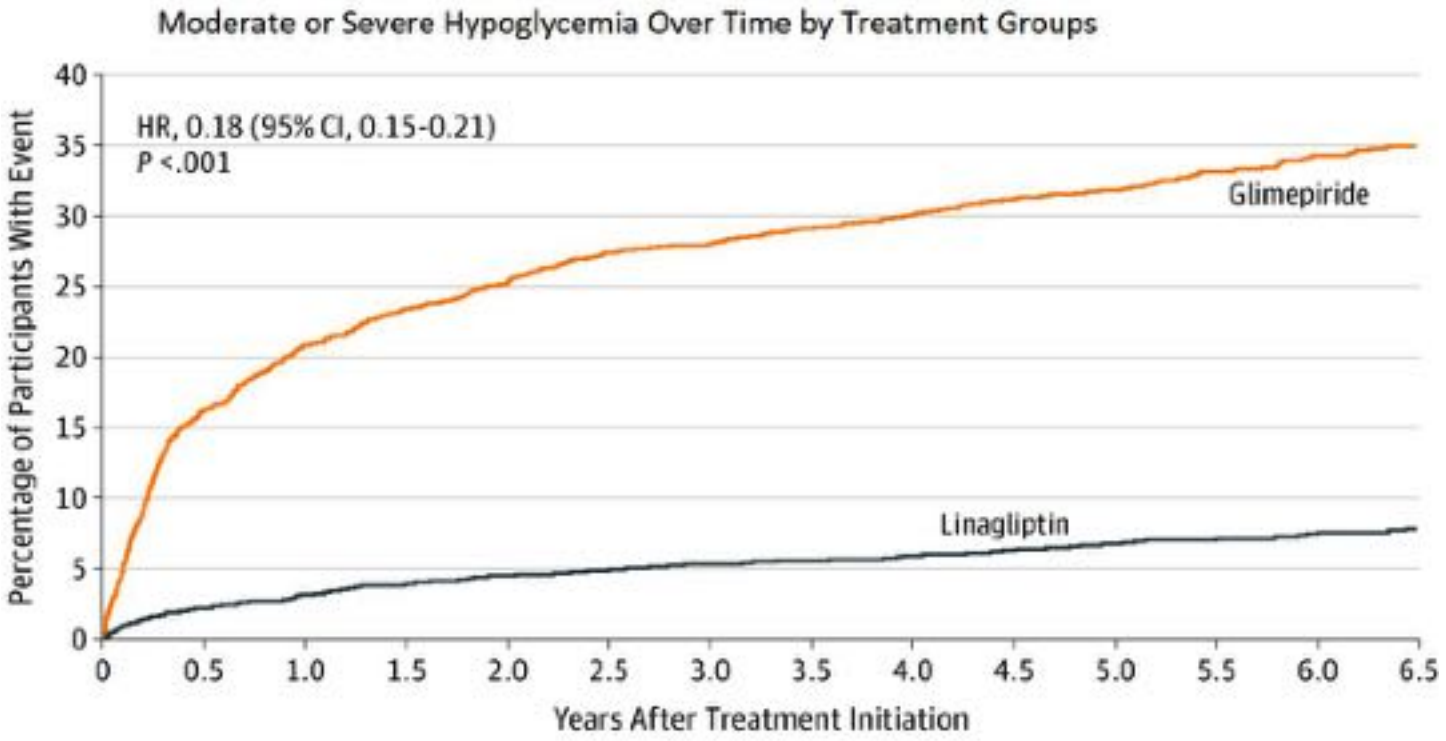
Outcome	Linagliptin (n = 3023) No. (%)	Linagliptin (n = 3023) Rate/100 Patient-Years	Glimepiride (n = 3010) No. (%)	Glimepiride (n = 3010) Rate/100 Patient-Years	Incidence Rate/ 100 Patient-Years Difference, Linagliptin – Glimepiride (95% CI)	HR[a]/Odds Ratio[b] (95% CI)
Other Secondary or Tertiary Cardiovascular End Points						
All-cause mortality	308 (10.2)	1.7	336 (11.2)	1.8	−0.2 (−0.4 to 0.1)	0.91 (0.78 to 1.06)
Cardiovascular mortality	169 (5.6)	0.9	168 (5.6)	0.9	0.0 (−0.2 to 0.2)	1.00 (0.81 to 1.24)
Noncardiovascular mortality	139 (4.6)	0.8	168 (5.6)	0.9	−0.2 (−0.4 to 0.0)	0.82 (0.66 to 1.03)
Nonfatal myocardial infarction	145 (4.8)	0.8	142 (4.7)	0.8	0.0 (−0.2 to 0.2)	1.01 (0.80 to 1.28)
Fatal or nonfatal myocardial infarction	153 (5.1)	0.9	148 (4.9)	0.9	0.0 (−0.2 to 0.2)	1.03 (0.82 to 1.29)
Nonfatal stroke	91 (3.0)	0.5	104 (3.5)	0.6	−0.1 (−0.2 to 0.1)	0.87 (0.66 to 1.15)
Fatal or nonfatal stroke	104 (3.4)	0.6	120 (4.0)	0.7	−0.1 (−0.3 to 0.1)	0.86 (0.66 to 1.12)
Transient ischemic attack	25 (0.8)	0.1	33 (1.1)	0.2	0.0 (−0.1 to 0.0)	0.75 (0.45 to 1.26)
Hospitalization for unstable angina	60 (2.0)	0.3	56 (1.9)	0.3	0.0 (−0.1 to 0.1)	1.07 (0.74 to 1.54)
Coronary revascularization procedure	202 (6.7)	1.2	189 (6.3)	1.1	0.1 (−0.2 to 0.3)	1.06 (0.87 to 1.29)
Hospitalization for heart failure	112 (3.7)	0.6	92 (3.1)	0.5	0.1 (−0.1 to 0.3)	1.21 (0.92 to 1.59)
Investigator-reported heart failure events[e]	166 (5.5)	1.0	155 (5.2)	0.9	0.1 (−0.1 to 0.3)	1.06 (0.85 to 1.32)
Hospitalization for heart failure or cardiovascular death	236 (7.8)	1.3	234 (7.8)	1.3	0.0 (−0.2 to 0.2)	1.00 (0.84 to 1.20)
Any adjudicated-confirmed cardiovascular event[f]	518 (17.1)	3.1	535 (17.8)	3.2	−0.1 (−0.5 to 0.3)	0.96 (0.85 to 1.09)

Weight Over Time by Treatment Groups



No. of participants																	
Glimepiride	2998	2933	2814	2740	2682	2621	2572	2534	2498	2434	2398	2341	2291	2257	2229	2193	2178
Linagliptin	3014	2936	2822	2741	2674	2620	2546	2522	2466	2433	2426	2378	2326	2280	2280	2236	2221
Total in follow-up analysis	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551

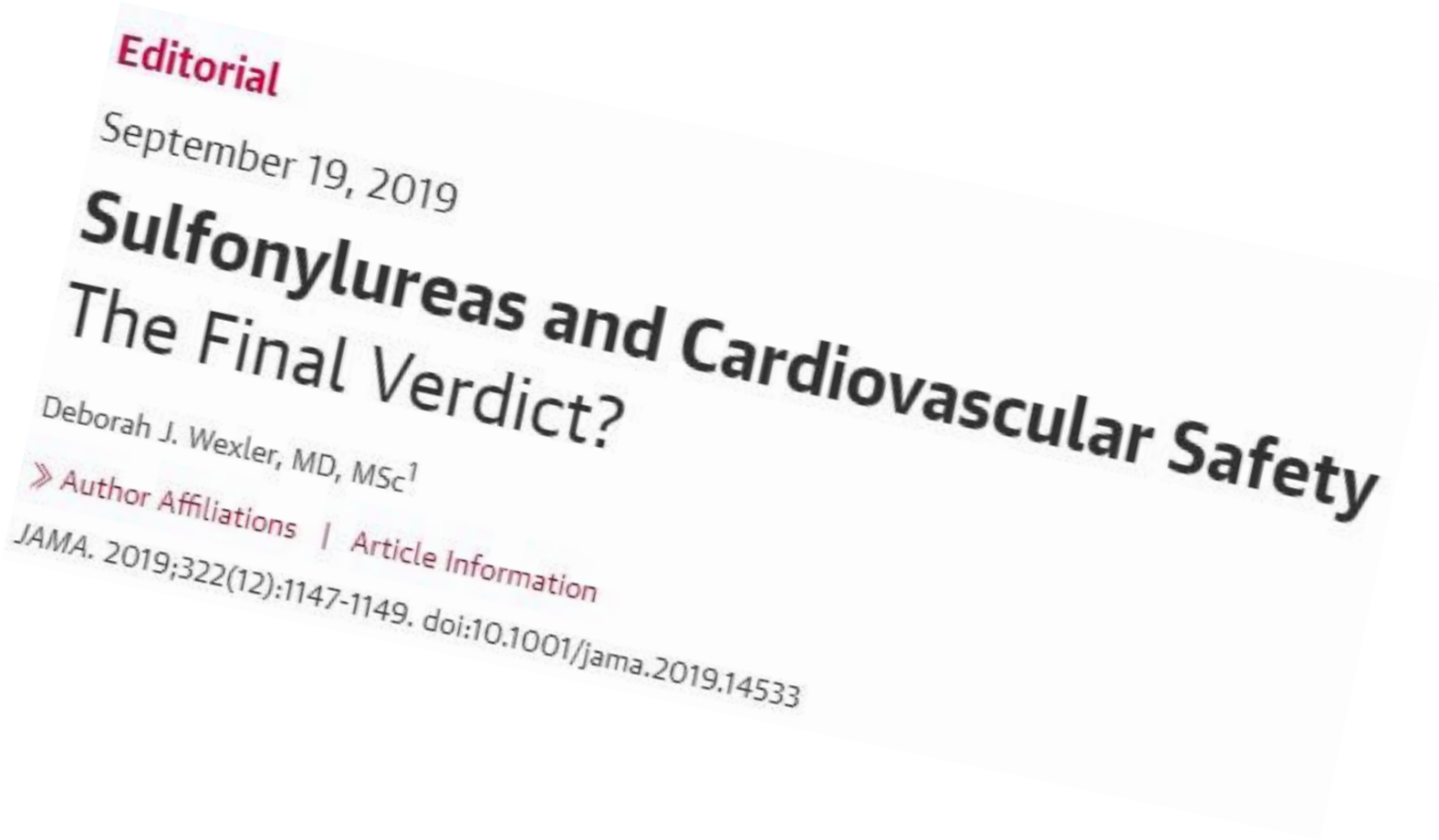
Resultados secundarios



Refuerzo con medicación adicional para el control de la DM en el 49.3% del grupo con linagliptina vs el 47.1% en el de la glimepirida, con un tiempo más corto de intensificación requerido en el grupo de linagliptina.

Comentarios

★ Se desconoce si este resultado puede generalizarse a toda la clase de sulfonilureas, aunque los estudios observacionales no han observado diferencias en el riesgo cardiovascular entre gliburida, glipizida o glimepirida.



Editorial

September 19, 2019

Sulfonylureas and Cardiovascular Safety
The Final Verdict?

Deborah J. Wexler, MD, MSc[1]

» Author Affiliations | Article Information

JAMA. 2019;322(12):1147-1149. doi:10.1001/jama.2019.14533

"las SU modernas (gliburida, glipizida y glimepirida) pueden continuar utilizándose con tranquilidad asociadas a la MET con la confianza de su eficacia en la reducción de las complicaciones microvasculares, así como por su seguridad cardiovascular"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SEP 19, 2019

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray J.J.V., Solomon S.D., Inzucchi S.E., et al. | 10.1056/NEJMoa1911303

...8 patients (5 in the **dapagliflozin** group and 3 in the placebo group) were excluded from the safety analyses because they did not receive **dapagliflozin** or placebo (Table 2). Serious adverse events related to volume depletion occurred in 29 patients (1.2%) in the **dapagliflozin** group and in 40 patients...

EDITORIAL

SEP 19, 2019

Heart-Failure Therapy — New Drugs but Old Habits?

Fang J.C. | 10.1056/NEJMe1912180

...subsequent trials of SGLT2 inhibitors involving patients with type 2 diabetes: the CANVAS trial of canagliflozin and the DECLARE–TIMI 58 trial of **dapagliflozin**. Since these heart-failure benefits were independent of glucose lowering, it was postulated that SGLT2 inhibitors might be a treatment for...

DAPA-HF - A global trial

4,744 patients 20 countries

Descripción:

El objetivo del ensayo fue evaluar la dapagliflozina (un inhibidor del SGLT2) en comparación con el placebo en pacientes con IC con FE reducida (HFrEF).

Diseño del estudio

- Aleatorizado
- Paralelo
- Placebo

Los pacientes con HFrEF (independientemente del estado de la diabetes) fueron asignados al azar a dapagliflozina 10 mg diarios (n = 2,373) versus placebo (n = 2,371).

- Número total de pacientes: 4.744
- Duración del seguimiento: 18,2 meses.
- Edad media del paciente: 66 años.
- Porcentaje femenino: 24%
- Porcentaje con DM2 conocida 42%; DM2 nueva 3%

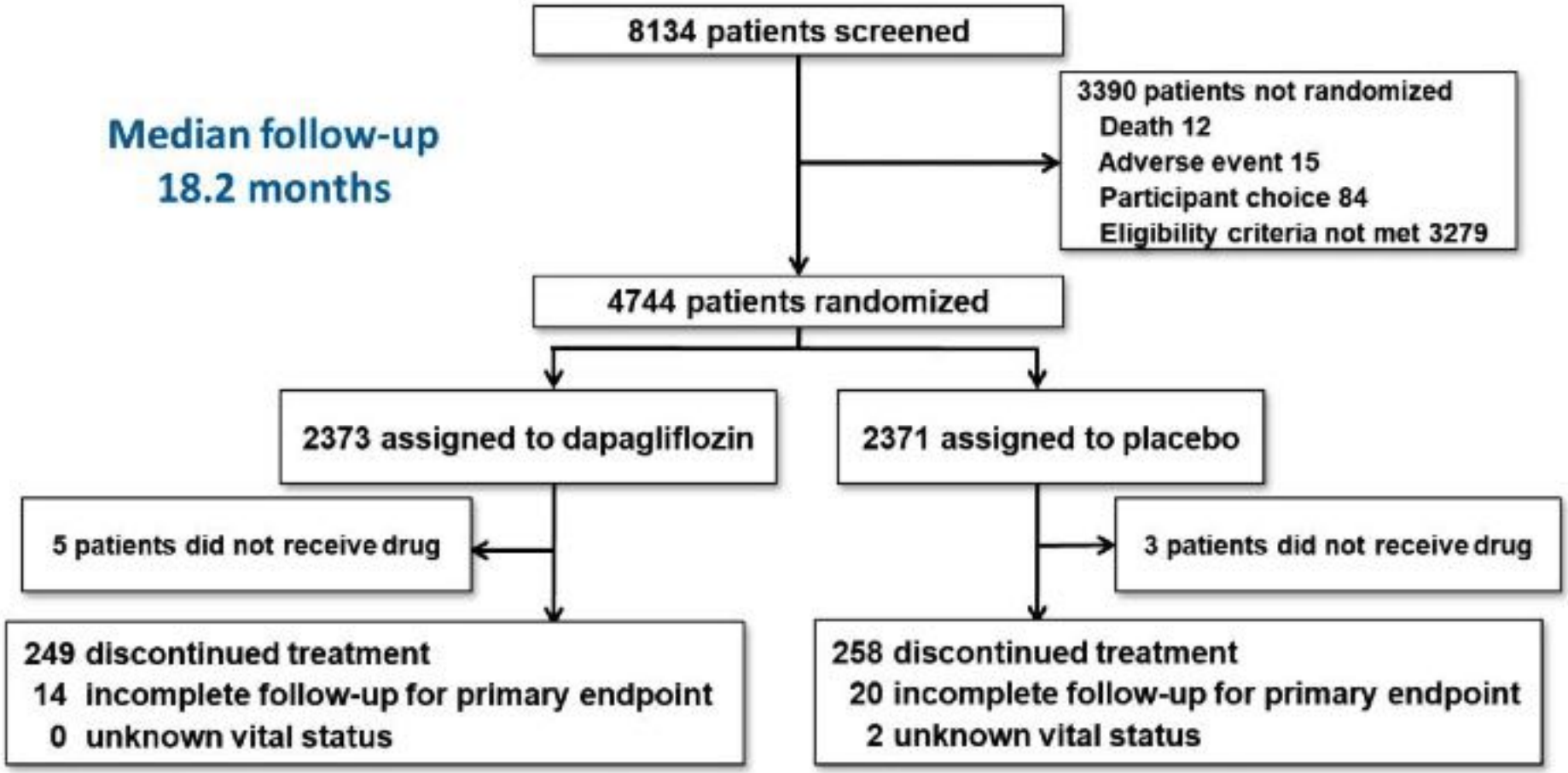
Criterios de inclusión:

- IC de clase II, III o IV de la NYHA
- FEVI ≤40%
- NT-proBNP ≥600 pg / ml (o ≥400 pg sí hospitalización el año previo por IC); si fibrilación / aleteo auricular ≥900 pg / ml)
- Solo se aceptan pacientes que estén recibiendo un tratamiento totalmente correcto segun las guias, incluyendo tanto la farmacoterapia como los dispositivos.

Criterio de exclusión:

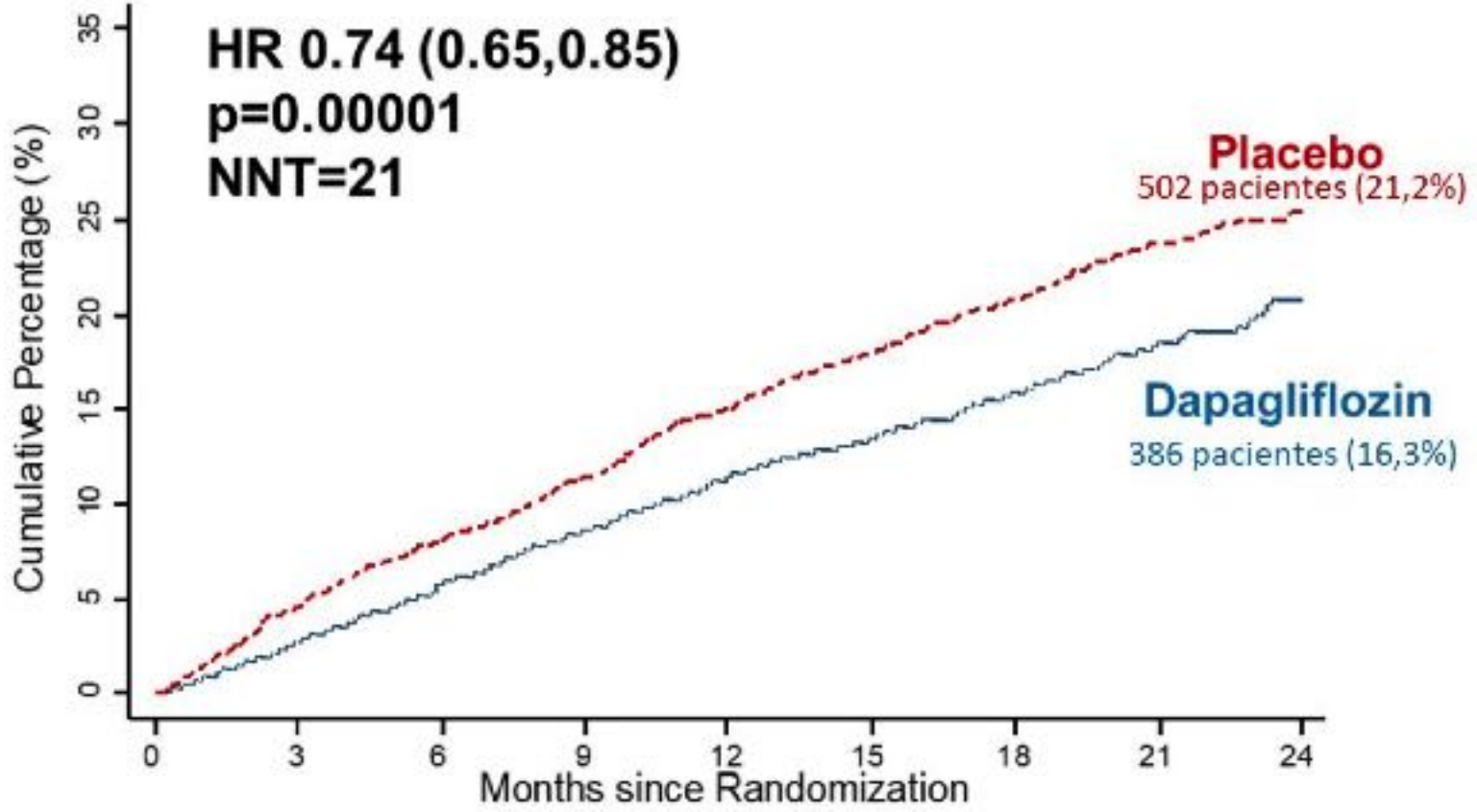
- FGE <30 ml / min / 1.73 m^2
- Hipotensión sintomática o TAs <95 mm Hg
- DM 1

Median follow-up
18.2 months



Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



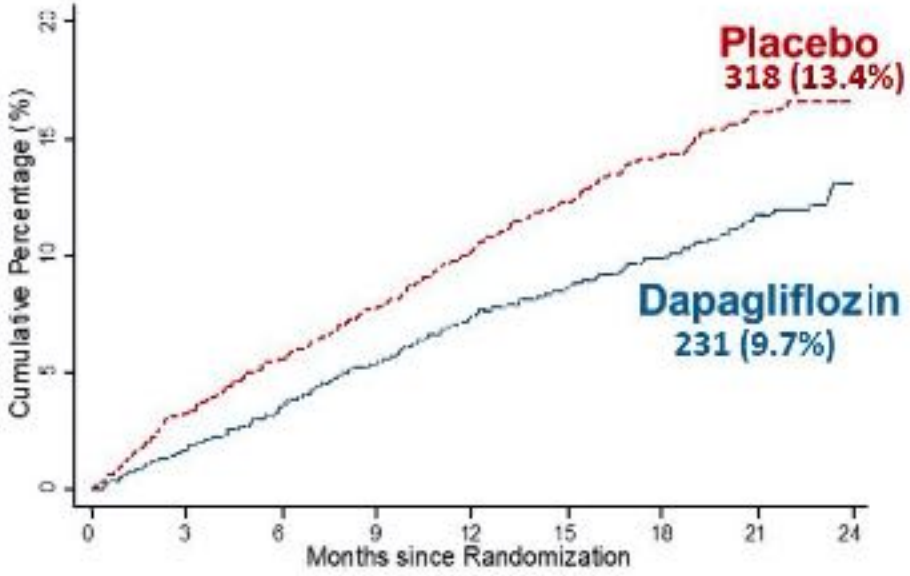
Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Components of primary outcome

Hospitalizaciones por IC

HR 0.70 (0.59, 0.83); p=0.00003

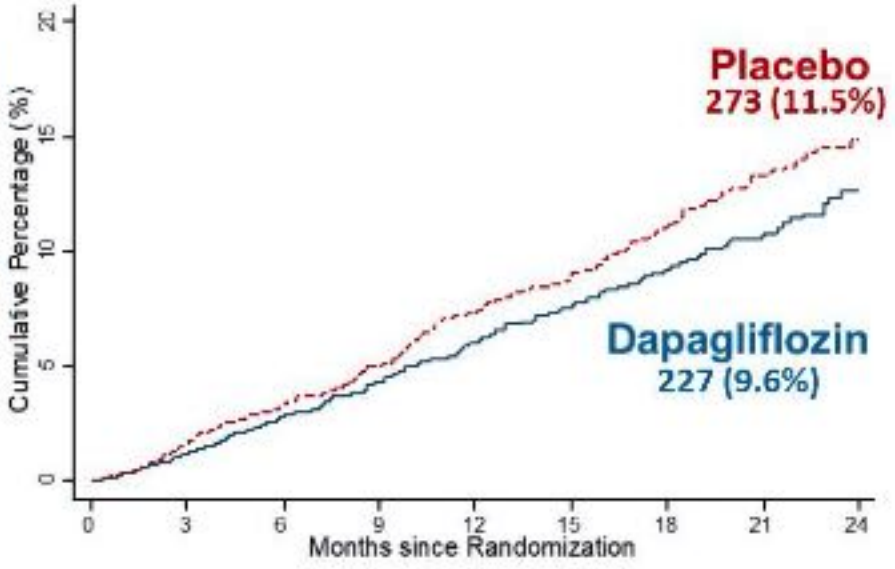


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

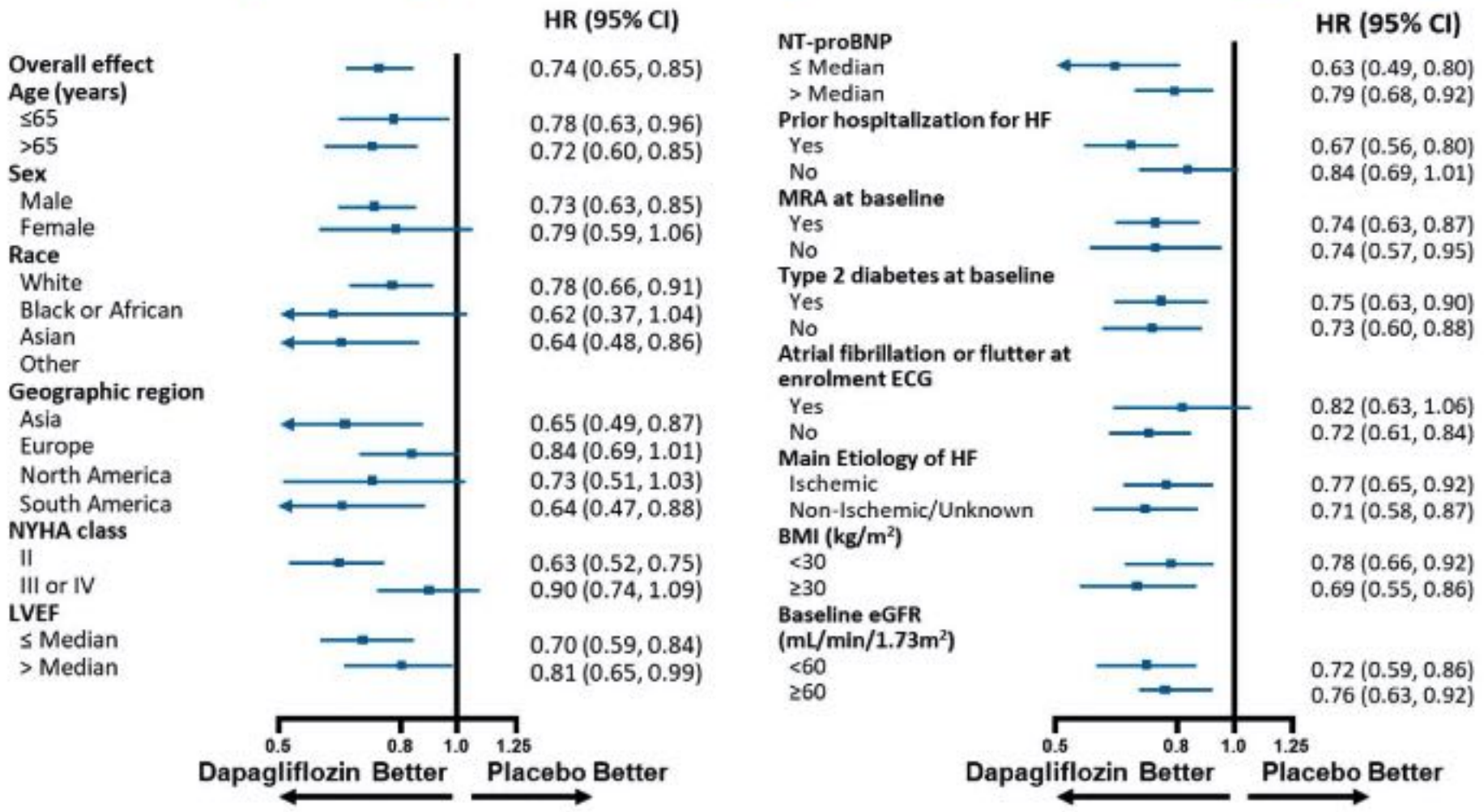
Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



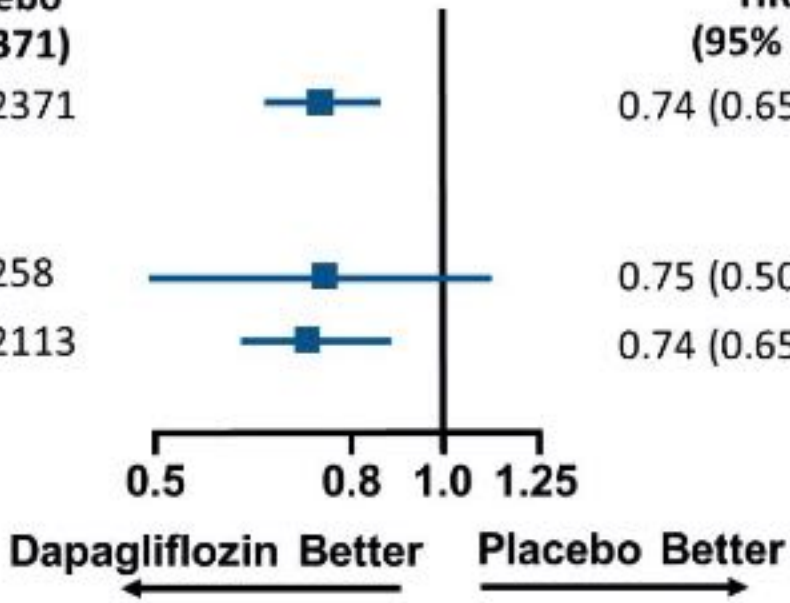
	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

Primary Endpoint: Prespecified subgroups

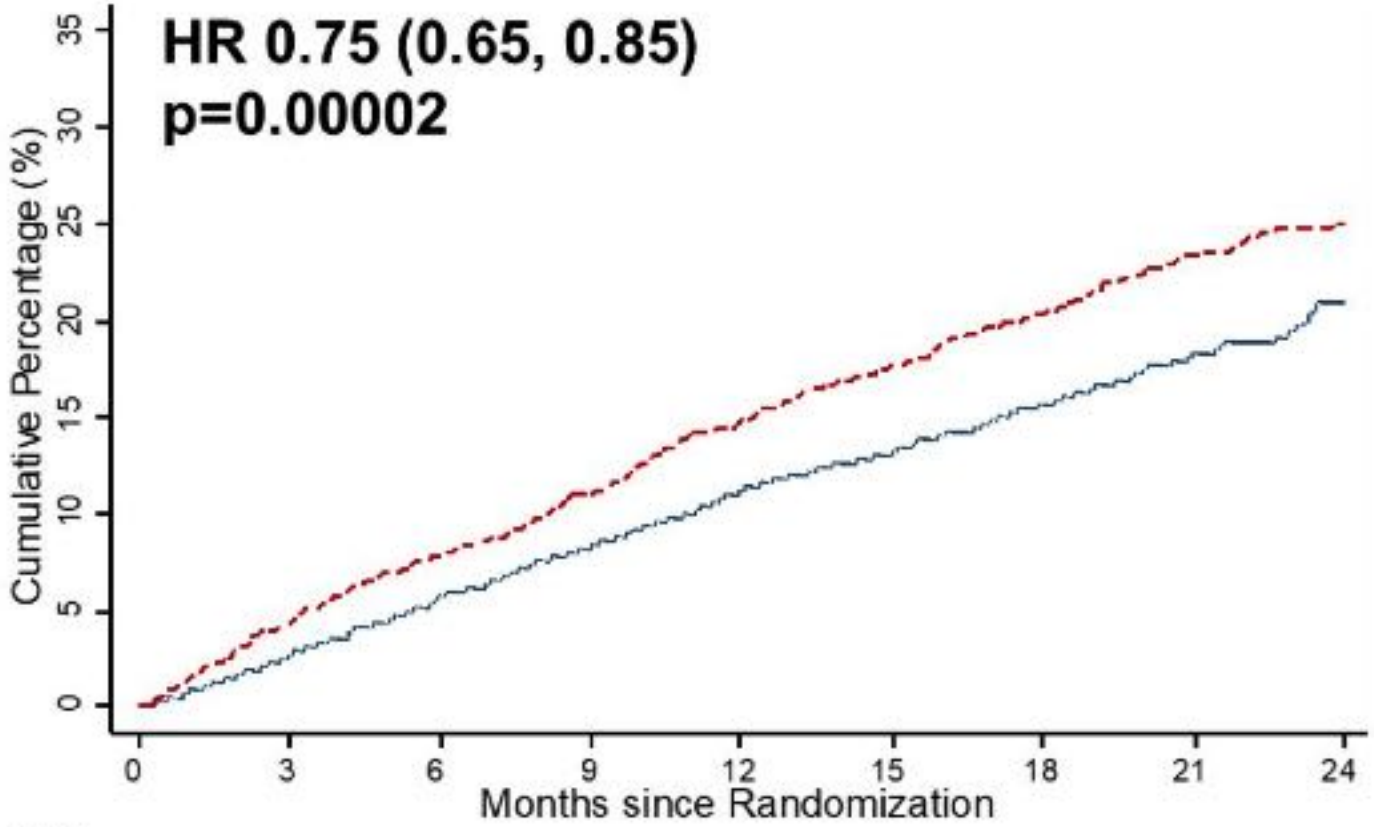


ARNI/no ARNI *post hoc* subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



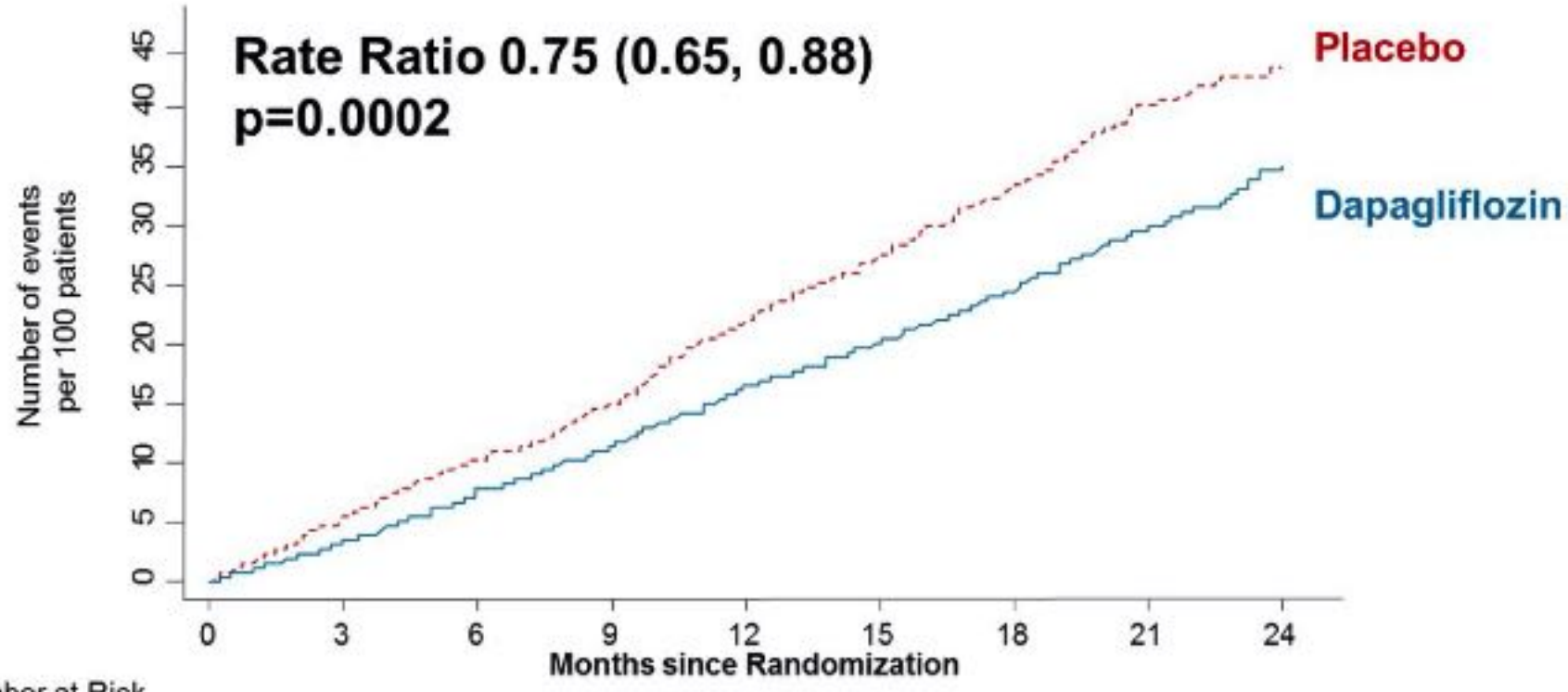
CV death or HF hospitalization



Number at Risk									
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212

Total HF hospitalizations and CV death

Including first and repeat hospitalizations



Number at Risk									
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference
2.8 points (95% CI 1.6, 4.0)
p<0.001*

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Treatment	Dapagliflozin	Placebo	Odds ratio (95% CI)
≥5 point improvement	58%	51%	1.15 (1.08, 1.23) p<0.001
≥5 point deterioration	25%	33%	0.84 (0.78, 0.90) p<0.001

*Taking account of death

Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

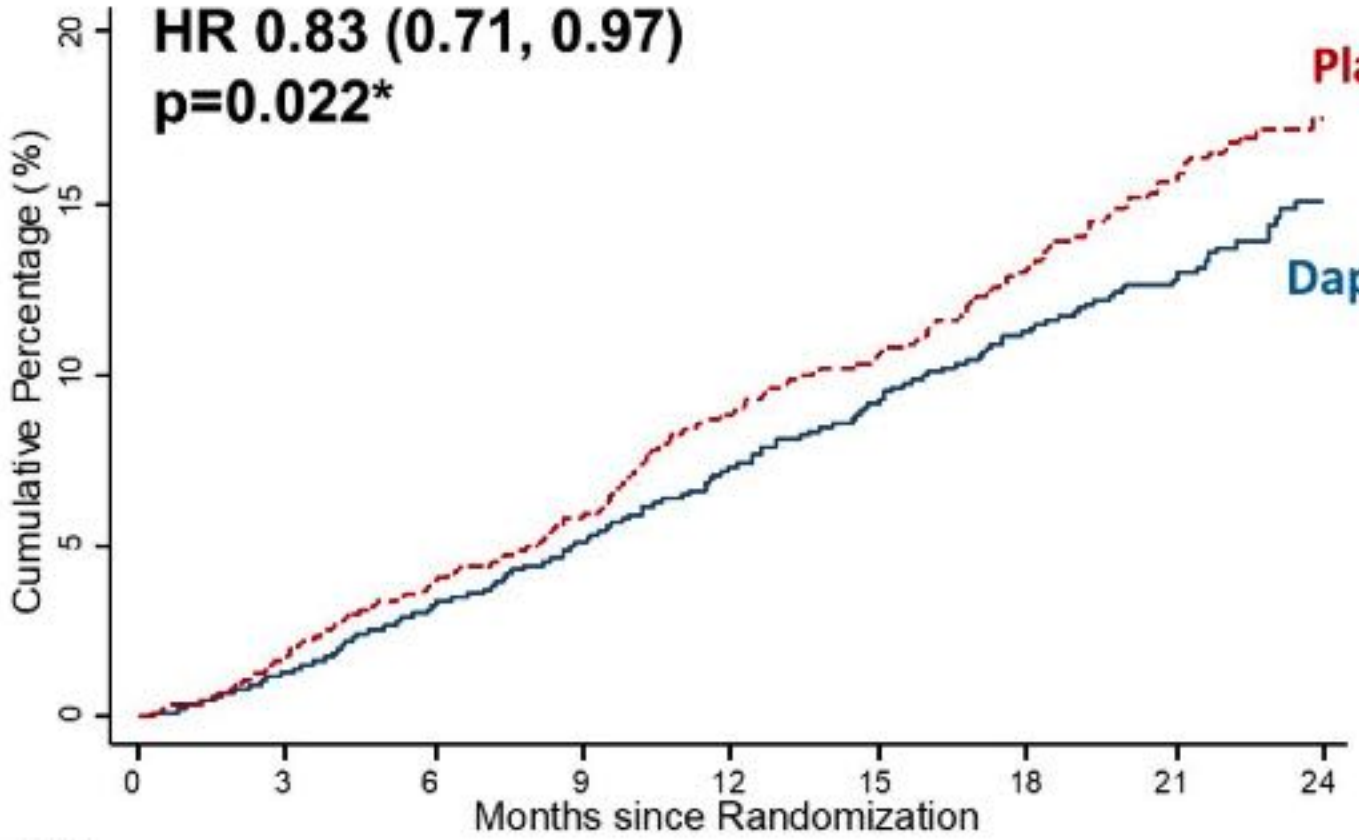
Treatment	No. (%)
Dapagliflozin	28 (1.2)
Placebo	39 (1.6)

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation

*Sustained = 28 days or more

All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

Resultados secundarios:

- Muerte cardiovascular: 9.6% con dapagliflozina vs. 11.5% con placebo
- Hospitalización por insuficiencia cardíaca: 9.7% con dapagliflozina vs. 13.4% con placebo
- Empeoramiento de la función renal: 1,2% con dapagliflozina frente a 1,6% con placebo (p = 0,17)

LIMITACIONES:

- Casi todos los pacientes tenían IC moderada, por lo que se necesitan más estudios para conocer sus efectos en la IC más grave.
- El uso de de sacubitril-valsartán fue limitado (en aproximadamente el 10% de los pacientes), por lo que se precisan más estudios para valorar el efecto en pacientes con este tratamiento.
- No se informaron datos sobre las dosis individuales de las terapias de insuficiencia cardíaca de fondo.