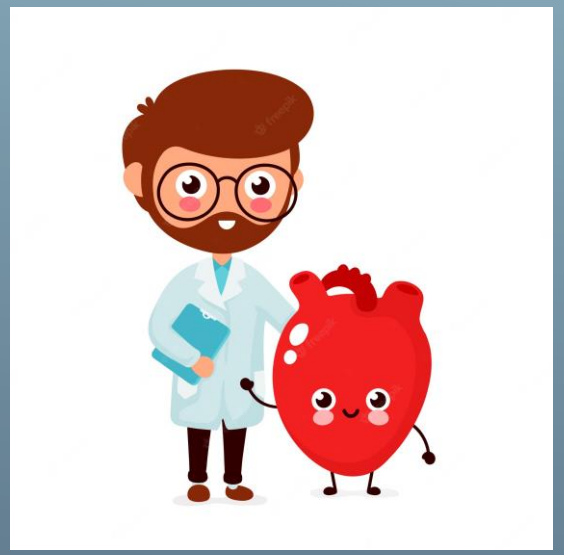
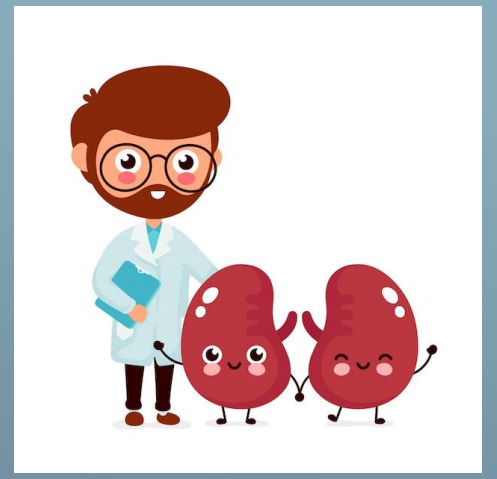
ISGLT2 : DESDE DISTINTAS MIRADAS

Dr. Atilio Castillo Ruiz

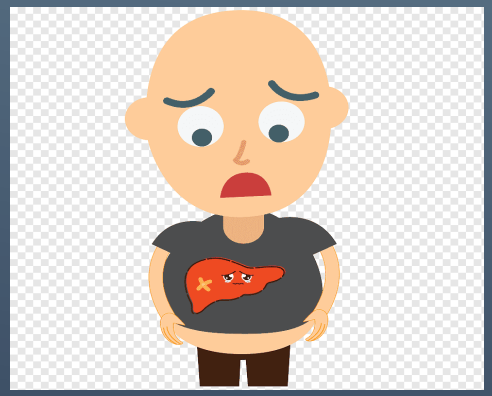
Medicina Interna- Diabetología

Educar-Actuar-Detener®






OJO CLÍNICO



CONFLICTO DE INTERÉS

Asesoría Médica: Servier, Boeringher Ingelheim, Abbott, Quimfa, PTC

Disertante: Abbott, Novo Nordisk , Sanofi, Quimfa, Eurofarma, PTC

Becas de Cursos y/o Congresos Nacionales e Internacionales: Sanofi, Servier, Boeringher Ingelheim, Novo Nordisk, Lilly ,Quimfa

Ningún laboratorio de la industria farmacéutica ha ejercido presión de cualquier índole para expresar el contenido de esta presentación

- En la Medicina Oriental:

✓Se utilizaba la corteza del **árbol de manzo**

✓**En 1835**

✓Compuesto activo: **Florizina**

✓Inhibidor No Selectivo de:SGLT-2 y SGLT-1

- Modelo de Inhibición de los SGLT2:
- **Glucosuria Familiar Renal**

✓Poco frecuente

✓Sin afectación renal a largo plazo

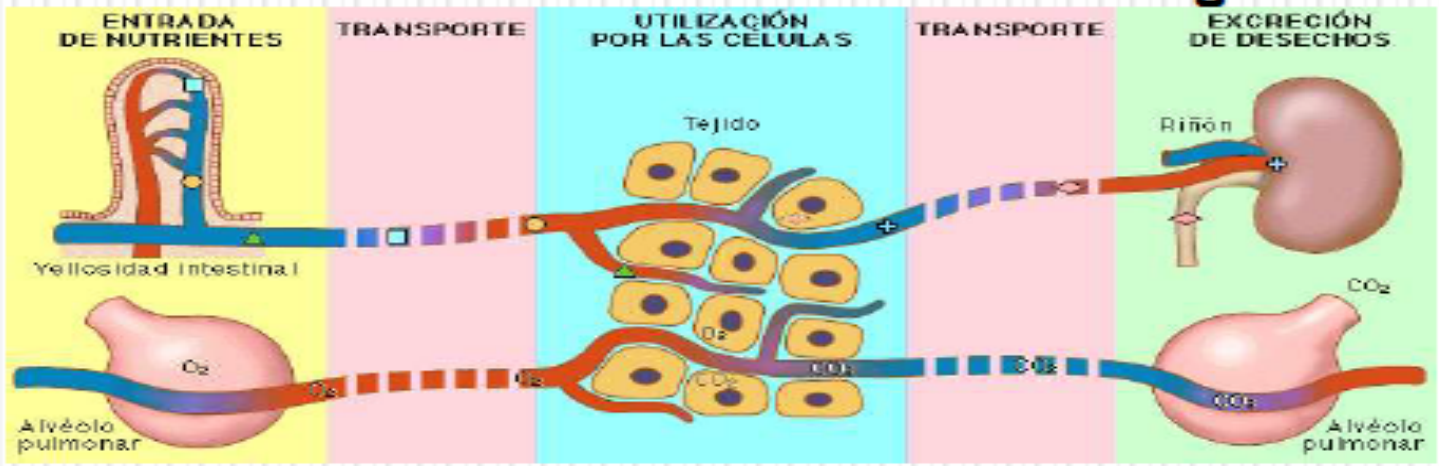
ISGLT2

MECANISMOS DE ACCION

Educar-Actuar-Detener®

- Riñones normalmente filtran 180g de glucosa al día

- Reabsorbida por una familia de proteínas transmembrana llamadas **cotransportadores de sodio-glucosa**



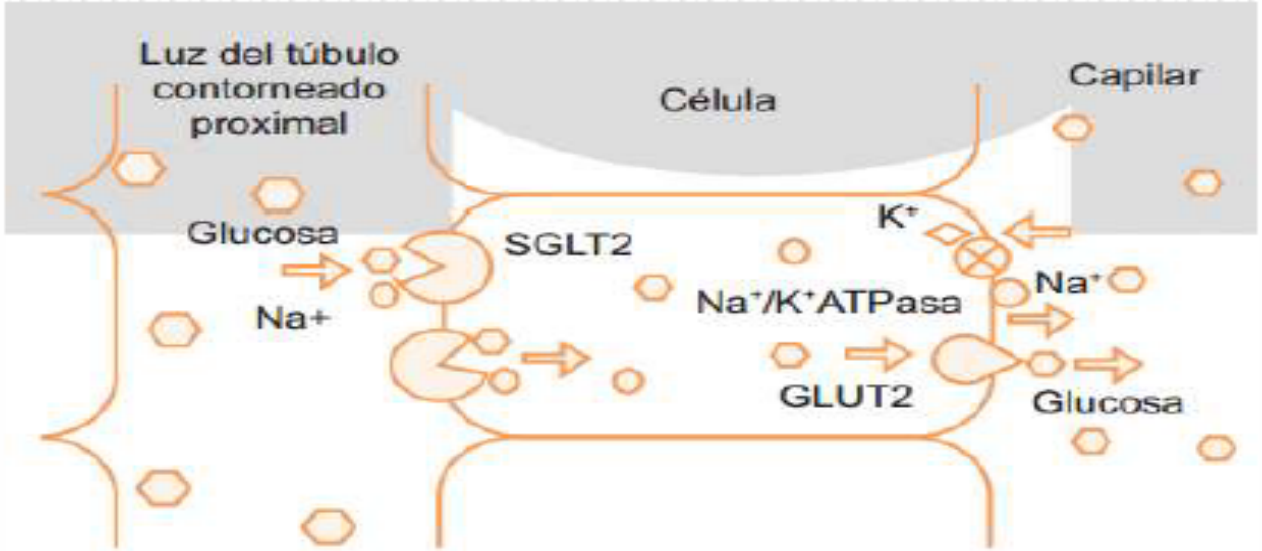
- Localizadas en el **túbulo contorneado proximal**

- ✓ Reabsorbida a la circulación casi en su totalidad
- ✓ Excreta por la orina menos de 1% de glucosa filtrada

SGLT : Reabsorben moléculas de glucosa a través de la membrana celular mediante el **sodio** como sustrato

Por **transporte activo** al acoplarse a este electrólito y transportarlo a favor de su gradiente electroquímico al interior de la célula epitelial.

Por la acción de la **bomba Na+/K+ ATPasa** que utiliza trifosfato de adenosina **(ATP)** como sustrato energético



- En los humanos, los inhibidores del transportador de sodio-glucosa tipo 2 inhiben sólo **30 a 50%** de la reabsorción renal de la glucosa

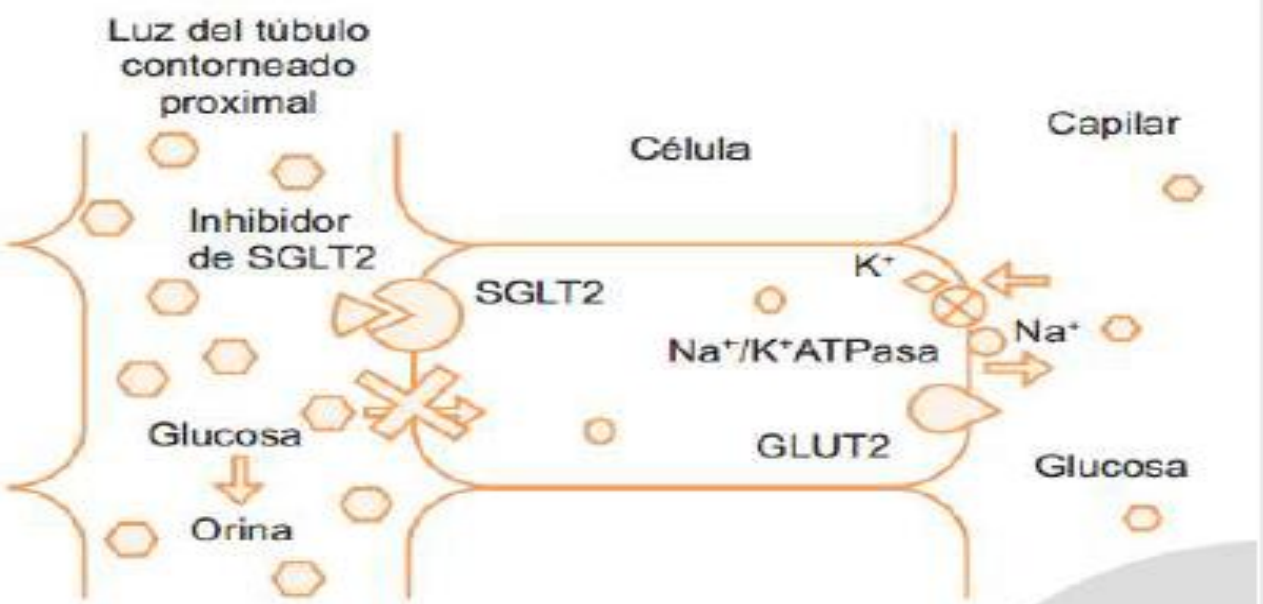
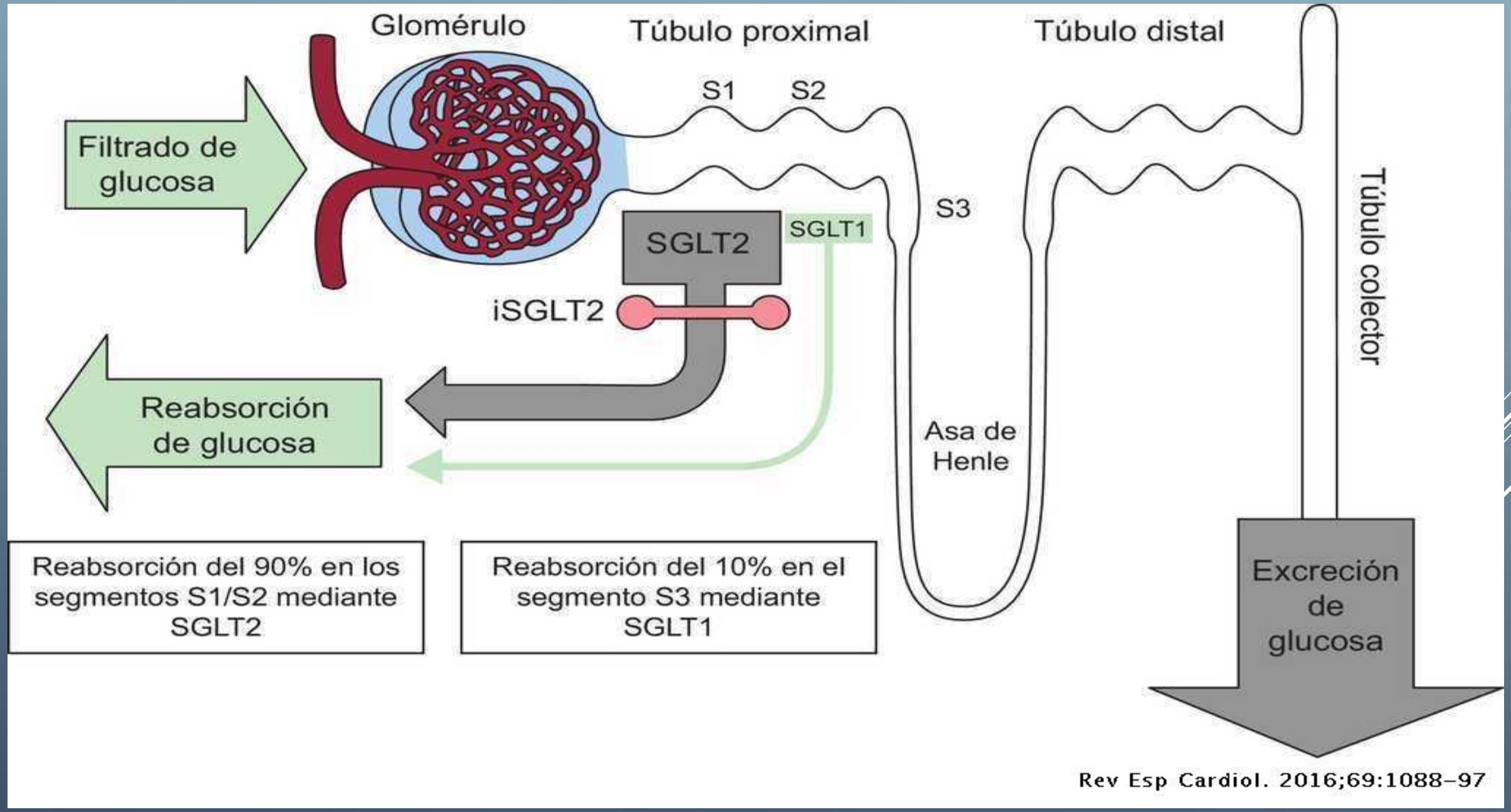
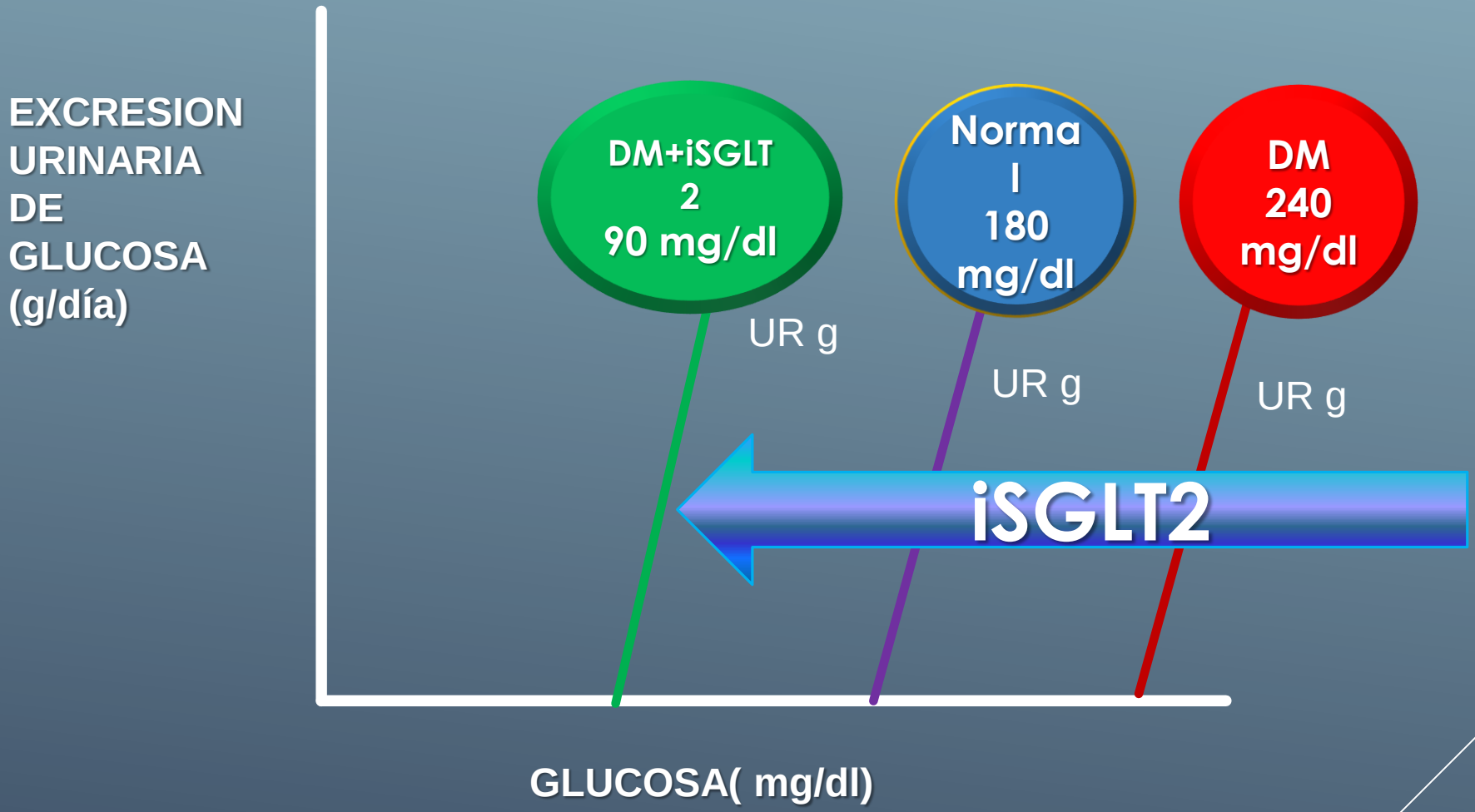


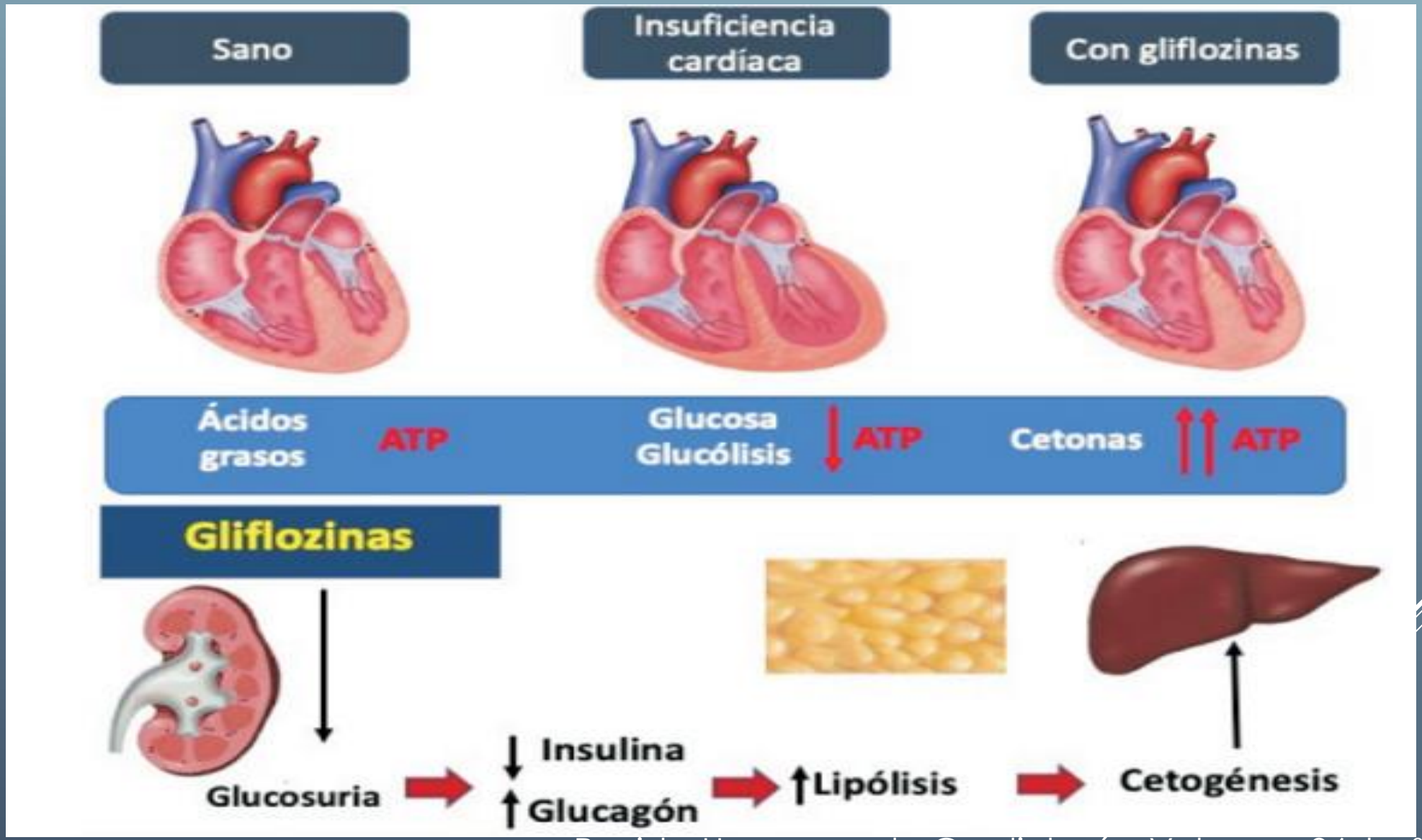
Figura 2. Los fármacos inhibidores del transportador de sodio-glucosa tipo 2, como la dapagliflozina y la canagliflozina, disminuyen en 30 a 50% la reabsorción de glucosa a partir de la luz del túbulo contorneado proximal, de esta manera se induce glucosuria y disminuye la concentración sérica de glucosa.

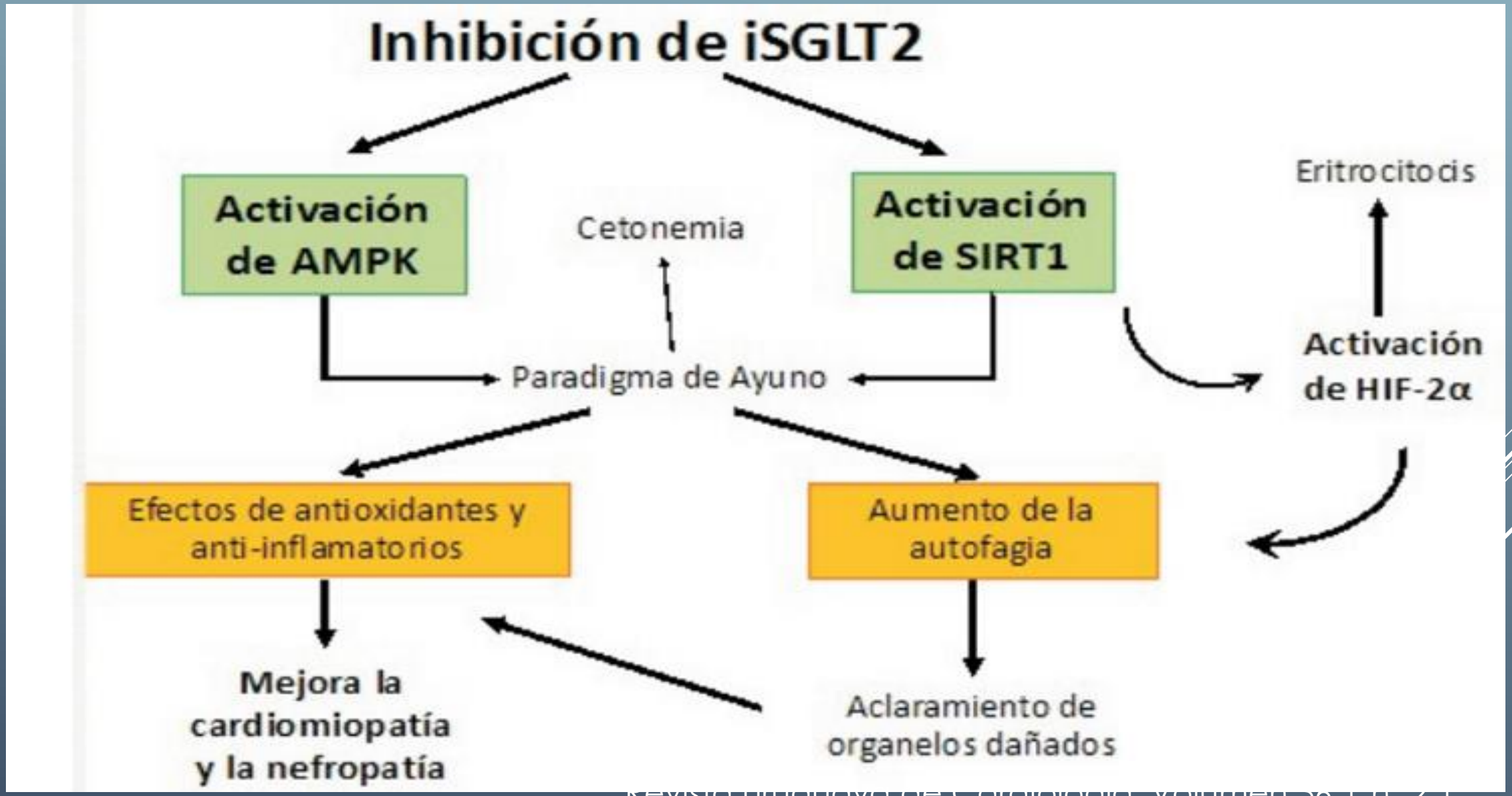


Rev Esp Cardiol. 2016;69:1088–97

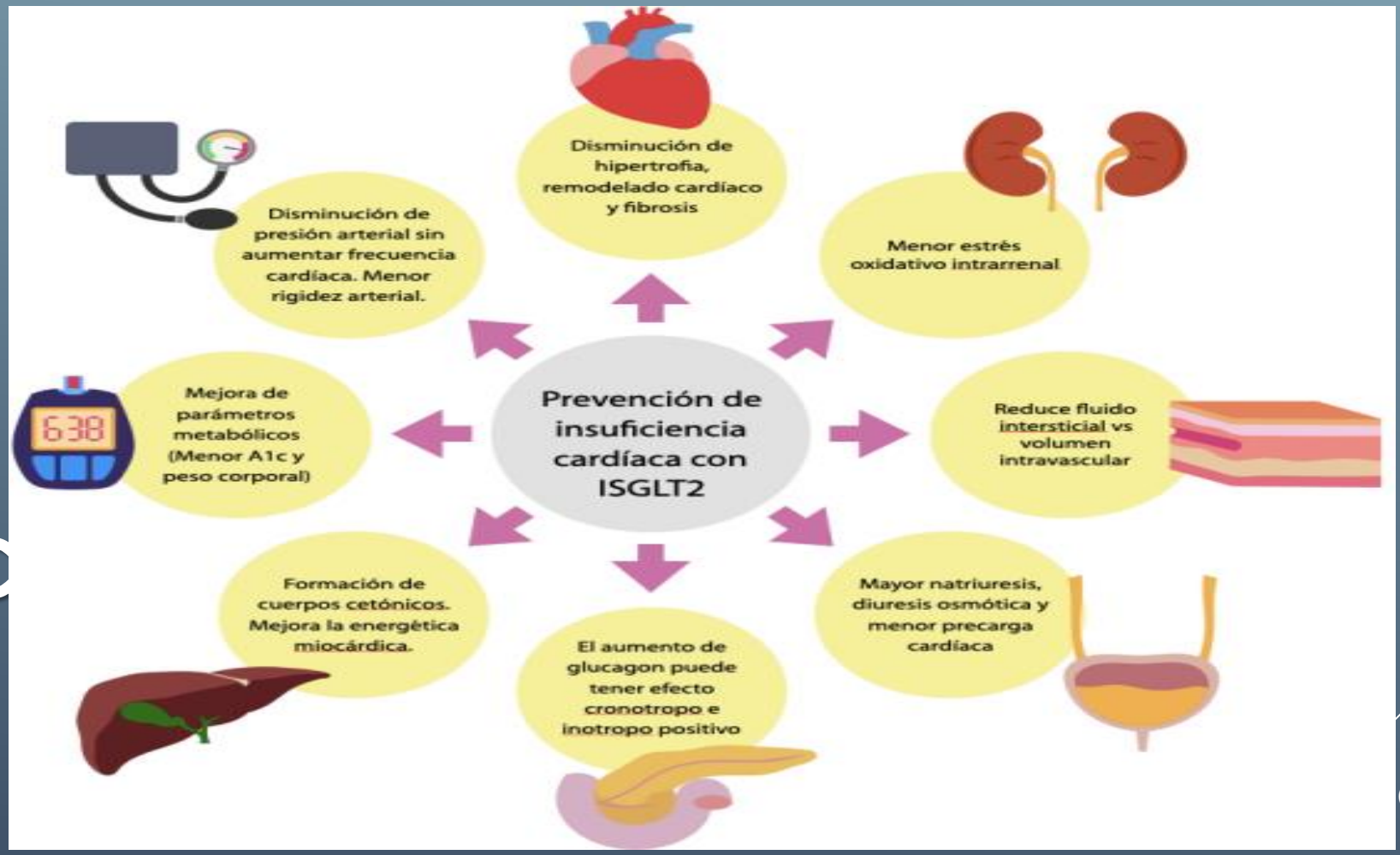

EXCRESION URINARIA DE GLUCOSA (g/día)
DM+iSGLT 2 90 mg/dl
Normal 180 mg/dl
DM 240 mg/dl
UR g
UR g
UR g
iSGLT2
GLUCOSA(mg/dl)


Efectos renales de los inhibidores SGLT2
Reducción de la albuminuria
Retraso del deterioro progresivo de la función renal durante el tratamiento a largo plazo
Disminución aguda, moderada y reversible de la TFGe durante las primeras 4 semanas de tratamiento

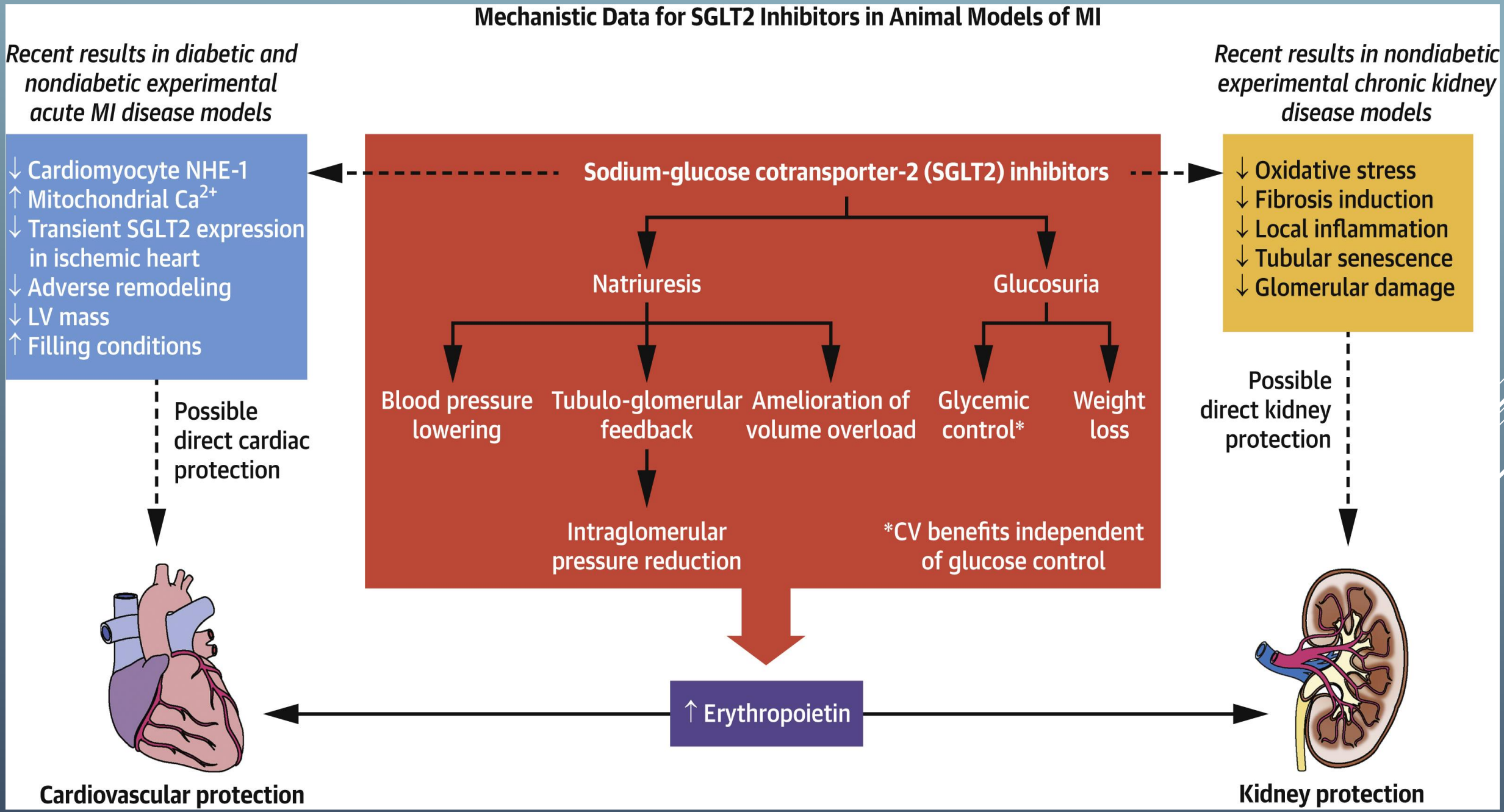

Sano
Insuficiencia cardíaca
Con gliflozinas
Ácidos grasos
ATP
Glucosa
Glucólisis
ATP
Cetonas
ATP
Gliflozinas
Glucosuria
Insulina
Glucagón
Lipólisis
Cetogénesis

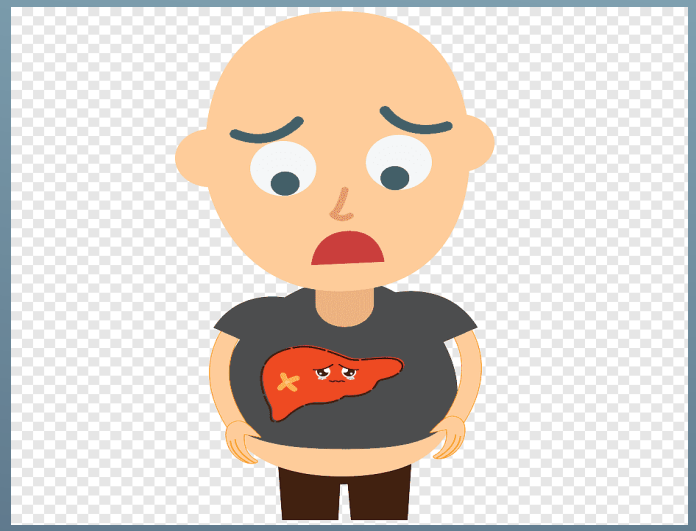

Inhibición de iSGLT2
Activación de AMPK
Cetonemia
Activación de SIRT1
Eritrocitosis
Paradigma de Ayuno
Activación de HIF-2α
Efectos de antioxidantes y anti-inflamatorios
Aumento de la autofagia
Mejora la cardiomiopatía y la nefropatía
Aclaramiento de organelos dañados

MEC



Card 2020;1(1):6-14


Mechanistic Data for SGLT2 Inhibitors in Animal Models of MI
Recent results in diabetic and nondiabetic experimental acute MI disease models
↓ Cardiomyocyte NHE-1
↑ Mitochondrial Ca^{2+}
↓ Transient SGLT2 expression in ischemic heart
↓ Adverse remodeling
↓ LV mass
↑ Filling conditions
Possible direct cardiac protection
Sodium-glucose cotransporter-2 (SGLT2) inhibitors
Natriuresis
Glucosuria
Blood pressure lowering
Tubulo-glomerular feedback
Amelioration of volume overload
Glycemic control*
Weight loss
Intraglomerular pressure reduction
*CV benefits independent of glucose control
Recent results in nondiabetic experimental chronic kidney disease models
↓ Oxidative stress
↓ Fibrosis induction
↓ Local inflammation
↓ Tubular senescence
↓ Glomerular damage
Possible direct kidney protection
↑ Erythropoietin
Cardiovascular protection
Kidney protection



DIABETES

Educar-Actuar-Detener®

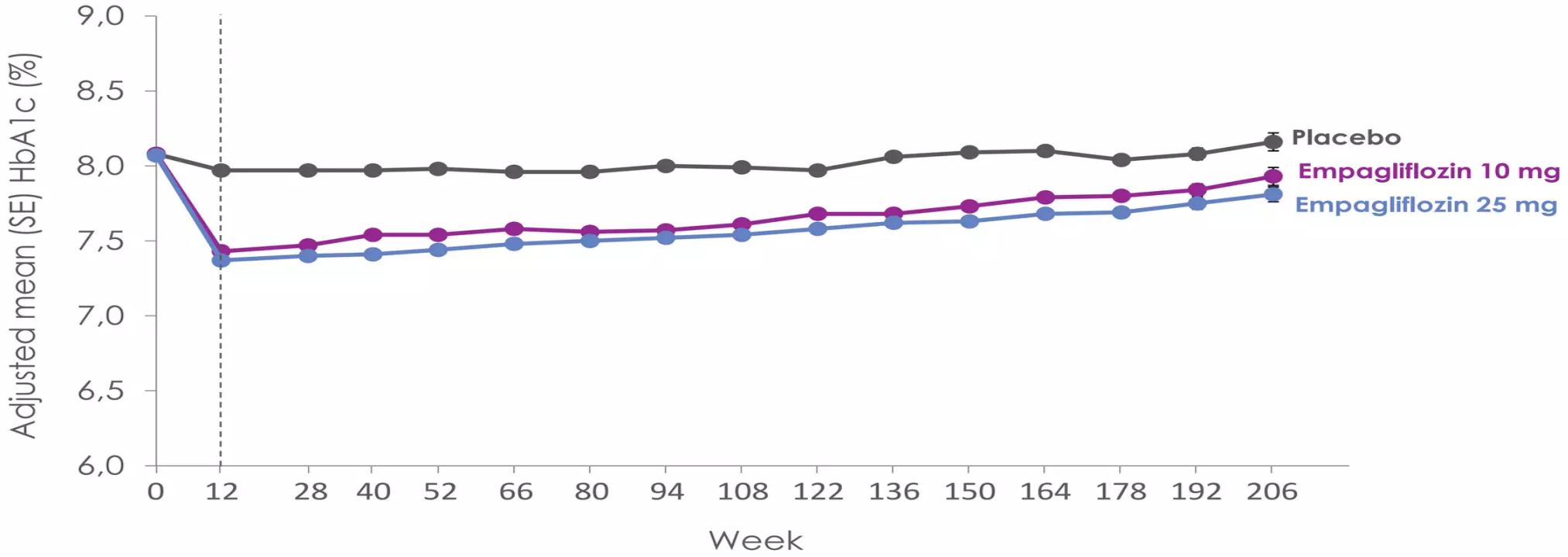
SGLT2 Inhibitors in T2DM

EMA-Approved[a-d]	MOA[e]	Clinical Effects[e]	Glycemic Efficacy[e]
• Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	• Blocks glucose reabsorption by the kidney, increasing glucosuria • ? Other tubulo-glomerular effects	↓Weight, BP • Effective at all stages of T2DM with preserved glomerular function ↓MACE, HF, CKD with some agents	• Intermediate to high (dependent on GFR)

a. Invokana SmPC; b. Forxiga SmPC; c. Jardiance SmPC; d. Steglatro SmPC; e. Davies MJ, et al. *Diabetologia*. 2018;61:2461-2498.

EMPA-REG OUTCOME®

HbA1c



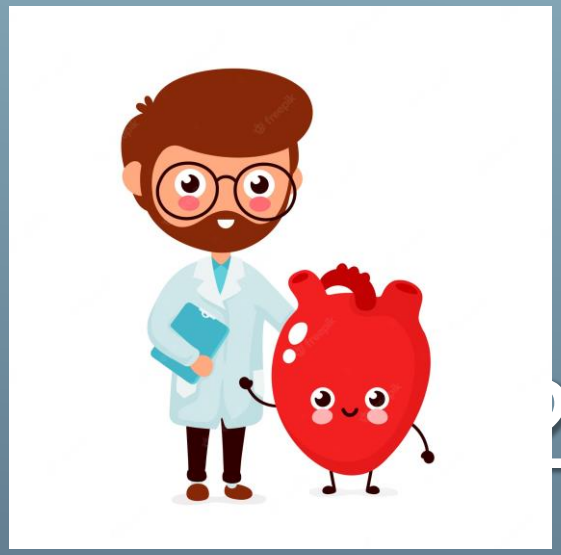
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

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

A1c 0,42%

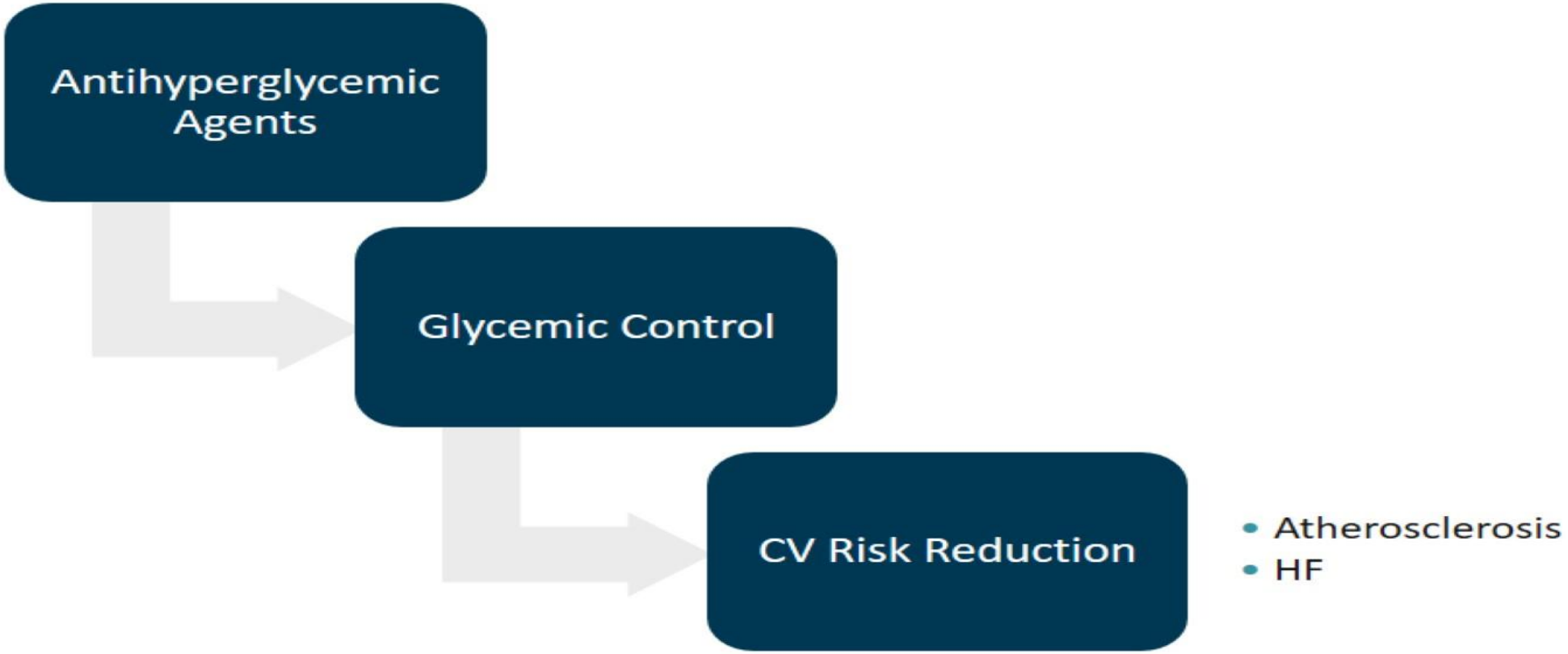


2

CARDIOVASCULAR

Educar-Actuar-Detener®

Glucose-Lowering Agents and CVD Risk Reduction in T2DM



Carboone S, et al. *Mayo Clin Proc*. 2018;93:1629-1647.

Main CVOTs With SGLT2 Inhibitors

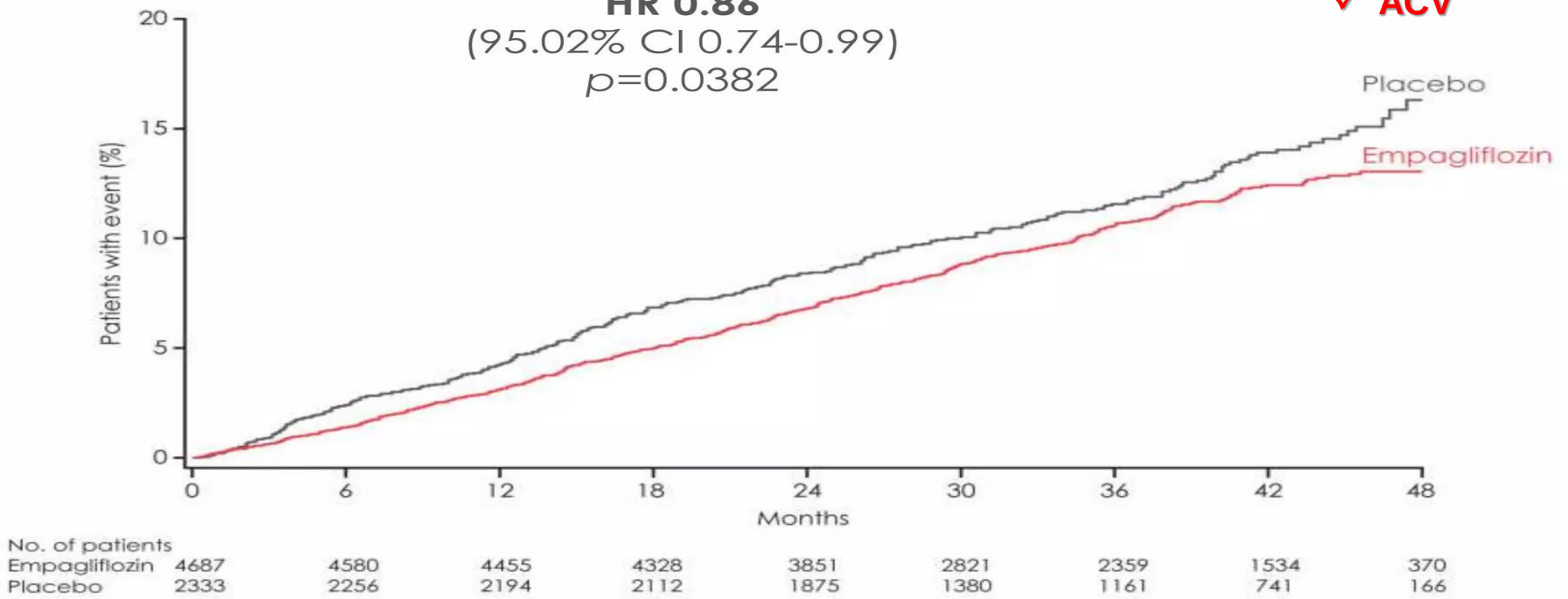
	EMPA-REG OUTCOME[a]	CANVAS[b]	DECLARE-TIMI 58[c]	VERTIS-CV[d]
Interventions	Empagliflozin /placebo	Canagliflozin /placebo	Dapagliflozin /placebo	Ertugliflozin /placebo
Main inclusion criteria	Established CVD	Est. vascular complications or ≥ 2 CV risk factors	High risk for CV event	Est. vascular complications
N	7020	10,142	17,160	~8000
Primary outcome	3P-MACE	3P-MACE	3P-MACE; CV death or HHF	3P-MACE
Key secondary outcome	4P-MACE	Progression of albuminuria	Renal composite outcome; all-cause death	4P-MACE
Follow-up	Median f/u 3.1 y	Mean 188.2 wk	Median f/u 4.2 y	5-7 y (estimated)

a. Zinman B, et al. *N Engl J Med*. 2015; 373:2117-2128; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. Cannon CP, et al. *Am Heart J*. 2018;206:11-23.

EMPA-REG OUTCOME®

primary outcome: 3-point MACE

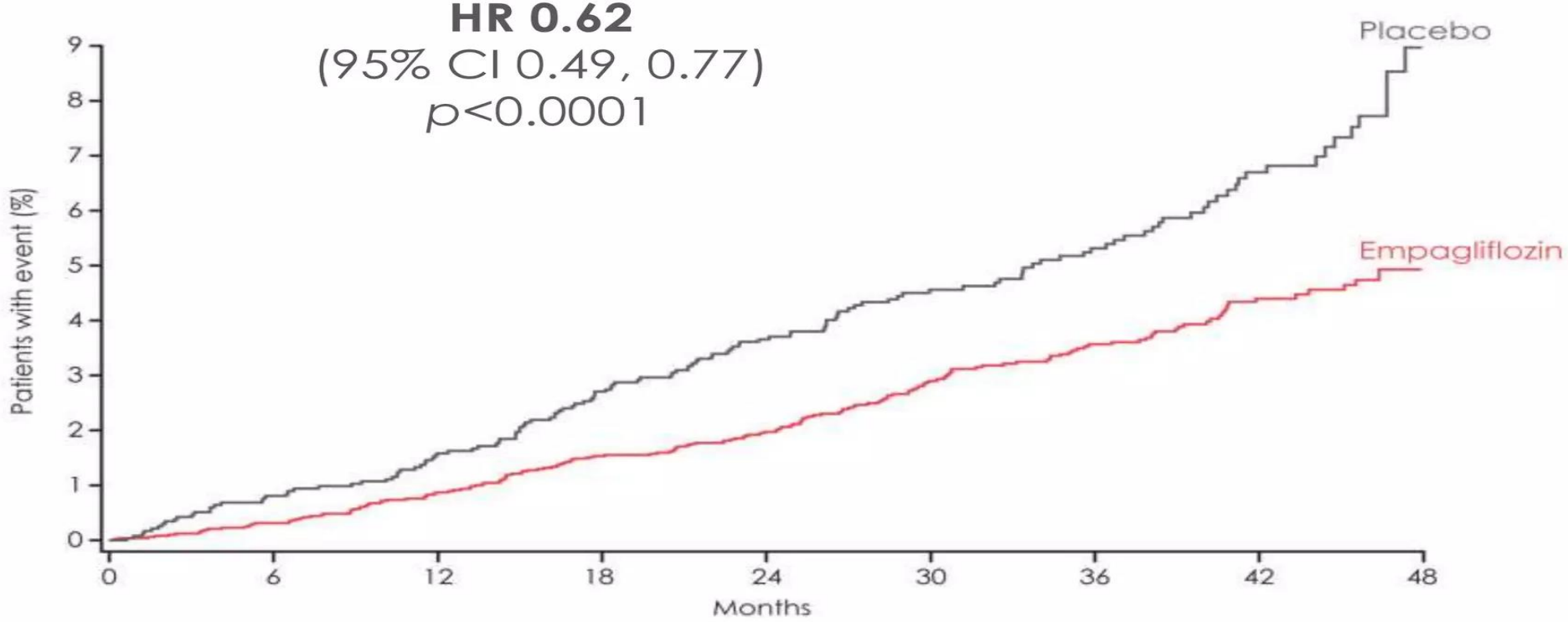
- ✓ **MUERTE**
- ✓ **IAM NO FATAL**
- ✓ **ACV**



EMPA-REG OUTCOME®

CV death

HR 0.62
(95% CI 0.49, 0.77)
$p<0.0001$

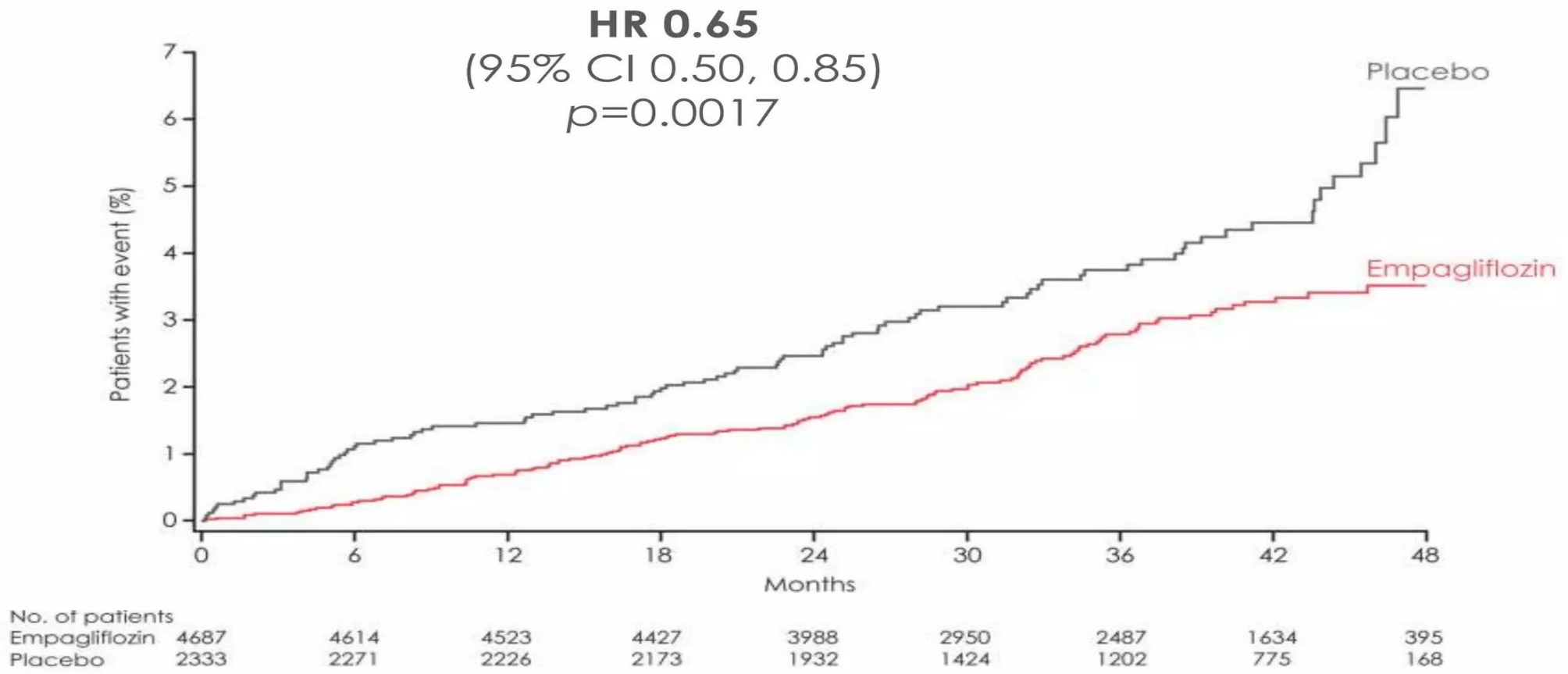


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

2015

EMPA-REG OUTCOME®

hospitalization for heart failure



2015

EMPA-REG OUTCOME: una nueva era

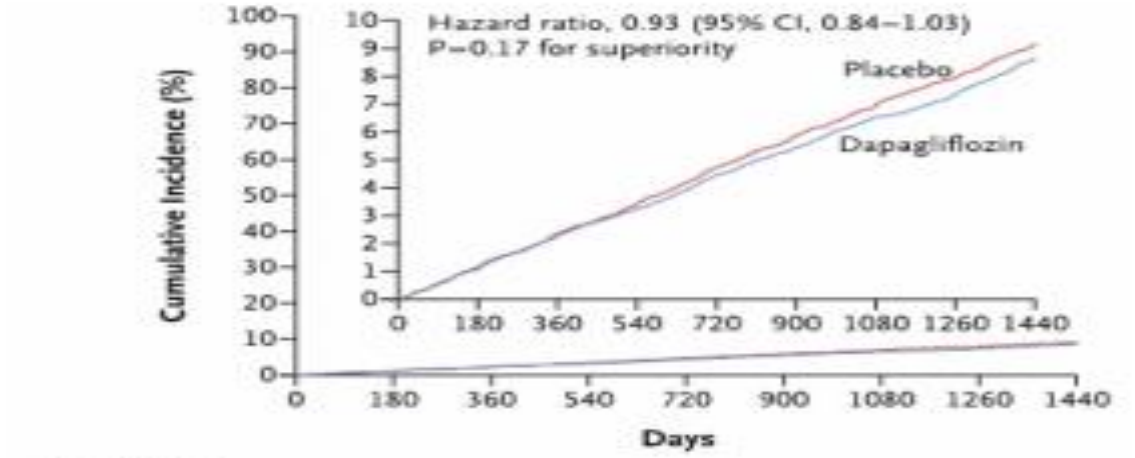
14%	38%	32%	35%	39%
				
↓ 3P-MACE[1]	↓ CV death[1]	↓ All-cause mortality[1]	↓ HF hospitalisations[1]	↓New or worsening nephropathy*,[2]

*Defined as new onset of macroalbuminuria, doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m2), initiation of renal replacement therapy or death due to renal disease; 3P-MACE, 3-point major adverse cardiovascular events

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016 (submitted)

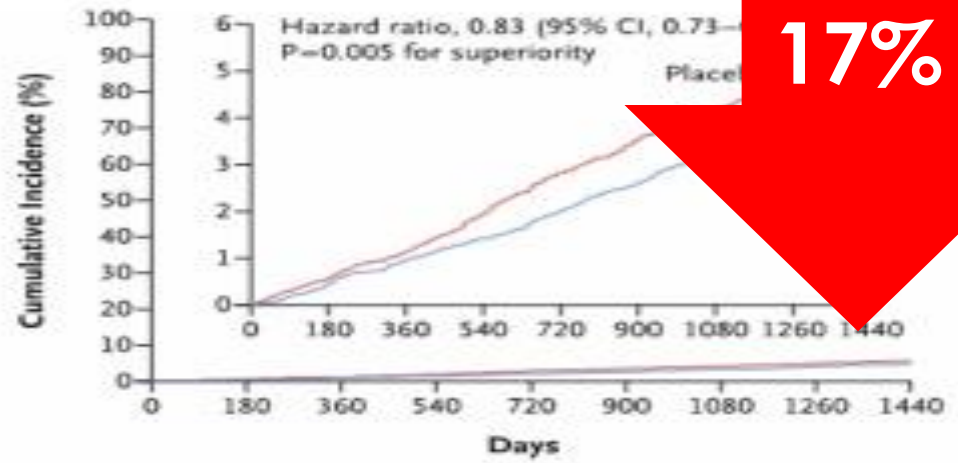
DECLARE TIMI-58: Co-Primary Outcomes

3-Point MACE: Death, Nonfatal MI, or Stroke



No. at Risk									
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

CV Death or HHF



17%

No. at Risk									
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357.

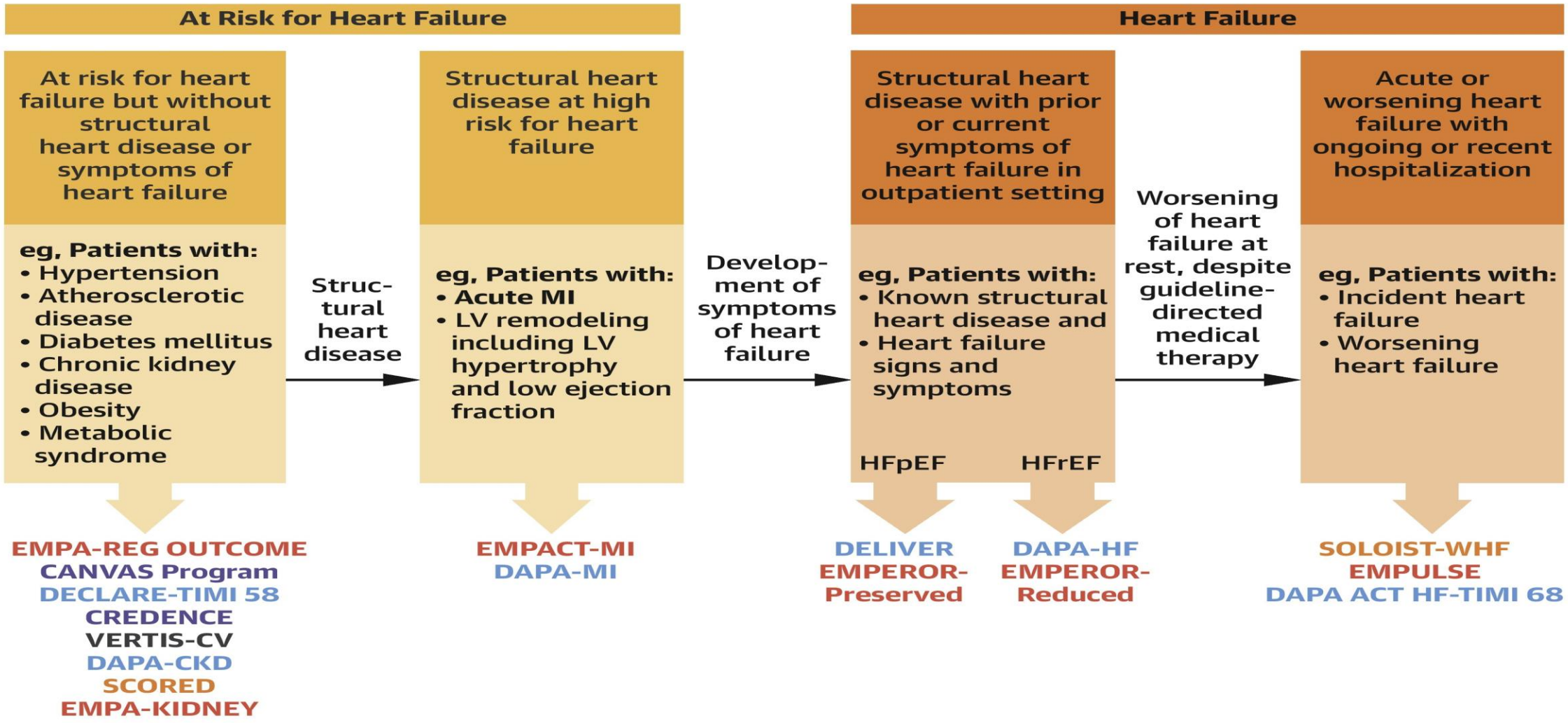
Se ha demostrado que los iSGLT2 mejoran los factores de riesgo CV en pacientes con DM2

SGLT2 inhibitor on top of metformin	Empagliflozin 10 mg[1]	Canagliflozin 100 mg[2]	Dapagliflozin 10 mg[3]	Ertugliflozin 5 mg[4]
HbA1c, %	-0.70*	-0.73†	-0.84‡	-0.7§
Weight, kg	-2.08*	-3.3†	-2.9‡	-3.0§
Systolic blood pressure, mmHg	-4.5*	-3.5†	-5.1¶	-4.4§
Diastolic blood pressure, mmHg	-2.0*	-1.8†	-1.8¶	-1.6§

Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

*Adjusted mean change from baseline at Week 24; †Least squares mean change from baseline at Week 52; ‡Adjusted mean change from baseline at Week 24; §Least squares mean change from baseline at Week 26; ¶Mean change from baseline at Week 24

CENTRAL ILLUSTRATION: Sodium Glucose Cotransporter-2 Inhibition Across the Spectrum of Cardiovascular Risk



Udell JA, et al. J Am Coll Cardiol. 2022;79(20):2058–2068.

Reducciones en los resultados CV, IC y renales observadas con inhibidores de SGLT2 en pacientes con DM2

	EMPA-REG OUTCOME[1,2] (empagliflozin)	CANVAS Program[3] (canagliflozin)	DECLARE-TIMI 58[4] (dapagliflozin)	VERTIS CV[5] (ertugliflozin)	CREDENCE[6*] (canagliflozin)
3P-MACE	▼ 14%†	▼ 14%†	NS†		▼ 20%‡
CV death	▼ 38%‡§	NS‡¶	NS‡¶		NS‡
HHF	▼ 35%‡§	▼ 33%‡¶	▼ 27%‡¶	▼ ‡	▼ 39%‡
Kidney outcomes	▼ 39%‡§	▼ 40%‡¶	▼ 47%‡¶	‡	▼ 30%**

▼ p<0.05 and/or upper 95% CI<1

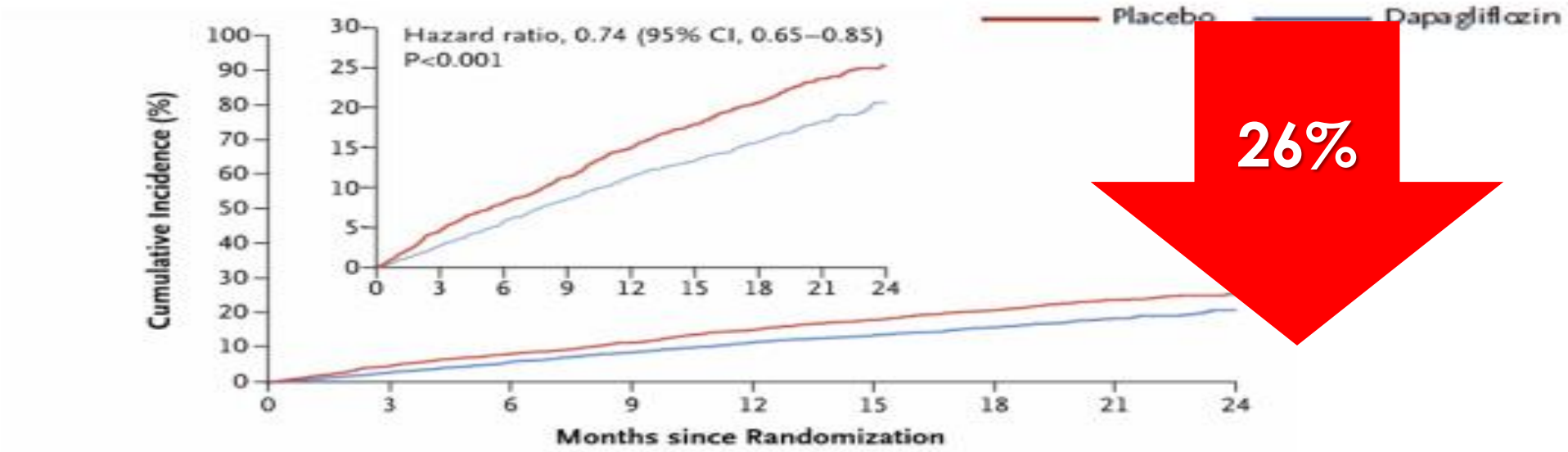
Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

*CREDENCE was a kidney outcomes trial in patients with T2D and albuminuric chronic kidney disease; †Testing for superiority for 3P-MACE was the primary endpoint in EMPA-REG OUTCOME and CANVAS Program (co-primary endpoint in DECLARE-TIMI 58), whereas testing for non-inferiority for 3P-MACE was the primary endpoint in VERTIS CV; ‡Secondary endpoints as defined in the study protocols; §Nominal *p*-value; ¶*p*-value not reported in publication; **Primary endpoint in CREDENCE

See slide notes for definitions of kidney outcomes, abbreviations and references

DAPA-HF: Primary Composite Endpoint

CV Death/HHF/Urgent HF Visit

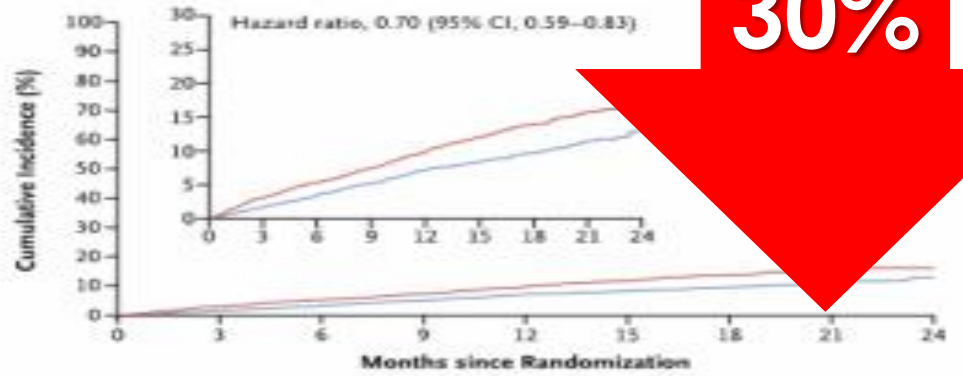


No. at Risk									
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

McMurray JJ, et al. *N Engl J Med.* 2019 Sept 19. [Epub ahead of print]

DAPA-HF: Components of Primary Endpoint

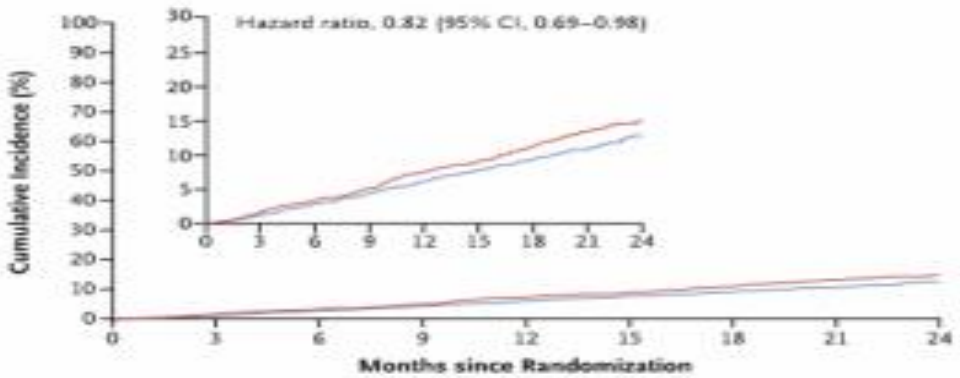
HHF



30%

No. at Risk									
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

CV Death



No. at Risk									
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232

Placebo Dapagliflozin

McMurray JJ, et al. *N Engl J Med*. 2019 Sept 19. [Epub ahead of print]

Sodium-glucose cotransporter-2 inhibitors in heart failure: an updated meta-analysis

iSGLT2 disminuyen **hospitalizaciones** por falla cardiaca

iSGLT2 disminuyen **mortalidad** por falla cardiaca sin importar FEVI

- Primera hospitalización por falla cardiaca o Muerte CV **19%**
- Primer episodio FC **29%**
- Hospitalizaciones totales por FC o Muerte CV **39%**

No hubo diferencia en:


Fracturas

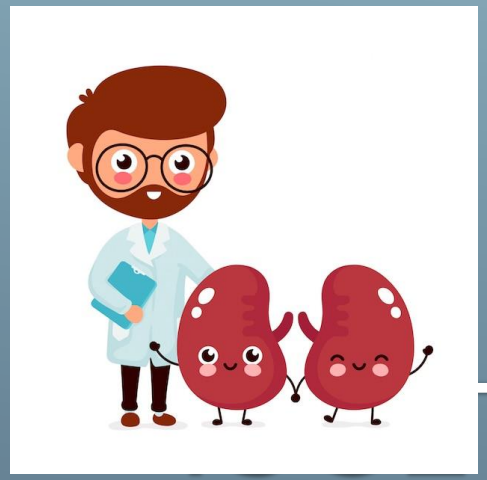

Hipoglicemia


Amputaciones


Infeccion del tracto urinario


Lesión renal aguda

ESC Heart Failure 2022; DOI: 10.100ehf2.13905



T2

RENAL

Educar-Actuar-Detener®

NEFROPATÍA EN PARAGUAY

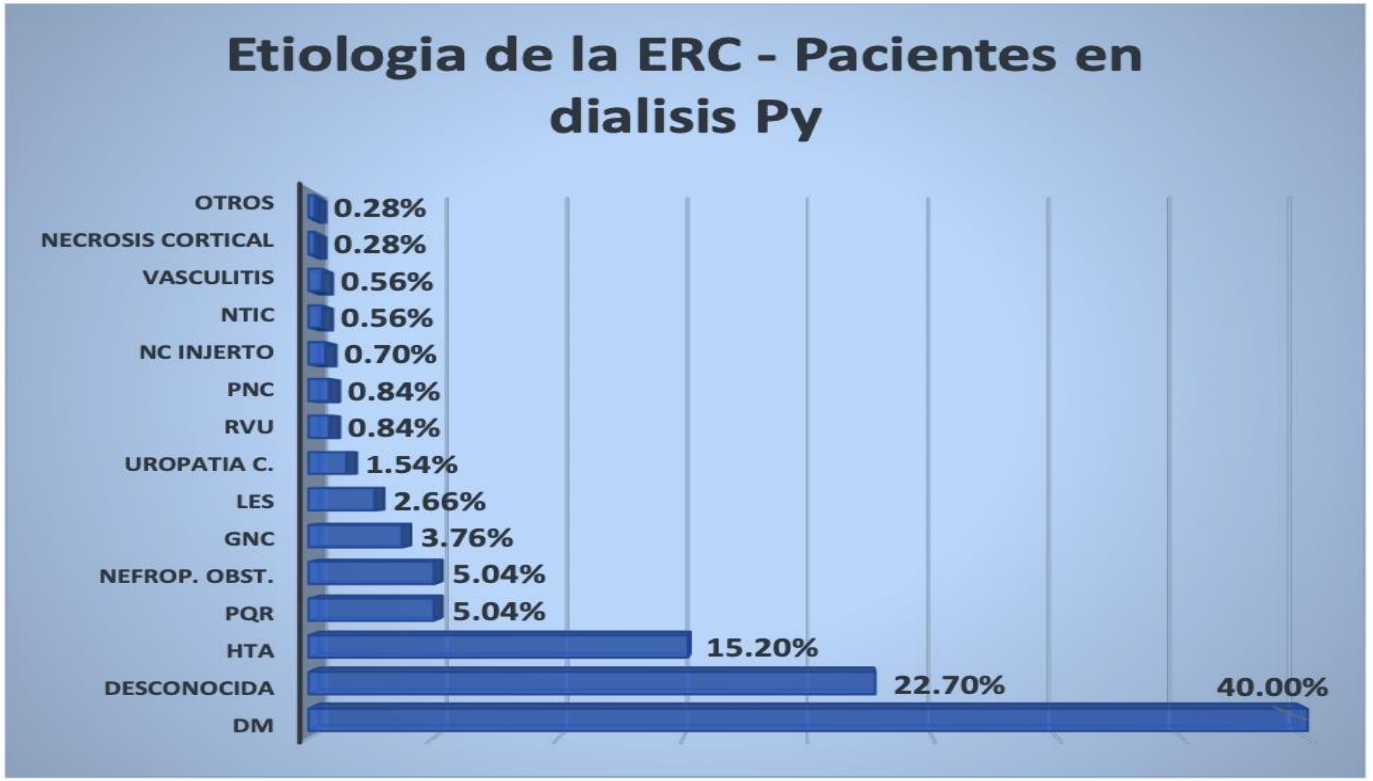
Ministerio de SALUD PÚBLICA Y BIENESTAR SOCIAL

GOBIERNO NACIONAL

Paraguay de la gente

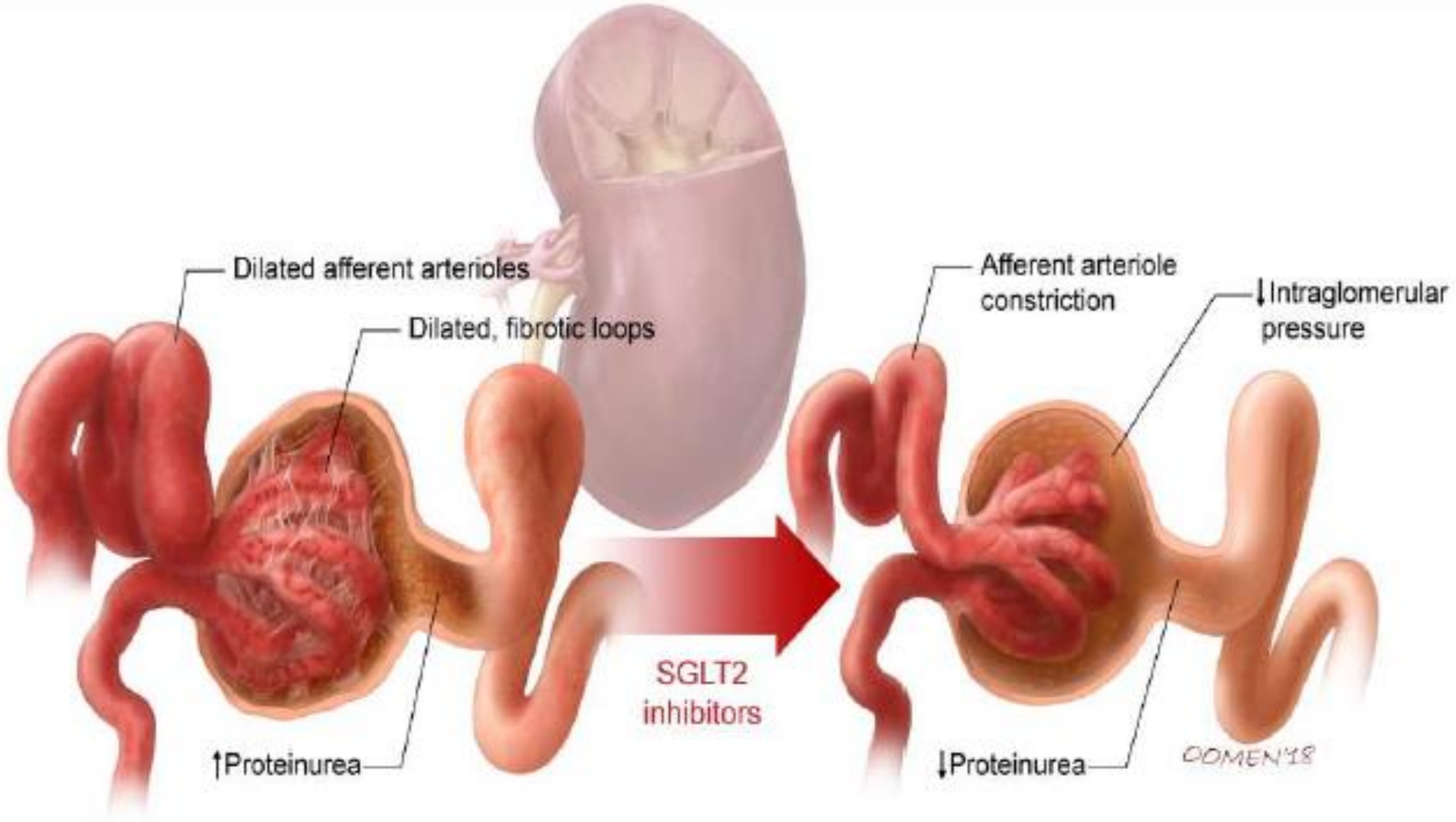
INSTITUTO NACIONAL DE NEFROLOGIA

Avda. Lombardo c/ Sacramento Telefax: 021 281758



Fuente: INSTITUTO NACIONAL DE NEFROLOGIA – REGISTRO NACIONAL DIALISIS Y TRASPLANTE PARAGUAY (RNDTPy)

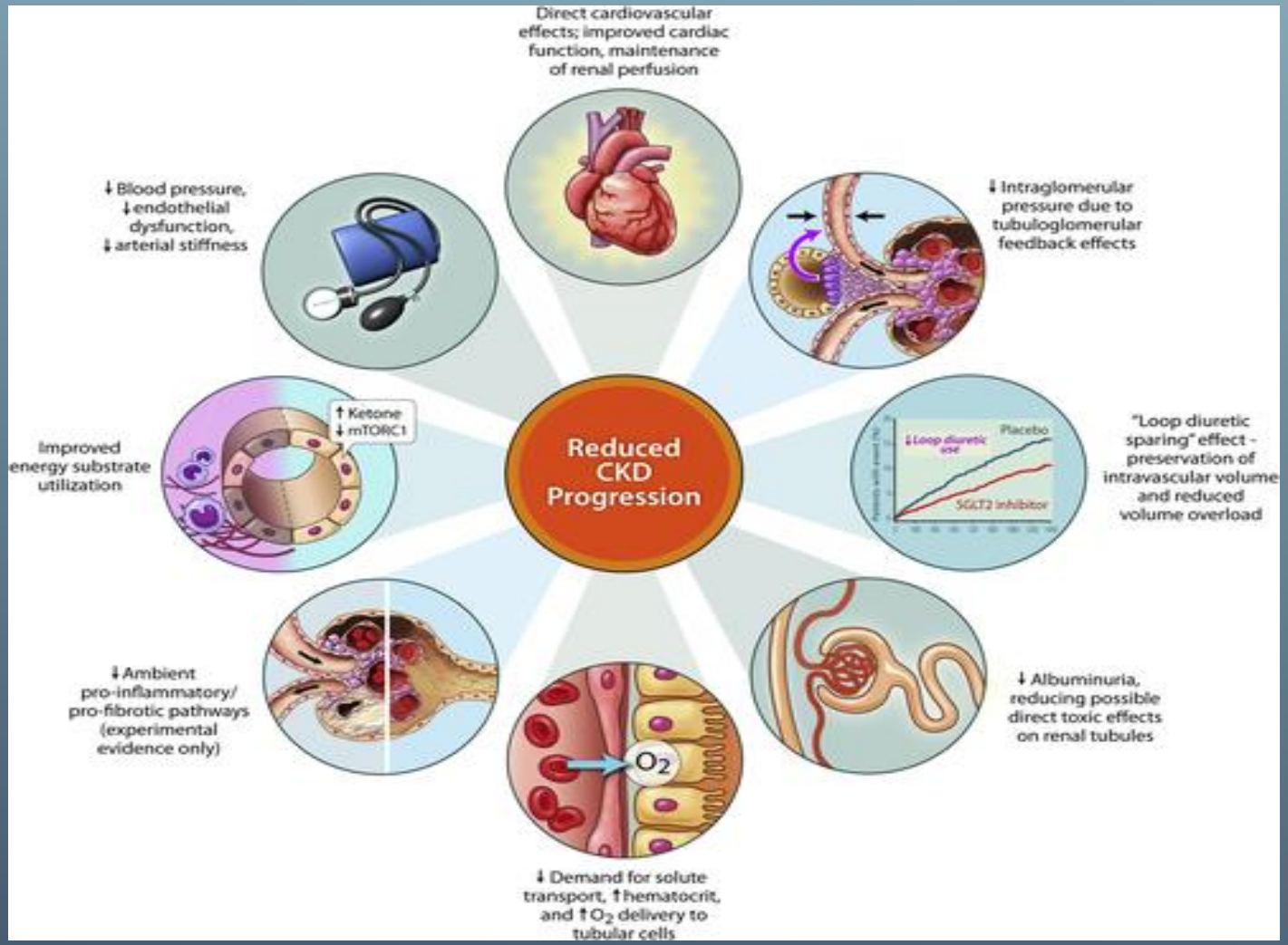
iSGLT2 improve renal conditions



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

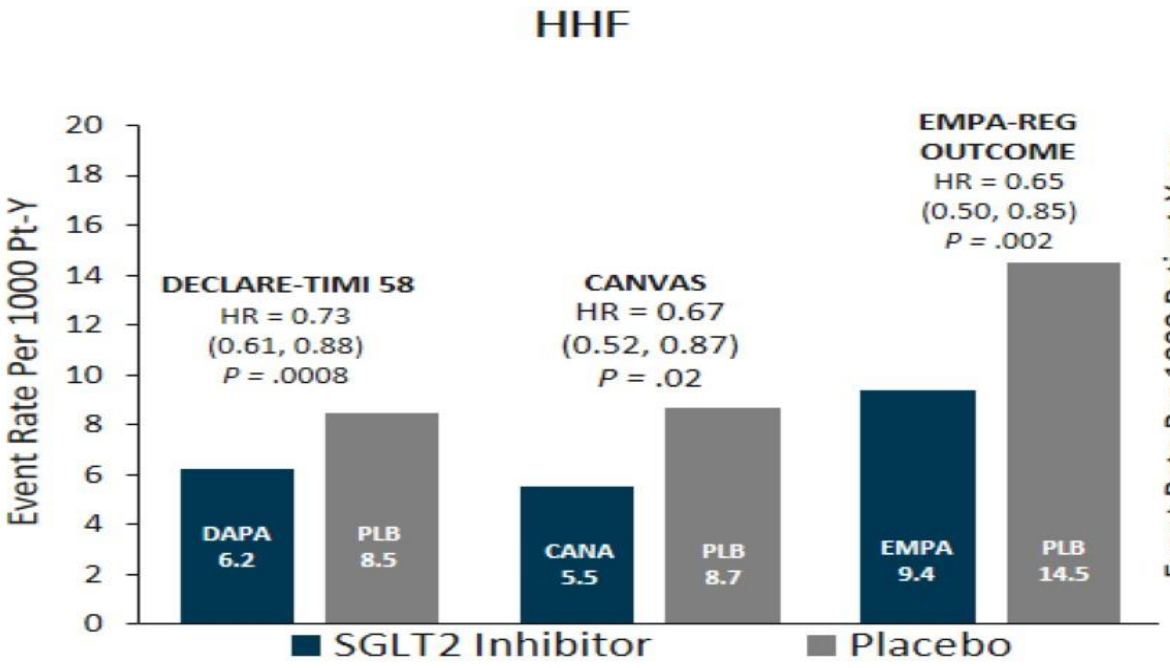
Diabetologia

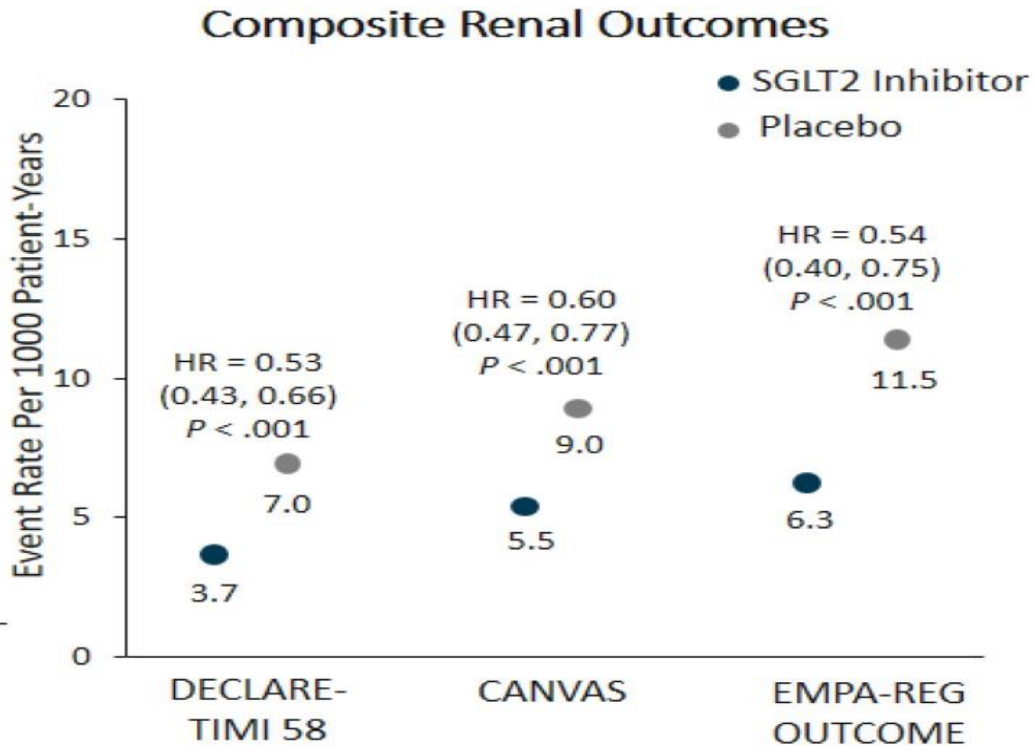
JACC
Basic to Translational Science
An Open Access Journal



David Z.I. Cherney et al. *J Am Coll Cardiol Basic Trans Science* 2021; 6:74-77.

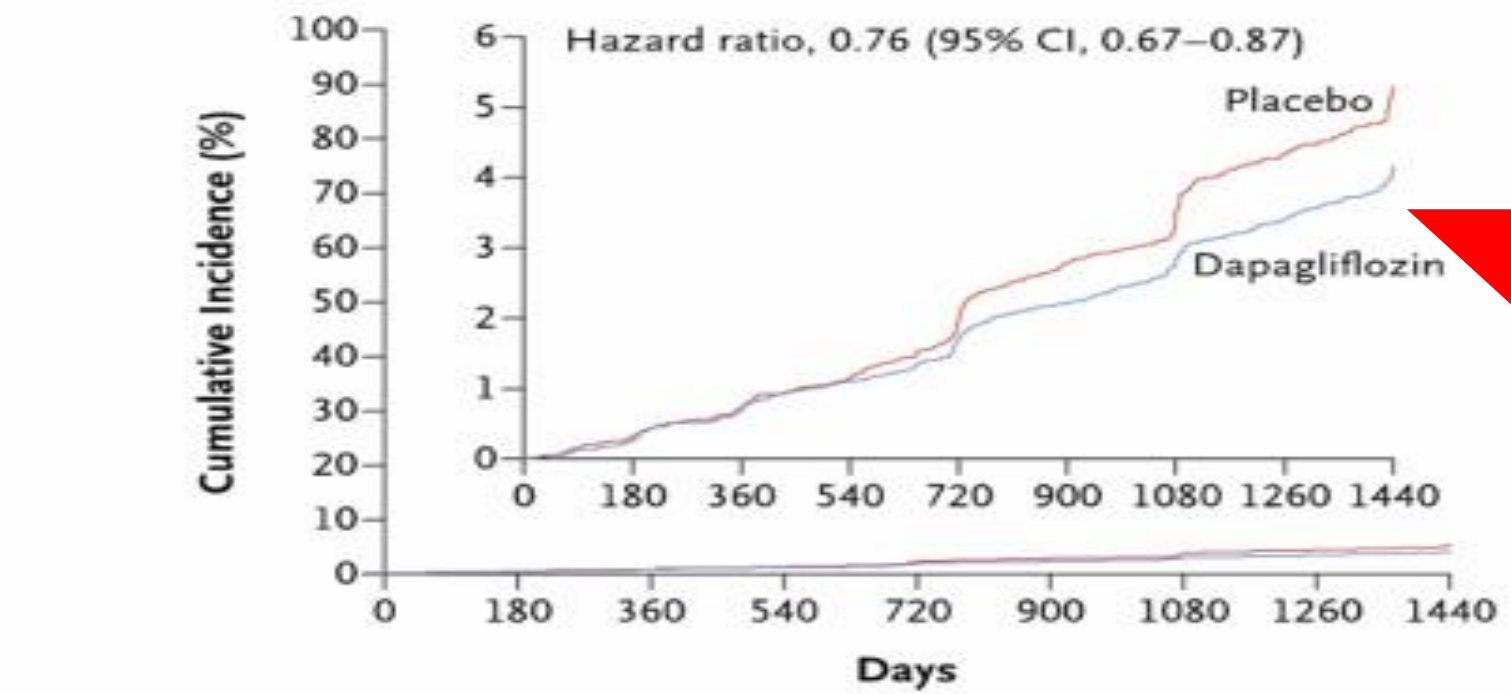
SGLT2 Inhibitor CVOTs: Cardiorenal Outcomes





Kluger AY, et al. *Cardiovasc Diabetol*. 2019;18:99.

DECLARE TIMI-58: Renal Composite Endpoint*



24%

No. at Risk

Placebo	8578	8508	8422	8326	8200	8056	7932	7409	5389
Dapagliflozin	8582	8533	8436	8347	8248	8136	8009	7534	5472

*≥ 40% decrease in eGFR to < 60 mL/min/1.73 m^2 of body-surface area, new ESRD, or death from renal or CV causes

Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357.

The NEW ENGLAND JOURNAL of MEDICINE

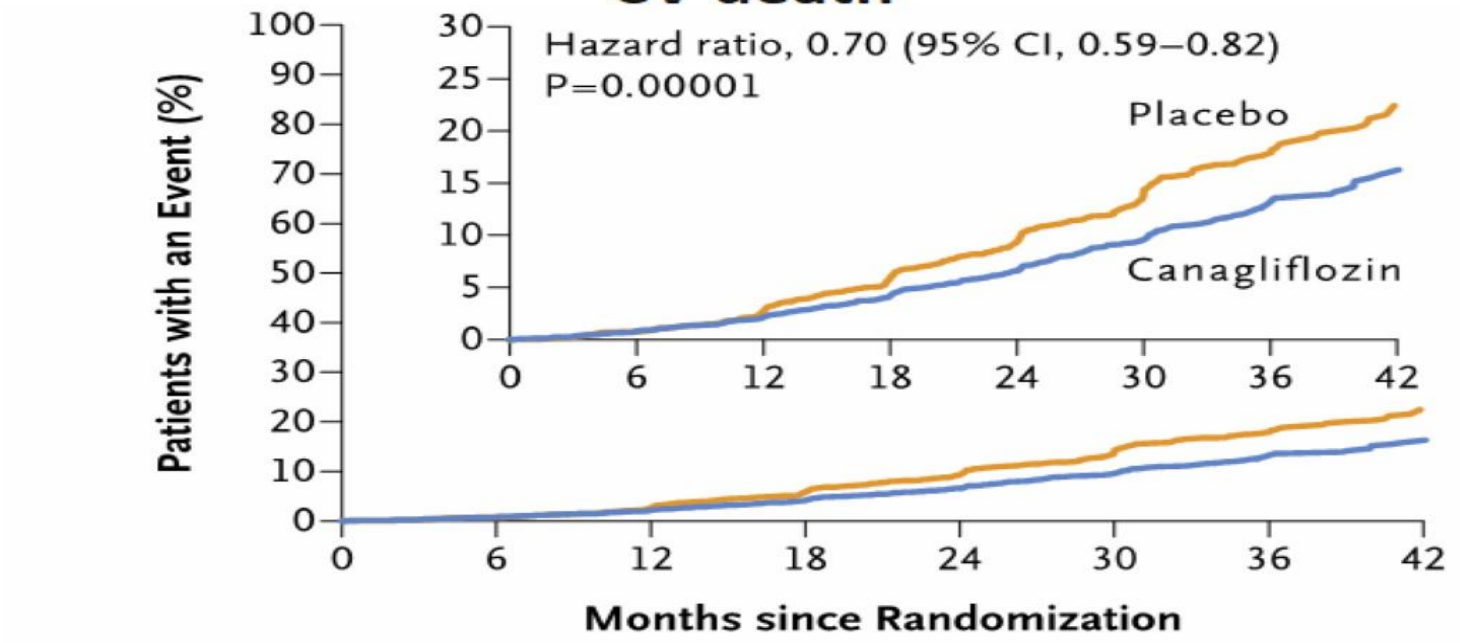
ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

CREDENCE: Canagliflozin and Renal Outcomes in T2DM and Nephropathy

Primary Composite Outcome: ESKD, Doubling of SCr, or Renal or CV death



No. at Risk

Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306.

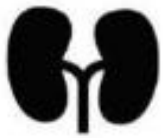
CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

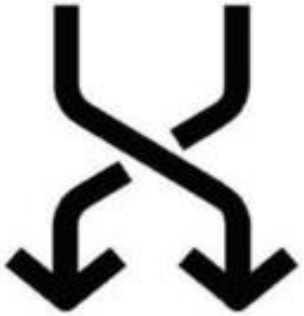


eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

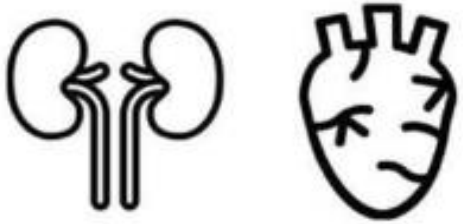


Canagliflozin **Placebo**

Outcomes

Primary outcome

(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

Fractures

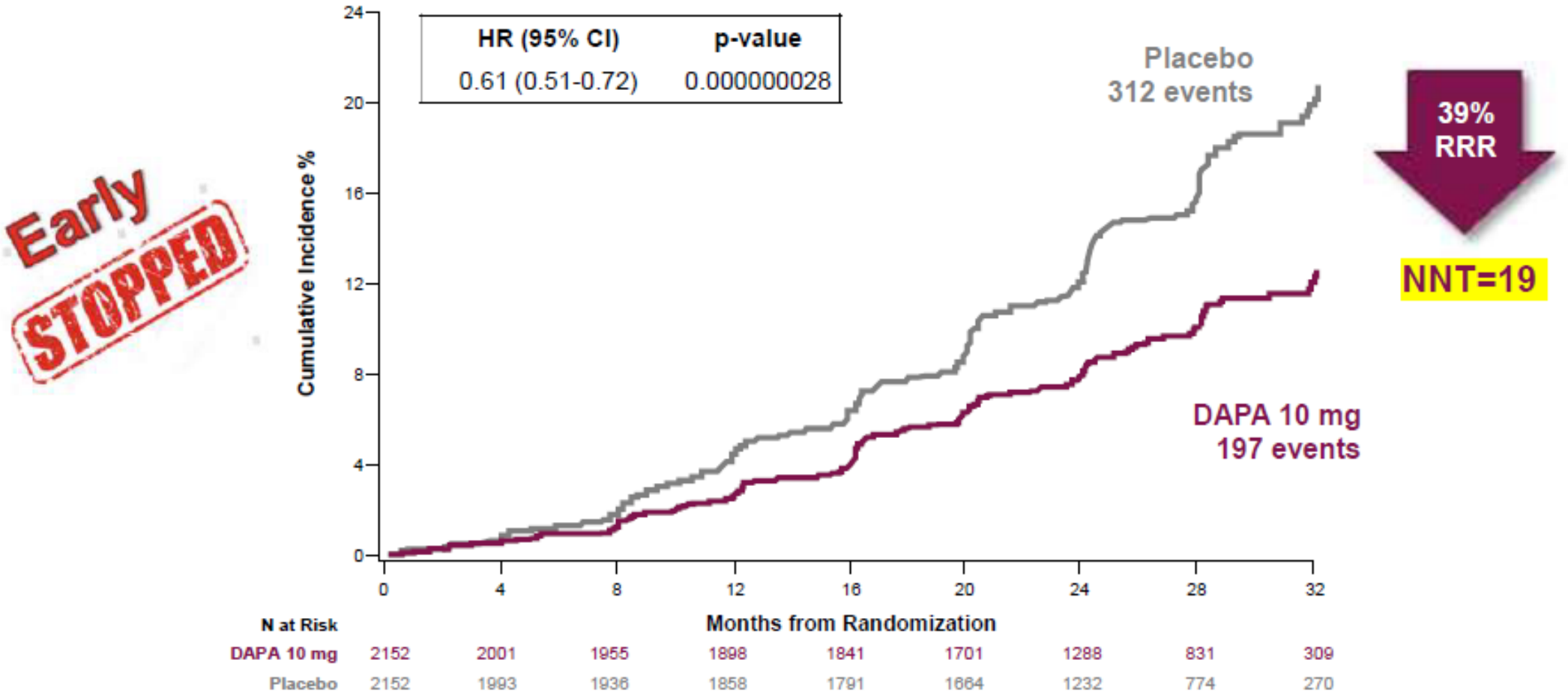
HR 0.98
(95% CI 0.70-1.37)

Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a]

DAPACKD



Early STOPPED

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

DAPA EN NEFROPATIA – DAPA CKD

39%

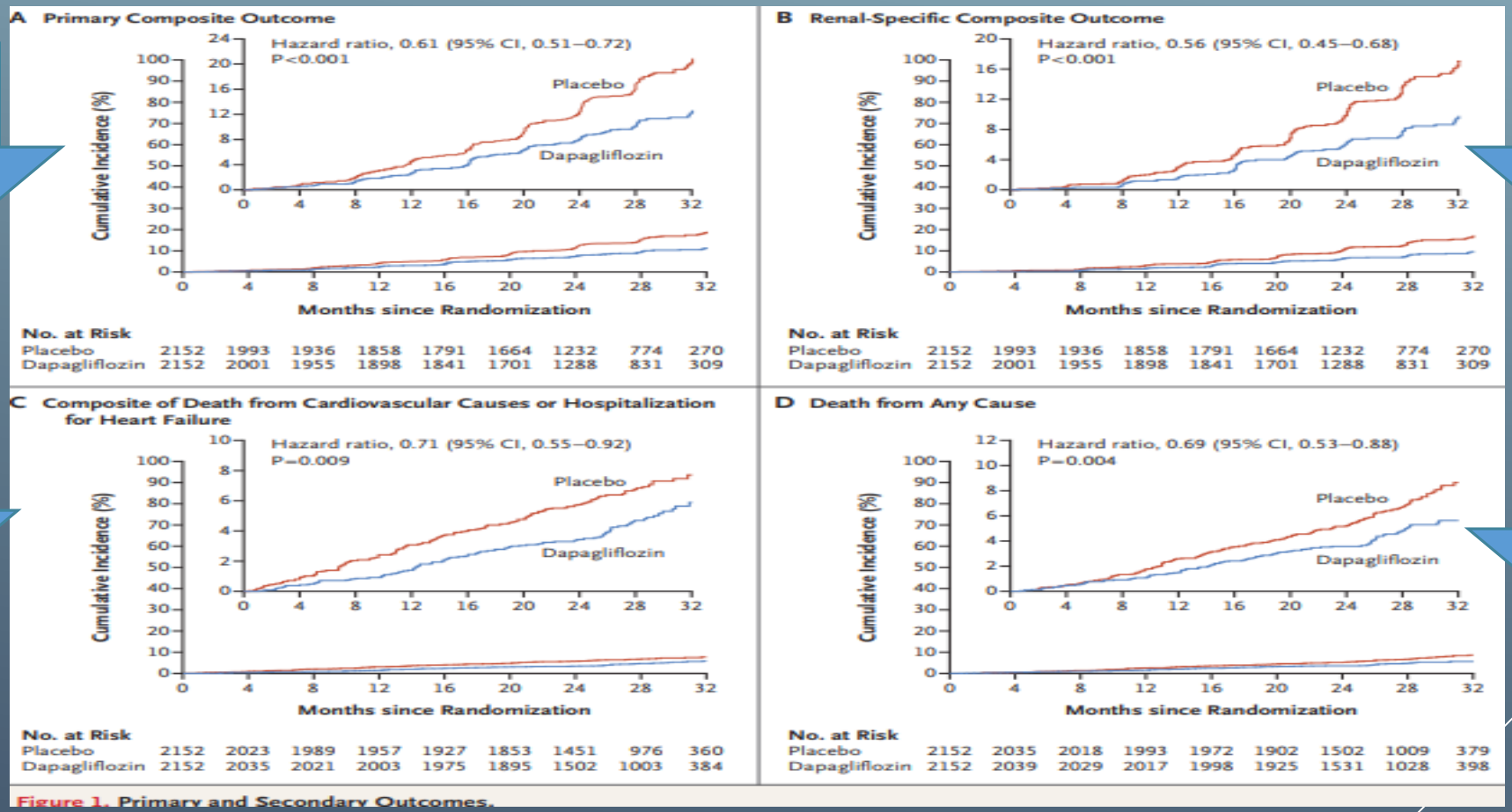


Figure 1. Primary and Secondary Outcomes.

44%

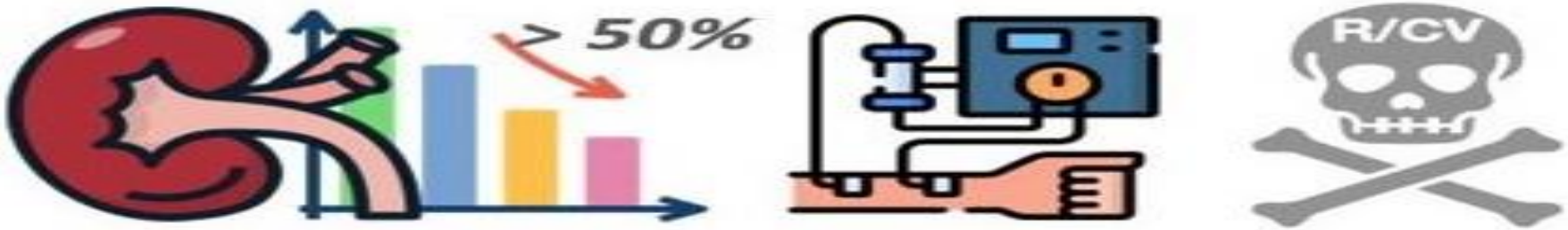
39%

31%

n engl j med 383;15 nejm.org October 8, 2020

Primary outcome

Composite Outcome



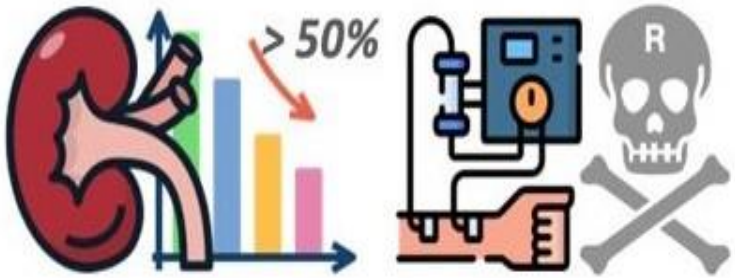
49% RRR

p<0.001

14.5% vs 9.2%

Secondary outcomes

Composite Renal Outcome



44% RRR

p<0.001

11.3% vs 6.6%

CV Renal Outcome

29% RRR

P=0.009

6.4% vs 4.6%

Total Death

31% RRR

P=0.004

6.8% vs 4.7%

EMPA-KIDNEY Early Stop

Study of heart and kidney protection with empagliflozin

BURDEN OF CHRONIC KIDNEY DISEASE

Kidney disease is a global public health issue, affecting nearly **850 million people**, which is more than **one in ten adults**[1]

Worldwide, **5 to 10 million people** die each year from chronic kidney disease (CKD)[2]

CKD is **closely linked with several metabolic and cardiovascular (CV) diseases**[3,4,5]

Prevention of kidney disease progression and reduction of CV risk remain significant unmet clinical needs[6]

ABOUT THE EMPA-KIDNEY TRIAL

EMPA-KIDNEY is the **largest and broadest** SGLT2 inhibitor trial in CKD to date[7]

EMPA-KIDNEY is evaluating the efficacy and safety of Jardiance® (empagliflozin) across a broad spectrum of adults with CKD[8]

The trial's Independent Data Monitoring Committee recommended that the trial be **stopped early** due to clear **positive efficacy**

Study design

EMPA-KIDNEY is a double-blind, randomized, placebo-controlled, academic-led trial, including more than **6,600 adults with CKD**[7]

The trial is being conducted, analyzed, and reported by the **Medical Research Council Population Health Research Unit at the University of Oxford**[7]

EMPA-KIDNEY endpoints

Primary endpoint:
a composite of kidney disease progression or CV death[7]

Key secondary endpoints:
CV death or hospitalization for heart failure, all-cause hospitalization, and all-cause mortality[7]

EMPA-KIDNEY includes adults with CKD who are **frequently seen in clinical practice but under-represented in previous SGLT2 inhibitor trials,** including people:[7,8]

- with mildly to severely reduced eGFR (a measure of kidney function);
- with normal and increased levels of albumin (a type of protein present in the urine);
- with and without diabetes;
- with CKD attributable to a wide range of underlying causes

CONCLUSION

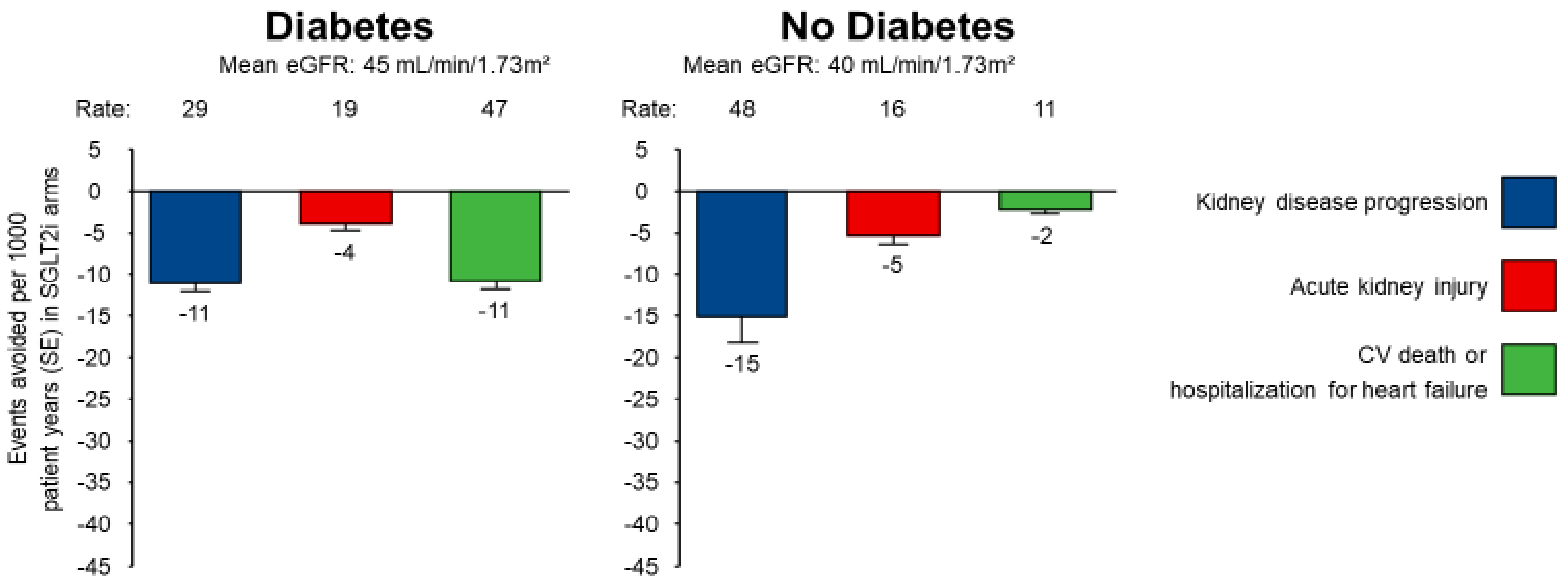
EMPA-KIDNEY follows the landmark EMPA-REG OUTCOME® and EMPEROR trials, all of which demonstrated cardio-renal benefits of empagliflozin[9,10,11]

Full results from EMPA-KIDNEY will be presented at an upcoming medical congress

References

1. Li PKT, *et al. Braz J Med Biol Res.* 2020; 53(3): e9614. **2.** Luyckx VA, *et al. Bull World Health Organ.* 2018;96(6):414–422D. **3.** Thomas MC, *et al. Nat Rev Nephrol.* 2016;12(2):73-81. **4.** Pugh D, *et al. Drugs.* 2019;79(4):365-379. **5.** Kovesdy CP, *et al. Am J Nephrol.* 2017;45:283-291 **6.** Levin A, *et al. The Lancet.* 2017;390:1888–917. **7.** The EMPA-KIDNEY Collaborative Group. [Published online ahead of print March 3 2022]. *Nephrol Dial Transplant.* 2022. DOI:10.1093/ndt/gfac040. **8.** Herrington WG, *et al. Clin Kidney J.* 2018;11(6):749–61. **9.** Wanner C, *et al. N Engl J Med.* 2016;375:323-34. **10.** Anker S, *et al. N Engl J Med.* 2021; 385:1451-1461. **11.** Packer MD, *et al. N Engl J Med.* 2020; 383:1413-1424.

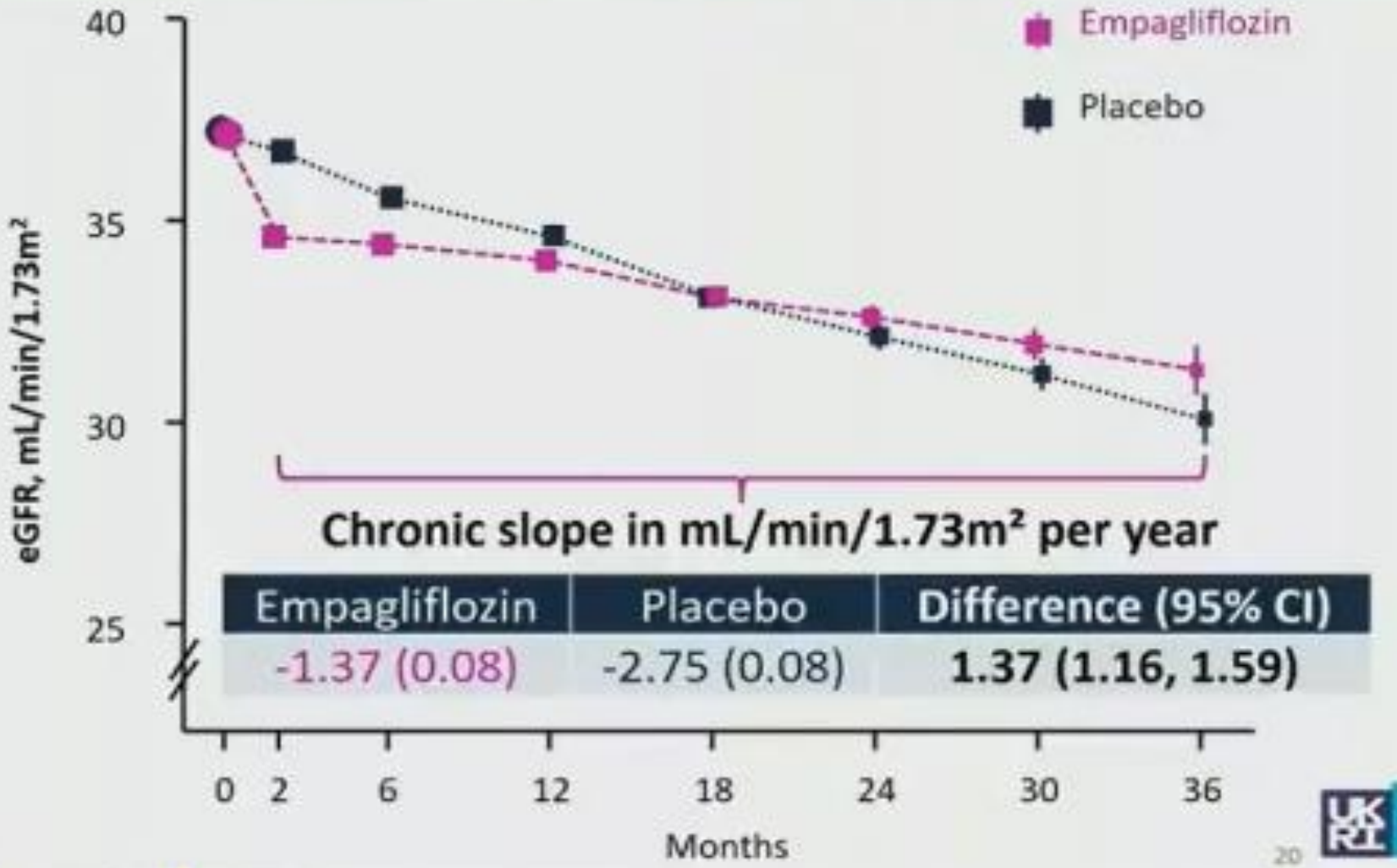
Absolute benefits: Chronic kidney disease



MRC Population Health Research Unit

SMART-C

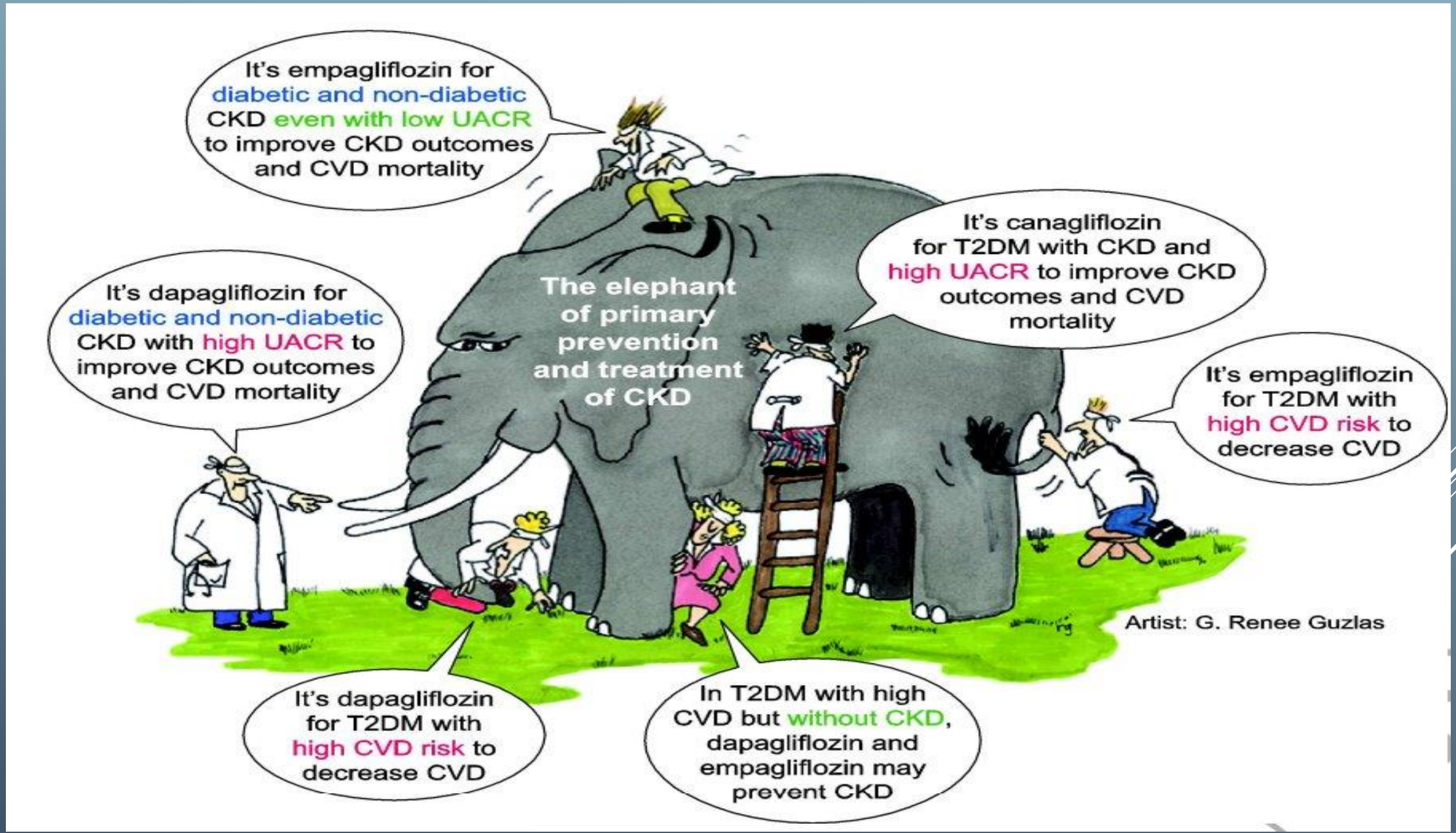
Annual rate of change of eGFR



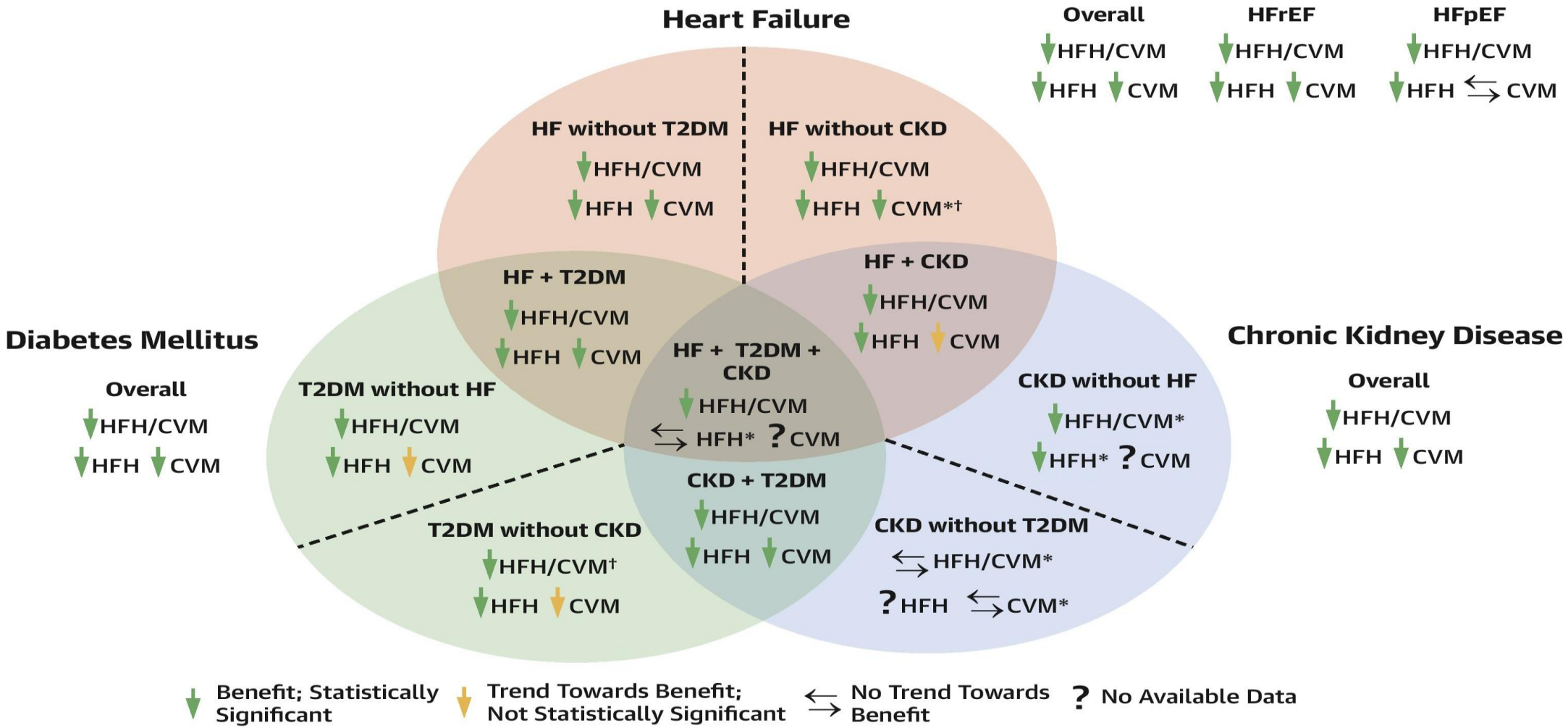
Empagliflozin	Placebo	Difference (95% CI)
-1.37 (0.08)	-2.75 (0.08)	**1.37 (1.16, 1.59)**

EMPA-KIDNEY

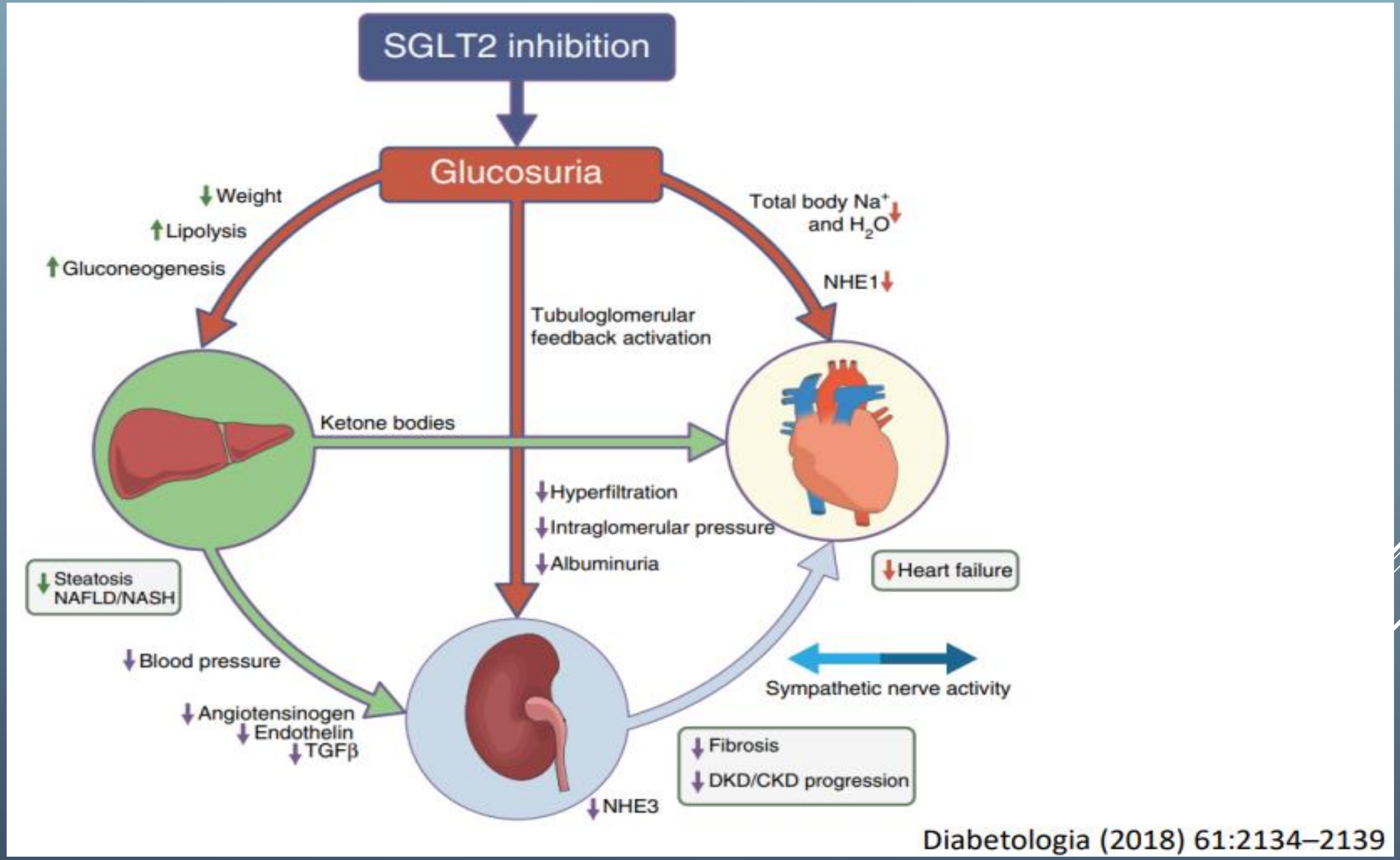
MRC Population Health Research Unit


It's empagliflozin for diabetic and non-diabetic CKD even with low UACR to improve CKD outcomes and CVD mortality
It's dapagliflozin for diabetic and non-diabetic CKD with high UACR to improve CKD outcomes and CVD mortality
The elephant of primary prevention and treatment of CKD
It's canagliflozin for T2DM with CKD and high UACR to improve CKD outcomes and CVD mortality
It's empagliflozin for T2DM with high CVD risk to decrease CVD
Artist: G. Renee Guzlas
It's dapagliflozin for T2DM with high CVD risk to decrease CVD
In T2DM with high CVD but without CKD, dapagliflozin and empagliflozin may prevent CKD

CENTRAL ILLUSTRATION: Effect of Sodium-Glucose Cotransporter-2 Inhibitors on Cardiovascular Outcomes Across Different Patient Populations



Usman MS, et al. J Am Coll Cardiol. 2023;81(25):2377–2387.



Diabetologia (2018) 61:2134–2139

iSGLT2

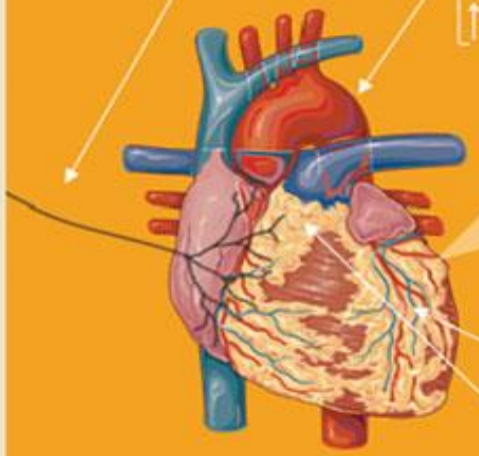
Efectos renales

↑ Diuresis/natriuresis
↓ Presión glomerular
↓ Proteinuria
↑ Eritropoyetina
↓ Progresión ERC

Efectos cardiovasculares

↓ Activación SNS

↓ Presión arterial
↓ Rigidez aórtica
↑ Función endotelial



↓ Actividad NHE I
↓ Inflamación
↓ Estrés oxidativo
↓ Apoptosis
↓ Fibrosis
↓ Hipertrofia
↑ Diástole

↑ Función endotelial coronaria

↓ Adiposidad en epicardio

Efectos metabólicos

↓ Peso corporal
↓ Adiposidad
↓ Sensibilidad a la insulina
↑ Cetogénesis
↓ Esteatosis hepática
↓ Ácido úrico

Mejora de las condiciones de carga cardíaca

↓ Precarga - ↓ Poscarga

Mejora de la viabilidad y el rendimiento del miocardio

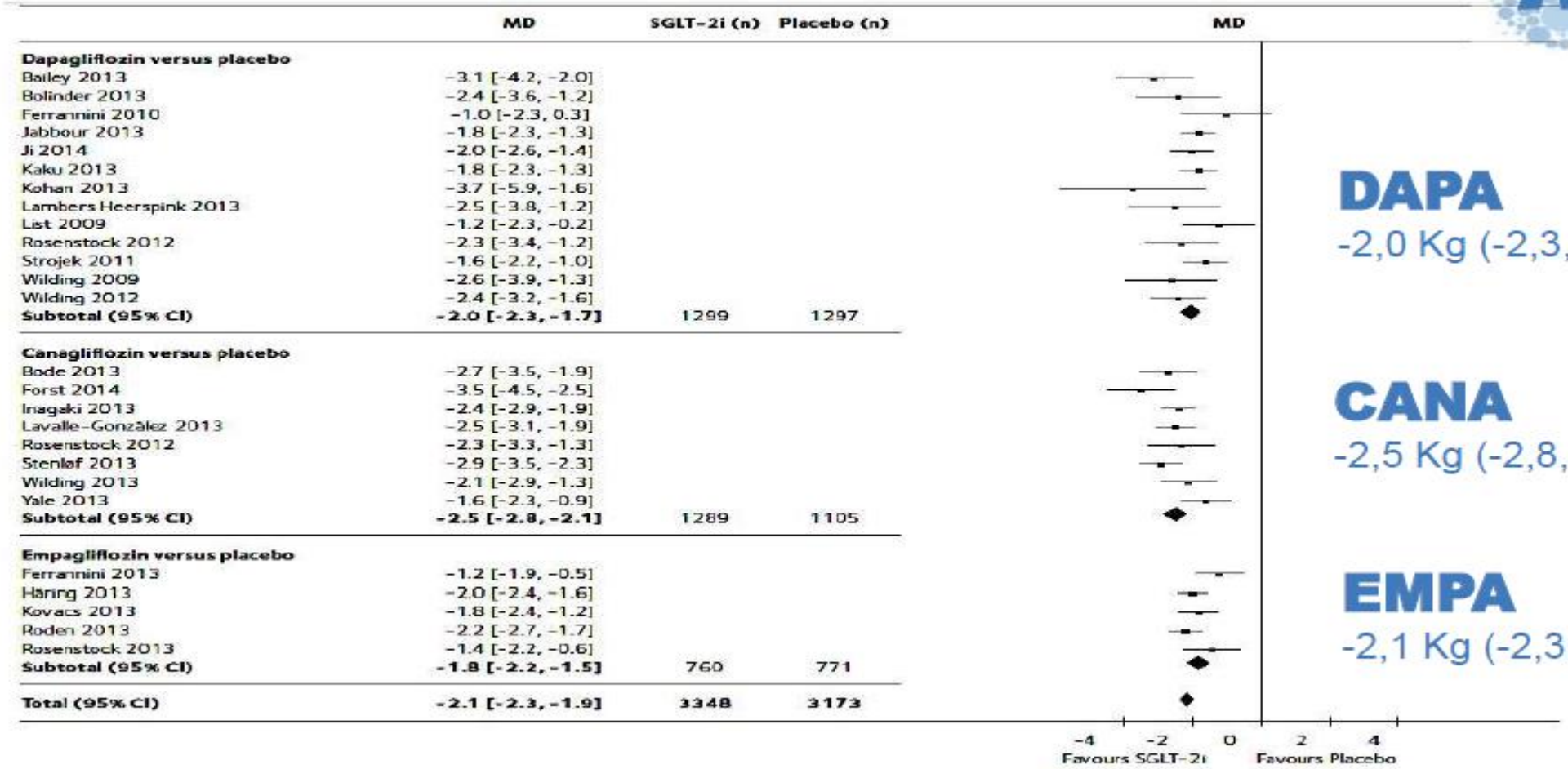
Mejores resultados cardiovasculares

ISGLT2

PESO

Educar-Actuar-Detener®

iSGLT-2: Reducción de peso *vs.* placebo



Cambio en el peso corporal (kg) después de, al menos, 12 semanas de tratamiento. Metaanálisis de los efectos aleatorios de los iSGLT-2 *versus* control activo. Los resultados se presentan como diferencias medias (DM), con intervalos de confianza (IC) del 95%. Dapa: dapagliflozina; Cana: canagliflozina; Empa: empagliflozina.

Storgaard H, et al. Effects of sodium glucose co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review with meta-analysis of randomised clinical trials. P856 EASD Vienna, 2014.

ISGLT2 Y CÁNCER

Article | Published: 10 February 2023

Epidemiology

Sodium-glucose cotransporter 2 (SGLT2) inhibitors and non-small cell lung cancer survival

Juhua Luo ✉, Michael Hendryx & Yi Dong

British Journal of Cancer **128**, 1541–1547 (2023) | Cite this article

419 Accesses | **2** Citations | **12** Altmetric | Metrics

Abstract

Background

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of antidiabetic drugs with demonstrated renal and cardiovascular disease benefit. This study evaluates the role of SGLT2 inhibitors on the survival of non-small cell lung cancer (NSCLC) patients.

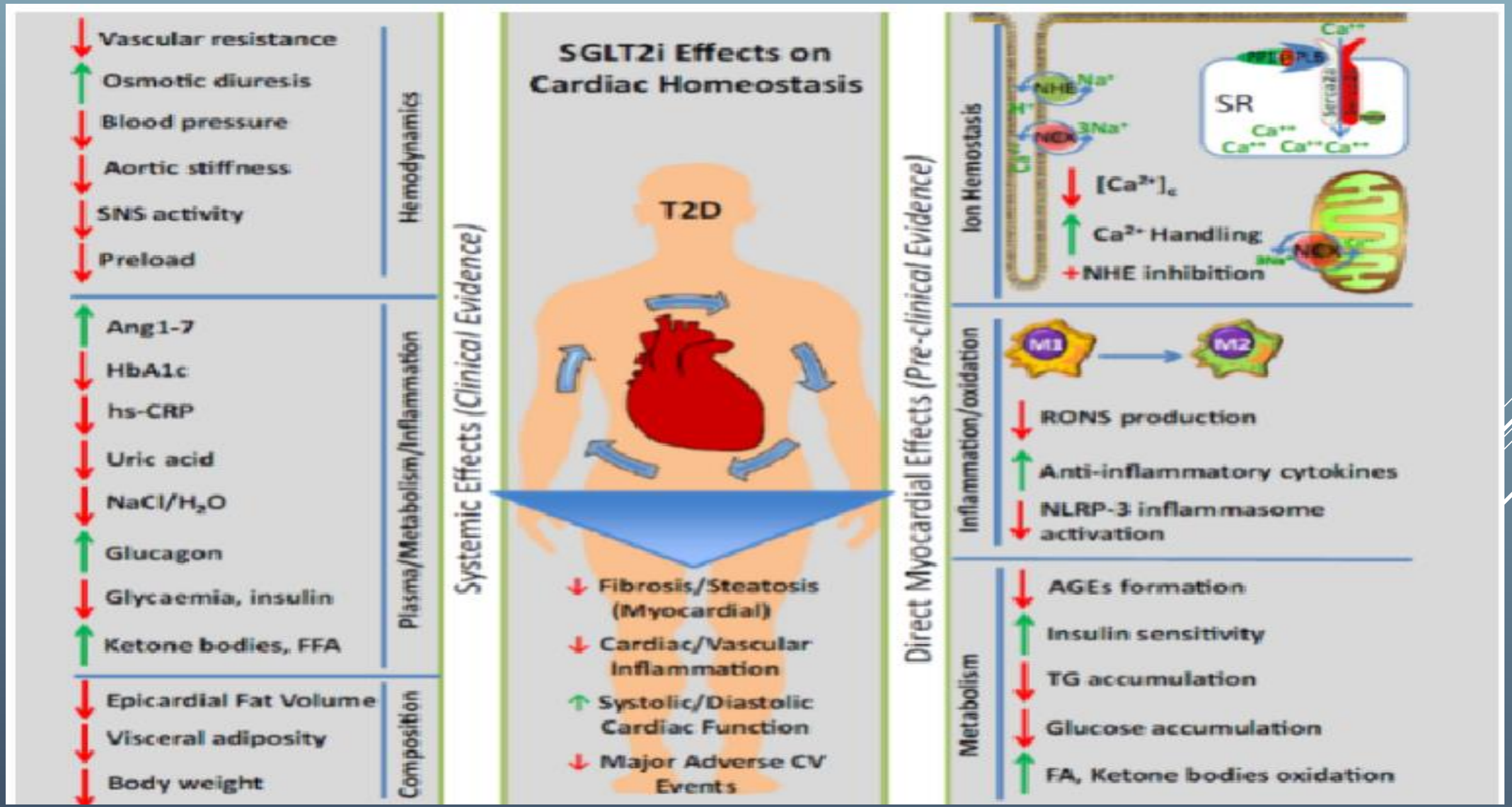
Effects of Dapagliflozin on NAFLD/NASH in Patients with T2D

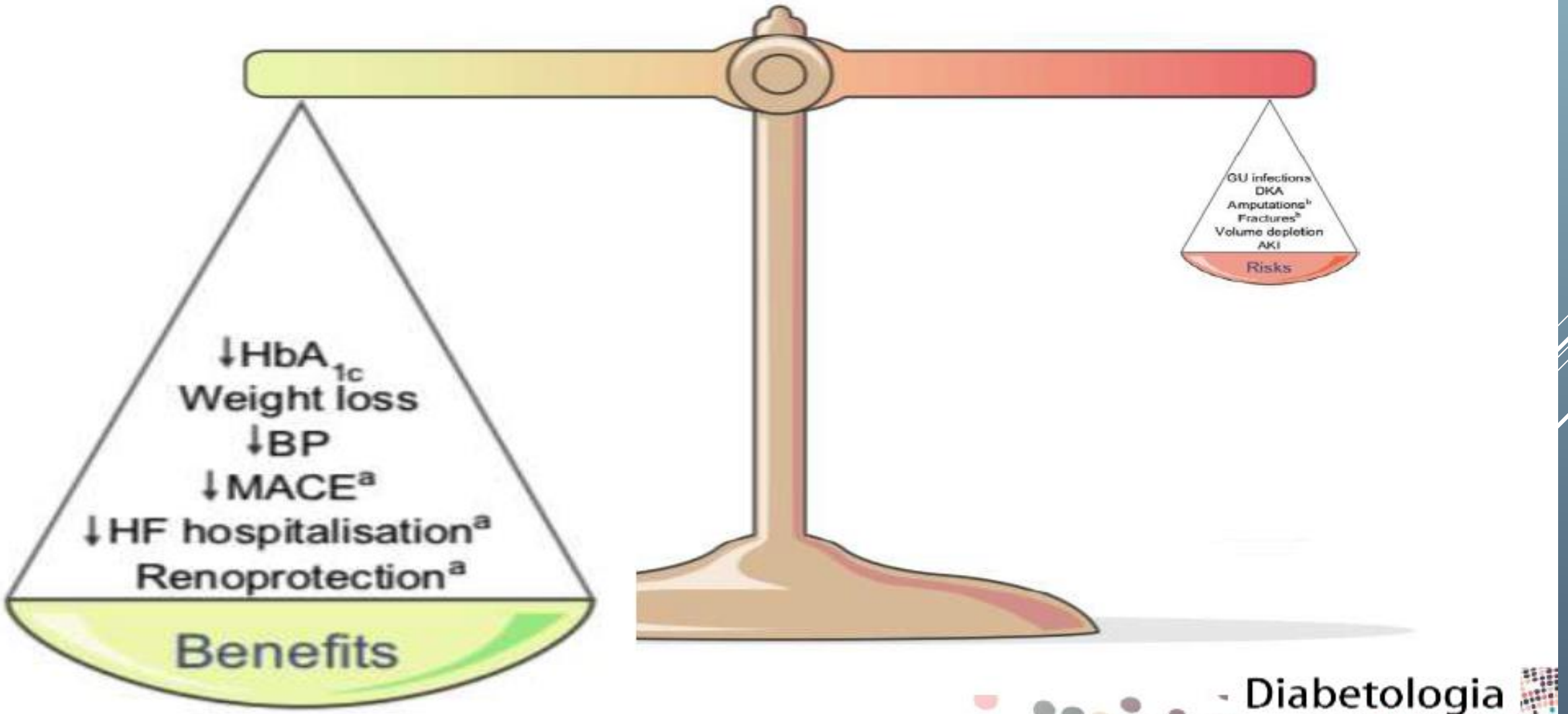
Author	Design/Comparator	Number of Patients	Study Duration	Method of Diagnosis	Outcome	Measure Method
Shimizu et al., 2019	RCT/placebo	57	24 weeks	FibroScan	Improvement of hepatic steatosis and fibrosis	CAP and LSM
Kinoshita et al., 2020	RCT/pioglitazone or glimepiride	98	28 weeks	CT	Improvement of NAFLD	Liver-to-spleen ratio
Johansson et al., 2020	RCT/glimepiride plus placebo	444/59 in the MRI substudy	52 weeks	MRI-PDFF	Improvement of NAFLD	Liver fat percentage and adipose tissue volumes
EFFECT-II/Eriksson et al., 2018	RCT/omega-3 carboxylic acids/ placebo	83	12 weeks	MRI-PDFF + PNPLA3 polymorphism	Improvement of NAFLD	Liver fat content
Rasku et al., 2019	RCT/placebo	32	8 weeks	MRI-PDFF	Improvement of NAFLD	Liver fat content
Gastaldelli et al., 2020	RCT/exenatide combination/placebo combination	695	52 weeks	FLI, FIB-4, NAFLD fibrosis score	Improvement in non-invasive steatosis and fibrosis score	Non-invasive scores
EXENDA/Harreiter et al., 2021	RCT/exenatide combination/placebo	30	24 weeks	MRS + FLI + FIB-4	Improvement in intrahepatic lipid content	HCL
Phrueksotsai et al., 2021	RCT/placebo	38	12 weeks	CT	Changes in intrahepatic lipid contents	Liver attenuation index
Frias et al., 2022	RCT	338	105 weeks	MRI	Changes in adipose tissue and liver fat	MRI

Dapagliflozin improved hepatic parameters

CAP, controlled attenuation parameter; CT, computed tomography; HCL, hepato-cellular lipid; LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging proton density fat fraction; MRS, magnetic resonance spectroscopy
Bica IC, et al. Medicina (Kaunas). 2023;59:1136

CMF Cardiometabolic Forum


Vascular resistance
Osmotic diuresis
Blood pressure
Aortic stiffness
SNS activity
Preload
Hemodynamics
Ang1-7
HbA1c
hs-CRP
Uric acid
NaCl/H2O
Glucagon
Glycaemia, insulin
Ketone bodies, FFA
Plasma/Metabolism/Inflammation
Epicardial Fat Volume
Visceral adiposity
Body weight
Composition
Systemic Effects (Clinical Evidence)
SGLT2i Effects on Cardiac Homeostasis
T2D
Fibrosis/Steatosis (Myocardial)
Cardiac/Vascular Inflammation
Systolic/Diastolic Cardiac Function
Major Adverse CV Events
Direct Myocardial Effects (Pre-clinical Evidence)
Ion Homeostasis
NHE
NCX
SR
[Ca2+]c
Ca2+ Handling
+NHE inhibition
Inflammation/oxidation
M1
M2
RONS production
Anti-inflammatory cytokines
NLRP-3 inflammasome activation
Metabolism
AGEs formation
Insulin sensitivity
TG accumulation
Glucose accumulation
FA, Ketone bodies oxidation



Diabetologia

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

— OR —

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate: DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High: Semaglutide, Tirzepatide

High: Dulaglutide, Liraglutide

Intermediate: GLP-1 RA (not listed above), SGLT2i

Neutral: DPP-4i, Metformin

If A1C above target

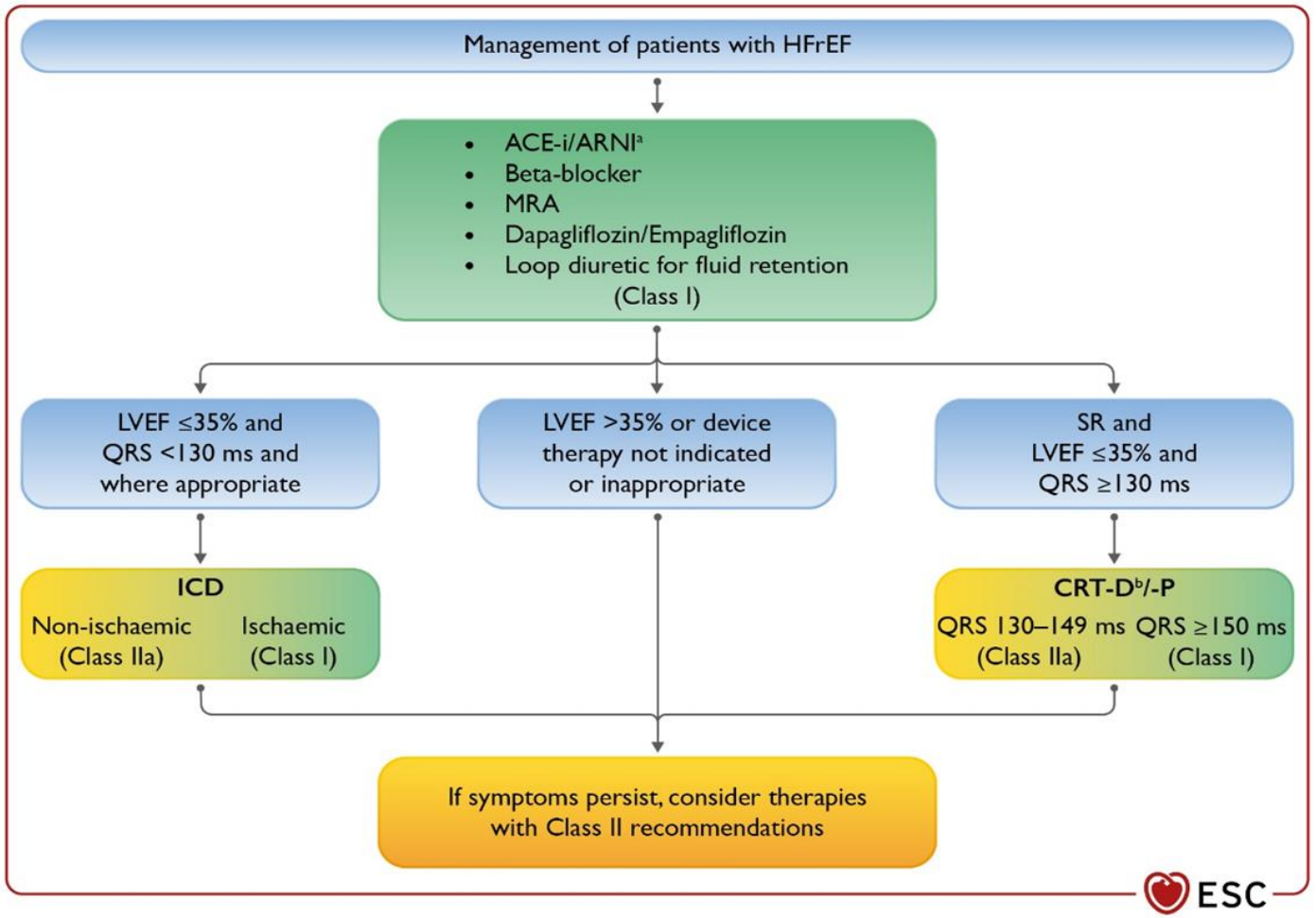
Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction



ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves of an ECG; SR = sinus rhythm.

[a]As a replacement for ACE-I.

[b]Where appropriate. Class I=green. Class IIa=Yellow.

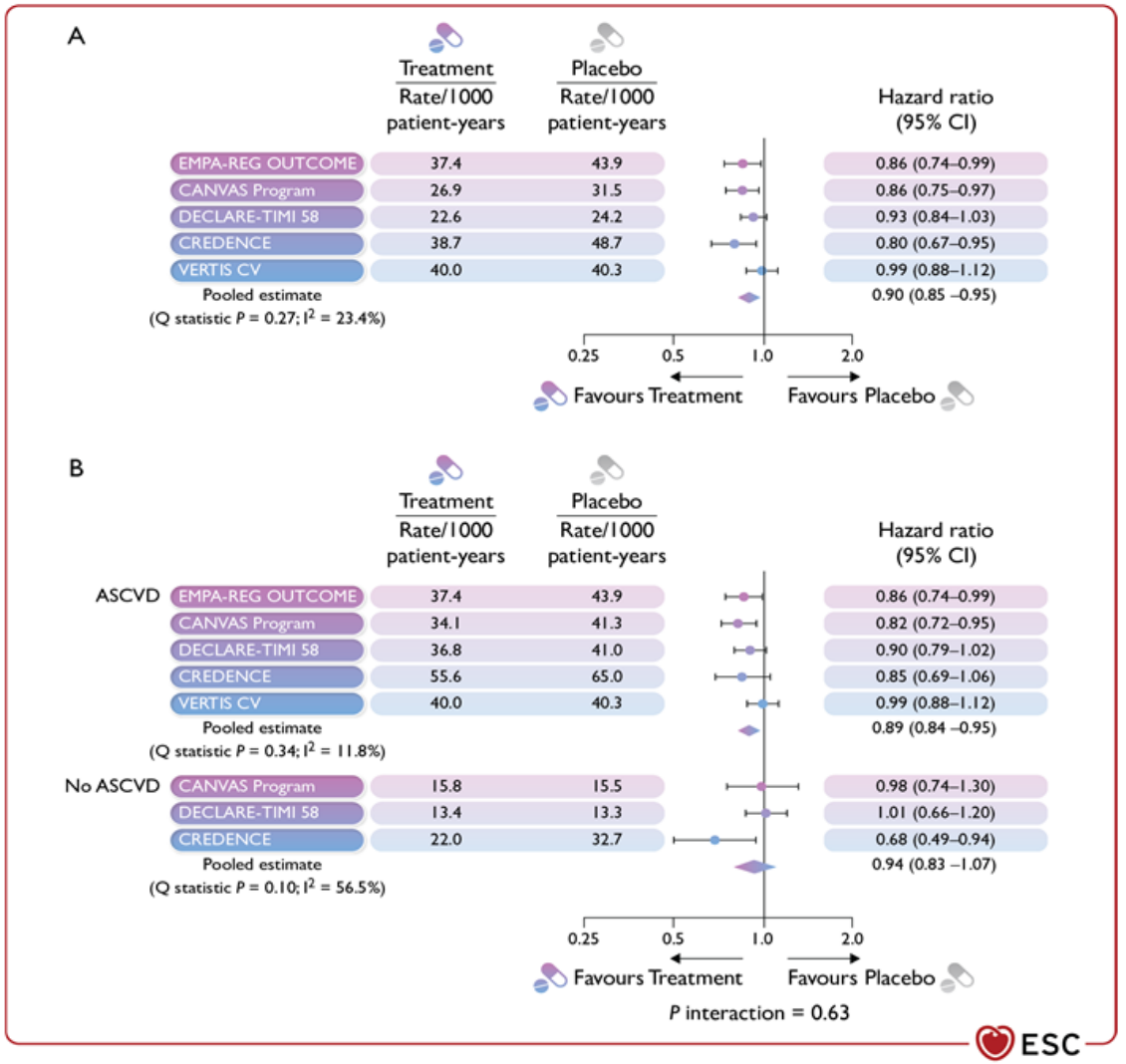
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Tabla 2. Tratamiento farmacológico

Recomendación	Clase	Nivel de evidencia
– Se recomienda el uso de diuréticos de asa para el alivio de síntomas de congestión en pacientes con IC-FEp	I	C
– Se recomienda la utilización de iSGLT2 para la reducción de internaciones	I	A
– Se podría iniciar tratamiento con ARNI para disminuir internación.	IIb	B
– Se podría iniciar tratamiento con antagonistas de los receptores mineralocorticoides para disminuir internación.	IIb	B
– Se podría iniciar tratamiento con antagonistas de los receptores de angiotensina II para disminuir internación.	IIb	B

Figure 5

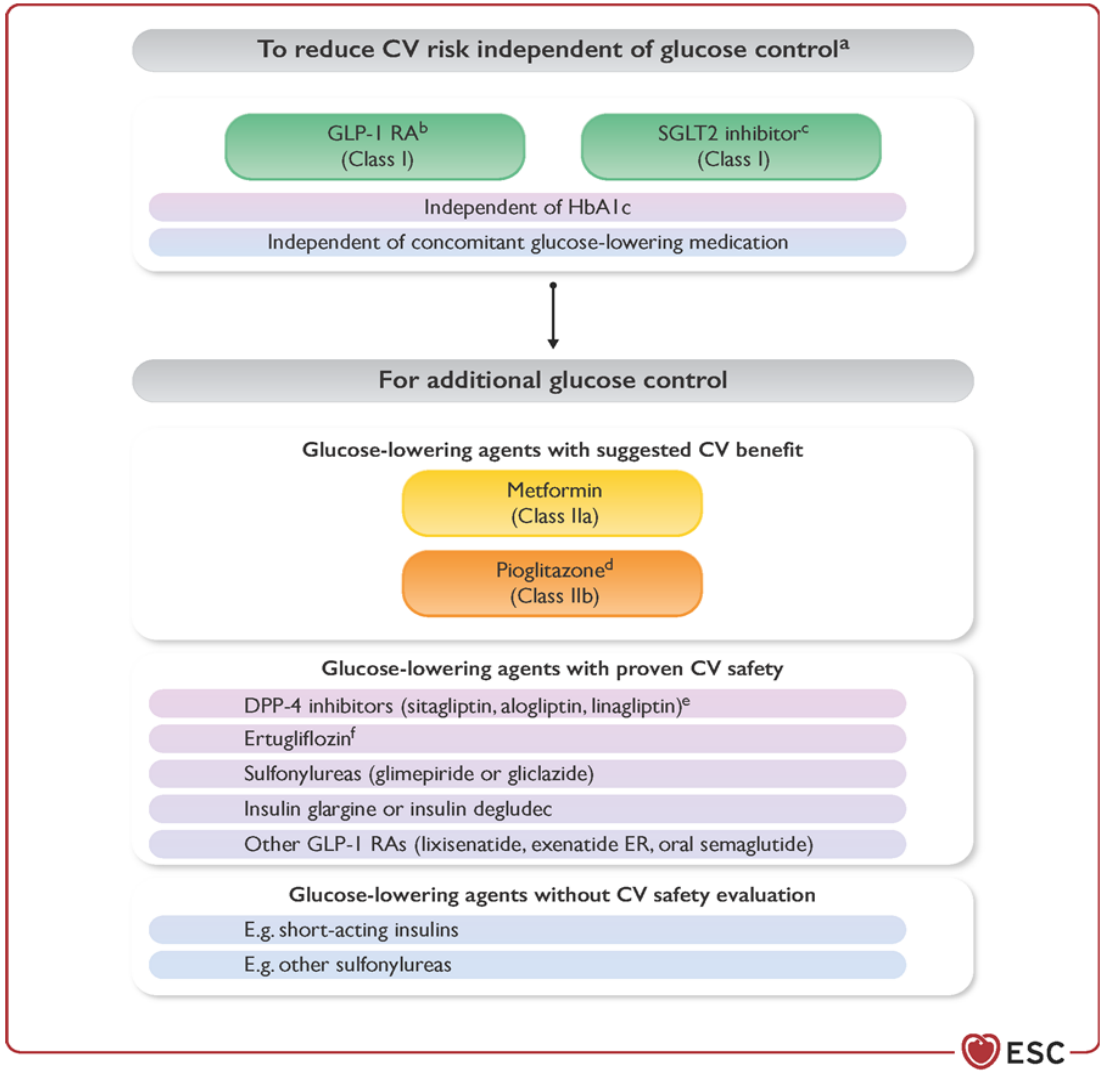
Meta-analysis of cardiovascular outcomes trials with sodium–glucose co-transporter-2 inhibitors. (A) Overall major adverse cardiovascular events; (B) Major adverse cardiovascular events by atherosclerotic cardiovascular disease status



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 8

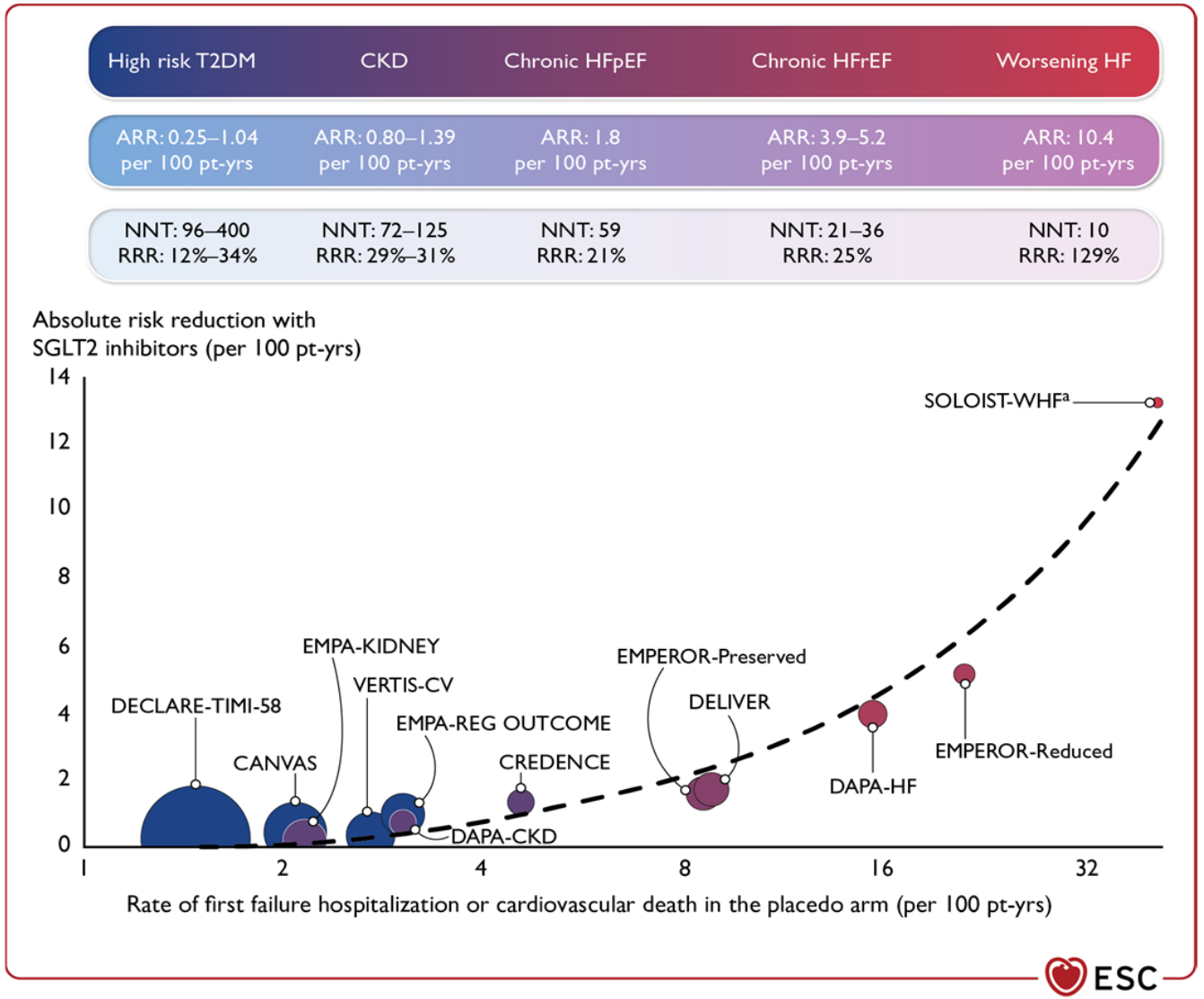
Glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 15

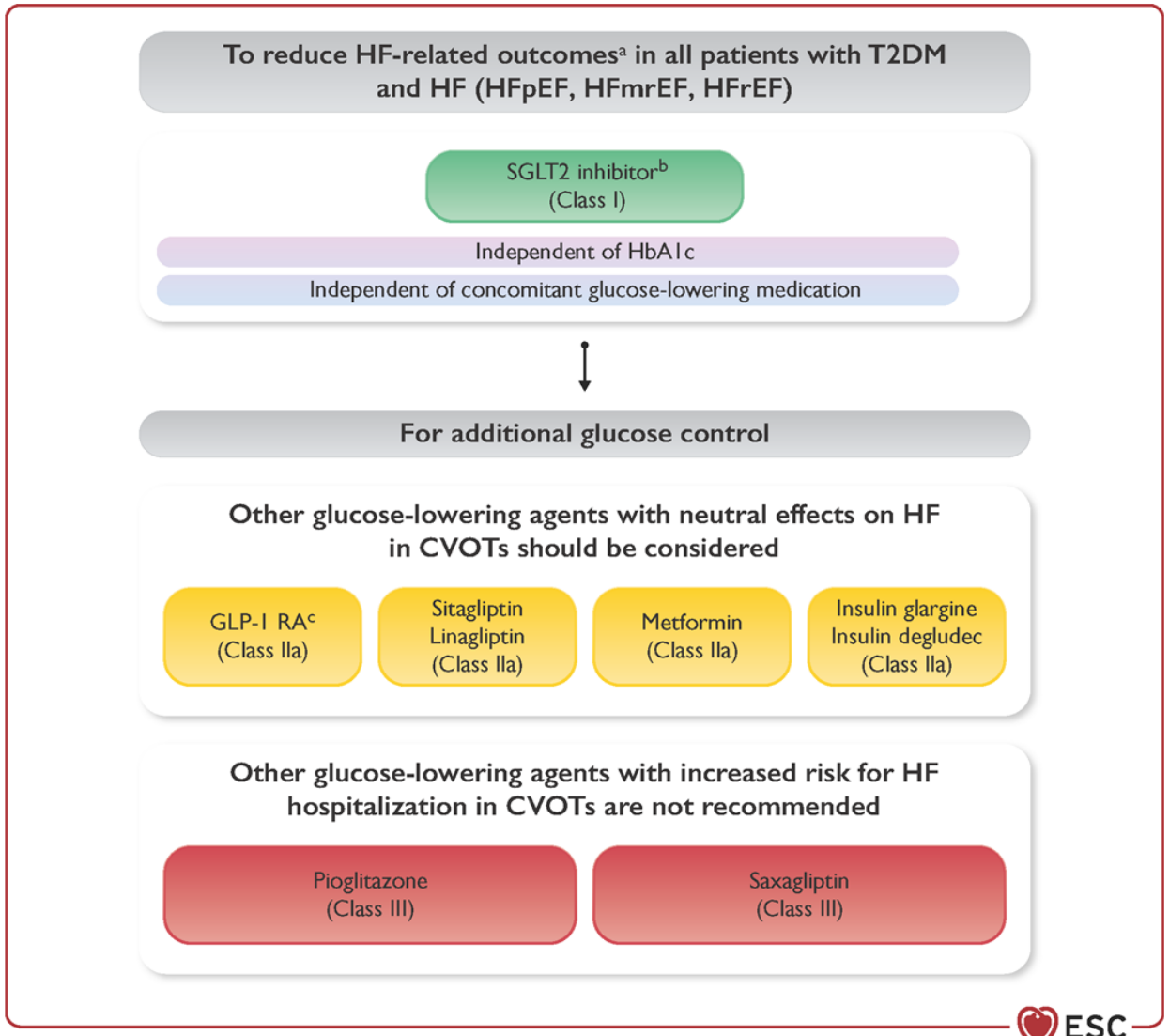
Absolute risk reduction with sodium–glucose co-transporter-2 inhibitors in relation to patient risk based on rate of heart failure-related endpoints in the placebo arm of the respective trials



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 16

Glucose-lowering treatment of patients with heart failure and type 2 diabetes



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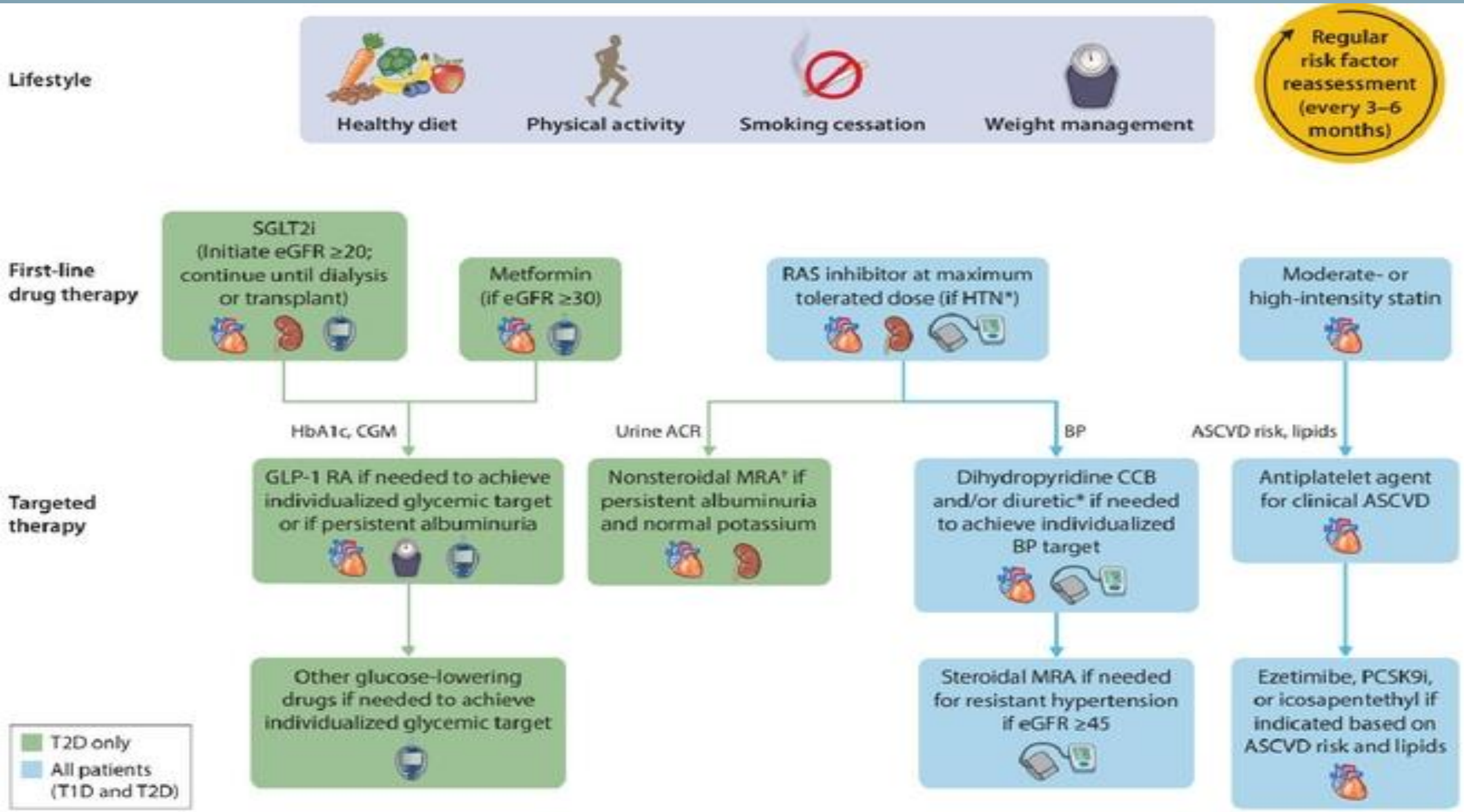

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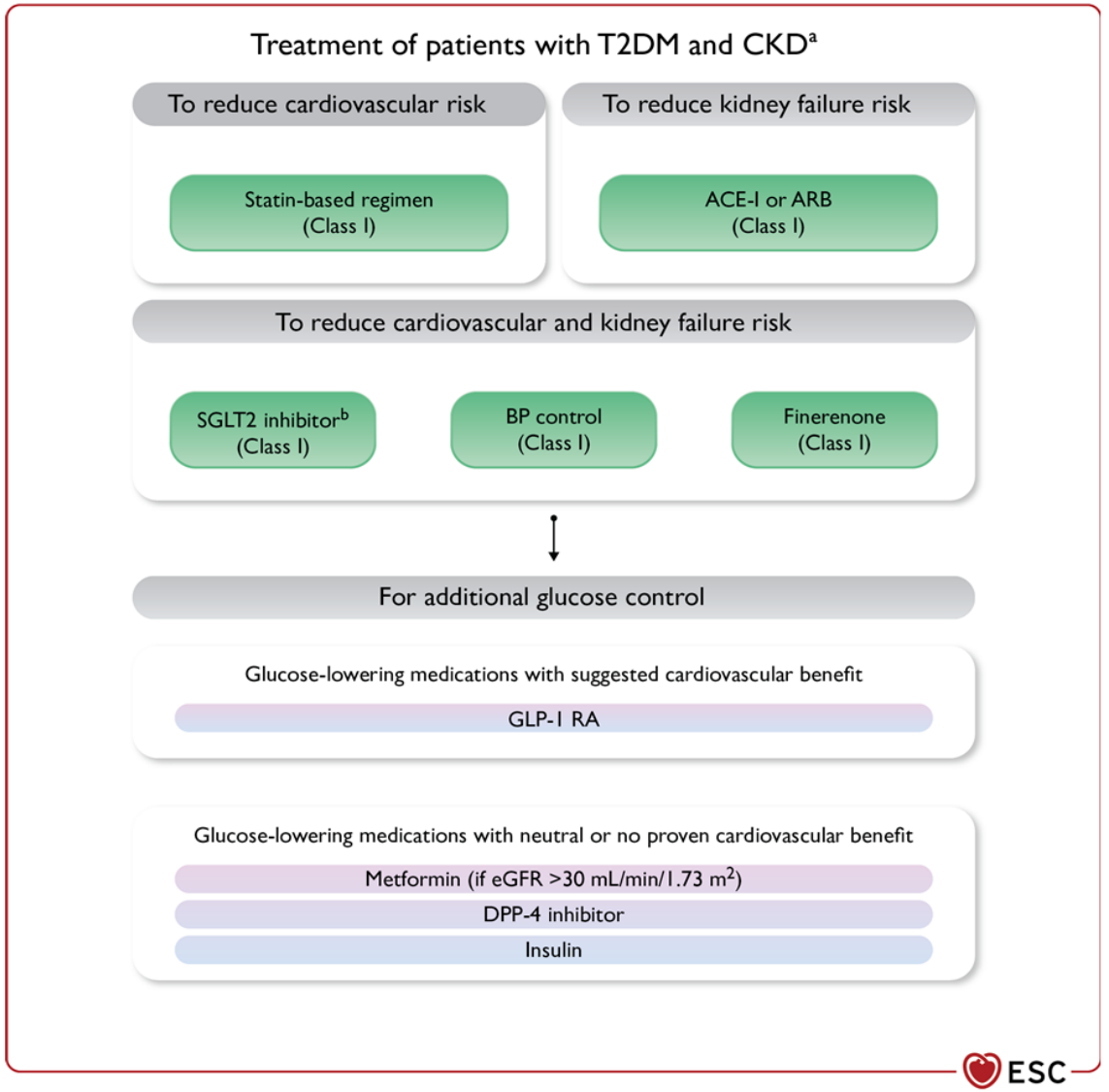
Figure 18

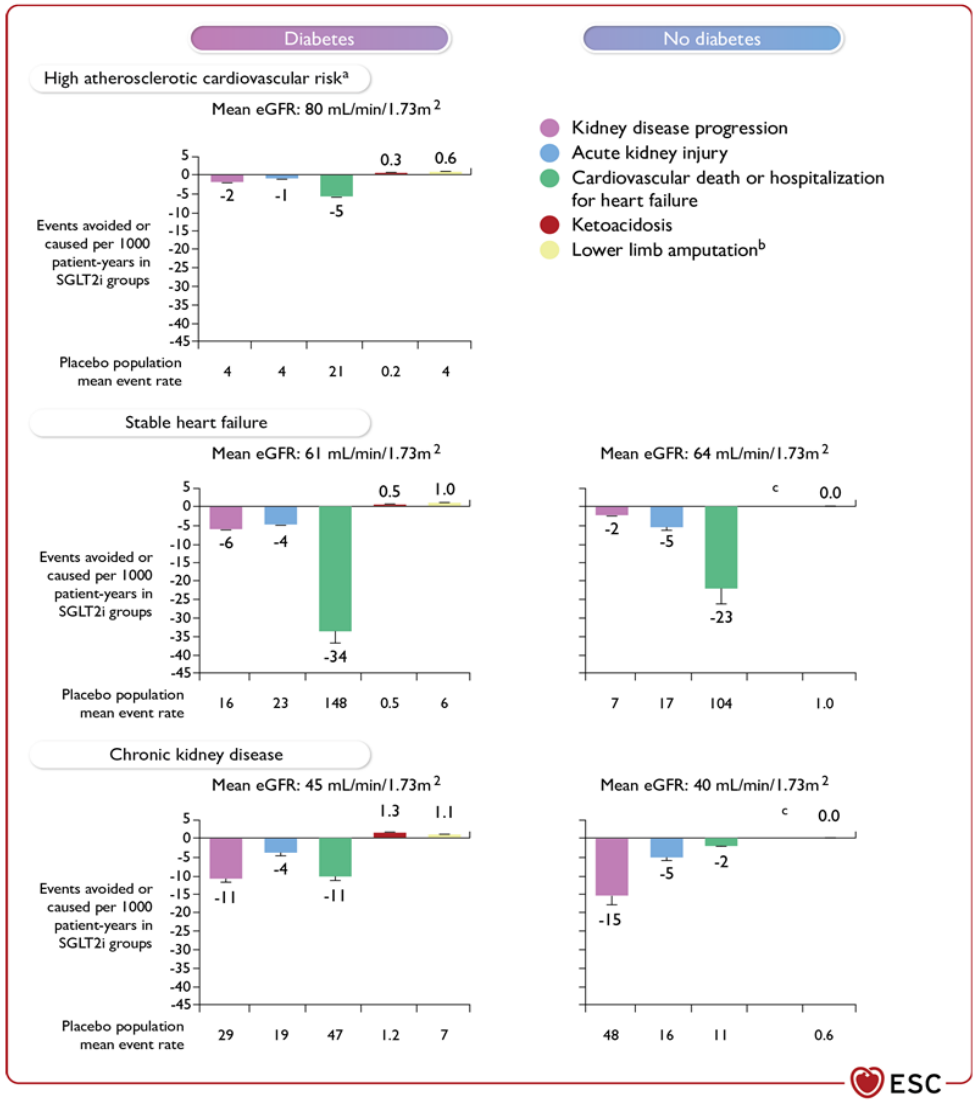
Pharmacological management to reduce cardiovascular or kidney failure risk in patients with type 2 diabetes and chronic kidney disease



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

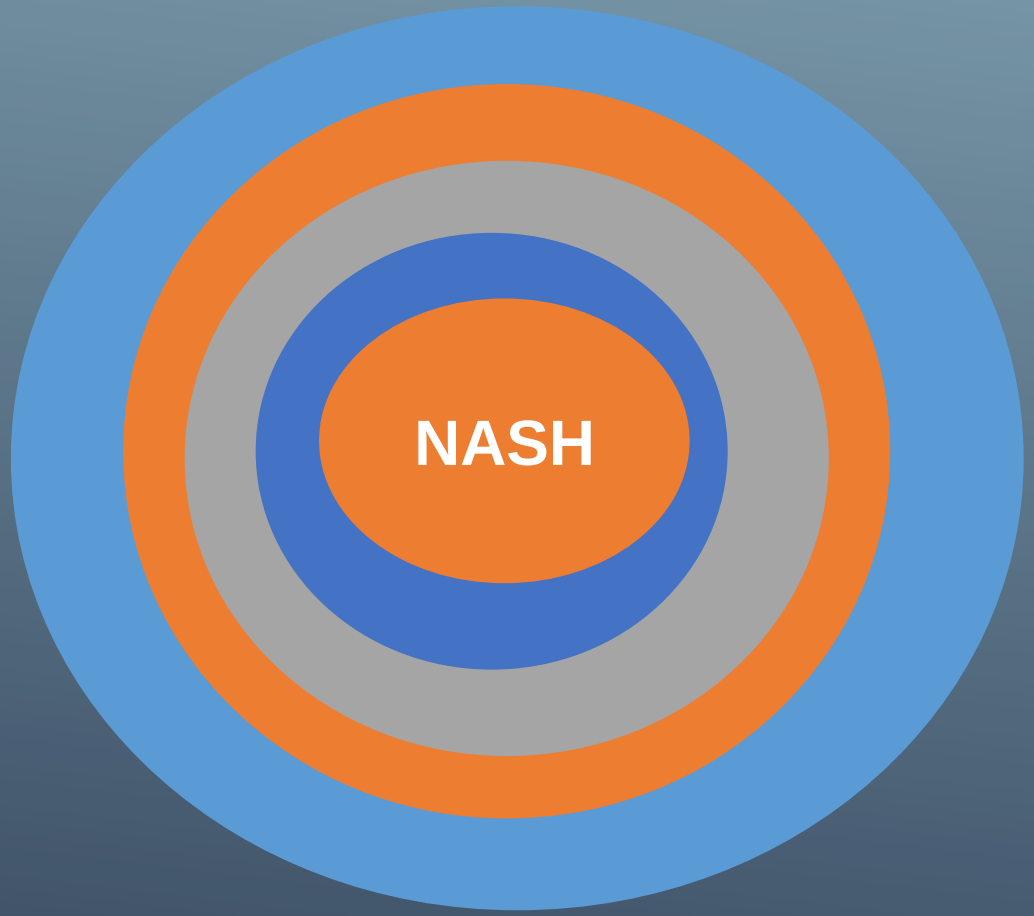
Figure 19

Absolute benefits and harms of sodium–glucose co-transporter-2 inhibitors in patients with and without diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

FÁRMACO MULTIFUNCIONAL



iSGLT2

LA EFICACIA NO DEPENDE DE LA RESERVA PANCREATICA DE INSULINA

SE PUEDEN UTILIZAR EN CUALQUIER MOMENTO Y CUALQUIER OTRA TERAPIA

BIEN TOLERADOS/ INFECCIONES GENITALES LEVES

PRECAUCIÓN POR EL RIESGO DE CETOSIS EUGLUCEMICA

MENSAJES PARA LA CASA

Hoy los iSGLT2 en nuestros pacientes y en base a las evidencias son fármacos:

1. **Dosis Única Diaria – casi sin necesidad de titulación.**
2. **En Nefrología posiblemente cuando mas precoz mejores resultados.**
3. **En Cardiología es parte de los 4 fantásticos**
4. **(IECA/ARA2/ARNI+BB+ARM).**
5. **Mejorar la calidad de vida y también la prolongan.**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