PAPEL DE LOS iSGLT2 y aR-GLP1 EN LA ERC.

Limitaciones y precauciones en su prescripción

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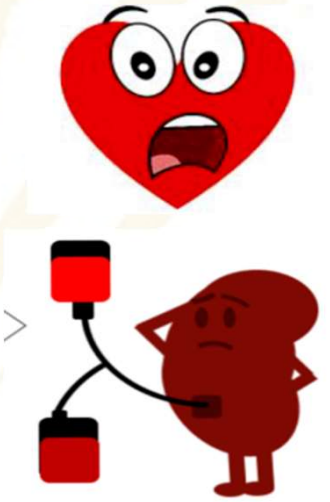
Adults with Diabetes, Hypertension, older than 60, or a family history of kidney disease → Request Kidney Profile (eGFR & ACR)

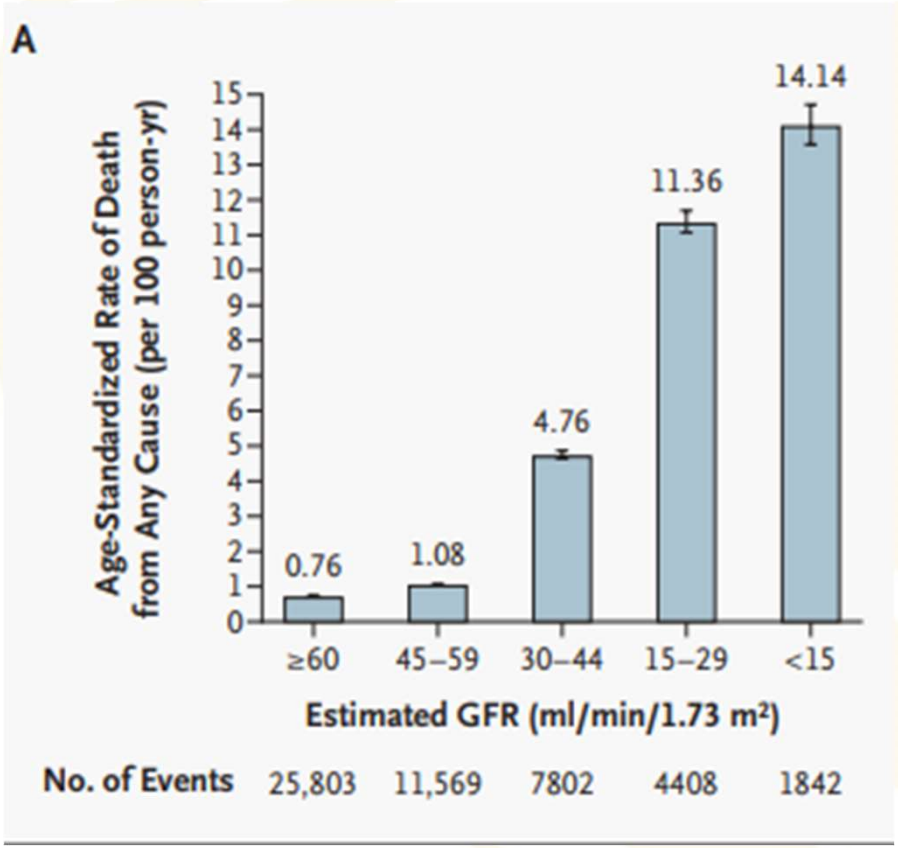
Low risk
Moderately increased risk
High risk
Very high risk
Highest risk

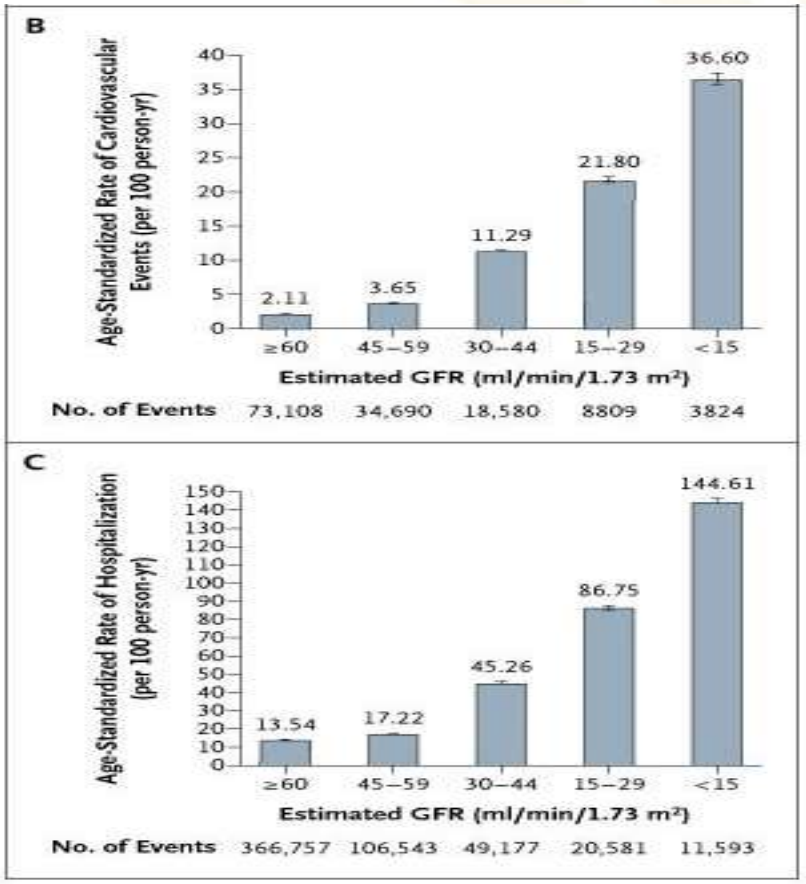
CKD is classified on the basis of:
- Cause (C)
- GFR (G)
- Albuminuria (A)

GFR categories (mL/min/1.73m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severly increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+



El riesgo de morbilidad y mortalidad aumentan drásticamente a medida que desciende el FGe





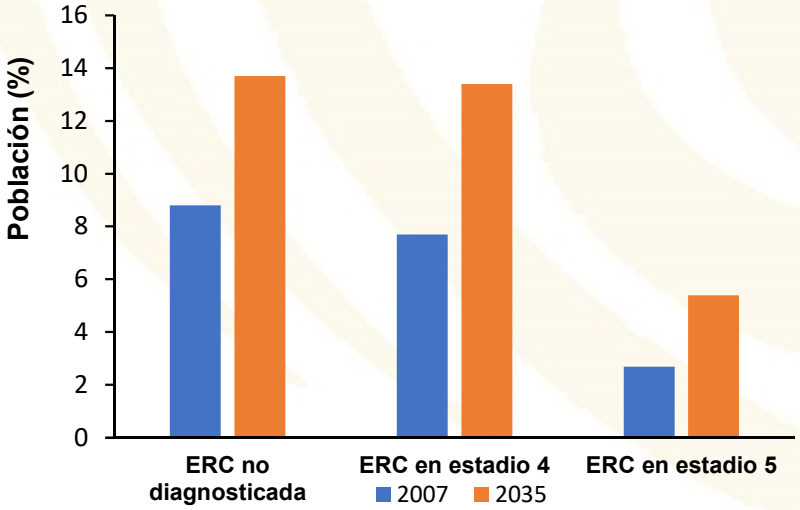
El evento cardiovascular se definió como la hospitalización por enfermedad coronaria, insuficiencia cardíaca, accidente cerebrovascular isquémico y enfermedad arterial periférica.
TFGe: tasa de filtración glomerular estimada

Go A, Chertow MG, Fan D, *et al.* N Engl J Med. 2004;351:1296-1305.

La enfermedad renal crónica es un problema de salud global[1-3]

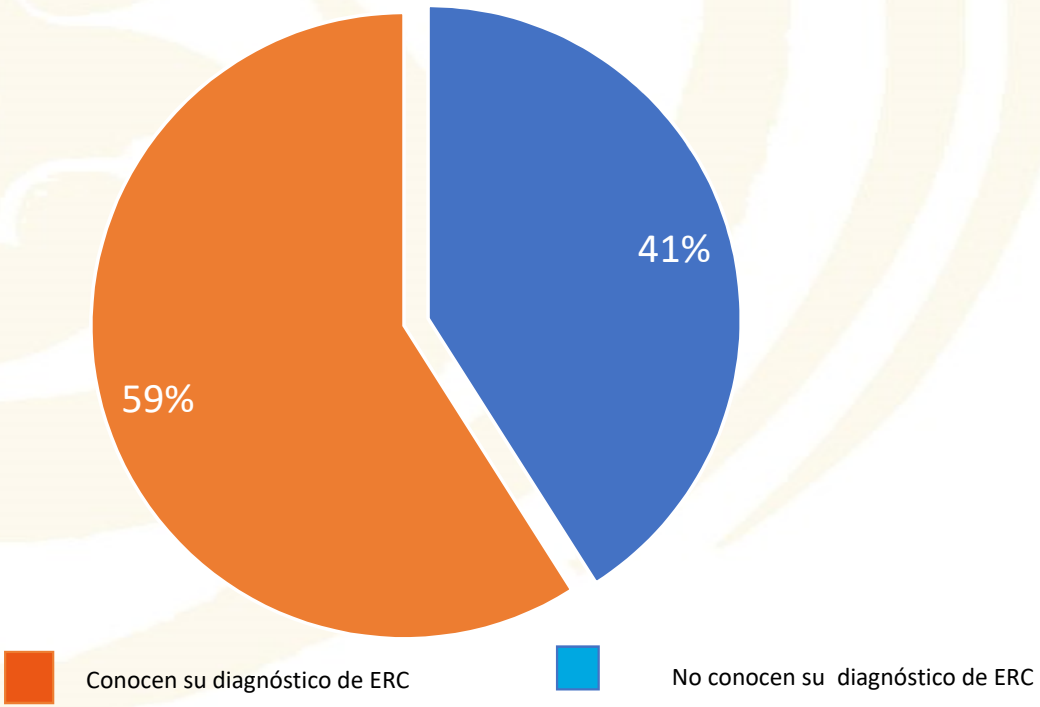
- La prevalencia mundial de la ERC es de aproximadamente **698 millones**[1] La incidencia mundial de la ERC supera los **19 millones**[1]

Prevalencia prevista de la ERC no diagnosticada y de la ERC en estadios 4 y 5[2]



Wong LY, *et al*.2018[2]

Pacientes de atención primaria con ERC conscientes de su diagnóstico[1],



British Journal of General Practice 2012; 62 (597): E227-E23

La diabetes es la principal causa de enfermedad renal crónica

Prevalencia mundial estandarizada por edad de ERC por causa por 100 000 personas en 2016[1]

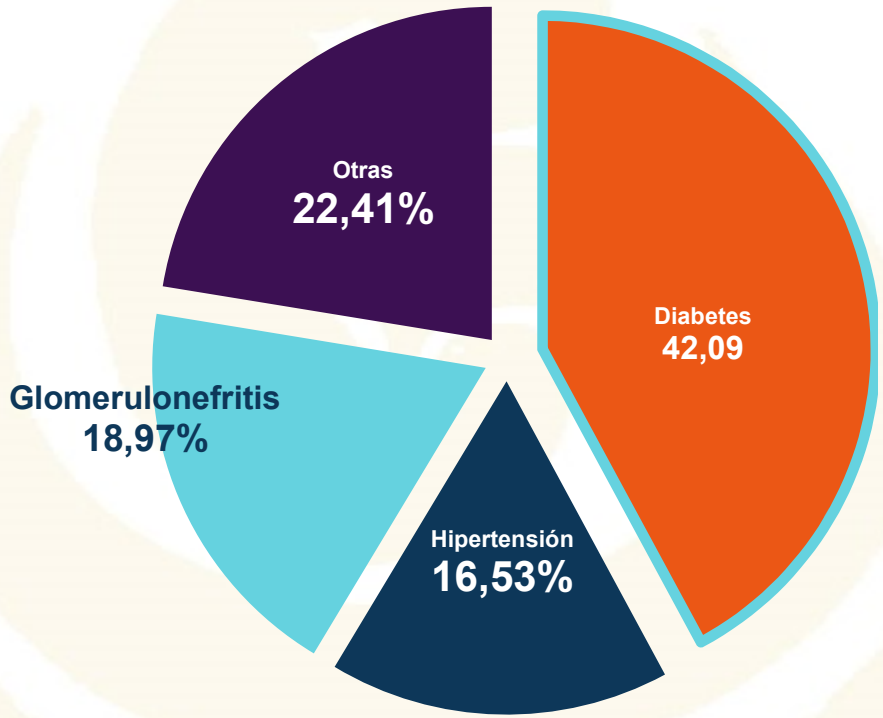
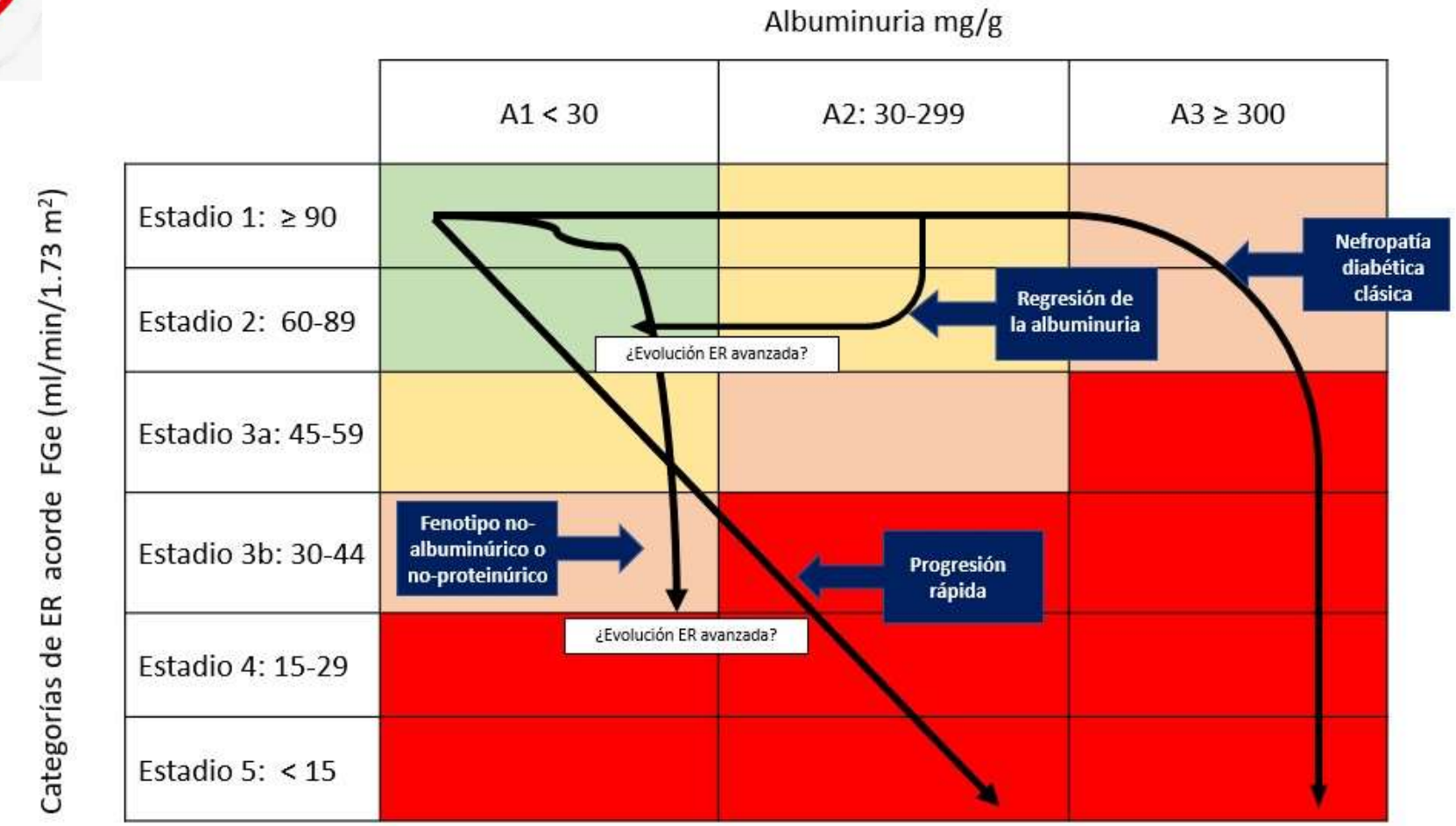
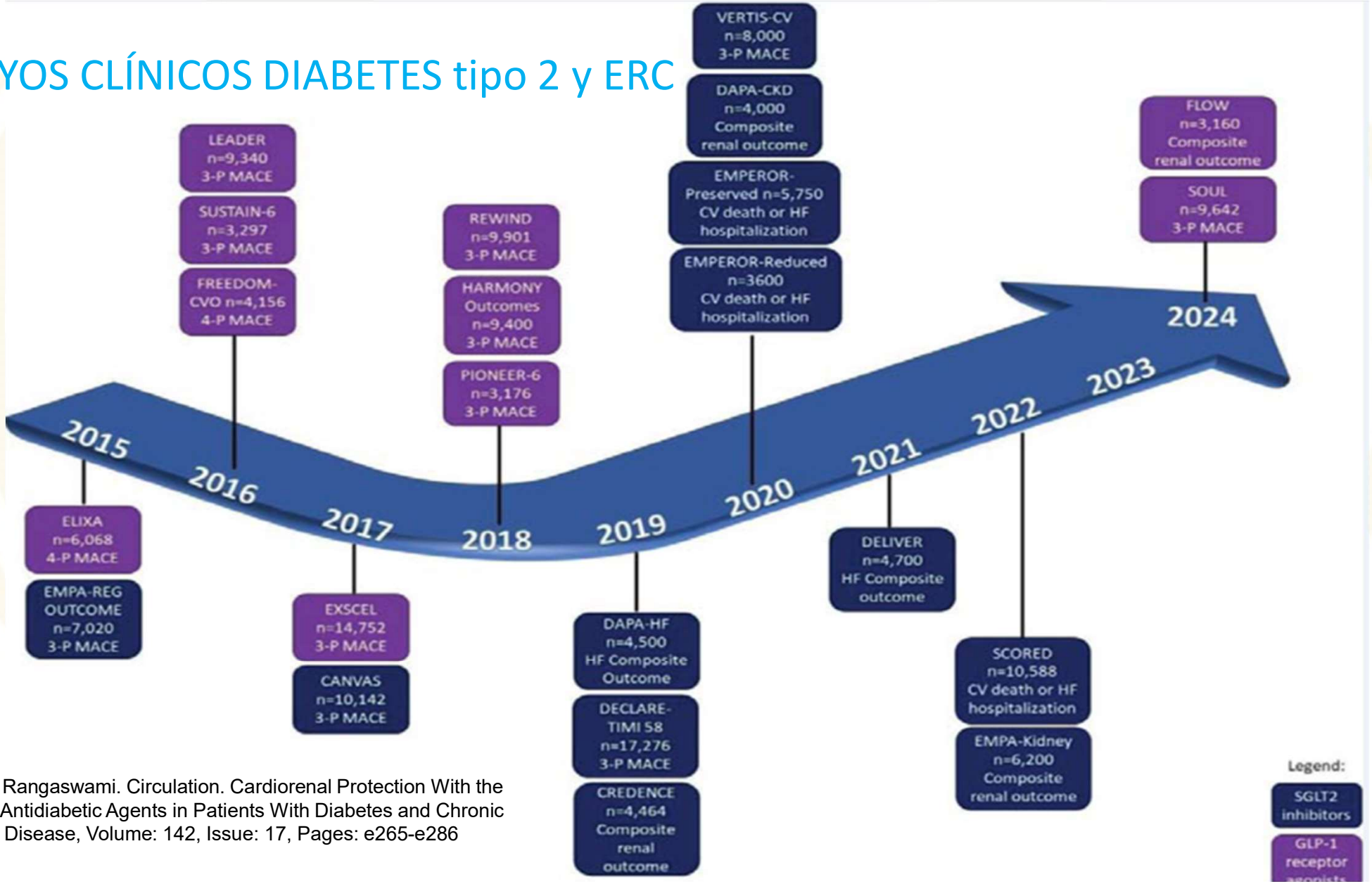


Figura 1: Evolución de los distintos fenotipos de enfermedad renal del paciente diabético



DM: Diabetes mellitus. ER: enfermedad renal. FGe: fitrado glomerular estimado. Adaptado de Osima et al, *Nature Reviews Nephrology* (Vol. 17, Issue 11, pp. 740–750) 2021

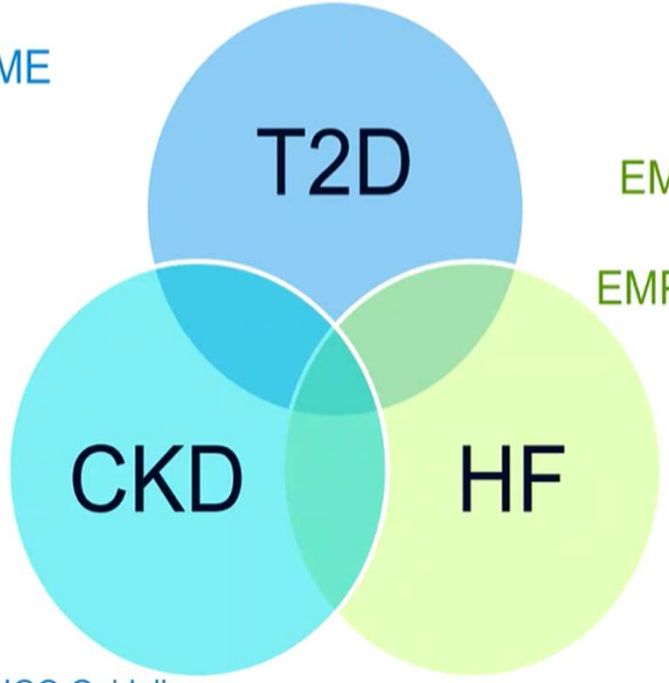
ENSAYOS CLÍNICOS DIABETES tipo 2 y ERC



Janani Rangaswami. Circulation. Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease, Volume: 142, Issue: 17, Pages: e265-e286

Large clinical trials of SGLT-2 inhibitors

EMPA-REG OUTCOME
CANVAS
DECLARE-TIMI 58
VERTIS-CV*



DAPA-HF
EMPEROR-Reduced*
SOLOIST*
EMPEROR-Preserved*
DELIVER**

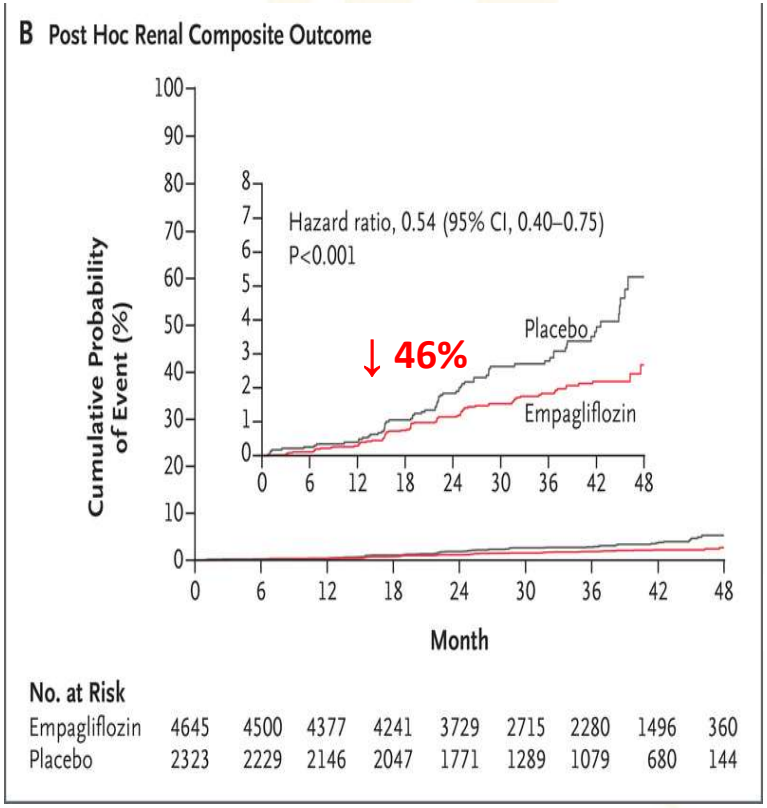
CREDENCE
DAPA-CKD*
SCORED*
EMPA-Kidney**

* Published since 2020 KDIGO Guideline
** Ongoing/pending, but positive press releases

i SGLT2. DM 2

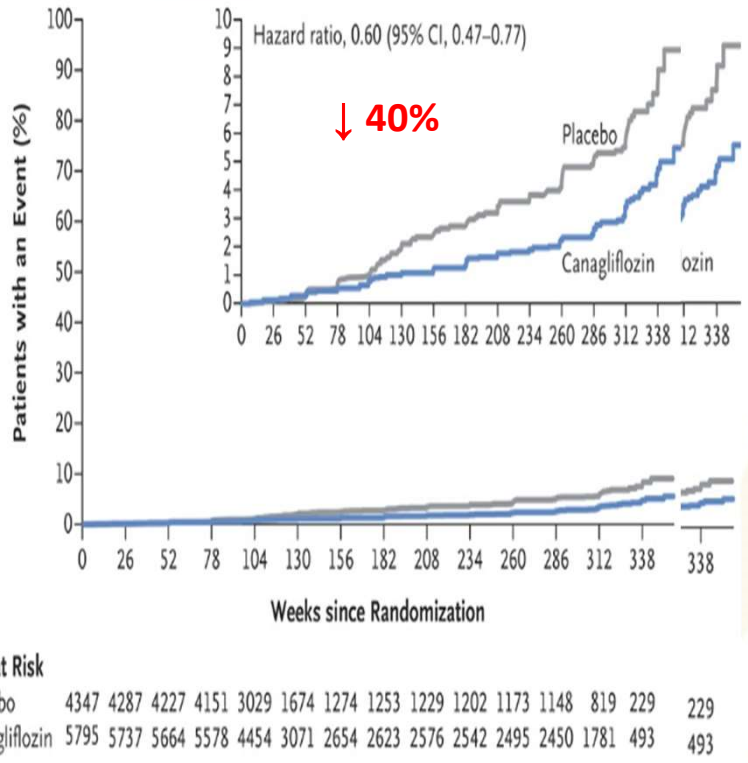
Composite Renal Outcome

EMPA-REG OUTCOME®



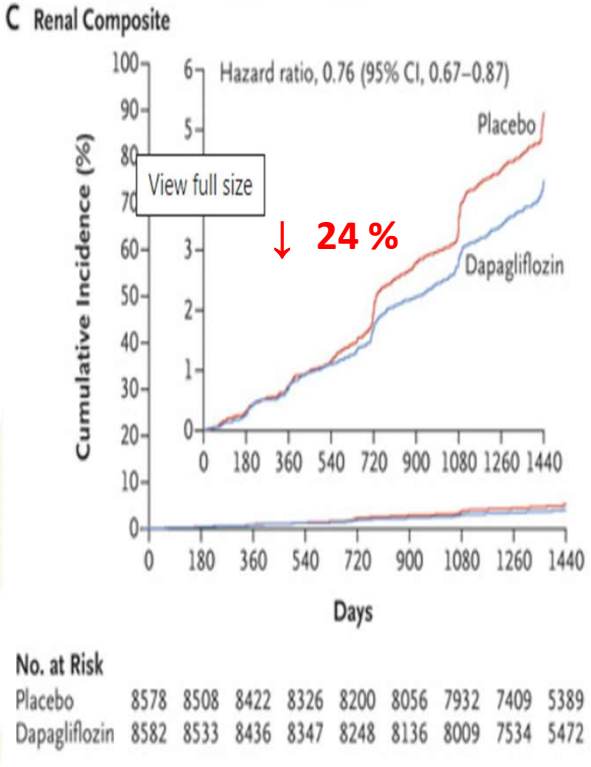
doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease

CANVAS Program



Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes

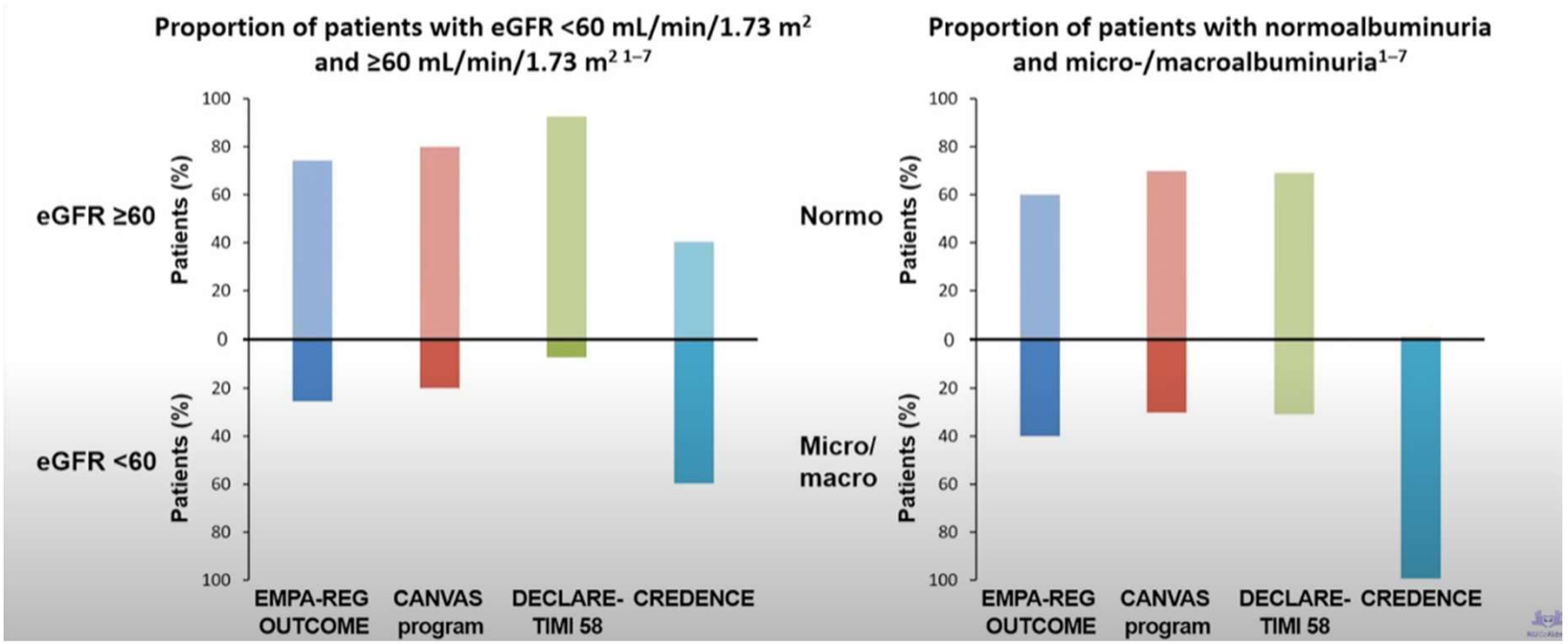
DECLARE TIMI-58 Dapagliflozin Effect on Cardiovascular Events



≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause

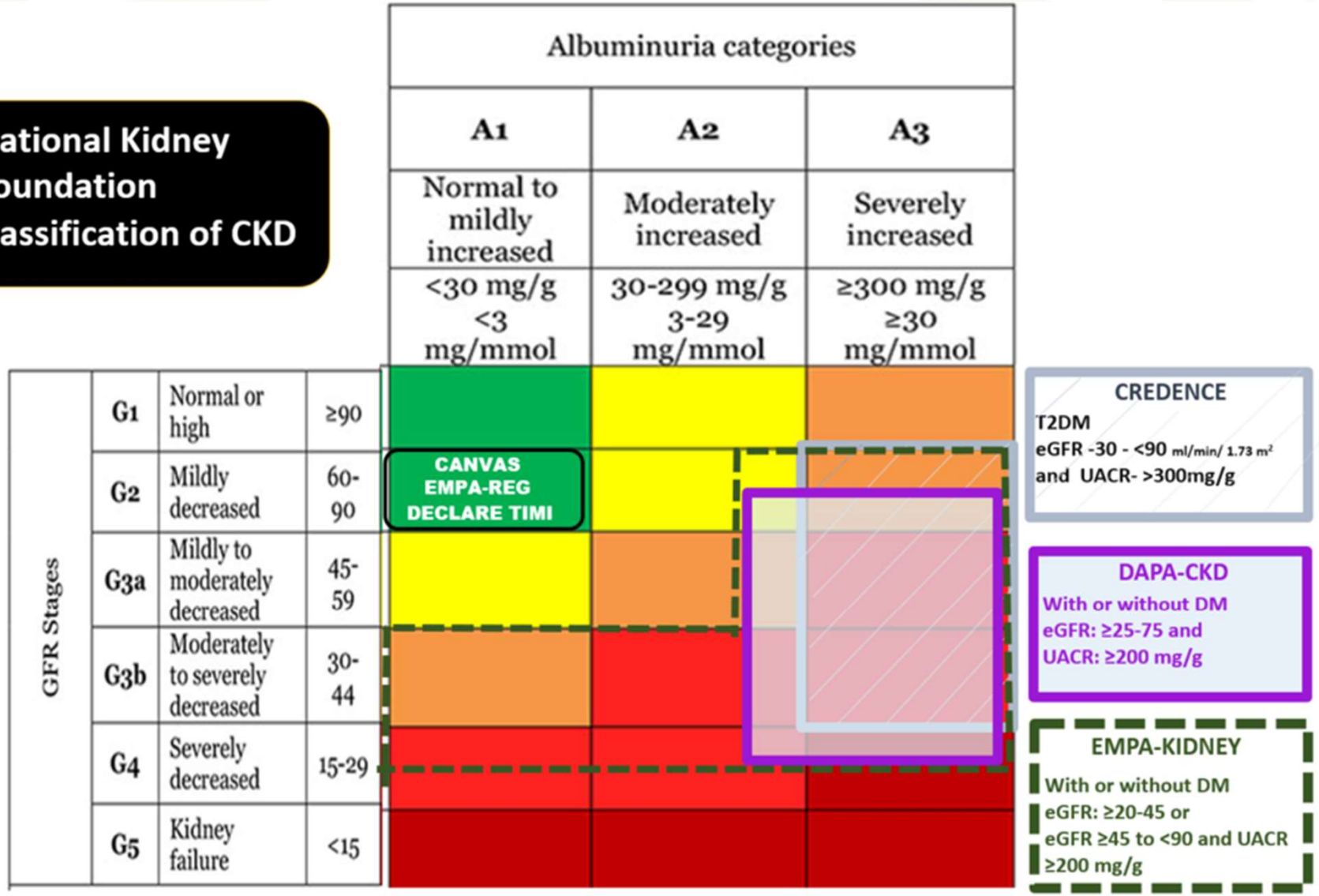
Wanner et al NEJM 2016; Neal B.et al NEJM 2017; Wiviott S.et al NEJM 2018

¡ SGLT2 EN DIFERENTES ESTADIOS ERC Y ALBUMINURIA EN DIABETES MELLITUS TIPO 2



JASN 2018; 29: 2755-2769; NEJM 2019,380: 347-357

National Kidney Foundation classification of CKD



Randomised controlled trials of SGLT2is in DKD/CKD

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
	Double-blind, Placebo-controlled, Multicentric RCT (N=4401)	Double-blind, Placebo-controlled, Multicentric RCT (N=4304)	Double-blind, Placebo-controlled, Multicentric parallel group RCT (N=5000)
Inclusion	Type 2 DM eGFR: ≥30- 90 and UACR: >300-≤5000 mg/g	With or without DM eGFR: ≥25-75 and UACR: ≥200-≤5000 mg/g	With or without DM eGFR: ≥20-45 or eGFR ≥45 to <90 with UACR ≥200 mg/g
Median follow up	2.62 yrs	2.4 yrs	
Intervention	Canagliflozin VS placebo	Dapagliflozin VS placebo	Empagliflozin VS placebo
Year	2019	2020	2022
			JUST PUBLISHED!
Primary outcomes	Composite of ESKD, 2 X S.cr , or kidney related or CV death HR 0.70; (0.59 to 0.82)	Composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal causes-HR 0.56; (0.45 to 0.68)	Primary outcomes: Kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40%
Secondary outcomes	CV death, MI, or stroke- HR 0.80, (0.67 -0.95) Hospitalization for heart failure HR 0.61; (0.47 to 0.80)	Composite of death from CV causes or hospitalization for heart failure HR 0.71; (0.55 to 0.92)	

CREDENCE: DM + eGFR of 30 to <90 ml/min/1.73 m^2 and albuminuria (UACR >300 to 5000)

Perkovic V *et al*. *N Engl J Med* 2019;380:2995

CREDENCE

Primary composite outcome

ESKD, doubling of serum creatinine, death from kidney causes or CV death

↓30% RRR

p=0.00001

Secondary outcomes

CV death or HHF

↓31% RRR

p<0.001

3P-MACE†

↓20% RRR

p=0.01

HHF

↓39% RRR

p<0.001

DAPA-CKD: noDM & DM + eGFR of 25 to <75 ml/min/1.73 m^2 and albuminuria (UACR >200 to 5000)

DAPACKD

Primary composite outcome

Decline in eGFR ≥50%; ESKD*; renal or CV death

↓39% RRR

p=0.000000028

*Defined as eGFR <15 ml/min/1.73 m^2, need for chronic dialysis and/or renal transplantation

Secondary outcomes

≥50% sustained decline in eGFR or reaching ESRD or renal death

↓44% RRR

P=0.000000018

CV death or HHF

↓29% RRR

p=0.008

TOTAL death

↓31% RRR

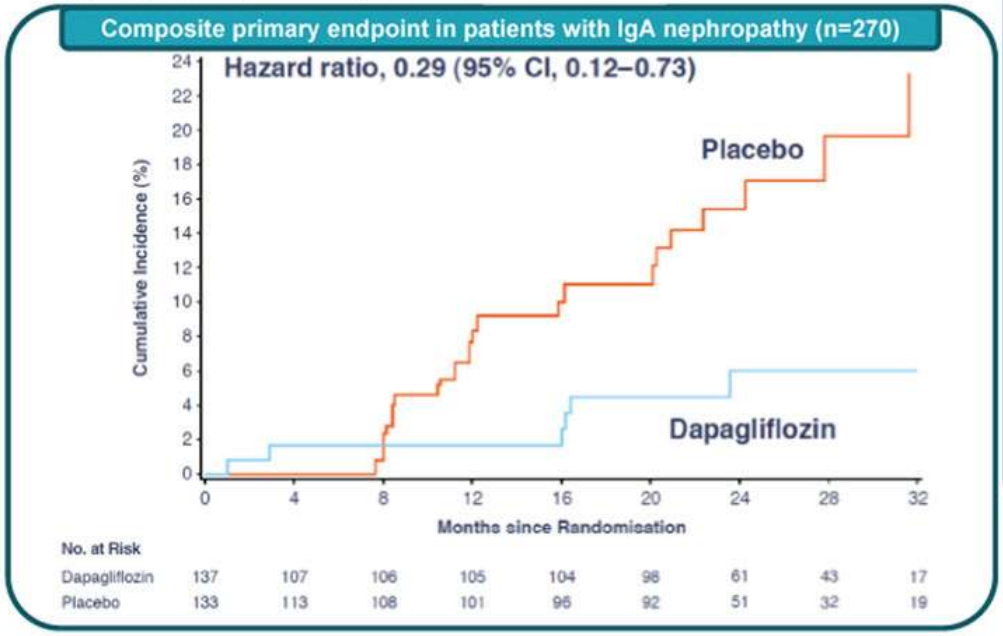
p 0.0035

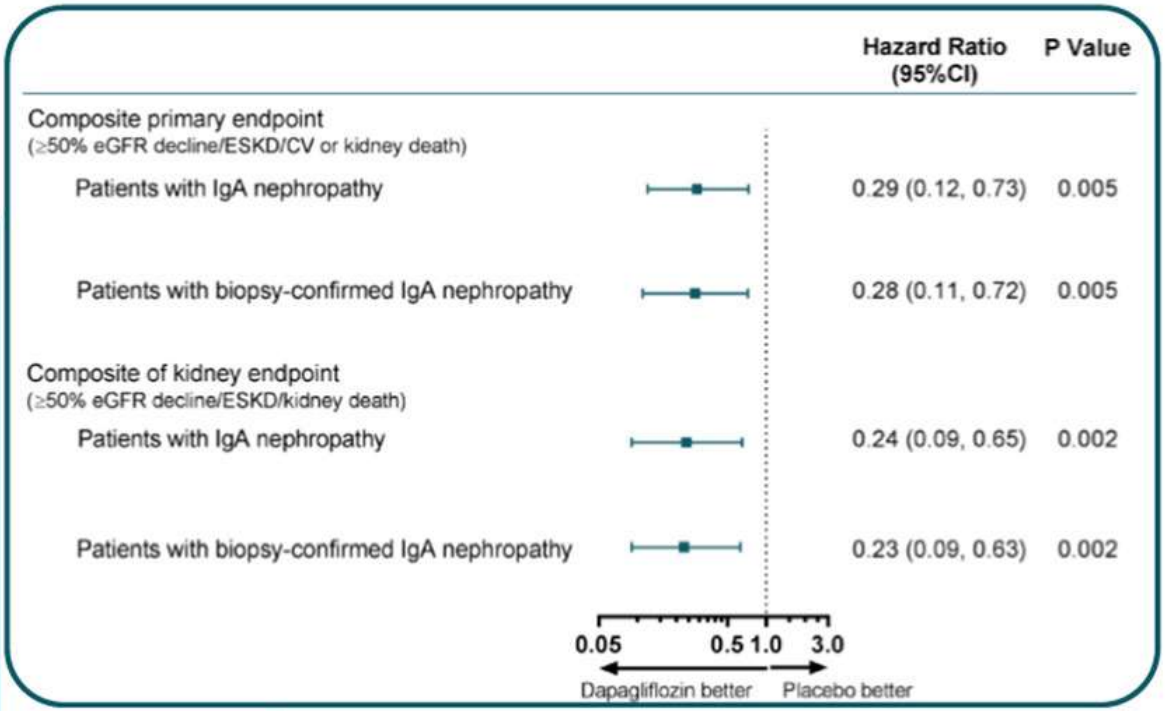
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**





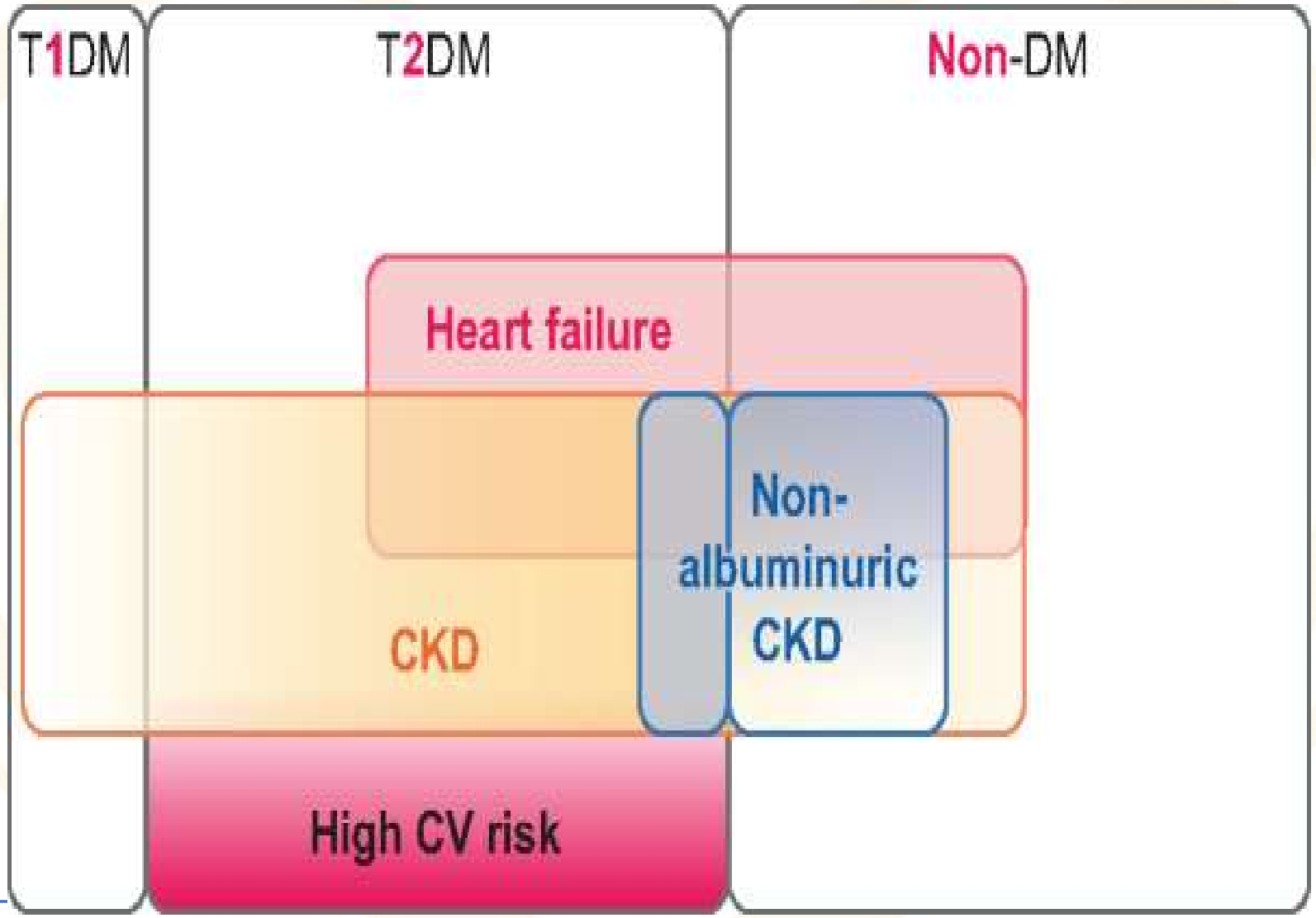
IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

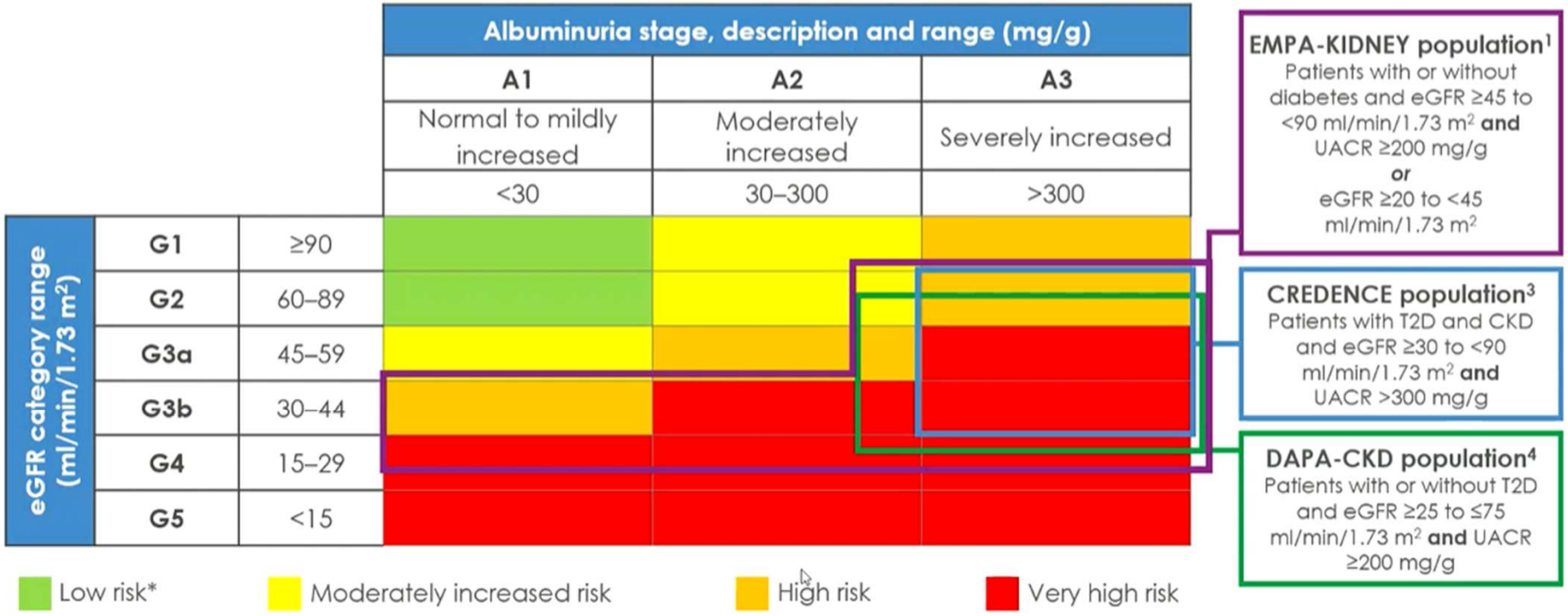
kidney INTERNATIONAL ISN

Wheeler et al, 2021


T1DM
T2DM
Non-DM
Heart failure
CKD
Non-albuminuric CKD
High CV risk

EMPA-KIDNEY enrolled a CKD population with a broad range of eGFR, with and without albuminuria

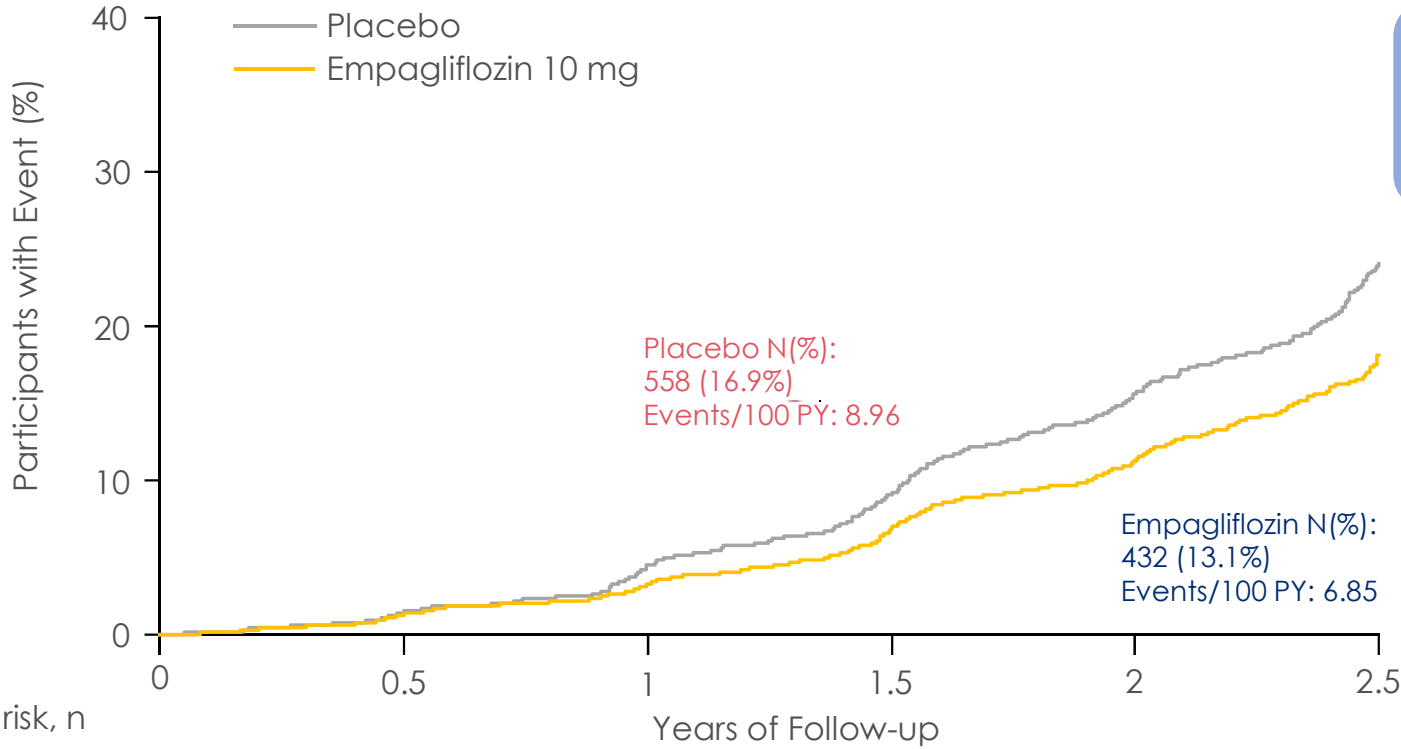
Prognosis of CKD by eGFR and albuminuria categories



1. The EMPA-KIDNEY Collaborative Group. Nephrol Dial Transplant 2022;
2. Perkovic V et al. N Engl J Med 2019; 3. Wheeler DC et al. Nephrol Dial Transplant 2020

Primary composite outcome
Kidney disease progression or CV death

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin



HR 0.72
(95% CI 0.64, 0.82)
P<0.001

RRR 28%

NNT=28*

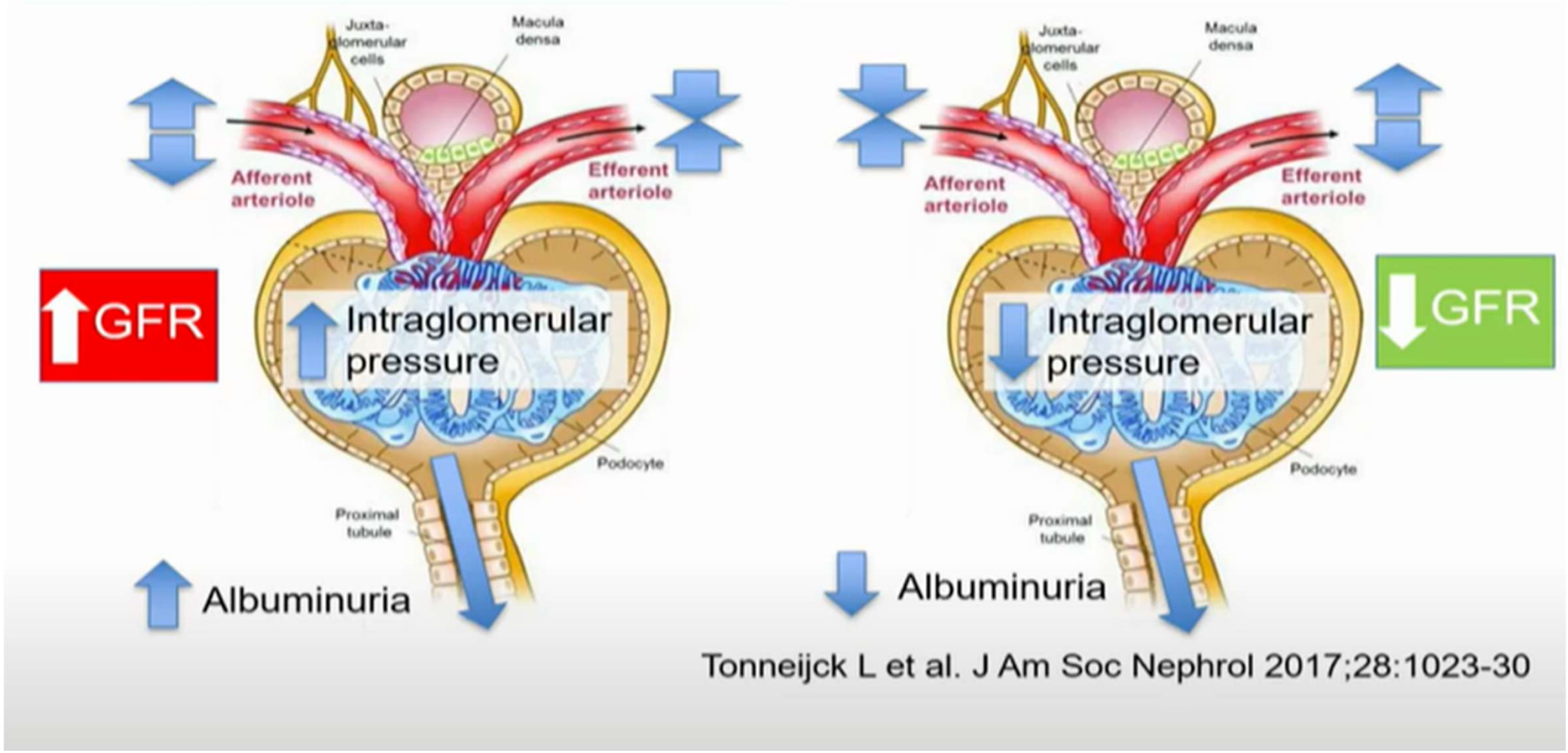
Patients at risk, n

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

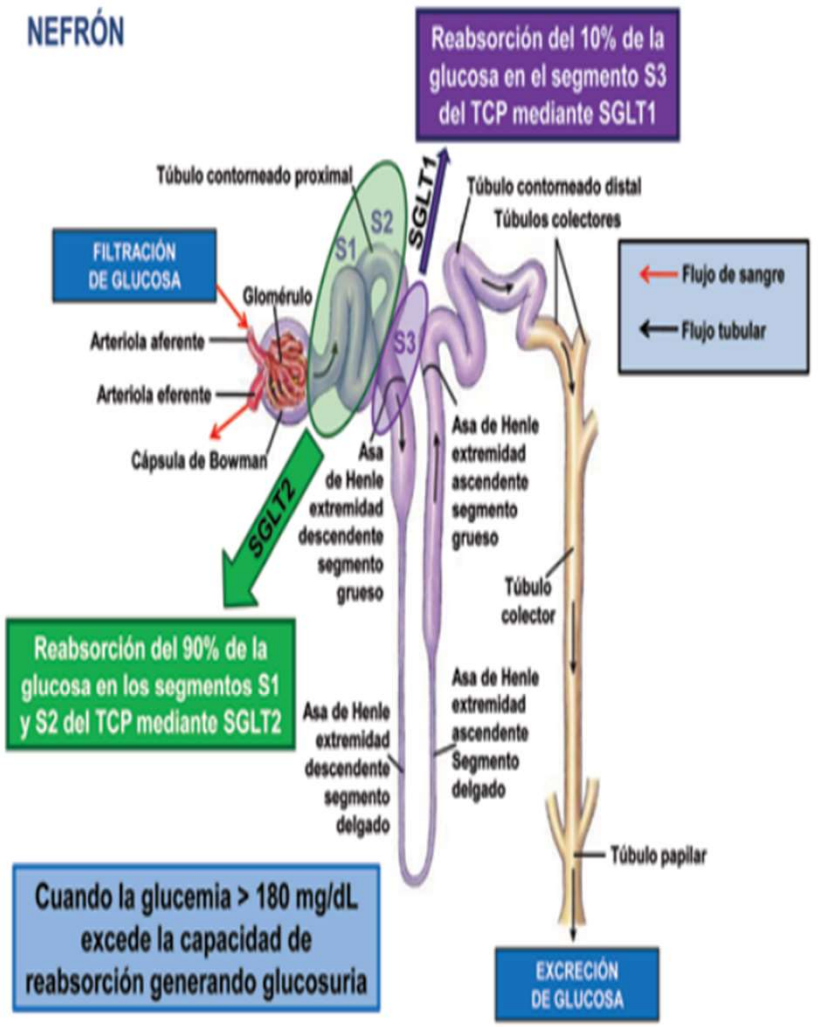
*NNT: 28 (95% CI 19, 53) per 2 years at risk
ARR for the primary composite outcome of kidney disease progression or CV death is 3.6% per patient year at risk
Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization
ARR, absolute risk reduction; CV, cardiovascular, eGFR, estimated glomerular filtration rate; NNT, number needed to treat; RRR, relative risk reduction; UACR, urine albumin-to-creatinine ratio
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022;XX:XXXX

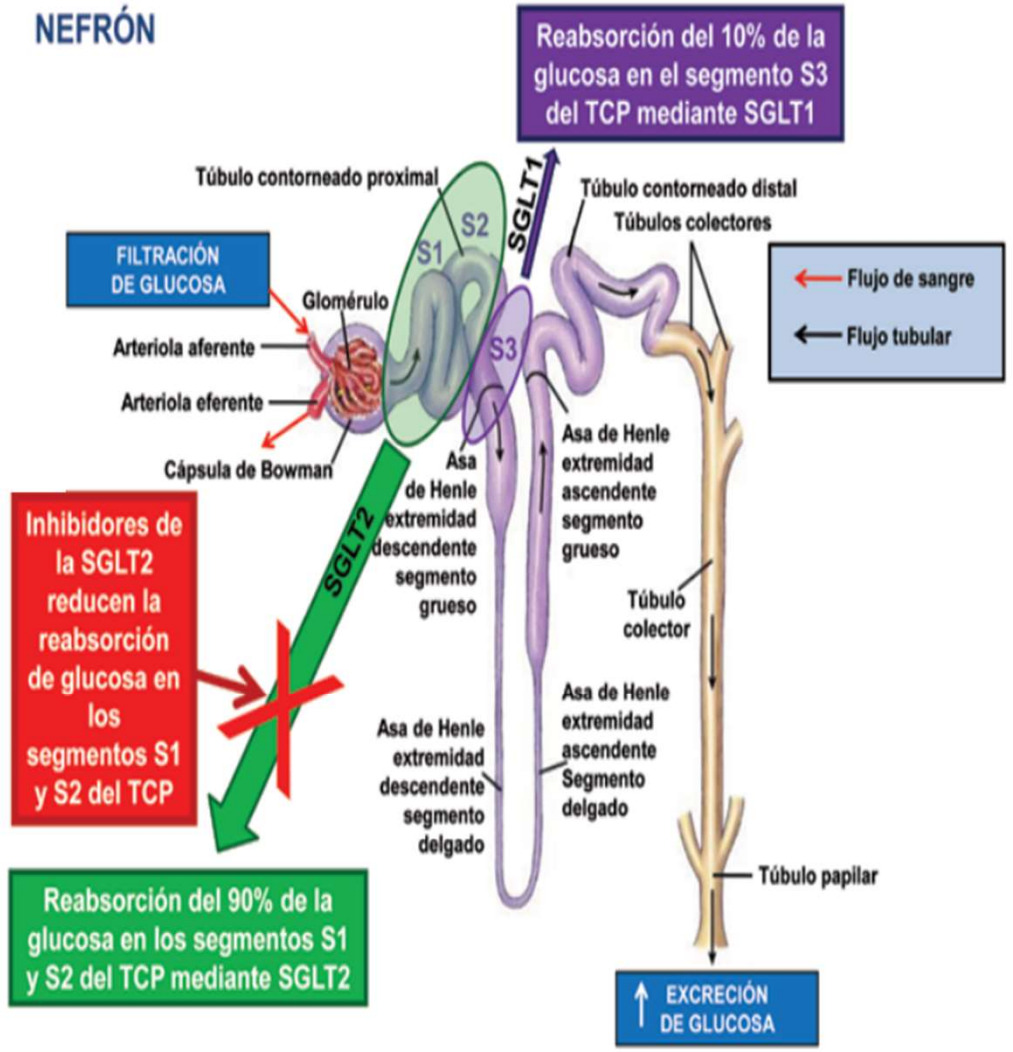
Increased filtration

Decreased filtration



Tonneijck L et al. J Am Soc Nephrol 2017;28:1023-30


NEFRÓN
Reabsorción del 10% de la glucosa en el segmento S3 del TCP mediante SGLT1
Túbulo contorneado proximal
S1
S2
S3
SGLT1
Túbulo contorneado distal
Túbulos colectores
FILTRACIÓN DE GLUCOSA
Glomérulo
Arteriola aferente
Arteriola eferente
Cápsula de Bowman
Flujo de sangre
Flujo tubular
SGLT2
Asa de Henle extremidad descendente segmento grueso
Asa de Henle extremidad ascendente segmento grueso
Túbulo colector
Reabsorción del 90% de la glucosa en los segmentos S1 y S2 del TCP mediante SGLT2
Asa de Henle extremidad descendente segmento delgado
Asa de Henle extremidad ascendente Segmento delgado
Túbulo papilar
Cuando la glucemia > 180 mg/dL excede la capacidad de reabsorción generando glucosuria
EXCRECIÓN DE GLUCOSA


NEFRÓN
Reabsorción del 10% de la glucosa en el segmento S3 del TCP mediante SGLT1
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S3
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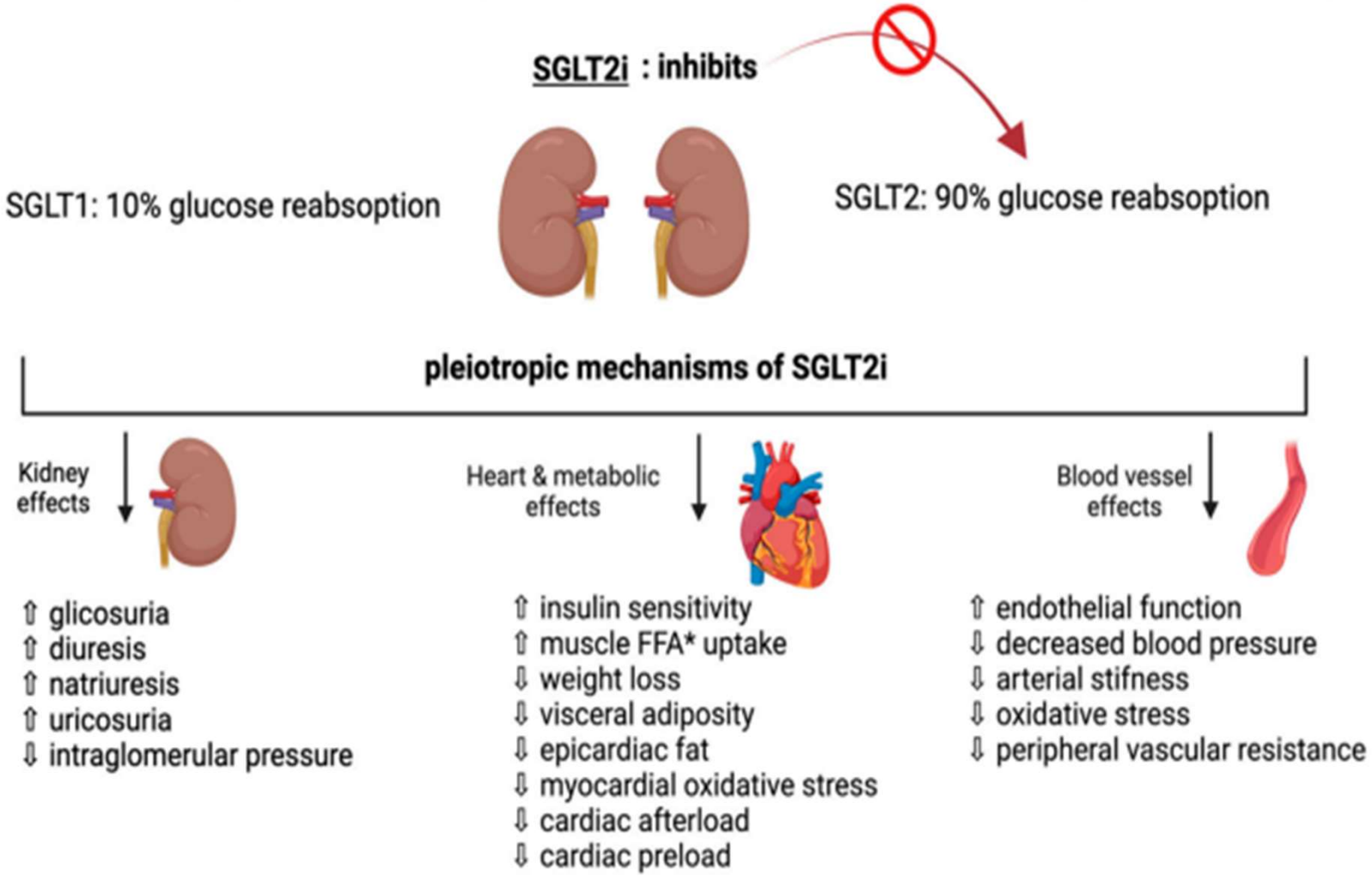
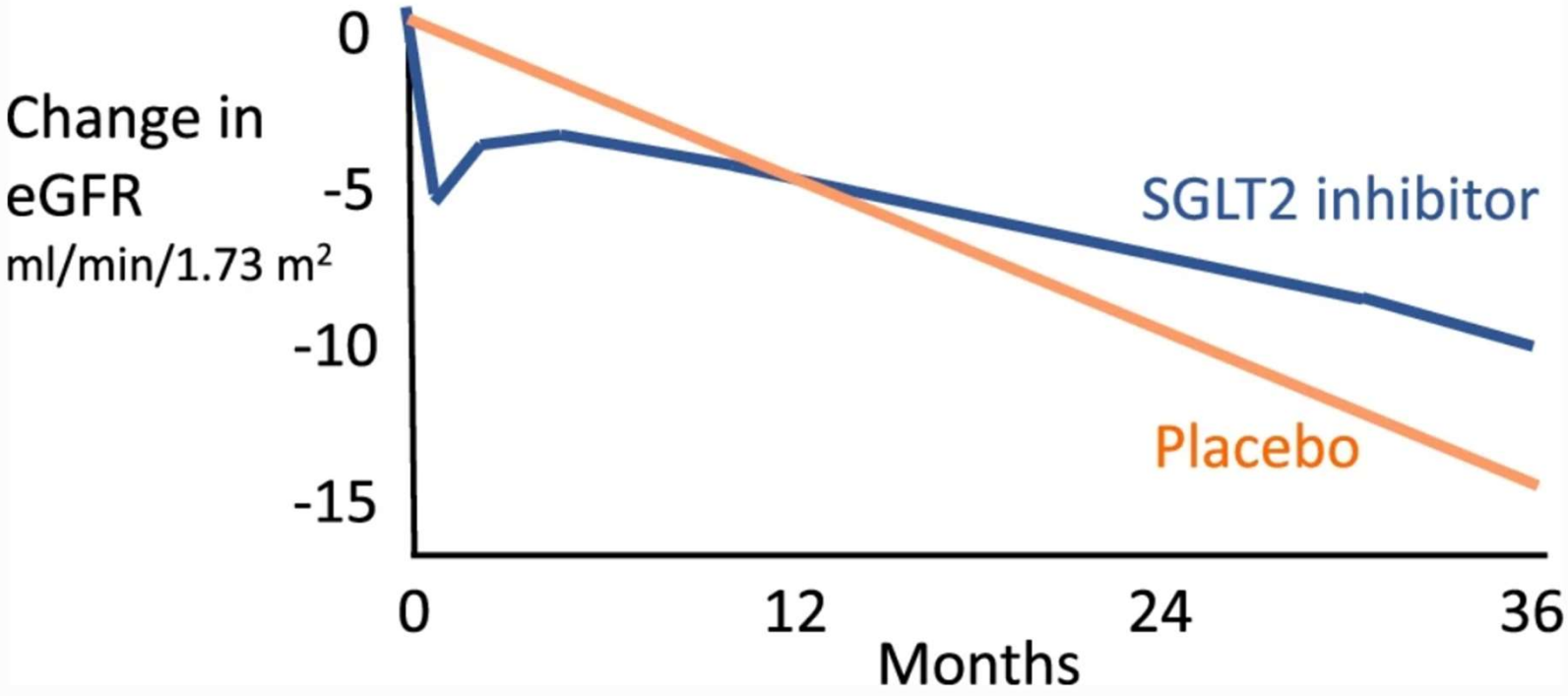
Túbulo contorneado distal
Túbulos colectores
FILTRACIÓN DE GLUCOSA
Glomérulo
Arteriola aferente
Arteriola eferente
Cápsula de Bowman
Flujo de sangre
Flujo tubular
Inhibidores de la SGLT2 reducen la reabsorción de glucosa en los segmentos S1 y S2 del TCP
SGLT2
Asa de Henle extremidad descendente segmento grueso
Asa de Henle extremidad ascendente segmento grueso
Túbulo colector
Asa de Henle extremidad descendente segmento delgado
Asa de Henle extremidad ascendente Segmento delgado
Túbulo papilar
Reabsorción del 90% de la glucosa en los segmentos S1 y S2 del TCP mediante SGLT2
EXCRECIÓN DE GLUCOSA



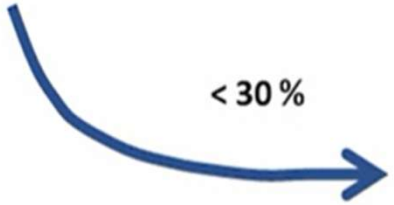
Pharmaceutics **2022**, *14*, 1730.

Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease



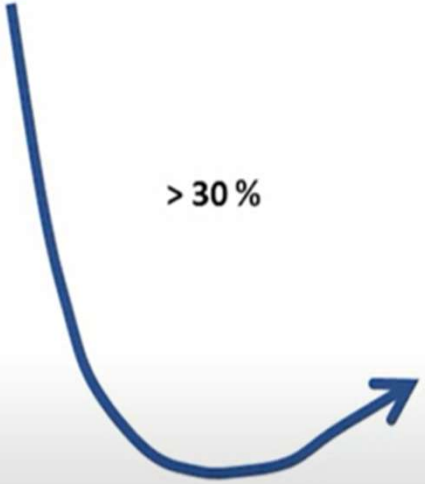
Current Diabetes Reports **22**, 39–52 (2022)

Caída del FGe < 30 % respecto a la basal tras inicio de un iSGLT2



No precisa control ni atención especial

Caída del FGe > 30 % respecto a la basal tras inicio de un iSGLT2



Descartar:

- Altas dosis de diuréticos
- Depleción hidrosalina
- Estenosis bilateral ateromatosa de la arterial renal

ASPECTOS BÁSICOS A TENER EN CUENTA ANTES DE INDICAR UN i SGLT2

Category	Clinical situation
SGLT2i therapy should be offered	First-line (metformin intolerant)
	Second-line to metformin or third-line as add-on to other second-line therapies, including in combination with GLP-1 RA and insulin
	Established CVD
	History of HF
	Overweight or obesity
	Prior stroke
	Vulnerable to the effects of hypoglycaemia
	Renal impairment/CKD/DKD
	No history of lower limb amputation
	No history of PAD
	Receiving loop diuretics
	Osteoporosis
	History of fractures
SGLT2i therapy can be considered	Frail/elderly/cognitive impairment
	History of PAD
	History of foot ulceration
	Previous lower limb amputation
	Existing diabetic foot ulcers
	Ketogenic/low calorie/low carbohydrate diet
	BMI <25 kg/m^2
	High HbA1c levels (>86 mmol/mol or 10%)
	Recurrent UTIs
	Recurrent genital mycotic infections
	Receiving systemic steroid therapy
SGLT2i therapy should not be prescribed	Acute illness
	DKA (or previous episode of DKA)
	Excessive alcohol intake
	Eating disorders
	Rapid progression to insulin (within 1 year)
	Multiple pre-disposing risks for Fournier's gangrene
	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding
	Recent major surgery

Tratamiento de la DM2 en el paciente hospitalizado

Unidades ENDOCARE - Abordaje integral multidisciplinar

ENDO: Endocrinología y Nutrición; CA: Cardiología; RE: Nefrología

Abordaje integral Diabetes tipo 2
Área de conocimiento de diabetes mellitus SEEN

@diabeteSEEN

El empleo de estos fármacos en el ambiente hospitalario, debe ser supervisado y monitorizado preferentemente por Endocrinología, en el marco de Unidades ENDOCARE

Cirugía mayor

iSGLT2	72 h
arGLP1	48 h
Metformina	24 h

Diabetes tipo 2
Objetivo general 140-180 mg/dL
Objetivos mas estrictos
< 140 mg/dL en casos seleccionados con bajo riesgo de hipoglucemia

STOP
Criterios
START

Reevaluación

Terapia adyuvante Insulínica

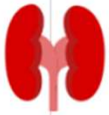
Terapia no-insulina
Metformina
iSGLT2
arGLP1
iDPP4

Monoterapia Insulínica

Si terapia no-insulina contraindicada

Cardiopatía Isquémica

iSGLT2 [E]
arGLP1 Liraglutida [B2]



Enfermedad Renal Diabética

iSGLT2 Dapaglifozina [E]
Canaglifozina [E]
arGLP1 Liraglutida [E]

ACV

arGLP1 Liraglutida [E]

Insuficiencia Cardiaca

iSGLT2 Empaglifozina [A1,C3]
Dapaglifozina [E]

Evidencia [A-E] disponible aplicable a:
1. Reducción objetivo compuesto: Muerte, Número de eventos de IC, tiempo hasta el primer evento de IC, cambios en KCCQ-TSS tras 90 días de tratamiento.
2. Mejor control metabólico frente a monoterapia con insulina.
3. Menor número de hipoglucemias frente a monoterapia con insulina.

arGLP1

START	STOP **No emplear** en estas situaciones
Indicación	**Cirugía mayor** en próximas **48 horas**
Cardiopatía isquémica [4] Ausencia de criterios de STOP	**FGe < 15** ml/min/m² superficie corporal
Enfermedad cerebrovascular Ausencia de criterios de STOP	**Insuficiencia Hepática** (Child – Pugh C)
Enfermedad Renal Diabética con contraindicación de iSGLT2 Ausencia de criterios de STOP	**Clínica digestiva** **Anorexia, Sd. Catabólico con pérdida de peso** (pacientes oncológicos, desnutrición, etc.) **Intolerancia a alimentación oral o enteral**
Sugerencia	
A valorar su inicio en cualquier paciente hospitalizado con **IMC ≥ 30 kg/m²** que carece de criterios de STOP	

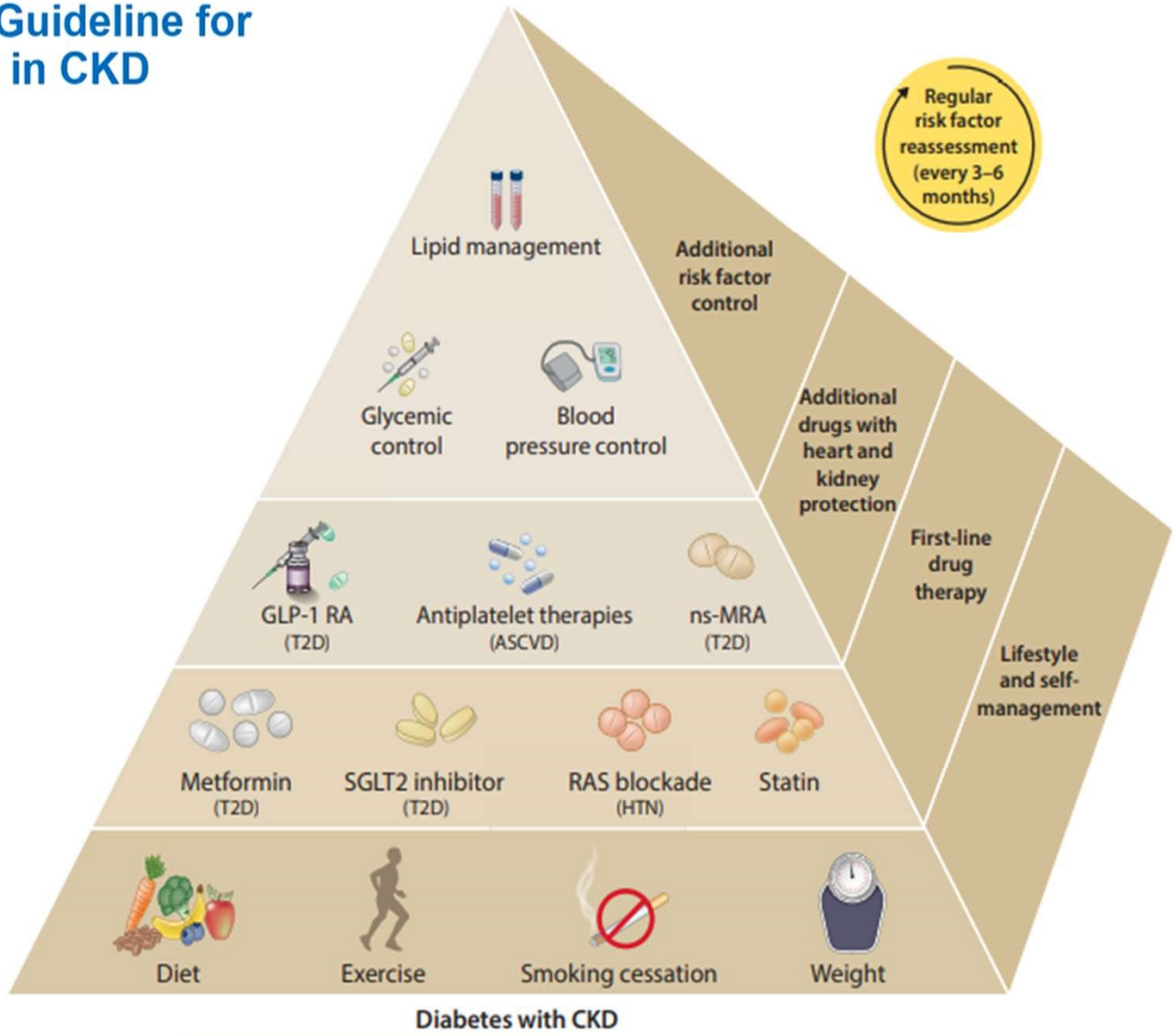
iSGLT2

START	STOP **No emplear** en estas situaciones
Indicación	**Cirugía mayor** en próximas **72 horas**
Insuficiencia Cardiaca con FEr en fase de estabilidad clínica [5] Ausencia de criterios de STOP	Metabolismo anaeróbico: **sepsis, hipoxia, shock** **Anorexia, Sd. Catabólico con pérdida de peso** (pacientes oncológicos, desnutrición, etc.) **Diarrea** **Insuficiencia renal aguda** **Insuficiencia Hepática** (Child – Pugh C) **Infección fúngica genital – perineal activa** **Arteriopatía periférica 2B o superior** **Hemodiálisis**
Cardiopatía isquémica [4] en fase de estabilidad clínica [6] Ausencia de criterios de STOP	
Enfermedad Renal Diabética en fase de estabilidad clínica con FG > 25 ml/min/m² SC DAPA 10 MG FG > 30 ml/min/m² SC CANA 100 MG FG > 30 ml/min/m² SC EMPA 10 MG Ausencia de criterios de STOP	
Sugerencia	
A valorar su inicio en **cualquier paciente hospitalizado** que carece de criterios de STOP	

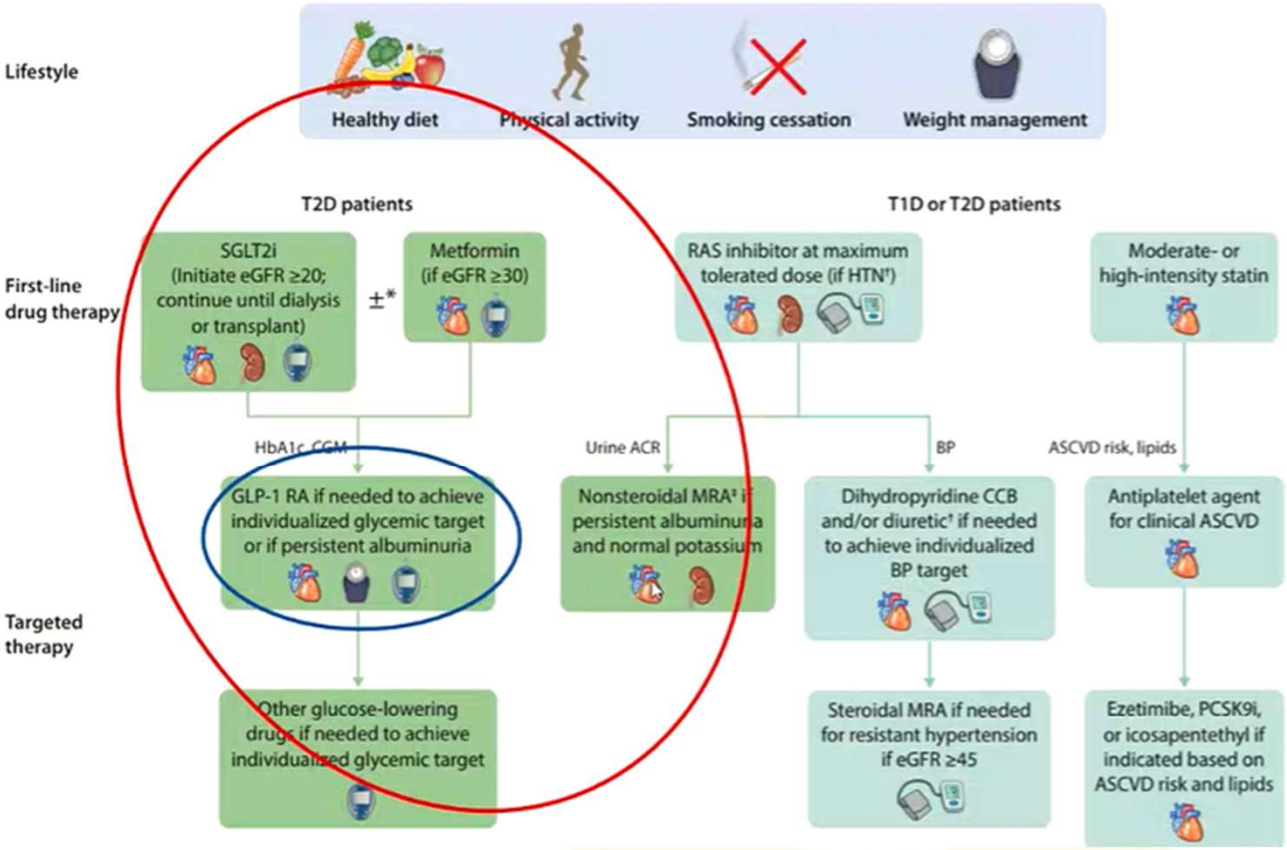
[4] Individualizar su indicación frente a arGLP1/ iSGLT2 como alternativa, o valorar combinación.
[5] Ausencia de inestabilidad hemodinámica, EAP no controlado o shock cardiogénico.
[6] Ausencia de signos de isquemia aguda o inestabilidad hemodinámica.
Al alta hospitalaria mantener - iniciar iSGLT2 / arGLP1 o ambos, según medicina basada en la evidencia (ver "Selección de fármacos en la DM2")

iSGLT2, inhibidores co-transportador Na/Glu tipo 2 (Empaglifozina, Dapaglifozina, Canagliflozina); arGLP1, agonistas del receptor de GLP1 (Liraglutida, Semaglutide sc / oral, Dulaglutida); iDPP4, inhibidores de la dipeptidil peptidasa-4 (Sitagliptina, Linagliptina); EAP: edema agudo de pulmón. SC: superficie corporal.

KDIGO 2022 Clinical Practice Guideline for Management of Diabetes in CKD



Holistic Approach for Improving Outcomes in Diabetes and CKD



de Boer IH *et al. Diabetes Care* 2022; In press

Agonistas receptor GLP-1 en DM tipo 2

- Reduce risk of major adverse CVD events.
  - Atherosclerotic CVD (3-point MACE: myocardial infarction, stroke, CVD death)
  - CVD death (liraglutide, semaglutide)
- Decrease macroalbuminuria and eGFR decline from early- to late-stage CKD (liraglutide, dulaglutide, semaglutide)
- CVD and CKD benefits are present in patients with CKD.

Tuttle KR *et al. Lancet Diabetes Endocrinol* 2018;6:605-617

Los agonistas del receptor del GLP-1 tienen efectos multifactoriales más allá del control de la glucemia

Corazón

- ↑ Contractilidad
- ↑ Función cardíaca
- ↑ Supervivencia de los miocitos
- ↑ Cardioprotección
- ↑ Utilización de glucosa
- ↑ Vasodilatación
- ↑ Recaptación de glucosa
- ↑ Función del ventrículo izquierdo
- ↑↓→ Presión arterial
- ↑↓→ Frecuencia cardíaca
- ↑ Producción de PNA

Páncreas

- ↑ Secreción de insulina
- ↑ Biosíntesis de insulina
- ↓ Secreción de glucagón
- ↑ Proliferación de células beta
- ↑ Supervivencia de las células beta
- ↓ Apoptosis

Hueso

- ↑ Osteogénesis
- ↑ Masa ósea

Tubo digestivo

- ↓ Vaciamiento gástrico
- ↓ Motilidad digestiva

Riñón

- ↑ Diuresis
- ↑ Natriuresis
- ↓ Albuminuria
- ↓ Inflamación renal

Cerebro

- ↓ Ingesta de alimentos
- ↓ Ingesta de agua
- ↑ Memoria y capacidad de aprender
- ↑ Neuroprotección
- ↓ Inflamación
- ↓ Conducta de gratificación
- ↓ Palatabilidad
- ↓ Apoptosis

Hígado

- ↓ Producción endógena de glucosa
- ↓ Esteatosis

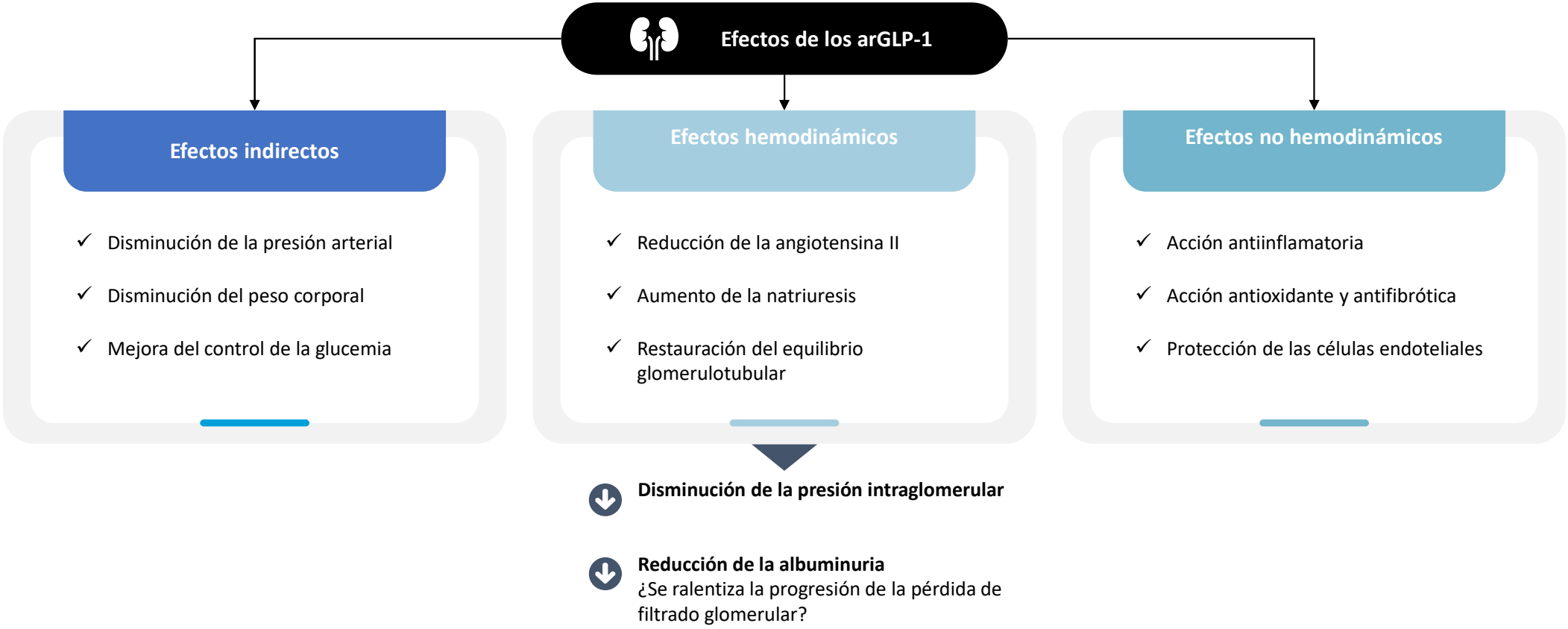
Músculo

- ↑ Sensibilidad a la insulina
- ↑ Recaptación de glucosa

arGLP-1: agonista del receptor del péptido similar al glucagón 1; PNA, péptido natriurético auricular.

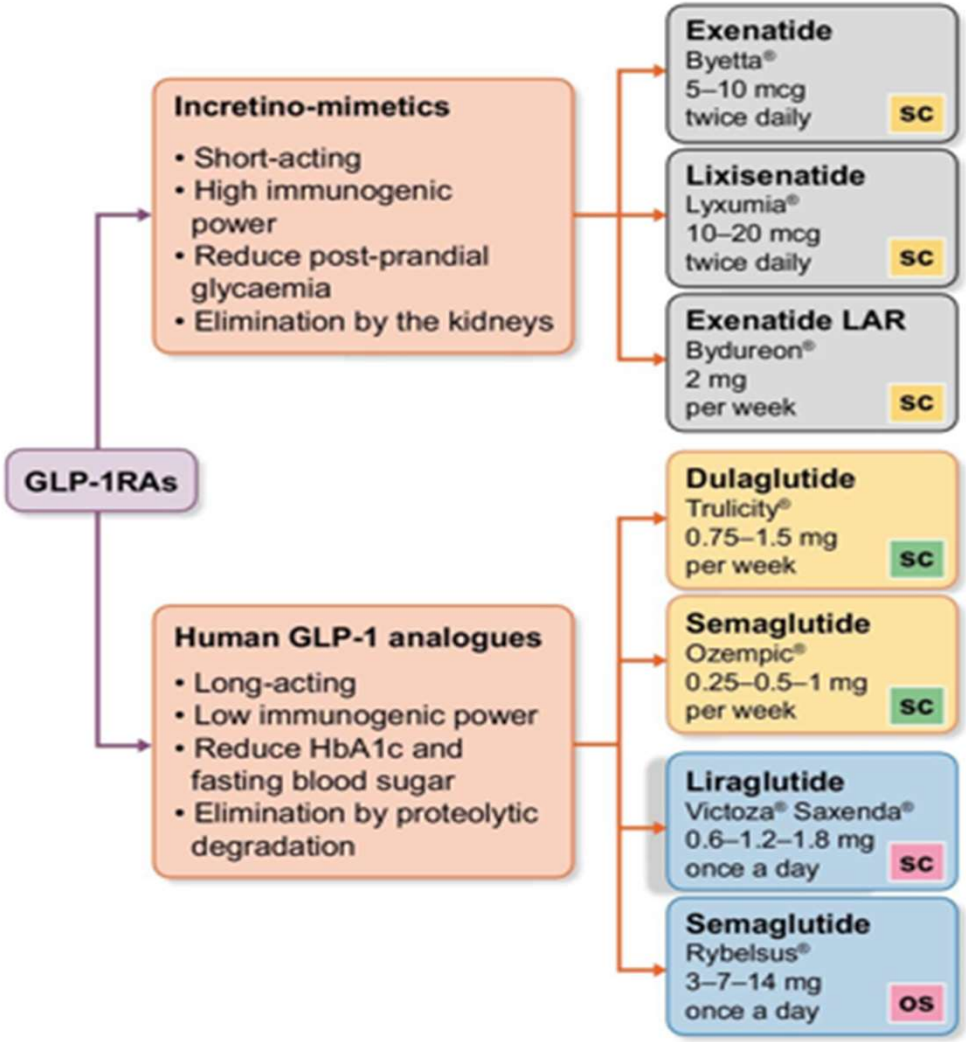
1. Müller TD, et al. *Mol Metab*. 2019;30:72-130; 2. Tsimihodimos V, et al. *Eur J Pharmacol*. 2018;818:103-109.

Los beneficios de los arGLP-1 en la enfermedad renal diabética no dependen de un control adecuado de la glucemia

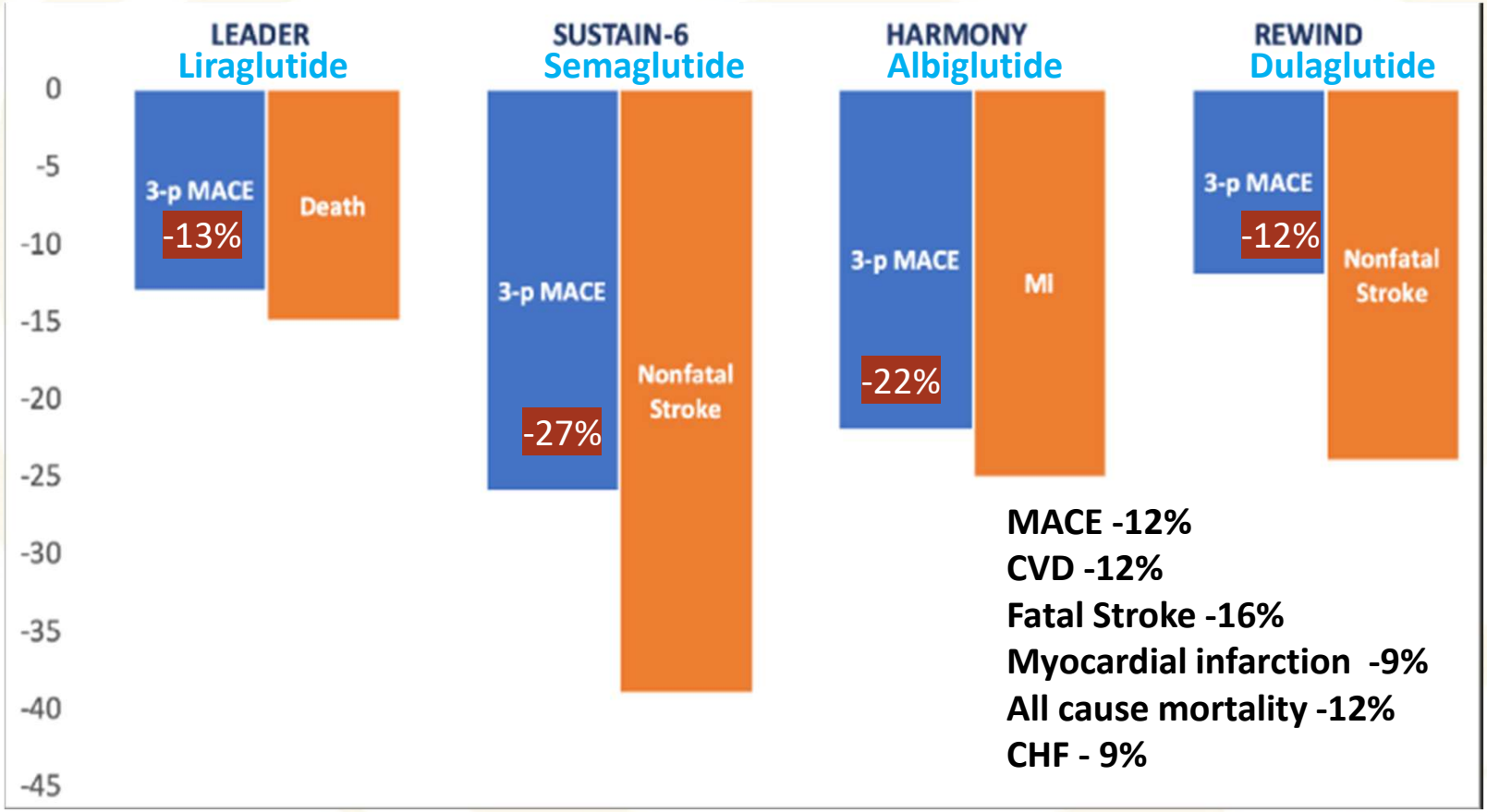


Adapted from Tsimihodimos V, et al. 2018. arGLP-1, agonista del receptor del péptido similar al glucagón 1.

1. Tsimihodimos V, et al. *Eur J Pharmacol.* 2018;818:103-109.

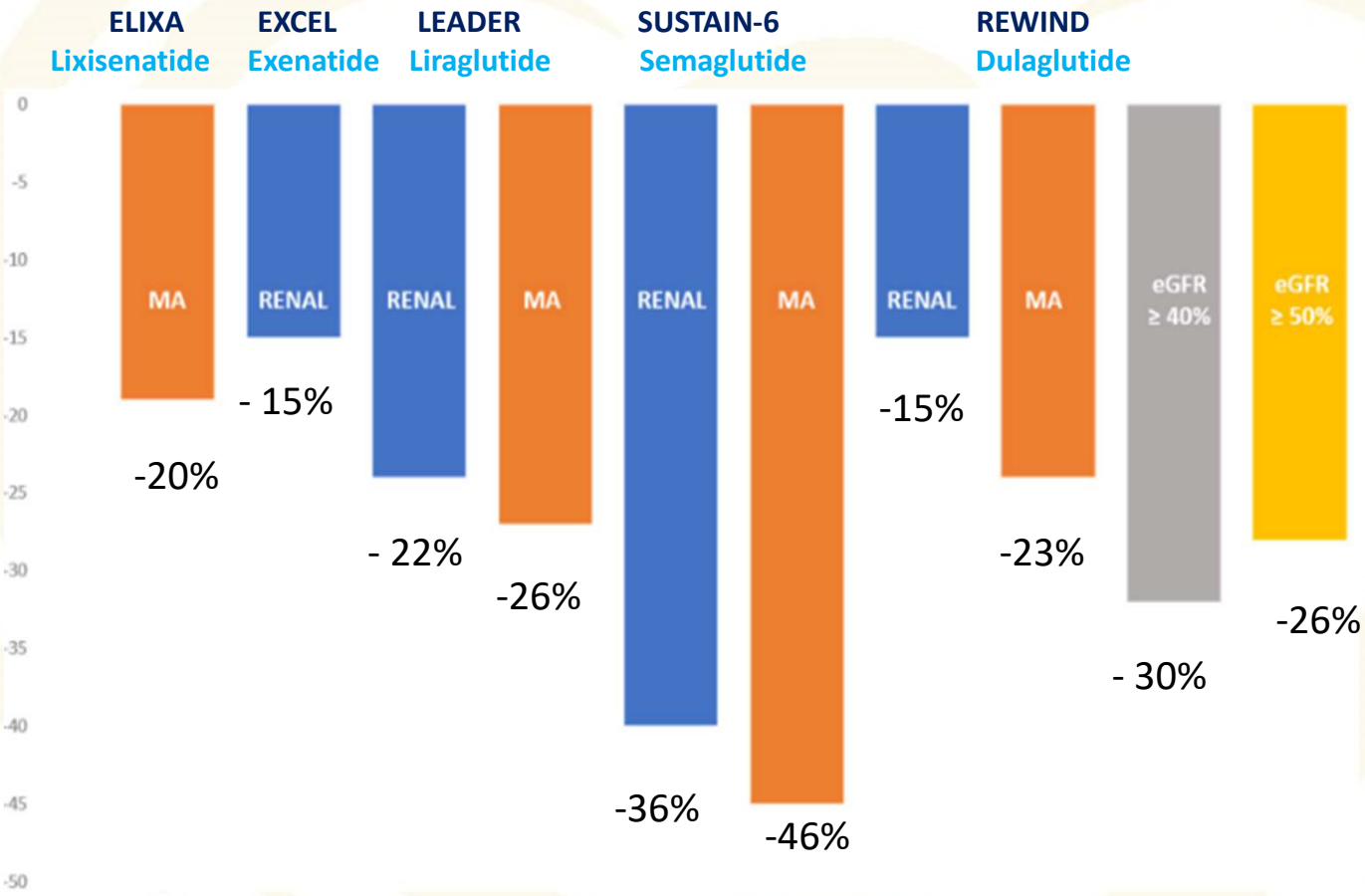

GLP-1RAs
Incretino-mimetics
• Short-acting
• High immunogenic power
• Reduce post-prandial glycaemia
• Elimination by the kidneys
Exenatide
Byetta®
5–10 mcg
twice daily
SC
Lixisenatide
Lyxumia®
10–20 mcg
twice daily
SC
Exenatide LAR
Bydureon®
2 mg
per week
SC
Human GLP-1 analogues
• Long-acting
• Low immunogenic power
• Reduce HbA1c and fasting blood sugar
• Elimination by proteolytic degradation
Dulaglutide
Trulicity®
0.75–1.5 mg
per week
SC
Semaglutide
Ozempic®
0.25–0.5–1 mg
per week
SC
Liraglutide
Victoza® Saxenda®
0.6–1.2–1.8 mg
once a day
SC
Semaglutide
Rybelsus®
3–7–14 mg
once a day
OS

Agonistas receptor GLP-1 : cardiovascular endpoints



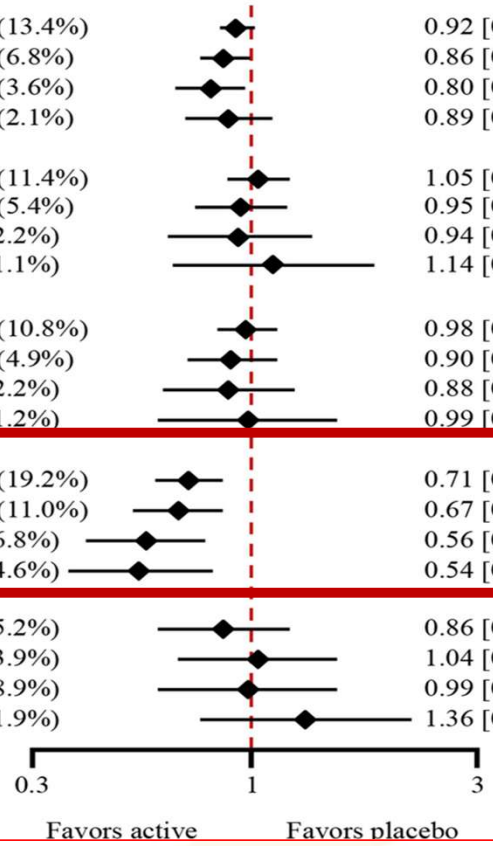
Górriz, JL, Soler MJ, Navarro-González JF. GLP1-receptor agonists and Diabetic Kidney disease: A call of attention to nephrologists. J Clin Med 2020 Mar 30; 9(4)

Agonistas receptor GLP-1 : renal endpoints



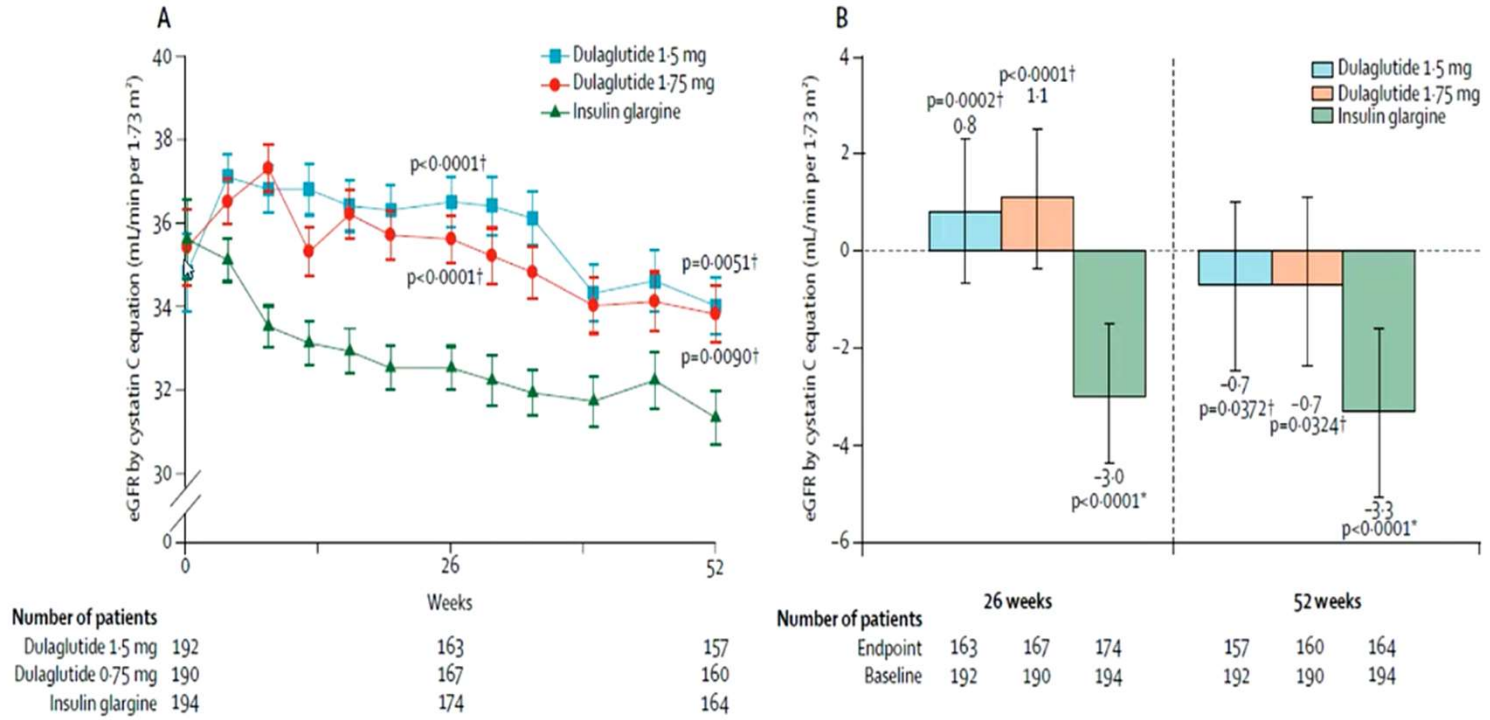
Semaglutide/ liraglutide: NEFROPROTECCION EN ERC

Subgroup/outcome	Events/N_{Active}	Events/$N_{Placebo}$	HR [95% CI]	*p* value	*p* value for interaction
Pooled population					
30% eGFR reduction	791/6316 (12.5%)	848/6321 (13.4%)	0.92 [0.84, 1.02]	0.10	
40% eGFR reduction	378/6316 (6.0%)	432/6321 (6.8%)	0.86 [0.75, 0.99]	0.039	
50% eGFR reduction	185/6316 (2.9%)	229/6321 (3.6%)	0.80 [0.66, 0.97]	0.023	
57% eGFR reduction	121/6316 (1.9%)	135/6321 (2.1%)	0.89 [0.69, 1.13]	0.34	
eGFR ≥90 mL/min/1.73m²					
30% eGFR reduction	255/2112 (12.1%)	246/2156 (11.4%)	1.05 [0.88, 1.25]	0.61	0.017
40% eGFR reduction	110/2112 (5.2%)	116/2156 (5.4%)	0.95 [0.73, 1.23]	0.71	0.16
50% eGFR reduction	45/2112 (2.1%)	48/2156 (2.2%)	0.94 [0.63, 1.41]	0.77	0.11
57% eGFR reduction	26/2112 (1.2%)	23/2156 (1.1%)	1.14 [0.65, 1.99]	0.66	0.035
eGFR >60—<90 mL/min/1.73m²					
30% eGFR reduction	279/2633 (10.6%)	290/2673 (10.8%)	0.98 [0.83, 1.16]	0.82	0.017
40% eGFR reduction	117/2633 (4.4%)	132/2673 (4.9%)	0.90 [0.70, 1.16]	0.42	0.16
50% eGFR reduction	52/2633 (2.0%)	60/2673 (2.2%)	0.88 [0.61, 1.28]	0.51	0.11
57% eGFR reduction	31/2633 (1.2%)	32/2673 (1.2%)	0.99 [0.60, 1.62]	0.97	0.035
eGFR 30—<60 mL/min/1.73m²					
30% eGFR reduction	202/1400 (14.4%)	256/1333 (19.2%)	0.71 [0.59, 0.85]	0.0003	0.017
40% eGFR reduction	108/1400 (7.7%)	146/1333 (11.0%)	0.67 [0.52, 0.86]	0.002	0.16
50% eGFR reduction	56/1400 (4.0%)	91/1333 (6.8%)	0.56 [0.40, 0.78]	0.001	0.11
57% eGFR reduction	36/1400 (2.6%)	61/1333 (4.6%)	0.54 [0.36, 0.81]	0.003	0.035
eGFR <30 mL/min/1.73m²					
30% eGFR reduction	55/171 (32.2%)	56/159 (35.2%)	0.86 [0.60, 1.25]	0.44	0.017
40% eGFR reduction	43/171 (25.1%)	38/159 (23.9%)	1.04 [0.67, 1.61]	0.86	0.16
50% eGFR reduction	32/171 (18.7%)	30/159 (18.9%)	0.99 [0.60, 1.62]	0.96	0.11
57% eGFR reduction	28/171 (16.4%)	19/159 (11.9%)	1.36 [0.76, 2.44]	0.30	0.035



Circulation. 2022 | Volume 145, Issue 8: 565–574,

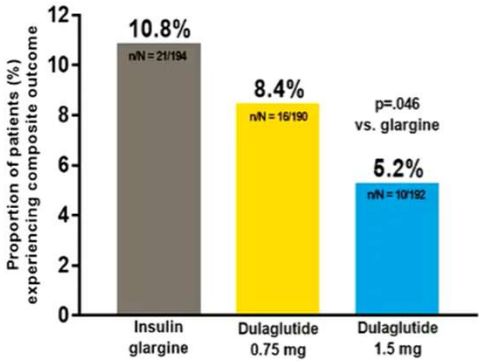
AWARD-7: Dulaglutide versus Insulin Glargine in Type 2 Diabetes and Moderate-to-Severe CKD



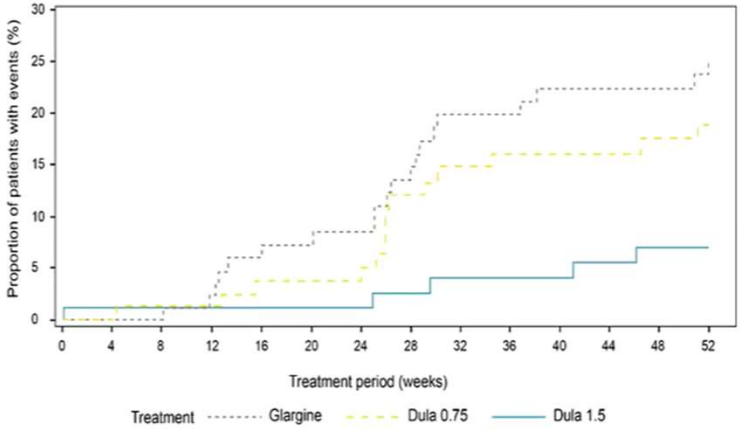
Tuttle KR *et al. Lancet Diabetes Endocrinol* 2018;6:605-617

AWARD 7: ≥40% eGFR Decline or ESKD with Dulaglutide versus Insulin Glargine

Overall



Macroalbuminuria

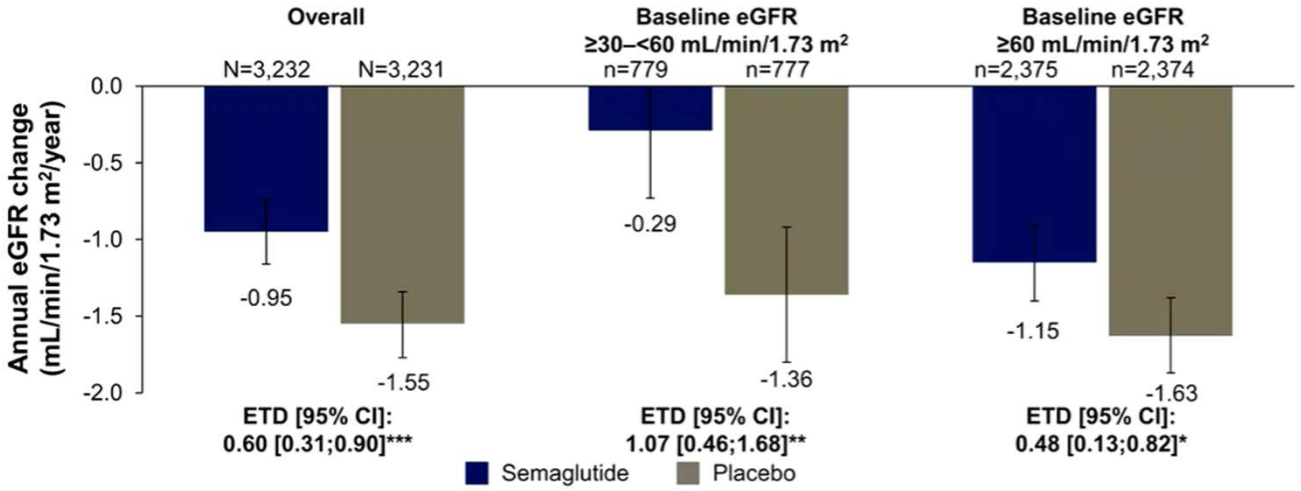


Dulaglutide 1.5 mg versus insulin glargine HR (95% CI): 0.25 (0.10-0.68); p=0.006

Dulaglutide 0.75 mg versus insulin glargine HR (95% CI): 0.72 (0.36-1.43); p=0.34

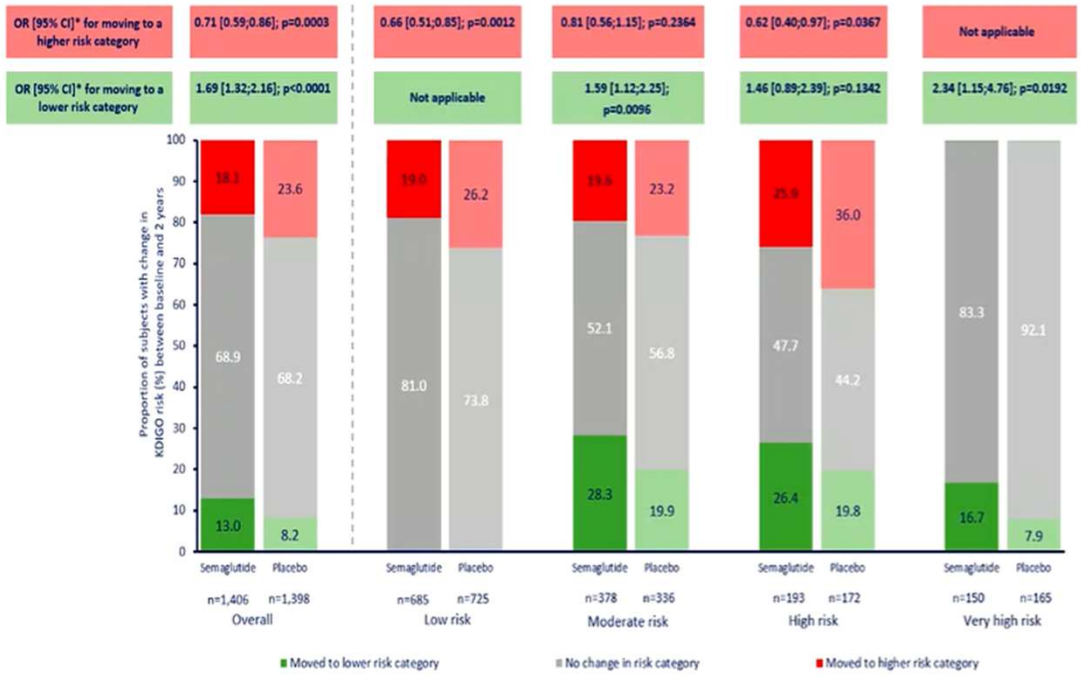
Tuttle KR *et al. Kidney 360* 2021;2:254-262

eGFR Slope with Semaglutide versus Placebo in SUSTAIN-6 and PIONEER-6



Tuttle KR *et al. Kidney Int* 2022 (In revision)

Change in KDIGO risk category with Semaglutide versus Placebo in SUSTAIN-6



Overall population

Participants receiving semaglutide vs placebo were:

- Less likely to move to a higher risk category
- More likely to move to a lower risk category

Across KDIGO risk categories**

Of participants receiving semaglutide vs placebo:

- Lower proportions moved to a higher risk category
- Greater proportions moved to a lower risk category

*Data from 2,804 of the 3,297 subjects randomised in SUSTAIN 6 were available for this post hoc analysis .*OR is obtained for OW semaglutide versus placebo by logistic regression. **Data stratified by baseline KDIGO risk categories.*

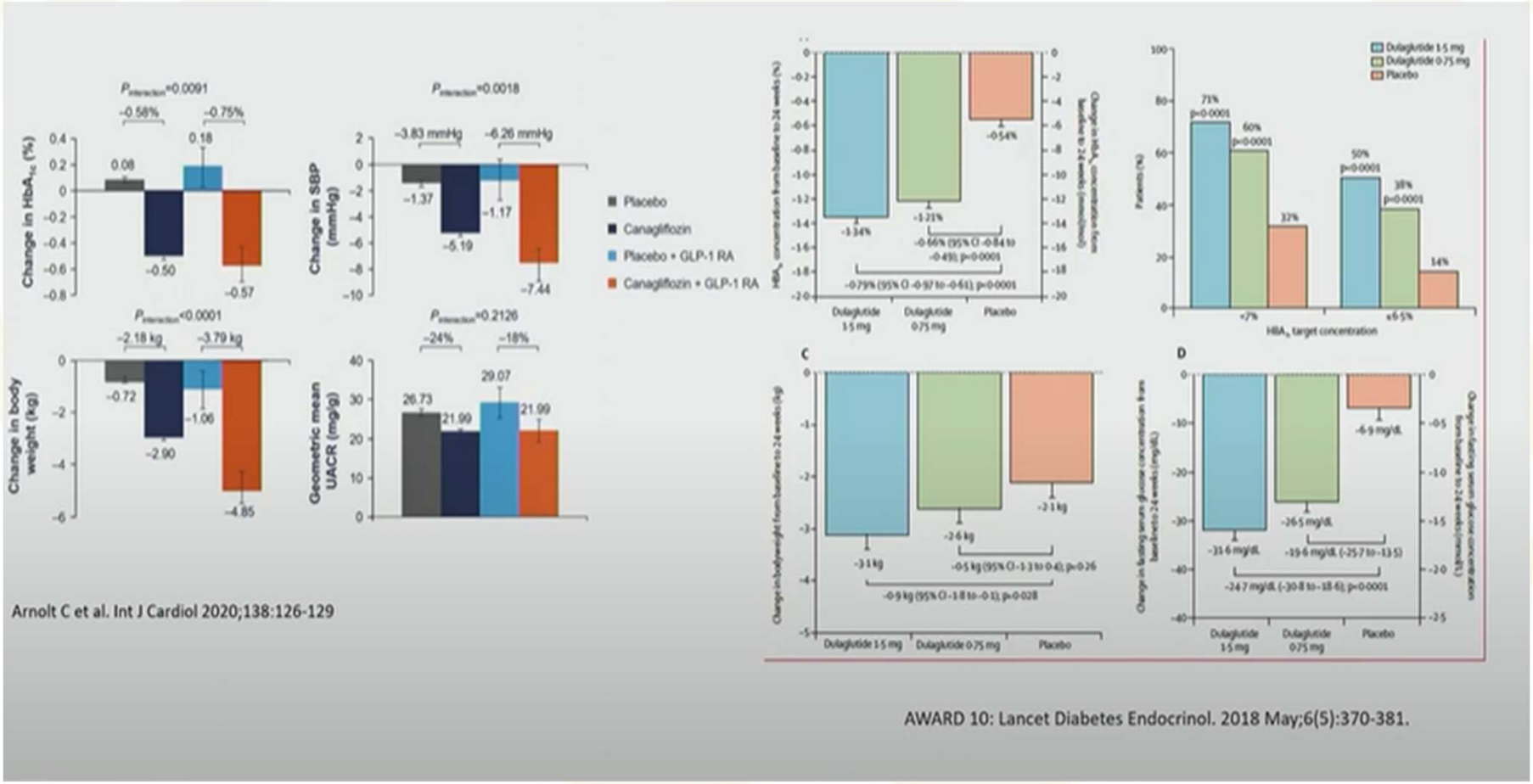
CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; OW, once weekly.

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int. 2020;98:S1–115.

Tuttle KR *et al.* ERA 2022; oral presentation, May 19, 2022

GLP1ra + SGLT2i:

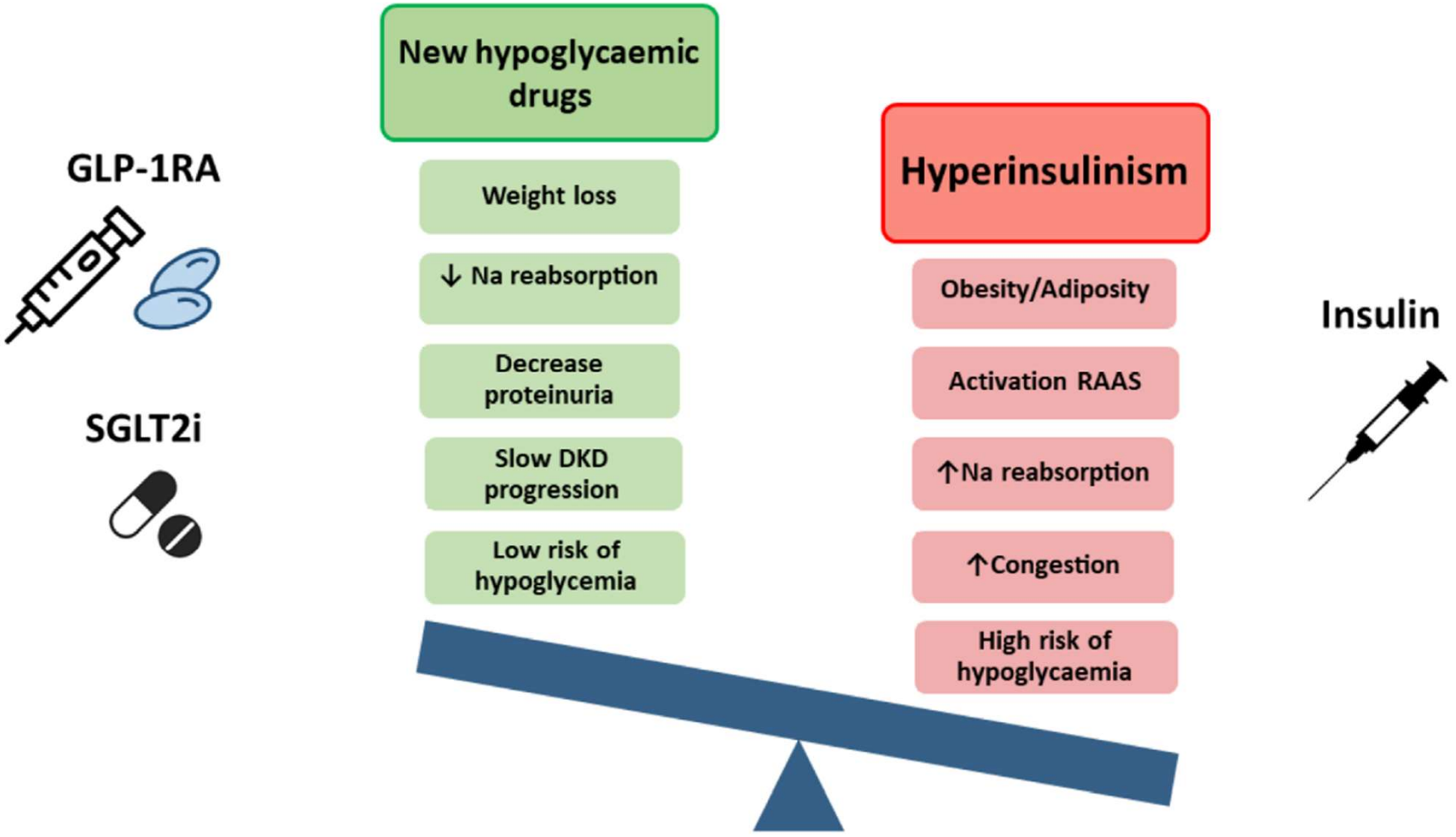
MEJOR JUNTOS



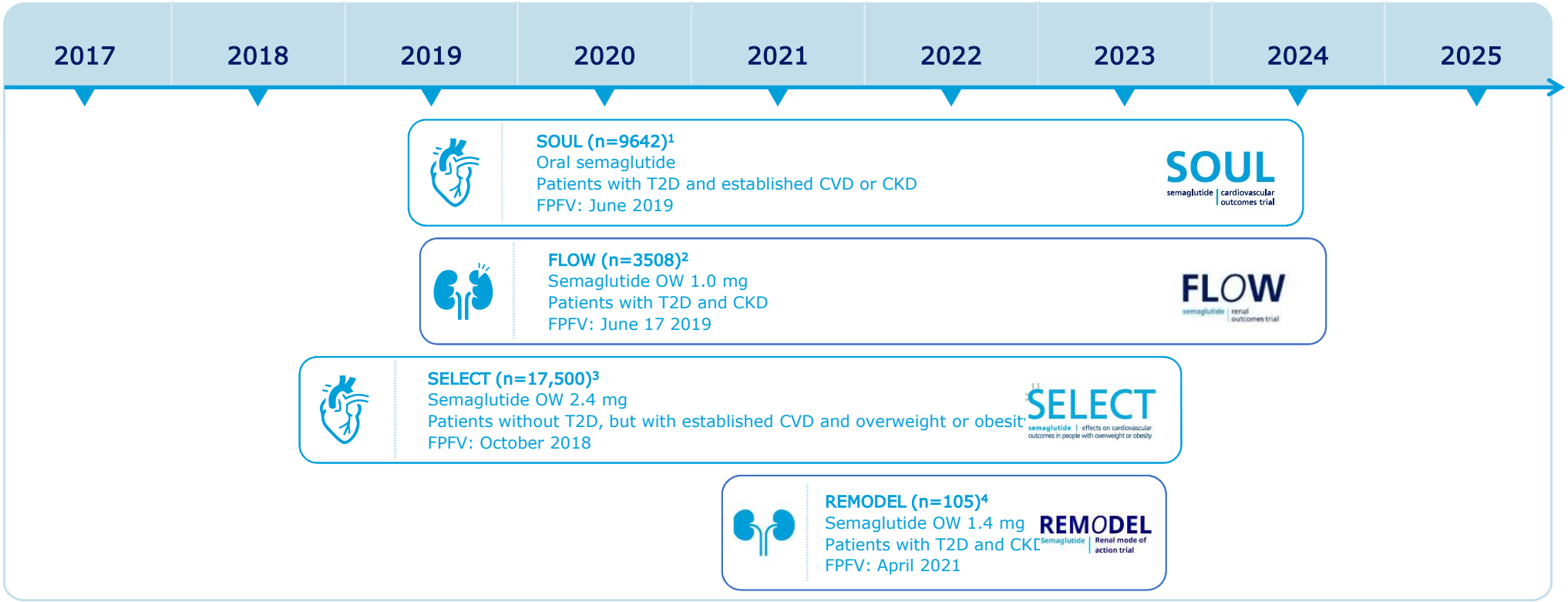
Arnolt C et al. Int J Cardiol 2020;138:126-129

AWARD 10: Lancet Diabetes Endocrinol. 2018 May;6(5):370-381.

New hypoglycaemic agents vs Insulin in DKD patients



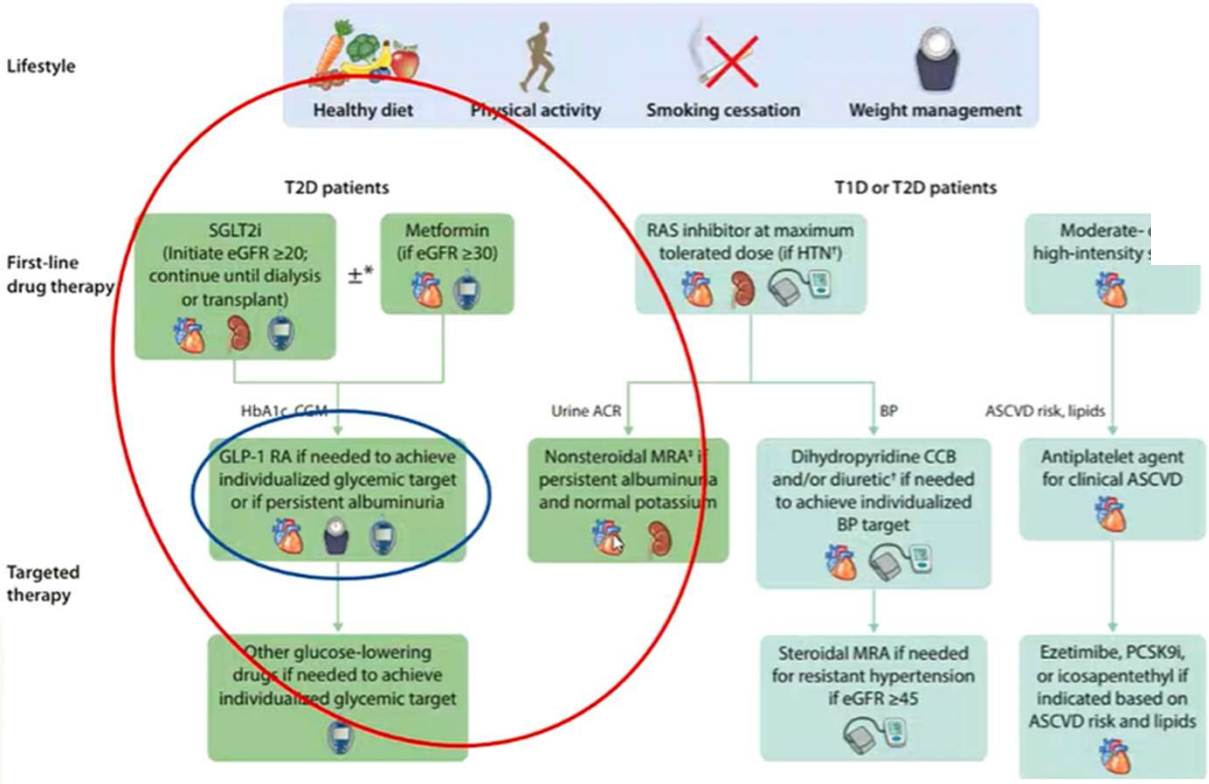
Renal outcomes will be evaluated in >30,000 patients in current semaglutide RCTs



FPFV, first patient first visit

1. ClinicalTrials.gov. NCT03914326; 2. ClinicalTrials.gov Identifier: NCT03819153. 3. ClinicalTrials.gov. NCT03574597; 4. ClinicalTrials.gov Identifier: NCT04865770

Holistic Approach for Improving Outcomes in Diabetes and CKD



de Boer IH *et al. Diabetes Care* 2022; In press