

Estrategias preventivas

¿Es posible enlentecer la
progresión de la enfermedad renal
crónica en la diabetes?

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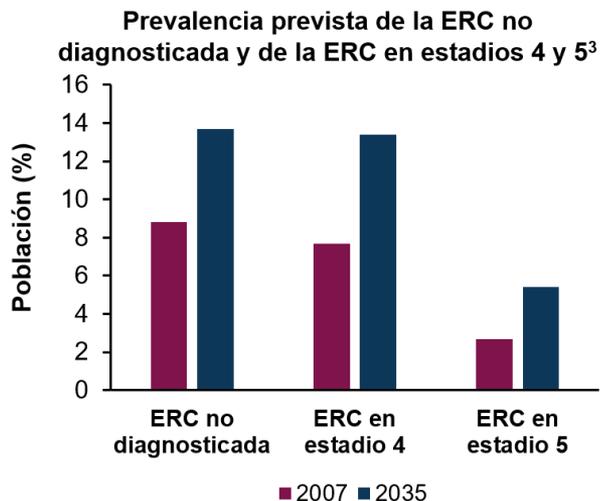
Conflictos de interés

Liliana Gutiérrez Carrasquilla participa ha participado como ponente con AstraZeneca, Boehringer, Lilly, Sanofi, Novonordisk y Esteve.



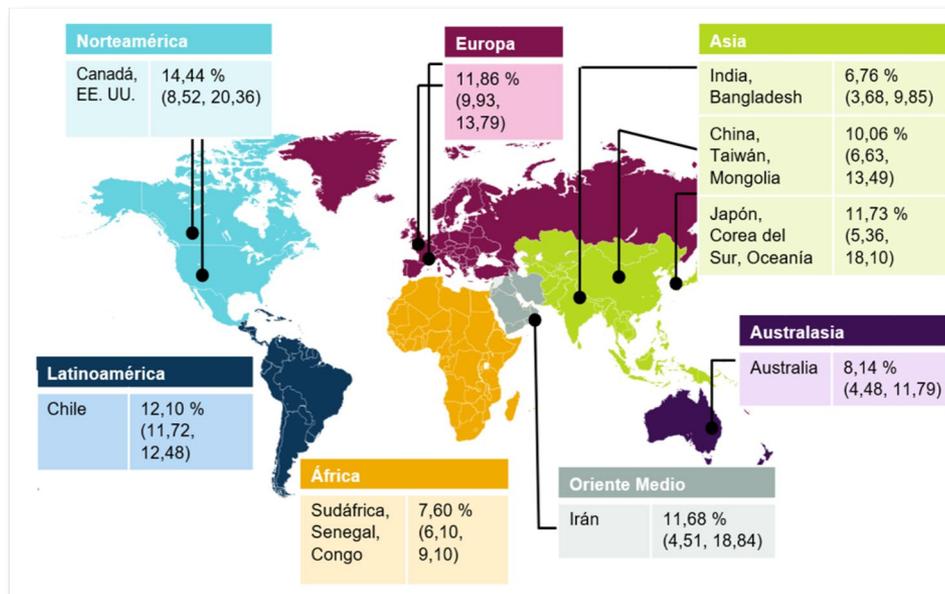
Enfermedad renal crónica: un problema de salud global.

- La prevalencia mundial de la ERC es de **698 millones**¹ (alrededor del 10 %); en España es del **15,1%**².



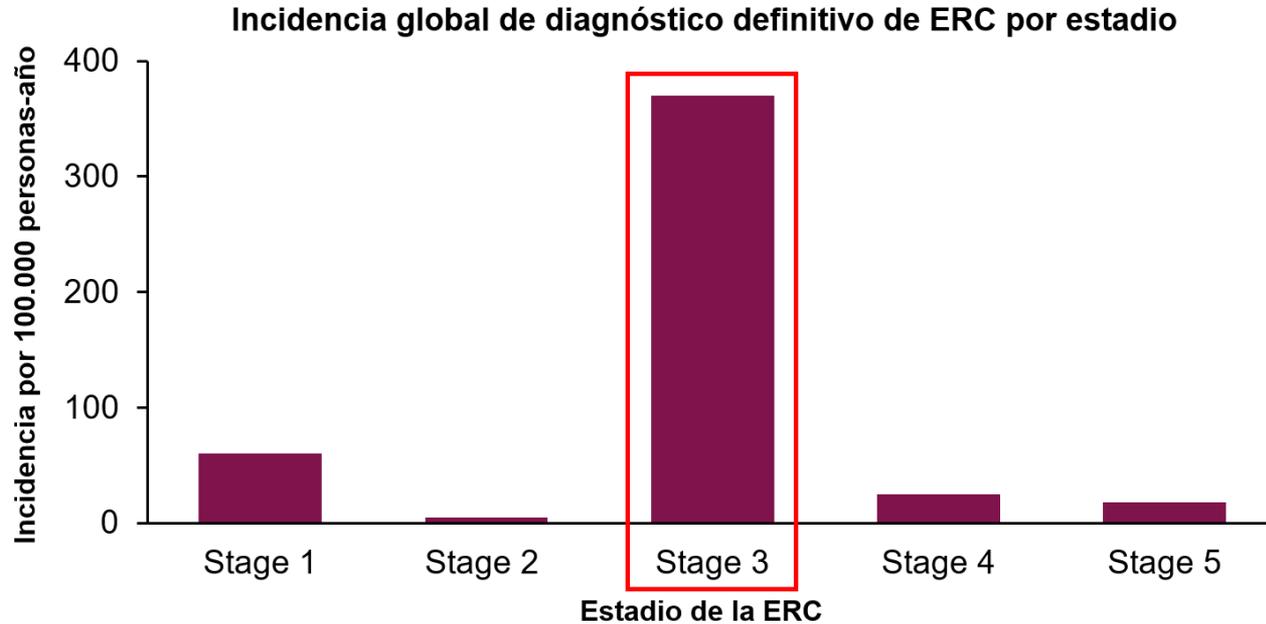
ERC, enfermedad renal crónica

Metaanálisis que estima la prevalencia mundial de la ERC (estadios 3-5)⁴



1. Global Burden of Disease Collaborators 2017. *Lancet* 2018;392:1789–1858; 2. Chronic kidney disease in Spain: Prevalence and impact of accumulation of cardiovascular risk factors. *Nefrología*. 2018 (38): 606-615; 3. Wong LY, et al. *Int J Nephrol* 2018;2018:5196285; 4. Hill NR, et al. *PLoS One* 2016;11:e0158765.

La incidencia de enfermedad renal crónica es superior en el estadio 3



ERC, enfermedad renal crónica

La albuminuria y la disminución del filtrado glomerular empeoran el pronóstico de la enfermedad renal crónica

Pronóstico de la ERC según FGe y albuminuria

				Descripción e intervalo de las categorías de albuminuria		
				A1	A2	A3
				Normal o ligero aumento <30 mg/g <3 mg/mmol	Aumento moderado 30-300 mg/g 3-30 mg/mmol	Aumento intenso >300 mg/g > 30 mg/mmol
Descripción e intervalo de las categorías de FG (ml/min/1,73 m ²)	G1	Normal o alta	≥90	No CKD	G1 A2	G1 A3
	G2	Leve	60-89	No CKD	G2 A2	G2 A3
	G3a	Descenso leve o moderado	45-59	G3a A1	G3a A2	G3a A3
	G3b	Descenso moderado o intenso	30-44	G3b A1	G3b A2	G3b A3
	G4	Descenso intenso	15-29	G4 A1	G4 A2	G4 A3
	G5	ERT	<15	G5 A1	G5 A2	G5 A3

Riesgo creciente

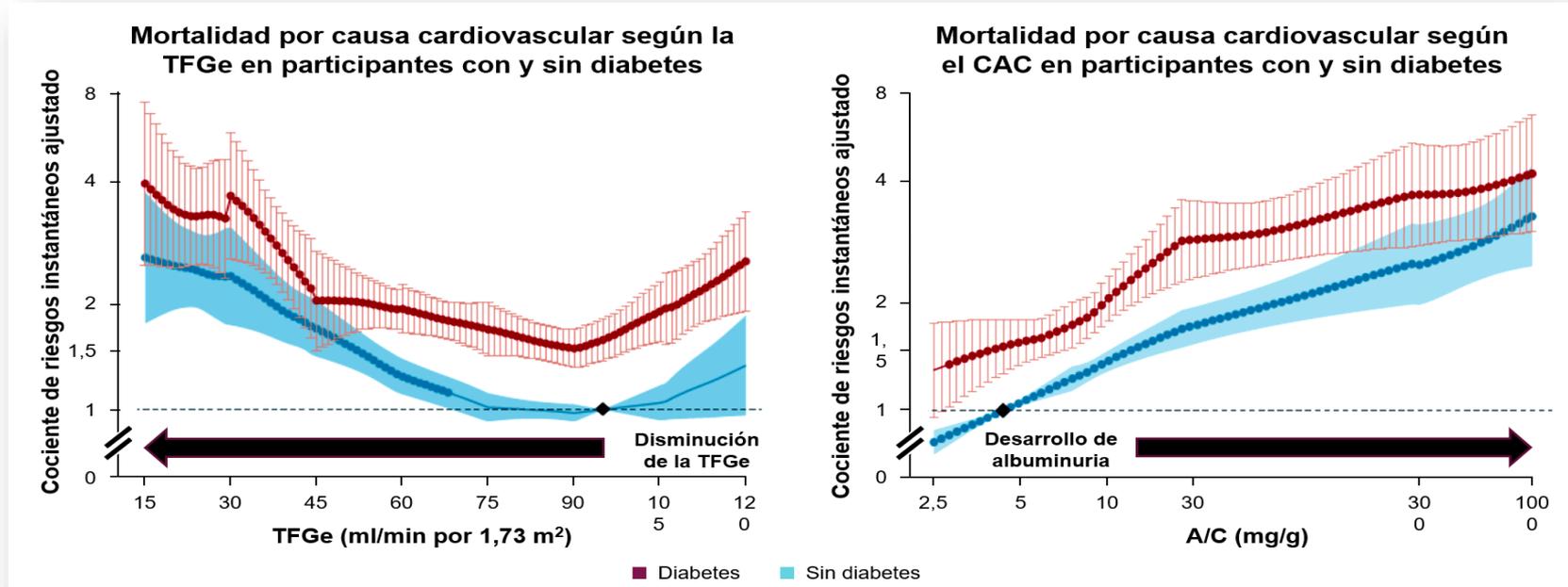
El pronóstico empeora al descender el FGe o aumentar la albuminuria

- Mortalidad global
- Mortalidad por causas CV
- ERT
- LRA
- ERC progresiva

1 vez/yr	Risk moderado
2 vez/yr	Risk alto
3 veces/yr	Risk muy alto

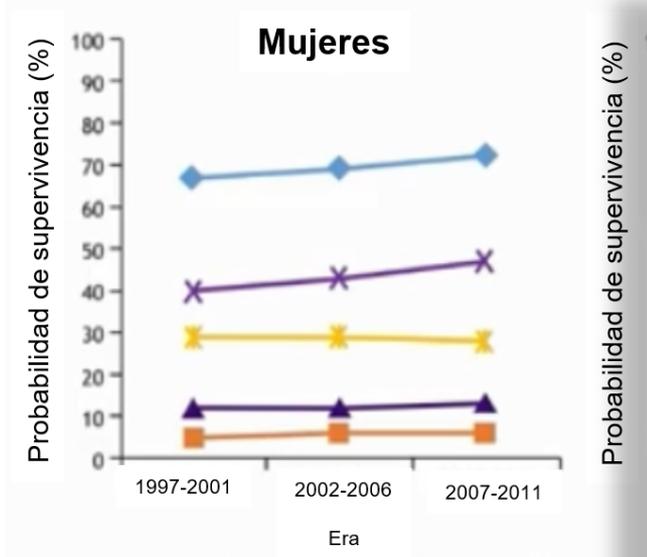
LRA, lesión renal aguda; ERC, enfermedad renal crónica; CV, cardiovascular; FGe, filtración glomerular estimada; ERT, enfermedad renal terminal; FG, filtración glomerular.

Tasa de filtrado glomerular y albuminuria: Indicador pronóstico de mortalidad

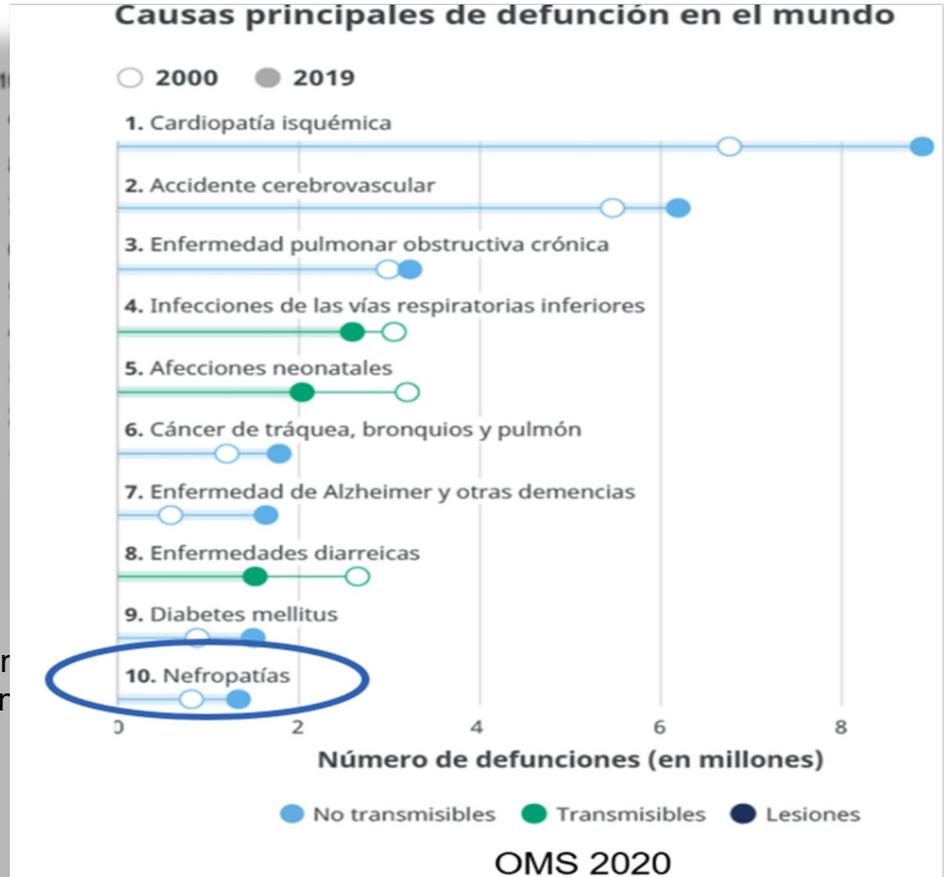


HR, razón de riesgos instantáneos; CAC = cociente albúmina/creatinina en orina; CV = cardiovascular; ERD = enfermedad renal diabética; IC, intervalo de confianza; ECV, enfermedad cardiovascular; FGe, filtración glomerular estimada; ERT, enfermedad renal terminal.

Enfermedad renal crónica y mortalidad

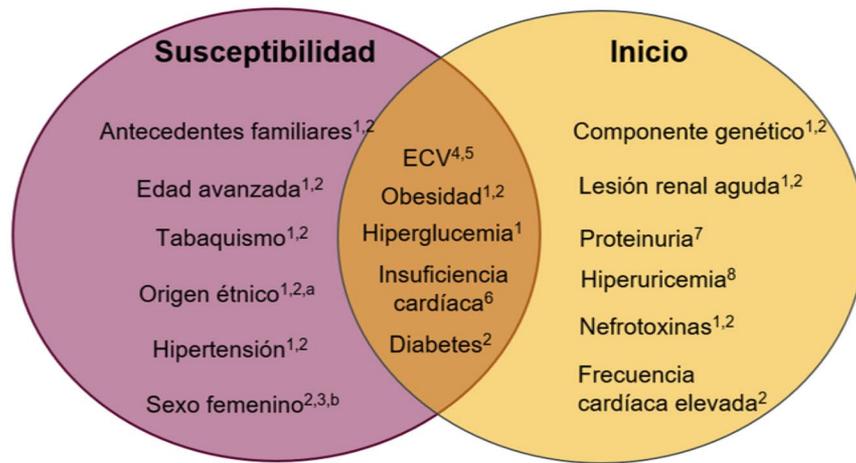


Supervivencia a 10 años sin ajustar para la r
N=33.500 pacientes en diálisis de mar



ERC: Enfermedad renal crónica

Factores de riesgo de la enfermedad renal crónica



Muchos de estos factores de riesgo son prevenibles o tratables como la obesidad, la DM, la IC o la hipertensión

ERC, enfermedad renal crónica; ECV, enfermedad cardiovascular

^aEl origen étnico comprende raza negra, indio americano, hispano, asiático/nativo de las islas del Pacífico

^bEn mujeres posmenopáusicas y pacientes con diabetes, la velocidad de progresión de la ERC es mayor

1. Alicic RZ, et al. *Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Kazancioğlu R. *Kidney Int Suppl* 2013;3:368–371; 3. Goldberg I, Krause I. *EMJ* 2016;1:58–64;

4. Nelson RG, et al. *JAMA* 2019;322:2104–2114; 5. Sud M, et al. *Circulation* 2014;130:458–465; 6. George LK, et al. *Circ Heart Fail* 2017;10:e003825; 7. Koye DN, et al. *Am J Kidney Dis* 2018;72:653–661; 8. Liu X, et al. *Ren Fail* 2018;40:289–297; 9. Nam KH, et al. *J Am Heart Assoc* 2019;8:e011162

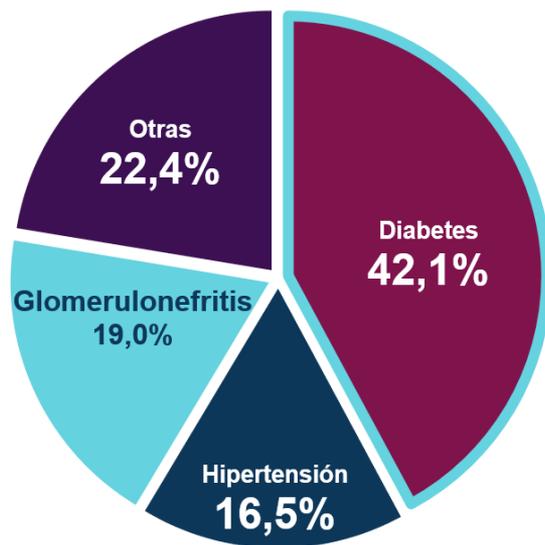
Factores que afectan la progresión de la enfermedad renal crónica



CV = cardiovascular; ERC = enfermedad renal crónica; ERD = enfermedad renal diabética; TFGe = tasa de filtración glomerular estimada

Diabetes: principal causa de enfermedad renal crónica

Prevalencia mundial estandarizada por edad de ERC por causa por 100 000 personas en 2016¹



Diabetes
Hiperglucemia crónica



La hiperglucemia crónica provoca daño renal estructural y funcional²



ERC
Degradación de las barreras de filtración y de la capacidad de reabsorción de los riñones²



La filtración alterada lleva a la pérdida de homeostasis de metabolitos y electrolitos²

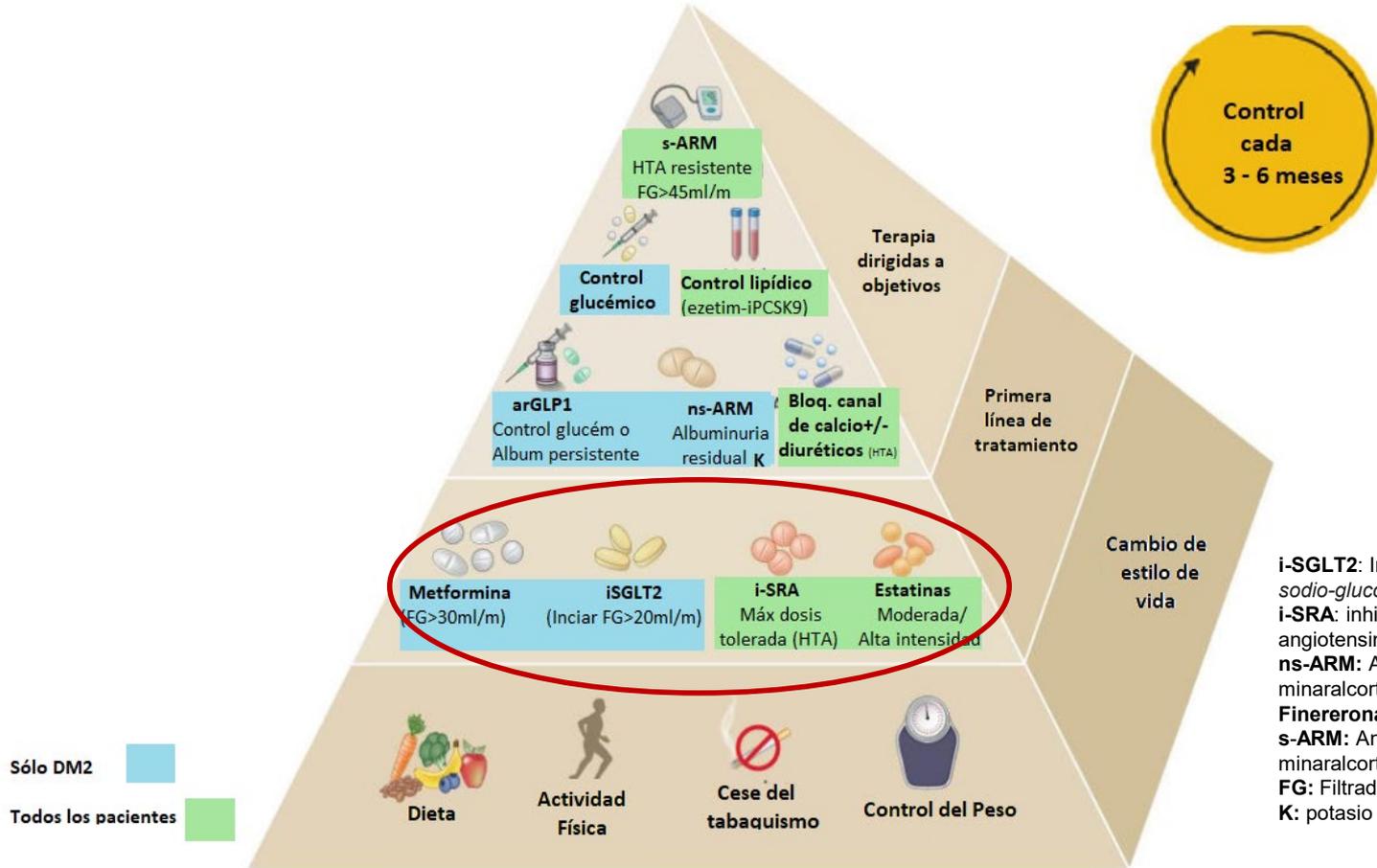
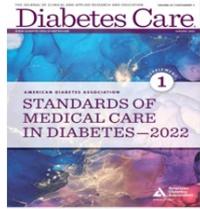


Múltiples enfermedades concomitantes
para el paciente

ERC, enfermedad renal crónica

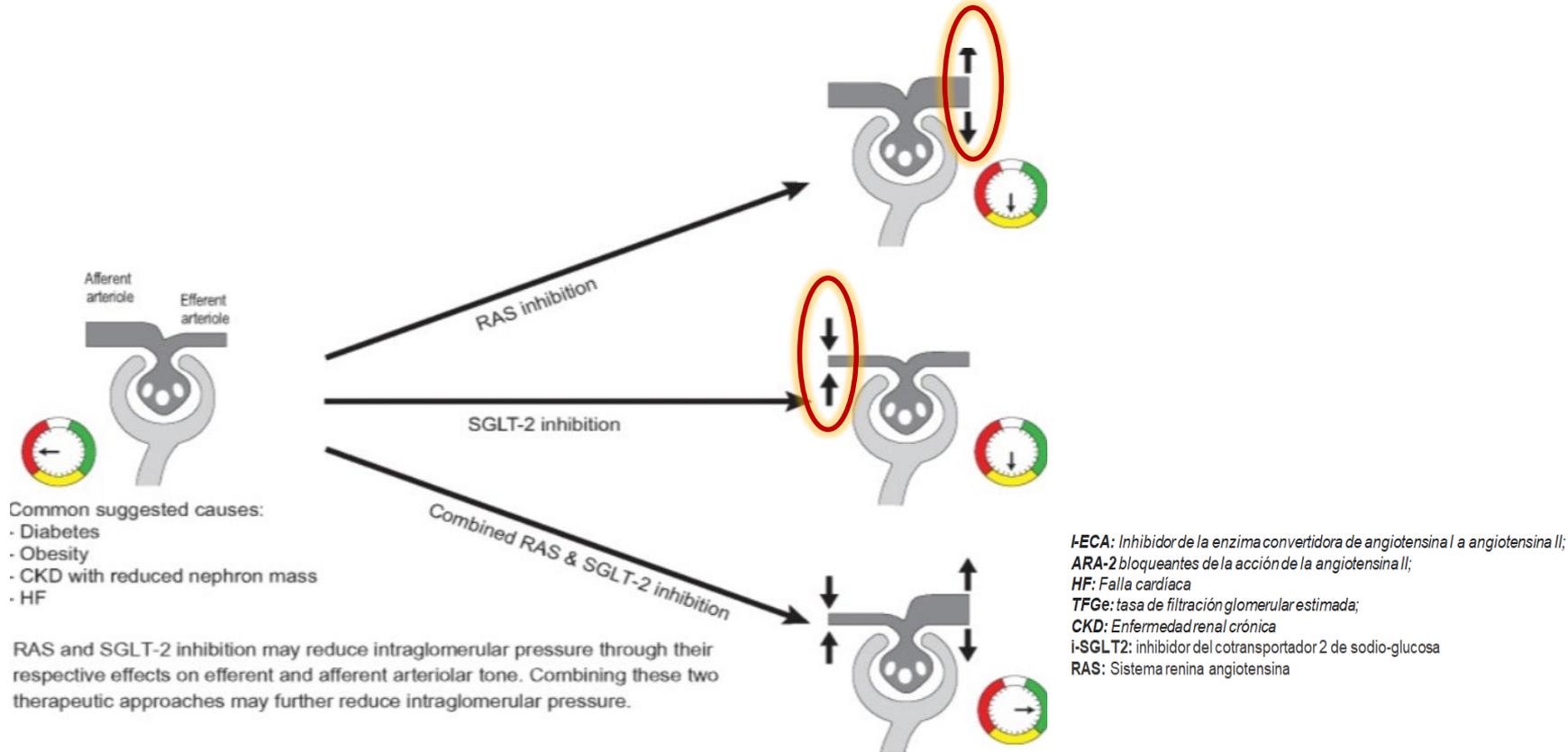
1. Xie Y *et al.* *Kidney Int.* 2018;94:567–81; 2. Alicic RZ *et al.* *Clin J Am Soc Nephrol.* 2017;12:2032-45

Tratamiento de la enfermedad renal diabética



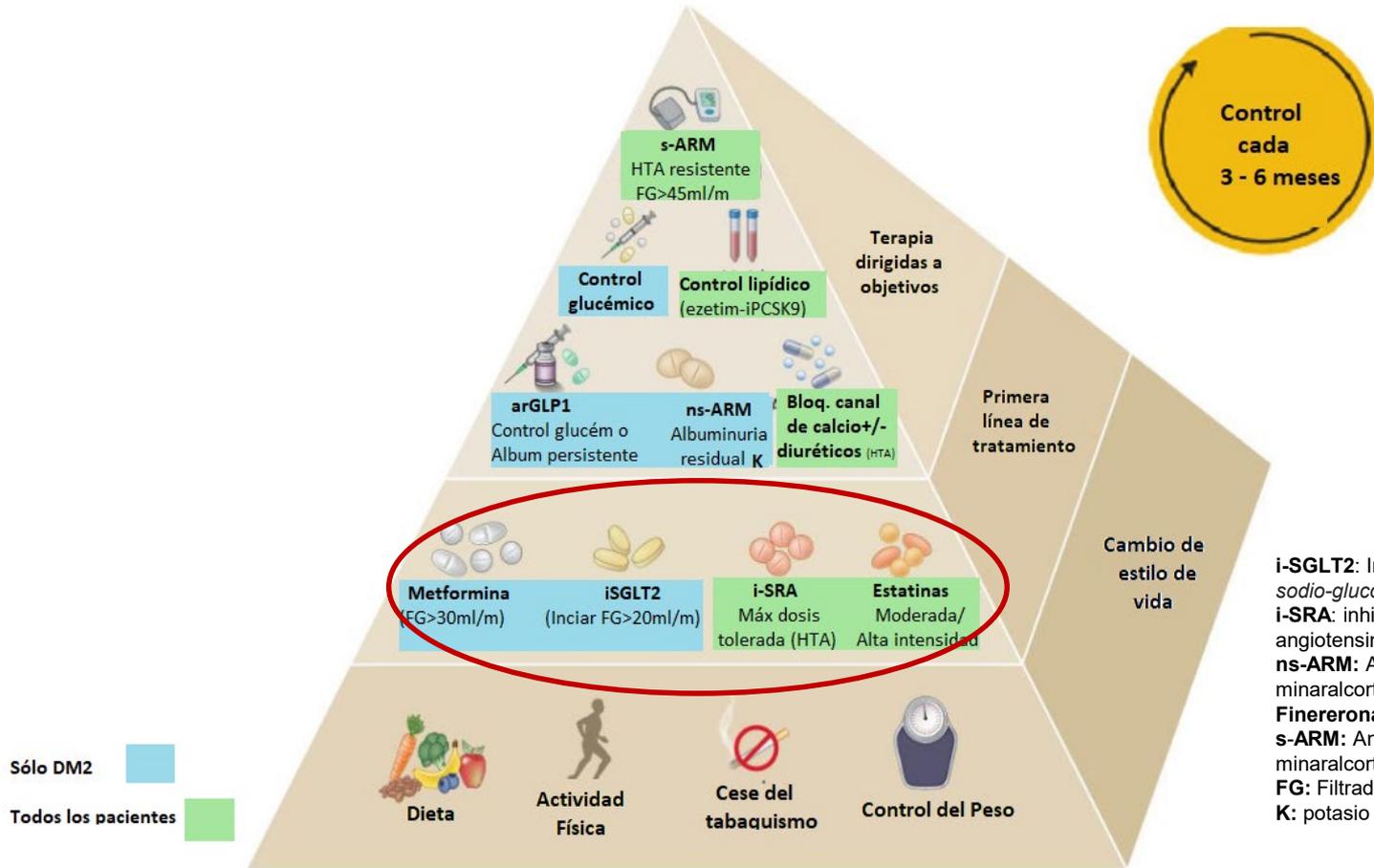
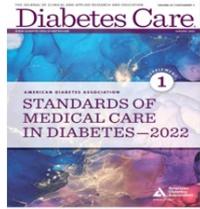
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Finererona
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FG: Filtrado glomerular
K: potasio

i-ECA/ARA2 e i-SGLT2: Sinergia renoprotectora



The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY Study. Clin Kidney J. 2018 Dec; 11(6): 749–761. PMID: PMC6275453

Tratamiento de la enfermedad renal diabética



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Control lipídico



European Treatment goals for LDL-C across categories of total cardiovascular disease risk*

LDL-C goal + $\geq 50\%$ reduction from baseline

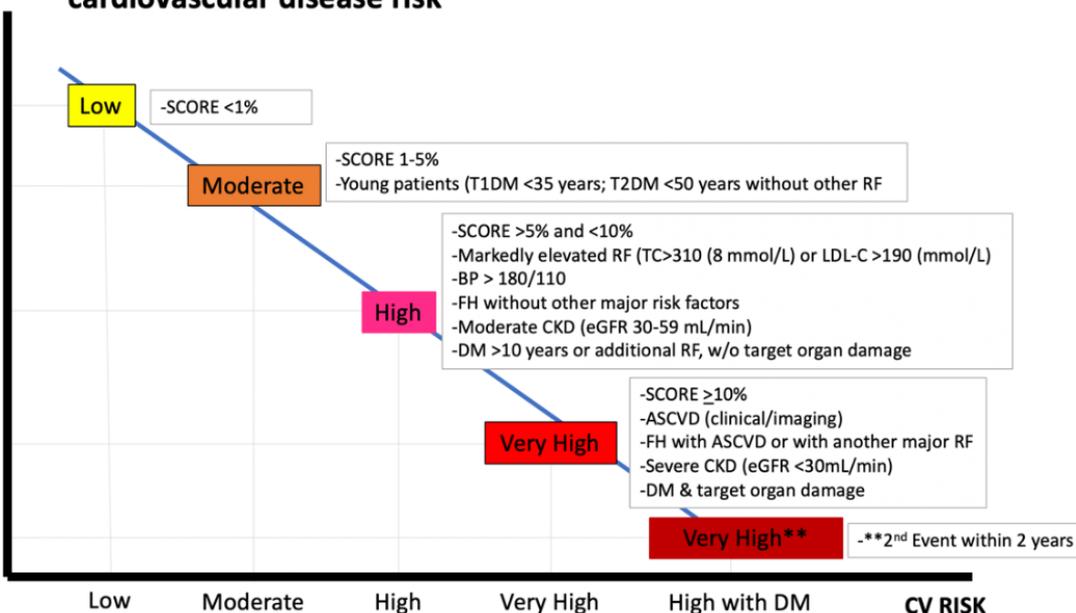
116 mg/dL
(3.0 mmol/L)

100 mg/dL
(2.6 mmol/L)

70 mg/dL
(1.8 mmol/L)

55 mg/dL
(1.4 mmol/L)

40 mg/dL
(1.0 mmol/L)



Very-high-risk

People with any of the following:
Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage,² or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m²).
A calculated SCORE $\geq 10\%$ for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

High-risk

People with:
Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP $\geq 180/110$ mmHg.
Patients with FH without other major risk factors.
Patients with DM without target organ damage,² with DM duration ≥ 10 years or another additional risk factor.
Moderate CKD (eGFR 30–59 mL/min/1.73 m²).
A calculated SCORE $\geq 5\%$ and <10% for 10-year risk of fatal CVD.

Moderate-risk

Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE $\geq 1\%$ and <5% for 10-year risk of fatal CVD.

Low-risk

Calculated SCORE <1% for 10-year risk of fatal CVD.



Hipolipemiantes en enfermedad renal

Filtrado Glomerular	Fenofibrato	Gemfibrozilo	AG omega 3	Ezetimibe	Atorvastatina	Fluvastatina	Lovastatina	Pravastatina	Rosuvastatina	Simvastatina	Pitavastatina
90	145-250mg/d	900mg-1500mg/d	2-4gr/d	10mg/d	10-80mg/d	20-80mg/d	10-80mg/d	10-40mg/d	5-40mg/d	5-40mg/d	1-4mg/d
60										5-20mg/d	
30	67-100mg/24h	600mg/d				20-40mg/d *	10-20mg/d*	10-20mg/d	5-10mg/d**	5-20mg/d	1-2mg/d
15	contraindicado	No recomendado									

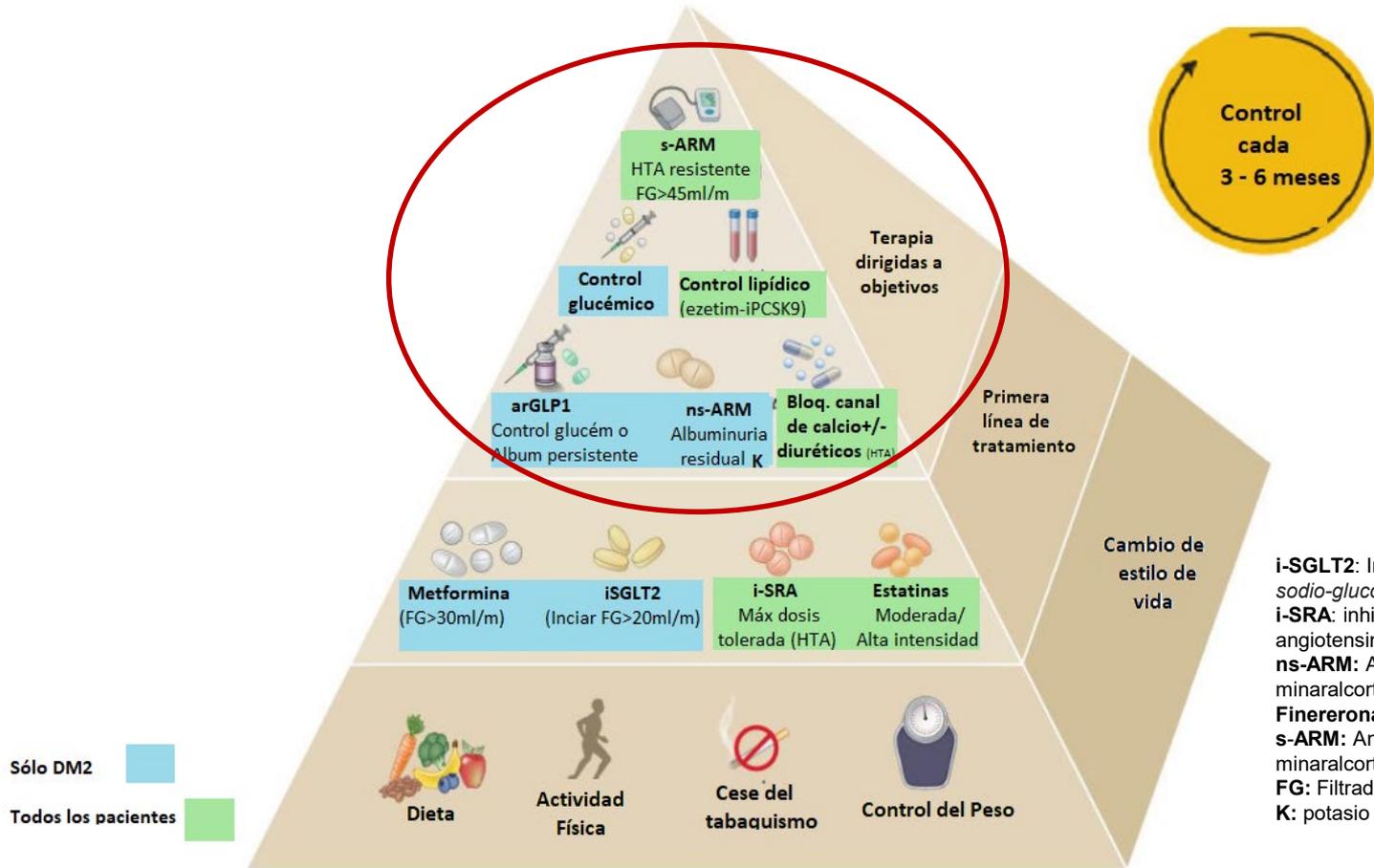
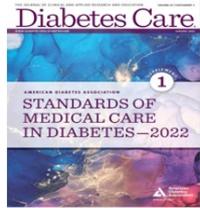
AG: Ácidos grasos.

*Experiencias limitadas con dosis superiores en ERC 4-5

**Contraindicada según ficha técnica

Bibliografía: Según ficha técnica.

Tratamiento de la enfermedad renal diabética

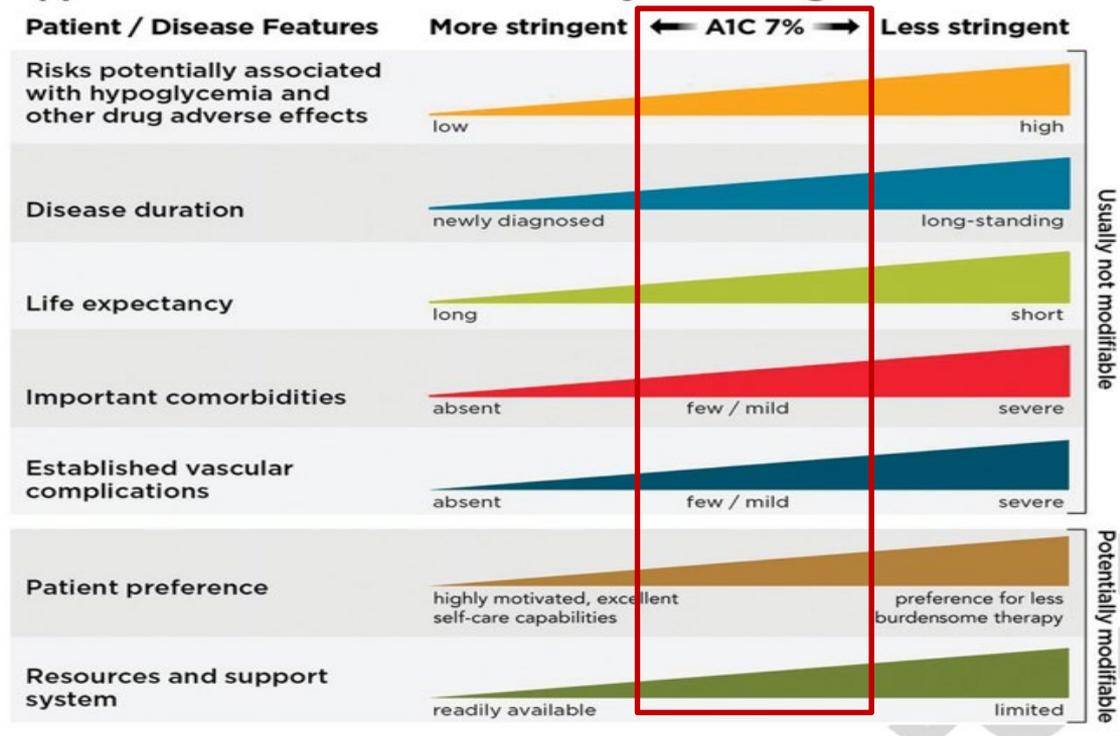


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Control de la glucemia

Approach to Individualization of Glycemic Targets



Optimizar el control de la glucosa (ralentiza la enfermedad renal): $HbA1c < 7\%$
Individualizar!!



PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification¹

ASCVD/INDICATORS OF HIGH RISK, HF, CKD†

RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡

+ASCVD/INDICATORS OF HIGH RISK*

GLP-1 RA with proven CVD benefit¹ **OR** **SGLT2i with proven CVD benefit¹**

IF A1C ABOVE TARGET

- For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa¹
- TZD⁵

+HF*

SGLT2i with proven benefit in this population¹

+CKD**

CKD and albuminuria (e.g., ≥200 mg/g creatinine) **OR** **CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)**

PREFERABLY SGLT2i with primary evidence of reducing CKD progression

OR SGLT2i with evidence of reducing CKD progression in CVOTs

OR GLP-1 RA with proven CVD benefit¹ if SGLT2i not tolerated or contraindicated

For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk

GLP-1 RA with proven CVD benefit¹ **OR** **SGLT2i with proven CVD benefit¹**

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

IF A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs

NONE

Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals

Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)

- Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:

MINIMIZE HYPOGLYCEMIA

No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia^{1,2}

IF A1C ABOVE TARGET

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

MINIMIZE WEIGHT GAIN/PROMOTE WEIGHT LOSS

PREFERABLY GLP-1 RA with good efficacy for weight loss **OR** SGLT2i

IF A1C ABOVE TARGET

For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
• If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs



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

CONSIDER COST AND ACCESS

Available in generic form at lower cost:
• Certain insulins: consider insulin available at the lowest acquisition cost
• SU
• TZD

IF A1C ABOVE TARGET

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / gargine U-300 < gargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs

¹For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended

(See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes) †Indicated whenever these become new clinical considerations regardless of background glucose-lowering medications

‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy

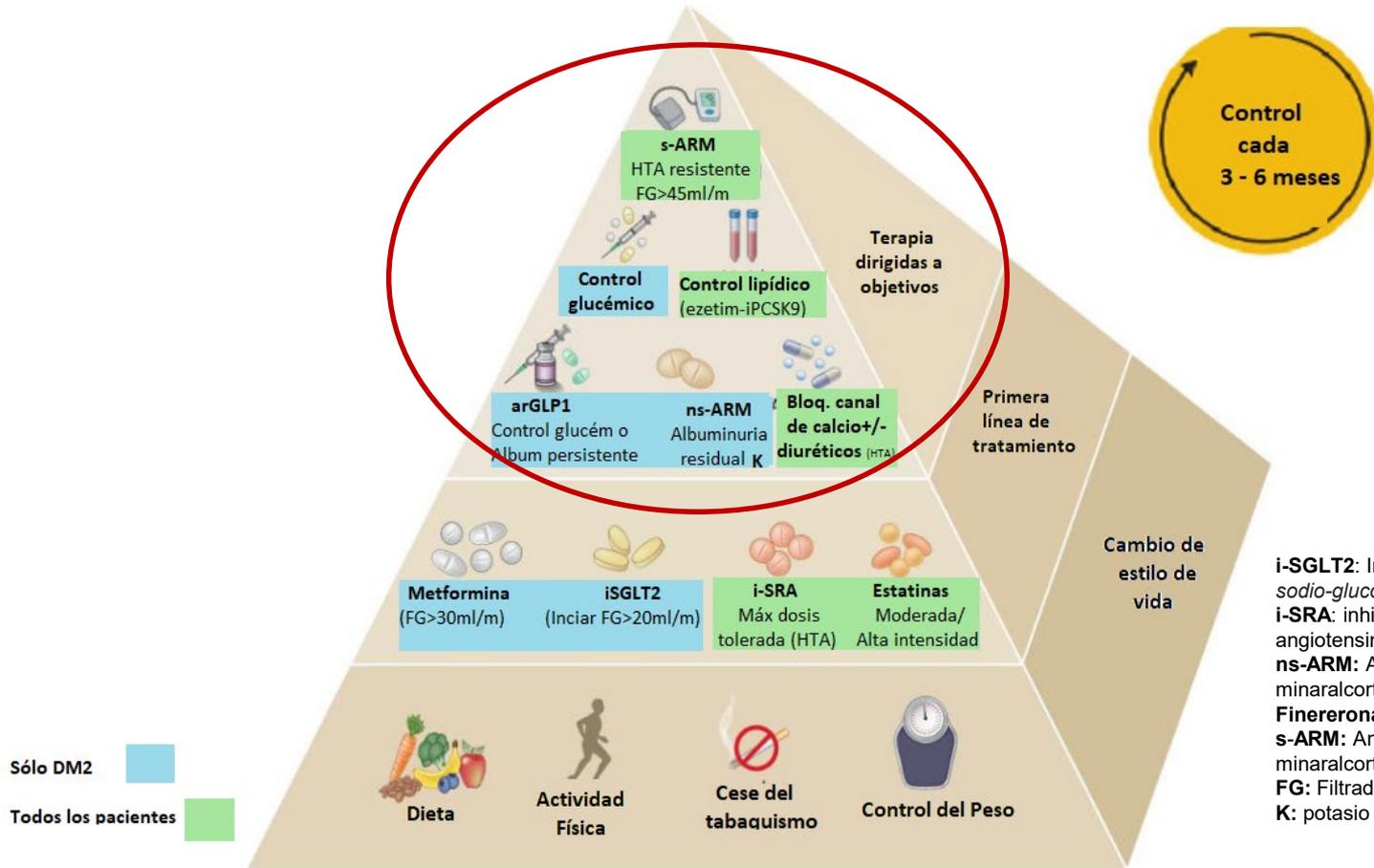
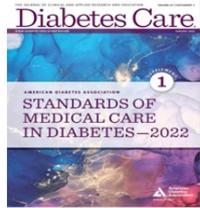
§Refer to Section 10: Cardiovascular Disease and Risk Management

**Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria

FG (ml/min/ /1,73m ²)	Met formina	Ertu glifozina	Empa glifozina	Cana glifozina	Dapa glifozina	Sita gliptina	Lina gliptina	Vilda gliptina	Saxa gliptina	Alo gliptina
≥ 60										
59-50										
49-45	2 g/d	No inicio 45-60	10 mg/d	100 mg/d		50 mg/d		50 mg/d		
44-30	1 g/d		No recomendado iniciar tratamiento			50 mg/d			2.5 mg/d	12.5 mg/d
29-15					No inicio <25	25 mg/d				6.25 mg/d
<15										
FG (ml/min/ /1,73m ²)	Lira glutida	Dula glutida	Sema glutida	Lixi senatida	Exe natida	Exenatid a -Lar	Albigluti da	Piogli tazona	Glicla zida	Repa glinida
≥ 60										
59-50										
49-45										
44-30										
29-15										
<15								15 mg/d		

Permitido SIN ajuste de dosis
 Permitido CON ajuste de dosis
 No recomendado

Tratamiento de la enfermedad renal diabética



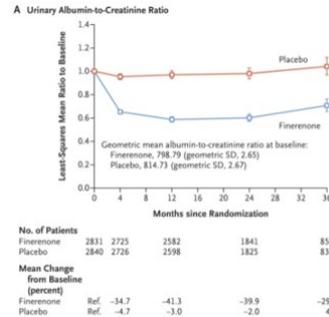
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Finererona
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Antagonista del receptor mineralcorticoide no esteroideo: FINERENONA

- Mayor selectividad por el receptor que la espironolactona
- Mejor afinidad por el receptor que la eplerenona in vitro.

Reducción de:

- La albúminuria hasta un 30% (2,5-10 mg/una vez/día)
- Resultados renales 15-23%
- 14% de ECV, 14% muerte CV,
- 14% Hx por ICC.



ESC

European Society of Cardiology

European Heart Journal (2022) 43, 474–484 **FASTTRACK CLINICAL RESEARCH**

<https://doi.org/10.1093/eurheartj/ehab777>

Diabetes and metabolic disorders

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



The NEW ENGLAND
JOURNAL of MEDICINE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

N Engl J Med 2020; 383:2219-2229

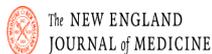
Original investigation

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy A Randomized Clinical Trial

JAMA. 2015;314(9):884-894. doi:10.1001/jama.2015.10081

i-SGLT2: inhibidor del cotransportador 2 de sodio-glucosa; **TFGe:** tasa de filtración glomerular estimada; **ERC:** Enfermedad renal crónica; **CAC:** Cociente albumina/creatinina; **Hx:** Hospitalización; **ICC:** Insuficiencia cardíaca; **ECV:** Eventos cardiovasculares

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

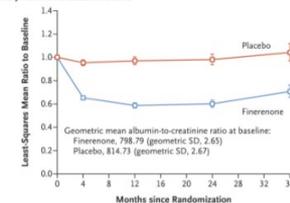
N Engl J Med 2020; 383:2219-2229

Se recomienda Finerenona:

- ERC estadios 3-4 con albuminuria asociada a DM tipo 2 o
- Progresión de la ERC o
- Cuando no es posible utilizar el i-SGLT2

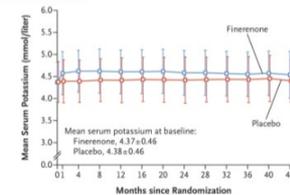
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A Urinary Albumin-to-Creatinine Ratio



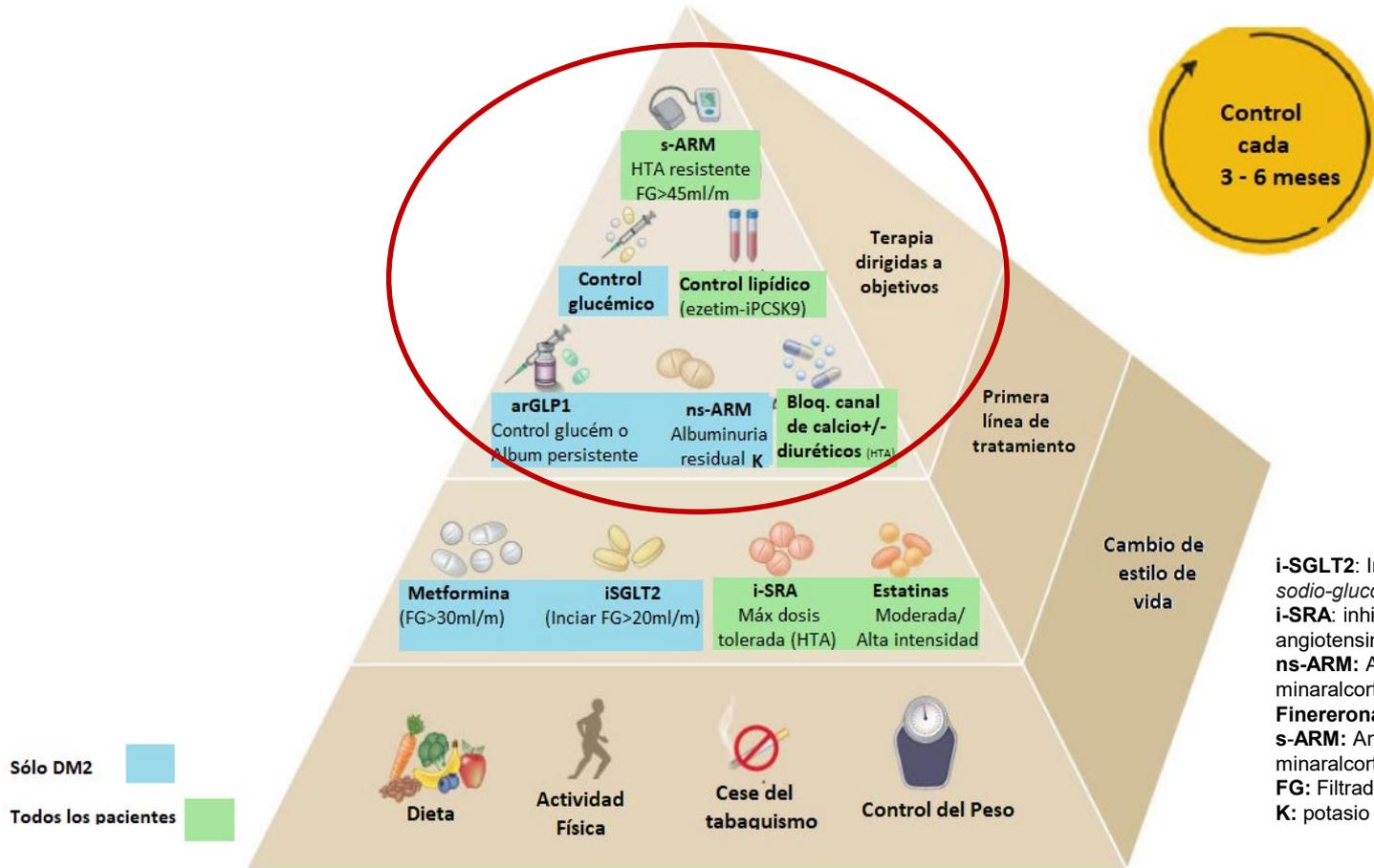
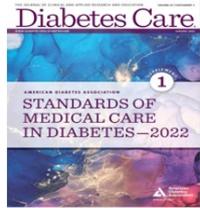
No. of Patients		2831		2725		2582		1841		856	
Finerenone		2840		2726		2598		1825		834	
Mean Change from Baseline (percent)		Ref.	-34.7	-41.3	-39.9	-29.3	Ref.	-4.7	-3.0	-2.0	-4.1
Finerenone		Placebo		Finerenone		Placebo		Finerenone		Placebo	

B Mean Serum Potassium



No. of Patients		2827		2708		2600		1872		882		344	
Finerenone		2831		2709		2596		1863		862		348	
Mean Change from Baseline (mmol/liter)		Ref.	0.25	0.24	0.21	0.21	0.21	0.02	0.04	0.05	0.07	0.07	
Finerenone		Placebo		Finerenone		Placebo		Finerenone		Placebo		Finerenone	

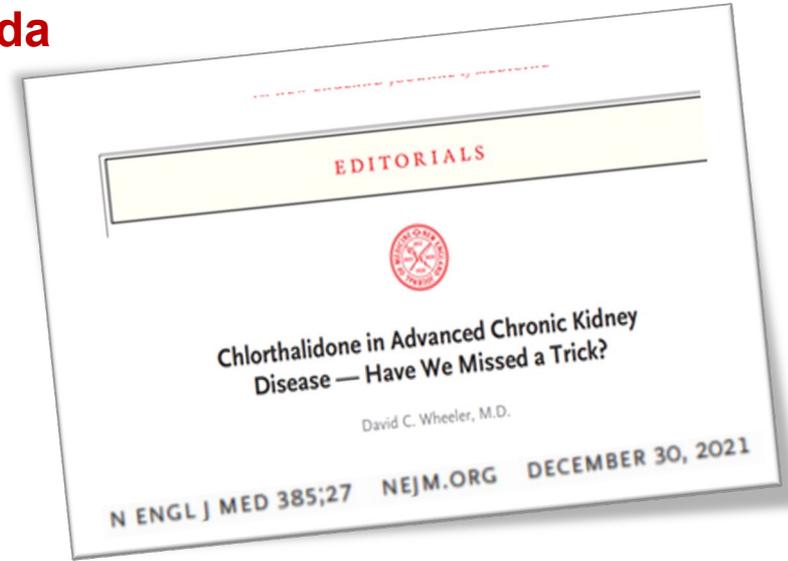
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Diuréticos: CLORTALIDONA en ERC avanzada

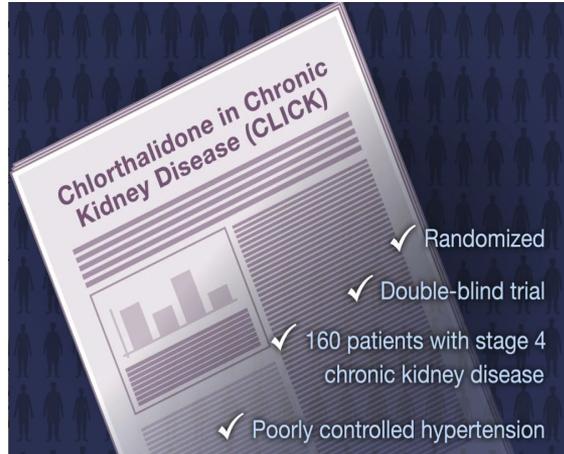
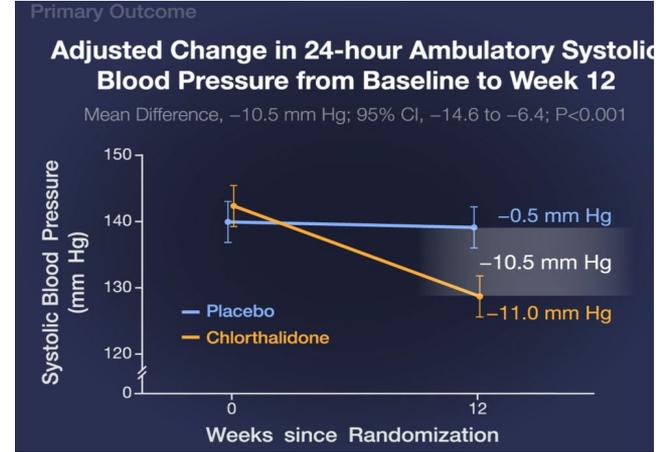
- “*Renuencia general a usar diuréticos de tipo tiazida en **ERC avanzada***” por **pérdida de eficacia diurética** a medida que disminuye la función renal. Se prefieren los diuréticos de asa.
- Inhibe el sistema de transporte $\text{Na}^+ \text{Cl}^-$ en el túbulo renal distal, disminuyendo la reabsorción de Na^+ y aumentando su excreción



Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

by R. Agarwal et al.

N Engl J Med 2021; 385:2507-2519



FG: 23,2 ± 4,2 ml/min/1,73m2

Chlorthalidone
(N=81)

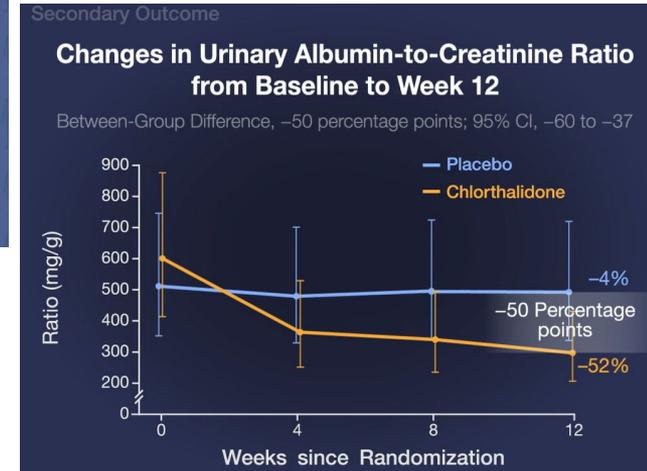
Placebo
(N=79)

Mean 3.4 prescriptions per patient

60% Of patients in each group received loop diuretics

99% Of patients in each group received:

- Angiotensin-converting-enzyme inhibitors
- Angiotensin-receptor blockers
- Beta-blockers



Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

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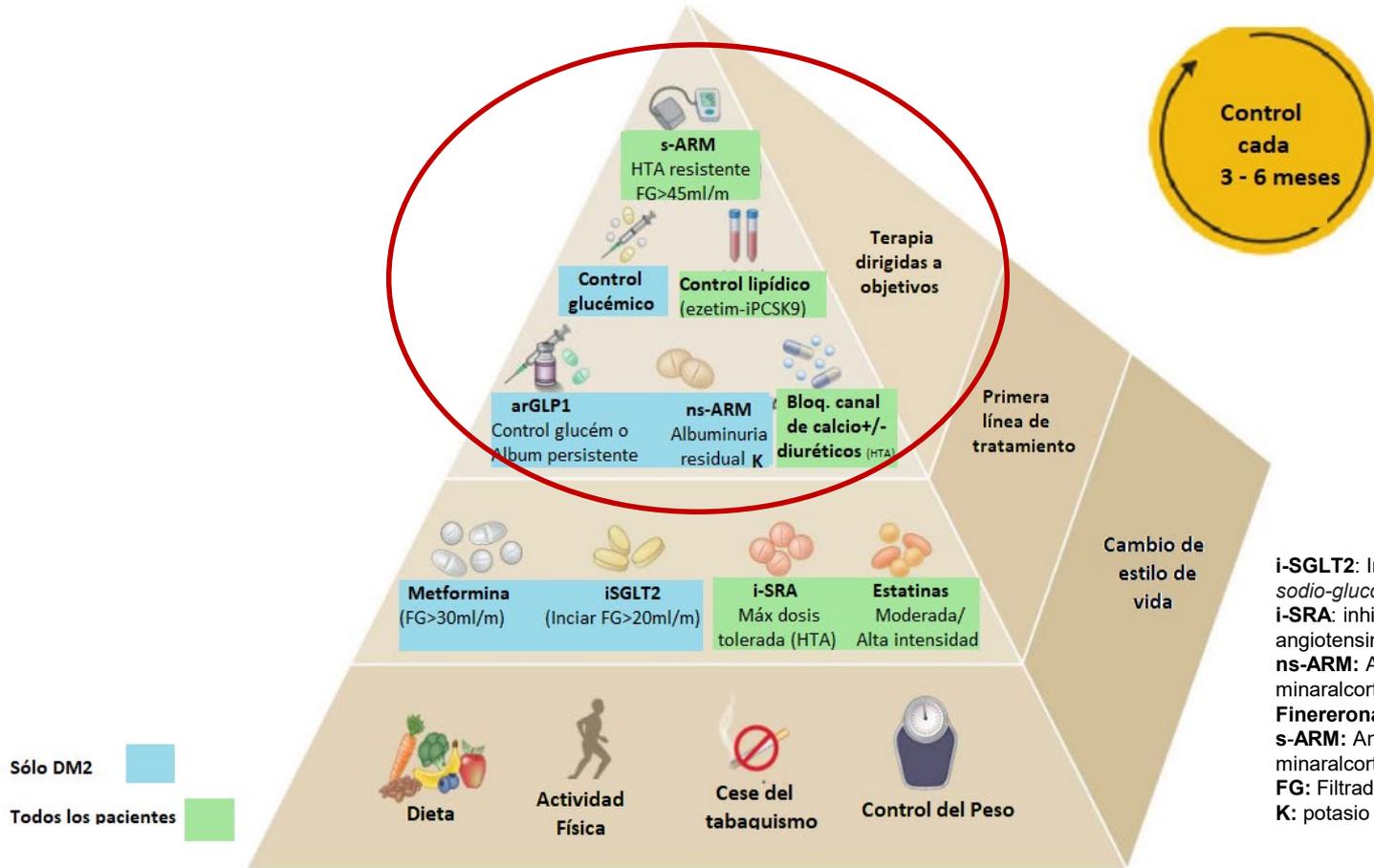
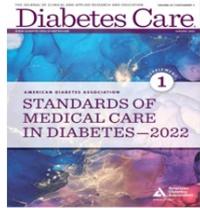
- La clortalidona es un agente reductor de la presión arterial **eficaz en pacientes con enfermedad renal crónica avanzada.**

Limitaciones:

- Estudio de muy corto tiempo y pocos pacientes.
- Determinar si la adición de clortalidona a los iECA o ARA2 ralentizará la progresión de la ERC y reducirá el RCV
- Valorar seguridad (más largo plazo).

La clortalidona podría resultar una valiosa adición en el tratamiento de la enfermedad renal crónica.

Tratamiento de la enfermedad renal diabética



i-SGLT2: Inhibidor *cotransportador de sodio-glucosa 2*.
i-SRA: inhibidor sistema renina angiotensina
ns-ARM: Antagonista del recept minaral corticoide **no esteroideo**:
Finererona
s-ARM: Antagonista del recept minaral corticoide **esteroideo**
FG: Filtrado glomerular
K: potasio

Otras terapias de uso limitado en la enfermedad renal diabética

Pentoxifilina:

- Inhibidor inespecífico de la fosfodiesterasa, agente antiinflamatorio
- Uso en la claudicación o hepatitis alcohólica.
- Varios estudios con nefropatía diabética con pentoxifilina (600 mg dos veces al día) mejoró o estabilizó la TFGe

El diseño del estudio no fue adecuado y se necesitan datos adicionales.

Vitamina D:

- El déficit de vitamina D aumenta la albuminuria (en modelos experimentales),
- La vit D (calcitriol o paricalcitol) se ha asociado a reducción en la albuminuria y propiedades antiinflamatorias.

La literatura escasa, pocos pacientes en los estudios. Se requieren mas ensayos clínicos para demostrar el beneficio nefroprotector de los derivados de la vitamina D sobre la ERC.

Otras terapias de uso limitado en la enfermedad renal diabética



A estudio...
Excepto
finerenona

NUEVAS ESTRATEGIAS

Bloqueo del SRAA (antialdosterónicos de tercera generación, Finerenona).

Antioxidantes

Moduladores inflamación (pentoxifilina, antagonista R CCR2/5, anticuerpo monoclonal anti IL-1)

Bloqueantes del receptor de endotelina de tipo A (atrasentán)

Antifibróticos

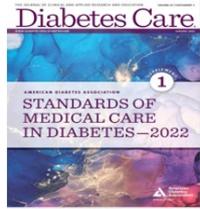
Inhibidores de los productos de glicosilación avanzada (aminoguanidina, piridoxamina)

Inhibidor del factor de adhesión vascular (ASP8232)

Inhibidores del cotransportador de sodio-glucosa tipo 2 (SGLT2)

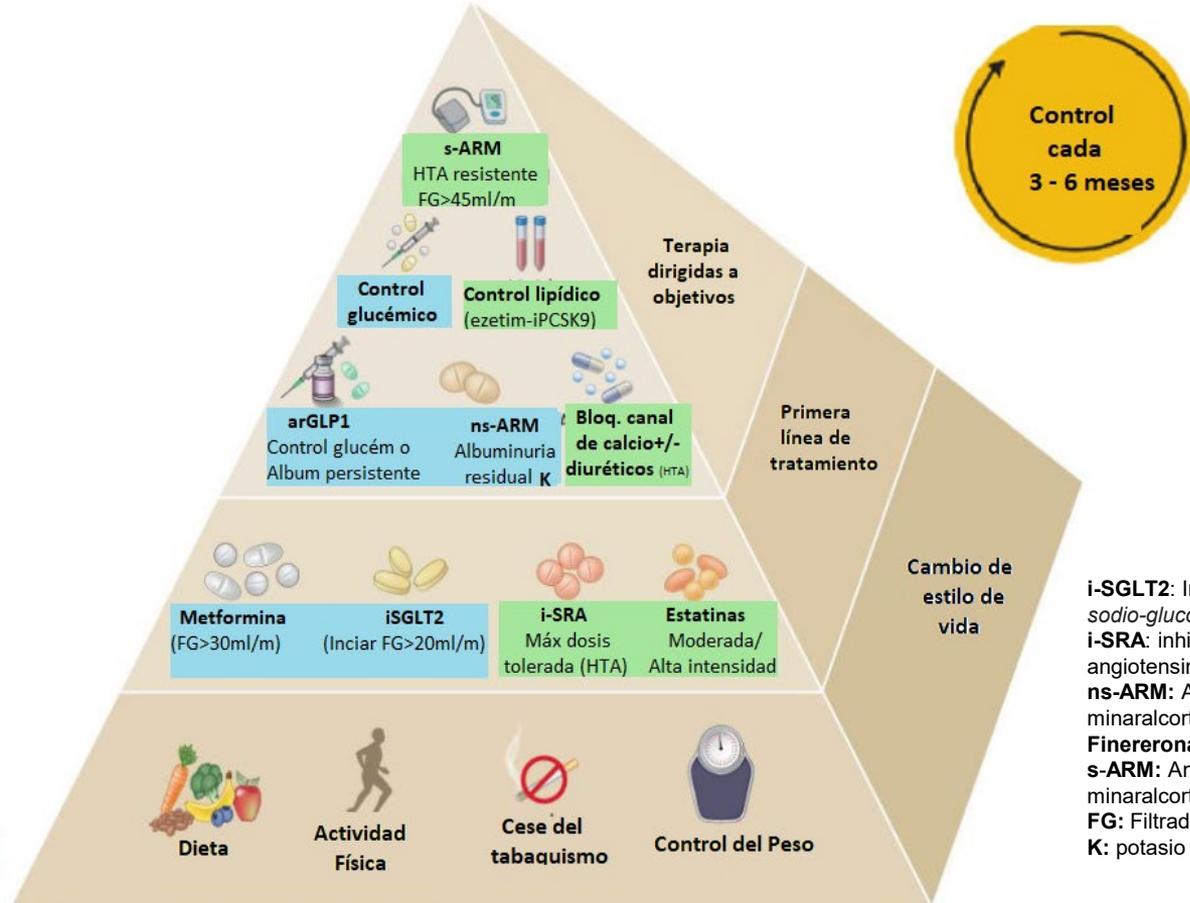
Agonistas del GLP-1 (glucagon like peptide-1)

Tratamiento de la enfermedad renal diabética

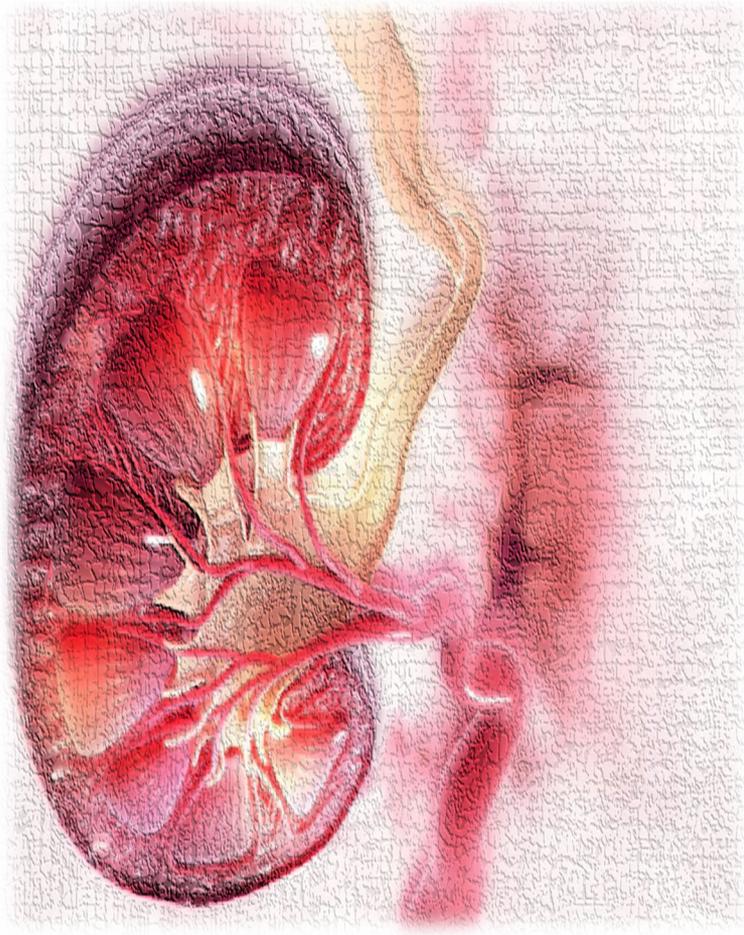


Sólo DM2

Todos los pacientes



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***¡Gracias por vuestra
Atención !***