Sesión Bibliográfica

04/03/2022

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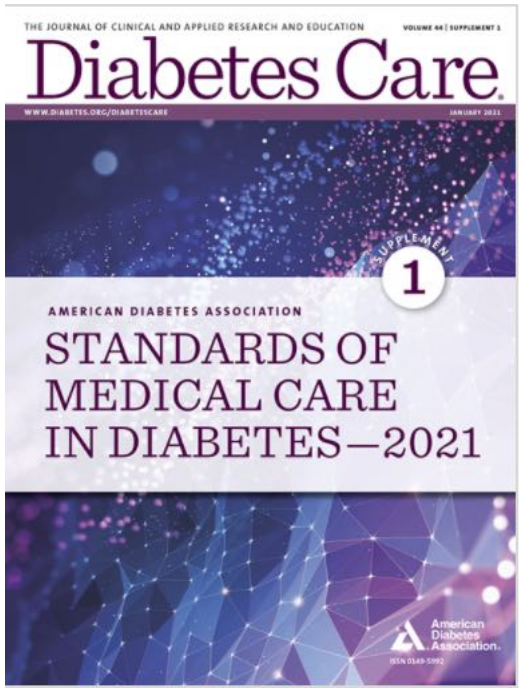
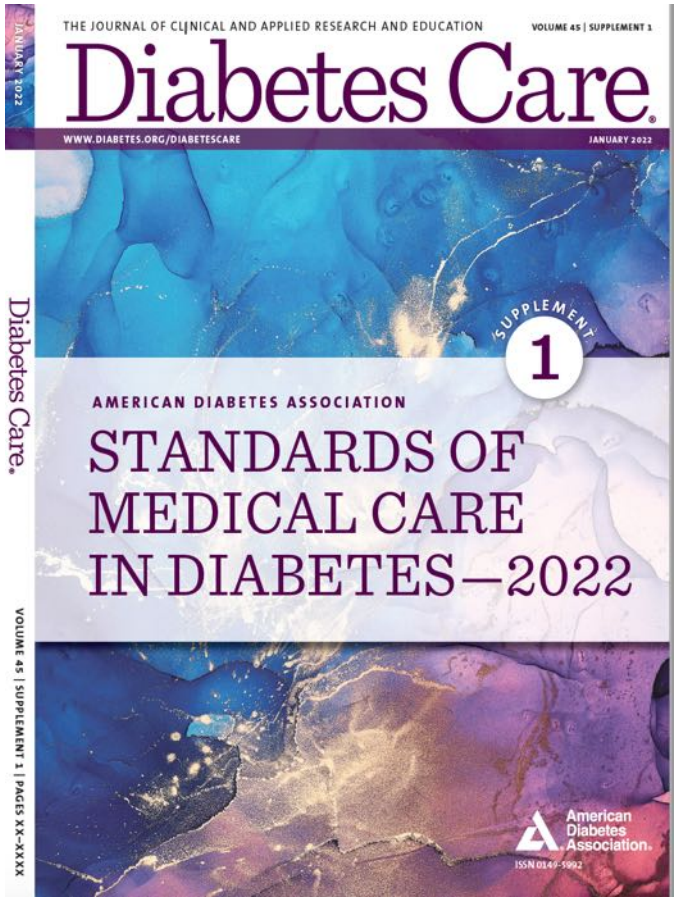


232 Páginas



264 Páginas Abajo

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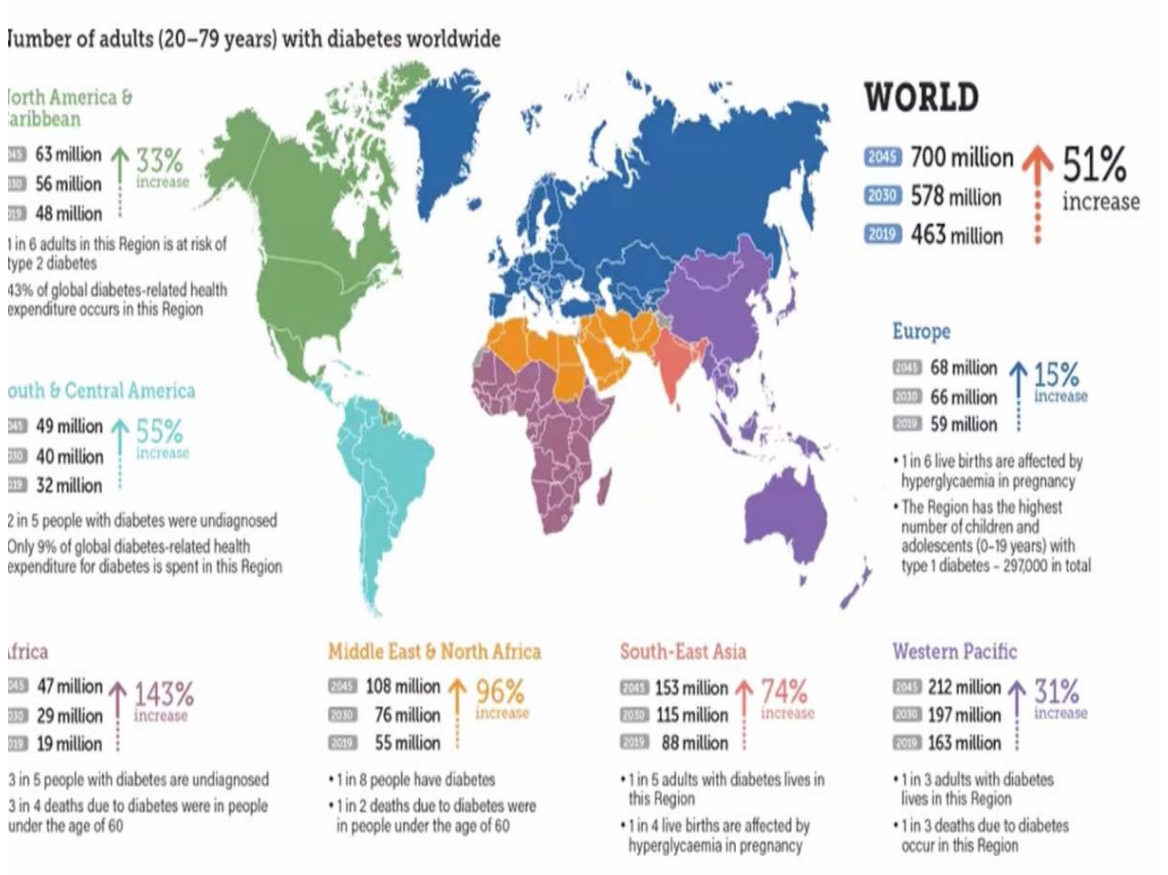

80% de pacientes con DM mueren de ECV

Diabetes Atlas. International Diabetes Federation. 9th edition (2019).

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- Los “Standards of Medical Care” la American Diabetes Association (ADA) es la Guía de Práctica Clínica más importante en el manejo del paciente con diabetes del mundo.

- Desde el 1989 se realiza una actualización constante y periódica sobre todo aquello que tiene que ver con el paciente con DM.

- Proporciona información relevante, contrastada y según evidencia científica a todo aquel clínico o no que tiene responsabilidad de asistir al paciente con DM.

Summary of Revisions: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S4–S7 | https://doi.org/10.2337/dc22-SREV

1- Clasificación y Diagnóstico Diabetes
2.- Prevención o Retraso de la DM 2
3- Abordaje de comorbilidades
4- Resultados de Salud
5- Objetivos Glucémicos
6- Tecnología
7- Sobrepeso/Obesidad
8- Tratamiento Farmacológico
9- Enfermedad Cardiovascular
10- Enfermedad Renal Crónica
11- Retinopatia, Neuropatía y Pie Diabético
12- Ancianos
13- Hospital

2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S17–S38 | https://doi.org/10.2337/dc22-S002

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

- **Repetidas en dos ocasiones (no en el cribado), salvo cuando existan signos inequívocos de DM2 en cuyo caso una glucemia al azar ≥ 200 mg/dl, es suficiente**
- **Si los resultados son discordantes en dos pruebas distintas, aquel que se encuentre por encima del umbral debe ser repetido**

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

2.4 Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes. **A**

2.8 Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more risk factors (**Table 2.3**). **B**

2.9 For all people, screening should begin at age 35 years. **B**

- Ingesta de 150 gr/día de hidratos de carbono 3 días antes de la sobrecarga
- Screening para la población general a partir de los 35 años

3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S39–S45 | https://doi.org/10.2337/dc22-S003

Recommendation

3.1 Monitor for the development of type 2 diabetes in those with prediabetes at least annually, modified based on individual risk/benefit assessment. **E**

Recommendations

3.2 Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program consistent with the DPP to achieve and maintain 7% loss of initial body weight, and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**

- Monitorizar la glucosa anualmente en los pacientes con prediabetes
- Programa intensivo en cambios en estilo de vida **pacientes con** en sobrepeso/Obesidad

(*lograr y mantener una pérdida de 7% del peso y realizar actividad física de moderada 150 min /semana (A)*

- Matizaciones en las recomendaciones de Metformina en Prediabetes (Edad 29-59 años, IMC ≧ 35, FGP ≧ 110, HbA1c ≧ 6% y antecedentes de DG (A)

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Table 4.1 (cont.)- Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics+	✓		✓

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S46–S59 | https://doi.org/10.2337/dc22-S004

- Inmunización COVID (Pfizer, Moderna, Janssen)
- Booster anual (recordatorio de 3ª dosis)
- NASH estadio 2-3 se recomienda Pioglitazona y aGLP1

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.5** for highly recommended vaccinations for adults with diabetes). **A**

Table 4.6—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFLD	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. [a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. [b]Among glucagon-like peptide 1 (GLP-1) receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. [c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution. Adapted from "Preparing for the NASH Epidemic: A Call to Action" (62).

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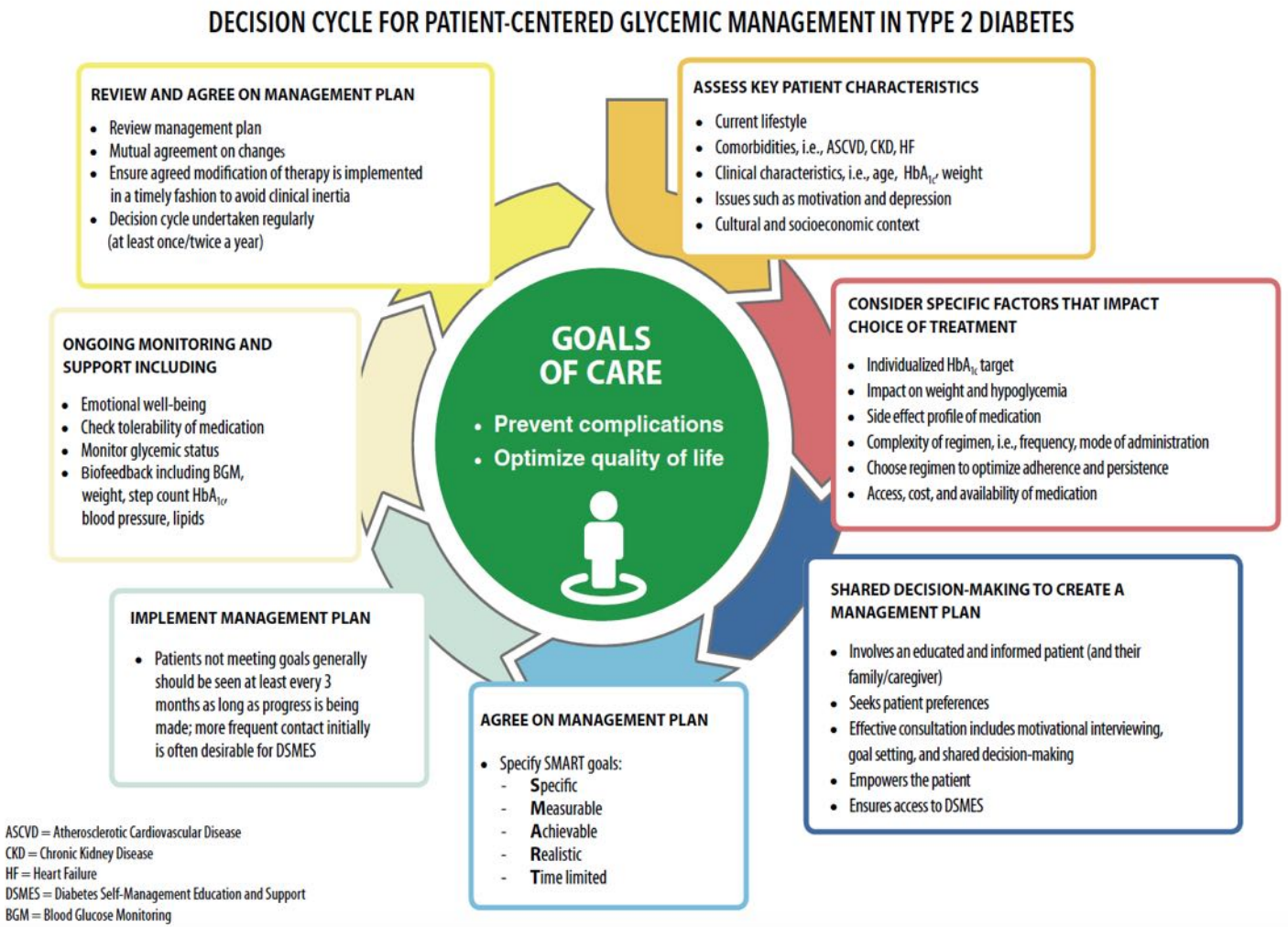
5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S60–S82 | https://doi.org/10.2337/dc22-S005



- ***Ciclo de decisión centrado en el paciente.*** Necesidad de una evaluación continua con decisiones compartidas que permita alcanzar los objetivos y evitando la inercia clínica

- Evaluación médica completa en la visita inicial al confirmar el diagnóstico (A), clasificación de la DM (A), complicaciones derivadas de la misma (A) y comorbilidades (A).

5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S60–S82 | https://doi.org/10.2337/dc22-S005

5.4 Diabetes self-management education and support should be patient-centered, may be offered in group or individual settings, and should be communicated with the entire diabetes care team. **A**

- Acepta y recomienda métodos digitales de auto-control como beneficiosos
- Da más peso a valoración cognitiva: evaluación e integración en la toma de decisiones

Cognitive Capacity/Impairment

Recommendations

5.51 Cognitive capacity should be monitored throughout the life span for all individuals with diabetes, particularly in those who have documented cognitive disabilities, those who experience severe hypoglycemia, very young children, and older adults. **B**

5.52 If cognitive capacity changes or appears to be suboptimal for provider-patient decision-making and/or behavioral self-management, referral for a formal assessment should be considered. **E**

6. Glycemic Targets: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S83–S96 | https://doi.org/10.2337/dc22-S006

- **Se mantiene la tabla clásica de individualización de objetivos**

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

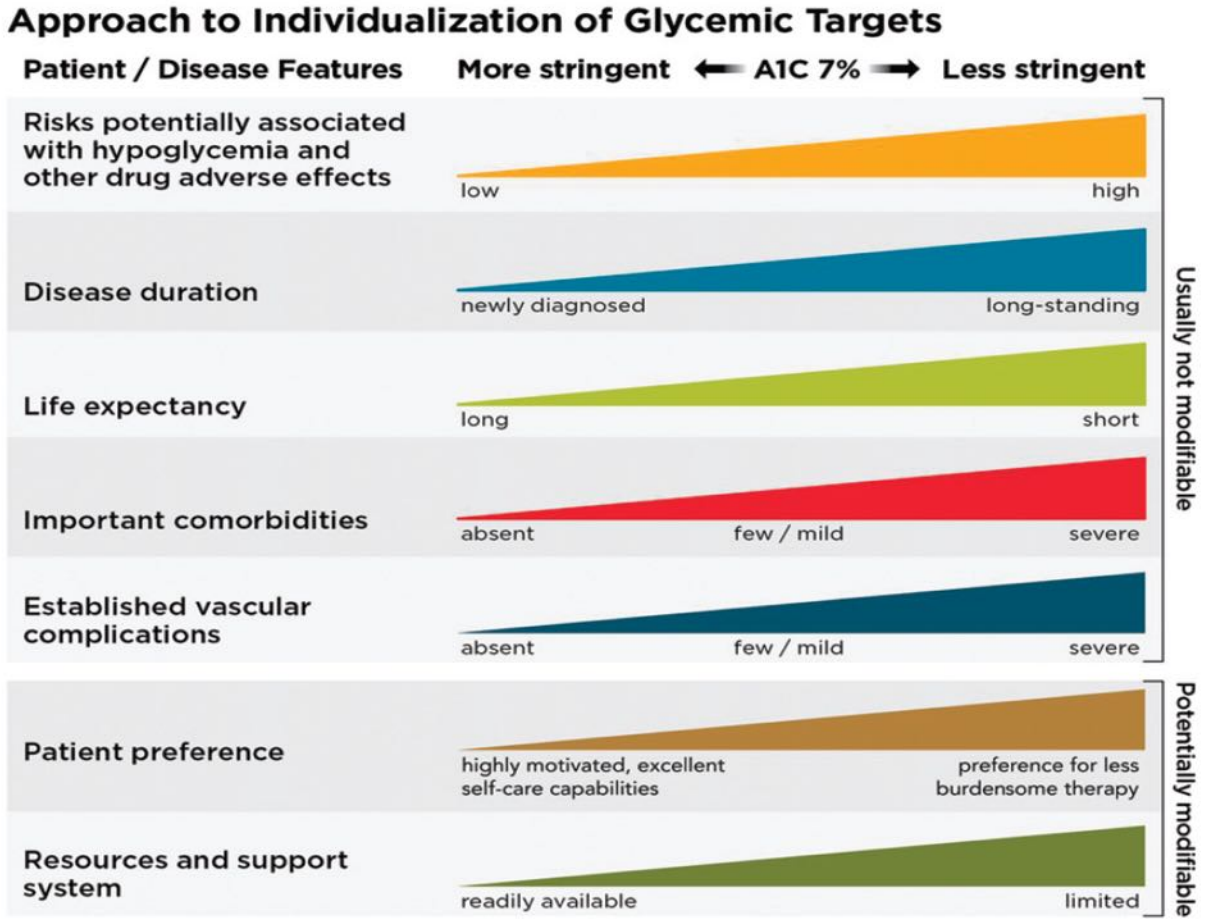


Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (68).

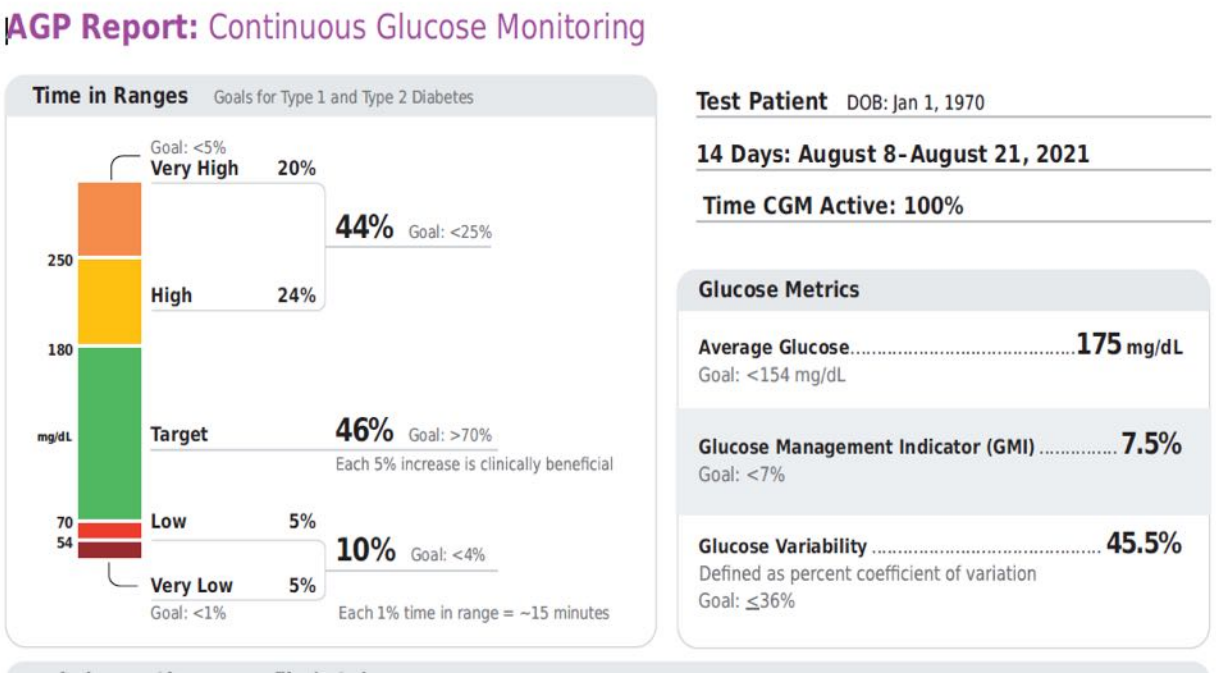
7. Diabetes Technology:
Standards of Medical Care in Diabetes—2022

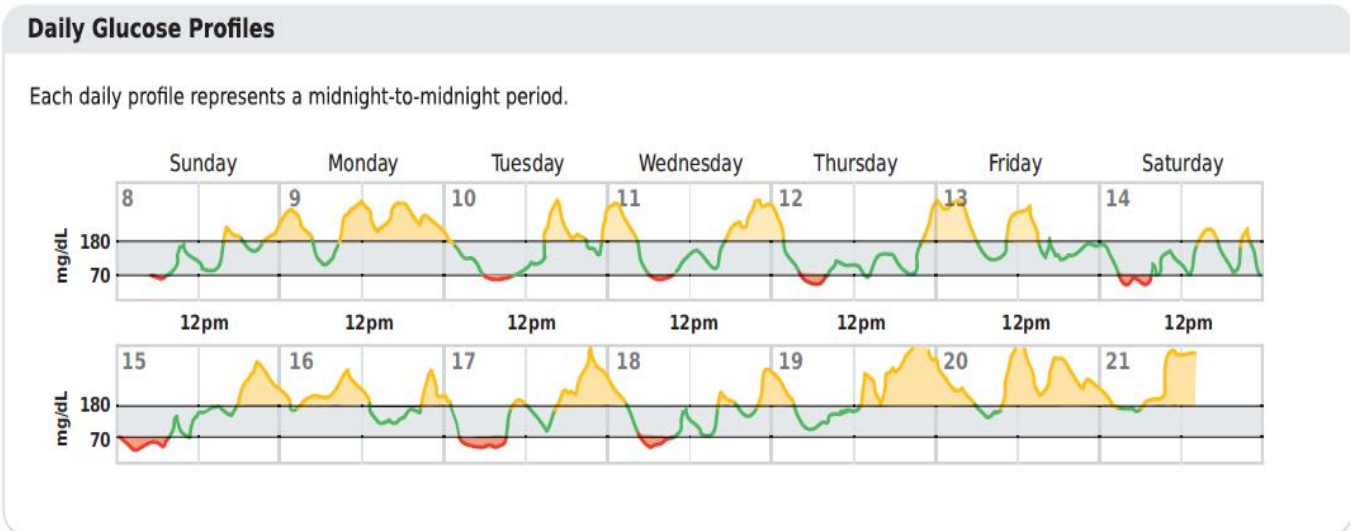
Diabetes Care 2022;45(Suppl. 1):S97–S112 | https://doi.org/10.2337/dc22-S007

1- Autocontrol de la glucemia

2- MCG

- Múltiples inyecciones diarias o una infusión subcutánea continua de INS
- DM con INSB
- DM2 jóvenes inyecciones diarias múltiples o INS subcutánea continua





- En la MCG resaltan:

→ **TER:** porcentaje de tiempo de la glucemia dentro del rango objetivo

→ **IGG** (indicador de gestión de la glucemia): nivel medio de HbA1c que cabría esperar basándose en la glucosa media medida

- Objetivo TER → dentro de rango superior a 70% y menor al 4%
- Los datos publicados sugieren una fuerte correlación entre TER (70%) y HbA1c (~7 %)
- *Relación estrecha entre la variabilidad glucémica y la hipoglucémica*

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8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2022*

8.12 There is no clear evidence that dietary supplements are effective for weight loss. **A**

- **Dieta, actividad física y terapia conductual para lograr y mantener una pérdida de peso del 7%**
- Relación entre obesidad y Covid 19
- ***No evidencia que los suplementos dietéticos sirvan para perder peso***
- ***La FDA aprueba semaglutide 2.4mg semanal para el tratamiento obesidad*** (Phentermine, Orlistat, Phentermine/topiramate, Naltrexone/bupropion, Liraglutide 3 mg)
- **Cirugía bariátrica: DM2 e IMC de 40 kg/m2 y a considerar en IMC de 30,0-34,9 kg/m2 si no logran sus objetivos con métodos no quirúrgicos.**

9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2022*

		Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
					ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors		Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs		High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: generally not recommended in chronic kidney disease ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human insulin**	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

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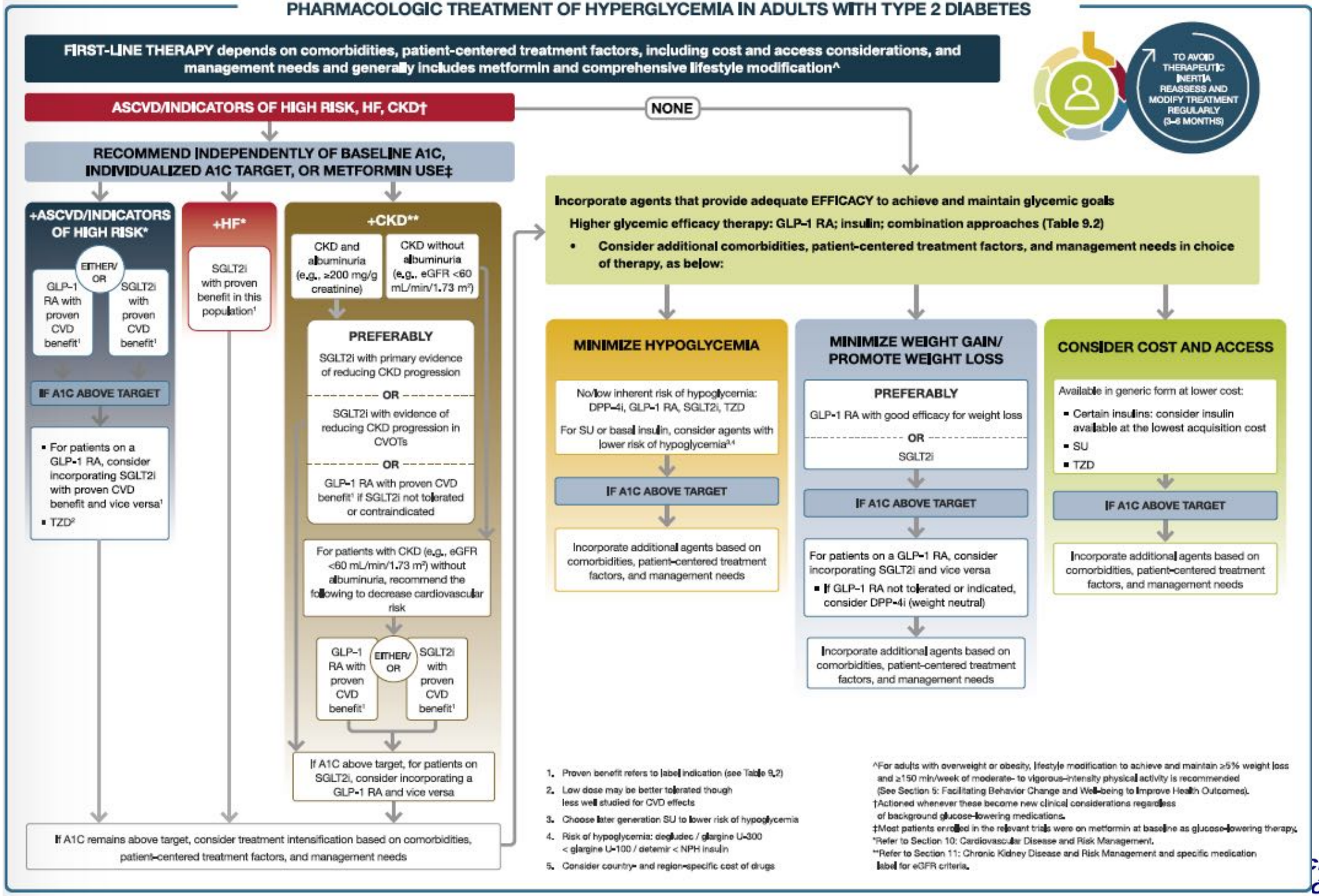
PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
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 benefit[1] 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 benefit[1]
EITHER/ OR
SGLT2i with proven CVD benefit[1]
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
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[3,4]
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
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 / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs
^For 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).
†Actioned 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.

- La terapia inicial de primera línea depende de las comorbilidades, preferencias del paciente, coste y acceso → **MEV Y MET**
- La elección de la medicación de segunda línea se basa en las características clínicas y preferencias del paciente. Pueden utilizarse seis familias farmacológicas
- El ***tratamiento combinado*** al inicio puede considerarse ***si HbA1c% es superior a 1,5%*** del objetivo
- Si glucemia basal > 300 mg/dL o HbA1c > 10% o síntomas de hiperglucemia (poliuria, polidipsia) o de catabolismo (pérdida de peso) → iniciar INS.
- El régimen terapéutico debe adaptarse a las comorbilidades (enfermedad cardiovascular aterosclerótica, enfermedad renal crónica y enfermedad cardiovascular) y centrado en el paciente

Recommendations

9.4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**

9.5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**

2021

Se acepta un enfoque terapéutico inicial alternativo a la MET, dependiendo de las comorbilidades

9.4a First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. **A**

9.4b Other medications (glucagon-like peptide 1 receptor agonists, sodium–glucose cotransporter 2 inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease (**Fig. 9.3**). **A**

9.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. **A**

2022
Nuevo

Recommendations

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy and durability of treatment effect. **A**

2022
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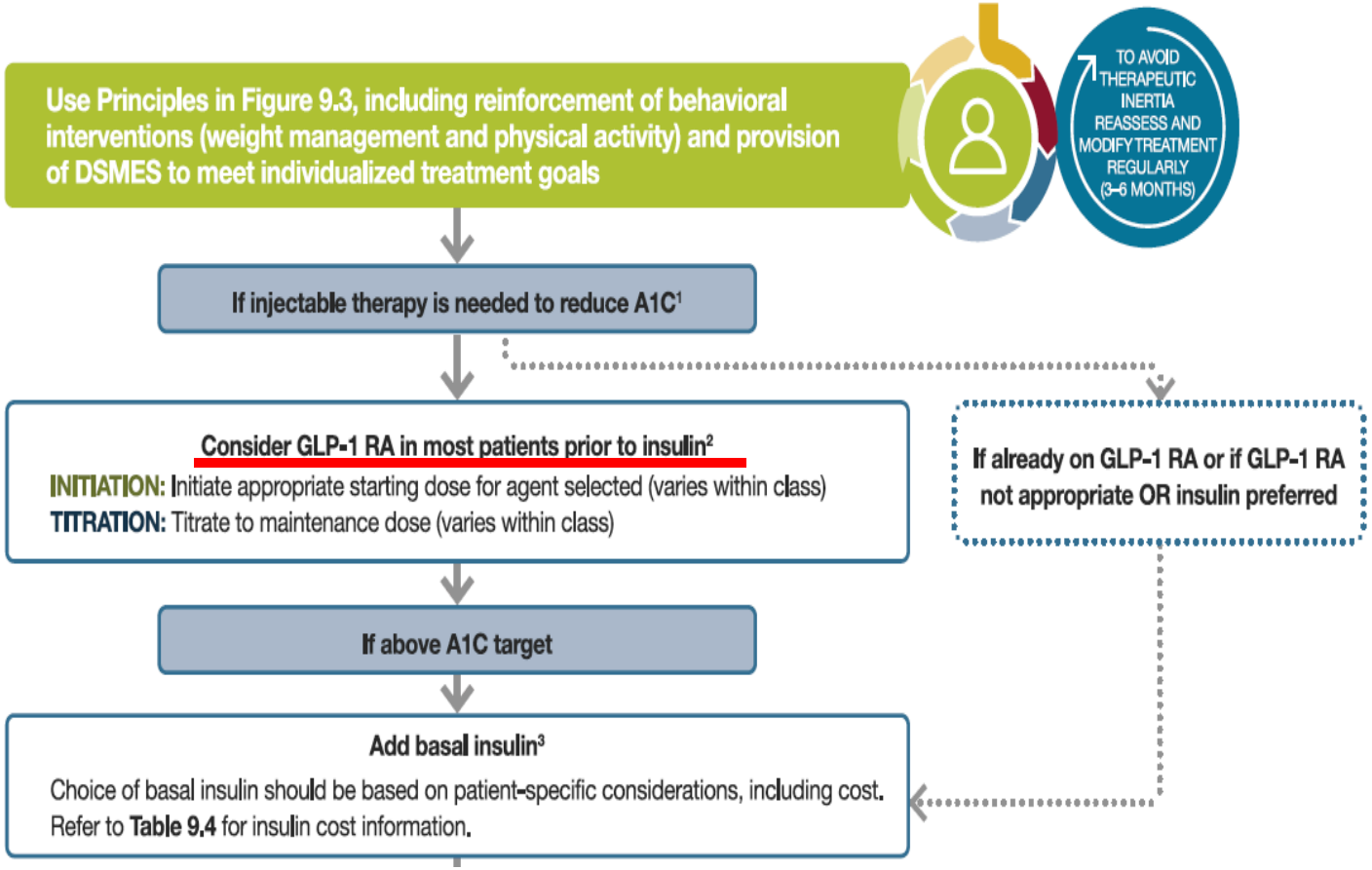
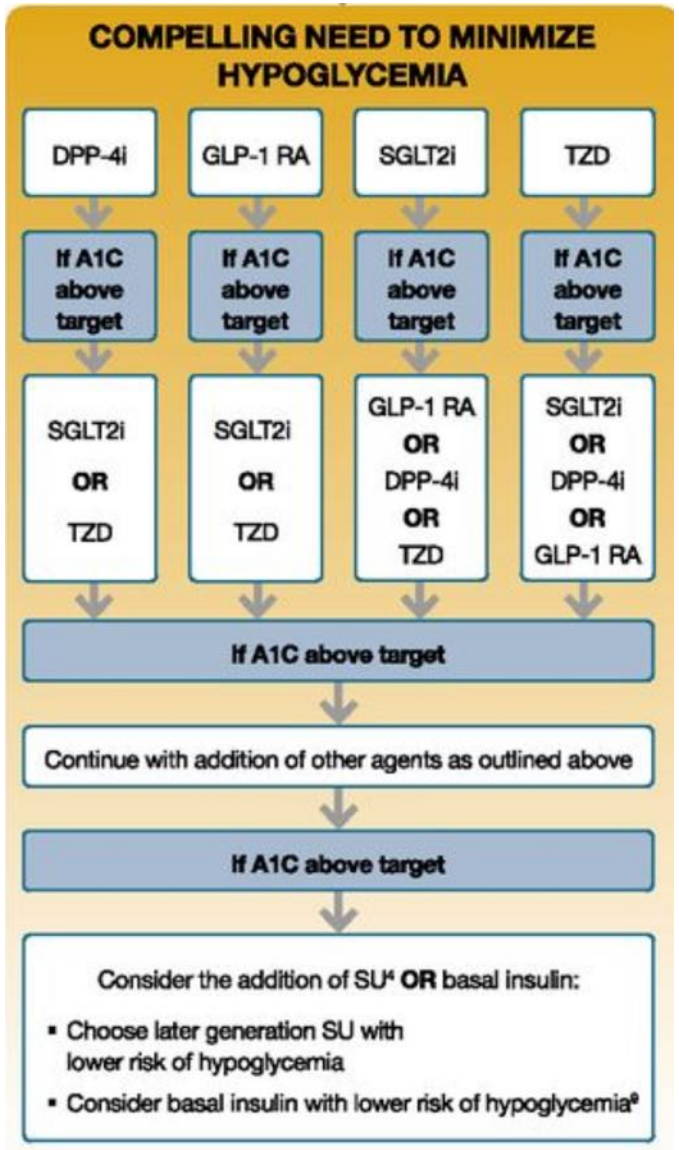


- Si se plantea terapia inyectable consideran antes aGLP1 que INS
- Se recomienda terapia combinada de INS + aGLP-1 para una mayor eficacia y la durabilidad del efecto del tratamiento



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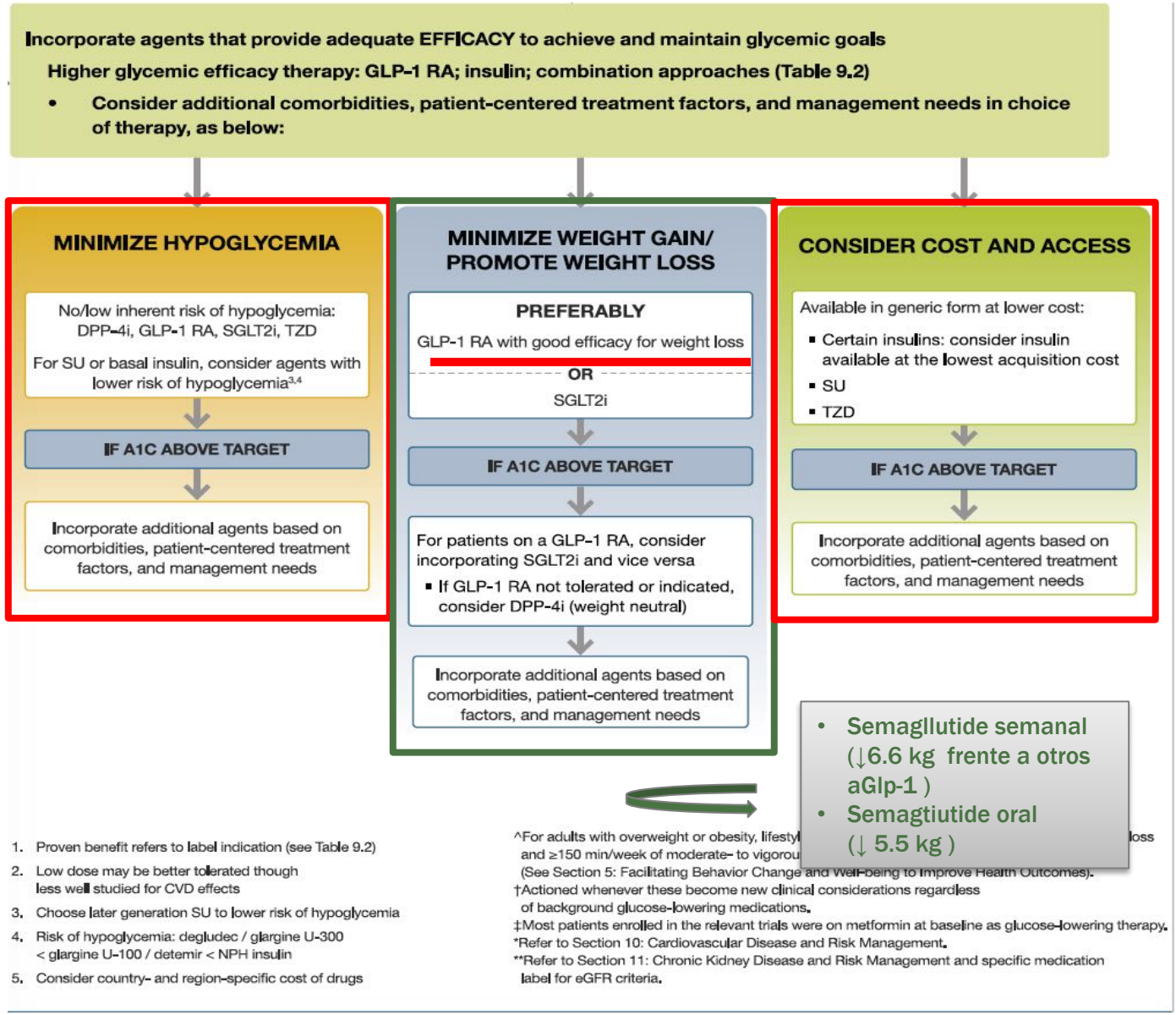

- Semaglutide semanal (↓6.6 kg frente a otros aGlp-1)
- Semagtiutide oral (↓ 5.5 kg)

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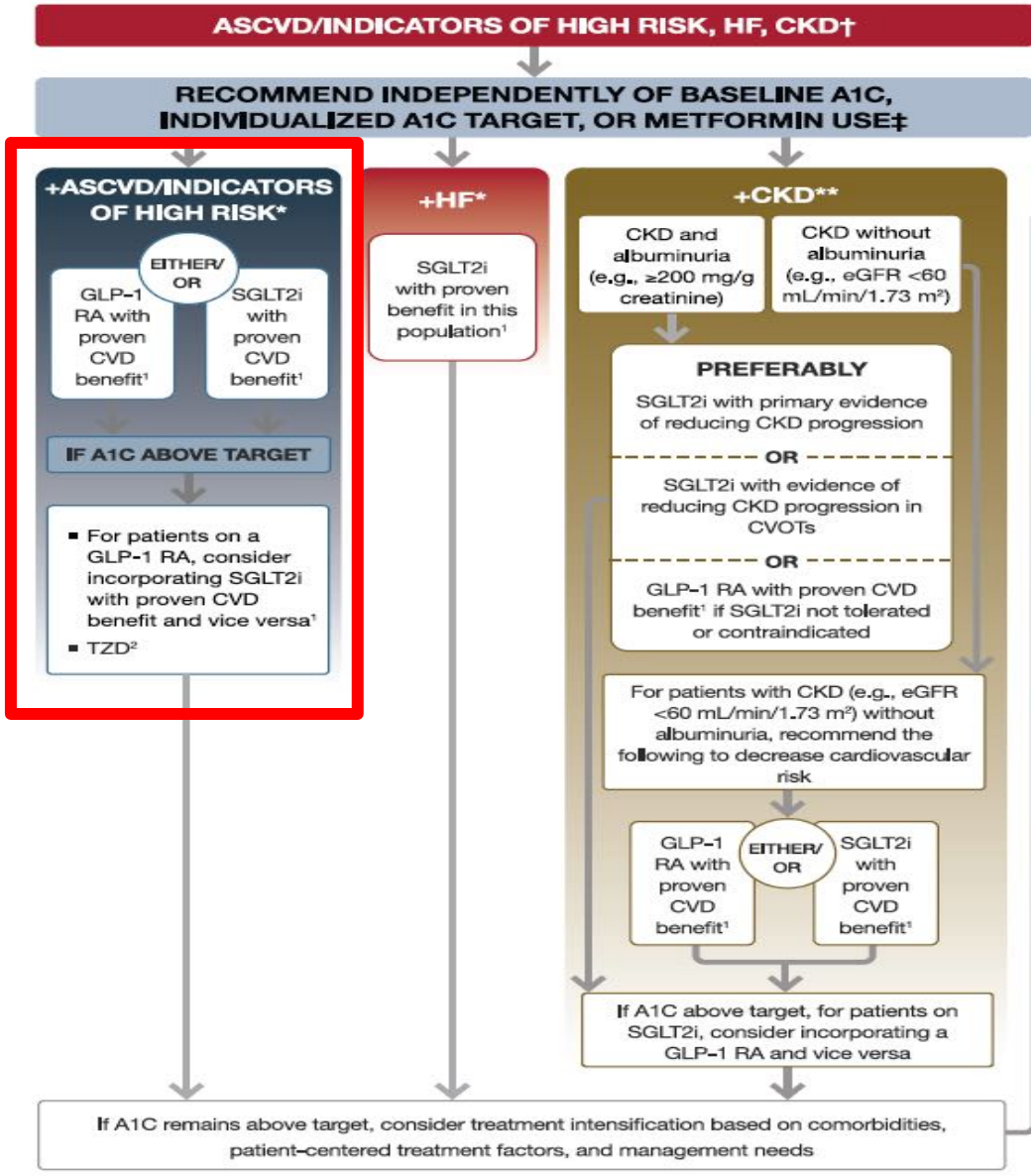
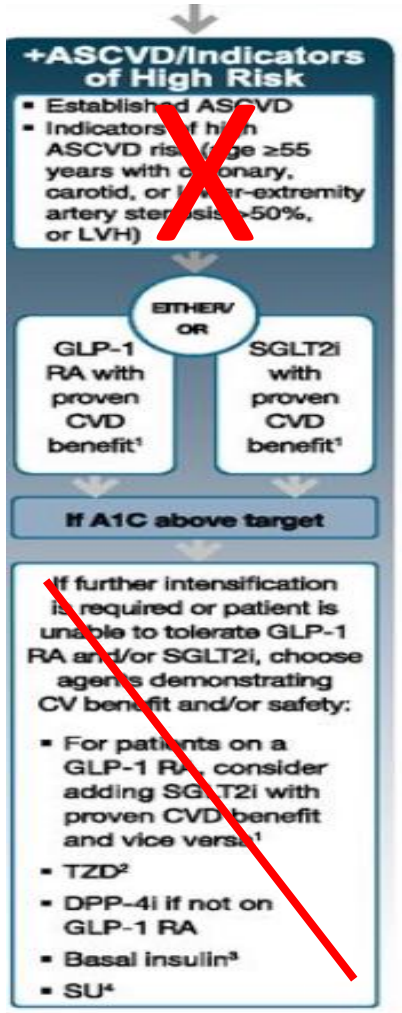
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^





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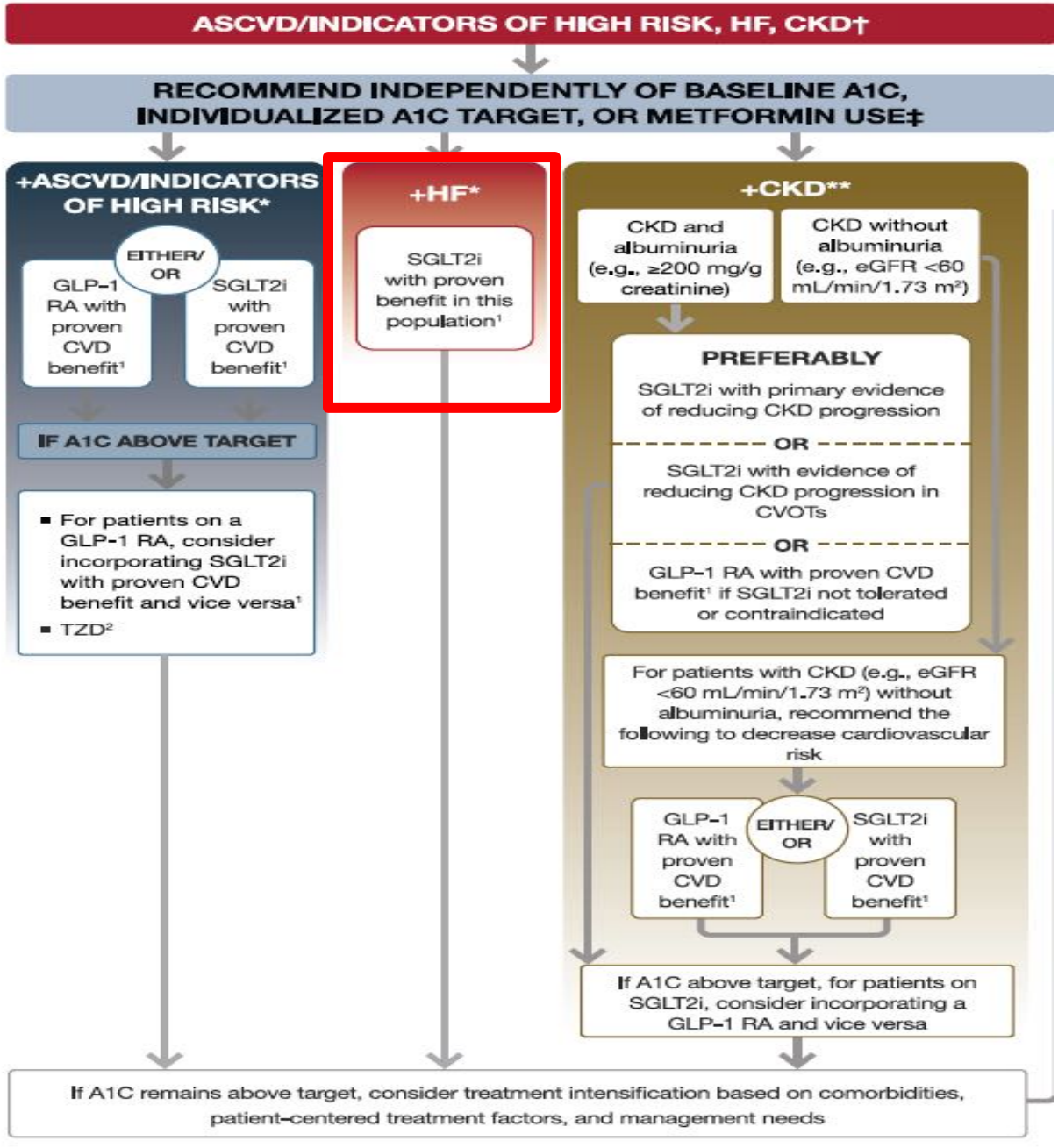

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The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

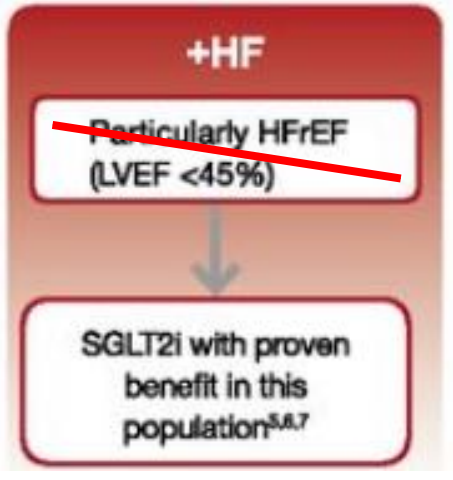
Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators*

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., et al., for the DAPA-HF Trial Committees and Investigators*

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., h.D., Hans-Peter Brunner-La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., et al., for the EMPEROR-Preserved Trial Investigators*



2021

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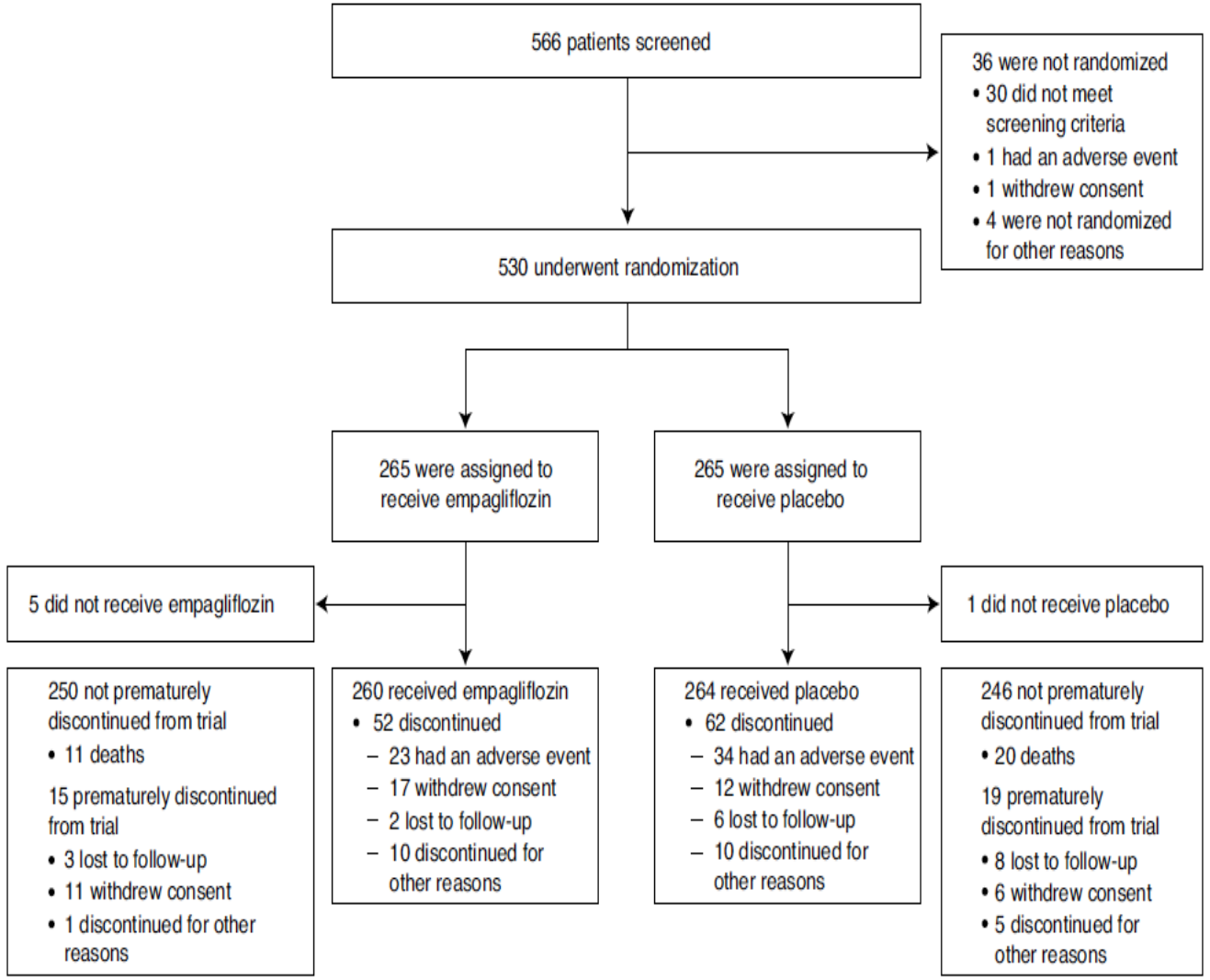
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01659-1

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Eficacia y seguridad de empagliflozina hospitalizados con ICC, independiente de FEVI (66,6% FEVI ≤ 40%, 33,3% FEVI > 40%), de DM2 (46% de pacientes con DM2 basal) y de si era una descompensación de una IC previa 66,6%) o de novo (33,3%).

Se randomizaban entre los días 1 – 5 tras la hospitalización y eran seguidos durante 90 días



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nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01659-1

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	

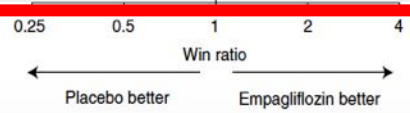

Fig. 3 | Primary efficacy outcome in all prespecified subgroups. Win ratios were calculated using a non-parametric generalized pairwise comparison

Endpoint primario: compuesto de
- Mortalidad CV
- Hospitalizaciones por IC
- Calidad de vida

- Pacientes tratados con empagliflozina presentaron un ***36% más de beneficio*** clínico que los pacientes tratados con placebo
- No diferencias en seguridad y tolerabilidad en el grupo de empagliflozina frente a placebo

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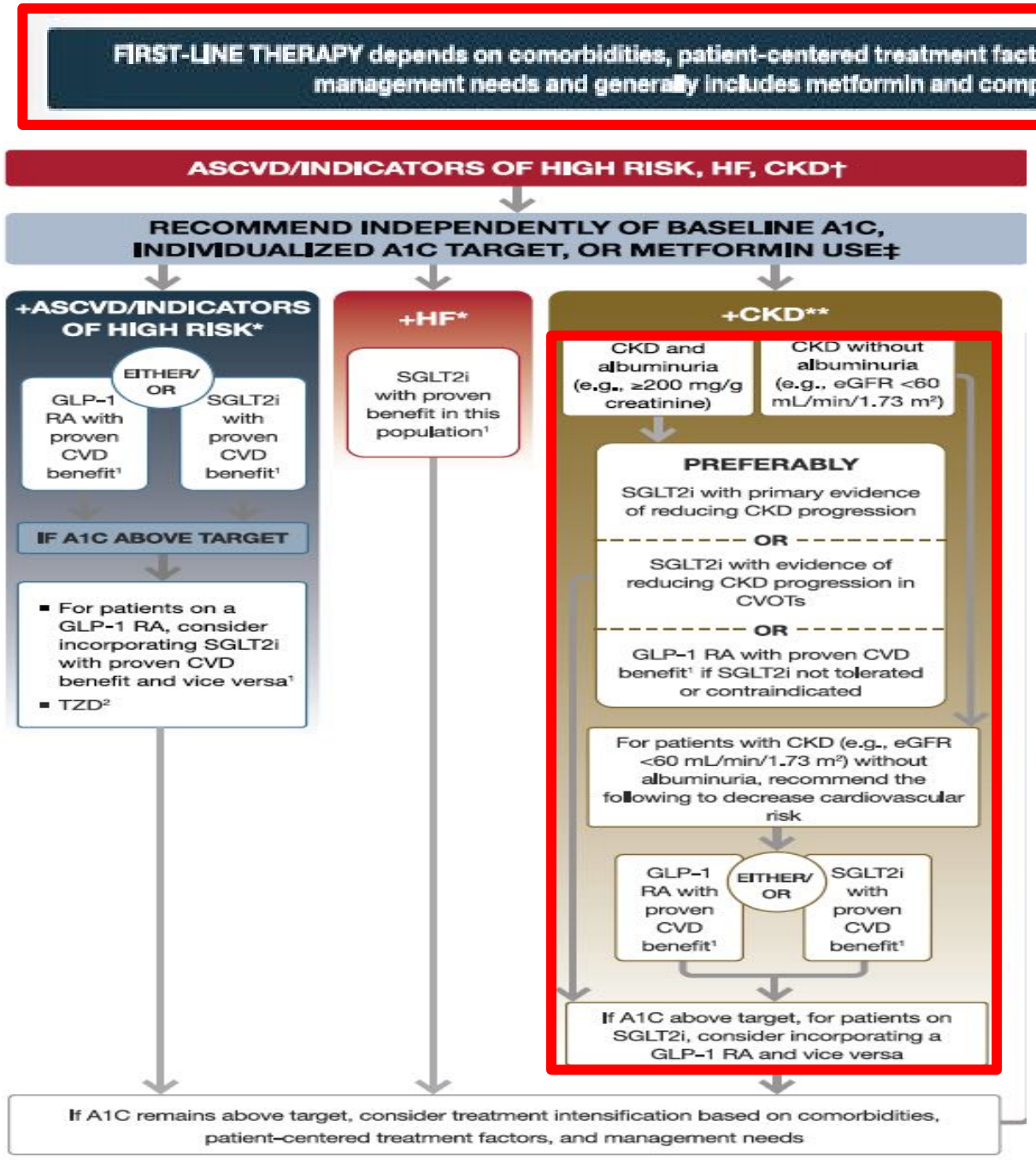

- i-SGLT2 y a-GLP1 reducen la albuminuria
- i-SGLT2 enlentecen el deterioro del FG y a-GLP1, en general, no llegan a hacerlo de forma significativa

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Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

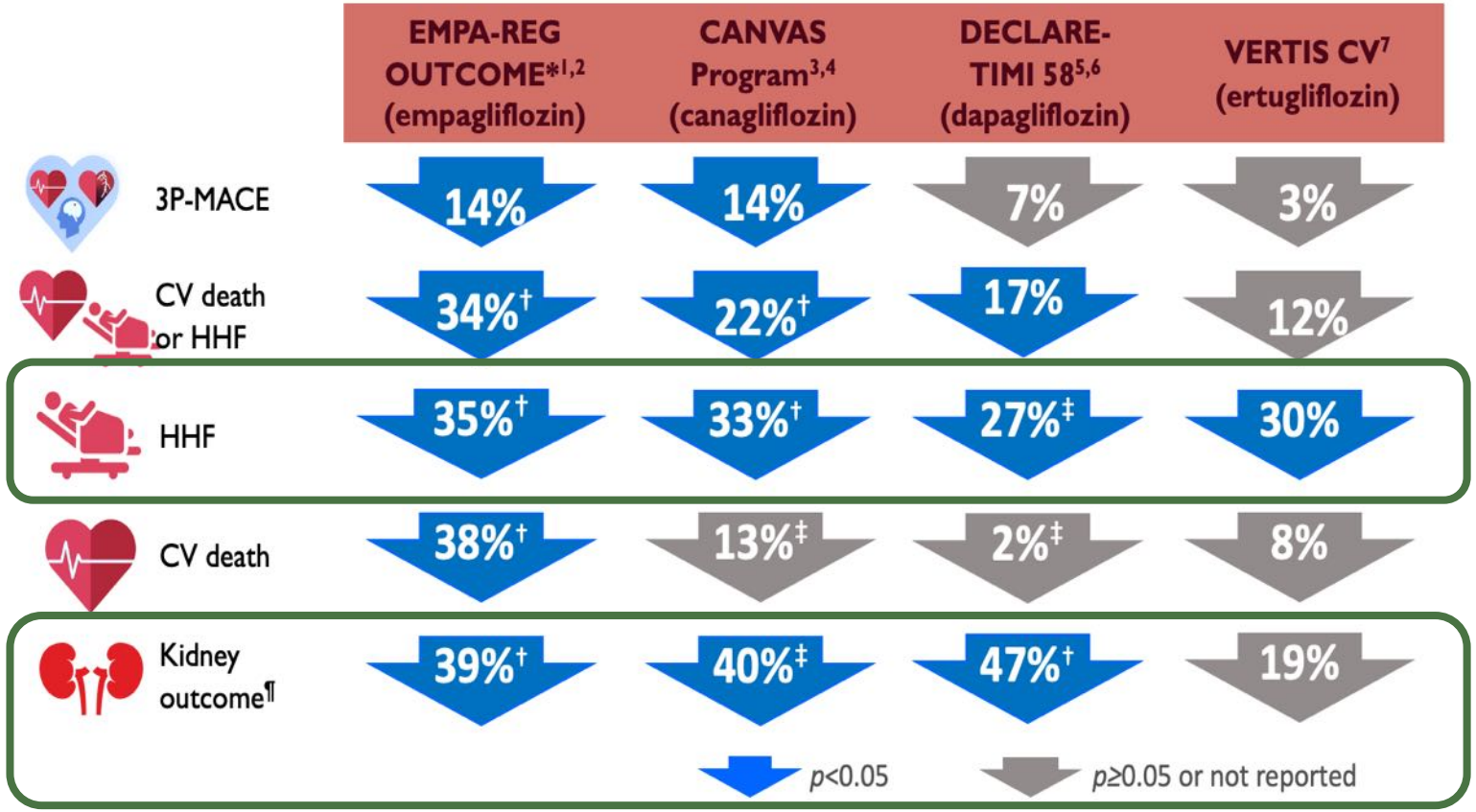
	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (189) (n = 17,160)	CREDENCE (187) (n = 4,401)	DAPA-CKD (190,226) (n = 4,304; 2,906 with diabetes)	VERTIS CV (192,227) (n = 8,246)	DAPA-HF (191) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (217,219) (n = 3,730; 1,856 with diabetes)
Intervention	Empagliflozin/ placebo	Canagliflozin/ placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/ placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or >2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6
Diabetes duration (years)†	57% >10	13.5	11.0	15.8		12.9		
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—
Metformin use (%)	74	77	82	57.8	29		51.2% (of patients with diabetes)	
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.58‡	−0.43‡	−0.31	N/A	−0.48 to −0.5	N/A	N/A
Year started/ reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020

Continued on p. S163

Table 10.3C—Continued

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (189) (n = 17,160)	CREDENCE (187) (n = 4,401)	DAPA-CKD (190,226) (n = 4,304; 2,906 with diabetes)	VERTIS CV (192,227) (n = 8,246)	DAPA-HF (191) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (217,219) (n = 3,730; 1,856 with diabetes)
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68)	CV death or HF hospitalization 0.88 (0.75–1.03)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85)
					Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.69 (0.53–0.88)	CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	Mean slope of change in eGFR 1.73 (1.10–2.37)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—		1.04 (0.86–1.26)	—	
Stroke§	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	—		1.06 (0.82–1.37)	—	
HF hospitalization§	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)		0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—			—	
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYHA, New York Heart Association. Data from this table was adapted from Cefalu et al. (225) in the January 2018 issue of *Diabetes Care*. *Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡Significant difference in A1C between groups ($P < 0.05$). ^A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ||Definitions of worsening nephropathy differed between trials.


EMPA-REG OUTCOME*[1,2] (empagliflozin)
CANVAS Program[3,4] (canagliflozin)
DECLARE-TIMI 58[5,6] (dapagliflozin)
VERTIS CV[7] (ertugliflozin)
3P-MACE
14%
14%
7%
3%
CV death or HHF
34%†
22%†
17%
12%
HHF
35%†
33%†
27%‡
30%
CV death
38%†
13%‡
2%‡
8%
Kidney outcome¶
39%†
40%‡
47%†
19%
p<0.05
p≥0.05 or not reported

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

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)

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

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Renal Outcomes from Clinical Trials: aGLP-1

	ELIXA[1]	LEADER[2]	FREEDOM-CVO[3]	SUSTAIN-6[4]	HARMONY[5]	REWIND[6]	AWARD-7[7]	EXSCEL[8]	PIONEER-6[9]
Criterio de valoración principal	4P-MACE	3P-MACE	4P-MACE	3P-MACE	3P-MACE	3P-MACE	*Cambio en HbA1c*	3P-MACE	3P-MACE
Key Secondary Outcomes	4P-MACE plus HHF, **UACR 4MACE , HHF, OR coronary revascularization procedures.**	**Expanded composite outcome**; individual components of the composite outcome; MI; fatal stroke; transient ischaemic attack; microvascular events (retinopathy and **nephropathy)**; all-cause mortality	-	Expanded composite CV outcome; individual components of the expanded composite CV outcome; all-cause mortality; retinopathy complications; **new or worsening nephropathy. Death from all causes, nonfatal myocardial infarction, or nonfatal stroke.**	3P-MACE for superiority; composite of 3P-MACE or revascularisation for unstable angina; individual components of the primary composite outcome; composite of CV death or hospitalisation for heart failure; all-cause mortality) Change in eGFR calculated using MDRD formula	**Composite microvascular outcome: diabetic retinopathy needing laser, anti-VEGF therapy, or vitrectomy; or clinical proteinuria; or a 30% decline in eGFR; or chronic renal replacement therapy;** hospitalisation for unstable angina; individual components of the primary composite outcome; all-cause mortality. heart failure requiring hospitalization or an urgent heart failure visit	HbA1c at 52 weeks, participants HbA1c<7% (53 mmol/mol) or <8% (64 mmol/mol), SMPG profiles, FBG, mean daily insulin lispro dose; **change in eGFR (calculated with CKD-EPI equation), UACR**, bodyweight, rate of hypoglycaemia, and allergic reactions.	All-cause mortality; individual components of the primary composite outcome; hospitalisation for ACS; and hospitalisation for heart failure)	Expanded composite CV outcome (3P-MACE, hospitalisation for unstable angina or heart failure); individual components of the expanded composite CV outcome; composite of all-cause mortality, non-fatal MI or non-fatal stroke
Follow-up	2.1 years	~3.8 years	~2.0 years	~2.1 years	~3 to 5 years	~6.5 years	-	~3.2 year	~1.7 years

Renal Outcomes from Clinical Trials: aGLP-1

LEADER - liraglutide

Compuesto renal:

- *Macroalbuminuria persistente de nueva aparición*
- *Duplicación persistente de la creatinina sérica*
- *ERT*
- *Muerte por causas renales*

SUSTAIN-6 - semaglutide

- Nefropatía nueva o que empeora

REWIND – dulaglutide

Compuesto renal:

- Proteinuria
- 30 % de disminución en TFGe
- ERT

AWARD-7 - dulaglutide

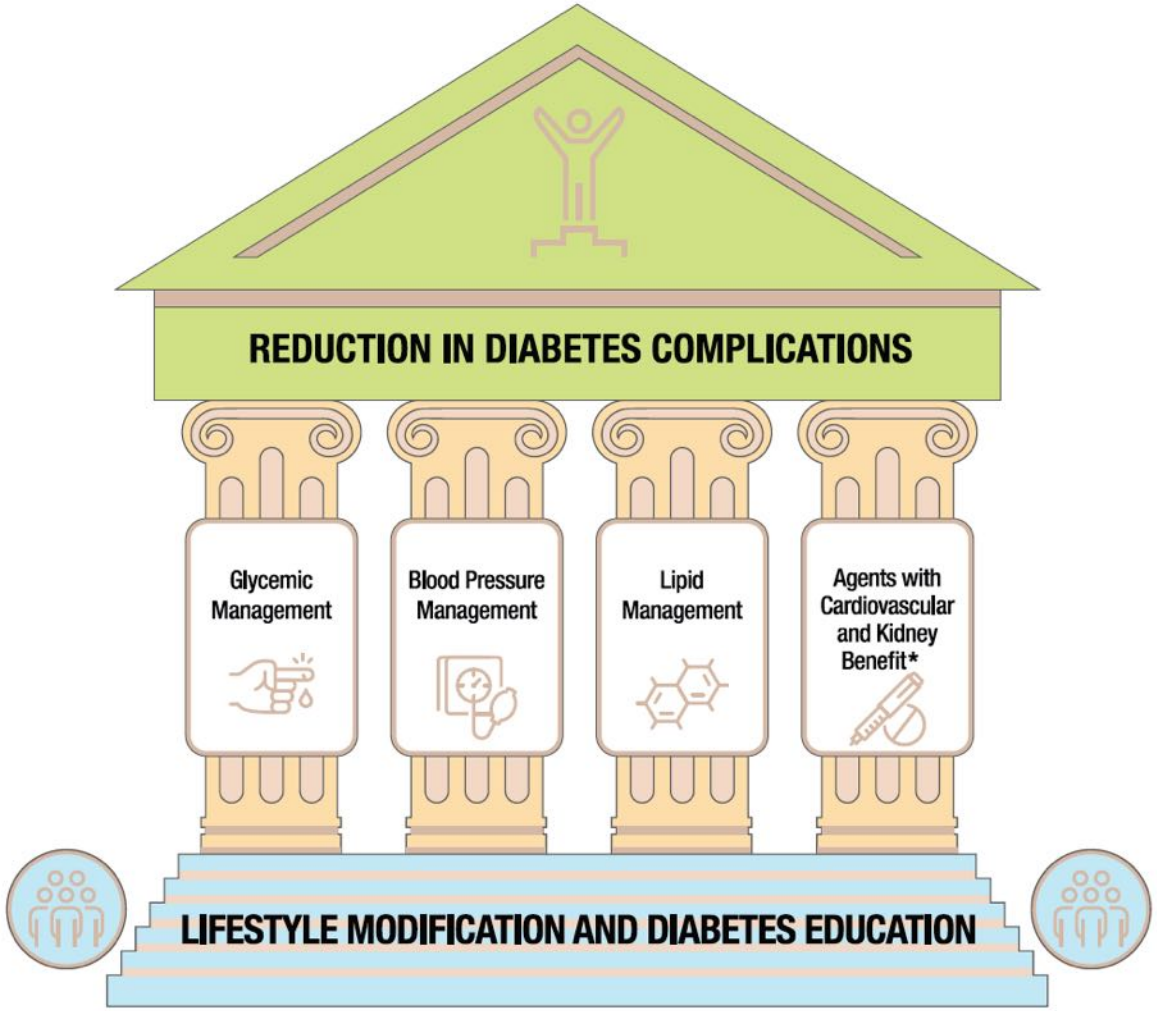
- Cambio desde la línea base en eGFR
- Cambio desde la línea base en ACR

Semaglutide 1 mg, Liraglutide 1.8 mg y dulaglutide → *Enlentecen el deterioro del FG sobre todo en ERD*

Semaglutide y dulaglutide → *disminuyen el ictus no mortal*

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S144–S174 | https://doi.org/10.2337/dc22-S010



HTA:

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**

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10.1 Blood pressure should be measured at every routine clinical visit. When possible, patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Patients with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

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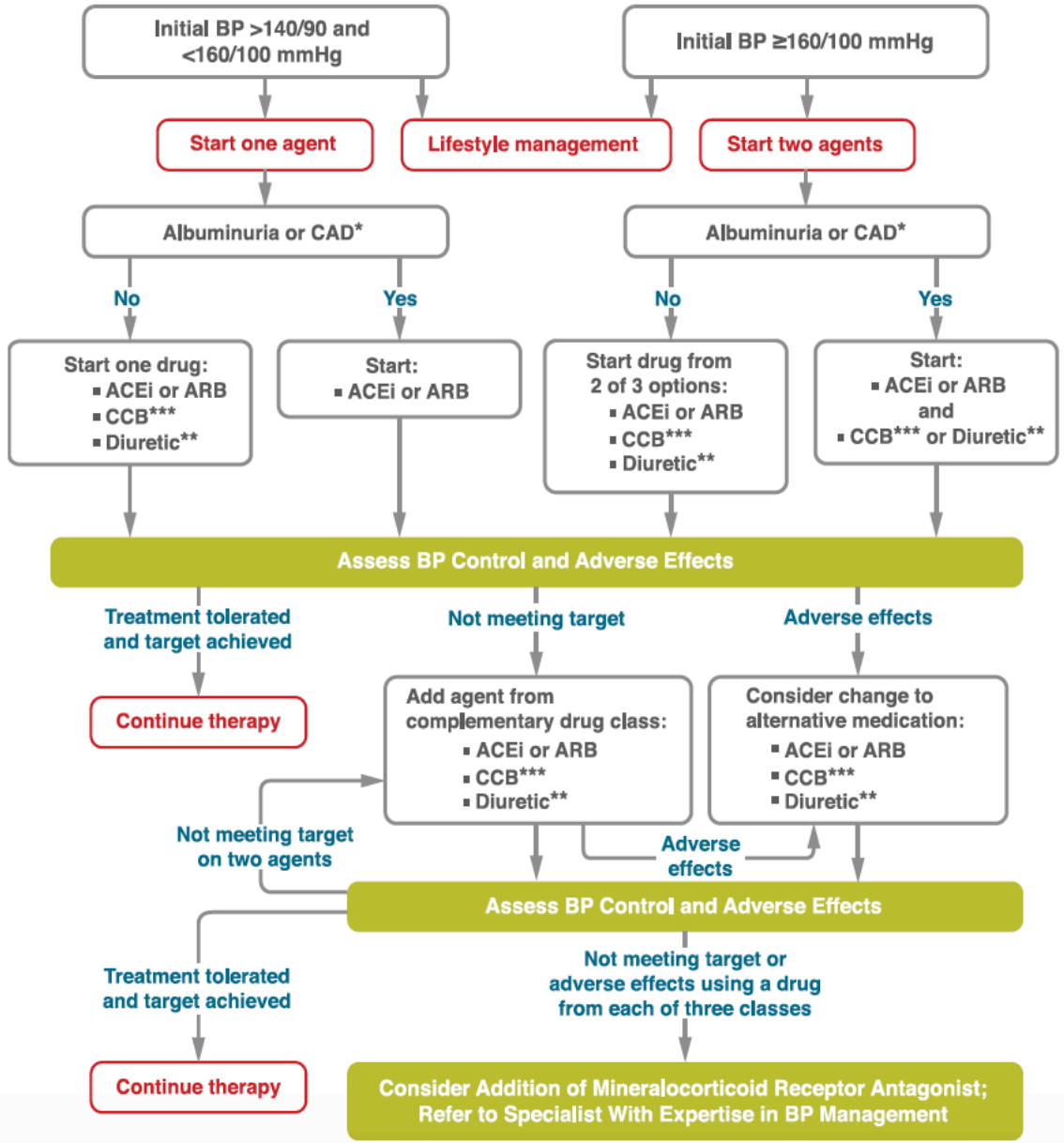
Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



Lípidos:

10.19 For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.21 In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. B

10.24 For patients with diabetes and atherosclerotic cardiovascular disease considered very high risk using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A

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Statins and Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (114). At this time, there are no completed trials demonstrating a cardiovascular outcomes benefit to use of this medication; however, this agent may be considered for patients who cannot use or tolerate other evidence-based LDL cholesterol–lowering approaches, or for whom those other therapies are inadequately effective (115).

Recommendations

10.42 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 10.3*B*** and **Table 10.3*C***) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. A

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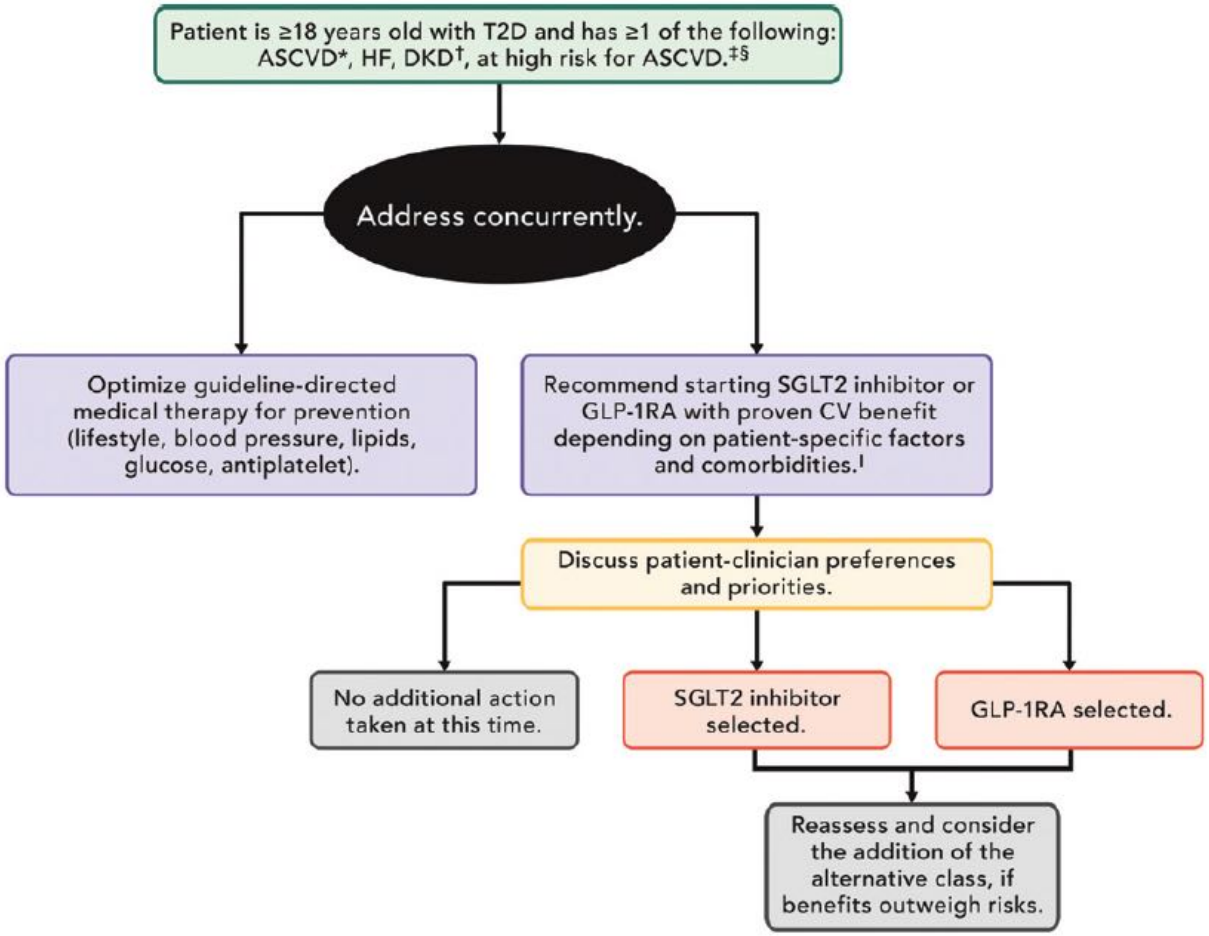
Enfoque clínico:



- En pacientes asintomáticos no se recomienda el cribado de rutina de la enfermedad coronaria
- En los pacientes con ECV o múltiples FRCV de ECV, combinar un iSGLT2 y un aGLP-1 con beneficio demostrado de reducción de ECV y eventos renales

11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2021;44(Suppl. 1):S151–S167 | https://doi.org/10.2337/dc21-S011

2021

11. Chronic Kidney Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S175–S184 | https://doi.org/10.2337/dc22-S011

12. Retinopathy, Neuropathy, and Foot Care: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S185–S194 | https://doi.org/10.2337/dc22-S012

2022

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11. Chronic Kidney Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S175–S184 | https://doi.org/10.2337/dc22-S011

Recommendations

11.3c In patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events (**Table 9.2**). **A**

2022

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Finerenona

Table 1 Characteristics of first-, second-, and third-generation mineralocorticoid receptor antagonists

	Spironolactone	Eplerenone	Finerenone
Trade name(s)	Aldactone	Inspra	
Class	Steroidal	Steroidal	Dihydropyridine
MR IC_{50} (nM)	24	990	17.8
AR IC_{50} (nM)	77	≥21 240	≥10 000
GR IC_{50} (nM)	2410	≥21 980	≥10 000
PR EC_{50} (nM)	740	≥31 210	≥10 000
Half-life (h)	1.4 (active metabolites 12–35)	4–6	≥10 000

European Journal of Heart Failure (2016) **18**, 28–37
doi:10.1002/ejhf.444

REVIEW

Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease

Peter Bramlage[1,2]*, Stephanie L. Swift[1†], Martin Thoenes[3], Joan Minguet[1], Carmen Ferrero[2], and Roland E. Schmieder[4]

European Heart Journal (2016) **37**, 2105–2114
doi:10.1093/eurheartj/ehw132

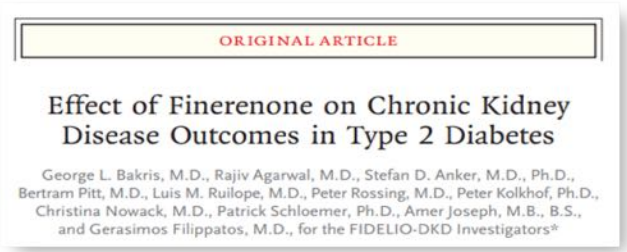
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease

Gerasimos Filippatos[1]*, Stefan D. Anker[2], Michael Böhm[3], Mihai Gheorghiade[4], Lars Køber[5], Henry Krum[6†], Aldo P. Maggioni[7], Piotr Ponikowski[8], Adriaan A. Voors[9], Faiez Zannad[10], So-Young Kim[11], Christina Nowack[11], Giovanni Palombo[12], Peter Kolkhof[13], Nina Kimmeskamp-Kirschbaum[14], Alexander Pieper[15], and Bertram Pitt[16]

European Journal of Heart Failure (2016) 18, 28
European Heart Journal (2016) 37, 2105

FIDELIO-CKD


ORIGINAL ARTICLE

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

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*


Circulation

ORIGINAL RESEARCH ARTICLE

Finerenone and Cardiovascular Outcomes in Patients With Chronic Kidney Disease and Type 2 Diabetes

- 5734 pctes, DM2, > 18 años
- Alb/Cr 30 – 300 + FG 25-60 ó Alb/Cr 300 – 5000 + FG 25-75
- K ≤ 4,8
- No: ICC FEVIr, nefropatía no diabética, diálisis, HTA no controlada
- Tto IECAS /ARA II: dosis máx, > 4 semanas estable
- Seguimiento 2,6 años

Con o sin Enfermedad CV

- **Eventos CV:** Muerte cardiovascular, IAM no fatal, ACVA no fatal, Hospitalización por ICC

- **Eventos renal:**

- *Descenso en la albuminuria*
- Inicio de diálisis durante > 90 días, trasplante, descenso > 40% del FG o muerte renal.
- Deterioro de la función renal en > 57% o Muerte renal

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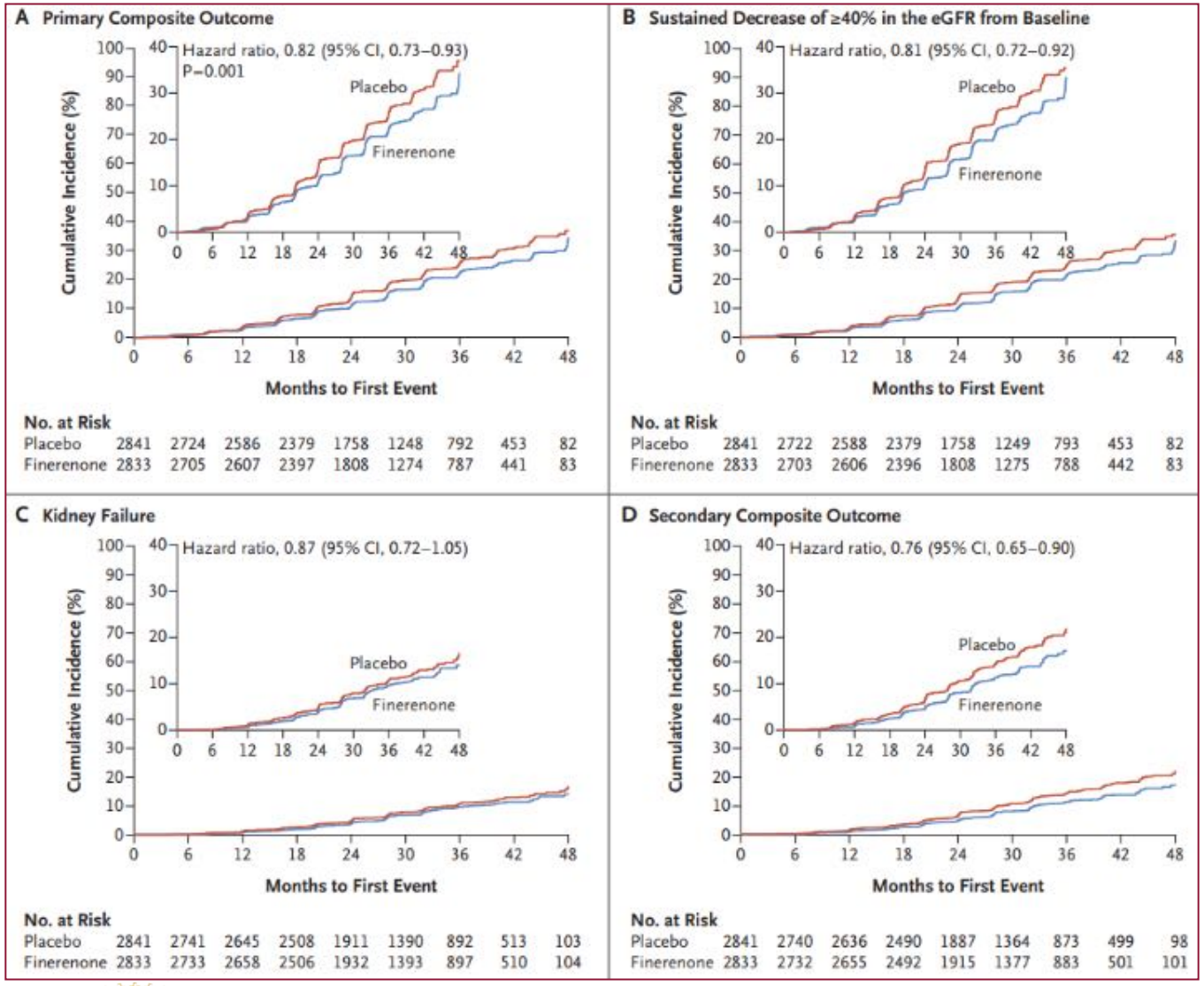
FIDELIO-CKD



- ↓ del riesgo de evento compuesto primario (↓ ≥ 40% en el FGe desde basal, muerte por causa renal o fallo renal terminal)
- ↓ riesgo de eventos cardiovasculares (tanto con ECV previa como en su ausencia)
- No relación con descenso de la tensión arterial

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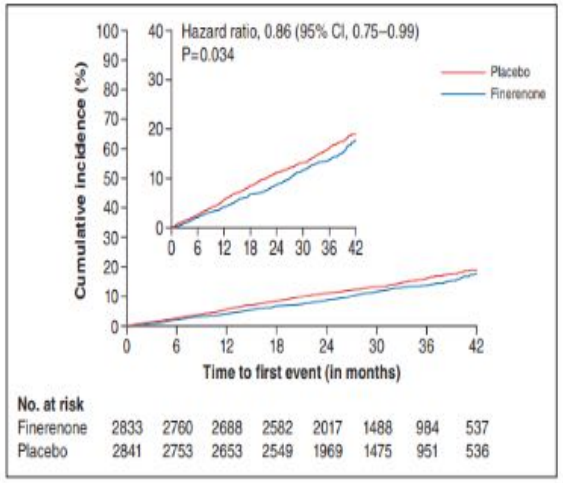
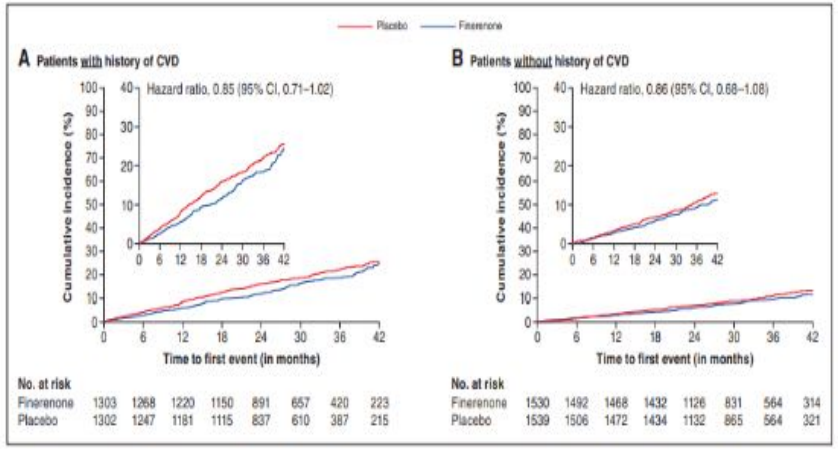
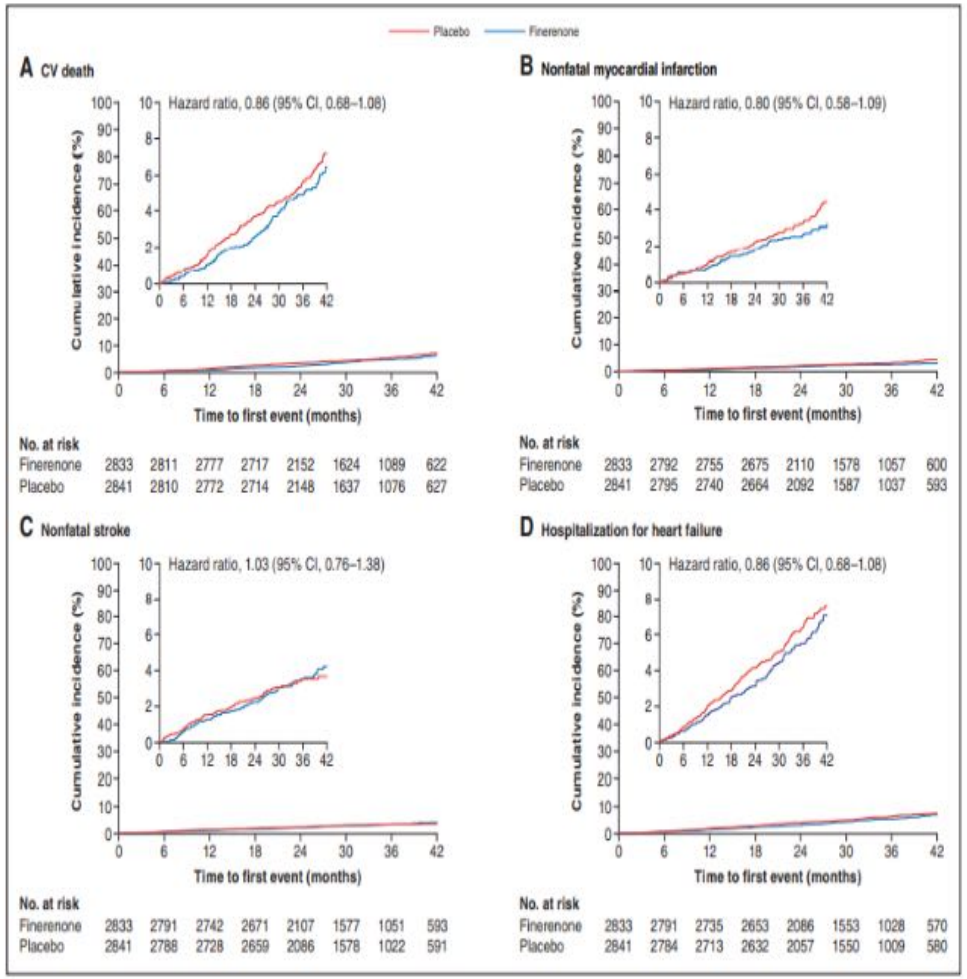
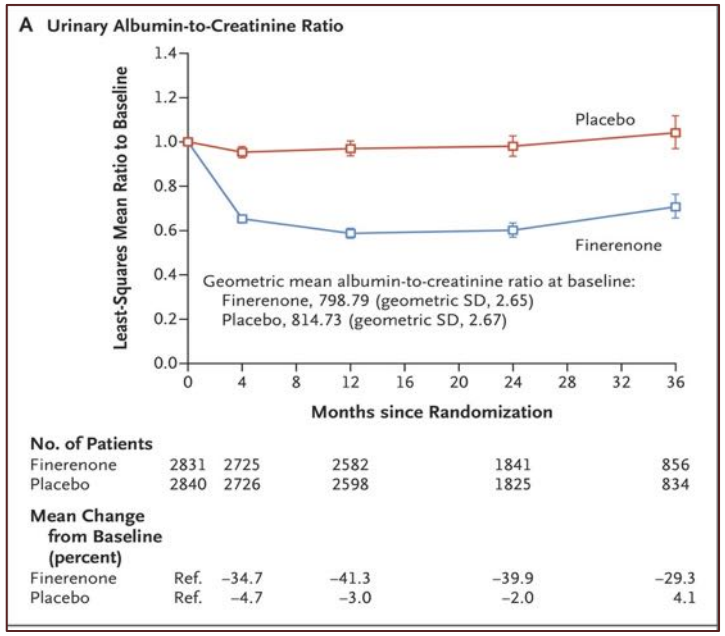
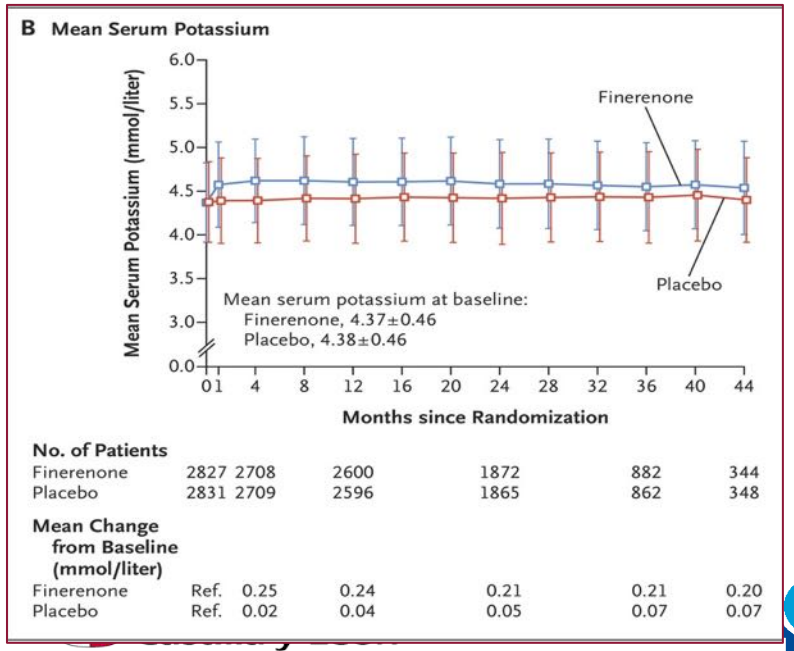
FIDELIO-CKD con o sin ECV











1º Eventos renales
- d 3,4% a 3 años
- NNT = 29

2º Eventos CV
- d 2,4% a 3 años
- NNT = 42

Reducción 22% de eventos global

Hiperpotasemia F vs P
- 18,3% vs 9,8%
- > 5,5 21%
- > 6 4,5%
- Suspensión del fármaco: 2,3%

Descenso de la **TAS** 2-3mmHg

No efectos sobre **HbA1c ni IMC**

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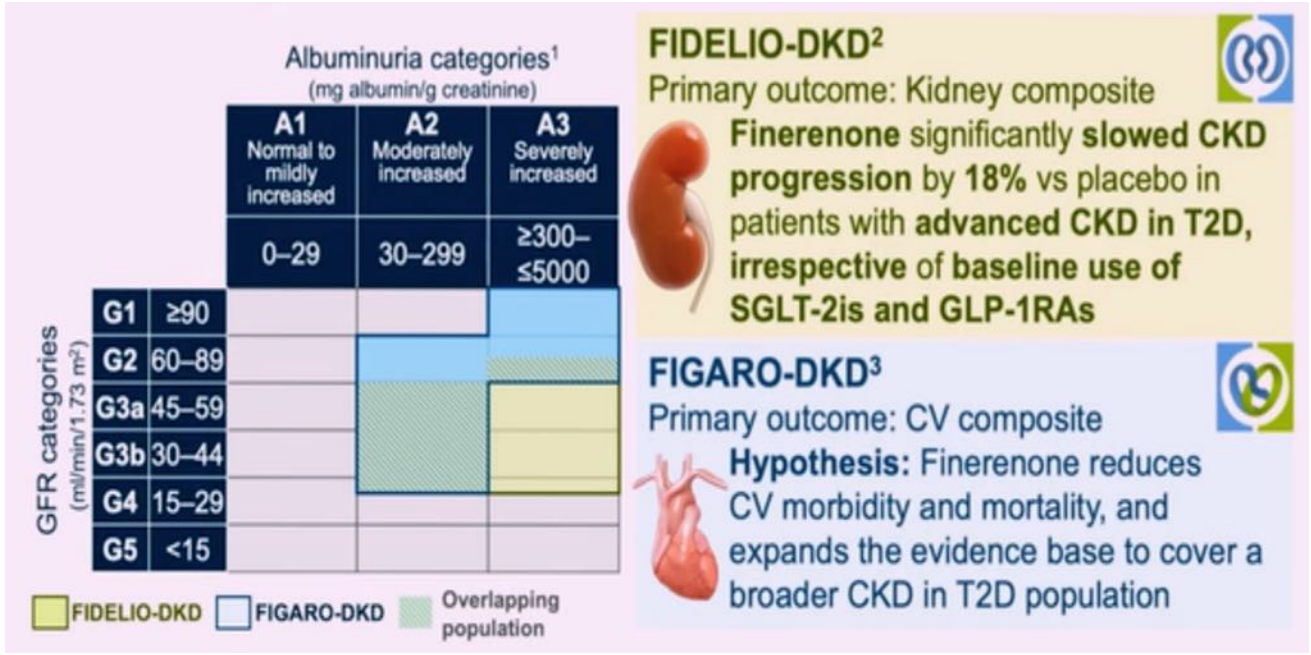
FIGARO-CKD

The NEW ENGLAND JOURNAL of MEDICINE

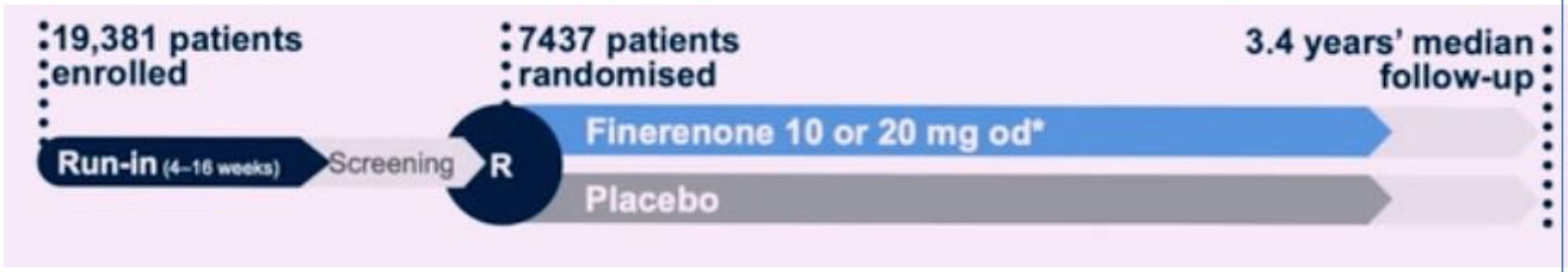
ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*



FIGARO-CKD

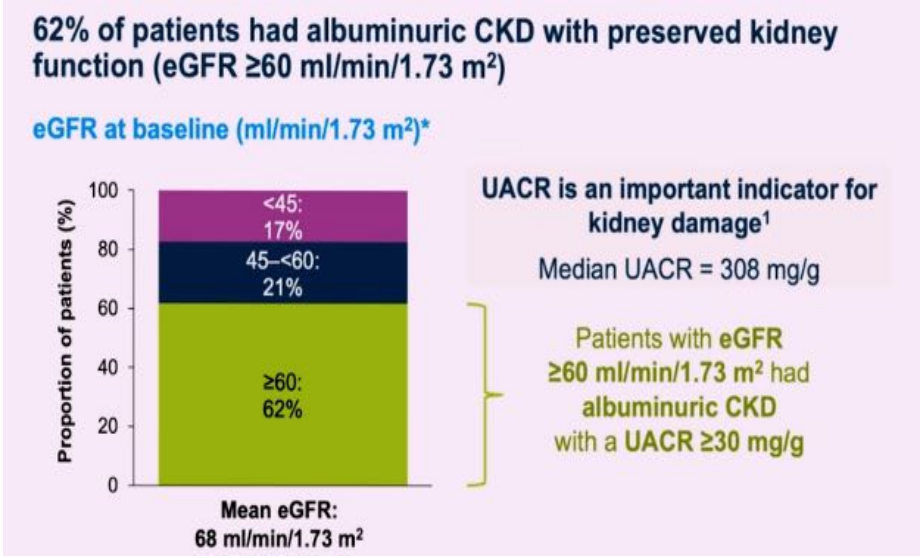


Endpoint primario: compuesto de
- Muerte CV
- IAM no fatal
- Ictus no fatal
- Hospitalización por IC

Endpoint secundario: compuesto de
- Descenso de >40% en FG
- Muerte por causa renal

- 18 años
- Alb/crea 30-300 con FG 30-90
- O Alb/crea 300-5000 con FG >60
- Máxima dosis de inhibidores SRAA

* K < 4.8
* Exclusión ICFEr NYHA 2-4



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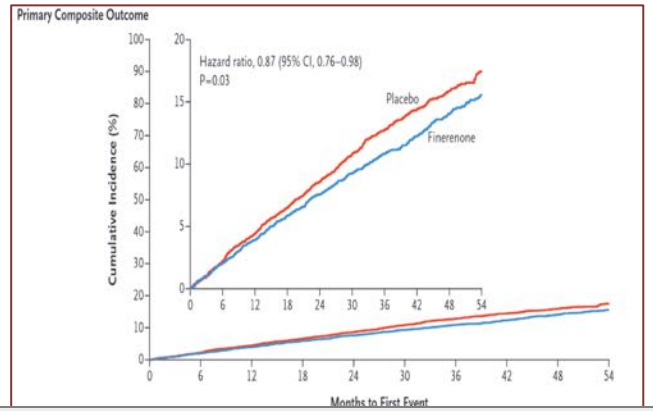
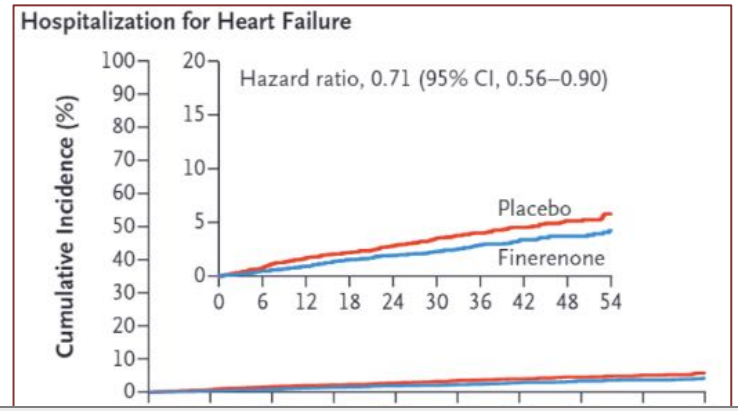
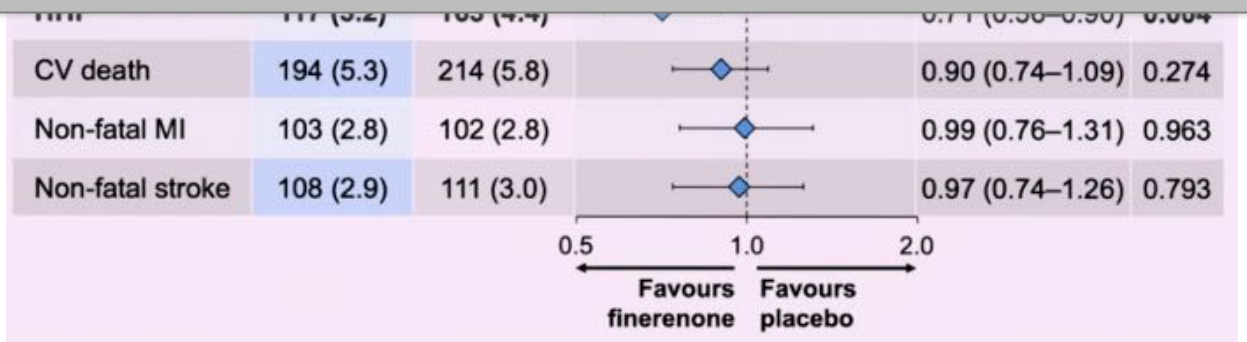




- ↓ morbi y mortalidad CV en un 13 % (reducción de hospitalizaciones por IC)
- Tendencia favorable en la progresión de enfermedad renal. No objetivo combinado del 40%
- ↓ enf renal terminal y un descenso sostenido de FG de ≥57% (p=0.041)
- Similar incidencia de efectos adversos que placebo



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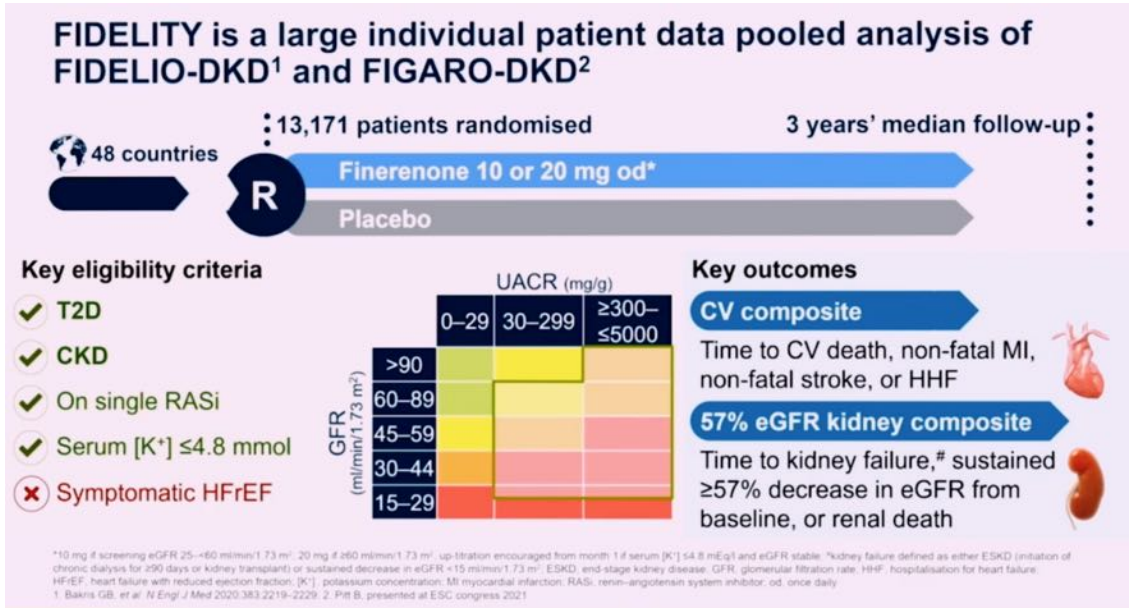
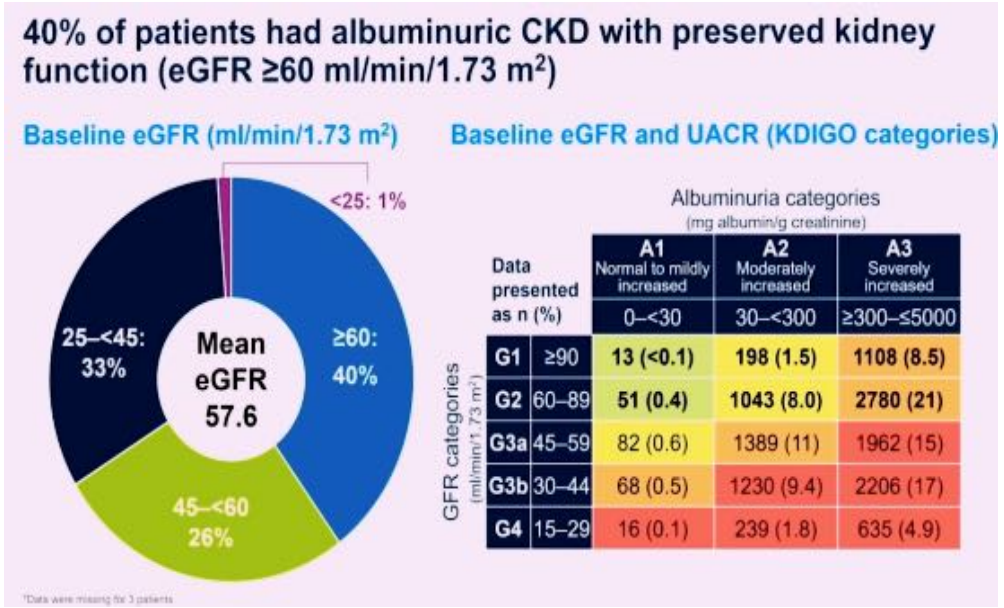
FIDELITY





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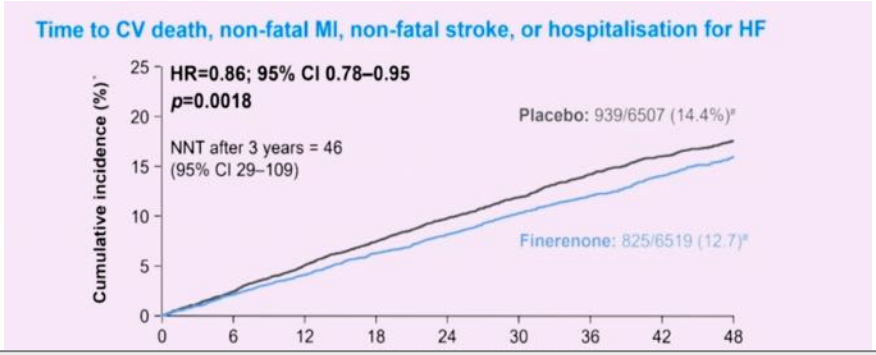
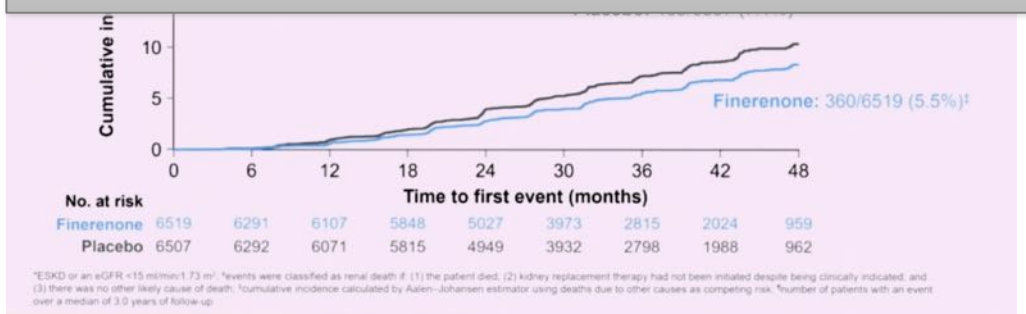
FIDELITY: Enpoints CV y renales



Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
Composite CV outcome	825 (12.7)	939 (14.4)	0.86 (0.76–0.95)	0.0018
HHF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.092
Non-fatal MI	173 (2.7)	189 (2.8)	0.91 (0.74–1.12)	0.36

En pacientes DM2 y ERC estadios I a IV o albuminuria ≧ 30mg/g:

- Redujo el riesgo de morbi-y mortalidad CV en un 14 % (reducción del 22% de hospitalizaciones por IC)
- Redujo el riesgo de progresión de enfermedad renal en un 23% (20% de ERT)
- Buen perfil de seguridad (Hiperpotasemia leve)



Kidney failure	254 (3.9)	297 (4.6)	(0.71–0.99)	0.039
ESKD#	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040‡
eGFR <15 ml/min/1.73 m²¶	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026‡
≥57% decrease in eGFR from baseline¶	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	–

≥57% decrease in eGFR is equivalent to doubling of serum creatinine

0.5 1.0 2.0

Favours finerenone Favours placebo

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13. Older Adults: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S195–S207 | https://doi.org/10.2337/dc22-S013

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

Recommendations

13.6 Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C less than 7.0–7.5% [53–58 mmol/mol]), while those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent glycemic goals (such as A1C less than 8.0% [64 mmol/mol]). **C**

- Objetivo glucémico 8% (en vez de8.5%)
- Valoración integral, especialmente la cognitiva
- Valorar el sobre-tratamiento de pacientes ancianos
- Monitorizar déficit de Vitamina B12 en uso prolongado de metformina
- Simplificar los regímenes insulínicos para evitar hipoglucemias

- En los pacientes mayores con DM2 que usan múltiples inyecciones diarias de INS y en pacientes con deterioro cognitivo o con limitaciones físicas. La MCG puede ser una opción.

- Se propone el uso del programa de ejercicio estructurado LIFE (Lifestyle Interventions and Independence for Elders Study) para paciente geriátrico donde el objetivo no será la pérdida de peso, sino la disminución de la fragilidad y el sedentarismo y la mejora en la funcionalidad.

- Se recomendan análogos de INS frente a NPH por menos hipoglucemias.

16. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S244–S253 | https://doi.org/10.2337/dc22-S016

Recommendations

16.1 Perform an A1C test on all patients with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital if not performed in the prior 3 months. **B**

16.2 Insulin should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations. **B**

- Iniciar ≧ 180 mg/dl
- Objetivo 140-180 mg/dl
- Plan al alta adaptado e individualizado

GLYCEMIC TARGETS IN HOSPITALIZED| PATIENTS

Recommendations

16.4 Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L) (checked on two occasions). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients. **A**

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

16.11 There should be a structured discharge plan tailored to the individual patient with diabetes. **B**

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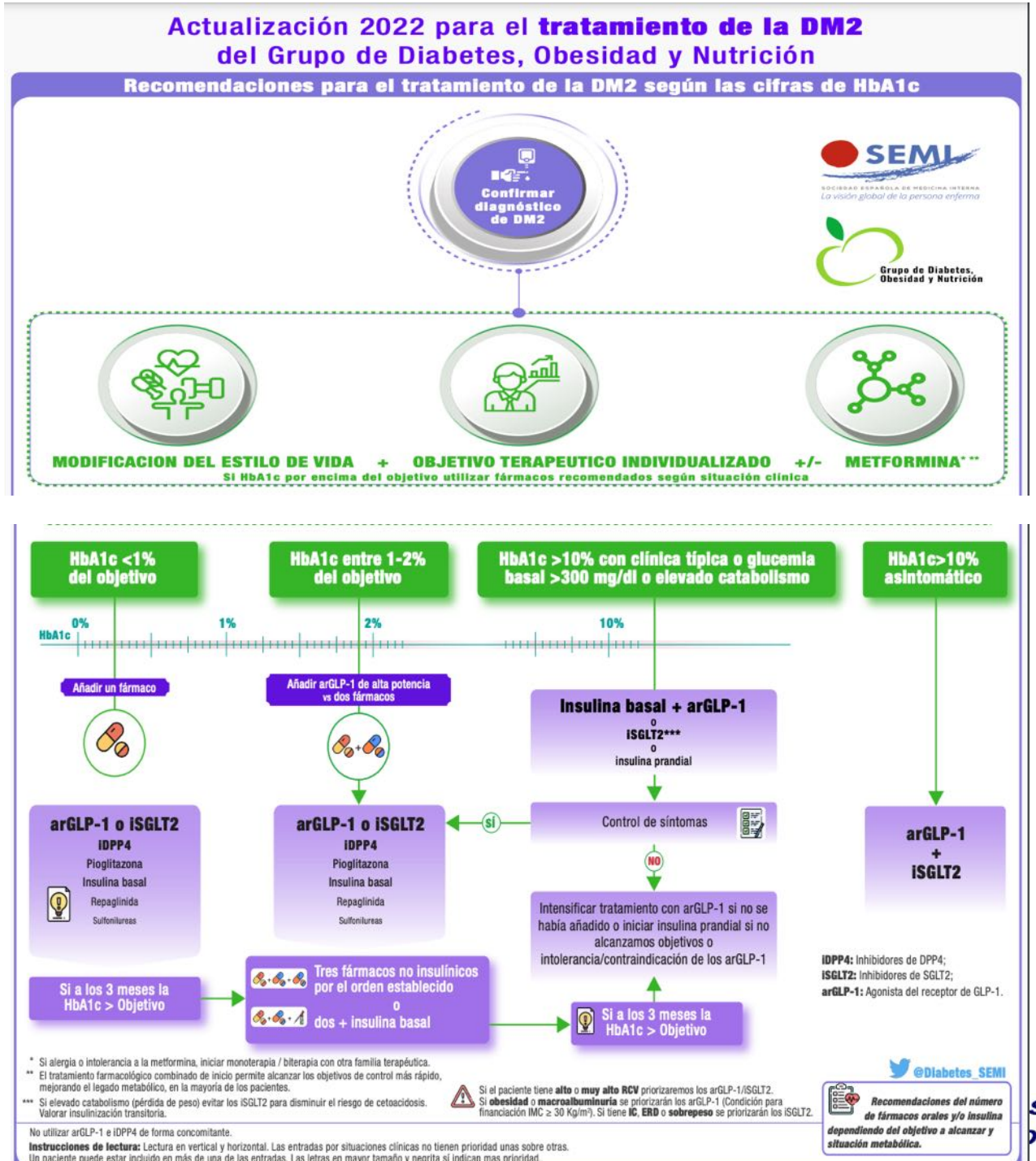
Arriba

D

I

Abajo



Si alto/muy alto RCV, IC y/o ERD se deben priorizar los arGLP-1 y/o iSGLT2 independientemente del objetivo de HbA1c y del uso de metformina.

Alto RCV / muy alto RCV	IC	ERD (FG ml/min/1,73 m² (CKD-EPI) 30)		Sobrepeso - Obesidad	>75 años		Minimizar la hipoglucemia	DM2 con más de 10 años de evolución
		FG ≥30	FG <30		Ausencia de fragilidad	Fragilidad y/o LET		
arGLP-1 sc/oral* y/o **iSGLT2** **iDPP4** Pioglitazona Insulinas basales (Glargina y Degludec)	**iSGLT2** **FEVI** ≤ 40% (empagliflozina/dapagliflozina) **FEVI** > 40% (empagliflozina) arGLP-1 sc/oral* iDPP4 Insulinas basales (Glargina y Degludec)	**iSGLT2** **arGLP-1** sc* iDPP4** Insulinas basales	**arGLP-1** sc* iSGLT2 iDPP4** Insulinas basales Pioglitazona Repaglinida	**arGLP-1*** **SEMANAL**: Semaglutida sc, Dulaglutida, Exenatide-LAR **DIARIO**: Semaglutida oral, Liraglutida **iSGLT2**	**arGLP-1** sc/oral * o **iSGLT2** **iDPP4** Insulina basal (Glargina U300 y Degludec)	**iDPP4** Insulina basal (Glargina U300 y Degludec)	**iDPP4** o **iSGLT2** o **arGLP-1** sc/oral * o **Pioglitazona** Insulina basal (Glargina U300 y Degludec)	**iSGLT2** **arGLP-1** sc/oral * Insulina basal Pioglitazona
a	b	c	d	e	f	g	h	i

Muy alto riesgo CV: ECV establecida, LOD severa (FG < 45 ml/min/1,73 m² independientemente del grado de albuminuria; FG 45-59 ml/min/1,73 m² y UACR 30-300 mg/g; macroalbuminuria (UACR > 300 mg/g) y/o enfermedad microvascular (microalbuminuria, retinopatía, neuropatía) y/o 3 o más FRCV.

Alto RCV: DM2 ≥ 10 años sin LOD y/o 1 FRCV adicional.

a Pacientes con alto o muy alto riesgo CV priorizar hipoglucemiantes con beneficio demostrado en la reducción de eventos CV. Los **arGLP-1 subcutáneos*** (semaglutida, liraglutida, dulaglutida) reducen eventos CV mayores (MACE) fundamentalmente por la prevención del ictus; **semaglutida oral*** demostró no inferioridad en MACE; liraglutida y semaglutida oral disminuyen la mortalidad total y CV. Los **iSGLT2** (empagliflozina y canagliflozina) reducen MACE; empagliflozina disminuye la mortalidad total y CV; dapagliflozina y ertugliflozina demostraron no inferioridad en MACE. La **pioglitazona** reduce MACE, pero como objetivo secundario. Los **iDPP4** demuestran seguridad CV. Recomendamos utilizar insulinas basales con seguridad CV demostrada (glargina y degludec).

b Recomendamos priorizar un **iSGLT2** en todos los pacientes con DM2 e IC o riesgo de desarrollarla. Todos los **iSGLT2** han demostrado reducción de hospitalizaciones por IC. En pacientes con **IC** y FEVI ≤ 40%, empagliflozina y dapagliflozina son los **iSGLT2** de elección. En pacientes con IC y FEVI > 40 % empagliflozina es el **iSGLT2** de elección. En pacientes sin IC establecida recomendamos cualquier **iSGLT2**.

Los **arGLP-1**, los **iDPP4**, excepto saxagliptina, y las **insulinas basales** (glargina y degludec) han demostrado seguridad respecto a las hIC.

c **ERD:** Definida por deterioro del FG y/o la presencia de albuminuria.

Los **iSGLT2** previenen el deterioro del FG y la progresión de albuminuria. Ertugliflozina no ha demostrado beneficio renal.

Recomendamos liraglutida, semaglutida sc y dulaglutida si UACR > 300 mg/g.

Los **iDPP4** solo deberían utilizarse cuando los hipoglucemiantes con beneficio renal están contraindicados o existe intolerancia.

Metformina precisa reducción de dosis (FG < 45 ml/min/1,73m², dosis máxima de 1000 mg/d).

d Los **arGLP-1** (semaglutida, dulaglutida y liraglutida) están indicados hasta FG >15 ml/min/1,73m².

Los **iSGLT2** están indicados según FG: Dapagliflozina >25ml/min/1,73 m², Empagliflozina >30 ml/min/1,73 m², Canagliflozina 100 >30 ml/min/1,73 m² y continuar si FG <30 ml/min/1,73 m² si estaba previamente en tratamiento.

Si **IC** y **ERD** : Dapagliflozina >25 ml/min/1,73 m², Empagliflozina >20 ml/min/1,73 m².

La metformina está contraindicada. Pioglitazona asocia riesgo de retención hidrosalina.

e Alcanzar dosis máximas de **arGLP-1**, si es necesario en combinación con **iSGLT2**. Los **iDPP4** tienen efecto ponderal neutro. La Pioglitazona, las SU y las insulinas inducen ganancia ponderal.

f No debe de haber limitación en la estrategia terapéutica basada solo en la edad. Los pacientes > 75 años con IC-FEVI ≤40% tratados con dapagliflozina o empagliflozina tienen un beneficio adicional en la hIC y en la protección renal.

g Minimizar el riesgo de hipoglucemia. Ver (h).

h Se priorizarán las insulinas con menor riesgo de hipoglucemia: degludec y glargina U300 < glargina U100 y detemir < NPH y mezclas.

i Los **iSGLT2** y los **arGLP-1** han demostrado efectos beneficiosos en pacientes con DM2 evolucionada. Valorar eficacia de los **iDPP4** en pacientes con baja reserva insulínica. Plantear Insulina prandial si no se alcanza el objetivo en 3 meses.

* Solo financiados para pacientes con IMC ≥ 30 Kg/m².

** Reducción de dosis según FG, excepto linagliptina.

@Diabetes_SEMI

arGLP-1: Agonista del receptor de GLP-1; **CV:** Cardiovascular; **DM2:** Diabetes mellitus tipo 2; **ECV:** Enfermedad cardiovascular; **ERD:** Enfermedad renal diabética; **FEVI:** Fracción de eyección del ventrículo izquierdo; **FG:** Filtrado glomerular; **FRCV:** Factores de riesgo cardiovascular; **hIC:** Hospitalización por insuficiencia cardíaca; **IC:** Insuficiencia cardiaca; **iDPP4:** Inhibidores de la DPP4; **IMC:** Indice de masa corporal; **iSGLT2:** Inhibidores del SGLT2; **LET:** Limitación del esfuerzo terapéutico; **LOD:** Lesión de órgano diana; **MACE:** Eventos cardiovasculares mayores; **SU:** Sulfonilurea; **UACR:** Ratio albúmina/creatinina.

Reevaluación periódica de objetivos, individualizar tratamientos, desprescribir las terapias ineficaces y evitar la inercia terapéutica. En pacientes con tratamientos instaurados previamente, reevaluar si la combinación es la más adecuada. Se recomienda realizar un péptido C en pacientes con diabetes evolucionada y/o cuando se sospeche insulinopenia antes de prescribir arGLP1 ó iSGLT2.

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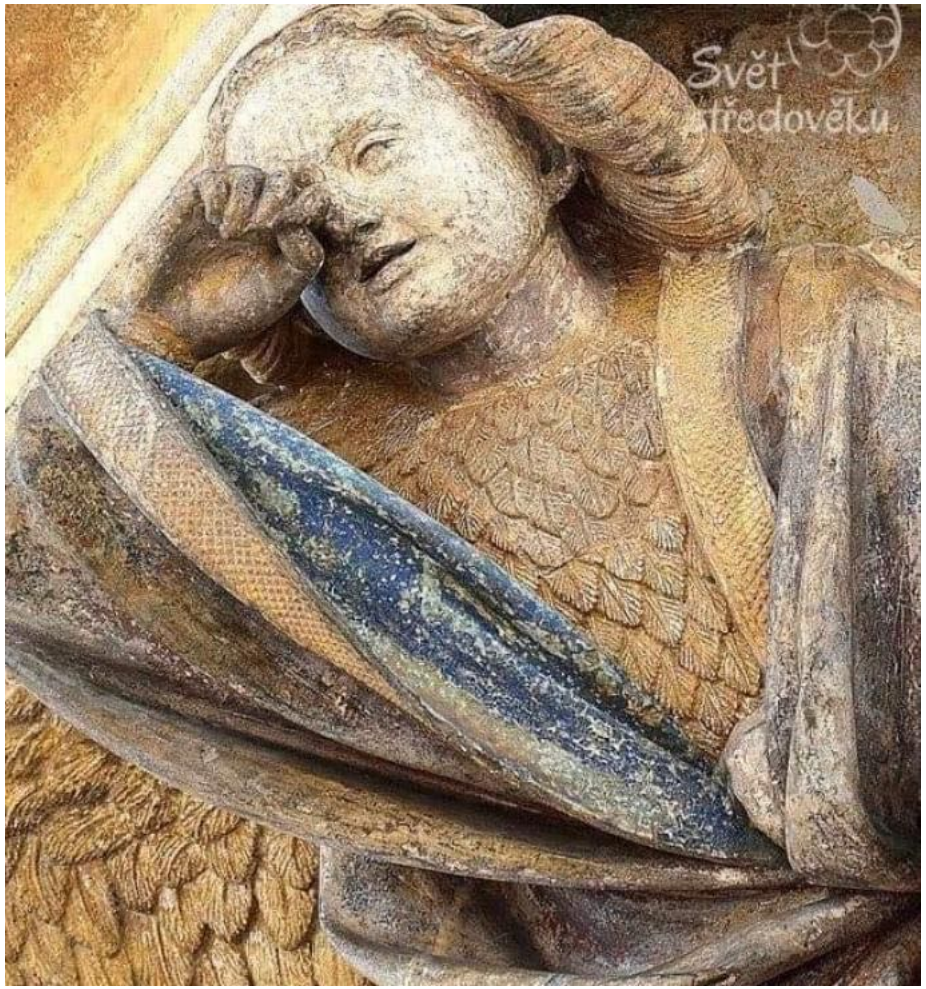
Svět
středověku