ACTUALITZACIÓ EN FACTORS DE RISC CARDIOVASCULAR: NOVES OPCIONS TERAPÈUTIQUES I INDICACIONS

Diabetis mellitus tipus 2

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CONFLICTO DE INTERES

☐ 1. No tengo ninguna relación con las entidades productoras, comercialización, reventa o distribución de bienes de atención médica o servicios consumidos por o utilizados en los pacientes.

☒ 2. A lo largo de los últimos 2 años, he mantenido relación comercial entendiendo como tal cualquier actividad profesional con contraprestación económica o con contraprestaciones en especie, con las siguientes empresas relacionadas con el mundo sanitario.

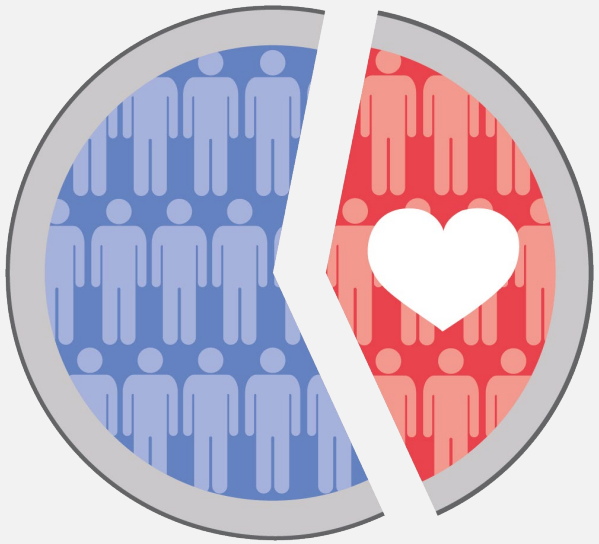
Tipo de Conflicto	***Detalles del posible conflicto de intereses***
Proyectos de investigación/Participación en ensayos clínicos	Novo Nordisk, Sanofi, Almirall, Esteve, Boehringer Ingelheim, Amgen, Menarini
Consultoría	Boehringer ingelheim, Novo Nordisk, Sanofi, Almirall, Merck Sharp & Dohme, Amgen, Pfizer, Amarin, Daiichi Sankyo
Pago por conferencias, por trabajos o informes	AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Almirall, Novartis, Esteve, Merck Sharp & Dohme, Amgen, Menarini, Gilead, Amarin, Daiichi Sankyo
Invitaciones a congresos, cursos, u actos educativos organizados por la industria, etc.	AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Almirall, Novartis, Esteve, Merck Sharp & Dohme, Amgen, Menarini
Cualquier otro tipo de relación económica	

.

AGENDA

- **Escenario clínico:** situación frecuente y resultados deficientes
- **Tratamiento por "el beneficio" e "individualizado" de la DM2.** ¿Cómo mejorar?
- **Inicio seguro fármacos hipoglucemiantes cardioprotectores**

PACIENTES CON DM2
RELEVANCIA ECV



≈1/3 pacientes con DM2 tiene enfermedad CV

La enfermedad CV en DM2 se asocia con:

- Inicio más temprano que en pacientes sin diabetes
- Peores resultados que en pacientes sin diabetes
- Costos elevados

Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83

Booth GL et al. Lancet 2006;368:29, Zhang XH et al. J Cardiothorac Vasc Anesth 2011;25:288
Zhu J et al. Diabetes Technol Ther 2016;18:62, Hex N et al. Diabet Med 2012;29:855

LA ECV SE ASOCIA A COSTOS ELEVADOS Y ES LA PRINCIPAL CAUSA DE MUERTE EN DM2

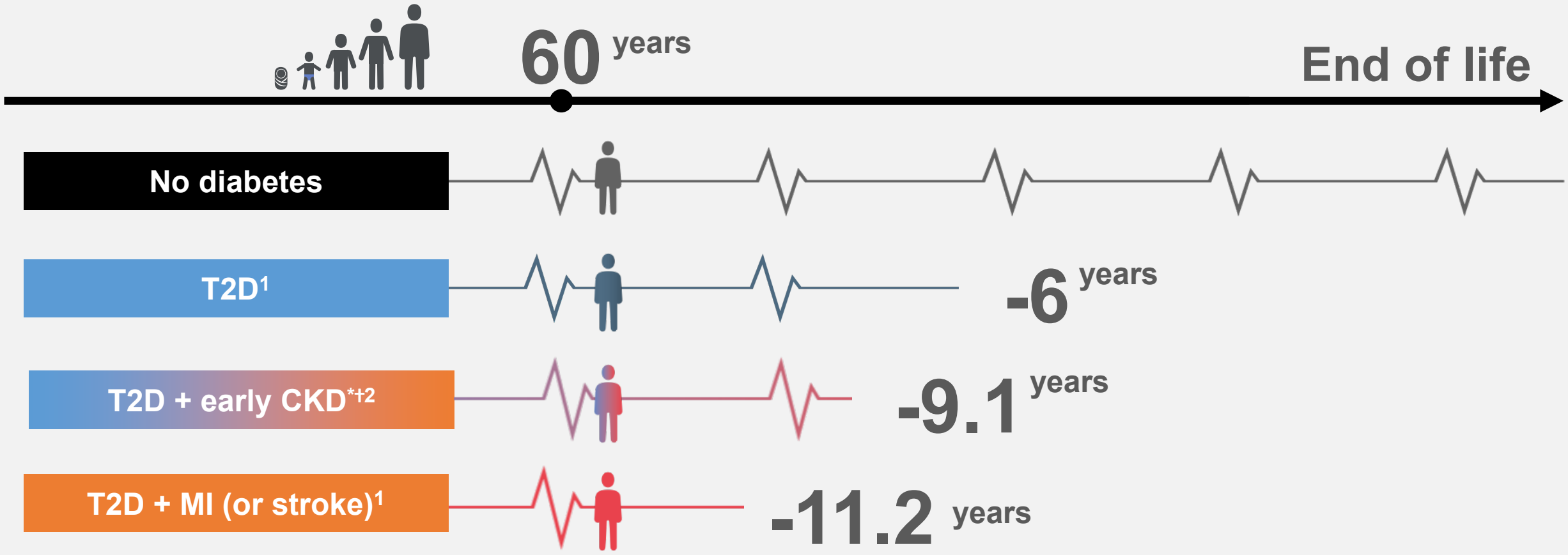
La ECV contribuye hasta **49 % costes directos** del tratamiento de la DM2

Einarson TR *et al. Value Health* 2018;21:881

Aproximadamente **1/2 de los pacientes con DM2 mueren por ECV**

Einarson TR et al. Cardiovas Diabetol 2018;17:83

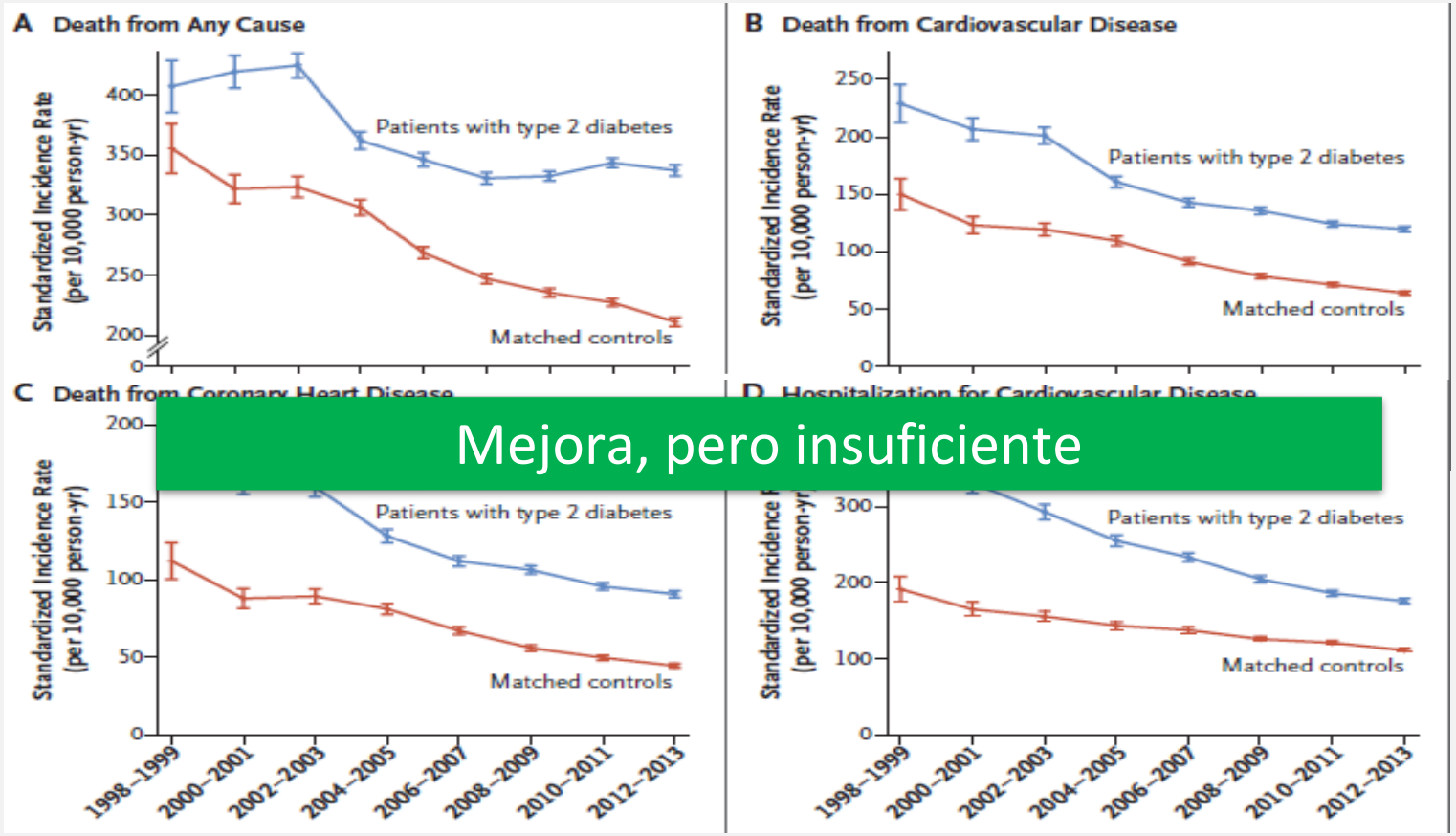
LA ESPERANZA DE VIDA SE REDUCE EN 11,2 AÑOS EN PACIENTES CON DIABETES Y ENFERMEDAD CV



*A 60-year-old man with diabetes and CVD or CKD dies, on average, 9–12 years earlier than a man without diabetes and CVD or CKD[1,2]; †CKD stages 1–3
CKD, chronic kidney disease; CRM, cardio-renal-metabolic; CVD, cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes
1. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52; 2. Wen C *et al. Kidney Int* 2017;92:388

A PESAR DE LA MEJORA DEL PRONÓSTICO CON LA MEJORA DE LA ATENCIÓN, LOS PACIENTES CON DM2 SIGUEN TENIENDO MAYOR MORTALIDAD CV

Registro Nacional Sueco de Diabetes desde 1998 hasta 2012 y seguimiento hasta 2014

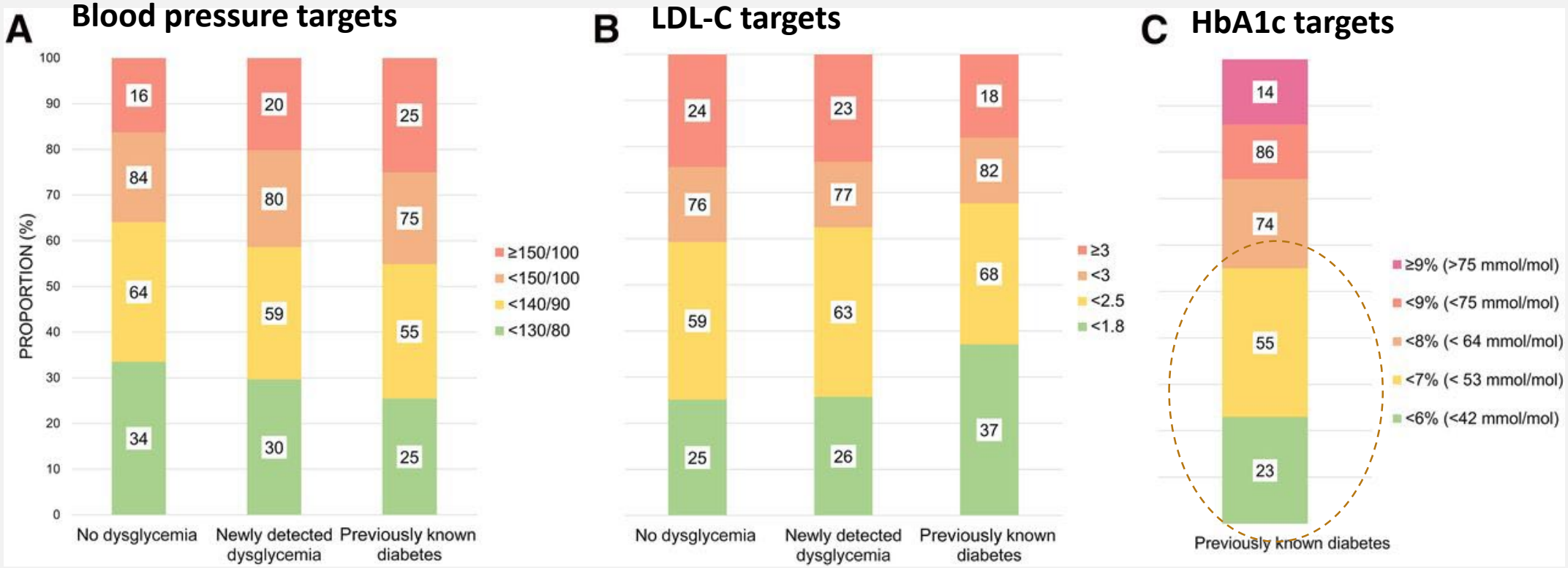


Mejora, pero insuficiente

Rawshani A. *et al.* N Engl J Med 2017; 376:1407-1418.

Control insuficiente de pacientes con DM2 y ECV

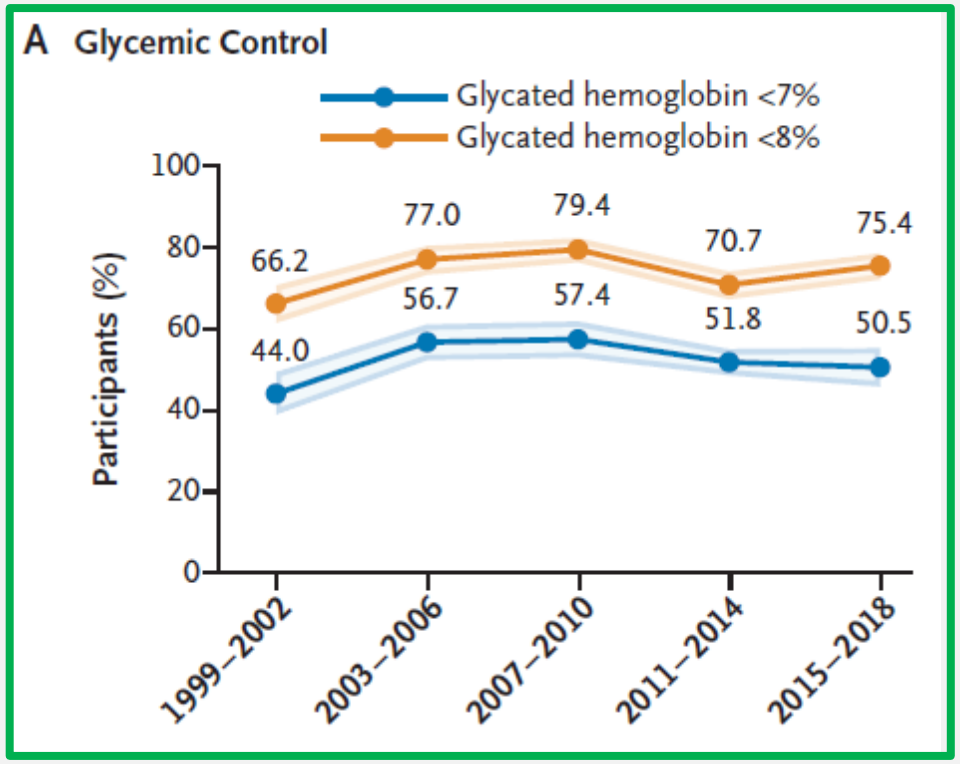
EUROASPIRE V (EAV) survey: Consecución de objetivos de control

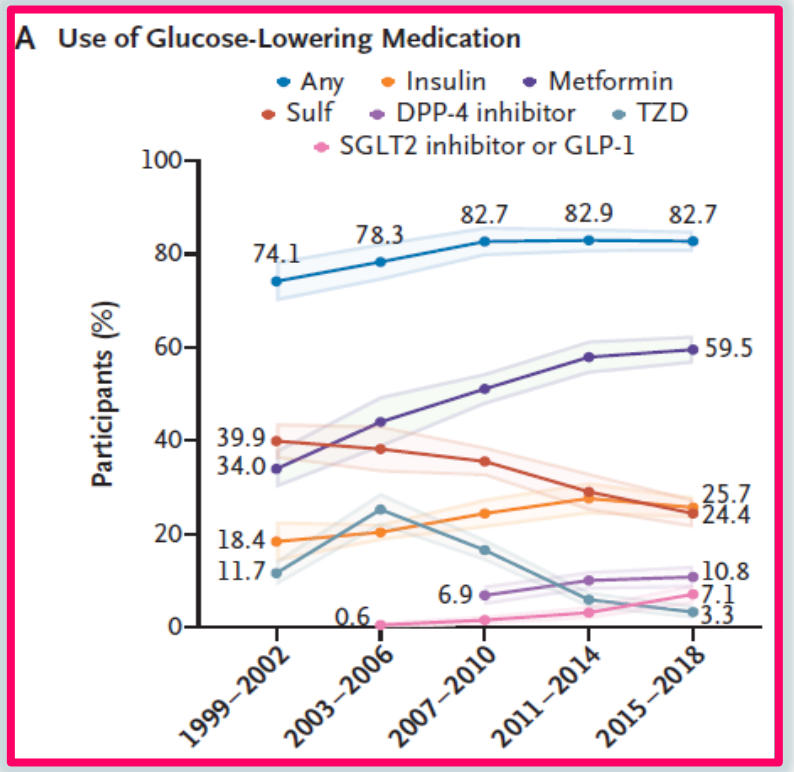


Giulia Ferrannini et al. Dia Care 2020;43:726-733

NO MEJORA/DETERIORO CONTROL GLUCEMICO

Adult NHANES Participants with Diagnosed Diabetes,1999–2002 to 2015–2018.

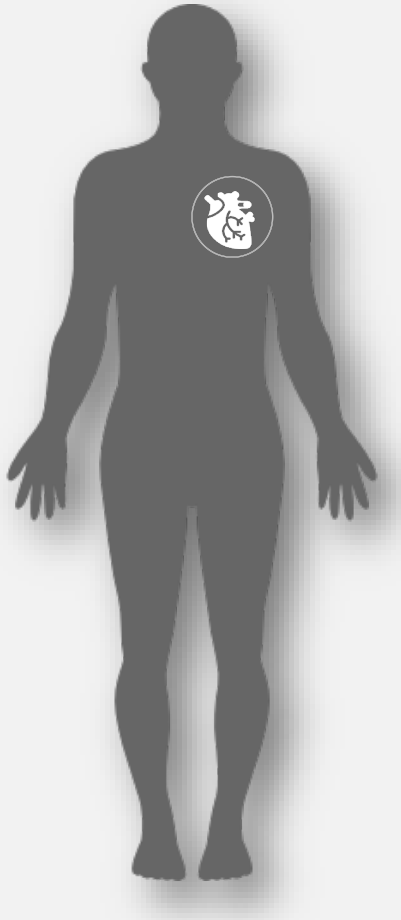




Necesidad de mejorar estrategias de tratamiento hiperglucemia

Fang M et al. N Engl J Med 2021;384:2219-2228

LA CARDIOPROTECCIÓN ES PRIORITARIA PARA LOS PACIENTES CON DM2



- *La mayoría de pacientes DM2 deben considerarse de **muy alto/alto riesgo CV**…*
- La ECV existe como **un continuo**
- *Necesidad enfoque **multifactorial precoz** dirigido a controlar FRCV*

PACIENTES CON DM2
LA MAYORÍA RCV ALTO/MUY ALTO

Muy alto riesgo	Pacientes con DM **y** ECV establecida • Lesión en otro órgano diana (LOD)† • ≥ 3 factores de riesgo importantes‡ • DM1 de aparición temprana o > 20 años)
Alto riesgo	Pacientes con DM ≥ 10 años duración sin LOD más cualquier otro FR adicional
Riesgo moderado	Pacientes con DM1 < 35 años o DM2 < 50 a y DM < 10 años duración, sin FR

ESC 2019: Eur Heart J. 2020; 41:111-88.

SIDIAP database in Catalonia (***N* = 373 185**)

Riesgo CV

- Muy alto: 53,4%
- Alto: 39,6%
- Moderado 7%

> 90%

Cebrián-Cuenca AM, et al. Eur J Prev Cardiol. 2022;28:e32-4.

GALIPDIA study (**274 pacientes DM2**)

Riesgo CV

- Muy alto: 72,1%
- Alto: 26,1%
- Moderado 1,8%

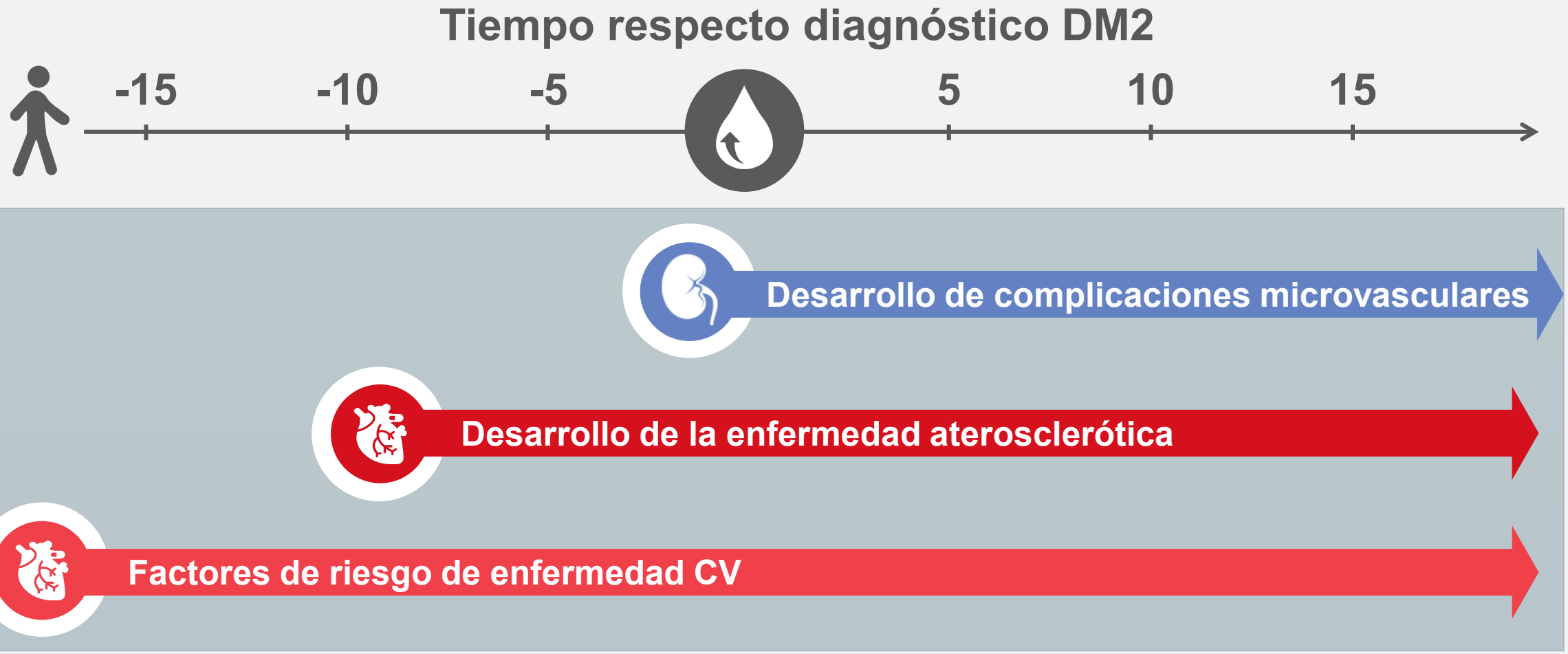
> 90%

R.Villar-Taibo et al. Endocrinología, Diabetes y Nutrición,https://doi.org/10.1016/j.endinu.2022.06.009Endinu

11

PREVENCIÓN ECV EN LA DM2

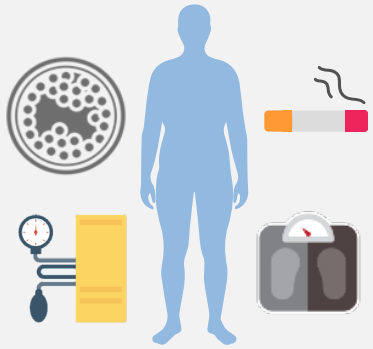
LA ECV EXISTE COMO UN CONTINUO DESDE ANTES DEL DIAGNÓSTICO



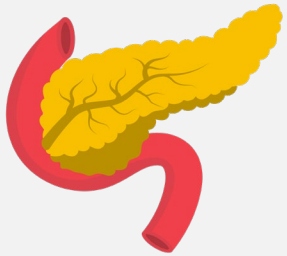
Adapted from Ramlo-Halsted BA & Edelman SV. *Prim Care* 1999;26:771; Nathan DM. *N Engl J Med* 2002;347:1342; UKPDS Group. *Diabetes* 1995;44:1249

El paciente con DM2 temprana

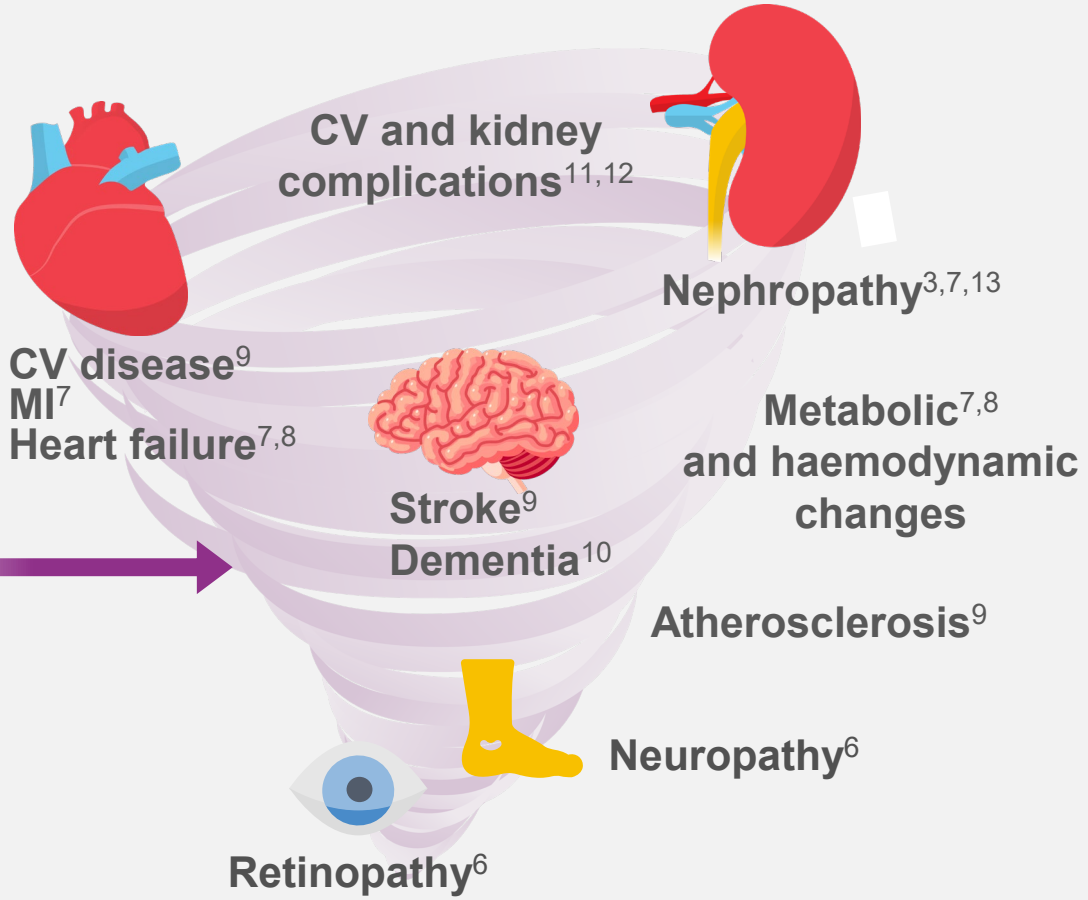
Mayor riesgo de complicaciones debido a alteraciones metabólicas y factores de riesgo interconectados[1,10]



- Overweight/obese
- Hypertension
- Dyslipidaemia
- Smoking[1–3]

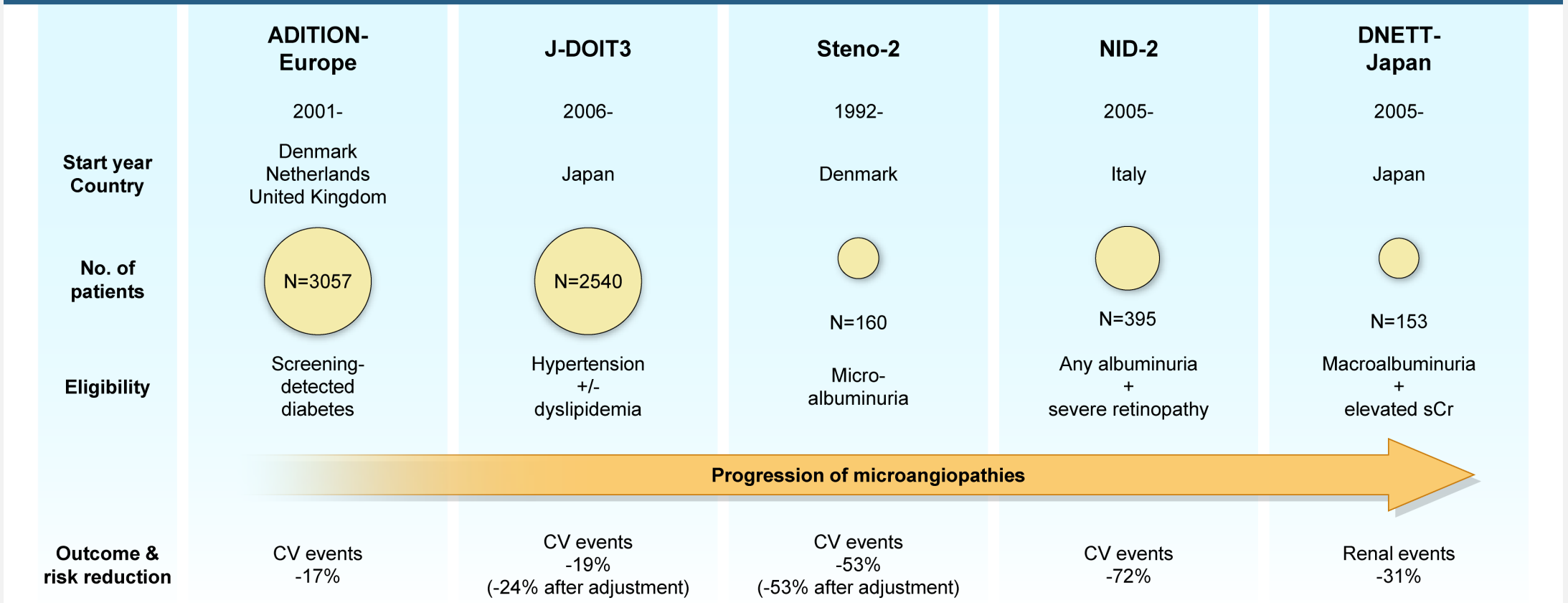


- β-cell dysfunction
- Insulin resistance
- Hyperglycaemia[4,5]



1. Leon BM & Maddox TM. *World J Diabetes* 2015;6:1246; 2. Sposito AC *et al. Cardiovasc Diabetol* 2018;17:157; 3. Cade WT. *Phys Ther* 2008;88:1322; 4. Marwick TH *et al. J Am Coll Cardiol* 2018;71:339; 5. DeFronzo RA *et al. Diabetes* 2009;58:773; 6. Fowler MJ. *Clinical Diabetes* 2011;29:116; 7. Song MK *et al. J Diabetes Res* 2014;2014:e313718; 8. Bugger H & Abel ED. *Diabetologia* 2014;57:660; 9. Galicia-Garcia U *et al. Int J Mol Sci* 2020;21:6275; 10. Hayden MR *et al. Cardiorenal Med* 2013;3:265; 11. Ronco C *et al. J Am Coll Cardiol* 2008;52:1527; 12. McCullough PA *et al. Contrib Nephrol* 2013;182:82; 13. Chen Y *et al. Kidney Dis* 2020;6:225

Intensified multifactorial intervention in patients with type 2 diabetes

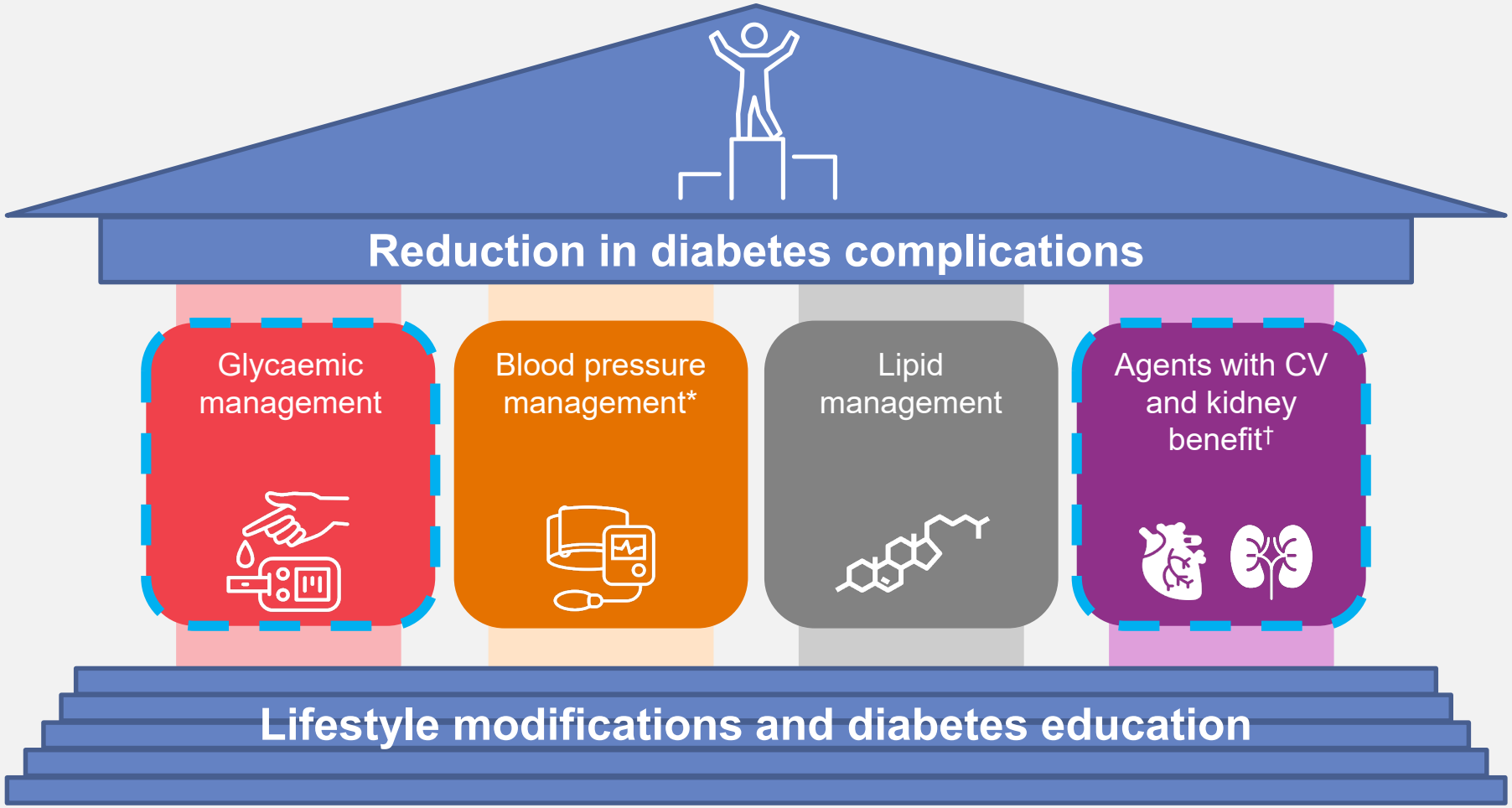


Conclusion

Intensified multifactorial intervention for major risk factors is expected to reduce the risk of not only macroangiopathies but also microangiopathies in patients with type 2 diabetes.

Diabetes & Metabolism Journal 2023;47(2):185-197. DOI: https://doi.org/10.4093/dmj.2022.0325

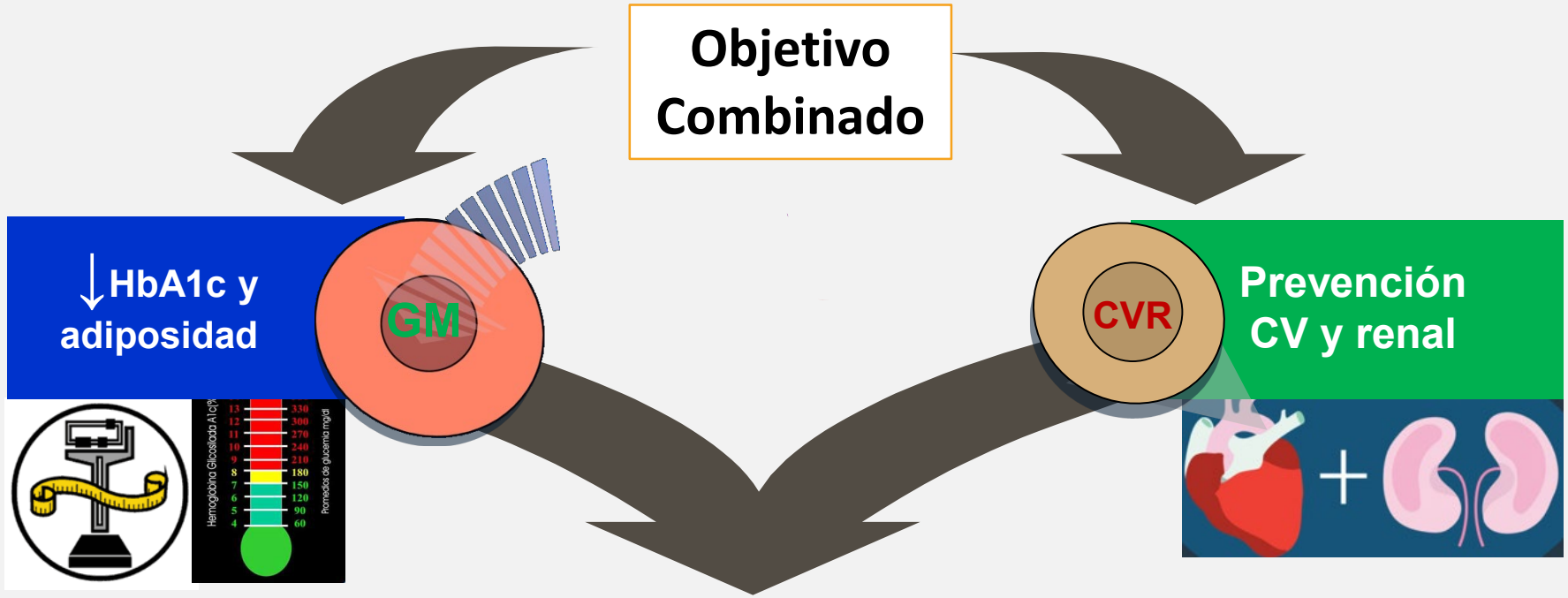
ADA 2023 STANDARDS OF MEDICAL CARE RECOMMENDS A MULTIFACTORIAL APPROACH TO REDUCTION IN THE RISK OF DIABETES COMPLICATIONS



*Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (120–129/<80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Hypertension is defined as ≥130/≥80 mmHg based on ≥2 measurements obtained on ≥2 occasions. Individuals with blood pressure ≥180/110 mmHg and CV disease could be diagnosed with hypertension at a single visit. All hypertensive people with diabetes should monitor their blood pressure at home, targets should be individualised through a shared decision-making process that addresses CV risk, potential adverse effects of antihypertensive medications and person preferences; †Risk reduction interventions to be applied as individually appropriate

American Diabetes Association. *Diabetes Care* 2023;46:S1

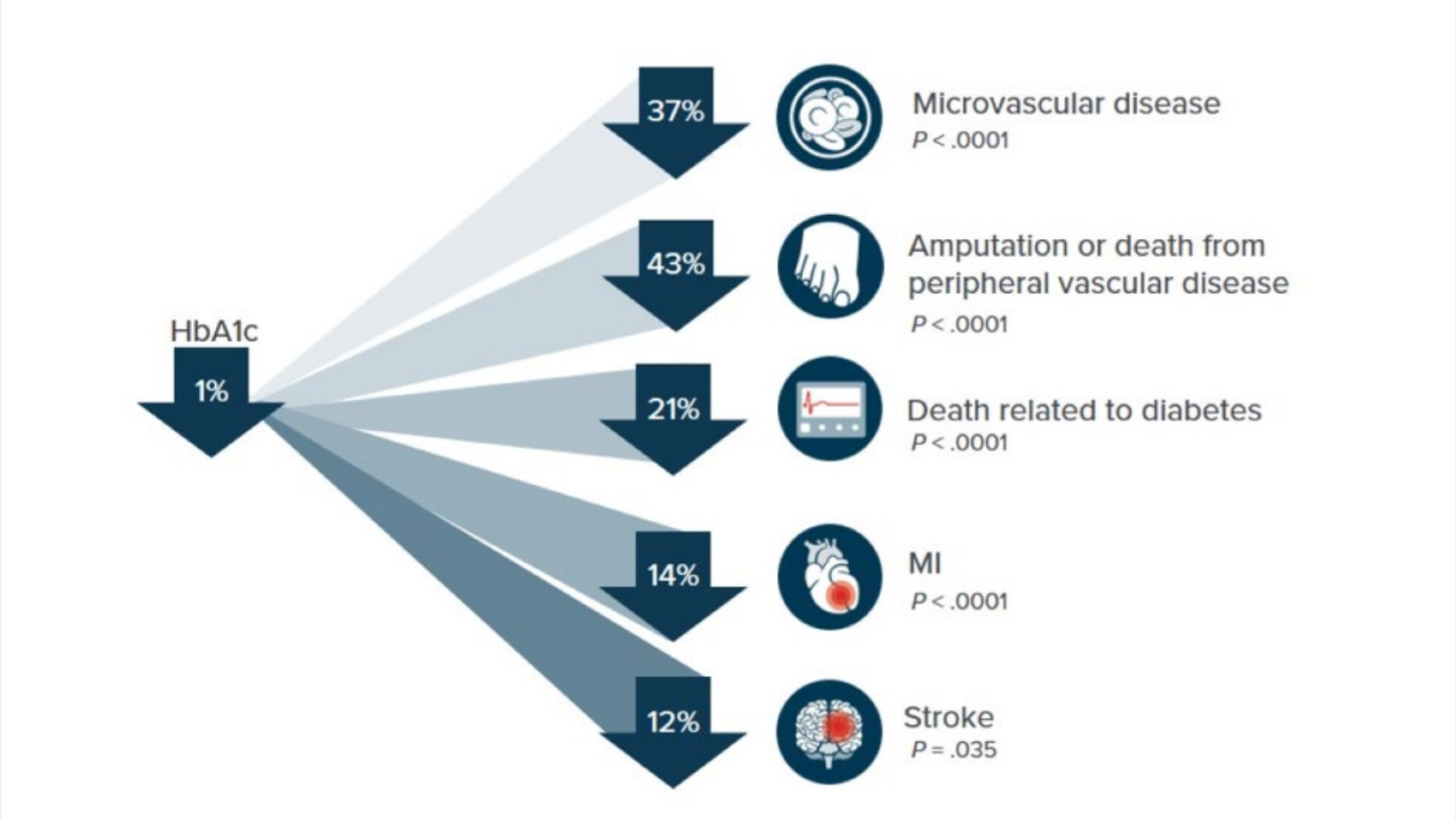
TERAPIA EN DM2: TRATAMIENTO POR EL *BENEFICIO* CLÍNICO



Tratamiento combinado inicial

-Beneficios micro y macrovasculares
-Reduce inercia terapéutica
-Efecto legado

BENEFICIOS DE REDUCIR HbA1c. UKPDS 35

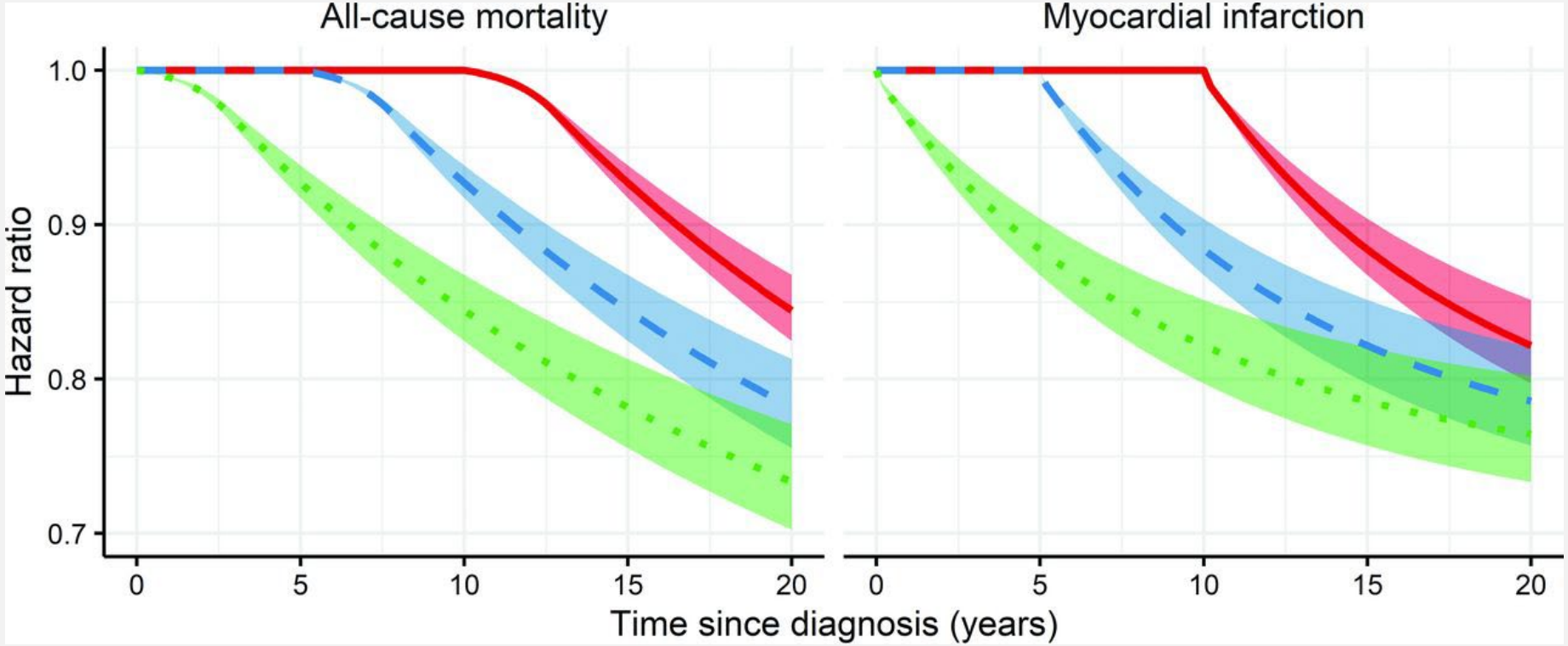


Stratton IM, et al. BMJ. 2000;321:405-412.

EVIDENCIA PARA INICIO PRECOZ DE LA TERAPIA.

Historical HbA_{1c} Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88

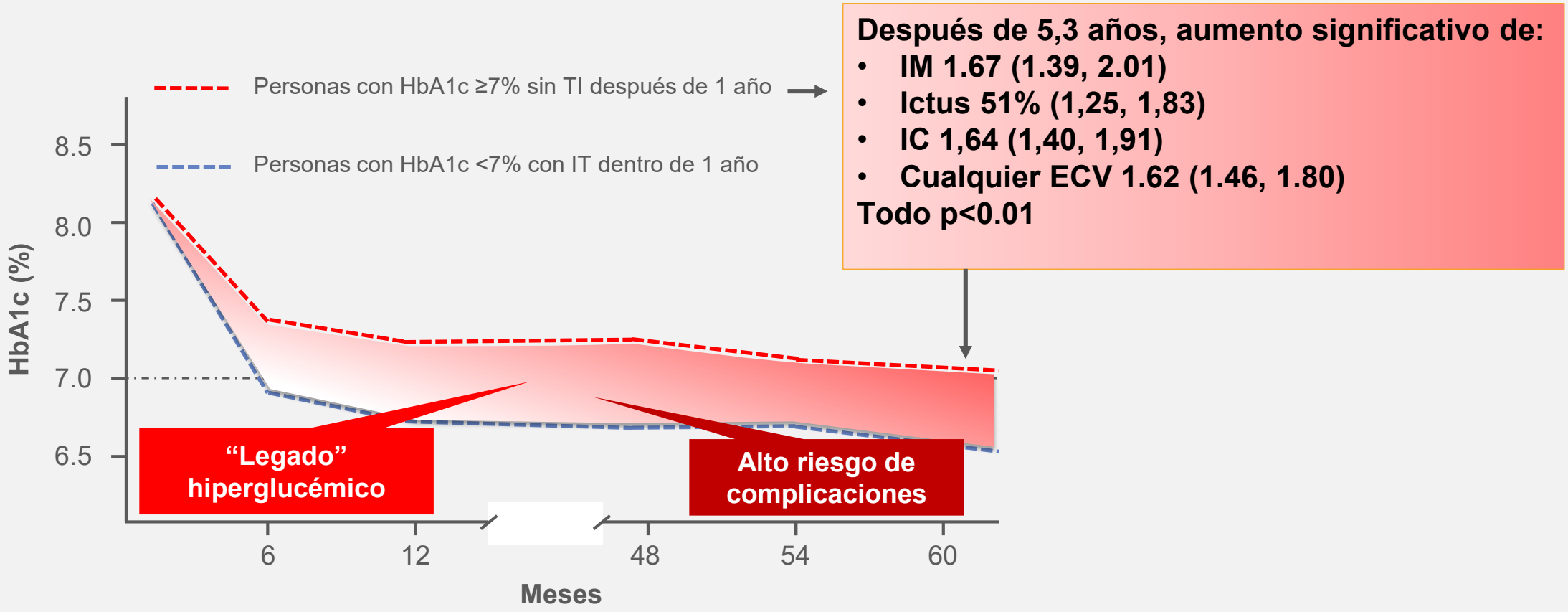
Time-dependent HRs from 0 to 20 years after diagnosis of type 2 diabetes



Diabetes Care. 2021;44(10):2231-2237. doi:10.2337/dc20-2439

DELAY IN T2D TREATMENT INTENSIFICATION BY 1 YEAR IN ADDITION TO POOR GLYCAEMIC CONTROL SIGNIFICANTLY INCREASED THE RISK OF HEART FAILURE, MI AND STROKE[1,2]

Estudio de cohorte retrospectivo de 105 477 personas con DT2 en el Reino Unido entre 1990 y 2012



Después de 5,3 años, aumento significativo de:

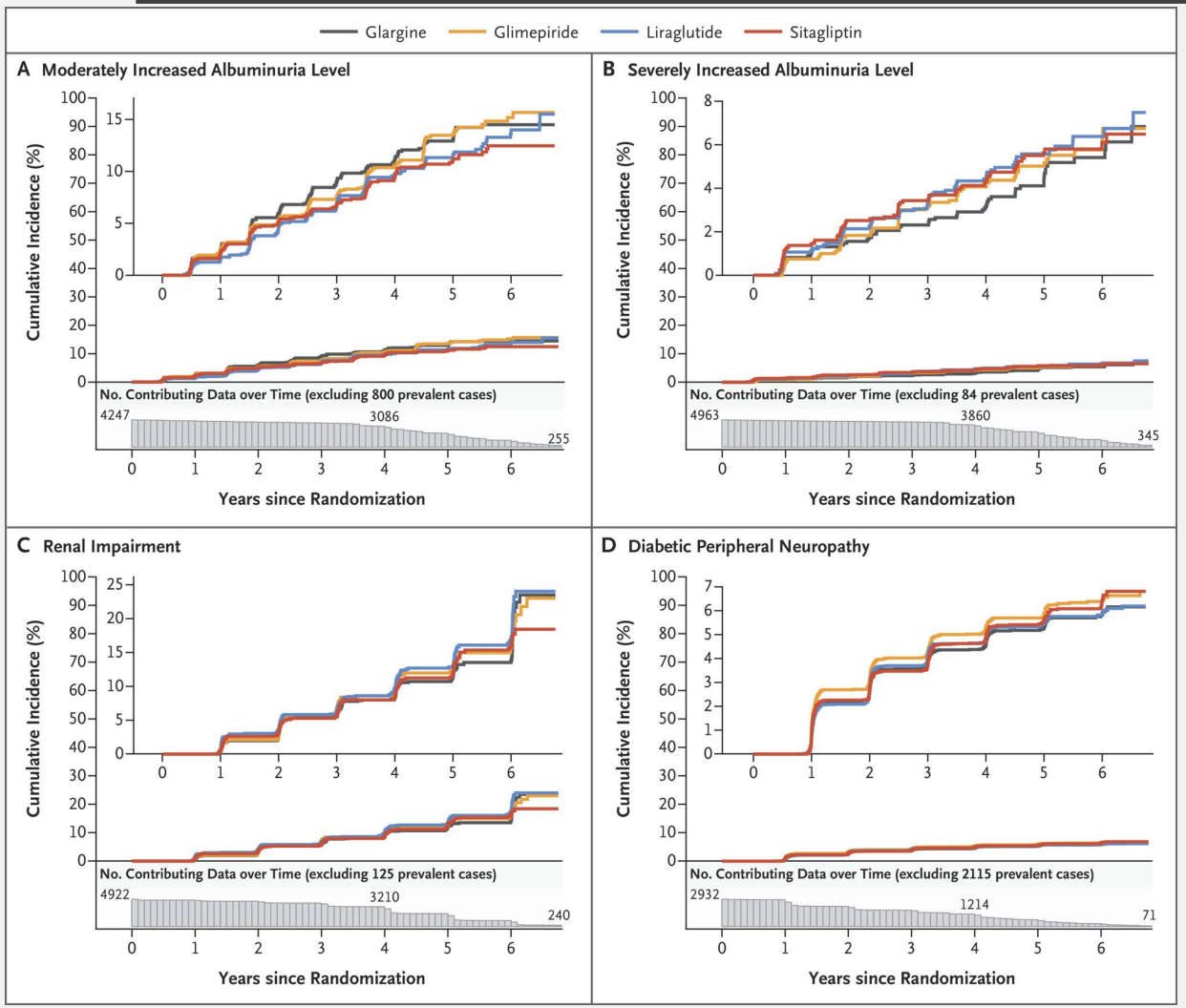
- **IM 1.67 (1.39, 2.01)**
- **Ictus 51% (1,25, 1,83)**
- **IC 1,64 (1,40, 1,91)**
- **Cualquier ECV 1.62 (1.46, 1.80)**

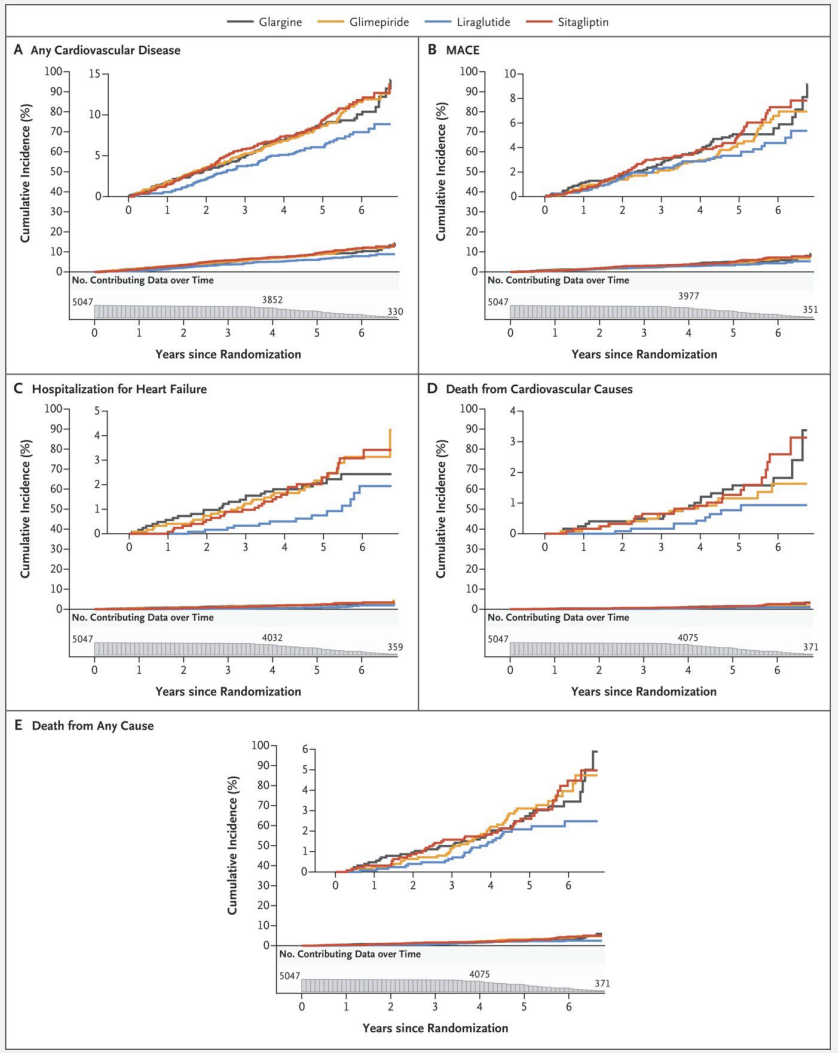
Todo p<0.01

Values in parentheses are 95% CI. The reference group was those with a time to treatment intensification <12 months and HbA1c <7 or 7.5% (<53 or 58 mmol/mol)
CVE, macrovascular event; HbA1c, glycated haemoglobin; IT, treatment intensification

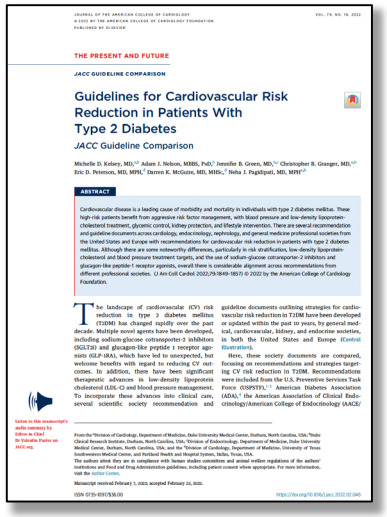
1. Paul SK *et al. Cardiovasc Diabetol* 2015;14:100; 2. Khunti K, Millar-Jones D. *Prim Care Diabetes* 2017;11:3

Cumulative Incidences of Microvascular and Macrovascular Outcomes in the Intention-to-Treat Analyses.
GRADE study





The GRADE Study Research Group. N Engl J Med2022;387:1075-1088



THE PRESENT AND FUTURE

JACC GUIDELINE COMPARISON

Guidelines for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

JACC Guideline Comparison

ABSTRACT

Cardiovascular disease is a leading cause of morbidity and mortality in individuals with type 2 diabetes mellitus. These high-risk patients benefit from aggressive risk factor management, with blood pressure and low-density lipoprotein-cholesterol treatment, glycemic control, kidney protection, and lifestyle intervention. There are several recommendation and guideline documents across cardiology, endocrinology, nephrology, and general medicine professional societies from the United States and Europe with recommendations for cardiovascular risk reduction in patients with type 2 diabetes mellitus. Although there are some noteworthy differences, particularly in risk stratification, low-density lipoprotein-cholesterol and blood pressure treatment targets, and the use of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, overall there is considerable alignment across recommendations from different professional societies. (J Am Coll Cardiol 2022;79:1849-1857) © 2022 by the American College of Cardiology Foundation.

The landscape of cardiovascular (CV) risk reduction in type 2 diabetes mellitus (T2DM) has changed rapidly over the past decade. Multiple novel agents have been developed, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA), which have led to unexpected, but welcome benefits with regard to reducing CV outcomes. In addition, there have been significant therapeutic advances in low-density lipoprotein cholesterol (LDL-C) and blood pressure management. To incorporate these advances into clinical care, several scientific society recommendation and guideline documents outlining strategies for cardiovascular risk reduction in T2DM have been developed or updated within the past 10 years, by general medical, cardiovascular, kidney, and endocrine societies, in both the United States and Europe (Central Illustration).

Here, these society documents are compared, focusing on recommendations and strategies targeting CV risk reduction in T2DM. Recommendations were included from the U.S. Preventive Services Task Force (USPSTF),[1,2] American Diabetes Association (ADA),[3] the American Association of Clinical Endocrinology/American College of Endocrinology (AACE/

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on JACC.org

From the [1]Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA; [2]Duke Clinical Research Institute, Durham, North Carolina, USA; [3]Division of Endocrinology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA; and the [4]Division of Cardiology, Department of Medicine, University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas, Texas, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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https://doi.org/10.1016/j.jacc.2022.02.049

TABLE 1 Comparison of Type 2 Diabetes Guideline Recommendations

	ACC/AHA[8,13,39]	ADA[4,17,38,43]
Hyperglycemia treatment and novel agents		
First line	SGLT2i/GLP-1RA may be beneficial regardless of background metformin	SGLT2i/GLP-1RA may be beneficial regardless of background metformin
Relative priority of SGLT2/GLP-1RA	SLGT2i >GLP-1RA for HF, renal disease, weight loss	SLGT2i >GLP-1RA for HF and renal disease

TABLE 1 Continued

	AACE/ACE[5,6]	KDIGO[10,11,33]
Hyperglycemia treatment and novel agents		
First line	SGLT2i/GLP-1RA may be beneficial regardless of background metformin	Metformin and SGLT2i in combination for those with CKD
Relative priority of SGLT2/GLP-1RA	SLGT2i >GLP-1RA for HF and renal disease	SGLT2 inhibitor first, GLP-1RA second line

iSGLT2 arGLP1 | **iSGLT2 arGLP1** | **iSGLT2 arGLP1** | **iSGLT2 arGLP1**

Pioglitazona: infra-representada…

Kelsey MD, et al. J Am Coll Cardiol. 2022;79(18):1849–1857

Beneficios clínicos nuevos HGNI

Resultados CV, IC y renales

	SGLT2i[1–5]	GLP-1 RA[6–14]	ACEi[15,16]	ARB[17–20]	Statins[21–24]
MACE	↓	↓	↓	↔	↓
CV death	↓ Empagliflozin only	↓ Liraglutide only*	↓	↓	↓
HHF	↓	↔	↓	↓	↔
Hard kidney outcomes†	↓	↔	↔	↓	↔
Albuminuria	↓	↓	↓	↓	↓‡
All-cause mortality	↓ Empagliflozin only	↓ Liraglutide only*	↓	↓	↓

†Most commonly doubling serum creatinine, ESKD, renal death; ‡Effect has been modest and variable across studies

Cardiovascular and Renal Benefits of Novel Diabetes Drugs by Baseline Cardiovascular Risk: A Systematic Review, Meta-analysis, and Meta-regression

Cardiovascular and renal benefits of novel diabetes drugs by baseline cardiovascular risk: A systematic review, meta-analysis, and meta-regression

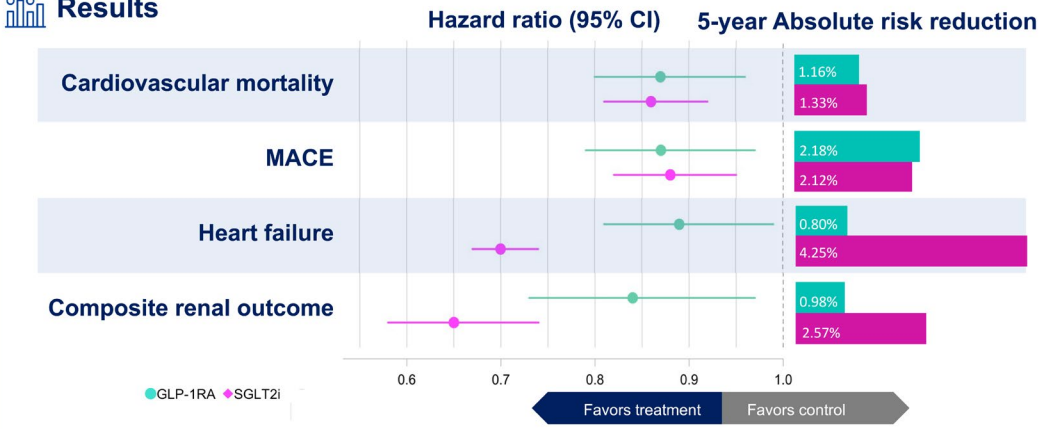
Summary Absolute, but not relative, treatment benefits of novel diabetes drugs depend on baseline cardiovascular risk, particularly regarding benefits for heart failure

Study design Systematic review, meta-analysis, followed by meta-regression

Data sources **34** reports on **22** RCTs
9 GLP-**1**RA, **13** SGLT2i
154,649 adult patients
Mean age **62-72** years
Low risk of bias
For all 22 RCTs

Comparison Intervention: Novel diabetes drugs (GLP-1RA, SGLT2i) Control: Placebo

Results



Largest 5-year absolute risk reduction for **heart failure** within SGLT2i trial participants at highest cardiovascular risk: **11.6%**

NNT **9** in high cardiovascular risk

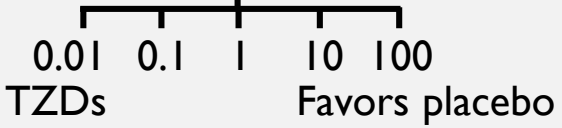
GLP-1RA, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular event; NNT, number needed to treat; tRCT, randomized controlled trial; SGLT2i, sodium–glucose cotransporter 2 inhibitors

Diabetes Care. 2023;46(6):1300-1310. doi:10.2337/dc22-0772

Preventing Recurrent Stroke With pioglitazone

- Meta-analysis of 3 RCTs evaluating stroke recurrence in patients with previous stroke or TIA receiving pioglitazone or placebo (n = 4979), followed for 25-57.6 months

Study or Subgroup	TZDs, n/N	Placebo, n/N	Risk Ratio M-H, Random, 95% CI	Weight, %	Risk Ratio M-H, Random (95% CI)
IRIS	127/1939	154/1937		56.6	0.82 (0.66-1.03)
J-SPIRIT	2/58	7/61		6.3	0.30 (0.07-1.39)
PROactive	27/486	51/498		37.1	0.54 (0.35-0.85)
Total	**2483**	**2496**		100	**0.66 (0.44-0.99)**

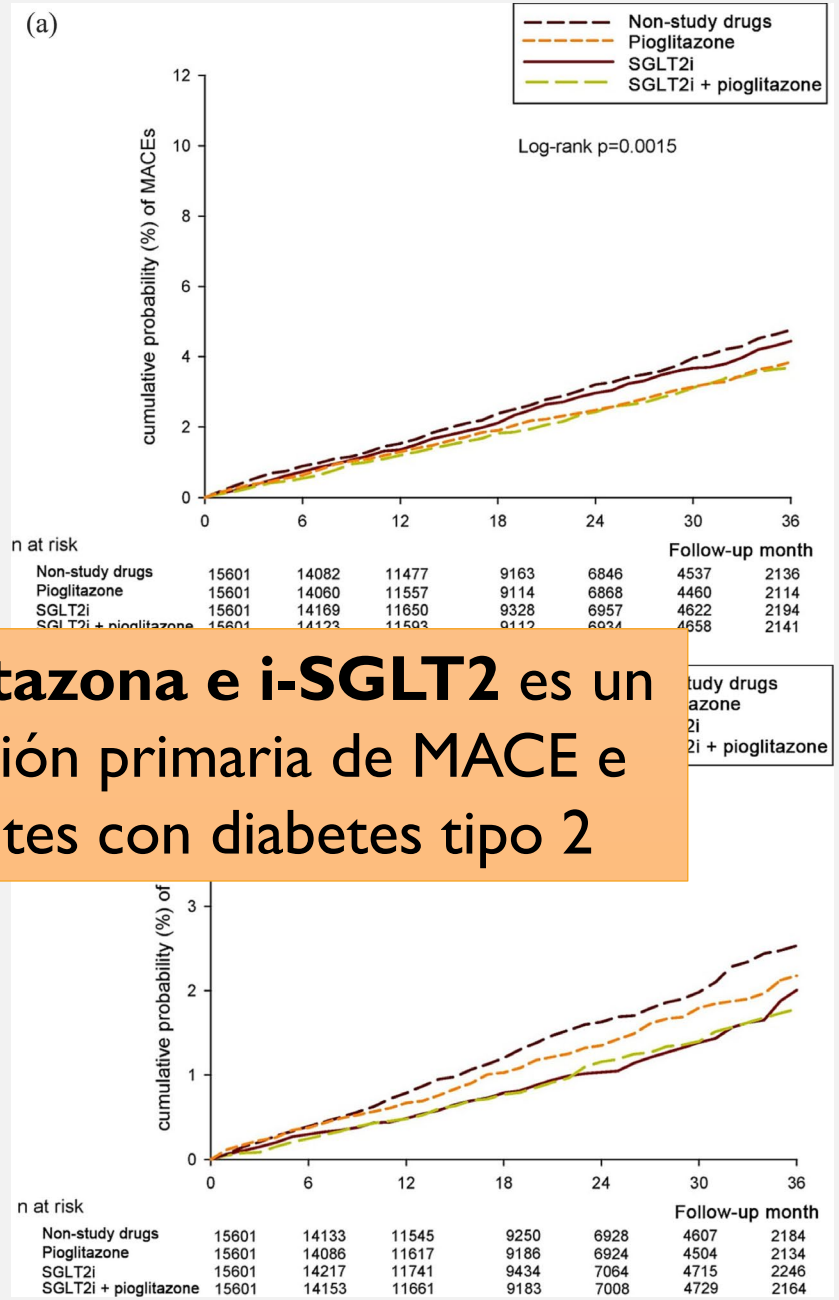


Liu J, Wang LN. Cochrane Database Syst Rev. 2017;12:CD010693.

Efecto de i-SGLT2 y pioglitazona sobre MACE e insuficiencia cardíaca en DM2

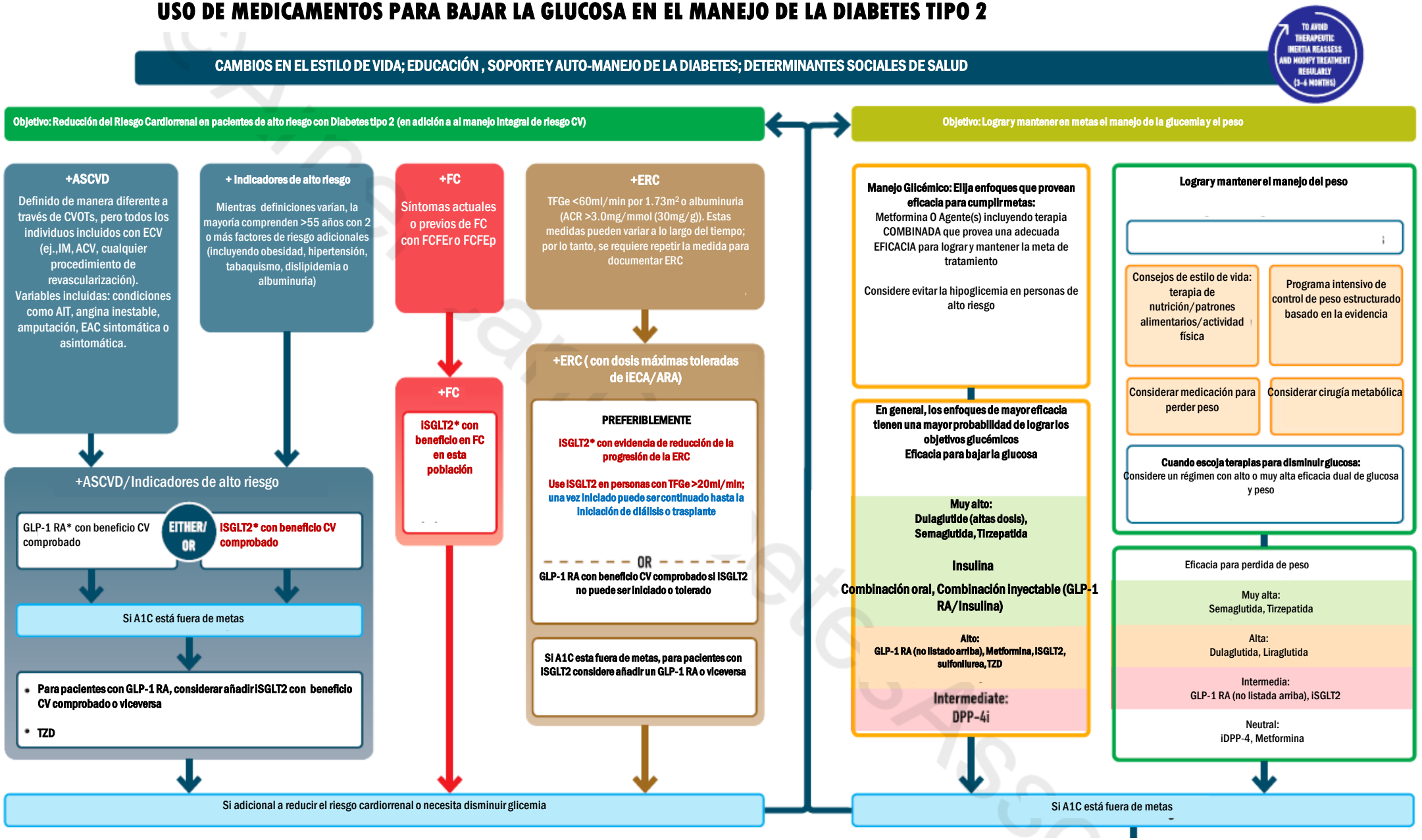
Real-world
col
(T2DM patients v

La terapia combinada con **pioglitazona e i-SGLT2** es un tratamiento eficaz en la prevención primaria de MACE e insuficiencia cardiaca en pacientes con diabetes tipo 2



Diabetes Res Clin Pract . 2023 Apr 24;200:110685. doi: 10.1016/j.diabres.2023.110685

USO DE MEDICAMENTOS PARA BAJAR LA GLUCOSA EN EL MANEJO DE LA DIABETES TIPO 2



Diabetes Care 2023;46(Supplement_1):S41–S48

THERE ARE SEVERAL TREATMENT OPTIONS RANKED BY LEVEL OF EFFICACY FOR GLYCAEMIC AND WEIGHT MANAGEMENT FOR PEOPLE WITH T2D

- ADA 2023 Standards of Medical Care and ADA–EASD Consensus Report[1,2]: Goal – achievement and maintenance of glycaemic and weight management goals

To avoid therapeutic inertia reassess and modify treatment regularly (3–6 months)

Glycaemia management: choose approaches that provide the efficacy to achieve goals

Metformin OR agent(s) including **combination** therapy that provide adequate **efficacy** to achieve and maintain goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

Achievement and management of weight-management goals

Set individualised weight-management goals and consider:

- Lifestyle advice
- Weight-management programme
- Medication for weight loss
- Metabolic surgery

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

Efficacy for glucose lowering

Very high:
Dulaglutide (high dose), semaglutide, tirzepatide
Insulin, combination oral, combination injectable (GLP-1 RA/insulin)

High:
GLP-1 RA (not listed above), metformin, SGLT2 inhibitor, sulphonylurea, TZD

Intermediate:
DPP-4i

Efficacy for weight loss

Very high:
Semaglutide, tirzepatide

High:
Dulaglutide, liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2 inhibitor

Neutral:
DPP-4i, metformin

Identify barriers to goals if HbA1c is above target

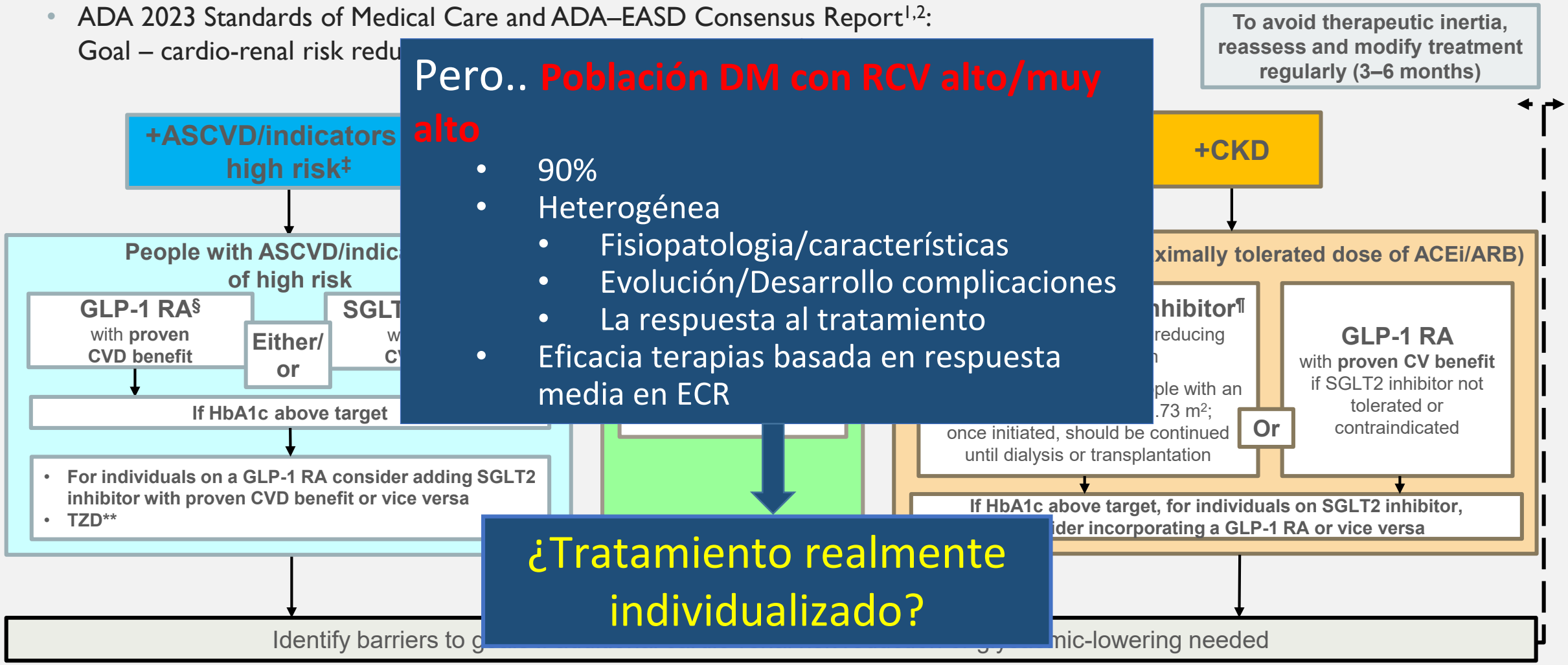
1. American Diabetes Association. *Diabetes Care* 2023;46:S1; 2. Davies MJ *et al. Diabetes Care* 2022;45:2753

SGLT2-I AND GLP-1 RA ARE RECOMMENDED AS A FIRST-LINE TREATMENT OPTION IN THE MANAGEMENT OF PEOPLE WITH T2D AT HIGH RISK OF CARDIO-RENAL EVENTS

- ADA 2023 Standards of Medical Care and ADA–EASD Consensus Report[1,2]:
  Goal – cardio-renal risk redu

Pero.. **Población DM con RCV alto/muy alto**

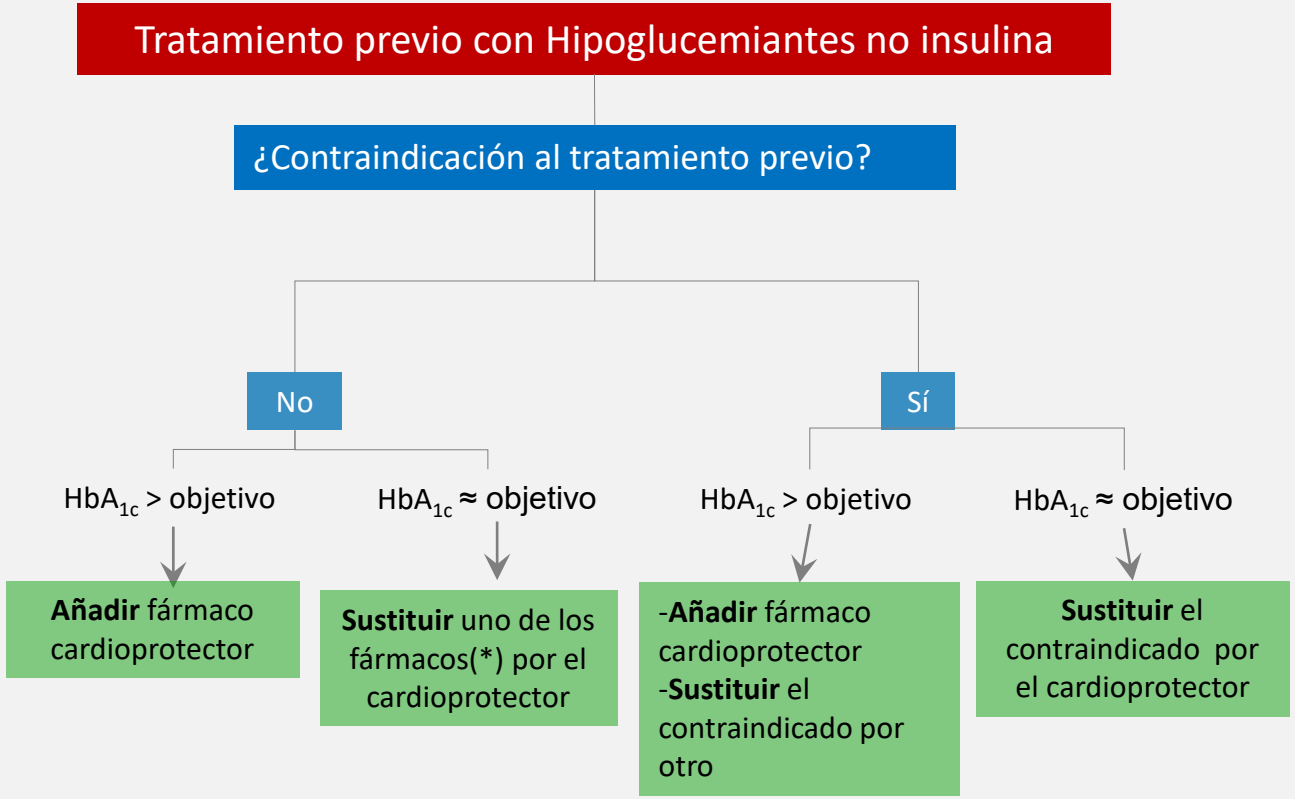
- 90%
- Heterogénea
  - Fisiopatologia/características
  - Evolución/Desarrollo complicaciones
  - La respuesta al tratamiento
- Eficacia terapias basada en respuesta media en ECR



¿Tratamiento realmente individualizado?

1. American Diabetes Association. *Diabetes Care* 2023;46:S1; 2. Davies MJ *et al. Diabetes Care* 2022;45:2753

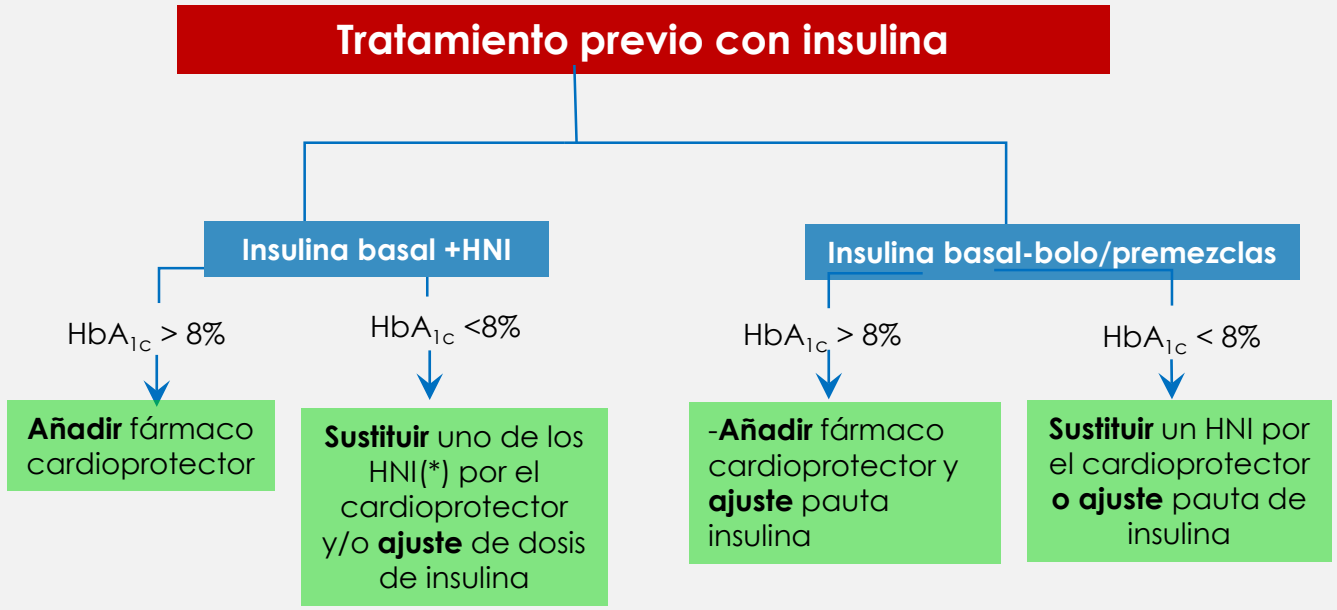
INICIO DE FÁRMACO CARDIOPROTECTOR EN DM2
AÑADIR VS SUSTITUIR/AJUSTAR



*Especialmente si riesgo de hipoglucemia

A. Pérez. Elaboración propia

Inicio de fármaco cardioprotector en DM2
Añadir vs Sustituir/Ajustar



*Especialmente si riesgo de hipoglucemia; HNI: hipoglucemiante no insulina

A. Pérez. Elaboración propia

I-SGLT2 Y ARGLP1: MANEJO DE EFECTOS ADVERSOS

	I-SGLT2 **Infección micótica genital**	**ArGLP1** **Efectos gastrointestinales**
Educación y explicación EA	• Frecuente leves • Buena respuesta a tratamiento • No necesario suspender	• Relación con la acción • Transitorio
Prevención	• Higiene personal • Evitar iniciar con hiperglucemia marcada	• Escalonamiento individualizado de la dosis • Evitar comidas copiosas
Tratamiento	• Antifúngico oral o en crema	• Modificaciones dietéticas -Disminuir volumen de ingesta -Dejar de comer cuando esté lleno • Hidratación adecuada
Suspender	• Infecciones graves/recurrentes	• Persistencia con reducción dosis/cambio preparado

Gracias

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