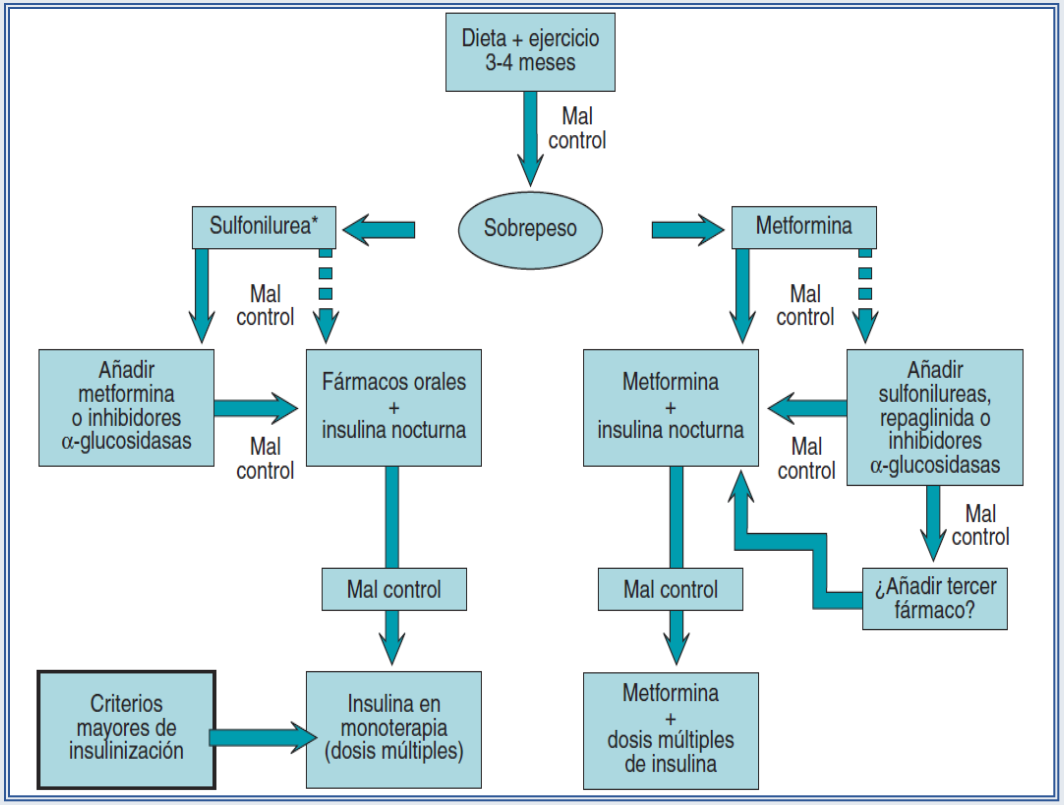
De les guies clíniques al tractament personalitzat de la diabetis: com incloure les aportacions dels nous fàrmacs?

Dra. María Teresa Julián
Servei d'Endocrinologia i Nutrició
Hospital de Mataró

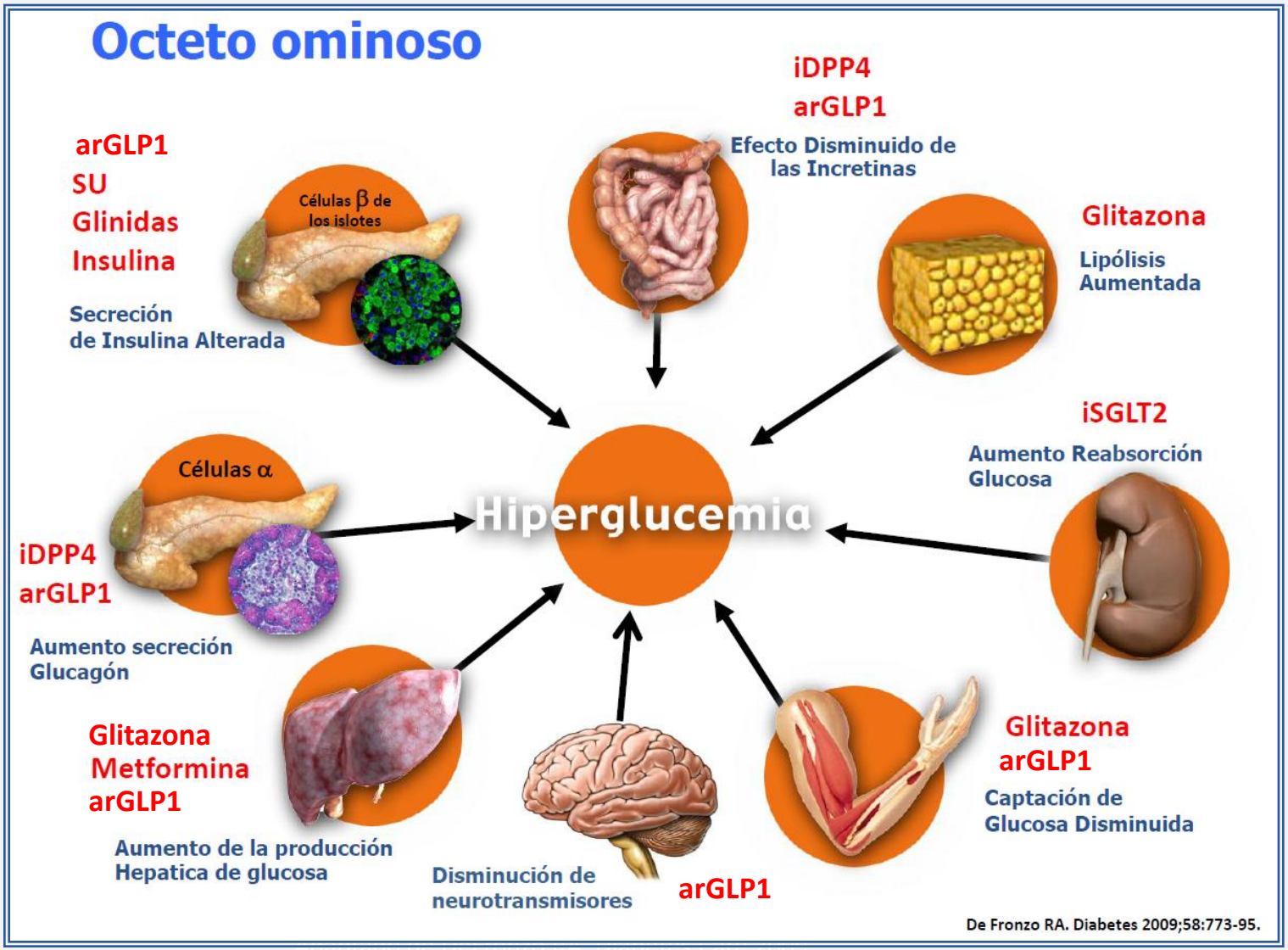
CONSORCI SANITARI DEL MARESME

ONCE UPON A TIME….

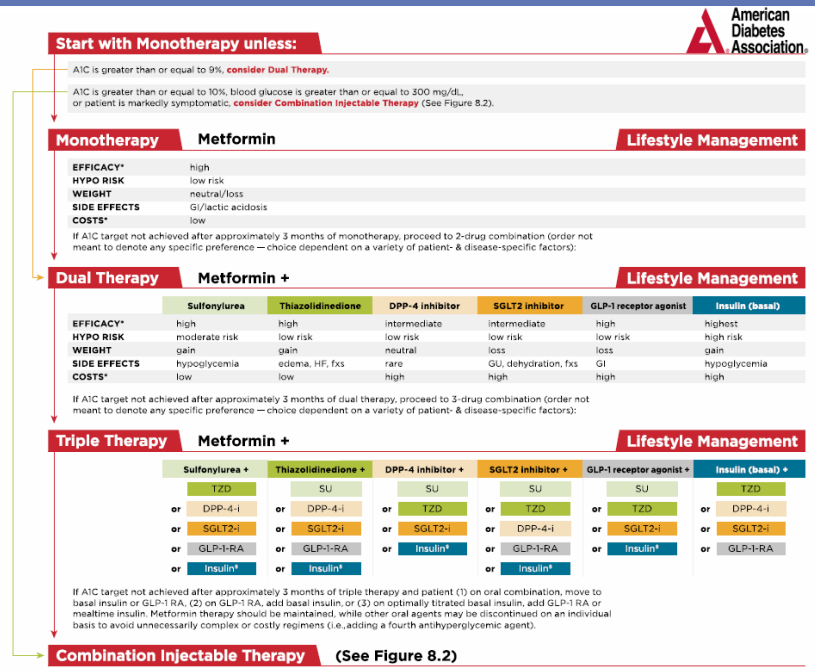


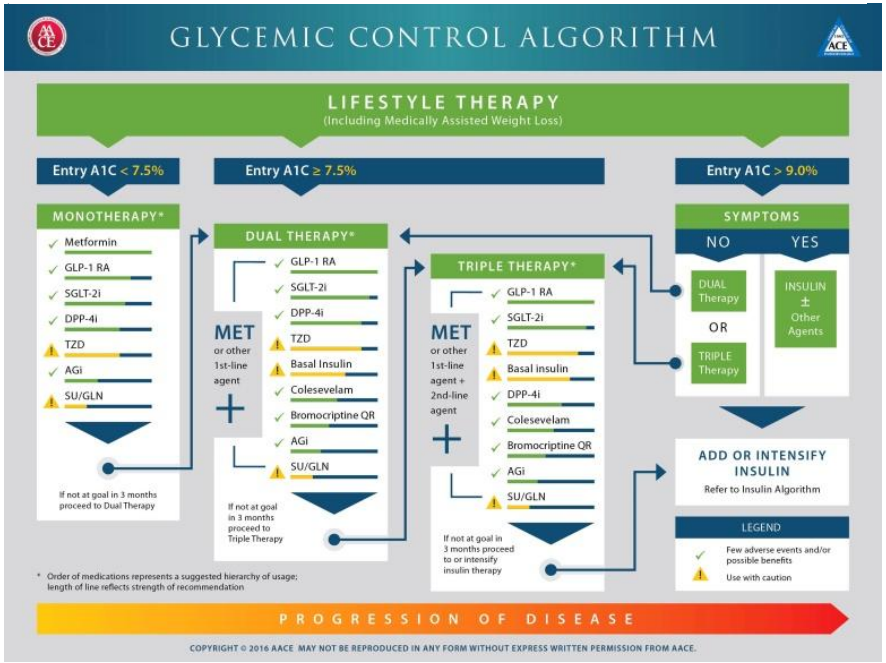
Adaptado Goday A. Med Clin .2004

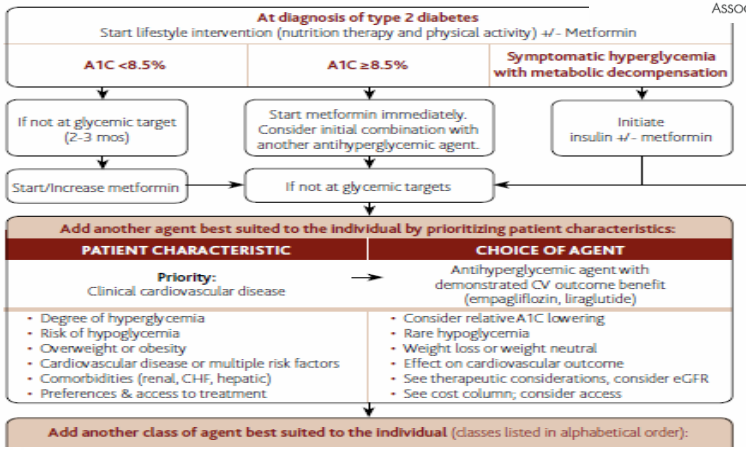
Fisiopatología compleja y multifactorial

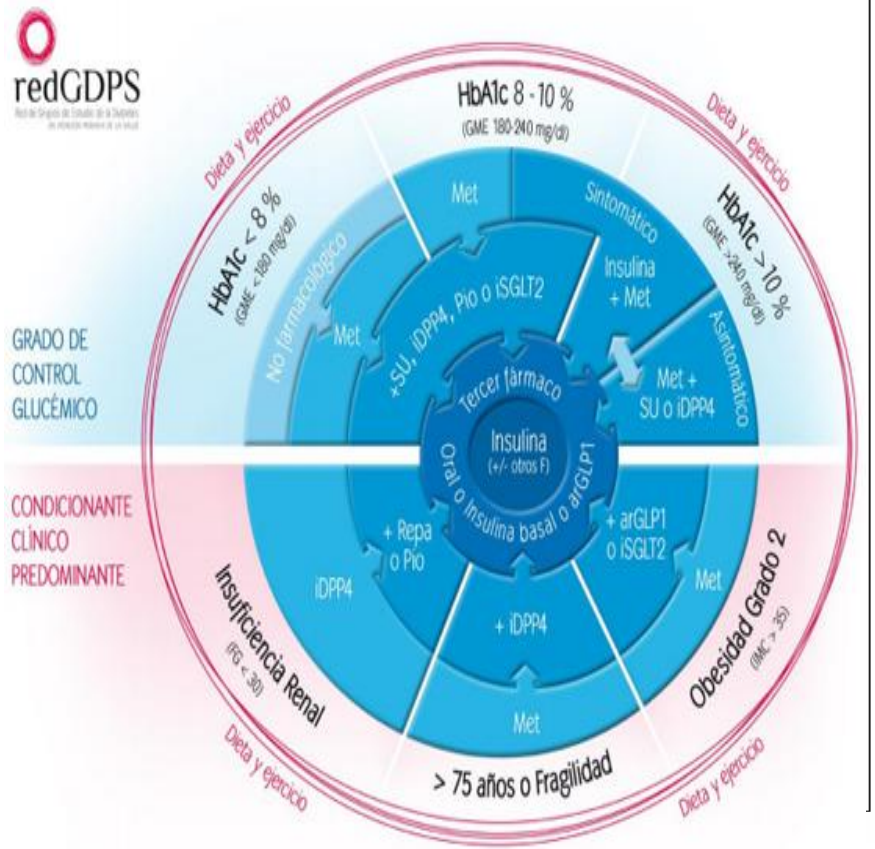


Guias clínicas







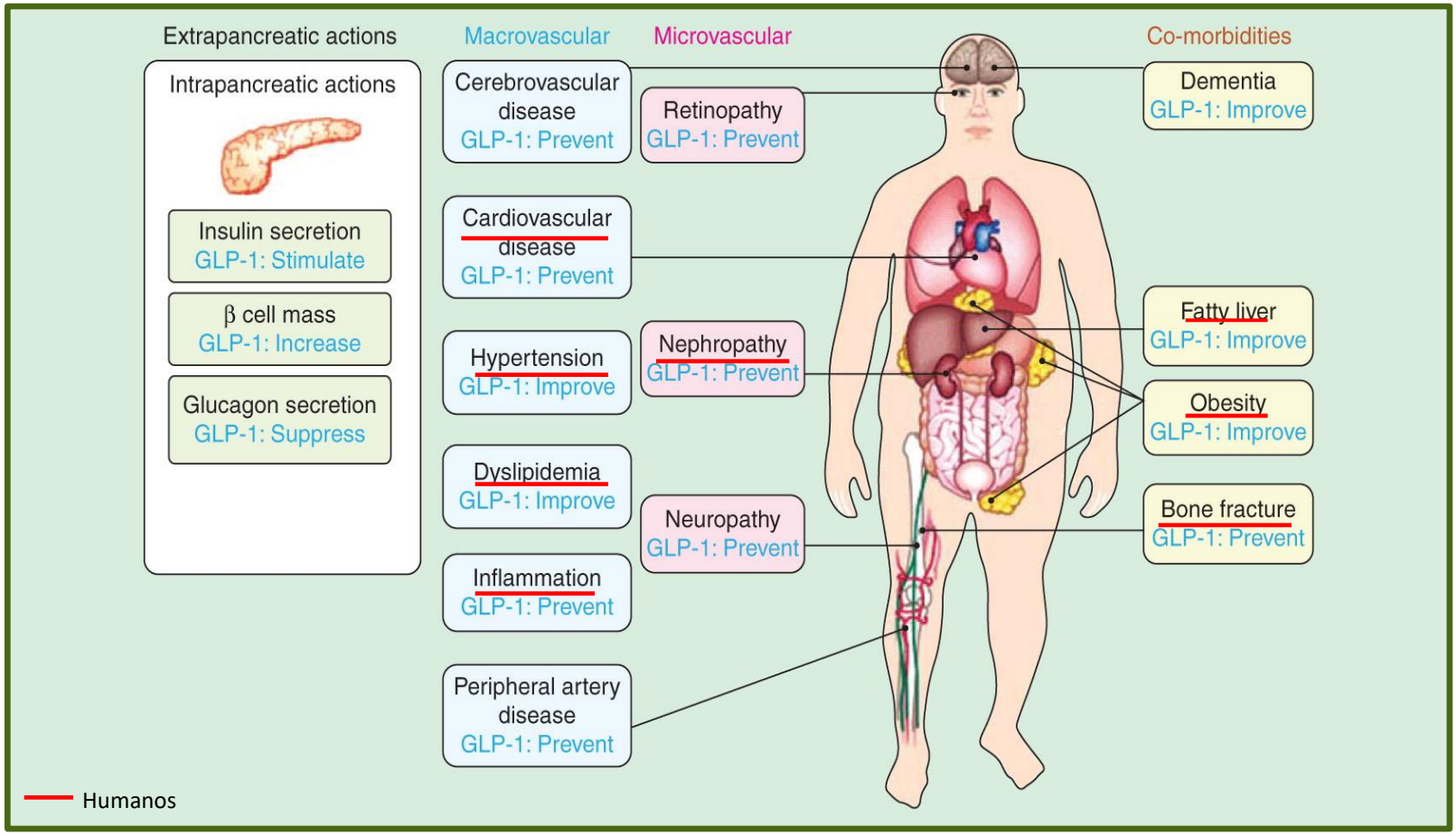


¿Qué nos aportan los nuevos fármacos hipoglucemiantes al tratamiento de la DM2?

Dual Therapy† According to ADA/EASD position statement	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑

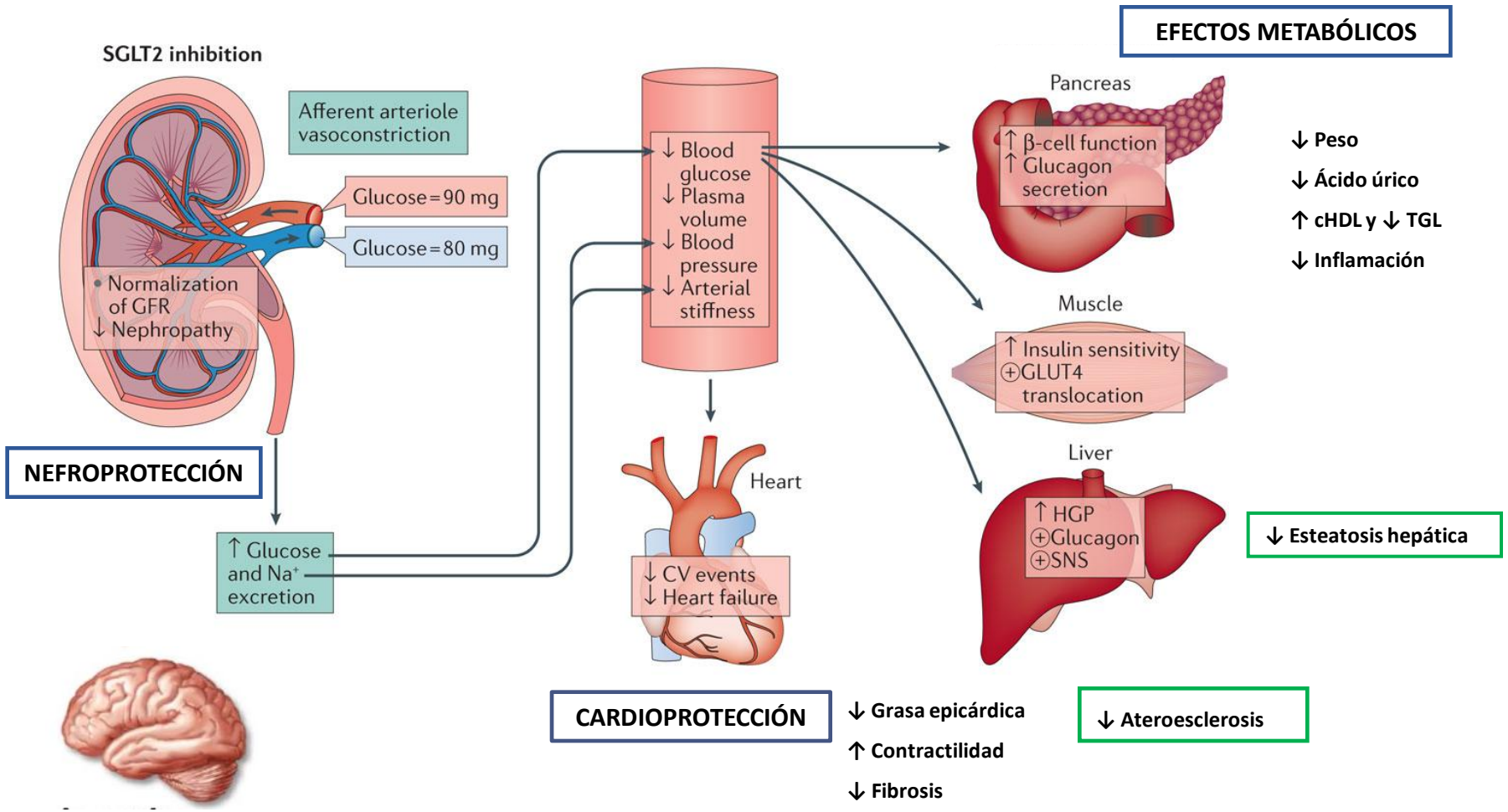
Mosenzon, O et at. Diabetes Care. 2016;39:S146-152

Efectos pleiotrópicos del GLP1/aGLP1



Adaptado de Daisuke Y et al. Expert Review of Endocrinology & Metabolism. 2014;9: 659-670

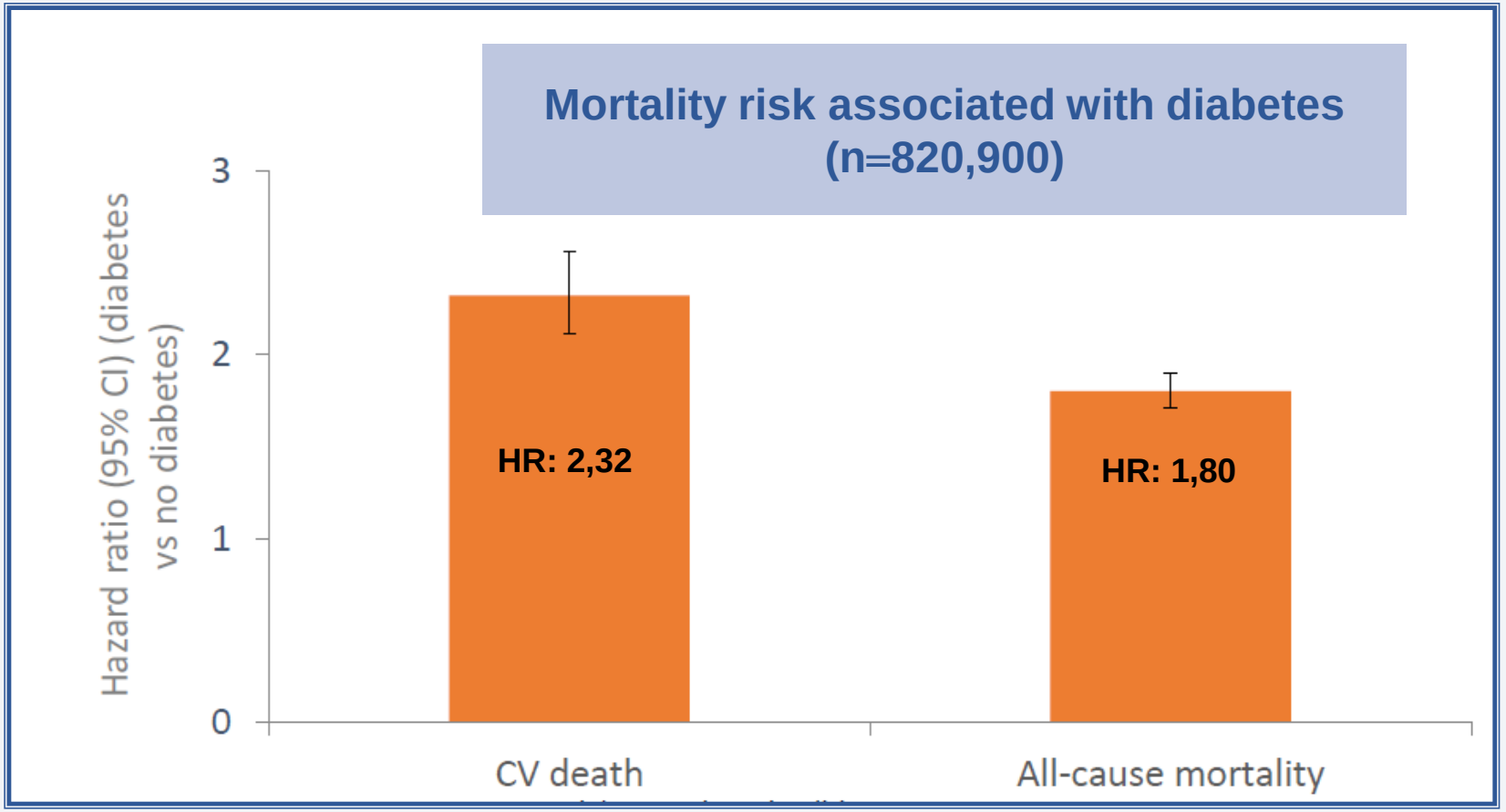
Efectos renales y extra-renales de los iSGLT2

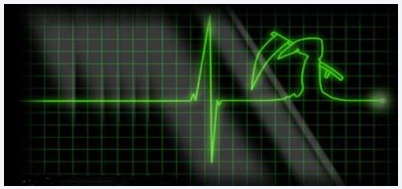


Adaptado de Daisuke Y et al. Expert Review of Endocrinology & Metabolism. 2014;9: 659-670;
Tahara A. EurJPharmacol. 2013;715:246-255; Harada S. Brain Research. 2013;1541:61-68

Mortalidad cardiovascular y diabetes

El 75% de la mortalidad a largo plazo de los diabéticos es de causa CV





Seshasai SR. ERFC. NEJM 2011;364:829; Morrish NJ. Diabetologia. 2001;44:S14-21

Hipoglucemiantes y seguridad cardiovascular

Effect of Rosiglitazo[illegible] Myocardial Infarction and D[illegible]ath from Cardiovascu[illegible] Causes

Steven E. Nissen, M.D., and Kath[illegible] Wolski, M.P.H.

ALERTA

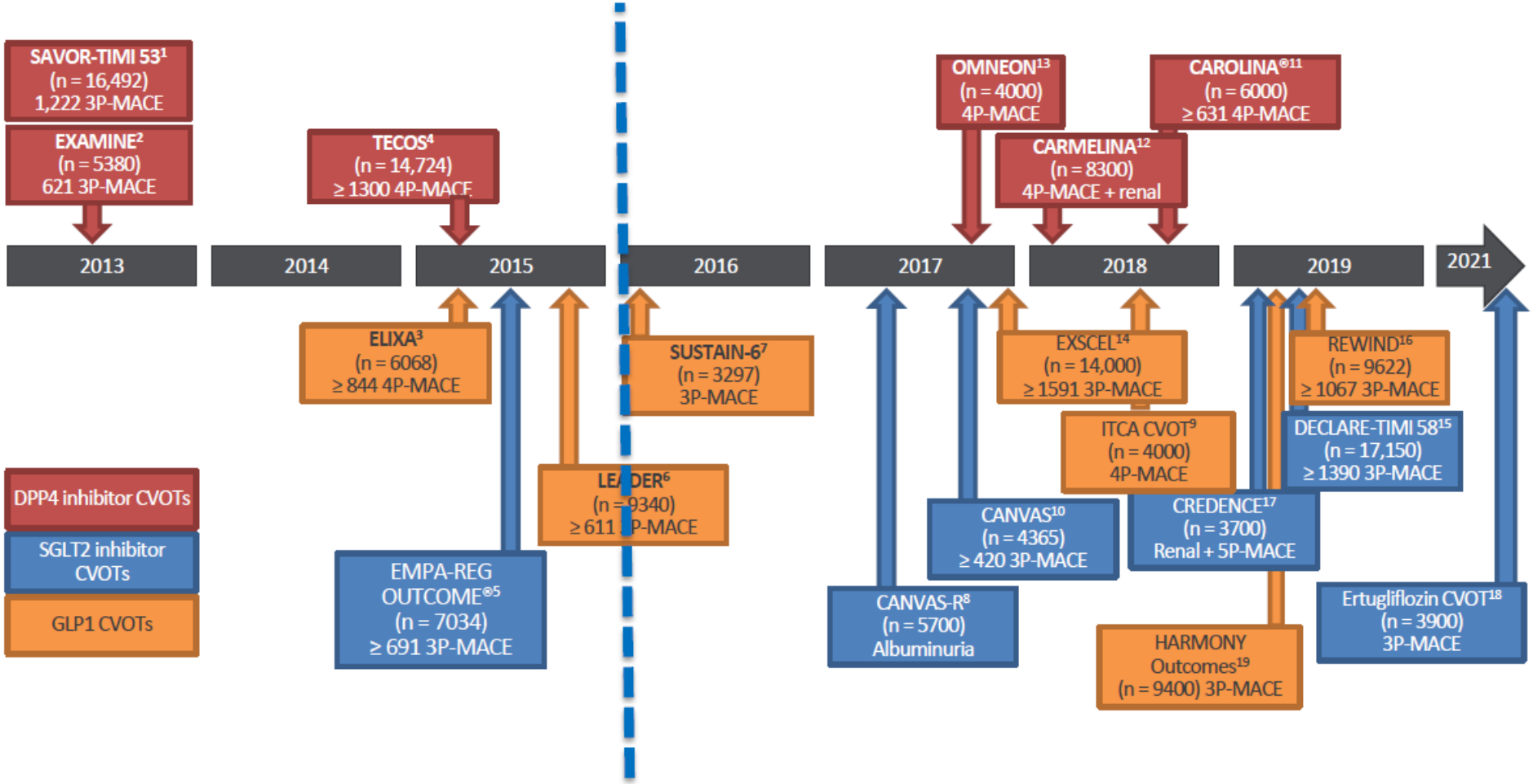
Table 4. Rat[illegible] Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Gro[illegible]	[illegible]ntrol G[illegible]	[illegible]io	P Value
	[illegible] of ev[illegible]	[illegible]%)		
Myocard[illegible]nfarction				
Small trials [illegible]ned	44[illegible]43)	[illegible]06 (0.36	1.45 (0.88–[illegible]9)	0.15
DREAM	15[illegible]5 (0.57)	9/[illegible]634 (0.34)	[illegible]65 (0.74–[illegible]8)	0.22
ADOPT	27/[illegible]	41/2895 (1.42)	[illegible].33 (0.80–[illegible]21)	0.27
Overall			1.43 (1.0[illegible].98)	0.03
Death fro[illegible]rdiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40[illegible]7–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1[illegible].52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	[illegible]0 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

The NEW ENGLAND JOURNAL of MEDICINE

Nissen SE. NEJM. 2007; 356Ç:2457-59

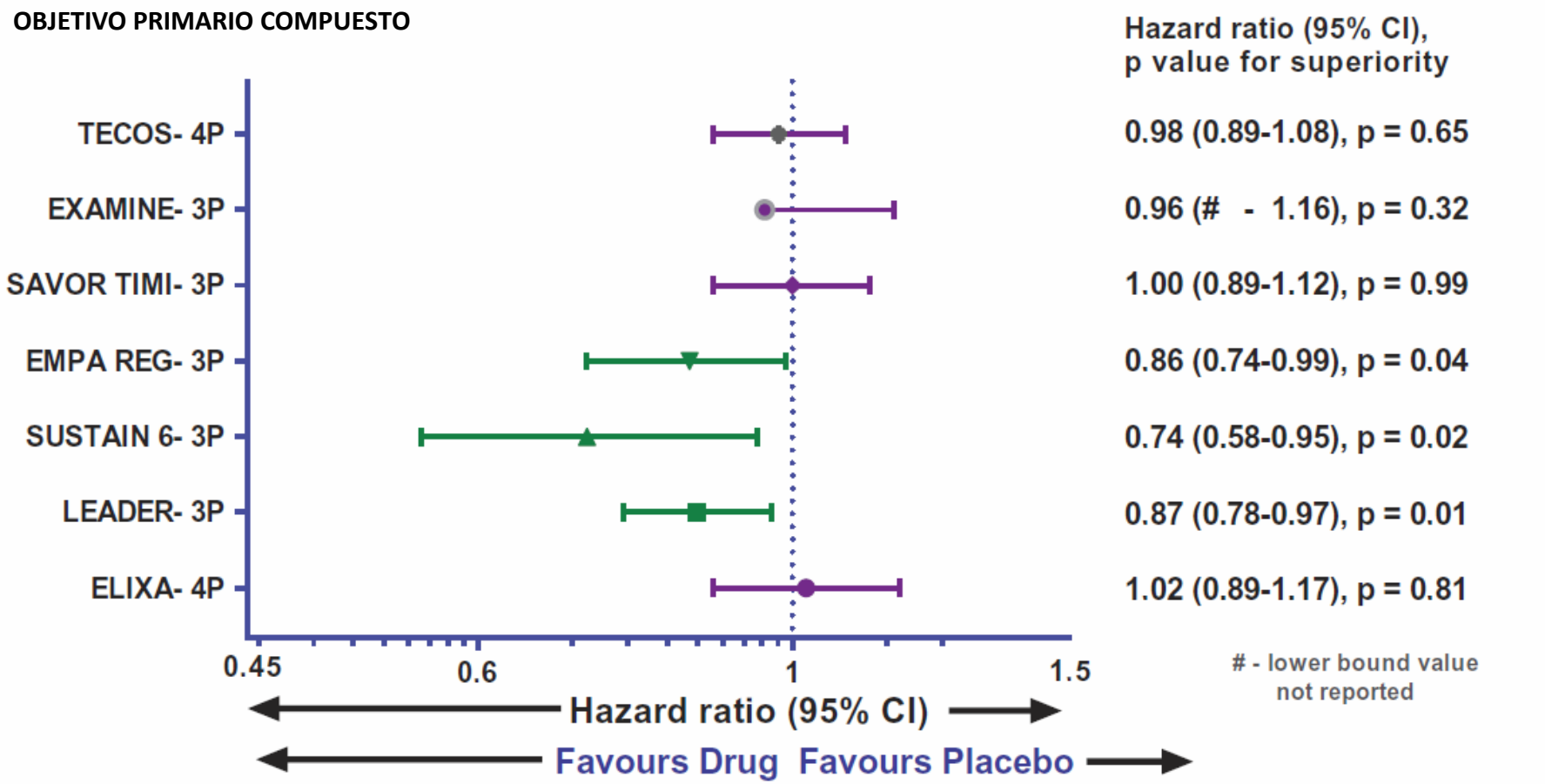
Estudios de seguridad CV finalizados y en marcha con los nuevos fármacos



Timings represent estimated completion dates as per ClinicalTrials.gov.

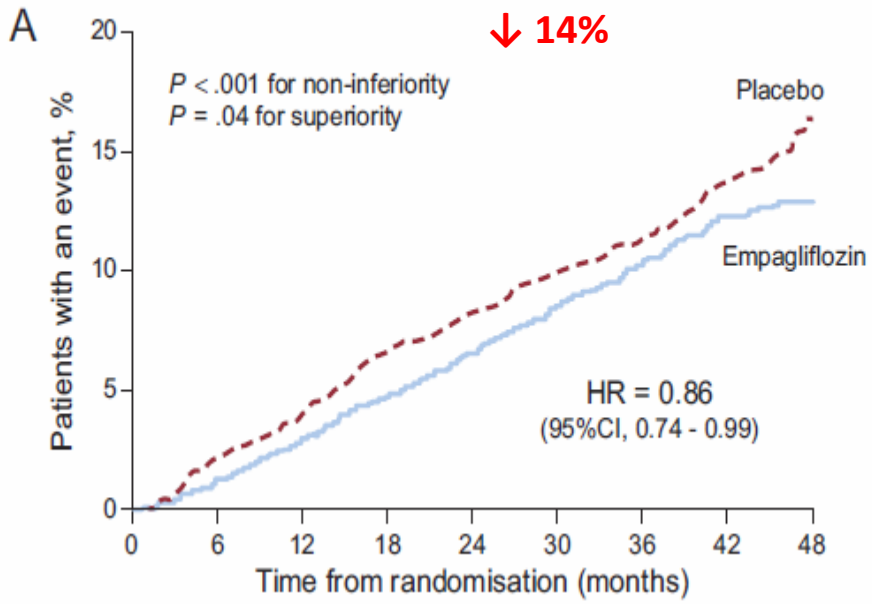
Adapted from Johansen. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)

Ensayos de seguridad CV en DM2



Sing AK. Expert Rev Clin Pharmacol. 2017;6:1-14

ESTUDIO EMPA-REG



- 7020 pacientes con DM2 + ECV
- Mediana de seguimiento: 3,1a
- OP compuesto: muerte por ECV, IAM no fatal, ictus no fatal

↓ 38% MORTALIDAD CV

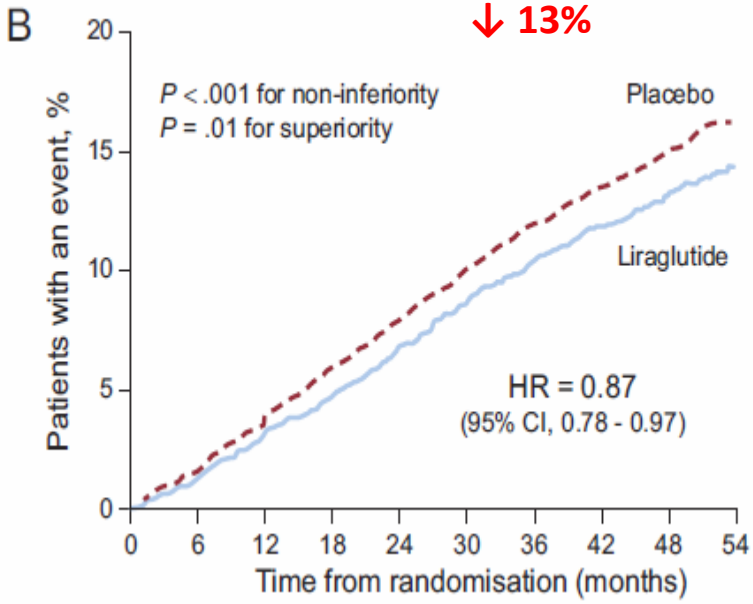
↓ 32% MORTALIDAD POR CUALQUIER CAUSA

↓ 35% HOSPITALIZACIÓN POR IC

∅ IAM no fatal, ictus no fatal

Zinman B. NEJM. 2015;373:2117-28

ESTUDIO LEADER



- 9342 pacientes con DM2: ECV (≥50a) o ≥ 1 FRCV (≥60a)
- Mediana de seguimiento: 3,8a
- OP compuesto: muerte por ECV, IAM no fatal, ictus no fatal

↓ 22% MORTALIDAD CV

↓ 15% MORTALIDAD POR CUALQUIER CAUSA

∅ HOSPITALIZACIÓN POR IC

∅ IAM no fatal, ictus no fatal

Marso S. NEJM. 2016;375:311-22

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

American Diabetes Association®

In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

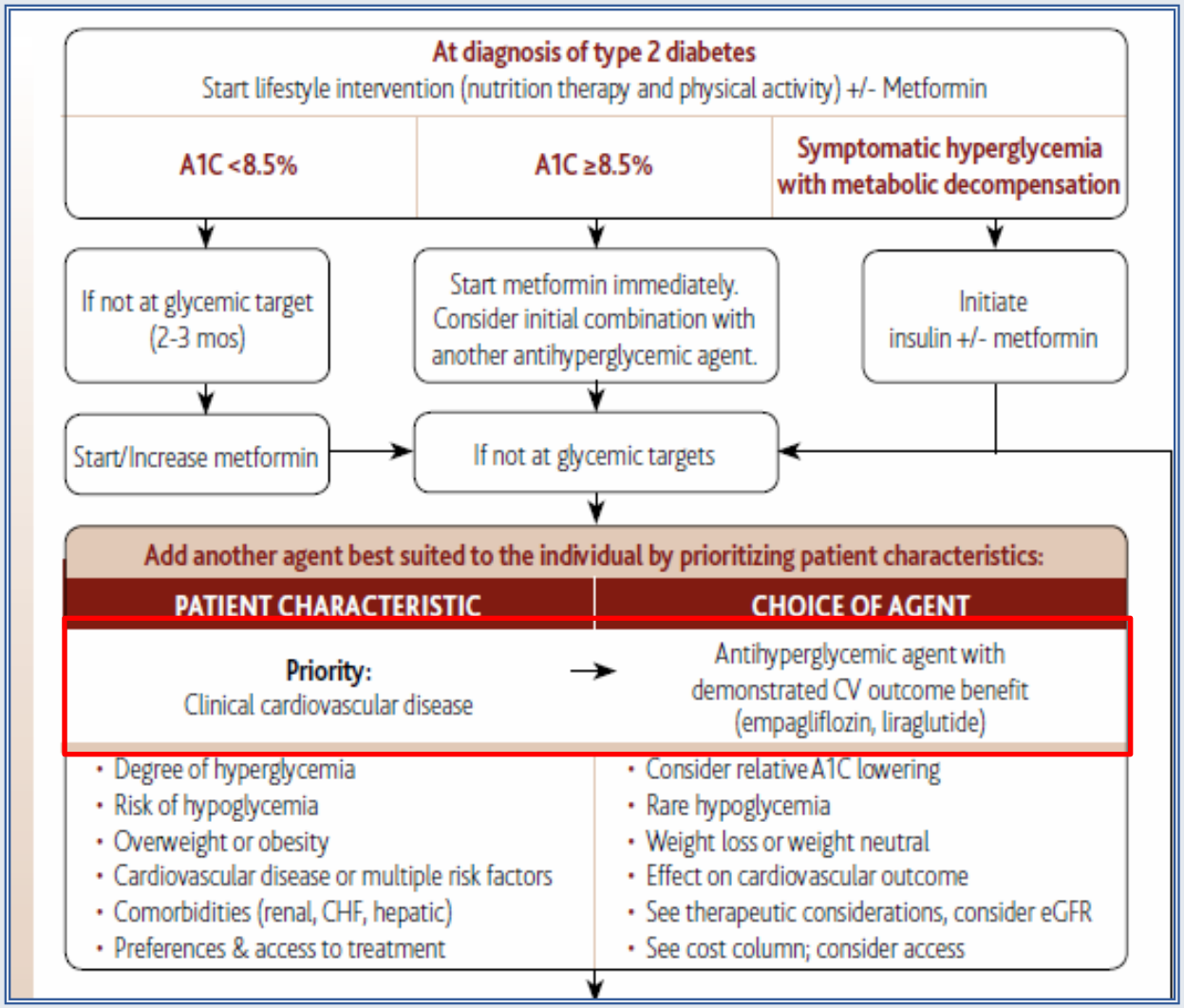
American Diabetes Association. Diabetes Care. 2017;40;S1

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain-dicated if eGFR < 30 mL/ min/1.73 m^2	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/ 1.73 m^2 Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA indication to prevent CVD death in diabetes plus prior CVD events

AACE/ACE. Endocrine Practice. 2017;



Canadian Diabetes Association Clinical Practice Guidelines. 2016

PASO 1: Un objetivo de control para cada paciente

Influencia del tratamiento intensivo de la diabetes: resumen de los principales ensayos clínicos

Estudio	Microvasc		ECV		Mortalidad	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Ensayo inicial

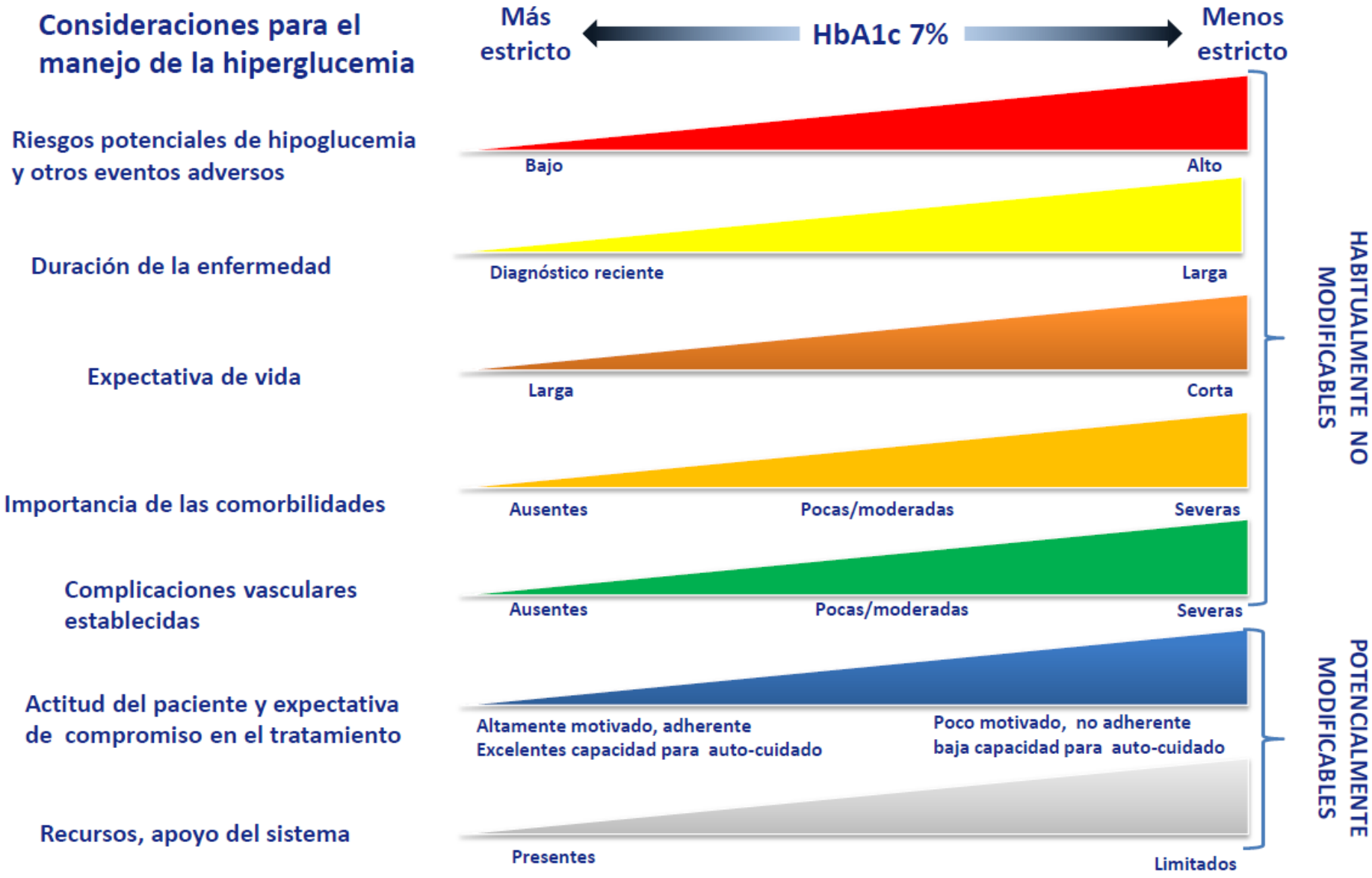
Seguimiento a largo plazo

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854.
Holman RR et al. N Engl J Med. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. N Engl J Med. 2005;353:2643. Gerstein HC et al. N Engl J Med. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129.
(erratum: Moritz T. N Engl J Med 2009;361:1024)

* En DMT1

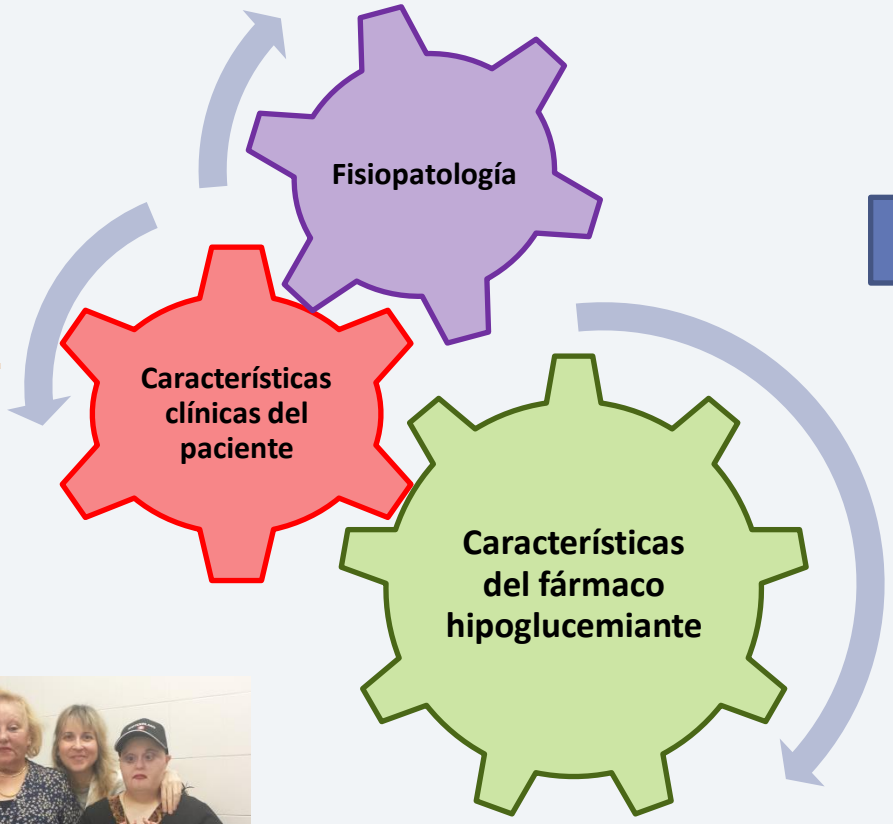
Abordaje de la hiperglucemia: ENFOQUE CENTRADO EN EL PACIENTE



Adaptado de ADA/EASD. Diabetes Care. 2015;38:140-49.

PASO 2: Un tratamiento para cada paciente

PACIENTES



FÁRMACOS

- Metformina
- SU
- Glinidas
- Glitazonas
- iαglicosidasa
- aGLP1
- iDPPIV
- iSGLT2
- Insulina

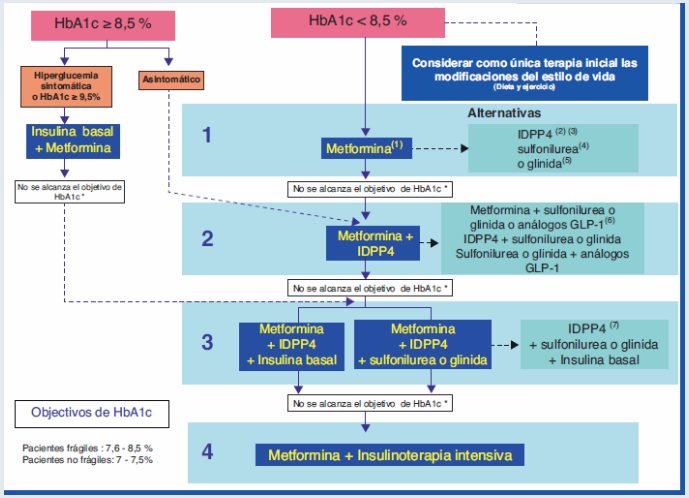
Un tratamiento para cada paciente: CONDICIONANTES CLÍNICOS

Sobrepeso/Obesidad

25-30 kg/m2	MTF + iDPP4 o iSGLT2
30-35 kg/m2	MTF + iSGLT2 o aGLP1 (iDPP4)
> 35 kg/m2	MTF + aGLP1 (iSGLT2)

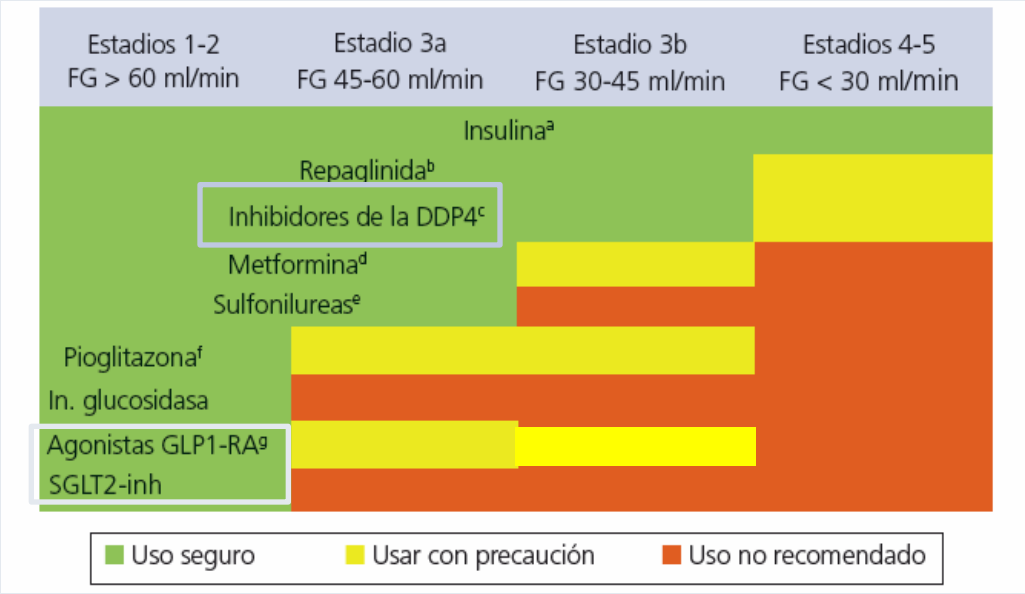
Mosenzon, O et at. Diabetes Care. 2016;39:S146-152

Ancianos



Gómez-Huelgas R. Med Clin. 2013;140:134e1-e12

Insuficiencia renal



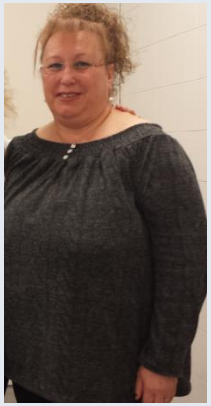
Gómez-Huelgas R. Nefrología. 2014;34:34-45

Enfermedad CV

- MTF + Empagliflozina
- MTF + Liraglutide
- MTF + iDPP4 (sitagliptina, saxagliptina, alogliptina)

American Diabetes Association. Diabetes Care. 2017;40;S1

Un tratamiento para cada paciente



45 años
DM2 de 2a
SOP, DG, SAHS, esteatosis hepática
FG> 60 ml/min
IMC 42 kg/m2
PC 102
Metformina 850 mg 1-0-1

HbA1c 9,5%

HbA1c < 7-6.5%

Resistencia a la insulina
↑↑↑↑

Riesgo alto de ↑ de peso
Riesgo bajo de hipoglucemias

aGLP-1	✓
iSGLT2	✓
iDPP-4	±
Pioglitazona	±
SU/Glinidas	X
Insulina basal	X

57 años
DM2 de 8a
HTA, SAHS, ECV estable (FE 40%)
FG> 60 ml/min
IMC 32 kg/m2
PC 105
Metformina 850 mg 1-0-1

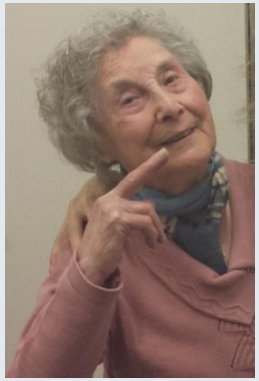
HbA1c 8,5%

HbA1c ~7 %

Resistencia a la insulina
↑↑

Riesgo intermedio

iSGLT2	✓
aGLP-1	✓
iDPP-4	✓
Pioglitazona	X
SU/Glinidas	±
Insulina basal	±



86 años
DM2 de 12 a
FG 40 ml/min
IMC 24 kg/m2
PC 80
Metformina 850 mg 1/2-0-1/2

HbA1c 8,5%

HbA1c < 8%

Resistencia a la insulina baja

Riesgo bajo de ↑ de peso
Riesgo alto de hipoglucemias

iSGLT2	X
aGLP-1	X
iDPP-4	✓
Pioglitazona	X
SU	X
Glinidas	±
Insulina basal	✓

Conclusió

Ecografia abdominal ?

Ecocardiograma ?

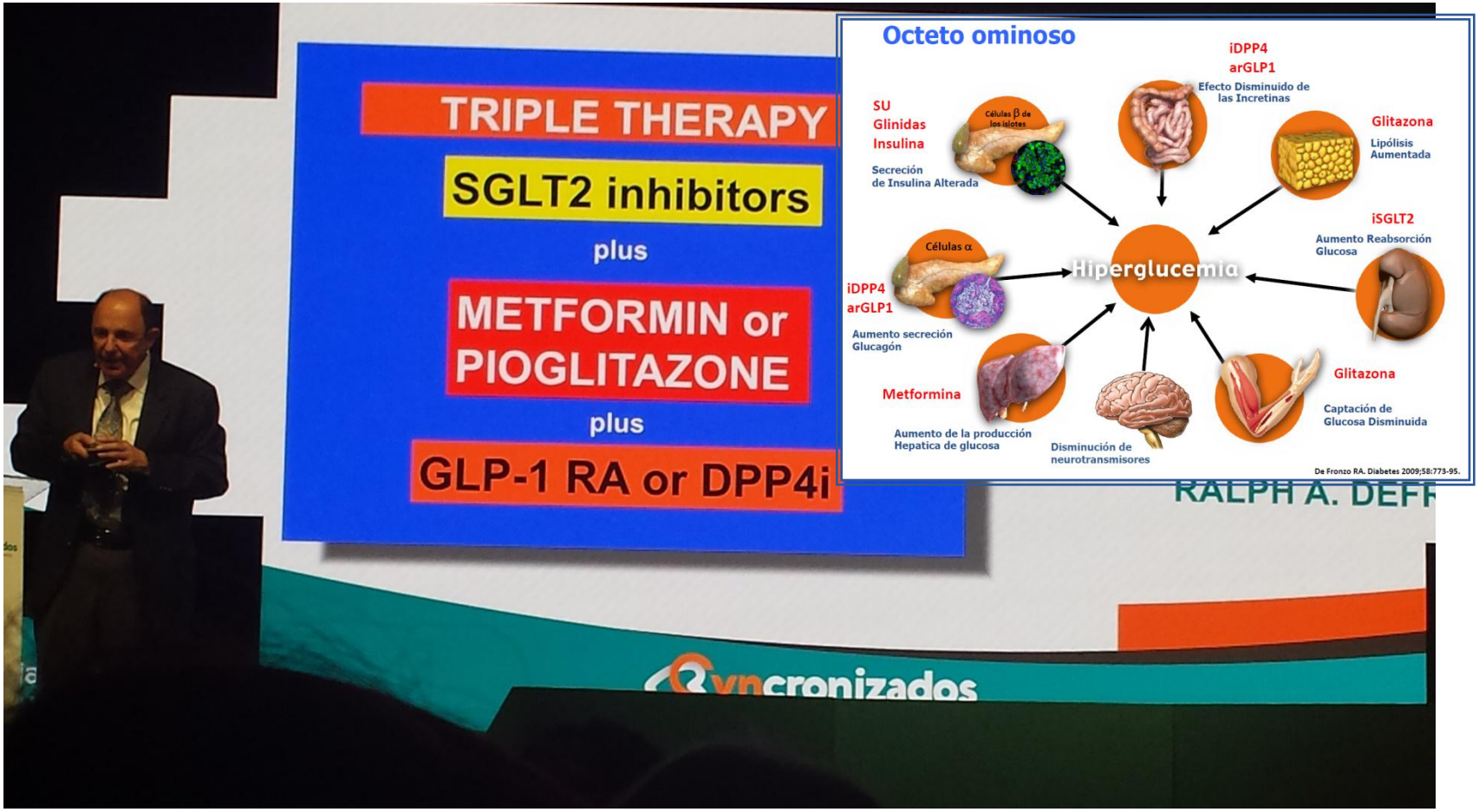
ECV subclínica ?

Péptido C y anti GAD ?

Análisis farmacogenómico ?

Moltes gràcies!

Abordaje fisiopatológico del paciente con DM2 de reciente diagnóstico



GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

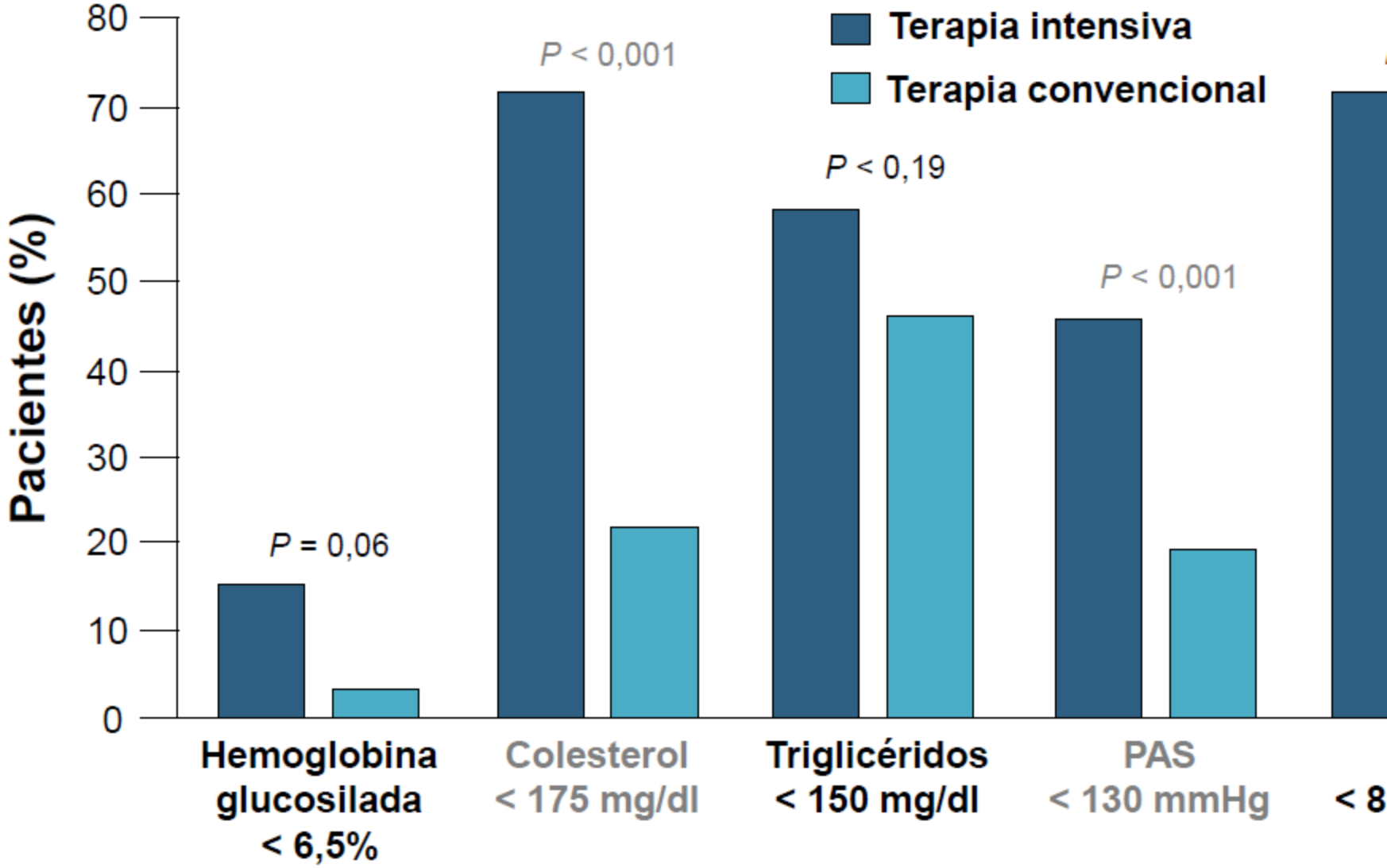
- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

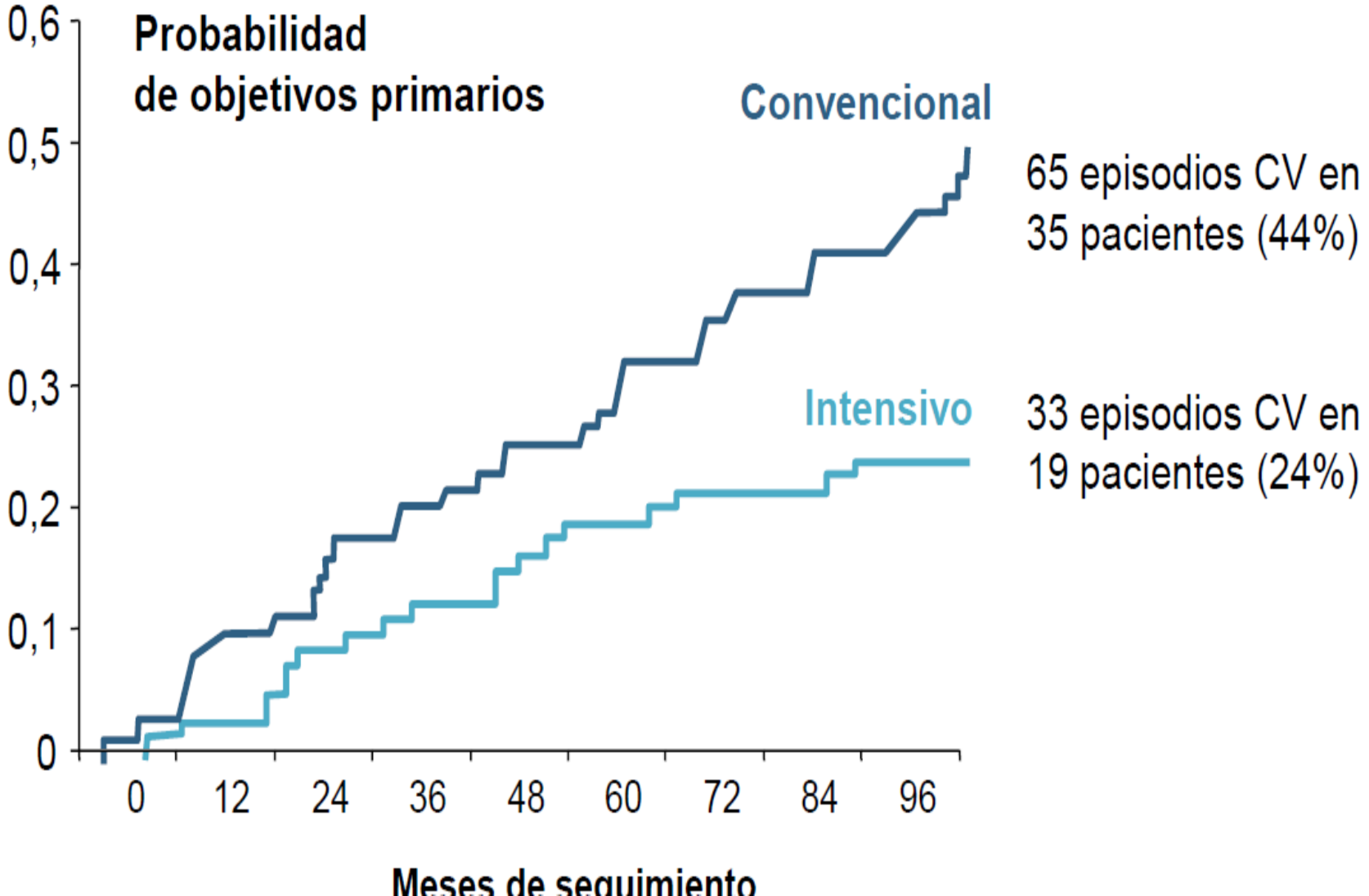
Abordaje global del tratamiento de la diabetes ti
Steno-2

Porcentaje de pacientes que alcanzan objetivos con tratamiento int

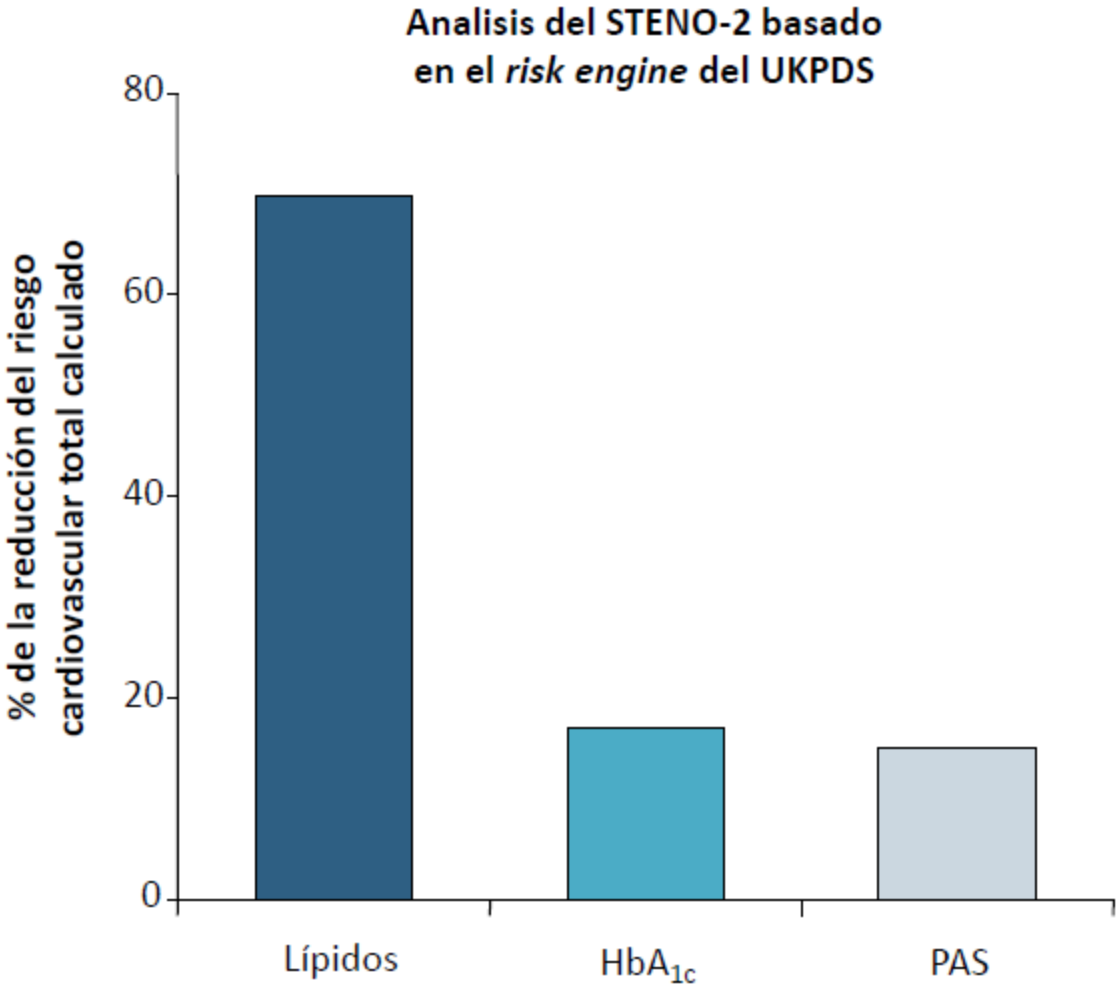


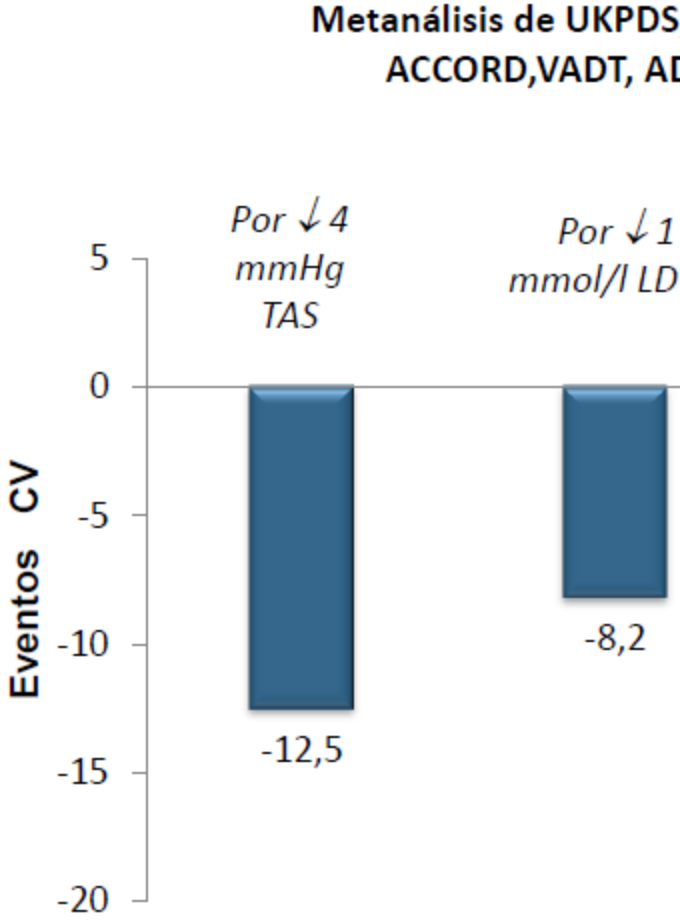
Media de seguimiento

Steno-2: Objetivos cardiovasculares después de 8 años de intervención



Intervenciones farmacológicas
Eficacia en RCV





Objetivos del tratamiento de la diabetes

Objetivos primarios

- **Evitar complicaciones**
- Mejorar la calidad de vida
- Reducir mortalidad
- Evitar los síntomas de la hiperglucemia

Objetivos intermedios

- Mejorar el control glucémico
- Mejorar el control de los factores de RCV:
  Presión arterial, Lípidos, Tabaco,
  Obesidad/Obesidad abdominal

Type 2 diabetes significantly increases the risk of cardiovascular disease

Overall, people with diabetes are 2-4 times more likely to develop cardiovascular disease than those without diabetes[1]

	Increased risk (x-fold)
Stroke[2,3]	2-4
Transient ischemic attack[1]	2-6
Coronary heart disease[3]	2
Coronary death[3,4]	2-3
Non-fatal myocardial infarction[3]	2
Heart failure[1]	2-3
Peripheral vascular disease[1]	
Lower-limb amputation	15-40
Intermittent claudication	3-9

1. International Diabetes Federation. Time to Act. 2001. Available at: http://www.idf.org/webdata/docs/Diabetes%20and%20CVD.pdf. Accessed: 6 Feb, 2013.
2. Folsom AR, et al. Diabetes Care 1999;22:1077-83.
3. Emerging Risk Factors Collaboration. Lancet 2010;375:2215-22.
4. Huxley R, et al. BMJ 2006;332:73-8.

Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people

Anoop Dinesh Shah, Claudia Langenberg, Eleni Rapsomaniki, Spiros Denaxas, Mar Pujades-Rodriguez, Chris P Gale, John Deanfield, Liam Smeeth, Adam Timmis, Harry Hemingway

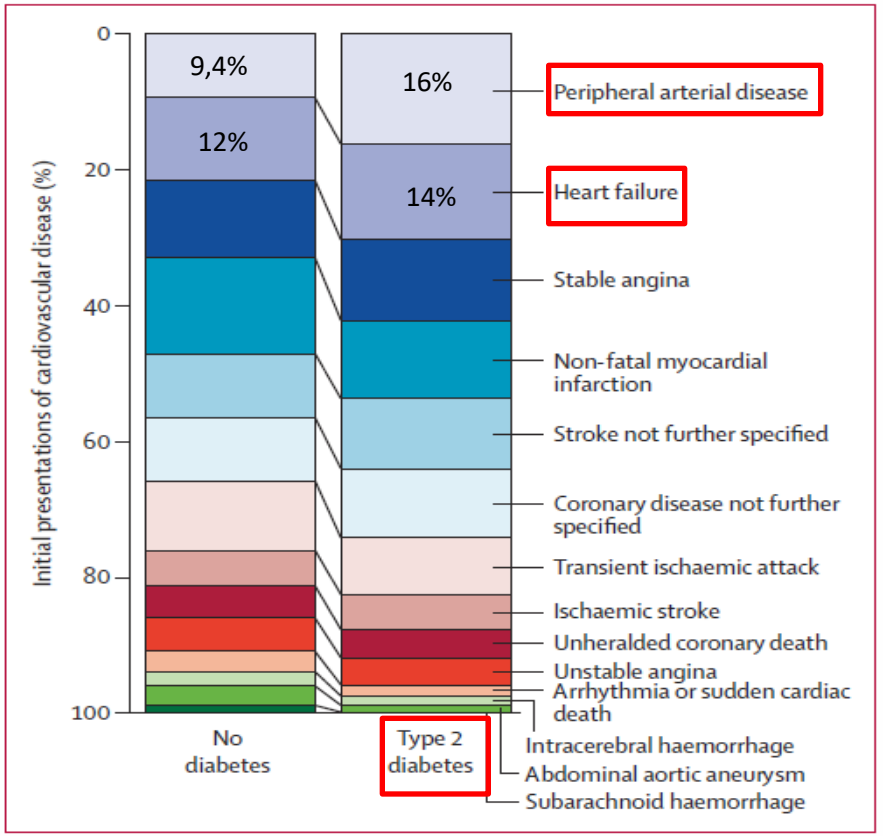


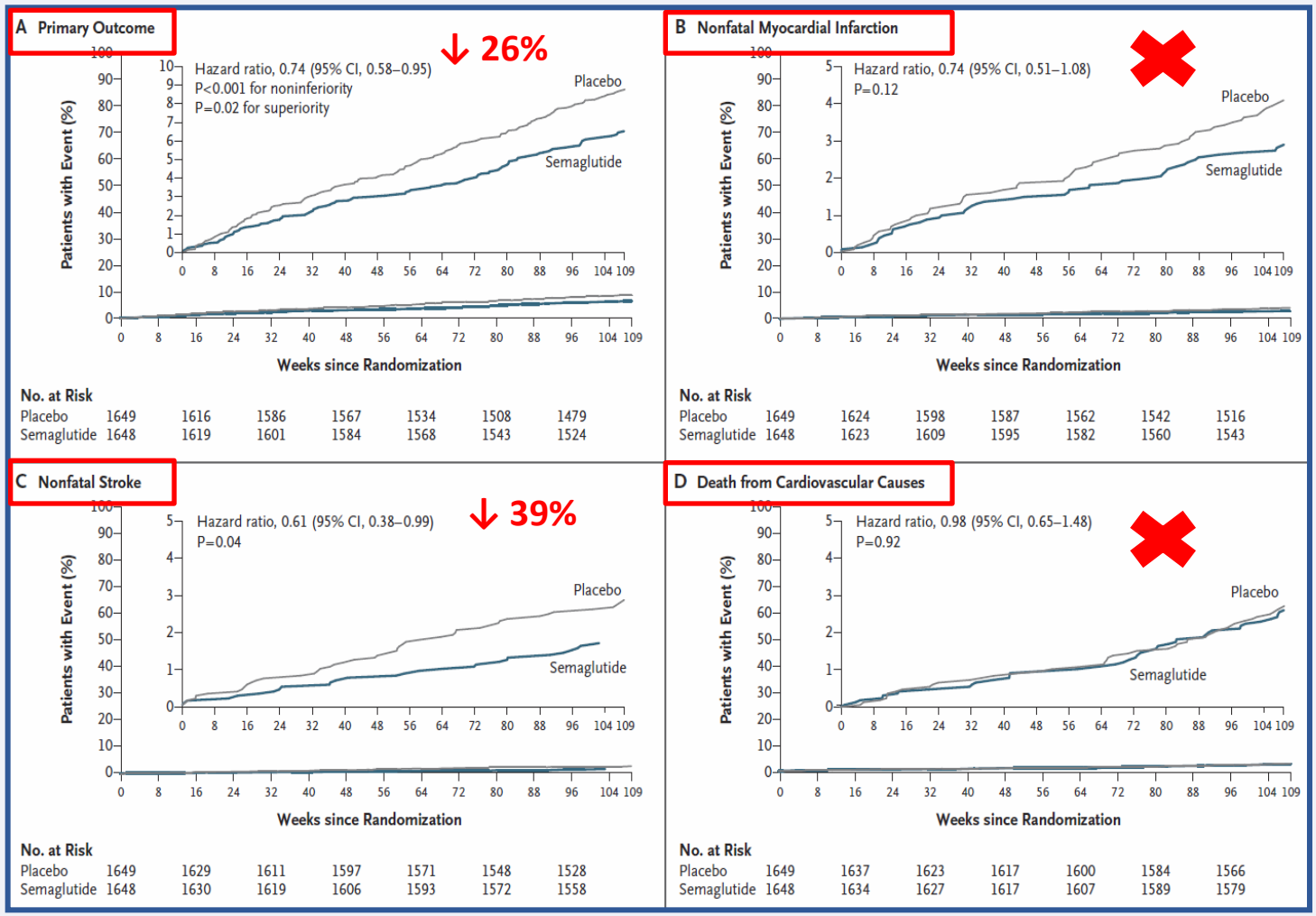
***Figure 1*: Distribution of initial presentations of cardiovascular diseases**
Distribution of initial presentations of cardiovascular disease in participants with and without type 2 diabetes and no history of cardiovascular disease.

Interpretation Heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes. The differences between relative risks of different cardiovascular diseases in patients with type 2 diabetes have implications for clinical risk assessment and trial design.

Shah AD. Lancet Diabetes Endocrinol. 2015;3:105-113

ESTUDIO SUSTAIN-6

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



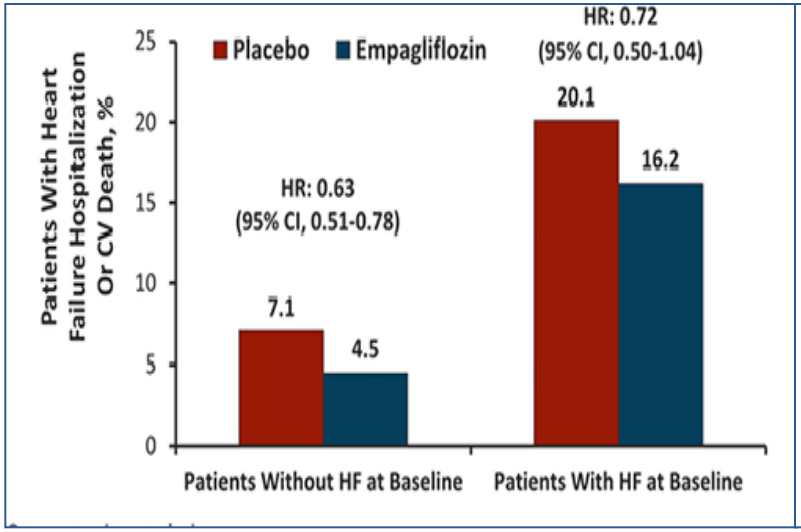
2700 pacientes con DM2 con ECV (≥50ª;83%) o ≥ 1 FRCV (≥60a).
Mediana de seguimiento: 2a
Objetivo primario compuesto

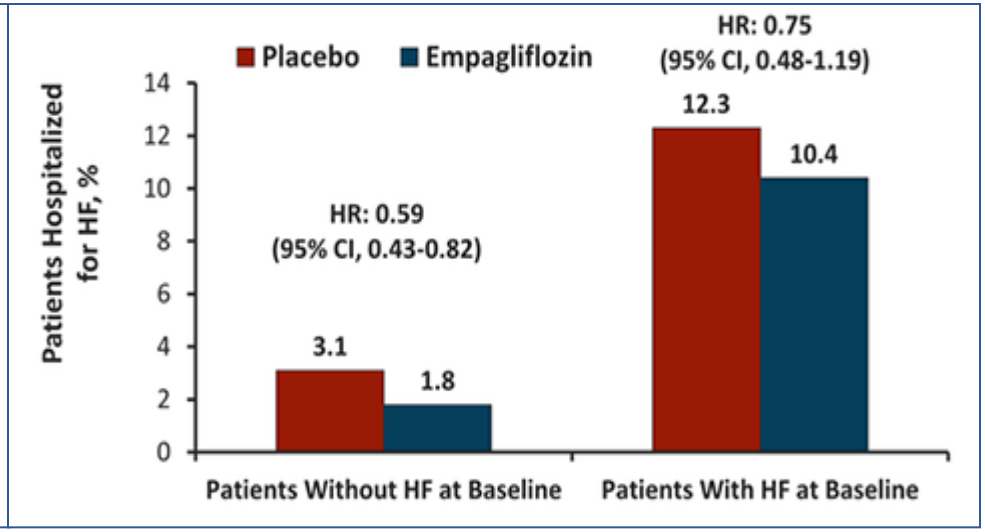
Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial

Table 1 Heart failure outcomes and all-cause hospitalization

Outcome	Placebo ($N = 2333$)		Empagliflozin ($N = 4687$)		HR (95% CI)	*P*-value
	n (%)	Rate/1000 patient-years	*n* (%)	Rate/1000 patient-years		
Heart failure hospitalization or cardiovascular death	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001
Hospitalization for or death from heart failure	104 (4.5)	15.8	129 (2.8)	9.6	0.61 (0.47–0.79)	<0.001
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Investigator-reported heart failure[a]	143 (6.1)	22.0	204 (4.4)	15.3	0.70 (0.56–0.87)	0.001
Investigator-reported serious heart failure[a,b]	136 (5.8)	20.9	192 (4.1)	14.4	0.69 (0.55–0.86)	0.001
All-cause hospitalization	925 (39.6)	183.3	1725 (36.8)	161.9	0.89 (0.82–0.96)	0.003

CI, confidence interval; HR, hazard ratio; MedDRA, Medical Dictionary for Regulatory Activities.
[a]Based on narrow standardized MedDRA query 'cardiac failure', which comprised these preferred terms: acute pulmonary oedema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary oedema; right ventricular failure.
[b]Adverse events reported as serious adverse events by investigator. Patients treated with at least one dose of study drug.





Fitchett D. Eur Heart J. 2016;37:1526-34

Comparison of Long-Term Mortality for Cardiac Diseases in Patients With Versus Without Diabetes Mellitus

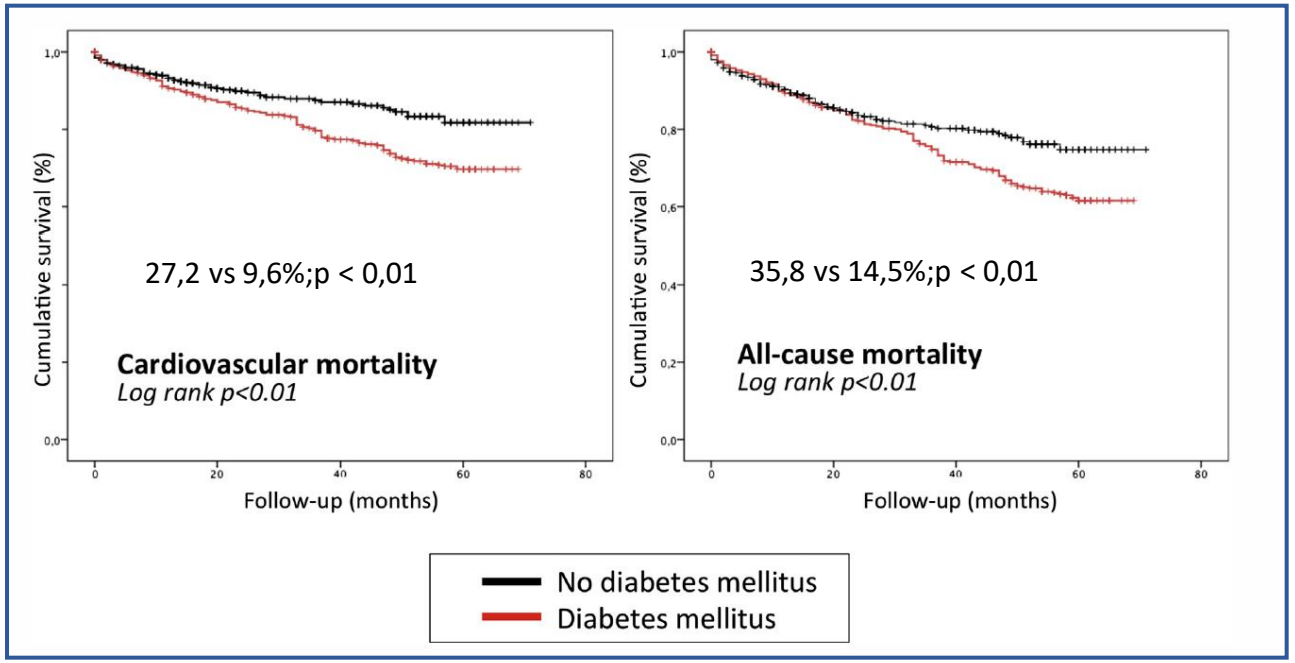
El 75% de la mortalidad a largo plazo de los diabéticos es de causa CV

- 1293 pacientes ingresados

(32% DM)

- Evaluar mortalidad CV y por todas las causas (Media de seguimiento de 58 m)

- ✓ La causa más frecuente de ingreso hospitalario fue el SCA, seguido de la IC.
- ✓ Mortalidad hospitalaria > en diabéticos (5,6% vs 1,7%; p< 0,01).

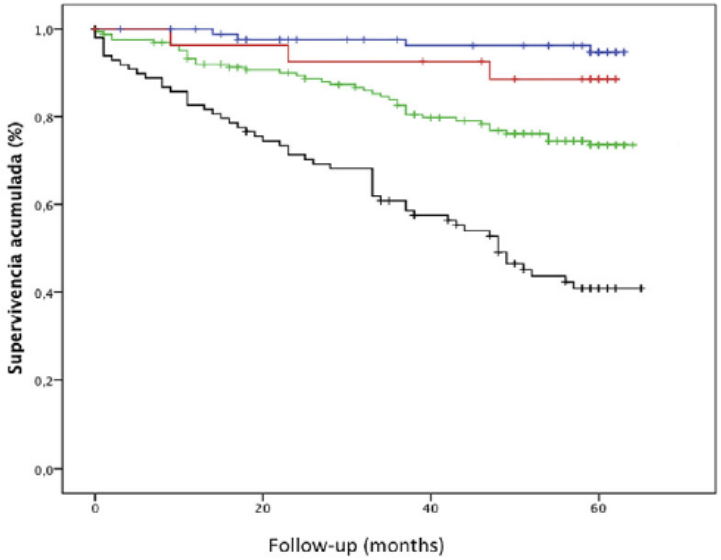


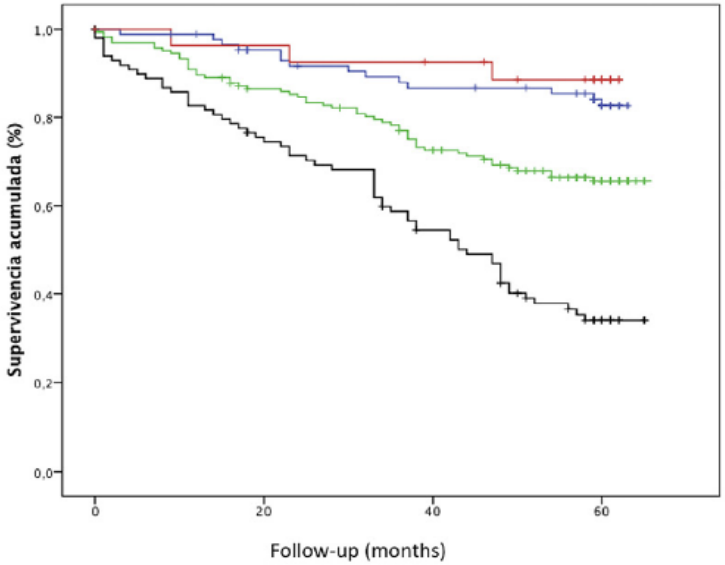
Cordero et al. Am J Cardiol;2016;117:1088-1094

Cardiovascular mortality

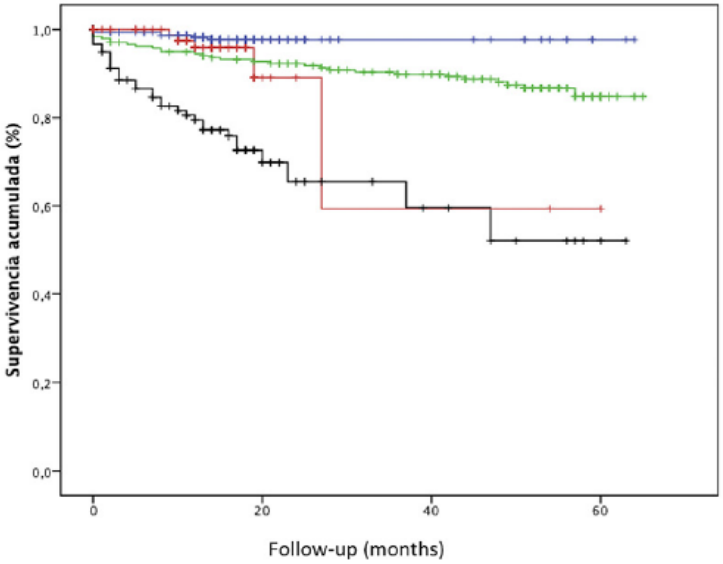
All-cause mortality

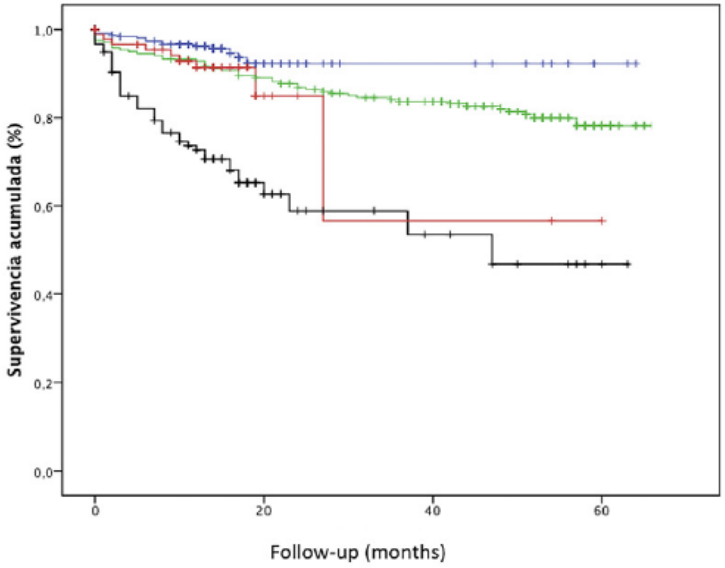
DM





No DM





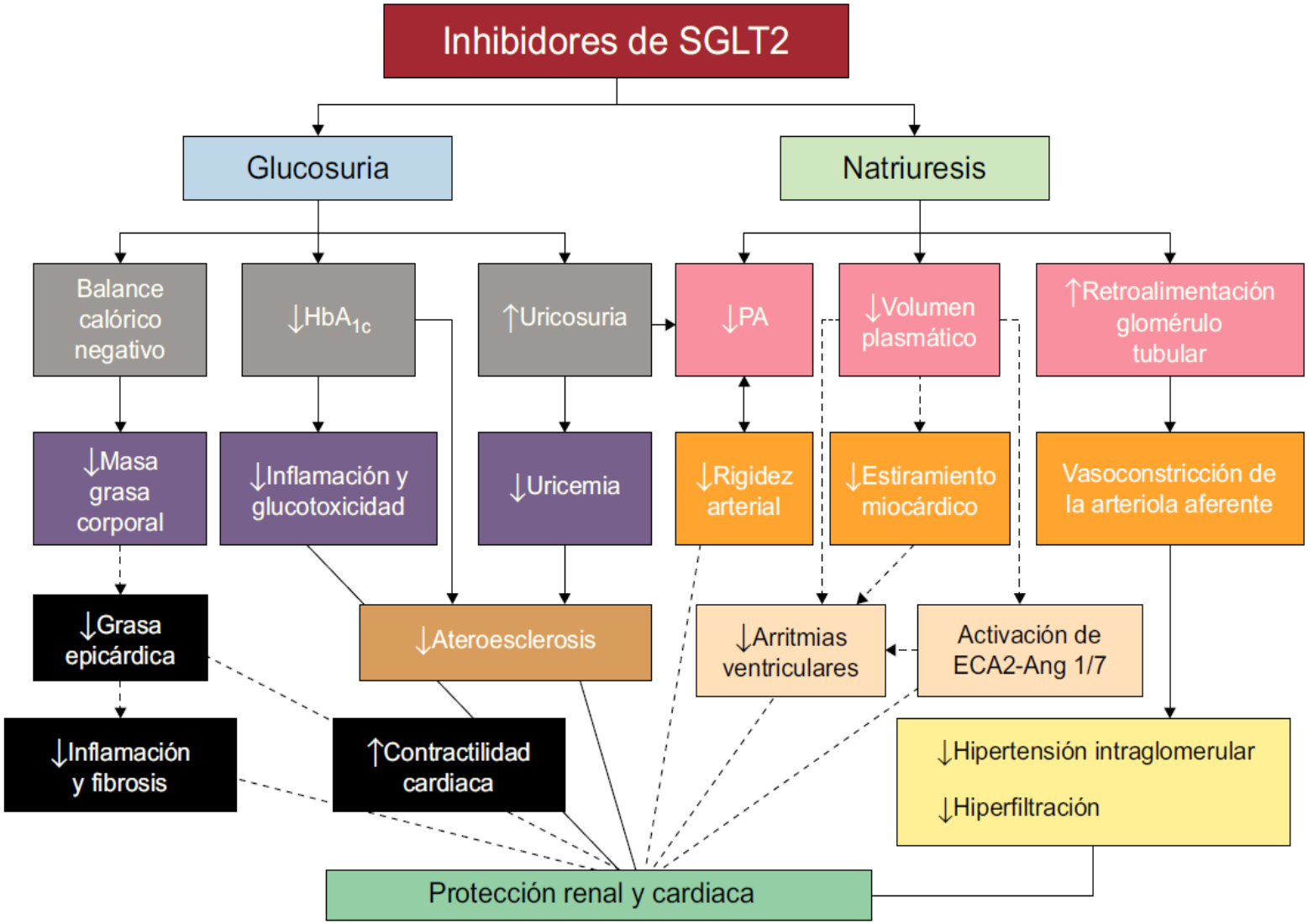
Acute Heart Failure

Acute Coronary Heart Disease

Rhythm disorders

No cardiac disease or syncope

Posibles mecanismos de la protección cardiovascular de los iSGLT2



Adaptado de Rakasejeran et al. Kidney Int. 2016;89:524-6

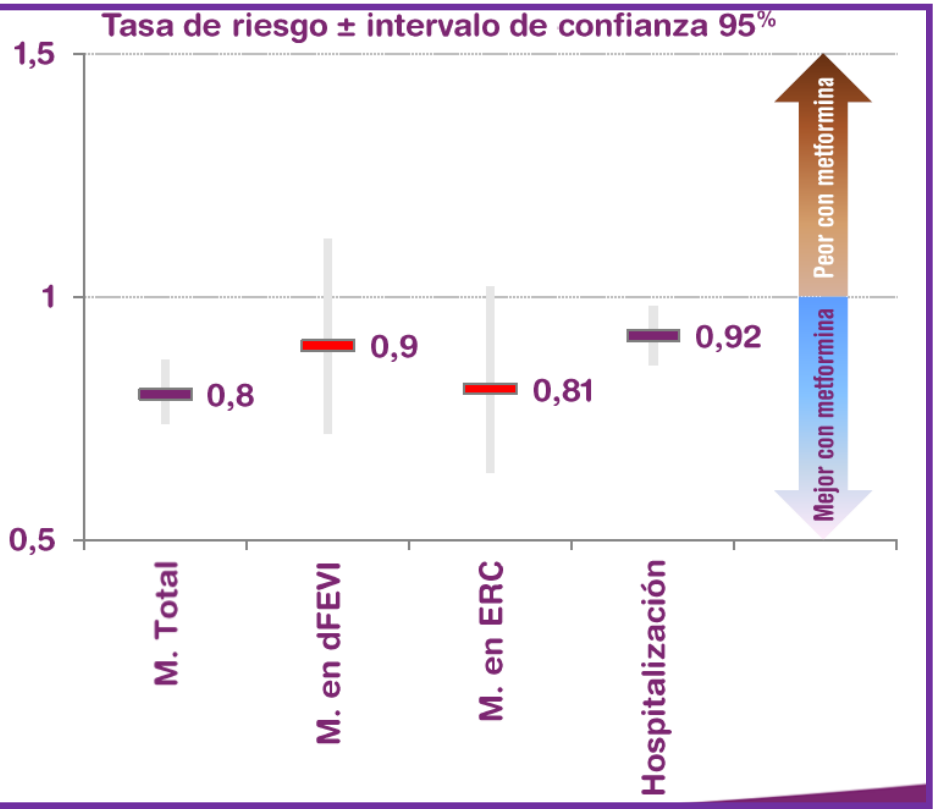
Circulation
Heart Failure

Metformina disminuye la mortalidad y la hospitalización en pacientes con DM2 e IC

Revisión sistemática de estudios observacionales en pacientes con DM2 e insuficiencia cardíaca

9 estudios: 34.504 pacientes

- ↓ Mortalidad (M) total.
- No incrementó mortalidad en pacientes con descenso de fracción de eyección (dFEVI) y enfermedad renal crónica (ERC)
- ↓ Hospitalización
- No aumento el riesgo de acidosis láctica ($p = 0.4$)



Adapted from Eurich DT. Circ Heart Fail. 2013;56: 395-402.

ENSAYOS CV TRADICIONALES FRENTE A ENSAYOS DE SEGURIDAD CV EN DIABETES

CV = cardiovascular; DPP-4 = dipeptidil peptidasa-4; LDL-C = colesterol unido a lipoproteínas de baja densidad.

1. Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7–22. 2. Heart Protection Study Collaborative Group. *Lancet*. 2003;361:2005–2016. 3. White WB et al. *N Engl J Med*. 2013;369:1327–1335. 4. Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326. 5. Green JB et al. *Am Heart J*. 2013;166:983–989.e7.