Centro de Hipertensión Arterial
del HOSPITAL UNIVERSITARIO AUSTRAL

UPDATE E INNOVACIONES EN DIABETES CUIDADO CARDIOVASCULAR Y ROL DE INHIBIDORES DE DPP-4 Y SGLT-2

Ma. de los Milagros Rubio

SANTA MARÍA DE LA SALUD

Problemas Actuales

PREVALENCIA MUNDIAL (18-99 AÑOS)		
	Año 2017	Año 2045
DM	451 millones (8,4%)	693 millones (9,9%)
Prediabetes	374 millones (7,7%)	587 millones (8,4%)

49,7% de personas con DM permanecen sin diagnostico

Cho N.H. Diabetes Res Clin Pract.2018;138:271-281.

Prevalencia

- 33% de los adultos > 65 años tienen DM tipo 2
- 50% de los adultos > 65 años tienen PREDIABETES
- Es una población con mas riesgo de complicaciones diabéticas

Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline

Derek LeRoith,[1] Geert Jan Biessels,[2] Susan S. Braithwaite,[3,4] Felipe F. Casanueva,[5] Boris Draznin,[6] Jeffrey B. Halter,[7,8] Irl B. Hirsch,[9] Marie E. McDonnell,[10] Mark E. Molitch,[11] M. Hassan Murad,[12] and Alan J. Sinclair[13]

J Clin Endocrinol Metab, May 2019, 104(5):1520–1574

DIABETES NO ATENDIDA

Año 2017
5 millones de muerte (20-99 años)
36,5% en menores de 60 años

Paciente, familias y salud pública
$850 billones a nivel mundial (2017)

Cho N.H. Diabetes Res Clin Pract.2018;138:271-281.

DIAGNOSTICO TEMPRANO

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 the 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).

diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Diabetes Care. 2019

- ≥65 años: Pesquisa de DM con dosaje de HbA1c y/o glucemia en ayunas
- PTOG en pacientes valores de prediabetes y con alto riesgo de DM :

- Sobrepeso u obesidad
- Familiares de 1º grado con DM
- Raza
- Enf. Cardiovascuar
- HTA (≥140/90 mmHg)
- HDL<35 mg/dl, y/o TAG > 250mg/dl
- SAOS
- Sedentarismo

LeRoith D. et al. JCEM. 2019. 104(5):1520–1574

Rol del Cardiólogo

1º) Pesquisa de DM2 en pacientes con ASCVD establecida o alto riesgo de ASCVD

2º) Tratamiento agresivo de los factores de riesgo CV

- ✓ Dieta
- ✓ Actividad Física
- ✓ Pérdida de peso
- ✓ Control dela presión arterial
- ✓ Control de lípidos
- ✓ Uso de agentes antiagregantes plaquetarios

3º) Conocimiento de los nuevos fármacos hipoglucemiantes con efecto CV

TRATAMIENTO ADECUADO

- ✓ Paciente comprometido
- ✓ Médico actualizado
- ✓ Sistema de salud

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

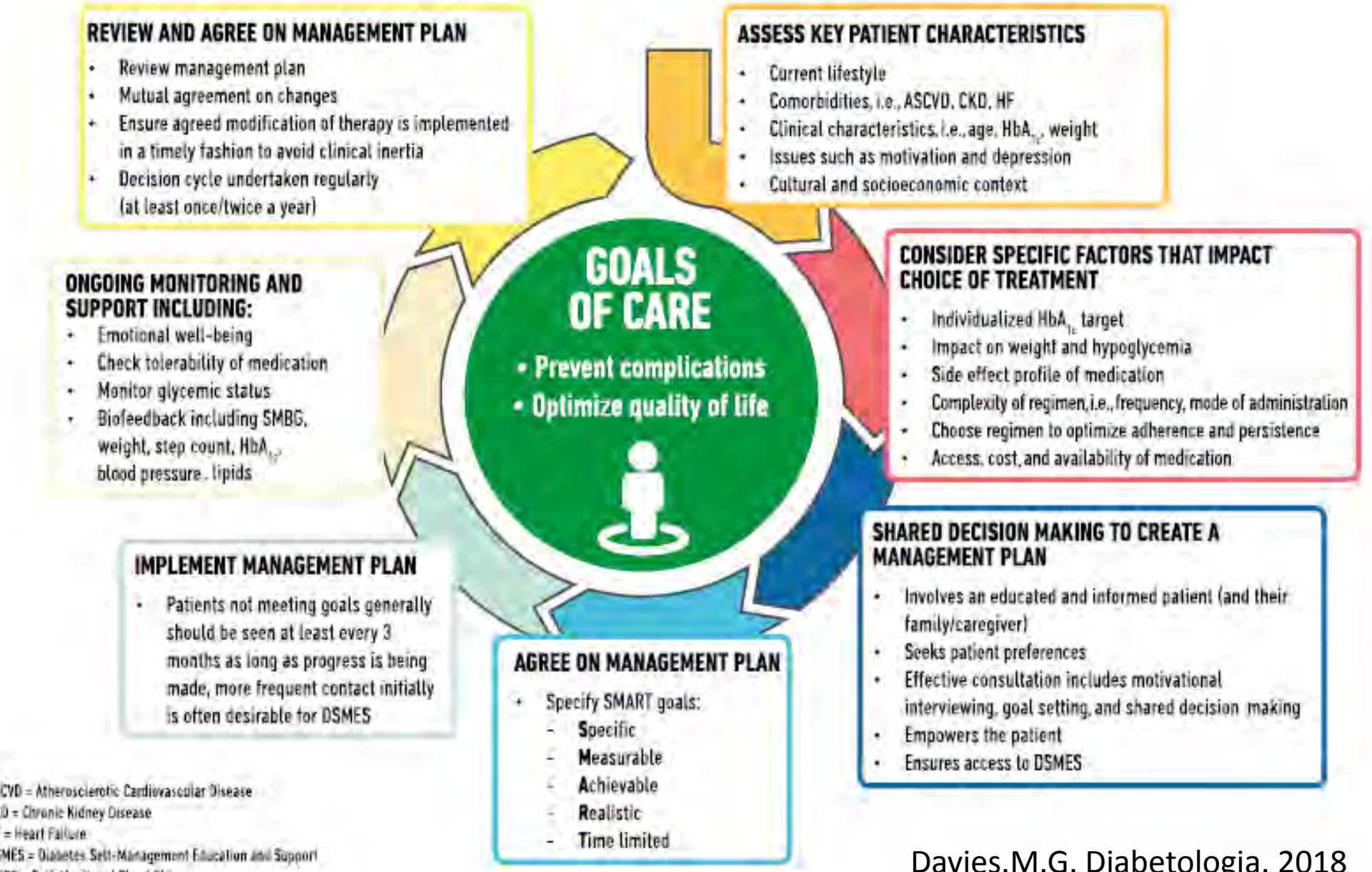
CONSENSUS REPORT

CrossMark

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

- Cambios en Estilo de Vida
- Diabetes Self Management Education (DSME)
- Tratamiento de la Obesidad
- Elección de Fármacos: 1ª evaluar comorbilidades (ASCVD, ERC, ICC)



CVD = Atherosclerotic Cardiovascular Disease
D = Chronic Kidney Disease
= Heart Failure
MES = Diabetes Self-Management Education and Support
BG = Self-Monitored Blood Glucose

Davies.M.G. Diabetologia. 2018

Smoking Cessation, Weight Change, Type 2 Diabetes, and Mortality

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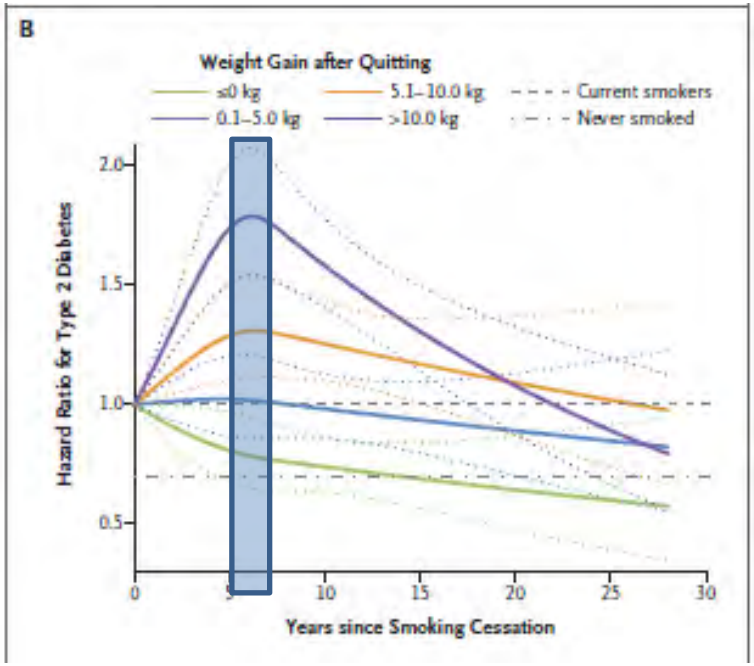
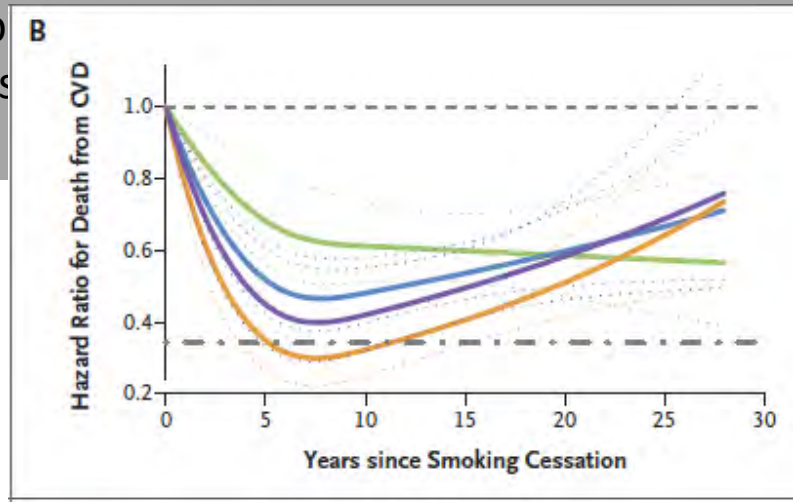
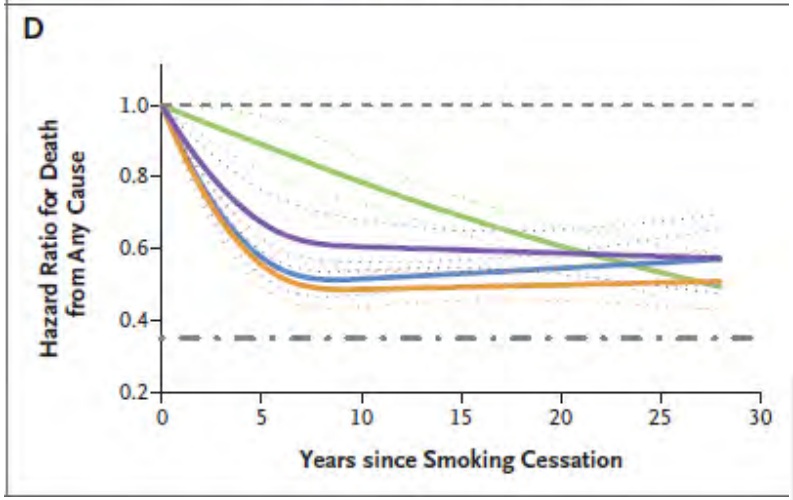
Riesgo de desarrollar DM luego de Abandonar Tb
Seguimiento de 19,6 años personas de 3 cohortes
12.384 casos de DM2 confirmados







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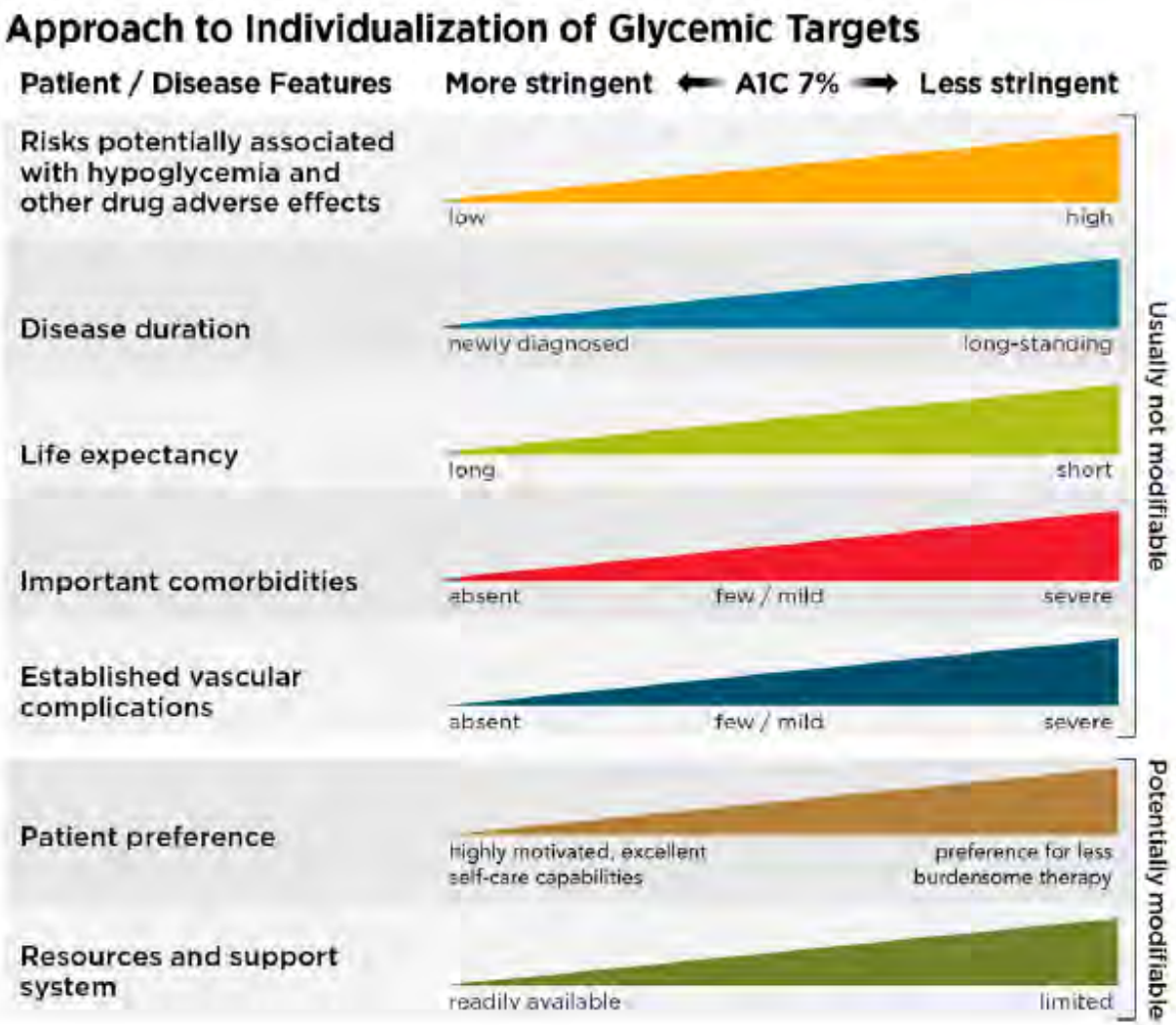
Yang Hu, S.M. et al. NEJM. 2018;379(7): 623-32

Metas de HbA1c



Diabetes Care 2019;42(Suppl. 1):S61–S70

Objetio de HbA1c en ≥ 65 años

Overall Health Category	Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Patient characteristics	No comorbidities **or** 1-2 non-diabetes chronic illnesses* **and** No ADL€ impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses* **and/or** Any one of the following: mild cognitive impairment or early dementia ≥2 IADL impairments	Any **one** of the following: End-stage medical condition(s)** Moderate to severe dementia ≥2 ADL impairments Residence in a long-term nursing facility

Reasonable glucose target ranges and HbA1c by group

Shared decision-making: individualized goal may be lower or higher

LeRoith D. et al. JCEM. 2019. 104(5):1520–1574

Objetio de HbA1c en ≥ 65 años

		Reasonable glucose target ranges and HbA1c by group Shared decision-making: individualized goal may be lower or higher		
Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)	No	Fasting: 90-130 mg/dL Bedtime: 90-150 mg/dL <7.5%	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL <8%	Fasting: 100-180 mg/dL Bedtime: 110-200 mg/dL <8.5%¥
	Yes£	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL ≥7.0 and <7.5%	Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL ≥7.5 and <8.0%	Fasting: 100-180 mg/dL Bedtime: 150-250 mg/dL ≥8.0 and <8.5%¥

LeRoith D. et al. JCEM. 2019. 104(5):1520–1574

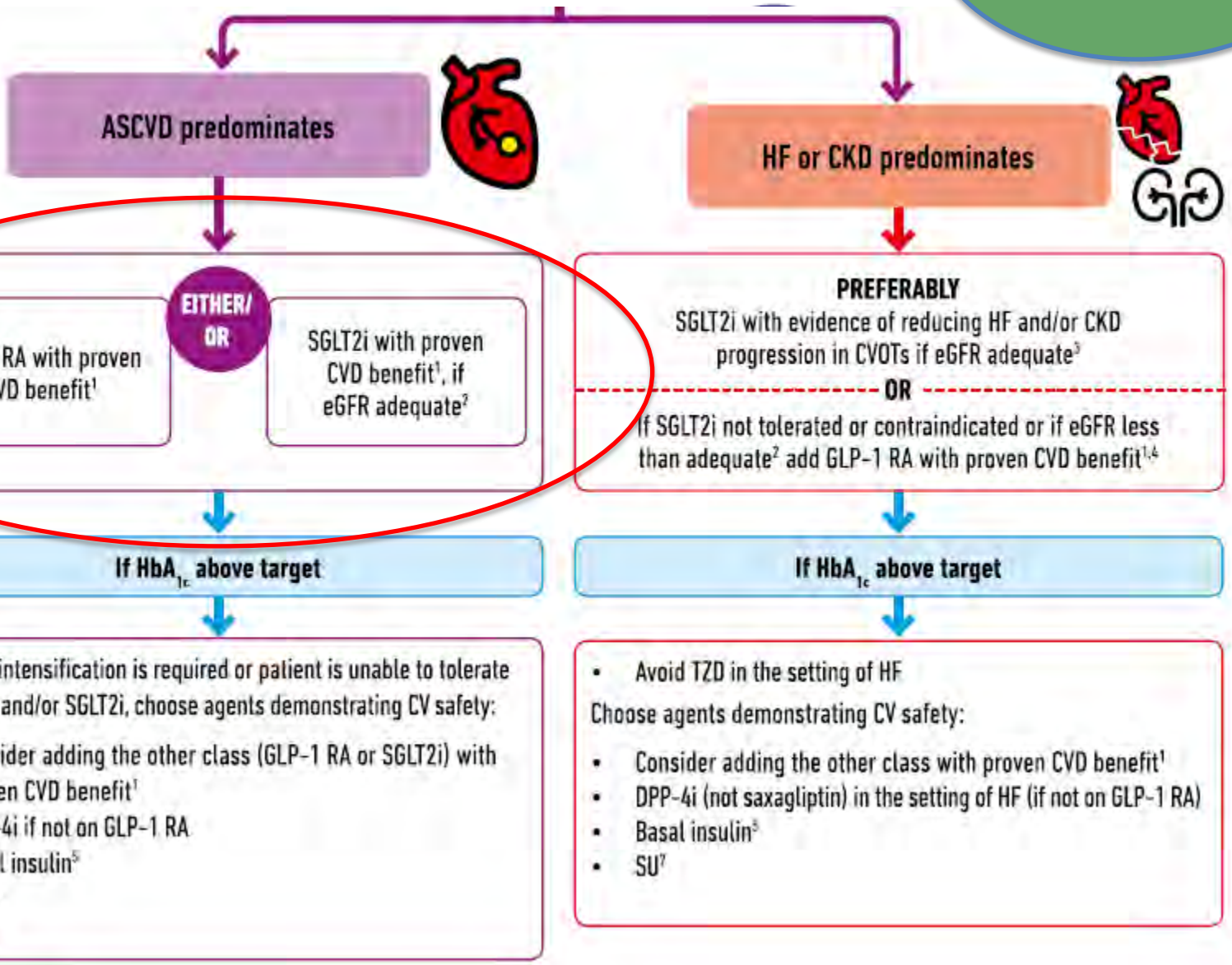
Tratamiento farmacológico

1ª Línea: METFORMINA

Si HbA1c > 1,5% del objetivo individualizado:
considerar tratamiento combinado

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

15-20%
de los pacientes



SGLT2-i

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

Pacientes con múltiples factores de riesgo CV	**0%**	**34%**	**59%**

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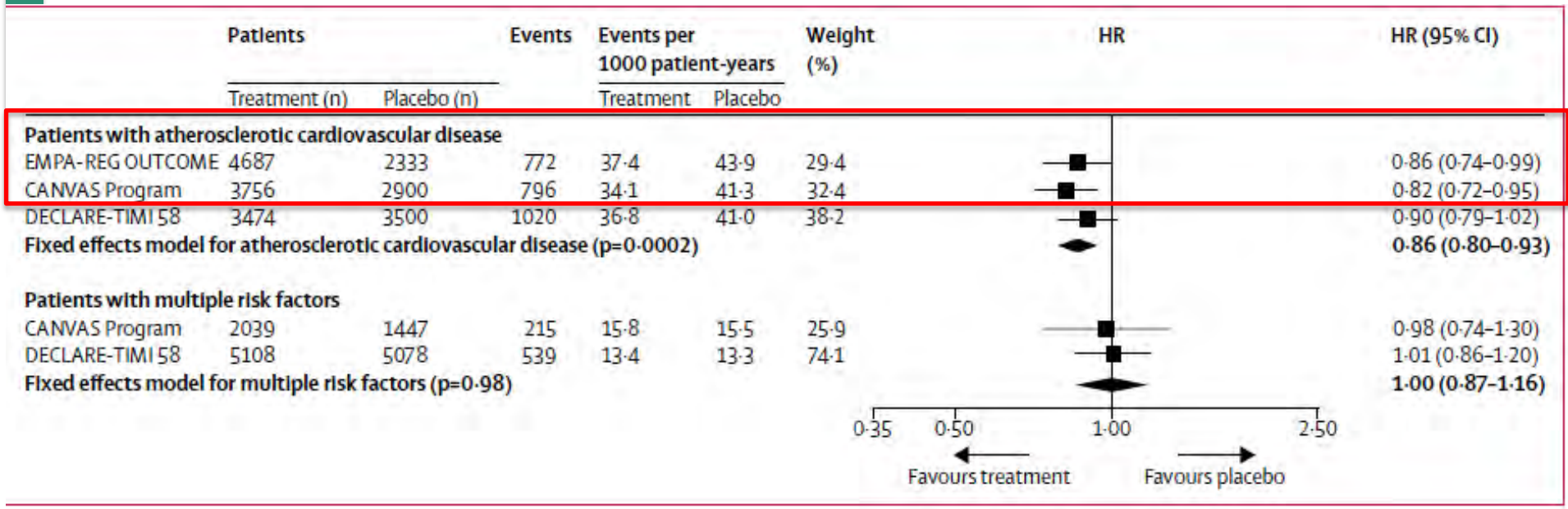
***Zelniker T.A. et al. Lancet* 2019; 393: 31–39c**

MACE (IAM no fatal, ACV no fatal y mortalidad CV)

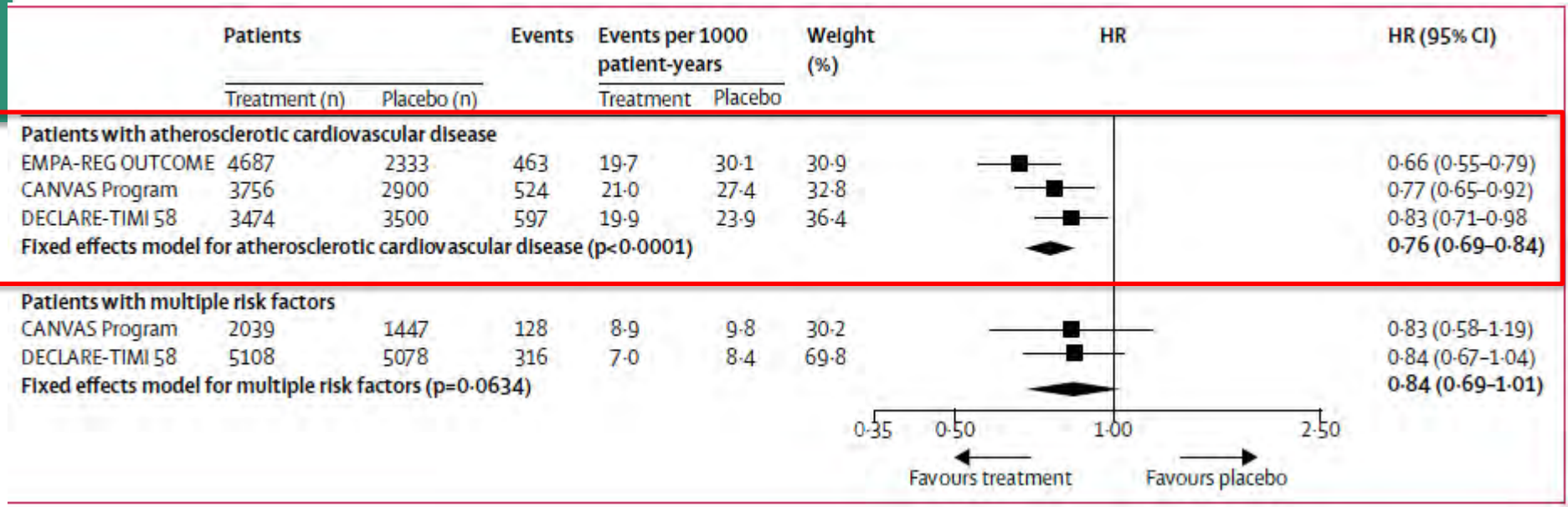


	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

Empaglifozina redujo un 14% el riesgo de MACE

***Zelniker T.A. et al. Lancet* 2019; 393: 31–39c**

Hospitalización por ICC y mortaidad CV



	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**

Empaglifozina

↓ un 38% la mortalidad CV

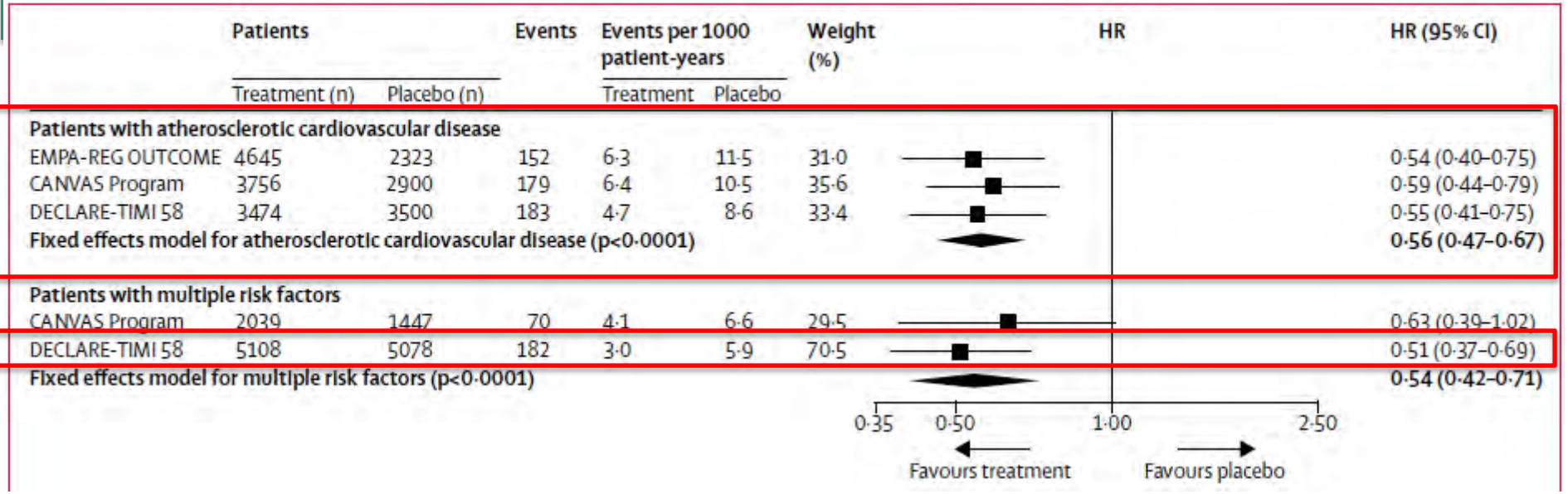
↓ riesgo de internación por ICC un 35% (HR: 0,65 [0,50-0,85]) en pacientes con o sin antecedentes de ICC

Dapaglifozina

↓ 5,8% mortalidad CV

***Zelniker T.A. et al. Lancet* 2019; 393: 31–39c**

Progresión de la Enf. Renal, ERC terminal o muerte por enfermedad renal



Zelniker T.A. et al. Lancet **2019; 393: 31–39c**

Empagliflozin And The Risk Of Heart Failure Hospitalization In Routine Clinical Care: A First Analysis From The Empagliflozin Comparative Effectiveness And Safety (EMPRISE) Study

Elisabetta Patorno[1], Ajinkya Pawar[1], Jessica M Franklin[1], Mehdi Najafzadeh[1], Anouk Déruaz-Luyet[2], Kimberly G Brodovicz[2], Dorothee B Bartels[2], Chandrasekar Gopalakrishnan[1], Martin Kulldorff[1], and Sebastian Schneeweiss[1]
[1]Brigham and Women's Hospital, Boston, MA, USA; [2] Boehringer Ingelheim, Ingelheim am Rhein, Germany

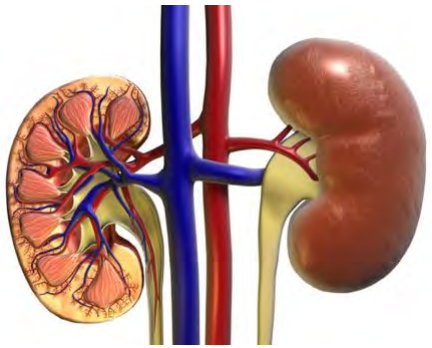
EMPRISE
EMPAGLIFLOZIN REAL-WORLD EFFECTIVENESS

Estudio en desarrollo

Evalúa riesgo de internaciones por insuficiencia cardíaca en pacientes que iniciaron tratamiento con Empagliflozina vs pacientes que iniciaron tratamiento con un iDPP4

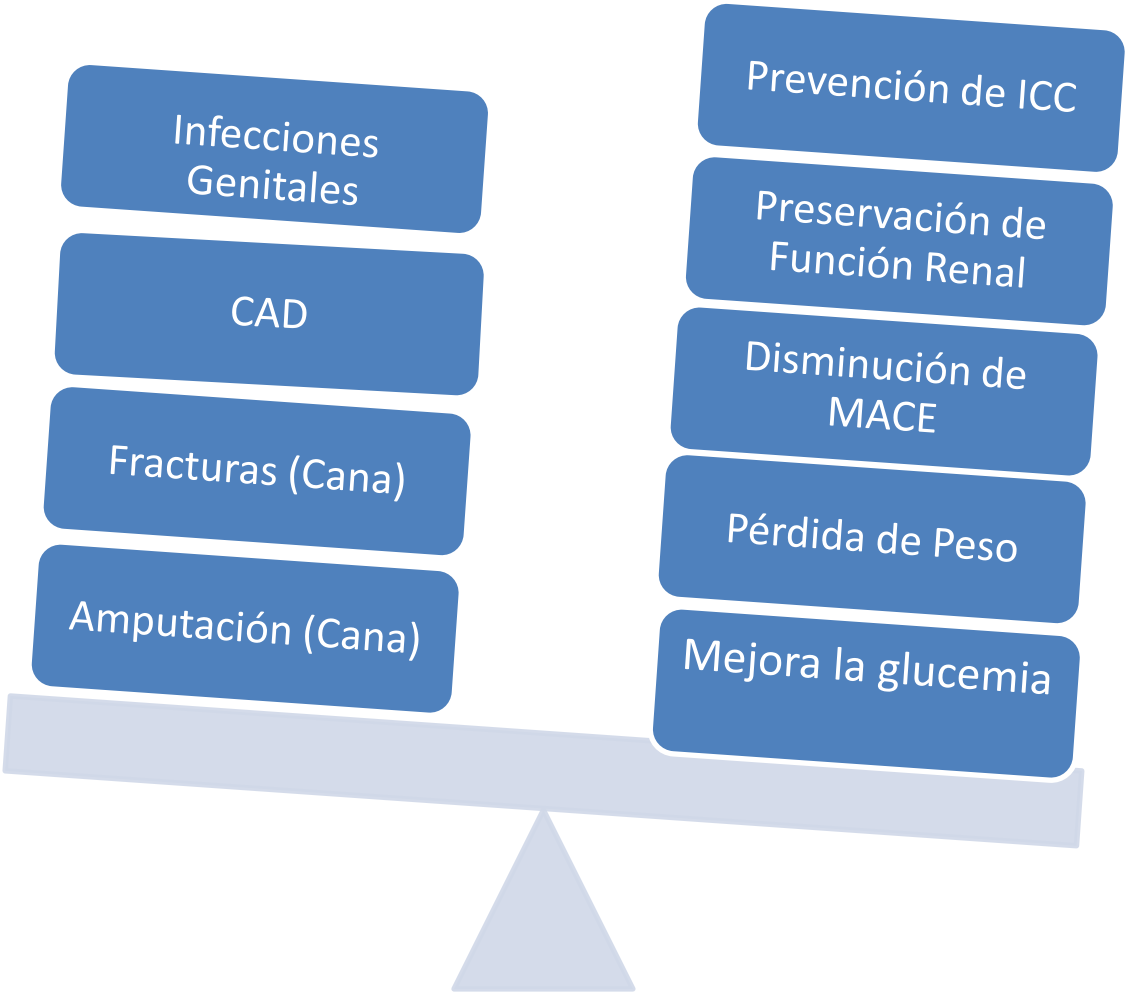
- ✓ Empagliflozina disminuyó en un 65% (HR 0,35, IC 0,20-0,61) el riesgo de internación por insuficiencia cardíaca vs iDPP4 en pacientes SIN enfermedad CV de base
- ✓ Empagliflozina diminuyó en un 47% (HR 0,53, IC 0,39-0,72) el riesgo de internación por insuficiencia cardíaca vs iDPP4 en pacientes CON enfermedad CV de base

↑ GLUCOSURIA → ↓ el VEC → ↑HTO
↓ la precarga
↓ poscarga
↓ rigidez arterial
↓ presión arterial
↓ masa del VI



VC de la arteriola aferente y dilatación de la eferente → ↓ de la presión intraglomerular → ↓ Albuminuria
↓ Fibrosis glomerular
Retrasa la progresión de la enfermedad renal

SGLT2-i


Infecciones Genitales
CAD
Fracturas (Cana)
Amputación (Cana)
Prevención de ICC
Preservación de Función Renal
Disminución de MACE
Pérdida de Peso
Mejora la glucemia

Análogos del Receptor de GLP-1

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COMUNICADOS DE PRENSA

	LEADER (10)	REWIND	PIONEER-6
Patients enrolled	9,340	9.901	3183
Drug	Liraglutide	Dulaglutida	Semaglutida (VO)
Dose	1.8 mg or max tolerated dose per day	1,5 mg/sem	14 mg/sem
Duration of follow up (years)	3.8	>5	1,5
Baseline A1C	8.7	7,3%	
Mean duration of diabetes (years)	12.8		
Baseline metformin use (%)	76		
Baseline statin use (%)	72		
Baseline prevalence of CV disease†/HF (%)	81/18	31%/	
Primary outcome, HR (95% CI)‡	3-point MACE 0.87 (0.78-0.97)		1P-MACE 0,79 (NS)
CV death, HR (95% CI)	0.78 (0.66-0.93)		0.49 (p=0,03)
Fatal or nonfatal MI, HR (95% CI)§	0.86 (0.73-1.00)		1,18 (NS)
Fatal or nonfatal stroke, HR (95% CI)§	0.86 (0.71-1.06)		0,74 (NS)
All-cause mortality, HR (95% CI)	0.85 (0.74-0.97)		0,51 (p=0,008)
HF hospitalization, HR (95% CI)	0.87 (0.73-1.05)		

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DPP4i

	SAVOR TIMI 53 (Saxagliptina)	EXAMINE (Alogliptina)	TECOS (Sitagliptina)	CARMELINA (Linagliptina)
n	16.492	5380	14671	6980
Seguimiento	2,1 años	1,5 años	3	continúa
Duración de la DM	10 años	7,35 años	11	14 años
HbA1c	8%	8,12%	6,5-8%	7,9%
ASCVD	78%	90%	100%	57%
ERC		28%		74%
Mortalidad CV, IAM o ACV no fatal, internación por AI (HR)	1 (IC 089-1,12)	0,98 (0,86-1,12)	0,98 (0,88-1,09)	1.02 (0,89-1,17)
Internación por ICC (HR)	HR: 1,27 (IC: 1,07-1,51)	1,07 (0,79-1,46)	1 (0,83-1,20)	

HTA

<u>OBJETIVOS DE PA INDIVIDUALIZADO</u>: Riesgo de ASCVD a 10 años

>15%: < 130/80 mmHg

<15%: <140/90mmHg

≥ 65 años: 140/90 mmHg

130/80 mmHg si ACV previo o IRC (<60ml/min o albuminuria)

- Control intensivo de la PAS: < 120 mmHg no redujo IAM o ACV no fatal y mortalidad CV Mayor riesgo de eventos adversos (ACCORD BP)

- SI PA > 120/80 mmHg: cambios en estilo de vida (Dieta DASH, disminuir el consumo de Na y aumentar el de K, consumo moderado de alchol, activ. Física)

- Drogas que demostraron beneficio CV en DM: IECA, ARA2, diuréticos tiazídicos, bloqueantes cálcicos dihidropiridinicos

- Si albuminuria (relación Cr/Album urinaria ≥ 30 mg/g)

  → incluir IECA o ARA2

- Si HTA severa (≥ 160/100 mmHg): iniciar tratamiento combinado

Manejo de Lípidos

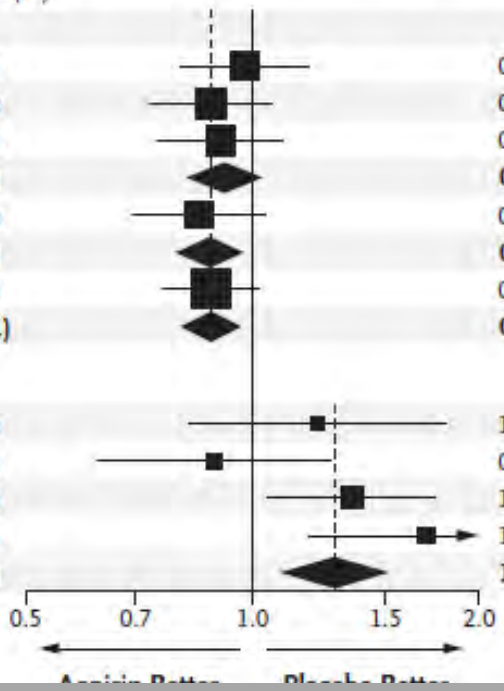
Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



Prevención 2ª en pacientes con antecedentes de ASCVD

Prevención 1ª: en pacientes con alto riesgo de ASCVD, luego de discutir con el paciente riesgos y beneficios

Conclusiones

- Encontrar pacientes con DM2 no diagnosticada
- Realizar tratamiento agresivo de los factores de riesgo cardiovascular
- Es la primera vez que se habla de tratamientos que, además de mejorar la glucemia, tienen un beneficio directo en la evolución de la patología CV
- Estos beneficios son independientes del efecto sobre la HbA1c
- Los cardiólogos deberían incorporar el uso de los SGLT2i y GLP1-RA en los pacientes diabéticos tipo 2 y ASCVD establecida para mejorar su evolución
- Los iDPP4 son drogas seguras a nivel cardiovascular, excepto la Saxagliptina que mostró un aumento del riesgo de internaciones por ICC

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