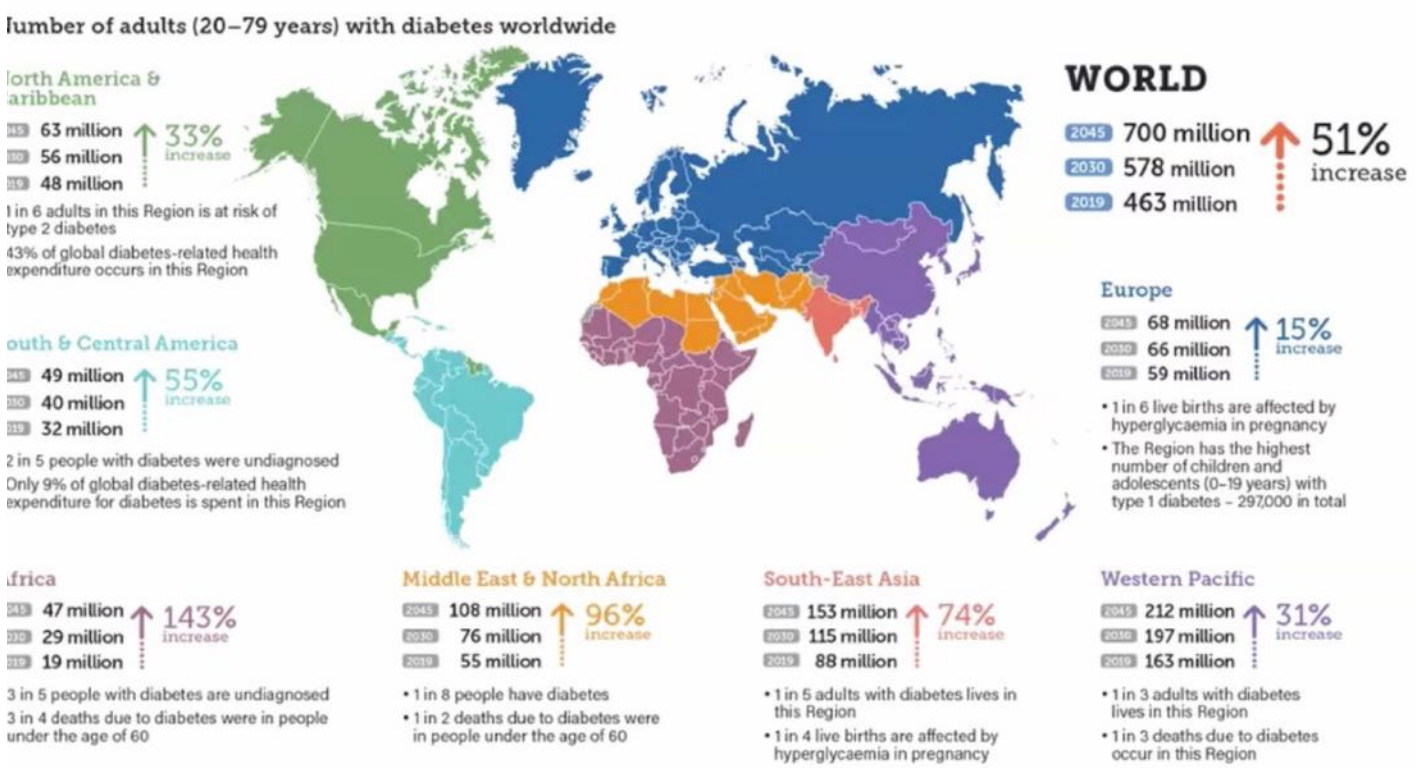
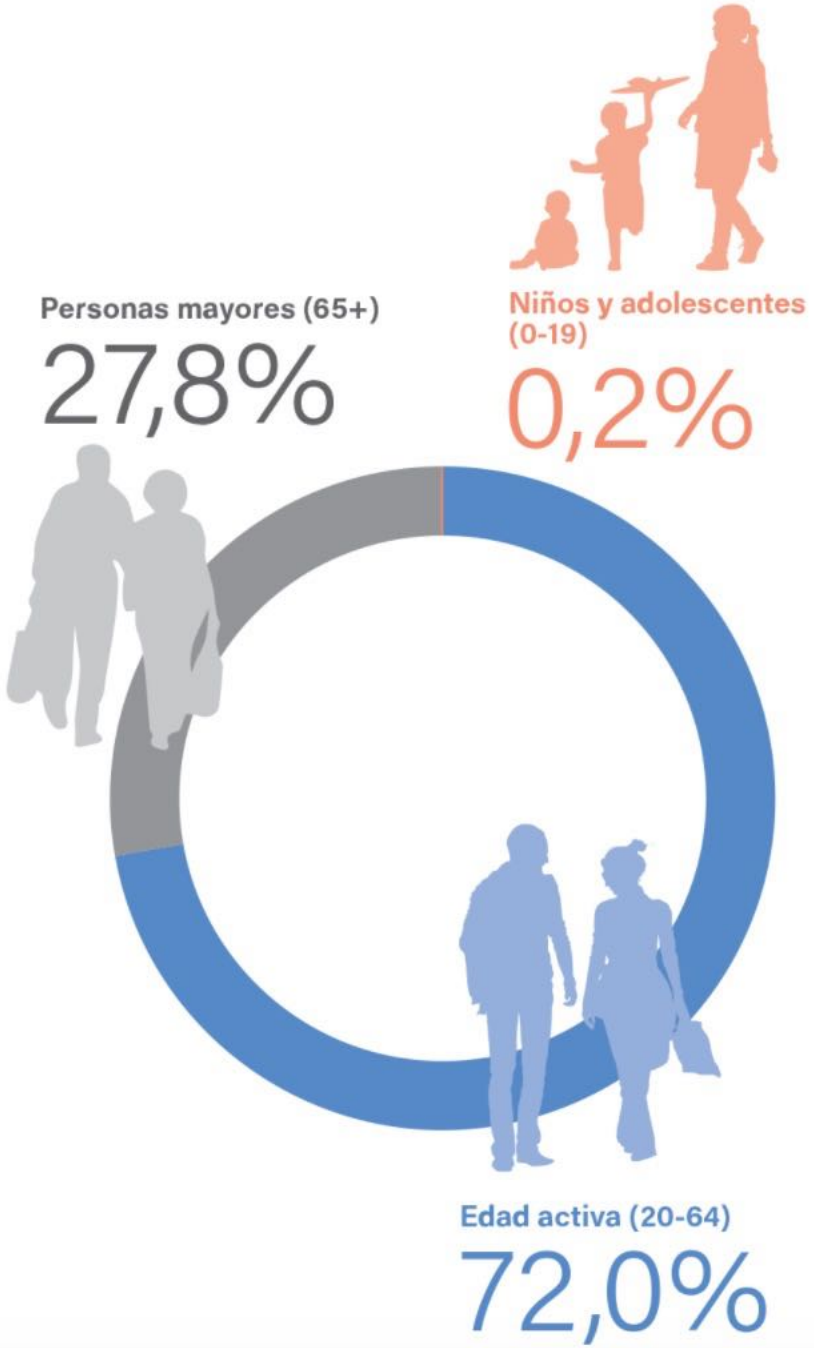
Uso de nuevos antidiabéticos en la enfermedad cardiovascular

Irene Toribio García
R1 de Cardiología
Sesión de Medicina Interna

14 de septiembre de 2021

Epidemiología de la DM



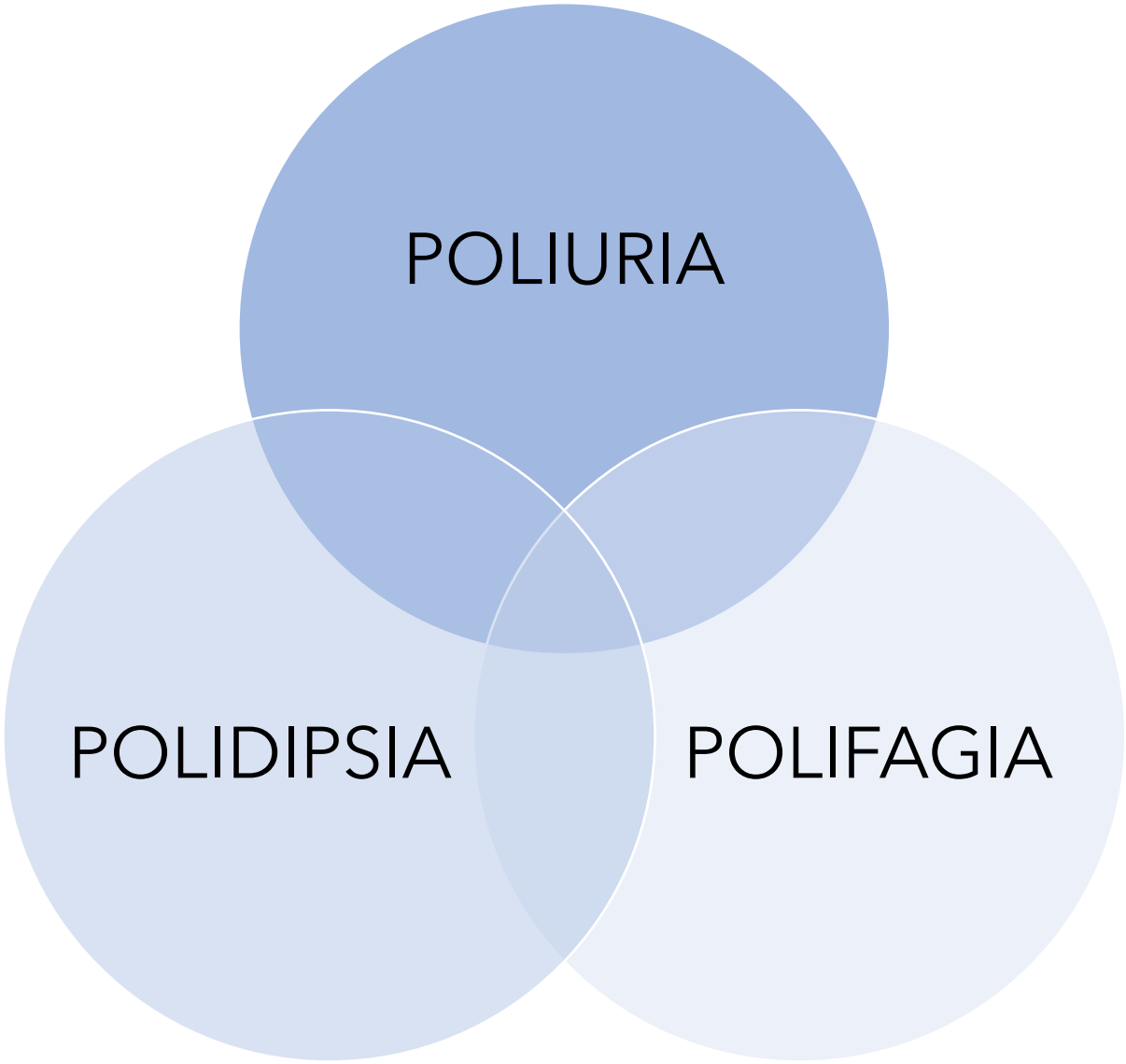


Diabetes Atlas. International Diabetes Federation. 9th edition (2019).

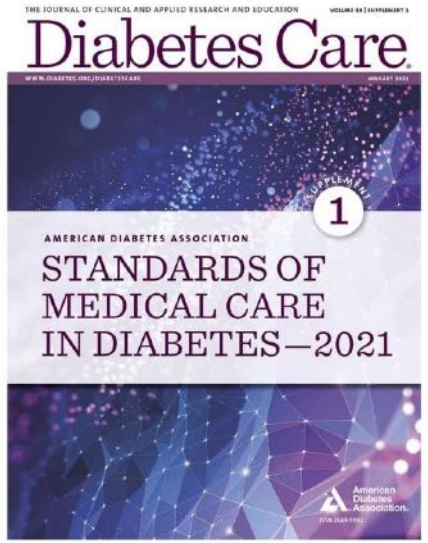
Epidemiología de la DM

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

Clínica y diagnóstico de la DM



Clínica y diagnóstico de la DM



- Hemoglobina glicosilada **> 6,5%**
- Test de sobrecarga oral de glucosa **>200 mg/dL** a los 120 minutos.
- Glucemia basal en ayunas **>126 mg/dL**

Necesarias dos determinaciones

- **Síntomas** cardinales + glucemia > **200 mg/dL** → Determinación única

American Diabetes Association. Diabetes Care 2021. Jan; 44 (Supplement 1): S15-S33.

Clínica y diagnóstico de la DM

- Debería considerarse en casos de **obesidad.**
- Debería realizarse 1 vez al año en casos de **prediabetes.**
- Debería realizarse 1 vez cada 3 años en **diabetes gestacional.**
- Debería realizarse de forma sistemática a todos los **mayores de 45 años.**

CRIBADO

American Diabetes Association. Diabetes Care 2021. Jan; 44 (Supplement 1): S15-S33.

Clínica y diagnóstico de la DM

CARACTERIZACIÓN DE LA DIABETES

- Historia personal y familiar.
- Comorbilidades **(FRCV).**
- Complicaciones (micro y macroangiopatía)

American Diabetes Association. Diabetes Care 2021. Jan; 44 (Supplement 1): S15-S33.

Clínica y diagnóstico de la DM

Clasificación de riesgo CV en pacientes con diabetes y pre-diabetes

Muy alto riesgo	Pacientes con **DM-2 y ECV**, u otro órgano diana dañado[b] o tres o más FRCV asociados[c] o inicio temprano de **DM-2 de larga duración (>20 años)**
Alto riesgo	Pacientes con **diabetes de ≥10 años** de duración sin daños en órgano diana **más cualquier otro factor de riesgo** adicional
Riesgo moderado	**Pacientes jóvenes** (DM-1 con <35 años de edad o DM-2 con <50 años de edad) **con diabetes de <10 años** de duración, sin otros factores de riesgo

Glucose-lowering treatment (a paradigm shift after recent CVOTs): "For the first time, we have evidence from several CVOTs that indicate **CV benefits from the use of SGLT2 inhibitors and GLP-1 Ras in patients with CVD, or at very high/high CV risk**"

[a]Modificado de 2016 European Guidelines on cardiovascular disease prevention in clinical practice.
[b]Proteinuria, daño renal definido como TFGe ≥30 ml/min/1,73 m^2, hipertrofia ventricular izquierda o retinopatía.
[c]Edad, hipertensión, dislipemia, tabaquismo, obesidad.

Cosentino F *et al. Eur Heart J* 2019; doi:10.1093/eurheartj/ehz486

Manejo de la DM

Postura ANTROPOCÉNTRICA

Basada en COMORBILIDADES

Manejo de la DM

PRIMER ESCALÓN

Dieta

Ejercicio

Metformina 850 mg

SEGUNDO ESCALÓN

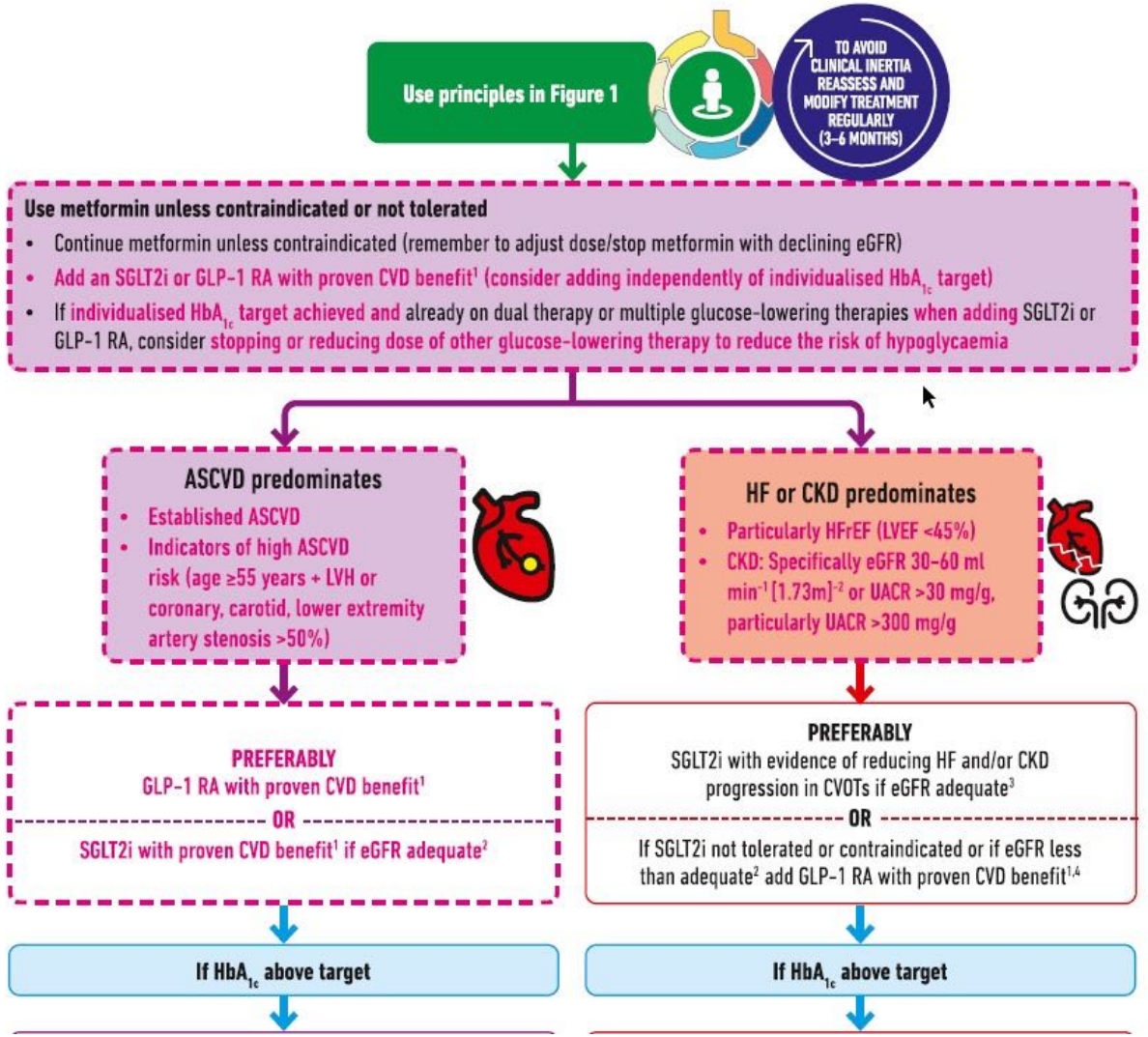
iSGLT2

aGLP1

TERCER ESCALÓN

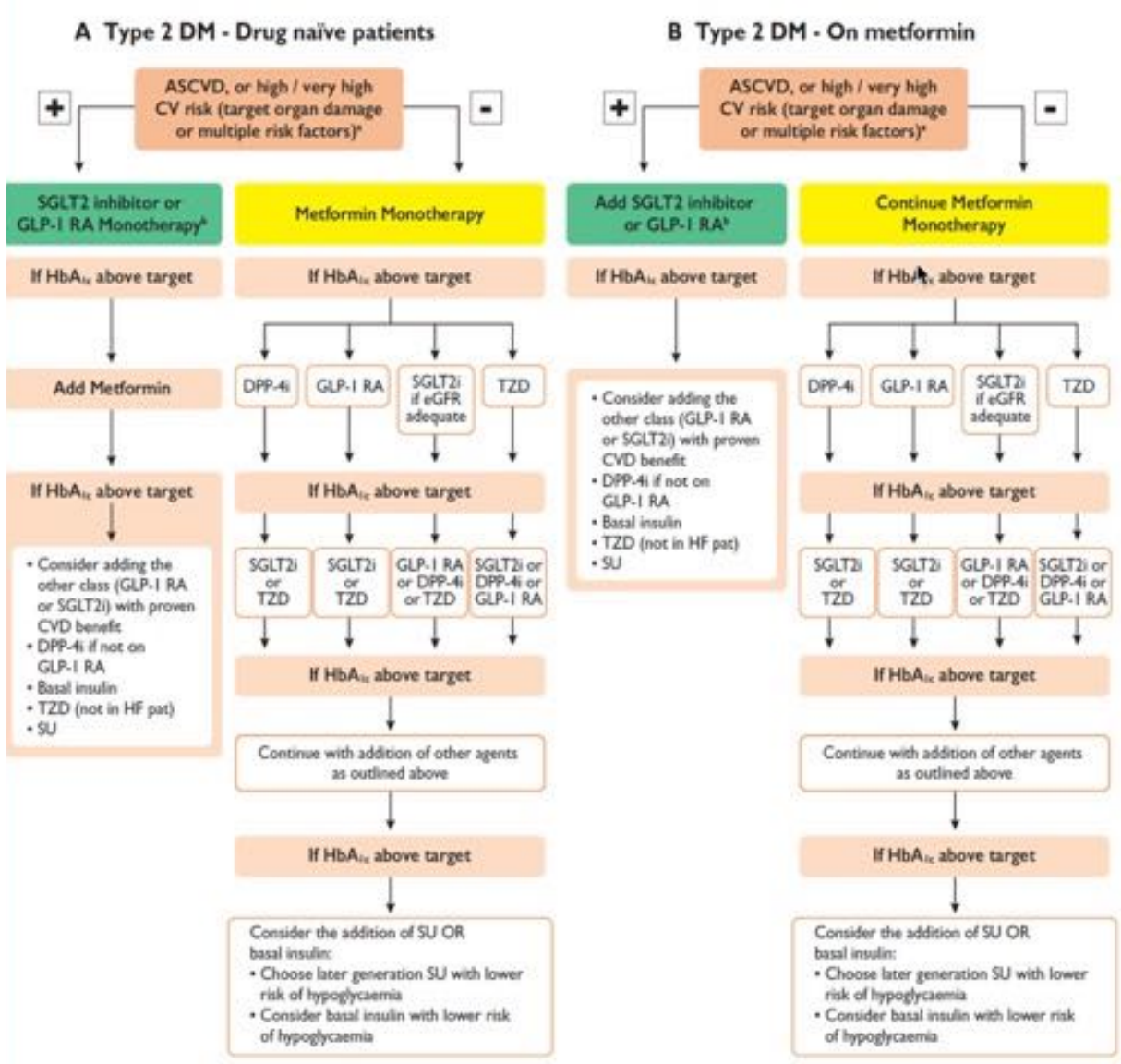
Coste

Manejo de la DM



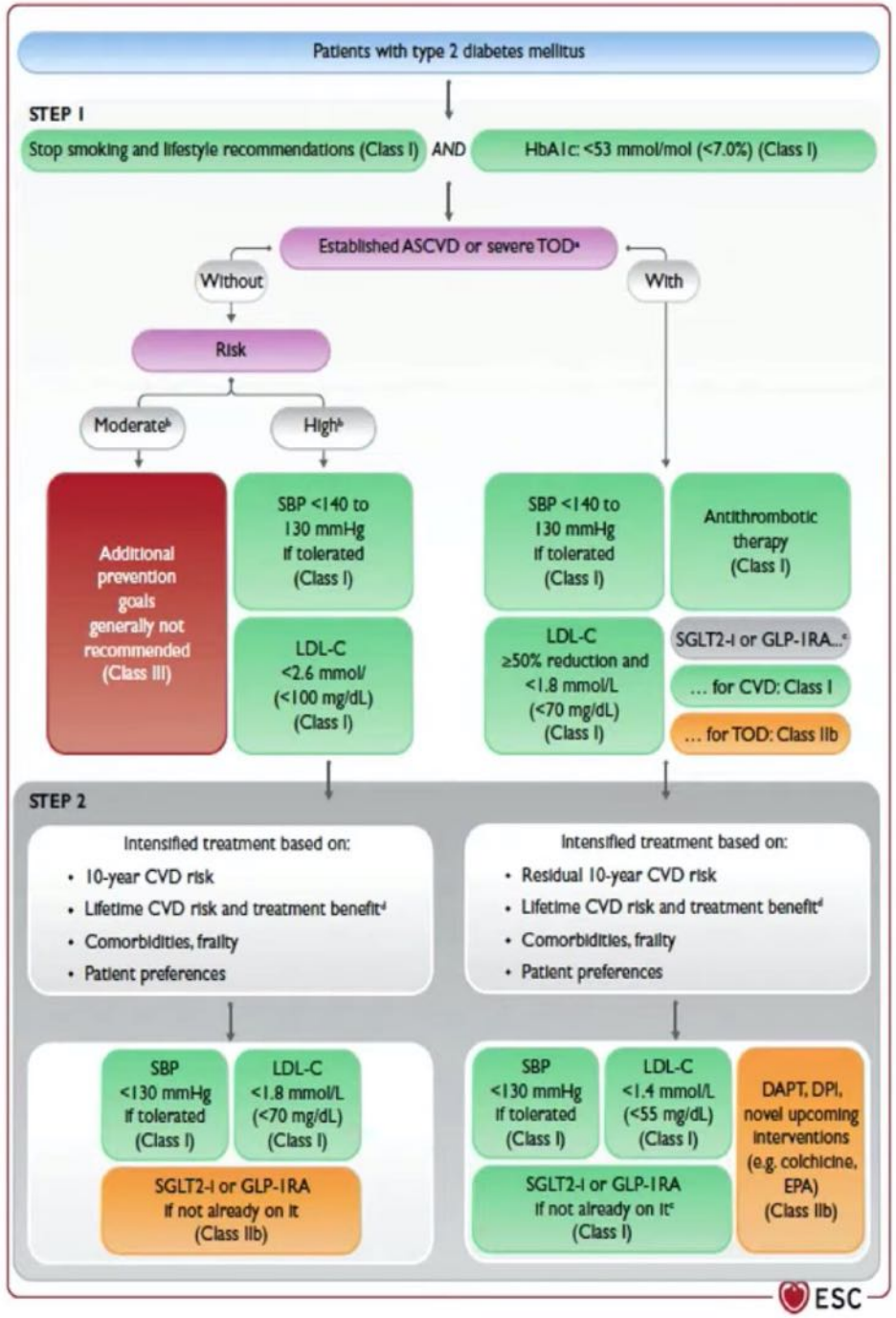
B. Buse et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018.

Manejo de la DM



Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.

Manejo de la DM



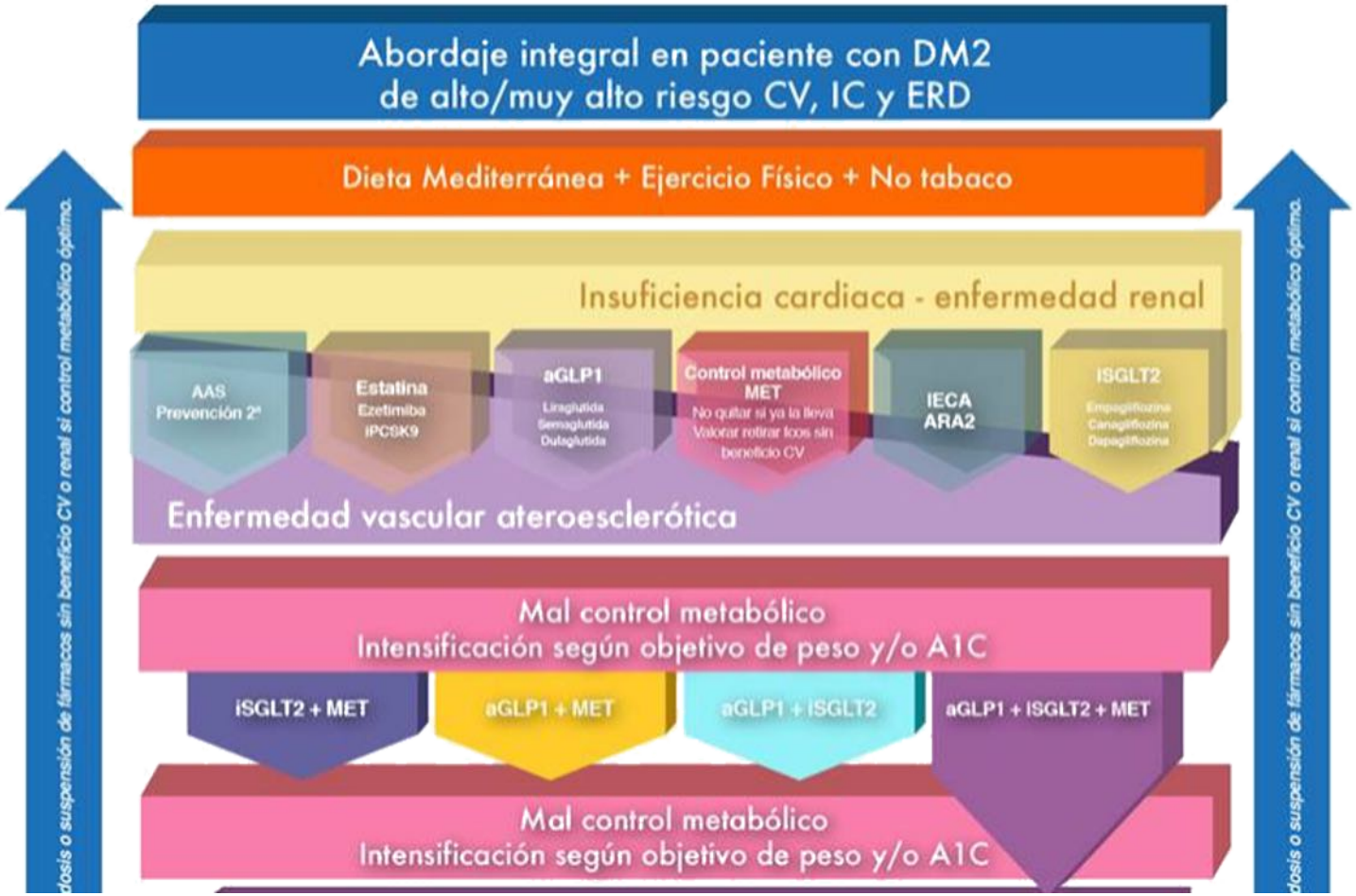
Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.

Manejo de la DM

Recomendaciones del Grupo de Diabetes, Obesidad y Nutrición de la SEMI. 2021.

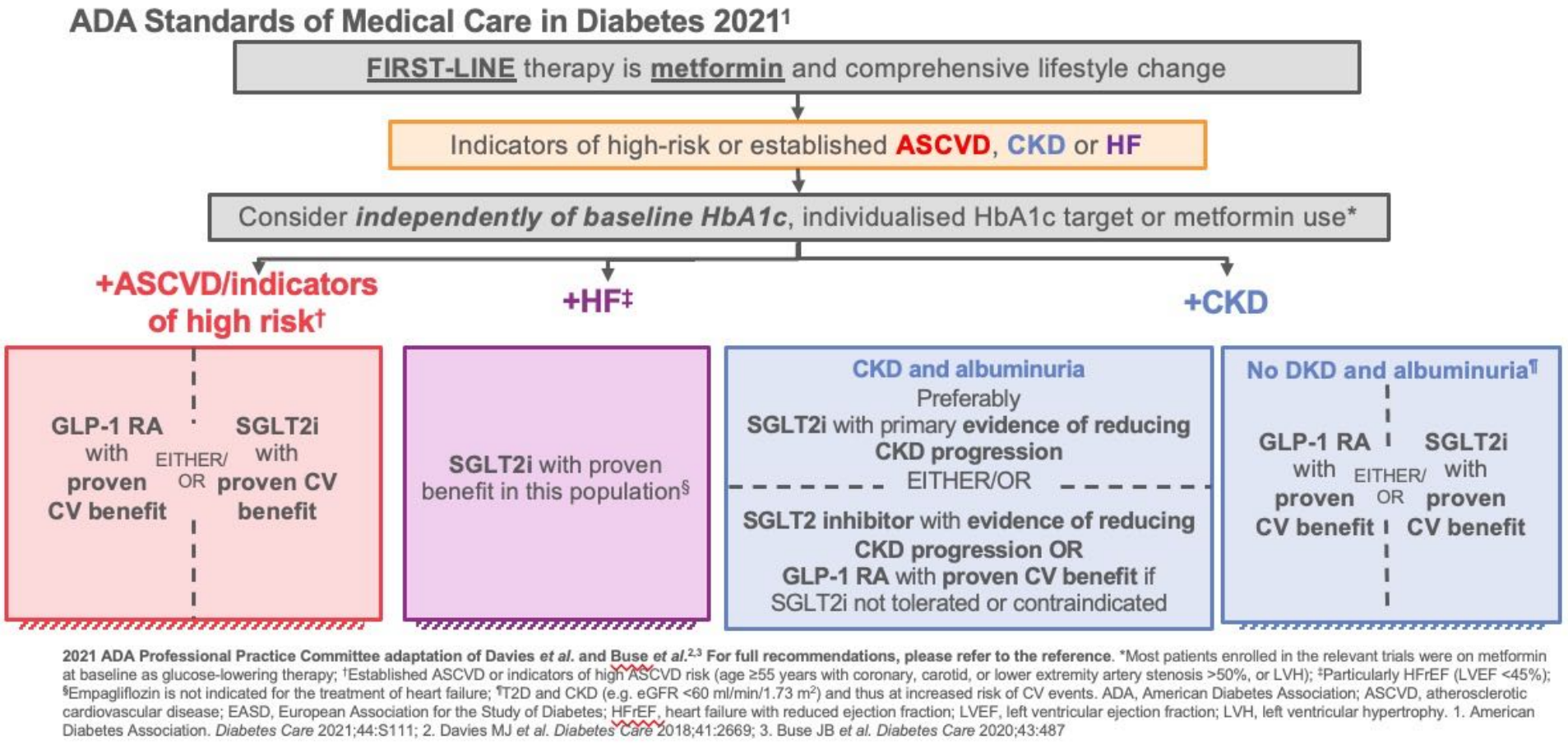
Manejo de la DM

Guías 2020 de manejo de DM2.



Guías 2020 de manejo de DM2. Grupo de trabajo de diabetes de SEC

ALGORITMO RESUMEN. ADA 2021

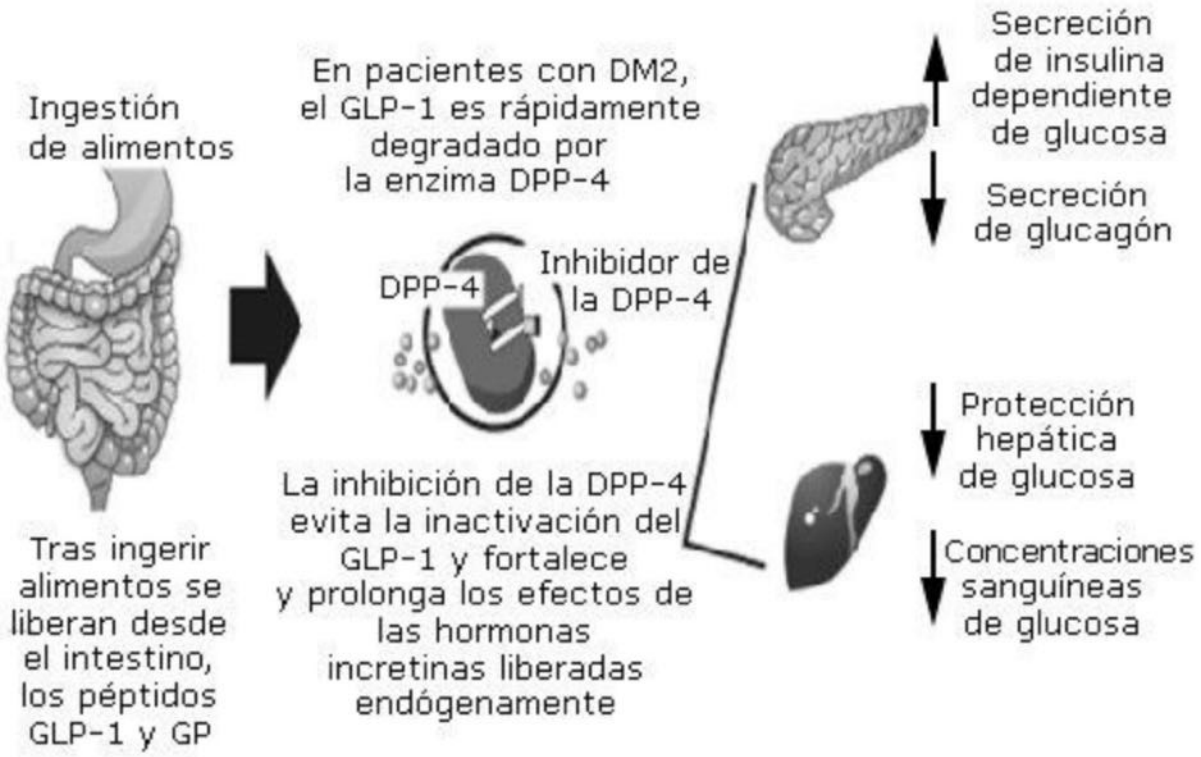


2021 ADA Professional Practice Committee adaptation of Davies *et al.* and Buse *et al.*[2,3] For full recommendations, please refer to the reference. *Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy; †Established ASCVD or indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower extremity artery stenosis >50%, or LVH); ‡Particularly HFrEF (LVEF <45%); §Empagliflozin is not indicated for the treatment of heart failure; ¶T2D and CKD (e.g. eGFR <60 ml/min/1.73 m^2) and thus at increased risk of CV events. ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; EASD, European Association for the Study of Diabetes; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy. 1. American Diabetes Association. *Diabetes Care* 2021;44:S111; 2. Davies MJ *et al. Diabetes Care* 2018;41:2669; 3. Buse JB *et al. Diabetes Care* 2020;43:487

Manejo de la DM

American Diabetes Association. Diabetes Care 2021;44:S111

Manejo de la DM



DPP-4: enzima dipeptidil peptidasa tipo 4. GLP-1: glucagón tipo 1 GLP-1.

Fuente: Zúñiga-Guajardo S. Med Int Mex. 2015;31(4):441-53.3

Fig. Efectos de la inhibición de la enzima dipeptidil peptidasa 4 (DPP-4) por parte de los iDPP-4.

Mecanismo de acción de iDPP4. Zúñiga-Guajardo S. Med Int Mex. 2015; 31 (4): 441-53.3.

EN RESUMEN…

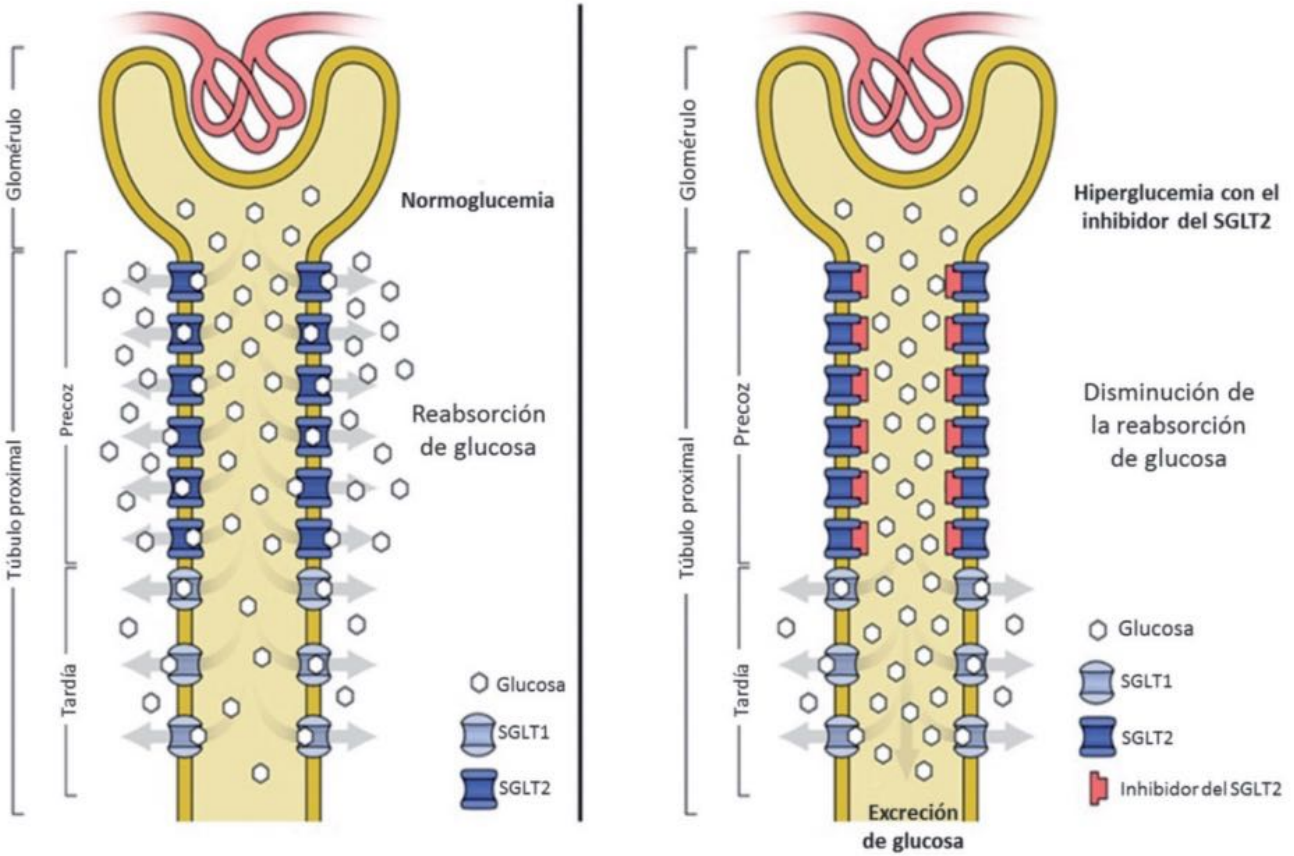
Tabla 1 Aspectos clave de los ensayos de resultados cardiovasculares con agentes antidiabéticos en pacientes con DM2

	Intervención	Objetivo principal	n	Edad media (años)	Criterios de inclusión	Mediana seguimiento (años)	HbA1c Media visita basal[a]	HbA1c alcanzada en el grupo de intervención	Cociente de riesgo para el objetivo principal (IC 95%); p
SAVOR-TIMI 53[38]	Adición de saxagliptina frente a placebo	Compuesto: muerte cardiovascular, infarto de miocardio o ictus	16.492	65,1	Enfermedad cardiovascular o alto riesgo cardiovascular	2,1	8,0%	7,7%	1,00 (0,89-1,12); 0,99
EXAMINE[37]	Adición de alogliptina frente a placebo	Compuesto: muerte cardiovascular, infarto de miocardio o ictus	5.380	61,0	Síndrome coronario agudo 15-90 días antes	1,5	8,0%	7,7%	0,96 (≤ 1,16); 0,32
TECOS[36]	Adición de sitagliptina frente a placebo	Compuesto: muerte cardiovascular, infarto de	14.724	65,4	Enfermedad cardiovascular preexistente	3	7,2%	7,2%	0,98 (0,89-1,08); 0,65
EXSCEL[44]	Exenatida LAR frente a placebo	Compuesto: muerte cardiovascular, infarto de miocardio o ictus	14.752	62	70% enfermedad cardiovascular preexistente	3,2	8,0%	7,6%	0,91 (0,83-1,00); 0,06

Manejo de la DM – Ensayos de nuevos AD

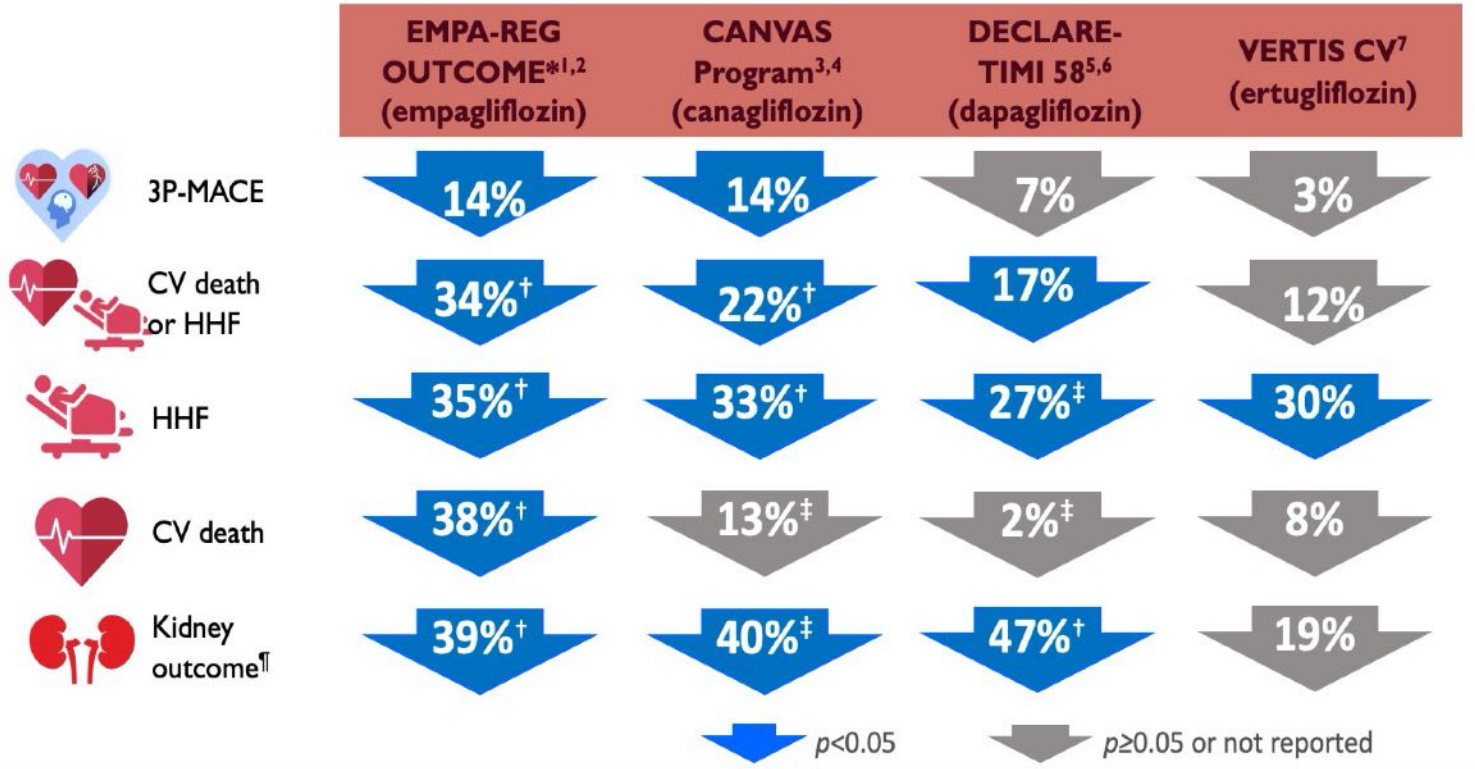
Gomez-Peralta F, et al. Recomendaciones de la Sociedad Espanola de Diabetes (SED) para el tratamiento farmacológico de la hiperglucemia en la diabetes tipo 2: Actualización 2018. Endocrinol Diabetes Nutr. 2018.

Manejo de la DM



Mecanismo de acción de iSGLT2.
Adaptada de Chao E C. et al. Nat Rev Drug Discov. 2010; 9(7):551-9.

Manejo de la DM – Ensayos de nuevos AD



Zinman B et al. N Engl J Med 2015;373:2117; 2. Wanner C et al. N Engl J Med 2016;375:323; 3. Neal B et al. N Engl J Med 2017;377:644; 4. Radholm K et al. Circulation 2018;138:458; 5. Wiviott SD et al. N Engl J Med 2019;380:347; 6. Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:606; 7. Cannon C. American Diabetes Association Scientific Sessions; June 16, 2020. Symposium

SOLOIST-WHF
(sotagliflozina)

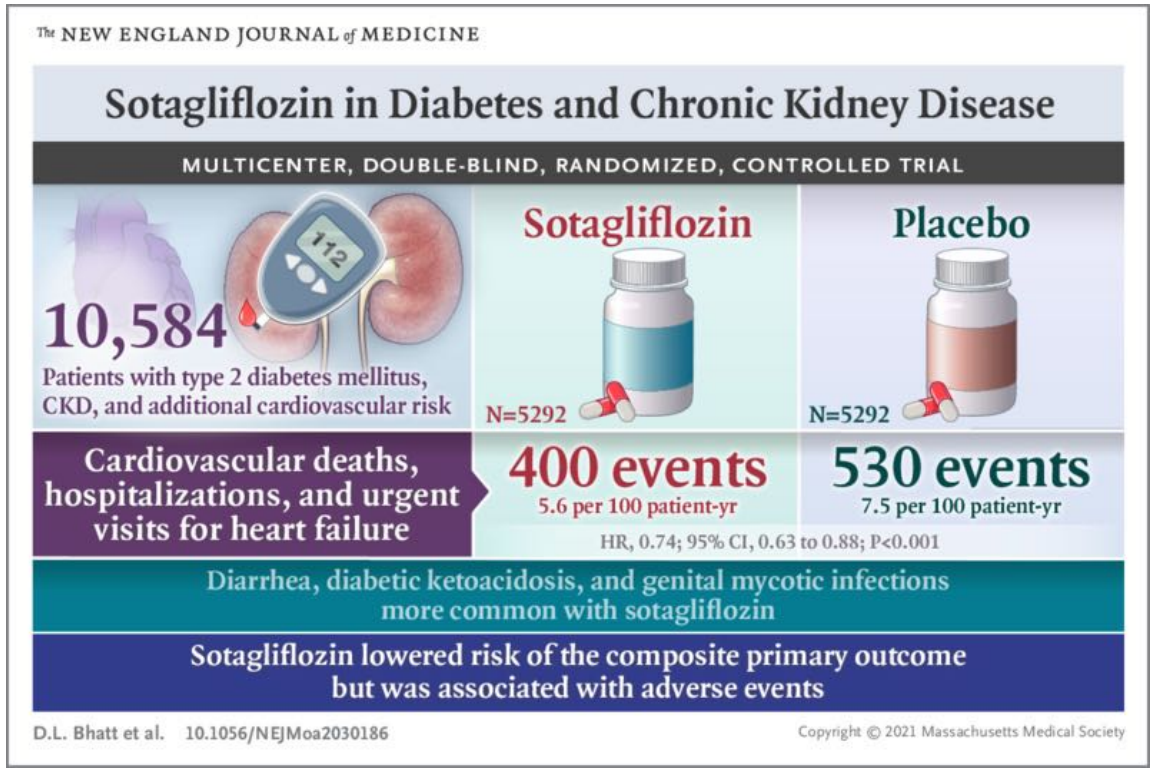


Table 2. Primary End Point and Secondary End Points.*

End Point	Sotagliflozin (N=5292)	Placebo (N=5292)	Hazard Ratio (95% CI)†	P Value
	no. of events/100 patient-yr (no. of events)			
Primary end point: total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF	5.6 (400)	7.5 (530)	0.74 (0.63–0.88)	<0.001
Major secondary end points, in order of hierarchical testing				
Total no. or hospitalizations for HF and urgent visits for HF	3.5 (245)	5.1 (360)	0.67 (0.55–0.82)	<0.001
Deaths from cardiovascular causes	2.2 (155)	2.4 (170)	0.90 (0.73–1.12)	0.35‡
Total no. of deaths from cardiovascular causes, hospitalizations for HF, nonfatal myocardial infarctions, and nonfatal strokes	7.6 (541)	10.4 (738)	0.72 (0.63–0.83)	—
Total no. of deaths from cardiovascular causes, hospitalizations for HF, urgent visits for HF, and events of HF during hospitalization	6.4 (453)	8.3 (589)	0.76 (0.65–0.89)	—
First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days	0.5 (37)	0.7 (52)	0.71 (0.46–1.08)	—
Deaths from any cause	3.5 (246)	3.5 (246)	0.99 (0.83–1.18)	—
Total no. of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes	4.8 (343)	6.3 (442)	0.77 (0.65–0.91)	—

* The term eGFR denotes estimated glomerular filtration rate, and HF heart failure.
† Results are presented as point estimates and 95% confidence intervals unadjusted for multiple comparisons, from which no definite conclusions regarding significant differences can be made.
‡ The hierarchical analysis stops after the first P value indicating nonsignificance.

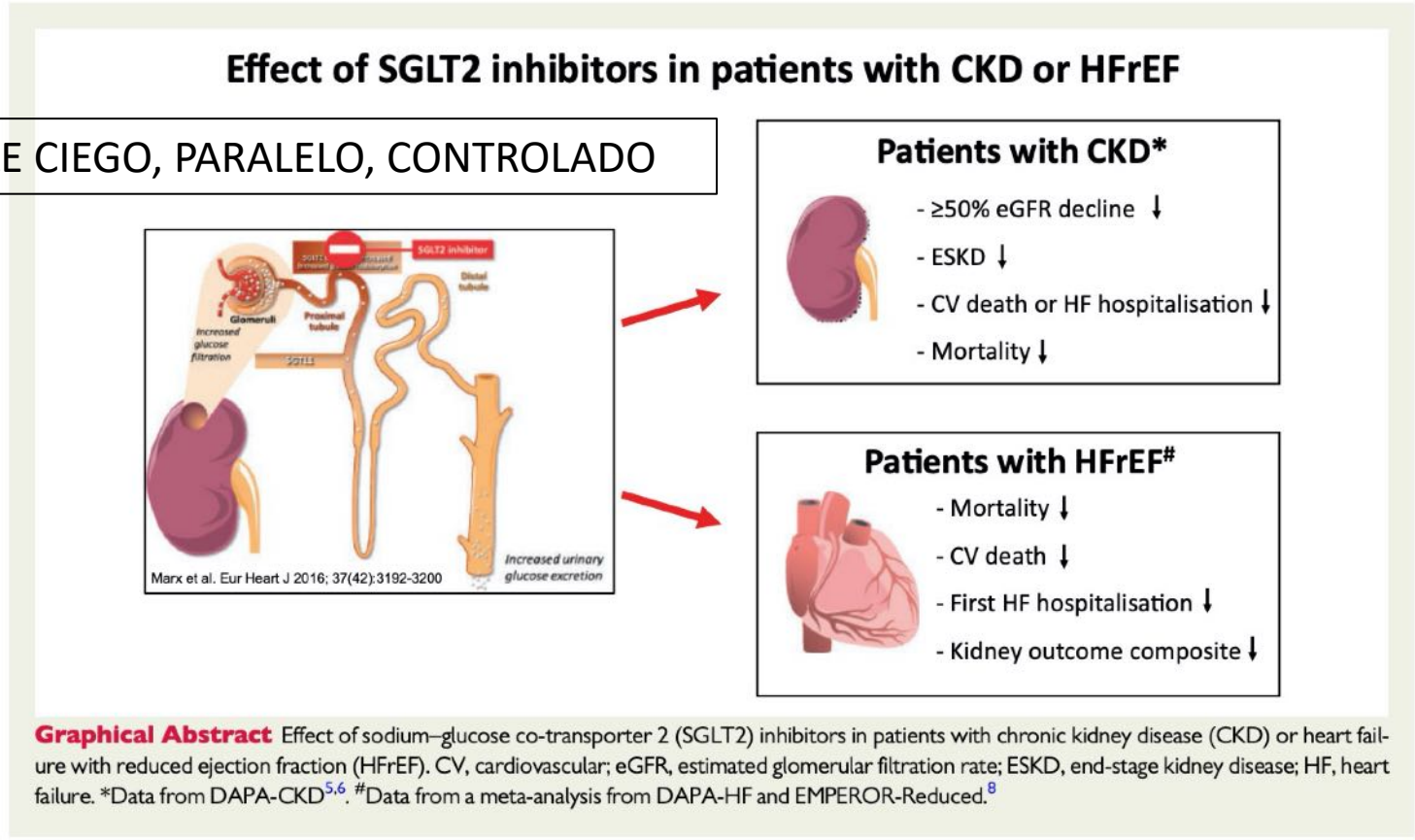
Manejo de la DM – Ensayos de nuevos AD

N Engl J Med 2021; 384:117-128. DOI: 10.1056/NEJMoa2030183

DAPA-CKD
(dapagliflozina)

ALEATORIZADO,, DOBLE CIEGO, PARALELO, CONTROLADO

4304



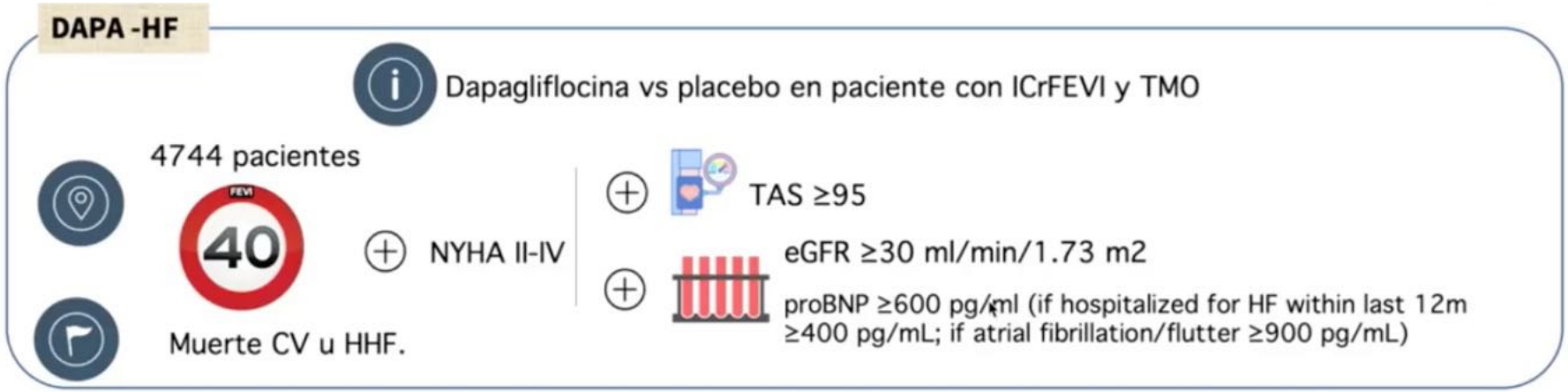
Graphical Abstract Effect of sodium–glucose co-transporter 2 (SGLT2) inhibitors in patients with chronic kidney disease (CKD) or heart failure with reduced ejection fraction (HFrEF). CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure. *Data from DAPA-CKD[5,6]. #Data from a meta-analysis from DAPA-HF and EMPEROR-Reduced.[8]

Manejo de la DM – Ensayos de nuevos AD

European Heart Journal (2021) 42, 1228–1230 EDITORIAL doi:10.1093/eurheartj/ehab092

DAPA-HF
(dapagliflozina)

ALEATORIZADO, PROSPECTIVO, DOBLE CIEGO, CONTROLADO



- **Primary endpoint:**

Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

Manejo de la DM – Ensayos de nuevos AD

N Engl J Med 2019;381:1995-2008. DOI: 10.1056/NEJMoa1911303

EMPEROR-REDUCED
(empagliflozina)

ALEATORIZADO, DOBLE CIEGO, PARALELO, CONTROLADO

3730

CRITERIOS DE INCLUSIÓN

- Pacientes con **IC con FEVI reducida** (≤40%).
- CF NYHA **II-IV.**
- **Tratamiento médico óptimo** instaurado.
- **Antecedente de hospitalización <12 meses/ NT-proBNP** ↑ (pacientes de alto riesgo).
- **TFG ≥ 20** mL/min/1.73 m2.

CRITERIOS DE EXCLUSIÓN

- Muy amplios: taqui/bradiarritmias mal tratadas, trasplante…

Manejo de la DM – Ensayos de nuevos AD

N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190

EMPEROR-REDUCED
(empagliflozina)

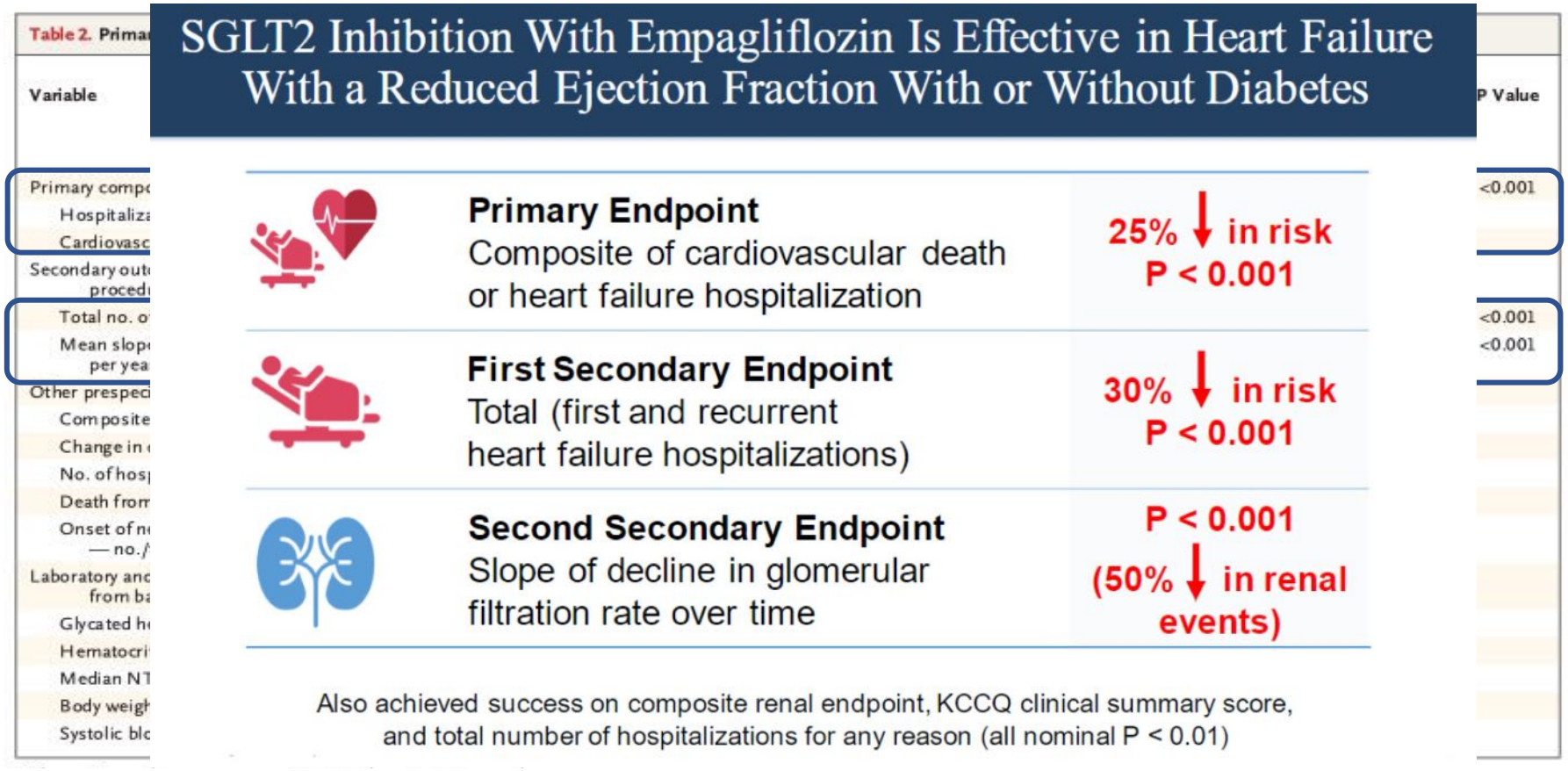
Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=1863)		Placebo (N=1867)		Hazard Ratio or Absolute Difference (95% CI)†	P Value
		events/100 patient-yr		*events/100 patient-yr*		
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	388	—	553	—	0.70 (0.58 to 0.85)	<0.001
Mean slope of change in eGFR — ml/min/1.73 m^2 per year‡	−0.55±0.23	—	−2.28±0.23	—	1.73 (1.10 to 2.37)	<0.001
Other prespecified analyses						
Composite renal outcome — no. (%)§	30 (1.6)	1.6	58 (3.1)	3.1	0.50 (0.32 to 0.77)	
Change in quality-of-life score on KCCQ at 52 weeks¶	5.8±0.4	—	4.1±0.4	—	1.7 (0.5 to 3.0)	
No. of hospitalizations for any cause	1364	—	1570	—	0.85 (0.75 to 0.95)	
Death from any cause — no. (%)	249 (13.4)	10.1	266 (14.2)	10.7	0.92 (0.77 to 1.10)	
Onset of new diabetes in patients with prediabetes — no./total no. (%)	71/632 (11.2)	9.3	80/636 (12.6)	10.6	0.86 (0.62 to 1.19)	
Laboratory and other measurements (adjusted change from baseline to 52 wk)						
Glycated hemoglobin in patients with diabetes — %	−0.28±0.03	—	−0.12±0.03	—	−0.16 (−0.25 to −0.08)	
Hematocrit (%)	1.98±0.10	—	−0.38±0.10	—	2.36 (2.08 to 2.63)	
Median NT-proBNP (IQR) — pg/ml‖	−244 (−890 to 260)		−141 (−784 to 585)	—	0.87 (0.82 to 0.93)	
Body weight — kg	−0.73±0.13	—	0.08±0.13	—	−0.82 (−1.18 to −0.45)	
Systolic blood pressure — mm Hg	−2.4±0.4	—	−1.7±0.4	—	−0.7 (−1.8 to 0.4)	

Manejo de la DM – Ensayos de nuevos AD

N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190

EMPEROR-REDUCED
(empagliflozina)



Manejo de la DM – Ensayos de nuevos AD

N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190

EMPEROR-PRESERVED
(empagliflozina)

ALEATORIZADO, MULTICÉNTRICO, DOBLE CIEGO, PARALELO

5988

CRITERIOS INCLUSIÓN

IC NYHA II-IV al menos 3 meses

FEVI >40% (y no previa ≤ 40%)

Alteración estructural ó **Hospitalización por IC Último año**

NTproBNP >300 en RS >900 en FA

CRITERIOS DE EXCLUSIÓN

Hipotensión sintomática	**FG < 20mL/min/1.73m2**
IC aguda	Historia de Cetoacidosis
Trasplantado Cardiaco	**IAM, CABG, ictus 3 meses previos**

- **Enf CV no tratada** que pueda influir en la IC
- **Tratamientos** que puedan influir en la IC
- **Comorbilidad** que influya el **pronóstico** independiente de la IC
- Cualquier condición que pudiera limitar la participación en el ensayo (ej seguridad)

Manejo de la DM – Ensayos de nuevos AD

Presentación ESC 2021 Congress. Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-PRESERVED
(empagliflozina)

OBJETIVOS

- Objetivo **PRIMARIO**
- Objetivos **Secundarios**
  - **Hospitalización** por insuficiencia cardíaca
  - Caída en la tasa de **filtrado glomerular**
  - **Mortalidad cardiovascular**
  - **EP renal** (HD, caída >40% FG < 10-15)
  - **Hospitalización** por cualquier causa
  - Debut **DM**
  - Calidad vida cuestionario **Kansas KCCQ**

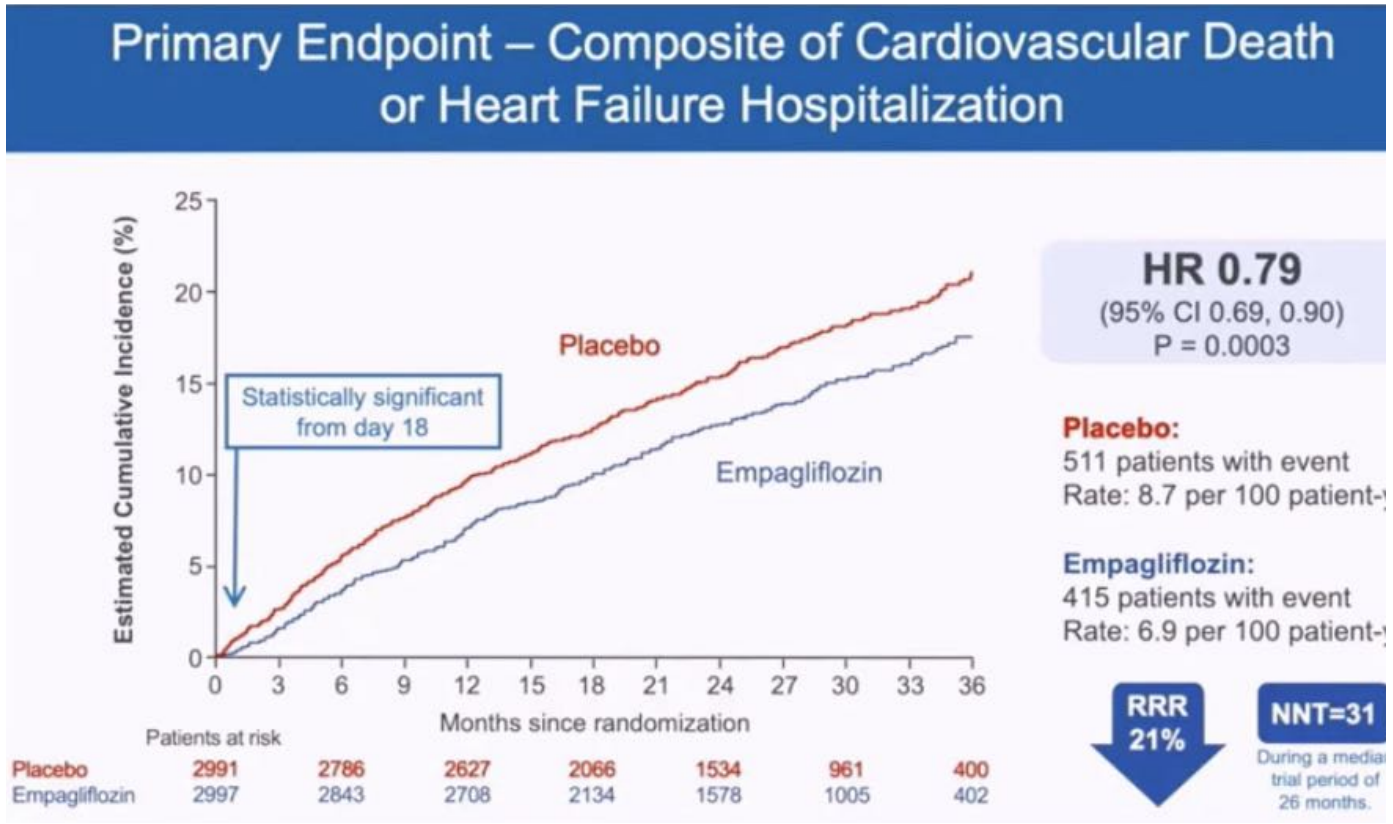
DISEÑO

Estudio muy bien estructurado, con grupos de pacientes muy parejos y comparables entre sí (disminución de sesgos estadísticos).

Manejo de la DM – Ensayos de nuevos AD

Presentación ESC 2021 Congress. Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-PRESERVED
(empagliflozina)



Manejo de la DM – Ensayos de nuevos AD

Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-PRESERVED
(empagliflozina)

Primary endpoint: individual components

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	0.0003
First hospitalization for heart failure	259 (8.6%)	4.3	352 (11.8%)	6.0	0.71 (0.60 – 0.83)	
Cardiovascular death	219 (7.3%)	3.4	244 (8.2%)	3.8	0.91 (0.76 – 1.09)	

Manejo de la DM – Ensayos de nuevos AD

Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-PRESERVED
(empagliflozina)

OBJETIVOS SECUNDARIOS

- **Hospitalización/rehospitalización por IC** descompensada (RRR 27%).
- **Reducción de la tasa de caída de FG.**

- Objetivo **compuesto renal** definido.

- **Mortalidad** por **todas** las causas.
- **Tasa de efectos adversos** mínima.

Manejo de la DM – Ensayos de nuevos AD

Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-PRESERVED
(empagliflozina)

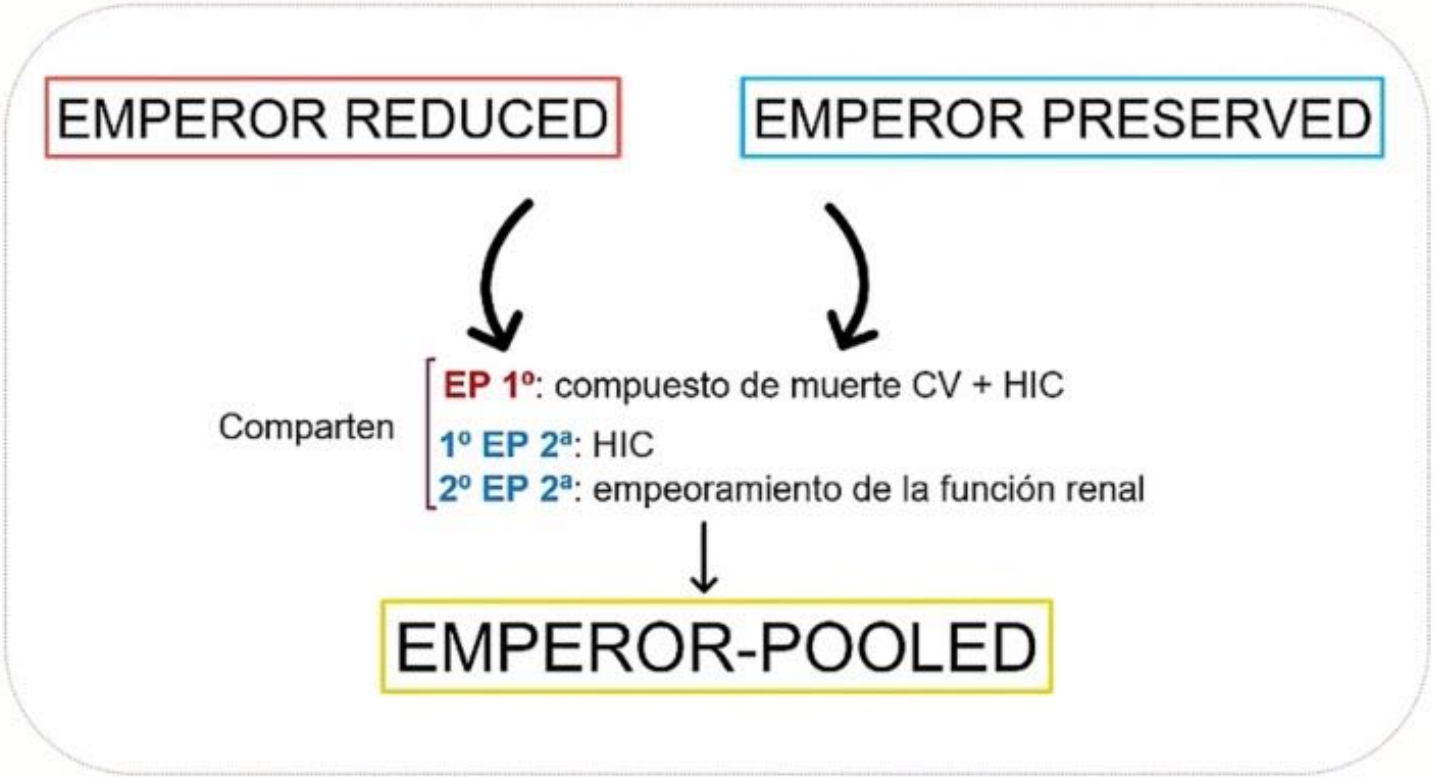
EN RESUMEN…

Trial	Treatment arms	Primary endpoint	Results (HR and 95% CI)	Risk reduction	P-value
EMPEROR-Preserved (2021)	**Empagliflozin vs placebo**	**CV death + HHF**	**0.79 (0.69–0.90)**	**-21%**	**0.0003**
PARAGON-HF (2019)	Sacubitril/valsartan vs valsartan	CV death + total (first and recurrent) HHF	0.87 (0.75–1.01)	-13%	0.06
TOPCAT (2014)	Spironolactone vs placebo	CV death + HHF + aborted cardiac arrest	0.89 (0.77–1.04)	-11%	0.14
I-PRESERVE (2008)	Irbesartan vs placebo	All-cause mortality + CV Hospitalization	0.95 (0.86–1.05)	-5%	0.35
PEP-CHF (2006)	Perindopril vs placebo	All-cause mortality + HHF	0.92 (0.70–1.21)	-8%	0.55
CHARM-Preserved (2003)	Candesartan vs placebo	CV death + HHF	0.86 (0.74–1.00)	-14%	0.05

Manejo de la DM – Ensayos de nuevos AD

Anke, SD et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

EMPEROR-POOLED
(empagliflozina)



Manejo de la DM – Ensayos de nuevos AD

Presentación ESC 2021 Congress. Packer M. et al. DOI: 10.1056/NEJMc2112411

Manejo de la DM – Ensayos de nuevos AD

EMPEROR-POOLED
(empagliflozina)

OBJETIVOS

EP 1º

Compuesto de eventos adversos **renales**

- Diálisis
- Trasplante renal
- ↓ 40% FG
- FG < 15 (si previo ≥ 30)
- FG < 10 (si previo < 30)

EP 2º

- Muerte por cualquier causa
- Muerte cardiovascular
- Nuevo dx de DM2 en pacientes con prediabetes

DISEÑO

9718

CRITERIOS INCLUSIÓN

- >18 años
- **NTproBNP**
- **IC crónica NYHA II-IV al menos 3 meses**

CRITERIOS DE EXCLUSIÓN

- **Enf CV no tratada** que pueda influir en la IC
- **Tratamientos** que puedan influir en la IC
- **Comorbilidad** que influya el **pronóstico** independiente de la IC
- Cualquier condición que pudiera limitar la participación en el ensayo (ej seguridad)

Packer M. et al. DOI: 10.1056/NEJMc2112411

EMPEROR-POOLED
(empagliflozina)

EN RESUMEN…

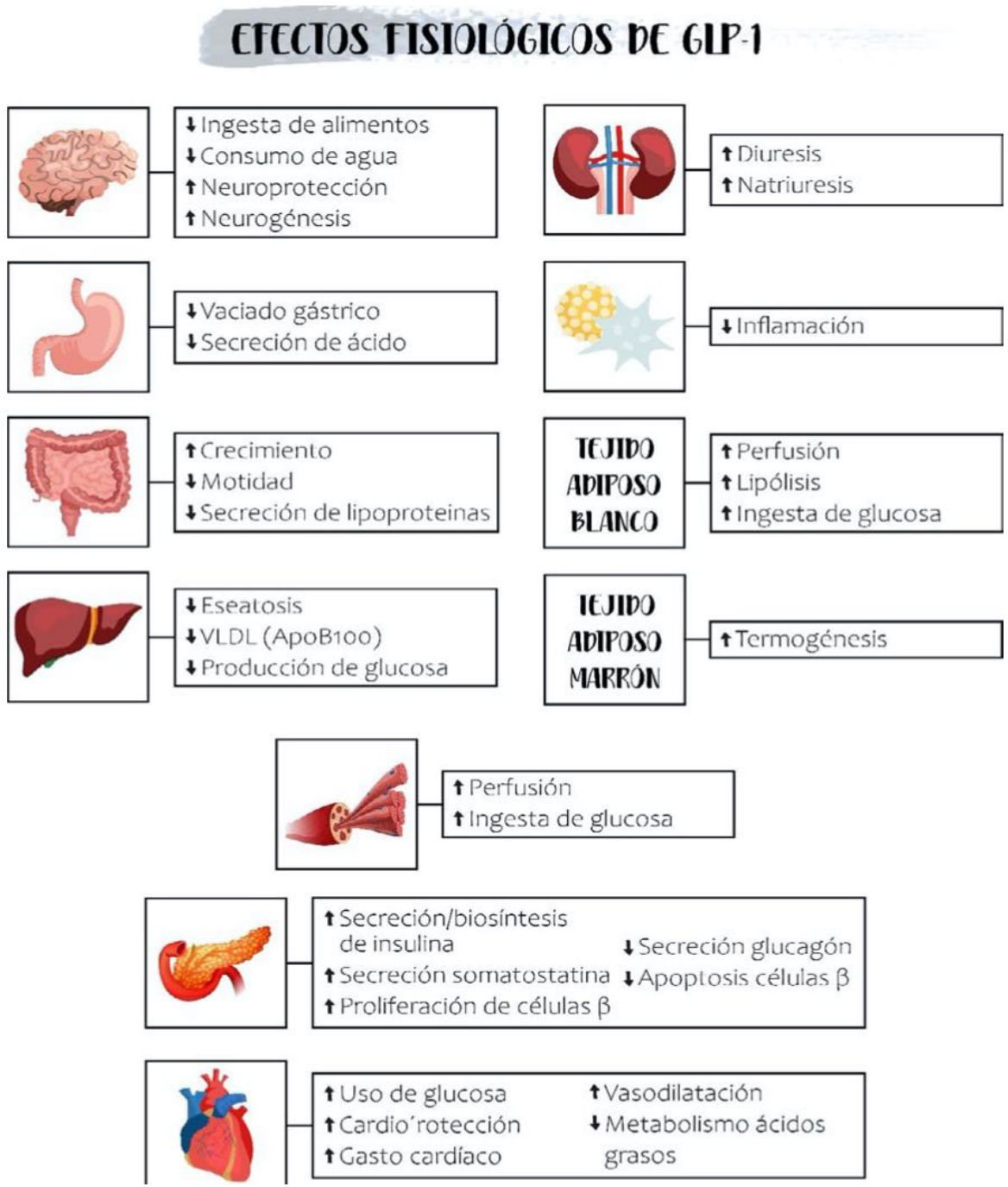
- Los **efectos** fueron **concordantes** entre ambos estudios en IC.
- El **tiempo hasta la primera hospitalización** se **reducía** hasta en un **30%** sobre todo en el espectro de **FEVI <65%.**
- **Endpoint primario renal: EMPEROR REDUCED** **EMPEROR PRESERVED**
- La **FEVI** influyó en los **eventos renales.**

Manejo de la DM – Ensayos de nuevos AD

Packer M. et al. DOI: 10.1056/NEJMc2112411

Manejo de la DM – Ensayos de nuevos AD

Manejo de la DM – Ensayos de nuevos AD



EN RESUMEN…

Estudio Clínico	EXSCEL (Exenatida)	ELIXA (Lixisenatida)	LEADER (Liraglutida)	SUSTAIN-6 (Semaglutida)	HARMONY (Albiglutida)	REWIND (Dulaglutida)
Número de pacientes	14752	6068	9340	3297	9463	9901
Diseño del estudio	Fase 3/4, multicéntrico, aleatorizado, doble ciego, controlado con placebo	Multicéntrico, aleatorizado, doble ciego, controlado con placebo	Multicéntrico, aleatorizado, doble ciego, controlado con placebo	Multicéntrico, aleatorizado, doble ciego, controlado con placebo	Multicéntrico, aleatorizado, doble ciego, controlado con placebo	Multicéntrico, aleatorizado, doble ciego, controlado con placebo
Desenlaces primarios	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal	MACE: Compuesto de Muerte Cardiovascular, Infarto del miocardio no fatal y Accidente cerebrovascular no fatal
Resultados del estudio	Efecto Neutro	Efecto neutro	Reducción del 13% del MACE vs placebo	Reducción del 26% del MACE vs placebo	Reducción del 22% del MACE vs placebo	Reducción del 12% del MACE vs placebo

Manejo de la DM – Ensayos de nuevos AD

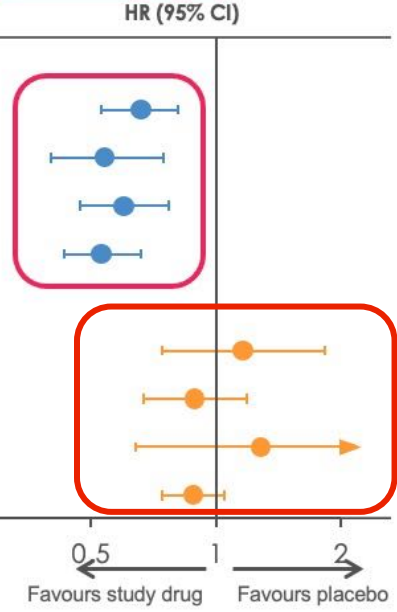
Manejo de la DM – Ensayos de nuevos AD

EN RESUMEN…

Hard kidney outcomes: SGLT2 inhibitor and GLP-1 receptor agonist CVOTs and cardio–renal trials in patients with T2D*

Reducción > 50% de FG – Iniciar diálisis – Necesidad de trasplante renal

	Patients	Events	Weights (%)	HR (95% CI)
SGLT2 inhibitor*†1				
CREDENCE (canagliflozin)[2]	4401	377	–	0.66 (0.53, 0.81)
EMPA-REG OUTCOME (empagliflozin)	6968	152	20.9	0.54 (0.40, 0.75)
CANVAS Program (canagliflozin)	10,142	249	34.0	0.60 (0.47, 0.77)
DECLARE-TIMI 58 (dapagliflozin)	17,160	365	45.1	0.53 (0.43, 0.66)
GLP-1 receptor agonist*‡§1				
ELIXA (lixisenatide)	6063	76	9.5	1.16 (0.74, 1.83)
LEADER (liraglutide)	9340	184	23.4	0.89 (0.67, 1.19)
SUSTAIN-6 (inj. semaglutide)	3297	32	4.0	1.28 (0.64, 2.58)
EXSCEL (exenatide)	12,914	519	63.1	0.88 (0.74, 1.05)



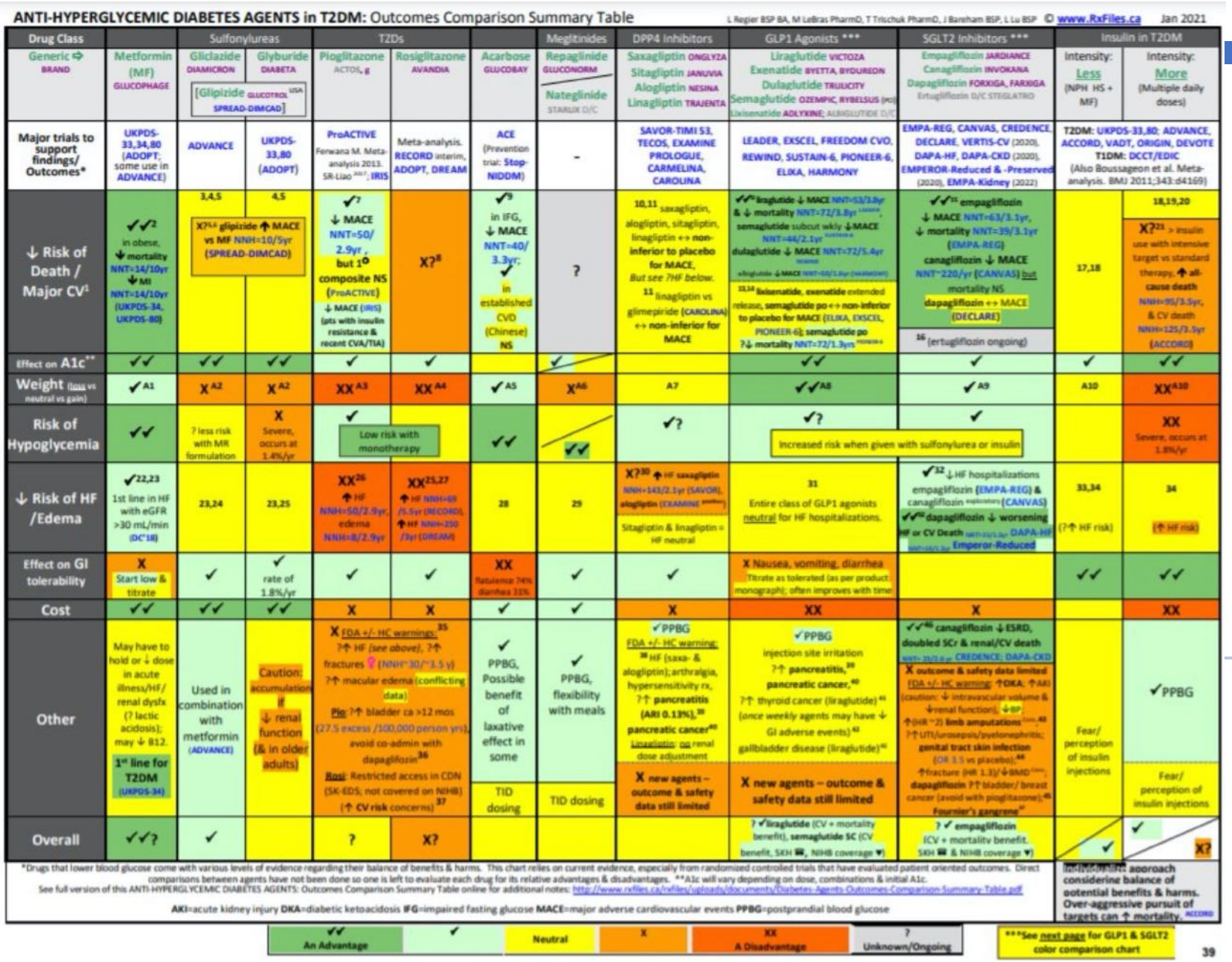
Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

p-value for subgroup differences between SGLT2 inhibitors and GLP-1 receptor agonists was <0.001 (excluding CREDENCE)

*Hard kidney outcomes (excluding albuminuria, including eGFR decline) were most commonly doubling of serum creatinine or need for chronic dialysis, ESKD and death due to kidney causes; †Q statistic=0.59; *p*=0.74, I^2=0% (excluding CREDENCE); ‡Q statistic=2.18; *p*=0.54, I^2=0%; §PIONEER 6 did not report any kidney outcomes ¶Doubling of serum creatinine, initiation of dialysis, renal transplantation or creatinine >6.0 mg/dl; **Sustained ESKD, sustained ≥40% decrease in eGFR from baseline or death from kidney failure

EN RESUMEN…

Manejo de la DM – Ensayos de nuevos AD



ANTI-HYPERGLYCEMIC DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

L Regier BSP BA, M LeBras PharmD, T Trischuk PharmD, J Bareham BSP, L Lu BSP © www.RxFiles.ca Jan 2021

Drug Class	Metformin	Sulfonylureas		TZDs		Acarbose	Meglitinides	DPP4 Inhibitors	GLP1 Agonists ***	SGLT2 Inhibitors ***	Insulin in T2DM	
Generic ⇨ BRAND	Metformin (MF) GLUCOPHAGE	Gliclazide DIAMICRON	Glyburide DIABETA	Pioglitazone ACTOS, g	Rosiglitazone AVANDIA	Acarbose GLUCOBAY	Repaglinide GLUCONORM / Nateglinide STARLIX D/C	Saxagliptin ONGLYZA, Sitagliptin JANUVIA, Alogliptin NESINA, Linagliptin TRAJENTA	Liraglutide VICTOZA, Exenatide BYETTA, BYDUREON, Dulaglutide TRULICITY, Semaglutide OZEMPIC, RYBELSUS (po), Lixisenatide ADLYXINE; ALBIGLUTIDE D/C	Empagliflozin JARDIANCE, Canagliflozin INVOKANA, Dapagliflozin FORXIGA, FARXIGA, Ertugliflozin D/C STEGLATRO	Intensity: Less (NPH HS + MF)	Intensity: More (Multiple daily doses)
Major trials to support findings/ Outcomes*	UKPDS-33,34,80 (ADOPT; some use in ADVANCE)	ADVANCE	UKPDS-33,80 (ADOPT)	ProACTIVE; Fonseca M. Meta-analysis 2013. SR-Liao 2017; IRIS	Meta-analysis. RECORD interim, ADOPT, DREAM	ACE (Prevention trial: Stop-NIDDM)	-	SAVOR-TIMI 53, TECOS, EXAMINE PROLOGUE, CARMELINA, CAROLINA	LEADER, EXSCEL, FREEDOM CVO, REWIND, SUSTAIN-6, PIONEER-6, ELIXA, HARMONY	EMPA-REG, CANVAS, CREDENCE, DECLARE, VERTIS-CV (2020), DAPA-HF, DAPA-CKD (2020), EMPEROR-Reduced & -Preserved (2020), EMPA-Kidney (2022)	T2DM: UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN, DEVOTE T1DM: DCCT/EDIC (Also Boussageon et al. Meta-analysis. BMJ 2011;343:d4169)	
↓ Risk of Death / Major CV[1]	✓✓[2] in obese, ↓ mortality NNT=14/10yr ↓ MI NNT=14/10yr (UKPDS-34, UKPDS-80)	3,4,5 X[3,4] glipizide ↑ MACE vs MF NNH=10/5yr (SPREAD-DIMCAD)	4,5	✓[7] ↓ MACE NNT=50/2.9yr, but 1↻ composite NS (ProACTIVE) ↓ MACE (IRIS) (pts with insulin resistance & recent CVA/TIA)	X?[8]	✓[9] in IFG, ↓ MACE NNT=40/3.3yr; ✓ in established CVD (Chinese) NS	?	10,11 saxagliptin, alogliptin, sitagliptin, linagliptin ↔ non-inferior to placebo for MACE, But see ?HF below. 11 linagliptin vs glimepiride (CAROLINA) ↔ non-inferior for MACE	✓✓[12] liraglutide ↓ MACE NNT=53/3.8yr & ↓ mortality NNT=72/3.8yr, semaglutide subcut wkly ↓ MACE NNT=44/2.1yr, dulaglutide ↓ MACE NNT=72/5.4yr; 13,14 lixisenatide, exenatide extended release, semaglutide po ↔ non-inferior to placebo for MACE (ELIXA, EXSCEL, PIONEER-6); semaglutide po ?↓ mortality NNT=72/1.3yrs	✓✓[15] empagliflozin ↓ MACE NNT=63/3.1yr, ↓ mortality NNT=39/3.1yr (EMPA-REG) canagliflozin ↓ MACE NNT~220/yr (CANVAS) but mortality NS. dapagliflozin ↔ MACE (DECLARE) [16] (ertugliflozin ongoing)	17,18	18,19,20 X?[21] > insulin use with intensive target vs standard therapy, ↑ all-cause death NNH=95/3.5yr, & CV death NNH=125/3.5yr (ACCORD)
Effect on A1c**	✓✓	✓✓	✓✓	✓	✓		✓		✓✓	✓	✓	✓✓
Weight (loss vs neutral vs gain)	✓ A1	X A2	X A2	XX A3	XX A4	✓ A5	X A6	A7	✓✓ A8	✓ A9	A10	XX A10
Risk of Hypoglycemia	✓✓	? less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓ Low risk with monotherapy		✓✓	✓✓	✓?	✓? Increased risk when given with sulfonylurea or insulin	✓		XX Severe, occurs at 1.8%/yr
↓ Risk of HF /Edema	✓[22,23] 1st line in HF with eGFR >30 mL/min (DC'18)	23,24	23,25	XX[26] ↑ HF NNH=50/2.9yr, edema NNH=8/2.9yr	XX[25,27] ↑ HF NNH=69 /5.5yr (RECORD), ↑ HF NNH=250 /3yr (DREAM)	28	29	X?[30] ↑ HF saxagliptin NNH=143/2.1yr (SAVOR), alogliptin (EXAMINE); Sitagliptin & linagliptin = HF neutral	31 Entire class of GLP1 agonists neutral for HF hospitalizations.	✓[32] ↓ HF hospitalizations empagliflozin (EMPA-REG) & canagliflozin (CANVAS) ✓✓[33] dapagliflozin ↓ worsening HF or CV Death DAPA-HF, Emperor-Reduced	33,34 (?↑ HF risk)	34 (↑ HF risk)
Effect on GI tolerability	X Start low & titrate	✓	✓ rate of 1.8%/yr	✓	✓	XX flatulence 74% diarrhea 33%	✓	✓	X Nausea, vomiting, diarrhea Titrate as tolerated (as per product monograph); often improves with time		✓✓	✓✓
Cost	✓✓	✓✓	✓✓	X	X	✓	✓	X	XX	X		XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx (? lactic acidosis); may ↓ B12. 1st line for T2DM (UKPDS-34)	Used in combination with metformin (ADVANCE)	Caution: accumulation if ↓ renal function (& in older adults)	X FDA +/- HC warnings;[35] ?↑ HF (see above), ?↑ fractures ♀ (NNH=30/~3.5 y) ?↑ macular edema (conflicting data) Pio: ?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs); avoid co-admin with dapagliflozin[36] Rosi: Restricted access in CDN (SK-EDS; not covered on NIHB) (↑ CV risk concerns)[37]		✓ PPBG, Possible benefit of laxative effect in some; TID dosing	✓ PPBG, flexibility with meals; TID dosing	✓PPBG FDA +/- HC warning: [38] HF (saxa- & alogliptin); arthralgia, hypersensitivity rx, ?↑ pancreatitis (ARI 0.13%),[39] pancreatic cancer[40] Linagliptin: no renal dose adjustment; X new agents – outcome & safety data still limited	✓PPBG injection site irritation ?↑ pancreatitis,[39] pancreatic cancer,[40] ?↑ thyroid cancer (liraglutide)[41] (once weekly agents may have ↓ GI adverse events)[42] gallbladder disease (liraglutide)[43]; X new agents – outcome & safety data still limited	✓✓[44] canagliflozin ↓ ESRD, doubled SCr & renal/CV death CREDENCE; DAPA-CKD; X outcome & safety data limited FDA +/- HC warning: ↑DKA; ↑AKI (caution: ↓ intravascular volume & ↓renal function), ↓BP, ↑(HR ~2) limb amputations,[45] ?↑ UTI/urosepsis/pyelonephritis; genital tract skin infection (OR 3.5 vs placebo);[46] ↑fracture (HR 1.3)/↓BMD, dapagliflozin ?↑ bladder/ breast cancer (avoid with pioglitazone);[45] Fournier's gangrene[47]	Fear/ perception of insulin injections	✓PPBG; Fear/ perception of insulin injections
Overall	✓✓?	✓		?	X?				? ✓liraglutide (CV + mortality benefit), semaglutide SC (CV benefit, SKH, NIHB coverage ▼)	? ✓ empagliflozin (CV + mortality benefit SKH & NIHB coverage ▼)	✓	✓ X?

*Drugs that lower blood glucose come with various levels of evidence regarding their balance of benefits & harms. This chart relies on current evidence, especially from randomized controlled trials that have evaluated patient oriented outcomes. Direct comparisons between agents have not been done so one is left to evaluate each drug for its relative advantages & disadvantages. **A1c will vary depending on dose, combinations & initial A1c.

See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional notes: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

AKI=acute kidney injury DKA=diabetic ketoacidosis IFG=impaired fasting glucose MACE=major adverse cardiovascular events PPBG=postprandial blood glucose

Individualize approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can ↑ mortality. ACCORD

✓✓ An Advantage | ✓ | Neutral | X | XX A Disadvantage | ? Unknown/Ongoing

***See next page for GLP1 & SGLT2 color comparison chart

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EN RESUMEN…

Manejo de la DM – Ensayos de nuevos AD

GLP1 Agonists & SGLT2 Inhibitors - SUBSET of DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

L Regier BSP BA - www.RxFiles.ca Oct 2020

Drug Class	GLP1 Agonists *				SGLT2 Inhibitors		
Generic ⇨ BRAND	Dulaglutide SC TRULICITY (SC WEEKLY)	Liraglutide SC VICTOZA (SC DAILY)	Semaglutide SC OZEMPIC (SC WEEKLY)	Semaglutide PO 14mg RYBELSUS (PO DAILY) FDA, now Canada	Canagliflozin INVOKANA	Dapagliflozin FORXIGA / FARXIGA FDA	Empagliflozin JARDIANCE
Major trial(s) to support findings/Outcomes*	REWIND n=9901 / 5.4 yr	LEADER n=9340 / 3.8 yr vs placebo (but ↑ insulin use)	SUSTAIN-6 n=3297 / 2 yr vs placebo (but ↑ insulin use)	PIONEER-6 n=3183 / 1.3 yr	CANVAS n=10142 / 3.6 yr CREDENCE n=4401 / 2.6 yr renal dx pts	DECLARE-TIMI n=17160 / 4.2 yr DAPA-HF n=4744 / 1.5 yr heart failure pts	EMPA-REG n=7020 / 3.1 yr Emperor-Reduced n=3730 / 1.3 yr ins heart failure pts
↓ Risk of Major CV - MACE	✓✓ ↓ MACE NNT=72/5.4yrs REWIND ? N. America - neutral HR: 1.14 (0.89-1.47)	✓✓ ↓ MACE NNT=53/3.8yr LEADER ? N. America - neutral HR: 1.01 (0.84-1.22)	✓✓ ↓ MACE NNT=44/2.1yr SUSTAIN-6 ? N. America – marginal HR: 0.87 (0.57-1.34)	Neutral for MACE: non-inferior to placebo 3.8% vs 4.8% PIONEER-6 HR: 0.79 (0.57-1.11) Many trial limitations, e.g. short	✓✓ ↓ MACE NNT~220/yr CANVAS (=NNT of 62 / 3.6yrs)	✓? Non-inferior to Placebo HR 0.93 (0.84-1.03) Superiority (NS) over 4.2yr	✓✓ ↓ MACE NNT=63/3.1yrs EMPA-REG 10mg as good as 25mg
↓ Risk of All-Death	HR 0.9 (0.80-1.01) 10.8% vs 12%/5.4 yrs (NS)	✓✓ NNT=72/3.8yrs LEADER	HR 1.05 (0.74-1.50) 3.8% vs 3.6%/2.1yrs (NS)	✓? 2° endpoint NNT=72/1.3yrs	HR 0.87 (0.74-1.01) CANVAS HR 0.83 (0.68-1.02) CREDENCE	HR 0.93 (0.82-1.04) DECLARE NNT=44/1.5yr DAPA-HF	✓✓ 2° endpoint NNT=39/3.1yr EMPA-REG
Less Renal Disease (composite/surrogates)	✓ NNT=40/5.4yrs 17.1 vs 19.6%/5.4 yrs	✓ NNT=67/3.8yr 5.7% vs 7.2% /3.8yrs	✓ NNT=44/2.1yr 3.8% vs 6.1% /3.8yr	?	✓✓ HR 0.66 (0.53-0.83) NNT= 23/2.6 yrs CREDENCE	✓✓?class effect HR 0.76 (0.67-0.87) NNT= 19/2.4 yrs DAPA-CKD	✓✓?class effect ↓acute renal failure NNT=71
Effect on A1c**	✓✓	✓✓	✓✓	✓✓	✓	✓	✓
Weight (loss vs neutral vs gain)	✓✓ ↓1.3-3 kg/5-52 wks	✓✓ ↓ 2.3 kg/3.8 yrs	✓✓ ↓ 3-4kg/2.1yrs	✓✓ ↓ 3.4kg/1.3 yrs	↓ 2.8-4 kg/4-52 wks CANTATA-M	↓ 2 kg/12-52 wks	↓ ~1.5-2 kg/3.1 yrs
Less Risk of Hypoglycemia	✓?	✓ Severe: 2.4% vs 3.3% p=0.02 (placebo group had more insulin)	✓?	✓? Severe: 1.4% vs 0.8%	✓ Risk when given with sulfonylurea or insulin		
Less Risk of HF /Edema	HR: 0.93 (0.77-1.22)	HR: 0.87 (0.73-1.05)	HR: 1.11 (0.77-1.61)	HR: 0.86 (0.48-1.55)	✓ 2° endpoint ↓ HF hospitalizations	✓✓ ↓ worsening HF or CV death NNT=21/1.5yr DAPA-HF	✓✓ ↓ worsening HF or CV death NNT=19/1.3yr Emperor-Reduced
Effect on GI & D/C due to Tolerability	X GI D/C due to AE 9% vs 6% NNH=36/5.4yrs	X GI D/C due to AE 9.5% vs 7.3% NNH=46/3.8yrs	X GI D/C due to AE 11.5-14.5% vs 5.7-7.6% NNH= ~14/2yrs	X D/C due to GI: 6.8% vs 1.6% D/C due to AE 11.6% vs 6.5%; NNH=20/1.3yrs	D/C due to AE 12% vs 13%; NNH= ? 100/2.6yrs	D/C due to AE 8.1% vs 6.9%; NNH=84/4.2yrs DECLARE	D/C due to AE 17.3 vs 19.4%; NNH= 48/3.1yrs
? AE Concerns Associated with Class	**Adverse Events**: injection site irritations if subcut. **Rare**/?: ?↑ pancreatitis, ?pancreatic cancer; ?↑ thyroid cancer (liraglutide);[42] gallbladder disease [46]; ?diabetic retinopathy complications.[SUSTAIN-6] See infographic pg 16. *Once weekly* agents may have ↓ GI adverse events.[42]				FDA +/- HC warning: ↑DKA; ↑AKI (caution: ↓ intravascular volume & ↓renal fx); **genital mycotic infections.** Rare: Fournier's gangrene;? ↑UTI/urosepsis/pyelonephritis. See infographic page 17.		
Cost – 1 month Some cost programs may be available	XX $225 ✗ ⊗	XX $90-$235 ✗ ⊗	XX $120-$220 ▼ NIHB	XX $260 ✗ ⊗	X $110 ▼	X $110 ▼ NIHB	X $110 ▼ NIHB
Other	Well tolerated, except GI. ↓BP 1.7/0.5 mmHg. Environmental impact - single use disposable pen	Gallbladder AE: NNH=84	NIHB open benefit	Smaller, shorter trial. SAE lower in tx group.	?↑(HR ~2) limb amputations ?↑fracture (HR 1.3)/↓BMD [108]	↑bladder/ breast cancer (avoid with pioglitazone). HF benefit similar in DM & non-DM patients. NIHB open benefit.	NIHB open benefit
Practical / Clinical Considerations	Upper GI effects often worse than lower GI effects; a low fat diet is better (small, frequent meals, gradual dose titration; patients may struggle with AEs in first ~2 weeks, but many will gain tolerability and do OK. Often insulin dose can be reduced 20% initially, and possibly more after that.				Uncertain multi-mechanism of action e.g. lower BP. Monitor BP and assess for postural hypotension, especially in older adults.		
Time Tested	X new agent – outcome & safety data still limited	X >10yr history, but... limited real world use	X new agent – outcome & safety data still limited	X new agent – outcome & safety data still limited	X new agents – outcome & safety data still limited		
Convenience	✓ Single Use Pen subcut once weekly	subcut once daily	✓ subcut once weekly	✓ 30min pre-am meal; ≤120mL H2O oral once daily	✓✓ Oral once daily		
Overall	?	?	?	?	? Safety	?	?

✓✓ An Advantage | ✓ | Neutral | X | XX A Disadvantage | ? Unknown/Ongoing

Note: the "Neutral" designation indicates little or no disadvantage; however, there is also little or no advantage.

‡ Lixisenatide not included in this GLP1 agonist chart due to neutral cardiovascular outcome data from the ELIXA trial, but coverage is ▬ &▼. See https://www.rxfiles.ca/RxFiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf

GLP1 Agonists

REWIND
Lower risk group; e.g. 21% had past CVD; others higher risk.
Renal: macroalbuminuria, eGFR decline 30+%, chronic renal replacement tx

LEADER
High risk group

SUSTAIN-6
High risk group: 83% had established CVD, CKD or both

PIONEER-6
MF: 77%, insulin 60%; Smaller, shorter trial; SAE leading to lower discontinuation rate in tx group, 2.6% vs 3%.
Higher risk group: CVD or CKD 84.7%

SGLT2 Inhibitors

CREDENCE
Patients with albuminuric CKD, eGFR 30-<90 mL/min, & albuminuria; High risk group: 50% had CVD
Renal: canagliflozin – composite primary endpoint: ↓ESRD, doubled SCr & renal/CV death

CANVAS
High risk group: 66% had established/hx of CVD [1° outcome if no CV disease history, HR= 0.98 (0.74-1.3)]

DECLARE-TIMI
High risk group: >40% had atherosclerotic CVD; 33% CAD, 6% PAD, 7.6% cerebrovascular dx, 10% HF

DAPA-HF
Both patients with and without diabetes studied; similar benefit in both groups.

EMPA-REG
High risk group: 100% had established CVD. Patients had not received glucose-lowering agents for >12 weeks

¡MUCHAS GRACIAS POR VUESTRA ATENCIÓN!

Irene Toribio García

R1 de Cardiología

Sesión de Medicina Interna

14 de septiembre de 2021