Efectos cardio-renales de los iSGLT2 en la práctica clínica

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Conflicto de interés

En el ultimo año he participado como:

- Ponente de:
  - Boehringer Ingelheim, Eli-Lilly, Sanofi, Astra Zeneca

- Asesor de:
  - Boehringer Ingelheim, Eli-Lilly, Sanofi, Abbott, Servier

Impacto de la ECV en DT2

La ECV es la principal causa de mortalidad y morbilidad en pacientes con DT2

Hasta 50% de pacientes con DT2 pueden desarrollar IC

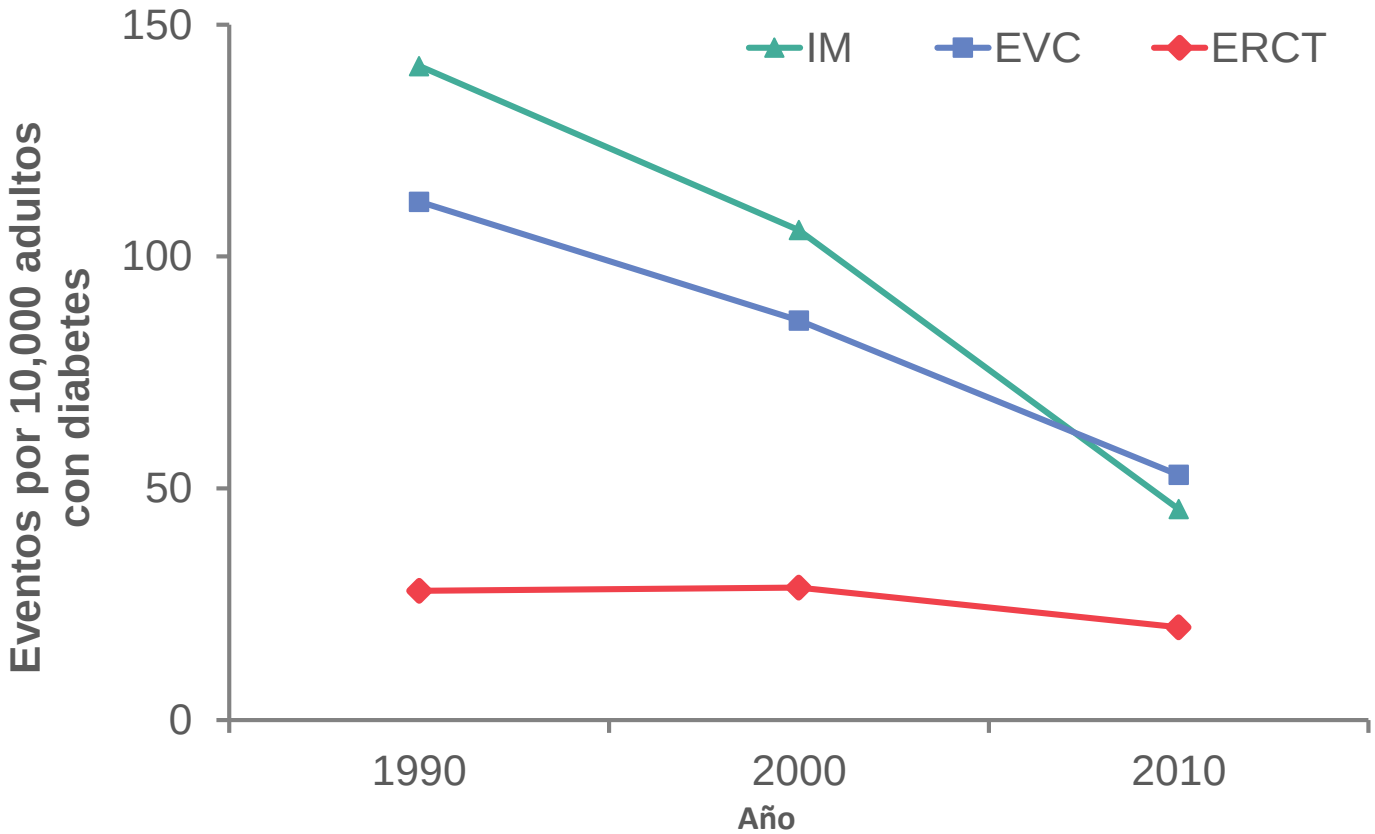
- Hospitalización por IC dos veces mayor en DM

Se ha expandido el tratamiento del paciente con T2D y ECV

- Inhibidores de SGLT2
- Agonistas del receptor de GLP-1

Cambio de paradigma: ir más allá del control de glucosa a una estrategia más amplia para reducir el riesgo CV

Disminución en IM y de EVC pero no de ERCT

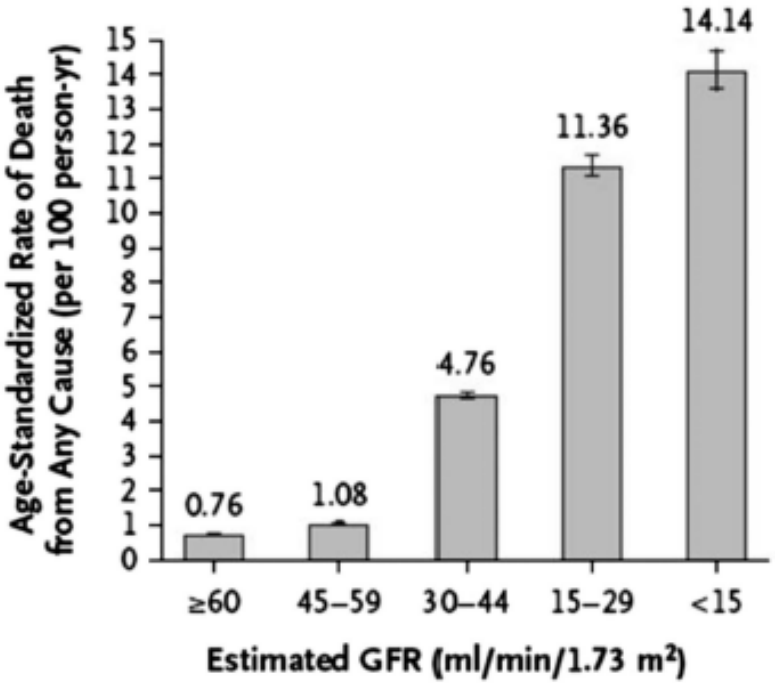


IM: infarto del miocardio, ECV: evento vascular cerebral, ERCT,enf renal crónica terminal

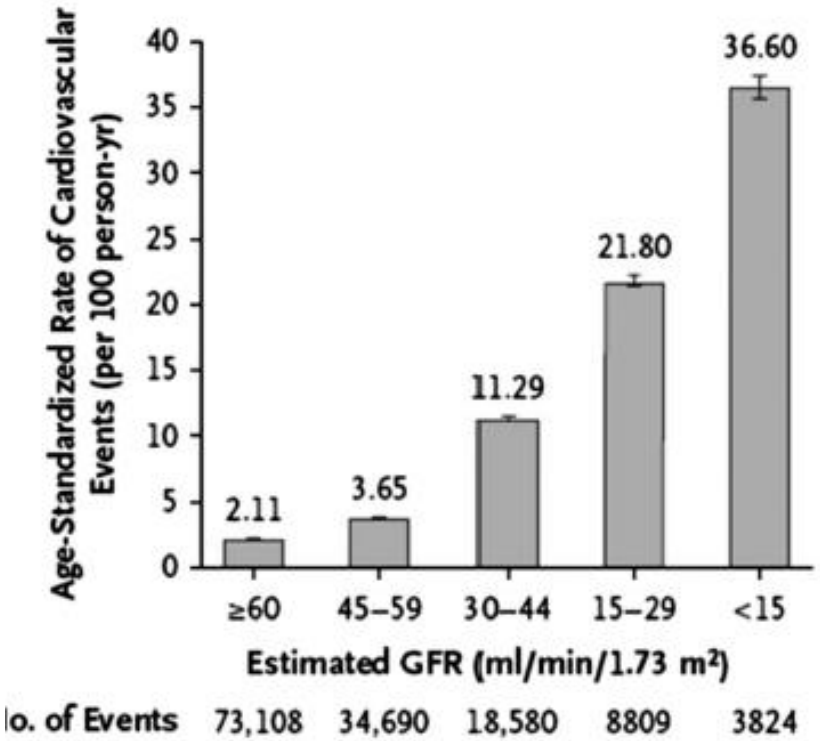
Adaptado de Gregg EW et al. N Engl J Med 2014;370:1514

Riesgo de muerte y eventos CV en función de la TFG

Mortalidad por cualquier causa



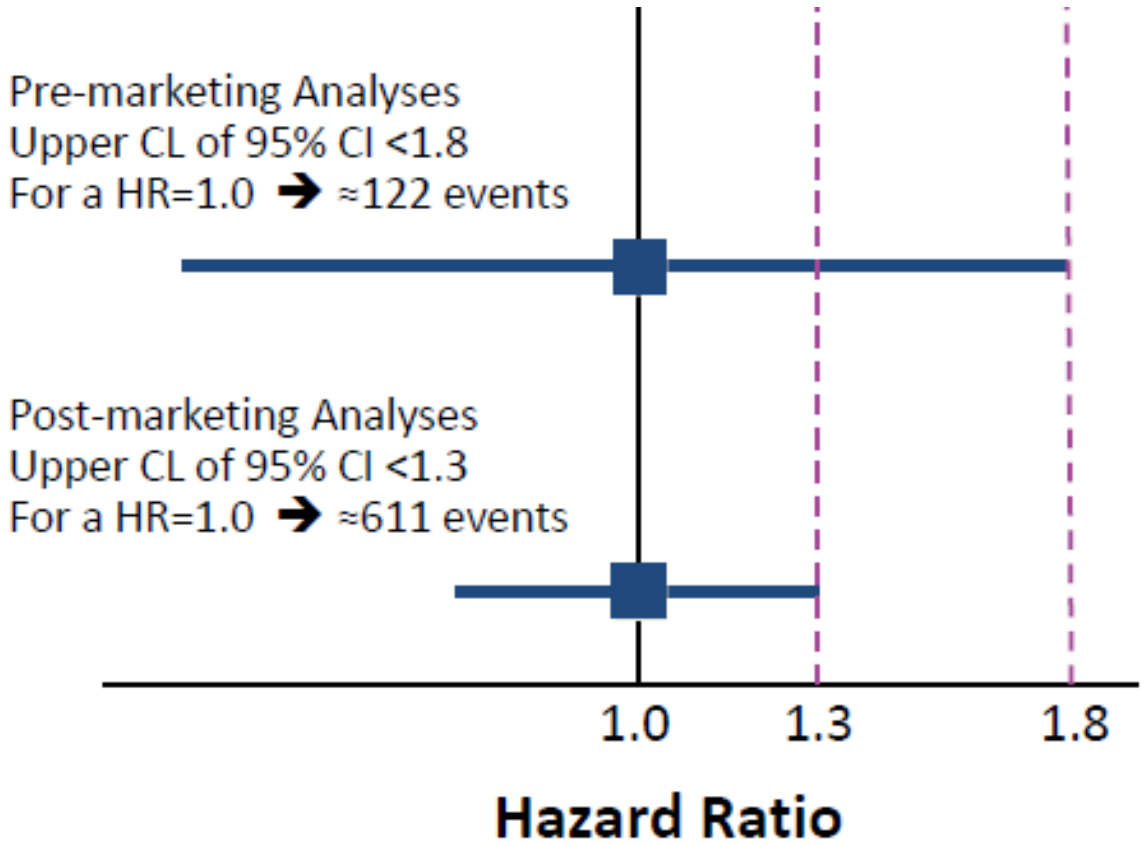
Eventos cardiovasculares



N Engl J Med, 2004; 351:1296-1305

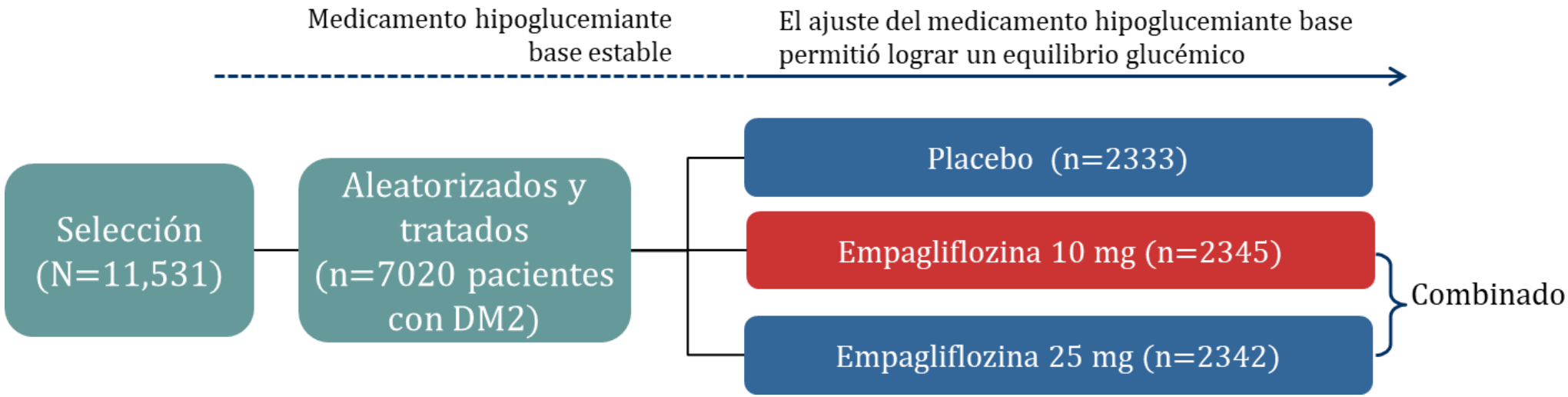
Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes



http://www.fda.gov/cder/guidance/index.htm

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



- HbA1c de 7–10%
- Enfermedad CV establecida: antecedente de enfermedad arterial coronaria, enfermedad arterial periférica, IM o accidente cerebrovascular
- TFGe ≥30 mL/min/1.73 m2

N Engl J Med 2015;373:2117-28

Desenlaces

Primario

- MACE de 3 puntos: muerte CV, IM no fatal o accidente cerebrovascular no fatal

Secundario

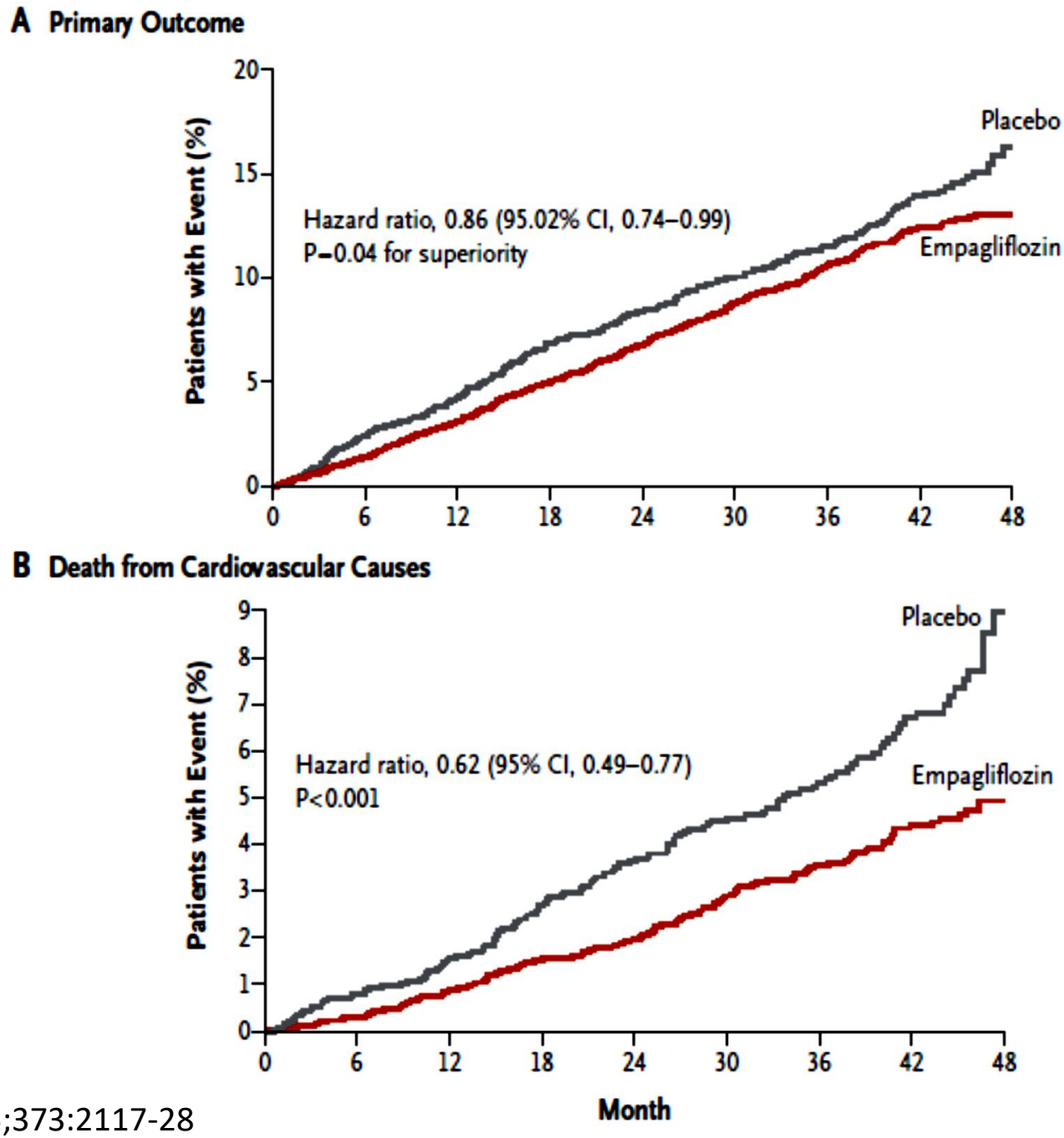
- MACE de 4 puntos: muerte CV, IM no fatal, accidente cerebrovascular no fatal u hospitalización por angina inestable

N Engl J Med 2015;373:2117-28

Características basales

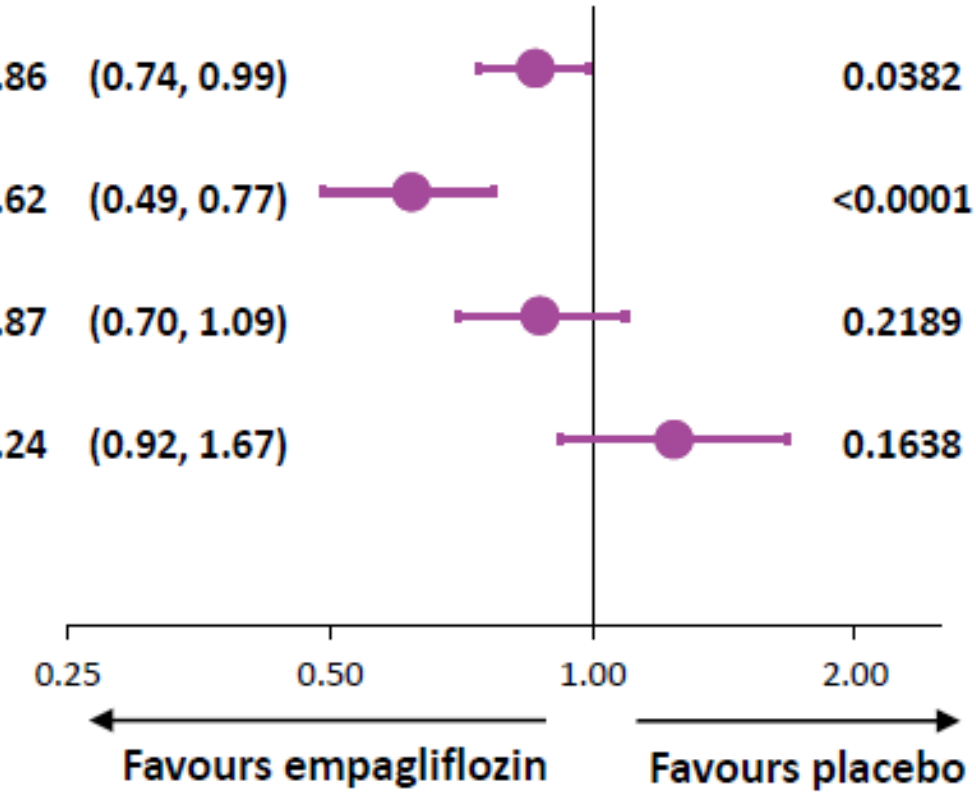
	Placebo + SOC (n=2333)		Empagliflozina 10 mg + SOC (n=2345)		Empagliflozina 25 mg + SOC (n=2342)	
HbA1c, % (±DE)	8.08	(0.84)	8.07	(0.86)	8.06	(0.84)
Índice de masa corporal, kg/m^2 (±DE)	30.7	(5.2)	30.6	(5.2)	30.6	(5.3)
PAS, mmHg (±DE)	135.8	(17.2)	134.9	(16.8)	135.6	(17.0)
PAD, mmHg (±DE)	76.8	(10.1)	76.6	(9.8)	76.6	(9.7)
Colesterol LDL, mg/L (±DE)	84.9	(35.3)	86.3	(36.7)	85.5	(35.2)
Colesterol HDL, mg/L (±DE)	44.0	(11.3)	44.7	(12.0)	44.5	(11.8)
TFGe, mL/min/1.73 m^2 (±DE)	73.8	(21.1)	74.3	(21.8)	74.0	(21.4)
≥90 mL/min/1.73 m^2, n (%)‡	488	(20.9)	519	(22.1)	531	(22.7)
60 a <90 mL/min/1.73 m^2, (%)	1238	(53.1)	1221	(52.1)	1202	(51.3)
30 a <60 mL/min/1.73 m^2, n (%)	607	(26.0)	605	(25.8)	607	(25.9)

N Engl J Med 2015;373:2117-28

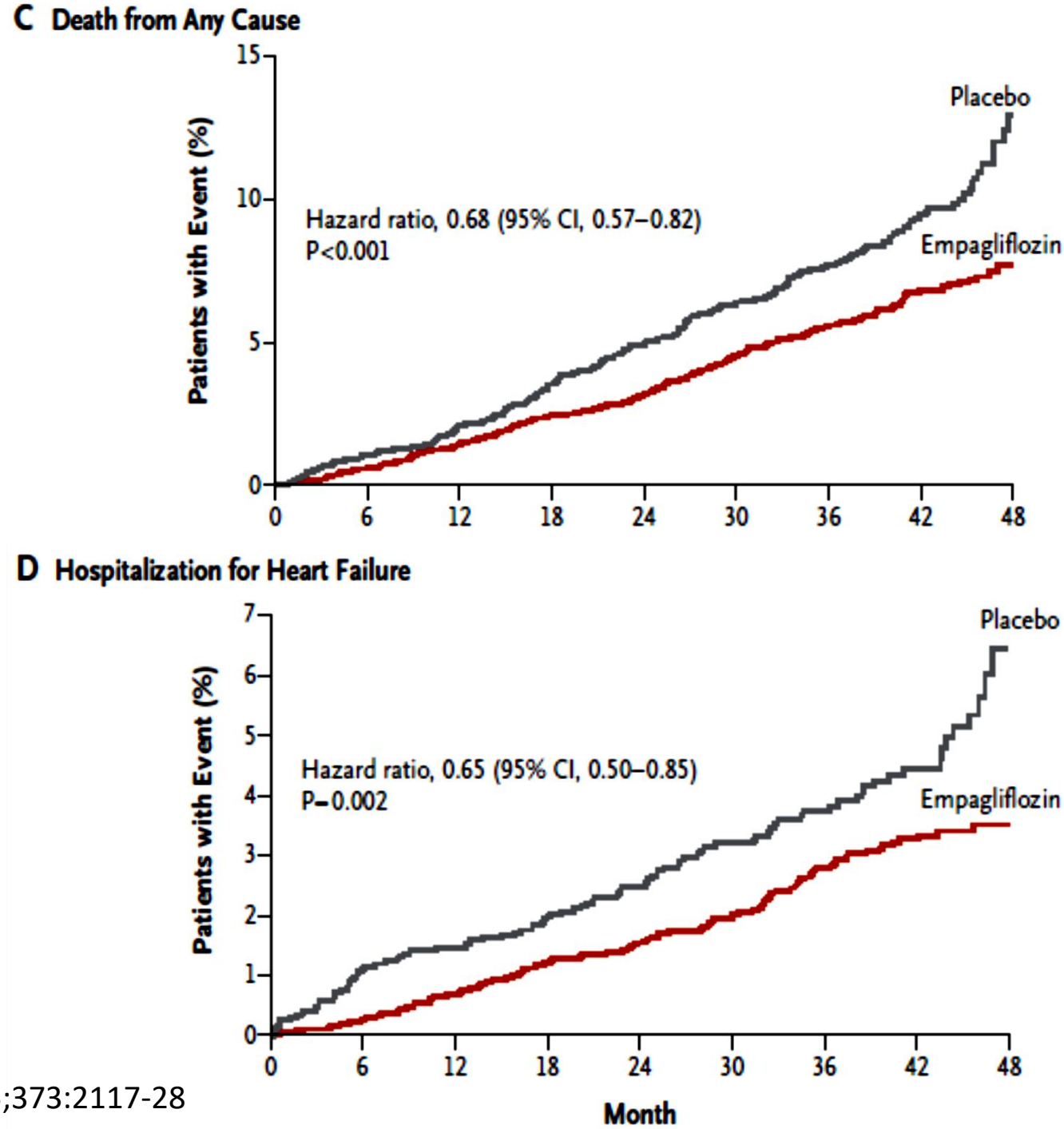


N Engl J Med 2015;373:2117-28

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638

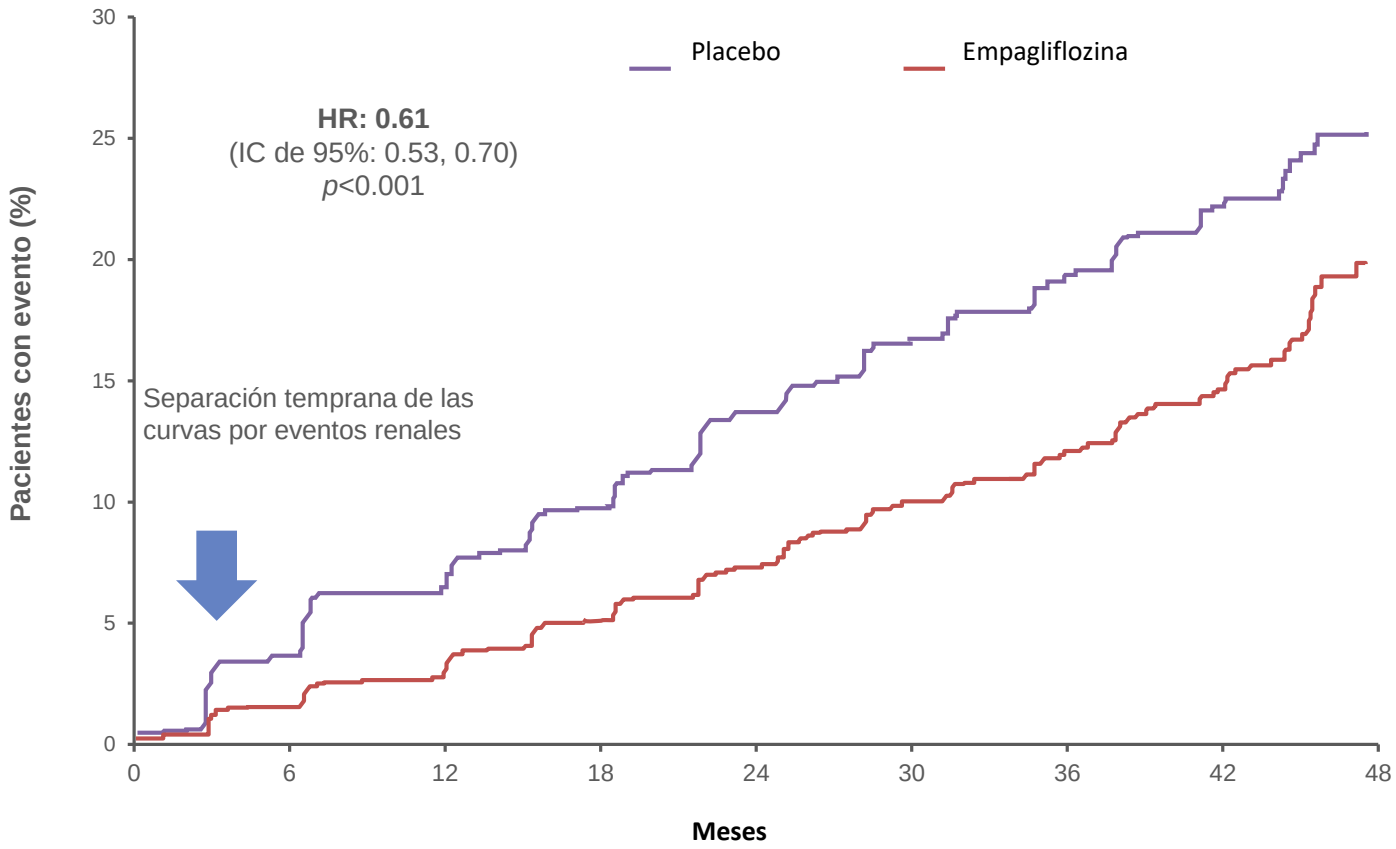


N Engl J Med 2015;373:2117-28



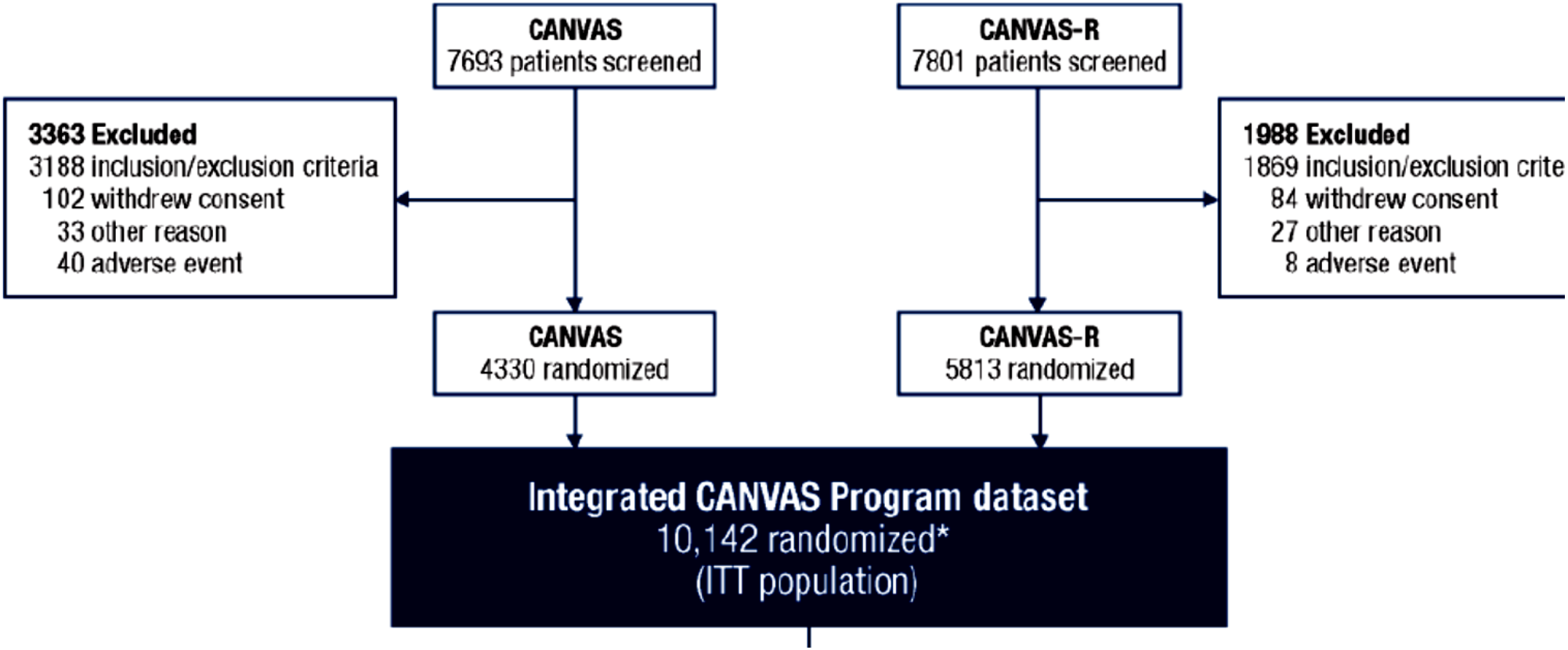
N Engl J Med 2015;373:2117-28

Progresión a macroalbuminuria, duplicación de la creatinina, inicio de la terapia de remplazo renal o muerte por enfermedad renal



N Engl J Med 2015;373:2117-28

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



N Engl J Med 2017;377:644-57

Criterios de selección

DT2

HbA1c ≥7% y ≤10%

≥30 años con antecedentes de enfermedad cardiovascular aterosclerótica

≥50 años con dos o más factores de riesgo para enfermedad cardiovascular (duración de DT2 >10 años, TAS >140 mmHg, tabaquismo, micro o macroalbuminuria, c-HDL <38.7 mg/dl)

TFGe >30 ml/min

N Engl J Med 2017;377:644-57

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

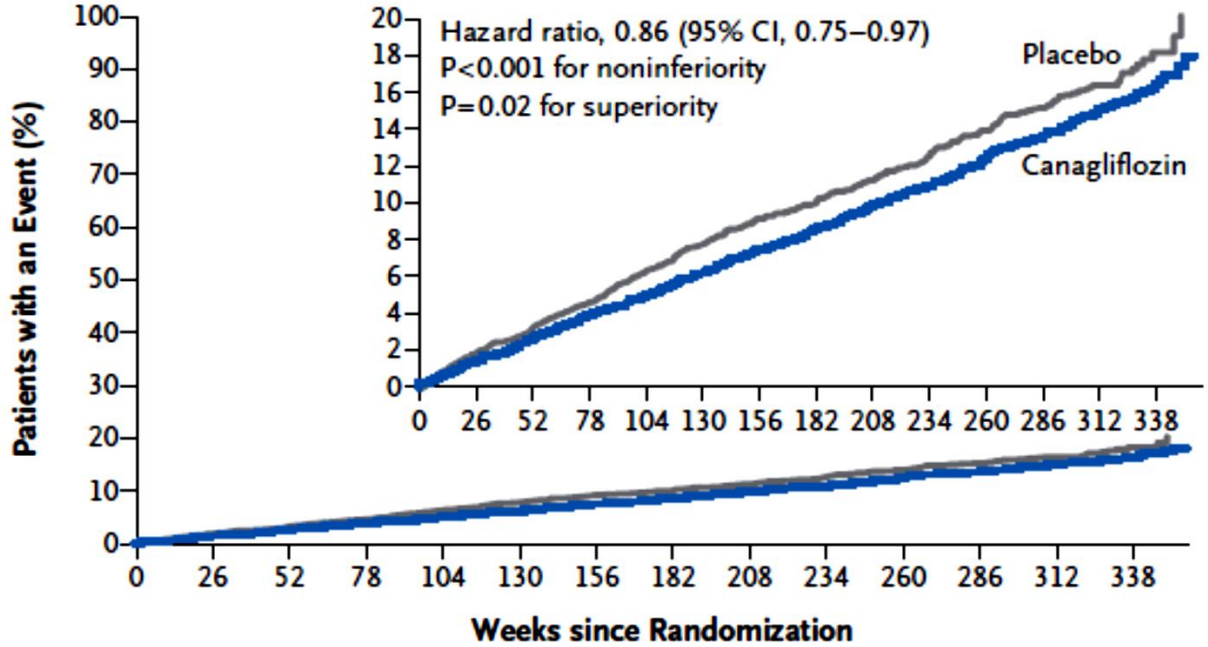
Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)	Total (N = 10,142)†
Age — yr	63.2±8.3	63.4±8.2	63.3±8.3
Female sex — no. (%)	2036 (35.1)	1597 (36.7)	3633 (35.8)
Race — no. (%)‡			
White	4508 (77.8)	3436 (79.0)	7944 (78.3)
Asian	777 (13.4)	507 (11.7)	1284 (12.7)
Black	176 (3.0)	160 (3.7)	336 (3.3)
Other	334 (5.8)	244 (5.6)	578 (5.7)
Current smoker — no. (%)	1020 (17.6)	786 (18.1)	1806 (17.8)
History of hypertension — no. (%)	5188 (89.5)	3937 (90.6)	9125 (90.0)
History of heart failure — no. (%)	803 (13.9)	658 (15.1)	1461 (14.4)
Duration of diabetes — yr	13.5±7.7	13.7±7.8	13.5±7.8
History of microvascular disease — no. (%)			
Retinopathy	1203 (20.8)	926 (21.3)	2129 (21.0)
Nephropathy	994 (17.2)	780 (17.9)	1774 (17.5)
Neuropathy	1787 (30.8)	1323 (30.4)	3110 (30.7)

N Engl J Med 2017;377:644-57

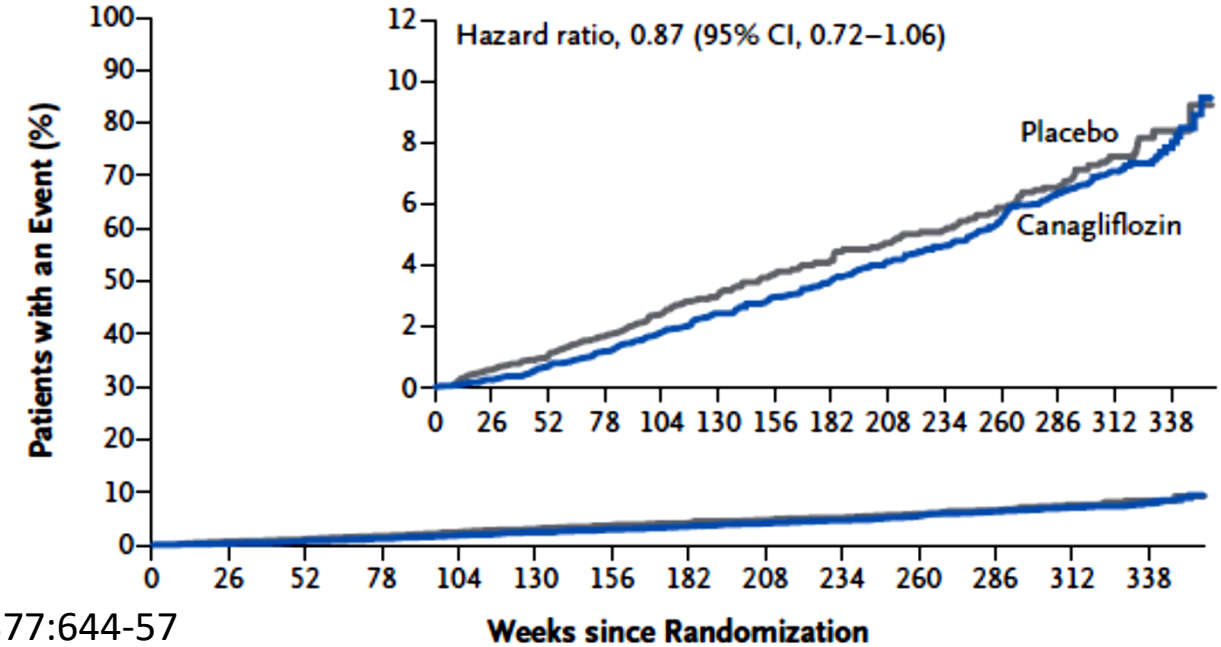
History of atherosclerotic vascular disease — no. (%)§			
Coronary	3234 (55.8)	2487 (57.2)	5721 (56.4)
Cerebrovascular	1113 (19.2)	845 (19.4)	1958 (19.3)
Peripheral	1176 (20.3)	937 (21.6)	2113 (20.8)
Any	4127 (71.2)	3197 (73.5)	7324 (72.2)
History of cardiovascular disease — no. (%)¶	3756 (64.8)	2900 (66.7)	6656 (65.6)
History of amputation — no. (%)	136 (2.3)	102 (2.3)	238 (2.3)
Body-mass index‖	31.9±5.9	32.0±6.0	32.0±5.9
Blood pressure — mm Hg			
Systolic	136.4±15.8	136.9±15.8	136.6±15.8
Diastolic	77.6±9.6	77.8±9.7	77.7±9.7
Glycated hemoglobin — %	8.2±0.9	8.2±0.9	8.2±0.9
Cholesterol — mmol/liter			
Total	4.4±1.1	4.4±1.2	4.4±1.2
HDL	1.2±0.3	1.2±0.3	1.2±0.3
LDL	2.3±0.9	2.3±0.9	2.3±0.9
Ratio of LDL to HDL	2.0±0.9	2.0±0.9	2.0±0.9
Triglycerides — mmol/liter	2.0±1.3	2.0±1.5	2.0±1.4
eGFR — ml/min/1.73 m **	76.7±20.3	76.2±20.8	76.5±20.5
Albumin measurements††			
Median albumin-to-creatinine ratio (interquartile range)	12.4 (6.71–40.9)	12.1 (6.57–43.9)	12.3 (6.65–42.1)
Normoalbuminuria — no./total no. (%)	4012/5740 (69.9)	2995/4293 (69.8)	7007/10,033 (69.8)
Microalbuminuria — no./total no. (%)	1322/5740 (23.0)	944/4293 (22.0)	2266/10,033 (22.6)
Macroalbuminuria — no./total no. (%)	406/5740 (7.1)	354/4293 (8.2)	760/10,033 (7.6)

N Engl J Med 2017;377:644-57

A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

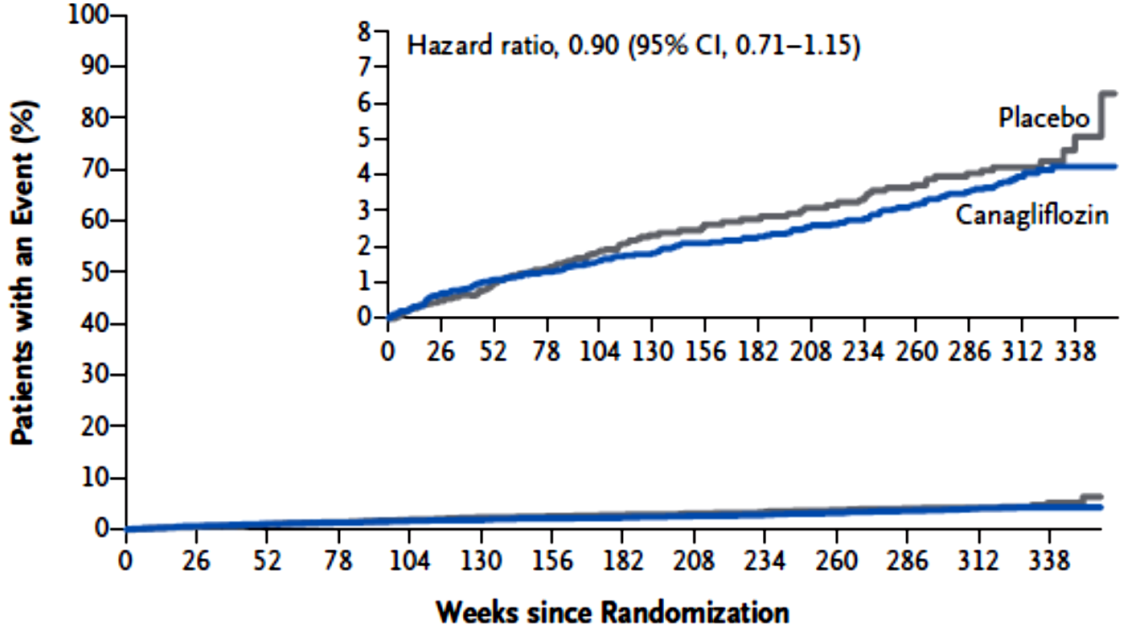


B Death from Cardiovascular Causes

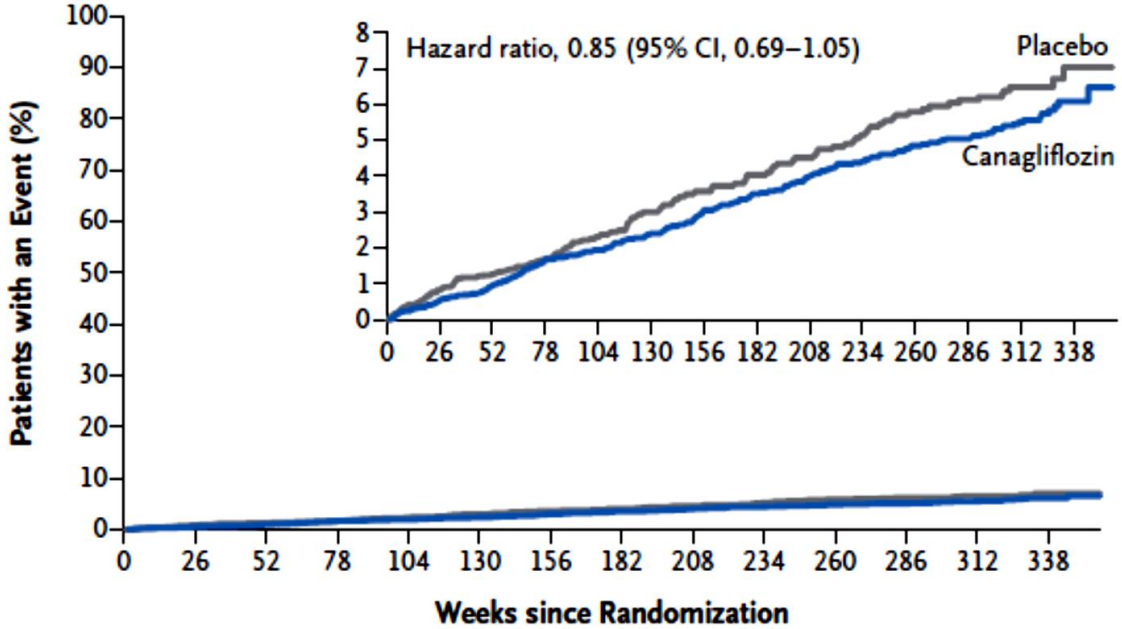


N Engl J Med 2017;377:644-57

C Nonfatal Stroke

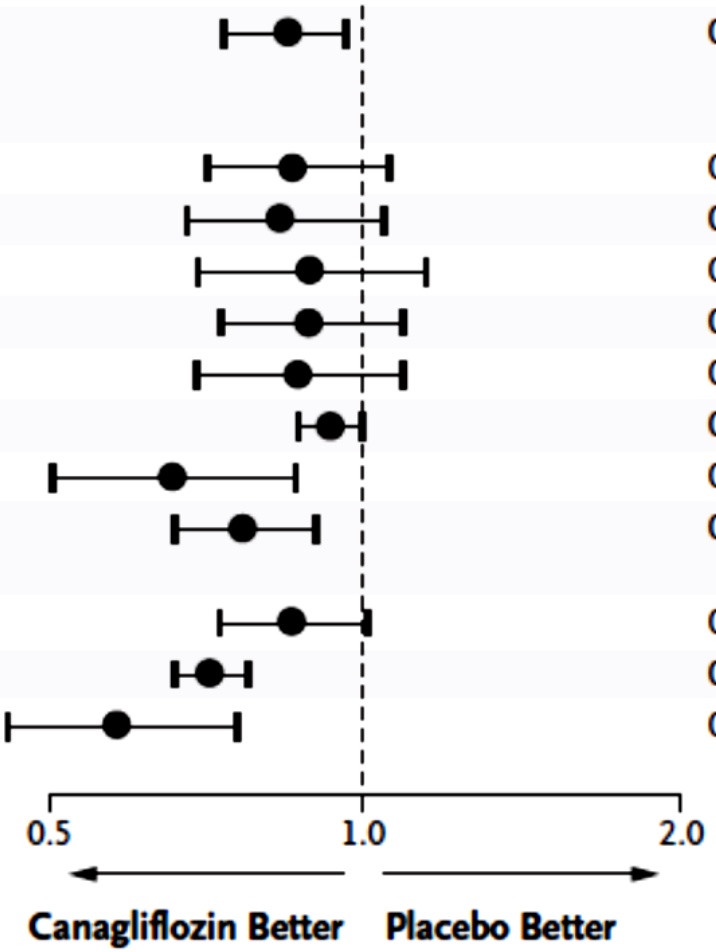


D Nonfatal Myocardial Infarction



N Engl J Med 2017;377:644-57

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



N Engl J Med 2017;377:644-57

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

17160 individuos con DM2
EVC (6794)
Factores de riesgo CV (10186)

Dapagliflozina 10 mg/día

Aleatorización 1:1
Doble ciego
Medicamentos para DM

Placebo

Duración hasta ≥1390 MACE

Seguimiento en persona cada 6 meses
Vía telefónica cada 3 meses

Mediana de seguimiento: 4.2 años

Desenlaces primarios
Seguridad: MACE (muerte CV, IAM, EVC)
Eficacia dual: muerte CV/hospitalización por IC

N Engl J Med. 2019 Jan 24;380(4):347-357

Criterios de selección

Diagnóstico de T2D

- A1c 6.5-12%
- Depuración de creatinina ≥60 ml/min

Enfermedad CV establecida (prevención secundaria)

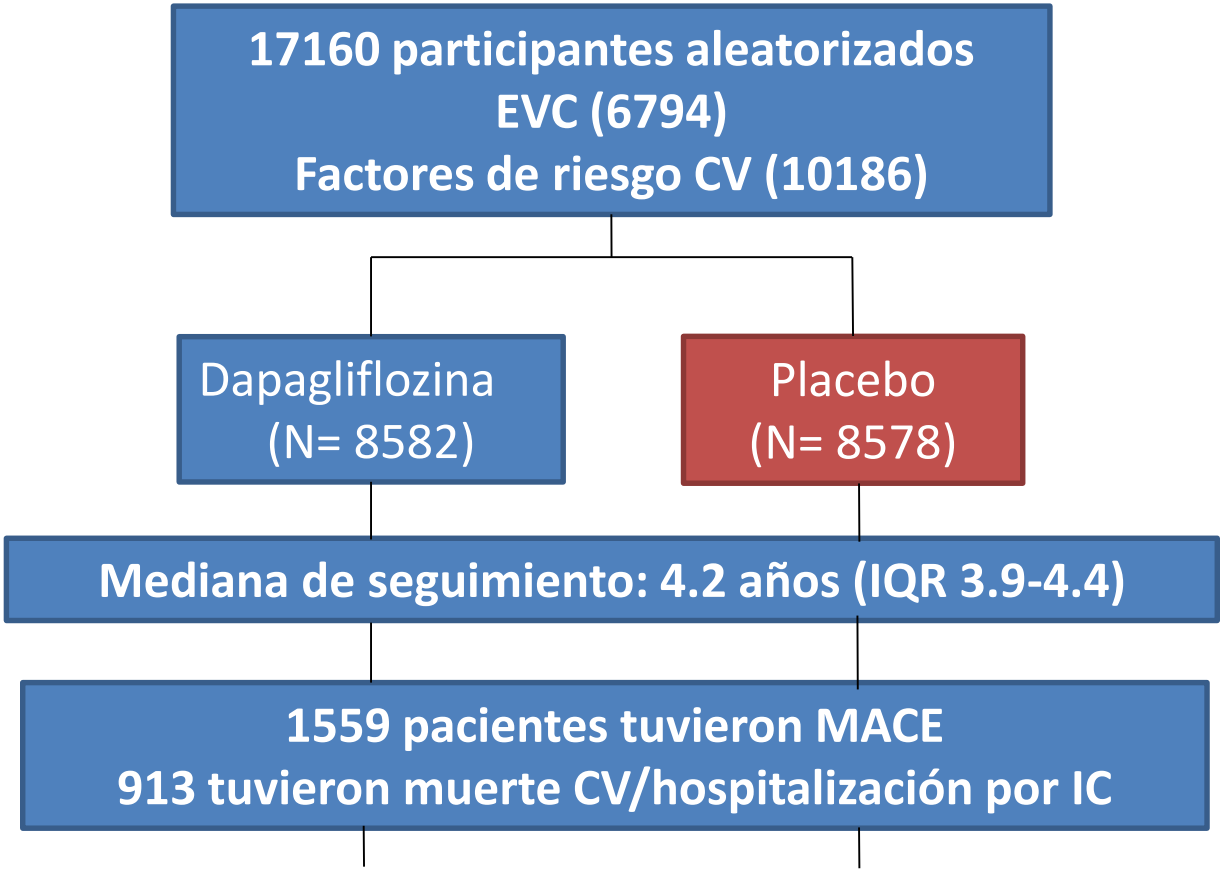
- Enfermedad isquémica cardiaca
- Enfermedad cerebrovascular
- Enfermedad arterial periférica

Múltiples factores de riesgo para ECV (prevención primaria)

- Hombres ≥55 años y mujeres ≥60 años con al menos un factor:
  - Dislipidemia
  - Hipertensión
  - Tabaquismo

N Engl J Med. 2019 Jan 24;380(4):347-357

Seguimiento



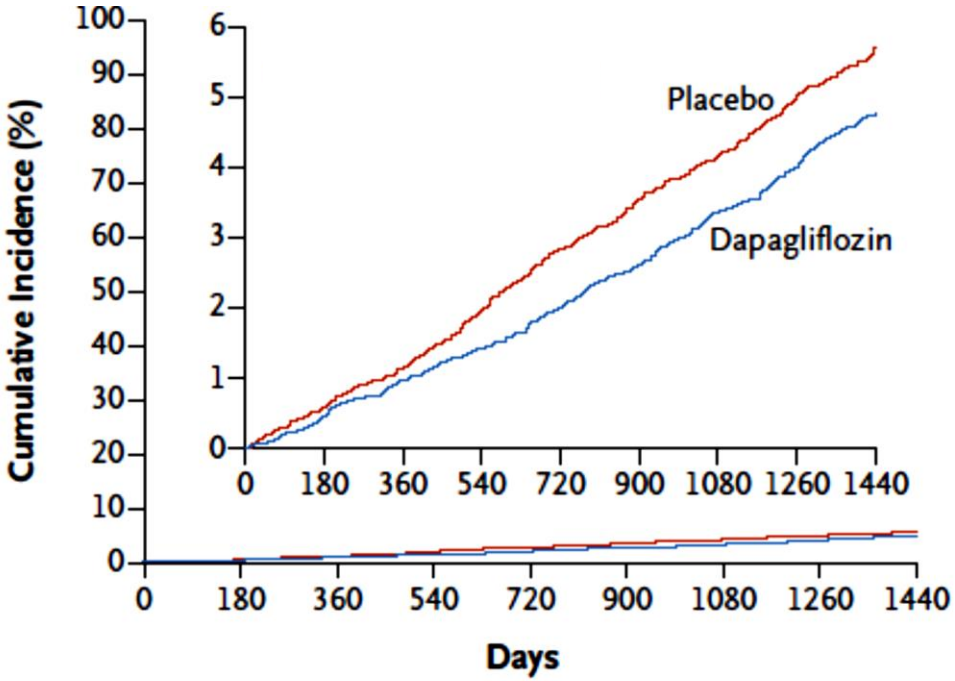
N Engl J Med. 2019 Jan 24;380(4):347-357

Características basales	N= 17160
Edad, años	64±7
Mujeres	37
IMC, kg/m2	32±6
Duración de T2D, años	11 (6, 16)
A1c, %	8.3±1.2
TFGe (CKD-EPI), ml/min	85±16
Norte América, %	32
Metformina	82
Insulina	41
Sulfonilureas	43
iDPP4	17
Agonistas receptor GLP-1	4
Anti-plaquetarios	61
iECA/ARAs	81
Beta-bloqueadores	53
Estatina/ezetimibe	75

N Engl J Med. 2019 Jan 24;380(4):347-357

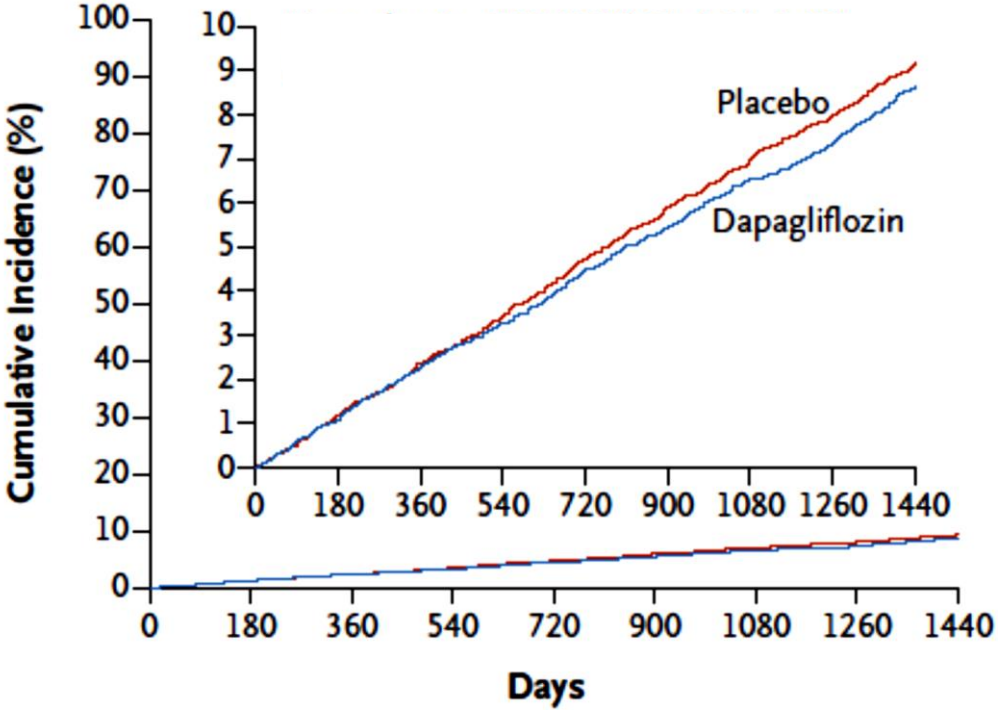
Desenlaces primarios

Muerte CV u hospitalización por IC



4.9% vs 5.8%
HR 0.83 (0.73 a 0.95, P= 0.005)

MACE

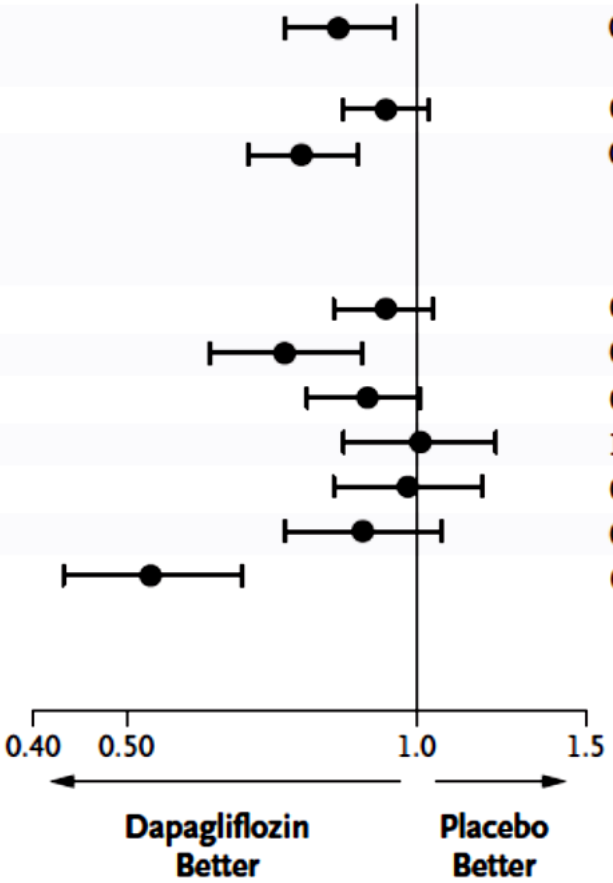


8.8% vs 9.4%
HR 0.93 (0.84 a 1.03, P= 0.17)

N Engl J Med. 2019 Jan 24;380(4):347-357

Componentes de los desenlaces

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



	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 m^2	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

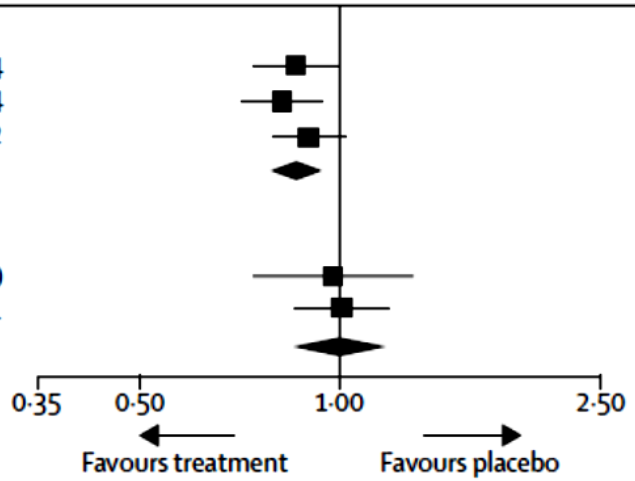
Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

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

Zelniker T.A Lancet 2019; 393: 31–39

Meta-análisis de estudios con i-SGLT2 en desenlace compuesto de IM, accidente cerebrovascular y muerte CV

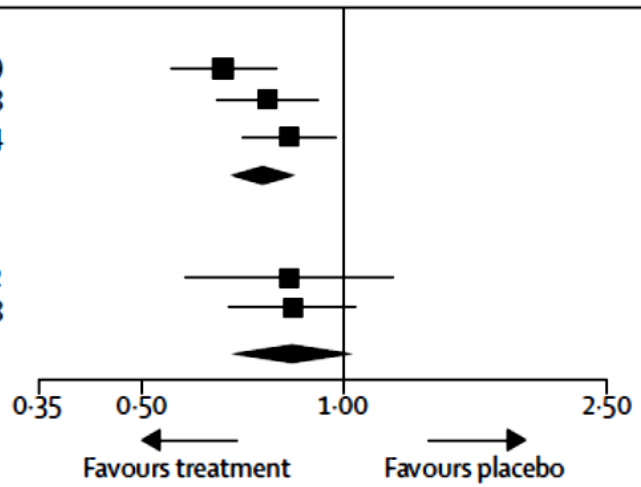
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	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	2039/3486	1447/3486	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	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)**



Zelniker T.A Lancet 2019; 393: 31–39

Meta-análisis de estudios con i-SGLT2 en hospitalización por IC y muerte CV

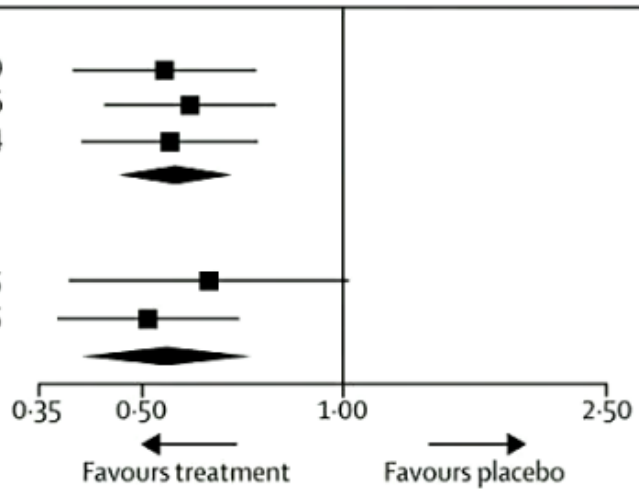
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	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	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	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)**



Zelniker T.A Lancet 2019; 393: 31–39

Meta-análisis de estudios con i-SGLT2 en desenlace renal compuesto

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0	0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6	0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4	0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·56 (0·47–0·67)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	70	4·1	6·6	29·5	0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5	0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)							**0·54 (0·42–0·71)**



Compuesto de empeoramiento de función renal, ERCT o muerte de origen renal

Zelniker T.A Lancet 2019; 393: 31–39

Reducción del RR de hospitalización por IC y progresión de enfermedad renal (45%)

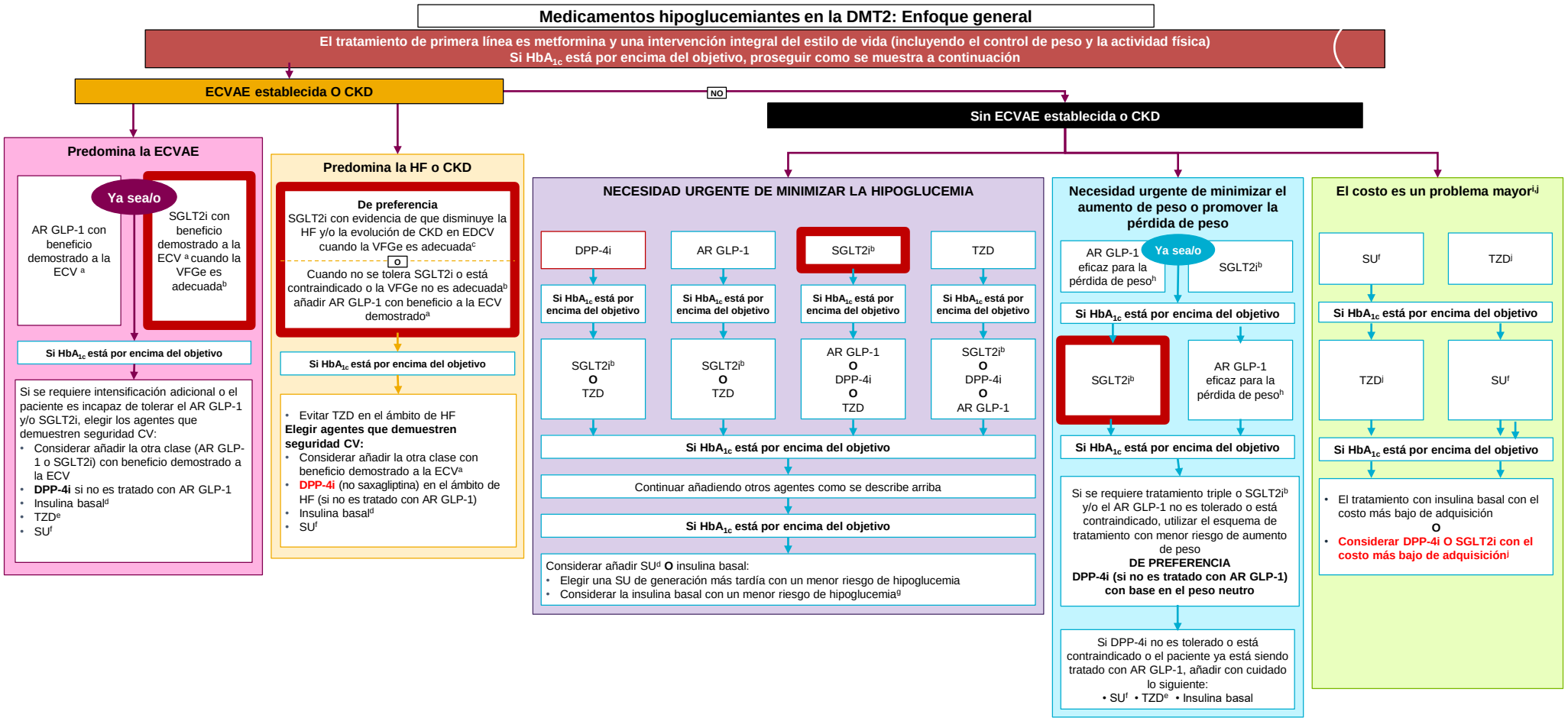
- Pacientes con y sin ECV establecida o historia de IC

Reducción del RR de 3-P MACE (IM, EVC, muerte CV) (11%)

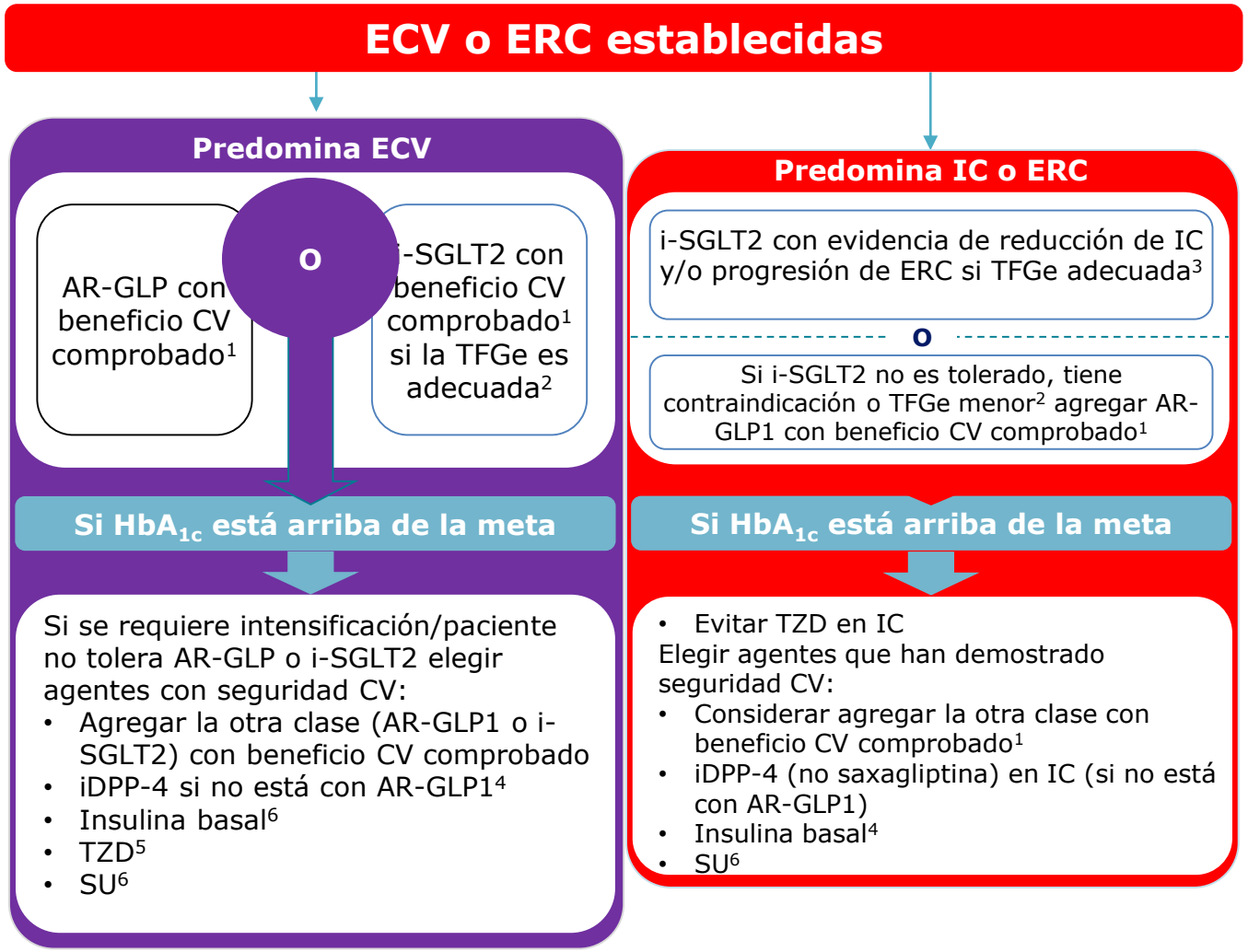
- Pacientes con ECV establecida

Zelniker T.A Lancet 2019; 393: 31–39

La adición de terapia antihiperglucémica requiere la consideración de potencia, riesgo de hipoglucemia, impacto en el peso, costo y seguridad y beneficio CV y/o renal



Diabetes Care. 2018; 41(12):2669-2701



1. Beneficio CV comprobado significa que cuenta con la indicación para reducir eventos CV
   - Análogos del receptor de GLP-1: liraglutida, semaglutida y exenatida de liberación prolongada
   - iSGLT2: empagliflozina, canagliflozina
2. La TFGe para iniciar/continuar iSGLT2 varía de acuerdo a la región y agente
3. Empagliflozina y canagliflozina han mostrado reducción de IC y en progresión de ERC
4. Degludec o glargina U100 han demostrado seguridad CV
5. Una dosis menor puede ser mejor tolerada pero ha sido menor estudiada en efectos CV
6. Elegir SU de última generación con menor riesgo de hipoglucemia

Diabetes Care. 2018; 41(12):2669-2701

Gracias