



Enfermedad cardiovascular, otra cara de la diabetes

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Universidad de Costa Rica

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Conflictos de interés

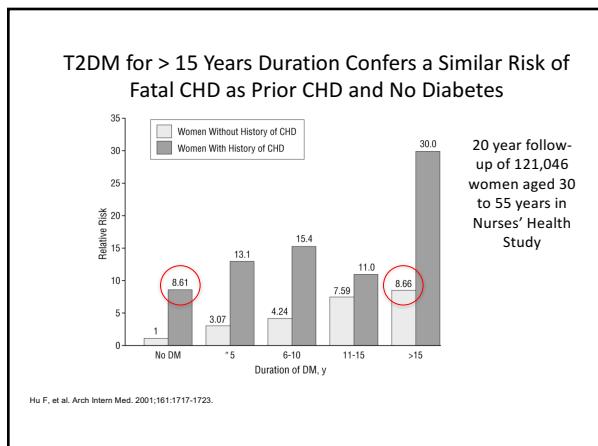
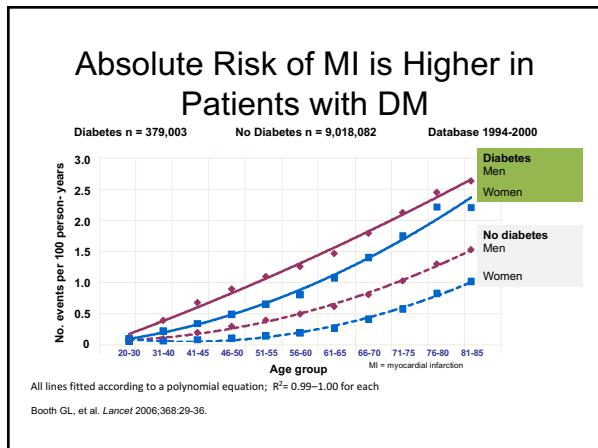
- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Janssen, Boehringer-Ingelheim
- Advisory Board: Novartis Oncology, Sanofi, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Janssen
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

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Agenda

- DM y enfermedad cardiovascular
- Evidencia más reciente en seguridad cardiovascular
 - Inhibidores de DPP-4
 - Análogos de GLP-1
 - Inhibidores de SGLT-2
- Cuáles son estos mecanismos?
- Actualización en seguridad

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Jackson Heart Study: HR ajustados

Outcome	N	Events	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Incident stroke					
No diabetes or CKD	2235	26	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	431	17	3.23 (1.75 to 5.97)	1.94 (0.96 to 3.93)	1.83 (0.90 to 3.74)
CKD but no diabetes	238	9	3.65 (1.70 to 7.82)	2.43 (1.06 to 5.74)	1.97 (0.80 to 4.35)
Diabetes and CKD	184	19	10.33 (5.70 to 18.73)	7.41 (3.87 to 14.18)	6.23 (3.22 to 12.09)
Ischemic cardiovascular heart disease					
No diabetes or CKD	2186	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	409	17	2.23 (1.26 to 3.95)	1.59 (0.84 to 3.03)	1.36 (0.74 to 2.60)
CKD but no diabetes	215	9	2.44 (1.18 to 5.05)	1.65 (0.73 to 3.75)	1.32 (0.58 to 3.00)
Diabetes and CKD	162	16	5.90 (3.30 to 10.56)	4.32 (2.33 to 8.04)	3.33 (1.79 to 6.20)
Cardiovascular mortality					
No diabetes or CKD	2297	30	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	456	16	2.52 (1.37 to 4.62)	2.06 (1.03 to 4.20)	1.90 (0.94 to 3.84)
CKD but no diabetes	257	22	7.00 (4.04 to 12.13)	5.04 (2.70 to 9.40)	4.22 (2.24 to 7.97)
Diabetes and CKD	201	30	13.38 (7.45 to 20.56)	7.46 (4.15 to 13.43)	6.44 (3.53 to 11.76)

Afkarian M. *Clin J Am Soc Nephrol*. 2016;11: early on line.

Doblamiento creatinina y riesgo de eventos

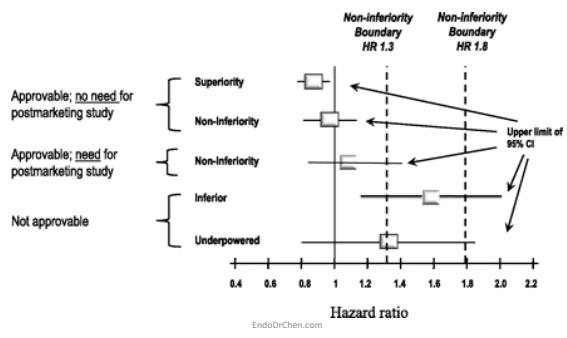
Outcome	No DSC*		DSC		HR	95% CI	P-value	HR adj.*	95% CI	P-value
	Cases	Censored	Cases	Censored						
Angina pectoris										
All	681	25,905	12	1,213	1.15	(0.64-2.09)	0.64	1.18	(0.66-2.10)	0.58
Females	282	11,655	3	610	0.62	(0.20-1.94)	0.41	0.60	(0.19-1.90)	0.39
Males	399	14,250	9	603	1.63	(0.83-3.18)	0.15	1.73	(0.88-3.38)	0.11
CHF										
All	1,009	25,699	60	1,043	3.59	(2.75-4.69)	<0.01	2.98	(2.27-3.89)	<0.01
Females	485	11,513	27	525	3.20	(2.15-4.76)	<0.01	2.71	(1.82-4.04)	<0.01
Males	524	14,186	33	518	4.02	(2.80-5.77)	<0.01	3.31	(2.30-4.77)	<0.01
Myocardial infarction										
All	487	26,103	21	1,200	2.58	(1.65-4.04)	<0.01	2.53	(1.62-3.96)	<0.01
Females	189	11,752	13	596	3.65	(2.05-6.51)	<0.01	3.32	(1.85-5.93)	<0.01
Males	298	14,351	8	604	1.79	(0.88-3.65)	0.11	1.84	(0.90-3.76)	0.10
Stroke										
All	932	25,681	38	1,160	2.12	(1.52-2.95)	<0.01	1.93	(1.38-2.69)	<0.01
Females	429	11,523	22	576	2.34	(1.51-3.63)	<0.01	2.09	(1.35-3.25)	<0.01
Males	503	14,158	16	584	1.86	(1.12-2.08)	0.02	1.70	(1.02-2.83)	0.04
TIA										
All	563	26,014	15	1,219	1.39	(0.82-2.33)	0.22	1.32	(0.78-2.22)	0.30
Females	267	11,662	8	613	1.45	(0.71-2.96)	0.31	1.31	(0.64-2.69)	0.46
Males	296	14,352	7	606	1.31	(0.61-2.79)	0.48	1.31	(0.61-2.79)	0.49

Schneider C. Clinical Epidemiology. 2016;8:177

CUÁL ES EL ORIGEN DE LA GRAN CANTIDAD DE ESTUDIOS CON DESENLAZES CARDIOVASCULARES?

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Requerimientos de seguridad cardiovascular por FDA



ESTUDIOS CON DESENLAES CARDIOVASCULARES

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Metformin: UKPDS 34

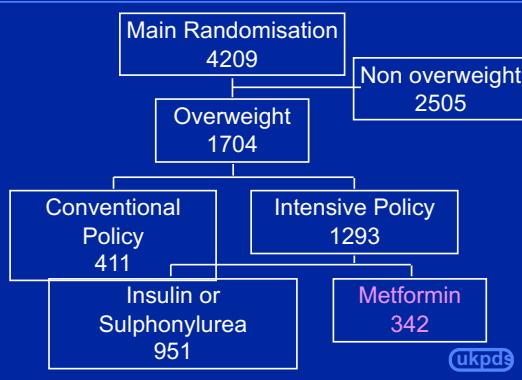
brief, between 1977 and 1991, general practitioners in 23 cities in the UK referred patients with newly diagnosed type 2 diabetes aged 25–65 years to the public sector in UKPDS. 5105 diabetes with FPG above 6.0 mmol/L on two mornings were recruited. The patients were advised to follow a diet high in carbohydrates and fibre and low in saturated fat. 4209 eligible patients with FPG above 6.0 mmol/L were randomised by a stratified design: 2022 (48%) were non-overweight and 2187 (52%) were overweight. Patients were allocated conventional treatment with diet or intensive treatment with sulphonylurea as the additional therapy option in overweight patients in the first 15 centres. We report here results for the overweight participants who had FPG above 7.8 mmol/L on diet treatment (n=1704) without symptoms of hyperglycaemia, after diet treatment.

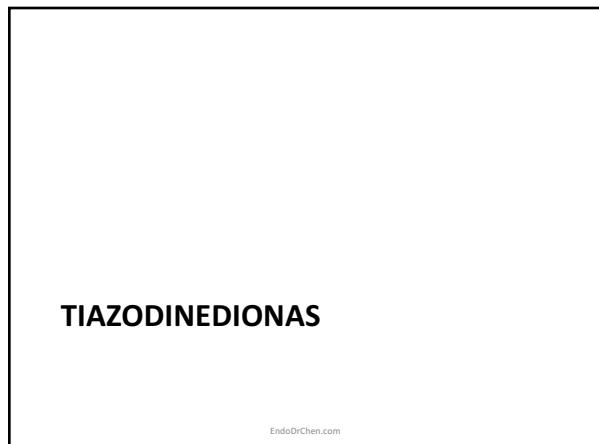
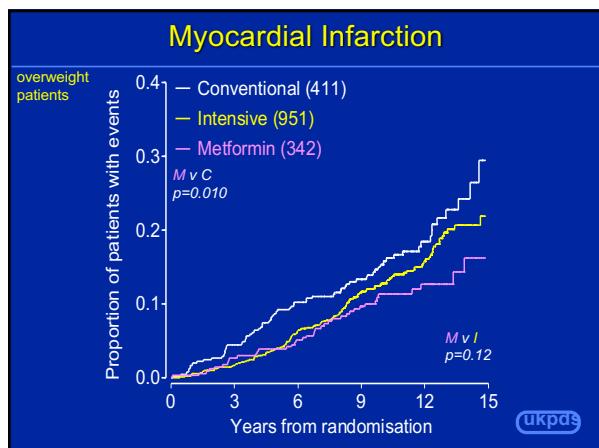
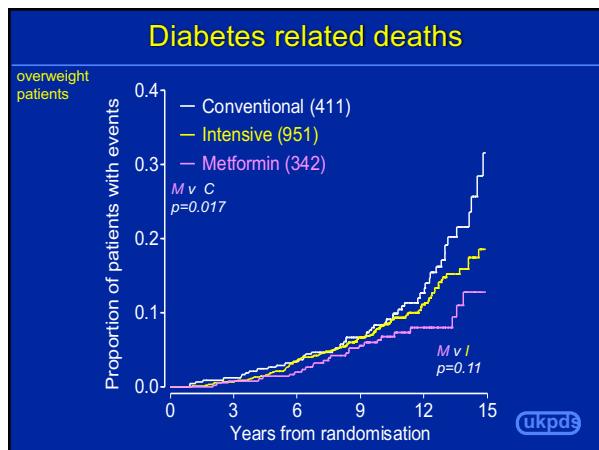
This paper reports on two randomised controlled trials in the first 15 centres, in which metformin was a therapeutic option.

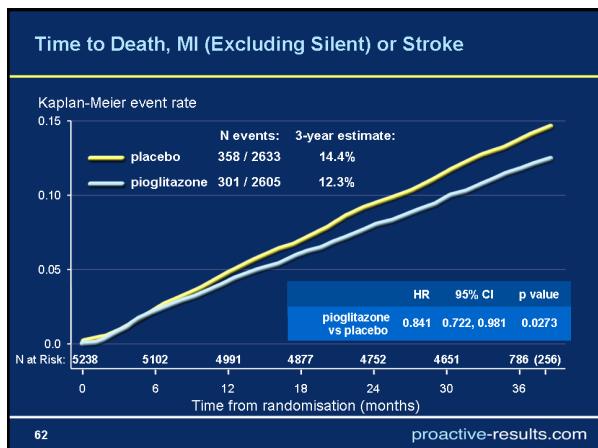
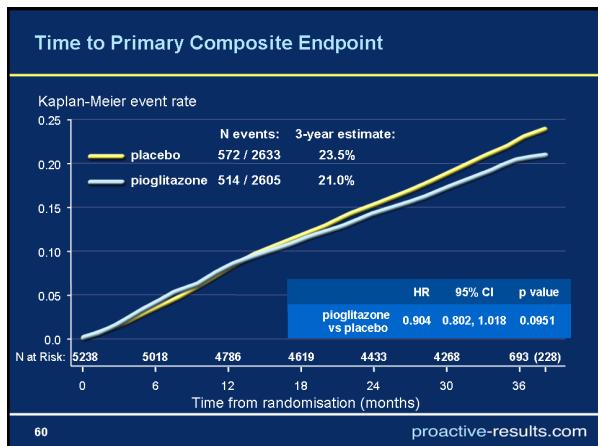
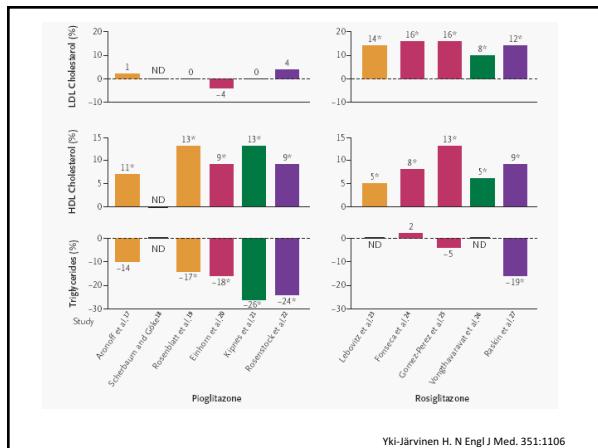
Trial in overweight, diet-treated patients of intensive blood glucose control with metformin versus conventional treatment

The 1704 overweight patients were randomly assigned conventional treatment, primarily with diet (24%), or intensive treatment with chlorpropamide (16%), glibenclamide (16%), insulin (24%), or metformin (20%). This report primarily compares the 411 overweight patients assigned conventional treatment with diet, or intensive treatment with sulphonylurea, treatment with metformin, as designated in the protocol⁶ (figure 1). The paper also reports the secondary analysis of the 1293 overweight patients assigned conventional treatment with metformin (n=342) with the 951 patients allocated intensive therapy with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409).

Randomisation



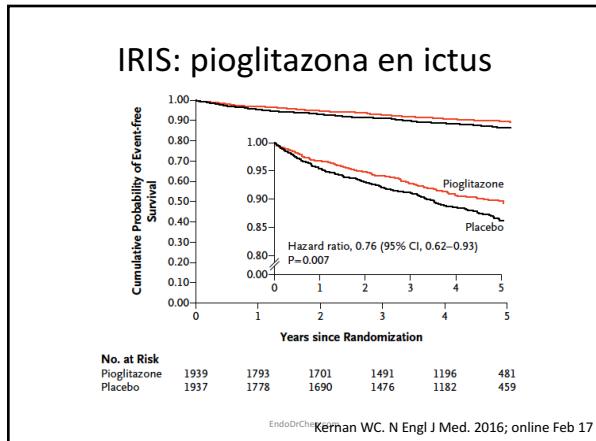




Serious Adverse Events Occurring in >1% of Patients (Excluding Endpoints)		
	Pioglitazone n (%)	Placebo n (%)
Heart failure	149 (5.7)	108 (4.1)
Hospitalisation for DM management	55 (2.1)	91 (3.5)
Angina pectoris	89 (3.4)	122 (4.6)
Accident	51 (2.0)	49 (1.9)
Atrial fibrillation	42 (1.6)	51 (1.9)
Pneumonia	53 (2.0)	35 (1.3)
Transient ischaemic attack	34 (1.3)	39 (1.5)
Malignant neoplasms	97 (3.7)	99 (3.8)

92

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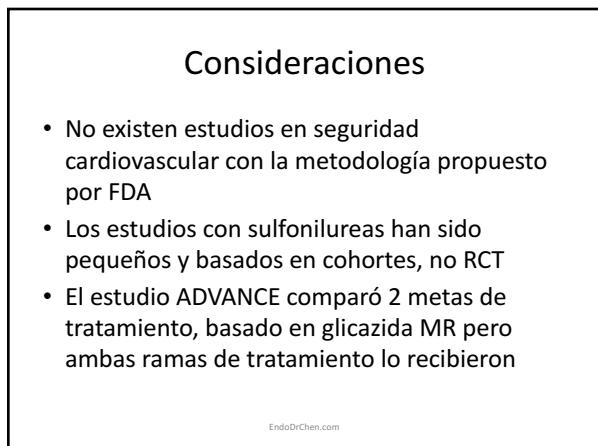


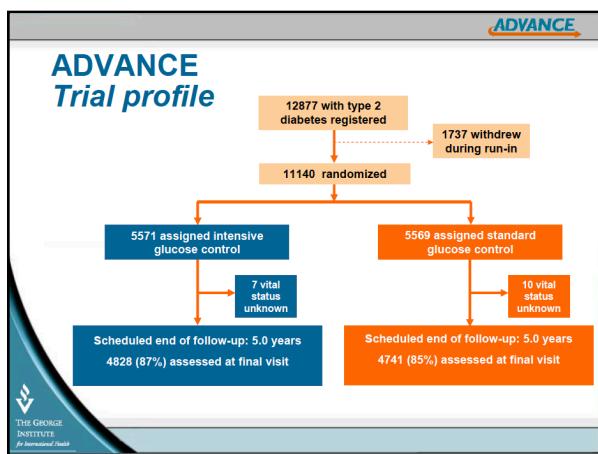
Aspectos prácticos

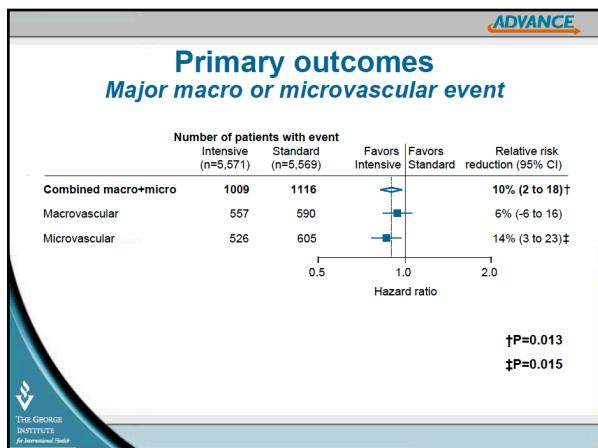
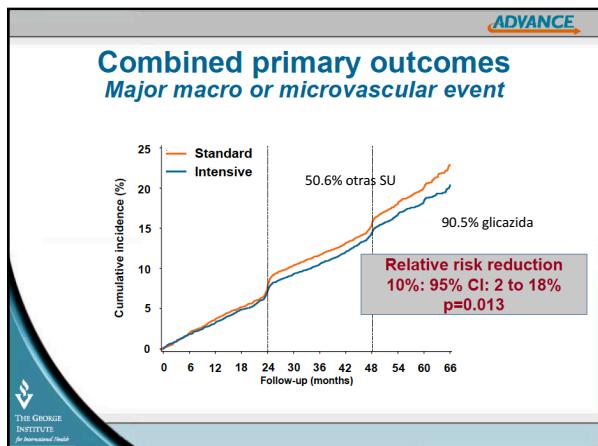
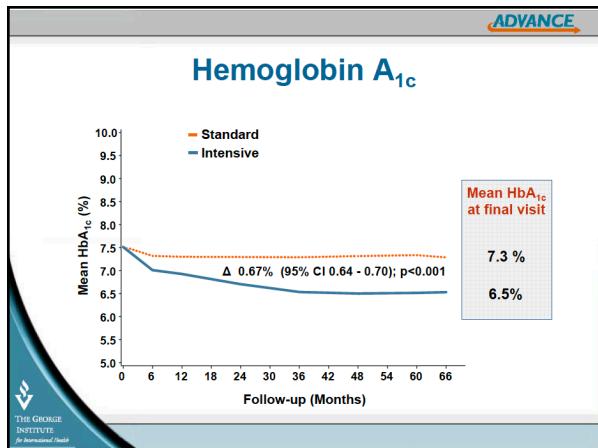
- Aumentan de peso
- Controversial si aumentan riesgo de cáncer de vejiga y fracturas
- Aumenta riesgo de insuficiencia cardíaca, especialmente combinado con insulina
- Mayor retención de agua en pacientes con insuficiencia renal
- Son la única terapia que ha mostrado enlentecer la progresión en la falla de la célula beta

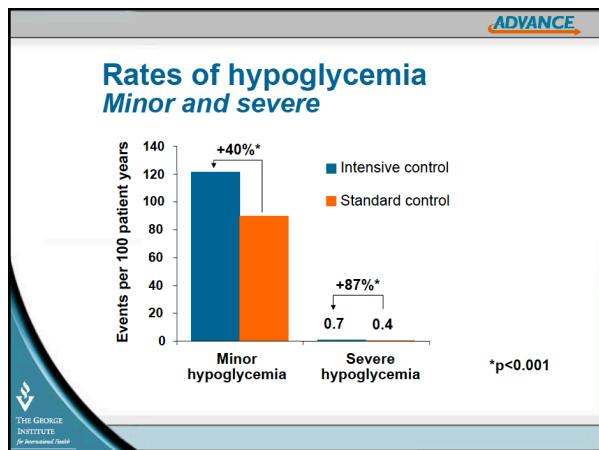
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LA ERA MODERNA DE LOS ESTUDIOS DE SEGURIDAD CARDIOVASCULAR

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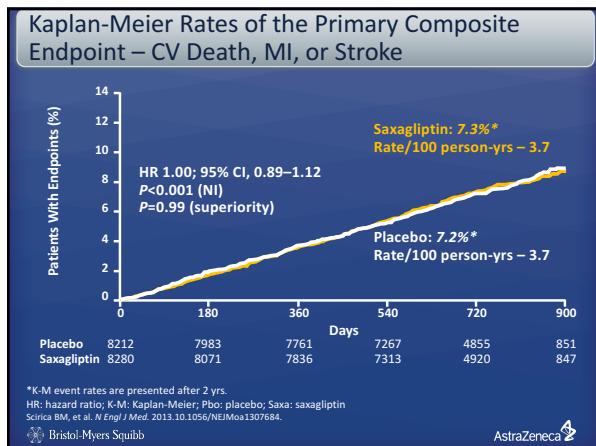
INHIBIDORES DE DPP-4

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Consideraciones

- Son muy bien tolerados
- Moderadamente eficaces
- No producen hipoglicemias
- Neutros en peso y presión arterial
- Amplia experiencia a nivel mundial

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Individual Components of the Composite Endpoints

Efficacy endpoint	Saxagliptin n (%) [*] (N = 8,280)	Placebo n (%) [*] (N = 8,212)	HR (95% CI)	P value
CV death	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
MI	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hosp for UA	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hosp for HF	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hosp for coronary revasc.	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

^{*}K-M event rates are presented after 2 yrs.

Scirica BM, et al. *N Engl J Med*. 2013;368:1307-1316.

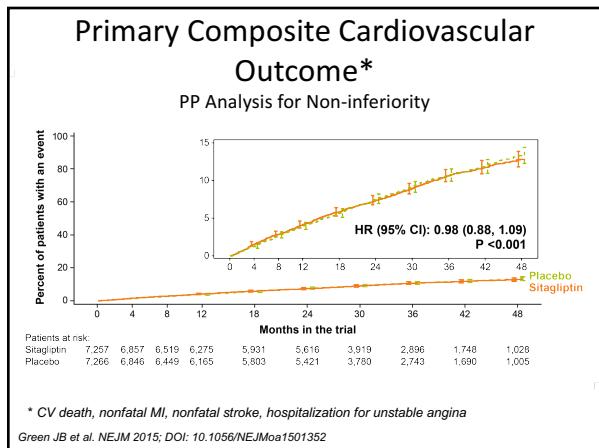
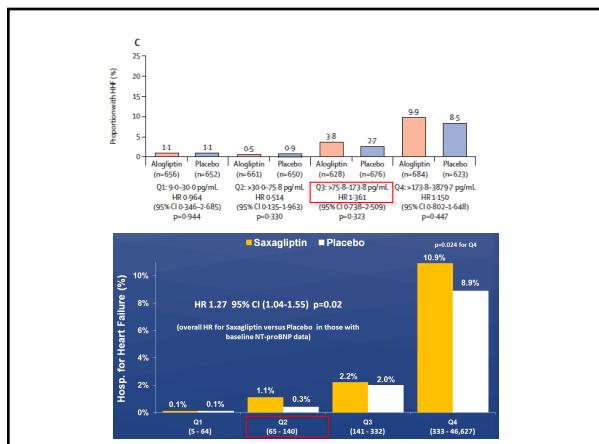
Bristol-Myers Squibb

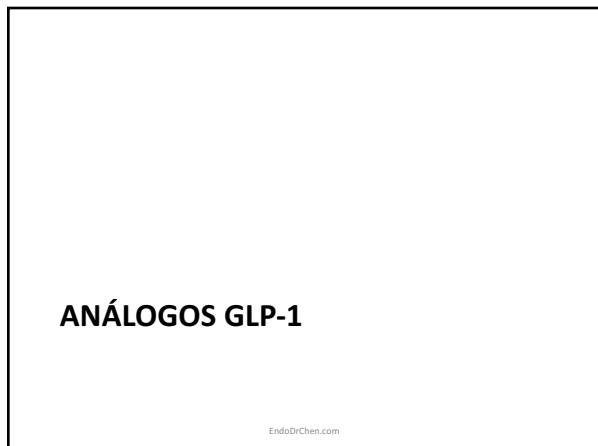
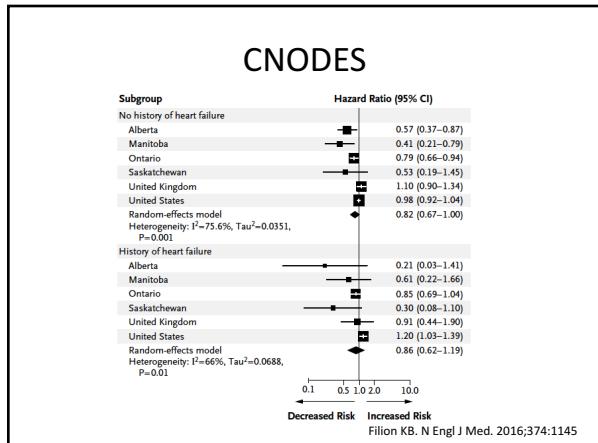
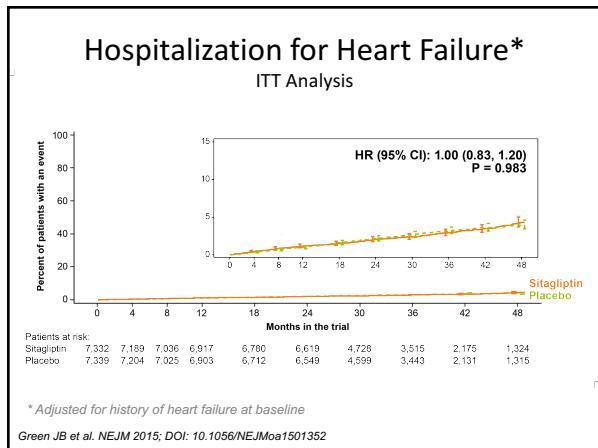
AstraZeneca

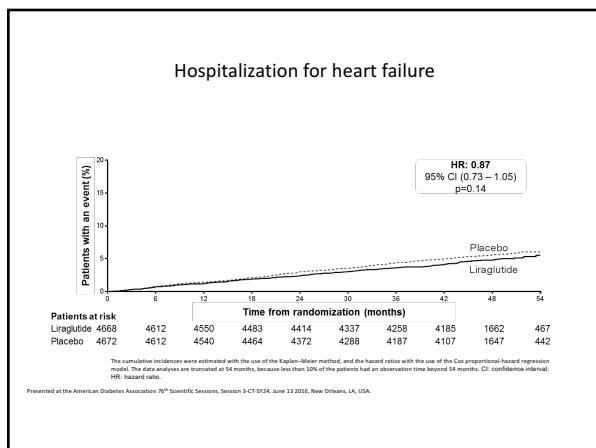
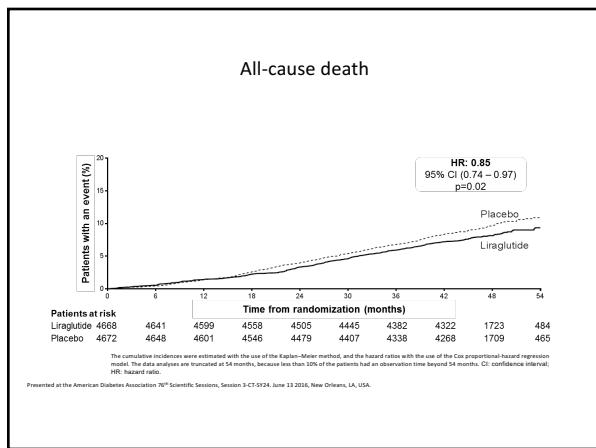
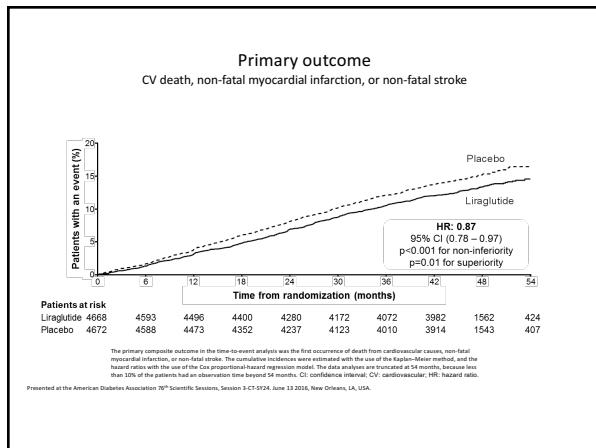
	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7.4)	201 (7.5)	107 (13.9)	120 (15.7)	94 (4.9)	81 (4.2)
Hazard ratio (95% CI)	1.00 (0.82-1.21)		0.90 (0.70-1.17)		1.14 (0.85-1.54)	
p value	0.976		0.446		0.337	
p _{interaction} for treatment and history of heart failure	-	-	0.221	-	-	-
Cardiovascular death*	112 (4.1)	130 (4.9)	55 (7.1)	69 (9.1)	57 (3.0)	61 (3.2)
Hazard ratio (95% CI)	0.85 (0.66-1.10)		0.77 (0.54-1.09)		0.92 (0.64-1.32)	
p value	0.212		0.141		0.643	
p _{interaction} for treatment and history of heart failure	-	-	0.508	-	-	-
Hospital admission for heart failure	106 (3.9)	89 (3.3)	63 (8.2)	65 (8.5)	43 (2.2)	24 (1.3)
Hazard ratio (95% CI)	1.19 (0.90-1.58)		1.00 (0.71-1.42)		1.76 (1.07-2.90)	
p value	0.220		0.996		0.026	
p _{interaction} for treatment and history of heart failure	-	-	0.068	-	-	-

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Zannad F. Lancet. 2015. Online Mar 15







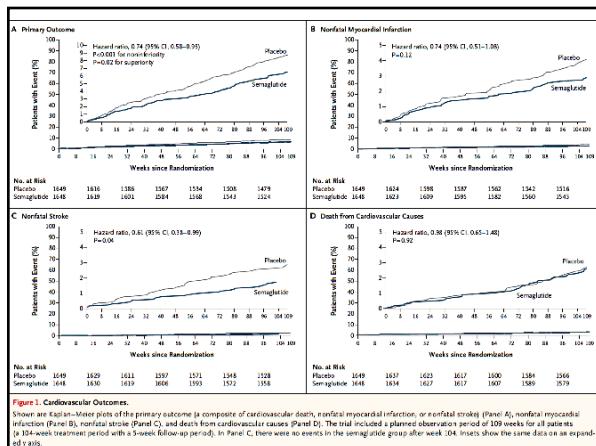
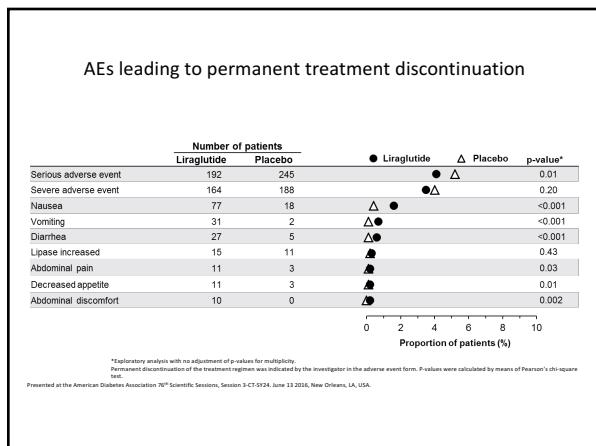
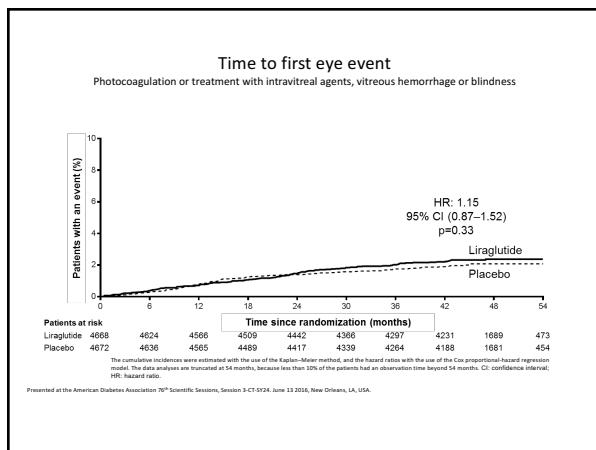


Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.						
Outcome	Semaglutide (N=1648)	Placebo (N=1649)	Hazard Ratio (95% CI) ^a	P Value		
	no. (%) no./100 person yr	no. (%) no./100 person yr				
Primary composite outcome ^b	108 (6.6) 3.24	146 (8.9) 4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority		
Expanded composite outcome ^c	199 (12.1) 6.17	264 (16.0) 8.36	0.74 (0.62–0.89)	0.002		
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4) 3.66	158 (9.8) 4.81	0.77 (0.61–0.97)	0.05		
Death						
From any cause	62 (3.8) 1.82	60 (3.6) 1.76	1.05 (0.74–1.50)	0.79		
From cardiovascular cause	44 (2.7) 1.29	46 (2.8) 1.33	0.98 (0.63–1.48)	0.92		
Nonfatal myocardial infarction	47 (2.9) 1.40	64 (3.9) 1.92	0.74 (0.51–1.08)	0.12		
Nonfatal stroke	27 (1.6) 0.80	44 (2.7) 1.31	0.61 (0.38–0.99)	0.04		
Hospitalization for unstable angina pectoris	22 (1.3) 0.65	27 (1.6) 0.80	0.82 (0.47–1.44)	0.49		
Revascularization	83 (5.0) 2.50	126 (7.6) 3.85	0.65 (0.50–0.86)	0.003		
Hospitalization for heart failure	59 (3.6) 1.76	54 (3.3) 1.61	1.11 (0.77–1.61)	0.57		
Retinopathy complications ^d	50 (3.0) 1.49	29 (1.8) 0.86	1.76 (1.11–2.78)	0.02		
New or worsening nephropathy ^e	62 (3.8) 1.86	100 (6.1) 3.06	0.64 (0.40–0.88)	0.005		

^a Hazard ratios and P values were estimated with the use of a Cox proportional hazards model with the study treatments as fixed factors and stratified according to all combinations of stratification factors used in the randomization.

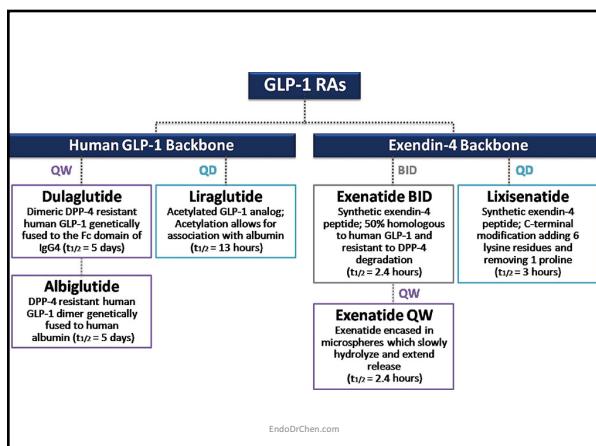
^b The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

^c The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.

^d Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation.

^e New or worsening nephropathy includes persistent microalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 mL per minute per 1.73 m² of body-surface area (according to the Modification of Diet in Renal Disease criteria).

^f or the need for continuous oral loop diuretic therapy.



Sin embargo...

- Los estudios de los análogos de GLP-1 basados en exendin 4 han sido neutros desde el punto de vista CV
 - ELIXA con lixisenatide
 - EXSCEL con exenatide semanal (datos no publicados)

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INHIBIDORES DE SGLT-2

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Key inclusion and exclusion criteria

- Key inclusion criteria
 - Adults with type 2 diabetes
 - BMI $\leq 45 \text{ kg/m}^2$
 - HbA1c 7–10%*
 - Established cardiovascular disease
 - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
- Key exclusion criteria
 - eGFR $<30 \text{ mL/min/1.73m}^2$ (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥ 12 weeks prior to randomisation or no change in dose for ≥ 12 weeks prior to randomisation or, in the case of insulin, unchanged by $>10\%$ compared to the dose at randomisation

EMPA-REG OUTCOME[®] 50

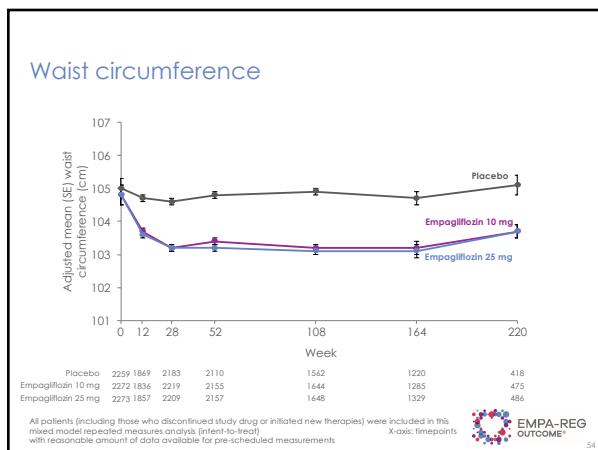
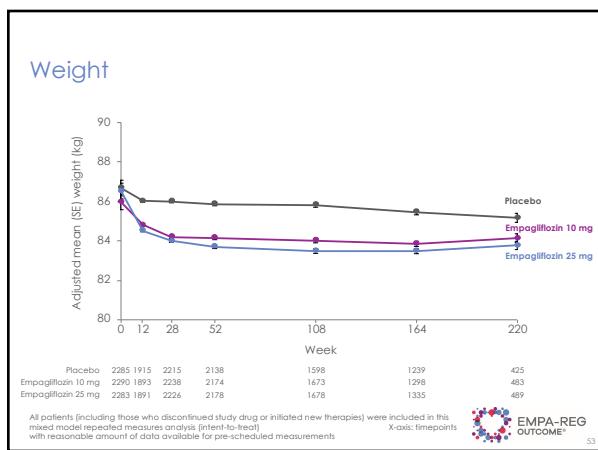
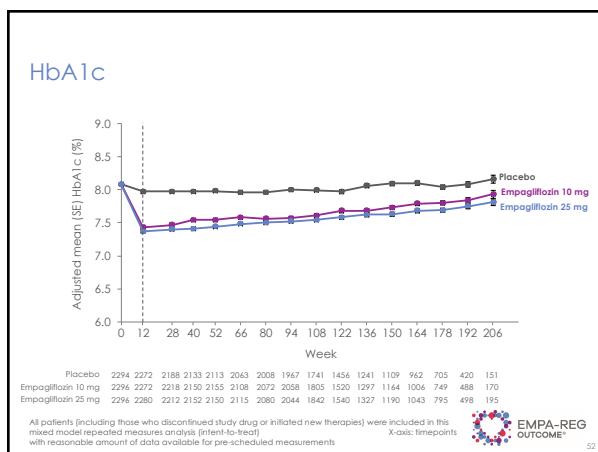
Trial design

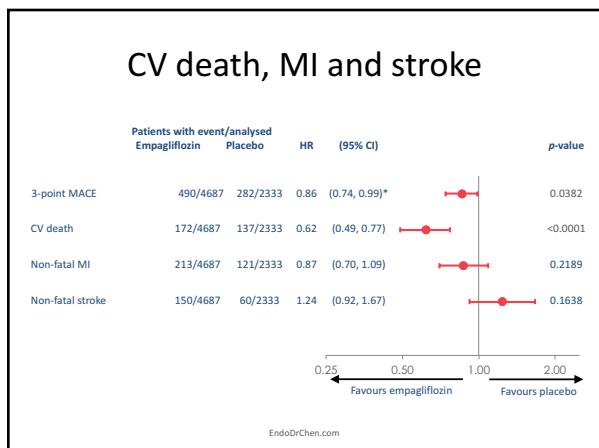
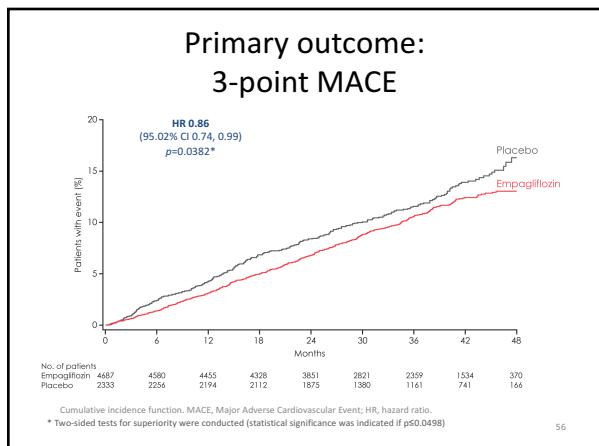
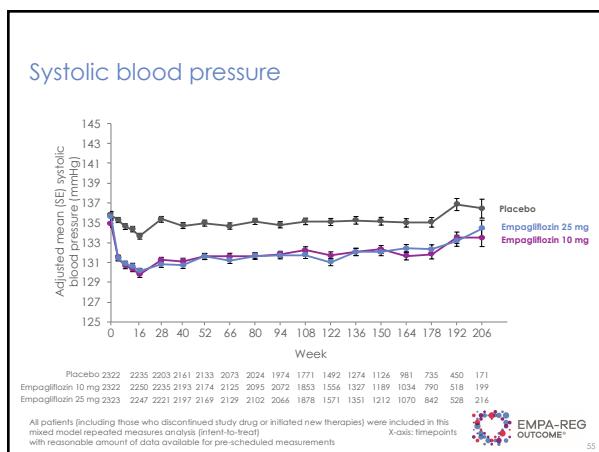
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graph LR
    A[Screening (n=11531)] --> B[Randomised and treated (n=7020)]
    B --> C[Placebo (n=2333)]
    B --> D[Empagliflozin 10 mg (n=2345)]
    B --> E[Empagliflozin 25 mg (n=2342)]
  
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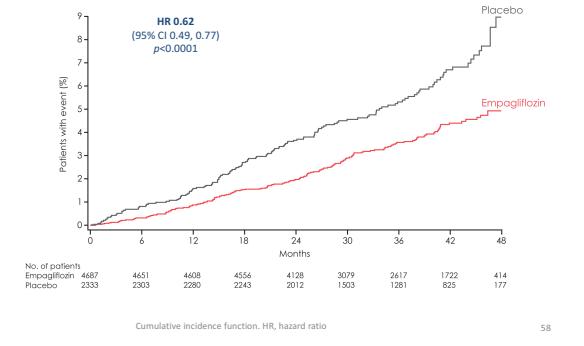
- Study medication was given in addition to standard of care
 - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

51

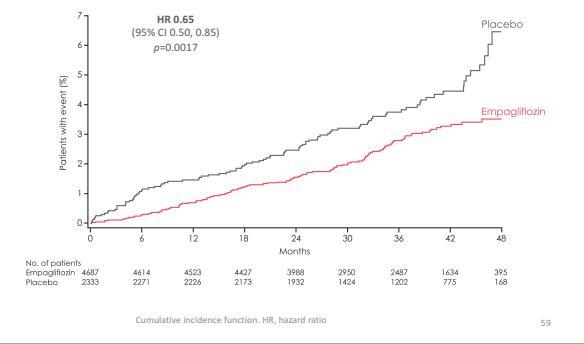




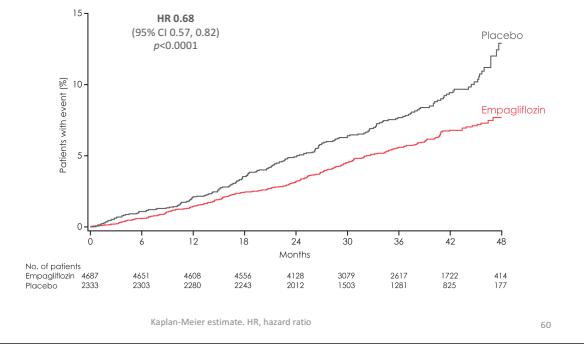
CV death

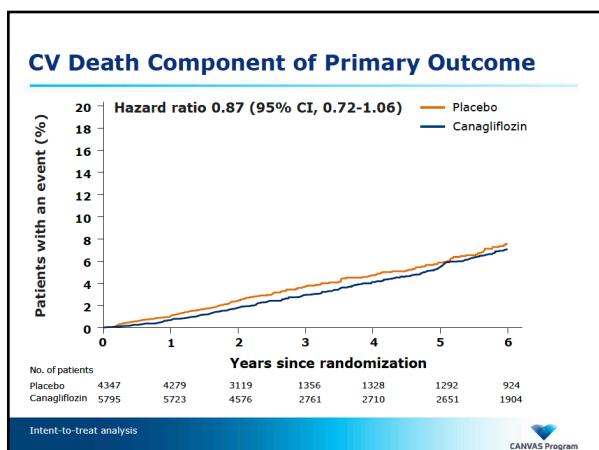
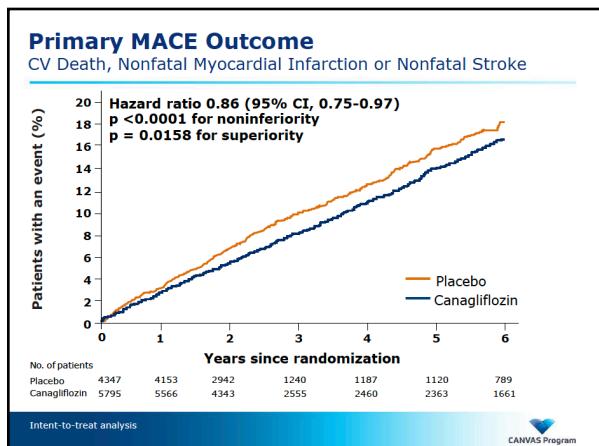
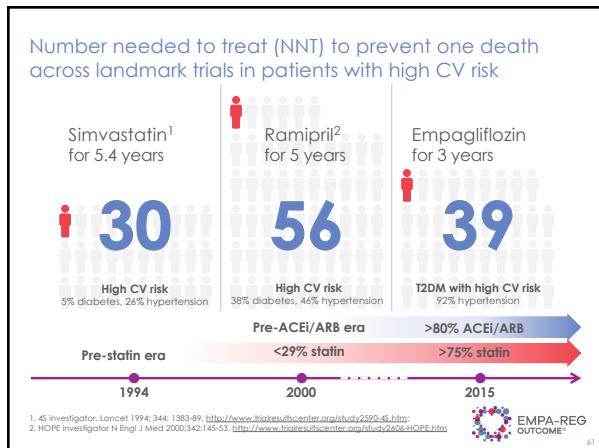


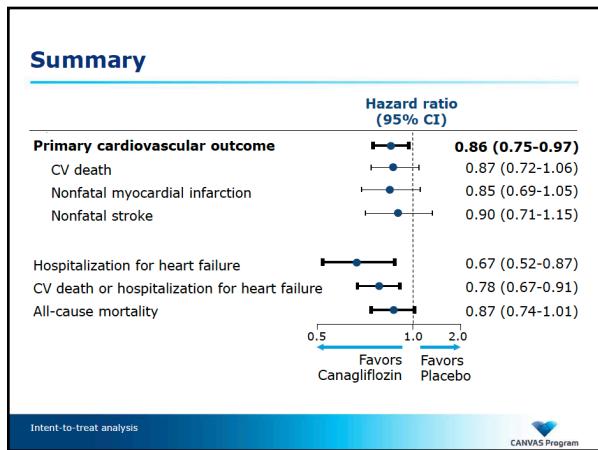
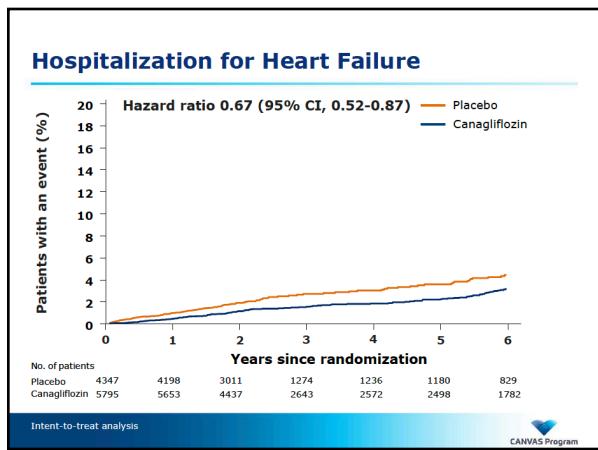
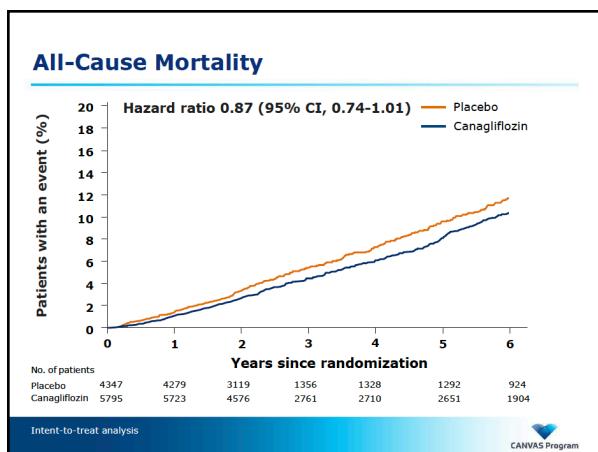
Hospitalisation for heart failure

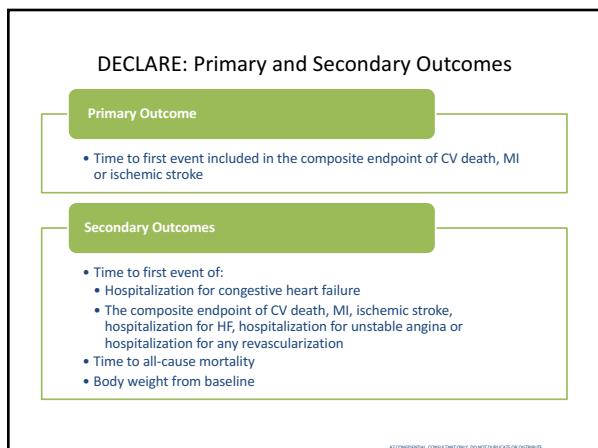
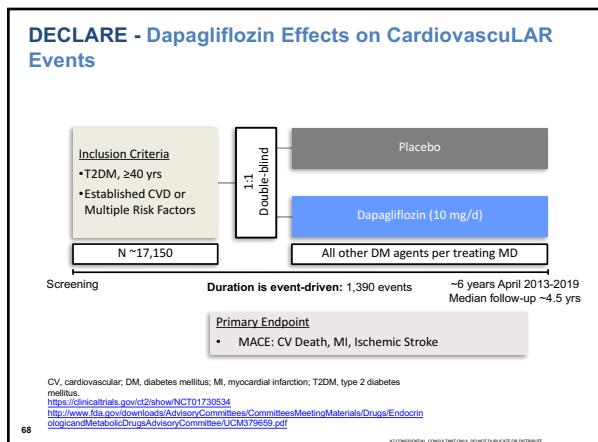
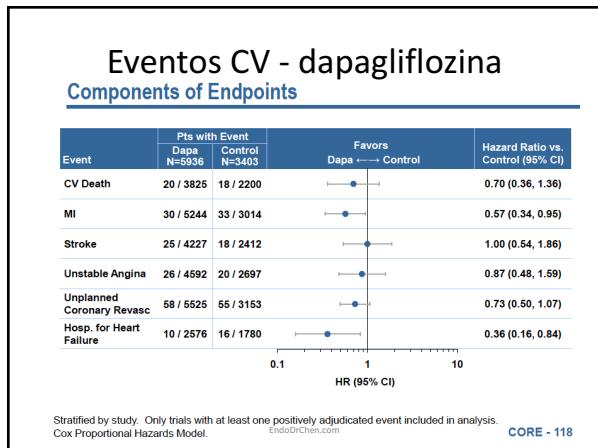


All-cause mortality









EVIDENCIAS EN LA VIDA REAL

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Real-world evidence de Dapagliflozina: datos de la práctica clínica rutinaria apoyan los resultados de ensayos clínicos aleatorizados¹⁻³

 Reducciones de HbA_{1c}, 1st
–0.8 to –1.16%

 ADDITIONAL BENEFITS
Pérdida de peso¹⁻³
–2.5 to –4.6 kg

 Reducciones de PAS¹⁺
–2.3 mmHg

 Bajas tasas de hospitalización por insuficiencia cardíaca y muerte por todas las causas en nuevos usuarios de ISGLT2:
CVDREAL

Data presentada en el "66th Annual Scientific Session of the American College of Cardiology", Washington, DC, 17-19 de Marzo, 2017

PDA: Puebla Acaral Diabetes.
1. Scheerer M, et al. Diabetologie und Stoffwechsel 2015;10:98. 2. Scheerer M, et al. Diabetologie und Stoffwechsel 2015;10:99. 3. Wilding JPH, et al. Poster presented at the 51st European Association for the Study of Diabetes, Stockholm, Sweden. 14-18 September 2015; Abstract A-15-209.

Población de Pacientes



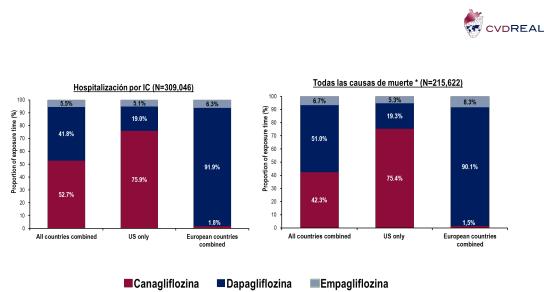
Más de 309,000 pacientes	Estudio de los inhibidores de SGLT2 versus otros fármacos hipoglicemiantes	Amplia población de pacientes	6 países
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Pacientes que usted ve a diario...

 Edad promedio 57 años	 Población libre de enfermedades CV en un 87%
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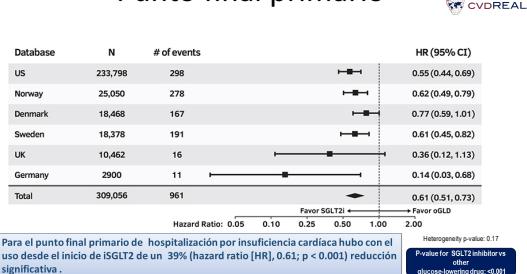
154.523 ISGLT2 154.523 Otros OAD

Contribución de los iSGLT2

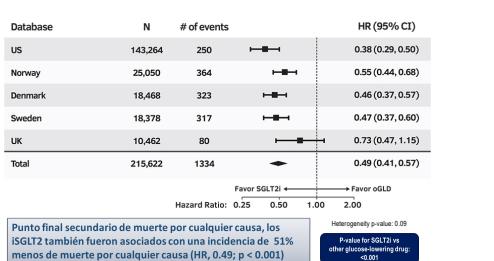


*Data shown are for all-cause death; data for HFHF or all-cause death are similar.

Hospitalización por Insuficiencia Cardíaca Punto final primario



Todas las causas de muerte – Punto final secundario



Registros nacionales suecos: Mortalidad por cualquier causa de los medicamentos hipoglucemiantes novedosos en comparación con insulina

Los medicamentos hipoglucemiantes novedosos se asociaron a un menor riesgo de mortalidad por cualquier causa en comparación con insulina

The graph shows the proportion of accumulated mortality risk over time (0.0 to 2.5 years) for two groups: Insulina (red line) and Novedoso (dapagliflozina/DPP-4) (blue line). The y-axis ranges from 0% to 10%. The x-axis is 'Tiempo desde el inicio del nuevo medicamento (años)' (Time since start of new medication (years)).

Tiempo (años)	Insulina (%)	Novedoso (%)
0.0	0	0
0.5	~2.5	~1.5
1.0	~4.5	~3.0
1.5	~6.5	~4.5
2.0	~7.5	~5.0
2.5	~8.0	~5.0

HR (IC 95%): 0.56 (0.49-0.64)

Nyström et al. Diabetez Obes Metab 2017 [En Impresión]
IC, intervalo de confianza; DPP-4, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgo instantáneo; SGLT-2, inhibidor del cotransportador de sodio-glucosa 2

76

Registros nacionales suecos: ECV mortal o no mortal de los medicamentos hipoglucemiantes novedosos en comparación con insulina

Los medicamentos hipoglucemiantes novedosos se asociaron a un menor riesgo de ECV mortal o no mortal en comparación con insulina

The graph shows the proportion of accumulated ECV risk (mortal or non-mortal) over time (0.0 to 1.5 years) for two groups: Insulina (red line) and Novedoso (dapagliflozina/DPP-4) (blue line). The y-axis ranges from 0% to 10%. The x-axis is 'Tiempo desde el inicio del nuevo medicamento (años)' (Time since start of new medication (years)).

Tiempo (años)	Insulina (%)	Novedoso (%)
0.0	0	0
0.5	~1.5	~1.0
1.0	~3.5	~3.0
1.5	~5.5	~5.0

HR (IC 95%): 0.85 (0.73-0.99)

Nyström et al. Diabetez Obes Metab 2017 [En Impresión]
IC, intervalo de confianza; ECV, enfermedad cardiovascular; DPP-4, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgo instantáneo; SGLT-2, inhibidor del cotransportador de sodio-glucosa 2

77

Registros nacionales suecos: Mortalidad por cualquier causa de dapagliflozina e inhibidores de DPP-4 en comparación con insulina

- Dapagliflozina se asoció con un 56% menos riesgo de mortalidad por cualquier causa en comparación con insulina
- Los inhibidores de DPP-4 se asociaron con un 41% menos riesgo de mortalidad por cualquier causa en comparación con insulina

The figure contains two side-by-side Kaplan-Meier survival plots.

Left plot: Mortality risk over 2.5 years for insulin vs. dapagliflozina. Y-axis: Proportion acumulada de mortalidad por cualquier causa (0% to 10%). X-axis: Tiempo desde el inicio del nuevo medicamento (años) (0.0 to 2.5).

Tiempo (años)	Insulina (%)	Dapagliflozina (%)
0.0	0	0
0.5	~1.5	~1.0
1.0	~3.5	~2.5
1.5	~5.5	~4.5
2.0	~7.5	~5.5
2.5	~8.0	~5.5

HR (IC 95%): 0.44 (0.28-0.70)
P < .001

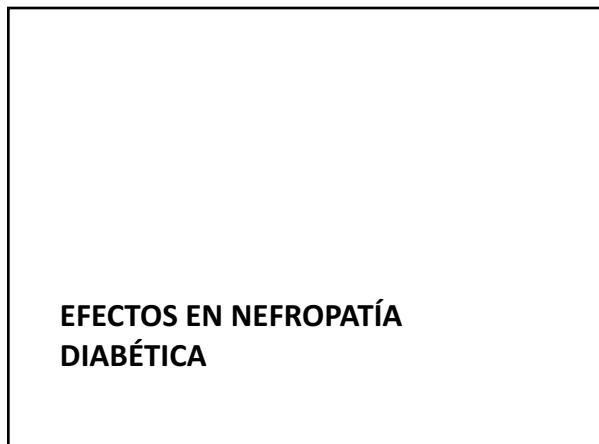
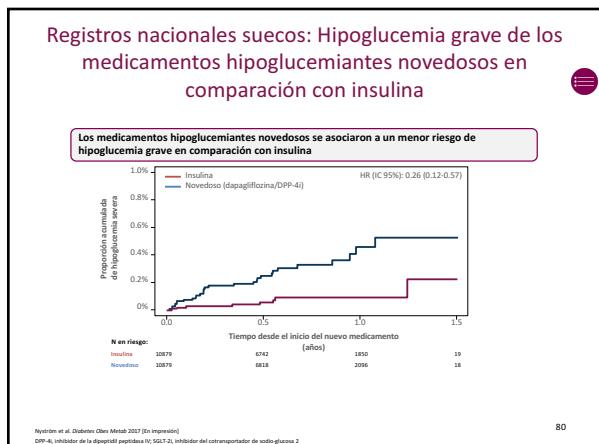
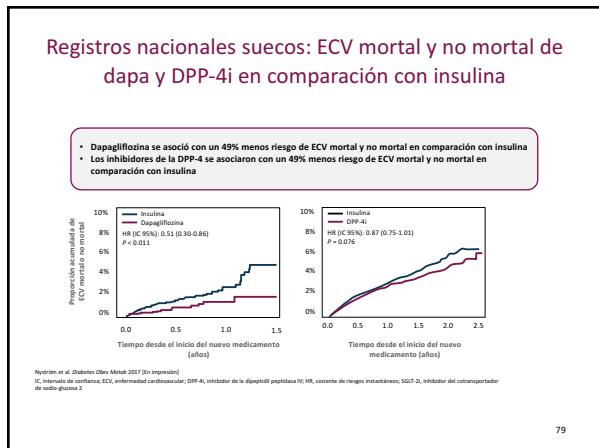
Right plot: Mortality risk over 2.5 years for insulin vs. DPP-4 inhibitors. Y-axis: Proportion acumulada de mortalidad por cualquier causa (0% to 10%). X-axis: Tiempo desde el inicio del nuevo medicamento (años) (0.0 to 2.5).

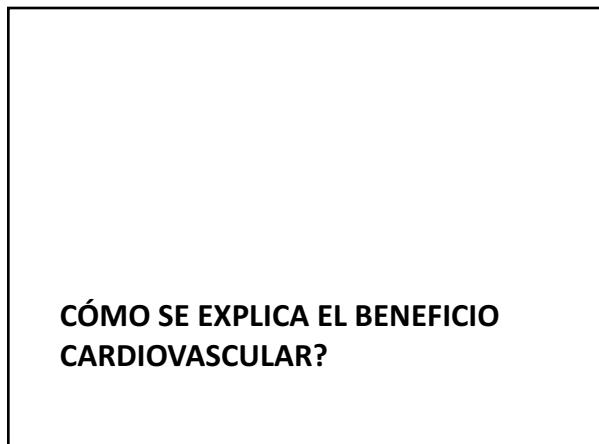
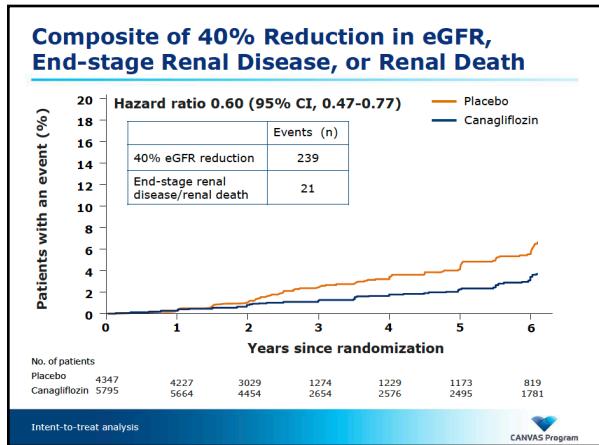
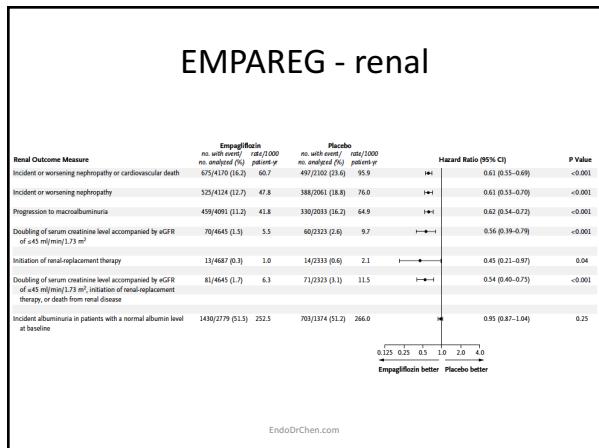
Tiempo (años)	Insulina (%)	Inhibidores DPP-4 (%)
0.0	0	0
0.5	~1.5	~1.0
1.0	~3.5	~3.0
1.5	~5.5	~4.5
2.0	~7.5	~5.5
2.5	~8.0	~5.5

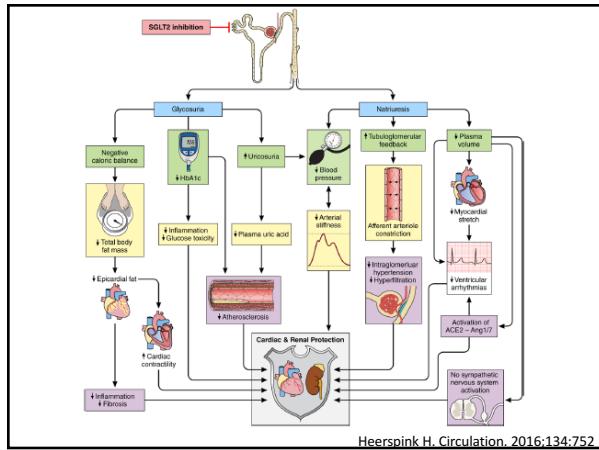
HR (IC 95%): 0.59 (0.51-0.67)
P < .001

Nyström et al. Diabetez Obes Metab 2017 [En Impresión]
IC, intervalo de confianza; DPP-4, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgo instantáneo

78



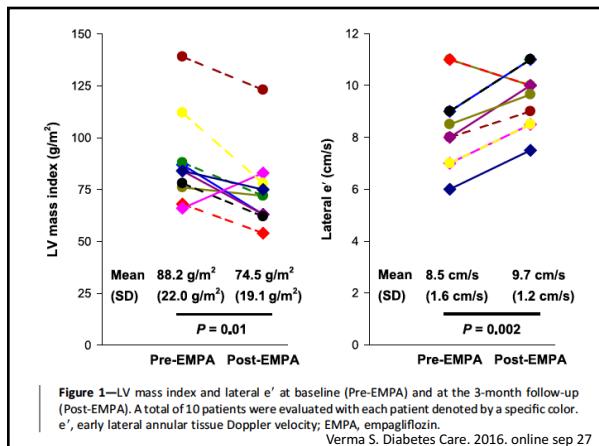




Hipótesis

- Presión arterial
 - Mayor impacto en ictus y no hubo diferencia
- Aterosclerosis y ácido úrico
 - No hay cambios tan tempranos
- Peso
 - No hay cambios tan tempranos
- Electrolitos?
- Sustrato energético?

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FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

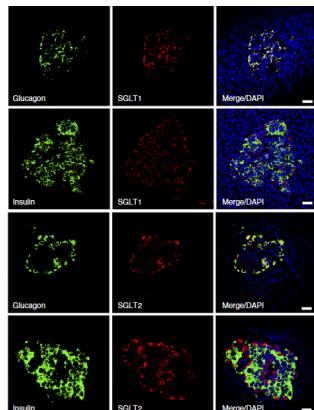
[05-15-2015]

Safety Announcement

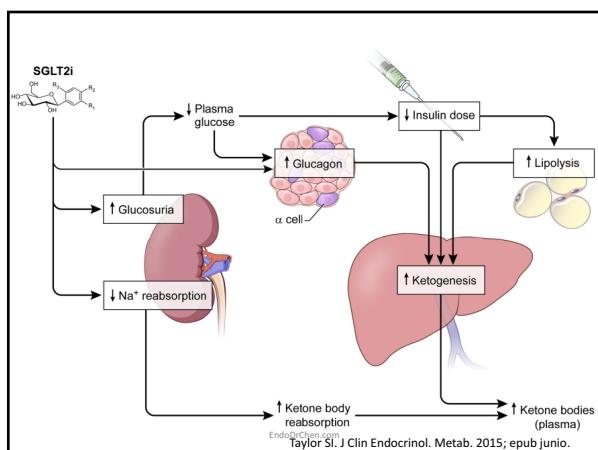
The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

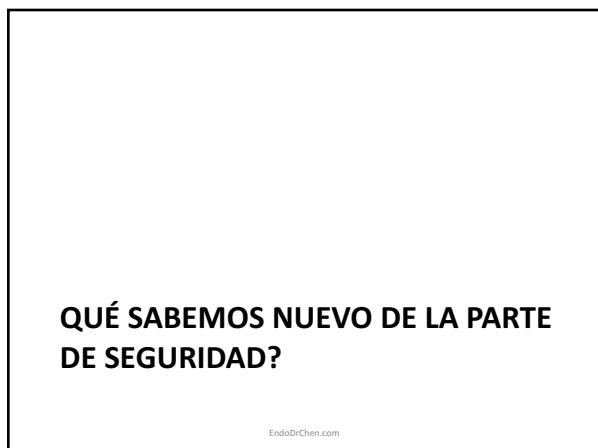
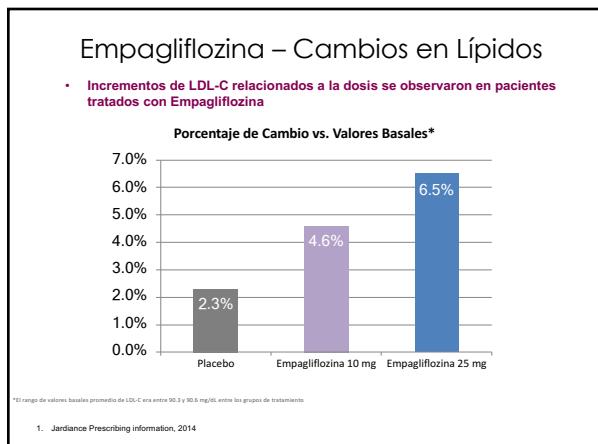
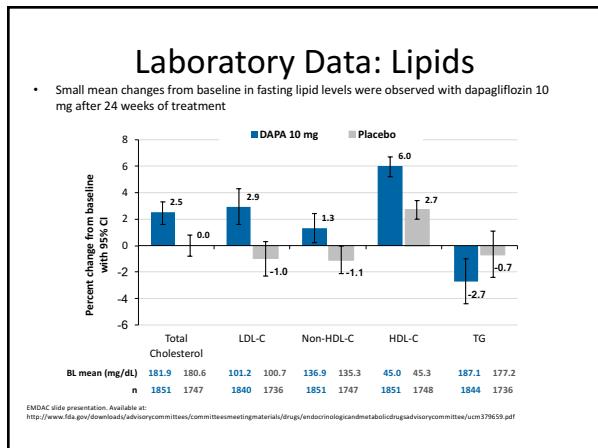
Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

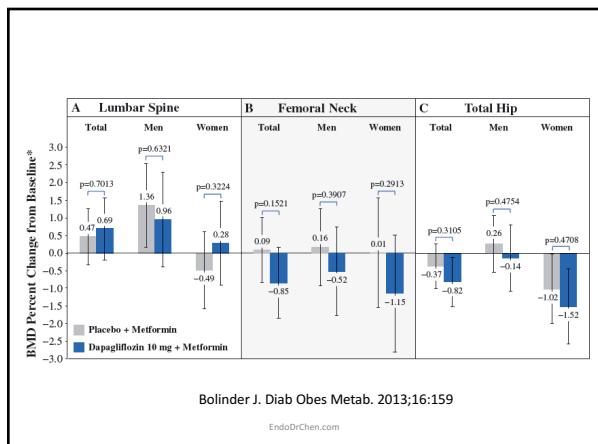
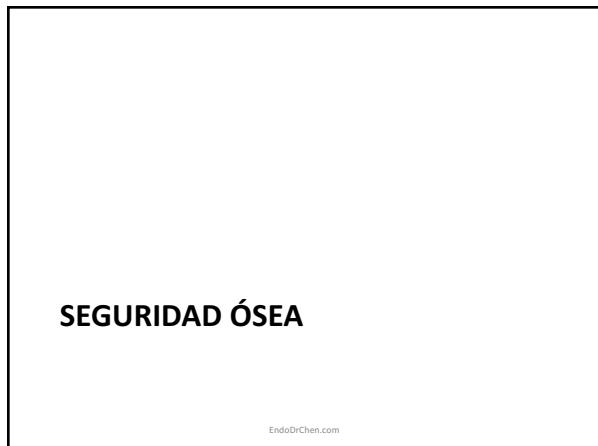
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Bonner C. Nat Med. 2015;21(5):512







Dapagliflozina: Eventos de Fracturas

- La proporción de pacientes con fracturas fue pequeña y equilibrada durante el tratamiento con Dapagliflozina versus placebo

	Colección de datos en estudios controlados con Placebo(corto-plazo)		Colección de datos en estudios controlados con Placebo(corto-plazo y largo-plazo)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Eventos, n (%)	N=2360 8 (0.3)	N=2295 17 (0.7)	N=2026 23 (1.1)	N=1956 32 (1.6)

DAPA=Dapagliflozina; PBO=Placebo.
EMDAC Documento de referencia disponible en:
<http://www.fda.gov/amedocs/advisorycommittees/commbeas/meetingmaterials/drugandbiologicsandmetabolizeddrugadvisorycommittee/ucm378079.pdf>.

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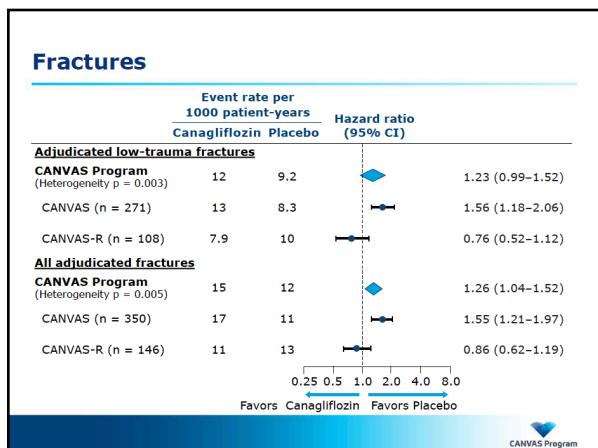
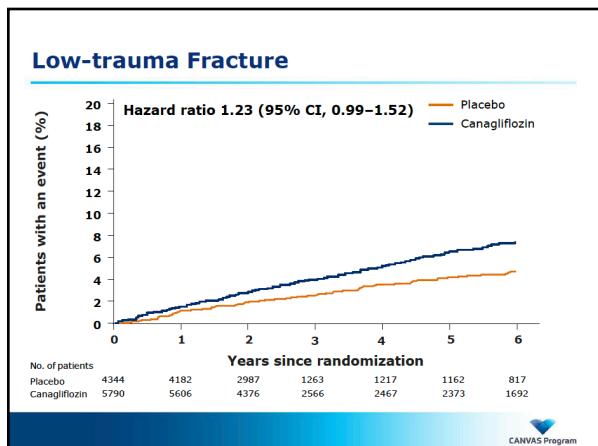
Other adverse events (2)

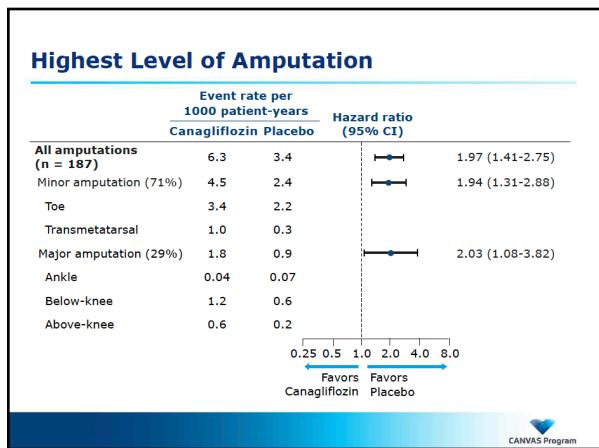
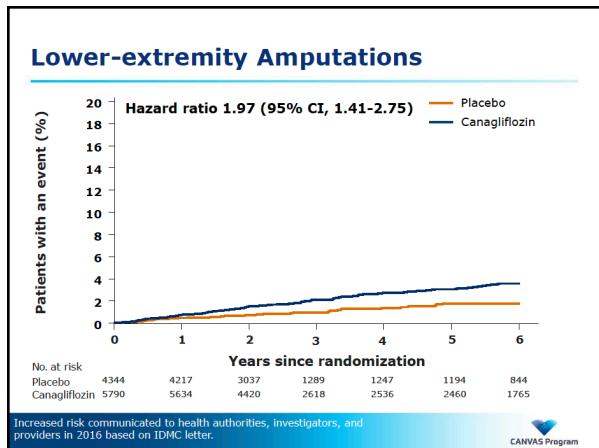
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Hepatic injury*	108 (4.6%)	1.91	80 (3.4%)	1.35	88 (3.8%)	1.48
Hypersensitivity*	197 (8.4%)	3.59	158 (6.7%)	2.75	181 (7.7%)	3.14
Bone fractures†	91 (3.9%)	1.61	92 (3.9%)	1.57	87 (3.7%)	1.46

Rate = per 100 patient-years

*Patients treated with ≥1 dose of study drug
†Based on standardised MedDRA queries
†Based on 62 MedDRA preferred terms

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Amputation Risk Factors - Multivariate Analysis

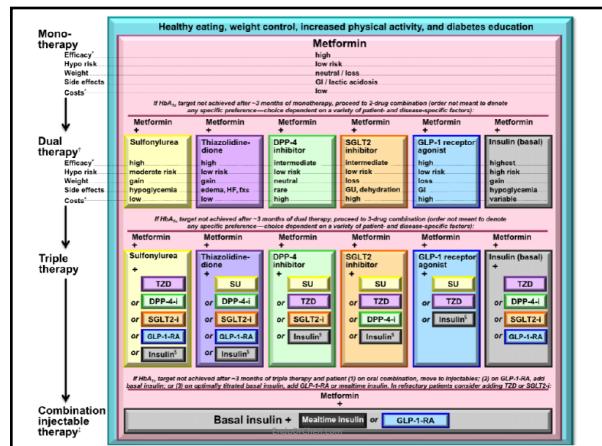
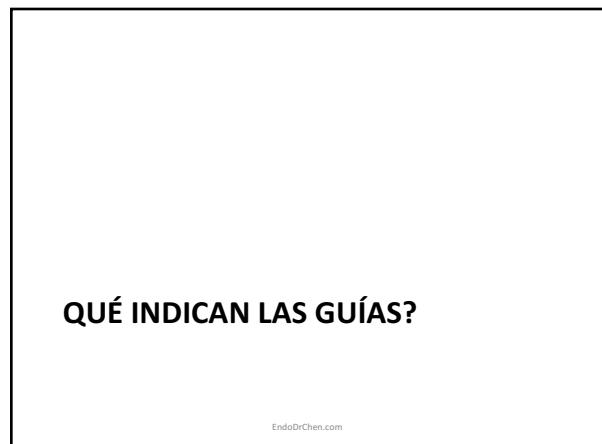
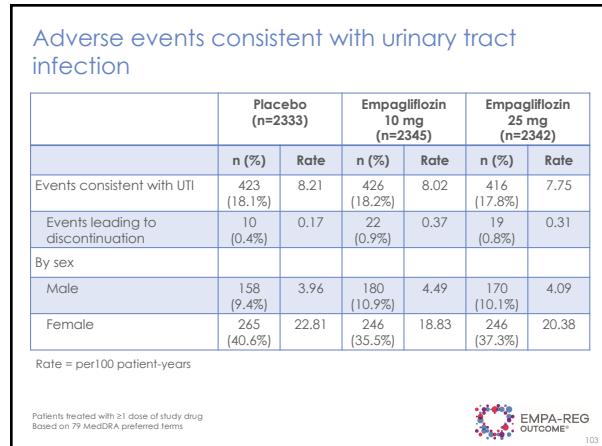
Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

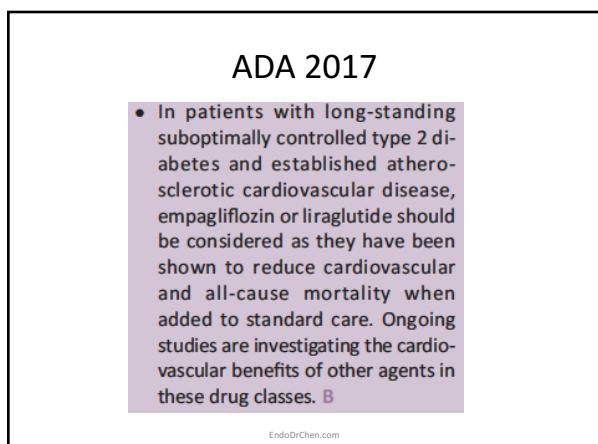
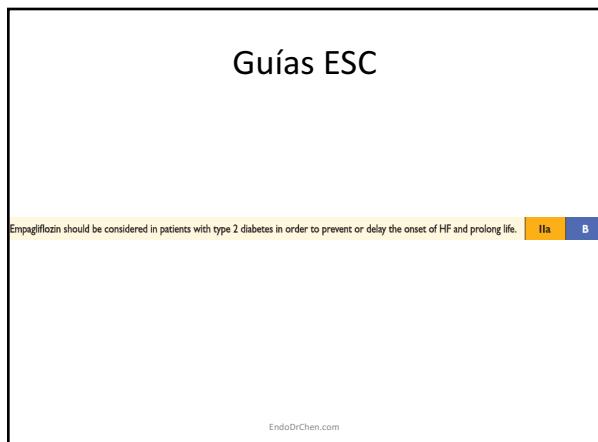
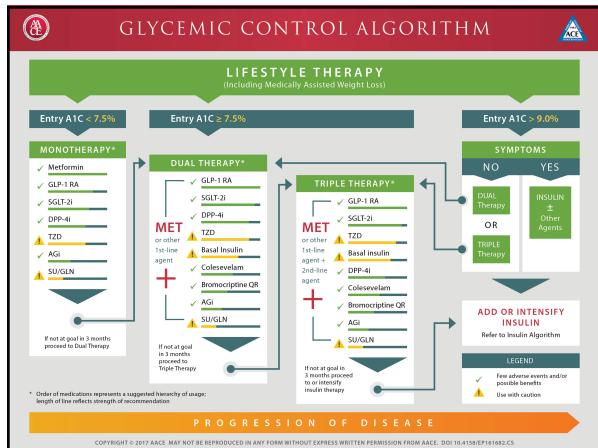
- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations

CANVAS Program





Conclusiones

- No todos los diabéticos son automáticamente de alto riesgo CV
 - Mayor riesgo con edad, ERC, mayor tiempo de evolución
- Seguridad CV de drogas más antiguas no han sido evaluadas tan extensamente
- Pioglitazona reduce MACE pero aumenta ICC
- Análogos de GLP-1 reduce MACE pero riesgo de empeoramiento retinopatía
- Inhibidores SGLT-2 reduce MACE, mortalidad total, hospitalización por falla cardíaca

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Preguntas...

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