



Seguridad cardiovascular, impactando los factores de riesgo cardiovascular

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

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Agenda

- Evidencia más reciente en seguridad cardiovascular
 - Inhibidores de DPP-4
 - Análogos de GLP-1
 - Inhibidores de SGLT-2
- Estudios de la vida real
- Cuáles son estos mecanismos?
- Actualización en seguridad

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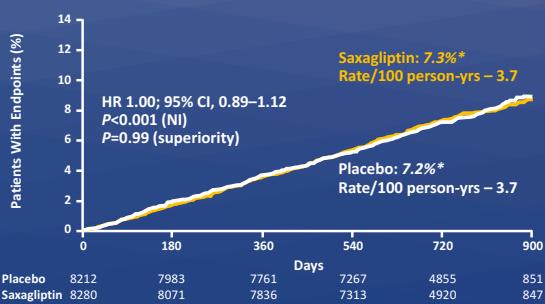
ESTUDIOS CON DESENLAES CARDIOVASCULARES

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INHIBIDORES DE DPP-4

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Kaplan-Meier Rates of the Primary Composite Endpoint – CV Death, MI, or Stroke



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

HR: hazard ratio; K-M: Kaplan-Meier; Pbo: placebo; Saha: saxagliptin

Seznic BM, et al. *N Engl J Med*. 2013;368:1056–1066.

Bristol-Myers Squibb



Individual Components of the Composite Endpoints				
Efficacy endpoint	Saxagliptin n (%)*	Placebo n (%)*	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(10):911–922.

Bristol-Myers Squibb

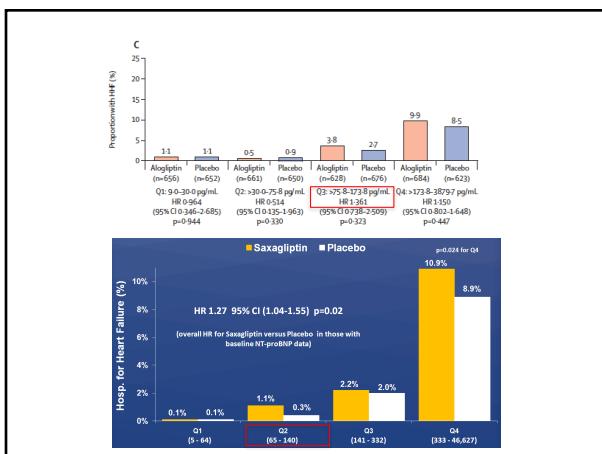
AstraZeneca

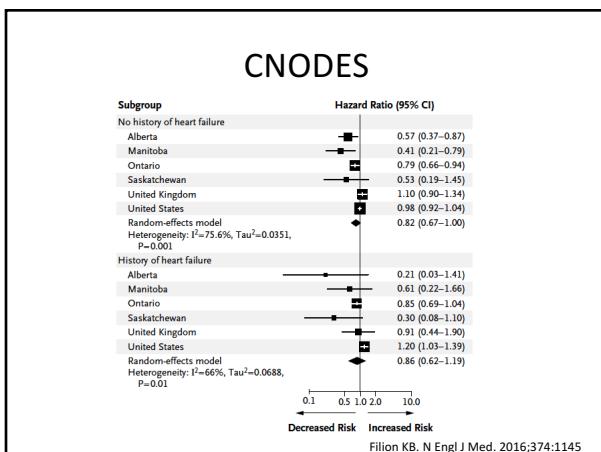
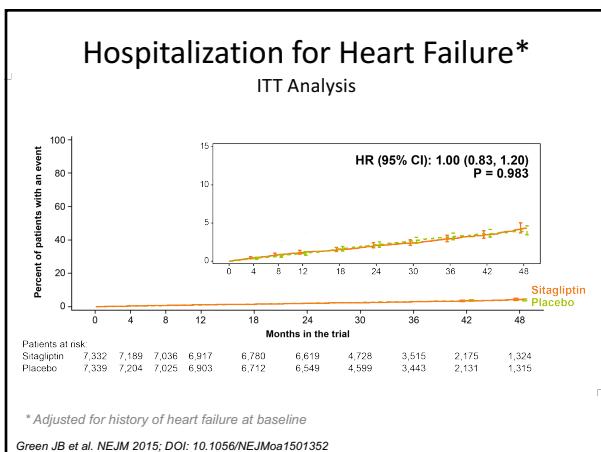
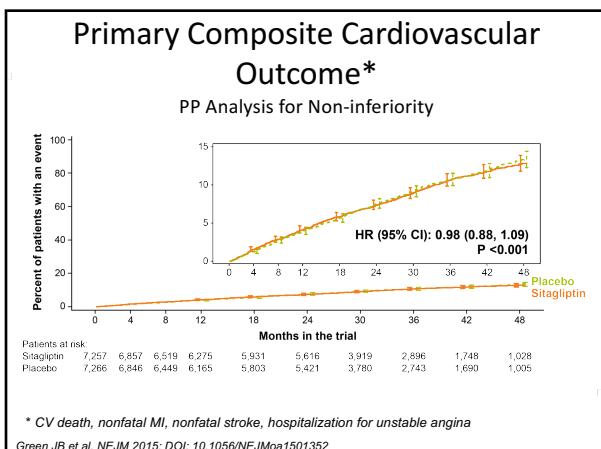
EXAMINE-análisis post hoc

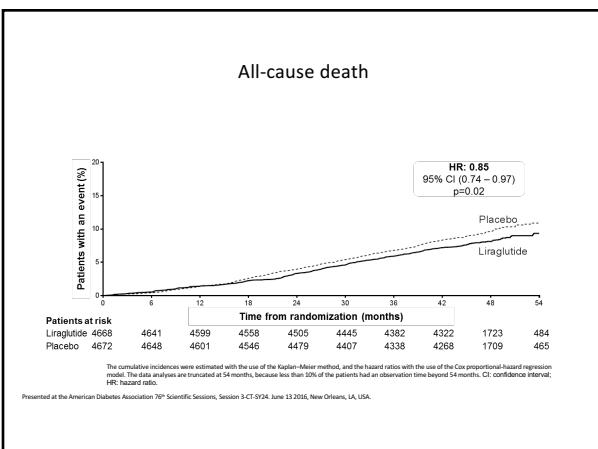
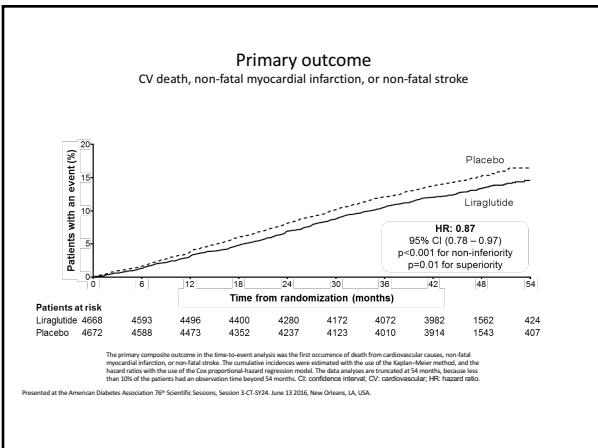
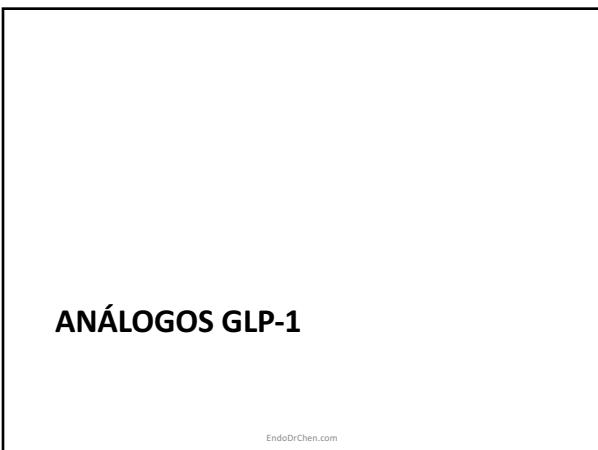
	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7.4)	201 (7.5)	107 (13.9)	120 (15.7)	94 (4.9)	81 (4.2)
Hazard ratio (95% CI)	1.00 (0.83–1.21)		0.90 (0.70–1.17)		1.14 (0.85–1.54)	
p value	0.976		0.446		0.337	
P_{strat} 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_{strat} 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_{strat} for treatment and history of heart failure	0.068

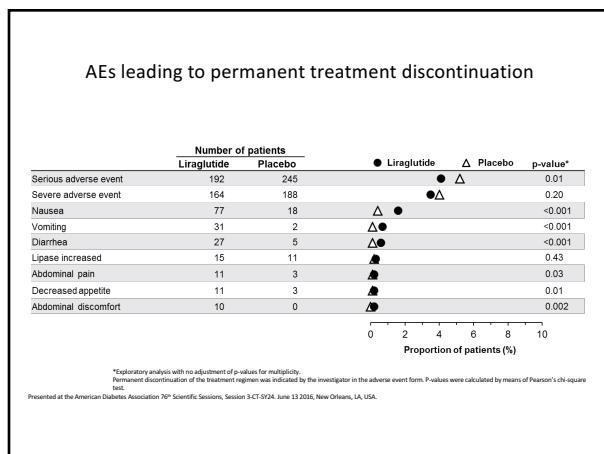
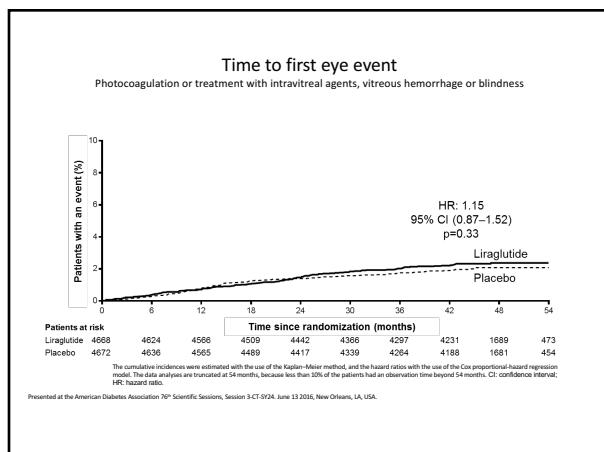
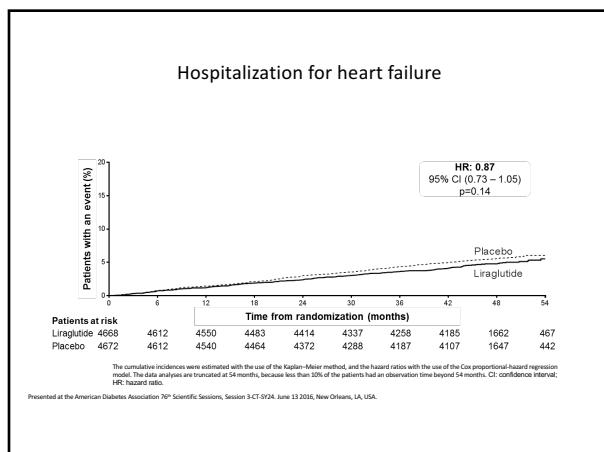
*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Zannad F. Lancet. 2015. Online Mar 15









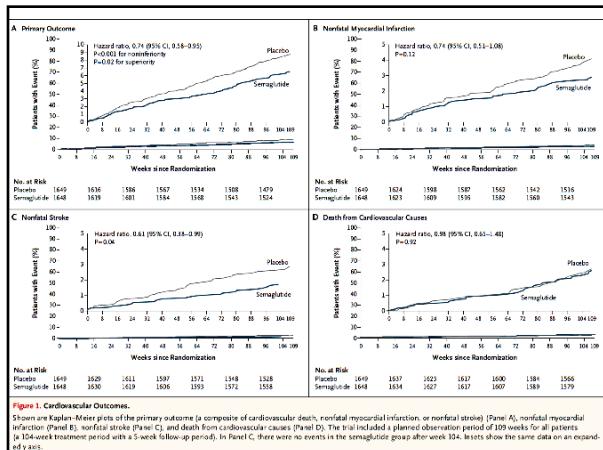


Figure 1

Figure 1. Cardiovascular Outcomes.
Source: Reprinted with permission of the primary outcome by composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (Panel A), non-fatal myocardial infarction (Panel B), non-fatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 104 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded x-axis.

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 ^b	No. (%)	No./100 person-yr ^b		
Primary composite outcome ^c	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for non-inferiority; 0.07 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, non-fatal myocardial infarction, or non-fatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
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)	1.35	0.98 (0.65–1.48)	0.92
Non-fatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Non-fatal stroke	27 (1.6)	0.80	44 (2.7)	1.11	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)	2.30	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 (0.46–0.88)	0.005

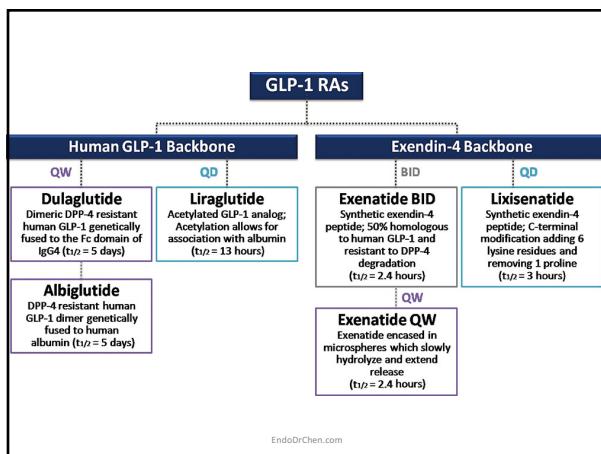
^a Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with the study treatments as fixed factors and strata according to all combinations of stratification factors used in the randomization.

^b The primary composite outcome was defined as the sum of deaths from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.

^c The expanded composite outcome included death from any cause, new or worsening non-fatal myocardial infarction, non-fatal 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/min per 1.73 m² of body-surface area (according to the Modification of Diet in Renal Disease criteria).



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Sin embargo...

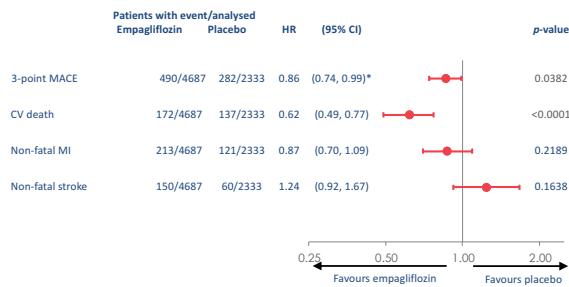
- Los estudios de los análogos de GLP-1 basados en exendin 4 han sido neutros desde el punto de vista CV
 - ELIXA con lixisenatide
 - EXSCEL con exenatide semanal (datos no publicados)

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INHIBIDORES DE SGLT-2

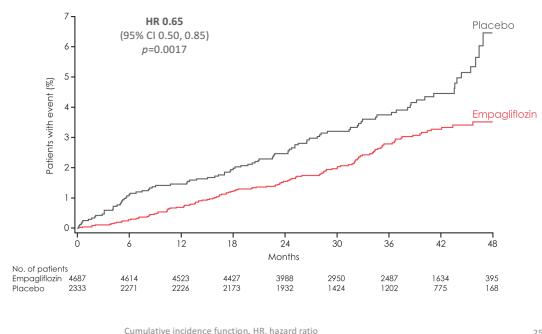
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CV death, MI and stroke

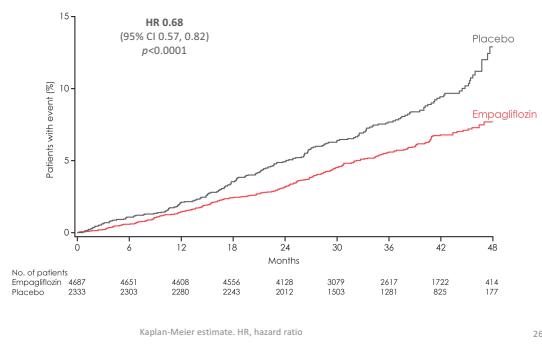


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Hospitalisation for heart failure

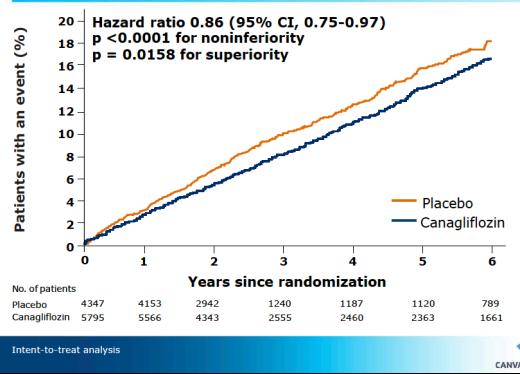


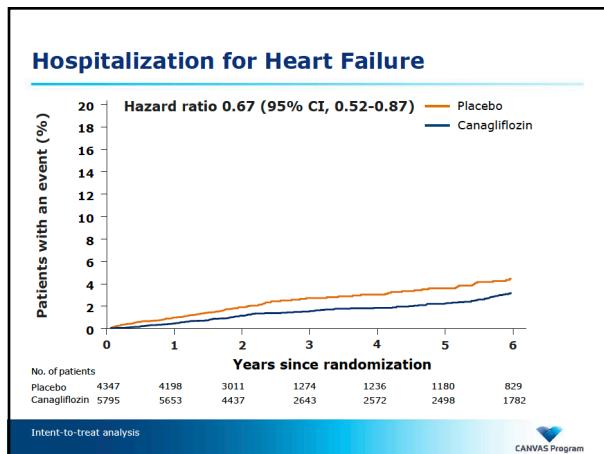
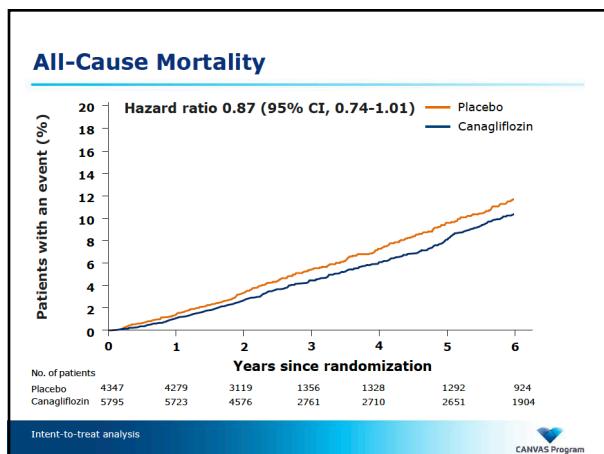
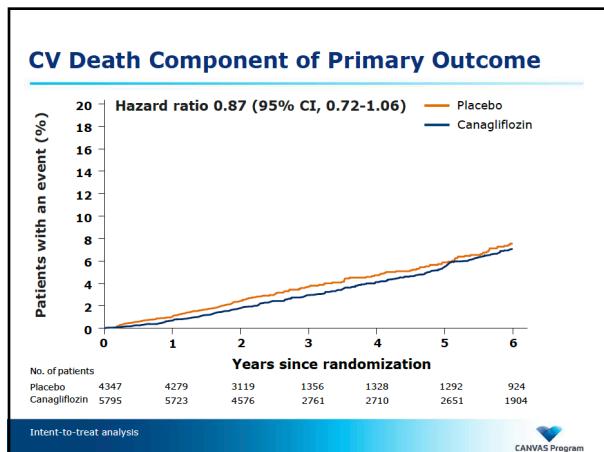
All-cause mortality

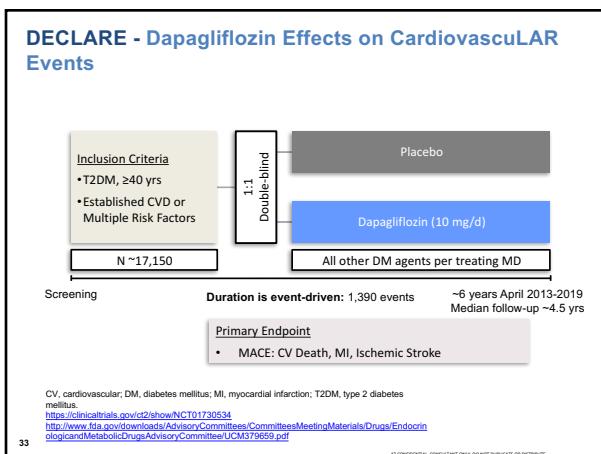
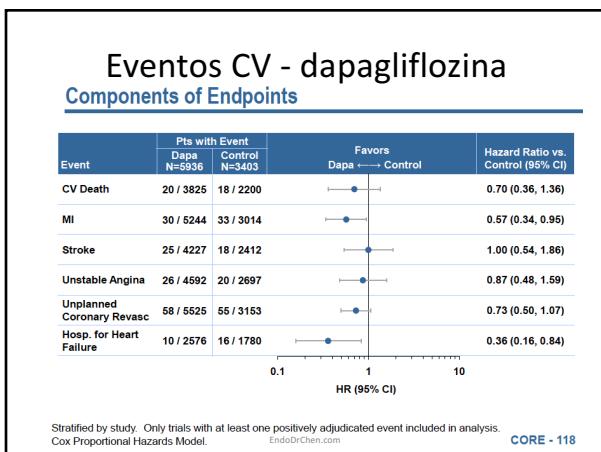
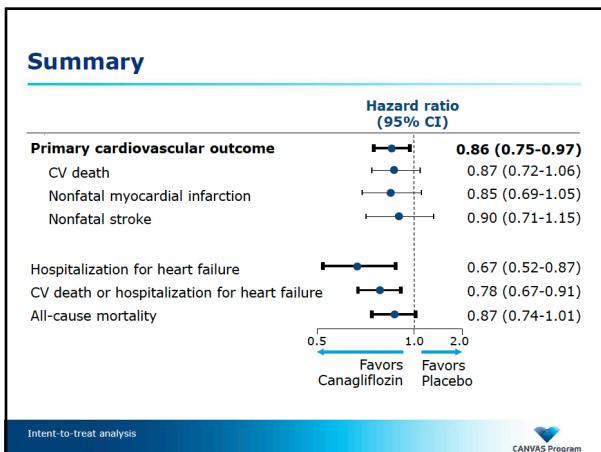


Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke







DECLARE: Primary and Secondary Outcomes

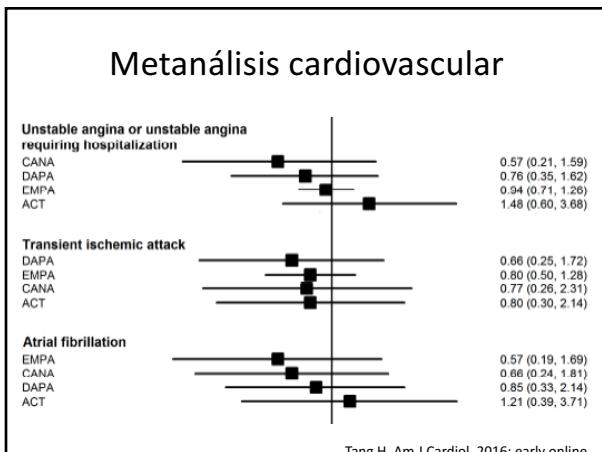
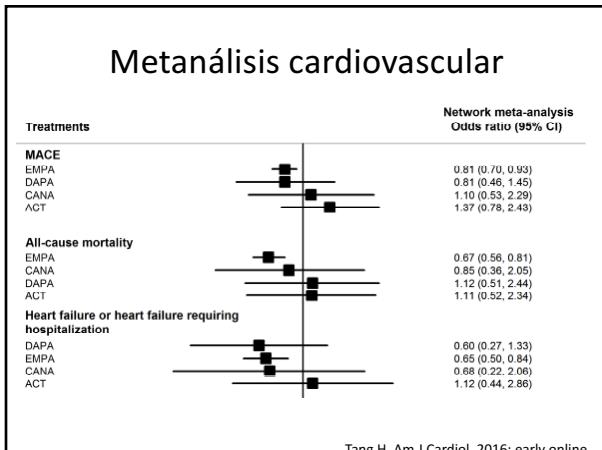
Primary Outcome

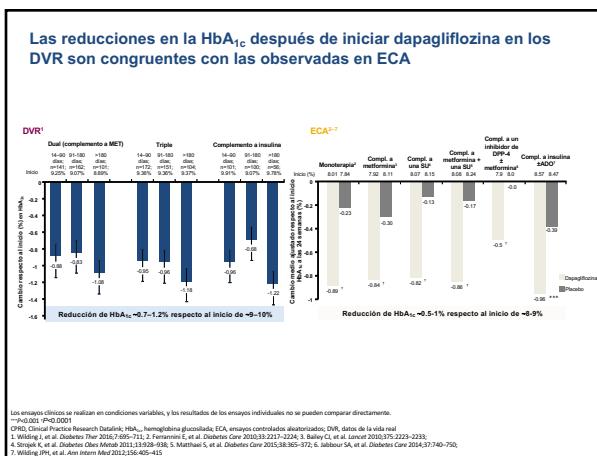
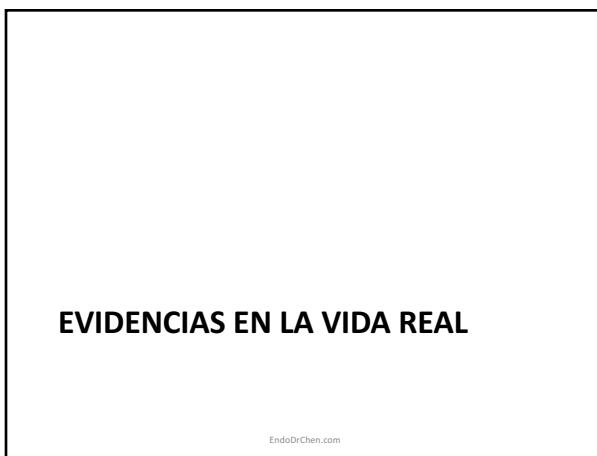
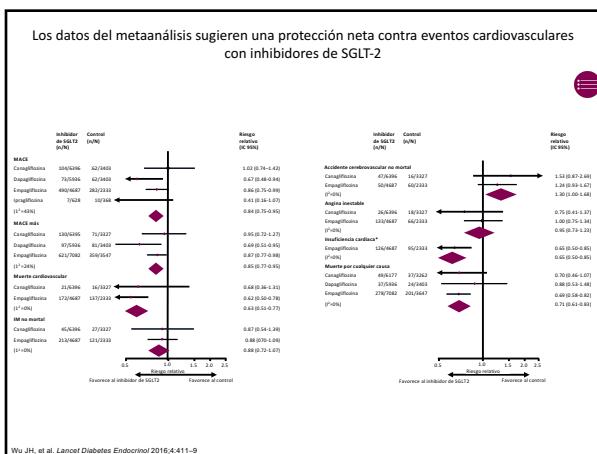
- Time to first event included in the composite endpoint of CV death, MI or ischemic stroke

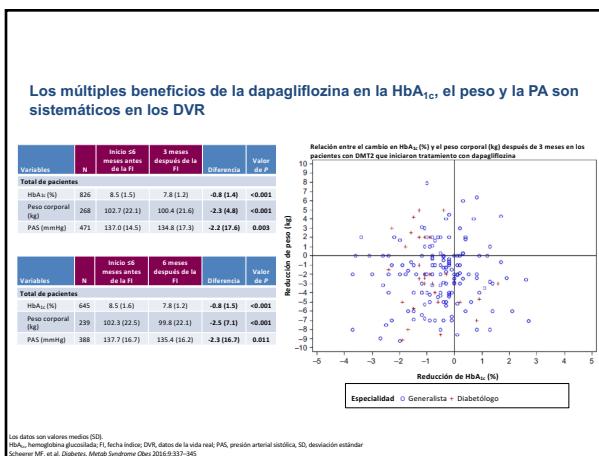
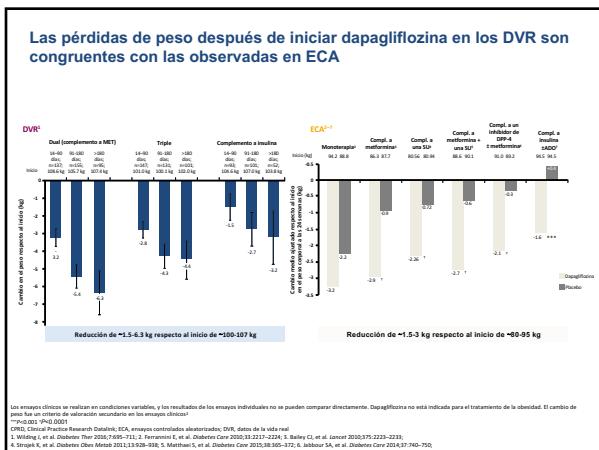
Secondary Outcomes

- Time to first event of:
 - Hospitalization for congestive heart failure
 - The composite endpoint of CV death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina or hospitalization for any revascularization
- Time to all-cause mortality
- Body weight from baseline

All CONFIDENTIAL - CONFIDENTIAL DATA DO NOT SUPPORT OR ENDORSE







Objetivos del estudio



- Primario:**

- Comparar el riesgo de hospitalización por Insuficiencia cardíaca en pacientes con DMT2 en pacientes nuevos iniciados con iSGLT2 versus otros agentes que reducen la glucosa.

- Secundario:**

- Comparar el riesgo de muerte por todas las causas entre los dos grupos de tratamiento.
- Comparar el riesgo de hospitalización por Insuficiencia cardíaca o muerte por todas las causas entre los dos grupos de tratamiento.

Fuente de Datos: Registros de salud en 6 países



Criterios de Inclusión y Exclusión

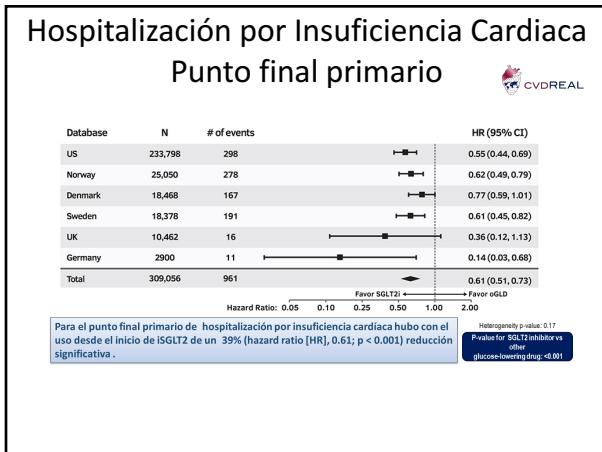
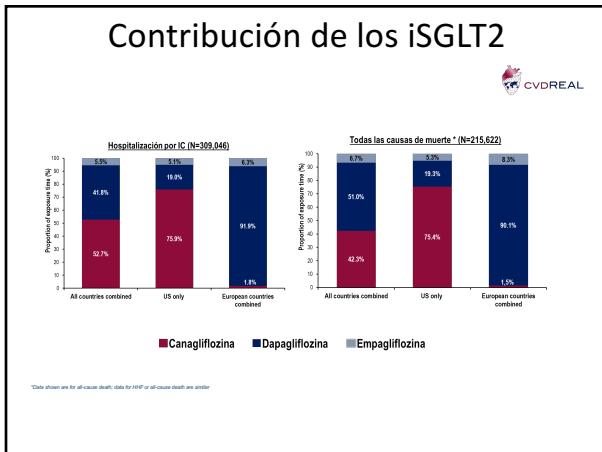
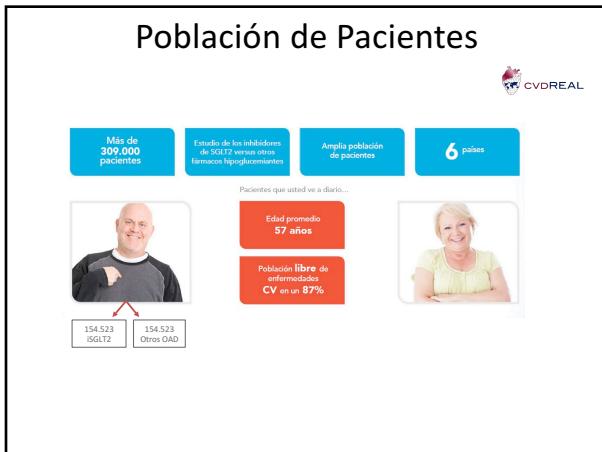


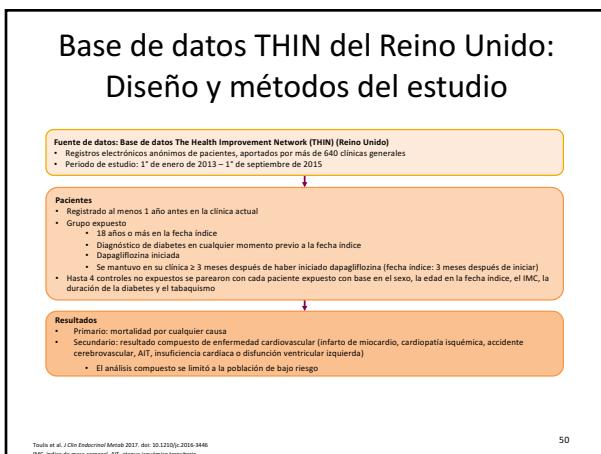
- Inclusión**

- Usuarios nuevos con iSGLT2 u otros medicamentos que reducen la glucosa
 - Diabetes tipo 2 establecida o antes de la selección
 - ≥18 años
 - > 1 año de data disponible antes de la selección

- Exclusión**

- Pacientes con diabetes tipo 1
- Pacientes con diabetes gestacional





Estudio de la base de datos THIN del Reino Unido: Características iniciales

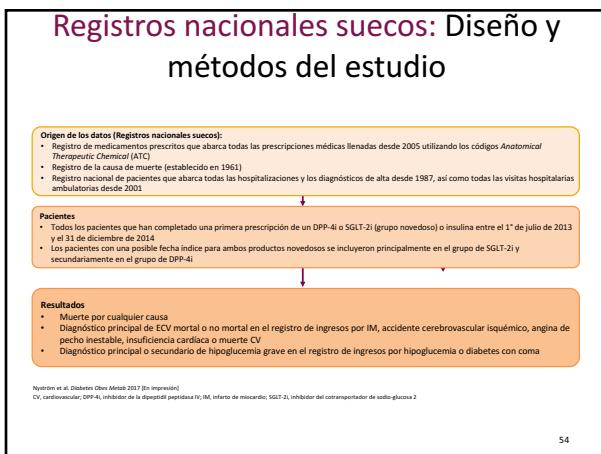
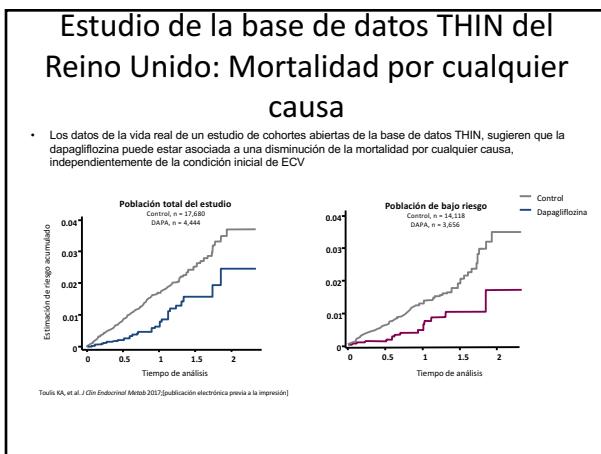
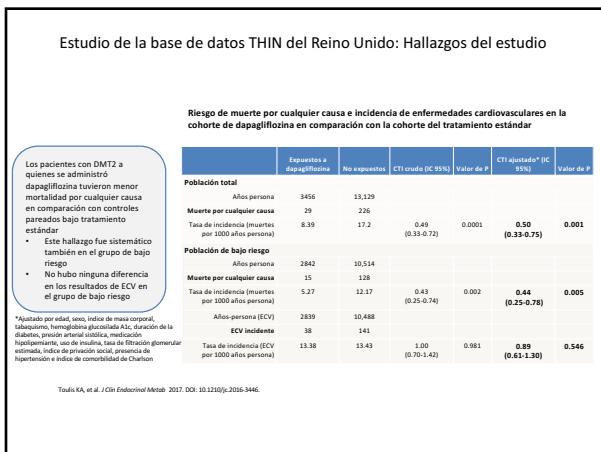
Variables	Expuesto a DAPA	No expuesto a DAPA
N	4444	17,680
Edad (años)	58.3 (10.4)	58.5 (10.4)
Indice IMC	26.65 (5.6)	26.36 (5.6)
Índice de masa corporal	31 (6.9)	34.7 (6.4)*
Presión arterial sistólica (mm Hg)	131.6 (12.9)	132.2 (14.1)*
Tabaquismo	600 (13.5)	2373 (13.4)*
Uso de medicamentos hipotensores	3931 (88.4)	14,966 (84.7)
Tasa filtración glomerular estimada	91.7 (22.0)	88.6 (24.8)*
Townsend		
1	99 (17.7)	3154 (17.7)
2	325 (18.5)	3124 (18.3)
3	1016 (21.2)	3744 (21.2)
4	885 (22.0)	3886 (22.0)
5	641 (16.8)	2966 (-16.8)
No disponible	173 (3.9)	709 (4.0)
Seguimientos (meses)	9.9 (6.5)	8.9 (6.3)*

*statísticamente significativo al nivel de 0.05.

Note: Baja riesgo de ECV se definió como la ausencia de cardiopatía isquémica, accidente cerebrovascular / accidente isquémico transitorio, insuficiencia cardíaca o disfunción ventricular izquierda. Los datos presentados se presentan el valor medio (desviación estándar), a menos que se especifique lo contrario. Los datos discontinuos y ordinarios se presentan como n (%). El índice de Townsend es una medida de privación material (1 = individuo menos privado, 5 = persona más privada).

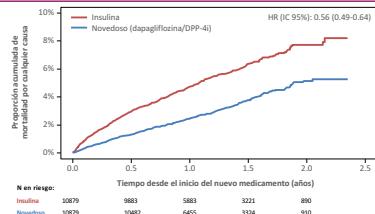
Toulis et al. J Clin Endocrinol Metab 2017; doi: 10.1210/jc.2016-3446
ECV: enfermedad cardiovascular; DAPA: dapagliflozina; IMC: Índice de masa corporal

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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

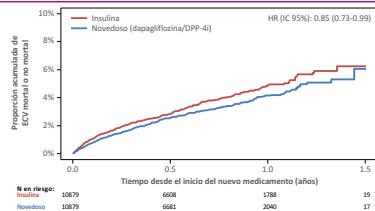


Nystrom et al. Diabetes Obes Metab 2017 [En impresión]
IC, intervalo de confianza; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos; SGLT-2, inhibidor del cotransportador de sodio-glucosa 2

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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

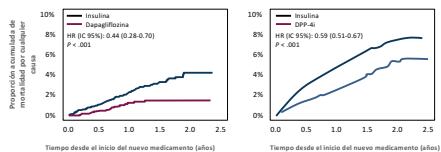


Nystrom et al. Diabetes Obes Metab 2017 [En impresión]
IC, intervalo de confianza; ECV, enfermedad cardiovascular; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos; SGLT-2, inhibidor del cotransportador de sodio-glucosa 2

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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

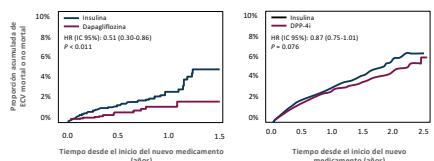


Nystrom et al. Diabetes Obes Metab 2017 [En impresión]
IC, intervalo de confianza; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos

57

Registros nacionales suecos: ECV mortal y no mortal de dapagliflozina y DPP-4i en comparación con insulina

- Dapagliflozina se asoció con un 49% menos riesgo de ECV mortal y no mortal en comparación con insulina
- Los inhibidores de la DPP-4 se asociaron con un 49% menos riesgo de ECV mortal y no mortal en comparación con insulina

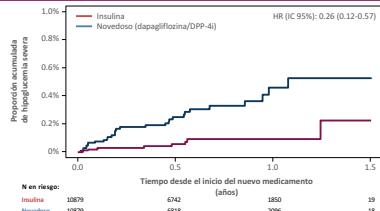


Nordin et al. Diabetes Obes Metab 2017 [En impresión]
IC, intervalo de confianza; ECV, enfermedad cardiovascular; DPP-4i, inhibidor de la dipeptidil peptidasa IV; HR, cociente de riesgos instantáneos; SGLT-2i, inhibidor del co-transportador de sodio-glucosa 2

58

Registros nacionales suecos: Hipoglucemia grave de los medicamentos hipoglucemiantes novedosos en comparación con insulina

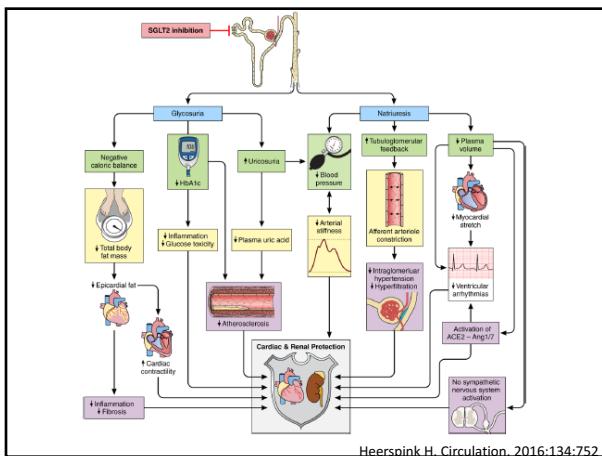
- Los medicamentos hipoglucemiantes novedosos se asociaron a un menor riesgo de hipoglucemia grave en comparación con insulina



Nordin et al. Diabetes Obes Metab 2017 [En impresión]
DPP-4i, inhibidor de la dipeptidil peptidasa IV; SGLT-2i, inhibidor del co-transportador de sodio-glucosa 2

59

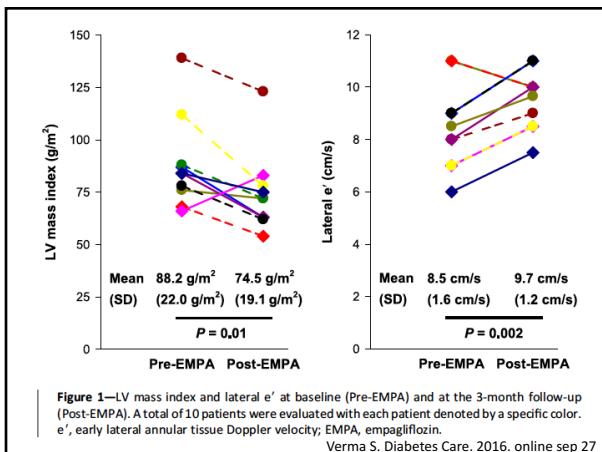
CÓMO SE EXPLICA EL BENEFICIO CARDIOVASCULAR?



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

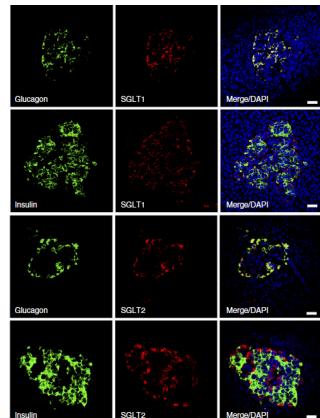
[05-15-2015]

Safety Announcement

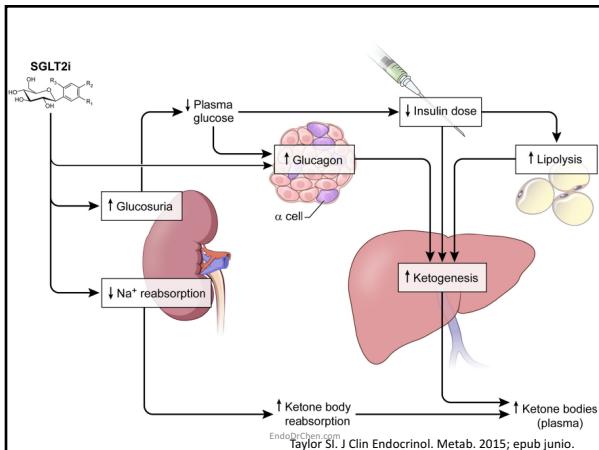
The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing 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.

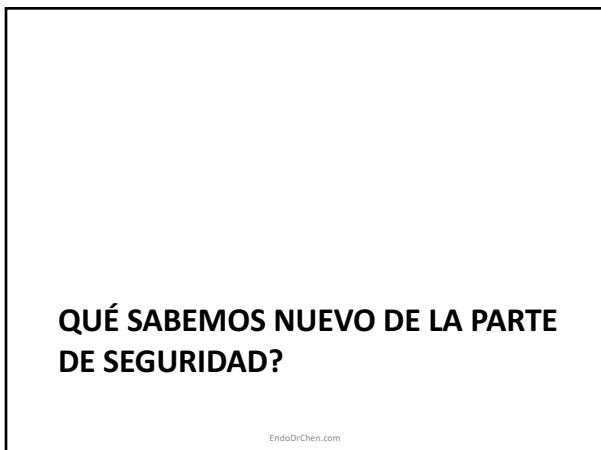
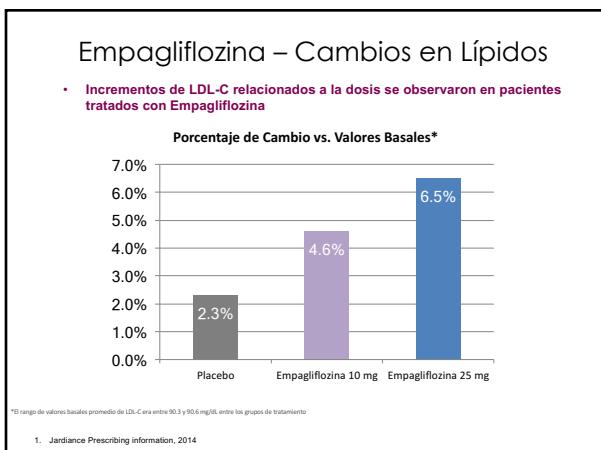
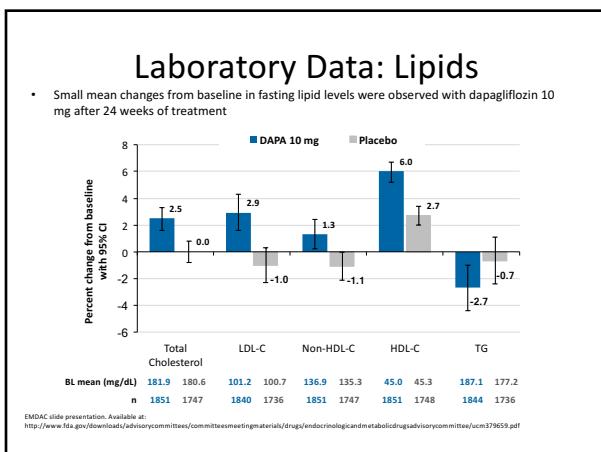
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Bonner C. Nat Med. 2015;21(5):512

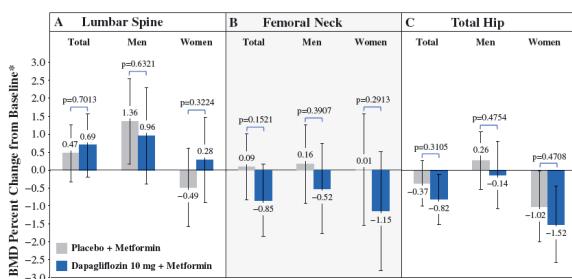


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Taylor Si. J Clin Endocrinol. Metab. 2015; epub junio.



SEGURIDAD ÓSEA

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Bolinder J. Diab Obes Metab. 2013;16:159

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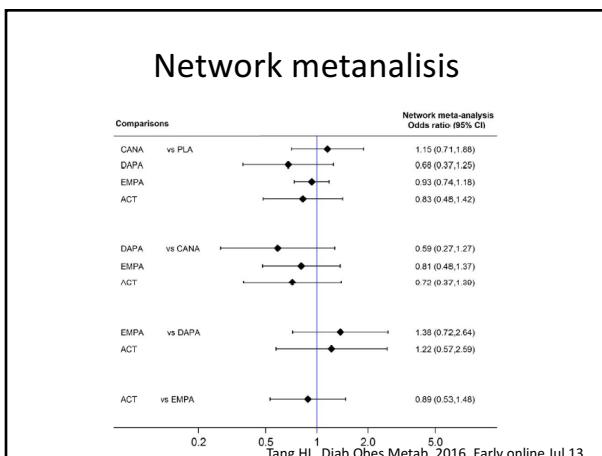
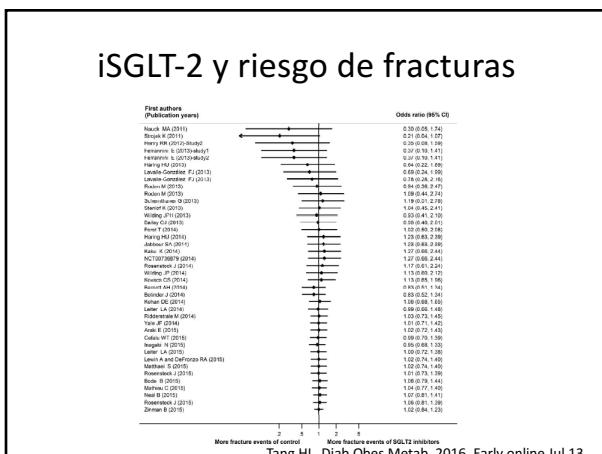
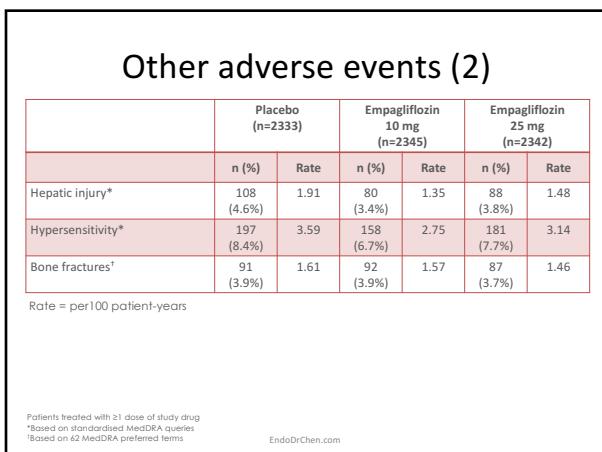
Dapagliflozina: Eventos de Fracturas

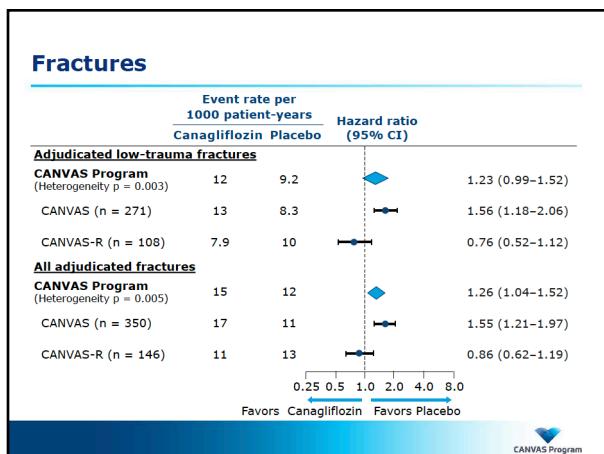
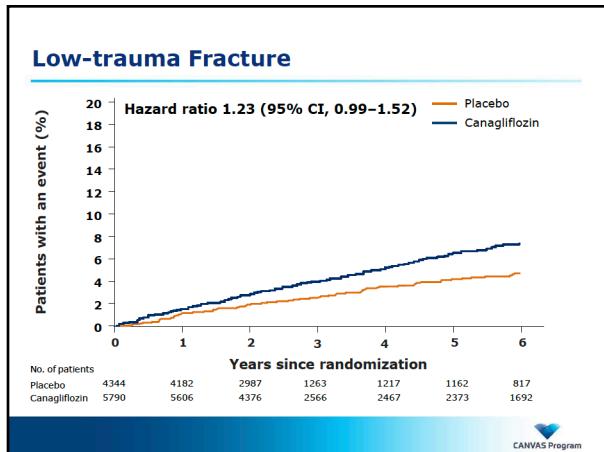
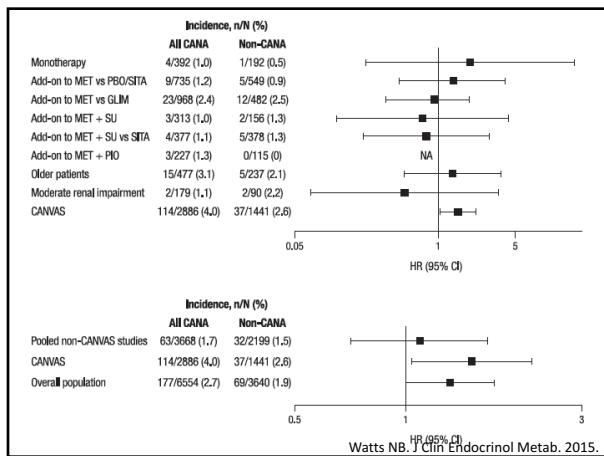
- La proporción de pacientes con fracturas fue pequeña y equilibrada durante el tratamiento con Dapagliflozina versus placebo

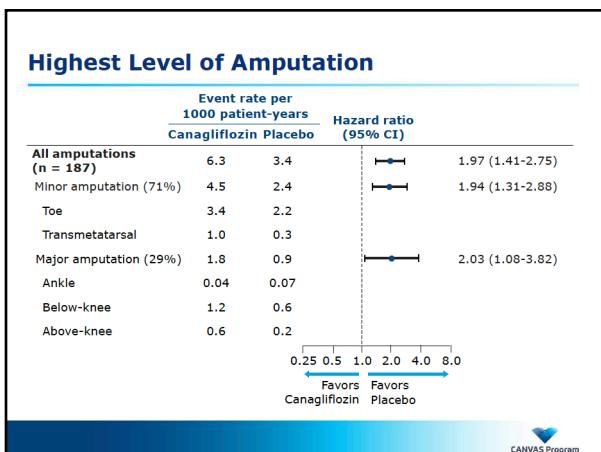
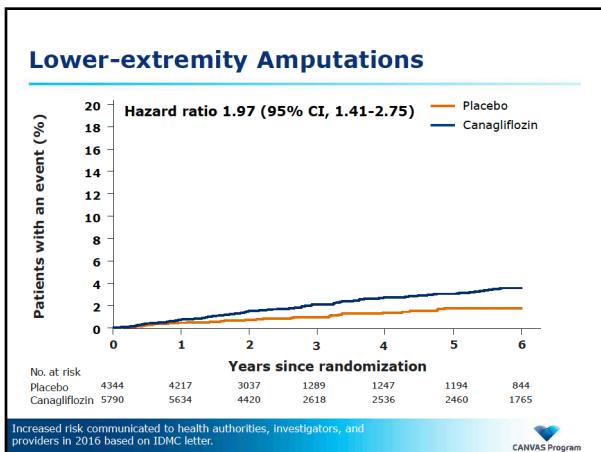
	Colección de datos en estudios controlados con Placebo(corto-plazo)		Colección de datos en estudios controlados con Placebo(corto-plazo y largo-plazo)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Eventos, n (%)	N=2360 8 (0.3)	N=2295 17 (0.7)	N=2026 23 (1.1)	N=1956 32 (1.6)

DAPA= Dapagliflozina; PBO= Placebo
EMDAC Documento de referencia disponible en:
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/u003780/79.pdf>

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Amputation Risk Factors - Multivariate Analysis

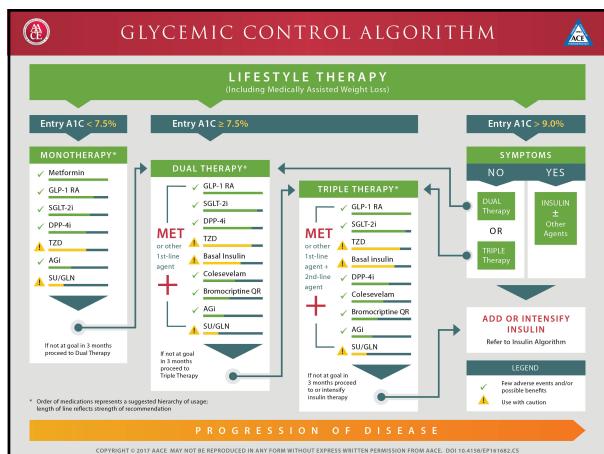
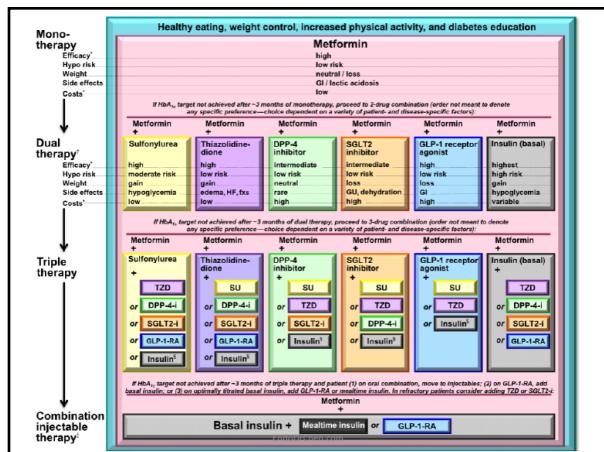
Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- 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



Guías ESC

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life. **IIa B**

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ADA 2017

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

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Conclusiones

- Los inhibidores de SGLT-2...
 - Producen reducción de Hba1c
 - Adicionalmente promueven pérdida de peso y reducen presión arterial
 - Están asociados a menor riesgo cardiovascular
 - Beneficios adicionales en ácido úrico y nefropatía diabética
- Precaución con infecciones urogenitales, hueso, amputaciones y cetosis euglicémia

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