



Actualización en nuevos antidiabéticos

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Conflictos de interés

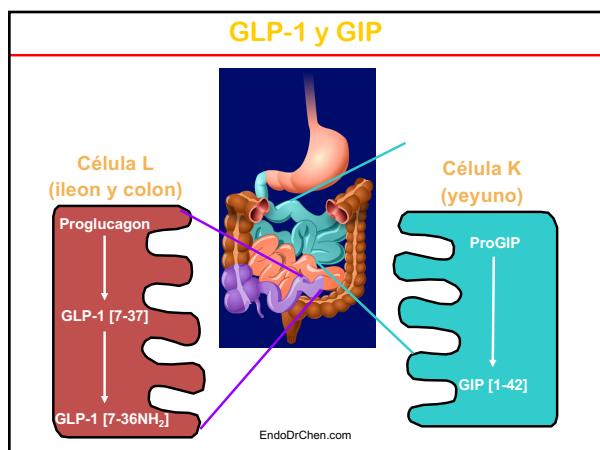
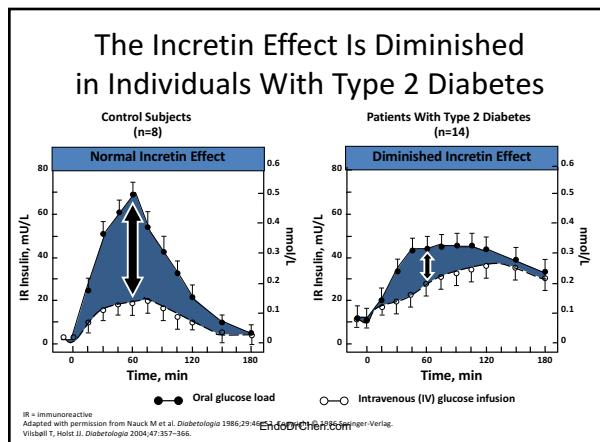
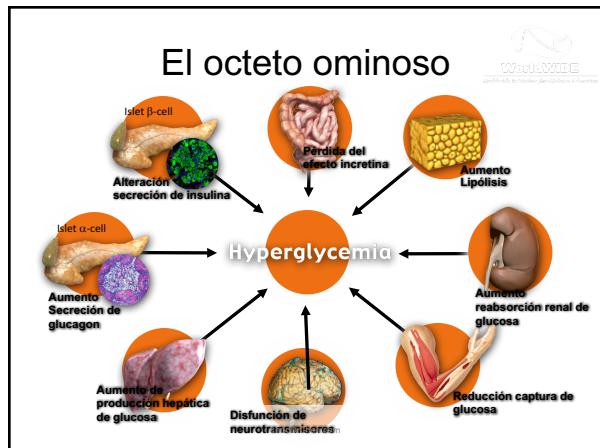
- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Janssen, Boehringer-Ingelheim
- Advisory Board: Novartis Oncology, Sanofi, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Janssen
- Investigación clínica: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

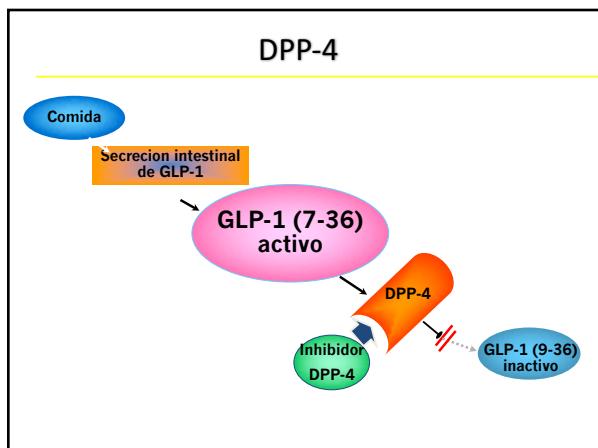
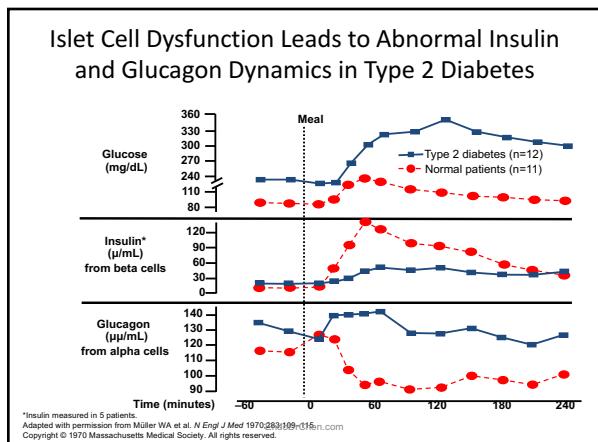
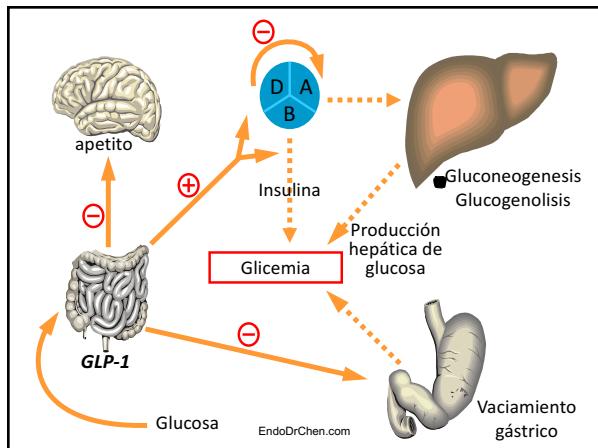
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Agenda

- Evidencia más reciente en
 - Inhibidores de DPP-4
 - Análogos de GLP-1
 - Inhibidores de SGLT-2
- Mecanismo acción
- Seguridad cardiovascular
- Alertas de seguridad

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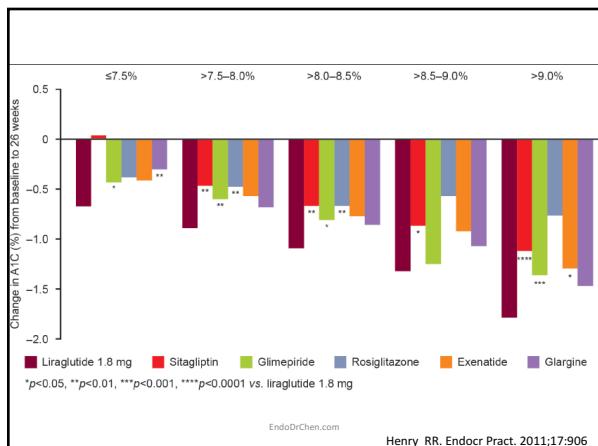




Modulación del sistema de incretinas

- Inhibiendo la enzima que degrada el GLP-1
 - Inhibidores de DPP-4
- Haciendo péptidos resistentes al DPP-4
 - Análogos de GLP-1

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INHIBIDORES DE DPP-4

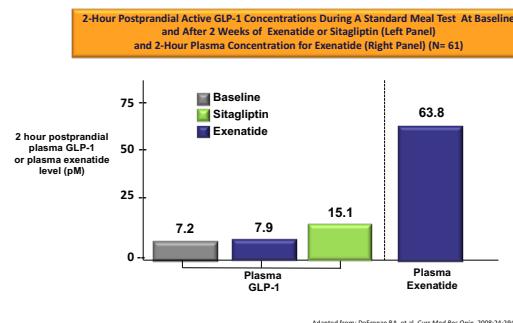
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Inhibidores de DPP-4

- DPP-4
 - Enzima encargada de degradar GLP-1 y otros péptidos gastrointestinales
 - Produce secreción de insulina
 - Efecto neutral sobre peso
 - Efecto a largo plazo desconocido
- Sitagliptina, vildagliptina, saxagliptina, linagliptina, alogliptina

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GLP-1 RA Plasma Levels are Much Higher Than GLP-1 Levels Achieved with a DPP-4 Inhibitor



	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Daily recommended dose	100 mg	100 mg	5 mg	25 mg	5 mg
Physicochemical properties					
Oral bioavailability	87%	85%	75%	70%	30%
Volume distribution	198 l	71 l	151 l	300 l	368 - 918 l
Fraction bound to proteins	38%	9.3%	< 10%	20%	70%
Half-life ($T_{1/2}$)	8 - 14 h	2 - 3 h	2.2 - 3.8 h	12.4 - 21.4 h	120 - 184 h
Kidney excretion	87%	85%	75%	76%	5%
Liver excretion	13%	4.5%	22%	13%	85%
Liver metabolized unchanged	20%	20%	20%	20%	20%
Substrate for CYP3A4/5	Low	No	Yes	No	No
Active metabolites	ND	No	Yes	ND	ND
Inactive metabolites	ND	Yes	No	ND	ND
Pharmacodynamic properties					
<i>In vitro</i> DPP-4 inhibition (IC_{50})	19 nM	62 nM	50 nM	24 nM	1 nM
Selectivity for DPP-4 versus DPP-8/DPP-9	> 2,600	< 100	< 100	> 14,000	> 10,000

Inhibidores de DPP-4

- A diferencia de los análogos de GLP-1, no hay pérdida de peso
- Efecto del DPP-4 no es exclusivo sobre GLP-1, puede haber acción sobre otros péptidos cuyo efecto se desconoce
- Son de administración oral
- No produce hipoglicemias
- Muy bien tolerados
- Seguridad pancreática

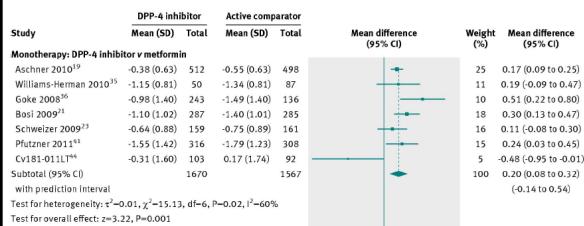
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Dosis

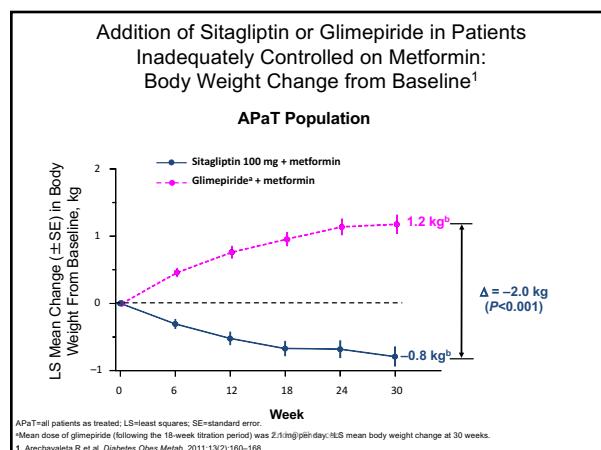
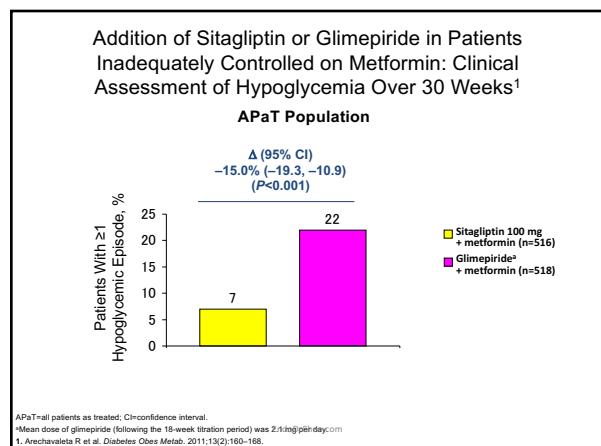
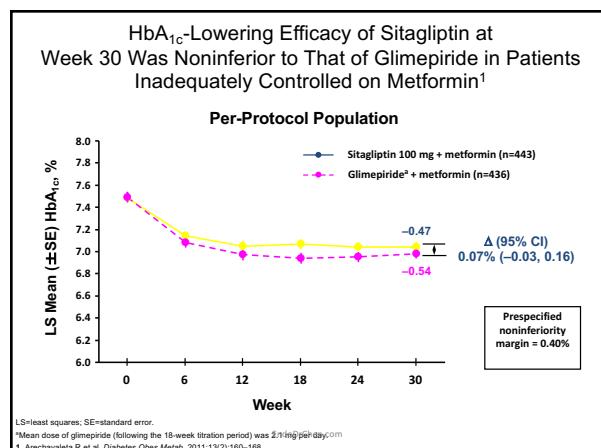
- Sitagliptina: 100 mg por día
- Saxagliptina: 5 mg por día
- Vildagliptina: 50 mg bid
- Linagliptina: 5 mg por día
- Todos requieren ajuste de dosis con AEC menor a 50 cc/min excepto linagliptina

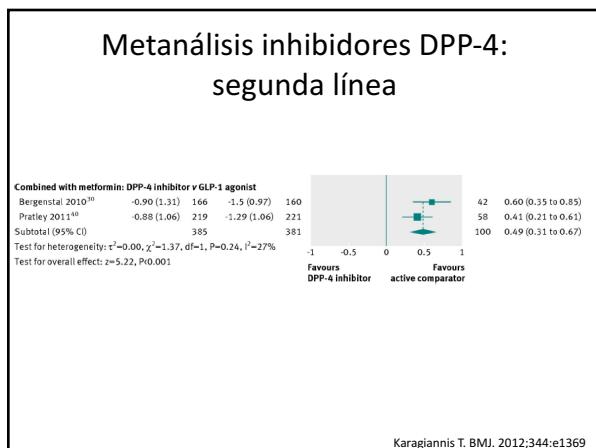
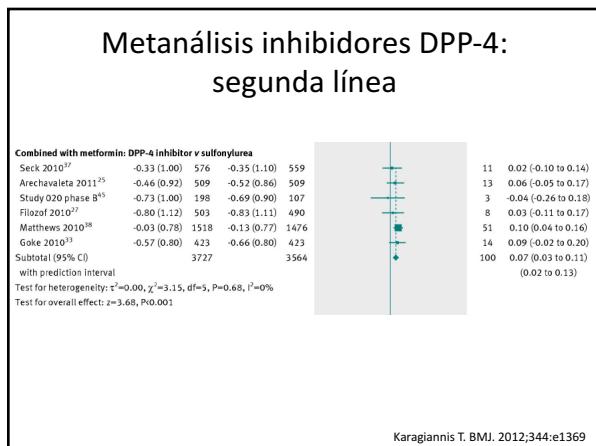
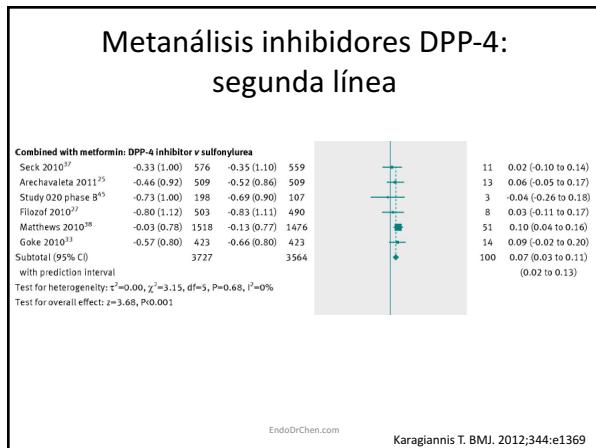
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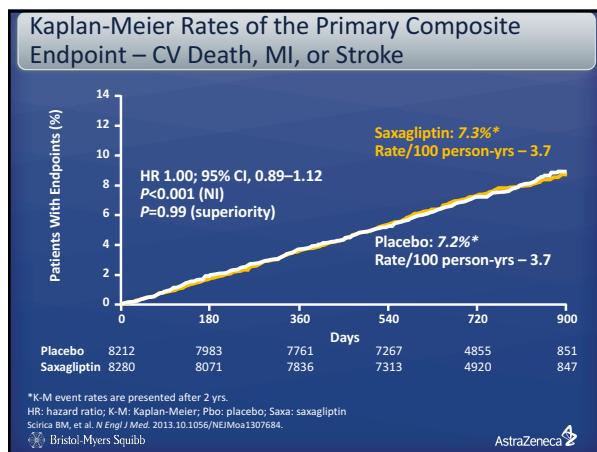
Metanálisis inhibidores DPP-4: terapia primera línea



Karagiannis T. BMJ. 2012;344:e1369







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.

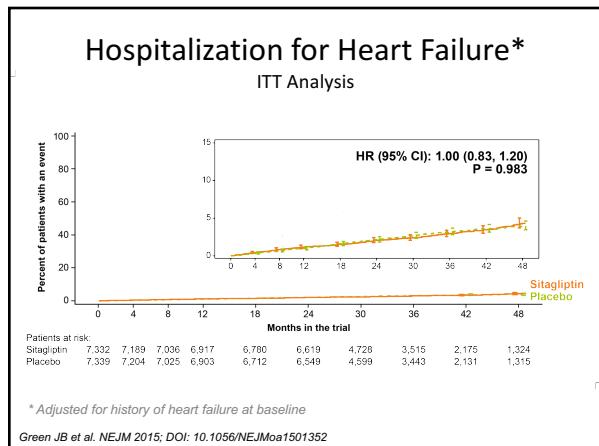
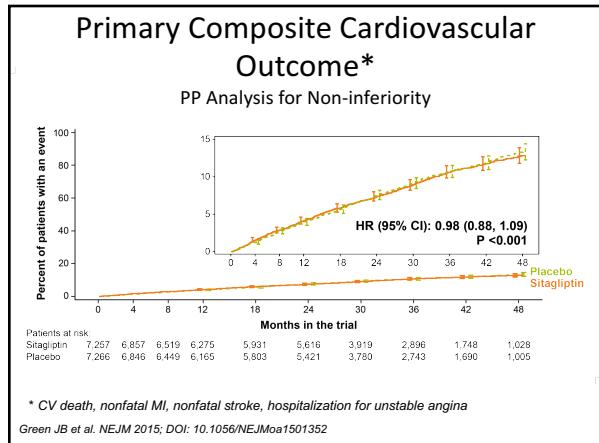
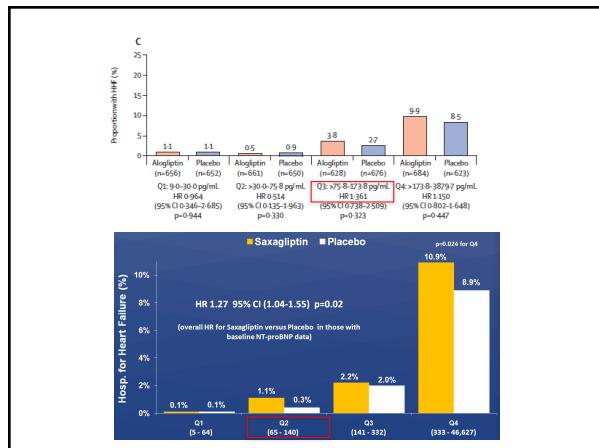
Bristol-Myers Squibb AstraZeneca

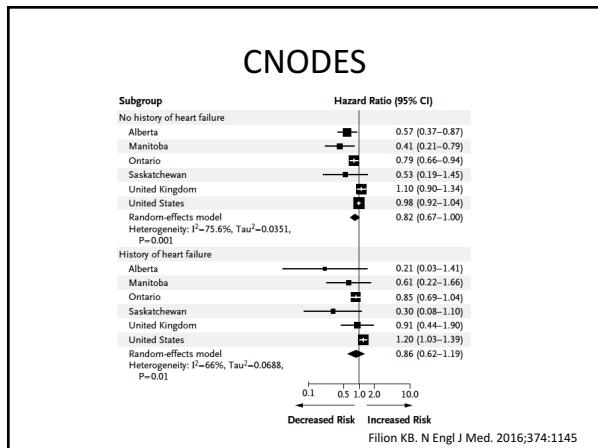
EXAMINE-análisis post hoc

	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 (0.82-1.21)		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





Inhibidores de DPP-4

- Insuficiencia cardíaca
 - Reportado con saxagliptina y alogliptina
 - No se presenta con sitagliptina
 - El mecanismo no está claro
 - Advertencia de FDA
 - Tener precaución en pacientes con falla cardíaca severa

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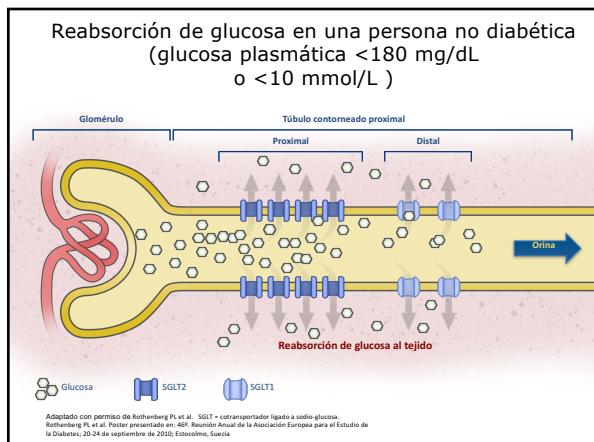
Inhibidores de DPP-4

- Muy bien tolerados en general
- Fallo a través del tiempo similar a sulfonilureas
- Precaución en ICC severa
- Eventos pancreáticos ya no son una preocupación

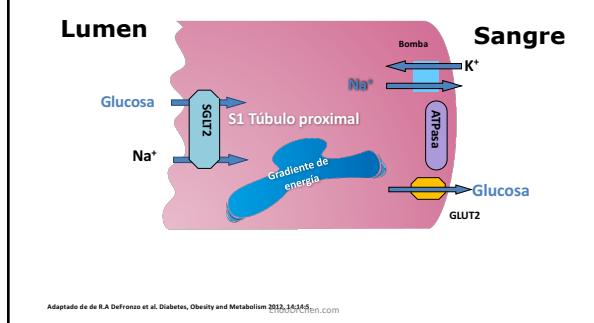
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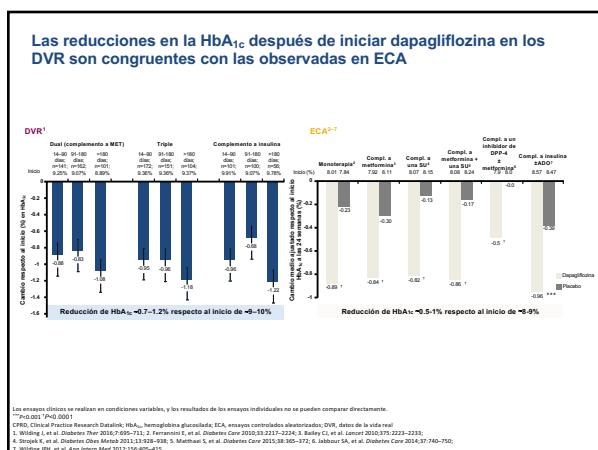
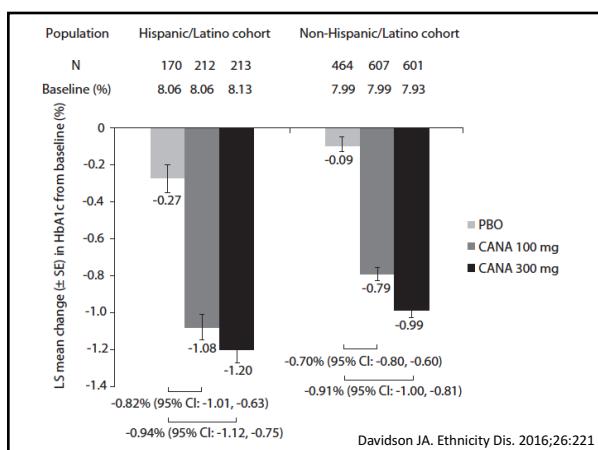
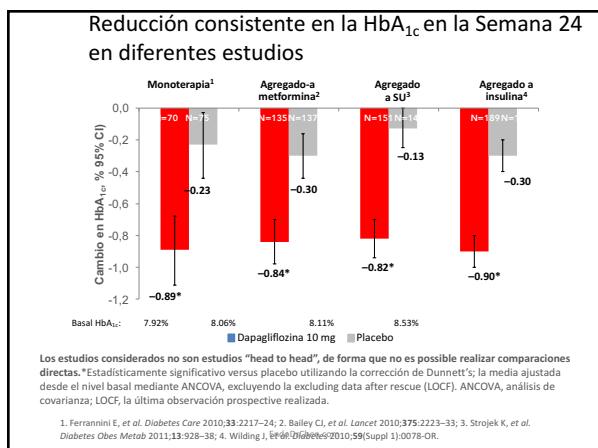
INHIBIDORES SGLT-2

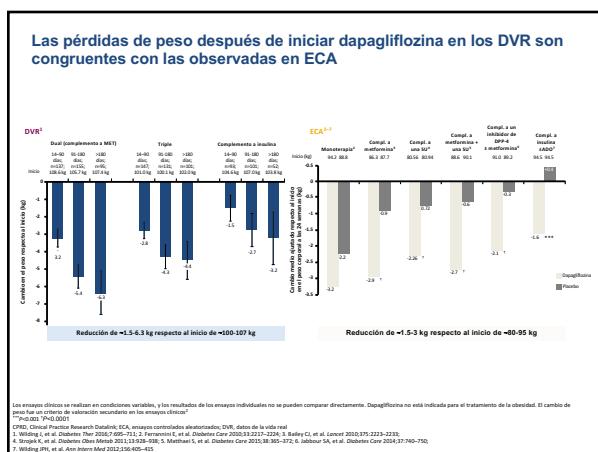
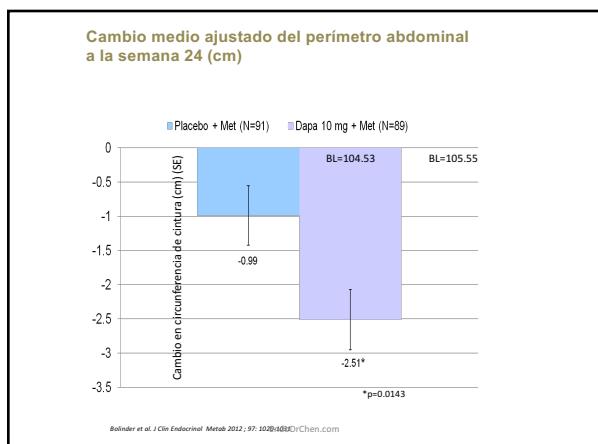
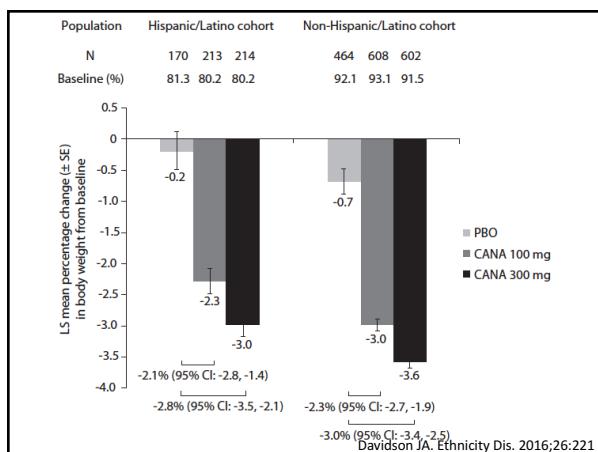
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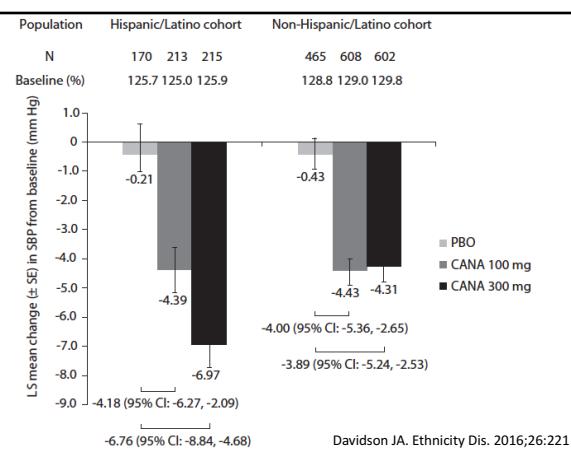
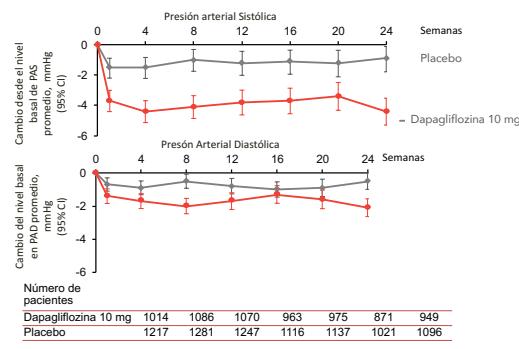
SGLT2 permite la reabsorción de glucosa renal





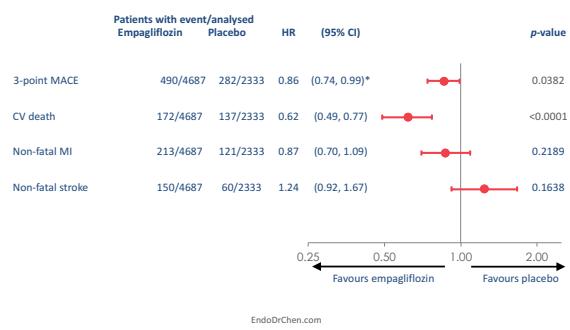


En el conjunto de los estudios, dapagliflozina redujo la TA a lo largo de las 24 semanas.

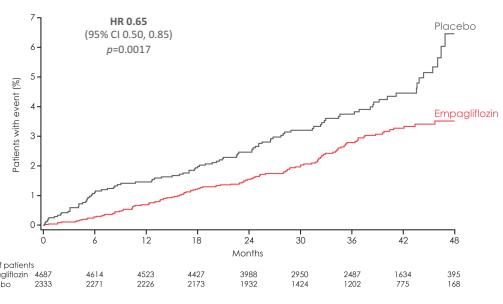


DESENLACES CARDIOVASCULARES

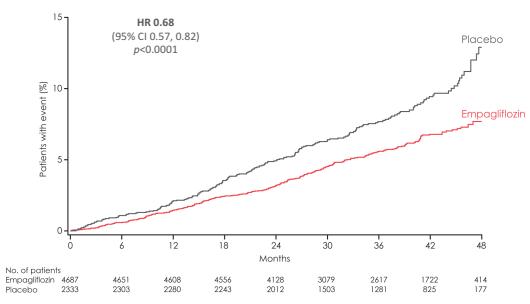
CV death, MI and stroke

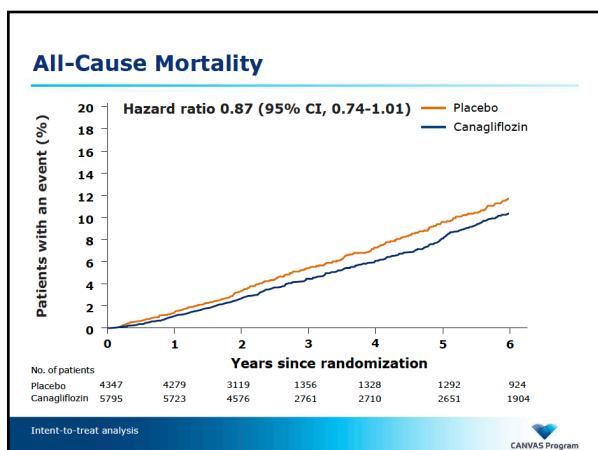
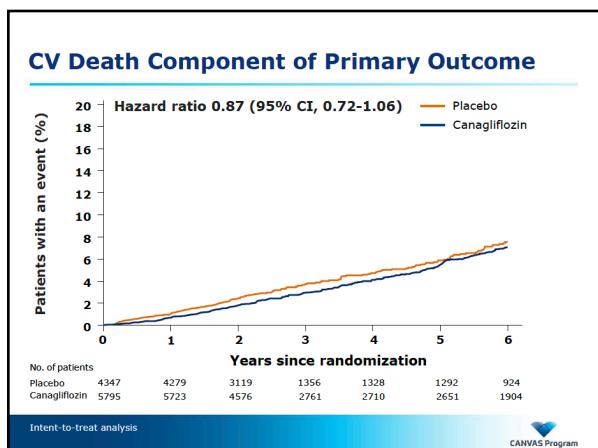
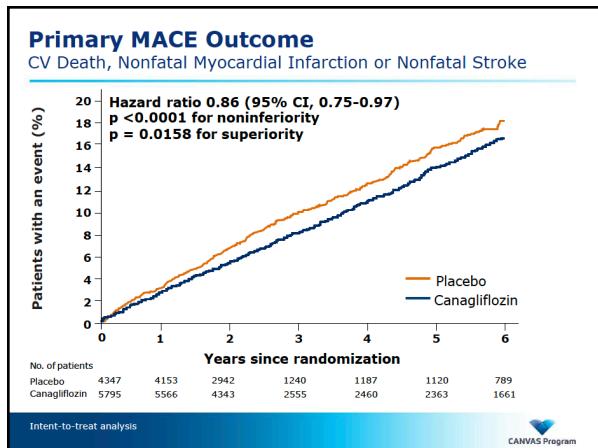


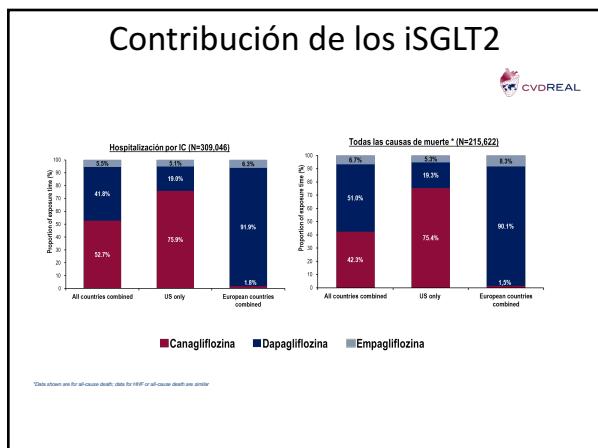
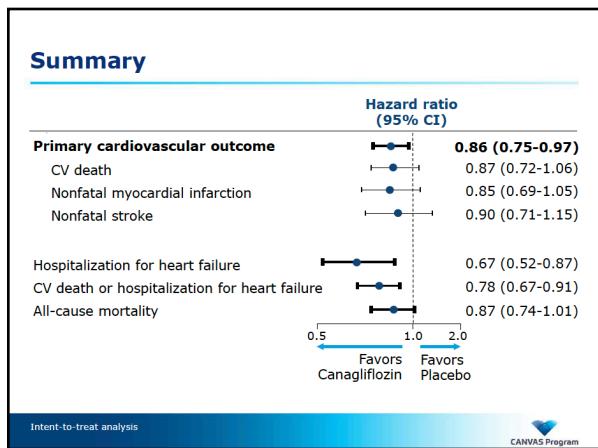
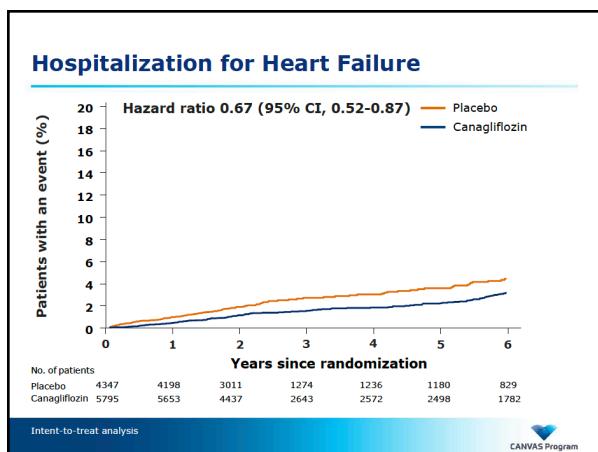
Hospitalisation for heart failure

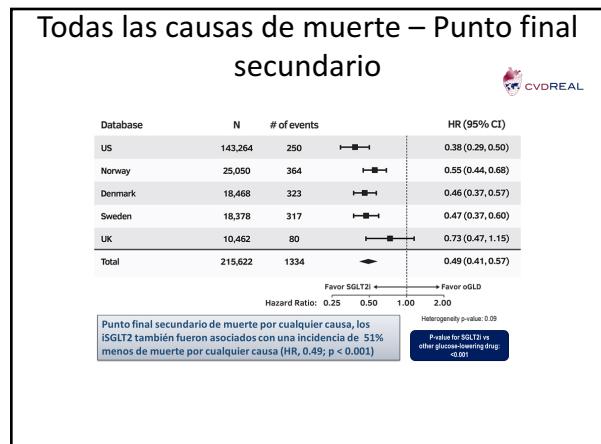
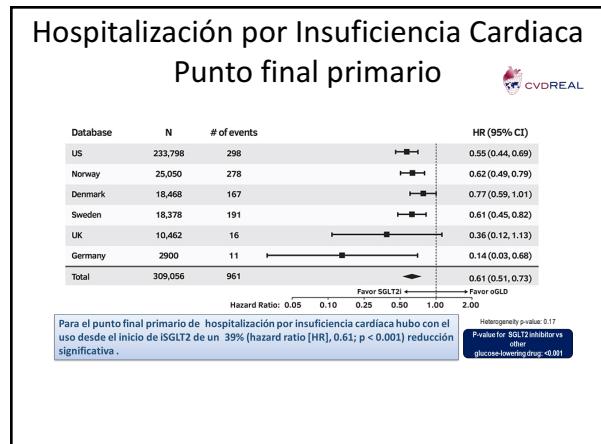


All-cause mortality

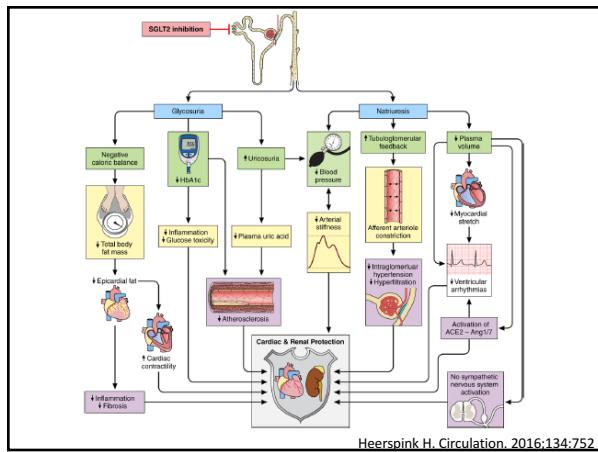








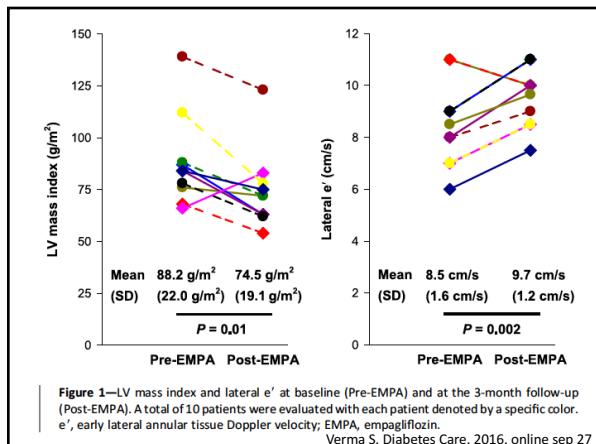
CÓMO SE EXPLICA EL BENEFICIO CARDIOVASCULAR?



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

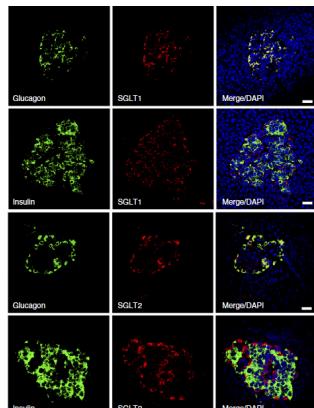
[05-15-2015]

Safety Announcement

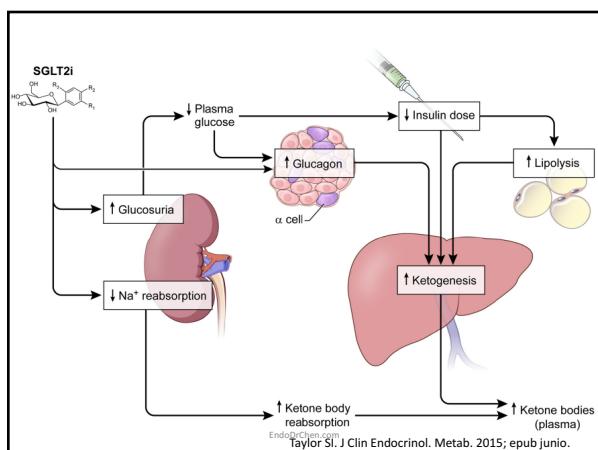
The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing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

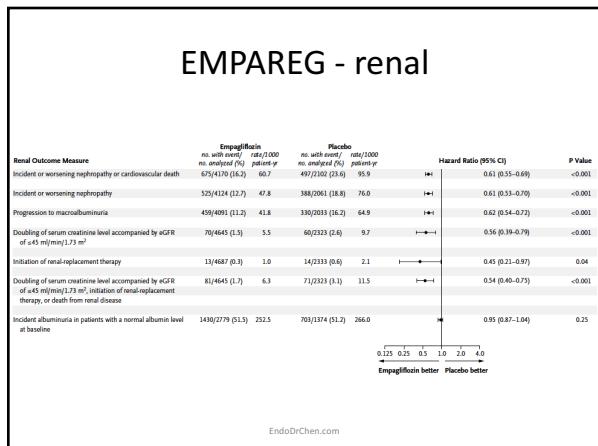
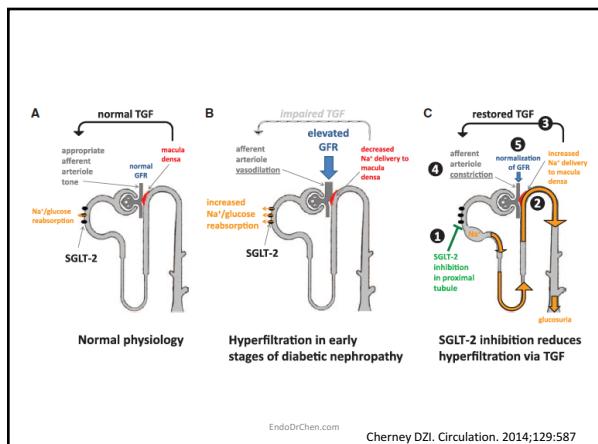
Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first 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.

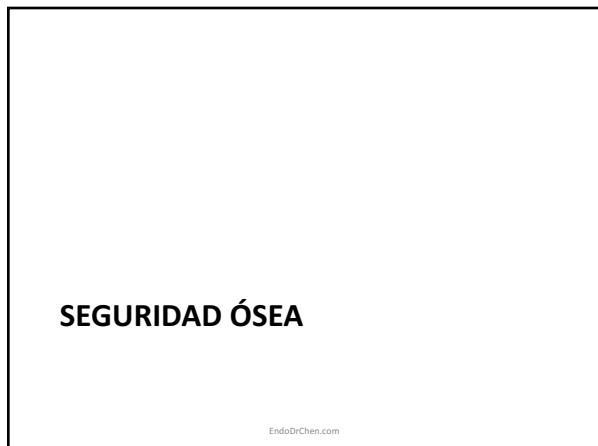
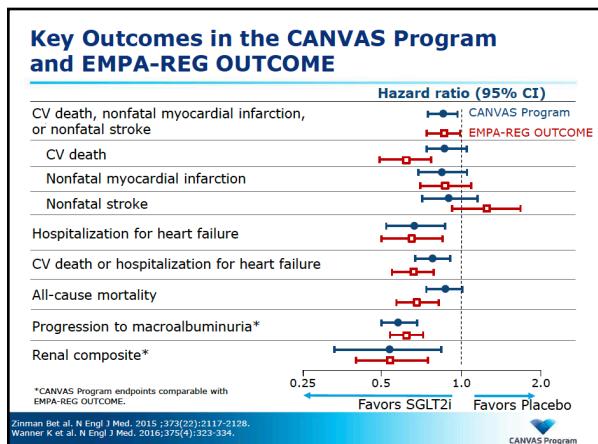
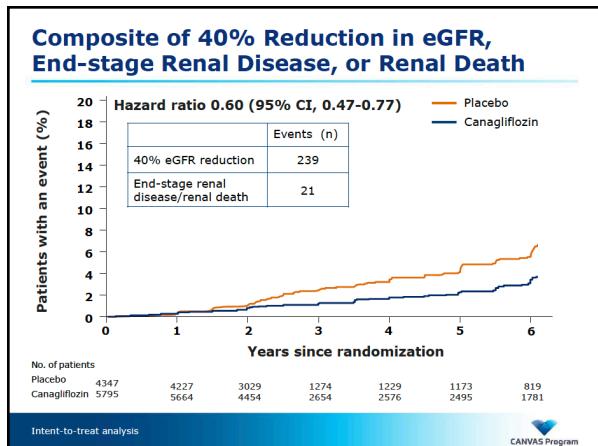
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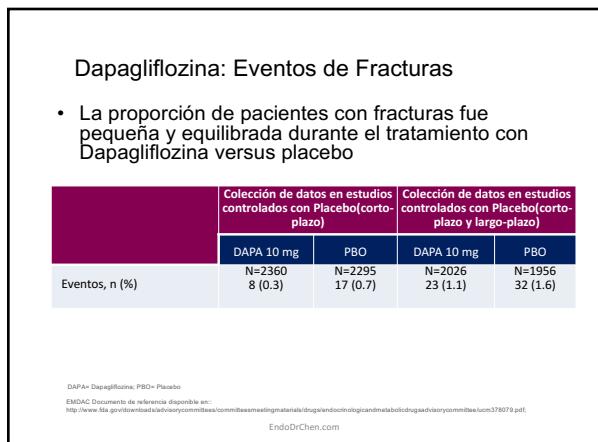
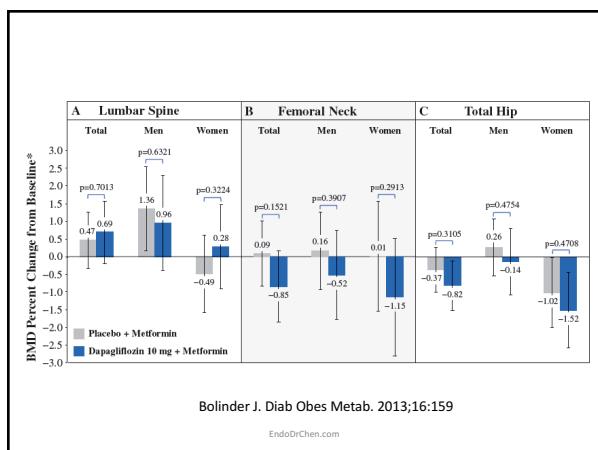


Bonner C. Nat Med. 2015;21(5):512









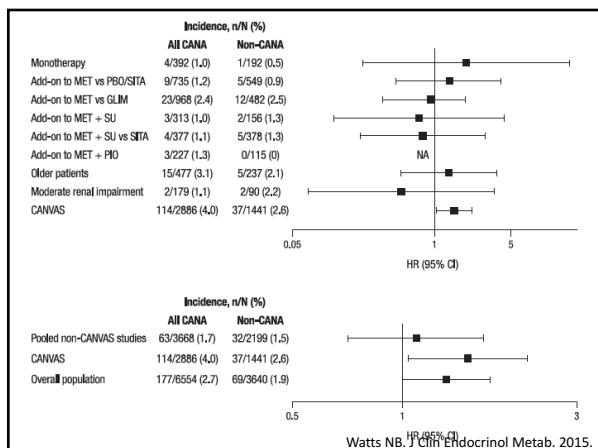
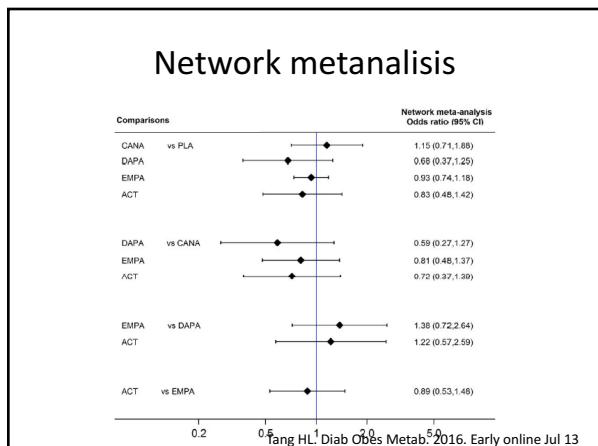
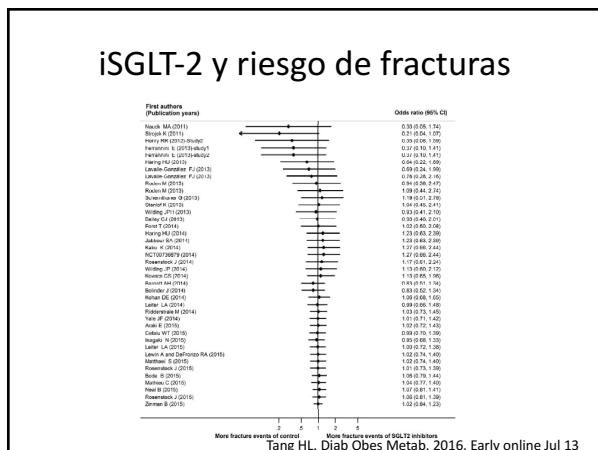
Other adverse events (2)

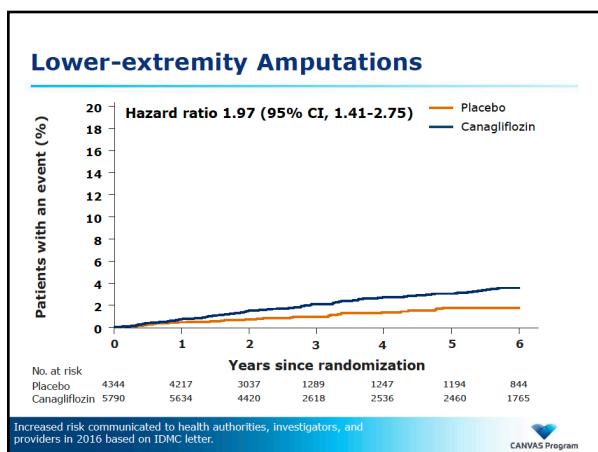
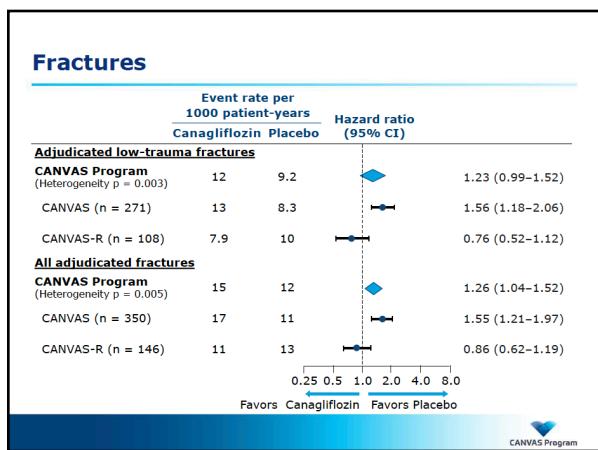
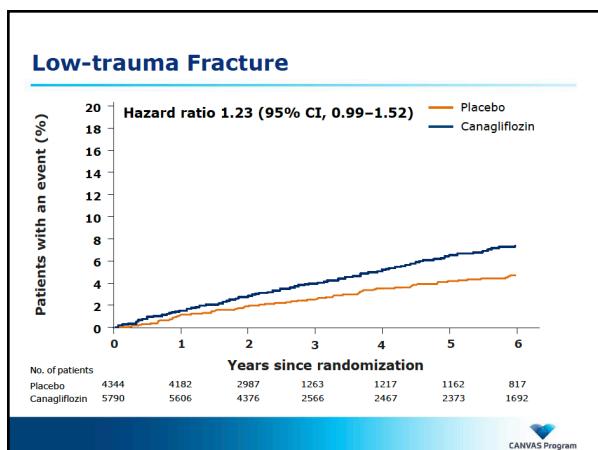
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Hepatic injury*	108 (4.6%)	1.91	80 (3.4%)	1.35	88 (3.8%)	1.48
Hypersensitivity*	197 (8.4%)	3.59	158 (6.7%)	2.75	181 (7.7%)	3.14
Bone fractures†	91 (3.9%)	1.61	92 (3.9%)	1.57	87 (3.7%)	1.46

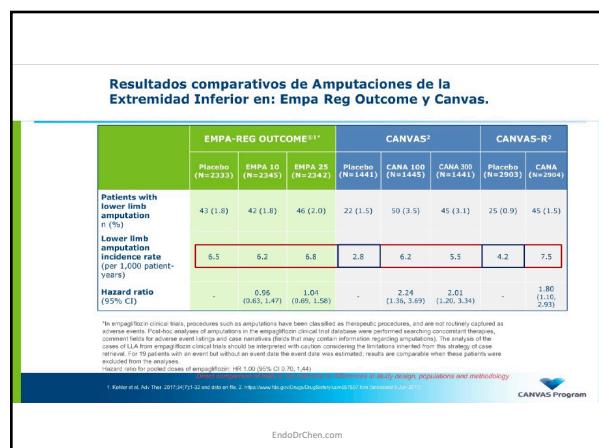
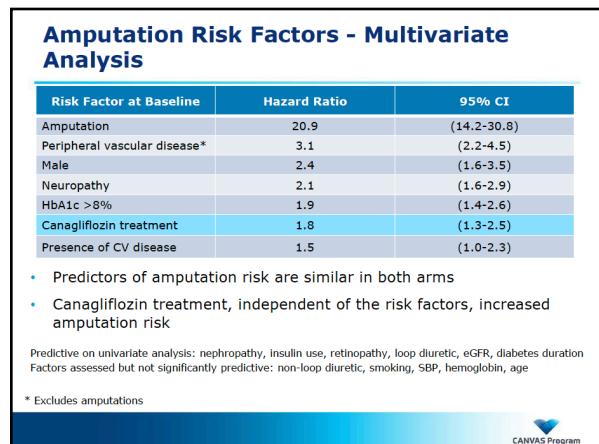
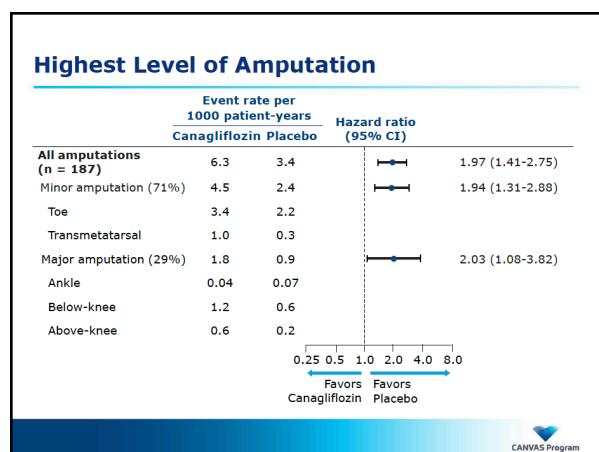
Rate = per100 patient-years

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

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Efectos adversos

- Infecciones genitales: 10% mujeres y 5% hombres
- Caída inicial de TFG e hipovolemia que luego normalizan
- Hipotensión postural: adultos mayores y diuréticos de asa

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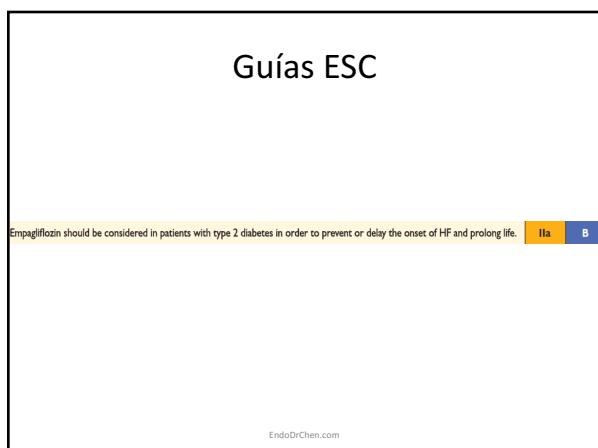
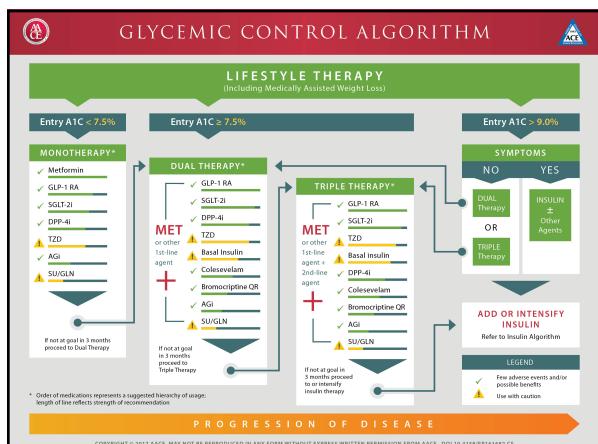
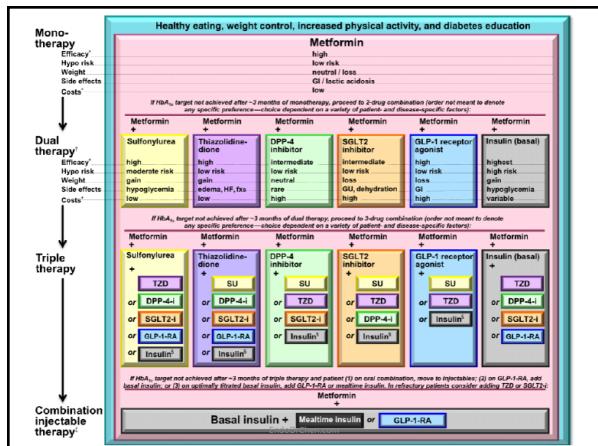
Cómo se usan?

- AEC mayor a 60 cc/min
 - Dapagliflozina 10 mg por día
 - Canagliflozina 300 mg por día
 - Empagliflozina 25 mg por día
- AEC 45-60 cc/min
 - Canagliflozina 100 mg por día
- Insuficiencia hepática
 - Dapagliflozina 5 mg por día
 - Canagliflozina 100 mg por día
 - Empagliflozian 10 mg por día

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QUÉ INDICAN LAS GUÍAS?

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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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Preguntas...

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