



## Inhibidores de SGLT-2, más allá del control glicémico

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### Conflictos de interés

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

### En estos momentos soy...

Estudiante de medicina

Interno universitario

Residente

Médico general

Especialista en medicina interna / diabetólogo

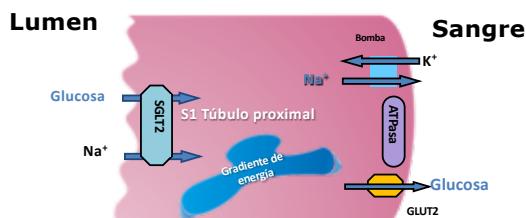
Otras especialidades médicas

## Agenda

- Mecanismo de los inhibidores de SGLT-2 y sus beneficios
- Eficacia comparativa contra los iDPP4
- Beneficios cardiovasculares
- Riesgos: euDKA, infecciones urogenitales, hueso

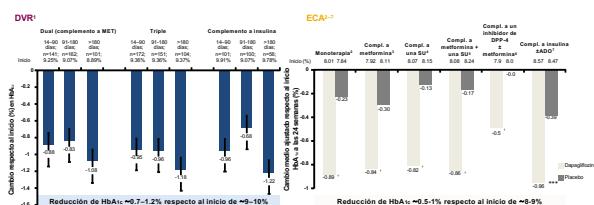
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## SGLT2 permite la reabsorción de glucosa renal



Adaptado de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012;28:83-93

## Las reducciones en la HbA<sub>1c</sub> después de iniciar dapagliflozina en los DVR son congruentes con las observadas en ECA



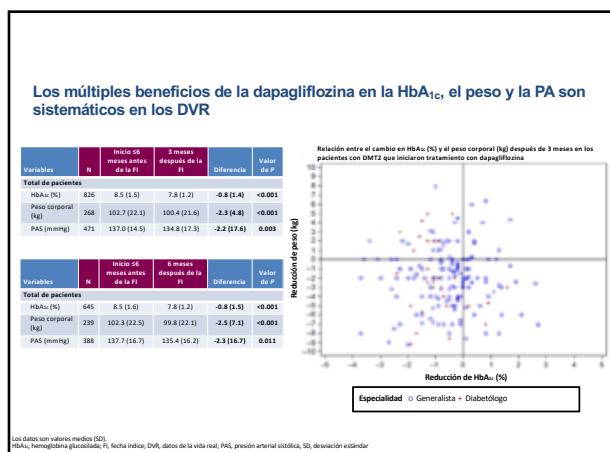
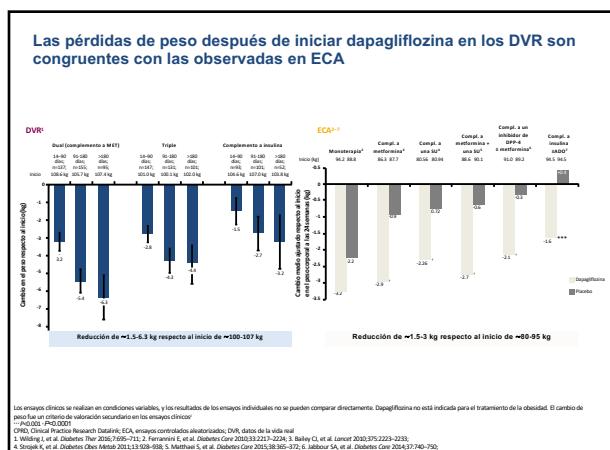
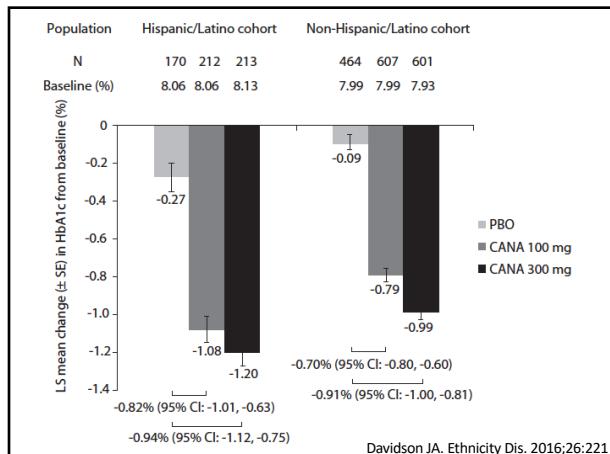
Los ensayos (DVR) se realizan en condiciones variables, y los resultados de los ensayos individuales no se pueden comparar directamente.  
\*P<0.05; \*\*P<0.001.

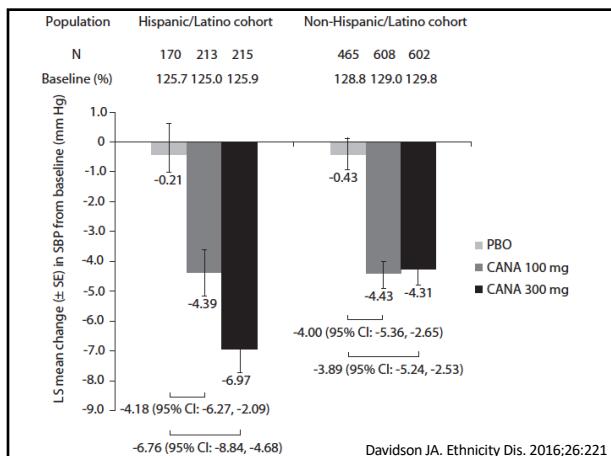
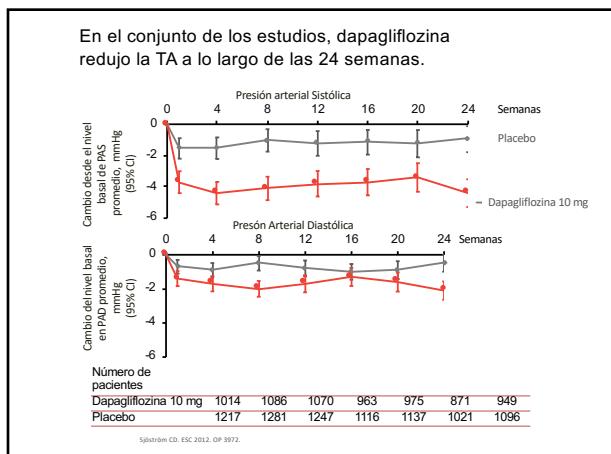
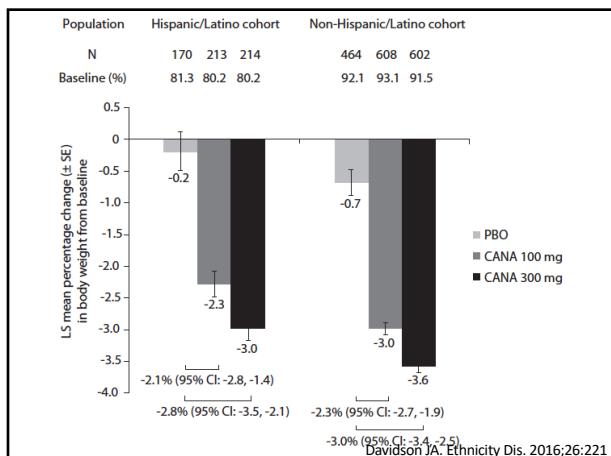
CPD, Clinical Practice Decision Definition; DKA, diabète ketoacidotique; ECA, ensayos controlados aleatorizados; DVR, diseño de la vida real.

1. M. M. Wintle et al. *Diabetologia* 2006; 49: 2215-2212. 2. Fennell E, et al. *Diabetes Care* 2010; 33: 2219-2224. 3. Bailey CJ, et al. *Lancet* 2010; 375: 2223-2233.

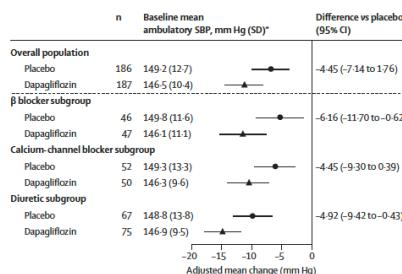
4. Strøm K, et al. *Diabetes Obes Metab* 2011; 13: 928-936. 5. Mattioli S, et al. *Diabetes Care* 2015; 38: 365-372; 6. Jobbar SA, et al. *Diabetes Care* 2014; 37: 740-750.

7. Whiting DR, et al. *Am J Med* 2012; 151: 405-415





## Efecto en PAS en MAPA



Weber MA. Lancet Diab Endocrinol. 2016;4:211

**QUIÉN DEBE SER HOY EL AGENTE DE SEGUNDA LÍNEA?**

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## Caso clínico

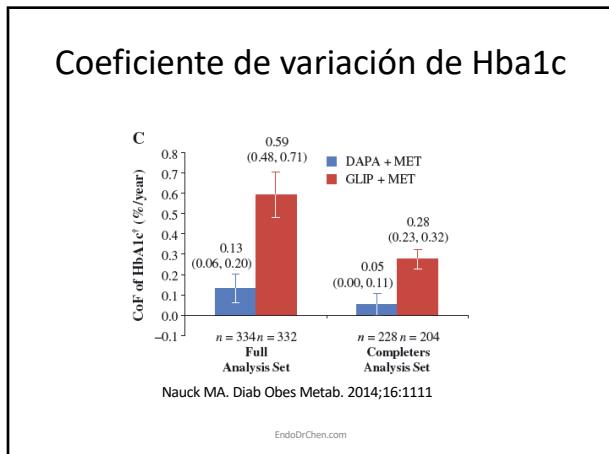
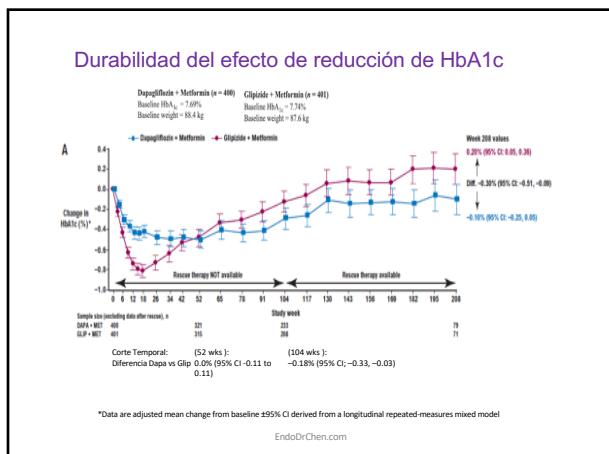
- Masculino de 57 años
- DM-2 de 5 años de evolución
- Tratamiento actual con metformin 500 mg tid
- Hba1c actual en 7.4%
- IMC 30 kg/m<sup>2</sup>
- Toma además atorvastatina 10 mg HS y amlodipina 5 mg por día

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Cuál es el paso a seguir? Qué le agregaría?

- insulina basal
- Sulfonilureas
- inhibidores de DPP4
- análogos de GLP1
- inhibidores de SGLT2

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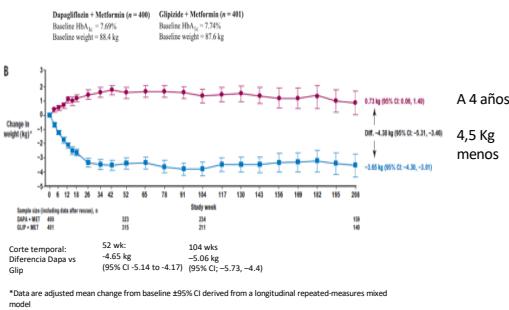
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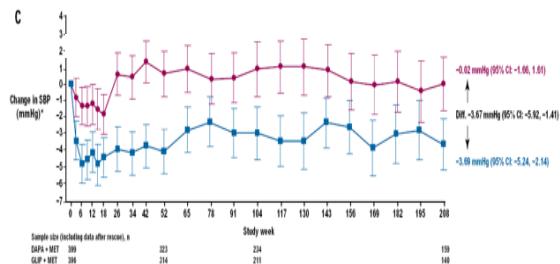
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### Durabilidad del efecto de reducción de peso



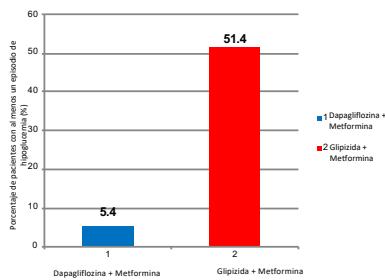
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### Durabilidad del efecto de reducción de PAS



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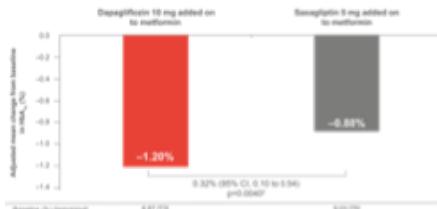
### Hipoglicemias



Todos los episodios de hipoglucemias severas (n=3) se dieron en el grupo de glipizida  
No hubo discontinuaciones debidas a las hipoglucemias en los pacientes tratados con dapagliflozina

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Dapagliflozina + metformina\* demostró reducciones importantes de la HbA<sub>1c</sub> a las 24 semanas vs. iDPP4 + metformina\*<sup>1</sup>



Phase II, 24 weeks, randomized, double-blind, active-controlled, parallel group study to compare the efficacy and safety of the dual add-on of canagliflozin and dapagliflozin with either canagliflozin or dapagliflozin alone on top of metformin in adults with Type 2 diabetes poorly controlled (HbA<sub>1c</sub> 8% to 11%) on metformin. Primary efficacy endpoint was adjusted mean change from baseline in HbA<sub>1c</sub> at 24 weeks.

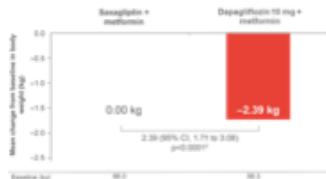
The study met its primary endpoint. This is a retrospective post-hoc analysis.

Mean change from baseline in HbA<sub>1c</sub> is expressed as adjusted mean change in HbA<sub>1c</sub> from baseline to observation carried forward.

CI: confidence interval; DPP4: dipeptidyl peptidase-4; LS: least squares mean.

1. Lavalle-González FJ, et al. Diabetologia. 2013;56(10):2453-2460. Atrialmeca, September 2014.

Dapagliflozina + metformina \* demostró una mayor pérdida de peso a las 24 semanas vs. iDPP4 + metformina



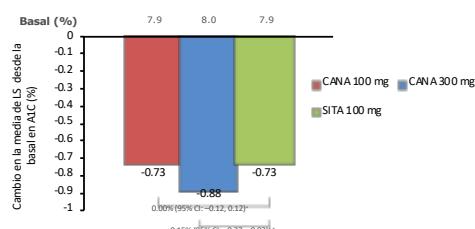
Forjaz y col. no están indicados para el tratamiento de la pérdida de peso. El cambio de peso fue un criterio de selección secundario.

Phase II, 24 weeks, randomized, double-blind, active-controlled, parallel group study to compare the efficacy and safety of the dual add-on of canagliflozin and dapagliflozin with either canagliflozin or dapagliflozin added alone in adults with Type 2 diabetes poorly controlled (HbA<sub>1c</sub> 8% to 11%) on metformin. Primary efficacy endpoint was adjusted mean change from baseline in HbA<sub>1c</sub> at 24 weeks.

This was a post-hoc analysis comparing dapagliflozina + metformina VS treatment group with the canagliflozin+metformina VS group.

1. Lavalle-González FJ, et al. Diabetologia. 2013;56(10):2453-2460. Atrialmeca, September 2014.

Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)  
Estudios comparativos de CANA  
Semana 52: A1C (LOCF)



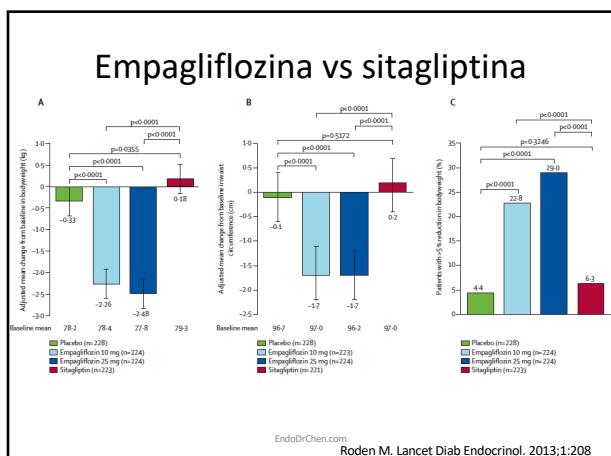
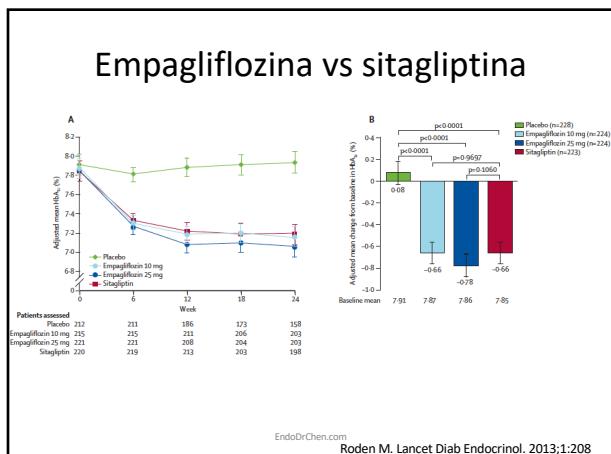
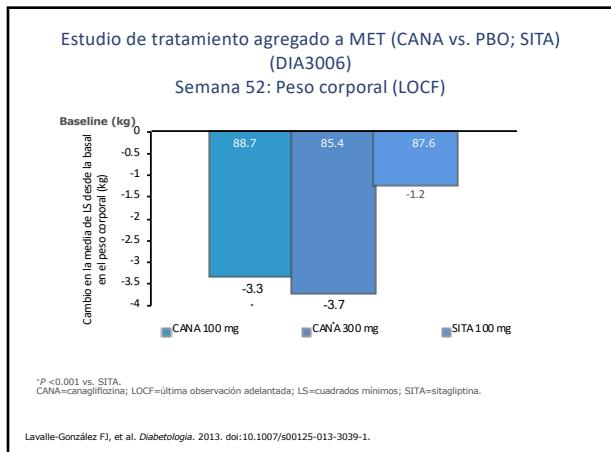
\*No inferior con respecto a SITA. (límite superior del 95% CI <0.3%).

<sup>1</sup>Superior vs. SITA. (límite superior del 95% CI >0.0%).

A1C=hemoglobina glucosilada; CANA=canafliglozina; CI=intervalo de confianza; LOCF=última observación adelantada; LS=cuadrados mínimos;

SITA=sitagliptina.

Lavalle-González FJ, et al. Diabetología. 2013. doi:10.1007/s00125-013-3039-1.



## EFFECTOS ADICIONALES Y POTENCIALES BENEFICIOS

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## EFFECTO URICOSÚRICO

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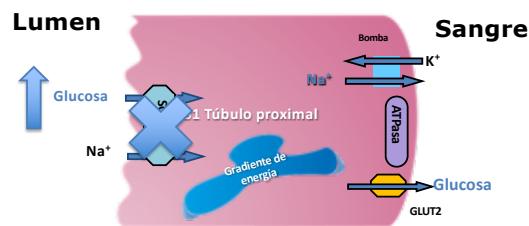


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**SGLT2** permite la reabsorción de glucosa renal



Adaptado de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012;38:83-93

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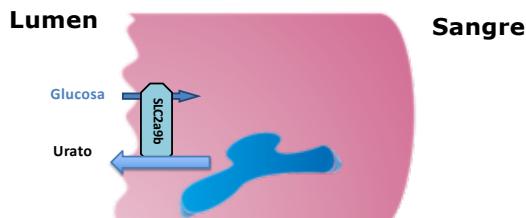


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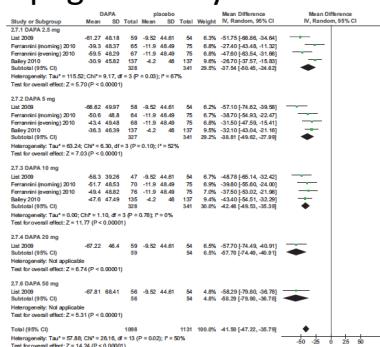
## Mecanismo uricosúrico



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Musso G. Ann Med. 2012;44:375

## Dapagliflozina y ácido úrico



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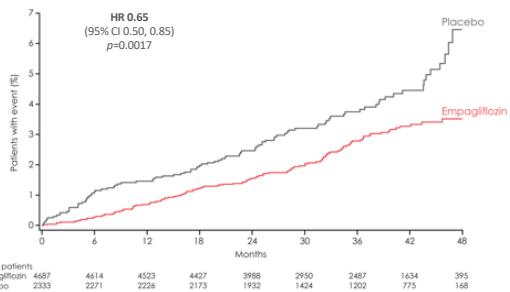
Equivalente a 2.4 mg/dl

Musso G. Ann Med. 2012;44:375

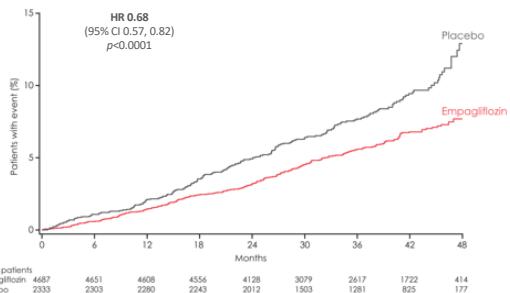
## IMPACTO CARDIOVASCULAR

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## Hospitalisation for heart failure

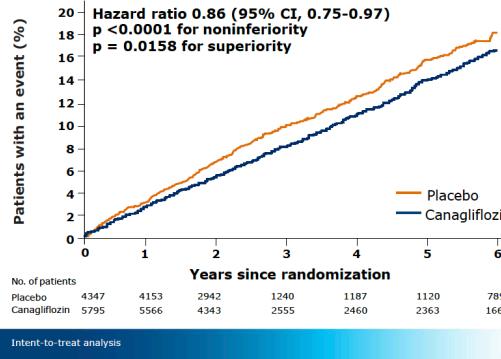


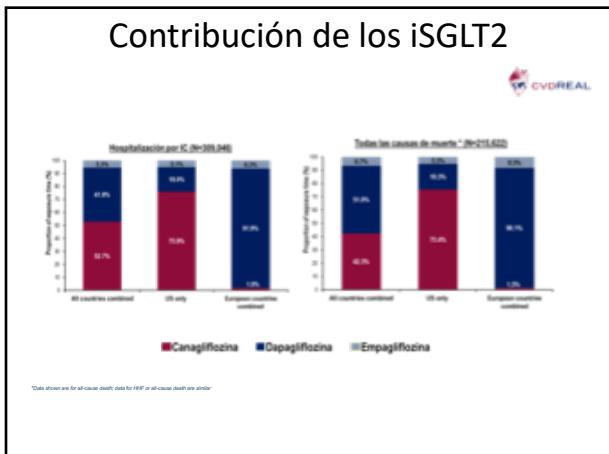
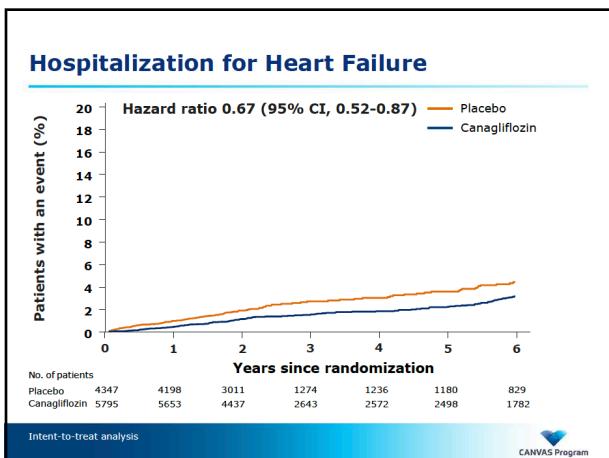
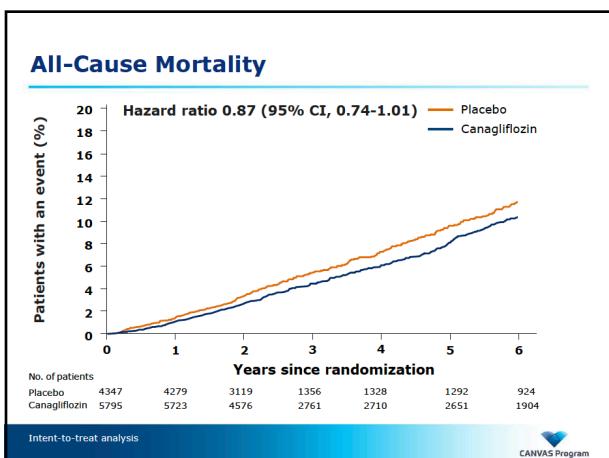
## All-cause mortality

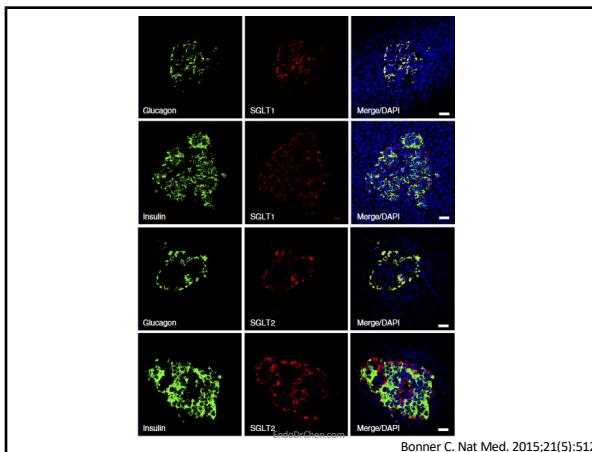
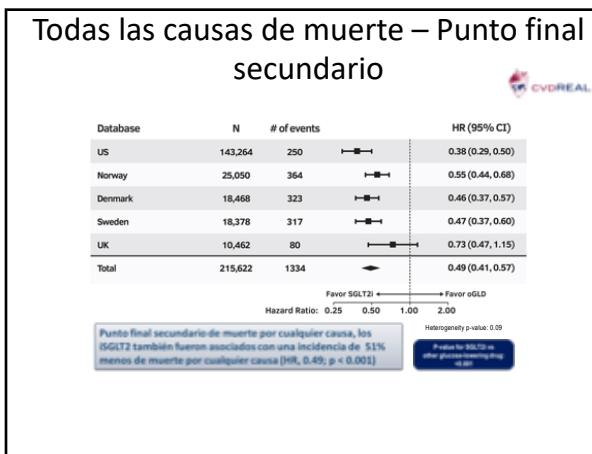
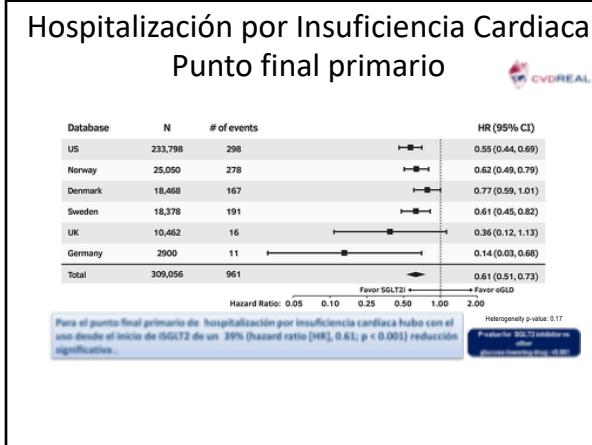


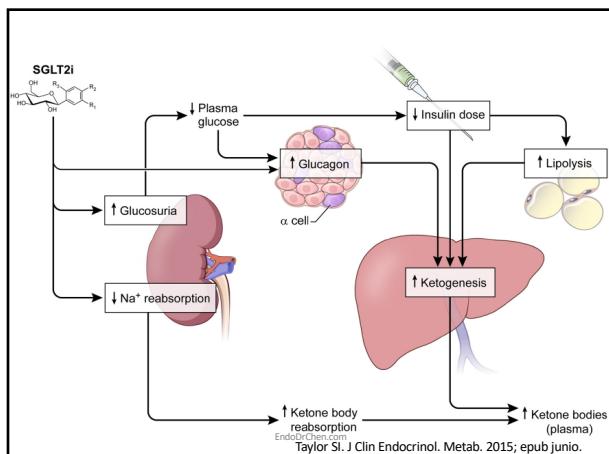
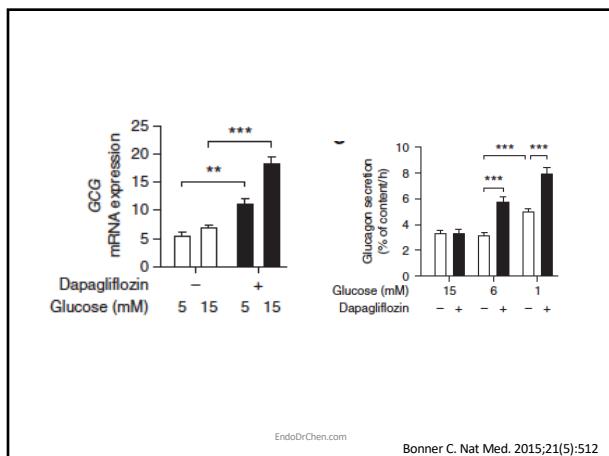
## Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke







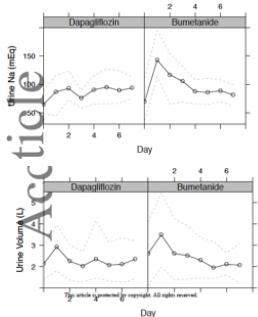


## Mecanismos en ICC

- Más allá de su mecanismo en el túbulo proximal... qué pasa en el túbulo distal?
  - Conforme se va reabsorbiendo agua, la concentración de glucosa en el filtrado aumenta y por lo tanto esto disminuye el gradiente y la reabsorción de agua
  - Contribuye a mayor efecto diurético osmótico
  - Mecanismo diferente a otros diuréticos que actúan preferentemente por natriuresis y arrastre de agua

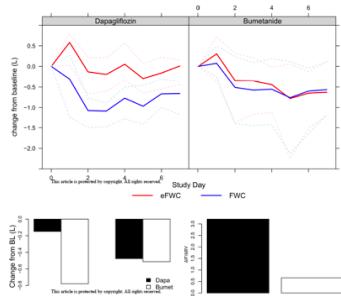
Hallow KM. Diab Obes Metab. Online 12 oct 2017

## Dapagliflozina vs bumetanida

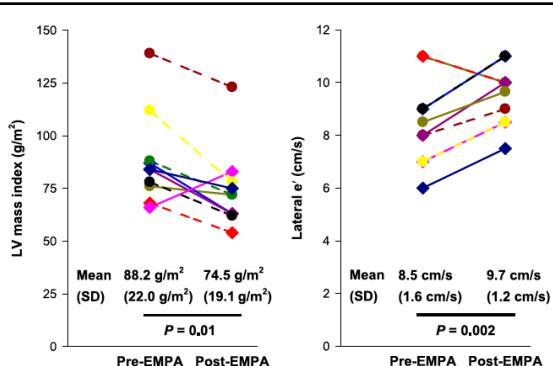


Hallow KM. Diab Obes Metab. Online 12 oct 2017

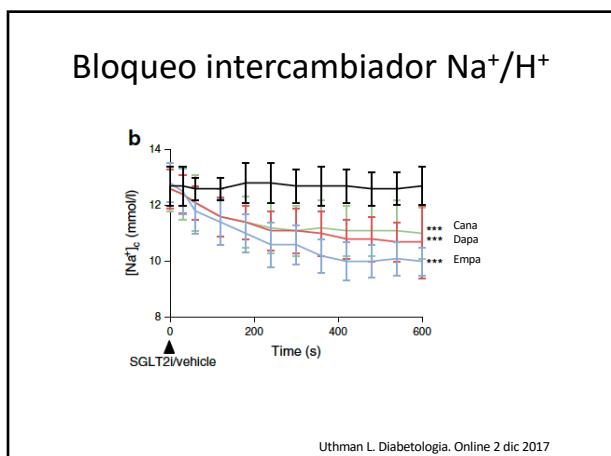
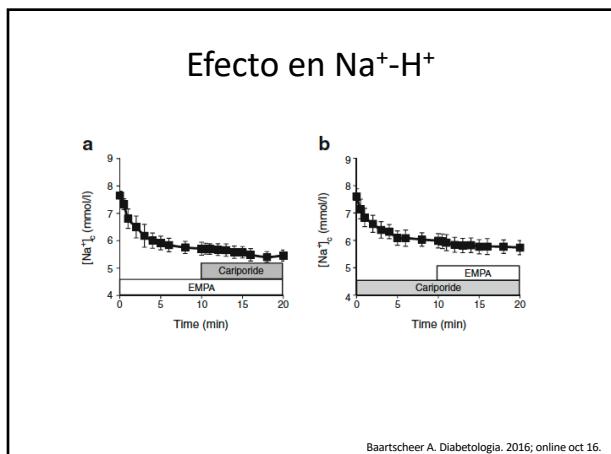
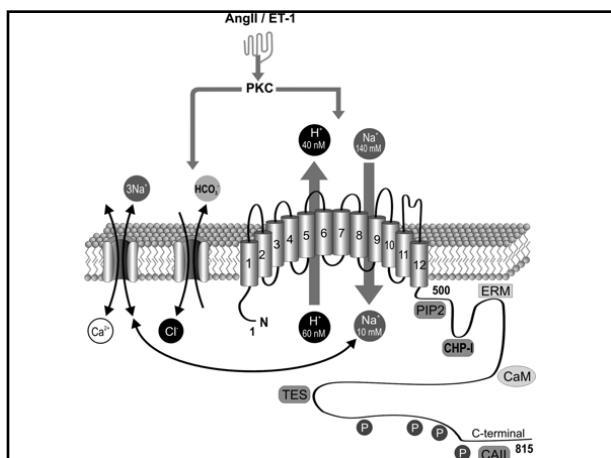
## Dapagliflozina vs bumetanida



Hallow KM. Diab Obes Metab. Online 12 oct 2017



**Figure 1—**LV mass index and lateral e' at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e', early lateral annular tissue Doppler velocity; EMPA, empagliflozin.  
Verma S. Diabetes Care. 2016. online sep 27



## EFFECTOS EN NEFROPATÍA DIABÉTICA: HIPERFLITRACIÓN Y PROTEINURIA

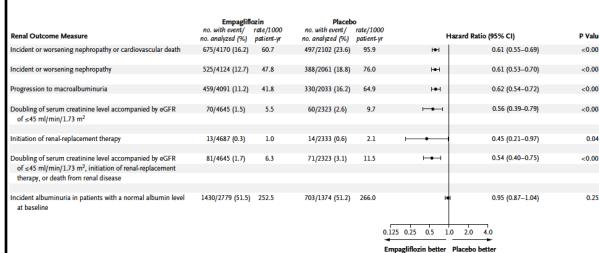
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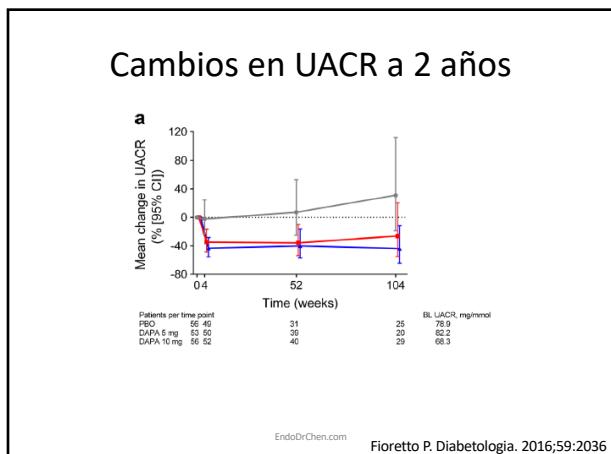
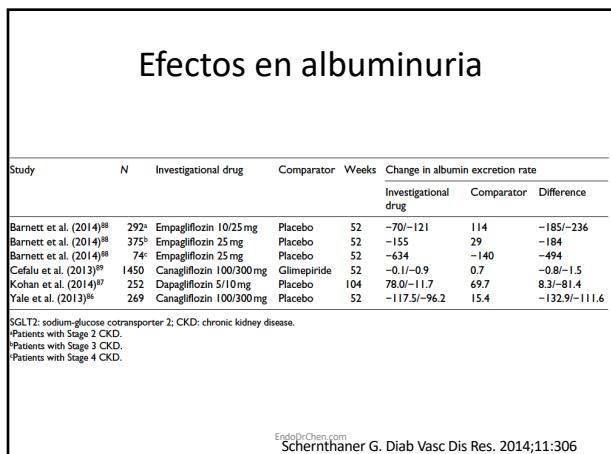
### Renal Outcomes Summary

- Canagliflozin compared to placebo
  - Induced sustained lowering of albuminuria
  - Prevented progression in albuminuria
  - Induced regression in albuminuria
  - Reduced renal function loss events
- Conclusion
  - These data suggest a potential renoprotective effect of canagliflozin treatment in patients with type 2 diabetes at high CV risk on top of ACE/ARBs

CANVAS Program

### EMPAREG - renal

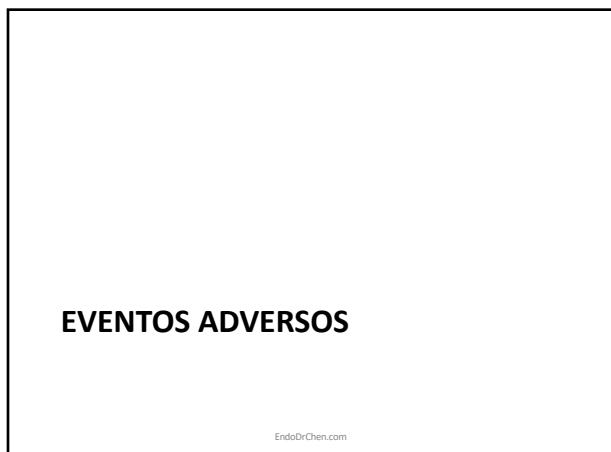
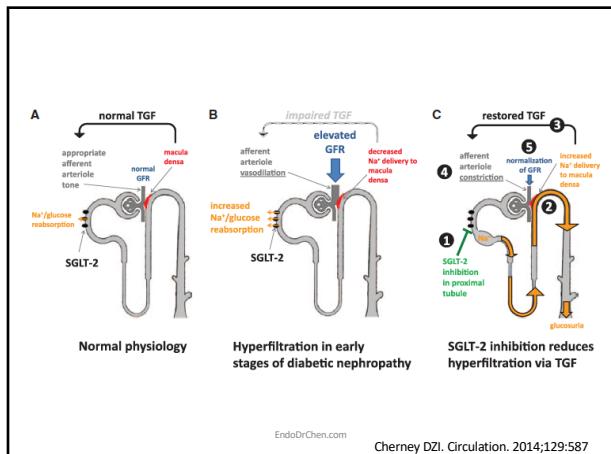




### IDNT and RENAAL Trial Comparison of Major Endpoints

	RRR (%)			
	RENAAL		IDNT	
	Losartan vs control	Irbesartan vs control	Irbesartan vs amlodipine	Amlodipine vs control
Doubling of Creat, ESRD, or death	16 (P=0.02)	20 (P=0.02)	23 (P=0.006)	-4 (P=0.69)
Doubling of Creat	25 (P=0.006)	33 (P=0.003)	37 (P<0.001)	-6 (P=0.60)
ESRD	28 (P=0.002)	23 (P=0.07)	23 (P=0.07)	0 (P=0.99)
Death	-2 (P=0.88)	8 (P=0.57)	-4 (P=0.8)	12 (P=0.4)
CV Morbidity & Mortality	10 (P=0.26)	9 (P=0.4)	-3 (P=0.79)	12 (P=0.29)

Lewis EJ et al. *N Engl J Med*. 2001;345:851-60.  
Brenner BM et al. *N Engl J Med*. 2001;345:861-9.



### Dapagliflozina - Infecciones de Vías Urinarias

- Se observó un leve incremento en infecciones de vías urinarias con dapagliflozina vs. placebo.

	Estudios controlados con Placebo (corto plazo)		Estudios controlados con Placebo (corto y largo plazo)	
	Dapagliflozina 10 mg	Placebo	Dapagliflozina 10 mg	Placebo
Infecciones de Vías Urinarias, n (%)	N=2360 110 (4.7)	N=2295 81 (3.5)	N=2026 174 (8.6)	N=1956 121 (6.2)
Mujeres, n (%)	N=1003 85 (8.5)	N=952 64 (6.7)	N=852 121 (14.2)	N=799 86 (10.8)
Hombres, n (%)	N=1357 25 (1.8)	N=1343 17 (1.3)	N=1174 53 (4.5)	N=1157 35 (3.0)

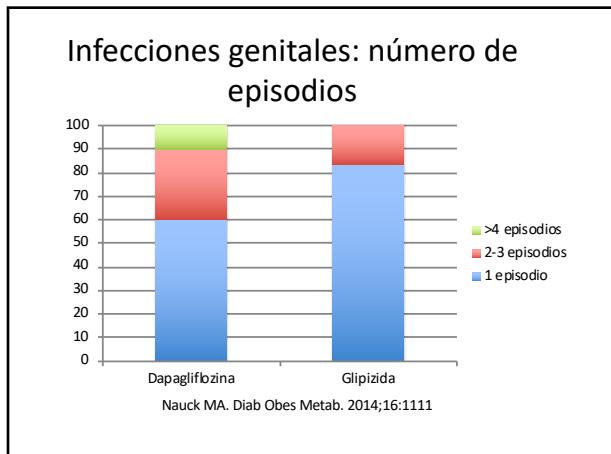
EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeemeetings/materials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf>  
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## Dapagliflozina - Infecciones Micóticas Genitales

• Las infecciones genitales se reportaron más frecuentemente con dapagliflozina vs. placebo

	Estudios controlados con Placebo (corto plazo)		Estudios controlados con Placebo (corto y largo plazo)	
	Dapagliflozina 10 mg	Placebo	Dapagliflozina 10 mg	Placebo
Infección genital n (%)	N=2360 130 (5.5)	N=2295 14 (0.6)	N=2026 156 (7.7)	N=1956 19 (1.0)
Mujeres, n (%)	N=1003 84 (8.4)	N=952 11 (1.2)	N=852 98 (11.5)	N=799 15 (1.9)
Hombres, n (%)	N=1357 46 (3.4)	N=1343 3 (0.2)	N=1174 58 (4.9)	N=1157 4 (0.3)

EMDAC Background document. Available at:  
<http://www.fda.gov/downloads/advisorycommittees/committees/meetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucom378079.pdf>  
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## Canagliflozina – Infecciones Urinarias y Genitales

Incidencia de Infecciones Urinarias y Genitales (DS1)

	Placebo	Canagliflozina 100 mg	Canagliflozina 300 mg
Infecciones Genitales – Hombres	0.6%	4.2%	3.7%
Infecciones Genitales - Mujeres	3.2%	10.4%	11.4%
Infecciones Urinarias	4.0%	5.9%	4.3%

1. Keon H. Canagliflozina: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting January 10, 2013.  
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm362231.htm>. Accesado Agosto 2, 2014.

2. FDA Briefing Information for the January 10, 2013 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)  
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm334549.htm>. Accesado Agosto 2, 2014.

## Empagliflozina – Infecciones Urinarias y Genitales

Incidencia de Infecciones Urinarias y Genitales

	Placebo	Empagliflozina 10 mg	Empagliflozina 25 mg
Infecciones Genitales – Hombres	0.4%	3.1%	1.6%
Infecciones Genitales - Mujeres	1.5%	5.4%	6.4%
Infecciones Urinarias	7.6%	9.3%	7.6%

Jardiance Prescribing Information, 2014.  
EFFICACY AND SAFETY OF SGLT2 INHIBITORS Riser Taylor and Harris PHARMACOTHERAPY Volume \*\*, Number \*\*, 2013  
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## Riesgo de DKA por reportes de FDA

SGLT2 inhibitors	Risk analysis	DPP4 inhibitors (sitagliptin and saxagliptin)
259 (192)	Reports of acidosis (ketoacidosis)	477(71)
\$1.5 billion	Total Sales (Approval – May, 2015)	\$38 billion
173	Risk (Reports per billion Dollars of Sales)	13
345,000	Estimated Patient Years (Extrapolated from sales)	8,740,000
0.75 (0.55)	Reports per est. Thousand Patient Years	0.055 (0.008)

Blau JE. Diab Metab Res Rev. 2017. Online Jul 24.

## Dinamarca 1995-2014

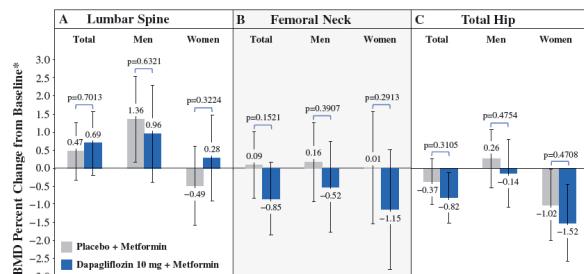
- Se excluyó a menores de 30 años
- 415670 pacientes con 4045 episodios de DKA (primer evento)
- Cetoacidosis:
  - Drogas no insulina: 1.3 (1.2-1.5)
  - Insulina monoterapia 6.0 (5.3-6.8)
  - Insulina + orales: 3.0 (2.7-3.4)
  - iSGLT-2 monoterapia: 0
  - iSGLT-2 combinación: 1.6 (0.7-3.5)
- De 1000 pacientes catalogados como DM-2, 1 tendrá un ingreso por DKA por año

Jensen ML. Diabetes Care. 2017;40(5):e57

Factores de riesgo: AEs de volumen intravascular reducido  
Grupo de datos amplio del período principal

eGFR (mL/min/1.73m <sup>2</sup> )	Sin CANA % (n/N)	CANA 100 mg % (n/N)	CANA 300 mg % (n/N)
<60	2.8 (12/436)	5.0 (19/382)	8.1 (33/405)
60 a <90	1.5 (26/1788)	2.4 (40/1686)	2.9 (48/1680)
≥90	1.2 (12/1035)	1.3 (13/1021)	2.4 (24/999)
Edad (años)			
<75	1.5 (46/3107)	2.2 (64/2929)	3.1 (90/2913)
≥75	2.6 (4/155)	4.9 (8/163)	8.7 (15/172)
Uso de diuréticos de asa			
No	1.2 (37/3006)	2.3 (65/2876)	2.9 (83/2835)
Sí	5.1 (13/256)	3.2 (7/216)	8.8 (22/250)
Edad <75, sin diuréticos de asa y con una eGFR ≥60 mL/min/1.73m <sup>2</sup>	1.1 (29/2604)	1.8 (45/2491)	2.2 (54/2434)

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm078079.pdf>  
EndoDrChen.com



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/ucm078079.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 = per100 patient-years

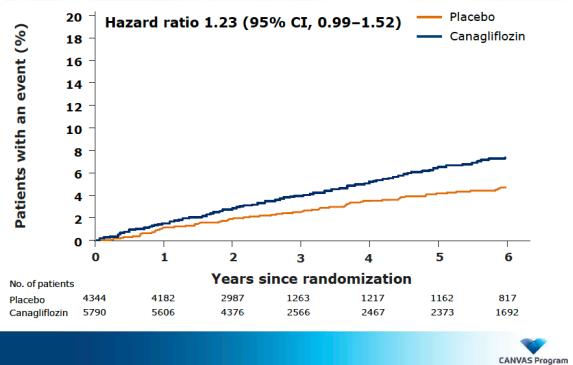
Patients treated with ≥1 dose of study drug

\*Based on standard MedDRA queries

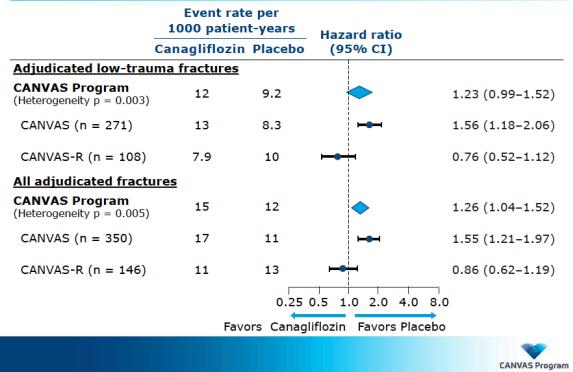
†Based on 62 MedDRA preferred terms

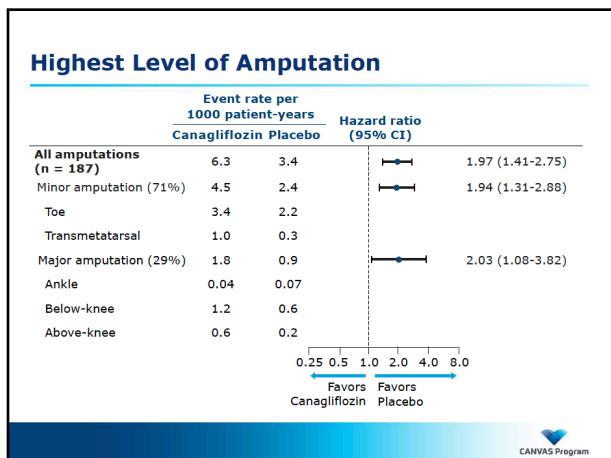
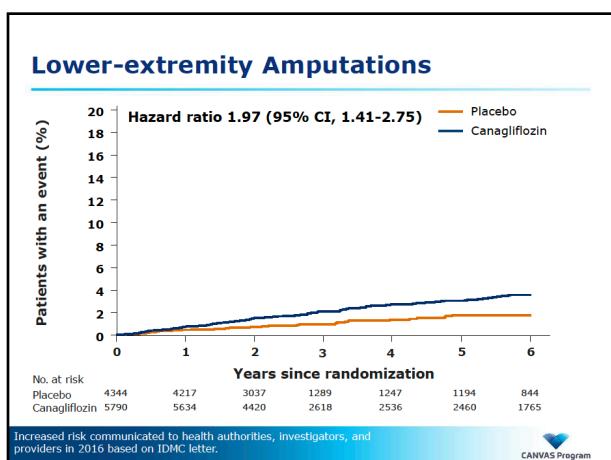
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## Low-trauma Fracture



## Fractures





**Amputation Risk Factors - Multivariate Analysis**

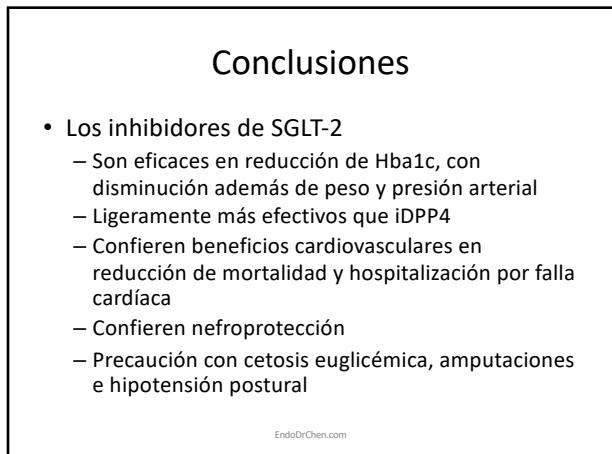
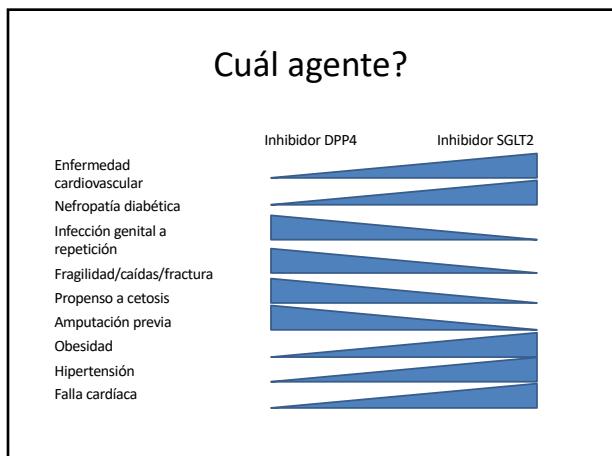
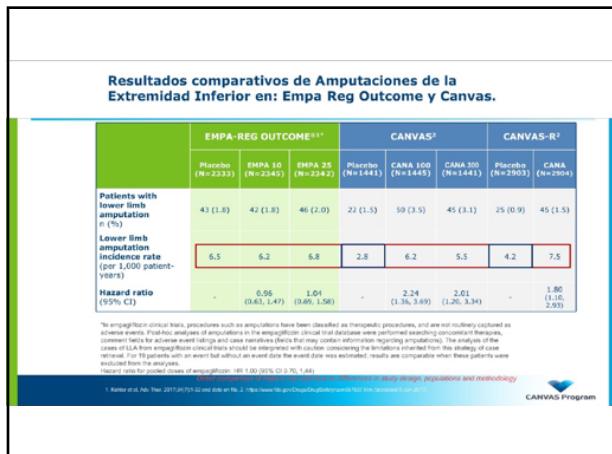
Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- 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



**PREGUNTAS...**

Puede descargar la  
presentación en:



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