Inhibidores de SGLT2 en el tratamiento de DM-2

Dr. Chih Hao Chen Ku, FACE

Servicio de Endocrinología, Hospital San Juan de Dios

Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica

Sistema de Estudios de Postgrado, Universidad de Costa Rica

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

Mi experiencia con los inhibidores de SGLT-2..

a sido buena

ha sido neutra

he tenido muy poca experiencia

los conozco pero no los he usado

no conozco la terapéutica

Start the presentation to activate live content

If you see this message in presentation mode, install the add-in or get help at PollEv.com/app

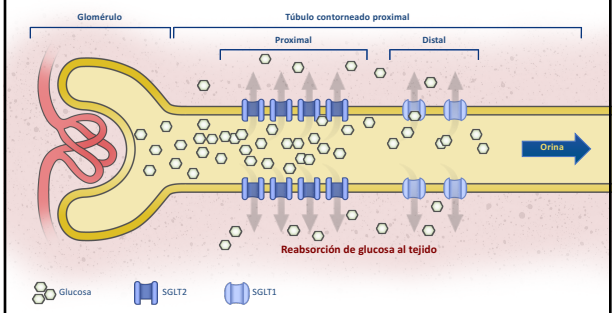
Poll Everywhere

Agenda

- Fisiología renal del manejo de glucosa
- Efectos farmacológicos de inhibidores de SGLT2
- Efectos cardiovasculares
- Efectos en nefropatía diabética
- Efectos adversos
- Cómo se usan?
- Papel en las guías de tratamiento

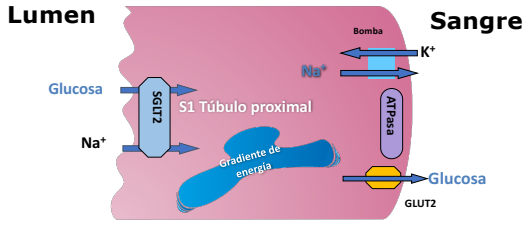
EndoDrChen.com

Reabsorción de glucosa en una persona no diabética (glucosa plasmática <180 mg/dL o <10 mmol/L)



Adaptado con permiso de Rothenberg PL et al. SGLT = cotransportador ligado a sodio-glucosa. Rothenberg PL et al. Poster presentado en: 46º. Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia

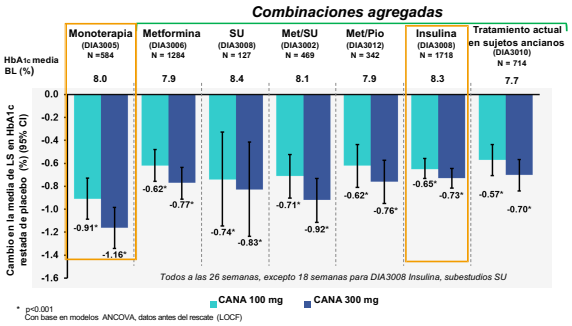
SGLT2 permite la reabsorción de glucosa renal



Adaptado de de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012; 14:1-5.

EndoDrChen.com

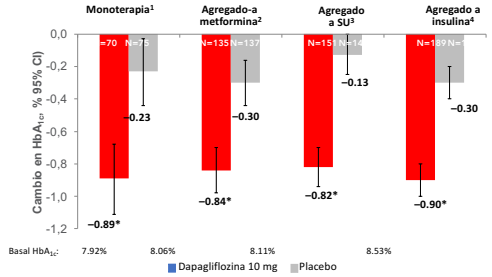
Cambio en HbA1c desde la basal
Estudios de Fase 3 controlados con placebo



* p<0.001
Con base en modelos ANCOVA, datos antes del rescate (LOCF)

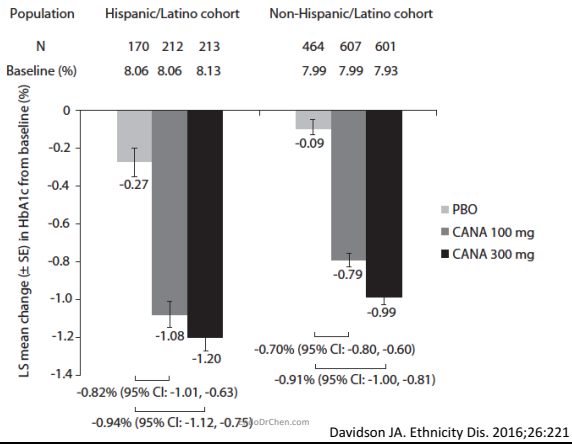
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs

Reducción consistente en la HbA_{1c} en la Semana 24 en diferentes estudios



Los estudios considerados no son estudios "head to head", de forma que no es possible realizar comparaciones directas. *Estadísticamente significativo versus placebo utilizando la corrección de Dunnett's; la media ajustada desde el nivel basal mediante ANCOVA, excluyendo la excluding data after rescue (LOCF). ANCOVA, análisis de covarianza; LOCF, la última observación prospective realizada.

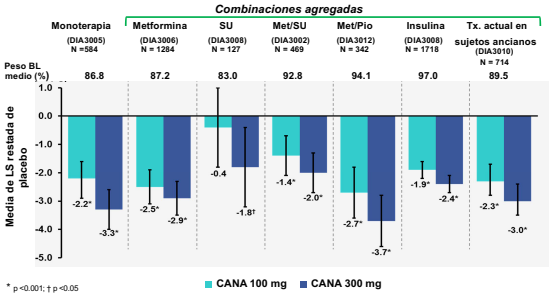
1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. Wilding J, *et al. Diabetes* 2010;**59**(Suppl 1):0078-OR.



Davidson JA. Ethnicity Dis. 2016;26:221

Cambio porcentual en el peso corporal desde la basal

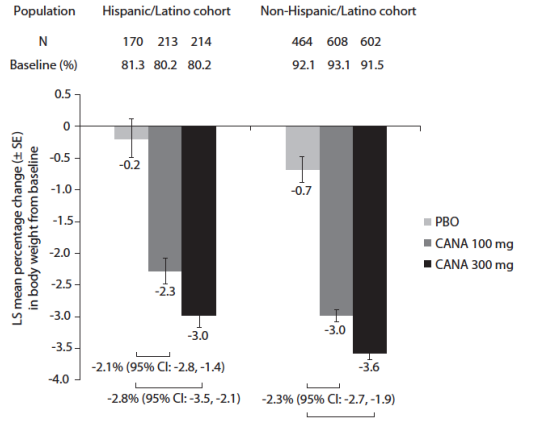
Estudios de Fase 3 controlados con placebo



* p <0.001; † p <0.05

Con base en modelos ANCOVA, datos previos al rescate (LOCF)

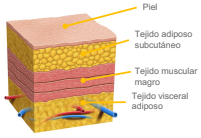
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs



EndoDrChen.com Davidson JA. Ethnicity Dis. 2016;26:221

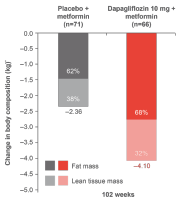
Dapagliflozina beneficia a su paciente con la pérdida de peso a partir de la masa de grasa[1]

- Las reducciones totales de peso corporal fueron más rápidas con Dapagliflozina durante las primeras semanas, seguido de una reducción más gradual a la semana 24.[1]
- El análisis exploratorio demostró que Dapagliflozina redujo la masa grasa en lugar de la pérdida de tejido magro o líquido, de manera sostenida a lo largo de 2 años[1]



El aumento de la **masa grasa** se asocia con disfunción metabólica[2]

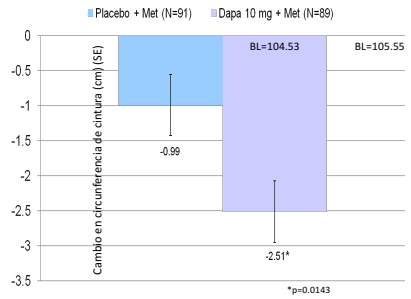
El aumento del tejido magro es protector[2]



- Forxiga y Xigduo® no están indicados para el tratamiento de la pérdida de peso. El aumento de peso fue un criterio de valoración secundario.

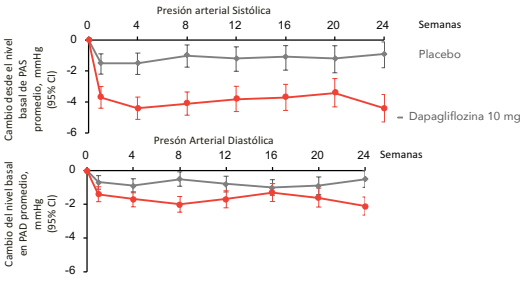
1. Bristol-Myers Squibb/AstraZeneca Data Sheet DS-00-11 Clear PI v1.0. Marzo 2014. Disponible en: www.medicines.org.uk/EMC/medicine/28148/SPC/Forxiga+10mg+film-coated+tablets/#PHARMACOLOGICAL+PROPERTIES. Último acceso: 10/04/2014.

Cambio medio ajustado del perímetro abdominal a la semana 24 (cm)



Bolinder et al. J Clin Endocrinol Metab 2012 ; 97: 1020-1031 EndoDrChen.com

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

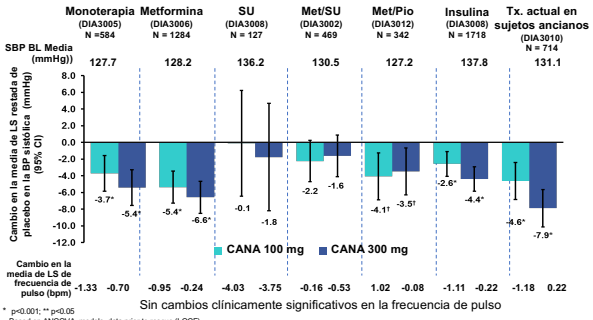


Número de pacientes							
Dapagliflozina 10 mg	1014	1086	1070	963	975	871	949
Placebo	1217	1281	1247	1116	1137	1021	1096

Sjöström CD. ESC 2012. OP 3972. EndoDrChen.com

Cambio en la presión arterial sistólica desde la basal

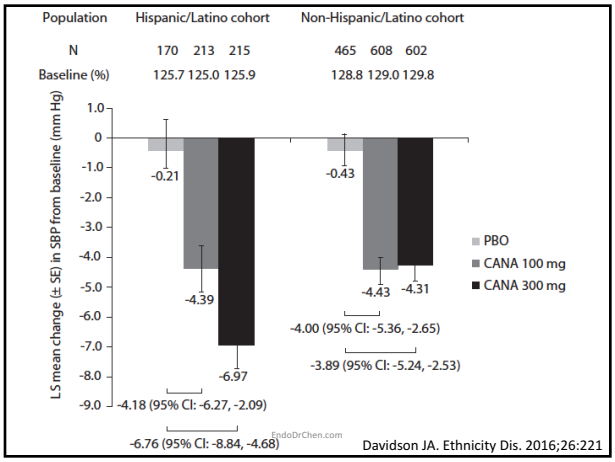
Estudios de Fase 3 controlados con placebo



Sin cambios clínicamente significativos en la frecuencia de pulso

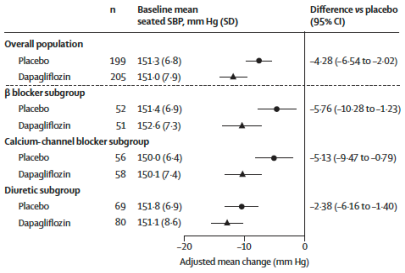
* p<0.001; ** p<0.05
Based on ANCOVA models, data prior to rescue (LOCF)

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs



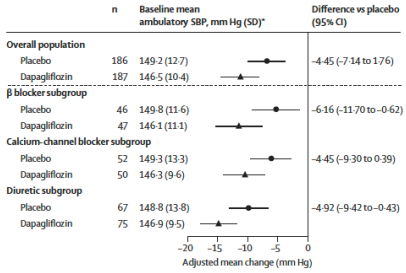
Davidson JA. Ethnicity Dis. 2016;26:221

Efecto en PAS



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

Efecto en PAS en MAPA

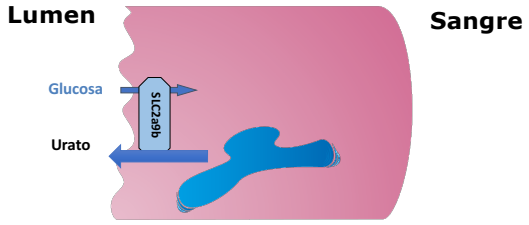


Weber MA. Lancet Diab Endocrinol. 2016;4:211

Efecto uricosúrico

EndoDrChen.com

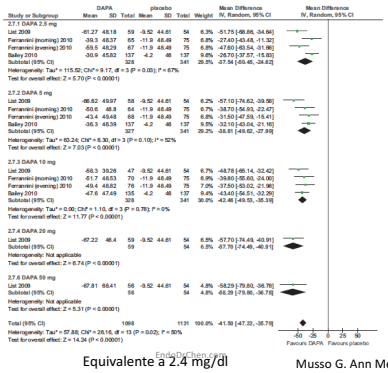
Mecanismo uricosúrico



EndoDrChen.com

Musso G. Ann Med. 2012;44:375

Dapagliflozina y ácido úrico



Equivalente a 2.4 mg/dl

EndoDrChen.com

Musso G. Ann Med. 2012;44:375

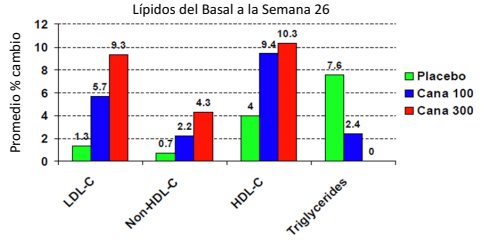
Efectos en lípidos

EndoDrChen.com

Canagliflozina: Cambios en Lípidos

Set de Datos de Estudios Controlados con Placebo de 26 Semanas

Cambio Porcentual del Promedio de CM en los Parámetros de Lípidos del Basal a la Semana 26



Cana = Canagliflozina; CM = Cuadrados mínimos; HDL-C = Colesterol HDL; LDL-C = Colesterol LDL; LS = Least squares ; Non-HDL-C = Colesterol No-HDL; TG= Triglicéridos

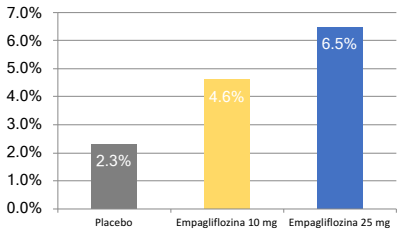
1. Kwon H, Canagliflozin: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting. January 10, 2013. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm Accesado Agosto 2, 2014
2. William T Cefalu. Lancet 2013

EndoDrChen.com

Empagliflozina – Cambios en Lípidos

- **Incrementos de LDL-C relacionados a la dosis se observaron en pacientes tratados con Empagliflozina**

Porcentaje de Cambio vs. Valores Basales*



*El rango de valores basales promedio de LDL-C era entre 90.3 y 90.6 mg/dL entre los grupos de tratamiento

1. Jardiance Prescribing information, 2014

EndoDrChen.com

Quién debe ser hoy el agente de segunda línea?

EndoDrChen.com

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/m2
- Toma además atorvastatina 10 mg HS y amlodipina 5 mg por día

EndoDrChen.com

ál es el paso a seguir? Cuál agente agregaría

ulina basal (NPH, glargina, degludec, detemir)

Sulfonilureas (glibenclamida, glimepiride, glicazida)

inhibidor de DPP-4 (sitagliptina, vildagliptina, linagliptina)

inhibidor de SGLT-2 (cangliflozina, dapagliflozina, empagliflozinma)

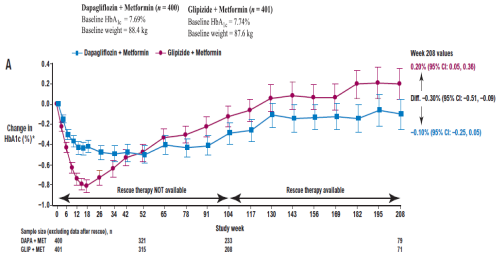
Start the presentation to activate live content

If you see this message in presentation mode, install the add-in or get help at PollEv.com/app

Poll Everywhere

EndoDrChen.com

Durabilidad del efecto de reducción de HbA1c

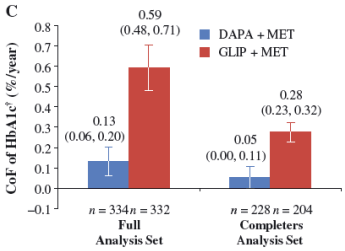


Corte Temporal: (52 wks): (104 wks):
Diferencia Dapa vs Glip 0.0% (95% CI -0.11 to 0.11) −0.18% (95% CI; −0.33, −0.03)

*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model

EndoDrChen.com

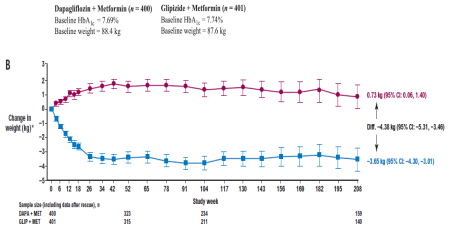
Coeficiente de variación de Hba1c



Nauck MA. Diab Obes Metab. 2014;16:1111

EndoDrChen.com

Durabilidad del efecto de reducción de peso



A 4 años

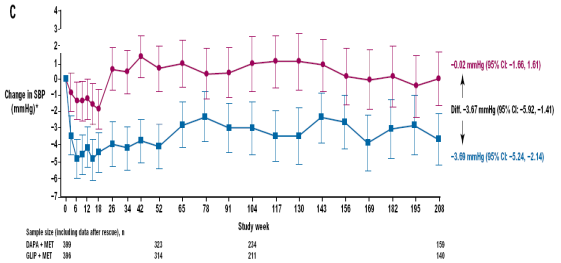
4,5 Kg menos

Corte temporal: 52 wk: 104 wks
Diferencia Dapa vs Glip −4.65 kg (95% CI -5.14 to -4.17) −5.06 kg (95% CI; −5.73, −4.4)

*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model

EndoDrChen.com

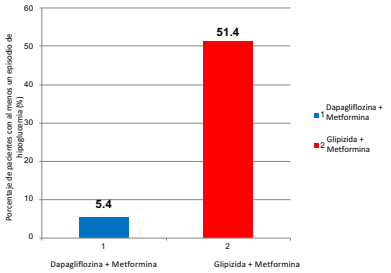
Durabilidad del efecto de reducción de PAS



*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model
DAPA, dapagliflozin; GLIP, glipizide; MET, metformin; SBP, systolic blood pressure

EndoDrChen.com

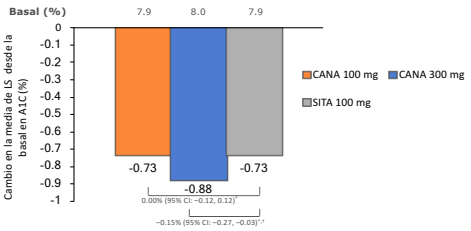
Hipoglicemias



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

EndoDrChen.com

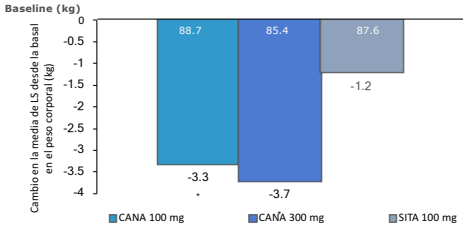
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Estudios comparativos de CANA
Semana 52: A1C (LOCF)



*No inferior con respecto a SITA (límite superior del 95% CI <0.3%).
†Superior vs. SITA (límite superior del 95% CI <0.0%).
A1C=hemoglobina glucosilada; CANA=canagliflozina; CI=intervalo de confianza; LOCF=última observación adelantada; LS=cuadrados mínimos; SITA=sitagliptina.

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

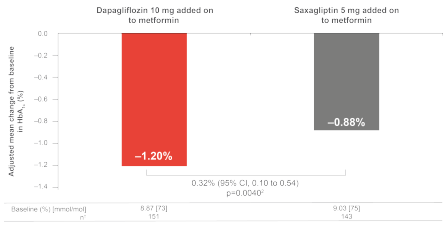
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Semana 52: Peso corporal (LOCF)



*P <0.001 vs. SITA.
CANA=canagliflozina; LOCF=última observación adelantada; LS=cuadrados mínimos; SITA=sitagliptina.

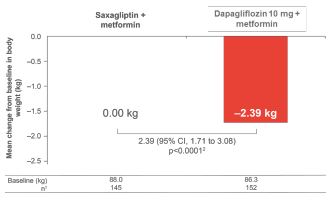
Lavalle-González FJ, et al. *Diabetologia*. 2013. doi:10.1007/s00125-013-3039-1.

Dapagliflozina + metformina* demostró reducciones importantes de la HbA_{1c} a las 24 semanas vs. iDPP4 + metformina*[1]



* Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual add-on of saxagliptin and dapagliflozin with either saxagliptin 5 mg or dapagliflozin 10 mg added on to metformin in patients with Type 2 diabetes poorly controlled (HbA1c ≥8% to ≤12%) on metformin. The primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks. The study met its primary endpoint. This is a retrospective post-hoc analysis.
*Metformin XR. †Number of randomised patients with non-missing baseline values and Week 24 values last observation carried forward.
CI, confidence interval; DPP4, dipeptidyl peptidase-4; XR, extended release.
1. Rosenstock J, *et al. Diabetes Care* 2014;**37**:1376–83. 2. Data on file 801453. AstraZeneca. September 2016.

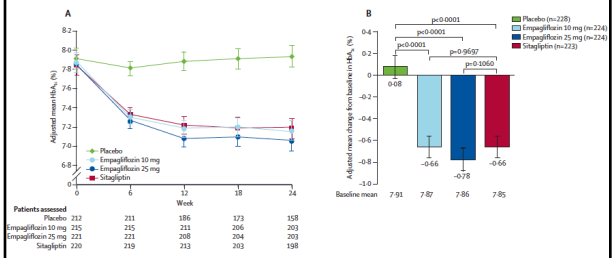
Dapagliflozina + metformina * demostró una mayor pérdida de peso a las 24 semanas vs. iDPP4 + metformina



* **Forxiga y XigduoXR no están indicados para el tratamiento de la pérdida de peso. El cambio de peso fue un criterio de valoración secundario.**

* Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual-add on of saxagliptin and dapagliflozin with either saxagliptin or dapagliflozin added alone in adults with Type 2 diabetes poorly controlled (HbA_{1c} ≥8% to ≤12%) on metformin. Primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks.
*Metformin XR. †Number of randomised patients with non-missing baseline values and Week 24 values last observation carried forward (LOCF).
This was a post-hoc analysis comparing dapagliflozin + metformin XR treatment group with the saxagliptin+metformin XR group.
CI, confidence interval; DPP4, dipeptidyl peptidase-4; XR, extended release.
1. Rosenstock J, *et al. Diabetes Care* 2015;**38**:376–82. 2. Data on file 801453. AstraZeneca. September 2016.

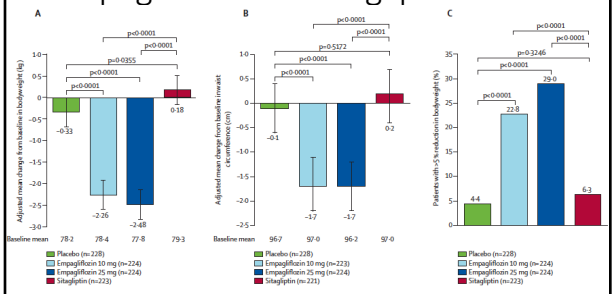
Empagliflozina vs sitagliptina



EndoDrChen.com

Roden M. Lancet Diab Endocrinol. 2013;1:208

Empagliflozina vs sitagliptina



EndoDrChen.com

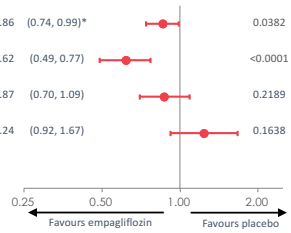
Roden M. Lancet Diab Endocrinol. 2013;1:208

Desenlaces cardiovasculares

EndoDrChen.com

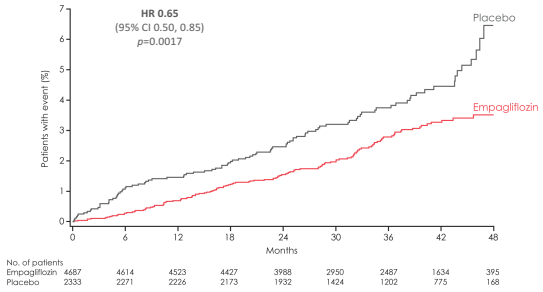
CV death, MI and stroke

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



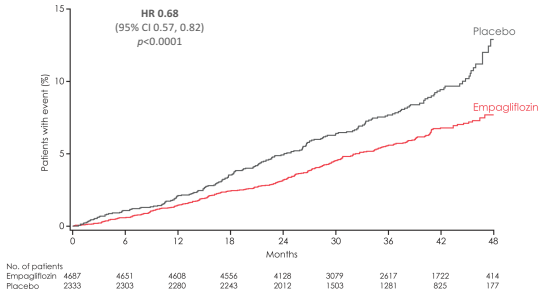
EndoDrChen.com

Hospitalisation for heart failure



EndoDrChen.com

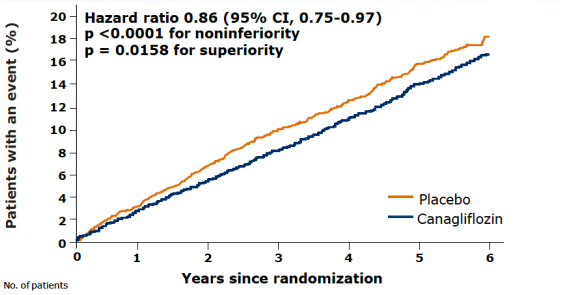
All-cause mortality



EndoDrChen.com

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



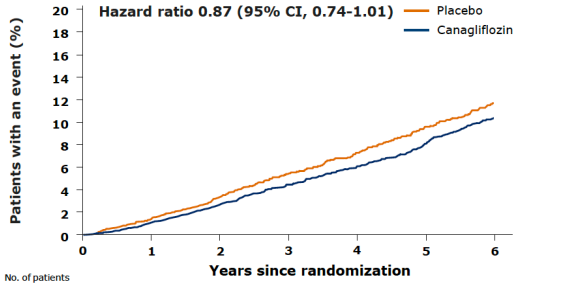
No. of patients

Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

CANVAS Program

All-Cause Mortality



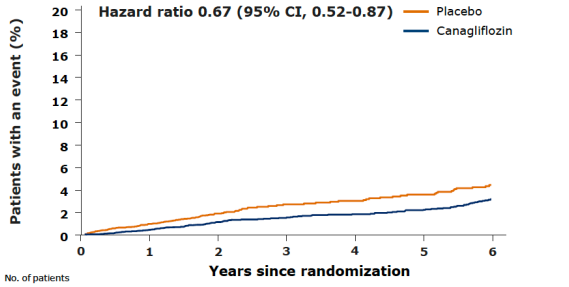
No. of patients

Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Intent-to-treat analysis

CANVAS Program

Hospitalization for Heart Failure



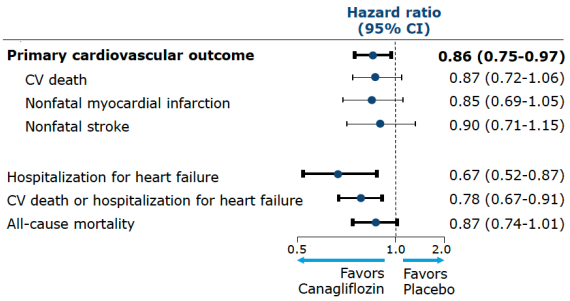
No. of patients

Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

Intent-to-treat analysis

CANVAS Program

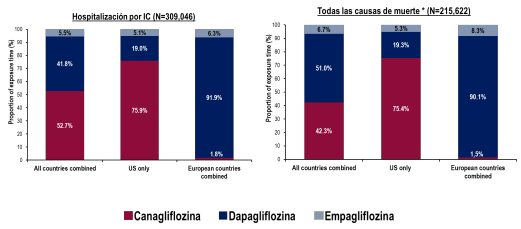
Summary



Intent-to-treat analysis

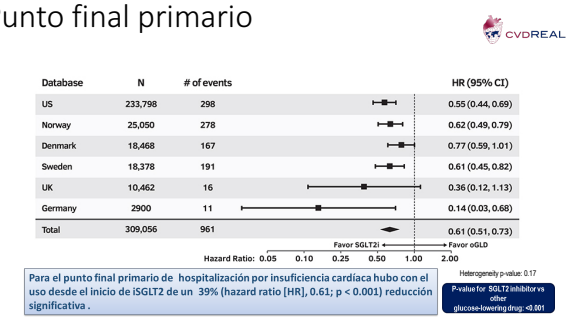
CANVAS Program

Contribución de los iSGLT2



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

Hospitalización por Insuficiencia Cardiaca Punto final primario



Para el punto final primario de hospitalización por insuficiencia cardíaca hubo con el uso desde el inicio de iSGLT2 de un 39% (hazard ratio [HR], 0.61; p < 0.001) reducción significativa .

Todas las causas de muerte – Punto final secundario

CVDREAL

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)

Favor SGLT2i ← → Favor oGLD

Hazard Ratio: 0.25 0.50 1.00 2.00

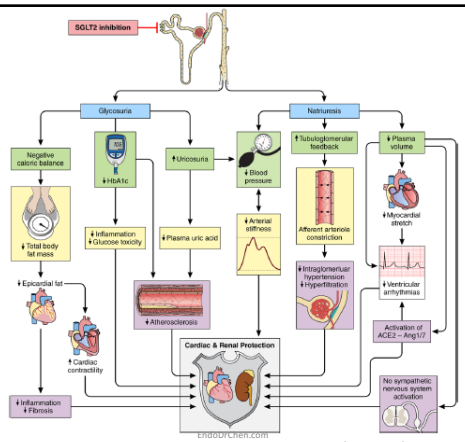
Heterogeneity p-value: 0.09

P-value for SGLT2i vs other glucose-lowering drug: <0.001

Punto final secundario de muerte por cualquier causa, los iSGLT2 también fueron asociados con una incidencia de 51% menos de muerte por cualquier causa (HR, 0.49; p < 0.001)

Cómo se explica el beneficio cardiovascular?

EndoDrChen.com



Heerspink H. Circulation. 2016;134:752

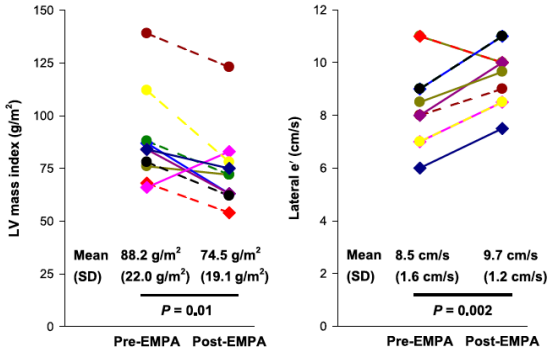


Figure 1—LV mass index and lateral e′ at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e′, early lateral annular tissue Doppler velocity; EMPA, empagliflozin.

Verma S. Diabetes Care. 2016. online sep 27

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

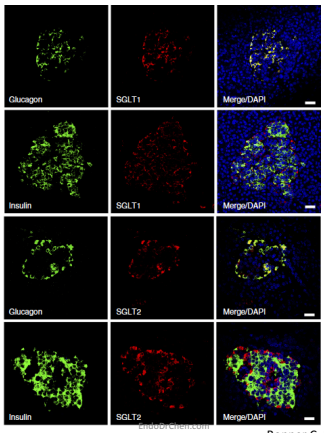
[05-15-2015]

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.

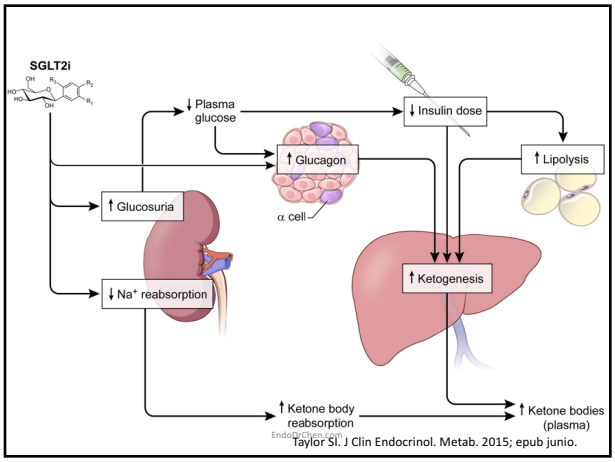
Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first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

EndoDrChen.com



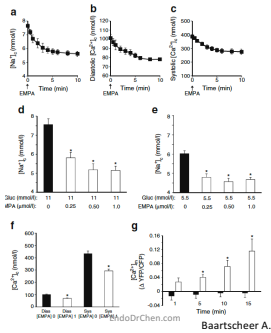
EndoDrChen.com

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

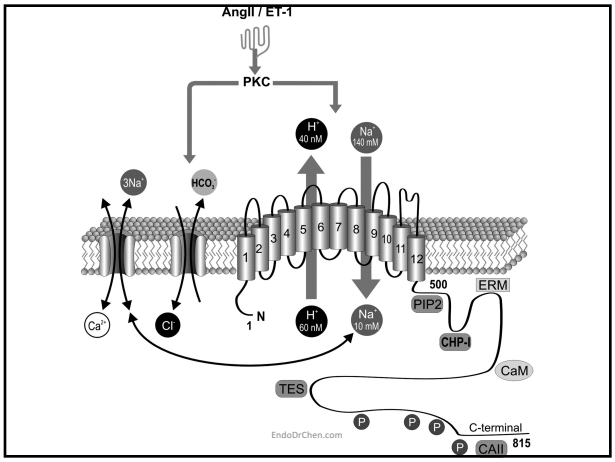


Taylor SI. J Clin Endocrinol. Metab. 2015; epub junio.

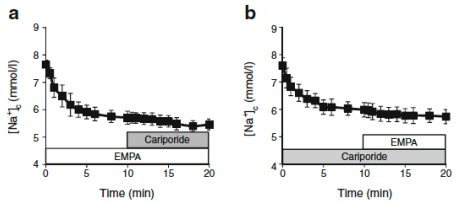
iSGLT-2 y Na^+ y Ca^{+2} intracelular



Baartscheer A. Diabetologia. 2016; online oct 16.



Efecto en Na^+-H^+



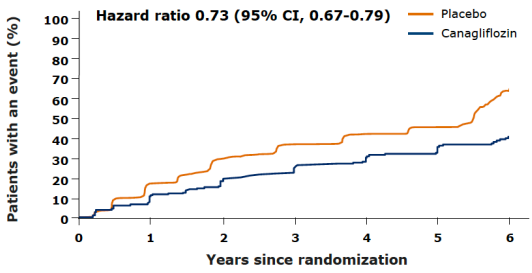
EndoDrChen.com

Baartscheer A. Diabetologia. 2016; online oct 16.

Riñón: efecto nefroprotector?

EndoDrChen.com

Progression of Albuminuria



No. of patients

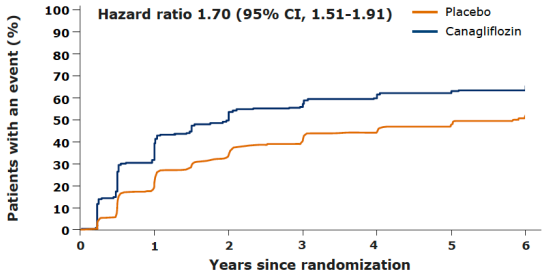
Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

Intent-to-treat analysis

EndoDrChen.com

CANVAS Program

Regression of Albuminuria

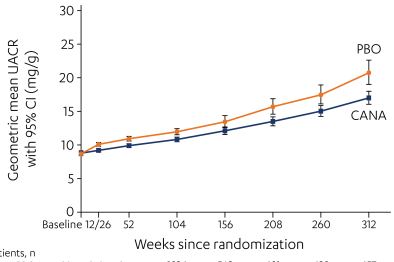


No. of patients							
Placebo	1257	913	426	163	144	123	59
Canagliflozin	1679	1009	518	276	227	198	112

Intent-to-treat analysis

CANVAS Program

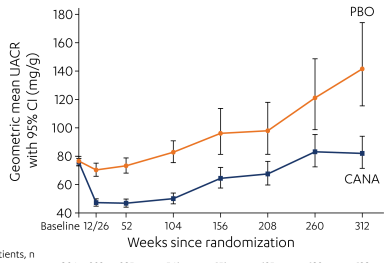
Effects of CANA on UACR in Patients With Normoalbuminuria at Baseline



Patients, n								
PBO	2846	2784	2645	1834	562	481	438	457
CANA	3844	3730	3571	2540	1249	1151	1064	1149

EndoDrChen.com

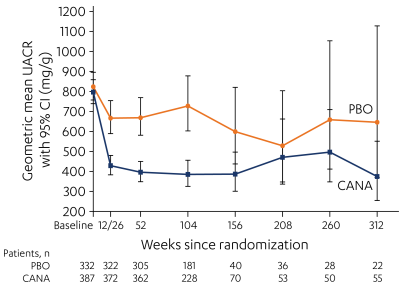
Effects of CANA on UACR in Patients With Microalbuminuria at Baseline



Patients, n								
PBO	906	883	825	541	151	135	128	139
CANA	1269	1239	1170	797	370	337	294	330

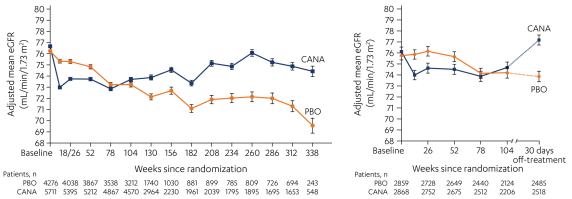
EndoDrChen.com

Effects of CANA on UACR in Patients With Macroalbuminuria at Baseline



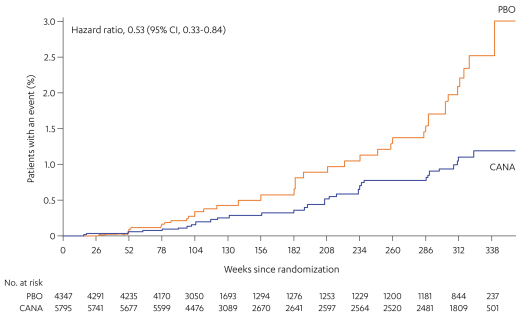
EndoDrChen.com

Effects of CANA on eGFR Over Time in the CANVAS Program (left) and Effects of CANA on eGFR Over Time and After a Median of 30 Days Off-treatment in CANVAS-R (right)



EndoDrChen.com

Effects of CANA on the Composite of dSCr, ESKD, or Renal Death



EndoDrChen.com

Renal Outcomes Summary

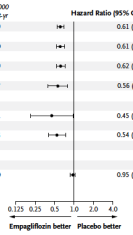
- Canagliflozin compared to placebo
  - Induced sustained lowering of albuminuria
  - Prevented progression in albuminuria
  - Induced regression in albuminuria
  - Reduced renal function loss events
- Conclusion
  - These data suggest a potential renoprotective effect of canagliflozin treatment in patients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

EndoDrChen.com

CANVAS Program

EMPAREG - renal

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.53–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

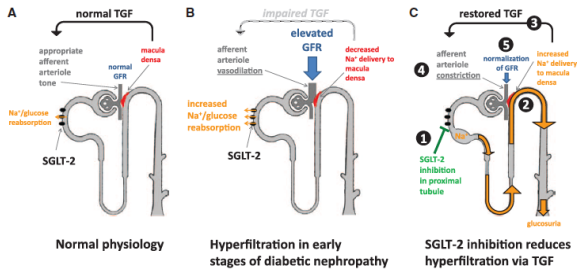


EndoDrChen.com

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.



Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

EndoDrChen.com

Cherney DZI. Circulation. 2014;129:587

Eventos adversos

EndoDrChen.com

Dapagliflozina - Infecciones Micóticas Genitales

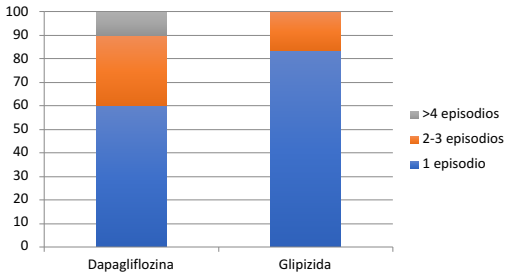
- Las infecciones genitales se reportaron más frecuentemente con dapagliflozina vs. placebo

	Estudios controlados con Placebo (corto plazo)		Estudios controlados con Placebo (corto y largo plazo)	
	Dapagliflozina 10 mg	Placebo	Dapagliflozina 10 mg	Placebo
Iinfección 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/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

EndoDrChen.com

Infecciones genitales: número de episodios



Nauck MA. Diab Obes Metab. 2014;16:1111

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/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

EndoDrChen.com

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. Kwon H. Canagliflozin: 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/ucm336233.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

EndoDrChen.com

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 SGLT-2 INHIBITORS Riser Taylor and HarrisPHARMACOTHERAPY Volume **, Number **, 2013

EndoDrChen.com

Hipotensión postural

EndoDrChen.com

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

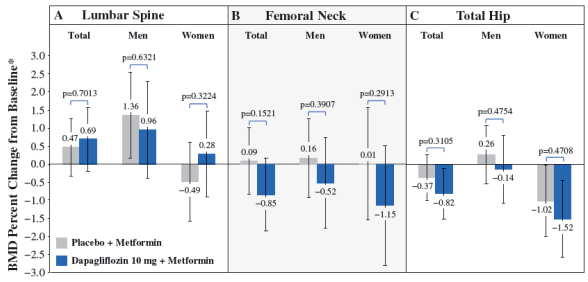
eGFR (mL/min/1.73m^2)	Sin CANA % (n/N)	CANA 100 mg % (n/N)	CANA 300 mg % (n/N)
<60	2.8 (12/436)	5.0 (19/382)	**8.1 (33/405)**
60 a <90	1.5 (26/1788)	2.4 (40/1686)	2.9 (48/1680)
≥90	1.2 (12/1035)	1.3 (13/1021)	2.4 (24/999)
Edad (años)			
<75	1.5 (46/3107)	2.2 (64/2929)	3.1 (90/2913)
≥75	2.6 (4/155)	4.9 (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^2	1.1 (29/2604)	1.8 (45/2491)	2.2 (54/2434)

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs

EndoDrChen.com

Seguridad ósea

EndoDrChen.com



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

EndoDrChen.com

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/ucm378079.pdf;

EndoDrChen.com

Other adverse events (2)

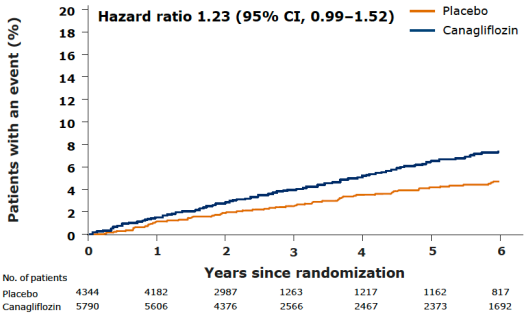
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Hepatic injury*	108 (4.6%)	1.91	80 (3.4%)	1.35	88 (3.8%)	1.48
Hypersensitivity*	197 (8.4%)	3.59	158 (6.7%)	2.75	181 (7.7%)	3.14
Bone fractures†	91 (3.9%)	1.61	92 (3.9%)	1.57	87 (3.7%)	1.46

Rate = per100 patient-years

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

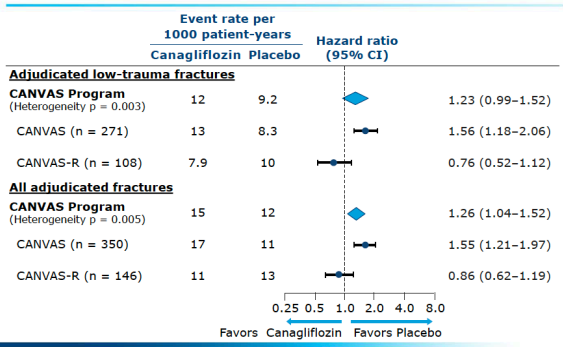
EndoDrChen.com

Low-trauma Fracture



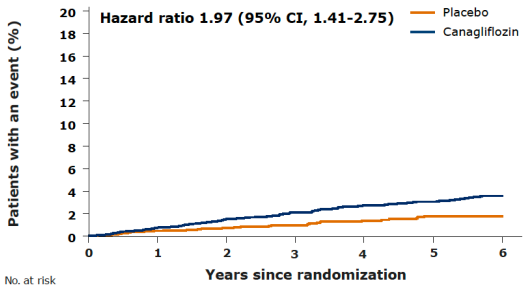
CANVAS Program

Fractures



CANVAS Program

Lower-extremity Amputations



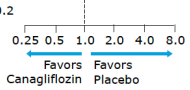
No. at risk							
Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozin	5790	5634	4420	2618	2536	2460	1765

Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

CANVAS Program

Highest Level of Amputation

	Event rate per 1000 patient-years: Canagliflozin	Event rate per 1000 patient-years: Placebo	Hazard ratio (95% CI)
All amputations (n = 187)	6.3	3.4	1.97 (1.41-2.75)
Minor amputation (71%)	4.5	2.4	1.94 (1.31-2.88)
Toe	3.4	2.2	
Transmetatarsal	1.0	0.3	
Major amputation (29%)	1.8	0.9	2.03 (1.08-3.82)
Ankle	0.04	0.07	
Below-knee	1.2	0.6	
Above-knee	0.6	0.2	



CANVAS Program

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

Resultados comparativos de Amputaciones de la Extremidad Inferior en: Empa Reg Outcome y Canvas.

	EMPA-REG OUTCOME[1,1*]			CANVAS[2]			CANVAS-R[2]	
	Placebo (N=2333)	EMPA 10 (N=2345)	EMPA 25 (N=2342)	Placebo (N=1441)	CANA 100 (N=1445)	CANA 300 (N=1441)	Placebo (N=2903)	CANA (N=2904)
Patients with lower limb amputation n (%)	43 (1.8)	42 (1.8)	46 (2.0)	22 (1.5)	50 (3.5)	45 (3.1)	25 (0.9)	45 (1.5)
Lower limb amputation incidence rate (per 1,000 patient-years)	6.5	6.2	6.8	2.8	6.2	5.5	4.2	7.5
Hazard ratio (95% CI)	-	0.96 (0.63, 1.47)	1.04 (0.69, 1.58)	-	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	-	1.80 (1.10, 2.93)

*In empagliflozin clinical trials, procedures such as amputations have been classified as therapeutic procedures, and are not routinely captured as adverse events. Post-hoc analyses of amputations in the empagliflozin clinical trial database were performed searching concomitant therapies, comment fields for adverse event listings and case narratives (fields that may contain information regarding amputations). The analysis of the cases of LLA from empagliflozin clinical trials should be interpreted with caution, considering the limitations inherited from this strategy of case retrieval. For 19 patients with an event but without an event date the event date was estimated; results are comparable when these patients were excluded from the analyses.
Hazard ratio for pooled doses of empagliflozin: HR 1.00 (95% CI 0.70, 1.44)

Differences in study design, populations and methodology

1. Kanter et al. Adv Ther. 2017;34(7):1-32 and data on file. 2. https://www.fda.gov/Drugs/DrugSafety/ucm556270.htm (accessed 6 Jun 2017)

CANVAS Program

EndoDrChen.com

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

EndoDrChen.com

Cambios en (A) HbA1c, (B) peso corporal y (C) BP sistólica para la población general con CKD en etapa 3 (LOCF)*

A

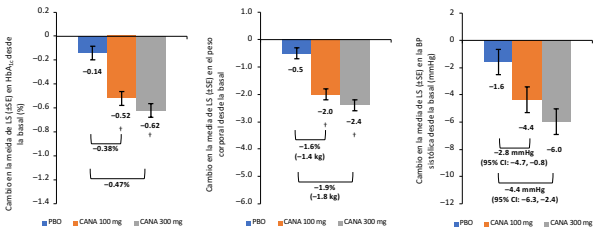
HbA_{1c}			
n	356	326	354
Basal (%)	8.0	8.1	8.1

B

Peso corporal			
n	376	335	360
Basal (kg)	92.4	90.3	90.1
Cambio en la media de LS (kg)	−0.5	−1.9	−2.3

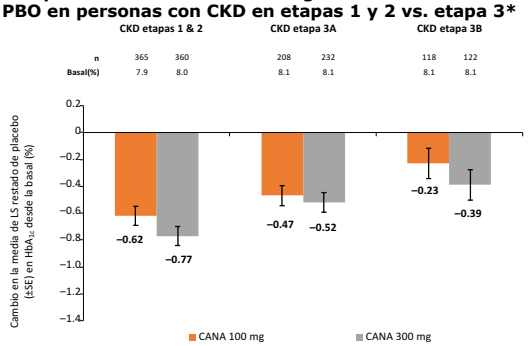
C

BP sistólica			
n	377	335	360
Basal (mmHg)	135.2	136.1	134.6



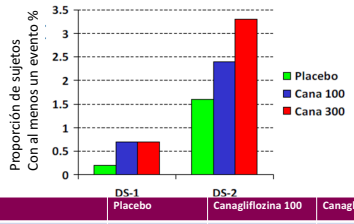
BP, presión arterial; CKD, enfermedad renal crónica; LOCF, última observación adelantada; LS, cuadrados mínimos; SE, error estándar, PBO, placebo; CANA, canagliflozina.
*Comparación estadística para cambios en la BP sistólica con CANA 100 mg y 300 mg vs. PBO no realizada (no pre-especificada).
†P <0.001 vs PBO.

Comparación del efecto de canagliflozina restado de PBO en personas con CKD en etapas 1 y 2 vs. etapa 3*



PBO, placebo; CKD, enfermedad renal crónica; LS, cuadrados mínimos; SE, error estándar; CANA, canagliflozina.
*Datos tomados de la Tabla Suplementaria 3 y del estudio de tratamiento agregado a metformina en sujetos normales.

Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



	Placebo	Canagliflozina 100	Canagliflozina 300
DS-1 Estudios Controlados con Placebo a 26 semanas	0.2% (N=646)	0.7% (N=833)	0.7% (N=834)
DS-2 Pacientes con Insuficiencia Renal Moderada	1.6% (N=382)	2.4% (N=338)	3.3% (N=365)

1. Kwon H. Canagliflozin: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting January 10, 2013. http://www.fda.gov/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm Accesado Agosto 2, 2014

EndoDrChen.com

Cómo manejamos las desventajas?

EndoDrChen.com

Manejo de desventajas

- ITU: aumento mínimo de riesgo, evitar usarlo en pacientes con ITU a repetición
- Infecciones genitales: extremar medidas de higiene, especialmente en hombres sin circuncisión
- Fracturas e hipotensión postural: evitar en adultos mayores que hacen ortostatismo o usan diuréticos de asa

EndoDrChen.com

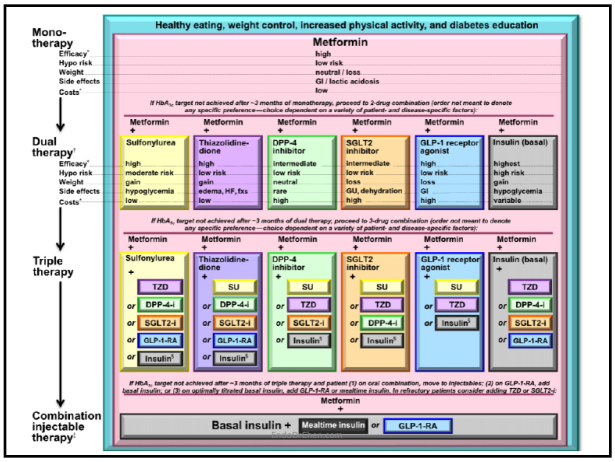
Manejo de desventajas

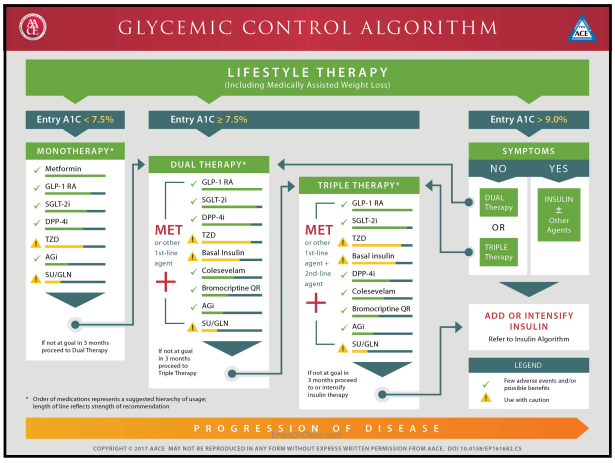
- Cetosis euglicémica
  - Evitar uso off label en DM-1 (dosis bajas?)
  - Probablemente suspensión en caso de enfermedad aguda o perioperatorio
  - Evitar consumo excesivo de alcohol

EndoDrChen.com

Qué indican las guías?

EndoDrChen.com





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

EndoDrChen.com

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

EndoDrChen.com

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com

EndoDrChen.com