Beneficios en reducción de riesgo cardiovascular con inhibidores de SGLT-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

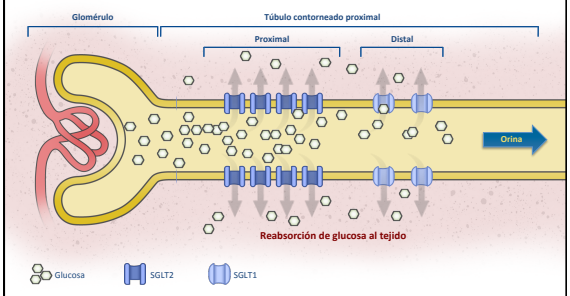
Conflictos de interés

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

Agenda

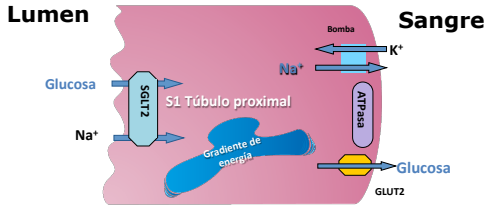
- Mecanismo de acción y efectos dependientes de su mecanismo
- Efecto sobre evento cardiovascular
  - Marcadores de riesgo
  - Puntos finales de duro
  - Cetosis: cambio de paradigma?
- Alertas existentes

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



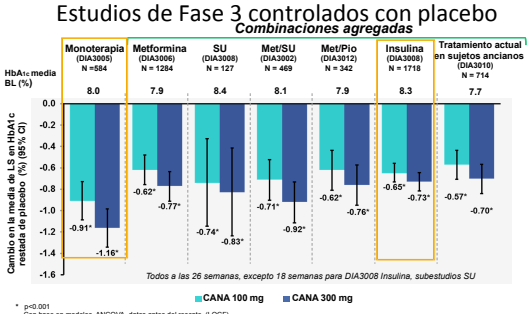
Adaptado con permiso de Rothenberg PL et al. SGLT = cotransportador ligado a sodio-glucosa.
Rothenberg PL et al. Poster presentado en: 46ª. Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia

SGLT2 permite la reabsorción de glucosa renal



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

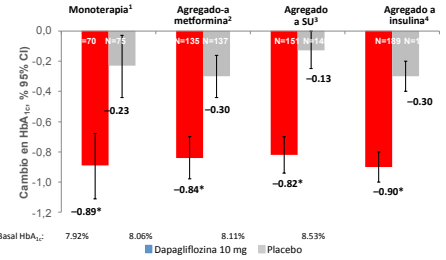
Cambio en HbA1c desde la basal
Estudios de Fase 3 controlados con placebo



* 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

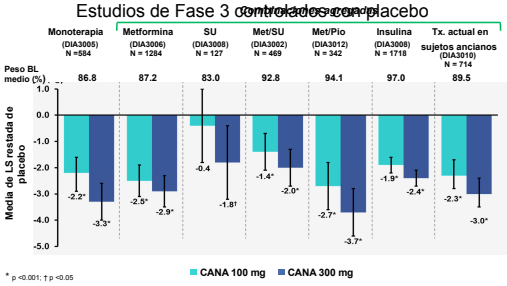


Los estudios considerados no son estudios "head to head", de forma que no es posible realizar comparaciones directas. *Estadísticamente significativo versus placebo utilizando la corrección de Dunnett's; la media ajustada desde el nivel basal mediante ANCOVA, excluyendo la excluding data after rescue (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. Diabetologia* 2010;**59**(Suppl 1):0078-OR.

Cambio porcentual en el peso corporal desde la basal

Estudios de Fase 3 controlados con placebo

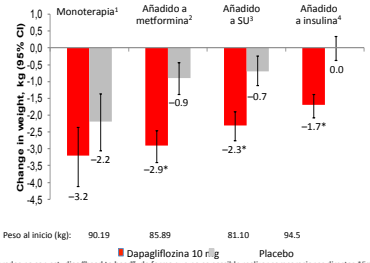


* p <0.001; † p <0.05

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

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

Reducción significativa de peso a la semana 24



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1. Ferrannini E, et al. Diabetes Care 2010;33:2217–24
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3. Strojek K, et al. Diabetes Obes Metab 2011;13:928–38
4. Wilding JPH, et al. Ann Intern Med 2012;156:405–15.

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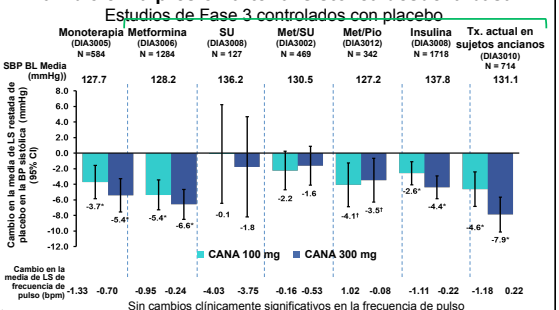
Cambio en la presión arterial sistólica desde la basal

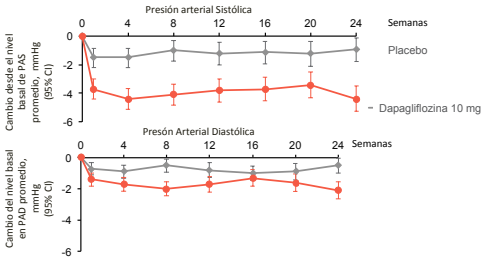
Estudios de Fase 3 controlados con placebo



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

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

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

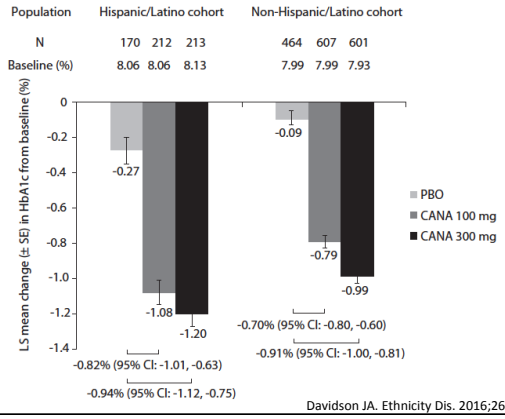
Sjöström CD. ESC 2012. OP 3972. EndoDrChen.com

CÓMO ES LA RESPUESTA EN POBLACIÓN HISPANA?

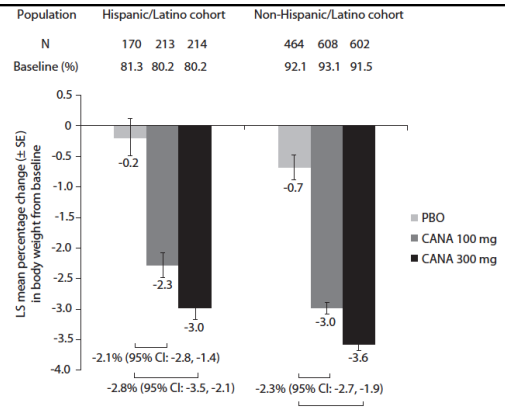
Canagliflozina en población hispana

Characteristics[a]	Hispanic/Latino, N=609			Non-Hispanic/Latino, N=1,695		
	Placebo n=175	CANA 100 mg n=213	CANA 300 mg n=221	Placebo n=471	CANA 100 mg n=615	CANA 300 mg n=609
Age, years	54.7 (9.7)	54.2 (10.4)	53.3 (9.5)	56.9 (9.8)	56.5 (9.9)	56.6 (9.4)
Duration of T2DM, years	7.6 (6.3)	7.4 (6.1)	7.2 (5.6)	7.4 (6.1)	7.1 (5.7)	7.4 (6.4)
Male sex, *n* (%)	76 (43.4)	73 (34.3)	76 (34.4)	258 (54.8)	332 (54.0)	324 (53.2)
Circumcision status, yes[a,b]	13 (17.1)	10 (13.7)	22 (28.9)	102 (39.5)	125 (37.7)	130 (40.1)
History of balanitis, yes[b,c]	1 (1.3)	2 (2.7)	2 (2.6)	4 (1.6)	13 (3.9)	9 (2.8)
HbA1c, %	8.1 (1.0)	8.1 (1.0)	8.1 (1.0)	8.0 (.9)	8.0 (.9)	7.9 (.9)
Body weight, kg	81.2 (19.1)	80.2 (18.8)	80.2 (18.9)	92.2 (21.9)	93.1 (22.5)	91.5 (22.4)
BMI, kg/m²	31.3 (6.1)	31.2 (5.6)	31.0 (6.1)	32.1 (6.5)	32.7 (6.6)	32.3 (6.6)
SBP, mm Hg	127.7 (12.5)	125.0 (13.0)	125.8 (13.3)	128.8 (13.6)	129.0 (12.6)	129.8 (12.5)
HDL-C, mg/dL	45.3 (9.9)	45.5 (11.5)	47.3 (11.7)	45.7 (11.4)	45.8 (11.9)	46.0 (11.5)
LDL-C, mg/dL	115.0 (33.3)	110.6 (32.7)	111.0 (33.0)	106.2 (40.0)	104.9 (36.6)	102.4 (35.9)
Triglycerides, mg/dL	214.9 (126.0)	208.2 (131.6)	194.8 (138.3)	175.2 (108.7)	173.6 (124.2)	176.8 (115.6)
eGFR, mL/min/1.73 m²	92.7 (18.7)	94.4 (18.5)	95.5 (20.1)	84.9 (19.9)	86.2 (18.6)	86.4 (17.8)

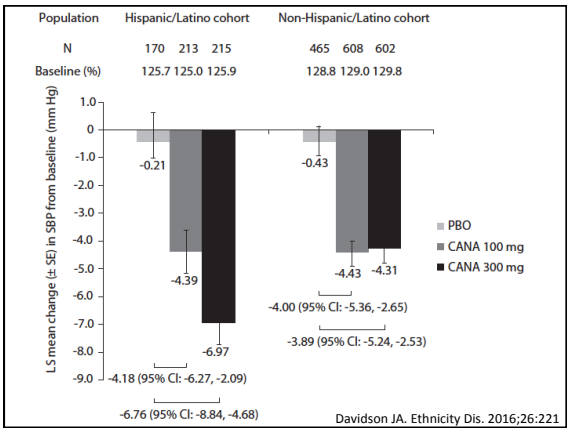
Davidson JA. Ethnicity Dis. 2016;26:221



Davidson JA. Ethnicity Dis. 2016;26:221



Davidson JA. Ethnicity Dis. 2016;26:221



Davidson JA. Ethnicity Dis. 2016;26:221

	Hispanic/Latino			Non-Hispanic/Latino		
	Placebo n=175	CANA 100 mg n=213	CANA 300 mg n=221	Placebo n=471	CANA 100 mg n=615	CANA 300 mg n=609
Any AE	98 (56.0)	126 (59.2)	126 (57.0)	286 (60.7)	370 (60.2)	364 (59.8)
AEs leading to discontinuation	3 (1.7)	3 (1.4)	6 (2.7)	17 (3.6)	32 (5.2)	24 (3.9)
AEs related to study drug[a]	19 (10.9)	36 (16.9)	40 (18.1)	66 (14.0)	132 (21.5)	150 (24.6)
Serious AEs	3 (1.7)	4 (1.9)	4 (1.8)	19 (4.0)	23 (3.7)	18 (3.0)
Deaths	0	0	0	2 (.4)	1 (.2)	1 (.2)
Genital mycotic infection	3 (1.7)	14 (6.6)	16 (7.2)	9 (1.9)	47 (7.6)	47 (7.7)
Female[b]	3 (3.0)	12 (8.6)	13 (9.0)	7 (3.3)	32 (11.3)	36 (12.6)
Male[c]	0	2 (2.7)	3 (3.9)	2 (.8)	15 (4.5)	11 (3.4)
Urinary tract infection	12 (6.9)	18 (8.5)	15 (6.8)	14 (3.0)	30 (4.9)	21 (3.4)
Female[b]	11 (11.1)	18 (12.9)	13 (9.0)	13 (6.1)	28 (9.9)	14 (4.9)
Male[c]	1 (1.3)	0	2 (2.6)	1 (.4)	2 (.6)	7 (2.2)
Osmotic diuresis-related AEs	1 (.6)	11 (5.2)	5 (2.3)	4 (.8)	44 (7.2)	42 (6.9)
Volume depletion-related AEs	0	1 (.5)	3 (1.4)	7 (1.5)	9 (1.5)	8 (1.3)

Davidson JA. Ethnicity Dis. 2016;26:221

EFICACIA VS INHIBIDORES DE DPP-4?

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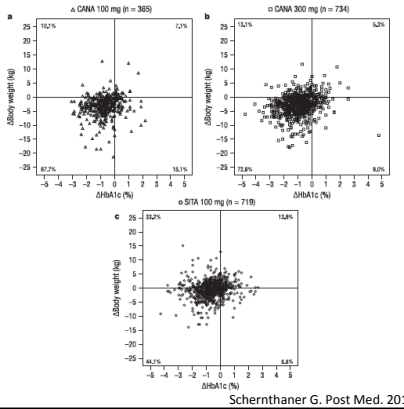


Schernthaner G. Post Med. 2016;128:725

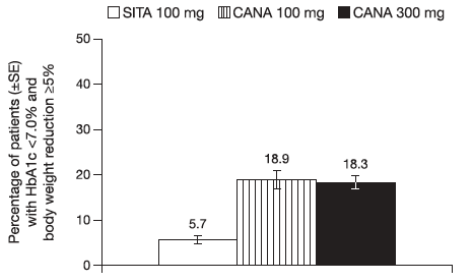
Sita vs cana con reducción de Hba1c y peso

	SITA 100 mg (n = 719)	CANA 100 mg (n = 365)	CANA 300 mg (n = 734)
Number of patients, n (%)	317 (44.1)	247 (67.7)	533 (72.6)
Difference vs. SITA (95% CI), %		23.6 (17.4–29.8)	28.5 (23.5–33.5)
OR vs. SITA (95% CI)		2.2 (1.7–2.9)	3.4 (2.8–4.3)

HbA1c: glycated hemoglobin; SITA: sitagliptin; CANA: canagliflozin; CI: confidence interval; OR: odds ratio.

Schernthaner G. Post Med. 2016;128:725

Sita vs cana con Hba1c <7% y pérdida de peso >5%



Schernthaner G. Post Med. 2016;128:725

EFECTOS ADICIONALES Y POTENCIALES BENEFICIOS

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EFECTO URICOSÚRICO

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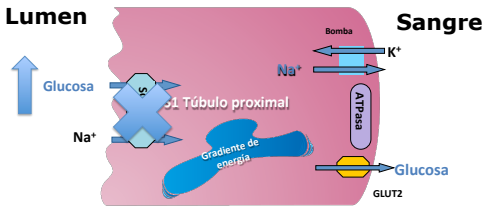
SGLT2 permite la reabsorción de glucosa renal



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

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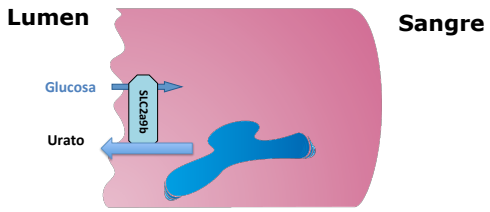
Mecanismo uricosúrico



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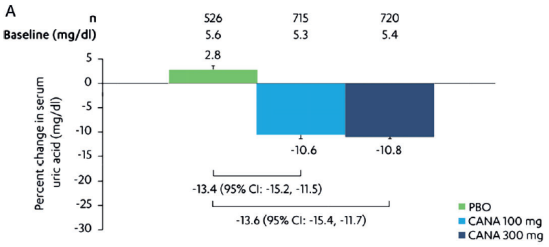
Musso G. Ann Med. 2012;44:375

Canagliflozina y ácido úrico: cohorte total



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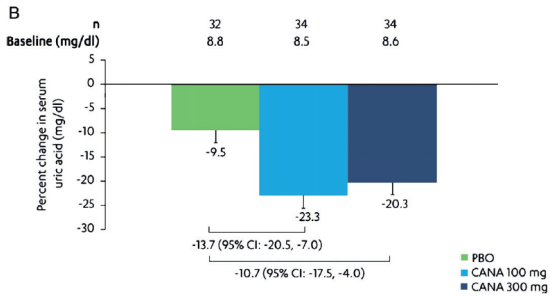
Davies MJ. Diab Obes Metab. 2015;17:426

Canagliflozina y ácido úrico: pacientes con hiperuricemia



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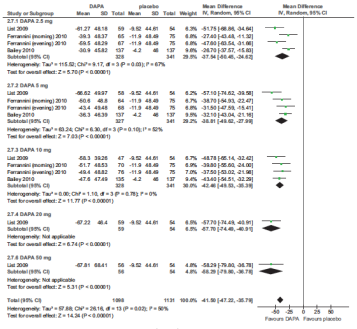
Davies MJ. Diab Obes Metab. 2015;17:426

Dapagliflozina y ácido úrico



Equivalente a 2.4 mg/dl

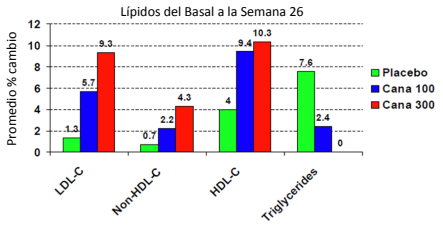
Musso G. Ann Med. 2012;44:375

EFECTOS EN LÍPIDOS

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

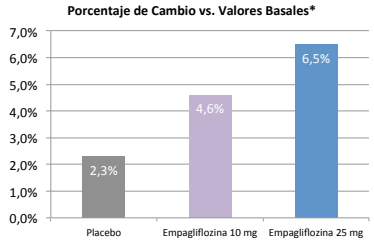


Cana = Canagliflozina; CM = Cuadrados mínimos; HDL-C = Colesterol HDL; LDL-C = Colesterol LDL; LS = Least squares ; Non-HDL-C = Colesterol No-HDL; TG= Triglicéridos

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/CommitteesMeeting/Materials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm Accesado Agosto 2, 2014
2. William T Cefalu. Lancet 2013

Empagliflozina – Cambios en Lípidos

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



*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

IMPACTO CARDIOVASCULAR

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Effect of Canagliflozin on potential CV risk factors

Parameters	Canagliflozin
BP reduction[1]	3.7/1.6 mm Hg
Weight reduction[1]	1.9 Kg
Fat mass[2]	2/3rd contribution to weight loss
Lean mass[2]	1/3rd contribution to weight loss
Change in LDL/HDL ratio[1]	Reduces LDL/HDL ratio by 5.8%
Albuminuria[3]	Decreased the urine albumin/creatinine ratio, and slowed the progression of albuminuria
Uric acid[4]	13% reduction

Disclaimer: Canagliflozin is not approved for treatment of Hypertension/Obesity/Dyslipidemia/ Albuminuria/Hyperuricemia

1. Stenlöf K, et al. Diabetes Obes Metab. 2013 Apr;15(4):372-82.
2. Cefalu et al. Lancet 2013; 382: 941–50
3. Yale JF, et al. Diabetes Obes Metab. 2013 May;15(5):463-73.
4. Davies MJ, et al. Diabetes Obes Metab. 2015 Apr;17(4):426-9.

Impacto cardiovascular

- Qué era lo esperable?
- Diseño de los estudios según lo establecido por la FDA, como estudios de no inferioridad

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TODO CAMBIA A PARTIR DEL SETIEMBRE 2015

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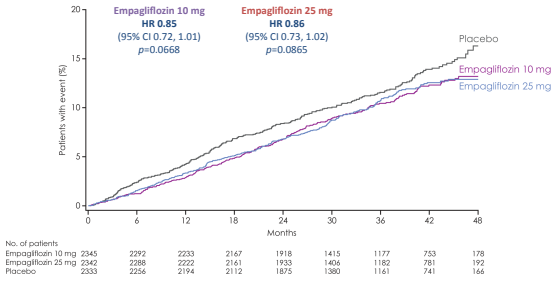
3-point MACE



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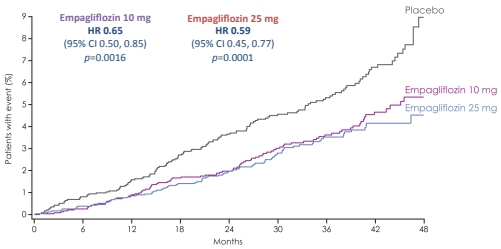
CV death



No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

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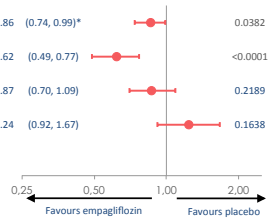
CV death, MI and stroke

	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



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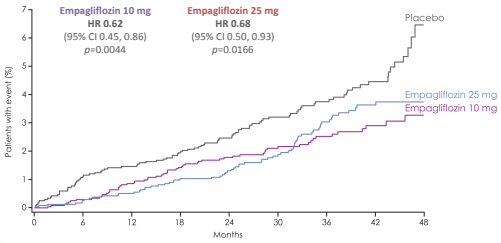
Hospitalisation for heart failure



No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

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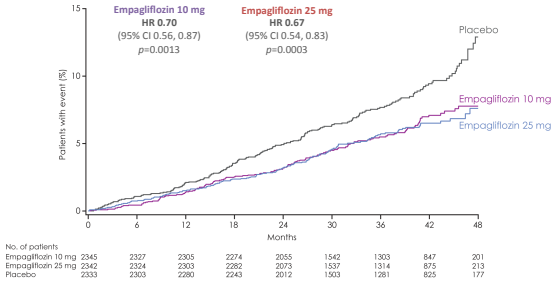
All-cause mortality



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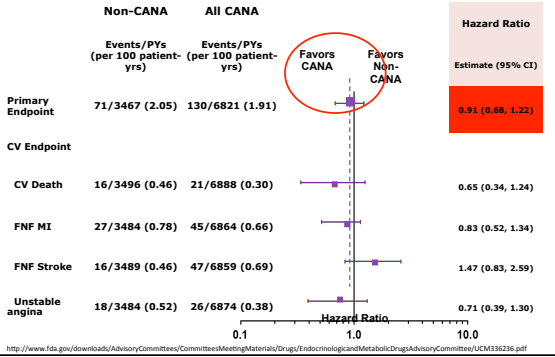
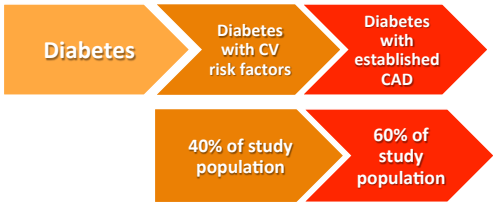
Canagliflozin CV safety data from interim meta-analysis of Phase 2/3 Studies



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf

CANVAS: Canagliflozin Cardiovascular Assessment Study
A close look at the study design



Am Heart J. 2013 Aug;166(2):217-223.e11.

Análisis interino

- Al 15 de setiembre 2011, frecuencia de muerte:
  - 0.7% en los grupos combinados de canagliflozina
  - 0.9% en el grupo placebo

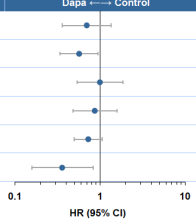
Table 21: MACE Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT)
JNJ-28431754 Phase 2/3 Studies (results through 31 Jan 2012)

	Control k/N (%)	CANA 100 mg k/N (%)	CANA 300 mg k/N (%)	CANA Pooled k/N (%)	Hazard Ratio (95% CI)[a]
CANVAS	38/1441(2.6)	46/1445(3.2)	40/1441(2.8)	86/2886(3.0)	1.11 (0.76,1.63)
Non-CANVAS(with CV risk similar to CANVAS)[b,c]	10/643(1.6)	7/580(1.2)	4/549(0.7)	11/1129(1.0)	0.61 (0.26,1.44)
Overall CV high risk population (CANVAS + non-CANVAS)[d]	48/2084(2.3)	53/2025(2.6)	44/1990(2.2)	97/4015(2.4)	**1.01** (0.71,1.43)
Non-CANVAS(without high CV risk)	5/1243(0.4)	2/1131(0.2)	5/1159(0.4)	7/2290(0.3)	**0.73** (0.23,2.29)

Eventos CV - dapagliflozina

Components of Endpoints

Event	Pts with Event: Dapa N=5936	Pts with Event: Control N=3403	Hazard Ratio vs. Control (95% CI)
CV Death	20 / 3825	18 / 2200	0.70 (0.36, 1.36)
MI	30 / 5244	33 / 3014	0.57 (0.34, 0.95)
Stroke	25 / 4227	18 / 2412	1.00 (0.54, 1.86)
Unstable Angina	26 / 4592	20 / 2697	0.87 (0.48, 1.59)
Unplanned Coronary Revasc	58 / 5525	55 / 3153	0.73 (0.50, 1.07)
Hosp. for Heart Failure	10 / 2576	16 / 1780	0.36 (0.16, 0.84)



Stratified by study. Only trials with at least one positively adjudicated event included in analysis.
Cox Proportional Hazards Model.

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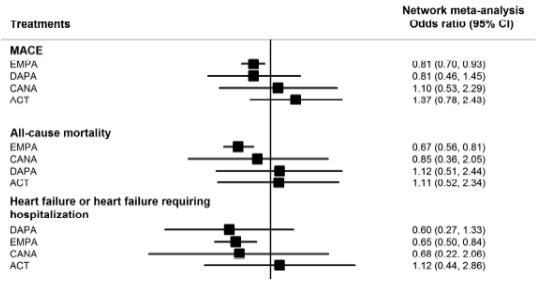
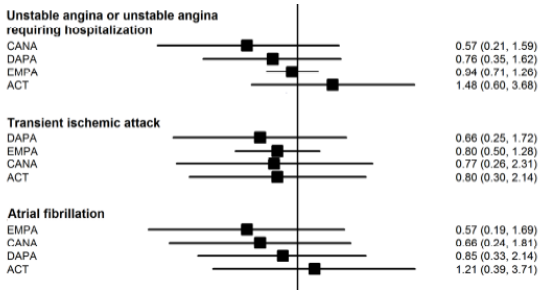
CORE - 118

Metanálisis cardiovascular

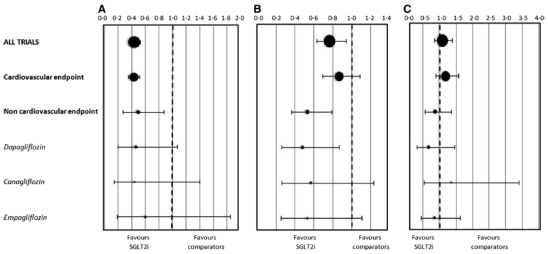


Tang H. Am J Cardiol. 2016; early online.

Metanálisis cardiovascular



Tang H. Am J Cardiol. 2016; early online.



	A: MH-OR [95%, CI]	A: p	B: MH-OR [95%, CI]	B: p	C: MH-OR [95%, CI]	C: p
All trials:	**0·43[0·36-0·53]**	**<0·001**	**0·77[0·63-0·94]**	**0·010**	**1·09[0·86-1·38]**	**0·50**
CV endpoint	0·43[0·35-0·52]	<0·001	0·87[0·69-1·09]	0·23	1·19[0·89-1·58]	0·23
Non CV endpoint	0·49[0·27-0·87]	0·016	0·53[0·36-0·79]	0·002	0·88[0·57-1·36]	0·57
Dapagliflozin	0·46[0·20-1·07]	0·071	0·48[0·26-0·87]	0·017	0·68[0·31-1·46]	0·32
Canagliflozin	0·44[0·14-1·40]	0·16	0·57[0·26-1·25]	0·15	1·36[0·54-3·40]	0·51
Empagliflozin	0·60[0·19-1·85]	0·37	0·53[0·25-1·11]	0·093	0·85[0·45-1·62]	0·63

Fig. 7 Subgroup analyses for cardiovascular mortality (**a**), myocardial infarction (**b**), and stroke (**c**) considering all randomized clinical trials with and without cardiovascular endpoints. *SGLT2i* sodium-glucose transporter 2 inhibitors

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Monami M. Acta Diabetol. 2016.Online Aug 4

CÓMO EXPLICAR EL IMPACTO?

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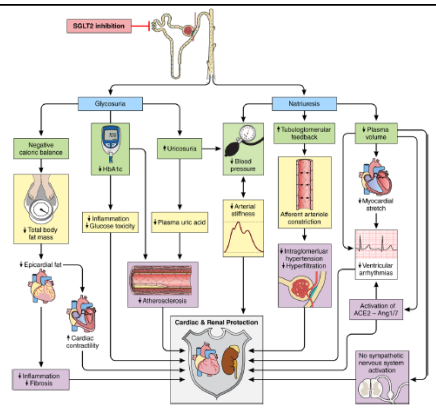

Heerspink H. Circulation. 2016;134:752

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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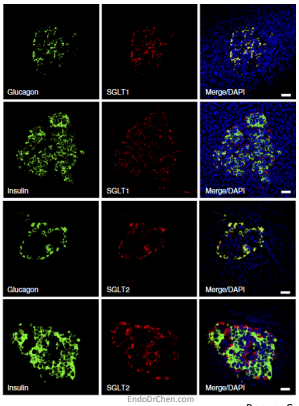
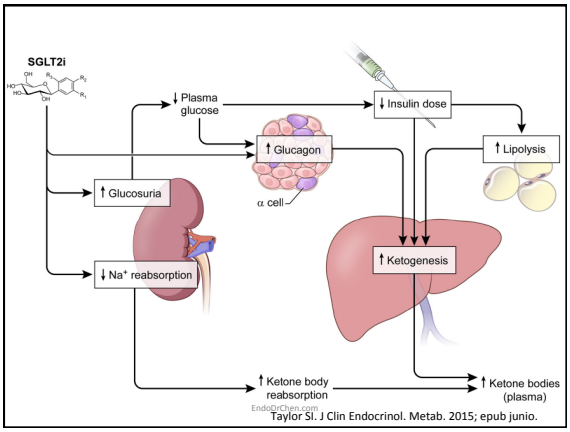


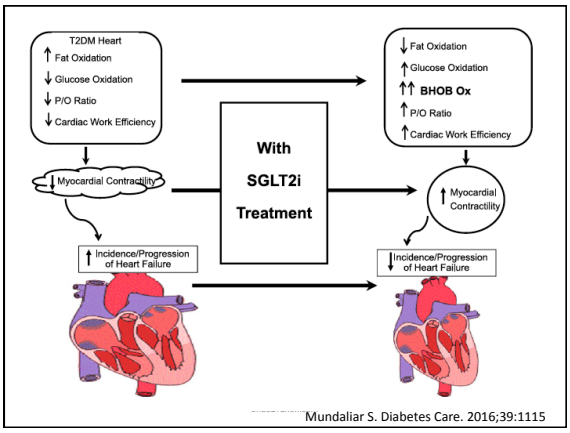
Bonner C. Nat Med. 2015;21(5):512



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

Cetosis

- Muchos de los casos fueron en DM-1
  - No está aprobado para usar en DM-1
  - Estudios fase III en DM-1 muestran que hasta 9% hacen DKA
- Usualmente hay causa precipitante
  - Cirugía, infecciones, alcohol
  - Suspender al menos 48 horas antes
- Ante sospecha, medir gases arteriales



Mundaliar S. Diabetes Care. 2016;39:1115

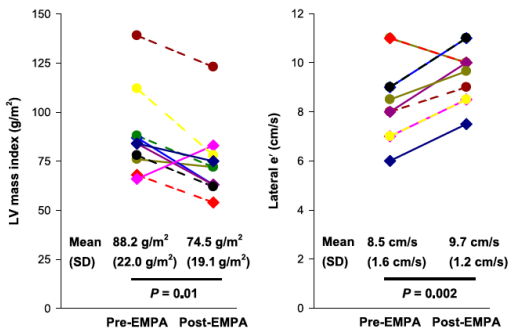


Figure 1—LV mass index and lateral e′ at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e′, early lateral annular tissue Doppler velocity; EMPA, empagliflozin.

Verma S. Diabetes Care. 2016. online sep 27

EFECTOS EN NEFROPATÍA DIABÉTICA: HIPERFLITRACIÓN Y PROTEINURIA

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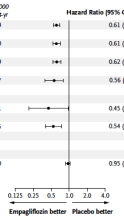
Puntos finales renales en EMPAREG

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 (0.40–0.73)	<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



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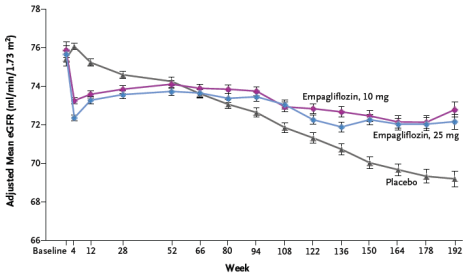
Wanner C. N Engl J Med. 2016; online Jun 14

AEC en EMPAREG



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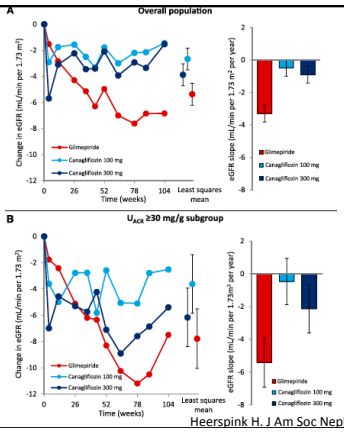
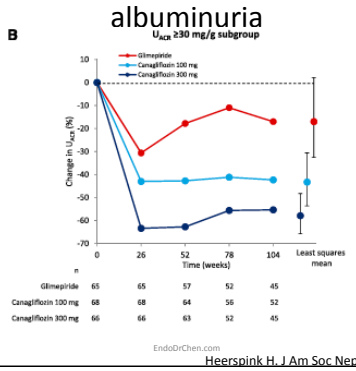
Wanner C. N Engl J Med. 2016; online Jun 14

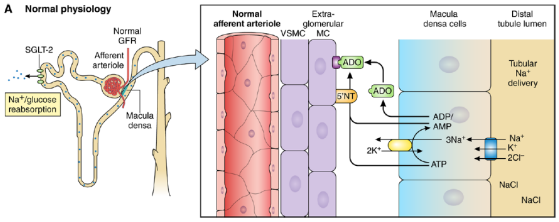


Heerspink H. J Am Soc Nephrol. 2017;28:368

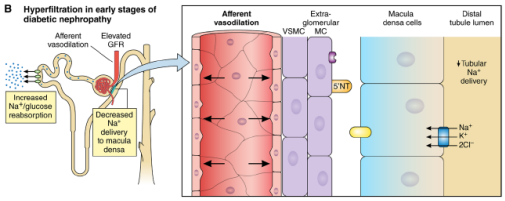
Canagliflozina vs glimepiride en albuminuria



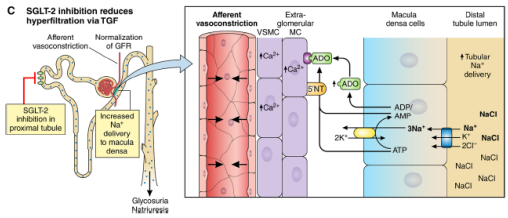
Heerspink H. J Am Soc Nephrol. 2017;28:368



Heerspink H. Circulation. 2016;134:752



Heerspink H. Circulation. 2016;134:752



Heerspink H. Circulation. 2016;134:752

Efectos en albuminuria

Study	N	Investigational drug	Comparator	Weeks	Change in albumin excretion rate		
					Investigational drug	Comparator	Difference
Barnett et al. (2014)[88]	292[a]	Empagliflozin 10/25 mg	Placebo	52	−70/−121	114	−185/−236
Barnett et al. (2014)[88]	375[b]	Empagliflozin 25 mg	Placebo	52	−155	29	−184
Barnett et al. (2014)[88]	74[c]	Empagliflozin 25 mg	Placebo	52	−634	−140	−494
Cefalu et al. (2013)[89]	1450	Canagliflozin 100/300 mg	Glimepiride	52	−0.1/−0.9	0.7	−0.8/−1.5
Kohan et al. (2014)[87]	252	Dapagliflozin 5/10 mg	Placebo	104	78.0/−11.7	69.7	8.3/−81.4
Yale et al. (2013)[86]	269	Canagliflozin 100/300 mg	Placebo	52	−117.5/−96.2	15.4	−132.9/−111.6

SGLT2: sodium-glucose cotransporter 2; CKD: chronic kidney disease.
[a]Patients with Stage 2 CKD.
[b]Patients with Stage 3 CKD.
[c]Patients with Stage 4 CKD.

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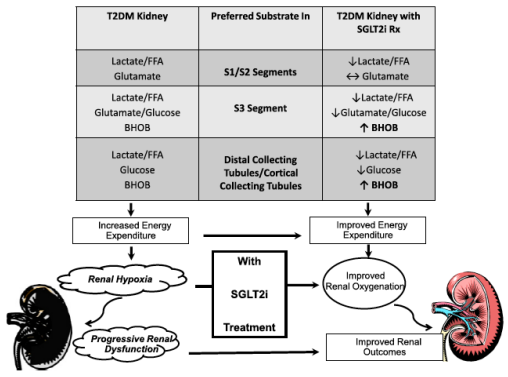
Schernthaner G. Diab Vasc Dis Res. 2014;11:306



Mundaliar S. Diabetes Care. 2016;39:1115

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

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[06-14-2016]

Safety Announcement

The U.S. Food and Drug Administration (FDA) has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. This is a serious condition in which the kidneys suddenly stop working, causing dangerous levels of wastes to build up in the body. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medicine without first talking to their health care professionals. Doing so can lead to uncontrolled blood sugar levels that can be harmful.

Health care professionals should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

HIPOTENSIÓN POSTURAL

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Factores de riesgo: AEs de volumen intravascular reducido

Grupo de datos amplio del período principal

eGFR (mL/min/ 1.73m²)	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/1.73m²	1.1 (29/2604)	1.8 (45/2491)	2.2 (54/2434)

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

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SEGURIDAD ÓSEA

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FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density

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[09-10-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana, Invokamet) related to the increased risk of bone fractures and added new information about decreased bone mineral density. Bone mineral density relates to the strength of a person's bones. To address these safety concerns, we added a new *Warning and Precaution* and revised the *Adverse Reactions* section of the Invokana and Invokamet drug labels.

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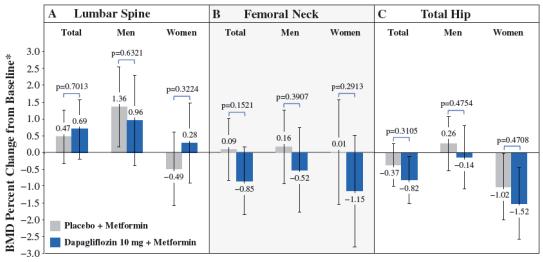

Bolinder J. Diab Obes Metab. 2013;16:159

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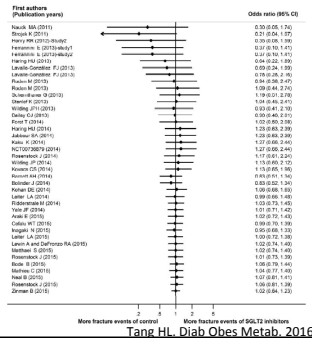
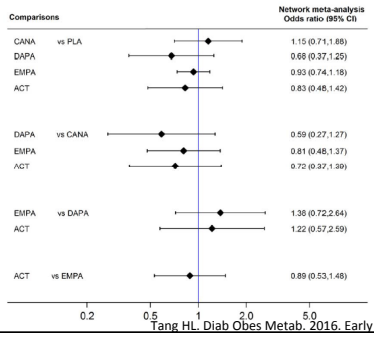
iSGLT-2 y riesgo de fracturas

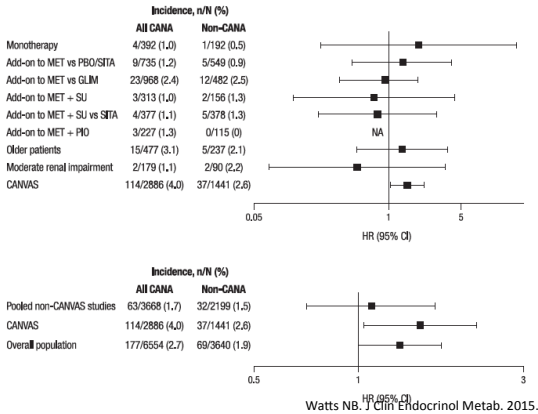


Tang HL. Diab Obes Metab. 2016. Early online Jul 13

Network metanalisis

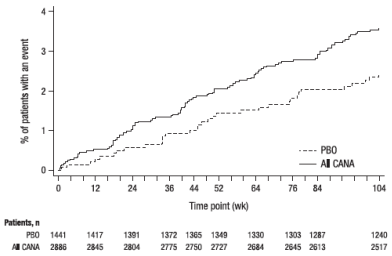


Tang HL. Diab Obes Metab. 2016. Early online Jul 13



Watts NB. J Clin Endocrinol Metab. 2015.

CANVAS: Tasa acumulada de fracturas



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Fracturas en CANVAS

- Las diferencias en tasa de fracturas empiezan tempranamente y se mantienen
- Se presentan en miembros superiores (1.6 vs 1.1%) y miembros inferiores (1.7 vs 1.2%)
- No hubo diferencias entre las dos dosis de canagliflozina
- No diferencias en otros sitios
- En ninguno de los sitios alcanzó significancia estadística

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FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate

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[05-18-2016]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with the diabetes medicine canagliflozin (Invokana, Invokamet). We have not determined whether canagliflozin increases the risk of leg and foot amputations. We are currently investigating this new safety issue and will update the public when we have more information.

Patients should not stop or change their diabetes medicines without first talking to their health care professional. Doing so can lead to uncontrolled blood sugar levels that can be harmful. Over time, this can cause serious problems, including blindness, nerve and kidney damage, and heart disease. Patients taking canagliflozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

Health care professionals should follow the recommendations in the canagliflozin drug labels. Monitor patients for the signs and symptoms described above and advise patients to seek medical advice if they experience them.

Canagliflozin is a prescription medicine used with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin lowers blood sugar by causing the kidneys to remove sugar from the body through the urine. It

Amputaciones

- Reporte de basado en análisis interino de CANVAS a 1 año de seguimiento:
  - 3 por cada 1000 pacientes en placebo
  - 5 por cada 1000 pacientes con canagliflozina 300 mg
  - 7 por cada 1000 pacientes con canagliflozina 100 mg
- CANVAS-R no ha mostrado los mismos resultados

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INFECCIONES UROGENITALES

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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. 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/CommitteesMeeting Materials/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

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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

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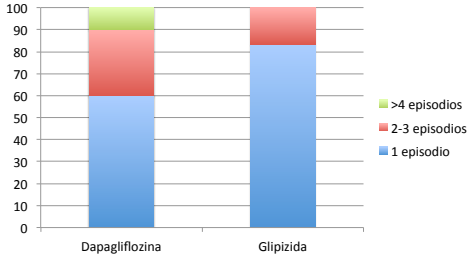
Infecciones genitales: número de episodios



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

Conclusiones

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

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Preguntas…
chenku2409@gmail.Com
EndoDrChen.Com

EndoDrChen.com