Actualización terapéutica en DM: inhibidores de SGLT-2

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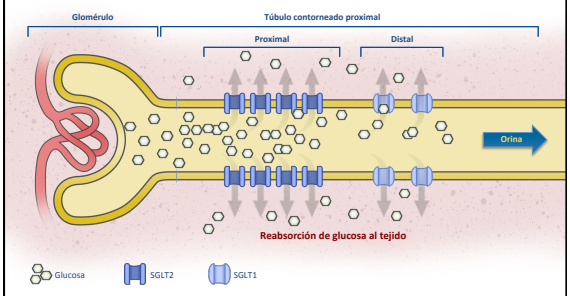
Conflictos de interés

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

Agenda

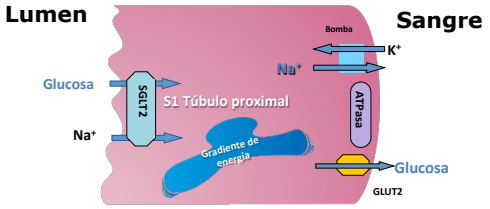
- Mecanismo de los inhibidores de SGLT-2 y sus beneficios
  - Control glicémico
  - Control peso
  - Reducción de presión arterial
  - Efecto uricosúrico
  - Reducción de nefropatía diabética
  - Eventos cardiovasculares
- Riesgos: euDKA, infecciones urogenitales, hueso

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



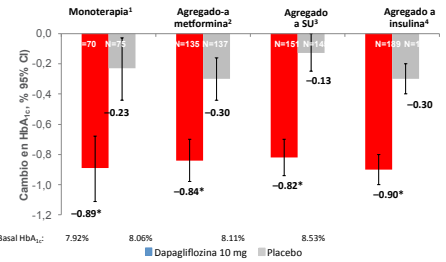
Adaptado con permiso de Rothenberg PL et al. SGLT = cotransportador ligado a sodio-glucosa.
Rothenberg PL et al. Poster presentado en: 46ª. Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia

SGLT2 permite la reabsorción de glucosa renal



Adaptado de de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012; 14:1-6.

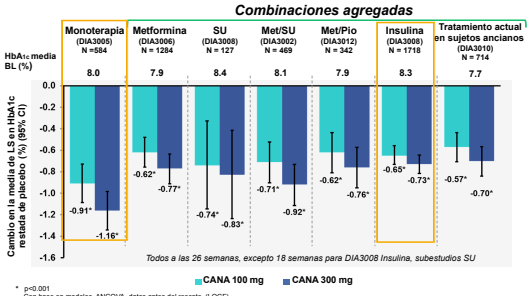
Reducción consistente en la HbA_{1c} en la Semana 24 en diferentes estudios



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 Metob* 2011;**13**:928–38; 4. Wilding J, *et al. Diabetes* 2010;**59**(Suppl 1):0078-OR.

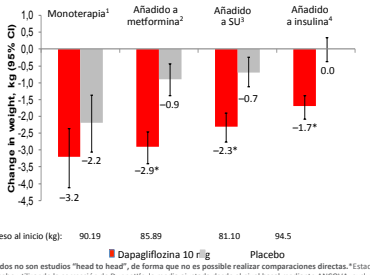
Cambio en HbA1c desde la basal
Estudios de Fase 3 controlados con placebo



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

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

Reducción significativa de peso a la semana 24



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 JPH, et al. Ann Intern Med 2012;156:405–15.

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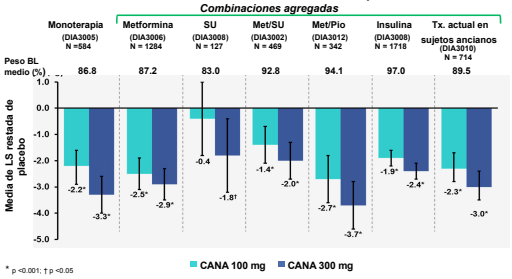
Cambio porcentual en el peso corporal desde la basal
Estudios de Fase 3 controlados con placebo

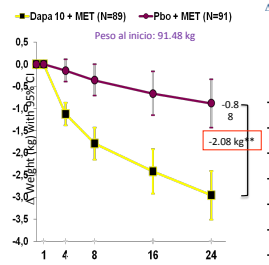


* p <0.001; † p <0.05
Con base en modelos ANCOVA, datos previos al rescate (LOCF)

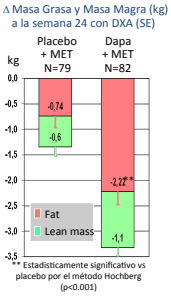
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs

Reducción de peso y grasa corporal a la semana 24

Estudio de composición corporal con DXA



** Estadisticamente significativo vs placebo (p<0.0001)



** Estadisticamente significativo vs placebo por el método Hochberg (p<0.001)

DXA = dual X-ray absorptiometry.
Adjusted mean change from baseline using ANCOVA, including data after rescue (LOCF)

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

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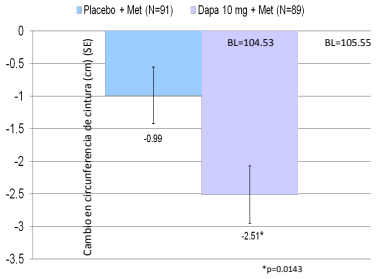
Cambio medio ajustado del perímetro abdominal a la semana 24 (cm)



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

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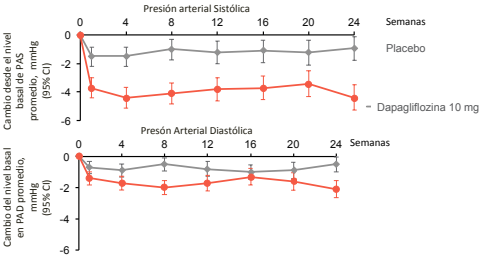
En el conjunto de los estudios, dapagliflozina redujo la TA a lo largo de las 24 semanas.



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.

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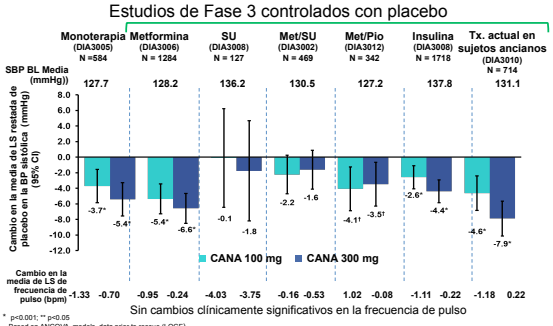
Cambio en la presión arterial sistólica desde la basal

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

PODEMOS POTENCIAR EL EFECTO EN PESO COMBINADO CON ANÁLOGOS GLP-1?

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Canagliflozina + análogo GLP-1

	HbA1C (%)	Weight (Kg)
GLP-1 Baseline	8.01	114.9
GLP-1 1 Year	7.45	112.8
Cana Baseline (mean 30 months GLP-1 therapy)	7.94	113.8
Cana Follow-up	7.55	109.2
Change from GLP-1 Baseline to Cana follow-up (mean 40 months)	- 0.46	- 5.7

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Saroka RM. Endocr Pract. 2015; early online.

Canagliflozina + análogo GLP-1

	Change, SD; p-values	
Primary outcome		
Change in HbA1c (%)	-0.39 ± 0.88;	p < 0.001
Secondary outcomes		
Change in weight (kg)	-4.6 ± 4.3;	p <0.001
% of patients with HbA1c < 7%	26.7%;	p < 0.001
Change in blood pressure (mmHg)		
Systolic	-4.0 ± 12;	p = 0.01
Diastolic	-2.7 ± 9;	p = 0.02
Changes in lipid parameters (mg/dL)		
TC	3 ± 30;	p = 0.47
LDL-C	0.6 ± 25.2;	p = 0.85
HDL-C	2.1 ± 4.5;	p < 0.001
TG	19 ± 15;	p = 0.32
Change in BUN	2.2 ± 4.6;	p < 0.001
Change in SCr	0.03 ± 0.17;	p = 0.15

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Saroka RM. Endocr Pract. 2015; early online.

USO EN IRC?

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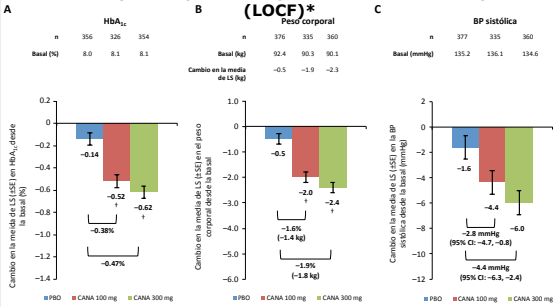
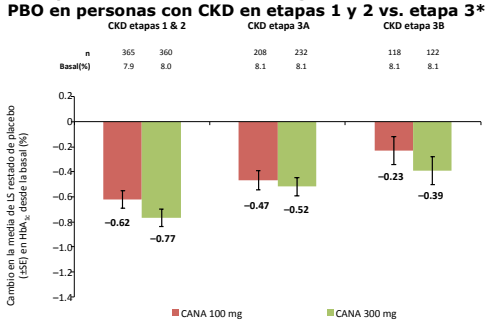
Cambios en (A) HbA1c, (B) peso corporal y (C) BP sistólica para la población general con CKD en etapa 3 (LOCF)*



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.

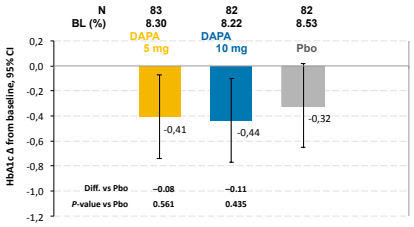
Comparación del efecto de canagliflozina restado de PBO en personas con CKD en etapas 1 y 2 vs. etapa 3*



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 tratamierrto agregado a metformina en sujetos normales.

Dapagliflozin in Patients with Moderate Renal Impairment: Change in HbA1c

- Mean change in HbA1c with dapagliflozin was not statistically different from placebo at week 24 in patients with moderate renal impairment



Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).
Kohan DE, et al. *Kidney Int.* 2013; epub ahead of print; EMDAC Background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

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Dapagliflozin in Patients with Moderate Renal Impairment: Efficacy by Baseline CKD Stage

- Post-hoc analysis showed a larger reduction in adjusted mean change in HbA1c and FPG from baseline to week 24 for dapagliflozin vs placebo for stage 3A CKD than for stage 3B CKD

	HbA1c (%)		FPG (mg/dL)		Weight (Kg)	
	n	Difference from PBO	n	Difference from PBO	n	Difference from PBO
Stage 3B: eGFR ≥ 30 and < 45 mL/min/1.73m²						
DAPA 5 mg	41	0.05 (0.21)	41	−2.66 (12.1)	41	−2.1 (0.69)
DAPA 10 mg	45	0.07 (0.21)	46	−1.49 (11.8)	47	-2.2 (0.68)
Stage 3A: eGFR ≥ 45 and < 60 mL/min/1.73m²						
DAPA 5 mg	35	−0.37 (0.23)	35	−24.8 (12.4)	35	−1.9 (0.66)
DAPA 10 mg	32	−0.33 (0.24)	33	−24.4 (12.7)	33	−2.3 (0.68)

CKD, chronic kidney disease. Data are differences in adjusted mean (SE) change from baseline (dapagliflozin vs PBO [LOCF]) excluding data after rescue based on ANCOVA model with treatment group and stratum as mean effects and baseline value as a covariate.

Kohan DE, et al. *Kidney Int.* 2013; epub ahead of print.

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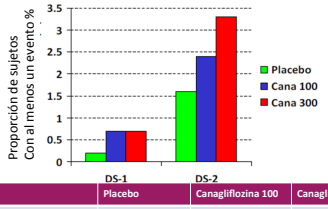
Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



	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/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm Accesado Agosto 2, 2014

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EFECTOS ADICIONALES Y POTENCIALES BENEFICIOS

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EFECTO URICOSÚRICO

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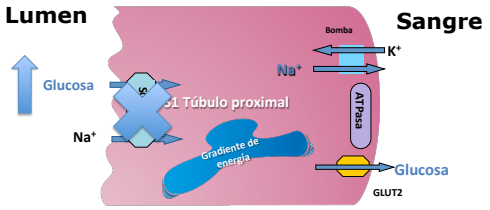
SGLT2 permite la reabsorción de glucosa renal



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

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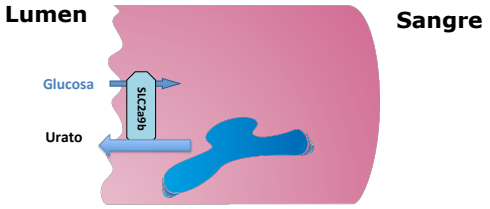
Mecanismo uricosúrico



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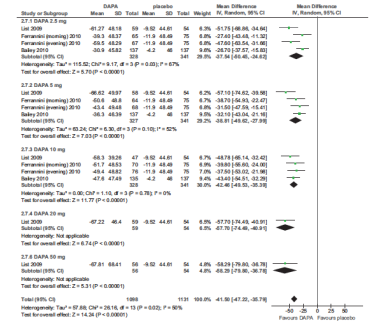
Musso G. Ann Med. 2012;44:375

Dapagliflozina y ácido úrico



Equivalente a 2.4 mg/dl

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Musso G. Ann Med. 2012;44:375

EFECTOS EN NEFROPATÍA DIABÉTICA: HIPERFLITRACIÓN Y PROTEINURIA

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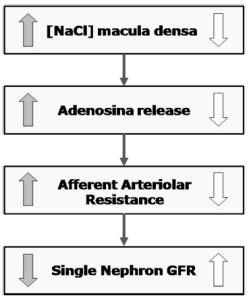
Reflejo tubuloglomerular



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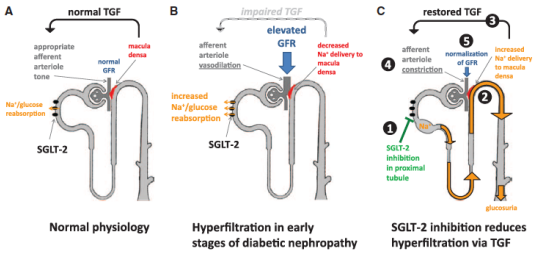
Nicola LD. Am J Kidney Dis. 2014;64:16-24



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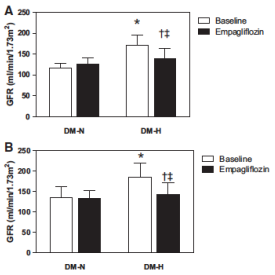
Cherney DZI. Circulation. 2014;129:587

DM-1 e hiperfiltración



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Cherney DZI. Circulation. 2014;129:587

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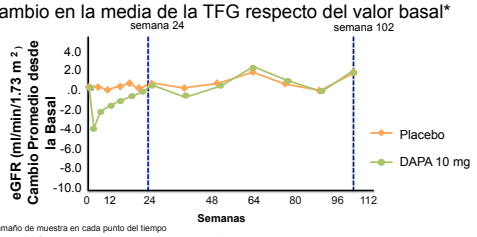
Schernthaner G. Diab Vasc Dis Res. 2014;11:306

Dapagliflozina - Seguridad Renal

Cambio en la media de la TFG respecto del valor basal*



Tamaño de muestra en cada punto del tiempo

PBO n=	785	627	682	617	305	271	242	164
DAPA 10 mg n=	859	719	758	717	405	372	338	249

Con DAPA, la eGFR media disminuyó en la Semana 1, para luego volver al valor basal en la Semana 24, donde se mantuvo hasta la Semana 102

*Incluye datos posrescate y contiene datos de los 6 estudios empleados en el análisis de hasta 102 semanas, en el que 2 estudios duraron 48 semanas.

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Expert Opin. Investig. Drugs (2013) 22(4):463-486

EVENTOS CARDIOVASCULARES: EMPA-REG

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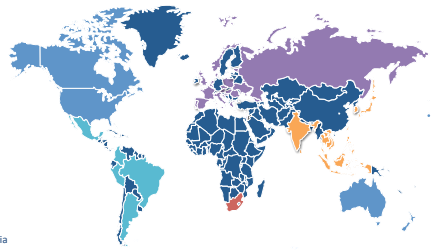
Participating countries

590 sites in 42 countries



- Asia
- North America, Australia, New Zealand
- Latin America
- Europe
- Africa

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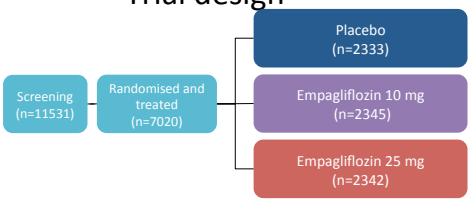
Trial design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

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Key inclusion and exclusion criteria

- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m^2
  - HbA1c 7–10%*
  - Established cardiovascular disease
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
- Key exclusion criteria
  - eGFR <30 mL/min/1.73m^2 (MDRD)

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EMPA-REG OUTCOME®

Pre-specified primary and key secondary outcomes

- Primary outcome
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- Key secondary outcome
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

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EMPA-REG OUTCOME®

Baseline characteristics

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Age, years	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)
Male	1680 (72.0)	1653 (70.5)	1683 (71.9)
Region			
Europe	959 (41.1)	966 (41.2)	960 (41.0)
North America*	462 (19.8)	466 (19.9)	466 (19.9)
Asia	450 (19.3)	447 (19.1)	450 (19.2)
Latin America	360 (15.4)	359 (15.3)	362 (15.5)
Africa	102 (4.4)	107 (4.6)	104 (4.4)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

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EMPA-REG OUTCOME®

Baseline characteristics: type 2 diabetes

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
HbA1c, %	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)
Time since diagnosis of type 2 diabetes, years			
≤5	423 (18.1)	406 (17.3)	434 (18.6)
>5 to 10	571 (24.5)	585 (24.9)	590 (25.2)
>10	1339 (57.4)	1354 (57.7)	1318 (56.3)
Glucose-lowering medication*			
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)
Sulphonylurea	992 (42.5)	985 (42.0)	1029 (43.9)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)
Mean daily dose, U**	65 (50.6)	65 (47.9)	66 (48.9)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

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Baseline characteristics: CV risk factors

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Body mass index, kg/m^2	30.7 (5.2)	30.6 (5.2)	30.6 (5.3)
Weight, kg	86.6 (19.1)	85.9 (18.8)	86.5 (19.0)
Waist circumference, cm	105.0 (14.0)	104.7 (13.7)	104.8 (13.7)
Systolic blood pressure, mmHg	135.8 (17.2)	134.9 (16.8)	135.6 (17.0)
Diastolic blood pressure, mmHg	76.8 (10.1)	76.6 (9.8)	76.6 (9.7)
Heart rate, bpm*	70.7 (0.2)	71.0 (0.2)	70.5 (0.2)
LDL cholesterol, mg/dL	84.9 (35.3)	86.3 (36.7)	85.5 (35.2)
HDL cholesterol, mg/dL	44.0 (11.3)	44.7 (12.0)	44.5 (11.8)
eGFR, mL/min/1.73m^2 (MDRD)	73.8 (21.1)	74.3 (21.8)	74.0 (21.4)
≥90 mL/min/1.73m^2	488 (20.9%)	519 (22.1%)	531 (22.7%)
60 to <90 mL/min/1.73m^2	1238 (53.1%)	1221 (52.1%)	1204 (51.4%)
<60 mL/min/1.73m^2	607 (26.0%)	605 (25.8%)	607 (25.9%)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

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Baseline characteristics: CV complications

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Any CV risk factor	2307 (98.9%)	2333 (99.5%)	2324 (99.2%)
Coronary artery disease	1763 (75.6%)	1782 (76.0%)	1763 (75.3%)
Multi-vessel coronary artery disease	1100 (47.1%)	1078 (46.0%)	1101 (47.0%)
History of MI	1083 (46.4%)	1107 (47.2%)	1083 (46.2%)
Coronary artery bypass graft	563 (24.1%)	594 (25.3%)	581 (24.8%)
History of stroke	553 (23.7%)	535 (22.8%)	549 (23.4%)
Peripheral artery disease	479 (20.5%)	465 (19.8%)	517 (22.1%)
Single vessel coronary artery disease	238 (10.2%)	258 (11.0%)	240 (10.2%)
Cardiac failure*	244 (10.5%)	240 (10.2%)	222 (9.5%)

Data are n (%) in patients treated with ≥1 dose of study drug

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Baseline characteristics: CV medication (1)

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Anti-hypertensive therapy	2221 (95.2%)	2227 (95.0%)	2219 (94.7%)
ACE inhibitors/ARBs	1868 (80.1%)	1896 (80.9%)	1902 (81.2%)
Beta-blockers	1498 (64.2%)	1530 (65.2%)	1526 (65.2%)
Diuretics	988 (42.3%)	1036 (44.2%)	1011 (43.2%)
Calcium channel blockers	788 (33.8%)	781 (33.3%)	748 (31.9%)
Mineralocorticoid receptor antagonists	136 (5.8%)	157 (6.7%)	148 (6.3%)
Renin inhibitors	19 (0.8%)	16 (0.7%)	11 (0.5%)
Other	191 (8.2%)	193 (8.2%)	190 (8.1%)

Data are n (%) in patients treated with ≥1 dose of study drug

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Baseline characteristics: CV medication (2)

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Lipid-lowering drugs	1864 (79.9%)	1926 (82.1%)	1894 (80.9%)
Statins	1773 (76.0%)	1827 (77.9%)	1803 (77.0%)
Fibrates	199 (8.5%)	214 (9.1%)	217 (9.3%)
Ezetimibe	81 (3.5%)	95 (4.1%)	94 (4.0%)
Niacin	35 (1.5%)	56 (2.4%)	35 (1.5%)
Other	175 (7.5%)	172 (7.3%)	193 (8.2%)
Anti-coagulants and anti-platelets	2090 (89.6%)	2098 (89.5%)	2064 (88.1%)
Acetylsalicylic acid	1927 (82.6%)	1939 (82.7%)	1937 (82.7%)
Clopidogrel	249 (10.7%)	253 (10.8%)	241 (10.3%)
Vitamin K antagonists	156 (6.7%)	141 (6.0%)	125 (5.3%)

Data are n (%) in patients treated with ≥1 dose of study drug

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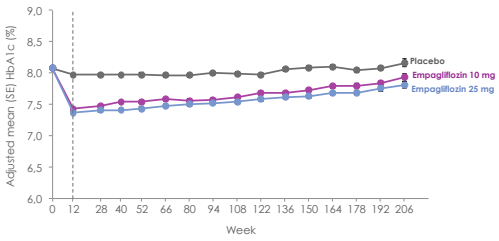
HbA1c



Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

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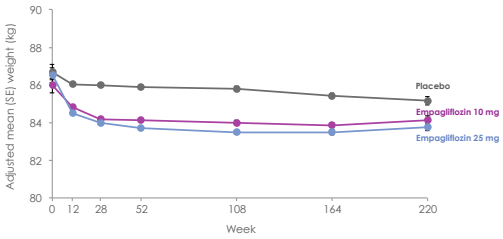
Weight



Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

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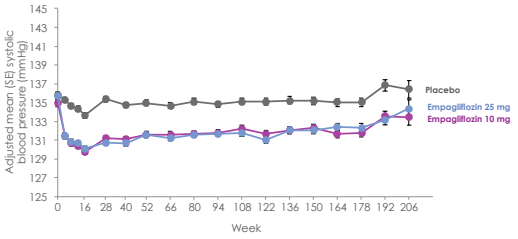
Systolic blood pressure



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

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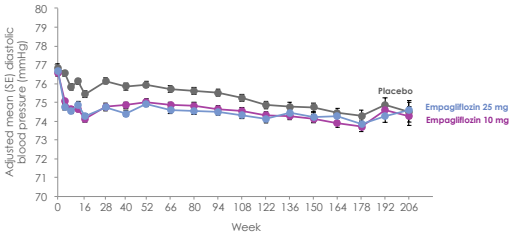
Diastolic blood pressure



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

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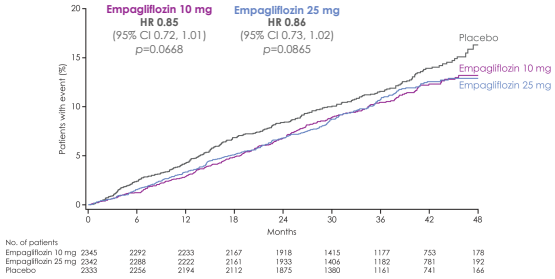
3-point MACE



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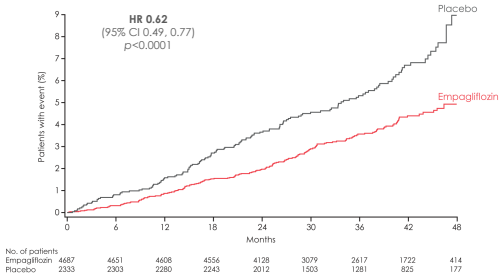
CV death



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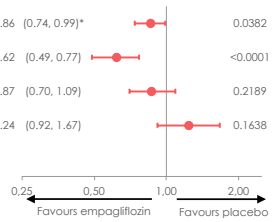
CV death, MI and stroke

	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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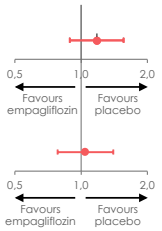
Fatal and non-fatal stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	p-value
Intent-to-treat population	164/4687	69/2333	1.18	(0.89, 1.56)	0.2567
On-treatment analysis*	141/4607	66/2308	1.04	(0.78, 1.40)	0.7849

Numerical difference largely driven by events occurring >30 days after treatment stop



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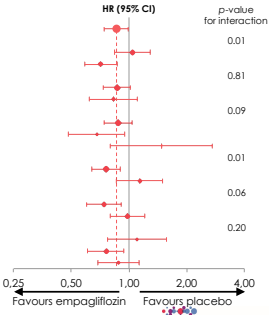
3-point MACE: subgroup analysis

	Empagliflozin	Placebo	p-value for interaction
All patients	4687	2333	
Age, years			0.01
<65	2596	1297	
≥65	2091	1036	
Sex			0.81
Male	3336	1680	
Female	1351	653	
Race			0.09
White	3403	1678	
Asian	1006	511	
Black/African-American	237	120	
HbA1c, %			0.01
<8.5	3212	1607	
≥8.5	1475	726	
Body mass index, kg/m²			0.06
<30	2279	1120	
≥30	2408	1213	
eGFR, mL/min/1.73m²			0.20
≥90	1050	488	
60 to <90	2425	1238	
<60	1212	607	



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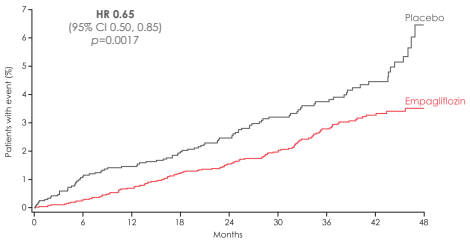
Hospitalisation for heart failure



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

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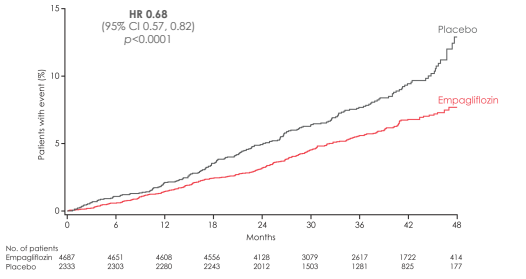
All-cause mortality



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EMPA-REG resultados renales

- 1800 pacientes con AEC <45 cc/min
- En el grupo de pacientes con AEC <60 cc/min
  - Punto compuesto: doblamiento creatinina, ESRD, muerte renal
    - HR 0.45 (IC 95% 0.4-0.75, p=0.002)
  - Empeoramiento de IRC más puntos anteriores
    - HR 0.61 (IC 95% 0.53-0.7)
  - MACE HR 0.88
  - Muerte cardiovascular HR 0.78
  - Falla cardíaca HR 0.59
  - Mortalidad total HR 0.80

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INHIBIDORES DE SGLT-2: DESVENTAJAS

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INFECCIONES URINARIAS Y GENITALES

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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

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Adverse events consistent with urinary tract infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with UTI	423 (18.1%)	8.21	426 (18.2%)	8.02	416 (17.8%)	7.75
Events leading to discontinuation	10 (0.4%)	0.17	22 (0.9%)	0.37	19 (0.8%)	0.31
By sex						
Male	158 (9.4%)	3.96	180 (10.9%)	4.49	170 (10.1%)	4.09
Female	265 (40.6%)	22.81	246 (35.5%)	18.83	246 (37.3%)	20.38

Rate = per100 patient-years

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Complicated urinary tract infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Complicated urinary tract infection*	41 (1.8%)	0.71	34 (1.4%)	0.57	48 (2.0%)	0.80
Urinary tract infection	16 (0.7%)	0.28	13 (0.6%)	0.22	16 (0.7%)	0.27
Pyelonephritis†	22 (0.9%)	0.38	15 (0.6%)	0.25	20 (0.9%)	0.33
Urosepsis	3 (0.1%)	0.05	6 (0.3%)	0.10	11 (0.5%)	0.18

Rate = per100 patient-years

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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
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

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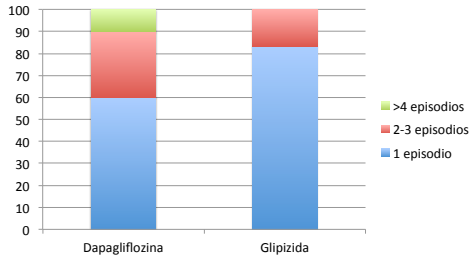
Infecciones genitales: número de episodios



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

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/ucm335233.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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Adverse events consistent with genital infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with genital infection	42 (1.8%)	0.73	153 (6.5%)	2.66	148 (6.3%)	2.55
Serious events	3 (0.1%)	0.05	5 (0.2%)	0.08	4 (0.2%)	0.07
Events leading to discontinuation	2 (0.1%)	0.03	19 (0.8%)	0.32	14 (0.6%)	0.23
By sex						
Male	25 (1.5%)	0.60	89 (5.4%)	2.16	77 (4.6%)	1.78
Female	17 (2.6%)	1.09	64 (9.2%)	3.93	71 (10.8%)	4.81

Rate = per100 patient-years

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SEGURIDAD ÓSEA

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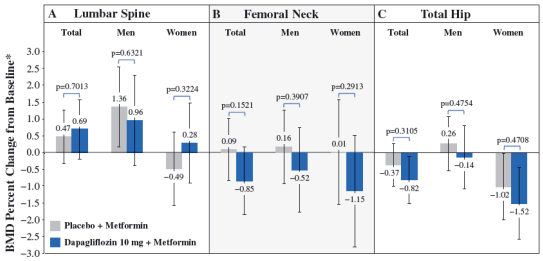

Bolinder J. Diab Obes Metab. 2013;16:159

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Dapagliflozina: Eventos de Fracturas

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

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

DAPA= Dapagliflozina; PBO= Placebo

EMDAC Documento de referencia disponible en: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm376079.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 standardised MedDRA queries
†Based on preferred MedDRA preferred terms

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Seguridad ósea

- Aún no está clara su relación
- Hay una advertencia de la FDA relacionado a fracturas con canagliflozina
- Lo más sensato es tener precaución en pacientes de alto riesgo

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EFECTOS EN LÍPIDOS

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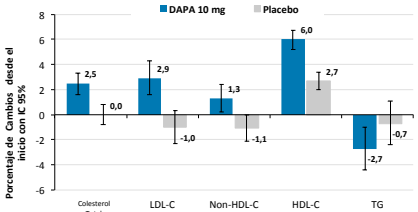
Dapagliflozina: Cambios en Lípidos

- Después de 24 semanas de tratamiento con Dapagliflozina 10mg, se observaron pequeños cambios en el promedio de lípidos en ayuno comparativamente con los valores iniciales.



	Colesterol Total		LDL-C		Non-HDL-C		HDL-C		TG	
Promedio BL (mg/dL)	181.9	180.6	101.2	100.7	136.9	135.3	45.0	45.3	187.1	177.2
n	1851	1747	1840	1736	1851	1747	1851	1748	1844	1736

BL = Linea basal; DAPA = Dapagliflozina; HDL-C = Colesterol HDL; IC = Intervalo de Confianza ; LDL-C = Colesterol LDL; Non-HDL-C = Colesterol No-HDL; TG= Triglicéridos

1. EMDAC slide presentation. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm079659.pdf

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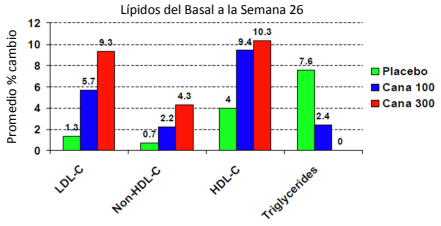
EFFICACY AND SAFETY OF SGLT-2 INHIBITORS Riser Taylor and HarrisPHARMACOTHERAPY Volume **, Number **, 2013

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

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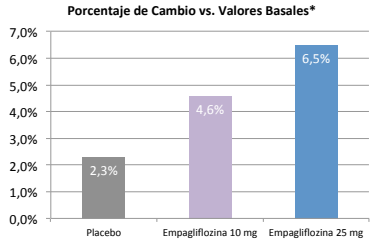
Empagliflozina – Cambios en Lípidos

- **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

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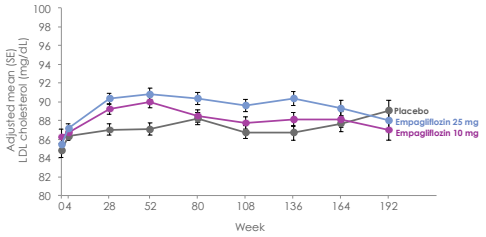
Low-density lipoprotein cholesterol



Placebo	2297	2273	2179	2104	2006	1932	1419	1086	694
Empagliflozin 10 mg	2294	2269	2205	2143	2072	1998	1474	1133	740
Empagliflozin 25 mg	2287	2256	2188	2132	2060	2020	1503	1169	779

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EMPA-REG OUTCOME®

HIPOTENSIÓN POSTURAL

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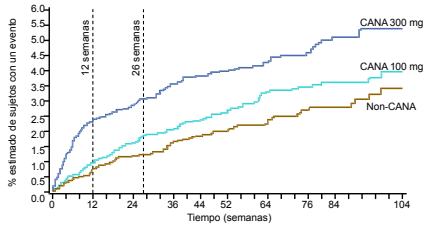
Tiempo al evento: EA de volumen intravascular reducido
Grupo de datos amplio hasta el 01 de julio de 2012

Estimación de KM



Sujetos en riesgo										
Sin CANA	3262	3097	2861	2679	2580	2506	1639	1303	995	344
CANA 100 mg	3092	2954	2791	2666	2582	2532	1750	1395	1060	369
CANA 300 mg	3085	2866	2692	2564	2491	2442	1671	1345	1014	370

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

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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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CETOACIDOSIS EUGLICÉMICA (EUDKA)

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Cetoacidosis euglicémica

- Casi 5% de DM-1 reportan al menos un episodio de DKA en los últimos 12 meses
- Reportado por FDA el 15 de mayo 2015
- euDKA es raro pero puede ser que no haya sido reconocido y por lo tanto subreportado
- euDKA:
  - Tratamiento parcial de DKA
  - Restricción de comidas
  - Consumo de alcohol
  - Inhibición de gluconeogénesis

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Peters AL. Diabetes Care. Online June 15th.

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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Table 1—Clinical Characteristics of euDKA Cases

Case patient	1	2	3		4		5	6	7			8	9
Age (years)	40	58	27		28		31	55	26			39	64
Sex	Female	Male	Female		Female		Female	Female	Female			Female	Female
T1/T2	T1	T2	T1		T1		T1	T1	T1			T1	T2
MDI/CSII	MDI	N/A	MDI		CSII		CSII	CSII	CSII			CSII	N/A
Duration years	17	2	25		6		15	18	13			26	6
BMI (kg/m^2)	26.5	26.5	24.3		25.9		33.2	22.0	22.0			26.1	32.8
Prior A1C (% [mmol/mol])	11.4 (101.1)	9.8 (83.6)	7.8 (61.7)		8.0 (63.9)		7.0 (53.0)	7.2 (55.2)	6.6 (48.6)			7.0 (53.0)	7.8 (62.0)
Canagliflozin dose (mg)	300	300	300	100	300	100	300	300	150			300	300
Potential contributors	URI	Surgery 1 week prior	URI, alcohol	Alcohol	Alcohol	Exercise, alcohol	Exercise	GI	None			URI	Surgery 12 h prior
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Yes	Unknown	No	No	No	Yes	N/A
Presenting plasma glucose (mg/dl; [mmol/L])	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	~125 (~6.9)	203 (11.3)	190 (10.6)	150 (8.3)		233 (12.9)	169 (9.4)
pH	6.9	7.12	6.89						7.15*				
P_{CO_2} (mmHg)	10								26*				
Bicarbonate (mEq/L)	6	10	6		11	18		15	9			9	13 and then 5
Anion gap (mmol/L)	25	17	35		22	18		26	21			24	16 and then 19
Ketones*	Yes (serum and urine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	Outpt.	Outpt.	ICU	ICU

CSII, continuous subcutaneous insulin infusion; GI, gastrointestinal, Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

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Peters AL. Diabetes Care. Online June 15th.

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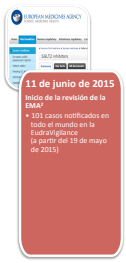
Inhibidores del SGLT-2 y CAD: revisión de la EMA



- 96 casos se relacionaron con Canagliflozina
  - 33 casos en DMT1 (excluidos del análisis adicional)
  - El tiempo hasta la aparición de síntomas osciló entre 3 días y 1 año (un tercio dentro del primer mes de tratamiento)
  - Todos los casos fueron graves; 53 requirieron hospitalización
- 46 casos se relacionaron con Dapagliflozina
  - 12 casos en DMT1
  - El tiempo hasta la aparición de síntomas osciló entre 3 días y 1 año (dentro de los primeros dos meses de tratamiento en 11 casos)
- 5 casos se relacionaron con Empagliflozina
  - 1 caso en DMT1
  - El tiempo hasta la aparición de síntomas osciló entre 1 día y 1.5 meses
- El tiempo hasta la aparición sugiere una relación causal
- Se informará por escrito a los profesionales sanitarios sobre el riesgo de CAD

DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose co-transporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus
European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/SGLT2_inhibitors/human_referral_prac_000053.jsp&mid=WC0b01ac058085c516f. Accessed June 2015

Puntos a resaltar

- Muchos son en DM-1, indicación donde no está aprobada el uso de inhibidores de SGLT-2
- No se conoce bien la fisiopatología
- Se recomienda que en presencia de náuseas medir cetonas
  - Potencialmente cetonuria puede no ser un marcador confiable

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Incidencia DKA en programa canagliflozina

- 12 pacientes con 13 eventos reportados como EAS
- 3 eventos aún no abiertos de CANVAS
- N=17596 pacientes totales
- Incidencia 0.07% (12/17596)
  - 0.07% con canagliflozina 100 mg
  - 0.11% con canagliflozina 300 mg
  - 0.03% con comparador
- 9/10 con glicemias >250 mg/dl

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Ngozi E. Diabetes Care. 2015;epub 1 agosto.

DKA en canagliflozina

- De los 12 pacientes con DKA
  - 6 fueron diagnosticados luego con LADA
  - 8 pacientes en CANVAS, 7 en insulina

	Patients with DKA (n = 12)	Patients without DKA (n = 17,584)
Sex, n (%)		
Male	9 (75.0)	7,182 (40.8)
Female	3 (25.0)	10,401 (59.2)
Age, years	69.5 (47, 78)	61.0 (20, 96)
Race, n (%)		
White	11 (91.7)	13,480 (76.7)
Black/African American	0	703 (4.0)
Asian	0	2,148 (12.2)
Other†	1 (8.3)	1,253 (7.1)
Ethnicity, n (%)		
Hispanic or Latino	2 (16.7)	3,118 (17.7)
Not Hispanic or Latino	10 (83.3)	14,385 (81.8)
Other‡	0	81 (0.5)
HbA_{1c}, %	8.9 (7, 11)	8.0 (5, 14)
HbA_{1c}, mmol/mol	74 (53, 97)	66 (31, 130)
BMI, kg/m^2	27.1 (23, 34)	31.3 (15, 73)
eGFR, mL/min/1.73 m^2	69.0 (33, 127)	79.0 (10, 227)
Duration of diabetes, years	13.5 (1, 29)	9.0 (0, 55)

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Ngozi E. Diabetes Care. 2015;epub 1 agosto.

DKA en DM-1

- Reportado con otros inhibidores de SGLT-2
- Ensayo de 12 semanas en DM-1 con canagliflozina
  - 100 mg 4.8% DKA
  - 300 mg 9% DKA
  - Uno de los factores predictores fue la mayor reducción de dosis de insulina

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POR QUÉ LA HIPERGLUCAGONEMIA? CÓMO SE PUEDE MANEJAR?

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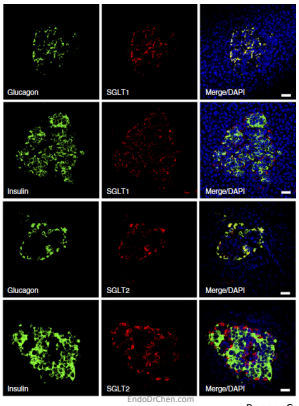

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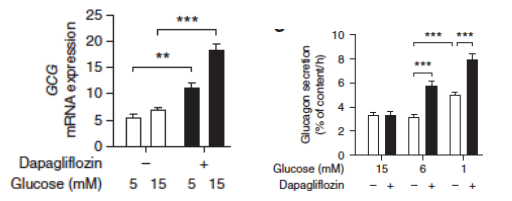
Bonner C. Nat Med. 2015;21(5):512



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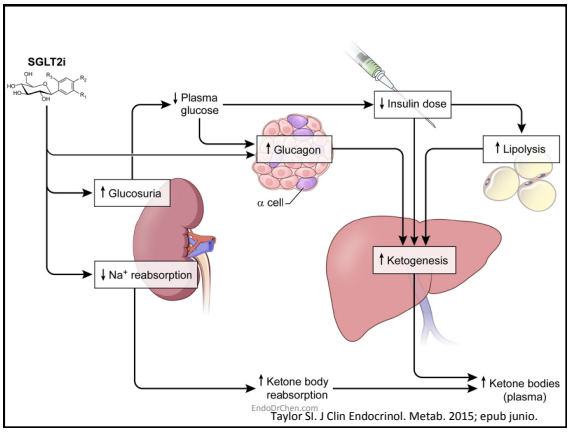
Bonner C. Nat Med. 2015;21(5):512



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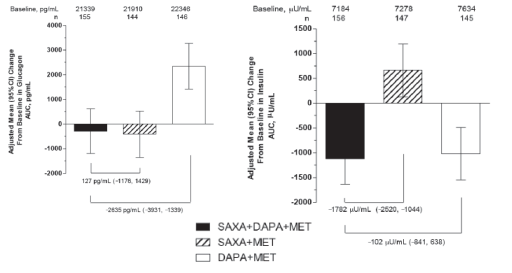
Taylor SI. J Clin Endocrinol. Metab. 2015; epub junio.

Saxa + dapa efectos en niveles de glucagon e insulina



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Hansen L. Endocr Pract. 2014;20:1187

CÓMO MANEJAMOS LAS DESVENTAJAS?

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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

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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

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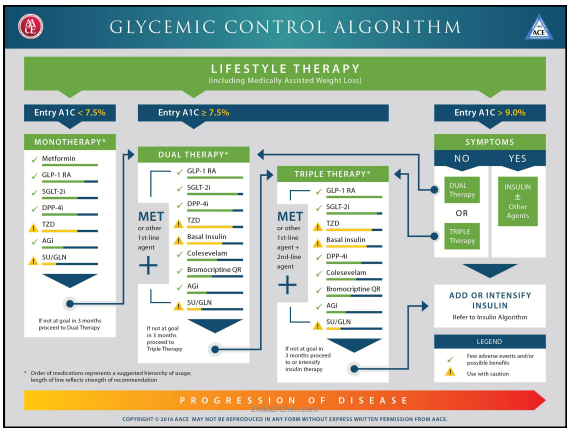

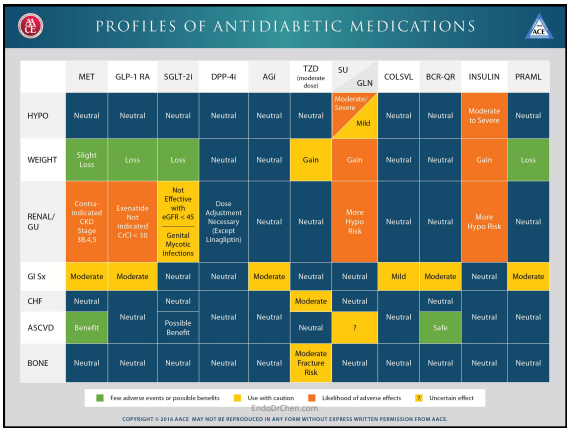

Conclusiones

- Los inhibidores de SGLT-2:
  - Reducción de Hba1c, peso, presión arterial, ácido úrico
  - Única clase terapéutica en DM que ha mostrado reducción de mortalidad TOTAL
  - Mecanismos nefroprotectores prometedores
- Precaución con cetosis euglicémica
- Precaución con uso en DM-1 o en situaciones no aprobadas

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Preguntas…
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