



Eficacia y seguridad de dapagliflozina más metformin

Dr. Chih Hao Chen Ku, FACE

Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica
Sistema de Estudios de Postgrado, Universidad de Costa Rica

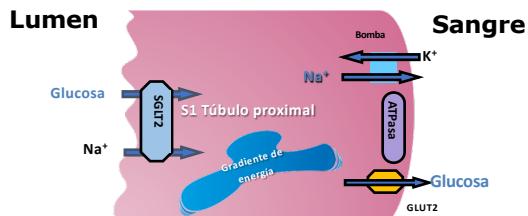
Conflictos de interés

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

Agenda

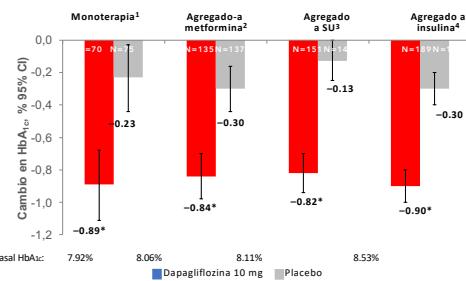
- Fisiología renal del manejo de glucosa
- Efectos farmacológicos de inhibidores de SGLT2
- Efectos cardiovasculares
- Efectos en nefropatía diabética
- Efectos adversos
- Cómo se usan?
- Papel en las guías de tratamiento

SGLT2 permite la reabsorción de glucosa renal



Adaptado de R.A. DeFronzo et al. Diabetes, Obesity and Metabolism 2012; 14:145.

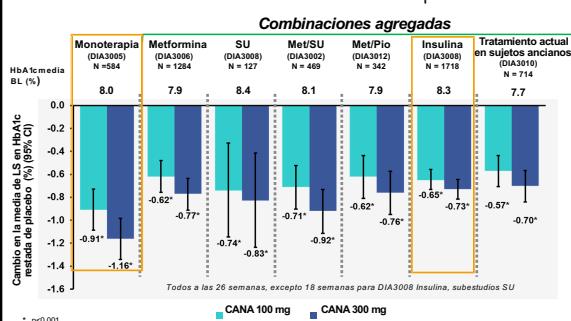
Reducción consistente en la HbA_{1c} en la Semana 24 en diferentes estudios



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 data after rescue (LOCF). ANCOVA, análisis de covariancia; LOCF, la última observación prospectiva realizada.

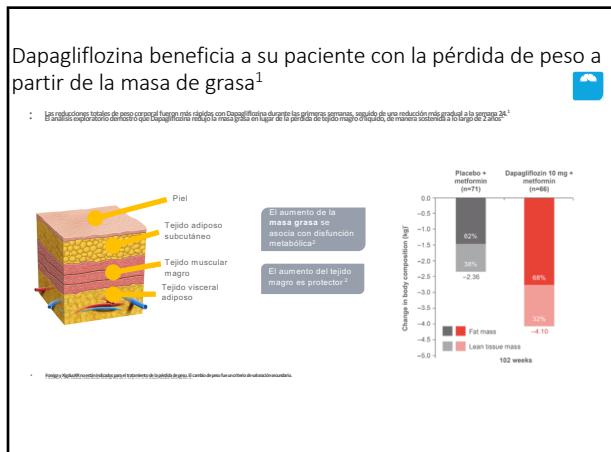
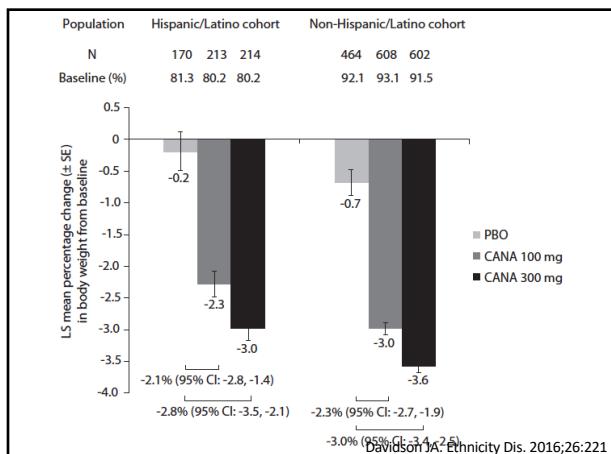
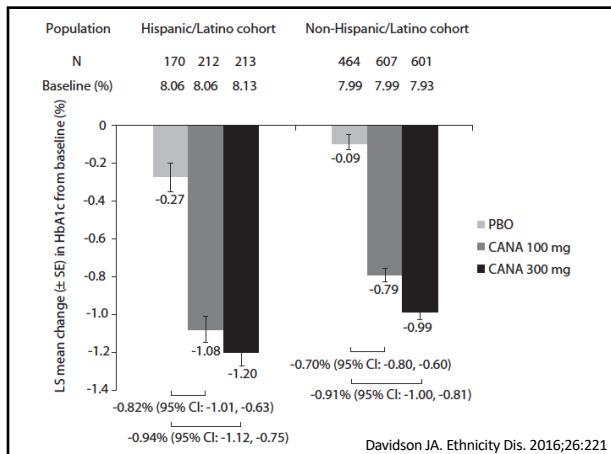
1. Ferrannini E, et al. Diabetes Care 2010;33:2217-24; 2. Bailey CJ, et al. Lancet 2010;375:2223-33; 3. Strojek K, et al. Diabetes Obes Metab 2011;13:928-38; 4. Wilding J, et al. Diabetes 2010;59(Suppl 1):0078-OR.

Cambio en HbA_{1c} desde la basal Estudios de Fase 3 controlados con placebo

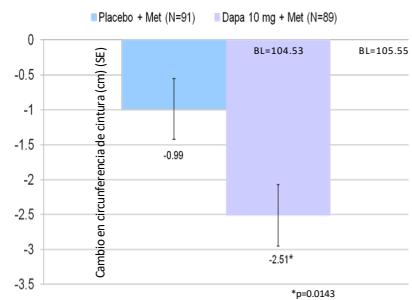


* p<0.001
Con base en modelos ANCOVA, datos antes del rescate (LOCF)

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

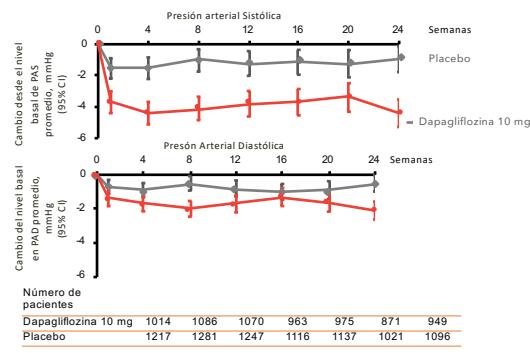


Cambio medio ajustado del perímetro abdominal a la semana 24 (cm)



Bolinder et al. J Clin Endocrinol Metab 2012; 97: 1020-1023

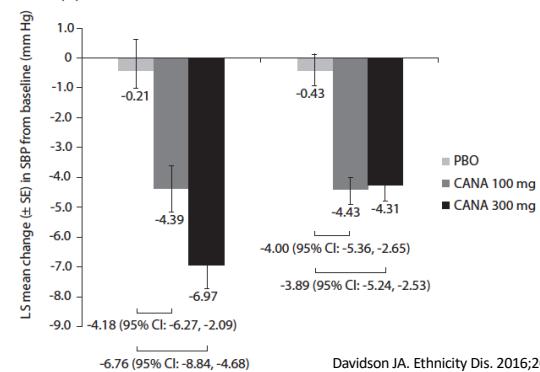
En el conjunto de los estudios, dapagliflozina redujo la TA a lo largo de las 24 semanas.



Sjöström CD. ESC 2012, OP 3972.

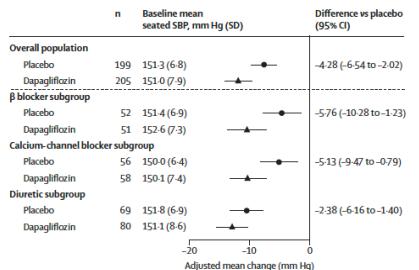
Population Hispanic/Latino cohort Non-Hispanic/Latino cohort

N 170 213 215 465 608 602
Baseline (%) 125.7 125.0 125.9 128.8 129.0 129.8



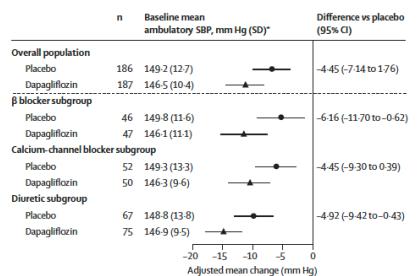
Davidson JA. Ethnicity Dis. 2016;26:221

Efecto en PAS



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

Efecto en PAS en MAPA

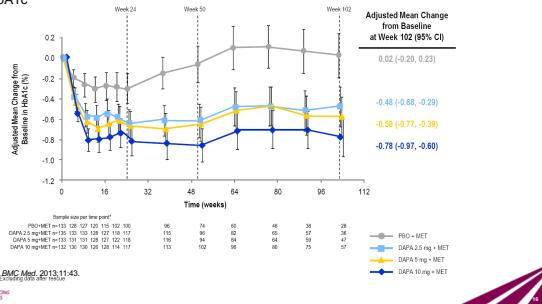


Weber MA. Lancet Diab Endocrinol. 2016;4:211

Quién debe ser hoy el agente de segunda línea?

Dapagliflozin as Add-on to Metformin: Change in HbA1c up to Week 102*

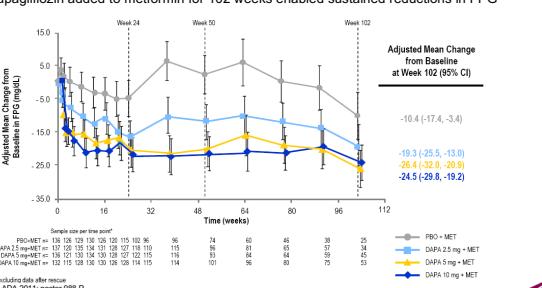
- Dapagliflozin added to metformin for 102 weeks enabled sustained reductions in HbA1c



Bailey, et al. *BMC Med.* 2013;11:43.
Including data after rescue

Dapagliflozin as Add-on to Metformin: Change in FPG up to Week 102*

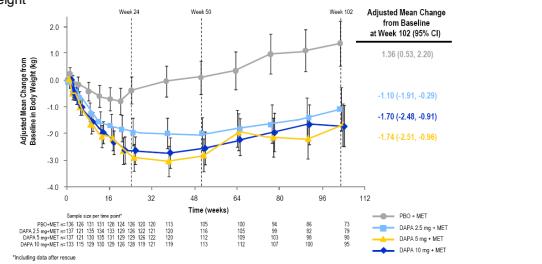
- Dapagliflozin added to metformin for 102 weeks enabled sustained reductions in FPG



*Excludes data after rescue
Bailey, et al. *ADA 2011; poster 988-P.*

Dapagliflozin as Add-on to Metformin: Change in Body Weight up to Week 102*

- Dapagliflozin added to metformin for 102 weeks enabled sustained reductions in body weight

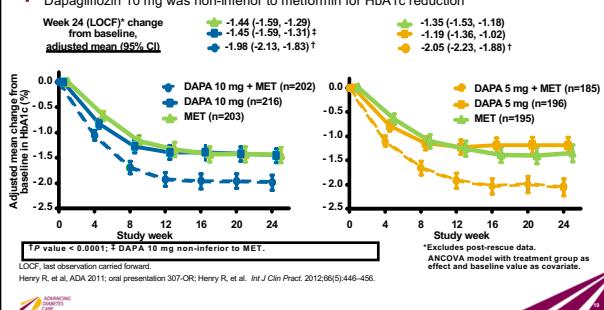


Bailey, et al. *BMC Med.* 2013;11:43.
Including data after rescue



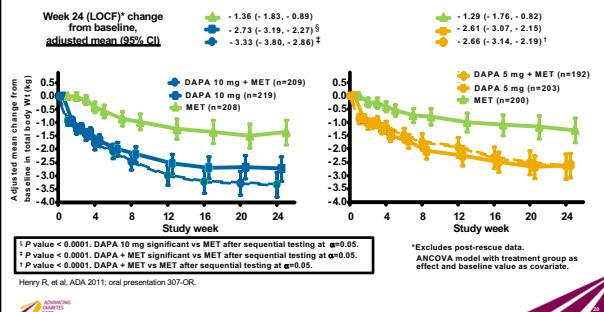
Dapagliflozin in Combination with Metformin: Change in HbA1c Over 24 Weeks

- Dapagliflozin plus metformin demonstrated mean HbA1c reductions significantly greater than either monotherapy
 - Dapagliflozin 10 mg was non-inferior to metformin for HbA1c reduction

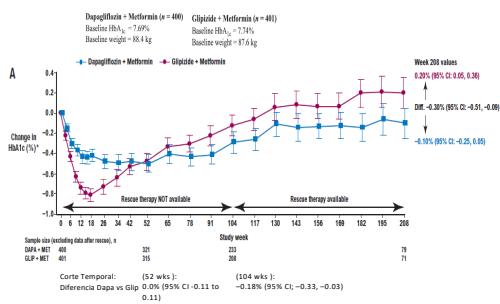


Dapagliflozin in Combination with Metformin: Change in Body Weight Over 24 Weeks

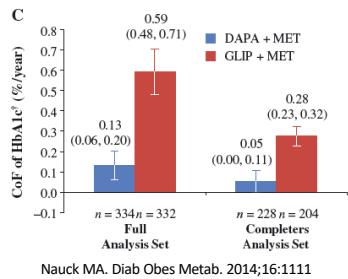
- Mean weight loss with combination therapy and dapagliflozin monotherapy was more than double the weight loss with metformin monotherapy



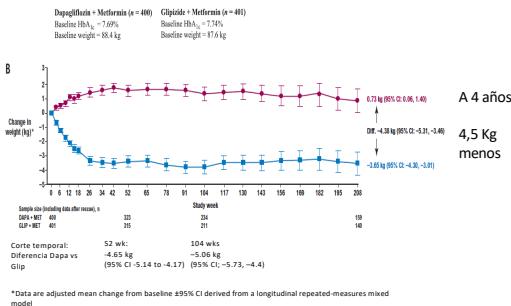
Durabilidad del efecto de reducción de HbA1c



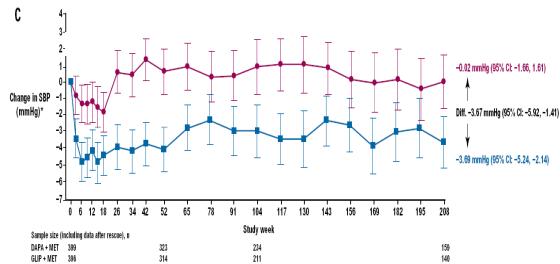
Coeficiente de variación de HbA1c



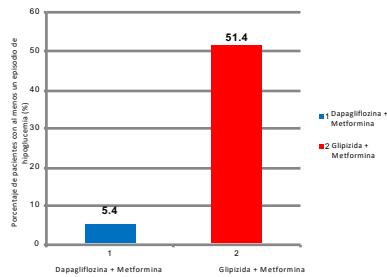
Durabilidad del efecto de reducción de peso



Durabilidad del efecto de reducción de PAS

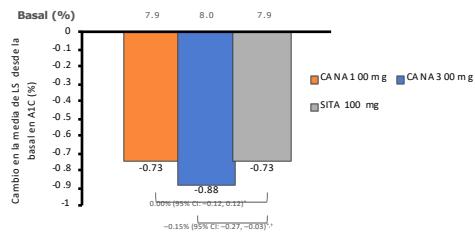


Hipoglicemias



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

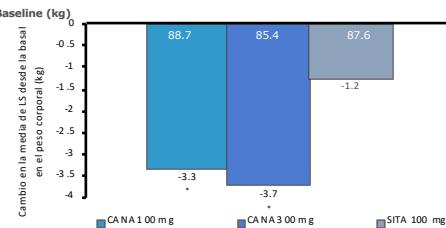
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Estudios comparativos de CANA
Semana 52: A1C (LOCF)



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

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

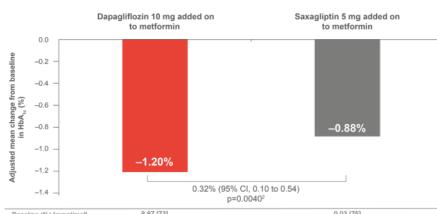
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Semana 52: Peso corporal (LOCF)



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

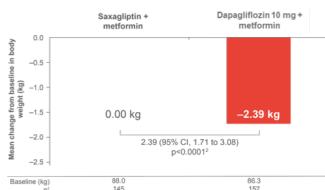
Lavalle-González FJ, et al. Diabetología. 2013. doi:10.1007/s00125-013-3039-1.

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



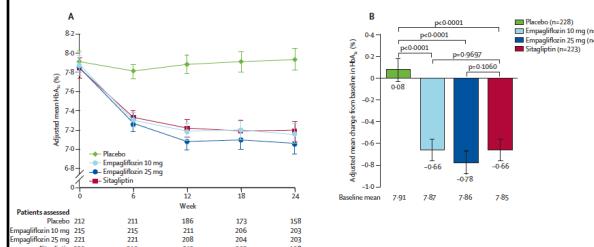
* Phase II, 24-week, randomized, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual-add-on of saxagliptin and dapagliflozin with either saxagliptin 5 mg or dapagliflozin 10 mg added alone in adults with Type 2 diabetes who had inadequately glycemic control (HbA_{1c} 6.8% to 12.7%) on metformin. The primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks. The study included 296 patients assigned to dapagliflozin 10 mg added on to metformin (n=145), saxagliptin 5 mg added on to metformin (n=143), and metformin monotherapy (n=126).
^a Number of randomized patients with non-missing baseline values and three 24 values last observation carried forward (LOCF).
1. Asociación Argentina de Endocrinología y Nutrición. Asociación Argentina de Endocrinología y Nutrición. September 2016.

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



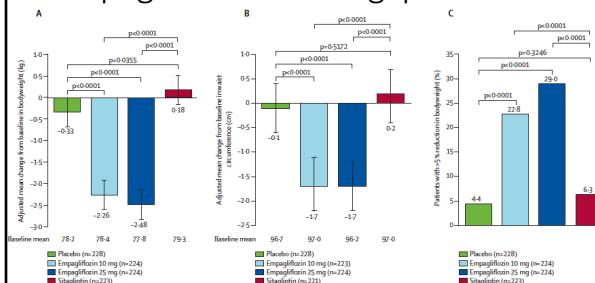
* Forxiga y Kijivir® no están indicados para el tratamiento de la pérdida de peso. El cambio de peso fue un criterio de valoración secundario.
• Phase II, 24-week, randomized, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual-add-on of saxagliptin and dapagliflozin with either saxagliptin or dapagliflozin added alone in adults with Type 2 diabetes who had inadequately glycemic control (HbA_{1c} 6.8% to 12.7%) on metformin. The primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks. The study included 296 patients assigned to dapagliflozin 10 mg added on to metformin (n=145), saxagliptin 5 mg added on to metformin (n=143), and metformin monotherapy (n=126).
1. Asociación Argentina de Endocrinología y Nutrición. Asociación Argentina de Endocrinología y Nutrición. September 2016.

Empagliflozina vs sitagliptina



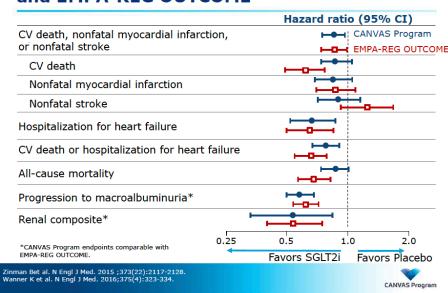
Roden M. Lancet Diab Endocrinol. 2013;1:208

Empagliflozina vs sitagliptina

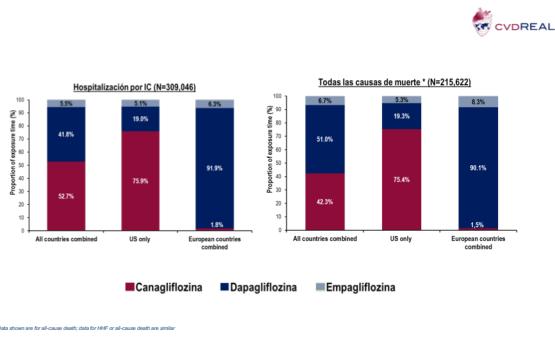


Desenlaces cardiovasculares

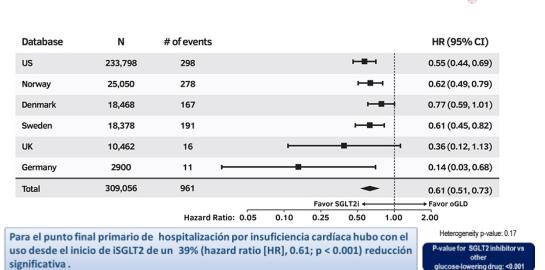
Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



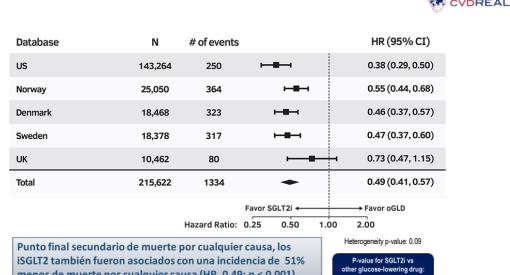
Contribución de los iSGLT2



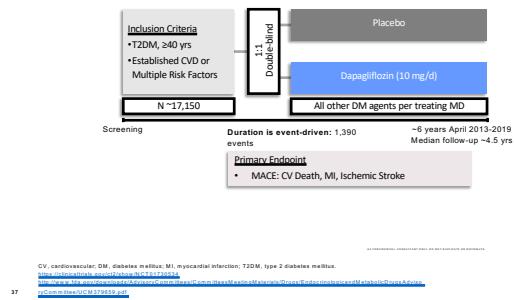
Hospitalización por Insuficiencia Cardiaca Punto final primario



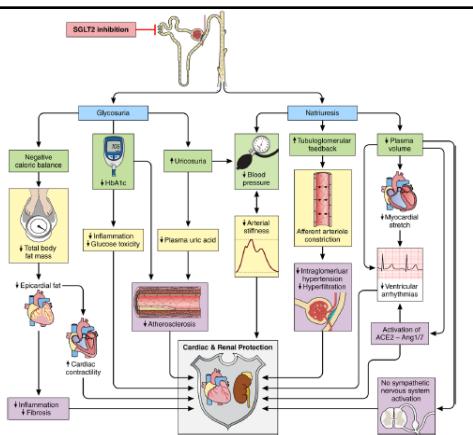
Todas las causas de muerte – Punto final secundario

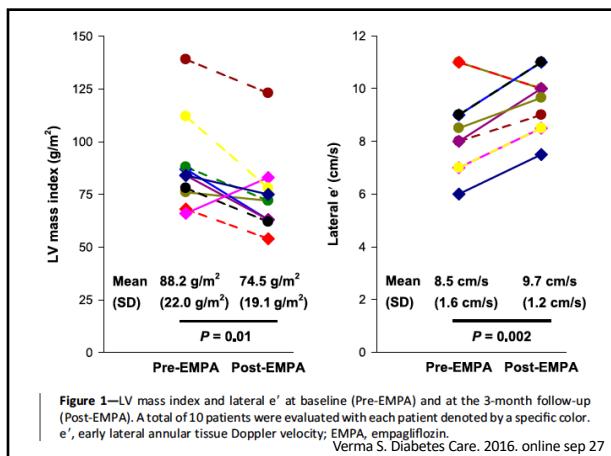


DECLARE - Dapagliflozin Effects on CardiovascuLAR Events



Cómo se explica el beneficio cardiovascular?





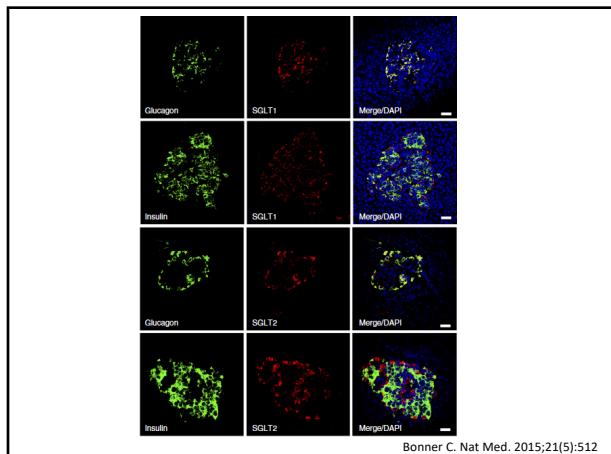
FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

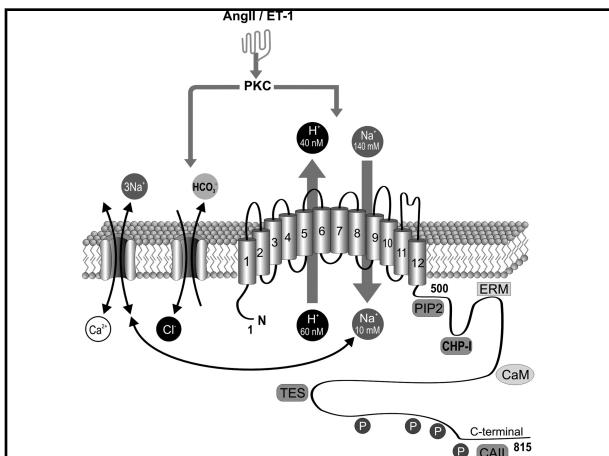
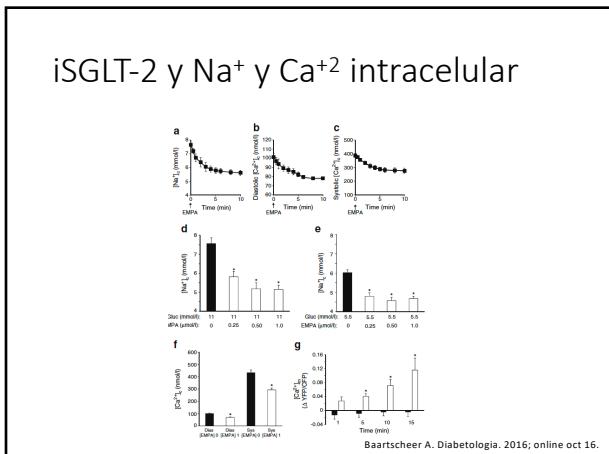
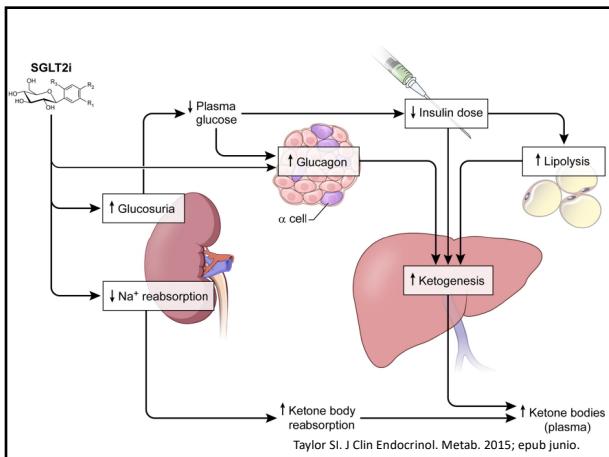
[05-15-2015]

Safety Announcement

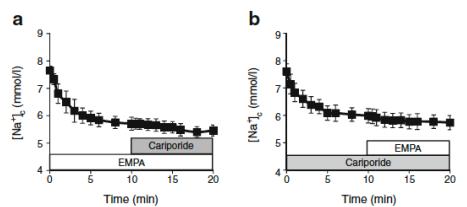
The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing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



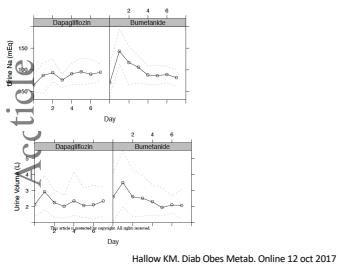


Efecto en Na⁺-H⁺



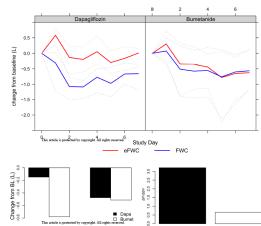
Baartscheer A. Diabetologia. 2016; online oct 16.

Dapagliflozina vs bumetanida



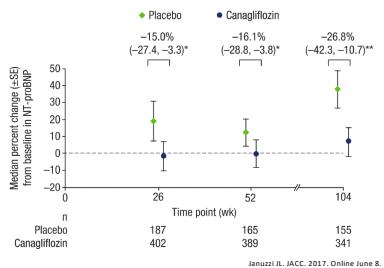
Hallow KM. Diab Obes Metab. Online 12 oct 2017

Dapagliflozina vs bumetanida

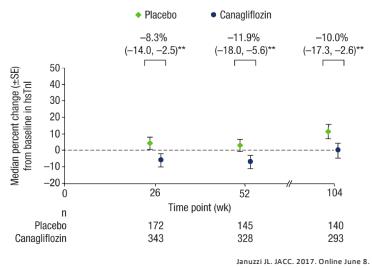


Holloway KA. *Dish-Offs Match*. Online 12 sept 2011.

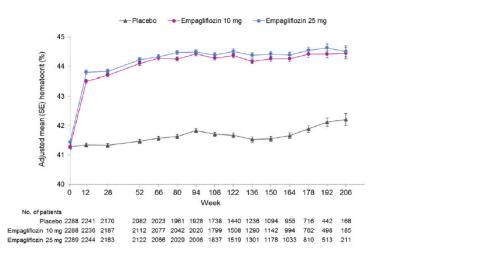
BNP



Troponina



EMPAREG: efecto en hematocrito



EMPAREG: análisis de variables

	Hazard ratio for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.915 (0.89, 0.970)	
Adjusted for		
HbA _{1c}	0.624 (0.49, 0.753)	3.0
PPG	0.625 (0.49, 0.757)	10.1
Age	0.593 (0.47, 0.724)	-7.5
DBP	0.614 (0.49, 0.739)	-0.3
Heart rate	0.623 (0.49, 0.750)	2.0
LDL-C	0.596 (0.47, 0.748)	-6.5
HDL-C	0.636 (0.56, 0.799)	6.9
log(TG)	0.604 (0.47, 0.730)	-4.7
FPG	0.586 (0.45, 0.741)	-8.9
log(UACr)	0.649 (0.51, 0.815)	11.1
eGFR (MDRD)	0.623 (0.49, 0.750)	5.3
eGFR (CKD-EPI)	0.632 (0.56, 0.791)	5.6
Weight	0.579 (0.46, 0.727)	-12.4
BMI	0.578 (0.46, 0.726)	-12.8
WC	0.598 (0.47, 0.750)	-3.8
Hemoglobin	0.791 (0.62, 1.000)	51.8
Hemopexin	0.789 (0.62, 0.989)	48.6
Albumin	0.696 (0.55, 0.873)	25.5
Uric acid	0.693 (0.53, 0.869)	24.6

Cox proportional hazards regression analysis in patients treated with one or more doses of study drug. PPG, first postprandial; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; WC, waist circumference.

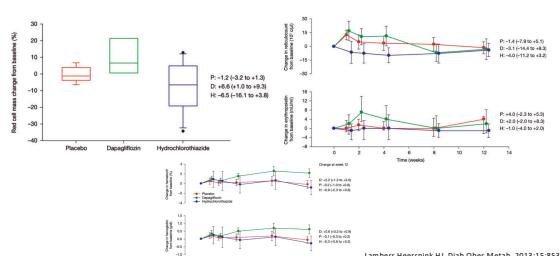
Inzucchi SE. Diabetes Care. 2018;41:356

Regulación de secreción de eritropoyetina

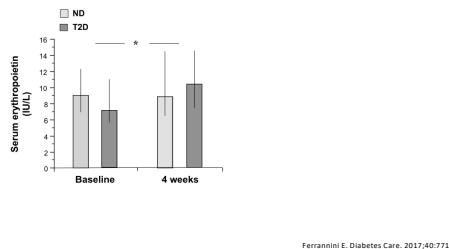
- Caída de perfusión renal
- Hipoxia
- Sales de cobalto
- Andrógenos
- Alcalosis
- catecolaminas

Ganong Physiology 2018. Chapter 38

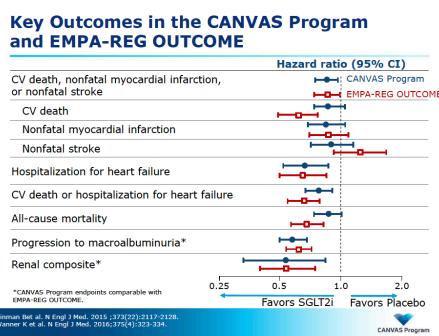
Masa de glóbulos rojos



Niveles de EPO con empagliflozina



Riñón: efecto nefroprotector?

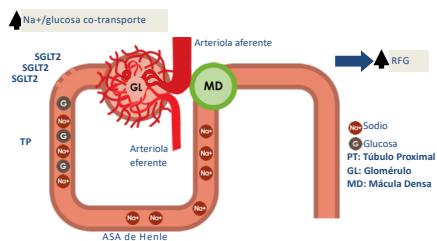


IDNT and RENAAL Trial Comparison of Major Endpoints

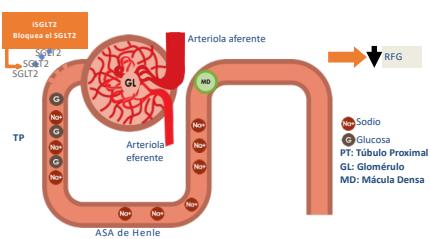
	RRR (%)			
	RENAAL	IDNT		
	Losartan vs control	Irbesartan vs control	Irbesartan vs amlodipine	Amlodipine vs control
Doubling of Creat, ESRD, or death	16 (P=0.02)	20 (P=0.02)	23 (P=0.006)	-4 (P=0.69)
Doubling of Creat	25 (P=0.006)	33 (P=0.003)	37 (P<0.001)	-6 (P=0.60)
ESRD	28 (P=0.002)	23 (P=0.07)	23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

Lewis EJ et al. *N Engl J Med*, 2001;345:851-60.

Brenner BM et al. *N Engl J Med*, 2001;345:851-9.



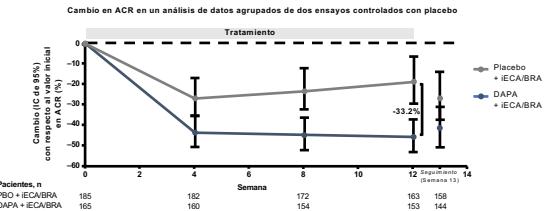
Adaptado de Cheriex O et al. Circulation 2014;129:587



Adaptado de Cheriex O et al. Circulation 2014;129:587

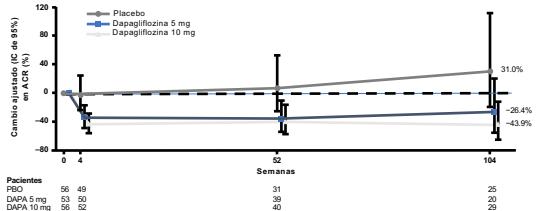
Dapagliflozina Reduce la Albuminuria en Pacientes con Diabetes e Hipertensión al Final de la Terapia con iECA/BRA

- Dapagliflozina reduce la albuminuria en pacientes con DMT2 e hipertensión recibiendo inhibidores de la ECA o BRA – sin que se incremente la frecuencia de eventos renales adversos



Dapagliflozina reduce la Albuminuria en la Etapa 3 de IRC

- Este análisis posterior incluyó 166 pacientes con IRC en Etapa 3 y el incremento de la albuminuria ($\geq 3.4 \text{ mg}/\text{mmol}$)



Recordar que...

- Metformin en disfunción renal:
 - >45 cc/min: dosis usual
 - 30-45 cc/min: reducir la dosis a la mitad y no iniciar pacientes nuevos, los que lo vienen tolerando se puede mantener

Eventos adversos

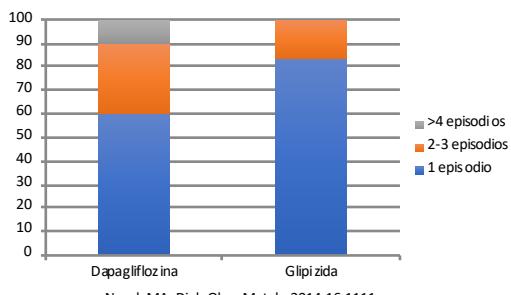
Dapagliflozina - Infecciones Micóticas Genitales

- 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
Infeción 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/endocrinologicandmetabolicdrugadvisorycommittee/ucm378079.pdf>

Infecciones genitales: número de episodios



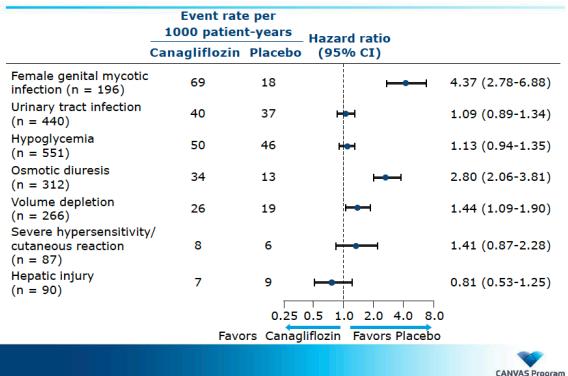
Dapagliflozina - Infecciones de Vías Urinarias

- 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>

Adverse Events (CANVAS)



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 = per 100 patient-years

Patients treated with ≥1 dose of study drug
 Based on 79 MedDRA preferred terms



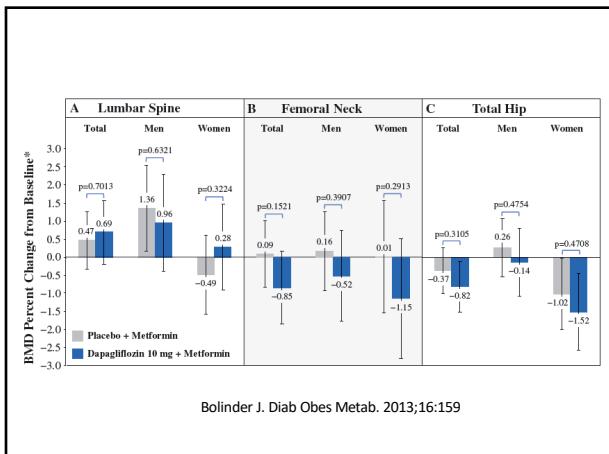
Hipotensión postural

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

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

<http://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM092004.pdf>

Seguridad ósea



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)

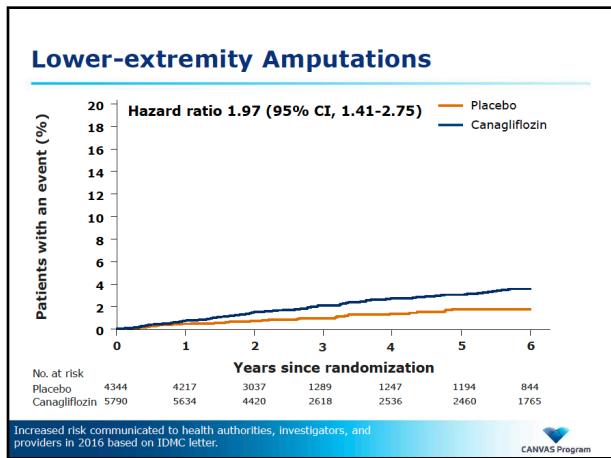
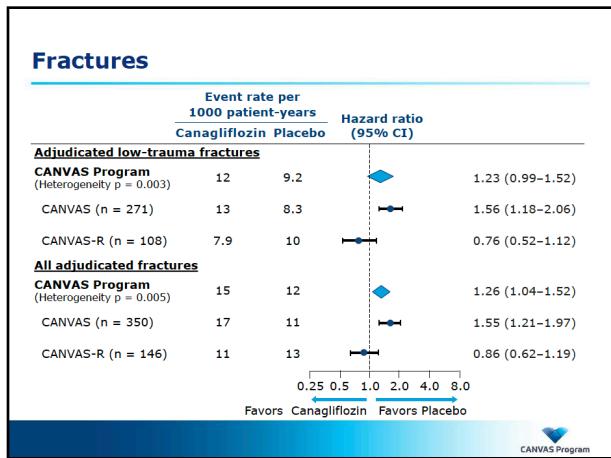
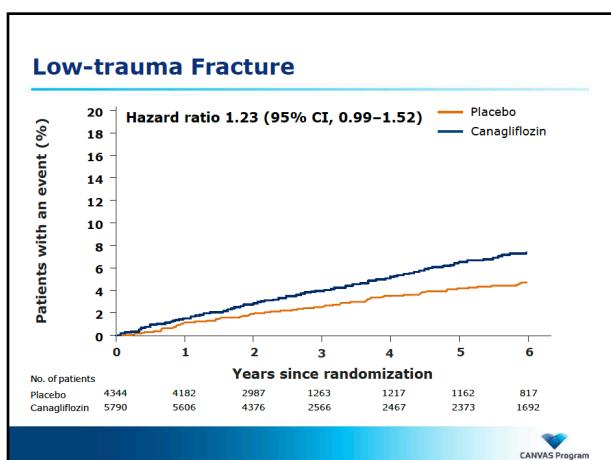
DAPA=Dapagliflozina; PBO=Placebo
EMDAC Documento de referencia disponible en:
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologycandmetabolicdrugsadvisorycommittee/ucm078079.pdf>

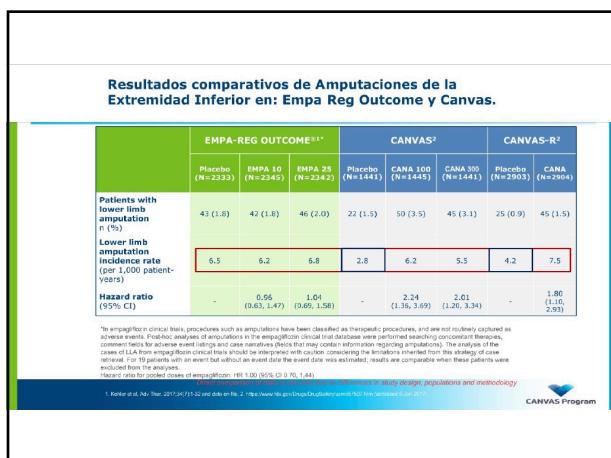
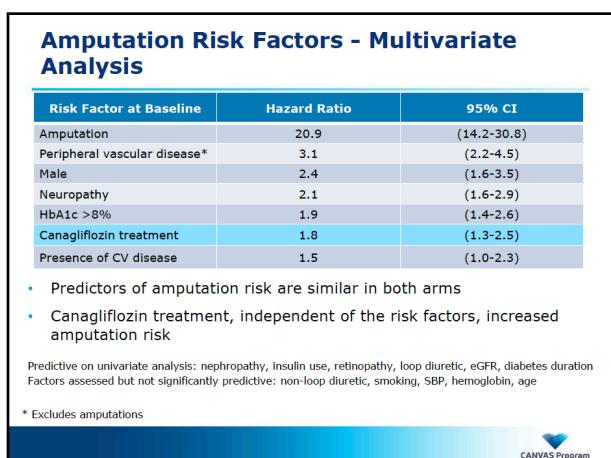
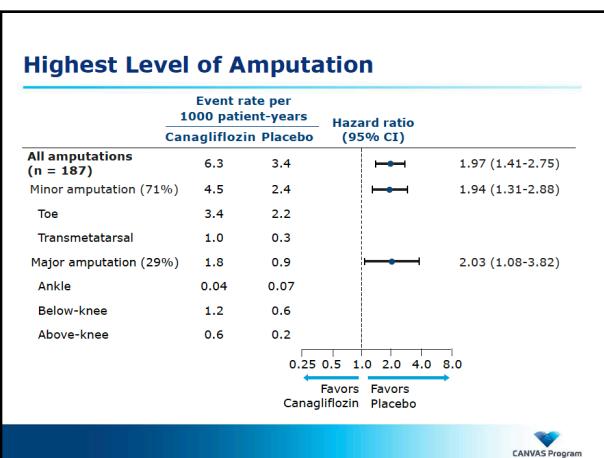
Other adverse events (2)

	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 standardized MedDRA queries
†Based on 62 MedDRA preferred terms





FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

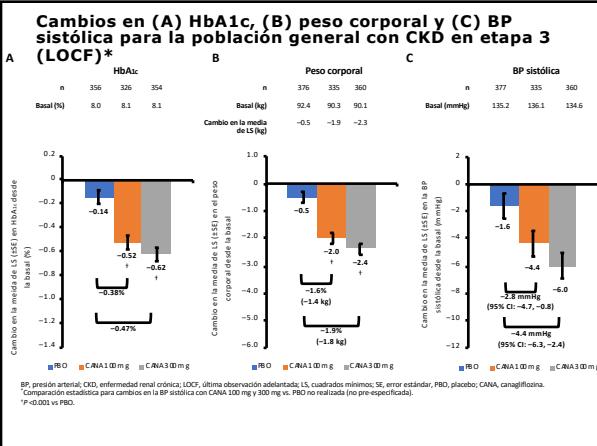
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Safety Announcement

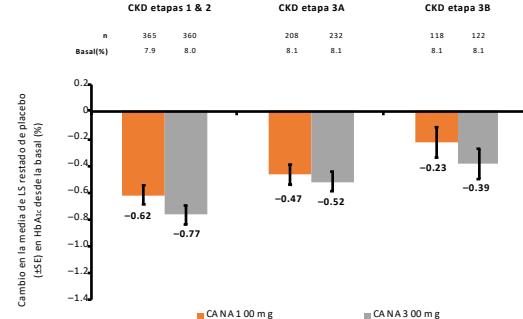
[8-29-2018] The U.S. Food and Drug Administration (FDA) is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.

Cómo se usan?

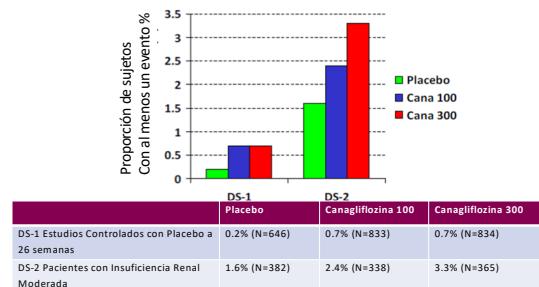
- AEC mayor a 60 cc/min
 - Dapagliflozina 10 mg por día
 - Canagliflozina 300 mg por día
 - Empagliflozina 25 mg por día
- AEC 45-60 cc/min
 - Canagliflozina 100 mg por día
- Insuficiencia hepática
 - Dapagliflozina 5 mg por día
 - Canagliflozina 100 mg por día
 - Empagliflozina 10 mg por día



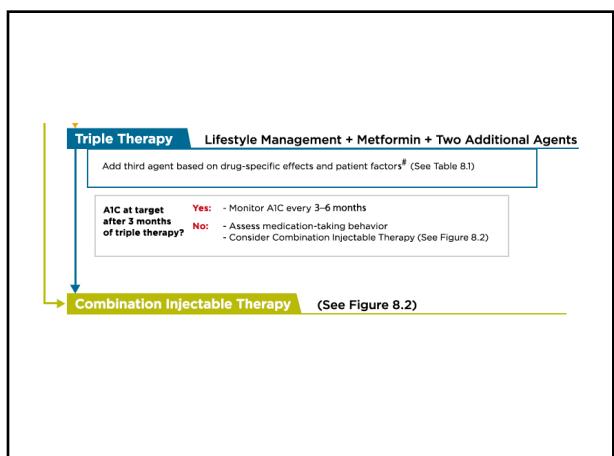
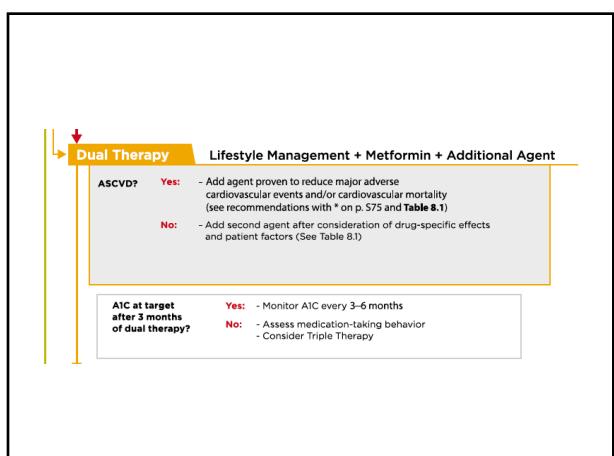
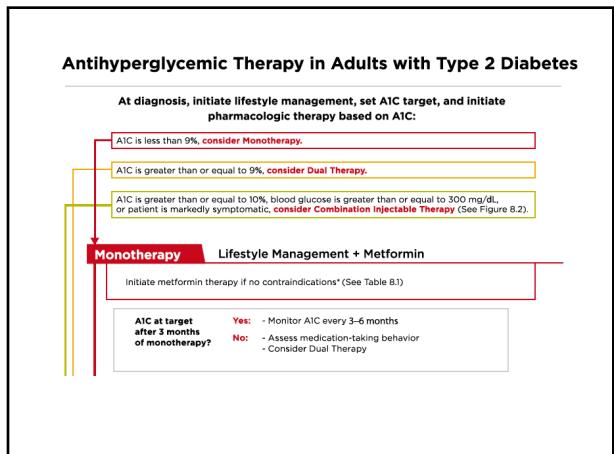
Comparación del efecto de canagliflozina restado de PBO en personas con CKD en etapas 1 y 2 vs. etapa 3*

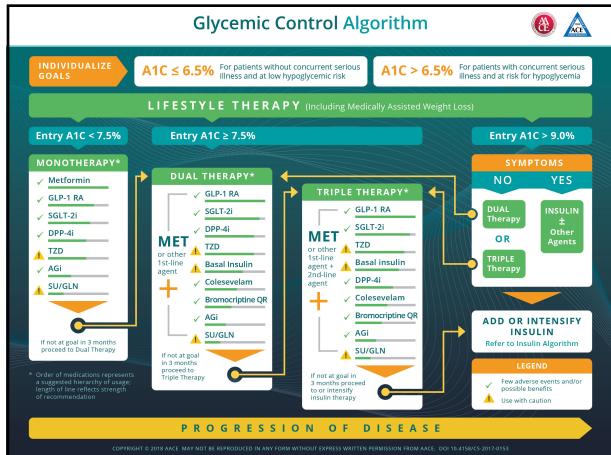


Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



Qué indican las guías?





Guías ESC

