Eficacia y seguridad de dapagliflozina más metformin

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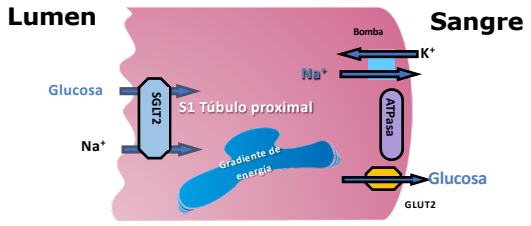
Conflictos de interés

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

Agenda

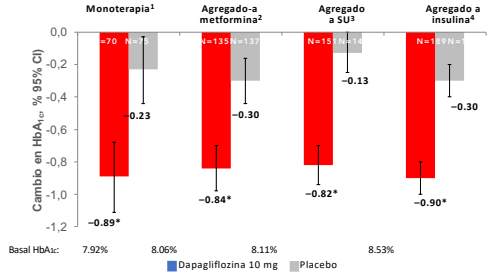
- Fisiología renal del manejo de glucosa
- Efectos farmacológicos de inhibidores de SGLT2
- Efectos cardiovasculares
- Efectos en nefropatía diabética
- Efectos adversos
- Cómo se usan?
- Papel en las guías de tratamiento

SGLT2 permite la reabsorción de glucosa renal



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

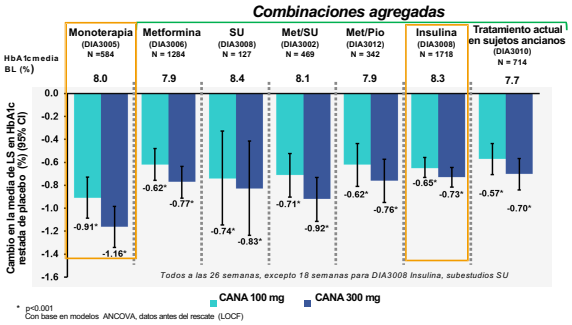
Reducción consistente en la HbA_{1c} en la Semana 24 en diferentes estudios



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

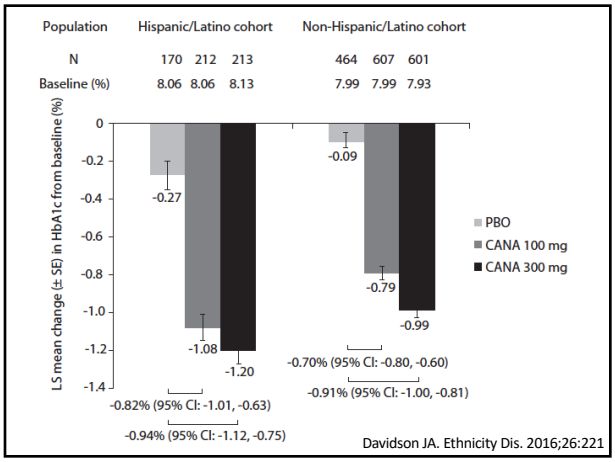
1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. Wilding J, *et al. Diabetes* 2010;**59**(Suppl 1):0078-OR.

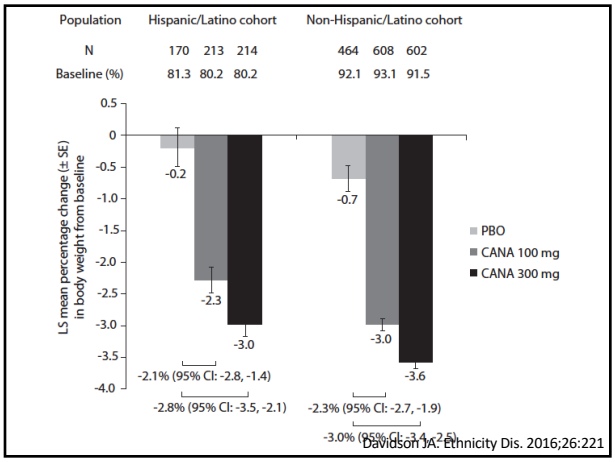
Cambio en HbA1c desde la basal
Estudios de Fase 3 controlados con placebo



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

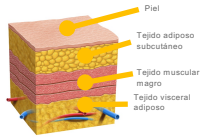
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs





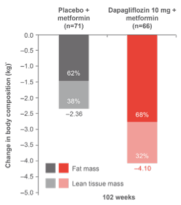
Dapagliflozina beneficia a su paciente con la pérdida de peso a partir de la masa de grasa[1]

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



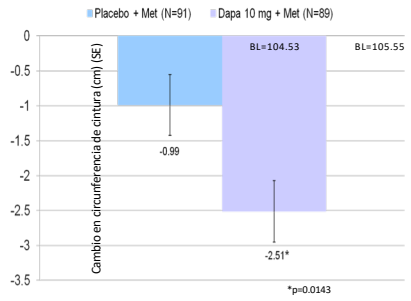
El aumento de la **masa grasa** se asocia con disfunción metabólica[2]

El aumento del tejido magro es protector[2]



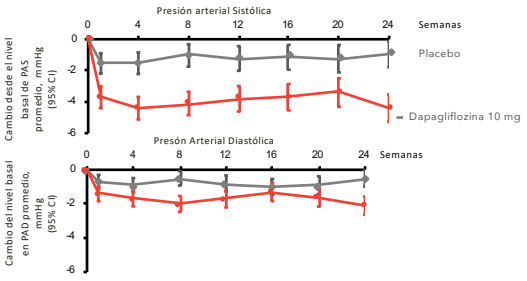
- Fenotipo Algodón: metáfora utilizada para el tratamiento de la pérdida de grasa. El cambio de peso fue un criterio de valoración secundario.

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



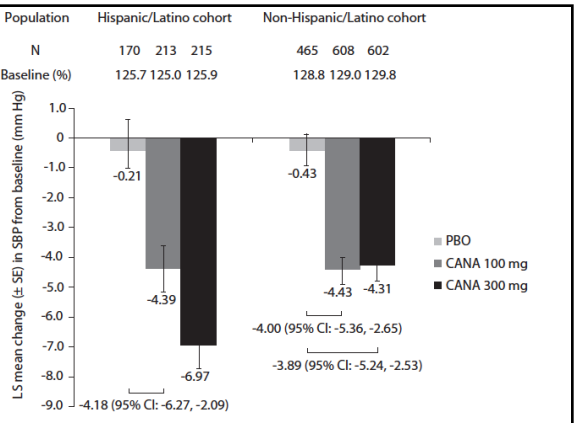
Bolinder et al. J Clin Endocrinol Metab 2012 ; 97: 1020-1031

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



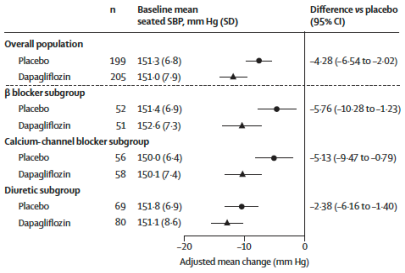
Número de pacientes							
Dapagliflozina 10 mg	1014	1086	1070	963	975	871	949
Placebo	1217	1281	1247	1116	1137	1021	1096

Sjöström CD. ESC 2012. OP 3972.



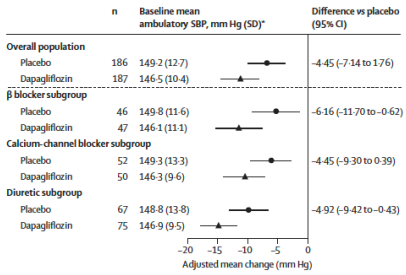
Davidson JA. Ethnicity Dis. 2016;26:221

Efecto en PAS



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

Efecto en PAS en MAPA

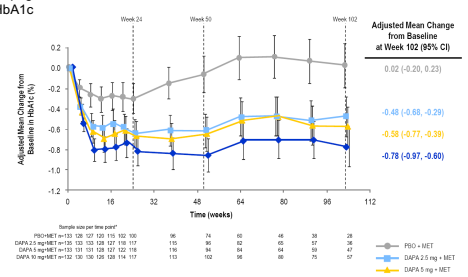


Weber MA. Lancet Diab Endocrinol. 2016;4:211

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

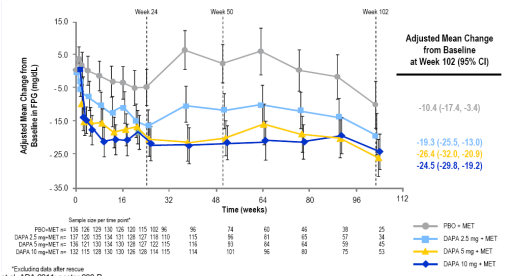


*Excluding data after rescue

Bailey, et al. *BMC Med.* 2013;11:43.

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

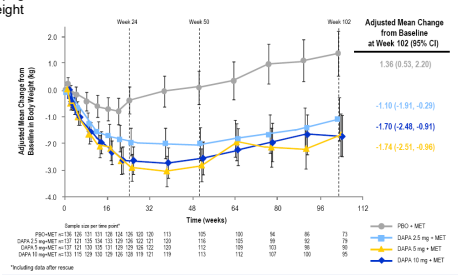


*Excluding data after rescue

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



*Including data after rescue

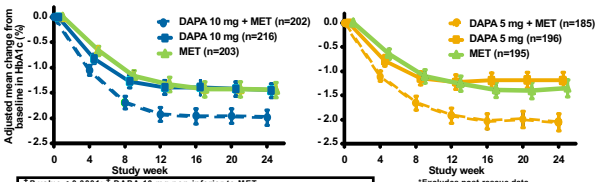
Bailey, et al. *BMC Med.* 2013;11:43.

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

Week 24 (LOCF)* change from baseline, adjusted mean (95% CI)

- -1.44 (-1.59, -1.29)
- -1.45 (-1.59, -1.31) ‡
- -1.98 (-2.13, -1.83) †
- -1.35 (-1.53, -1.18)
- -1.19 (-1.36, -1.02)
- -2.05 (-2.23, -1.88) †



†*P* value < 0.0001; ‡ DAPA 10 mg non-inferior to MET.

*Excludes post-rescue data.
ANCOVA model with treatment group as effect and baseline value as covariate.

LOCF, last observation carried forward.

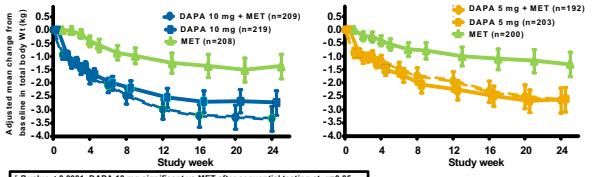
Henry R, et al, ADA 2011; oral presentation 307-OR; Henry R, et al. *Int J Clin Pract.* 2012;66(5):446–456.

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

Week 24 (LOCF)* change from baseline, adjusted mean (95% CI)

- - 1.36 (- 1.83, - 0.89)
- - 2.73 (- 3.19, - 2.27) §
- - 3.33 (- 3.80, - 2.86) ‡
- - 1.29 (- 1.76, - 0.82)
- - 2.61 (- 3.07, - 2.15)
- - 2.66 (- 3.14, - 2.19) †

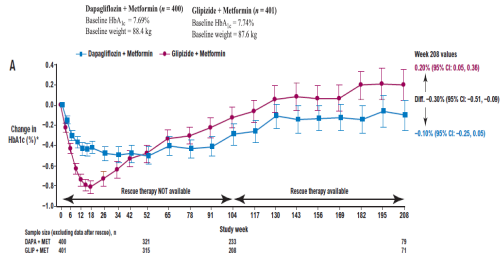


§ *P* value < 0.0001. DAPA 10 mg significant vs MET after sequential testing at α=0.05.
‡ *P* value < 0.0001. DAPA + MET significant vs MET after sequential testing at α=0.05.
† *P* value < 0.0001. DAPA + MET vs MET after sequential testing at α=0.05.

*Excludes post-rescue data.
ANCOVA model with treatment group as effect and baseline value as covariate.

Henry R, et al, ADA 2011; oral presentation 307-OR.

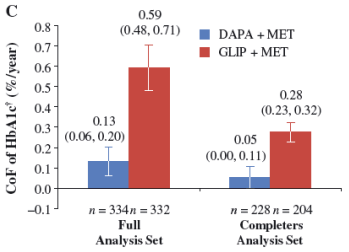
Durabilidad del efecto de reducción de HbA1c



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

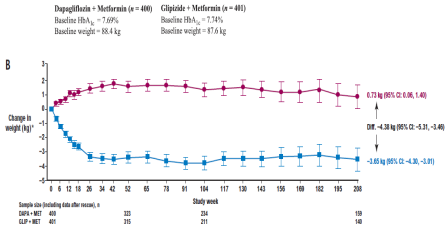
*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model

Coeficiente de variación de Hba1c



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

Durabilidad del efecto de reducción de peso



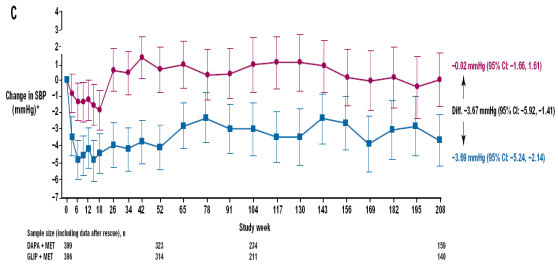
A 4 años

4,5 Kg menos

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

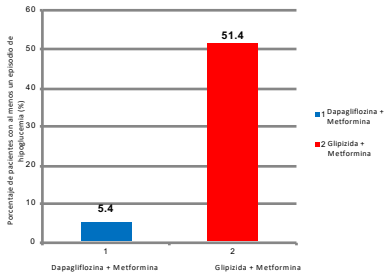
*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model

Durabilidad del efecto de reducción de PAS



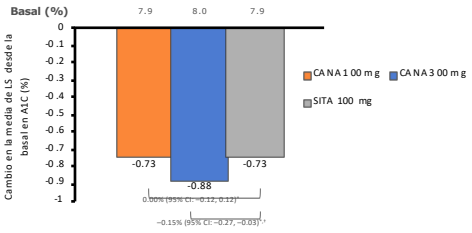
*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model
DAPA, dapagliflozin; GLIP, glipizide; MET, metformin; SBP, systolic blood pressure

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

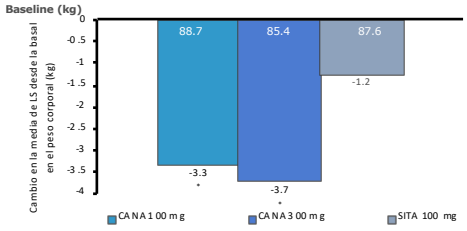
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Estudios comparativos de CANA
Semana 52: A1C (LOCF)



†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=canagliflozina; CI=intervalo de confianza; LOCF=última observación adelantada; LS=cuadrados mínimos; SITA=sitagliptina.

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

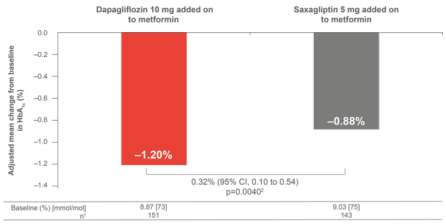
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Semana 52: Peso corporal (LOCF)



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

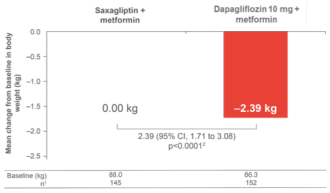
Lavalle-González FJ, et al. *Diabetologia*. 2013. doi:10.1007/s00125-013-3039-1.

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



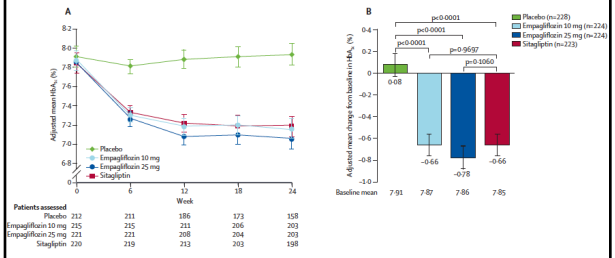
- Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual add-on of saxagliptin and dapagliflozin with either saxagliptin 5 mg or dapagliflozin 10 mg added alone in adults with Type 2 diabetes who had inadequate glycaemic control (HbA1c ≥8% to ≤12%) on metformin. The primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks. The study met its primary endpoint. This is a retrospective post-hoc analysis.
  *Metformin XR. †Number of randomised patients with non-missing baseline values and Week 24 values (last observation carried forward).
  CI, confidence interval; DPP4, dipeptidyl peptidase-4; XR, extended release.
  1. Rosenstock J, et al. Diabetes Care 2014;**37**:1276–83. 2. Data on file 801653. AstraZeneca. September 2016.

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



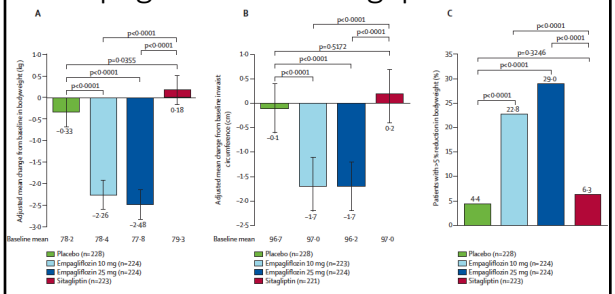
- Forxiga y XigduoXR no están indicados para el tratamiento de la pérdida de peso. El cambio de peso fue un criterio de valoración secundario.
- Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual-add on of saxagliptin and dapagliflozin with either saxagliptin or dapagliflozin added alone in adults with Type 2 diabetes poorly controlled (HbA1c ≥8% to ≤12%) on metformin. Primary efficacy endpoint was adjusted mean change from baseline in HbA_{1c} at 24 weeks.
  *Metformin XR. †Number of randomised patients with non-missing baseline values and Week 24 values (last observation carried forward (LOCF)
  This was a post-hoc analysis comparing dapagliflozin + metformin XR treatment group with the saxagliptin+metformin XR group.
  CI, confidence interval; DPP4, dipeptidyl peptidase-4; XR, extended release.
  1. Rosenstock J, et al. Diabetes Care 2014;**37**:1276–83. 2. Data on file 801653. AstraZeneca. September 2016.

Empagliflozina vs sitagliptina



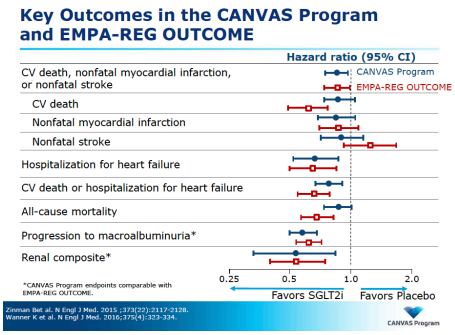
Roden M. Lancet Diab Endocrinol. 2013;1:208

Empagliflozina vs sitagliptina

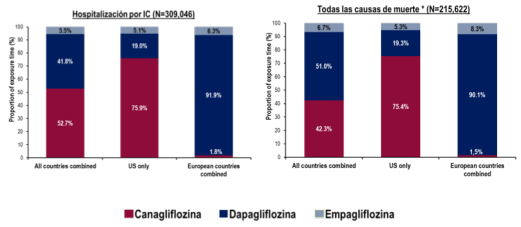


Roden M. Lancet Diab Endocrinol. 2013;1:208

Desenlaces cardiovasculares



Contribución de los iSGLT2



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

Hospitalización por Insuficiencia Cardiaca Punto final primario

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)

Favor SGLT2i ← → Favor oGLD

Hazard Ratio: 0.05 0.10 0.25 0.50 1.00 2.00

Heterogeneity p-value: 0.17

P-value for SGLT2 inhibitor vs other glucose-lowering drug: <0.001

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

Todas las causas de muerte – Punto final secundario

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

Favor SGLT2i ← → Favor oGLD

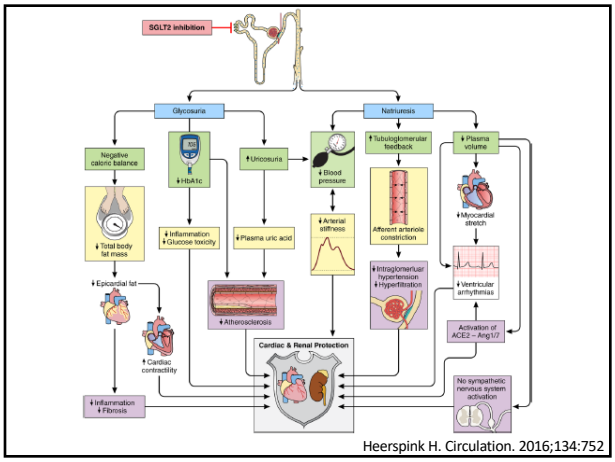
Hazard Ratio: 0.25 0.50 1.00 2.00

Heterogeneity p-value: 0.09

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

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

Cómo se explica el beneficio cardiovascular?



Heerspink H. Circulation. 2016;134:752

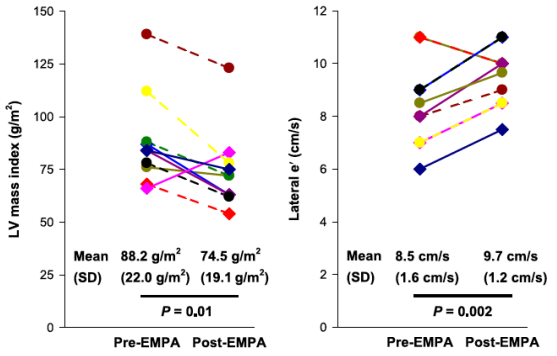


Figure 1—LV mass index and lateral e′ at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e′, early lateral annular tissue Doppler velocity; EMPA, empagliflozin.

Verma S. Diabetes Care. 2016. online sep 27

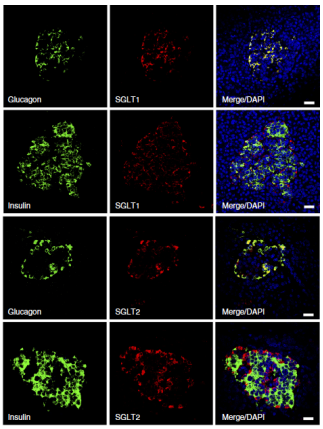
FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

[05-15-2015]

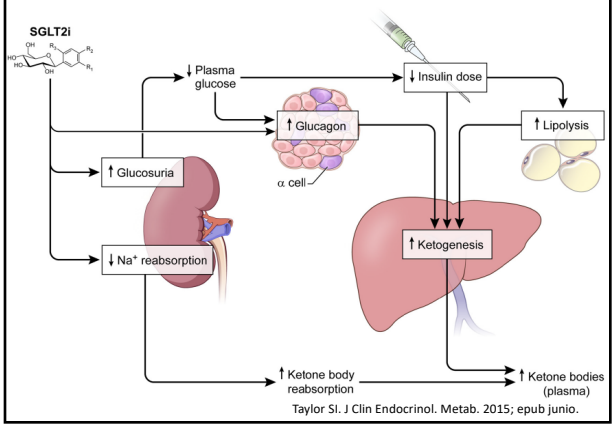
Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

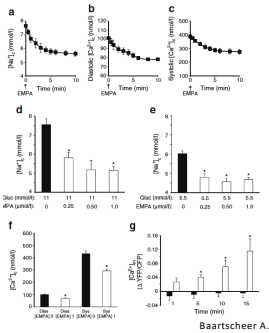


Bonner C. Nat Med. 2015;21(5):512

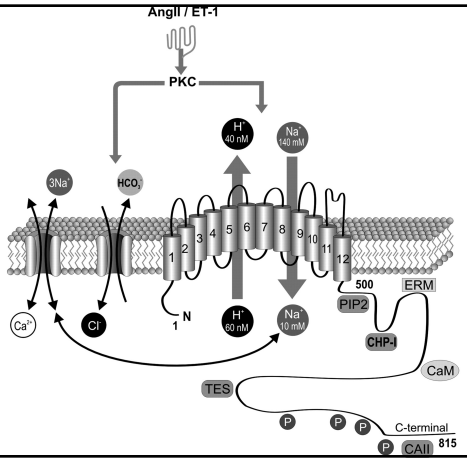


Taylor SI. J Clin Endocrinol. Metab. 2015; epub junio.

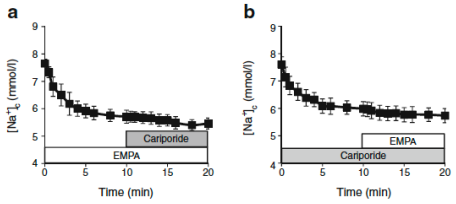
iSGLT-2 y Na^+ y Ca^{+2} intracelular



Baartscheer A. Diabetologia. 2016; online oct 16.

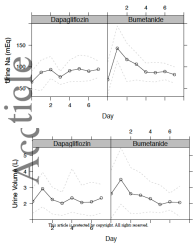


Efecto en Na^+-H^+



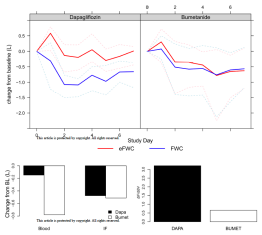
Baartscheer A. Diabetologia. 2016; online oct 16.

Dapagliflozina vs bumetanida



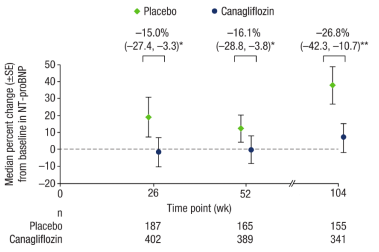
Hallow KM. Diab Obes Metab. Online 12 oct 2017

Dapagliflozina vs bumetanida



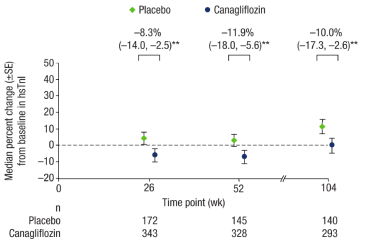
Hallow KM. Diab Obes Metab. Online 12 oct 2017

BNP



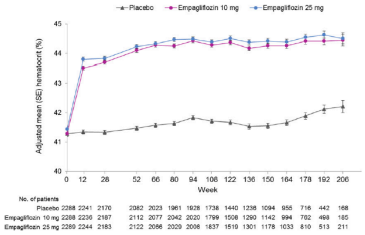
Januzzi JL. JACC. 2017. Online June 8.

Troponina



Januzzi JL. JACC. 2017. Online June 8.

EMPAREG: efecto en hematocrito



Inzucchi SE. Diabetes Care. 2018;41:356

EMPAREG: análisis de variables

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	−7.5
DBP	0.614 (0.490, 0.769)	−0.3
Heart rate	0.621 (0.495, 0.780)	2.0
LDL-C	0.596 (0.475, 0.748)	−6.5
HDL-C	0.636 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	−3.7
FFAs	0.586 (0.463, 0.741)	−9.9
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (MDRD)	0.631 (0.504, 0.790)	5.3
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
Weight	0.579 (0.461, 0.727)	−12.4
BMI	0.578 (0.460, 0.726)	−12.8
WC	0.598 (0.477, 0.750)	−5.8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.619, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

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

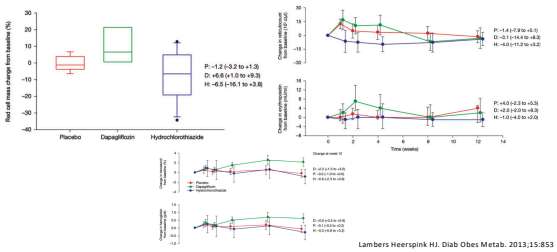
Inzucchi SE. Diabetes Care. 2018;41:356

Regulación de secreción de eritropoyetina

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

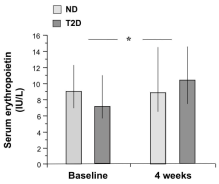
Ganong Physiology 2018. Chapter 38

Masa de glóbulos rojos



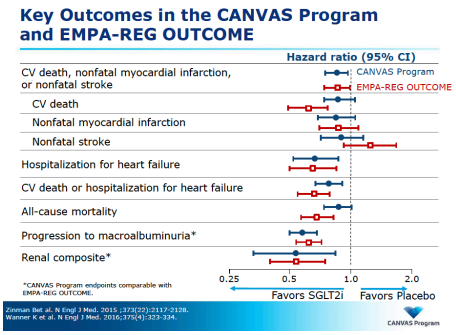
Lambers Heerspink HJ. Diab Obes Metab. 2013;15:853

Niveles de EPO con empagliflozina



Ferrannini E. Diabetes Care. 2017;40:771

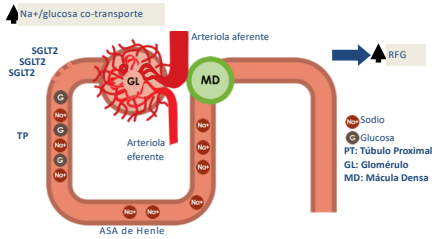
Riñón: efecto nefroprotector?



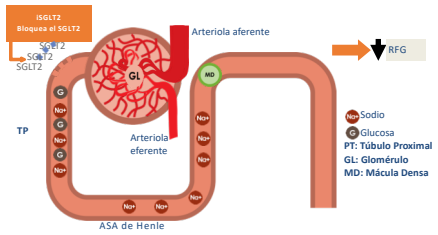
IDNT and RENAAL Trial Comparison of Major Endpoints

	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;345:861-9.



Adaptado de Cherney D et al. *Circulation* 2014;129:587

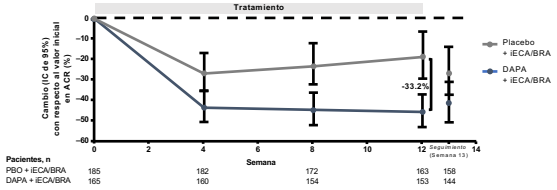


Adaptado de Cherney D et al. *Circulation* 2014;129:587

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

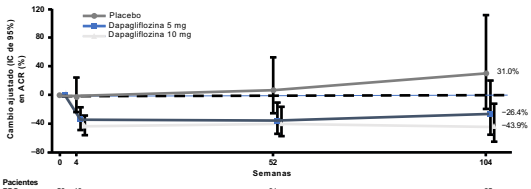
- Dapagliflozina reduce la albuminuria en pacientes con DMT2 e hipertensión recibiendo inhibidores de la ECA o BRA – sin que se incremente la frecuencia de eventos renales adversos

Cambio en ACR en un análisis de datos agrupados de dos ensayos controlados con placebo



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 (≥3.4 mg/mmol)



Pacientes				
PBO	56	49	31	25
DAPA 5 mg	53	50	39	20
DAPA 10 mg	56	52	40	29

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

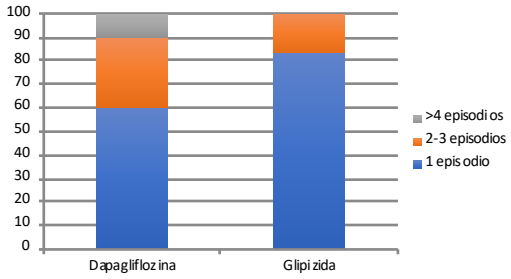
Dapagliflozina - Infecciones Micóticas Genitales

- 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
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

Infecciones genitales: número de episodios



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

Dapagliflozina - Infecciones de Vías Urinarias

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

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

EMDAC Background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

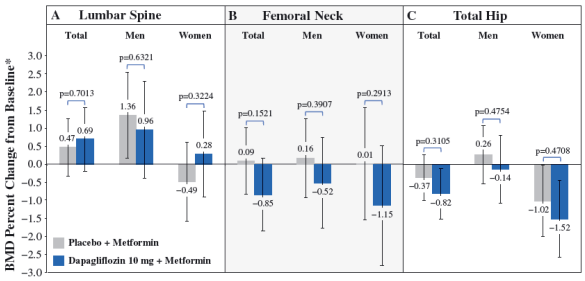
Hipotensión postural

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/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs

Seguridad ósea



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

Dapagliflozina: Eventos de Fracturas

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

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

DAPA= Dapagliflozina; PBO= Placebo

EMDAC Documento de referencia disponible en::
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf;

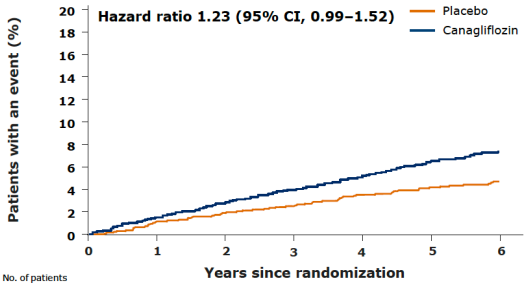
Other adverse events (2)

	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 ≥2 MedDRA preferred terms

Low-trauma Fracture

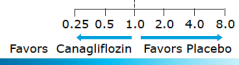


No. of patients							
Placebo	4344	4182	2987	1263	1217	1162	817
Canagliflozin	5790	5606	4376	2566	2467	2373	1692

CANVAS Program

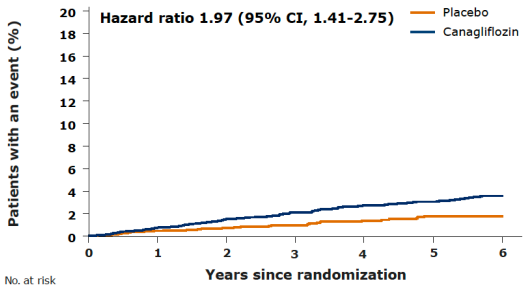
Fractures

	Event rate per 1000 patient-years: Canagliflozin	Event rate per 1000 patient-years: Placebo	Hazard ratio (95% CI)
Adjudicated low-trauma fractures			
CANVAS Program (Heterogeneity p = 0.003)	12	9.2	1.23 (0.99–1.52)
CANVAS (n = 271)	13	8.3	1.56 (1.18–2.06)
CANVAS-R (n = 108)	7.9	10	0.76 (0.52–1.12)
All adjudicated fractures			
CANVAS Program (Heterogeneity p = 0.005)	15	12	1.26 (1.04–1.52)
CANVAS (n = 350)	17	11	1.55 (1.21–1.97)
CANVAS-R (n = 146)	11	13	0.86 (0.62–1.19)



CANVAS Program

Lower-extremity Amputations



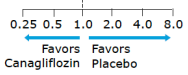
No. at risk							
Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozin	5790	5634	4420	2618	2536	2460	1765

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

CANVAS Program

Highest Level of Amputation

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



CANVAS Program

Amputation Risk Factors - Multivariate Analysis

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

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations

CANVAS Program

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

	EMPA-REG OUTCOME[3,1*]			CANVAS[2]			CANVAS-R[2]	
	Placebo (N=2333)	EMPA 10 (N=2345)	EMPA 25 (N=2342)	Placebo (N=1441)	CANA 100 (N=1445)	CANA 300 (N=1441)	Placebo (N=2903)	CANA (N=2904)
Patients with lower limb amputation n (%)	43 (1.8)	42 (1.8)	46 (2.0)	22 (1.5)	50 (3.5)	45 (3.1)	25 (0.9)	45 (1.5)
Lower limb amputation incidence rate (per 1,000 patient-years)	6.5	6.2	6.8	2.8	6.2	5.5	4.2	7.5
Hazard ratio (95% CI)	-	0.96 (0.63, 1.47)	1.04 (0.69, 1.58)	-	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	-	1.80 (1.10, 2.93)

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

Differences in study design, populations and methodology

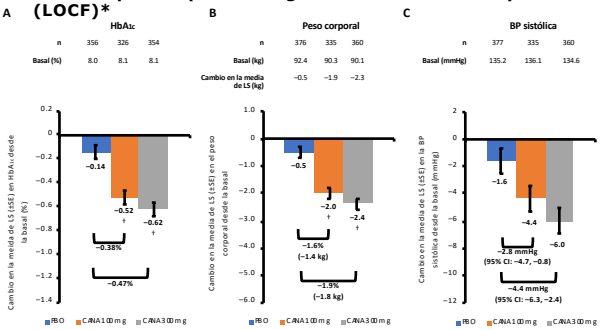
1. Rahkar et al, Adv Ther. 2017;34(7):1-22 and data on file. 2. https://www.fda.gov/Drugs/DrugSafety/ucm535167.htm (accessed 6 Jun 2017)

CANVAS Program

Cómo se usan?

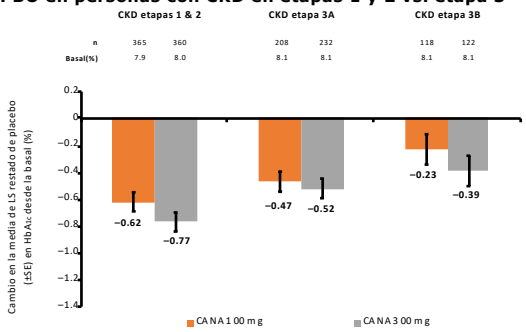
- AEC mayor a 60 cc/min
  - Dapagliflozina 10 mg por día
  - Canagliflozina 300 mg por día
  - Empagliflozina 25 mg por día
- AEC 45-60 cc/min
  - Canagliflozina 100 mg por día
- Insuficiencia hepática
  - Dapagliflozina 5 mg por día
  - Canagliflozina 100 mg por día
  - Empagliflozian 10 mg por día

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



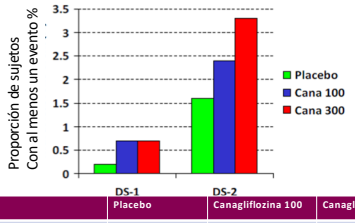
BP, presión arterial; CKD, enfermedad renal crónica; LOCF, última observación adelantada; LS, cuadrados mínimos; SE, error estándar, PBO, placebo; CANA, canagliflozina.
*Comparación estadística para cambios en la BP sistólica con CANA 100 mg y 300 mg vs. PBO no realizada (no pre-especificada).
†P <0.001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

Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



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

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

Qué indican las guías?

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure B.2).

Monotherapy Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table B.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?
- **Yes:** - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)
- **No:** - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

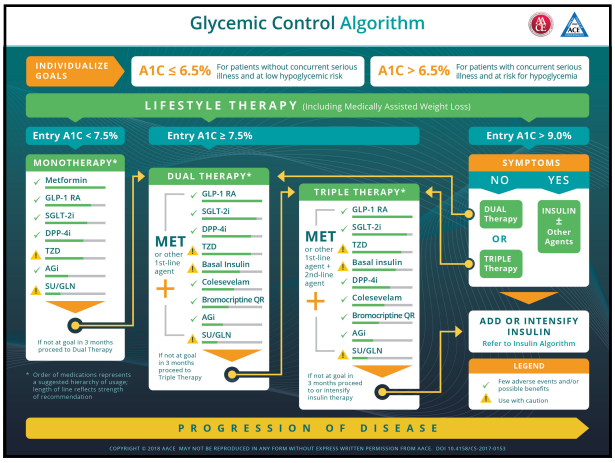
A1C at target after 3 months of dual therapy?
- **Yes:** - Monitor A1C every 3–6 months
- **No:** - Assess medication-taking behavior
  - Consider Triple Therapy

Triple Therapy Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?
- **Yes:** - Monitor A1C every 3–6 months
- **No:** - Assess medication-taking behavior
  - Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)



Guías ESC

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B

Preguntas…

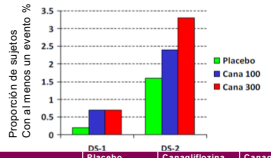
chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com

EndoDrChen.com

Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



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1. Kaon 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/CommitteeMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm338233.htm Accesado Agosto 2, 2014

News > Medscape Medical News

Canagliflozin Renal Outcomes Study Is Halted Early for Efficacy

Miriam E. Tucker
July 17, 2018

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An early halt has been called for a phase 3 randomized clinical trial investigating renal outcomes for the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin (*Invokana*, Janssen) in patients with type 2 diabetes and kidney disease because of achievement of prespecified efficacy criteria.

The Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial is evaluating the efficacy and safety of adding canagliflozin 100 mg/day versus placebo to standard of care, which includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).