La importancia del riñón en diabetes, enfocando el tratamiento con 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

Caso clínico

- Femenina de 64 años, costarricense, a quien se le diagnosticó DM-2 en 2005
- Tratada inicialmente con glicazida MR + metformin hasta noviembre 2011
- Se cambió a insulina NPH+ metformin
- Noviembre 2009: insulina premezcla bid + metformin
- 2011: Basal bolo + metformin

Caso clínico

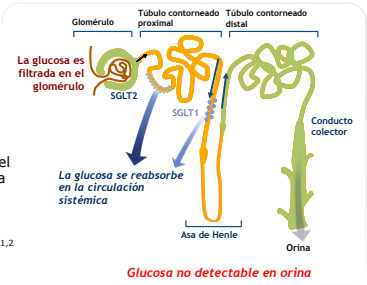
- Desde el 2011, su hba1c ha estado en 10%, 10.8%, 8.9%, 8.6%, 8.9%, 8.9%, 8.7%
- Septiembre 2014: hba1c 8.3%
- Dosis total diaria de insulina: 144 units (1.6 u/kg)
- Peso actual 90 kg
- Qué opciones de tratamiento quedan?

Agenda

- Manejo renal de glucosa
- SGLT-2 en pacientes diabéticos
- Inhibidores de SGLT-2
  - Eficacia, sobre todo comparado con otros agentes
  - Seguridad
  - Nuevas alertas: cetoacidosis euglicémica

Cotransportadores de sodio-glucosa (SGLT) y manejo renal normal de la glucosa

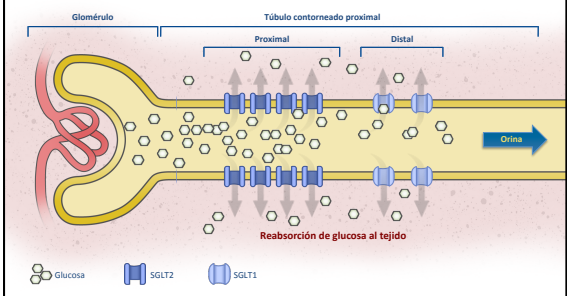
- 180 g/día/1.73 m^2 es la carga de glucosa filtrada.[1]
- SGLT2 transporta 90% de la glucosa filtrada fuera del lumen tubular.[1-4]
- SGLT1 transporta el 10% restante de la glucosa filtrada.[1-4]
  - SGLT1 es el SGLT principal en el intestino delgado.[1,2]



SGLT = cotransportador de sodio-glucosa.

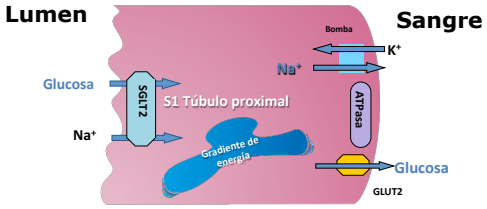
1. Wright EM *et al. J Intern Med.* 2007;261(1):32-43. 2. Kanai Y *et al. J Clin Invest.* 1994;93(1):397-404.
3. You G *et al. J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

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



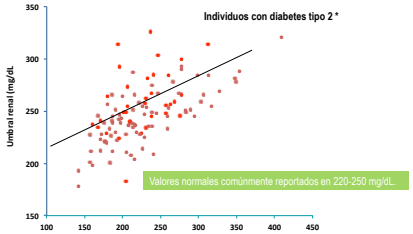
Adaptado con permiso de Rothenberg PL et al. SGLT = cotransportador ligado a sodio-glucosa.
Rothenberg PL et al. Poster presentado en: 46ª. Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia

SGLT2 permite la reabsorción de glucosa renal



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

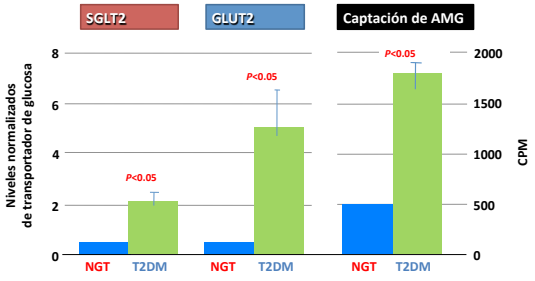
El umbral renal de glucosa está elevado en los individuos diagnosticados con diabetes tipo 2.



*Sujetos con diabetes tipo 2 no tratados previamente con antihiperglucémicos o después reposo farmacológico del tratamiento antihiperglucémico.
UGE, Excreción urinaria de glucosa; PG, Glucosa plasmática; GFR, Tasa de filtración glomerular.

Polidori D *et al.* 2010. Abstract 2186-PO. American Diabetes Association. June 25-29, 2010; Orlando, Florida.
Polidori D et al. 2010. Presentado en: 46ª. Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia.

Aumento del número y actividad de los transportadores en T2DM



AMG = metil-α-D-[U-^{14}C]-glucopiranósido; CPM = recuentos por minuto.
Rahmouna H, et al. Diabetes. 2005;54:3427-3434.

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INHIBIDORES DE SGLT-2

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Introducción

- En la medicina oriental, se utilizaba la corteza del árbol de manzano para tratar la diabetes
  - Compuesto activo florizina
  - Inhibidor no selectivo, tanto de SGLT-1 como SGLT-2
  - Diarrea como efecto adverso
- Modelo de la inhibición de SGLT-2 es la glucosuria familiar renal
  - Enfermedad poco frecuente
  - No consecuencias renales a largo plazo

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Inhibidores de SGLT-2

- Agentes disponibles
  - Dapagliflozina 5 y 10 mg
  - Canagliflozina 100 y 300 mg
  - Empagliflozina 10 y 25 mg
  - Ertogliflozina
  - tofogliflozina

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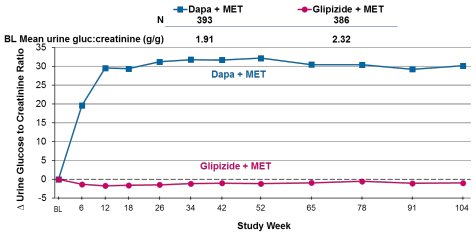
Increase in Glucose Excretion Observed Over 2 Years



Sample Size Per Time Point

Dapa + MET	393	379	355	362	352	337	329	319	305	264	240	228
Glip + MET	386	373	346	351	352	341	329	310	297	244	221	205

Repeated measures mixed model analysis.

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

EFICACIA DE GRUPO TERAPÉUTICO: DATOS EN HBA1C, PESO Y PRESIÓN ARTERIAL

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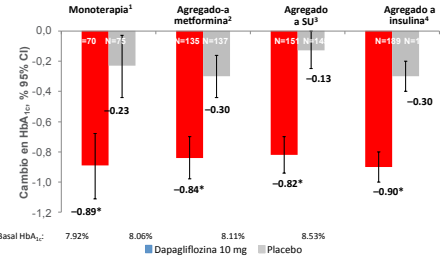
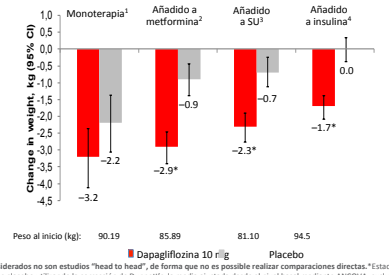
Reducción consistente en la HbA_{1c} en la Semana 24 en diferentes estudios



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. Diabetologia* 2010;**59**(Suppl 1):0078-OR.

Reducción significativa de peso a la semana 24



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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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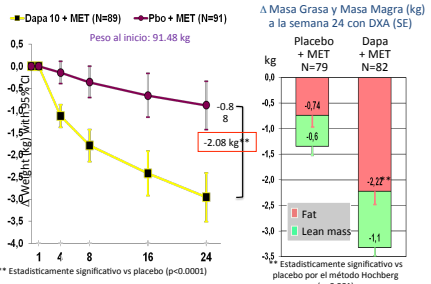
Reducción de peso y grasa corporal a la semana 24

Estudio de composición corporal con DXA



** Estadísticamente significativo vs placebo (p<0.0001)

** Estadísticamente 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: 1020-1029

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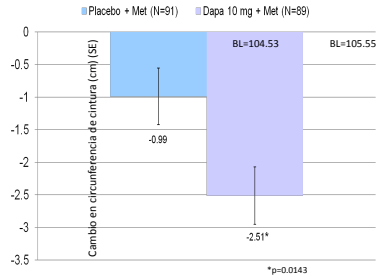
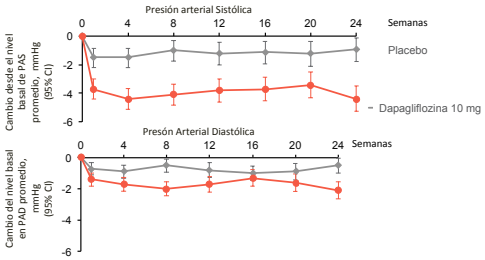
Cambio medio ajustado del perímetro abdominal a la semana 24 (cm)



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

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



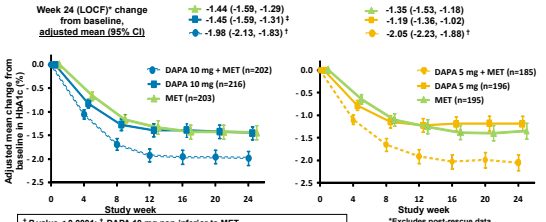
Número de pacientes							
Dapagliflozina 10 mg	1014	1086	1070	963	975	871	949
Placebo	1217	1281	1247	1116	1137	1021	1096

Sjöström CD. ESC 2012. OP 3972.

ESTUDIOS CONTRA COMPARADOR ACTIVO: PRIMERA LÍNEA VS METFORMIN XR

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



† *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.

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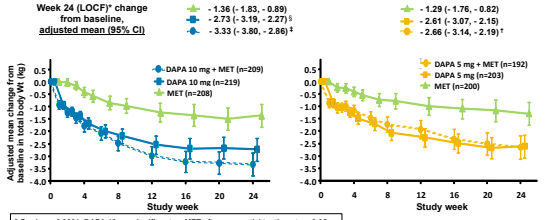
Dapagliflozin in Combination with Metformin: Change in Body Weight Over 24 Weeks

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



§ *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.

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EFICACIA CONTRA COMPARADOR ACTIVO EN SEGUNDA LÍNEA: SU E INHIBIDORES DE DPP-4

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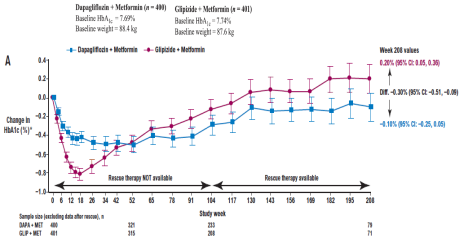
Durabilidad del efecto de reducción de HbA1c



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

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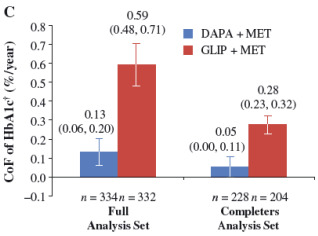
Coeficiente de variación de Hba1c



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

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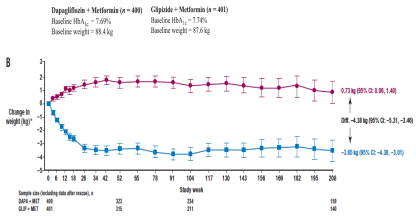
Durabilidad del efecto de reducción de peso



A 4 años

4,5 Kg menos

Corte temporal: Diferencia Dapa vs Glip 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

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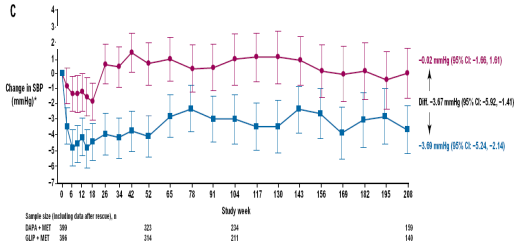
Durabilidad del efecto de reducción de PAS



*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

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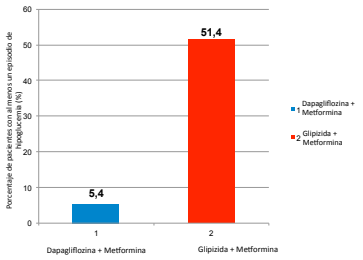
Hipoglicemias



- 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

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COMPARADO CON INHIBIDORES DE DPP-4 EN SEGUNDA LÍNEA

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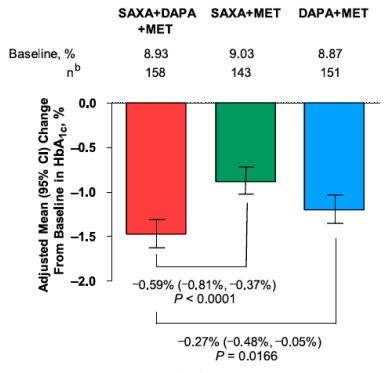
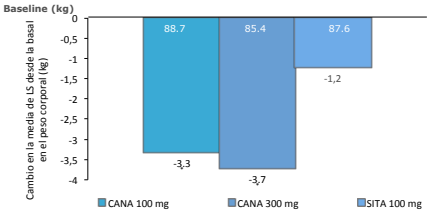


Rosenstock J. Diabetes Care. 2015;38:376

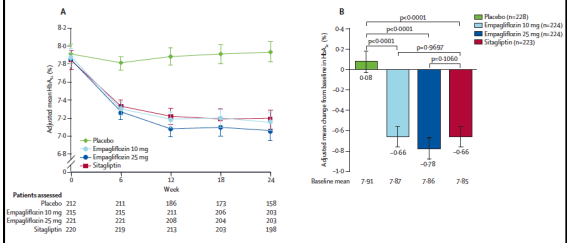
Estudio de tratamiento agregado a MET (CANA vs. PBO; SITA) (DIA3006)
Semana 52: Peso corporal (LOCF)



*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.

Empagliflozina vs sitagliptina



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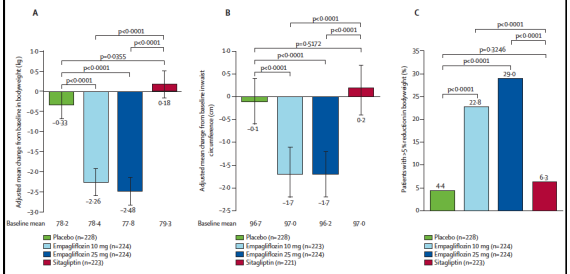
Roden M. Lancet Diab Endocrinol. 2013;1:208

Empagliflozina vs sitagliptina



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

TERCERA LÍNEA DE TRATAMIENTO

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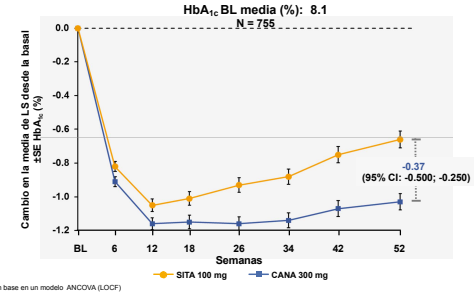
Estudio controlado con sitagliptina de tratamiento agregado a metformina + SU (DIA3015)

Cambio en HbA1c desde la basal en el tiempo

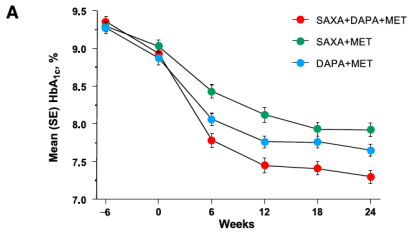


Con base en un modelo ANCOVA (LOCF)

Schernthaner G, et al. Diabets Care, 2013.

INHIBIDORES DE SGLT-2 AGREGADO A INHIBIDORES DE DPP-4

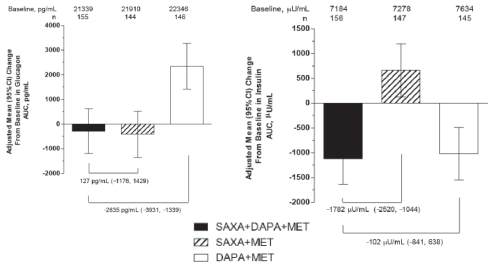
Dapa + saxa vs dapa vs saxa



Number of patients with measurements[a]						
SAXA+DAPA+MET	174	176	174	169	165	158
SAXA+MET	173	175	174	165	155	143
DAPA+MET	171	172	171	163	159	151

Rosenstock J. Diabetes Care. 2015;38:376

Saxa + dapa efectos en niveles de glucagon e insulina



Hansen L. Endocr Pract. 2014;20:1187

DATOS ASOCIADOS A INSULINA

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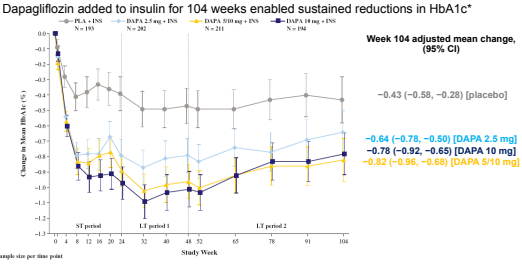
Dapagliflozin as Add-on to Insulin: Change in HbA1c Over 104 Weeks

- Dapagliflozin added to insulin for 104 weeks enabled sustained reductions in HbA1c*



*Including data after insulin uptitration
Wilding et al. *Diabetes Obes Metab.* 2013; epub ahead of print.

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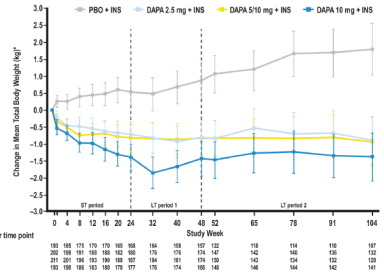
Fase III Agregado INS ± Antidiabéticos orales vs pcb: Pérdida de peso sostenida en 24 semanas, y contrasta el increment constant con insulina



Wilding J, *et al.* ADA 2012: Poster 1042-P.

*Data are adjusted mean change from baseline ± 95% CI derived from a mixed model and include data after insulin up-titration. DAPA, dapagliflozin; INS, insulin; PBO, placebo; ST, short-term; LT, long-term.

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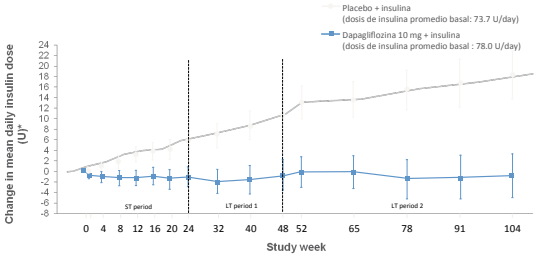
Fase Agregado INS ± Antidiabéticos orales vs pcb : Dapagliflozina reduce el increment de los requerimientos de insulina en un período de 48 semanas



N at each week	0	4	8	12	16	20	24	32	40	48	52	65	78	91	104
Dapagliflozin 10 mg + insulin	194	189	185	183	180	178	177	175	173	166	145	146	144	142	140
Placebo + insulin	191	185	176	171	170	165	168	164	158	157	121	118	114	110	104

*Data are adjusted mean change from baseline ± 95% CI derived from a mixed model and include data after insulin up-titration.

Wilding J.P.H et al Ann Intern Med. 2012;156:405-415.

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EVENTOS ADVERSOS

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Hipoglicemia

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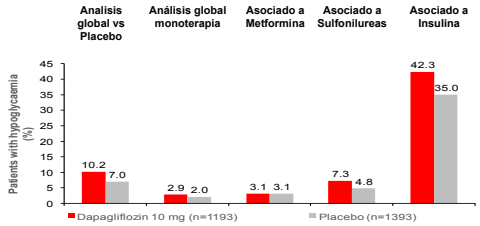
Baja capacidad intrínseca para generar hipoglicemia



The above are not head to head studies and direct comparisons should not be made.

Food & Drug Administration. Endocrinologic and Metabolic Drugs Advisory Committee: Dapagliflozin BMS-512148. Available at: http://tinyurl.com/7kd5j7. Last accessed October 2012.

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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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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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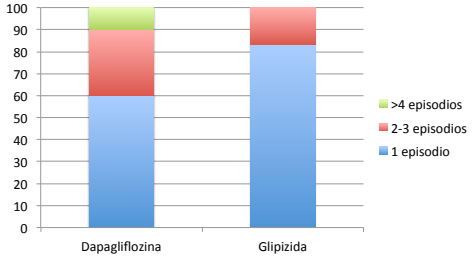
Infecciones genitales: número de episodios



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

SEGURIDAD ÓSEA

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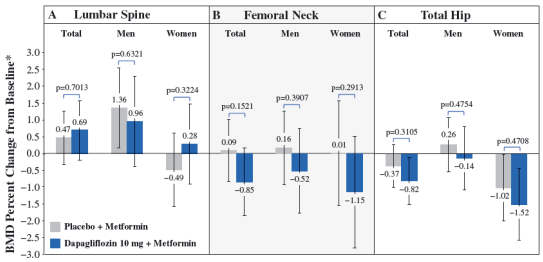

Bolinder J. Diab Obes Metab. 2013;16:159

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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/ucm378679.pdf;

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CAMBIOS EN FUNCIÓN RENAL

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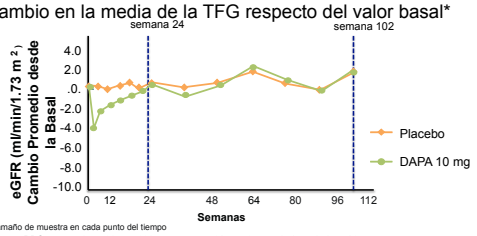
Dapagliflozina - Seguridad Renal

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

Renal Function: Events of Renal Impairment

- AEs of renal impairment/failure were more frequent in subjects receiving dapagliflozin 10 mg versus placebo
  - Most events were of mild or moderate intensity, were transient and were not accompanied by marked abnormalities of renal function

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)*	N=2360 76 (3.2)	N=2295 42 (1.8)	N=2026 136 (6.7)	N=1956 82 (4.2)

*Incidence of specific preferred terms for AEs of renal impairment shown on the following slide.
EMDAC Background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

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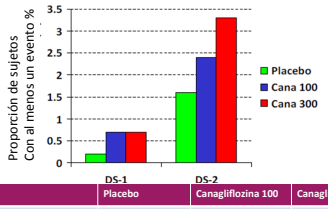
Canagliflozina – Eventos Adversos Relacionados a Hiperkalemia



	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/ucm538233.htm Accesado Agosto 2, 2014

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EN EL RIÑON, HAY ALGÚN EFECTO ADICIONAL?

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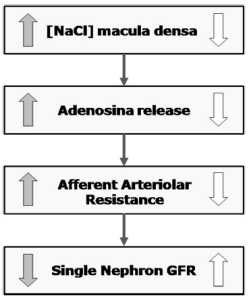
Reflejo tubuloglomerular



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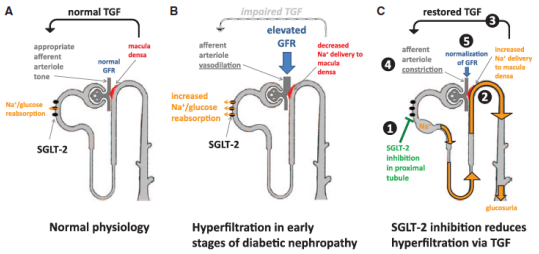
Nicola LD. Am J Kidney Dis. 2014;64:16-24



Normal physiology | Hyperfiltration in early stages of diabetic nephropathy | SGLT-2 inhibition reduces hyperfiltration via TGF

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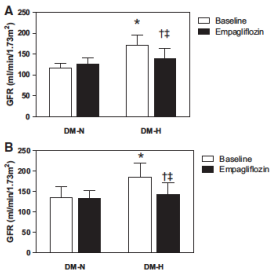
Cherney DZI. Circulation. 2014;129:587

DM-1 e hiperfiltración



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Cherney DZI. Circulation. 2014;129:587

EFECTOS EN PERFIL DE LÍPIDOS

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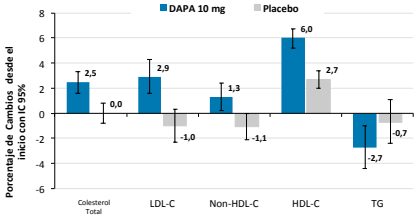
Dapagliflozina: Cambios en Lípidos

- 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 = Línea 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/ucm279659.pdf

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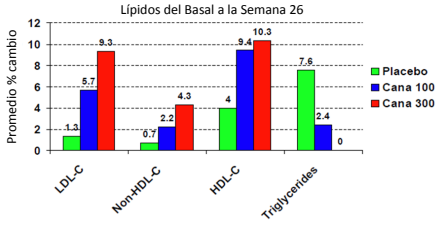
EFFICACY AND SAFETY OF SGLT-2 INHIBITORS Riser Taylor and HarrisPHARMACOTHERAPY Volume **, Number **, 2013

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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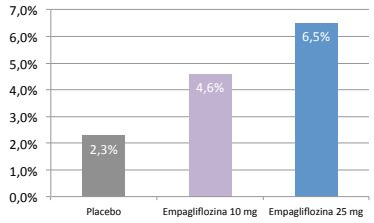
Empagliflozina – Cambios en Lípidos

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

Porcentaje de Cambio vs. Valores Basales*



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

1. Jardiance Prescribing information, 2014

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HIPOTENSIÓN POSTURAL

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Events of Volume Depletion

- Events of volume depletion (hypotension/hypovolemia/dehydration) were infrequent but more common in patients treated with dapagliflozin than placebo
  - Most events were mild of moderate in intensity
  - In the short-term and short- plus long-term placebo-controlled pool, most events were "hypotension" in the dapagliflozin 10-mg (0.6% and 0.9%) and placebo (0.2% and 0.3%) groups, respectively

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)	N=2360 27 (1.1)	N=2295 17 (0.7)	N=2026 38 (1.9)	N=1956 27 (1.4)

- In the all phase 2b and 3 pool, serious AEs of volume depletion were infrequent and occurred in 6 (0.1%) patients treated with dapagliflozin and 8 (0.2%) patients treated with control

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

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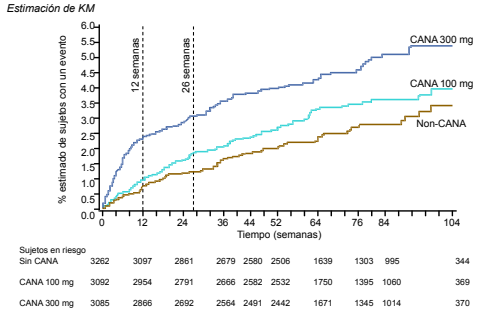
Tiempo al evento: EA de volumen intravascular reducido
Grupo de datos amplio hasta el 01 de julio de 2012



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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SEGURIDAD CARDIOVASCULAR

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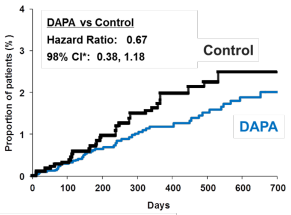
Meta-análisis de seguridad Cardiovascular



Number of patients								
DAPA	4097	3826	2767	2350	1532	1368	1062	585
Control	1850	1696	1197	1004	622	538	415	233

	DAPA		Control	
	First Event	Event Rate	First Event	Event Rate
Total	48	1.11%	30	1.64%
CV death	8	0.19%	4	0.22%
MI	18	0.42%	18	1.00%
Stroke	11	0.26%	5	0.28%
Unstable angina*	11	0.26%	3	0.17%

*Hospitalization for unstable angina

*98% CI is based on alpha spending function (one-sided alpha of 0.01 at the 1st look) to meet the US regulatory guidance to establish no unacceptable increase in CV risk by an upper bound of 1.8

Cox proportional hazards model and composite event rates are stratified by study

Johnsson K et al. Diabetologia 2012;55(Suppl1)743-P

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Inhibidores de SGLT2 – Seguridad CV

- ✓ Los datos disponibles sobre los efectos de los iSGLT2 en eventos macrovasculares es limitada[1]
- ✓ Los datos sometidos por Dapagliflozin a la FDA son los más completos disponibles hasta ahora.
- ✓ Ensayos clínicos multicéntricos, en desarrollo, proveerán más información sobre el impacto de iSGLT2 sobre ECV en pacientes con DM 2 y alto riesgo CV.
  - ✓ Dapagliflozina (DECLARE NCT01730534)
  - ✓ Canagliflozina (CANVAS NCT01032629)
  - ✓ Empagliflozina (EMPA-REG OUTCOME NCT01131676)
  - ✓ Ertugliflozin (NCT01986881)
- ✓ El estudio EMPA-REG OUTCOME espera que reporte resultados en 2015 y el resto entre 2017-2020[2]

1. Foote C et al. *Diab Vasc Dis Res.* 2012;9(2):117-123; 2. Zinman et al. *Cardiovascular Diabetology* 2014, 13:102

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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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Data Summary

FDA searched the FDA Adverse Event Reporting System (FAERS) database from March 2013 (approval of the first drug in the class) through June 6, 2014, and identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis reported with the sodium-glucose cotransporter-2 (SGLT2) inhibitors. Type 2 diabetes mellitus was noted as the indication in most of the cases, type 1 diabetes mellitus was noted in a few cases, and some cases did not specify the indication.

In all cases, a diagnosis of DKA or ketoacidosis was made by a health care professional, and hospitalization of the patients was required to treat the episode. A temporal association with SGLT2 inhibitor initiation was noted in all cases. The median time to onset of symptoms following initiation of drug therapy was 2 weeks (range 1 to 175 days). DKA case presentations were atypical in that glucose levels were only mildly elevated at less than 200 mg/dL in some reports, while patients with type 1 diabetes who have DKA typically have glucose levels greater than 250 mg/dL. In addition, DKA is not typically observed in patients with type 2 diabetes.

In most cases, a high anion gap metabolic acidosis accompanied by elevated blood or urine ketones was reported. Potential DKA-triggering factors that were identified in some cases included acute illness or recent significant changes such as infection, urosepsis, trauma, reduced caloric or fluid intake, and reduced insulin dose. Potential factors, other than hypoinsulinemia, contributing to the development of a high anion gap metabolic acidosis identified in the cases included hypovolemia, acute renal impairment, hypoxemia, reduced oral intake, and a history of alcohol use. Half of cases did not identify a triggering factor for DKA.

We are continuing to investigate this safety issue. Additional reports of DKA continue to be submitted to us, and we will determine whether changes are needed in the labeling for this class of drugs.

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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.

Características en común

- Los pacientes no reconocieron DKA por no tener franca hiperglicemia
- En lugar de aumentar dosis de insulina, en muchas ocasiones se reduce o no se cambió
- Los proveedores de salud tampoco reconocieron la entidad
- Mayoría de las ocasiones en DM-1 pero hubo 2 casos de DM-2 en postoperatorios

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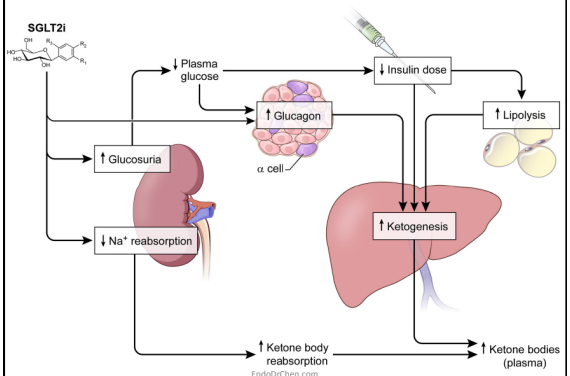
Peters AL. Diabetes Care. Online June 15th.

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_000012.jsp&mid=WC0b01ac058001c1d1. Accessed June 2015.



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

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

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.

Caso clínico

- Se empezó a tratar con dapagliflozina 10 mg por día desde noviembre 2014
- Última hba1c 7.8%
- Dosis total diaria de insulina: 128 unidades (era 144)
- Peso actual 89 kg (era 90 kg)

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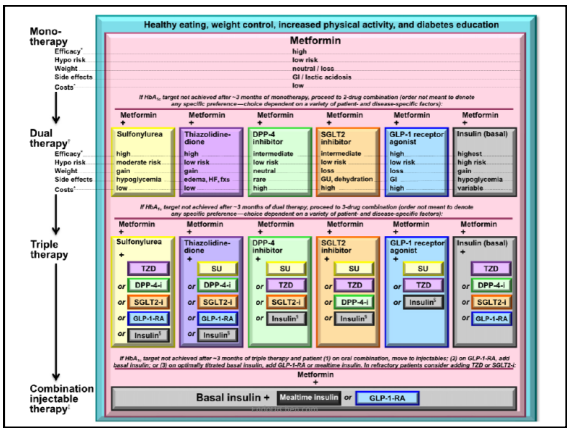

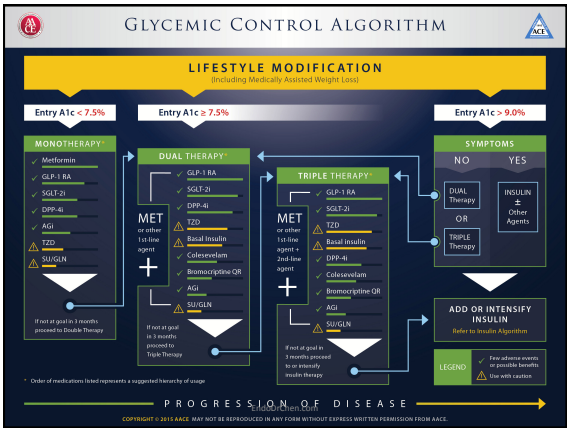

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

1.7 In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as GLP-1 analogs or SGLT-2 inhibitors) in addition to the first-line agent for T2DM and obesity, metformin (63). (2|⊕⊕⊕○)

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Apovian CM. J Clin Endocrinol Metab. 2015;100:342-62.

Conclusiones

- El riñón ya no sólo es la víctima en DM-2 sino que juega un papel activo en el control glicémico
- Inhibición de SGLT-2 provee reducción sostenida de la glicemia, con pérdida de peso y reducción de presión arterial, en todo el espectro de la DM-2 (1era, 2da y 3ra línea)
- Efectos adversos principales relacionados a infecciones urogenitales, aumento de LDL
- Tener mucho cuidado con el uso no aprobado en DM-1 y riesgo de euDKA

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