

## Casos clínicos orientados a 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

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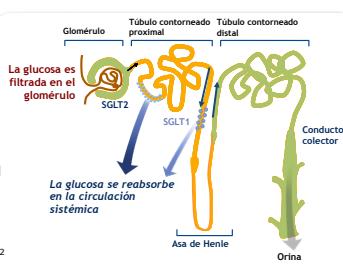
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### Cotransportadores de sodio-glucosa (SGLT) y manejo renal normal de la glucosa

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



**SGLT = cotransportador de sodio-glucosa.**  
 1. Wright EM et al. J Intern Med. 2007;261(1):32-43. 2. Kasiske B et al. J Clin Invest. 1998;91(3):397-404.  
 3. Nephrol Dial Transplant. 1995;10(4):2985-2987. 4. Wright EM. Am J Physiol Renal Physiol. 2001;280(1):F150-F158.

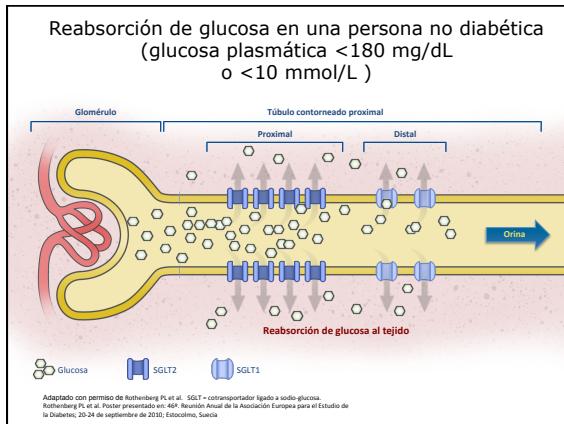
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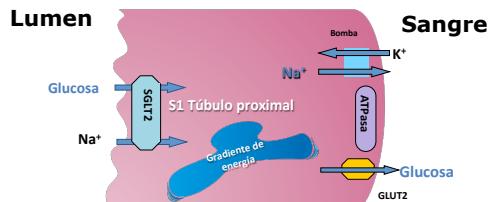
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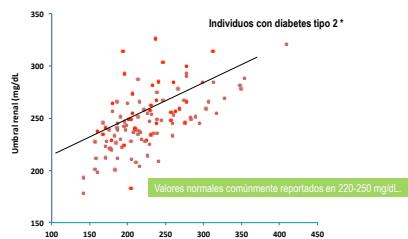
Adaptado con permiso de Rothenberg PT et al. SGLT = cotransportador ligado a sodio-glucosa. Rothenberg PT et al. Poster presentado en: 46º Reunión Anual de la Asociación Europea para el Estudio de la Diabetes; 20-24 de septiembre de 2010; Estocolmo, Suecia

**SGLT2** permite la reabsorción de glucosa renal



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

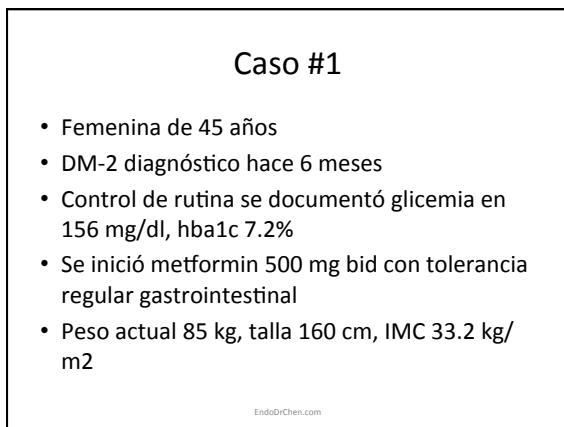
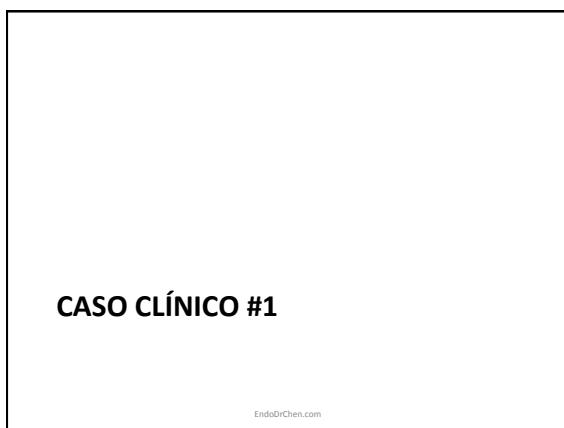
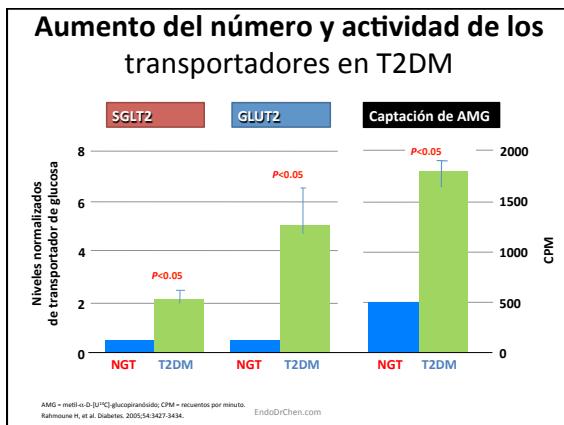
El umbral renal de glucosa está elevado en los individuos diagnosticados con diabetes tipo 2.



\*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.

GCE, excreción urinaria de glucosa; FG, glucosa plasmática; GFR, tasa de filtración glomerular.

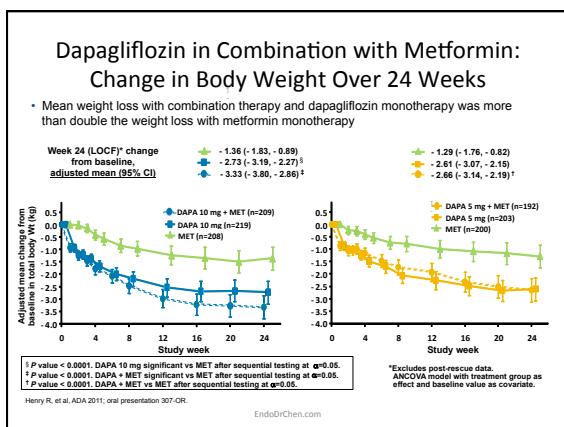
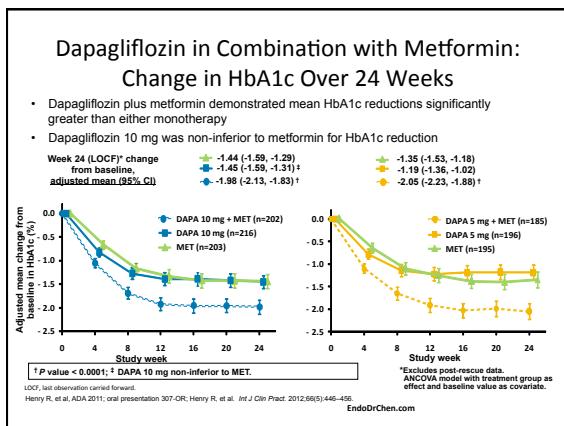
Polidori D et al. 2010. Abstract 2186-PO. American Diabetes Association. June 25-29, 2010; Orlando, Florida.  
Polidori D et al. 2010. Presentado en: 46<sup>a</sup> Reunión Anual de la Asociación Europea para el Estudio de la Diabetes. 20-24 de octubre de 2010; Estocolmo, Suecia.

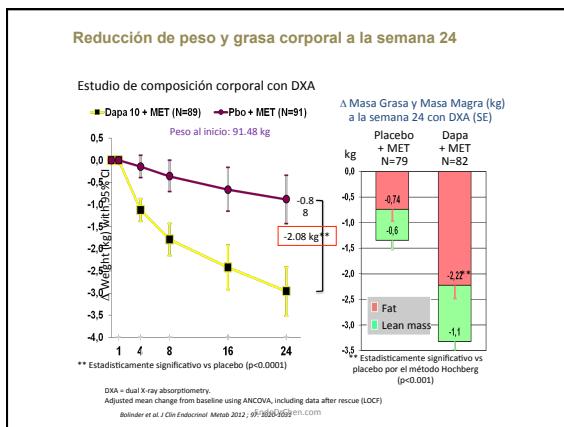
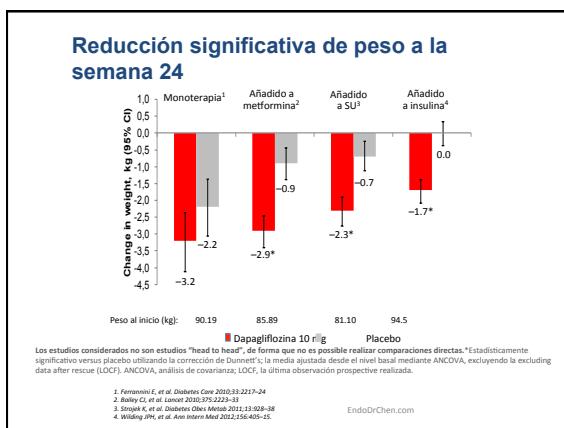
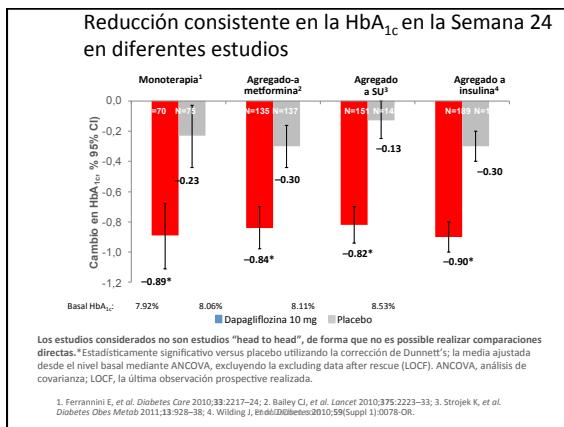


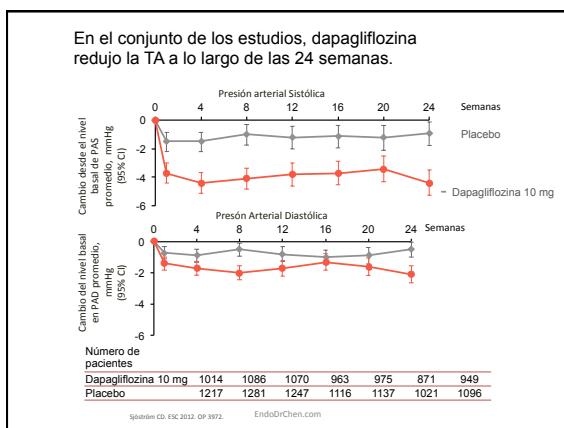
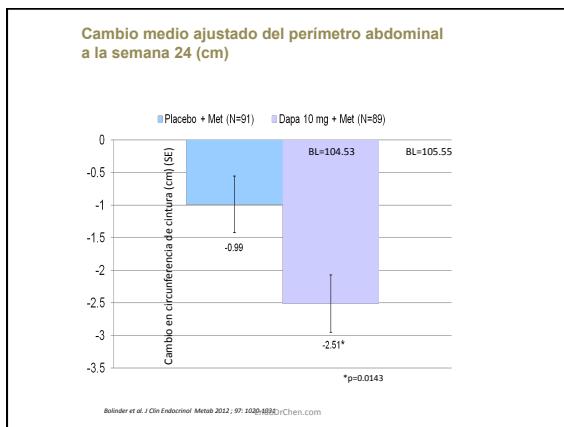
## Caso #1

- Tiene además hipertensión para lo cual toma irbesartan 150 mg por día
  - Hba1c actual 6.4%
  - Cuál es la conducta a seguir?
    - Seguir con metformin
    - Cambiar a:
      - Inhibidores de DPP-4?
      - Sulfonilureas?
      - Inhibidores de SGLT2?

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## CASO #2

## Caso #2

- Masculino de 57 años
- DM-2 de 5 años de evolución
- Tratamiento actual con metformin 500 mg tid
- Hba1c actual en 7.4%
- IMC 30 kg/m<sup>2</sup>
- Toma además lovastatina 40 mg HS y amlodipina 5 mg por día

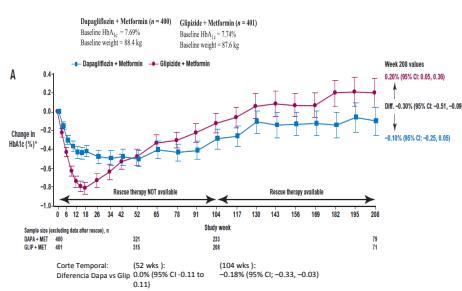
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## Caso #2

- Cuál es el paso a seguir?
  - Agregar
    - Insulina basal?
    - Sulfonilureas?
    - Inhibidores de DPP-4?
    - Inhibidores de SGLT2?

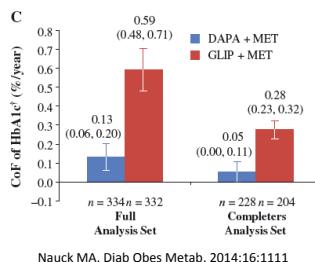
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### Durabilidad del efecto de reducción de HbA1c



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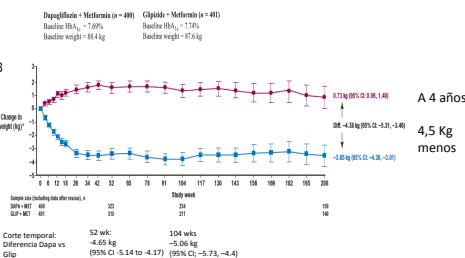
## Coeficiente de variación de HbA1c



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

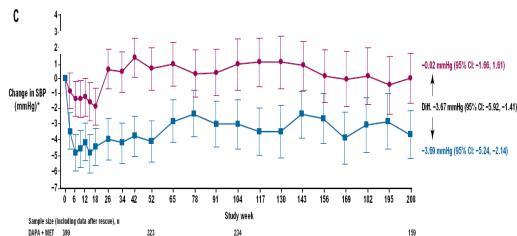
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## Durabilidad del efecto de reducción de peso

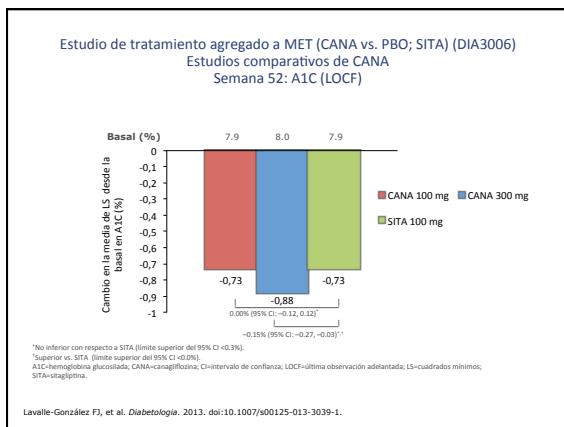
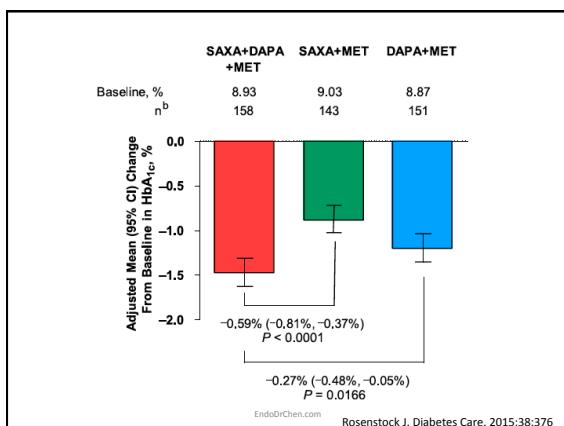
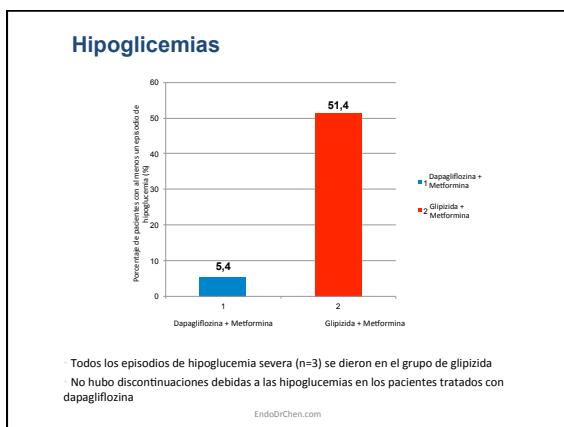


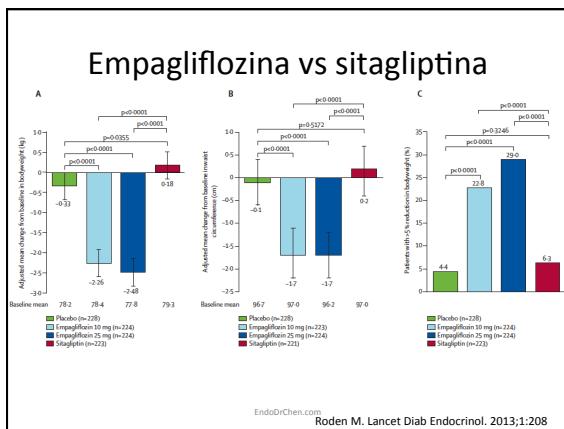
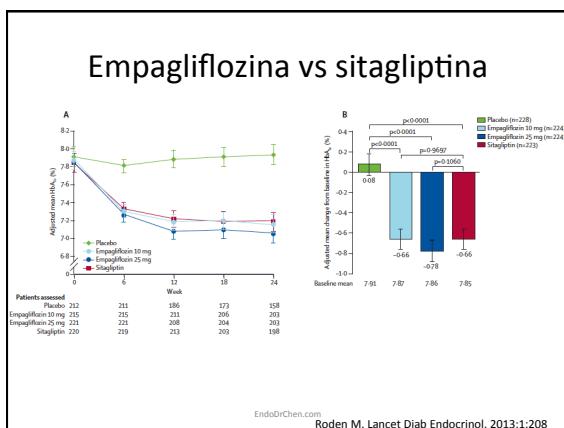
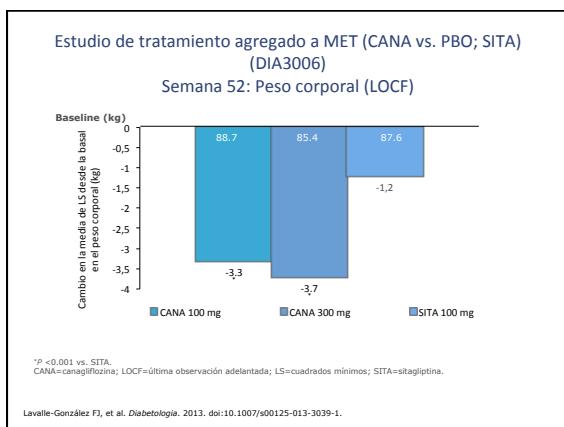
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## Durabilidad del efecto de reducción de PAS



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**CASO #3**

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**Caso #3**

- Femenina de 64 años, costarricense, a quien se le diagnosticó DM-2 en 2005
- Tratada inicialmente con glicazida MR + metformin hasta noviembre 2008
- Se cambió a insulina NPH+ metformin
- Noviembre 2009: insulina premezcla bid + metformin
- 2011: Basal bolo + metformin

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**Caso #3**

- 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

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**Caso #3**

- Cuáles son las opciones de tratamiento?
  - Agregar análogo GLP-1?
  - Agregar inhibidores de DPP-4?
  - Aumentar dosis de insulina?
  - Cambiar a bomba de insulina?
  - Agregar inhibidores de SGLT-2?

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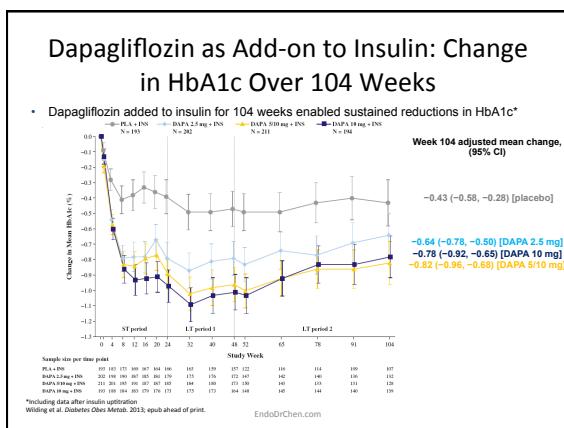
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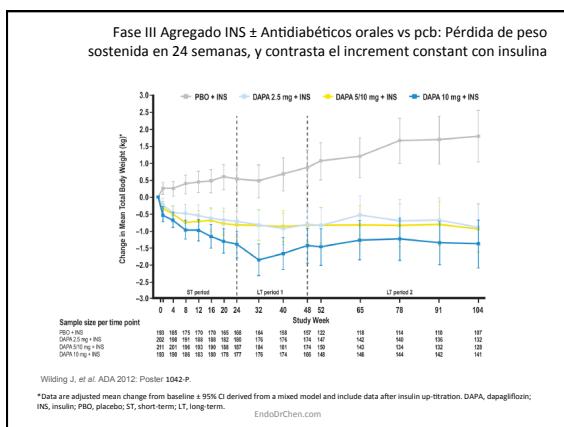
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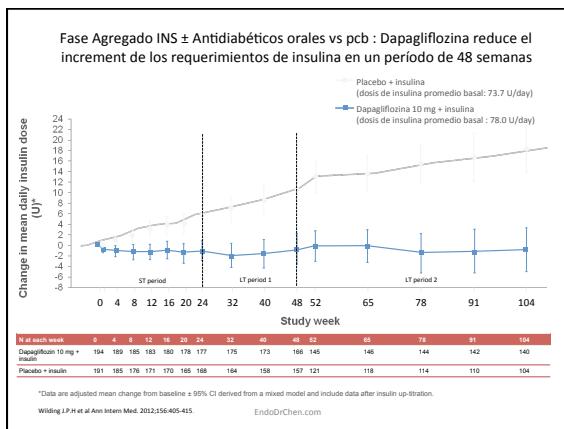
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### Caso #3

- Paciente tolera bien fármaco y tiene Hba1c en 7.8%
- Peso actual 88 kg
- Sin embargo presenta 1 episodio de vulvovaginitis
- Cuál es la conducta?

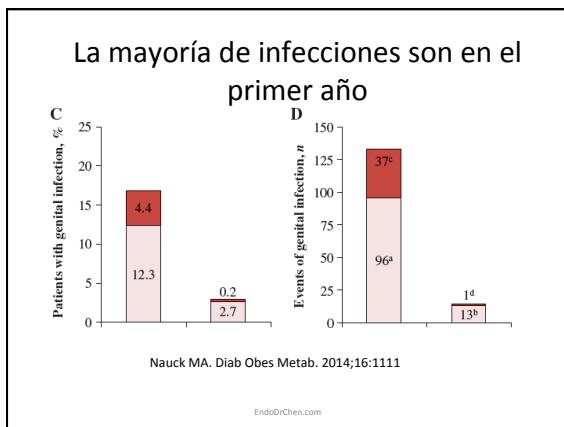
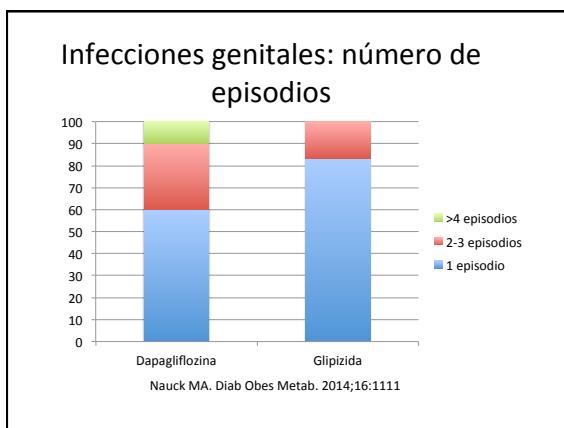
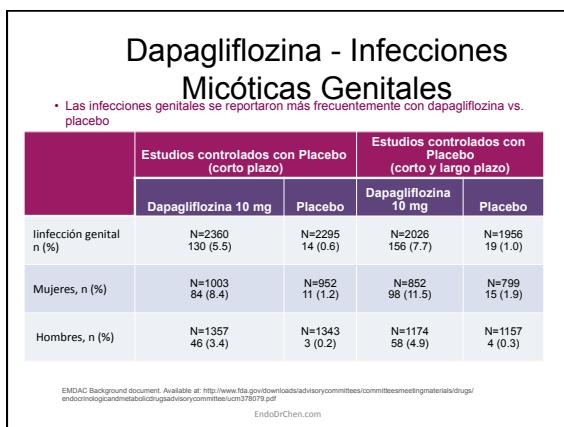
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### Dapagliflozina - Infecciones de Vías Urinarias

• 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/endocrinologycardometabolicdrugsadvisorycommittee/ucm378079.pdf>  
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**SEGURIDAD CARDIOVASCULAR**

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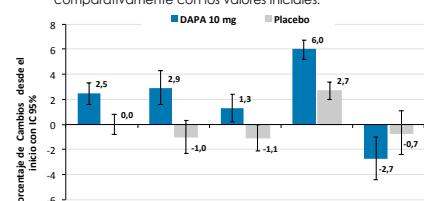
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### Dapagliflozina: Cambios en Lípidos

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



Parámetro	Promedio BL (mg/dL)	n	DAPA 10 mg (%)	Placebo (%)
Colesterol Total	181.9	1851	2.5	0.0
LDL-C	180.6	1747	2.9	-1.0
Non-HDL-C	101.2	1736	1.3	-1.1
HDL-C	100.7	1851	6.0	2.7
TG	136.9	1747	-4.0	-0.7

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

ENDDC slide presentation. Available at: <http://www.fda.gov/downloads/industry/advisorycommittees/meetingmaterials/drugs/endocrinologyparacmetabolicdrugsandendocrinologycommittee/ucm079589.pdf>

Efficacy and Safety of SGLT-2 Inhibitors Riser Taylor and Harris PHARMACOTHERAPY Volume \*\*, Number \*\*, 2013

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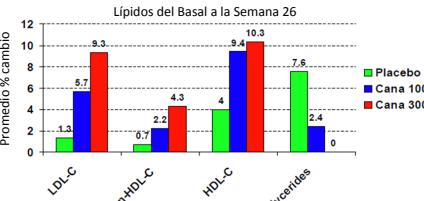


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### Canagliflozina: Cambios en Lípidos

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



Parámetro	Placebo (%)	Cana 100 (%)	Cana 300 (%)
LDL-C	1.1	5.7	9.3
Non-HDL-C	0.7	2.2	4.3
HDL-C	4	9.1	10.3
Triglycerides	7.6	2.4	0

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

1. Kevin H. Canagliflozine: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting January 10, 2013. <http://www.fda.gov/industry/advisorycommittees/meetingmaterials/drugs/endocrinologyparacmetabolicdrugsandendocrinologycommittee/ucm35223.htm> Accessed August 2, 2014.

2. William T Cefalu. Lancet 2013

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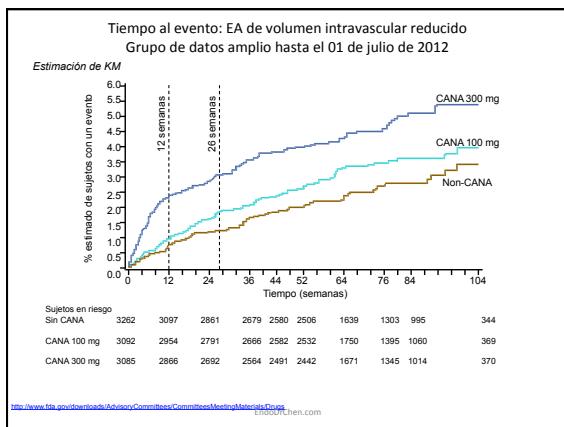
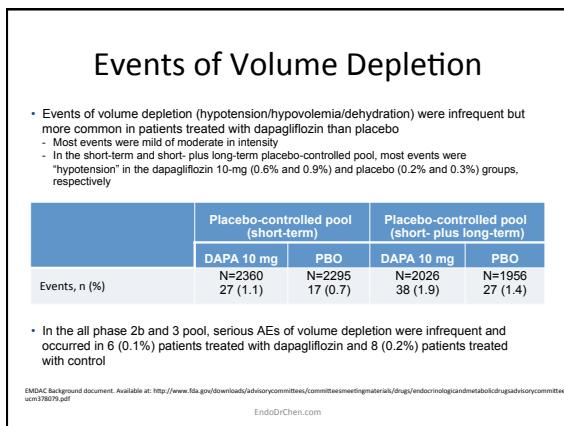
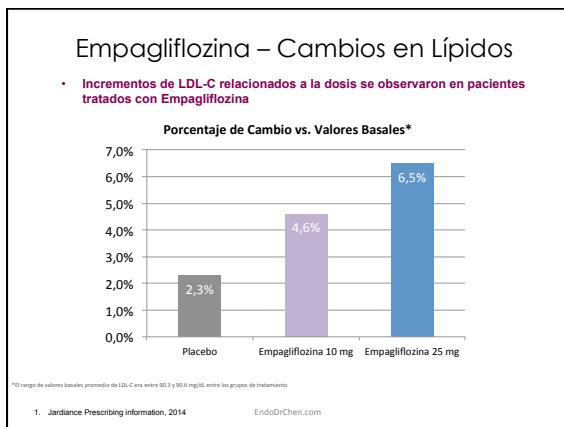
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Factores de riesgo: AEs de volumen intravascular reducido Grupo de datos amplio del período principal			
eGFR (mL/min/ 1.73m <sup>2</sup> )	Sin CANA % (n/N)	CANA 100 mg % (n/N)	CANA 300 mg % (n/N)
<60	2.8 (12/436)	5.0 (19/382)	8.1 (33/405)
60 a <90	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 <sup>2</sup>	1.1 (29/2604)	1.8 (45/2491)	2.2 (54/2434)

<http://www.fda.gov/endo/cad/advisoryCommittees/CommitteesMeetingMaterials/Drugs>  
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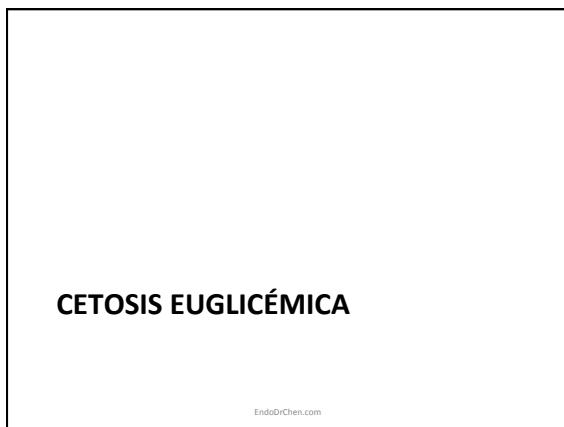
**EMPA-REG OUTCOME trial demonstrates superiority of Jardiance in T2D patients at risk for CV events**

Published on August 20, 2015 at 8:12 AM · No Comments

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Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) today announced positive top-line results from EMPA-REG OUTCOME®. This is a long-term clinical trial investigating cardiovascular (CV) outcomes for Jardiance® (empagliflozin) in more than 7,000 adults with type 2 diabetes (T2D) at high risk for CV events. EMPA-REG OUTCOME met its primary endpoint and demonstrated superiority of JARDIANCE, when added to standard of care, in CV risk reduction. The primary endpoint was defined as time to first occurrence of either CV death, or non-fatal myocardial infarction or non-fatal stroke.

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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

EndoDrChen.com Peters AL. Diabetes Care. Online June 15<sup>th</sup>.

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

[ 05-15-2015 ]

### Safety Announcement

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

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

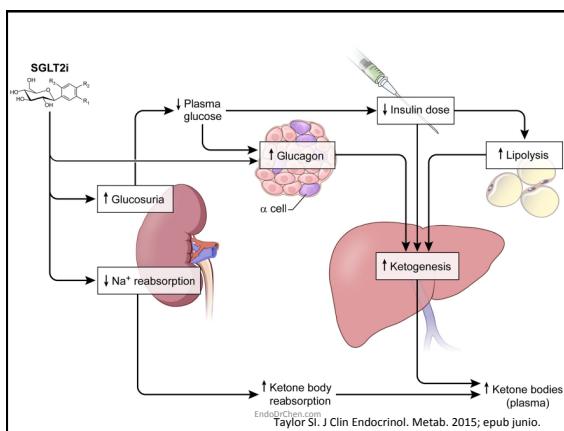
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Table 1—Clinical Characteristics of euDKA Cases										
Case patient	1	2	3	4	5	6	7	8	9	10
Age (year)	40	58	27	28	31	55	26	39	64	
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female	
T1/T2	T1	T2	T1	T1	T1	T1	T1	T1	T2	
HbA1C (%)	10.0	NA	NA	NA	NA	NA	NA	NA	NA	
Duration (years)	17	2	25	6	15	18	13	26	6	
BMI (kg/m <sup>2</sup> )	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 (91.7)	8.0 (83.4)	7.0 (85.0)	7.2 (85.2)	6.6 (48.6)	7.0 (85.0)	7.8 (86.2)	
Continuous insulin	100	100	100	100	100	100	100	100	100	
Potential contributors	100	Surgery 1 wks prior	URI, alcohol	Alcohol	Alcohol	Exercise	Exercise	None	URI	Surgery 12 h prior
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Unknown	No	No	Yes
Presenting plasma glucose (mmol/L)	200 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	-325 (-6.9)	201 (11.0)	190 (10.6)	150 (8.3)
pH	6.9	7.12	6.89				7.15*			
Ptgs (meq/L)	8	10	6	11	18	15	9	9	13 and then 5	
Bicarbonate (meq/L)	6	10	6	11	18	15	9	9	13 and then 5	
Anion gap (meq/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 (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	ICU

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

EndoDrChen.com Peters AL. Diabetes Care. Online June 15<sup>th</sup>.

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



## 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)	3,259 (17.1)
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 <sub>1c</sub> , %	8.9 (7, 11)	8.0 (5, 14)
HbA <sub>1c</sub> , mmol/mol	74 (53, 97)	66 (51, 130)
BMI, kg/m <sup>2</sup>	27.1 (23, 34)	31.3 (15, 73)
eGFR, mL/min/1.73 m <sup>2</sup>	68.0 (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.

## Conclusiones

- Inhibidores de SGLT-2 son una nueva alternativa para el tratamiento de DM-2 y se puede usar en cualquier momento combinado con cualquier otra terapia
- Bien tolerados, mayoría de infecciones genitales son leves
- Seguridad cardiovascular
- Precaución con el uso en DM-1 por el riesgo de cetosis euglicémica

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