Seguridad renal de los inhibidores de SGLT-2

Dr. Chih Hao Chen Ku, FACE
Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica

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Conflictos de interés

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

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Agenda

- Mecanismo de los inhibidores de SGLT-2 y sus beneficios renales
- Endpoints renales evaluados
- Comparación con otros agentes

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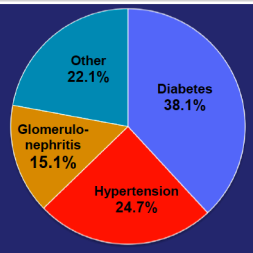
ESRD in the United States

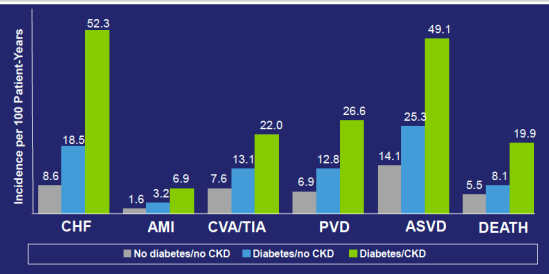


Diabetes is responsible for 44% of all new cases of ESRD[1]

1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

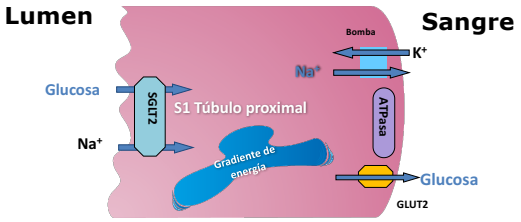
USRDS. 2009 Annual Data Report. Volume 3: Reference Tables on ESRD in the United States. Bethesda, MD: NIH, NIDDK; 2009:453-468. http://www.usrds.org/2009/ref B_Ref_09.pdf. Accessed November 9, 2010.

Greatest CV Risk with both Diabetes and Renal Impairment



AMI=acute myocardial infarction; ASVD=atherosclerotic vascular disease (defined as the first occurrence of AMI, CVA/TIA, or PVD); CHF=congestive heart failure; CVA/TIA=cerebrovascular accident/transient ischemic attack; PVD=peripheral vascular disease.
Foley RN et al. *J Am Soc Nephrol*. 2005;16:489-95.

SGLT2 permite la reabsorción de glucosa renal



Adaptado de de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012, 14:14-9

EFECTO URICOSÚRICO

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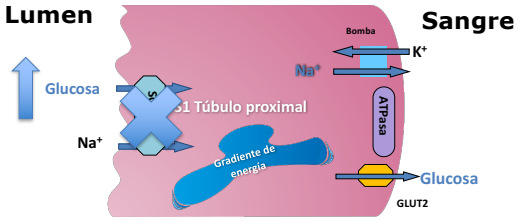
SGLT2 permite la reabsorción de glucosa renal



Adaptado de de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012; 14:1-15

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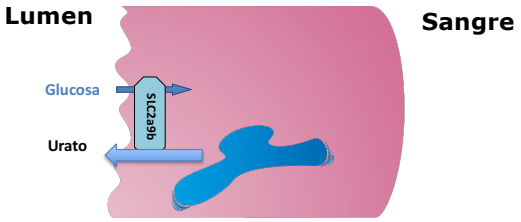
Mecanismo uricosúrico



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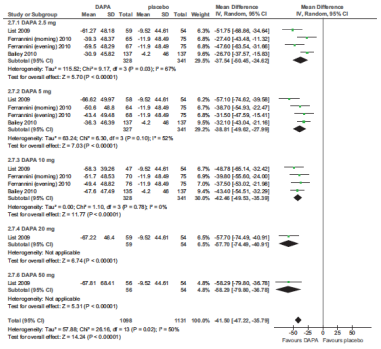
Musso G. Ann Med. 2012;44:375

Dapagliflozina y ácido úrico



Equivalente a 2.4 mg/dl

Musso G. Ann Med. 2012;44:375

EFECTOS EN NEFROPATÍA DIABÉTICA: HIPERFLITRACIÓN Y PROTEINURIA

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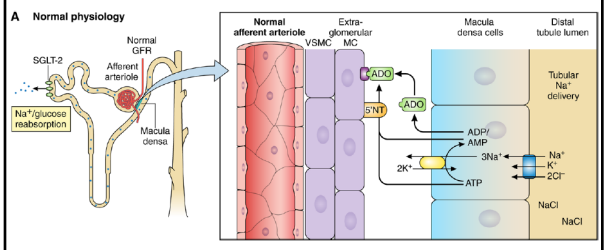
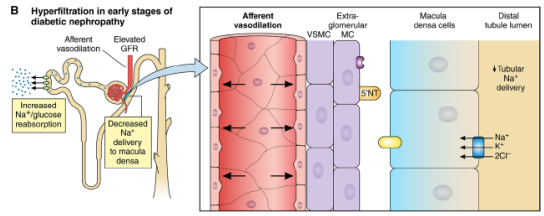
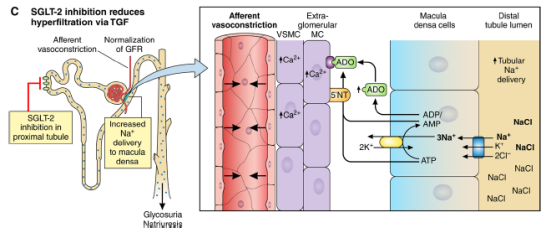


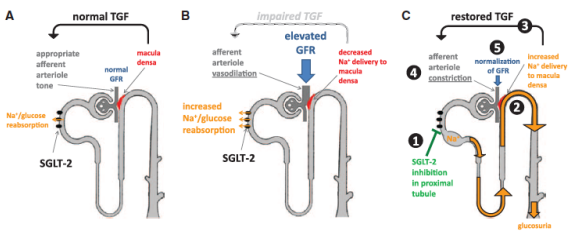
Heerspink H. Circulation. 2016;134:752



Heerspink H. Circulation. 2016;134:752



Heerspink H. Circulation. 2016;134:752



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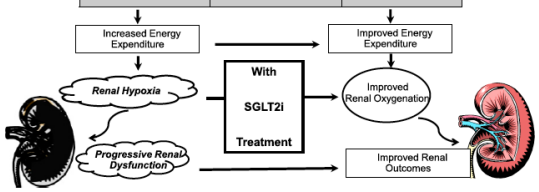
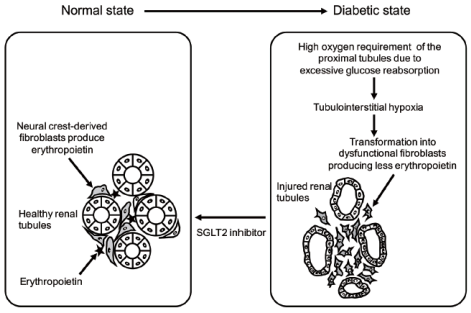
Cherney DZI. Circulation. 2014;129:587

T2DM Kidney	Preferred Substrate In	T2DM Kidney with SGLT2i Rx
Lactate/FFA Glutamate	S1/S2 Segments	↓Lactate/FFA ↔ Glutamate
Lactate/FFA Glutamate/Glucose BHOB	S3 Segment	↓Lactate/FFA ↓Glutamate/Glucose ↑ BHOB
Lactate/FFA Glucose BHOB	Distal Collecting Tubules/Cortical Collecting Tubules	↓Lactate/FFA ↓Glucose ↑ BHOB



Mundaliar S. Diabetes Care. 2016;39:1115

Cambios en Hto y mejoría de función renal



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Sano M. J Clin Med Res.2016;8:844

MODELOS ANIMALES Y MECANISMOS

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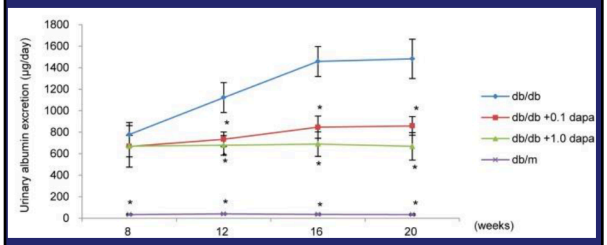
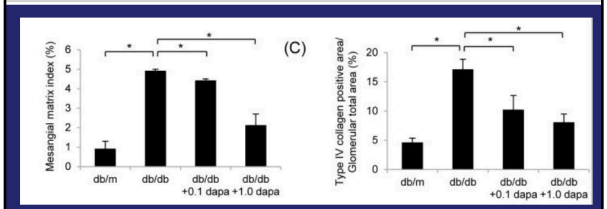
Effect of Dapagliflozin on Urinary Albumin Excretion (UAE)



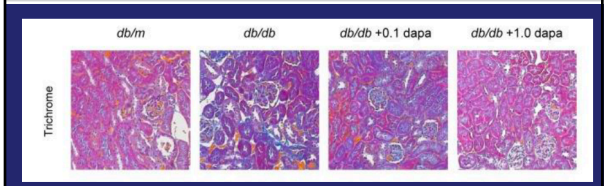
*P<0.05.
Terami N et al. *PLoS One*. 2014;9:e100777.

Dapagliflozin Suppresses Mesangial Matrix Accumulation and Interstitial Fibrosis



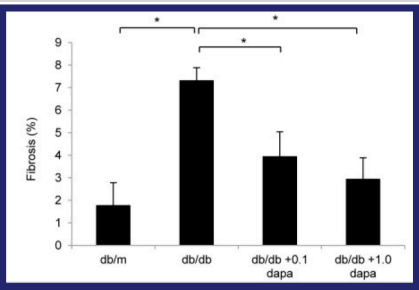
*P<0.05.
Terami N et al. *PLoS One*. 2014;9:e100777.

Dapagliflozin Suppresses Mesangial Matrix Accumulation and Interstitial Fibrosis



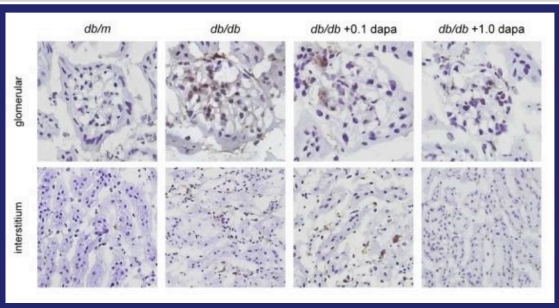
Terami N et al. *PLoS One*. 2014;9:e100777.

Dapagliflozin Inhibits Fibrosis in the Renal Cortex



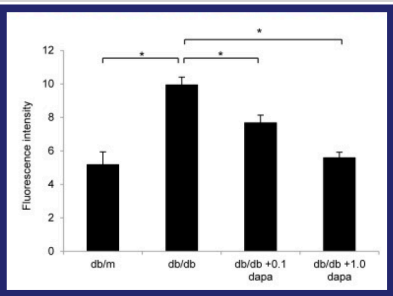
*P<0.05.
Terami N et al. *PLoS One*. 2014;9:e100777.

Dapagliflozin Inhibits Proinflammatory Macrophage Infiltration in the Renal Cortex



Terami N et al. *PLoS One*. 2014;9:e100777.

Dapagliflozin Inhibits Oxidative Stress in the Kidney



*P<0.05.
Terami N et al. *PLoS One*. 2014;9:e100777.

EVIDENCIA EN HUMANOS

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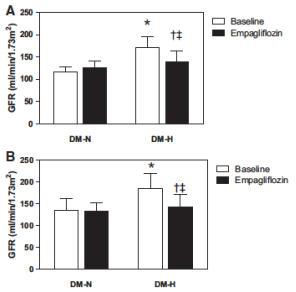
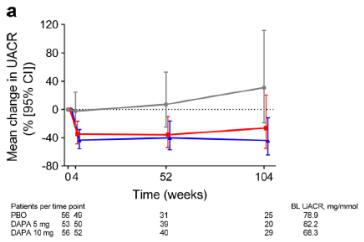
DM-1 e hiperfiltración



Cherney DZI. Circulation. 2014;129:587

Cambios en UACR a 2 años



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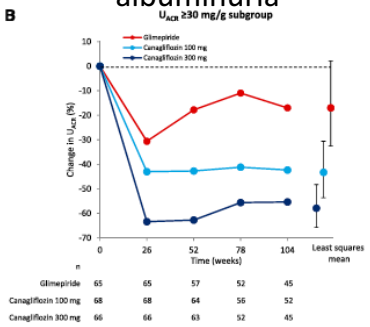
Fioretto P. Diabetologia. 2016;59:2036

Canagliflozina vs glimepiride en albuminuria



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Heerspink H. J Am Soc Nephrol. 2017;28:368

Efectos en albuminuria

Study	N	Investigational drug	Comparator	Weeks	Change in albumin excretion rate		
					Investigational drug	Comparator	Difference
Barnett et al. (2014)[88]	292[a]	Empagliflozin 10/25 mg	Placebo	52	−70/−121	114	−185/−236
Barnett et al. (2014)[88]	375[b]	Empagliflozin 25 mg	Placebo	52	−155	29	−184
Barnett et al. (2014)[88]	74[c]	Empagliflozin 25 mg	Placebo	52	−634	−140	−494
Cefalu et al. (2013)[89]	1450	Canagliflozin 100/300 mg	Glimepiride	52	−0.1/−0.9	0.7	−0.8/−1.5
Kohan et al. (2014)[87]	252	Dapagliflozin 5/10 mg	Placebo	104	78.0/−11.7	69.7	8.3/−81.4
Yale et al. (2013)[86]	269	Canagliflozin 100/300 mg	Placebo	52	−117.5/−96.2	15.4	−132.9/−111.6

SGLT2: sodium-glucose cotransporter 2; CKD: chronic kidney disease.
[a]Patients with Stage 2 CKD.
[b]Patients with Stage 3 CKD.
[c]Patients with Stage 4 CKD.

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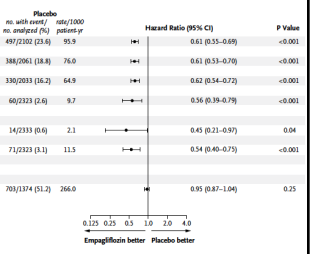
Schernthaner G. Diab Vasc Dis Res. 2014;11:306

EMPAREG - renal



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Measurement of Renal Outcomes

Albuminuria
- Urine albumin:creatinine ratio (UACR)

Progression/Regression of albuminuria
- Change in albuminuria class (normo-, micro-, macroalbuminuria) plus >30% UACR change from baseline

40% decrease in GFR
- Sustained more than 40% decrease in estimated GFR (eGFR)

End-stage renal disease
- Reaching dialysis or transplantation or sustained eGFR <15 mL/min/1.73 m^2

Renal death
- Death due to kidney disease

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Renal Baseline Characteristics

Similar for Canagliflozin and Placebo

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	**77**	**76**
Median albumin:creatinine ratio, mg/g	**12.4**	**12.1**
ACE inhibitor/ARB use, %	**80**	**80**

CANVAS Program

Low Renal Risk Population

High Percentage of "Normal" eGFR and Albuminuria

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	**77**	**76**
≥90 mL/min/1.73 m², %	*25*	*24*
60 to <90 mL/min/1.73 m², %	*56*	*54*
45 to <60 mL/min/1.73 m², %	*14*	*16*
<45 mL/min/1.73 m², %	*5*	*6*
Median albumin:creatinine ratio, mg/g	**12.4**	**12.1**
Normoalbuminuria (<30 mg/g), %	*70*	*70*
Microalbuminuria (30 to 300 mg/g), %	*23*	*22*
Macroalbuminuria (>300 mg/g), %	*7*	*8*

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Results

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

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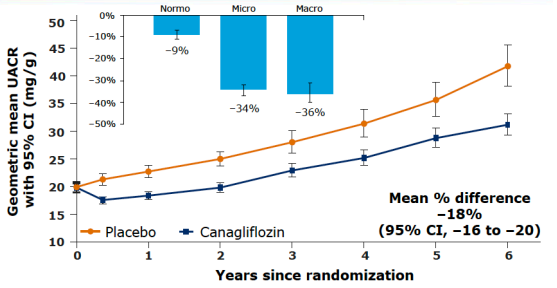
Change in Albumin:Creatinine Ratio (UACR)

Percent Change in UACR per Albuminuria Class (inset)



No. of patients

Placebo	4084	3775	2556	753	652	594	618
Canagliflozin	5500	5103	3565	1689	1541	1408	1534

Mixed model for repeated measures (MMRM) analysis
Excluding those below detection level

CANVAS Program

Results

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

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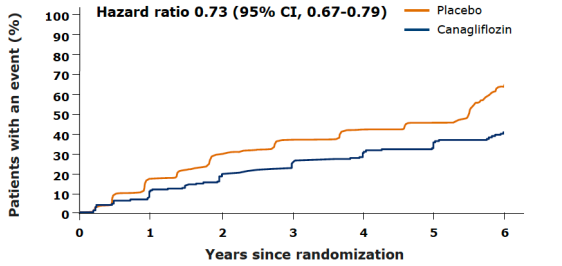
Progression of Albuminuria



No. of patients

Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

Intent-to-treat analysis

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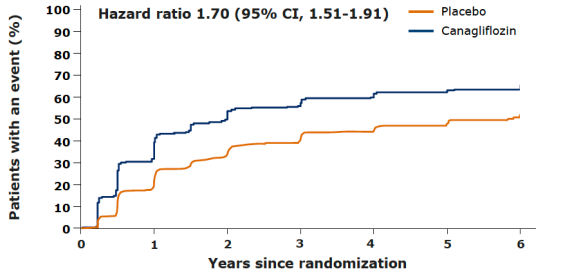
Regression of Albuminuria



No. of patients

Placebo	1257	913	426	163	144	123	59
Canagliflozin	1679	1009	518	276	227	198	112

Intent-to-treat analysis

CANVAS Program

Results

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

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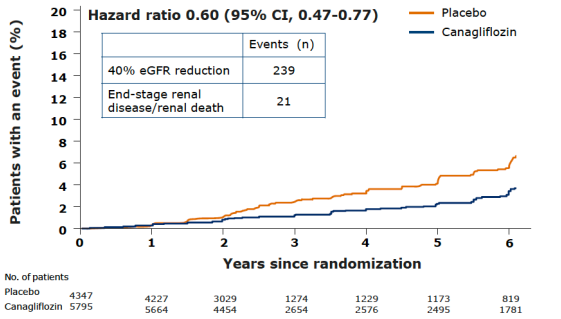
Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

No. of patients

Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

Intent-to-treat analysis

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Renal Outcomes Summary

- Canagliflozin compared to placebo
  - Induced sustained lowering of albuminuria
  - Prevented progression in albuminuria
  - Induced regression in albuminuria
  - Reduced renal function loss events
- Conclusion
  - These data suggest a potential renoprotective effect of canagliflozin treatment in patients with type 2 diabetes at high CV risk on top of ACE/ARBs

CANVAS Program

EFECTOS SOBRE FILTRACIÓN GLOMERULAR

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EFECTO AGUDO

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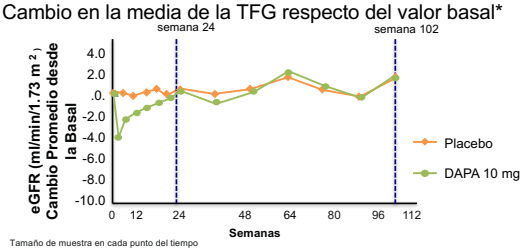
Dapagliflozina - Seguridad Renal

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

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

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[06-14-2016]

Safety Announcement

The U.S. Food and Drug Administration (FDA) has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. This is a serious condition in which the kidneys suddenly stop working, causing dangerous levels of wastes to build up in the body. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medicine without first talking to their health care professionals. Doing so can lead to uncontrolled blood sugar levels that can be harmful.

Health care professionals should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

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

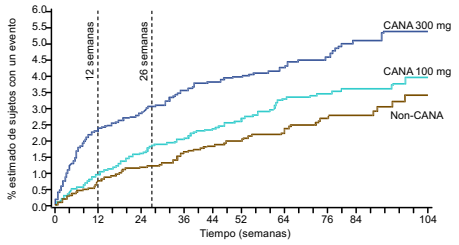
	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)	N=2360 27 (1.1)	N=2295 17 (0.7)	N=2026 38 (1.9)	N=1956 27 (1.4)

- 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

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

Estimación de KM



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

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

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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Laboratory Data: Electrolytes

- Dapagliflozin had no clinically relevant impact on serum electrolytes
  - No clinically meaningful changes from baseline were observed in mean serum sodium, potassium, calcium, bicarbonate, or chloride after 24 weeks of treatment
  - Small changes from baseline in mean serum phosphorous and magnesium were observed
- There was no increased risk of hyperkalemia with dapagliflozin

	Placebo-controlled pool (short-term)	
	DAPA 10 mg (N=2360)	PBO (N=2295)
Sodium Mean change from BL	N=1966 0.065 (3.172)	N=1858 –0.429 (3.192)
Potassium Mean change from BL	N=1965 –0.047 (0.454)	N=1854 –0.023 (0.433)
Calcium, total, (mg/dL) Mean change from BL	N=1954 0.037 (0.493)	N=1845 –0.006 (0.523)
Bicarbonate, (MEQ/l) Mean change from BL (SD)	N=1949 0.159 (3.047)	N=1847 0.442 (2.907)
Chloride, serum (MEQ/l) Mean change from BL	N=1966 0.101 (3.227)	N=1858 –0.307 (3.176)
Magnesium, serum (MEQ/l) Mean change from BL	N=1956 0.092 (0.192)	N=1849 –0.023 (0.164)
Phosphorous, inorganic (mg/dL) Mean change from BL	N=1954 0.132 (0.509)	N=1844 –0.043 (0.647)

BMS/AZ data on file; EMDAC Background document Available at:
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf;

EFECTO A LARGO PLAZO

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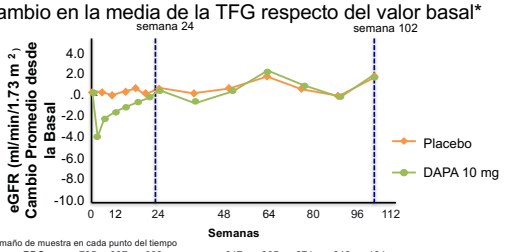
Dapagliflozina - Seguridad Renal

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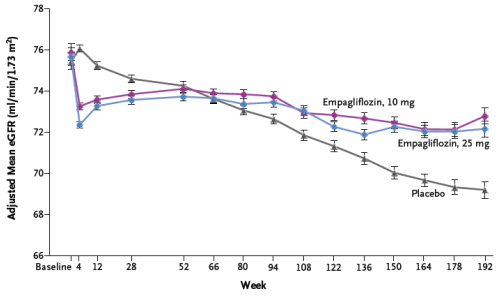
Expert Opin. Investig. Drugs (2013) 22(4):463-486

AEC en EMPAREG



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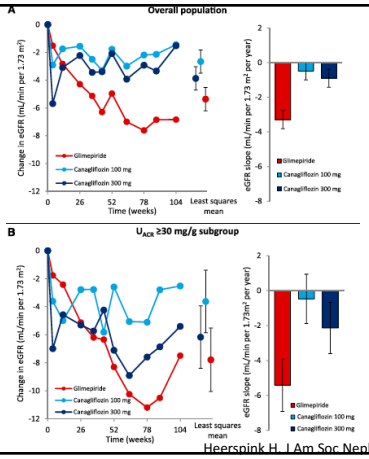
Wanner C. N Engl J Med. 2016; online Jun 14



Heerspink H. J Am Soc Nephrol. 2017;28:368

EFICACIA EN PACIENTES CON AEC DISMINUIDO

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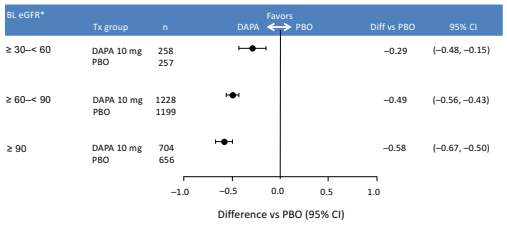
Effect of Baseline eGFR Category on HbA1c Reduction

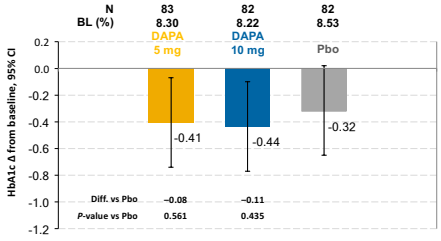
- Consistent with the mechanism of action, efficacy of dapagliflozin is dependent on renal function



*eGFR, estimated glomerular filtration rate (unit: ml/min/1.73m^2); ANCOVA model, excluding data after rescue
EMDAC Background document. Available at:
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

Dapagliflozin in Patients with Moderate Renal Impairment: Change in HbA1c

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



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

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

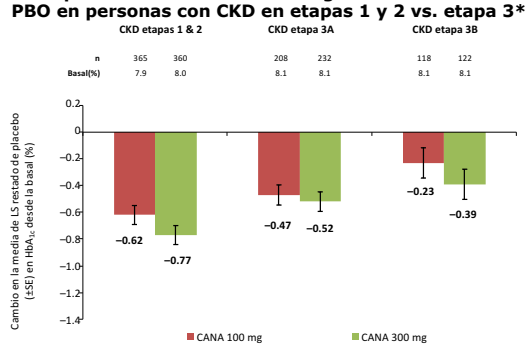
- Post-hoc analysis showed a larger reduction in adjusted mean change in HbA1c and FPG from baseline to week 24 for dapagliflozin vs placebo for stage 3A CKD than for stage 3B CKD

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

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

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

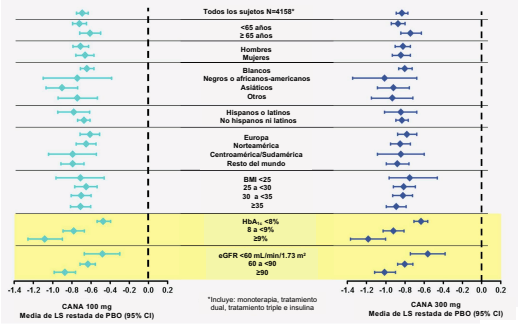
Comparación del efecto de canagliflozina restado de PBO en personas con CKD en etapas 1 y 2 vs. etapa 3*



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.

Bakris G, et al. *Am J Nephrol.* 2014; In Press.

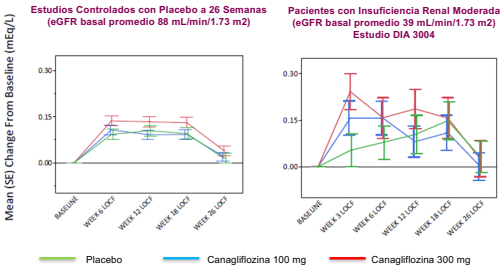
Cambio en HbA1c desde la basal por factores de subgrupo Estudios de eficacia controlados con placebo acumulados



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

Canagliflozina – Manejo de Potasio

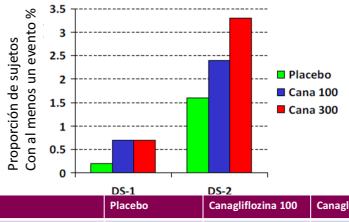
Cambio Promedio en Potasio Sérico en Cada Visita



eGFR = tasa estimada de filtración glomerular

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

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

A PESAR DE LO CUAL… EN LOS DESENLACES MACE

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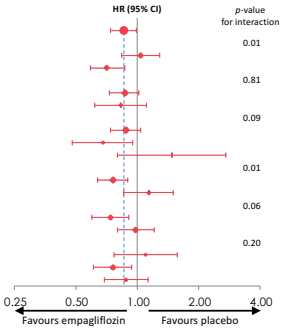
3-point MACE: subgroup analysis

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

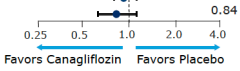


For the test of homogeneity of the treatment group difference among subgroups with no adjustment for multiple tests. eGFR, estimated glomerular filtration rate (according to Modification of Diet in Renal Disease equation)

64

Risk Factor Subgroups (Primary Outcome)

	Hazard ratio (95% CI)	p value for interaction
BMI		**0.29**
<30 kg/m²	0.97 (0.79-1.20)	
≥30 kg/m²	0.79 (0.67-0.93)	
BP control		**0.64**
SBP ≥140 mmHg or DBP ≥90 mmHg	0.84 (0.70-1.01)	
SBP <140 mmHg and DBP <90 mmHg	0.88 (0.74-1.04)	
Duration of diabetes		**0.33**
≥10 y	0.81 (0.70-0.95)	
<10 y	0.96 (0.76-1.22)	
HbA1c		**0.29**
<8%	0.94 (0.77-1.15)	
≥8%	0.80 (0.68-0.94)	
eGFR		**0.20**
30 to <60 mL/min/1.73 m²	0.70 (0.55-0.90)	
60 to <90 mL/min/1.73 m²	0.95 (0.80-1.13)	
≥90 mL/min/1.73 m²	0.84 (0.62-1.12)	



Intent-to-treat analysis

CANVAS Program

SIMILAR A ARA?

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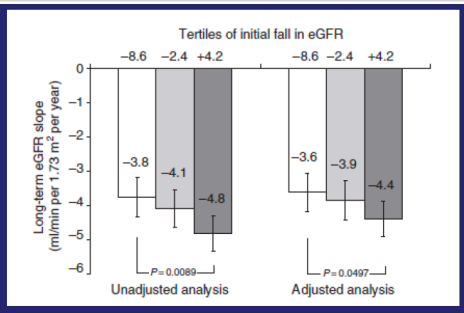
Long-term eGFR Slope Stratified by Acute Fall in eGFR in Losartan-assigned Patient



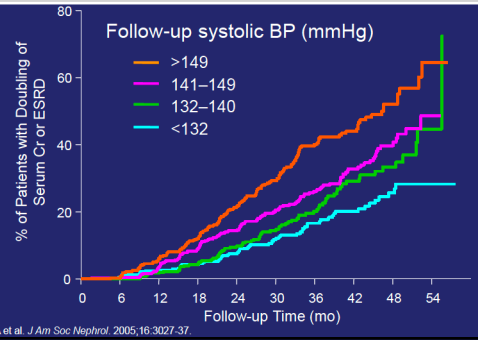
Hollkamp FA et al. *Kidney Int.* 2011;80:282-7.

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.

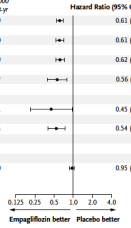
IDNT: Impact of Quartile of Achieved Mean Systolic Blood Pressure on Time to Renal Endpoint



Pohl MA et al. *J Am Soc Nephrol.* 2005;16:3027-37.

EMPAREG - renal

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.53–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



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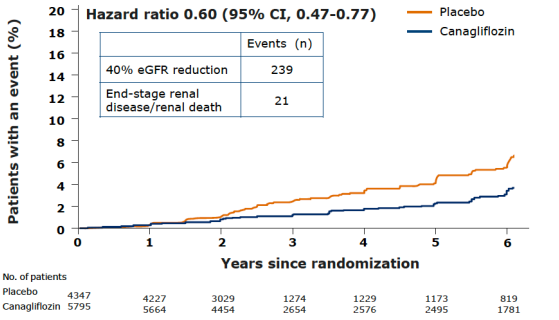
Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



Intent-to-treat analysis

CANVAS Program

1314-P — 2017 [Board 1314-P] ADA

The Effect of Sodium-Glucose Cotransporter 2 Inhibitors on the Alteration of Plasma Renin Activity and Aldosterone Concentration in Type 2 Diabetes Mellitus

Map

Clinical Therapeutics/New Technology - Pharmacologic Treatment of Complications
Presented on Saturday, June 10, 2017 11:30 AM

Author(s): **ICHIRO MORI**, MARIKO TANGIKU, MASAYUKI FUWA, KEI FUJIOKA, DAIKI ANDO, TATSUO ISHIZUKA, *Gifu, Japan*

Objective: The purpose of this study is to examine alterations of plasma renin activity (PRA) and aldosterone concentration (PAC) after treatment with SGLT2 inhibitor in type 2 diabetes mellitus (T2D).
Methods: We measured PRA and PAC after resting at supine position for 30 minutes in 18 T2D patients (age 68±18 years old, men: female = 12:6) after treatment with SGLT2i (tofogliflozin: 9 cases, empagliflozin: 4 cases, canagliflozin: 4 cases dapagliflozin: 1 case) for more than 1 month, and also selected as control 18 nondiabetic patients adjusted for age and sex from 2014 to 2016. Moreover, we could measure each metabolic parameter such as blood glucose, HbA1c, urinary Na/creatinine and blood pressure, and PRA and PAC before and after treatment with SGLT2i for 1 month in 6 T2D patients. We analyzed these results with paired and unpaired t test using JMP12.2.0.
Results: SGLT2i significantly increased PRA and decreased PAC levels compared with control as follows; PRA in control group and SGLT2i group 0.9±0.5 ng/ml/h and 5.8±8.9 ng/ml/h, p<0.04, PAC in control group and SGLT2i group 99±44 pg/ml and 72±36 pg/ml, p<0.05. Moreover, when we examined each metabolic parameter before and after treatment with SGLT2i for 1 month in 6 T2D patients, each body weight, blood pressure, and HbA1c was significantly decreased compared with before treatment in 6 TSD patients (p<0.04). PRA value after treatment with SGLT2i was significantly increased compared with before (before 3.25±3.13, after 5.98±4.78, p<0.05), but not PAC.
Discussion and Conclusions: SGLT2i increases urinary sodium excretion, which affects macula densa in juxta-glomerular apparatus, and finally stimulates secretion of renin, but not aldosterone. SGLT2i-induced decreases in the circulating plasma volume, renal blood flow and osmotic diuresis also may affect stimulation of renin secretion

Disclosure: **I. Mori:** None. **M. Tangiku:** None. **M. Fuwa:** None. **K. Fujioka:** None. **D. Ando:** None. **T. Ishizuka:** None.

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EVENTOS ADVERSOS

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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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Complicated urinary tract infection

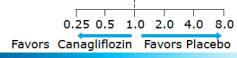
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Complicated urinary tract infection*	41 (1.8%)	0.71	34 (1.4%)	0.57	48 (2.0%)	0.80
Urinary tract infection	16 (0.7%)	0.28	13 (0.6%)	0.22	16 (0.7%)	0.27
Pyelonephritis†	22 (0.9%)	0.38	15 (0.6%)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

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
Events reported in >0.1% of patients in any group are shown
*Pyelonephritis, urosepsis or serious adverse event consistent with urinary tract infection

Adverse Events (CANVAS)

	Event rate per 1000 patient-years: Canagliflozin	Event rate per 1000 patient-years: Placebo	Hazard ratio (95% CI)
Female genital mycotic infection (n = 196)	69	18	4.37 (2.78-6.88)
Urinary tract infection (n = 440)	40	37	1.09 (0.89-1.34)
Hypoglycemia (n = 551)	50	46	1.13 (0.94-1.35)
Osmotic diuresis (n = 312)	34	13	2.80 (2.06-3.81)
Volume depletion (n = 266)	26	19	1.44 (1.09-1.90)
Severe hypersensitivity/ cutaneous reaction (n = 87)	8	6	1.41 (0.87-2.28)
Hepatic injury (n = 90)	7	9	0.81 (0.53-1.25)



CANVAS Program

Conclusiones

- Los inhibidores de SGLT-2…
  - El paradigma ha cambiado, pasando a ser más bien nefroprotectores
  - Mecanismo no bien establecido
  - Mayoría de pacientes están recibiendo moduladores del SRAA de base
  - No produce ITU
  - Precaución con AEC bajos por mayor riesgo de EAs

EndoDrChen.com

Preguntas…
chenku2409@gmail.Com
EndoDrChen.Com

EndoDrChen.com