Tratamiento con iSGLT2: la nueva frontera de tratamiento

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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, Pfizer, Novartis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Siegfried
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Novo Nordisk

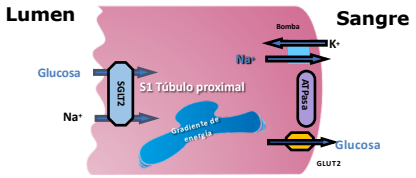
Agenda

- Ilustrar conceptos cambiantes de iSGLT2
- Beneficios metabólicos de los iSGLT2
- Estudios de seguridad cardiovascular
- Cuándo, cómo y en quién iniciar iSGLT2?

Beneficios metabólicos de los iSGLT2

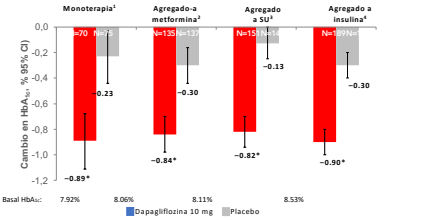
1er concepto: mecanismo de acción “clásico”

SGLT2 permite la reabsorción de glucosa renal



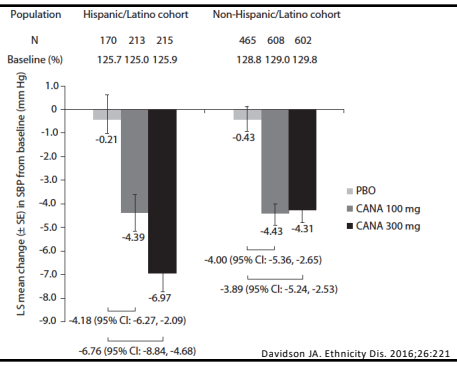
Adaptado de de R.A DeFronzo et al. Diabetes, Obesity and Metabolism 2012, 14:14:5.

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



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

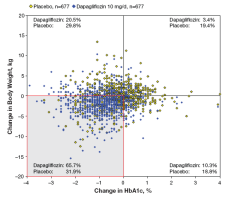
1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. Wilding J, *et al. Diabetes* 2010;**59**(Suppl 1):0078-OR.



Davidson JA. Ethnicity Dis. 2016;26:221

Changes in Individual HbA1c and Body Weight in Patients Receiving Dapagliflozin or Placebo

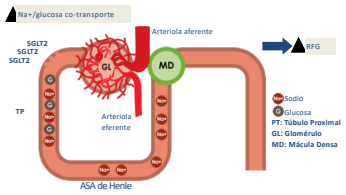
- ~65% of dapagliflozin-treated patients achieved reductions in both HbA1c and body weight



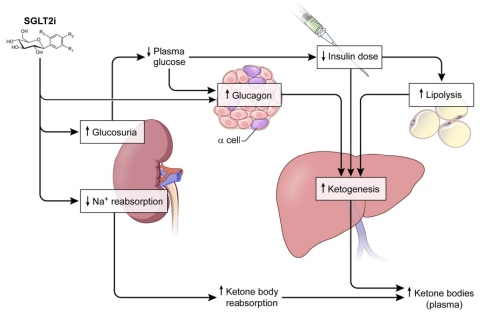
Data are not adjusted for study. Data not shown: 1 patient receiving placebo with ΔHbA1c = −1.7%, ΔWeight = −27.6 kg; 1 patient receiving placebo with ΔHbA1c = 4.4%, ΔWeight = −3.1 kg; and 1 patient receiving dapagliflozin 10 mg/d with ΔHbA1c = 0.2%, ΔWeight = −20.7 kg.

Hardy E, et al. ADA 2012; poster 987-P.

2do concepto: nuevos mecanismos



Adaptado de Cherney D et al. *Circulation* 2016;129:587



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

Glucagon y efectos vasculares

- Niveles altos de glucagon:
  - Vasodilatación
  - Aumento de flujo plasmático renal
  - Aumento de TFG
  - Aumento de natriuresis en estados de ayuno

Wanner C. Am J Med. 2017;130:563

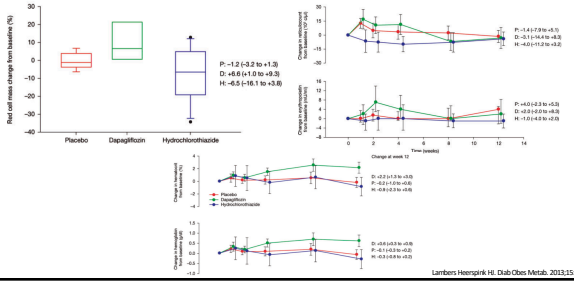
EMPAREG: análisis de variables

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for:		
HbA1c	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	−7.5
DBP	0.614 (0.490, 0.769)	−0.5
Heart rate	0.621 (0.495, 0.780)	2.0
LDL-C	0.596 (0.475, 0.748)	−6.5
HDL-C	0.636 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	−3.7
FFAs	0.586 (0.463, 0.741)	−9.9
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (MDRD)	0.631 (0.504, 0.790)	5.3
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
Weight	0.579 (0.461, 0.727)	−12.4
BMI	0.578 (0.460, 0.726)	−12.8
WC	0.598 (0.477, 0.750)	−3.8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.615, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

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

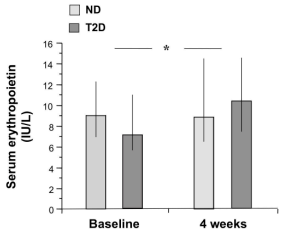
Inzucchi SE. Diabetes Care. 2018;41:356

Masa de glóbulos rojos



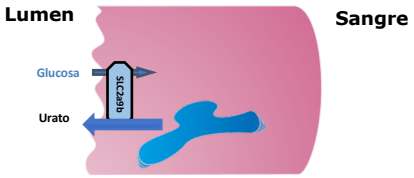
Lambers Heerspink HJ. Diab Obes Metab. 2013;15:853

Niveles de EPO con empagliflozina

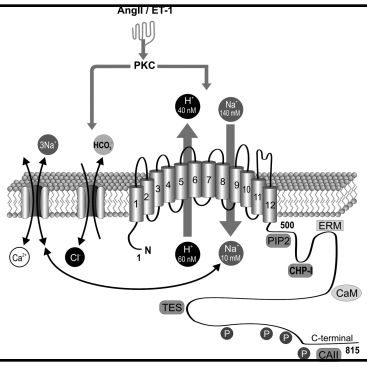


Ferrannini E. Diabetes Care. 2017;40:771

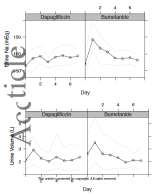
Mecanismo uricosúrico



Musso G. Ann Med. 2012;44:375

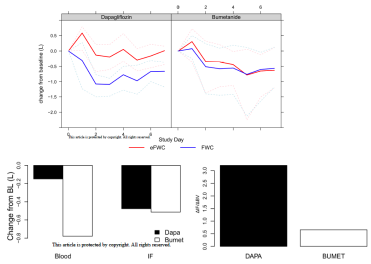


Dapagliflozina vs bumetanida



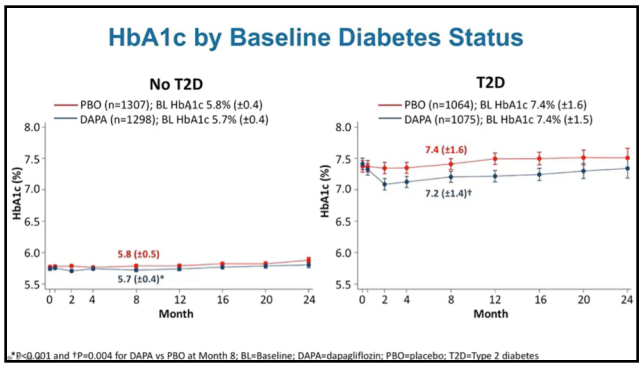
Hallow KM. Diab Obes Metab. Online 12 oct 2017

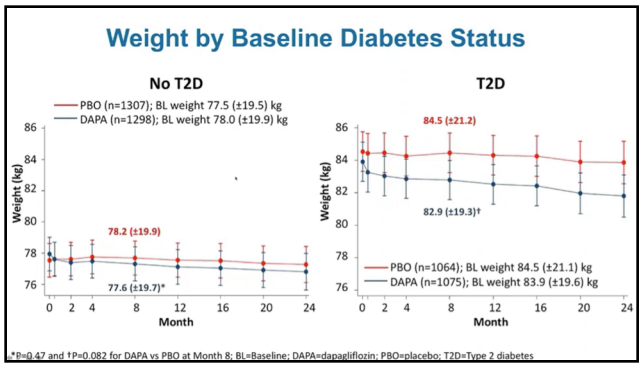
Dapagliflozina vs bumetanida

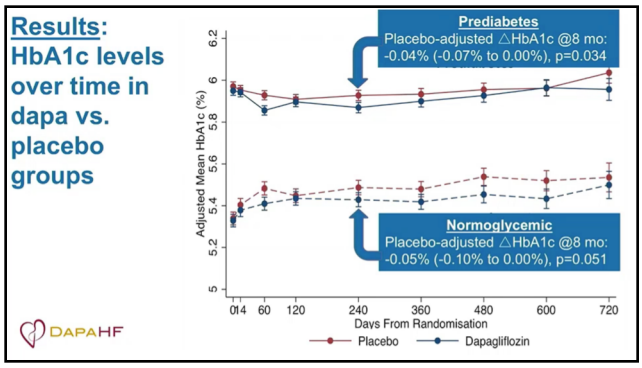


Hallow KM. Diab Obes Metab. Online 12 oct 2017

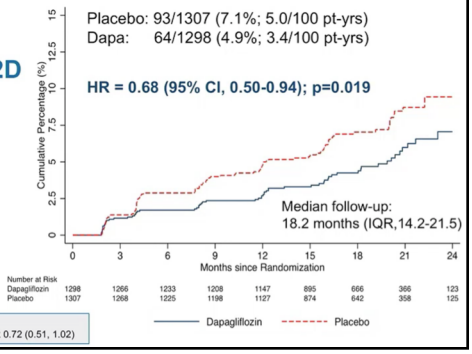
3er concepto: efectos en personas sin diabetes


HbA1c by Baseline Diabetes Status
No T2D
PBO (n=1307); BL HbA1c 5.8% (±0.4)
DAPA (n=1298); BL HbA1c 5.7% (±0.4)
5.8 (±0.5)
5.7 (±0.4)*
T2D
PBO (n=1064); BL HbA1c 7.4% (±1.6)
DAPA (n=1075); BL HbA1c 7.4% (±1.5)
7.4 (±1.6)
7.2 (±1.4)†
HbA1c (%)
Month
*P<0.001 and †P=0.004 for DAPA vs PBO at Month 8; BL=Baseline; DAPA=dapagliflozin; PBO=placebo; T2D=Type 2 diabetes


Weight by Baseline Diabetes Status
No T2D
PBO (n=1307); BL weight 77.5 (±19.5) kg
DAPA (n=1298); BL weight 78.0 (±19.9) kg
78.2 (±19.9)
77.6 (±19.7)*
T2D
84.5 (±21.2)
82.9 (±19.3)†
PBO (n=1064); BL weight 84.5 (±21.1) kg
DAPA (n=1075); BL weight 83.9 (±19.6) kg
Weight (kg)
Month
*P=0.47 and †P=0.082 for DAPA vs PBO at Month 8; BL=Baseline; DAPA=dapagliflozin; PBO=placebo; T2D=Type 2 diabetes


Results: HbA1c levels over time in dapa vs. placebo groups
Prediabetes
Placebo-adjusted △HbA1c @8 mo: -0.04% (-0.07% to 0.00%), p=0.034
Normoglycemic
Placebo-adjusted △HbA1c @8 mo: -0.05% (-0.10% to 0.00%), p=0.051
Adjusted Mean HbA1c (%)
Days From Randomisation
Placebo
Dapagliflozin
DAPA HF

Results: Incidence of new onset T2D in dapa vs. placebo groups



Fine & Gray: HR 0.69 (0.50-0.95)
LR adjusted for baseline HbA1c: OR 0.72 (0.51, 1.02)

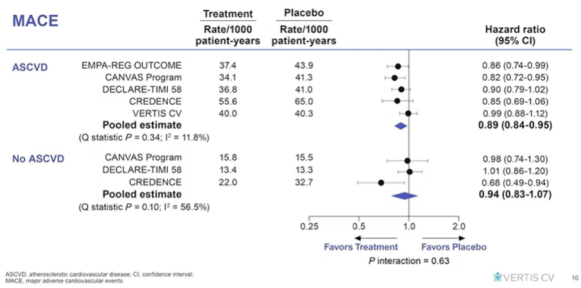
Seguridad cardiovascular

4to concepto: protección cardiovascular y reducción en falla cardíaca

Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardíaca
Inhibidores de SGLT2						
EMPAREG (empagliflozina)	0.86 (0.74-0.99)	0.87 (0.70-1.09)	1.24 (0.92-1.67)	0.62 (0.49-0.77)	0.68 (0.57-0.82)	0.65 (0.5-0.85)
CANVAS (canagliflozina)	0.86 (0.75-0.97)	0.85 (0.69-1.05)	0.90 (0.71-1.15)	0.87 (0.72-1.06)	0.87 (0.74-1.01)	0.67 (0.52-0.87)
DECLARE (dapagliflozina)	0.93 (0.84-1.03)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.98 (0.82-1.17)	0.93 (0.82-1.04)	0.73 (0.61-0.88)
VERTIS (ertugliflozina)	0.97 (0.95-1.11)	1.0 (0.86-1.27)	1.0 (0.76-1.32)	0.92 (0.77-1.11)	NA	0.70 (0.54-0.90)

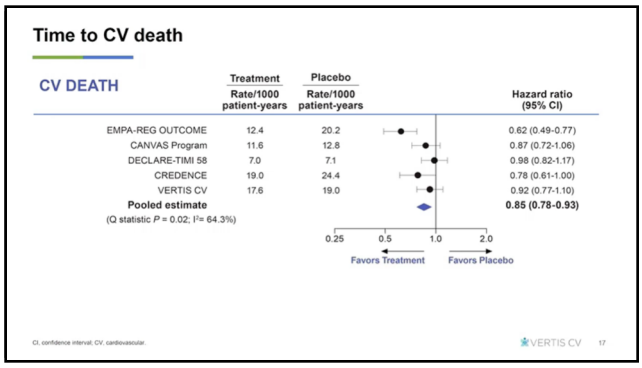
5to concepto: efecto de clase?

Time to first MACE – subgroup analysis by ASCVD



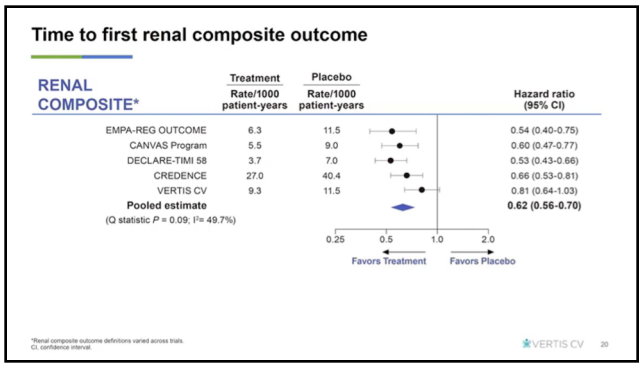
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MACE, major adverse cardiovascular events.

VERTIS CV 16



6to concepto: del temor de lesión renal a ser renoprotectores

	Desenlace compuesto microvascular	Desenlace compuesto renal	Nueva aparición microalbuminuria	Doblamiento creatinina	Terapia reemplazo renal	Muerte renal
Inhibidores de SGLT2						
EMPAREG (empagliflozina)	0.62 (0.54-0.70)	0.61 (0.53-0.70)	0.62 (0.54-0.72)	0.56 (0.39-0.79)	0.45 (0.21-0.97)	NA
CANVAS (canagliflozina)	0.86 (0.75-0.97)	0.60 (0.47-0.77)	0.80 (0.79-0.88)	0.50 (0.30-0.84)	0.77 (0.30-1.97)	NA
DECLARE (dapagliflozina)	NA	0.53 (0.43-0.66)	NA	NA	NA	NA
CREDENCE (canagliflozina)	NA	0.66 (0.53-0.81)	NA	0.60 (0.48-0.76)	0.74 (0.55-1.00)	NA
VERTIS (ertugliflozina)	NA	0.81 (0.63-1.04)	NA	NA	NA	NA
Análogos de GLP1						
ELIXA (lixisenatide) [32]	NA	NA	NA	1.16 (0.74-1.82)	NS	NS
LEADER (liraglutide)	0.84 (0.79-0.97)	0.78 (0.67-0.92)	0.74 (0.60-0.91)	0.88 (0.66-1.18)	0.87 (0.6-1.24)	1.59 (0.52-4.87)
SUSTAIN-6 (semaglutide)	NA	0.64 (0.46-0.88)	0.54 (0.37-0.77)	1.28 (0.64-2.58)	0.91 (0.40-2.07)	NA
HARMONY (albiglutide)	NA	NA	NA	NA	NA	NA



Lesión renal aguda

	iSGLT2	Placebo	P
EMPAREG	5.3%	6.6%	NA
CANVAS	1.6 x 1000 pts año	2.5 x 1000 pts año	HR 0.68 (0.45-1.02)
DECLARE	1.5%	2.0%	0.002
VERTIS	1.9%	2.2%	NA
CREDENCE	3.9%	4.4%	HR 0.85 (0.64-1.13)

7mo concepto: efectos adversos, no produce ITU

ITU

	iSGLT2	Placebo	P
EMPAREG	18.1%	18.2%	NA
CANVAS	40 x 1000 pts año	37 x 1000 pts año	HR 1.09 (0.89-1.34)
DECLARE	1.5%	1.6%	NS
VERTIS	12.2%	10.2%	NA
CREDENCE	11.1%	10.0%	HR 1.08 (0.90-1.29)

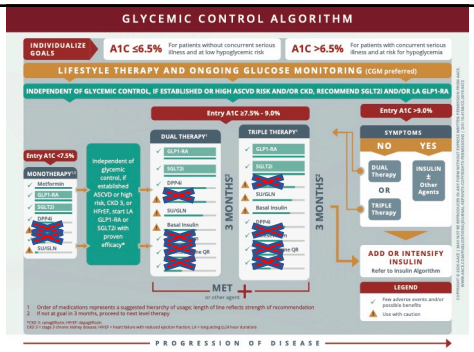
Infección genital

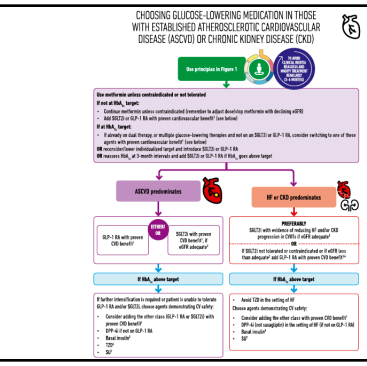
	iSGLT2	Placebo	P
EMPAREG	6.5%	1.8%	NA
CANVAS	69 x 1000 pts año (F) 35 x 1000 pts año (M)	18 x 1000 pts año (F) 11 x 1000 pts año (M)	HR 4.37 (2.78-6.88) (F) HR 3.76 (2.91-4.86) (M)
DECLARE	0.9%	0.1%	<0.001
VERTIS	7.8% (F) 5.1% (M)	2.4% (F) 1.2% (M)	NA NA
CREDENCE	2.27%	0.59%	

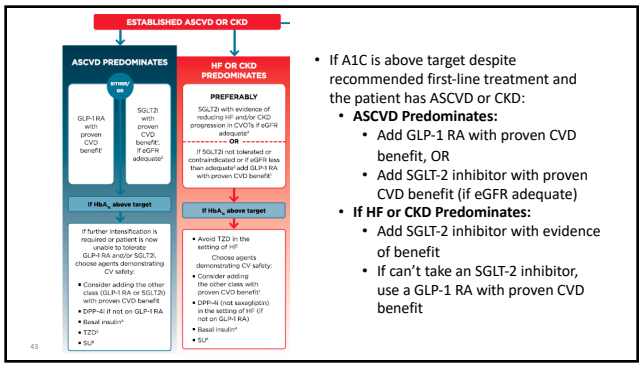
Otros efectos adversos

- Hipotensión postural
  - Adultos mayores, diuréticos de asa, AEC <60 cc/min
- Fracturas
  - Parece que es secundario a hipotensión postural
- Amputaciones
  - No está claro, parece que sólo en CANVAS
- Cetoacidosis
  - Aumento muy discreto
- Gangrena de Fournier
  - No significativo en estos estudios de desenlaces CV

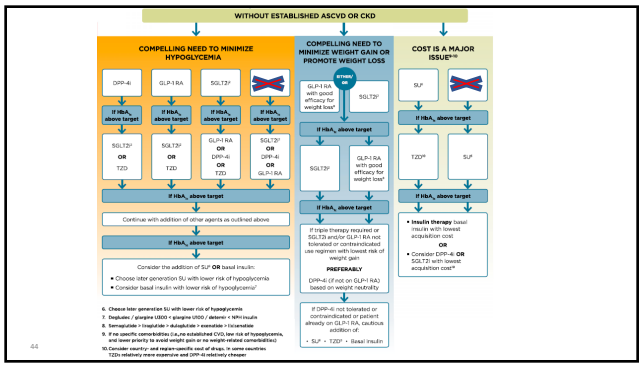
Cuándo, cómo y en quién iniciar iSGLT2?

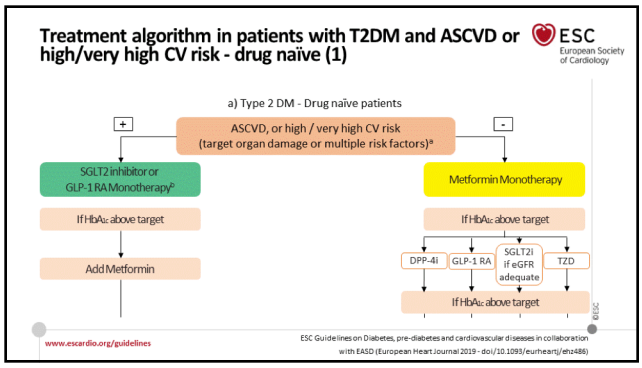






- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor with evidence of benefit
    - If can't take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit





Cuál agente para quién?

	iSGLT2	GLP1RA (basado en estructura GLP1)	iDPP4
Enfermedad aterosclerótica			
Insuficiencia cardíaca			
Nefropatía diabética			
Peso			
Propenso a cetosis			
Fragilidad/fractura previa/caídas			
Amputación previa			
Insuficiencia renal crónica (estadio 4-5)			
Infección genital a repetición			

Conclusiones

- Los iSGLT2 han pasado de ser agentes glucosúricos a tener una serie de cambios hemodinámicos importantes que producen nefroprotección y cardioprotección
- Los efectos metabólicos se presentan predominantemente en la población con DM, no tenemos muchos datos de población sin DM
- Previene aparición de DM en pacientes con HFrEF
- Presencia de falla renal, proteinuria o falla cardíaca son indicaciones absolutas para el uso de iSGLT2
- Por sus efectos metabólicos, pueden ser 1ra ó 2da línea de tratamiento en todos los pacientes con DM

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com