iSGLT2 y su impacto en comorbilidades

Dr. Chih Hao Chen Ku, FACE
Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica
Sistema de Estudios de Postgrado, Universidad de Costa Rica

Conflictos de interés (últimos 5 años)

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

Agenda

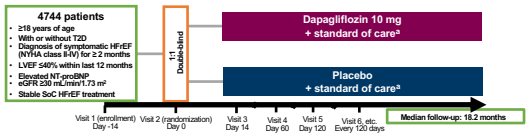
- Revisar el impacto que tienen los inhibidores de SGLT2 en:
  - Insuficiencia cardíaca
  - Nefropatía diabética
  - Enfermedad cardiovascular

Insuficiencia cardíaca

Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardíaca
Inhibidores de SGLT2						
EMPAREG (empaglifozina)	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)
SCORED (sotagliflozina)	0.77 (0.65-0.91)	NA	NA	0.90 (0.63-0.83)	0.99 (0.83-1.18)	0.67* (0.55-0.82)
SOLIST-WHF (sotagliflozina)	NA	NA	NA	0.84 (0.58-1.22)	0.82 (0.59-1.14	0.64 * (0.49-0.83)

DAPA-HF

Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D[1,2]



Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

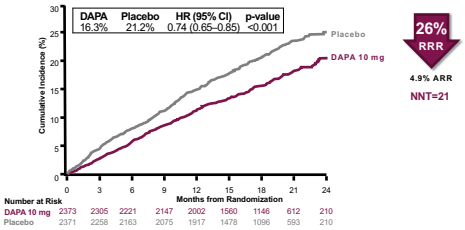
Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD[b] or renal death
- Time to death from any cause

[a]Patients were treated according to regional standard of care for HF. Dose reduction or discontinuation of standard of care therapy was discouraged unless all other measures failed. Changes in standard of care medications was at the discretion of the investigator. [b]Defined as sustained eGFR <15 mL/min/1.73m², chronic dialysis treatment, or receiving a renal transplant.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray JJV et al. Article and study protocol. *N Engl J Med.* 2019;381:1995-2008.

Primary Endpoint: CV Death or hHF or an Urgent HF Visit



4.9% ARR

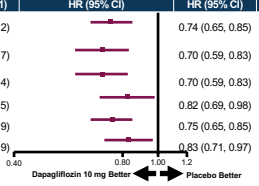
NNT=21

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008.

Effects of Dapagliflozin on Worsening HF[a] and Mortality[1]

Outcome, n (%)	Dapagliflozin 10 mg (n=2373)	Placebo (n=2371)	HR (95% CI)	p-value
CV death, hHF, or urgent HF visit	386 (16.3)	502 (21.2)	0.74 (0.65, 0.85)	<0.001
hHF or urgent HF visit	237 (10.0)	326 (13.7)	0.70 (0.59, 0.83)	0.00003[2]
Hospitalization for HF	231 (9.7)	318 (13.4)	0.70 (0.59, 0.83)	0.0001[3]
CV death	227 (9.6)	273 (11.5)	0.82 (0.69, 0.98)	0.029[2]
CV death or hHF	382 (16.1)	495 (20.9)	0.75 (0.65, 0.85)	<0.001
Death from any cause	276 (11.6)	329 (13.9)	0.83 (0.71, 0.97)	0.022[2,b]



[a]Worsening HF includes hHF or urgent HF visit; [b]Nominal p-value.

CV = cardiovascular; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

1. McMurray JJV et al. Supplementary material. *N Engl J Med.* 2019;381:1995-2008; 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France; 3. In House Data, AstraZeneca Pharmaceuticals LP. CSR D1699C00001.

Primary Outcome by Diabetes Status[1]

Dapagliflozin significantly reduced the primary endpoint, regardless of diabetes status and HbA1c in the no T2D group

CV death or hHF or urgent HF visit

Outcome	Dapagliflozin 10 mg, n/N (%)	Placebo, n/N (%)	HR (95% CI)	Interaction p-value[a]
Total population	386/2373 (16.3)	502/2371 (21.2)	0.74 (0.65-0.85)	
T2D[b]	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63-0.90)	0.80
No T2D	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60-0.88)	
Normo-glycemic (HbA1c <5.7%)	53/438 (12.1)	71/419 (16.9)	0.67 (0.47-0.96)	0.72
Pre-diabetes (HbA1c ≥5.7-<6.5%)	118/860 (13.7)	160/888 (18.0)	0.74 (0.59-0.94)	

[a]Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
CV = cardiovascular; HbA1c = glycated hemoglobin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; T2D = type 2 diabetes.

1. Petrie MC et al. *JAMA*. 2020;323:1353-1368; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

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Safety Outcomes[a]

Event, n (%)	Dapagliflozin 10 mg (n=2368)	Placebo (n=2368)	p-value
AE leading to treatment discontinuation	111 (4.7)	116 (4.9)	0.79
AE of interest			
Volume depletion[b]	178 (7.5)	162 (6.8)	0.40
Renal AE[c]	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (0.5)	1.00
Major hypoglycemia[d]	4 (0.2)	4 (0.2)	-
Diabetic ketoacidosis[e]	3 (0.1)	0 (0)	-

[a]Safety population included all patients who had undergone randomization and received at least one dose of dapagliflozin or placebo. [b]Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%); p=0.23; [c]Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%); p=0.009. Serious adverse events of acute kidney injury were reported in 23 dapagliflozin patients (1.0%) and 46 placebo patients (1.9%). [d]Defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline. [e]All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline and were adjudicated as definite or probable.
AE = adverse event.

Mc Murray JJV et al. Article and supplementary material. *N Engl J Med*. 2019;381:1995-2008.

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EMPEROR-REDUCED

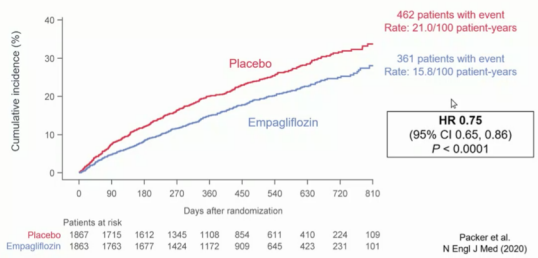
Trial inclusion and exclusion criteria

Inclusion criteria

EMPEROR-Reduced[1,2]	DAPA-HF[3]
Age ≥18 years (Japan, age ≥20 years) at screening	Age ≥18 years
Chronic HF NYHA class II–IV	Chronic HF NYHA class II–IV
HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)
Elevated NT-proBNP **EF (%)** — **NT-proBNP (pg/ml)** Patients without AF* ≥36 to ≤40 — ≥2500 ≥31 to ≤35 — ≥1000 ≤30 — ≥600 ≤40% + HHF within 12 months — ≥600	**NT-proBNP ≥600 pg/ml or NT-proBNP ≥400 pg/ml in patients with HHF within 12 months** Patients without AF†
Further inclusion criteria apply	Further inclusion criteria apply
EMPEROR-Reduced **eGFR <20 ml/min/1.73 m²** or requiring dialysis	**DAPA-HF** **eGFR <30 ml/min/1.73 m²** or rapidly declining renal function

*The cut off for patients with AF is doubled in EMPEROR-Reduced. †In DAPA-HF patients with AF or atrial flutter were required to have NT-proBNP ≥900 pg/ml regardless of history of HHF
See slides notes for abbreviations
1. ClinicalTrials.gov. NCT03057977 (Accessed Aug 2020). 2. Zannad F et al. EHJ-HF 2018; doi:ehjhf.2018.0054. 3. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008.

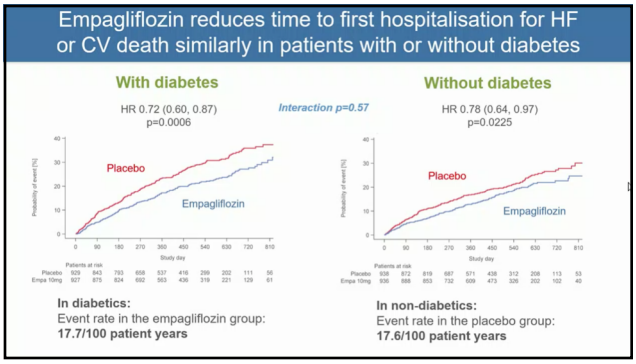
EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



Packer et al.
N Engl J Med (2020)

EMPEROR-Reduced: Effect on Individual Components of the Primary Endpoint

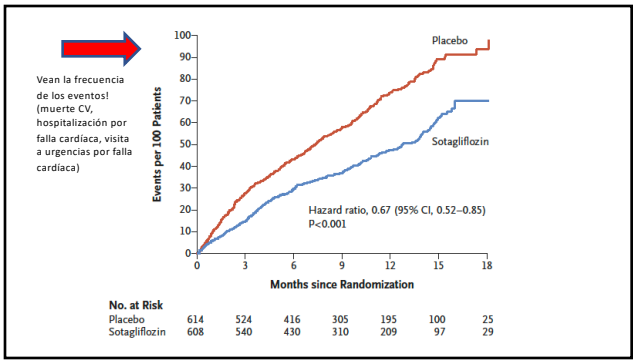
	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.0001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	



SOLOIST-WHF

Introducción

- Sotagliflozin es un inhibidor de SGLT2 (riñón) y SGLT1 (intestinal)
- Ensayo realizado en el contexto del paciente con hospitalización reciente por falla cardíaca
- Con HFrEF ó HFpEF
- Todos con DM-2
- Debían tener PAS >100 mm Hg, sin O2 suplementario, sin necesidad de soporte inotrópico IV y con transición hacia diuréticos orales
- Aleatorizado durante la hospitalización o durante los primeros 3 días post egreso a sotagliflozin 200 mg por día vs placebo



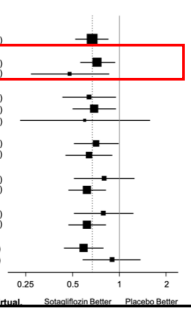
Efficacy Testing Hierarchy

Endpoint	Sotagliflozin Rate [Events]	Placebo Rate [Events]	HR (95% CI)	P-value
Total CV death, HHF, and urgent HF visit	**51.0 [245]**	**76.3 [355]**	**0.67 (0.52-0.85)**	**0.0009**
Total HHF and urgent HF visit	40.4 [194]	63.9 [297]	0.64 (0.49-0.83)	0.0008
CV death	10.6 [51]	12.5 [58]	0.84 (0.58-1.22)	0.36
Total CV death, HHF, NFMI, and non-fatal stroke	51.4 [247]	71.0 [330]	0.72 (0.56-0.92)	0.008*
Total CV death, HHF, urgent HF visit, and HF while hospitalized	54.7 [263]	80.6 [375]	0.68 (0.54-0.86)	0.001*
All-cause death	13.5 [65]	16.3 [76]	0.82 (0.59-1.14)	0.23*
Change in KCCQ-12 score, points	17.7	13.6	4.1 (1.3-7.0)	0.005*
Change in eGFR, mL/min/1.73m^2	-0.34	-0.18	-0.16 (-1.30-0.98)	0.78*

*Nominal p-value. Rate = number of events per 100 patient-years. Values in table for change in KCCQ-12 score and change in eGFR are least squares means, difference in least squares means, and 95% CI for difference in least squares means

Primary Efficacy Subgroups

Subgroup	Patients	Events Per 100 py Sotagliflozin	Events Per 100 py Placebo	HR (95% CI)
Overall	1222	51.0	76.3	0.67 (0.52, 0.85)
LVEF (%)				
< 50	966	56.9	79.9	0.72 (0.56, 0.94)
≥ 50	256	30.6	64.0	0.48 (0.27, 0.86)
Geographic Region				
Americas	346	68.3	103.0	0.64 (0.43, 0.95)
Europe	800	44.1	64.7	0.69 (0.50, 0.95)
Rest of World	76	48.4	78.3	0.60 (0.23, 1.58)
First Study Drug Dose				
Before Discharge	596	52.1	76.6	0.71 (0.51, 0.99)
After Discharge	626	50.0	76.1	0.64 (0.45, 0.90)
Sex				
Female	412	41.9	52.0	0.80 (0.51, 1.25)
Male	810	55.7	89.3	0.62 (0.47, 0.82)
Age (years)				
< 65	364	57.1	71.1	0.79 (0.51, 1.23)
≥ 65	858	48.0	78.5	0.62 (0.47, 0.82)
eGFR (ml/min/1.73m2)				
< 60	854	50.1	85.8	0.59 (0.44, 0.79)
≥ 60	368	53.1	58.1	0.90 (0.58, 1.37)



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med*. 2020. Bhatt DL. AHA 2020. virtual.

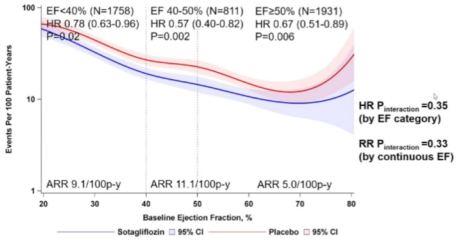
Adverse Events of Special Interest

Composite Term	Sotagliflozin N=605 n (%)	Placebo N=611 n (%)	P-value
Bone fractures	12 (2.0)	9 (1.5)	0.52
Diabetic ketoacidosis	2 (0.3)	4 (0.7)	0.69
Genital mycotic infections	5 (0.8)	1 (0.2)	0.12
Urinary tract infections	52 (8.6)	44 (7.2)	0.40
Volume depletion	57 (9.4)	54 (8.8)	0.77
Diarrhea	42 (6.9)	25 (4.1)	0.032
Pancreatitis	0	3 (0.5)	0.25
Venous thrombotic events	0	7 (1.1)	0.015
Malignancies	4 (0.7)	4 (0.7)	1.00
Adverse event leading to amputation	4 (0.7)	1 (0.2)	0.22
Severe hypoglycemia	9 (1.5)	2 (0.3)	0.037

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med*. 2020. Bhatt DL. AHA 2020, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4,500 Patients with History of HF

SOLOIST SCORED



HR $P_{interaction}$ =0.35 (by EF category)

RR $P_{interaction}$ =0.33 (by continuous EF)

For this analysis, patients from SCORED with any history of HF are included.

Bhatt DL. ACC 2021, virtual.

Breakthrough results for empagliflozin confirm EMPEROR-Preserved as first and only successful trial for heart failure with preserved ejection fraction

- *The EMPEROR-Preserved Phase III trial met its primary endpoint and demonstrated significant risk reduction with empagliflozin for the composite of cardiovascular death or hospitalization for heart failure in patients with heart failure with preserved ejection fraction (HFpEF)*
- *HFpEF has been classified as "the single largest unmet need in cardiovascular medicine"[1] based on prevalence, poor outcomes and the absence of clinically proven therapies to date[2]*
- *With approval, empagliflozin would become the first and only clinically proven therapy to improve outcomes for the full spectrum of heart failure patients regardless of ejection fraction*

Efectos en nefropatía diabética

	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
SCORED	NA	0.71 (0.46-1.08)	NA	NA	NA	NA

Estudios con desenlaces renales: pacientes con DM y proteinuria (CREDENCE)

Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m²
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in → R (Double-blind randomization (1:1)) → Canagliflozin 100 mg / Placebo

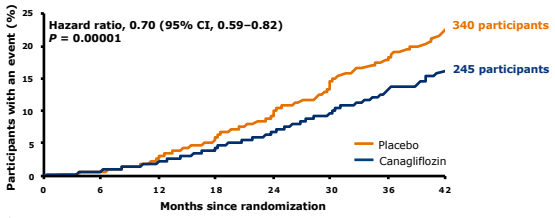
Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

Jardine MJ, et al. *Am J Nephrol.* 2017;46(6):462-472.

CREDENCE

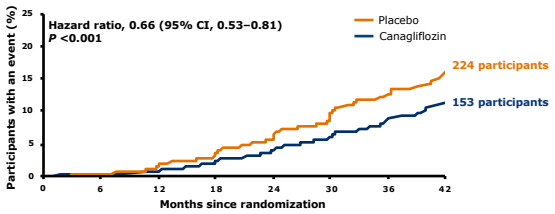
Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

CREDENCE

ESKD, Doubling of Serum Creatinine, or Renal Death



No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

CREDENCE

Summary Forest Plot

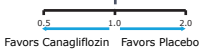
	Hazard ratio (95% CI)	*P* value
Primary composite outcome	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine	0.60 (0.48–0.76)	<0.001
ESKD	0.68 (0.54–0.86)	0.002
eGFR <15 mL/min/1.73 m^2	0.60 (0.45–0.80)	–
Dialysis initiated or kidney transplantation	0.74 (0.55–1.00)	–
Renal death	0.39 (0.08–2.03)	–
CV death	0.78 (0.61–1.00)	0.0502
ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001
Dialysis, kidney transplantation, or renal death*	0.72 (0.54–0.97)	–

*Post hoc analysis.

CREDENCE

Renal Safety

	Number of participants with an event, n: Canagliflozin (N = 2200)	Placebo (N = 2197)	Hazard ratio (95% CI)
All renal-related AEs	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)

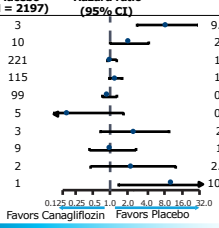


Includes all treated participants through 30 days after last dose.

CREDENCE

Other AEs of Interest

	Number of participants with an event, n: Canagliflozin (N = 2200)	Placebo (N = 2197)	Hazard ratio (95% CI)
Male genital mycotic infections*	28	3	9.30 (2.83–30.60)
Female genital mycotic infections†	22	10	2.10 (1.00–4.45)
Urinary tract infections	245	221	1.08 (0.90–1.29)
Volume depletion–related AEs	144	115	1.25 (0.97–1.59)
Malignancies‡	98	99	0.98 (0.74–1.30)
Renal cell carcinoma	1	5	0.20 (0.02–1.68)
Breast†	8	3	2.59 (0.69–9.76)
Bladder	10	9	1.10 (0.45–2.72)
Acute pancreatitis	5	2	2.44 (0.47–12.59)
Diabetic ketoacidosis	11	1	10.80 (1.39–83.65)



Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1468).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.

CREDENCE

Pacientes con DM y ERC independientemente de proteinuria (SCORED)

Key Inclusion and Exclusion Criteria

SCORED

Inclusion:
- Type 2 diabetes with HbA1c≥7%
- eGFR 25-60 mL/min/1.73m^2
  - with no requirement for macro- or micro-albuminuria
- CV risk factors

Exclusion:
- Planned start of SGLT2 inhibitor

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med*. 2020. Bhatt DL. AHA 2020. virtual.

Efficacy Testing Hierarchy

SCORED

Endpoint	Sotagliflozin Rate [Events]	Placebo Rate [Events]	HR (95% CI)	P-value
Total CV death, HHF, and urgent HF visit	**5.6 [400]**	**7.5 [530]**	**0.74 (0.63-0.88)**	**0.0004**
Total HHF and urgent HF visit	3.5 [245]	5.1 [360]	0.67 (0.55-0.82)	0.0001
CV death	2.2 [155]	2.4 [170]	0.90 (0.73-1.12)	0.35
Total CV death, HHF, non-fatal MI, and non-fatal stroke	7.6 [541]	10.4 [738]	0.72 (0.63-0.83)	0.000008*
Total CV death, HHF, urgent HF visit, and HF while hospitalized	6.4 [453]	8.3 [589]	0.76 (0.65-0.89)	0.0005*
First sustained** ≥50% decrease in eGFR, chronic dialysis, renal transplant or sustained* eGFR <15 mL/min/1.73m^2	0.5 [37]	0.7 [52]	0.71 (0.46-1.08)	0.11*
All-cause death	3.5 [246]	3.5 [246]	0.99 (0.83-1.18)	0.93*
Total CV death, non-fatal MI, and non-fatal stroke	4.8 [343]	6.3 [442]	0.77 (0.65-0.91)	0.002*

**For ≥30 days. *Nominal p-value. Rate = number of events per 100 patient-years.

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med*. 2020. Bhatt DL. AHA 2020. virtual.

Adverse Events of Special Interest

SCORED

Composite Term	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)	P-value
Urinary tract infections	610 (11.5)	585 (11.1)	0.45
Diarrhea	448 (8.5)	315 (6.0)	<0.0001
Volume depletion	278 (5.3)	213 (4.0)	0.003
Bone fractures	111 (2.1)	117 (2.2)	0.68
Genital mycotic infections	125 (2.4)	45 (0.9)	<0.0001
Severe hypoglycemia	53 (1.0)	55 (1.0)	0.84
Malignancies	47 (0.9)	42 (0.8)	0.60
Venous thrombotic events	31 (0.6)	37 (0.7)	0.46
Adverse event leading to amputation	32 (0.6)	33 (0.6)	0.89
Diabetic ketoacidosis	30 (0.6)	14 (0.3)	0.022
Pancreatitis	12 (0.2)	20 (0.4)	0.16

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med*. 2020. Bhatt DL. AHA 2020. virtual.

Pacientes con proteinuria con y sin DM (DAPA-CKD)

Objectives

- To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in people with CKD with or without type 2 diabetes, and who are receiving standard of care including a maximum tolerated dose of an ACE inhibitor or ARB
- **Primary outcome**
  - Composite outcome of sustained ≥50% eGFR decline, ESKD, renal or CV death
- **Secondary outcomes (in hierarchical order)**
  - Composite outcome of sustained ≥50% eGFR decline, ESKD or renal death
  - CV death or hospitalizations for heart failure
  - All-cause mortality

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.
Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

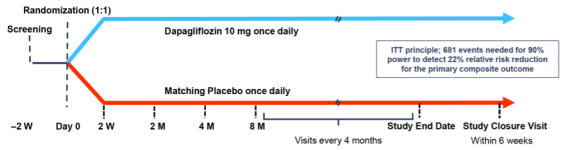
No es una indicación aprobada para Costa Rica

DAPACKD

Study Design

Key inclusion criteria:
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73m^2
- UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)
- Stable maximum tolerated labelled dose of ACEi or ARB for ≥4 weeks (if not contraindicated)

Key exclusion criteria:
- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrollment



- Outcome analysis based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

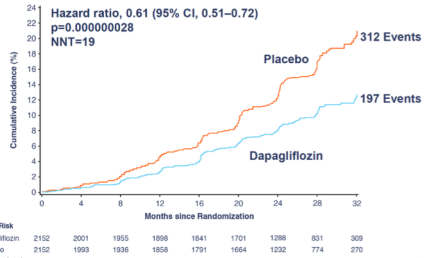
No es una indicación aprobada para Costa Rica

ANCA, anti-neutrophil cytoplasmic antibody; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282; Wheeler DC, et al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234.

DAPACKD

Primary outcome: Sustained ≥50% eGFR decline, ESKD, renal or CV death

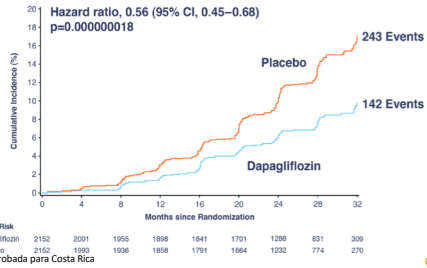


No es una indicación aprobada para Costa Rica

Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

Secondary outcome: Sustained ≥50% eGFR decline, ESKD, renal death

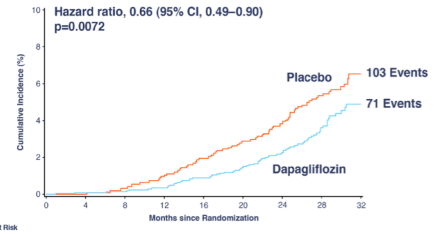


No es una indicación aprobada para Costa Rica

Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

Chronic dialysis, kidney transplantation, renal death



No. at Risk									
Dapagliflozin	2152	2035	2021	2004	1977	1887	1481	985	373
Placebo	2152	2031	2006	1971	1936	1849	1444	955	356

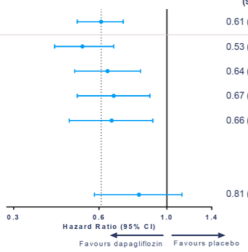
No es una indicación aprobada para Costa Rica

Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

Summary of the primary outcome and its components

	Dapagliflozin events	Placebo events	Hazard Ratio (95% CI)	p-value
Primary composite endpoint	197	312	0.61 (0.51, 0.72)	0.000000028
≥50% eGFR decline	112	201	0.53 (0.42, 0.67)	<0.0001
ESKD	109	161	0.64 (0.50, 0.82)	0.0004
eGFR <15 mL/min/1.73m^2	84	120	0.67 (0.51, 0.88)	0.0045
Chronic dialysis	68	99	0.66 (0.48, 0.90)	0.0080
Transplantation	3	8	NC	
Renal death	2	6	NC	
CV death	65	80	0.81 (0.58, 1.12)	0.2029



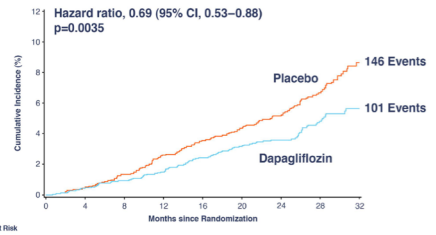
No es una indicación aprobada para Costa Rica

NC, not calculable

Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

Secondary outcome: All-cause mortality



No. at Risk									
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379

No es una indicación aprobada para Costa Rica

Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

FDA NEWS RELEASE

FDA Approves Treatment for Chronic Kidney Disease

Approval is First to Cover Many Causes of Disease

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For Immediate Release: April 30, 2021

Today, the U.S. Food and Drug Administration approved Farxiga (dapagliflozin) oral tablets to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression.

Enfermedad cardiovascular

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)

Reflexiones

- Podemos seguir hablando de efecto de clase?
- Por qué ertugliflozina fue negativo en VERTIS a pesar de tener criterios de inclusión casi idénticos a EMPAREG?
- SOLOIST y SCORED no tenían poder para demostrar efectos en enfermedad cardiovascular porque se tuvo que reducir el número de pacientes y cambiar el desenlace a falla cardíaca

Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardiaca
Análogos de GLP1						
ELIXA (lixisenatide)	1.02 (0.89-1.17) &	1.03 (0.87-1.22)	1.12 (0.79-1.58)	0.98 (0.78-1.22)	0.94 (0.78-1.13)	0.96 (0.75-1.23)
LEADER (liraglutide)	0.87 (0.76-0.97)	0.88 (0.75-1.03)	0.89 (0.72-1.11)	0.78 (0.66-0.93)	0.85 (0.74-0.97)	0.87 (0.73-1.05)
SUSTAIN-6 (semaglutide SC)	0.74 (0.58-0.95)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	0.98 (0.65-1.48)	1.05 (0.74-1.50)	1.11 (0.77-1.61)
PIONEER-6 (semaglutide oral)	0.79 (0.57-1.11)	1.18 (0.73-1.90)	0.74 (0.35-1.57)	0.49 (0.27-0.92)	0.51 (0.31-0.84)	0.86 (0.48-1.55)
EXSCEL (exenatide)	0.91 (0.83-1.00)	0.95 (0.84-1.09)	0.86 (0.70-1.07)	0.88 (0.73-1.05)	0.86 (0.77-0.97)	0.94 (0.78-1.13)
HARMONY (albiglutide)	0.78 (0.68-0.90)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	0.93 (0.73-1.19)	0.93 (0.73-1.19)	0.95 (0.79-1.16)
REWIND (dulaglutide)	0.88 (0.79-0.99)	0.96 (0.79-1.15)	0.75 (0.61-0.95)	0.91 (0.78-1.06)	0.90 (0.80-1.01)	0.93 (0.77-1.12)
AMPLITUDE-O (efpeglenatide)	0.73 (0.58-0.92)	0.78 (0.55-1.10)	0.74 (0.47-1.16)	0.72 (0.50-1.03)	0.78 (0.58-1.06)	0.61 (0.38-0.98)

Consideraciones prácticas y reflexiones finales

Consideraciones prácticas

- A pesar de su efecto nefroprotector, el efecto en reducción de glucosa va bajando entre menor sea TFG
  - La reducción es mínima con TFG <45 cc/min/1.73 m2
  - Se sigue manteniendo el efecto en reducción de peso y presión arterial
    - No está claro los mecanismos
  - En nefroprotección, todos los estudios con TFG >25 cc/min/1.73 m2
- Algunos efectos adversos se presentan con más frecuencia en TFG <45 cc/min/1.73 m2
  - Hipotensión postural: ajustar dosis de diuréticos
  - Algunos datos de hiperkalemia: no así demostrado en los estudios con desenlaces renales, sólo en los fases III

Consideraciones prácticas

- En quiénes tener más cuidado?
  - Adultos mayores y personas frágiles
  - pacientes con amputación previa
- Parece que está claramente establecido el papel que tiene en insuficiencia cardíaca,
  - Independiente de si tiene o no DM
  - Independiente de fracción de eyección
  - Lo que no está tan claro es la secuencia de fármacos
- Seguridad en pacientes aún sin diabetes

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com