CONGRESO INTERNACIONAL DE

"DIABETES Y CONTROVERSIAS EN ENDOCRINOLOGÍA AECE 2021"

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Resultados de estudios CV y renales con iSGLT2

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

EndoDrChen.com

Agenda

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

Enfermedad cardiovascular y falla 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)

Endpoints and Components

En una población con >60% de pacientes en prevención primaria, hospitalización por falla cardíaca fue al menos igual de frecuente como ictus, muerte no cardiovascular y muerte cardiovascular y más común que los desenlaces renales! (sólo 10% de pacientes tenían historia de falla cardíaca)

	P value
CV deat	0.005*
MACE	<0.001**
40% dec ESRD, c	0.17*
All-caus	
HHF	
Myocard	
Ischemic	
CV deat	
Non-CV	
40% decrease in eGFR to <60 mL/min/1.73 m², ESRD, or renal death	0.7 / 7.0 / 0.93 (0.43-2.00)

0.40 0.50 1.0 1.5
Favors Dapagliflozin ← → Favors Placebo

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

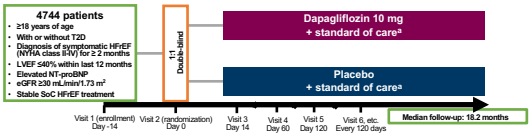
*P for superiority, **P for non-inferiority

Por qué nos da la impresión que hay menos falla cardíaca?

- Subdiagnóstico!
- Paciente con obesidad, diabetes y disnea de esfuerzos… no siempre pensamos en falla cardíaca
- Se confunde el diagnóstico clínico
- Definitivamente hay que pensar en falla cardíaca
  - Tratamientos que modifican la historia natural de la enfermedad
  - Tratamientos que mejoran sobrevida y tasa de rehospitalización

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.

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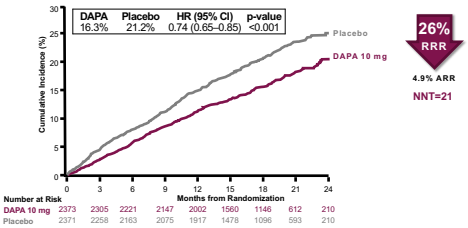
Primary Endpoint: CV Death or hHF or an Urgent HF Visit



26% RRR

4.9% ARR

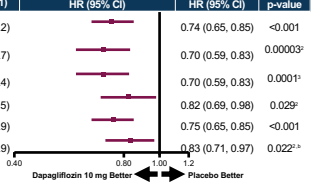
NNT=21

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.

11 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[1]
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. CSP 0169SC0001.

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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.[7]
CV = cardiovascular; HbA1c = glycated hemoglobin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; T2D = type 2 diabetes.

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

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 49 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.

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

EMPEROR-REDUCED

Trial inclusion and exclusion criteria

Inclusion criteria

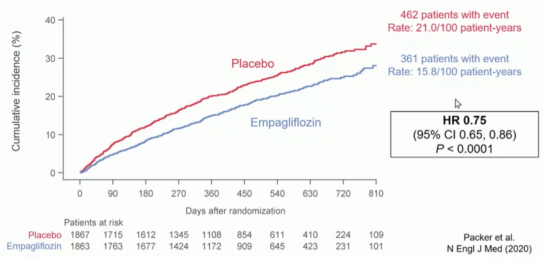
EMPEROR-Reduced[1,2]	DAPA-HF[3]
Age ≥18 years (Japan, age ≥20 years) at screening	Age ≥18 years
Chronic HF NYHA class II–IV	Chronic HF NYHA class II–IV
HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)
Elevated NT-proBNP **EF (%)** — **NT-proBNP (pg/ml)** Patients without AF* ≥36 to ≤40 — ≥2500 ≥31 to ≤35 — ≥1000 ≤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[1]
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. ESC-HF 2018; poster P1755 3. McMurray JJV et al. N Engl J Med. 2019;381(21):1995-2008

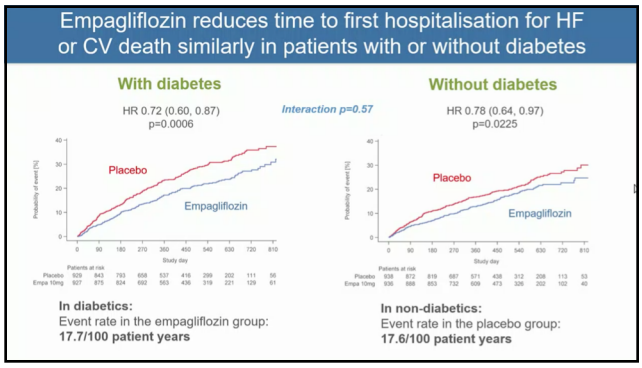
EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



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)	

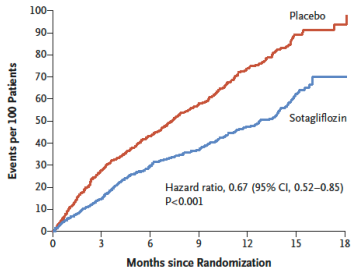


SOLOIST-WHF

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

Vean la frecuencia de los eventos! (muerte CV, hospitalización por falla cardíaca, visita a urgencias por falla cardíaca)



No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

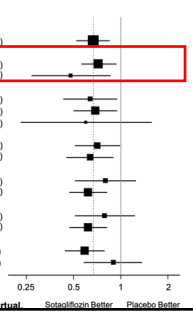
Efficacy Testing Hierarchy

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*

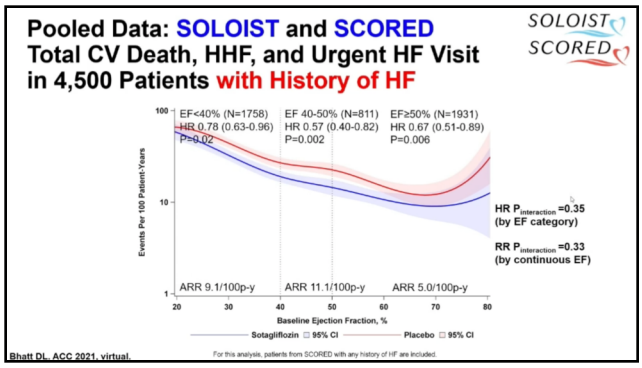
*Nominal p-value. Rate = number of events per 100 patient-years. Values in table for change in KCCQ-12 score and change in eGFR are least squares means, difference in least squares means, and 95% CI for difference in least squares means

Primary Efficacy Subgroups

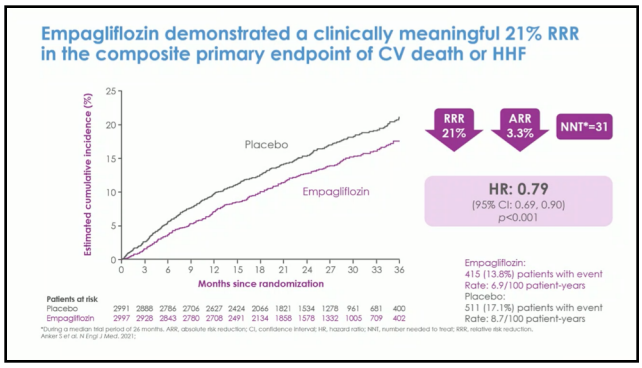
Subgroup	Patients	Events Per 100 py Sotagliflozin	Events Per 100 py Placebo	HR (95% CI)
Overall	1222	51.0	76.3	0.67 (0.52, 0.85)
LVEF (%)				
< 50	966	56.9	79.9	0.72 (0.56, 0.94)
≥ 50	256	30.6	64.0	0.48 (0.27, 0.86)
Geographic Region				
Americas	346	68.3	103.0	0.64 (0.43, 0.95)
Europe	800	44.1	64.7	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.



EMPEROR-PRESERVED

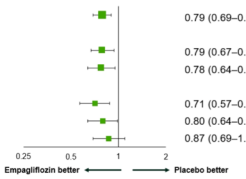


Primary endpoint: individual components

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	0.0003
First hospitalization for heart failure	259 (8.6%)	4.3	352 (11.8%)	6.0	0.71 (0.60 – 0.83)	
Cardiovascular death	219 (7.3%)	3.4	244 (8.2%)	3.8	0.91 (0.76 – 1.09)	

EMPEROR-Preserved: Results

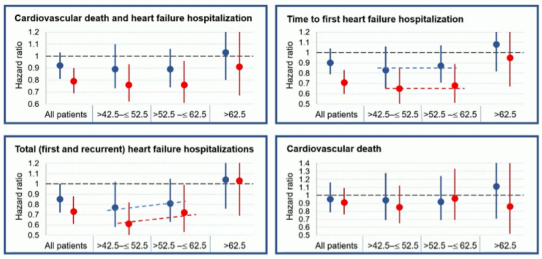
Subgroup	Empagliflozin	Placebo	HR (95% CI)
	No. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)



Consistent results across diabetes status and LVEF at baseline (interaction *P*>0.10)

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction
Anker S, et al. *N Engl J Med* 2021. doi: 10.1056/NEJMoa2107038 [Epub ahead of print]

Side-by-Side Display of EMPEROR-Preserved and PARAGON-HF in Ejection Fraction Subgroups (Post Hoc)



Solomon Circulation 2020;141:352-361
Packer Circulation 2021;doi:10.1161/CIRCULATIONAHA.121.056657

PRESERVED-HF: Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with Preserved Ejection Fraction Heart Failure[1,2]

324 Patients
- HF with NYHA class II-IV symptoms (with or without T2D)
- LVEF ≥45%
- eGFR ≥20 mL/min/1.73m^2
- NT-proBNP ≥225 pg/mL or BNP ≥75 pg/mL[a]
- Requirement for diuretic therapy
- At least 1 of the following:
  - Recent HF hospitalization or urgent HF visit requiring IV diuretic
  - Elevated filling pressures by right or left heart catheterization
  - Structural heart disease by echocardiography

1:1 randomization

- Dapagliflozin 10 mg + standard of care
- Placebo + standard of care

Primary Endpoint
- Change from BL in KCCQ-CSS at 12 weeks

Key Secondary Endpoints
- Change from BL in KCCQ-OSS at 12 weeks
- Proportion of patients with a ≥5-point increase[b] in KCCQ at 12 weeks
- Change from BL in 6MWD at 12 weeks
- Change from BL in NT-proBNP and BNP at 6 and 12 weeks
- Change from BL in HbA1c at 12 weeks
- Change from BL in Weight and SBP at 6 and 12 weeks

[a]If atrial fibrillation, NT-proBNP ≥370 pg/mL or BNP ≥120 pg/mL; [b]a 5-point increase is considered a clinically meaningful change.
6MWD = 6-minute walking distance; BL = baseline; BNP =B-type natriuretic peptide; HbA1c = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; IV = intravenous; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; T2D = type 2 diabetes.
1. Reshaw M. Presented at HFSA 2021 Annual Scientific Meeting, September 10-13, 2021. Poster 126. 2. Study NCT03619616. ClinicalTrials.gov website.

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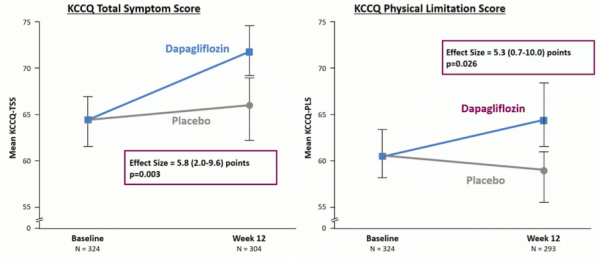
Dapagliflozin Improved Both Symptoms and Physical Limitations Scores



Therapies successful in HFrEF have not demonstrated success in full range of HFpEF

Intervention	HFrEF[1–14]	HFpEF[15–25]
Beta blocker	✓	✗
ACEI/ARB	✓	✗
ARNI	✓	✓
Cardiac glycosides	?	✗
MRA	✓	?
Vasodilators	✓	✗
CRT	✓	?
ICD	✓	?
Exercise	✓	?
Intravenous iron	✓	?

✓ Evidence of clinical efficacy*
✓ Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal
✗ No evidence of clinical efficacy
? Clinical efficacy uncertain

Empagliflozin is not approved to reduce the risk of CV death or hospitalization for heart failure in adult patients with heart failure with preserved ejection fraction; or to slow kidney function decline in adults with heart failure with preserved ejection fraction.
*Clinical efficacy was evidenced if primary endpoints were met
ACEI: angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HHF, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist

1. Pfeffer MD et al. Eur Heart J 2005;26:215. 2. Granger CB et al. Lancet 2003;362:772. 3. McMurray et al. N Engl J Med 2014;371:993. 4.Digitalis Investigation Group. N Engl J Med 1997;336:525. 5. Pitt B et al. N Engl J Med 1999;341:709. 6.Jannuzzi F et al. N Engl J Med 2011;364:11. 7.Taylor AL et al. N Engl J Med 2004;351:2049. 8.Cohn JN et al. N Engl J Med 1986;314:1547. 9.Mao AJ et al. N Engl J Med 2011;364:1115. 10.Packer M et al. N Engl J Med 1996;334:1349. 11.Packer M et al. N Engl J Med 1996;334:1443. 12.Packer M et al. Circulation 1993;87:1420. 13.Packer M et al. Circ Heart Fail 2010;3:377. 14.Ferreira-Filho LP et al. Eur Heart J 2015;36:2457. 15.Patel S et al. Int J Cardiol 2014;170:393. 16.Bacchi TA et al. Circ Heart Fail 2013;6:377. 17.Cleland JG et al. Eur Heart J 2006;27:2338. 18.Solomon SD et al. N Engl J Med 2019;381:1609. 19.Ahmed A et al. Circulation 2006;114:397. 20.Pitt B et al. N Engl J Med 2014;370:1383. 21.Edelmann F et al. JAMA 2013;309:781. 22.Redfield MM et al. N Engl J Med 2013;373:24. 23.Chung ES et al. Eur J Heart Failure 2010;12:385. 24.Pandey A et al. Circ Heart Fail 2018;8:33. 25.ClinicalTrials.gov. NCT03057691 (accessed Aug 2021).

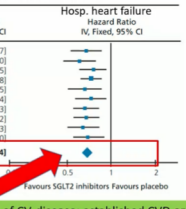
Meta-analyses in of SGLT-2i in 10 RCT with T2 diabetes

Effects in Type 2 diabetes (n= 65 708)

Pooled HR for heart failure hospitalisation 0.69 (0.64-0.74)

Study of subgroup	log (Hazard Ratio)	SE	SGLT2 Inhibitor Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS	-0.4004775	0.1312919	5795	4347	8.1%	0.67 [0.52, 0.87]
CREDENCE	-0.4942963	0.1356834	2202	2199	7.6%	0.61 [0.47, 0.80]
DAPA-HF	-0.2744369	0.113011	1075	1064	11.0%	0.76 [0.61, 0.95]
DECLARE-TIMI 58	-0.3147107	0.0934854	8582	8578	16.0%	0.73 [0.61, 0.88]
EMPA-REG	-0.4307829	0.1353644	4687	2333	7.6%	0.65 [0.50, 0.85]
EMPEROR-Preserved	-0.3147	0.1276	1466	1472	8.6%	0.73 [0.57, 0.94]
EMPEROR-Reduced	-0.4004775	0.1096573	927	929	11.6%	0.67 [0.54, 0.83]
SCORED	-0.4004775	0.10188	5292	5292	13.5%	0.67 [0.55, 0.82]
SOLOIST	-0.4462871	0.134444	608	614	7.7%	0.64 [0.49, 0.83]
VERTIS-CV	-0.356675	0.1303126	5499	2747	8.2%	0.70 [0.54, 0.90]
Total (95% CI)			**36133**	**29575**	**100.0%**	**0.69 [0.64, 0.74]**

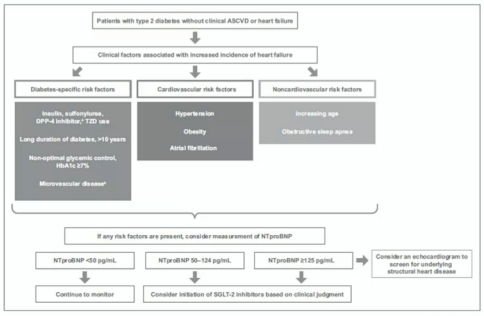
Heterogeneity: Chi² = 2.83, df = 9 (p = 0.97); I² = 0%
Test for overall effect: Z = 10.02 (p < 0.00001)



Consistent results regardless of type of CV-disease; established CVD or HF!
31% reduced risk for heart failure hospitalisation in type 2 diabetes
HR 0.69 (0.64-0.74)

Courtesy from Robert Ryder, Thomas Crabtree & Robert Ryder, Br J Diabetes 2021;21:ONLINE

Prediction of HF in T2D: practical clinical approach



Curr Opin Cardiol. 2019; 34: 578-583.

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**

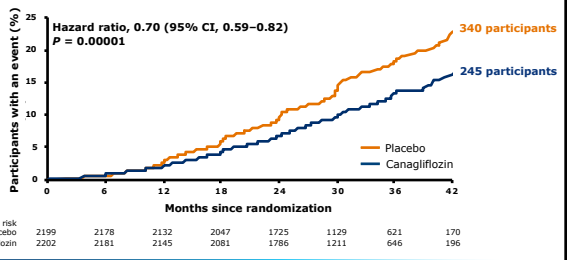
Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

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

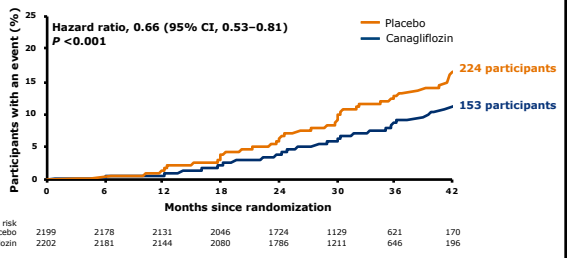
Jardine MJ, et al. *Am J Nephrol.* 2017;46(6):462-472.

CREDENCE

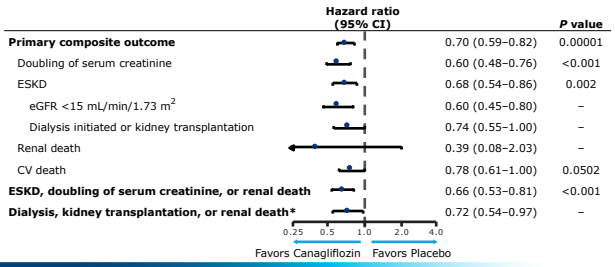
Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



ESKD, Doubling of Serum Creatinine, or Renal Death



Summary Forest Plot



*Post hoc analysis.

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.

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

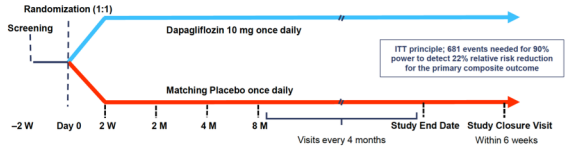
eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.
Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

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



ITT principle; 681 events needed for 90% power to detect 22% relative risk reduction for the primary composite outcome

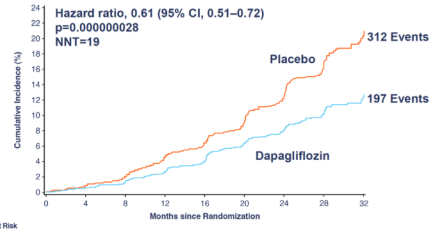
- Outcome analysis based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

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



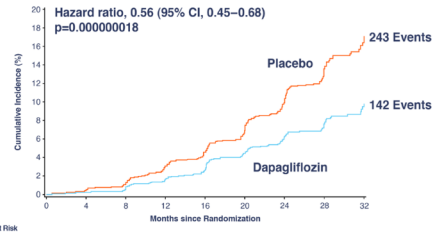
No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

No es una indicación aprobada para Costa Rica

DAPACKD

Heerspink HJL, et.al. Presented at ESC 2020.

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



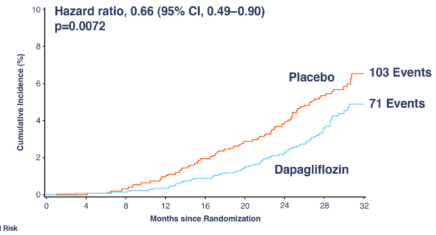
No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

No es una indicación aprobada para Costa Rica

DAPACKD

Heerspink HJL, et.al. Presented at ESC 2020.

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

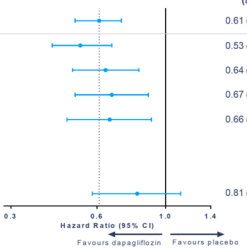
No es una indicación aprobada para Costa Rica

DAPACKD

Heerspink HJL, et.al. Presented at ESC 2020.

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

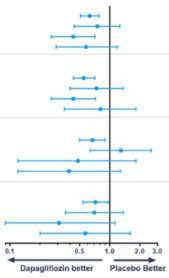


NC, not calculable
Heerspink HJL, et al. Presented at ESC 2020.

DAPACKD

Consistent effect of dapagliflozin across CKD aetiology

	Dapagliflozin	Placebo	Hazard ratio (95% CI)	Interaction P-value
	No. of participants/total no			
Primary composite outcome				
Diabetic nephropathy	139/1271	207/1239	0.63 (0.51, 0.78)	0.53
Ischaemic/hypertensive CKD	24/324	35/363	0.75 (0.44, 1.26)	
Glomerulonephritides	22/343	49/352	0.43 (0.26, 0.71)	
Other/unknown	12/214	21/198	0.58 (0.29, 1.19)	
Kidney-specific outcome				
Diabetic nephropathy	93/1271	157/1239	0.55 (0.43, 0.71)	0.67
Ischaemic/hypertensive CKD	18/324	26/363	0.74 (0.40, 1.36)	
Glomerulonephritides	21/343	46/352	0.43 (0.26, 0.72)	
Other/unknown	10/214	14/198	0.81 (0.35, 1.83)	
Cardiovascular death or heart failure hospitalisation				
Diabetic nephropathy	76/1271	107/1239	0.67 (0.50, 0.90)	0.24
Ischaemic/hypertensive CKD	17/324	15/363	1.29 (0.64, 2.60)	
Glomerulonephritides	3/343	7/352	0.48 (0.12, 1.84)	
Other/unknown	4/214	9/198	0.39 (0.12, 1.28)	
All-cause mortality				
Diabetic nephropathy	78/1271	104/1239	0.72 (0.54, 0.97)	0.55
Ischaemic/hypertensive CKD	14/324	22/363	0.70 (0.36, 1.37)	
Glomerulonephritides	3/343	11/352	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	0.57 (0.20, 1.61)	

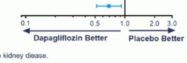


Wheeler DC, et al. *Lancet Diabetes Endocrinol* 2021;9:22-31.

DAPACKD

Consistent effect of dapagliflozin across CKD stages

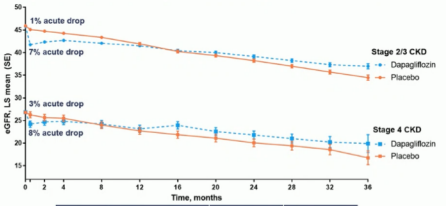
	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	Interaction P-value
	No. of participants/total no.			
Primary outcome				
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
Stage 4	59/293	87/331	0.73 (0.53, 1.02)	0.22
Stage 2/3	138/1859	225/1821	0.58 (0.47, 0.71)	
Kidney-specific outcome				
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
Stage 4	49/293	73/331	0.71 (0.49, 1.02)	0.13
Stage 2/3	93/1859	170/1821	0.51 (0.40, 0.66)	
Cardiovascular death or heart failure hospitalization				
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
Stage 4	18/293	24/331	0.83 (0.45, 1.53)	0.63
Stage 2/3	82/1859	114/1821	0.69 (0.52, 0.92)	
All-cause mortality				
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	0.69 (0.52, 0.92)	



Stage 4 CKD, eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD, eGFR ≥30 mL/min/1.73m^2
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease.
Cherney DM. *JASN* 2021; doi:https://doi.org/10.1681/ASN.2021020167.

DAPACKD

Lesser declines in eGFR over the study with dapagliflozin

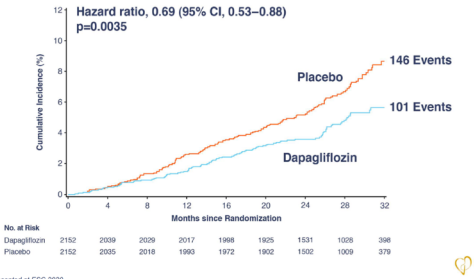


Between slope difference* (SE)	Stage 4 CKD	Stage 2/3 CKD
Acute, mL/min/1.73m²/2 weeks	–1.4 (0.5)	–2.6 (0.2)
Chronic, mL/min/1.73m²/year	1.8 (0.4)	1.9 (0.2)
Total, mL/min/1.73m²/year	1.2 (0.4)	0.9 (0.2)

*dapagliflozin vs placebo
Stage 4 CKD, eGFR <30 mL/min/1.73m²; Stage 2/3 CKD, eGFR ≥30 mL/min/1.73m²
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Chertow GM. JASN 2021; doi:https://doi.org/10.1681/ASN.2021020167.

DAPACKD

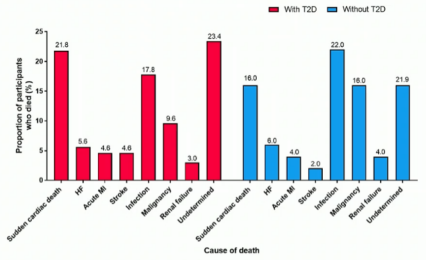
Secondary outcome: All-cause mortality



DAPACKD

Heerspink HJL. et.al. Presented at ESC 2020.

Main causes of death in DAPA-CKD participants were sudden cardiac death and infections

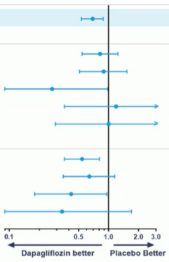


DAPACKD

HF, heart failure; MI, myocardial infarction

Benefit of dapagliflozin on all-cause mortality driven by reduction in non-cardiovascular death

	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	No. of participants/total no.		
All-cause mortality	**101/2152**	**146/2152**	**0.69 (0.53, 0.88)**
Cardiovascular death	**41/2152**	**50/2152**	**0.82 (0.54, 1.24)**
Sudden cardiac death	24/2152	27/2152	0.89 (0.51, 1.53)
Heart failure	3/2152	11/2152	0.27 (0.08, 0.98)
Acute myocardial infarction	6/2152	5/2152	1.19 (0.36, 3.91)
Stroke	5/2152	5/2152	1.00 (0.29, 3.45)
Non-cardiovascular death	**36/2152**	**66/2152**	**0.54 (0.36, 0.81)**
Infection	18/2152	28/2152	0.64 (0.35, 1.15)
Malignancy	8/2152	19/2152	0.42 (0.18, 0.96)
Renal failure	2/2152	6/2152	0.34 (0.07, 1.70)



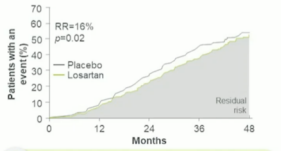
DAPACKD

Heerspink HJL et al. *European Heart Journal*. 2021;42:1216-27.

Despite RAS blockade, patients with T2D and advanced CKD are at risk of CKD progression

RENAAL: Losartan vs placebo[1]

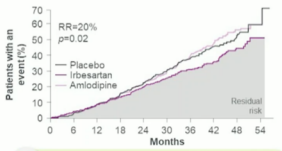
Primary composite endpoint: Doubling of SCr, kidney failure or death



Patients with severely increased albuminuria: 100%
Median UACR: 1249 mg/g

IDNT: Irbesartan vs amlodipine vs placebo[2]

Primary composite endpoint: Doubling of SCr, kidney failure or death



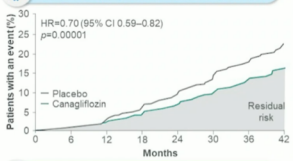
Patients with severely increased albuminuria: 100%
Median UACR: 1900 mg/g

RAS, renin–angiotensin system; RR, risk reduction; SCr, serum creatinine; SOC, standard of care
1. Brenner BM, *et al. N Engl J Med* 2001;345:861–869; 2. Lewis EJ, *et al. N Engl J Med* 2001;345:851–860

Reducing residual risk of renal events

CREDENCE: Canagliflozin (+ ACEi/ARB) vs placebo[1]

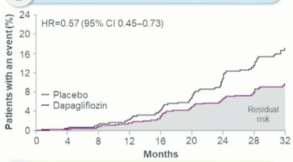
Primary composite outcome: Kidney failure, doubling of SCr or death from kidney/CV causes



Patients with severely increased albuminuria: 88%
Median UACR: 927 mg/g

DAPA-CKD: Dapagliflozin (+ACEi/ARB) vs placebo (T2D subgroup)[2]

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



Patients with severely increased albuminuria: 89.7%
Median UACR: 949 mg/g

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; NNT, number needed to treat; SGLT-2, sodium-glucose co-transporter-2
1. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306; 2. Wheeler DC, *et al. Lancet Diabetes Endocrinol* 2021;9:22–31

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.

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…

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Puede descargar la presentación en:

www.EndoDrChen.com