# Caso clínico: paciente con DM2 de muy alto riesgo CV y lesión de órgano blanco

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EndoDrChen.com

## Conflictos de interés (últimos 5 años)

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

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## Presentación de caso

- Visto por primera vez en agosto 2015, 63 años, con historia de DM-2 de 10 años de evolución
  - Metformin 500 mg tid + glibenclamida 5 mg tid, hasta 4 meses previo a la cita
  - Cambio a sitagliptina/metformin 50/1000 mg bid
  - Hace 1 mes le agregaron insulina glargina U100 12 u al día
- En el último año ha perdido unos 8 kg con modificación de estilos de vida. Hba1c en atención primaria entre 7.5% y 8.5%
- Usa ademá ezetimibe/simvastatina 10/20 mg 1 tab por día, enalapril 5 mg por día y AAS 100 mg por día
- Peso 76.5 kg, talla 172 cm, PA 130/70

## Caso clínico

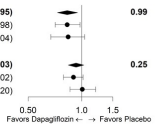
- Vuelve a consulta 4 meses después
- Se le hizo prueba de esfuerzo, fue positivo, se llevó a cateterismo y le colocaron 4 stents
- En rehabilitación cardíaca en CENARE
- Ha perdido 4 kg
- Peso 72.7 kg PA 120/70
- Hba1c 6.1%, LDL 42 mg/dl, HDL 23 mg/dl, triglicéridos 173 mg/dl
- Viene usando atorvastatina 80 mg, atenolol 25 mg, enalapril 5 mg, AAS 100 mg por día, clopidogrel 75 mg, glargina 8 u, sitagliptina/metformin 50/1000 mg bid

## Caso clínico

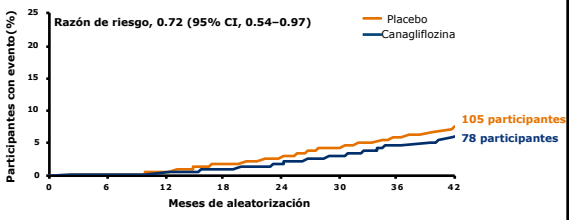
- 8 meses después se presenta asintomático
- Peso 77 kg, PA 130/70 mm Hg
- Hba1c 6.9%, proteinuria 195 mg/24 horas, AEC 128 cc/min
- Al repetir la proteinuria está en 350 mg/24 horas
- Cuál sería la conducta?

## Primary Efficacy Endpoints by Presence of ASCVD vs MRF

| Outcomes | Dapagliflozin Events per 1000 pt years | Placebo Events per 1000 pt years | Hazard Ratio (95% CI) | P value for interaction |
|---|---|---|---|---|
| **CV death/HHF** | **12.2** | **14.7** | **0.83 (0.73-0.95)** | **0.99** |
| ASCVD | 19.9 | 23.9 | 0.83 (0.71-0.98) | |
| MRF | 7.0 | 8.4 | 0.84 (0.67-1.04) | |
| **MACE** | **22.6** | **24.2** | **0.93 (0.84-1.03)** | **0.25** |
| ASCVD | 36.8 | 41.0 | 0.90 (0.79-1.02) | |
| MRF | 13.4 | 13.3 | 1.01 (0.86-1.20) | |



## Diálisis, transplante renal o muerte renal*




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 2199 | 2183 | 2147 | 2077 | 1776 | 1178 | 653 | 180 |
| Canagliflozin | 2202 | 2184 | 2148 | 2100 | 1811 | 1236 | 661 | 199 |

*Post hoc analysis.

CREDENCE

| Area | Risk Parameter | Treatment Objectives or Goals | | |
|---|---|---|---|---|
| | | 3 | 2 | 1 |
| Metabolic | HbA1c | >8% | 7%-8% | <7% |
| | Hypoglycemia | Severe hypoglycemia | Mild hypoglycemia | Without hypoglycemia |
| Cardiac | BP (mm Hg) | >140/90 | >130/80 and <140/90 | <130/80 and >120/70 |
| | LDL-C (mg/dL) | >130 | >100 and <130 | <100 |
| Renal | GFR (mL/min/1.73 m$^2$) | <30 to >150 | 30-90 | 90-150 |
| | Albuminuria | Macroalbuminuria >300 mg/g (albumin/creatinine) | Microalbuminuria from 30 to 300 mg/g (albumin/creatinine) | Absent or <30 mg/g |

Mehta R, Pichel R, Chen-Ku CH. Diabetes Ther. 2021;12:1-20

Cuáles son las intervenciones que benefician a este paciente?

# Perspectiva renal

| | 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 | NA | 0.66 (0.53-0.81) | NA | 0.60 (0.48-0.76) | 0.74 (0.55-1.00) | NA |
| Inhibidores de DPP4 | | | | | | |
| SAVOR (saxagliptina) [31] | NA | 1.08 (0.88-1.32) | NA | 1.1 (0.89-1.36) | 0.90 (0.61-1.32) | NA |
| EXAMINE (alogliptina) | NA | NA | NA | NA | NA | NA |
| TECOS (sitagliptina) | NA | NA | NA | NA | NA | NA |
| CARMELINA (linagliptina) | 0.86 (0.78-0.95) | 0.98 (0.82-1.18) | NA | NA | 0.87 (0.69-1.10) | NS |
| 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 |

# 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

**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.

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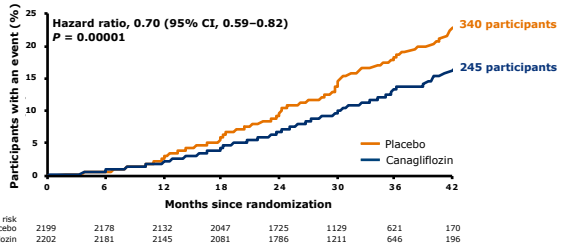
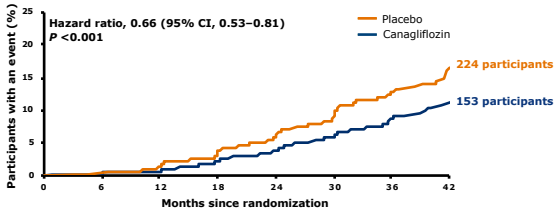
## Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death




| 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

# 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.

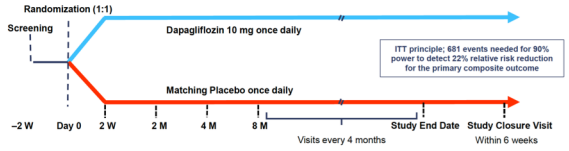
Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med*. 2020. Bhatt DL. AHA 2020. virtual.

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

## 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, Honduras, Panamá, Guatemala, República Dominicana

DAPACKD

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.*

## Baseline characteristics

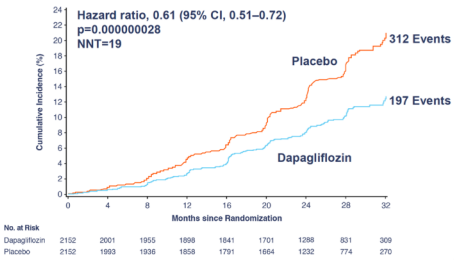
| | Dapagliflozin (N=2152) | Placebo (N=2152) |
|---|---|---|
| **Age, years, mean** | 62 | 62 |
| **Sex, female, %** | 33 | 33 |
| **Race, %** | | |
| White | 52 | 54 |
| Black or African-American | 5 | 4 |
| Asian | 35 | 33 |
| Other | 8 | 8 |
| **Type 2 diabetes, %** | 68 | 67 |
| **Systolic blood pressure, mmHg, mean** | 137 | 137 |
| **eGFR, mL/min/1.73m$^2$, mean** | 43 | 43 |
| **UACR, mg/g, median** | 965 | 934 |
| **ACEi or ARB, %** | 97 | 97 |

No es una indicación aprobada para Costa Rica, Honduras, Panamá, Guatemala, República Dominicana

DAPACKD

*Wheeler DC, et al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234.*

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

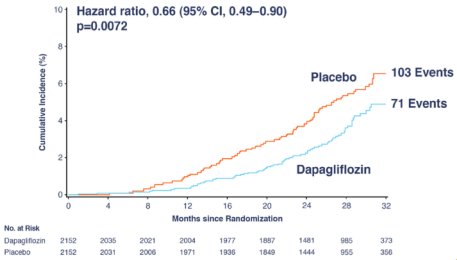



No es una indicación aprobada para Costa Rica, Honduras, Panamá, Guatemala, República Dominicana

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

DAPACKD

## Chronic dialysis, kidney transplantation, renal death



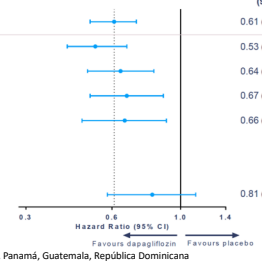

No es una indicación aprobada para Costa Rica, Honduras, Panamá, Guatemala, República Dominicana

*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, Honduras, Panamá, Guatemala, República Dominicana

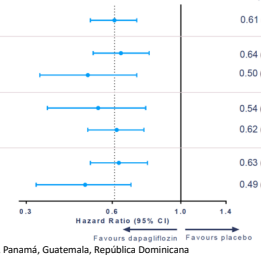
NC, not calculable

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

DAPACKD

## Primary outcome – pre-specified subgroup analysis

| | Dapagliflozin events | Placebo events | Hazard Ratio (95% CI) | p-value interaction |
|---|---|---|---|---|
| All patients | 197 | 312 | 0.61 (0.51, 0.72) | |
| With type 2 diabetes | 152 | 229 | 0.64 (0.52, 0.79) | |
| Without type 2 diabetes | 45 | 83 | 0.50 (0.35, 0.72) | 0.24 |
| UACR ≤1000 mg/g | 44 | 84 | 0.54 (0.37, 0.77) | |
| UACR >1000 mg/g | 153 | 228 | 0.62 (0.50, 0.76) | 0.52 |
| eGFR <45 mL/min/1.73m² | 152 | 217 | 0.63 (0.51, 0.78) | |
| eGFR ≥45 mL/min/1.73m² | 45 | 95 | 0.49 (0.34, 0.69) | 0.22 |

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

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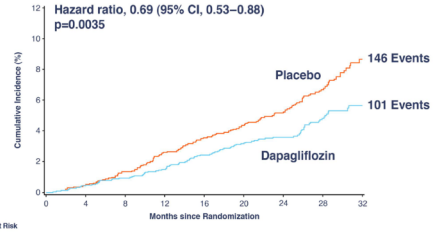
## Secondary outcome: All-cause mortality




| 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, Honduras, Panamá, Guatemala, República Dominicana

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

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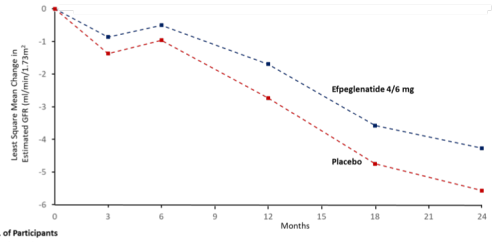
# Otros andiabéticos

| | Desenlace compuesto microvascular | Desenlace compuesto renal | Nueva aparición microalbuminuria | Doblamiento creatinina | Terapia reemplazo renal | Muerte renal |
|---|---|---|---|---|---|---|
| Inhibidores de DPP4 | | | | | | |
| SAVOR (saxagliptina) [31] | NA | 1.08 (0.88-1.32) | NA | 1.1 (0.89-1.36) | 0.90 (0.61-1.32) | NA |
| EXAMINE (alogliptina) | NA | NA | NA | NA | NA | NA |
| TECOS (sitagliptina) | NA | NA | NA | NA | NA | NA |
| CARMELINA (linagliptina) | 0.86 (0.78-0.95) | 0.98 (0.82-1.18) | NA | NA | 0.87 (0.69-1.10) | NS |
| 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 |

## Effect of Efpeglenatide on Change in eGFR

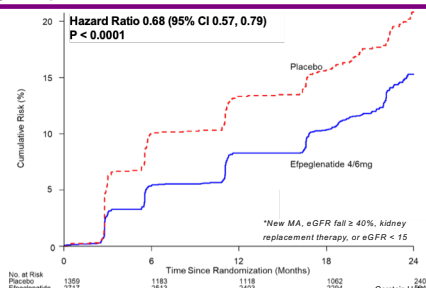



| No. of Participants | | | | | | |
|---|---|---|---|---|---|---|
| Efpeglenatide | 2717 | 2566 | 2520 | 2453 | 2024 | 490 |
| Placebo | 1357 | 1274 | 1250 | 1194 | 953 | 225 |

Gerstein H. N Engl J Med. 2021; online Jun 28.

## Efpeglenatide 4 or 6 mg *versus* Placebo

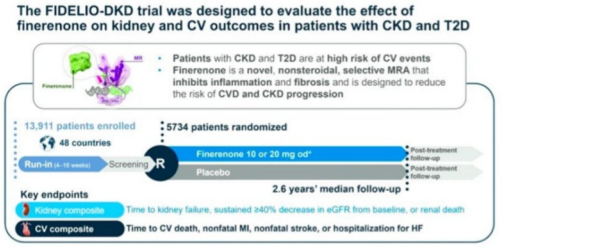
**Kidney Composite Outcome***



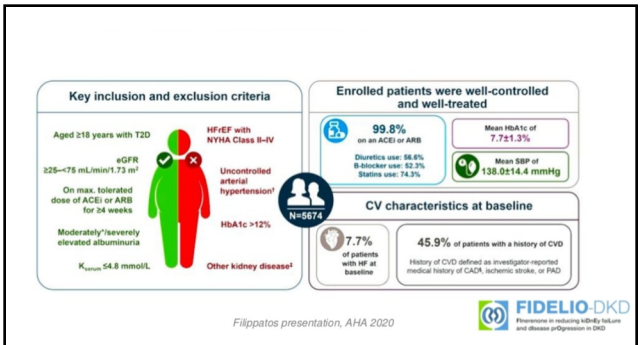

| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 1359 | 1183 | 1118 | 1062 | 240 |
| Efpeglenatide | 2717 | 2513 | 2403 | 2294 | 596 |

Gerstein H. N Engl J Med. 2021; online Jun 28.

# Finerenona: estudio FIDELIO

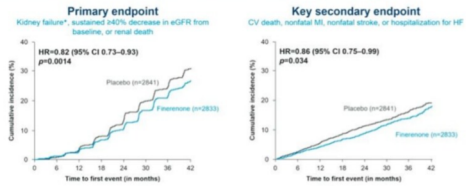



*Filippatos presentation, AHA 2020*




*Filippatos presentation, AHA 2020*

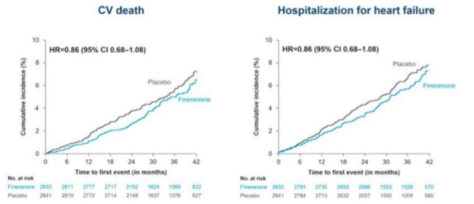
## FIDELIO-DKD met its primary and key secondary endpoint with relative risk reductions of 18% and 14%, respectively




*Filippatos presentation, AHA 2020*

FIDELIO-DKD
Finerenone in reducing kiDney failure and disease prOgression in DKD

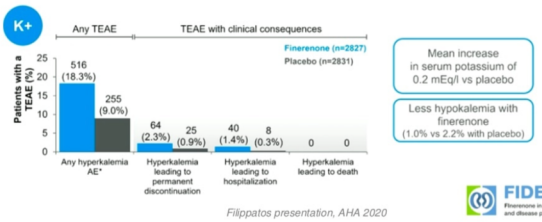
## There was a 14% relative risk reduction for both CV death and hospitalization for heart failure with finerenone




*Filippatos presentation, AHA 2020*

FIDELIO-DKD
Finerenone in reducing kiDney failure and disease prOgression in DKD

## Overall treatment-emergent adverse events were similar between treatment arms with a manageable increase in hyperkalemia




*Filippatos presentation, AHA 2020*

FIDELIO-DKD
Finerenone in reducing kiDney failure and disease prOgression in DKD

# 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) |
| 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) |

## 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 cardíaca |
|---|---|---|---|---|---|---|
| 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) |

## Evolución del caso clínico

- Estábamos con DM-2 de 12 años de evolución
  - Enfermedad coronaria revascularizado recientemente
  - Lesión renal con proteinuria 350 mg/24 horas
  - Bien controlado LDL (42 mg/dl), PA (130/70 mm Hg), beta bloqueado
- A finales del 2016 se le agregó dapagliflozina 10 mg por día y se suspendió glargina (tenía 8 u al día) para ayudar a controlar lesión renal

## Evolución del caso

- Se presenta en marzo 2021
- Disnea de grandes esfuerzos (trota todos los días en plano 5 km)
- Tuvo COVID19 en enero 2021, no se complicó y resolvió bien
- Peso 68.5 kg, PA 110/70 mm Hg
- Hba1c 6.4%, HDL 42 mg/dl, LDL 70 mg/dl, proteinuria 174 mg/24 horas
- Tratamiento actual:
  - Valsartan 80 mg, bisoprolol 5 mg, eplerenona 25 mg por día
  - AAS 81 mg
  - Atorvastatina 80 mg
  - Dapagliflozina/metformin 5/1000 mg 2 tab por día

## Evolución del caso

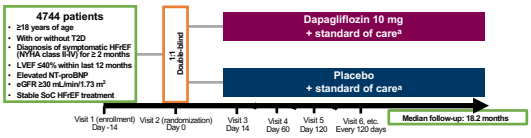
- Se le realiza nuevo ecocardiograma por la disnea de grandes esfuerzos y post COVID19
- Eco stress post ejercicio
  - Inducción de nuevos trastornos de la contractilidad al 100% de FCMT en segmento septal medio, sin cambios en ECG de isquemia
  - FEVI 60%, con disfunción diastólica
- Al cardiólogo no le parece que requiera nuevo cateterismo
- Cuál sería la conducta?

# 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;21:445-475; 2. McMurray JJV et al. Article and study protocol. *N Engl J Med.* 2019;381:1995-2008.

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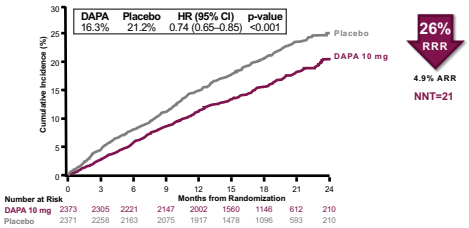
## Primary Endpoint: CV Death or hHF or an Urgent HF Visit




**26% RRR**

**4.9% ARR**

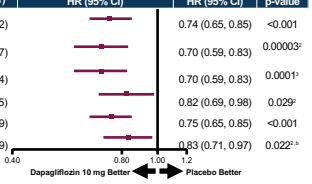
**NNT=21**

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.

46 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. CSP D1689C00001.

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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[b] |
|---|---|---|---|---|
| Total population | 386/2373 (16.3) | 502/2371 (21.2) | 0.74 (0.65-0.85) | |
| T2D[a] | 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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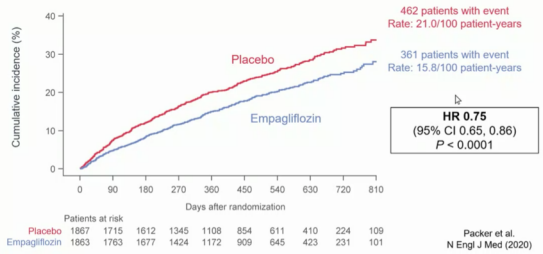
EMPEROR-REDUCED

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

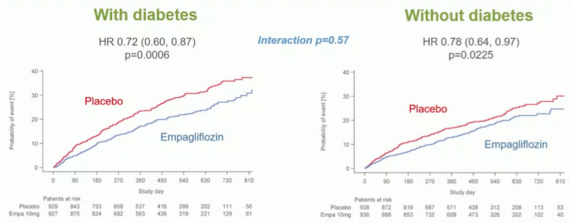



Packer et al.
N Engl J Med (2020)

## 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) | |

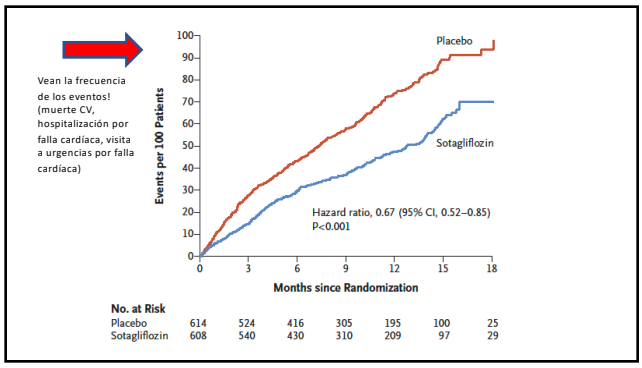
## Empagliflozin reduces time to first hospitalisation for HF or CV death similarly in patients with or without diabetes




**In diabetics:**
Event rate in the empagliflozin group:
**17.7/100 patient years**

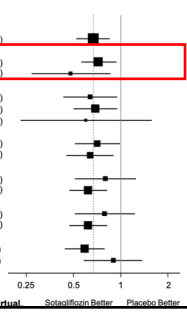
**In non-diabetics:**
Event rate in the placebo group:
**17.6/100 patient years**

# SOLOIST-WHF



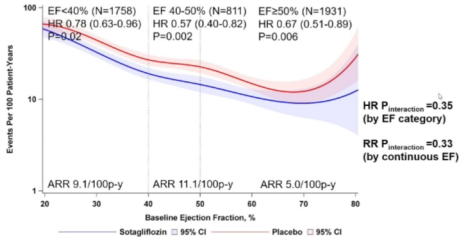

## Primary Efficacy Subgroups

| 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.

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




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

Bhatt DL. ACC 2021, virtual.

## EMPEROR-PRESERVED

| Variable | Empagliflozin (N=2997) | | Placebo (N=2991) | | Hazard Ratio or Difference (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | | *events per 100 patient-yr* | | *events per 100 patient-yr* | | |
| Primary composite outcome — no. (%) | 415 (13.8) | 6.9 | 511 (17.1) | 8.7 | 0.79 (0.69–0.90) | <0.001 |
| 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) | |
| Secondary outcomes specified in hierarchical testing procedure | | | | | | |
| Total no. of hospitalizations for heart failure | 407 | — | 541 | — | 0.73 (0.61–0.88) | <0.001 |
| eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 $m^2$‡ | −1.25±0.11 | — | −2.62±0.11 | — | 1.36 (1.06–1.66) | <0.001 |
| Other prespecified analyses | | | | | | |
| Change in KCCQ clinical summary score at 52 wk‡ | 4.51±0.31 | — | 3.18±0.31 | — | 1.32 (0.45–2.19) | |
| Total no. of hospitalizations for any cause | 2566 | — | 2769 | — | 0.93 (0.85–1.01) | |
| Composite renal outcome — no. (%) | 108 (3.6) | 2.1 | 112 (3.7) | 2.2 | 0.95 (0.73–1.24) | |
| Onset of new diabetes in patients with prediabetes — no. (%) | 120 (12.0) | 6.1 | 137 (14.0) | 7.4 | 0.84 (0.65–1.07) | |
| Death from any cause — no. (%) | 422 (14.1) | 6.6 | 427 (14.3) | 6.7 | 1.00 (0.87–1.15) | |

Anker SD. N Engl J Med. Online Aug 27 2021

## EMPEROR-PRESERVED

| Subgroup | Empagliflozin | Placebo | Hazard Ratio (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) |

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## Conclusiones

- Podemos estratificar el riesgo metabólico-cardio-renal de cada paciente para definir las prioridades de tratamiento
- El uso de iSGLT2 ha venido a cambiar el paradigma del tratamiento de la diabetes con protección de órgano blanco
  - Falla cardíaca
  - Muerte cardiovascular
  - Lesión renal
- Incluso usado en pacientes sin DM-2 con proteinuria o falla cardíaca, independientemente de la FE

## Preguntas…

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Puede descargar la presentación en:

www.EndoDrChen.com