



## Evidencia de los iSGLT2 en falla cardíaca

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## Conflictos de interés

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

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## Agenda

- Interrelación entre DM y falla cardíaca
- Impacto de antidiabéticos en falla cardíaca
- iSGLT2 en falla cardíaca con y sin diabetes
- iSGLT2 en HFpEF
- Nuevos mecanismos

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### El mal matrimonio entre DM y falla cardíaca

**DM**

- 30 millones en Estados Unidos
- 9.4% población general
- 25.2% de la población >65 años
- Prevalencia falla cardíaca comparado con población general
  - 2x en hombres
  - 5x en mujeres

**Falla cardíaca**

- 5.7 millones en Estados Unidos
- 1.7% población general
- Prevalencia 3x mayor en >60 años
- Prevalencia de hasta 44%

Mehta A. Clin Geriatr Med. 2020;36:447

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### Efecto de glucosa

- Cada 1% de aumento de Hba1c está asociado a 12% mayor riesgo de hospitalización por falla cardíaca
- Impacto del control glicémico?

Mehta A. Clin Geriatr Med. 2020;36:447

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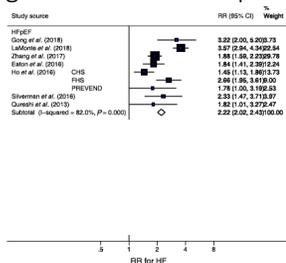
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### DM y riesgo de desarrollar HFpEF



Kodama S. ESC Heart Failure 2020; online apr 28

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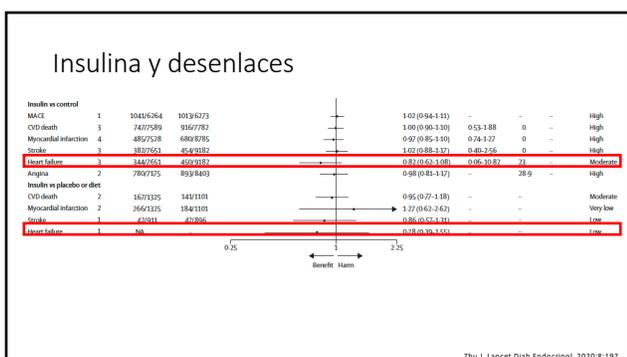
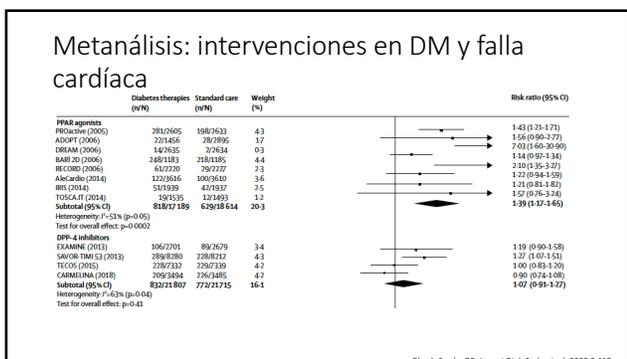
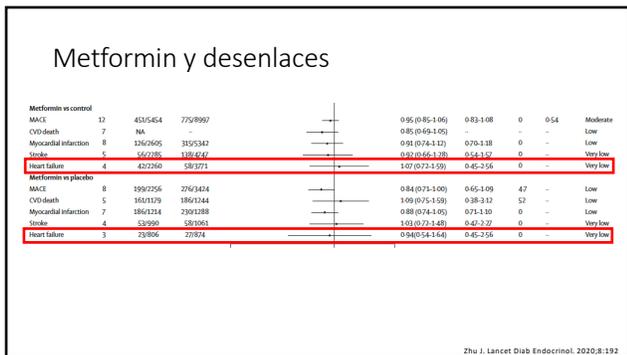
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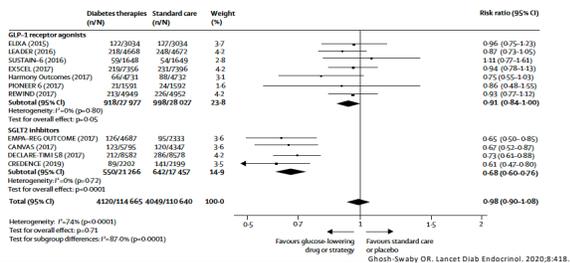
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### Metanálisis: intervenciones en DM y falla cardíaca




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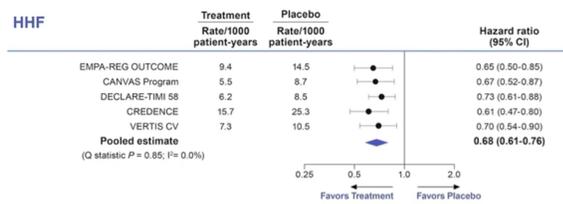
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### Time to first HHF




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### iSGLT2 y falla cardíaca con y sin diabetes

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# DAPA-HF



### Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D<sup>1,2</sup>

**4744 patients**

- ≥18 years of age
- With or without T2D
- Diagnosis of symptomatic HFrEF (NYHA class II-IV) for ≥ 2 months
- LVEF ≤40% within last 12 months
- Elevated NT-proBNP
- eGFR ≥30 mL/min/1.73 m<sup>2</sup>
- Stable SOC HFrEF treatment

**1:1 Double-blind**

**Dapagliflozin 10 mg + standard of care<sup>a</sup>**

**Placebo + standard of care<sup>a</sup>**

Visit 1 (enrollment) Day -14 | Visit 2 (randomization) Day 0 | Visit 3 Day 14 | Visit 4 Day 60 | Visit 5 Day 120 | Visit 6, etc. Every 120 days | Median follow-up: 18.2 months

**Primary Endpoint**

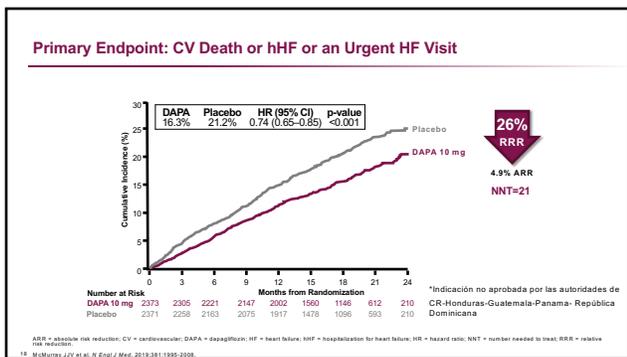
- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

**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 6 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<sup>b</sup> or renal death
- Time to death from any cause

<sup>a</sup>Indicación no aprobada por las autoridades de CR-Honduras-Guatemala-Panamá-República Dominicana

<sup>b</sup>Patients were treated according to regional standards of care for HF. Some patients in the dapagliflozin or placebo arms received additional or other measures beyond standard of care medications when at the discretion of their investigator. <sup>c</sup>Defined as sustained eGFR <15 mL/min/1.73 m<sup>2</sup> without dialysis treatment, or reaching a final renal transplant.



### Effects of Dapagliflozin on Worsening HF<sup>a</sup> and Mortality<sup>1</sup>

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

<sup>a</sup>Indicación no aprobada por las autoridades de CR-Honduras-Guatemala-Panamá- República Dominicana

<sup>b</sup>Worsening HF includes hHF or urgent HF visit. <sup>c</sup>Residual p-value.

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

1. McMurray JJV et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995-2009. 2. McMurray JJ. Presented at ESC Congress, August 31-September 4, 2019, Paris, France. 3. In House Data.

19. <https://doi.org/10.1016/j.eurj.2019.08.008>

### Primary Outcome by Diabetes Status<sup>1</sup>

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 <sup>a</sup> |
|----------------------------------|------------------------------|------------------|------------------|----------------------------------|
| Total population                 | 386/2373 (16.3)              | 502/2371 (21.2)  | 0.74 (0.65-0.85) |                                  |
| T2D <sup>b</sup>                 | 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) |                                  |

<sup>a</sup>Indicación no aprobada por las autoridades de CR-Honduras-Guatemala-Panamá- República Dominicana

<sup>b</sup>Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visit 1 and 2). <sup>c</sup>Non-significant result for an interaction between the intervention and diabetes status.

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

20. <https://doi.org/10.1016/j.eurj.2019.08.008>

### Safety Outcomes<sup>a</sup>

| 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 <sup>b</sup>           | 178 (7.5)                    | 162 (6.8)        | 0.40    |
| Renal AE <sup>c</sup>                   | 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 <sup>d</sup>         | 4 (0.2)                      | 4 (0.2)          | -       |
| Diabetic ketoacidosis <sup>e</sup>      | 3 (0.1)                      | 0 (0)            | -       |

<sup>a</sup>Indicación no aprobada por las autoridades de CR-Honduras-Guatemala-Panamá- República Dominicana

<sup>b</sup>Study population included all patients who had undergone randomization and received at least one dose of dapagliflozin or placebo. <sup>c</sup>Volume depletion serious AEs in 28 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23. <sup>d</sup>Renal serious AEs in 38 dapagliflozin patients (1.6%) and 61 placebo patients (2.6%), p=0.009. Serious adverse events of acute kidney injury were reported in 23 dapagliflozin patients (1.0%) and 40 placebo patients (1.7%). <sup>e</sup>Required an hypoglycemic requiring the assistance of another person to actively administer carbohydrates or glucose or to take other corrective action. All cases occurred in patients with diabetes at baseline. <sup>f</sup>All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline and were adjudicated as definite or probable.

AE = adverse event. 21. <https://doi.org/10.1016/j.eurj.2019.08.008>

# EMPEROR-REDUCED

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**DAPA-HF and EMPEROR-Reduced:  
SGLT2 Inhibitors in Heart Failure With Reduced EF**

| DAPA-HF  | EMPEROR-Reduced  |
|--|--|
| 4744 patients, with or without diabetes  | 3730 patients, with or without diabetes                          |
| Primary endpoint: CV death, hospitalization for heart failure and urgent heart failure visit | Primary endpoint: CV death and hospitalization for heart failure |
| ≈ 10% taking sacubitril-valsartan  | ≈ 20% taking sacubitril-valsartan                                |
| Increased levels of natriuretic peptides   | Markedly increased levels of natriuretic peptides                |
| Focus on patients with EF >30%   | Focus on patients with EF ≤ 30%                                  |
| Annual placebo event rate ≈ 15%  | Annual placebo event rate ≈ 21%                                  |

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**Trial inclusion and exclusion criteria**

| Inclusion criteria  |  |
|---|--|
| EMPEROR-Reduced <sup>1,2</sup>                            | DAPA-HF <sup>3</sup>   |
| 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%)  |
| <b>Elevated NT-proBNP</b>                                 |  |
| EF (%)  |  |
| NT-proBNP (pg/ml)   | NT-proBNP ≥600 pg/ml or NT-proBNP ≥400 pg/ml in patients with HFrEF within 12 months |
| Patients without AF*                                      | Patients without AF <sup>1</sup>   |
| ≥34 to ≤40  |  |
| ≥2500   |  |
| ≥31 to ≤35  |  |
| ≥1000   |  |
| ≤30   |  |
| ≥600  |  |
| ≤40% + HFrEF within 12 months                             |  |
| ≥600  |  |
| Further inclusion criteria apply                          | Further inclusion criteria apply   |
| <b>EMPEROR-Reduced</b>                                    | <b>DAPA-HF</b>   |
| eGFR <20 ml/min/1.73 m <sup>2</sup> or requiring dialysis | eGFR <30 ml/min/1.73 m <sup>2</sup> or rapidly declining renal function              |

\*Not 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 ≥500 pg/ml regardless of history of HFrEF. <sup>1</sup>Not included for discontinuation. <sup>2</sup>Not included for discontinuation. <sup>3</sup>Not included for discontinuation.

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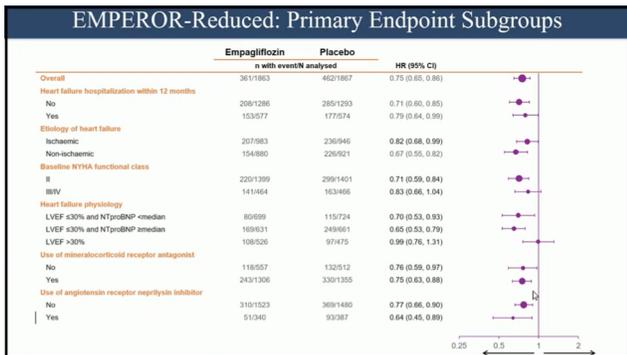
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### SGLT2 Inhibition With Empagliflozin Is Effective in Heart Failure With a Reduced Ejection Fraction With or Without Diabetes

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|--|---|--|
|  | <b>Primary Endpoint</b><br>Composite of cardiovascular death or heart failure hospitalization | <b>25% ↓ in risk</b><br>P < 0.001              |
|  | <b>First Secondary Endpoint</b><br>Total (first and recurrent heart failure hospitalizations) | <b>30% ↓ in risk</b><br>P < 0.001              |
|  | <b>Second Secondary Endpoint</b><br>Slope of decline in glomerular filtration rate over time  | <b>P &lt; 0.001</b><br>(50% ↓ in renal events) |

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

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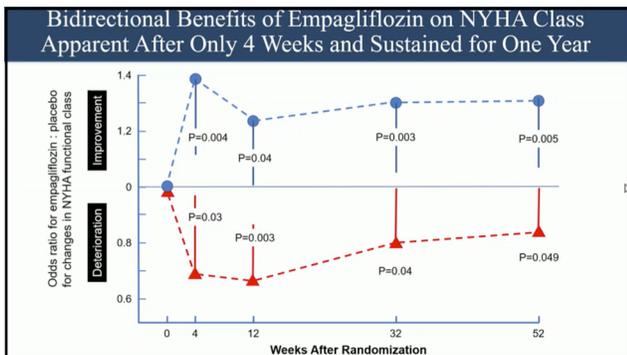
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| Trials in Heart Failure and a Reduced Ejection Fraction (With or Without Diabetes) |   |   |
|--|---|---|
|  | DAPA-HF (dapagliflozin)                   | EMPEROR-Reduced (empagliflozin)           |
| Cardiovascular death or hospitalization for heart failure                          | <b>0.75 (0.65 – 0.85)</b><br>[877 events] | <b>0.75 (0.65 – 0.86)</b><br>[823 events] |
| First hospitalization for heart failure  | <b>0.70 (0.59 – 0.83)</b><br>[549 events] | <b>0.69 (0.59 – 0.81)</b><br>[588 events] |
| Renal composite endpoint   | 0.71 (0.44 – 1.16)                        | 0.50 (0.32 – 0.77)                        |
| Cardiovascular death   | 0.82 (0.69 – 0.98)                        | 0.92 (0.75 – 1.12)                        |
| Trials in Type 2 Diabetes (With or Without Heart Failure)                          |   |   |
|  | DECLARE-TIMI38 (dapagliflozin)            | EMPA-REG OUTCOME (empagliflozin)          |
| Cardiovascular death or hospitalization for heart failure                          | 0.83 (0.73 – 0.95)                        | 0.66 (0.55 – 0.79)                        |
| First hospitalization for heart failure  | <b>0.73 (0.61 – 0.88)</b><br>[499 events] | <b>0.65 (0.50 – 0.85)</b><br>[221 events] |
| Renal composite endpoint   | 0.53 (0.43 – 0.66)                        | 0.54 (0.40 – 0.75)                        |
| Cardiovascular death in patients with prior myocardial infarction                  | 0.92 (0.69 – 1.23)                        | 0.59 (0.44 – 0.79)                        |

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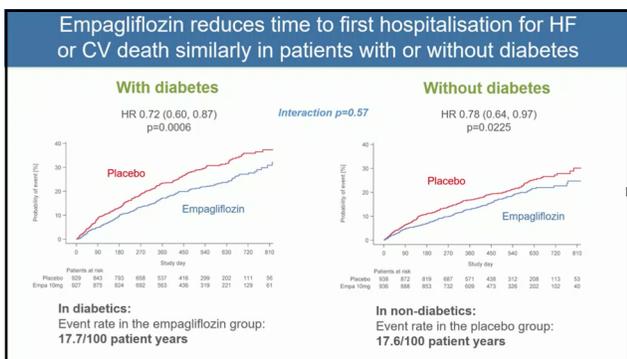
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**EMPEROR-Reduced: Serious Adverse Events and Adverse Events of Special Interest**

|   | Empagliflozin (n=1883) | Placebo (n=1883)  |
|---|------------------------|-------------------|
| Serious adverse events                      | 772 (41.4)             | 806 (48.1)        |
| Related to cardiac disorder                 | <b>500 (26.6)</b>      | <b>634 (34.0)</b> |
| Related to worsening renal function         | <b>59 (3.2)</b>        | <b>95 (5.1)</b>   |
| Adverse events of special interest          |                        |                   |
| Volume depletion                            | 197 (10.6)             | 184 (9.9)         |
| Hypotension                                 | 176 (9.4)              | 163 (8.7)         |
| Symptomatic hypotension                     | 106 (5.7)              | 103 (5.5)         |
| Confirmed hypoglycemia*                     | 27 (1.4)               | 28 (1.5)          |
| Ketoacidosis                                | 0 (0.0)                | 0 (0.0)           |
| Urinary tract infections                    | 91 (4.9)               | 83 (4.5)          |
| Genital tract infections                    | 31 (1.7)               | 12 (0.6)          |
| Bone fractures                              | 45 (2.4)               | 42 (2.3)          |
| Lower limb amputations (until end of trial) | 13 (0.7)               | 10 (0.5)          |

\*Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <20 mg/dL (3.9 mmol/L) or required assistance.

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### EMPEROR-Reduced: Symptomatic Hypotension Was Not Increased by Empagliflozin, Even in High-Risk Patients

|  | Empagliflozin (n=1863) | Placebo (n=1863) |
|--|------------------------|------------------|
| All events                               | 106 ( 5.7)             | 103 ( 5.5)       |
| Events within first 30 days of treatment | 30 ( 1.6)              | 28 ( 1.5)        |

Not influenced by

- Diabetes
- Renal function
- Age
- Ejection fraction
- Systolic blood pressure
- Nephrylsin inhibition

Patients at risk

| Study day | 0    | 90   | 180  | 270  | 360  | 450 | 540 | 630 | 720 | 810 |
|-----------|------|------|------|------|------|-----|-----|-----|-----|-----|
| Placebo   | 1863 | 1687 | 1578 | 1324 | 1108 | 856 | 615 | 411 | 210 | 93  |
| Empa 10mg | 1863 | 1707 | 1605 | 1363 | 1115 | 867 | 628 | 415 | 210 | 98  |

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### Metanálisis DAPA-HF y EMPEROR-REDUCED

**A All cause mortality**

|                 | Number with event/number of patients (%) |                  | HR (95% CI)             |
|-----------------|--|------------------|-------------------------|
|                 | SGLT2 inhibitor                          | Placebo          |                         |
| EMPEROR-Reduced | 249/1863 (13.4%)                         | 266/1867 (14.2%) | 0.92 (0.77-1.10)        |
| DAPA-HF         | 276/2373 (11.6%)                         | 339/2371 (13.9%) | 0.83 (0.71-0.97)        |
| <b>Total</b>    |  |                  | <b>0.87 (0.77-0.98)</b> |

Test for overall treatment effect p=0.018  
Test for heterogeneity of effect p=0.39

**B Cardiovascular death**

|                 | Number with event/number of patients (%) |                  | HR (95% CI)             |
|-----------------|--|------------------|-------------------------|
|                 | SGLT2 inhibitor                          | Placebo          |                         |
| EMPEROR-Reduced | 187/1863 (10.0%)                         | 202/1867 (10.8%) | 0.92 (0.75-1.12)        |
| DAPA-HF         | 227/2373 (9.6%)                          | 273/2371 (11.5%) | 0.82 (0.69-0.98)        |
| <b>Total</b>    |  |                  | <b>0.86 (0.76-0.98)</b> |

Test for overall treatment effect p=0.027  
Test for heterogeneity of effect p=0.40

Zamjad F. Lancet. 2020. Online Aug 20.

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### Metanálisis DAPA-HF y EMPEROR-REDUCED

**C First hospitalisation for heart failure or cardiovascular death**

|                 | Number with event/number of patients (%) |                  | HR (95% CI)             |
|-----------------|--|------------------|-------------------------|
|                 | SGLT2 inhibitor                          | Placebo          |                         |
| EMPEROR-Reduced | 361/1863 (19.4%)                         | 462/1867 (24.7%) | 0.75 (0.65-0.86)        |
| DAPA-HF         | 386/2373 (16.3%)                         | 502/2371 (21.2%) | 0.74 (0.65-0.85)        |
| <b>Total</b>    |  |                  | <b>0.74 (0.68-0.82)</b> |

Test for overall treatment effect p<0.0001  
Test for heterogeneity of effect p=0.89

**D First hospitalisation for heart failure**

|                 | Number with event/number of patients (%) |                  | HR (95% CI)             |
|-----------------|--|------------------|-------------------------|
|                 | SGLT2 inhibitor                          | Placebo          |                         |
| EMPEROR-Reduced | 246/1863 (13.2%)                         | 342/1867 (18.3%) | 0.69 (0.59-0.81)        |
| DAPA-HF         | 231/2373 (9.7%)                          | 318/2371 (13.4%) | 0.70 (0.59-0.83)        |
| <b>Total</b>    |  |                  | <b>0.69 (0.62-0.78)</b> |

Test for overall treatment effect p<0.0001  
Test for heterogeneity of effect p=0.90

Zamjad F. Lancet. 2020. Online Aug 20.

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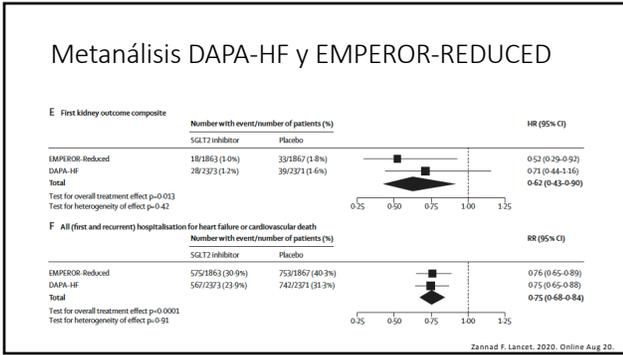
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iSGLT2 y HFpEF

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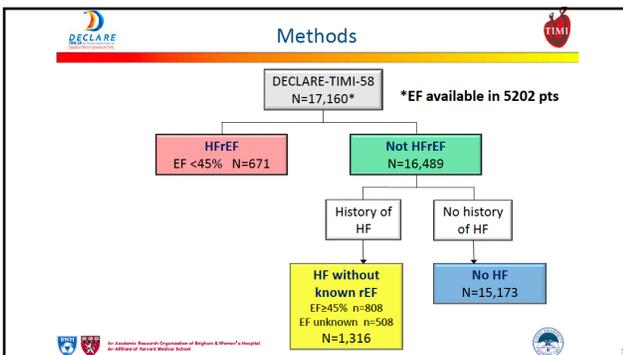
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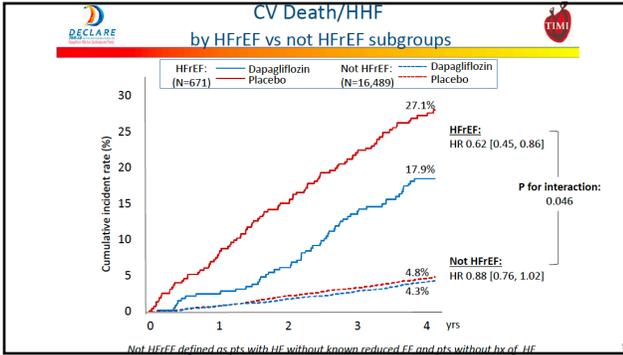
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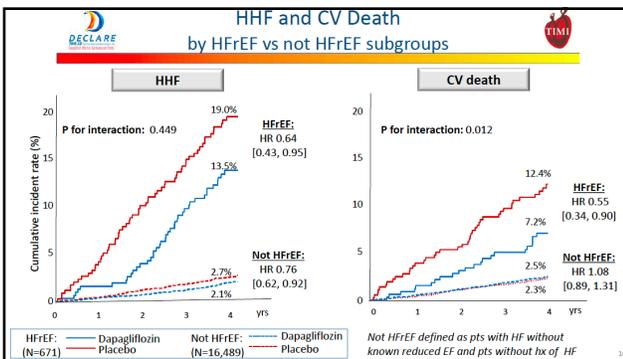
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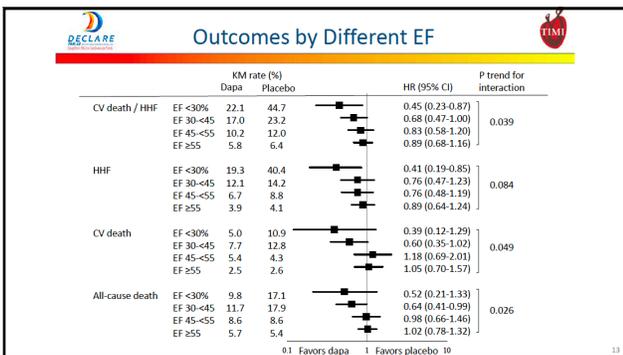
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### MUSCAT-HF

- RCT abierto
- Luseogliflozina 2.5 mg OD vs voglibosa 0.2 mg TID
- DM-2, >20 años de edad
- FEVI >45%, BNP >35 pg/ml y síntomas
- Desenlace primario: cambio en el ratio de BNP a las 12 semanas comparado con el basal

Ejiri K. J Am Heart Assoc. 2020;9:e015103

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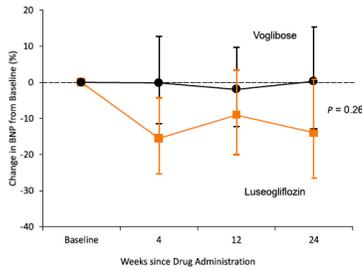
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### MUSCAT-HF



Ejiri K. J Am Heart Assoc. 2020;9:e015103

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Nuevos mecanismos propuestos:  
cómo integrarlos las piezas del  
rompecabezas?

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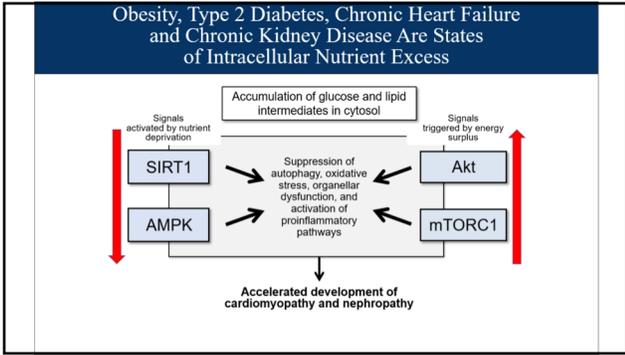
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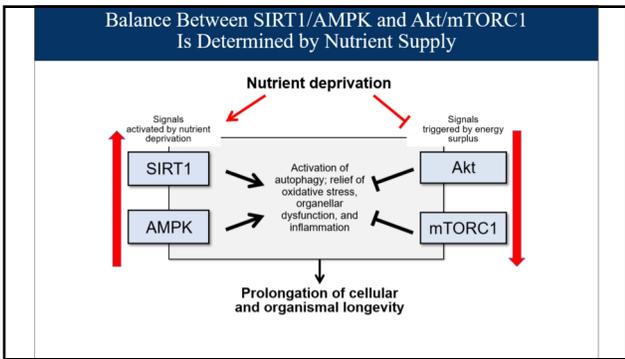
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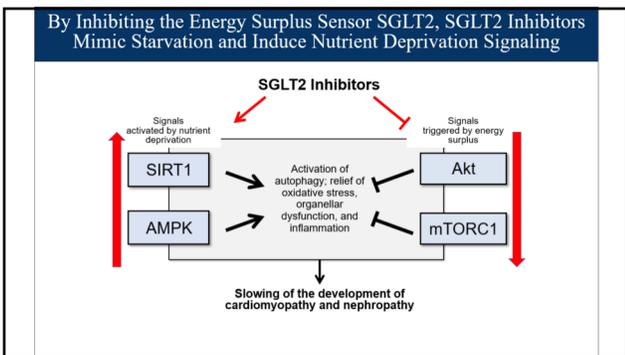
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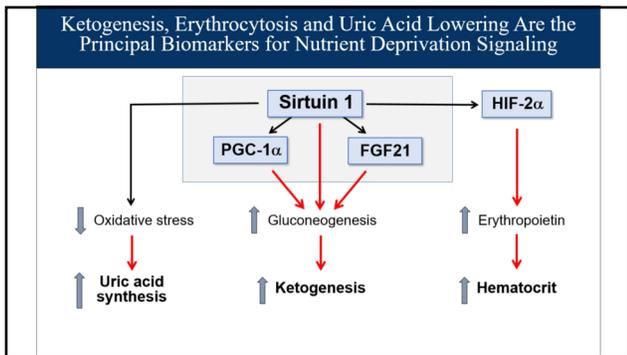
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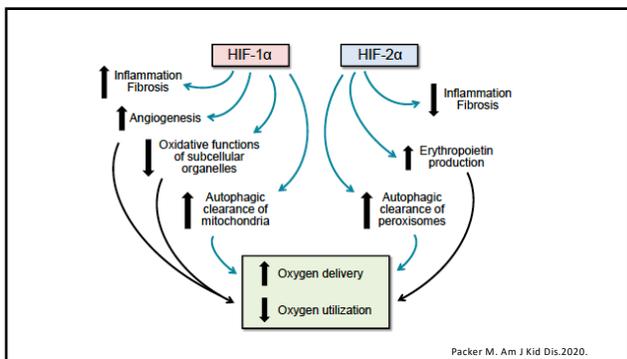
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**Ketogenesis, Erythrocytosis and Uric Acid Lowering Are the Hallmarks of SGLT2 Inhibitors**

SGLT2 inhibitors are the only antihyperglycemic drugs that

- Promote gluconeogenesis and ketogenesis
- Increase hematocrit — through an action to stimulate erythropoietin and erythrocytosis
- Reduce serum uric acid

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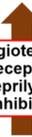
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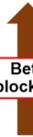
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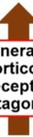
**Future Paradigm of Quadruple Therapy For Heart Failure With Reduced Ejection Fraction**



**Angiotensin  
receptor  
neprilysin  
inhibitor**



**Beta  
blockers**



**Mineralo-  
corticoid  
receptor  
antagonist**



**SGLT2  
inhibitor**

Adding spironolactone, a neprilysin inhibitor and SGLT2 inhibitor reduces mortality by an extra 45% above that achieved by an ACE inhibitor and a beta-blocker

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**Conclusiones**

- DM y falla cardíaca es un mal matrimonio
- Los iSGLT2 se están posicionando como parte de la terapia para pacientes con falla cardíaca con o sin diabetes, especialmente en HFREF
- Hay que caracterizar mejor falla cardíaca y necesitamos más datos en HFpEF

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**Preguntas...**

[chenku2409@gmail.com](mailto:chenku2409@gmail.com)

Puede descargar la presentación en:



www.EndoDrChen.com

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