

SAC 27 y 28 mayo 2022



Congreso de la
Sociedad Asturiana
de **Cardiología**
Sede: Parador de Corias

Congreso de la
Sociedad Asturiana
de **Cardiología**
Cangas de Narcea



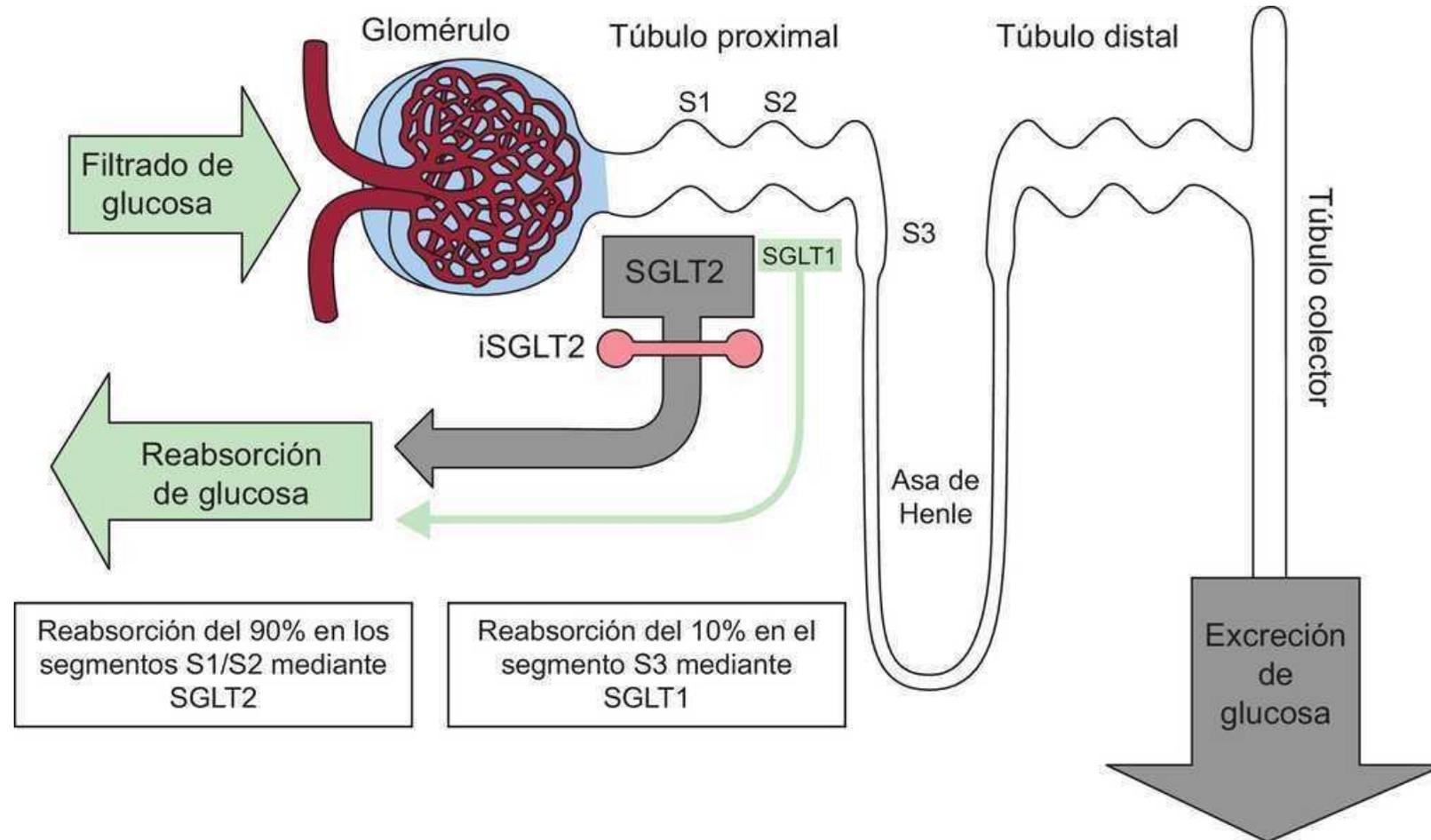
En FEVI reducida: MI PRIORIDAD ES INTRODUCIR ISGLT2

Vanesa Alonso Fernández

Área del Corazón

Hospital Universitario Central de Asturias

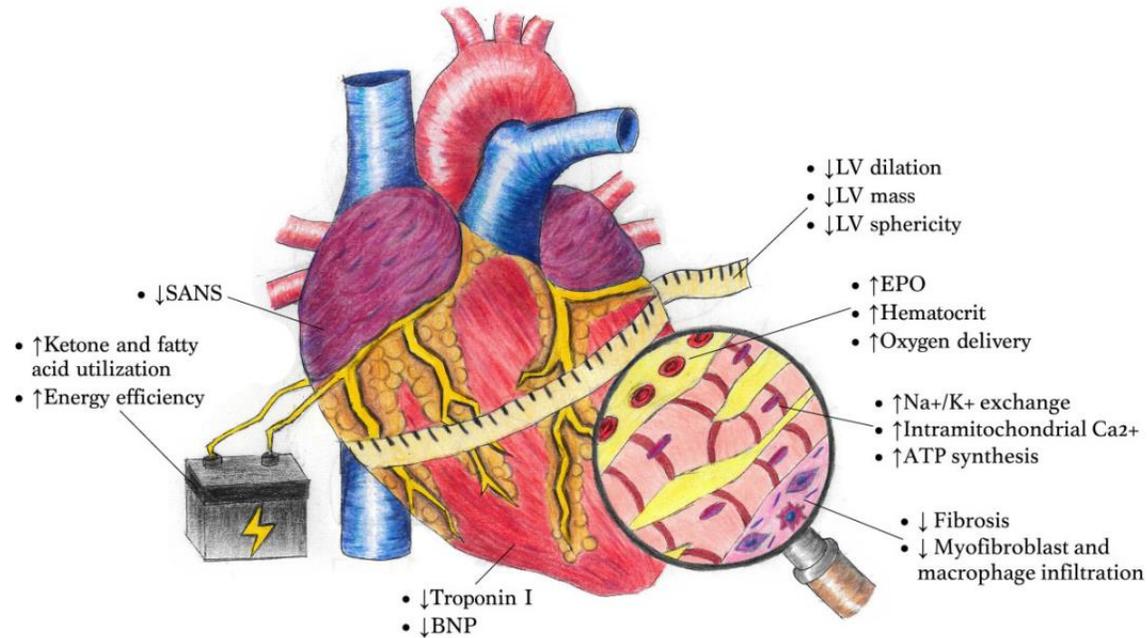
Un breve repaso...del mecanismo inicial



Rev Esp Cardiol. 2016;69:1088-97

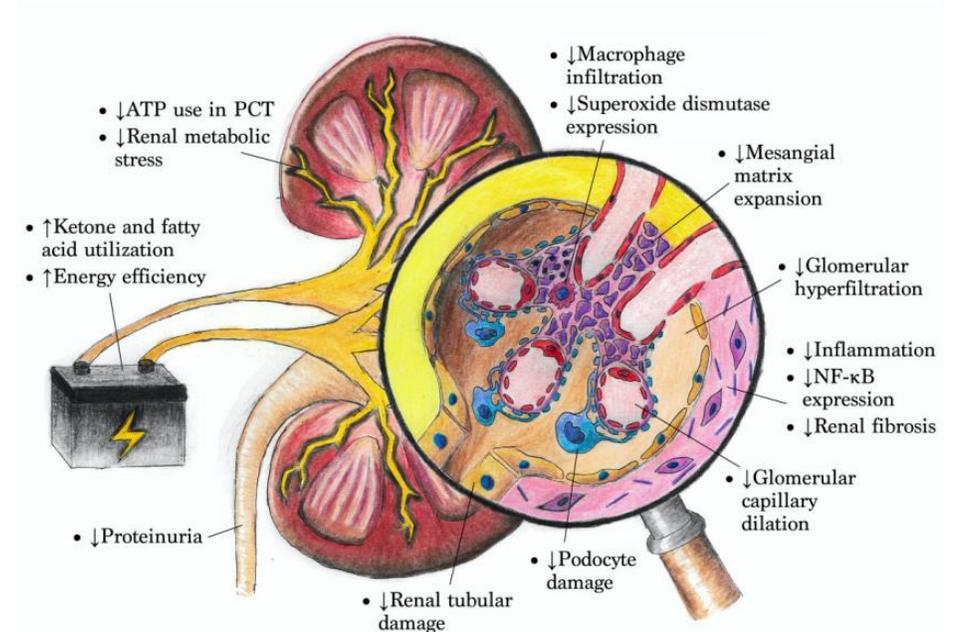
Un breve repaso...al efecto cardio-nefro protector

Cardiac Mechanisms of Benefit of SGLT2 Inhibitors



EPO= Erythropoietin, LV= Left ventricular, SANS= Sympathetic autonomic nervous system

Renal Mechanisms of Benefit of SGLT2 Inhibitors



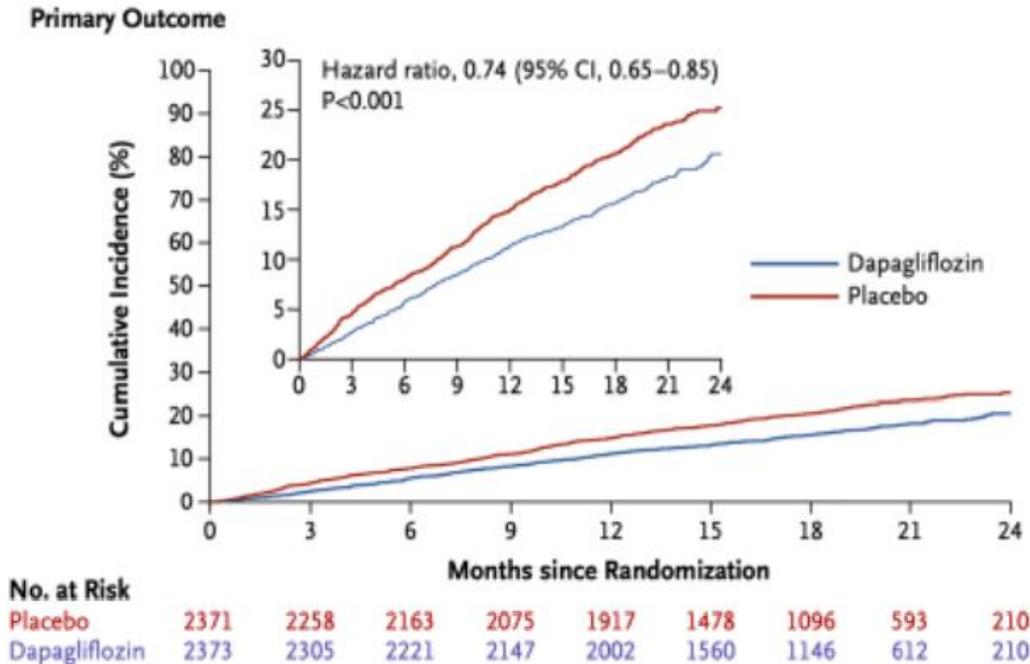
ATP= Adenosine triphosphate, NF-κB = Nuclear factor κB, PCT= Proximal convoluted tubule

Aguilar Gallardo et al. European Heart Journal - Cardiovascular Pharmacotherapy (2022) 8, 311–321

Evidencia de los ISGLT-2 en ICFEr

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

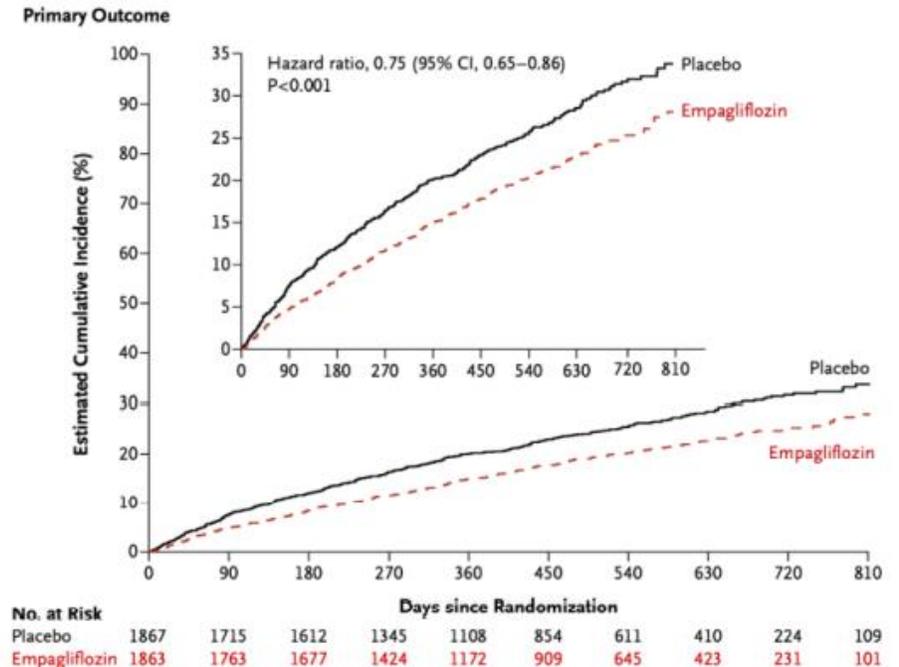
J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Böhlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozd, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*



Mc Murray et al NEJM 381 (2019): 1995-2008

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*



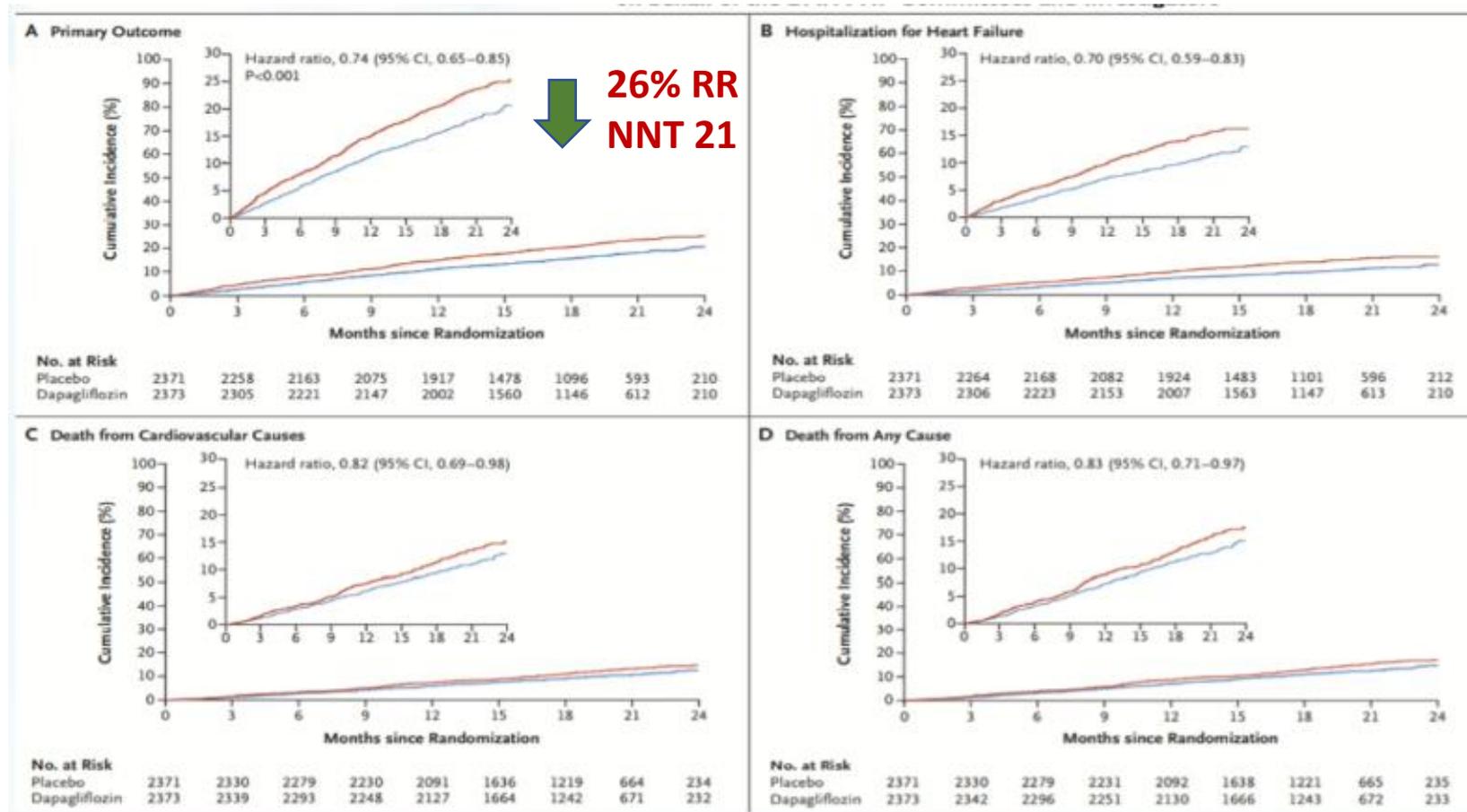
Packer et al. NEJM 383 (2020): 1414-1424

Evidencia de los ISGLT-2 en ICFEr

DAPA-HF

4744 pacientes
 IC FEVI < 40% con y sin DM
 FG > 30 ml/min
 Dapa vs placebo sobre TMO
 18 meses

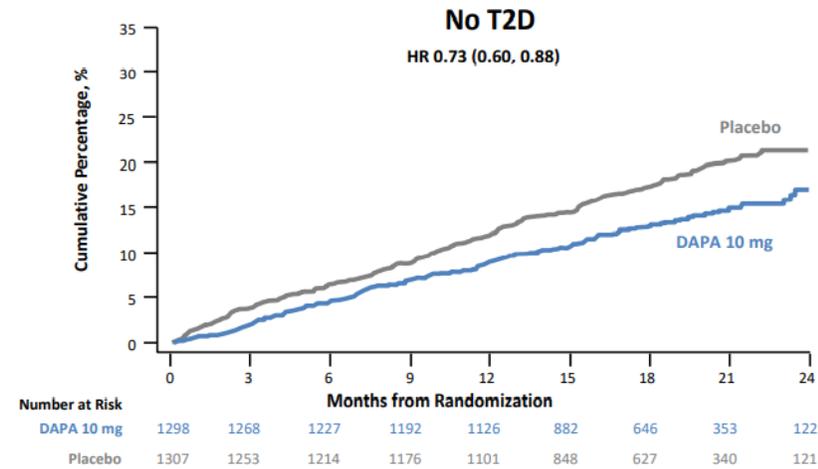
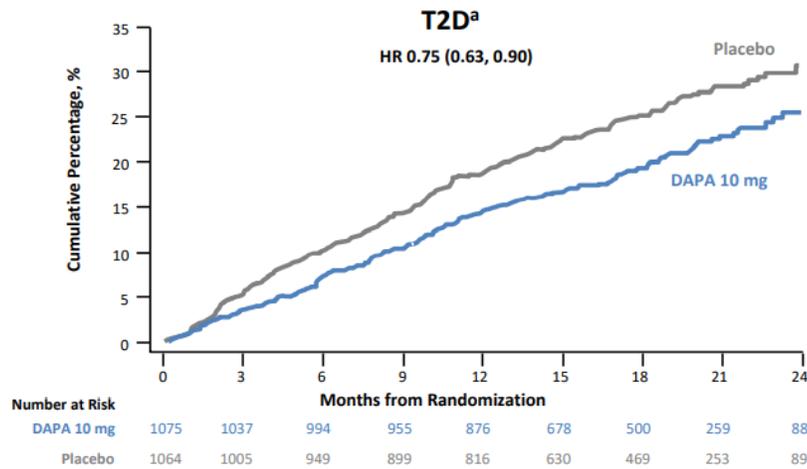
Edad media 67 años
 76% varones
 68% en CF II. FEVI media 31%
42% no DM
 NT proBNP 1428
 94% iSRAA (11% SV), 96% BB,
 71% ARM. TRC 8 %.
 15% sin diuréticos



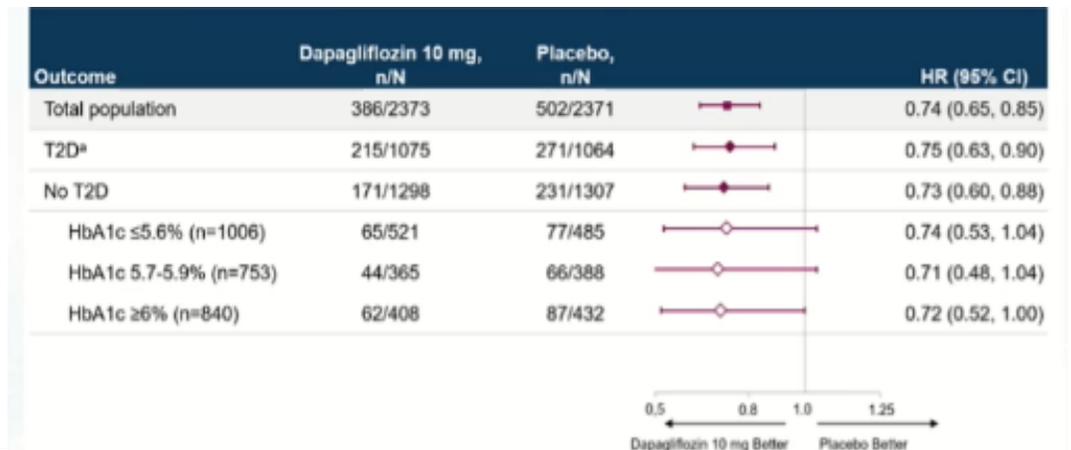
Mc Murray et al NEJM 381 (2019): 1995-2008



Evidencia de los ISGLT-2 en ICFEr Sin diferencias entre DM y no DM

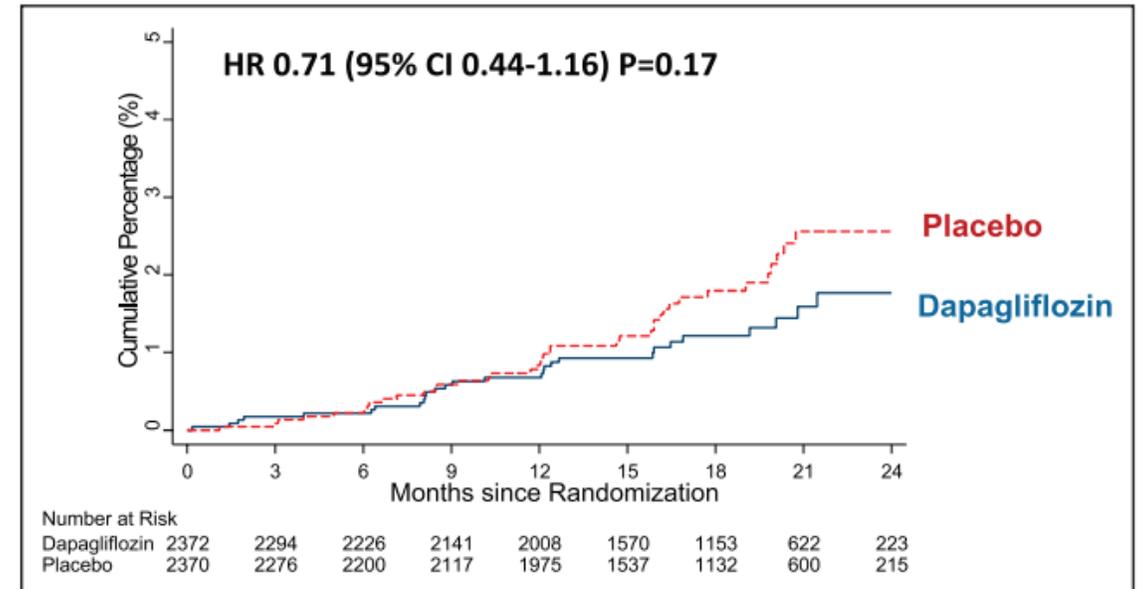
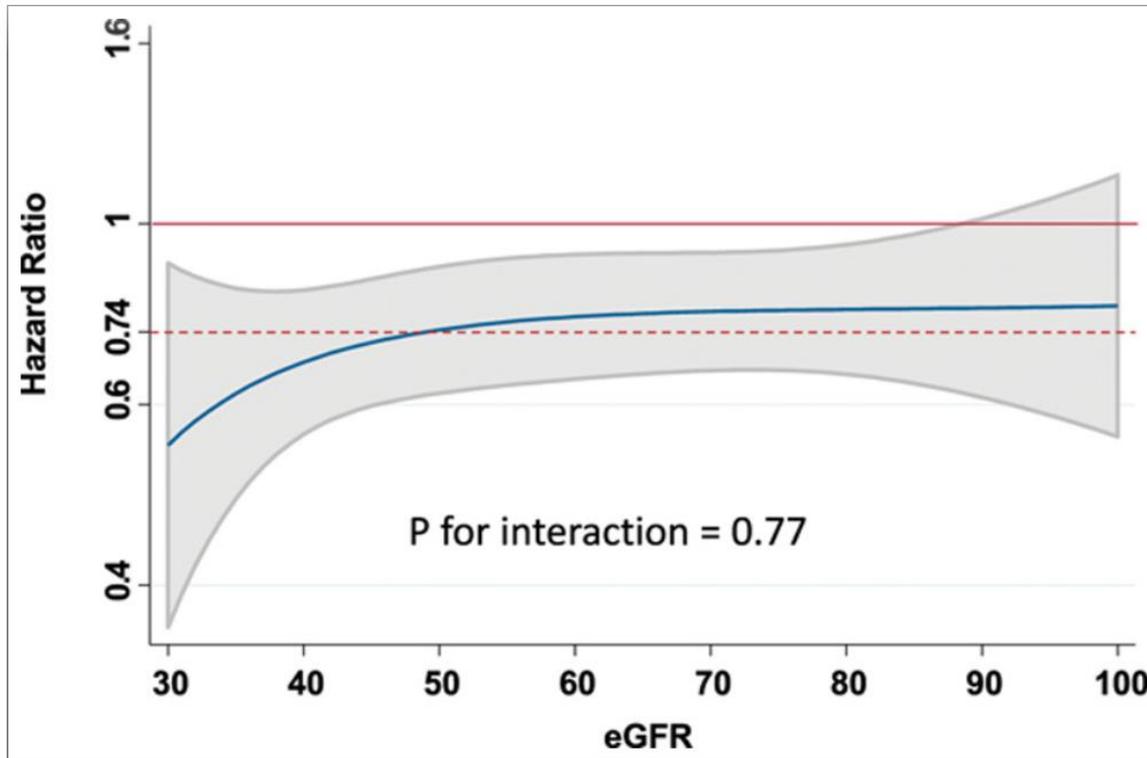


p-interaction=0.80



Mc Murray et al. NEJM 381 (2019): 1995-2008
Petrie et al. JAMA 2020. Apr 14;323 (14): 1353-1368

En ICfEr : Beneficio con independencia de la función renal



Renal outcome was a composite of $\geq 50\%$ sustained decline estimated glomerular filtration rate or end-stage renal disease or renal death in DAPA-HF

Jhund P and McMurray J. *Circulation* 2021;143:298–309

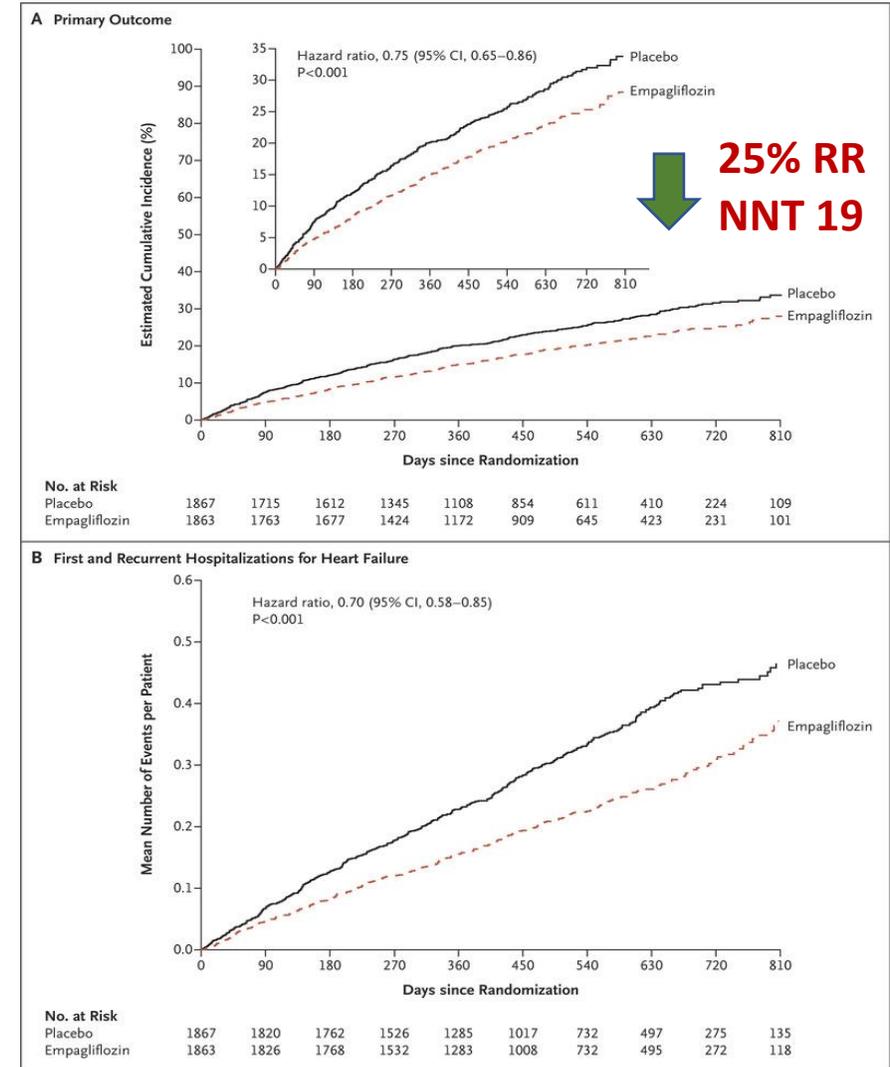
Evidencia de los ISGLT-2 en ICFEr

EMPEROR-Reduced

3730 pacientes IC FEVI < 40% con y sin DM
FG > 20 ml/min
Empa vs placebo sobre TMO. 16 meses

Edad media 67 años. 76% varones
72% en CF II. FEVI media 27%
49% no DM
NT ProBNP 1906
70% IECAs/ARA II, 20% ARNI, 96% BB, 71% ARM
TRC 12 %

Packer et al. NEJM 383 (2020): 1414-1424



Cambio en las guías de práctica clínica

Management of HFrEF



Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF <40%)

| Recommendations | Class ^a | Level ^b |
|---|--------------------|--------------------|
| An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{110–113} | I | A |
| A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death. ^{114–120} | I | A |
| An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{121,122} | I | A |
| Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. ^{108,109} | I | A |
| Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death. ¹⁰⁵ | I | B |

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European Heart Journal (2021) 00, 1128

¿Qué podemos esperar al iniciar un ISGLT2?

1. Seguridad

Selected Adverse Events of Interest

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

| Variable | Dapagliflozin (N=2373) | | Placebo (N=2371) | | Hazard or Rate Ratio or Difference (95% CI) | P Value |
|--|------------------------|-----------------------|------------------|-----------------------|---|---------|
| | values | events/100 patient-yr | values | events/100 patient-yr | | |
| Safety outcomes | | | | | | |
| Discontinuation due to adverse event — no./total no. (%) | 111/2368 (4.7) | — | 116/2368 (4.9) | — | — | 0.79 |
| Adverse events of interest — no./total no. (%) | | | | | | |
| Volume depletion | 178/2368 (7.5) | — | 162/2368 (6.8) | — | — | 0.40 |
| Renal adverse event | 153/2368 (6.5) | — | 170/2368 (7.2) | — | — | 0.36 |
| Fracture | 49/2368 (2.1) | — | 50/2368 (2.1) | — | — | 1.00 |
| Amputation | 13/2368 (0.5) | — | 12/2368 (0.5) | — | — | 1.00 |
| Major hypoglycemia** | 4/2368 (0.2) | — | 4/2368 (0.2) | — | — | NA |
| Diabetic ketoacidosis†† | 3/2368 (0.1) | — | 0 | — | — | NA |
| Fournier's gangrene | 0 | — | 1/2368 (<0.1) | — | — | NA |

| | Empagliflozin (n=1863) | Placebo (n=1863) |
|---|------------------------|------------------|
| | N (%) | N (%) |
| Patients with any adverse event | 1420 (76.2) | 1463 (78.5) |
| Patients with any serious adverse event | 772 (41.4) | 896 (48.1) |

Selected adverse events of interest

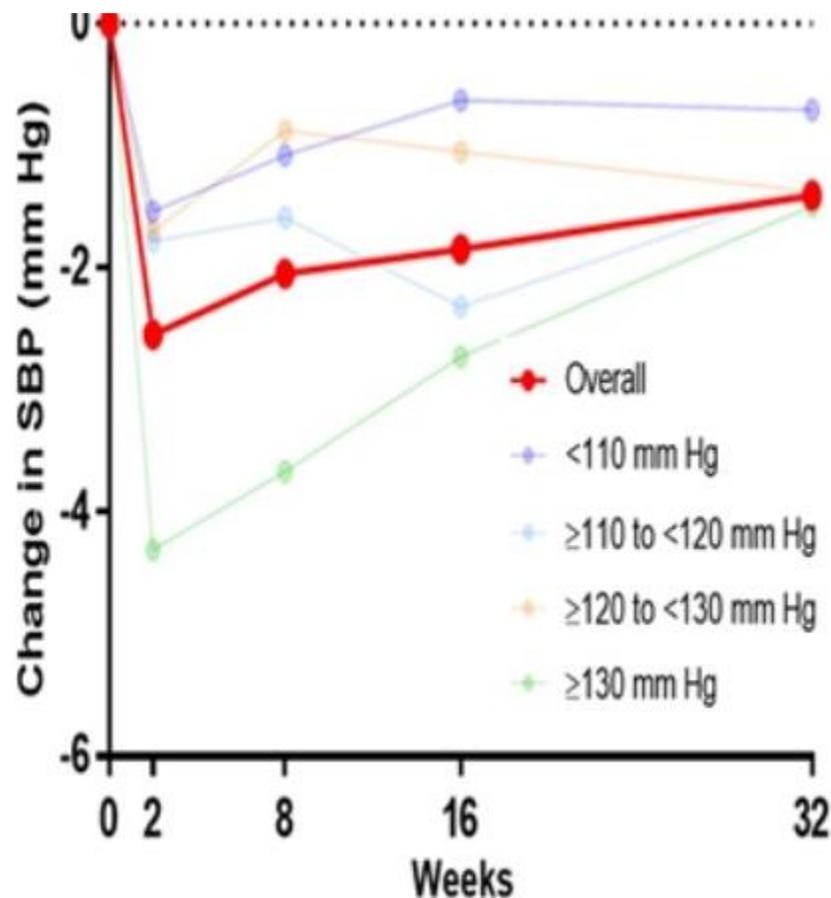
| | | |
|---|------------|-----------|
| Hypotension | 176 (9.4) | 163 (8.7) |
| Symptomatic hypotension | 106 (5.7) | 103 (5.5) |
| Volume depletion | 197 (10.6) | 184 (9.9) |
| Ketoacidosis | 0 (0.0) | 0 (0.0) |
| Hypoglycemic events* | 27 (1.4) | 28 (1.5) |
| In patients with type 2 diabetes | 20 (2.2) | 22 (2.4) |
| In patients without type 2 diabetes | 7 (0.7) | 6 (0.6) |
| Urinary tract infections | 91 (4.9) | 83 (4.5) |
| Complicated urinary tract infections | 19 (1.0) | 15 (0.8) |
| Genital infections | 31 (1.7) | 12 (0.6) |
| Complicated genital infections | 6 (0.3) | 5 (0.3) |
| Bone fractures | 45 (2.4) | 42 (2.3) |
| Events leading to lower limb amputation | 13 (0.7) | 10 (0.5) |

Mc Murray et al NEJM 381 (2019): 1995-2008

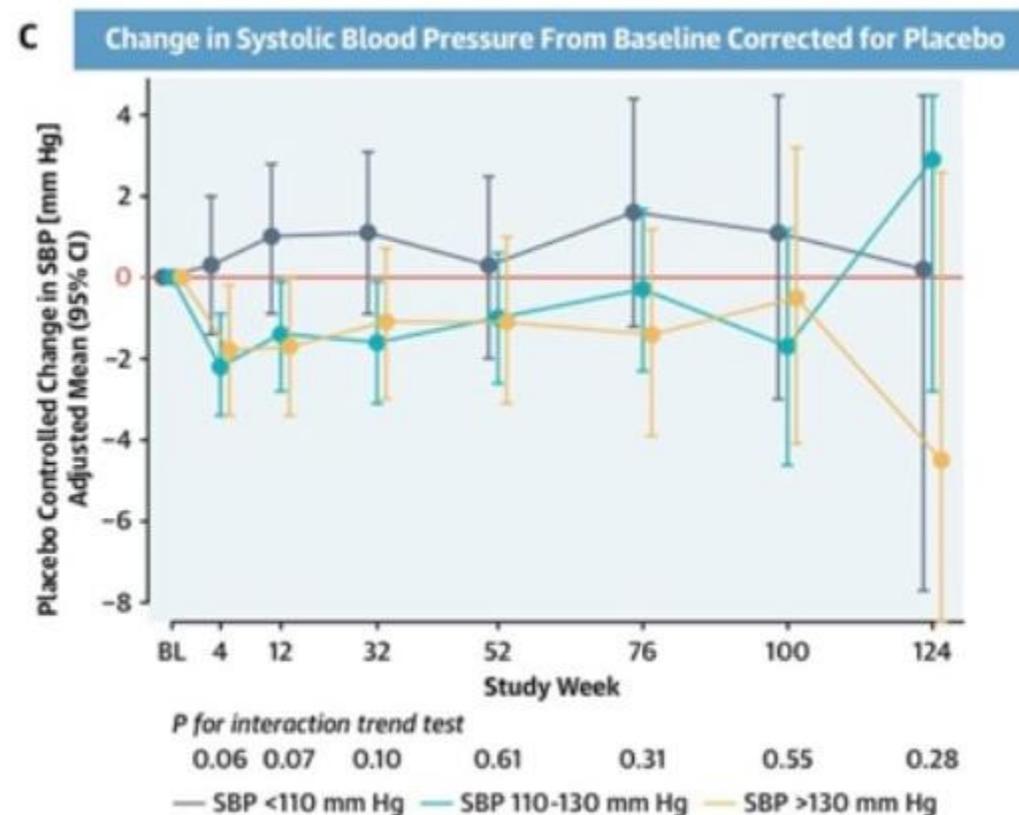
Packer et al. NEJM 383 (2020): 1414-1424

¿Qué podemos esperar al iniciar un ISGLT2?

2. Buen perfil hemodinámico



Serenelli et al. European Heart Journal (2020) 41, 3402–3418

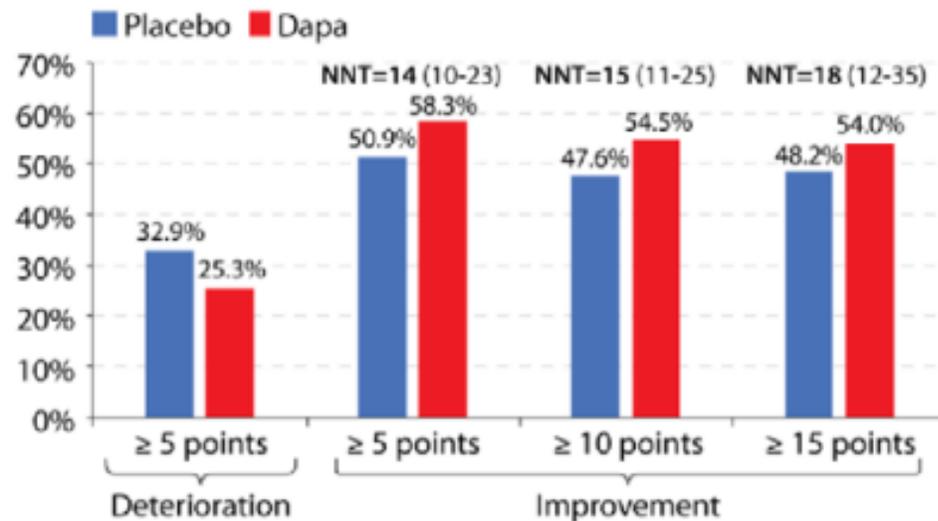


Böhm et al. J Am Cardiol 2021 Sep, 78 (13) 1337–1348

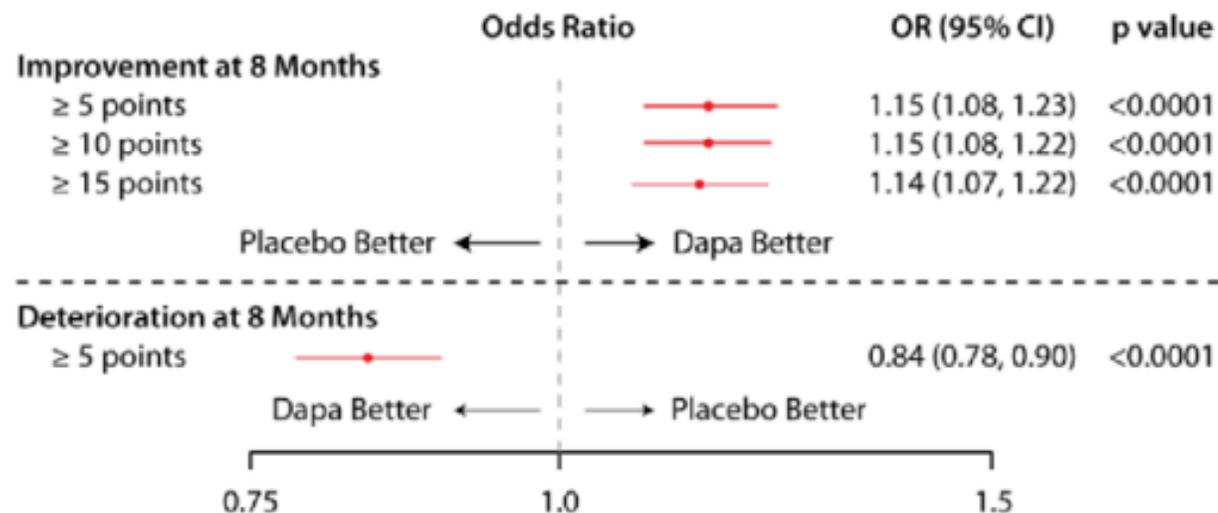
¿Qué podemos esperar al iniciar un ISGLT2?

3. Mejoría en calidad de vida

A KCCQ Total Symptom Score



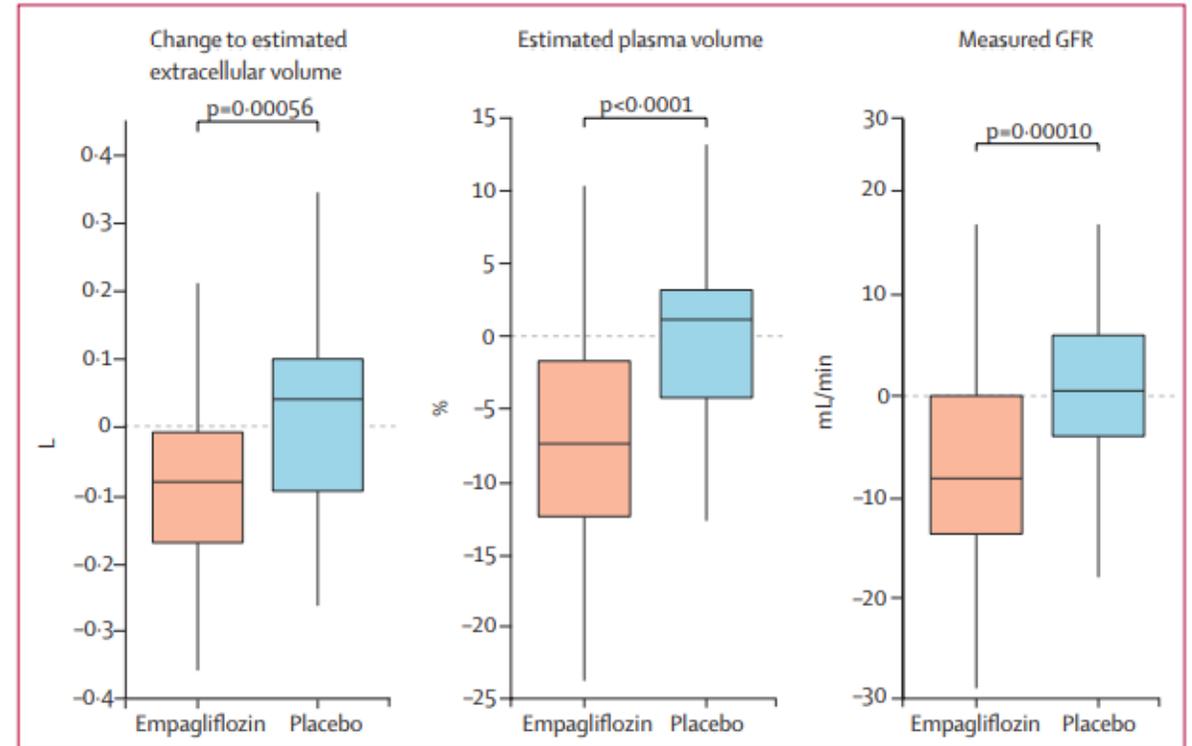
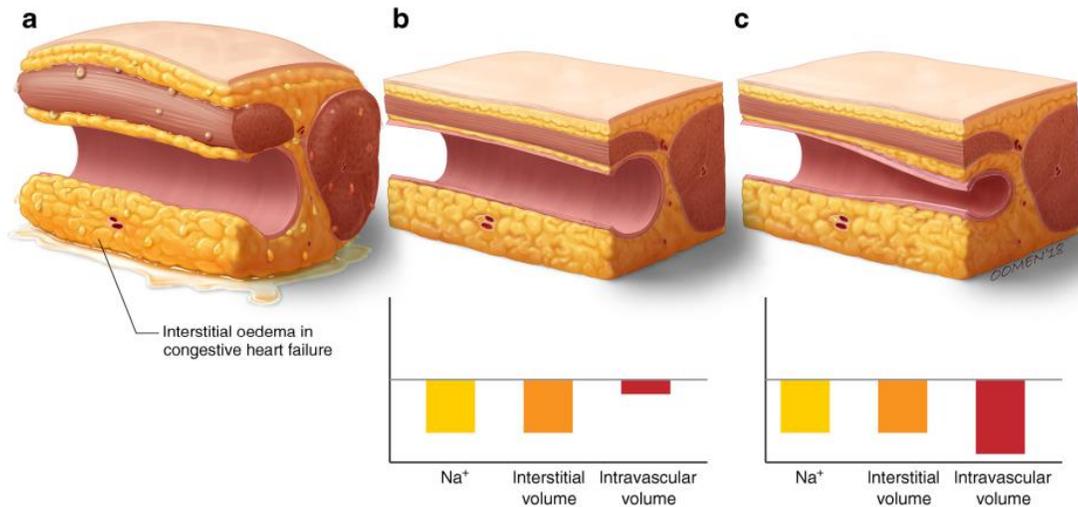
B KCCQ Total Symptom Score



Kosiborod et al. Circulation. 2020 Jan 14; 141(2): 90–99.

¿Qué podemos esperar al iniciar un ISGLT2?

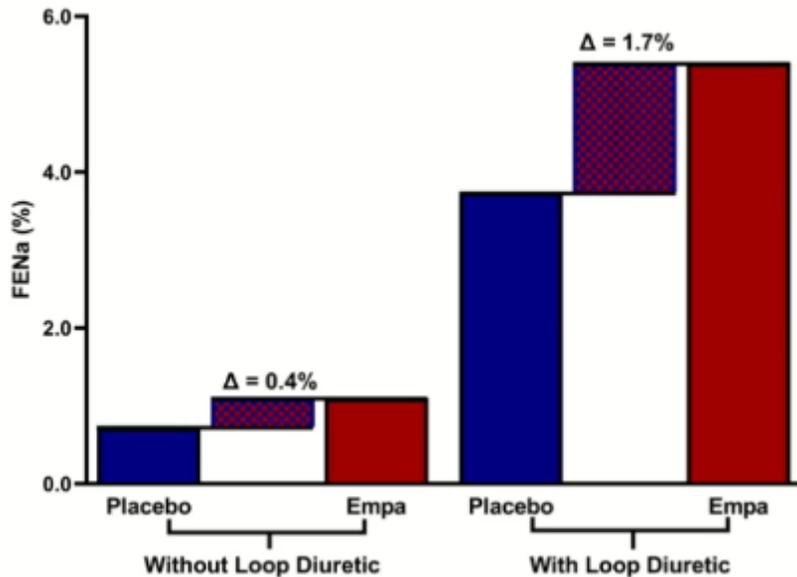
4. Efecto “diurético inteligente”



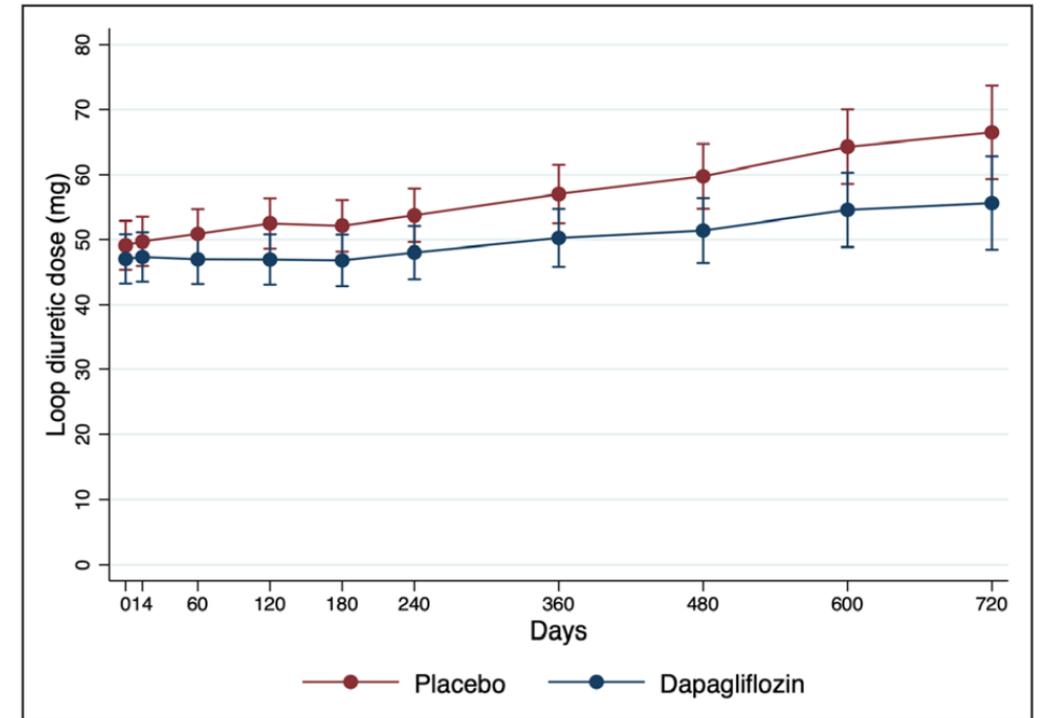
Verma S, Mc Murray J. Diabetologia (2018) 61:2108–2117

Berg et al. JAMA Cardiol. 2021;6(5):499-507

¿Qué podemos esperar al iniciar un ISGLT2? Efecto diurético junto con diuréticos de asa



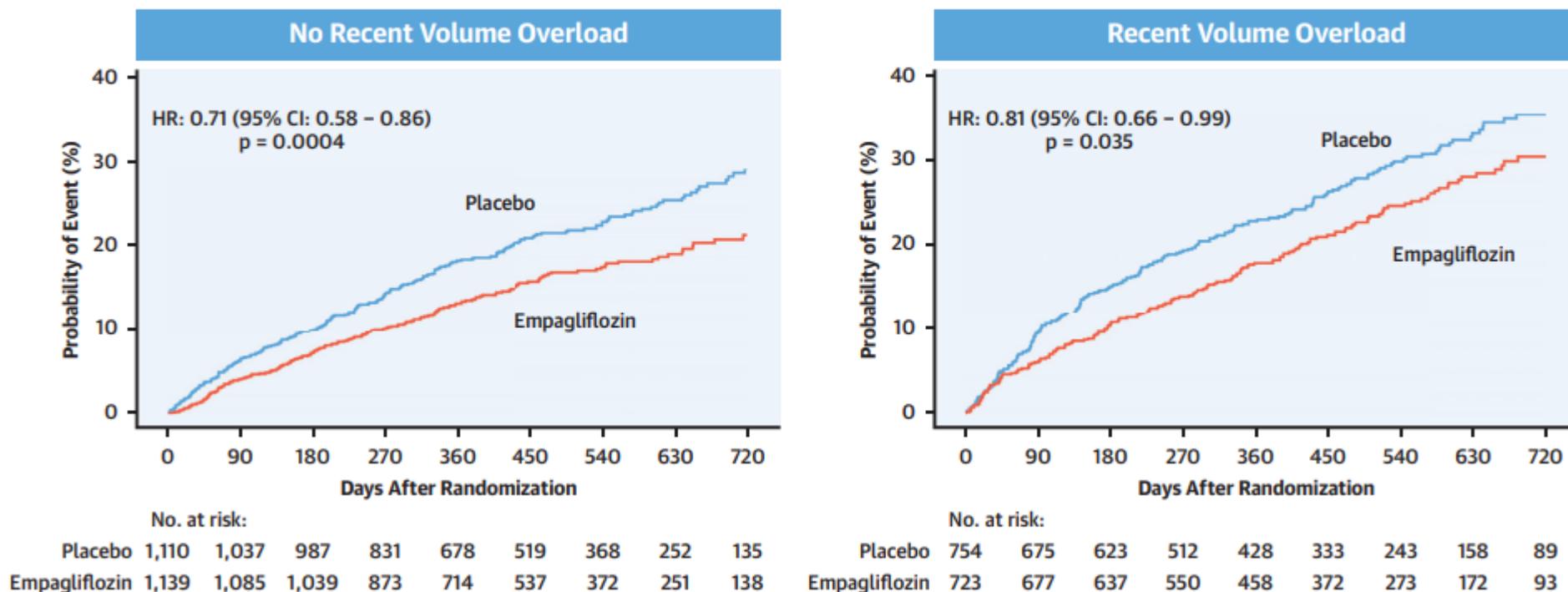
Griffin M, Rao VS, Ivey-Miranda J, et al. Circulation 2020.



Jackson et al. Circulation. 2020;142:1040–1054

¿Qué podemos esperar al iniciar un ISGLT2? Beneficio se mantiene sin congestión

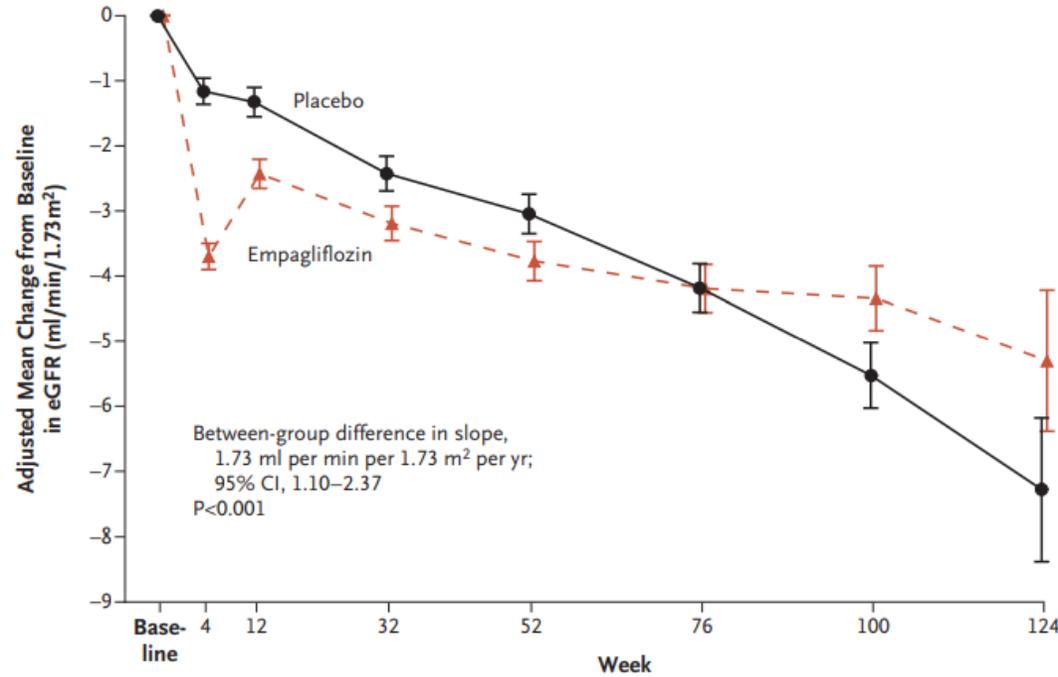
CENTRAL ILLUSTRATION Effect of Empagliflozin on the Combined Risk of Cardiovascular Death or Hospitalization for Heart Failure in Patients With or Without Recent Volume Overload at Baseline



Packer et al. J Am Coll Cardiol. 2021;77(11):1381–92

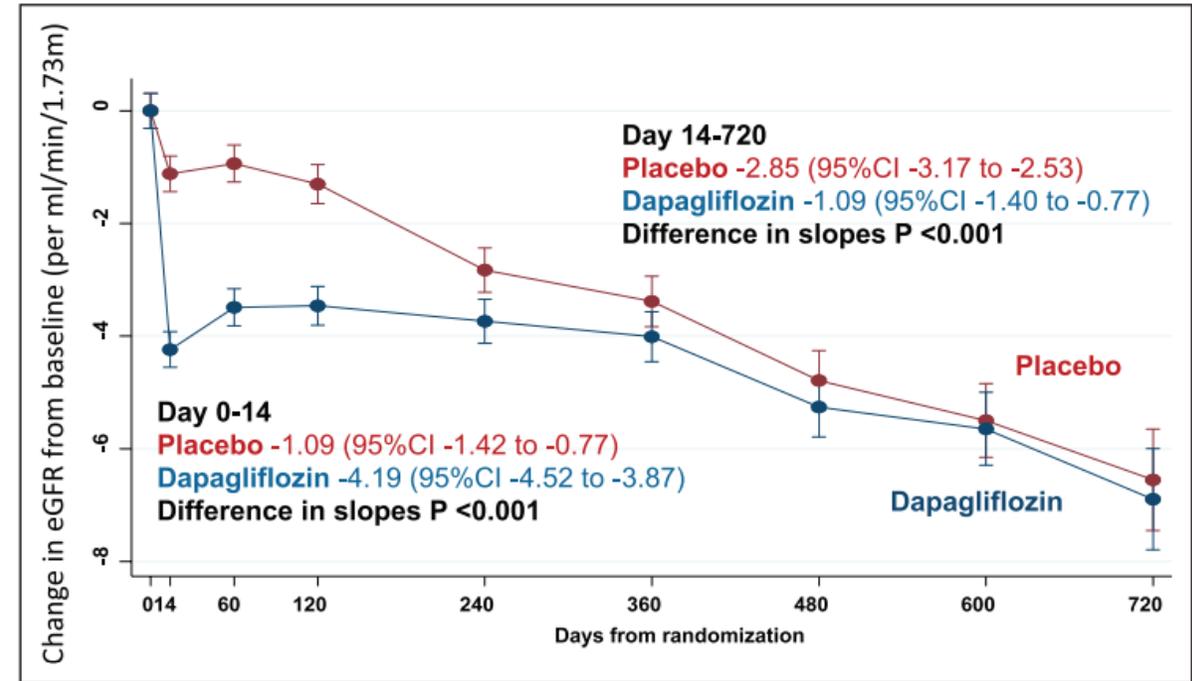
¿Qué podemos esperar al iniciar un ISGLT2?

5. Efecto protector renal



No. at Risk

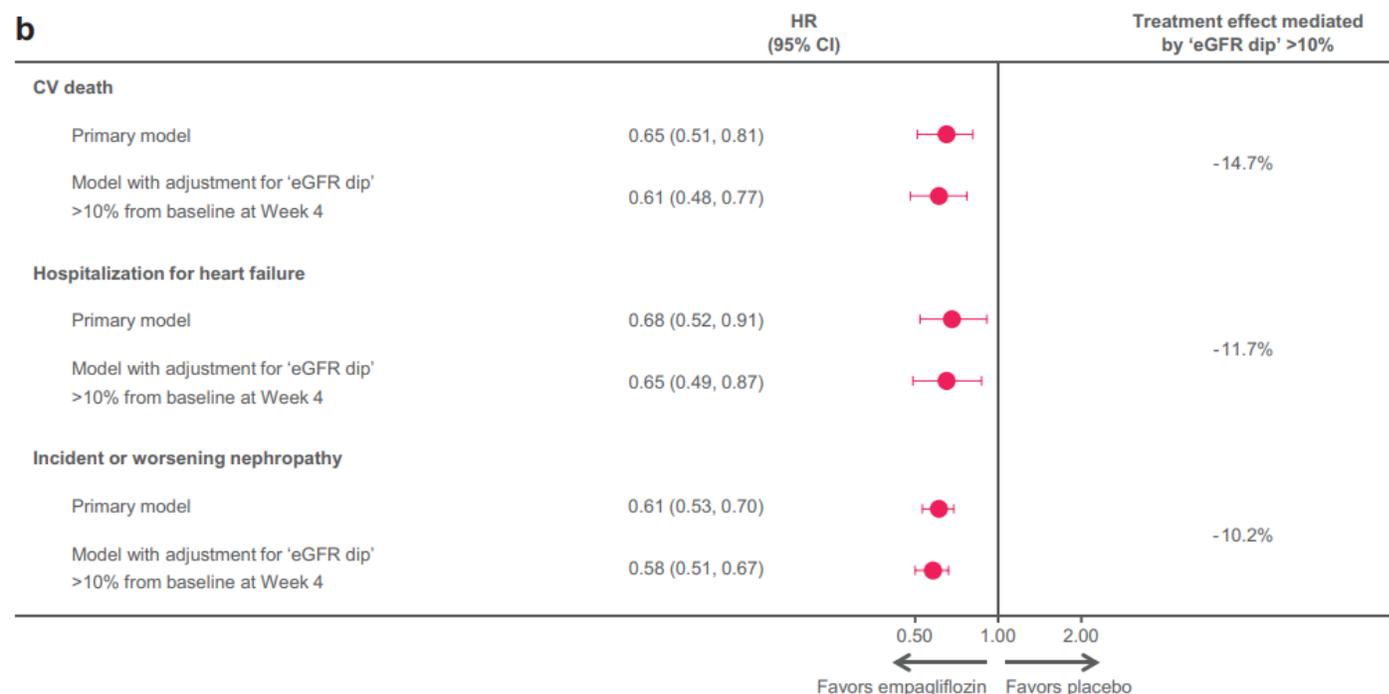
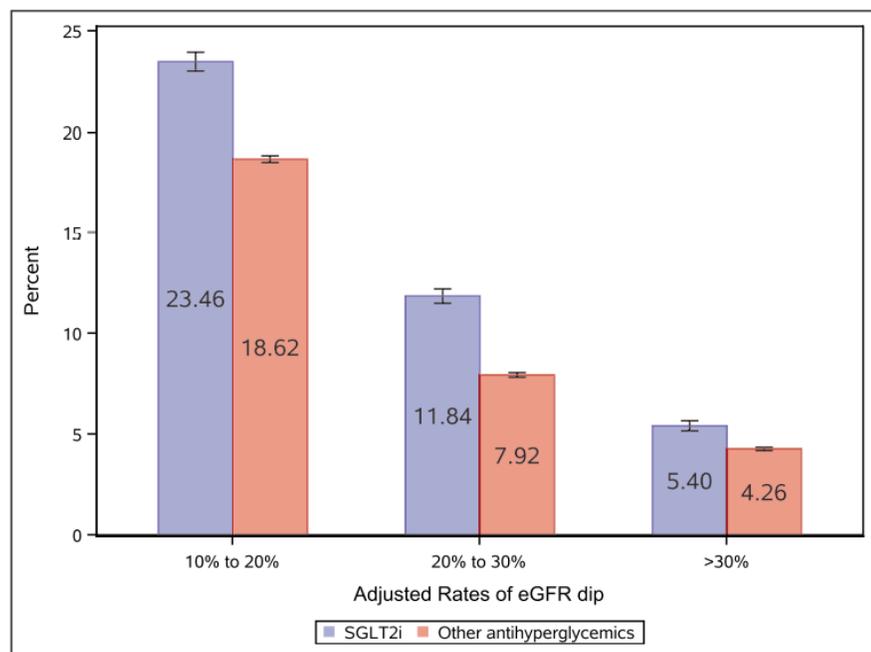
| | | | | | | | | |
|---------------|------|------|------|------|------|-----|-----|----|
| Placebo | 1792 | 1765 | 1683 | 1500 | 1146 | 745 | 343 | 76 |
| Empagliflozin | 1799 | 1782 | 1720 | 1554 | 1166 | 753 | 356 | 80 |



Jhund P and McMurray J. Circulation 2021;143:298–309

Packer et al. NEJM 383 (2020): 1414-1424

¿Qué podemos esperar al iniciar un ISGLT2? Efecto protector renal sin más eventos con dip <30%



Xie et al. JAm Heart Assoc. 2021;10:e020237

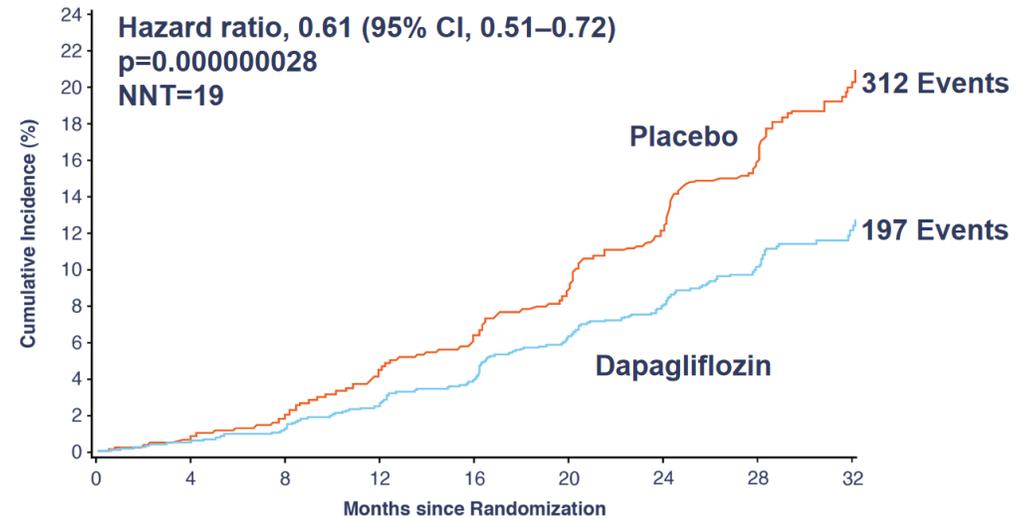
Krasus et al. Kidney International (2021) 99, 750–762

¿Qué podemos esperar al iniciar un ISGLT2? Beneficio en ERC: Retrasar progresión

DAPA-CKD
4304 pacientes
FG 25-75 ml/min 1.73
293 vs 331 con FG<30
67% DM
ACR 200-5000 g

C
DIA
eG
and U
ESK
S-cre
Rep

**Primary outcome:
Sustained $\geq 50\%$ eGFR decline, ESKD, renal or CV death**



| No. at Risk | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 |
|---------------|------|------|------|------|------|------|------|-----|-----|
| Dapagliflozin | 2152 | 2001 | 1955 | 1898 | 1841 | 1701 | 1288 | 831 | 309 |
| Placebo | 2152 | 1993 | 1936 | 1858 | 1791 | 1664 | 1232 | 774 | 270 |

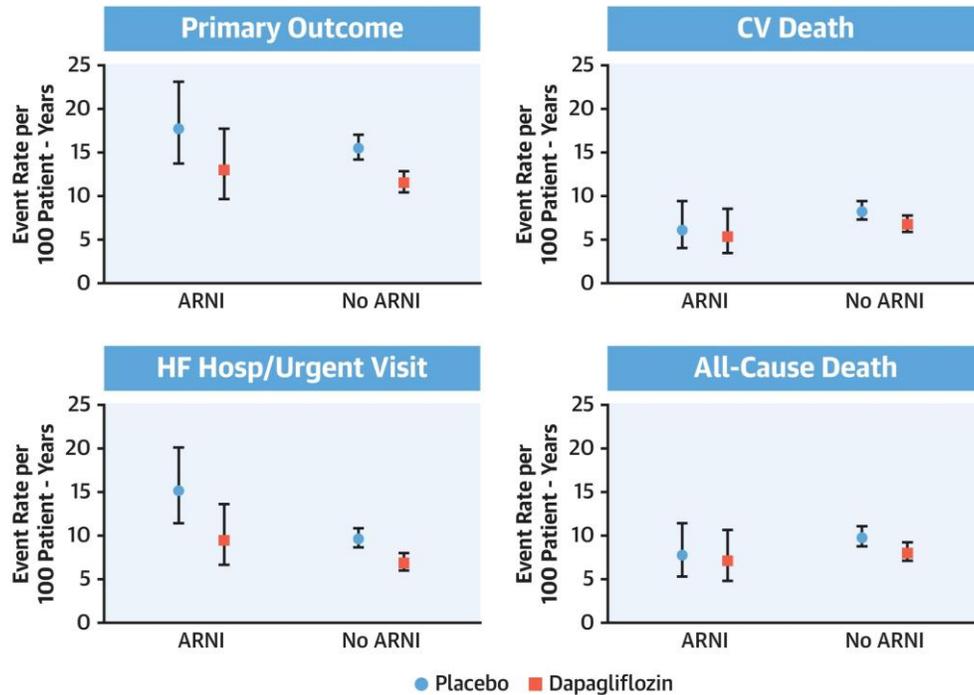
Heerspink HJL, et al. Presented at ESC 2020.



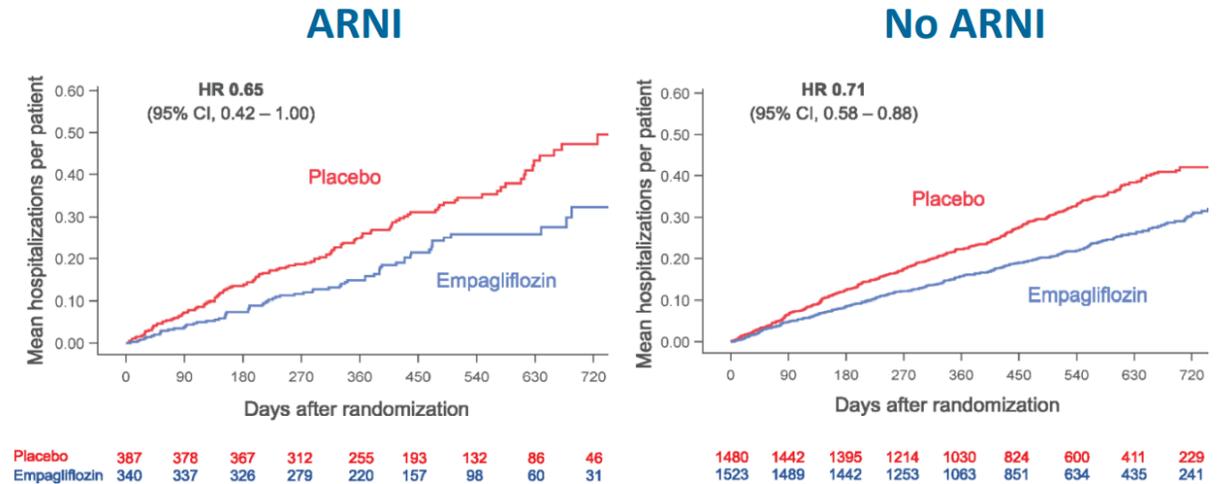
¿Qué podemos esperar al iniciar un ISGLT2?

6. Beneficio independiente del resto de terapias

CENTRAL ILLUSTRATION: Event Rates in Patients Taking and Not Taking Sacubitril/Valsartan at Baseline in Both Placebo and Dapagliflozin Groups



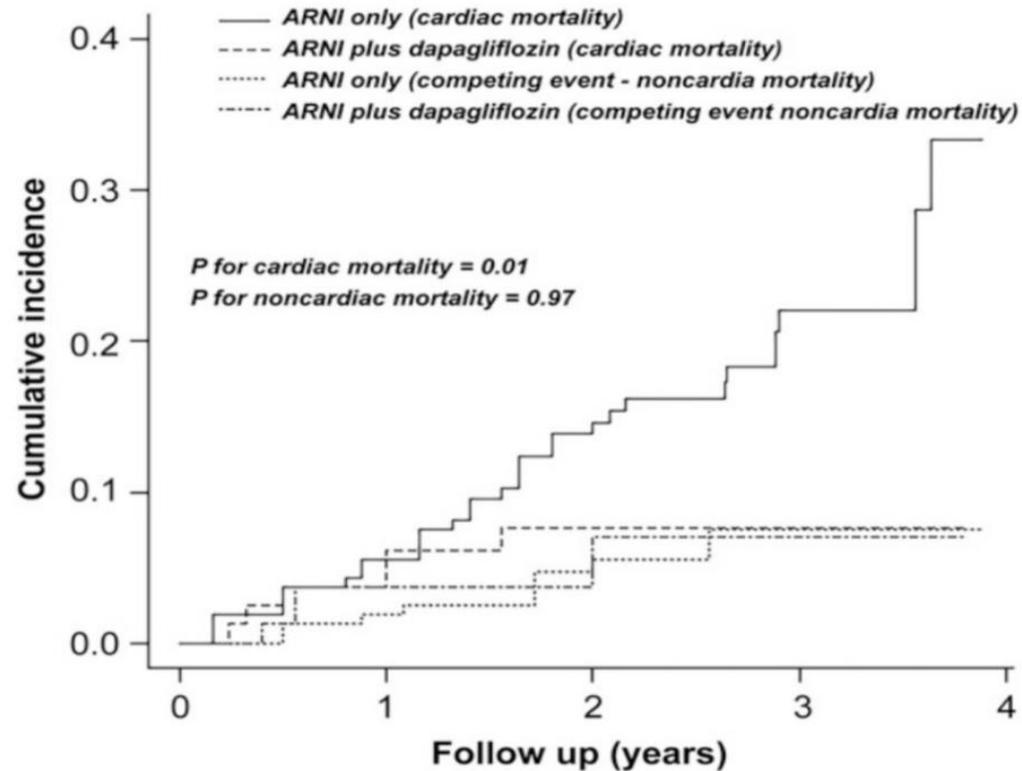
Solomon, S.D. et al. J Am Coll Cardiol HF. 2020;8(10):811-8.



Interaction p-value = 0.72

Packer et al. Eur Heart J 2021;42:671-680

¿Qué podemos esperar al iniciar un ISGLT2? Beneficio añadido al sacubitrilo/valsartan

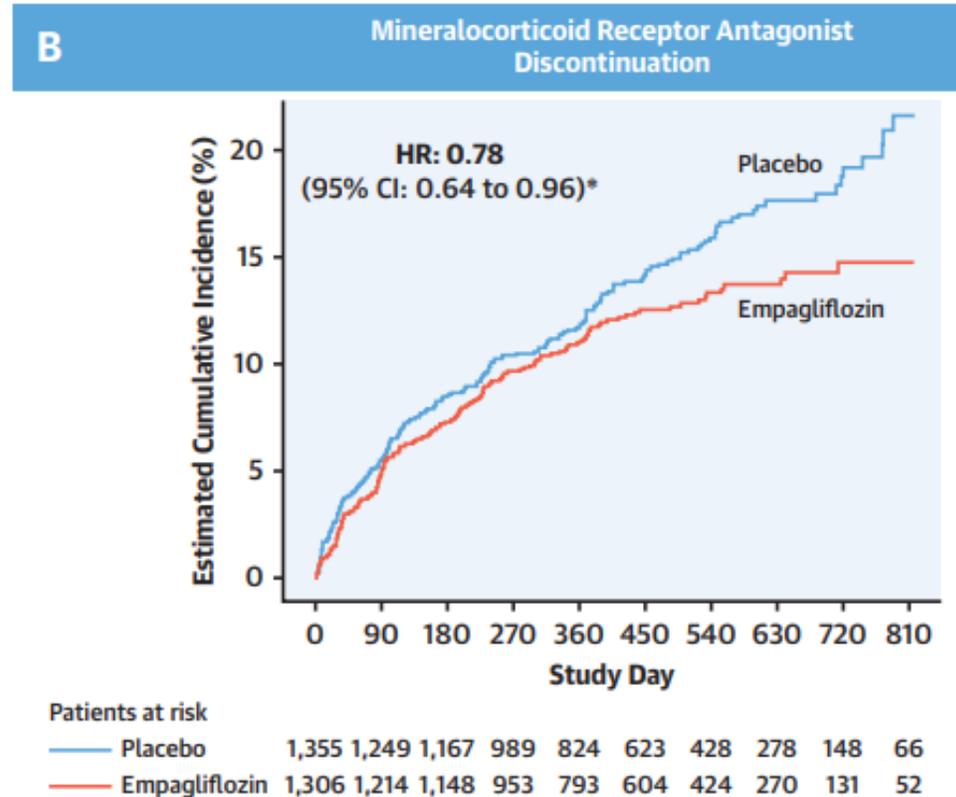


Karabulut et al. Angiology. 2021 Sep Vol 0. 1-7

| | Number at risk | | | | | |
|---|----------------|-----|-----|----|---|--|
| | 0 | 1 | 2 | 3 | 4 | |
| 0 | 163 | 148 | 105 | 52 | 0 | |
| 1 | 81 | 75 | 54 | 36 | 0 | |

¿Qué podemos esperar al iniciar un ISGLT2?

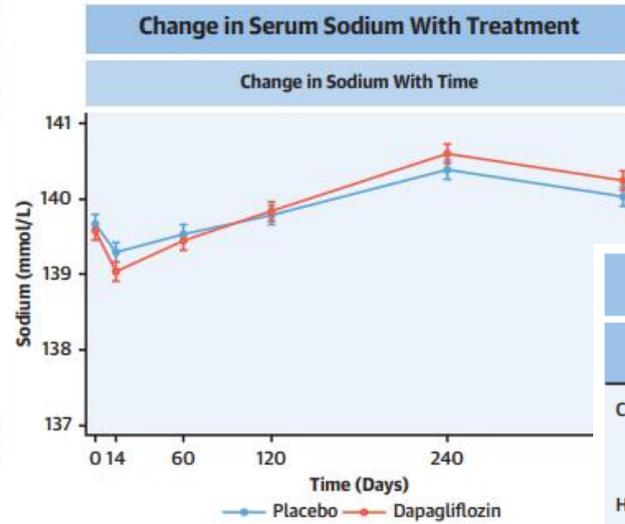
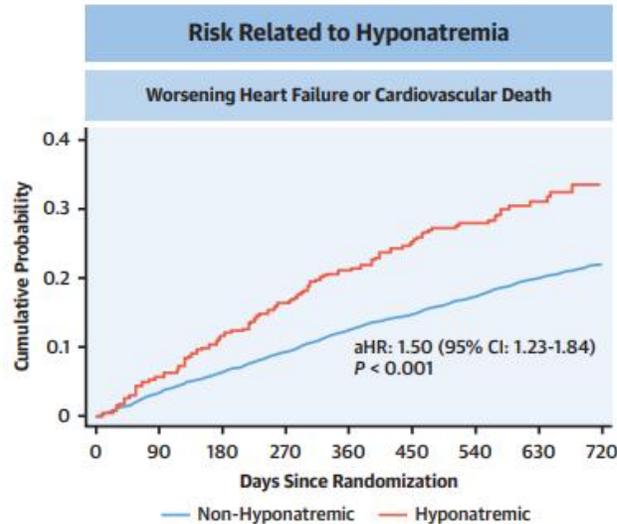
7. Perfil beneficioso ante hiperpotasemia



Ferreira, J.P. et al. J Am Coll Cardiol. 2021;77(11):1397-407.

¿Qué podemos esperar al iniciar un ISGLT2?

8. Beneficio independiente del estado del Na



| Effects of Dapagliflozin According to Baseline Sodium Level | | | | |
|---|------------------|------------------|------------------|---------------------|
| Outcomes | Dapagliflozin | Placebo | HR (95% CI) | Interaction P Value |
| CV Death or HF Hospitalization or Urgent HF Visit | | | | |
| Overall | 386/2,371 (16.3) | 501/2,369 (21.1) | 0.74 (0.65-0.85) | 0.54 |
| Na ⁺ ≤135 mmol/L | 54/205 (26.3) | 61/193 (31.6) | 0.83 (0.57-1.19) | |
| Na ⁺ >135 mmol/L | 332/2,166 (15.3) | 440/2,176 (20.2) | 0.73 (0.63-0.84) | |
| HF Hospitalization or Urgent HF Visit | | | | |
| Overall | 237/2,371 (10.0) | 325/2,369 (13.7) | 0.70 (0.59-0.83) | 0.95 |
| Na ⁺ ≤135 mmol/L | 29/205 (14.2) | 39/193 (20.2) | 0.69 (0.43-1.11) | |
| Na ⁺ >135 mmol/L | 208/2,166 (9.6) | 286/2,176 (13.1) | 0.70 (0.59-0.84) | |
| Cardiovascular Death | | | | |
| Overall | 227/2,371 (9.6) | 273/2,369 (11.5) | 0.82 (0.69-0.98) | 0.73 |
| Na ⁺ ≤135 mmol/L | 35/205 (17.1) | 38/193 (19.7) | 0.89 (0.56-1.40) | |
| Na ⁺ >135 mmol/L | 192/2,166 (8.9) | 235/2,176 (10.8) | 0.81 (0.67-0.98) | |
| All-Cause Death | | | | |
| Overall | 276/2,371 (11.6) | 329/2,369 (13.9) | 0.83 (0.71-0.97) | 0.96 |
| Na ⁺ ≤135 mmol/L | 41/205 (20.0) | 47/193 (24.4) | 0.85 (0.56-1.29) | |
| Na ⁺ >135 mmol/L | 235/2,166 (10.9) | 282/2,176 (13.0) | 0.83 (0.70-0.98) | |

Yeoh S et al. J Am Coll Cardiol HF 2022;10:306–318

¿Qué podemos esperar al iniciar un ISGLT2?

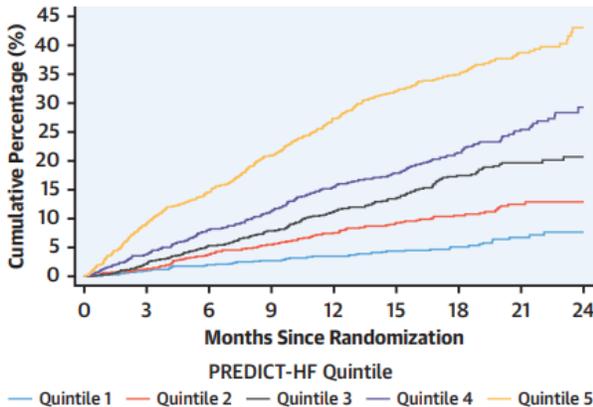
9. Beneficio independiente del riesgo de eventos

2 DAPA-HF Patients With a 2-Year History of HF and 1 Previous HF Hospitalization

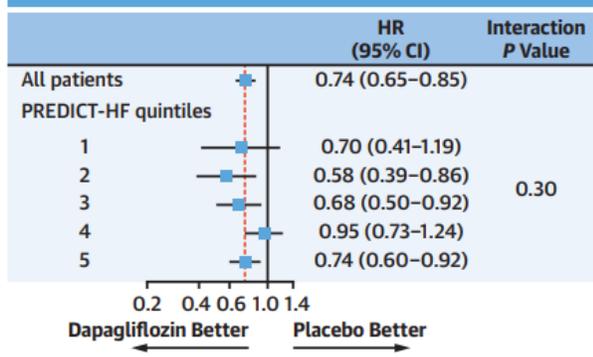


| | | |
|--|-------------|-------------|
| Age | 71y | 68y |
| LVEF | 26% | 24% |
| NYHA | II | II |
| NT-proBNP | 1,500 pg/mL | 1,600 pg/mL |
| T2DM | - | + |
| Beta-blocker | + | + |
| ARNI | + | - |
| PREDICT-HF risk of CV death at 2 years | 2.6% | 7.3% |
| PREDICT-HF risk of HFH/CV death at 2 years | 6.8% | 17.7% |

DAPA-HF Enrolled Patients Across a Wide Spectrum of Baseline Risk of CV Death or Worsening HF Events



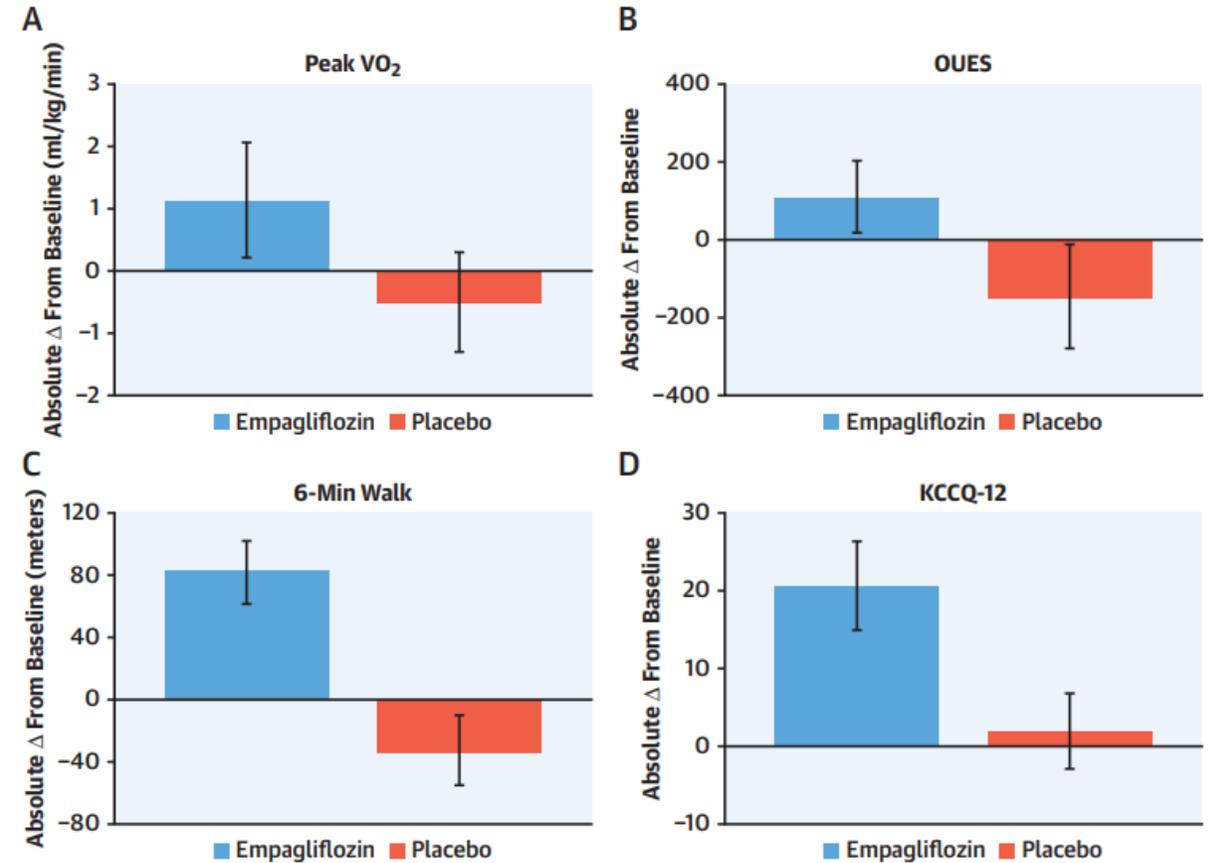
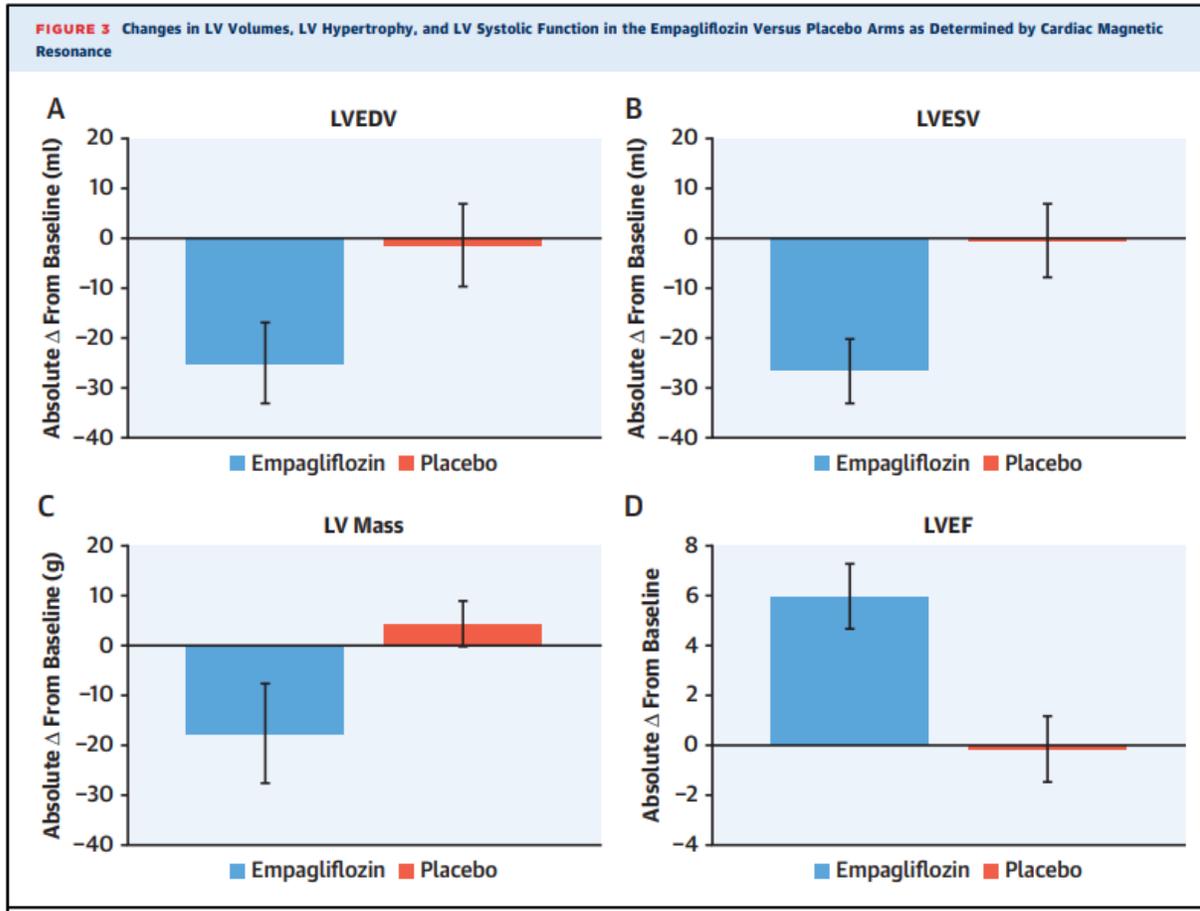
Dapagliflozin, Compared With Placebo, Was Effective at Reducing the Risk of CV Death or Worsening HF Events Across the Spectrum of Baseline Risk in DAPA-HF



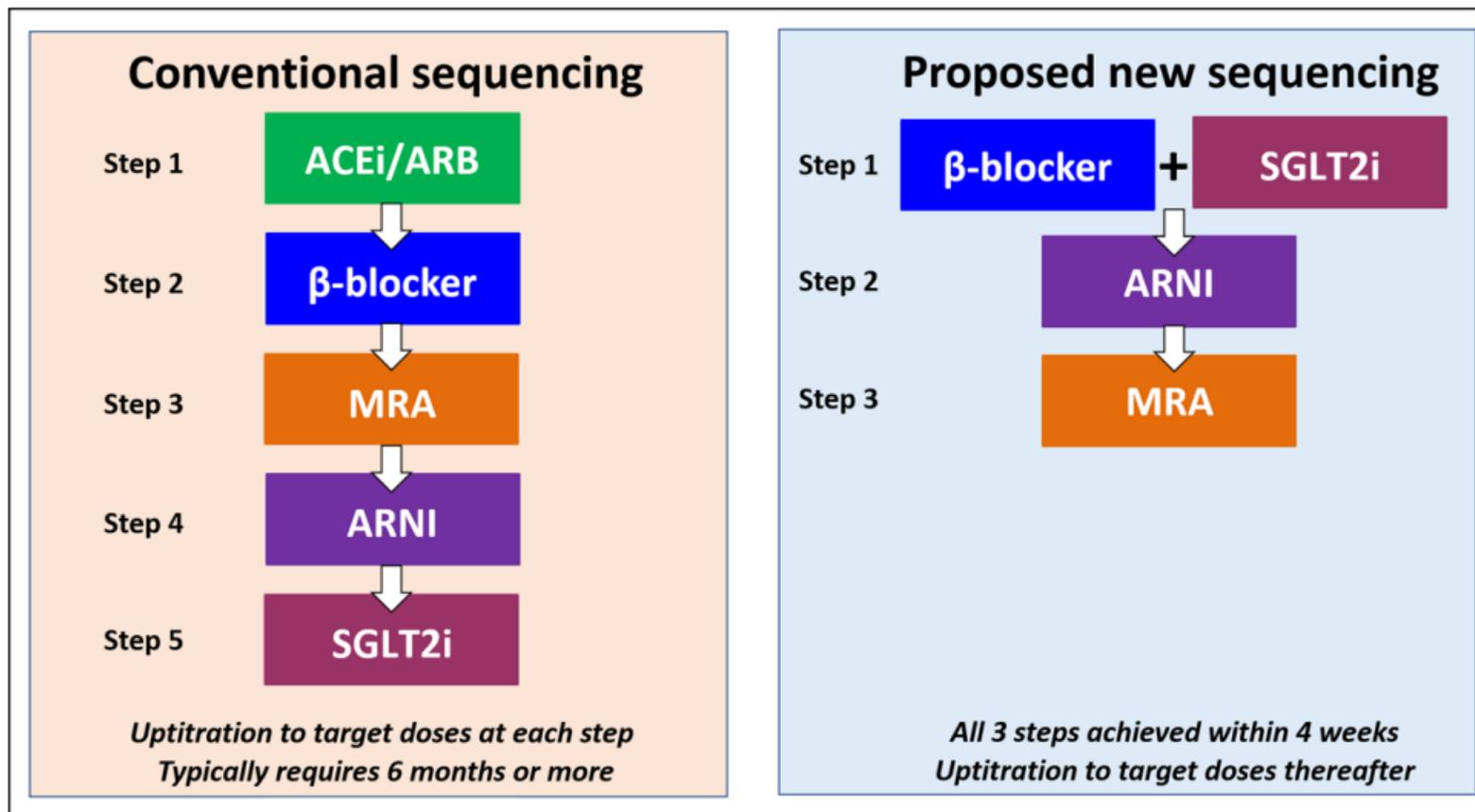
Docherty, K.F. et al. J Am Coll Cardiol HF. 2022;10(2):104–118

¿Qué podemos esperar al iniciar un ISGLT2?

10. Remodelado



¿Cuándo iniciar un ISGLT2? Inicio precoz

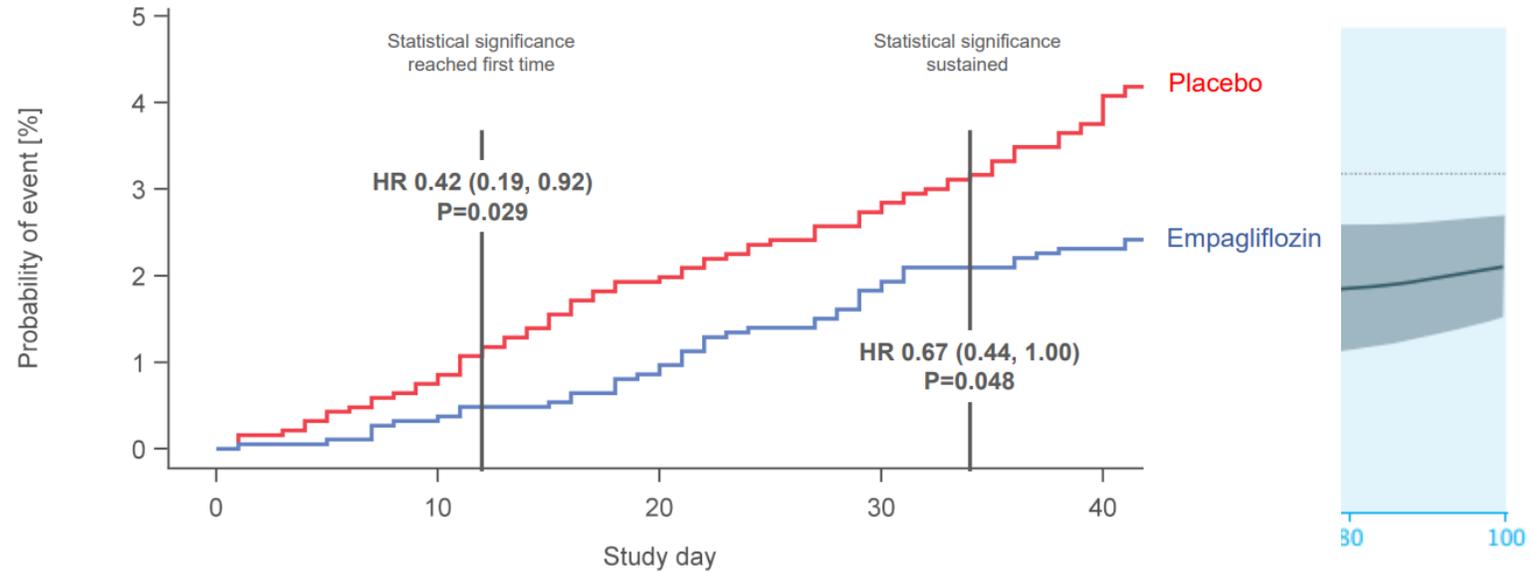
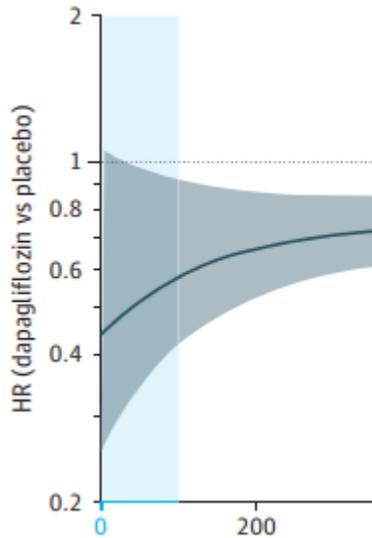


McMurray and Packer. *Circulation*. 2021;143:875–877

Inicio precoz: Beneficio precoz

Time to all-cause mortality, heart failure hospitalization or emergent/urgent care visit for worsening heart failure requiring IV therapy

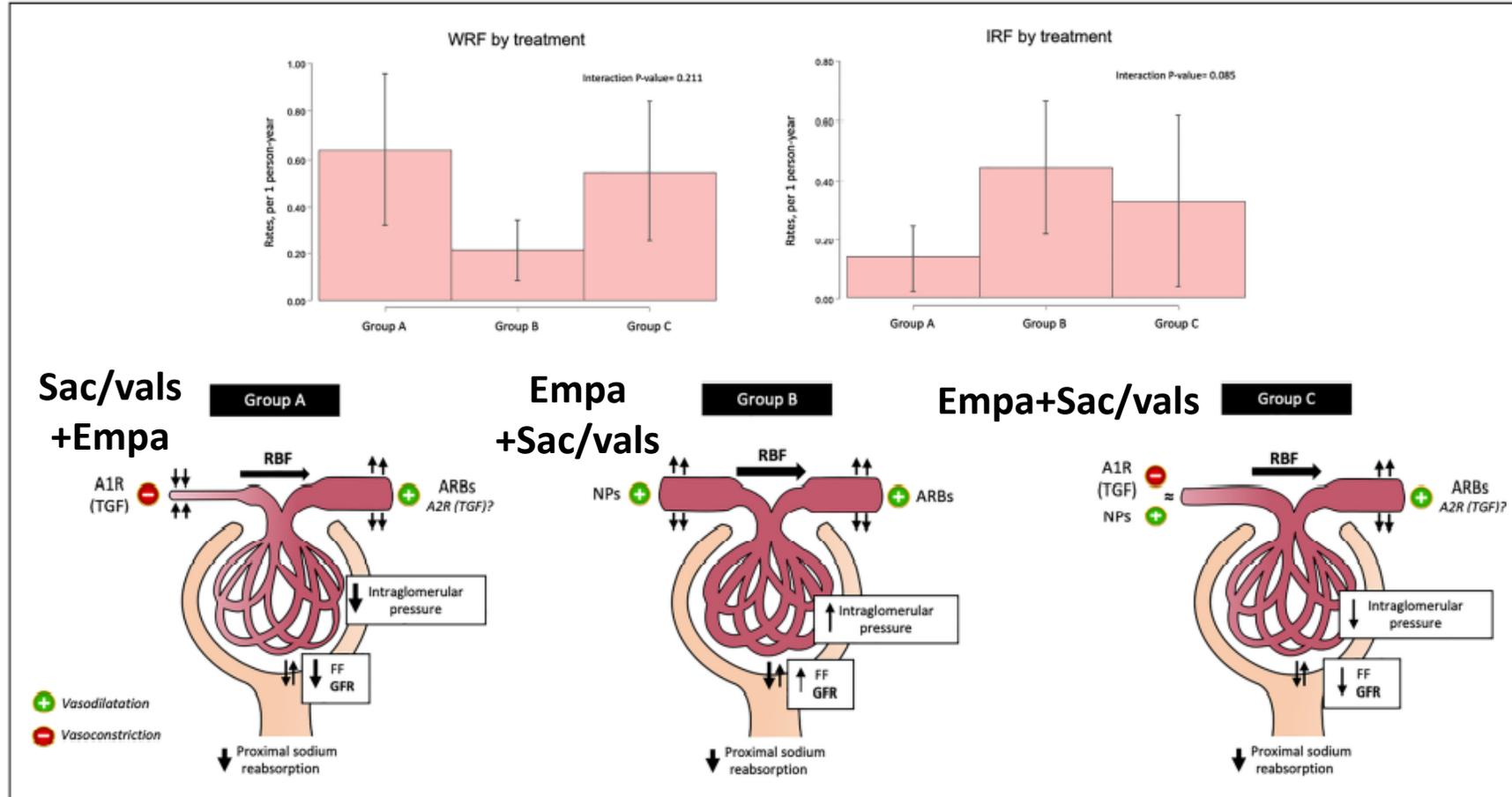
A Worsening heart failure or car



| | Patients at risk | | | | |
|---------------|------------------|------|------|------|------|
| | 0 | 10 | 20 | 30 | 40 |
| Placebo | 1867 | 1852 | 1830 | 1811 | 1792 |
| Empagliflozin | 1863 | 1855 | 1845 | 1826 | 1815 |

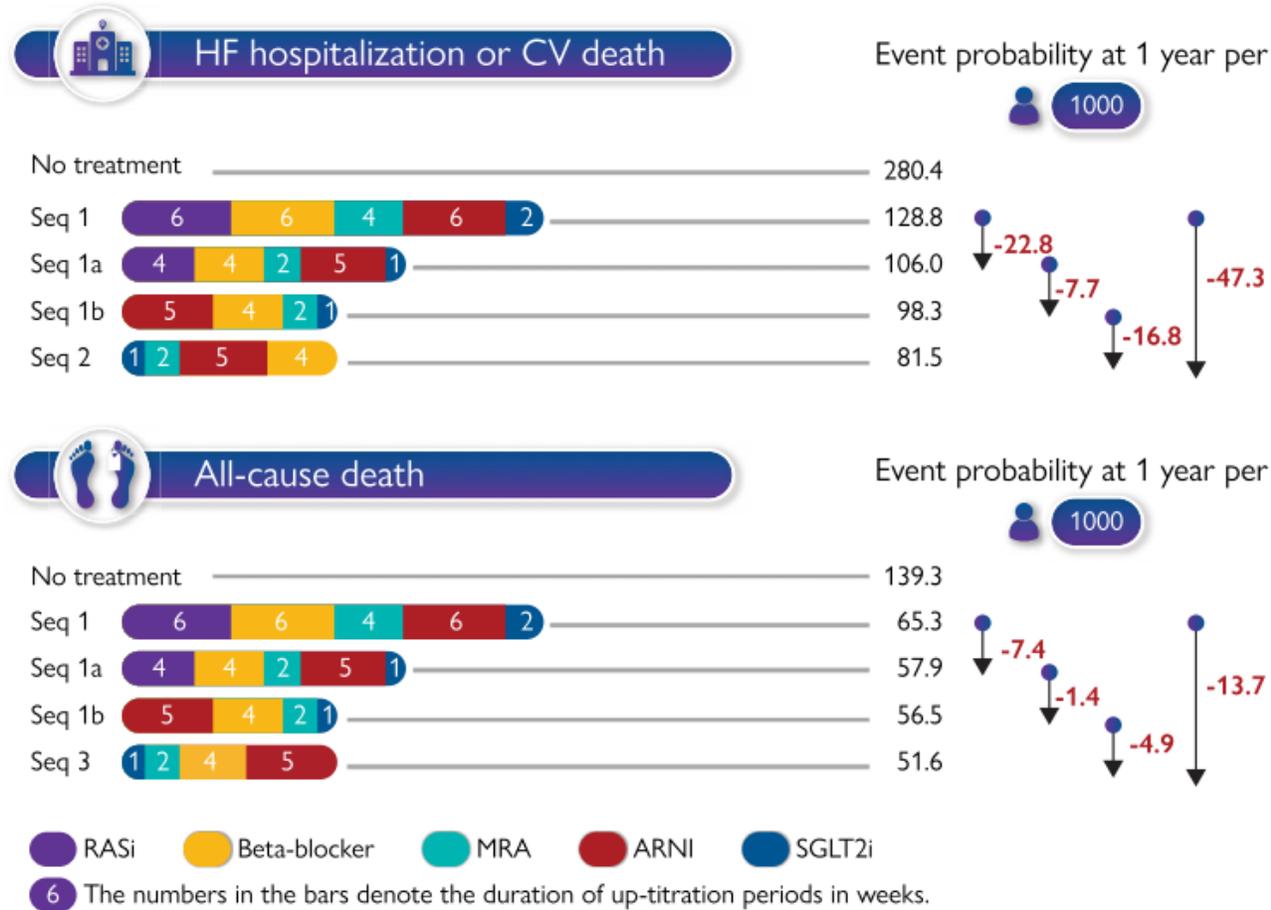
Berg et al. JAMA Cardiol. 2021;6(5):499-507

Inicio precoz: Efecto en la HD glomerular



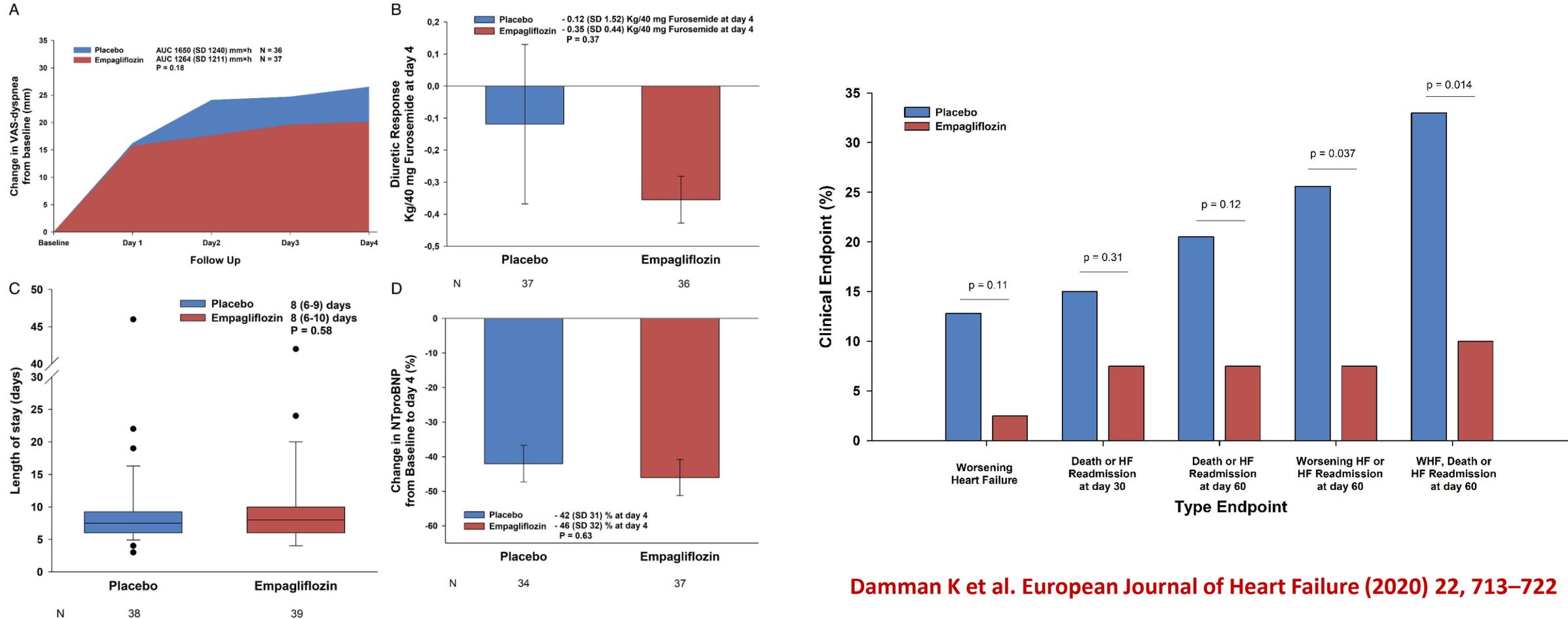
Esriella et al. ESC Heart Failure 2020; 7: 3792–3800

Inicio precoz y secuencia rápida: mayor beneficio



Shen L et al. European Heart Journal (2022) 00, 1–15

Evidencia IC Aguda: EMPA RESPONSE HF

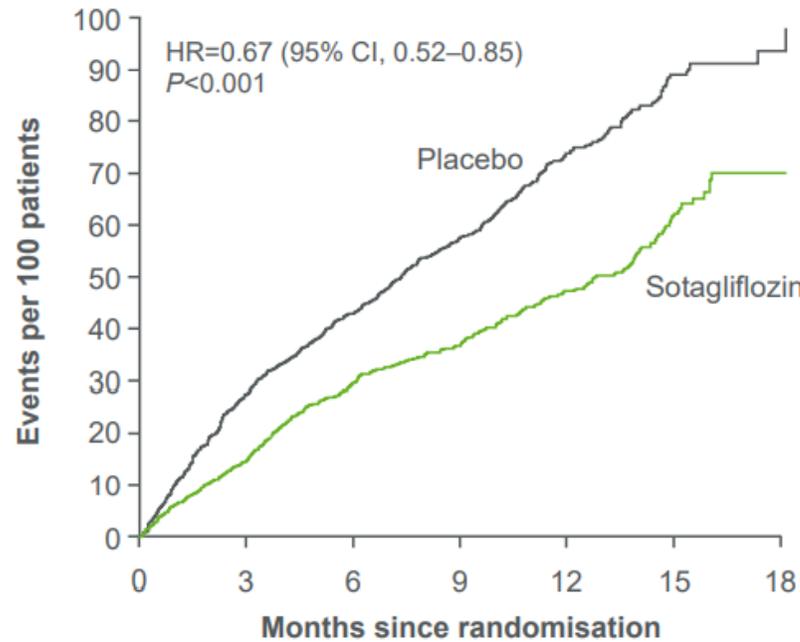


Damman K et al. European Journal of Heart Failure (2020) 22, 713–722

Evidencia IC Aguda: SOLOIST

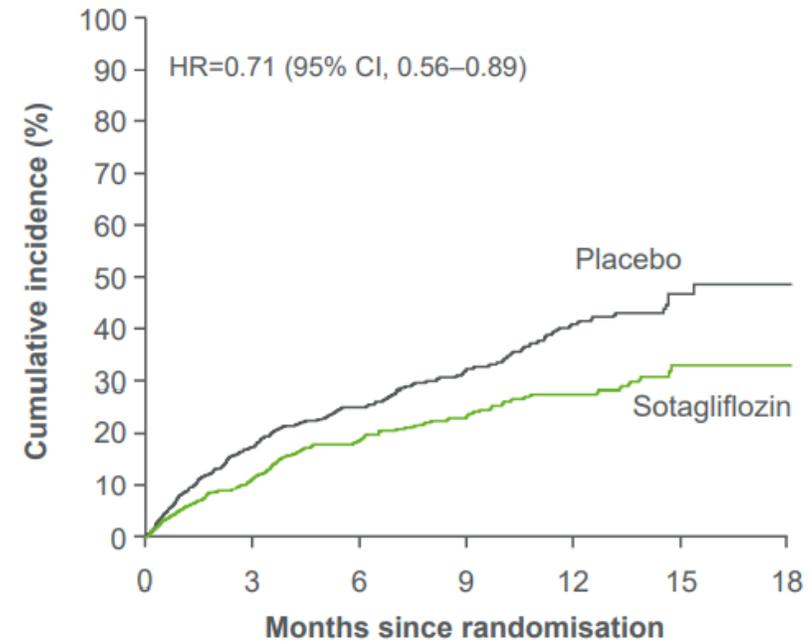
Primary endpoint

Total number of CV deaths and hospitalisations and urgent visits for HF (first and subsequent events)



| No. at risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 |
|---------------|-----|-----|-----|-----|-----|-----|----|
| Placebo | 614 | 524 | 416 | 305 | 195 | 100 | 25 |
| Sotagliflozin | 608 | 540 | 430 | 310 | 209 | 97 | 29 |

First occurrence of either CV death or HFH



| No. at risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 |
|---------------|-----|-----|-----|-----|-----|----|----|
| Placebo | 614 | 461 | 345 | 241 | 144 | 66 | 14 |
| Sotagliflozin | 608 | 498 | 374 | 266 | 171 | 76 | 25 |

Bhatt et al. N Engl J Med 2021; 384:117-128

Evidencia IC Aguda: EMPULSE Trial



EMPULSE

24h-5 d

> 100mmHg (6h)

No aumento iv 6h

No 24h

ICr/ICm/ICp



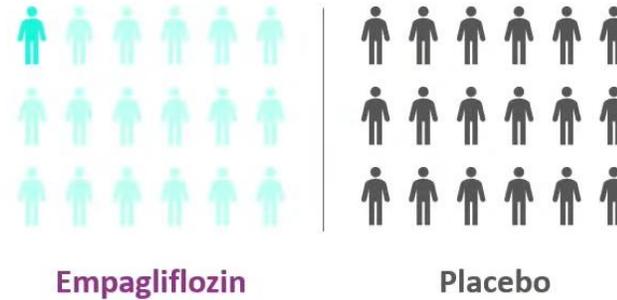
NT-proBNP ≥ 1600 pg/mL o BNP ≥ 400 o 72h previa

NT-proBNP ≥ 2400 pg/mL o BNP ≥ 600 pg/mL

Criteria

- 1 Death**
If neither patient is superior based on death
- 2 Number of HFEs**
If neither patient is superior based on death or number of HFEs
- 3 Time to first HFE**
If neither patient is superior based on 1-3
- 4 KCCQ-TSS mean change from baseline after 90 days**

Pairwise comparison



Each patient in the empagliflozin group is compared against every patient in the placebo group
Total number of comparisons: 39162

Calculation

Win ratio

=

Total number of wins in the empagliflozin group

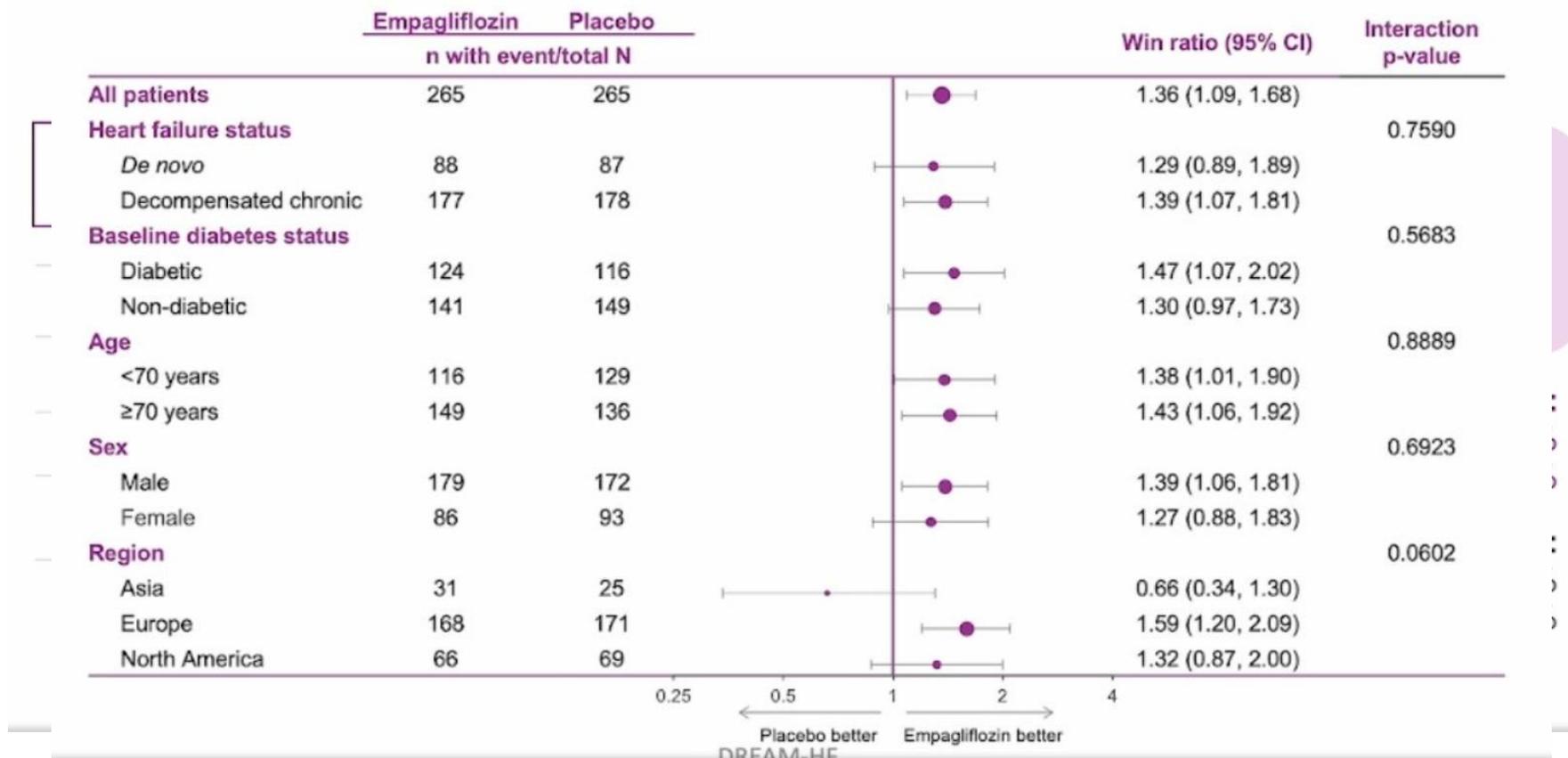
Total number of wins in the placebo group

Voors A et al. Nat Med 2022; 28(3): 568-574



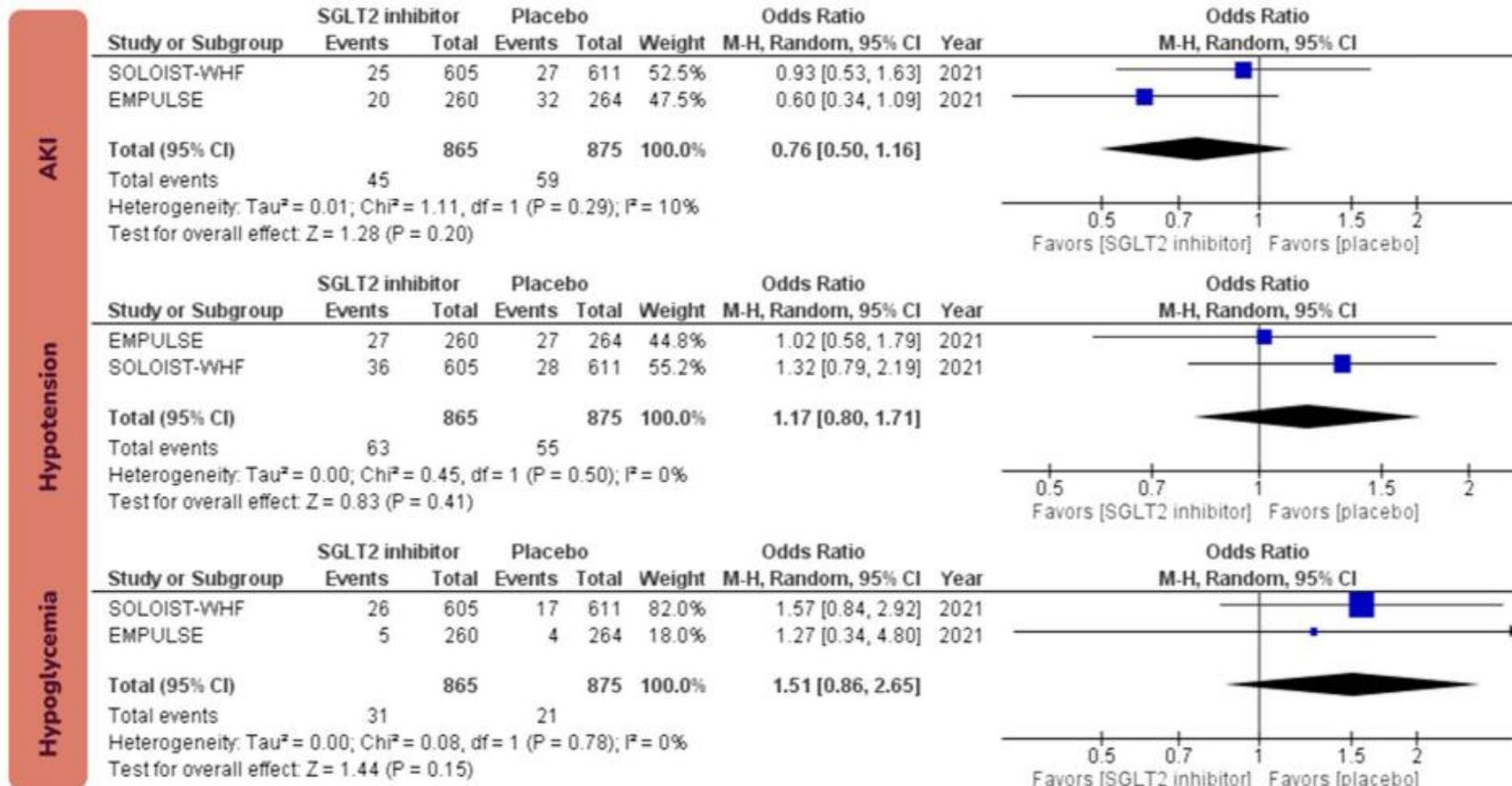
Evidencia IC Aguda: EMPULSE Trial

Primary endpoint by subgroup



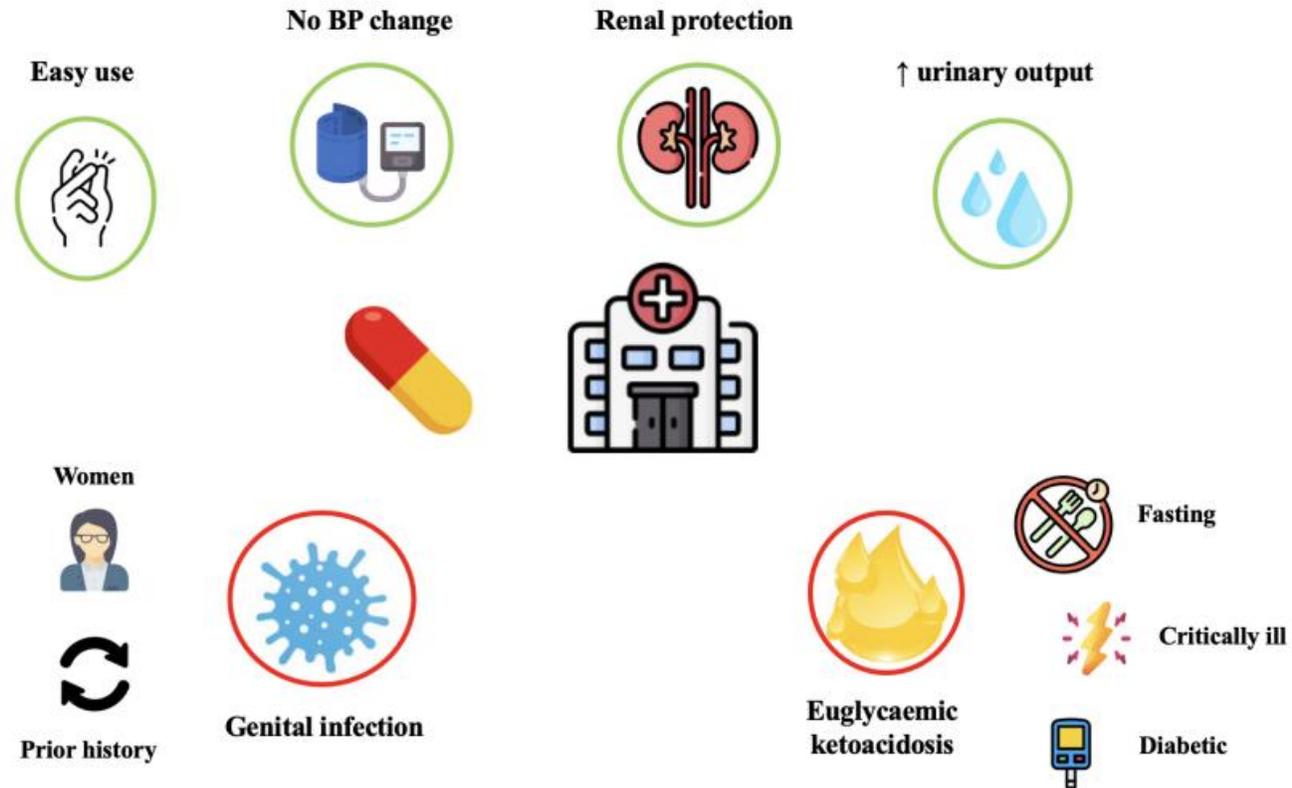
Voors A et al. Nat Med 2022; 28(3): 568–574.

Evidencia IC Aguda: ISGLT2 es Eficaz y Seguro



Salah et al. Cardiovascular Diabetology (2022) 21:20

ISGLT2: Riesgo/Beneficio en Hospitalización



Morillas H et al. Rev. Cardiovasc. Med. 2022; 23(4): 139

¿Y a nivel práctico? ¿Cómo y cuando lo inicio?

When and how initiate SGLT2 inhibitors?



Based on EMPULSE trial

- No increase in diuretic dose in prior 6 hours
- No intravenous vasodilators or inotropic agents in prior 24 hours
- Systolic blood pressure ≥ 100 mm Hg
- eGFR ≥ 20 mL/min/1.73 m²



Based on DAPA-HF and EMPEROR REDUCED trials

- Symptomatic HFrEF regardless of background therapy
- Systolic blood pressure > 100 mmHg (empagliflozin) or ≥ 95 mmHg (dapagliflozin)
- eGFR ≥ 20 mL/min/1.73 (empagliflozin) or ≥ 25 mL/min/1.73 (dapagliflozin)

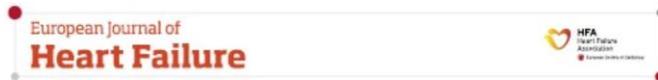
Which drug? Dapagliflozin 10 mg daily or Empagliflozin 10 mg daily

Advices. Monitor renal function at 1-2 weeks if low eGFR at baseline although initial 10-15% declines are common/expected, do not reflect acute kidney injury and therapy should be continued unless major fall in eGFR. Prevention of genital tract infection or mycosis.

Follow-up: Encourage adherence to guideline-recommended therapies. Adjust diuretic therapy based on volume status.

Tomasoni et al. European Journal of Heart Failure (2021)

¿Y a nivel práctico? ¿En algún perfil mejor?



Position Paper

Patients profiling in Heart Failure for tailoring medical therapy A consensus document of the Heart Failure Association of the European Society of Cardiology

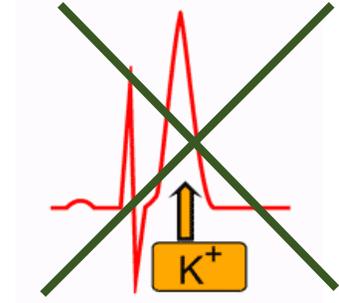
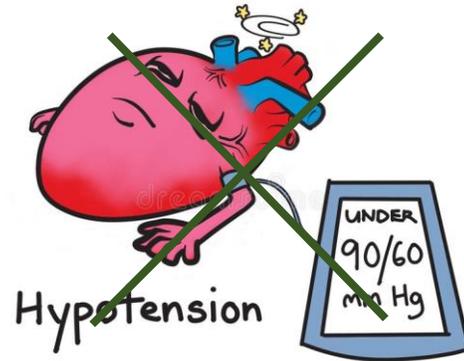
Giuseppe M.C. Rosano, Brenda Moura, Marco Metra, Johann Bauersachs, Tuvia Ben Gal ... See all authors >

First published: 01 May 2021

<https://doi.org/10.1002/ejhf.2206>



¿Por qué mi prioridad es introducir un ISGLT2 frente al resto de tratamiento?



Conclusiones

- Los ISGLT-2 que empezaron como fármacos hipoglucemiantes han cambiado su papel en la práctica clínica para convertirse en fármacos cardio-reno protectores.
- En insuficiencia cardiaca con FE reducida disminuyen la hospitalización y muerte cardiovascular, mejoran en la calidad de vida, destacando su efecto beneficioso a nivel renal y favoreciendo el remodelado.
- Su seguridad, tolerabilidad, buen perfil hemodinámico y su precoz beneficio, los posiciona en 1º línea de tratamiento, sin penalización del resto de tratamiento neurohormonal.
- Existe evidencia de su beneficio y seguridad cuando se emplea de forma precoz tanto en el escenario de la hospitalización como en el marco ambulatorio.
- Ante un paciente con Insuficiencia cardiaca debemos pensar ¿Por qué no tiene pautado un ISGLT2?