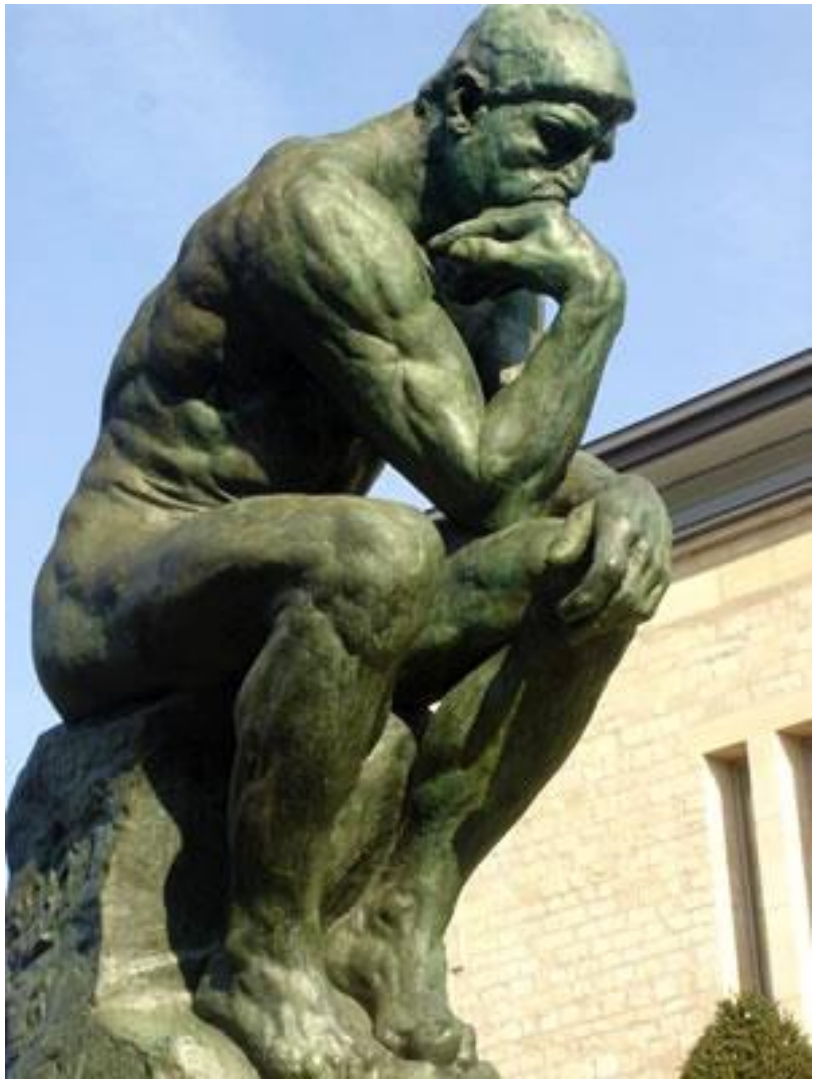
7th Advances in Heart Failure 2024
10 e 11 de Outubro
FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

# erapêuticas independentes da Fração de Ejeção

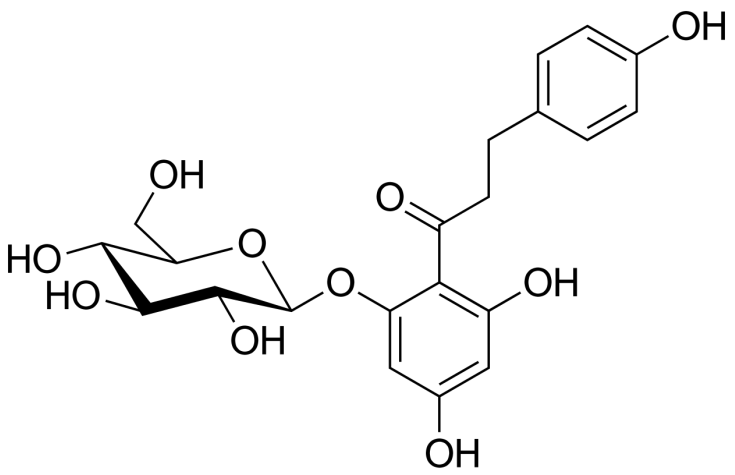
## Inibidores do SGLT-2

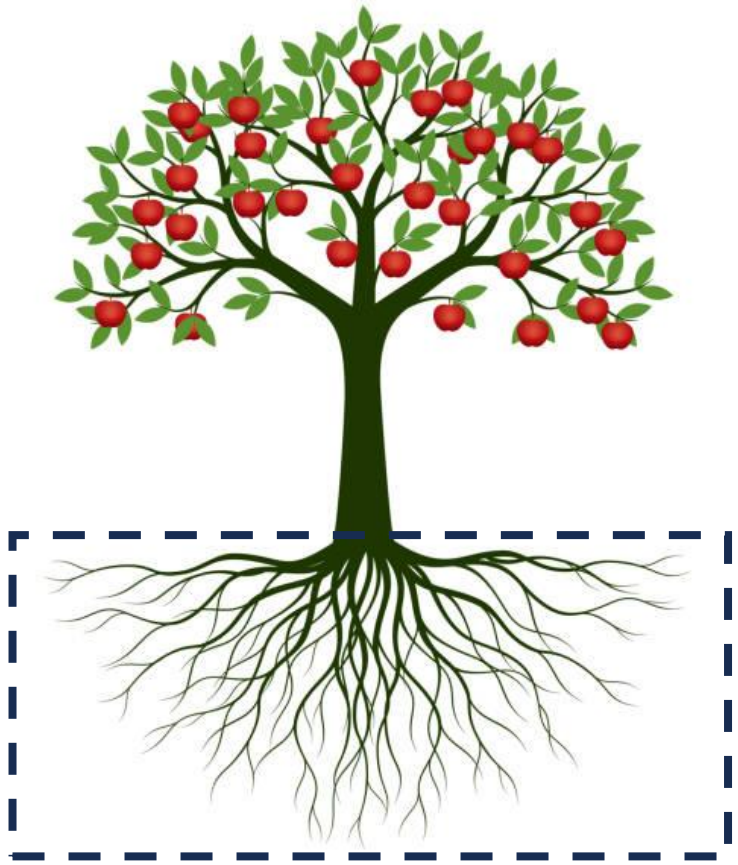
Francisco Vasques-Nóvoa



?

# Florizina



## Casca + Raiz

Φλοιός (*floiós*) + ρίζα (*riza*)

**Flo + Rizina**

**De Koninck LG**: Über das Phloridzin (Phlorrhizin) Annalen der Pharmacie. Heidelberg, **1835**, vol 15, pp 75–77.

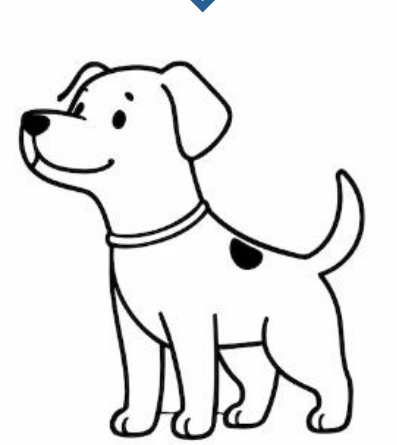
**Prof. Josef von Mering**
*1849-1908*

| **Diabetes** | | **“Phlorizin-Diabetes”** *20g Florizina* |
|---|---|---|
| Glicosuria | = | Glicosuria |
| Hiperglicemia | ≠ | Hipoglicemia<br>Cetose |

**Dr. Oskar Minkowski**

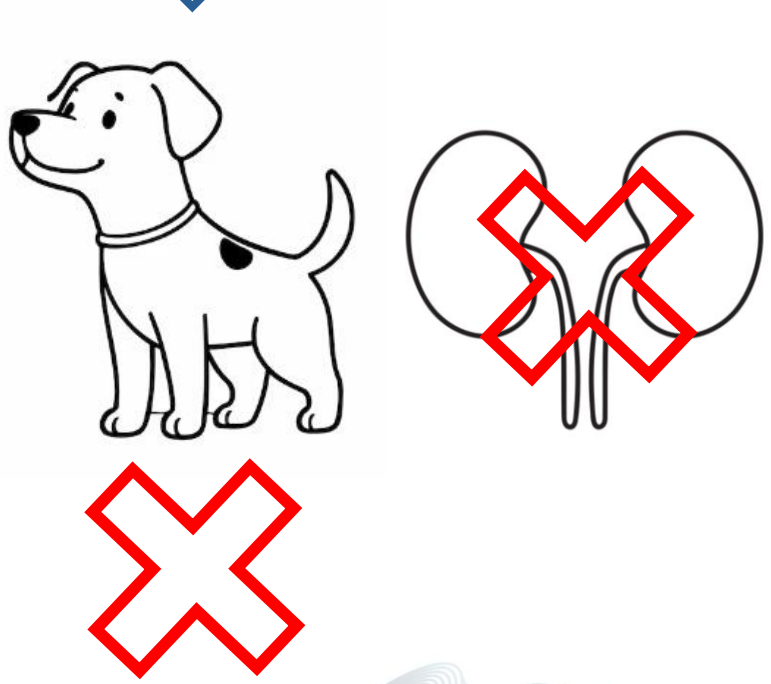
*1858-1931*

**Florizina**



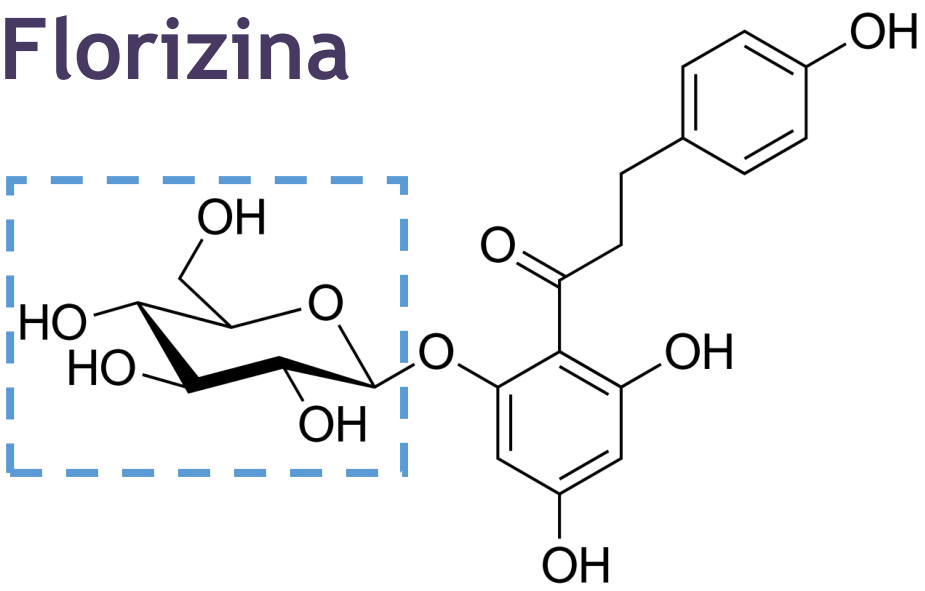
**Hipoglicemia**
**Glicosuria**

**Florizina**

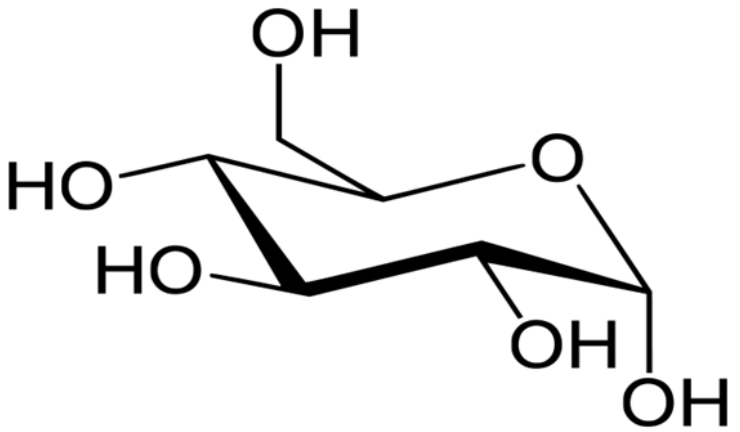


**Hipoglicemia**
**Glicosuria**

## Florizina



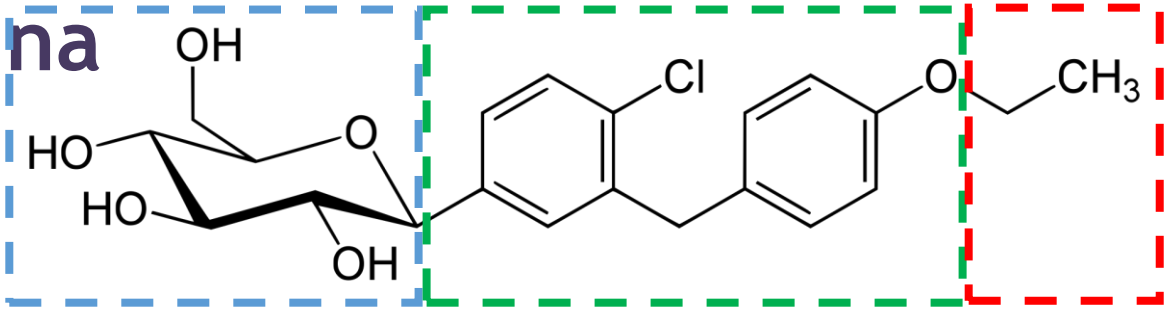

## Glicose




## Dapagliflozina

AstraZeneca

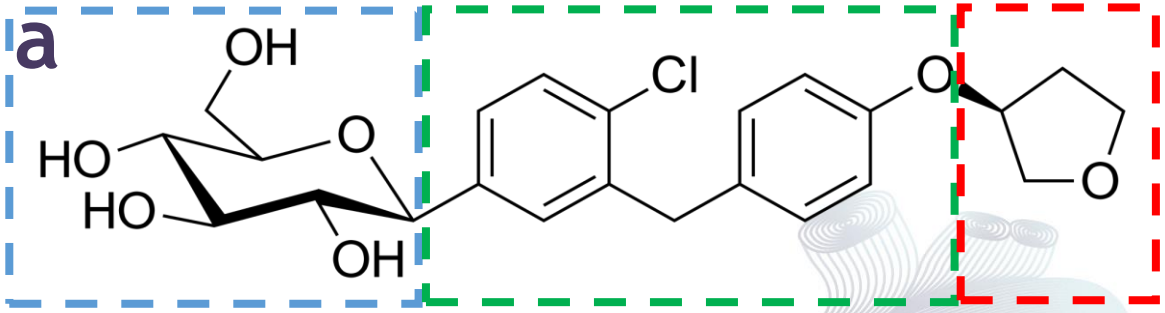
Bristol Myers Squibb®




## Empagliflozina

Lilly

Boehringer Ingelheim



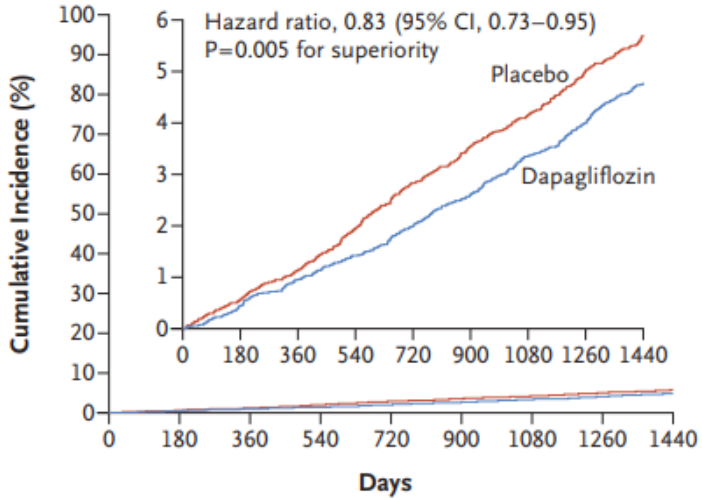
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

**A Cardiovascular Death or Hospitalization for Heart Failure**




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 8578 | 8485 | 8387 | 8259 | 8127 | 8003 | 7880 | 7367 | 5362 |
| Dapagliflozin | 8582 | 8517 | 8415 | 8322 | 8224 | 8110 | 7970 | 7497 | 5445 |

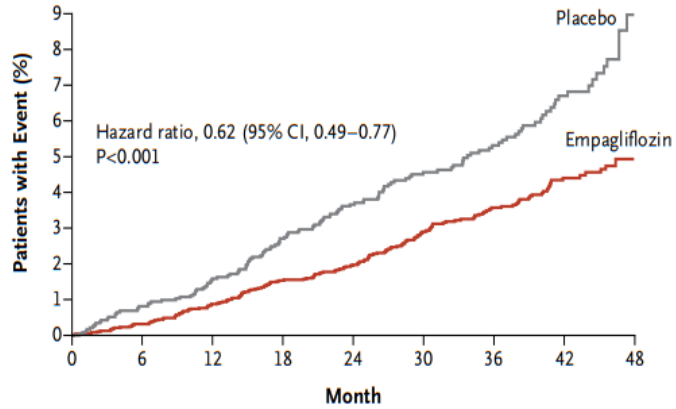
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

**B Death from Cardiovascular Causes**




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4687 | 4651 | 4608 | 4556 | 4128 | 3079 | 2617 | 1722 | 414 |
| Placebo | 2333 | 2303 | 2280 | 2243 | 2012 | 1503 | 1281 | 825 | 177 |

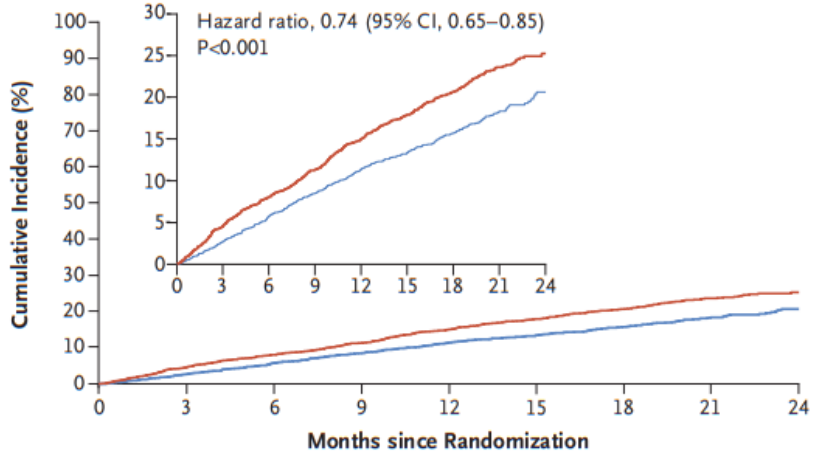
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

# 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. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, 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*

**A Primary Outcome**




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2371 | 2258 | 2163 | 2075 | 1917 | 1478 | 1096 | 593 | 210 |
| Dapagliflozin | 2373 | 2305 | 2221 | 2147 | 2002 | 1560 | 1146 | 612 | 210 |

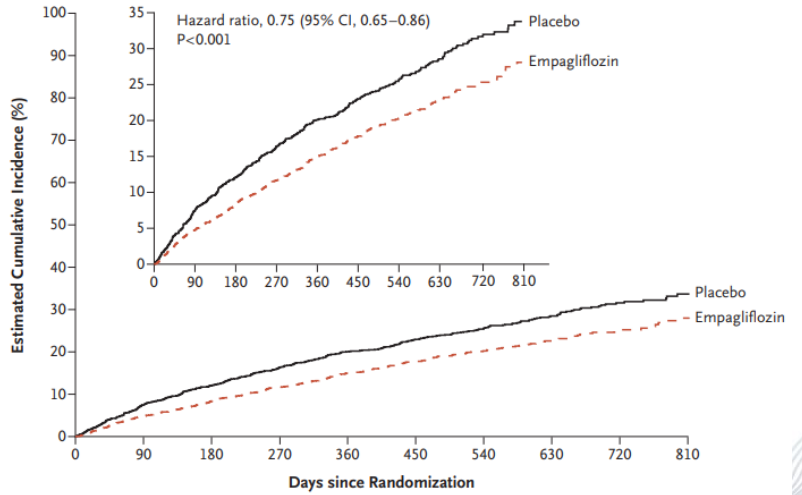
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

# 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*

**A Primary Outcome**



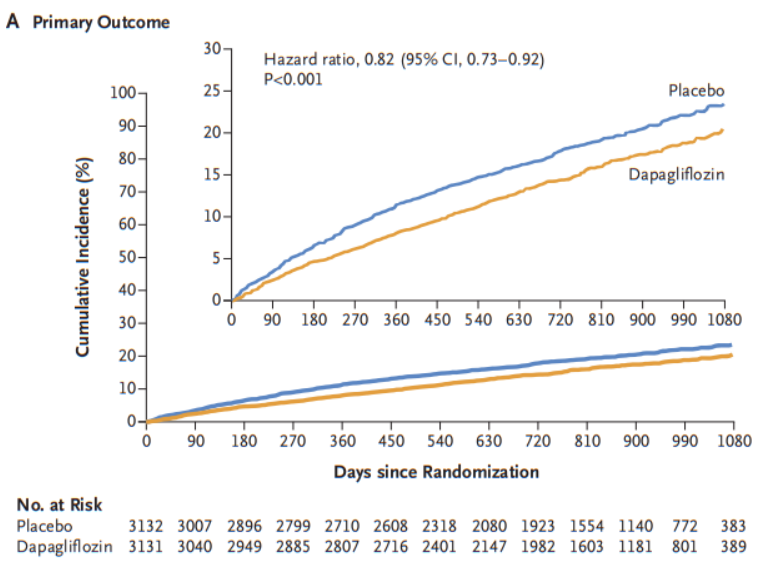

**No. at Risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 1867 | 1715 | 1612 | 1345 | 1108 | 854 | 611 | 410 | 224 | 109 |
| Empagliflozin | 1863 | 1763 | 1677 | 1424 | 1172 | 909 | 645 | 423 | 231 | 101 |

ORIGINAL ARTICLE

# Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

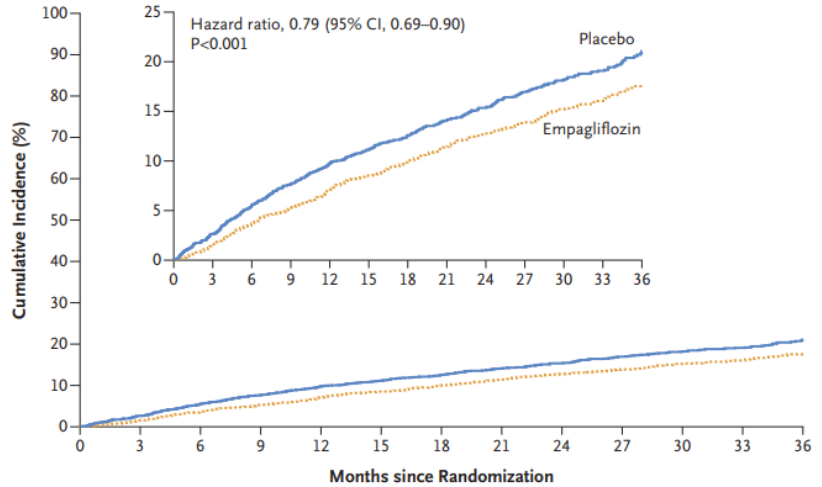
S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*




The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

# Empagliflozin in Heart Failure with a Preserved Ejection Fraction

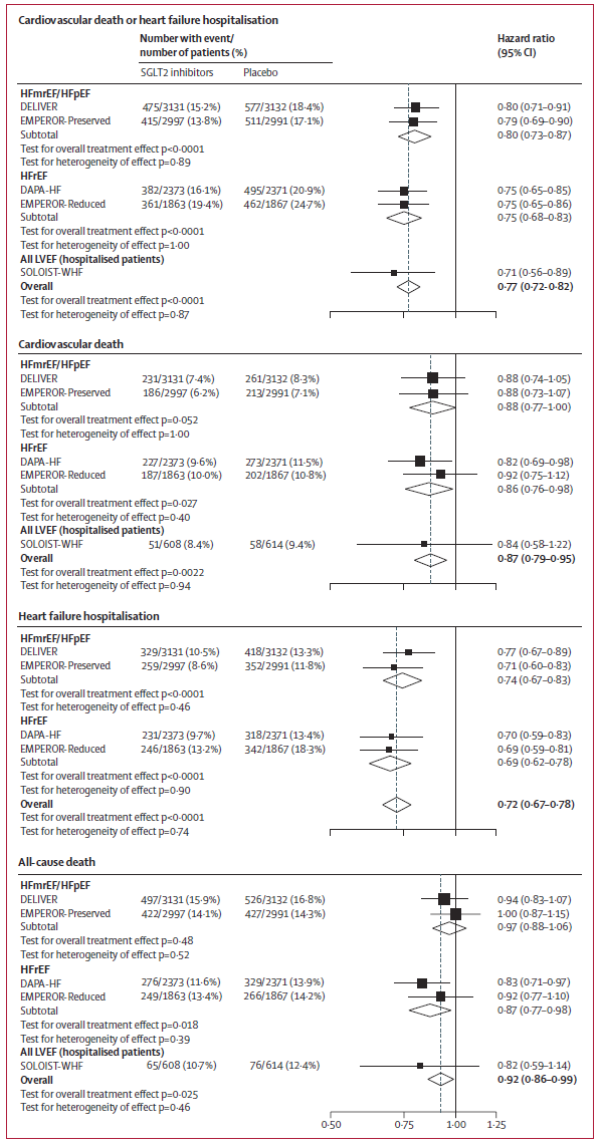
S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

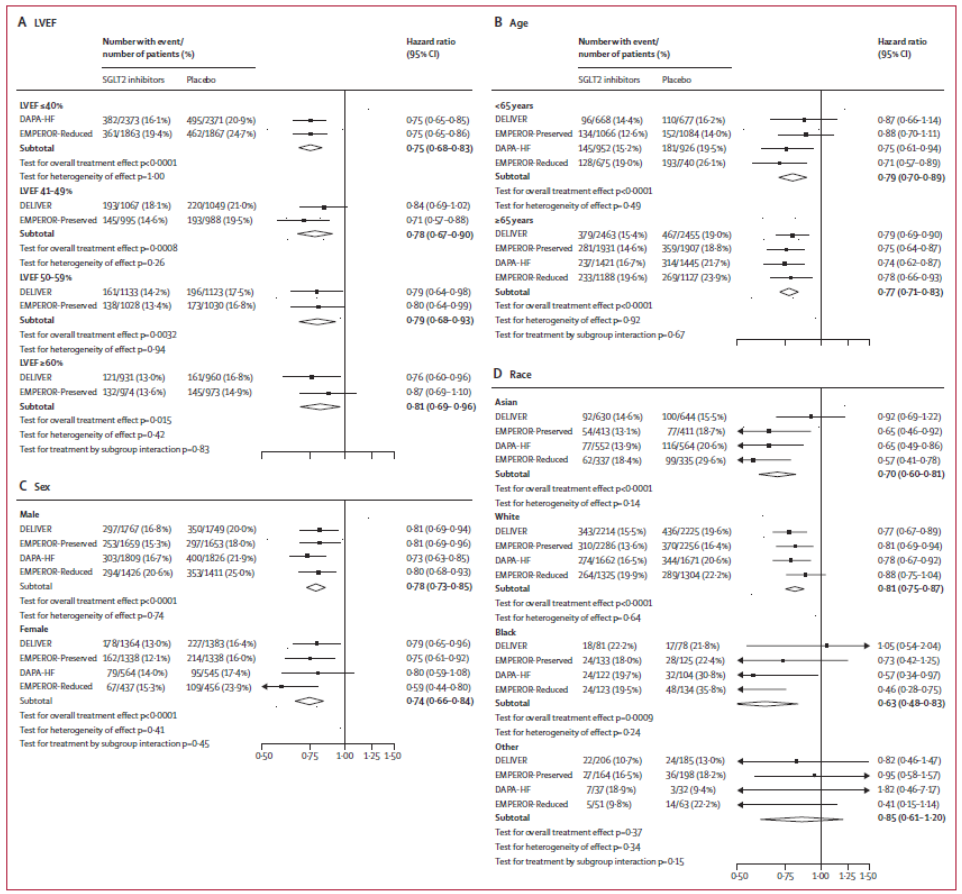


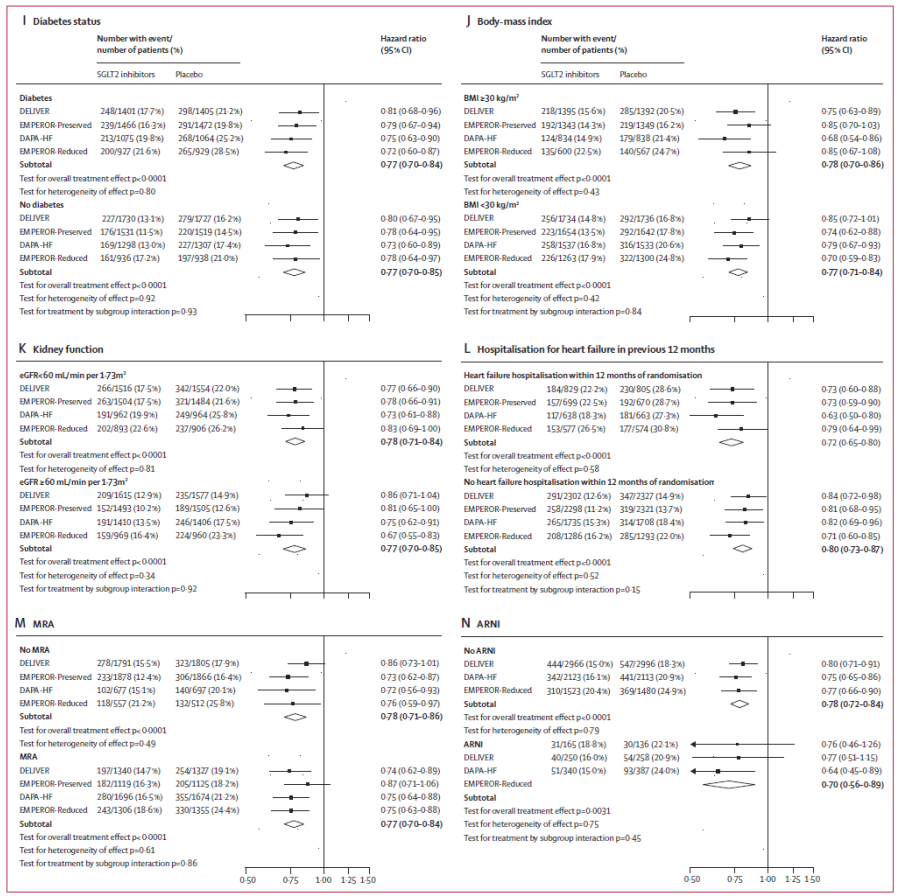
7th Advances in Heart Failure 2024
10 e 11 de Outubro

# SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

*Muthiah Vaduganathan*, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*



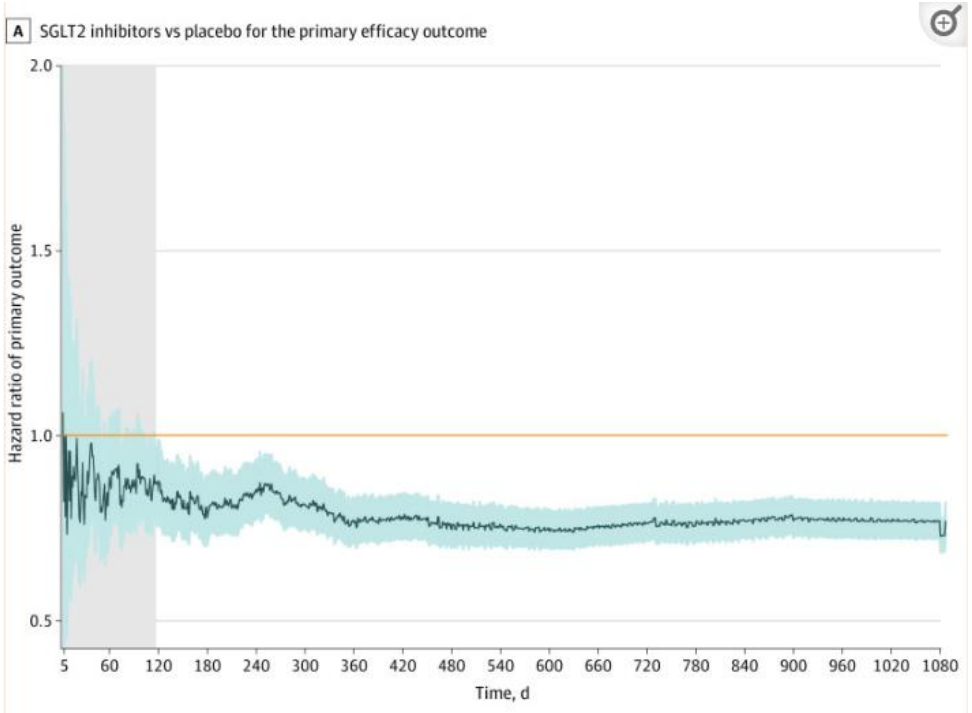



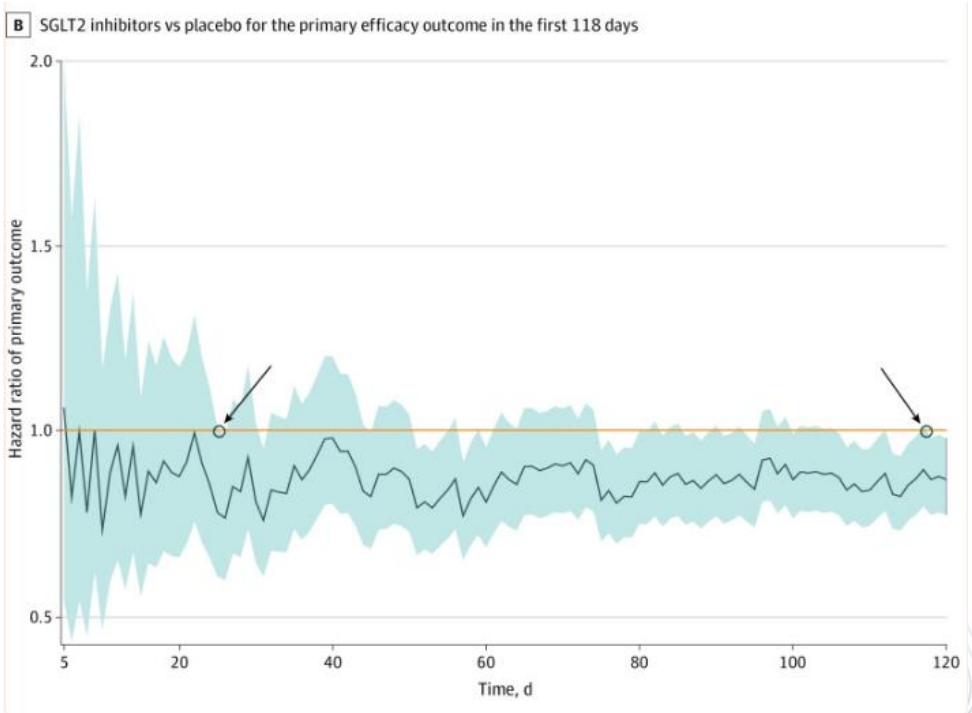
JAMA Network Open

Original Investigation | Pharmacy and Clinical Pharmacology

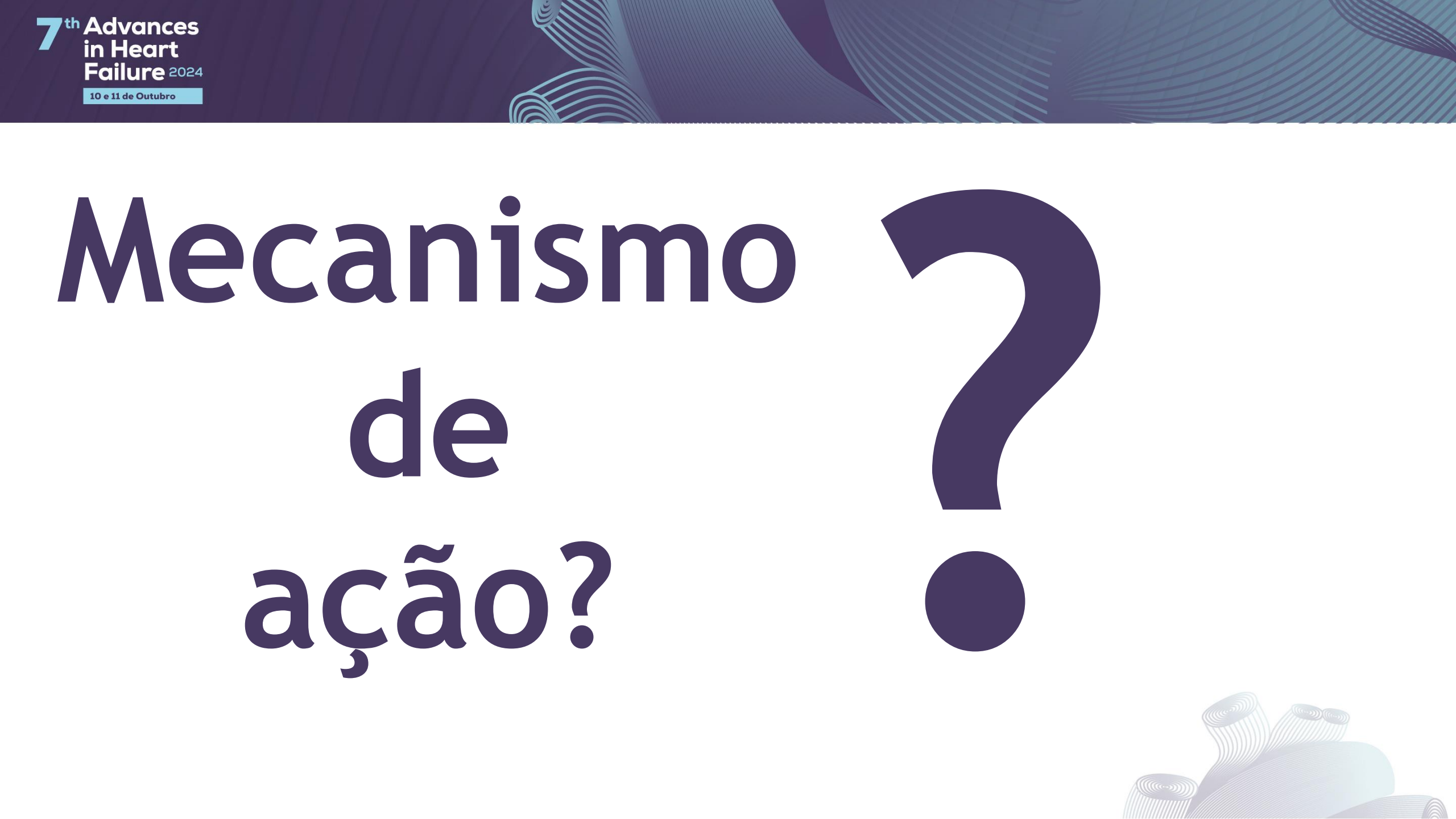
# Time to Benefit of Sodium-Glucose Cotransporter-2 Inhibitors Among Patients With Heart Failure

KangYu Chen, PhD; Zhiqiang Nie, PhD; Rui Shi, PhD; Dahai Yu, PhD; Qi Wang, PhD; Fang Shao, PhD; Guohong Wu, Msc; Zhenqiang Wu, PhD; Tao Chen, PhD; Chao Li, PhD



# Mecanismo de ação?

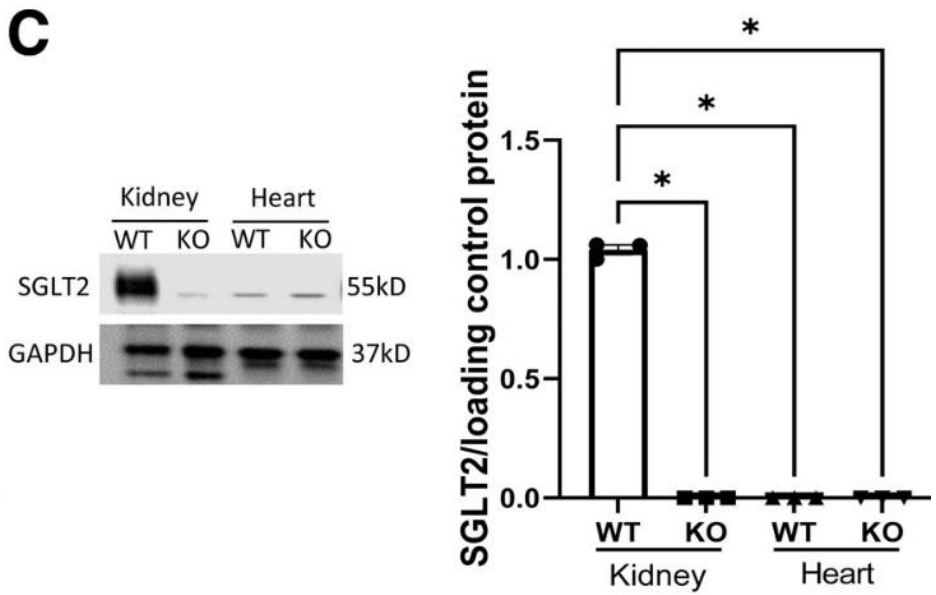


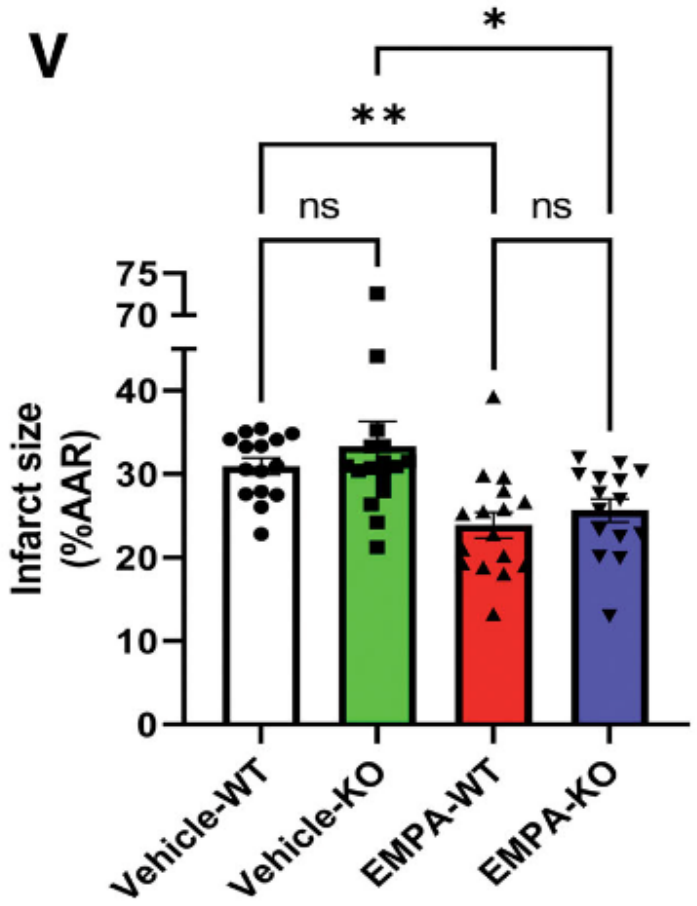
Circulation
Volume 147, Issue 3, 17 January 2023; Pages 276-279
https://doi.org/10.1161/CIRCULATIONAHA.122.061688

RESEARCH LETTER

# Sodium Glucose Cotransporter-2 Inhibitor Empagliflozin Reduces Infarct Size Independently of Sodium Glucose Cotransporter-2

Sha Chen, MD*, Qian Wang, MD*, Andriana Christodoulou, BSc*, Nikolaos Mylonas, BSc, Diane Bakker, BSc, Rianne Nederlof, PhD, Markus W. Hollmann, MD, PhD, Nina C. Weber, PhD, Ruben Coronel, MD, PhD, Vincent Wakker, BSc, Vincent M. Christoffels, PhD, Ioanna Andreadou, PhD†, and Coert J. Zuurbier, PhD †



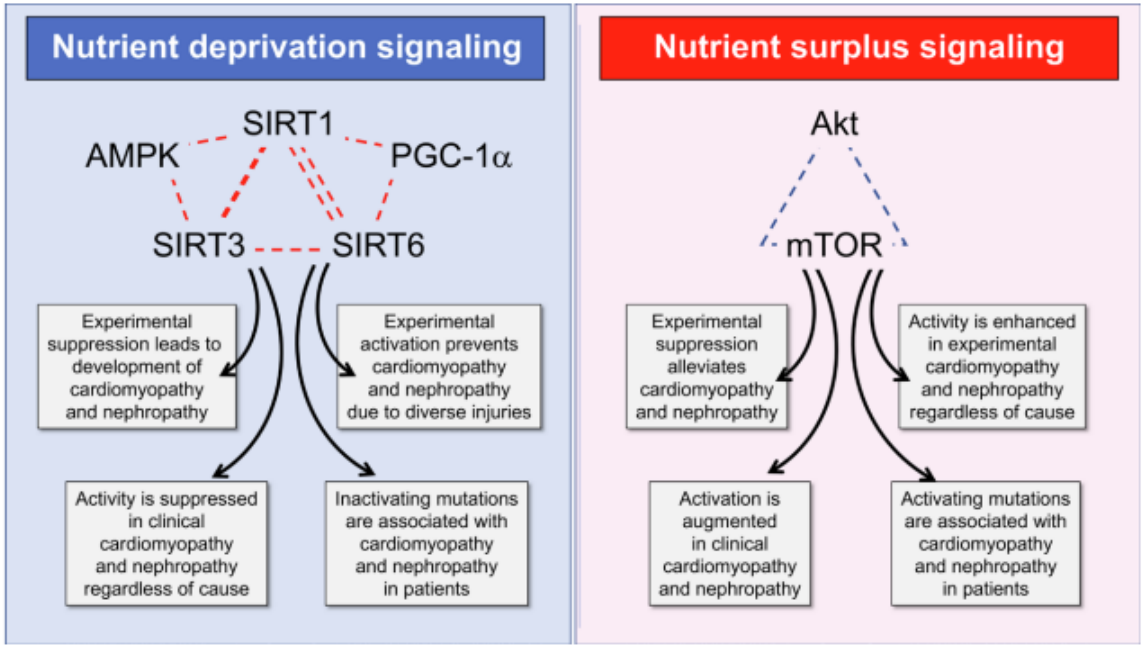



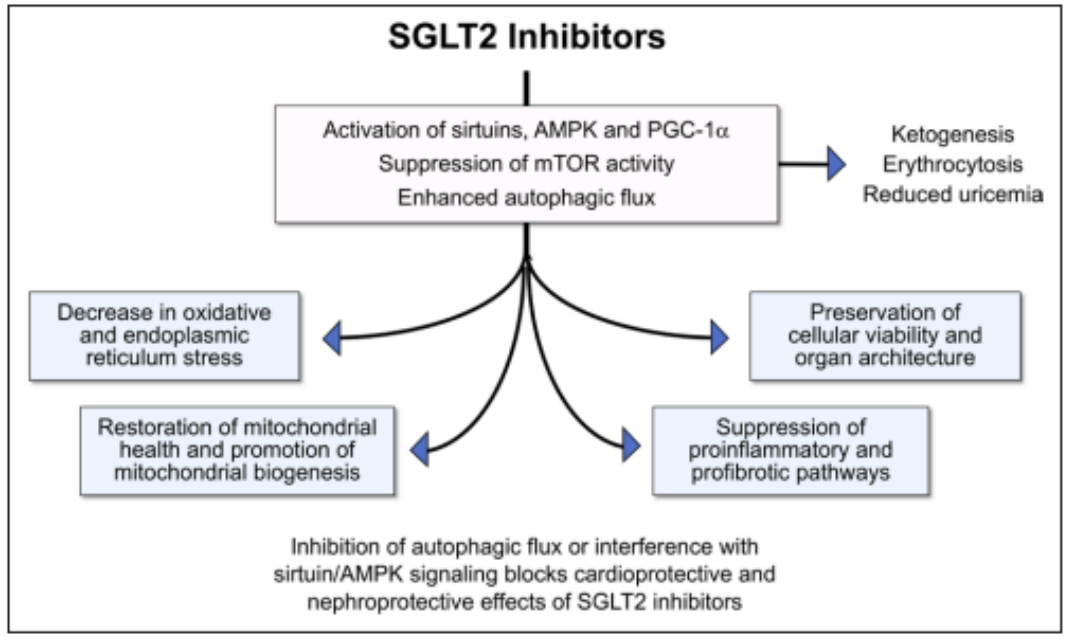
Circulation

FRONTIERS

# Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis

Milton Packer, MD



ESC European Society of Cardiology
European Heart Journal (2022) **43**, 4991–5002
https://doi.org/10.1093/eurheartj/ehac495

*FAST*TRACK CLINICAL RESEARCH
*clinical trials*

# Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme

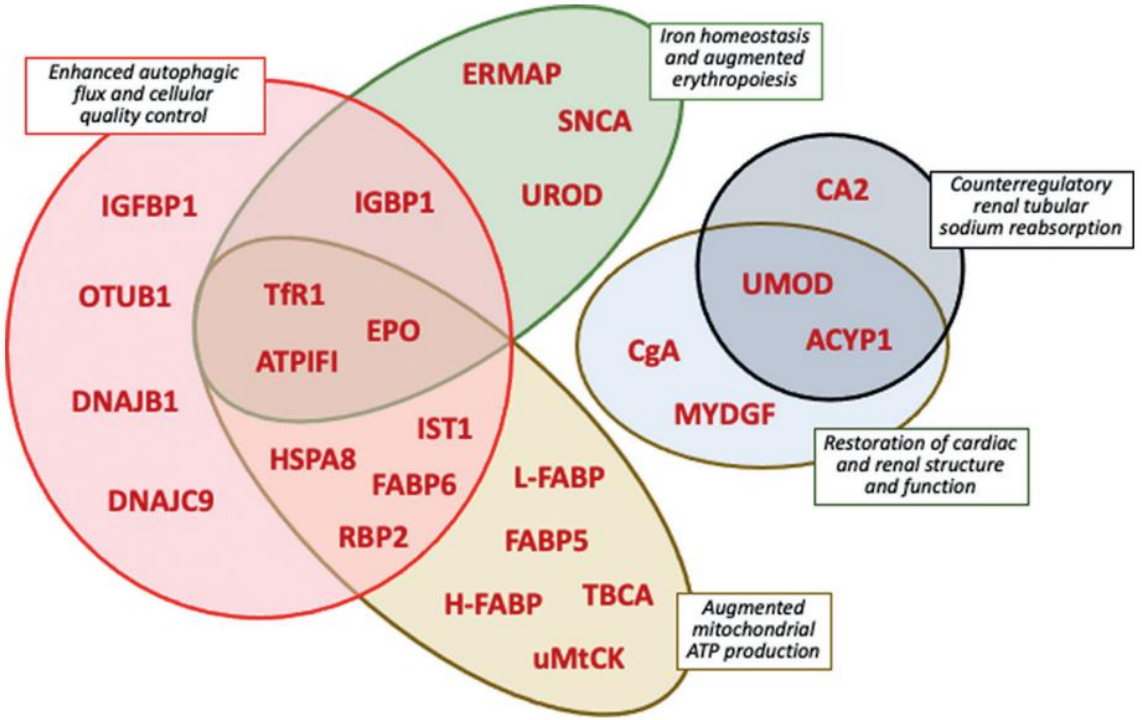
**Faiez Zannad [1*†], João Pedro Ferreira [1,2,3*†], Javed Butler [4,5], Gerasimos Filippatos [6], James L. Januzzi [7,8], Mikhail Sumin [9], Matthias Zwick [10], Maral Saadati [11], Stuart J. Pocock[12], Naveed Sattar [13], Stefan D. Anker [14,15], and Milton Packer [16,17]**

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2024


# Reaffirmation of Mechanistic Proteomic Signatures Accompanying SGLT2 Inhibition in Patients With Heart Failure

## A Validation Cohort of the EMPEROR Program

Milton Packer, MD,[a,b] João Pedro Ferreira, MD, PhD,[c,d] Javed Butler, MD, MPH,[d,e] Gerasimos Filippatos, MD, PhD,[f] James L. Januzzi, Jr, MD,[f,g] Sandra González Maldonado, PhD,[h] Marina Panova-Noeva, MD, PhD,[i,j] Stuart J. Pocock, PhD,[k] Jürgen H. Prochaska, MD,[l,m] Maral Saadati, PhD,[n] Naveed Sattar, MD, PhD,[o] Mikhail Sumin, MD, PhD,[l] Stefan D. Anker, MD,[p] Faiez Zannad, MD, PhD[q,r]

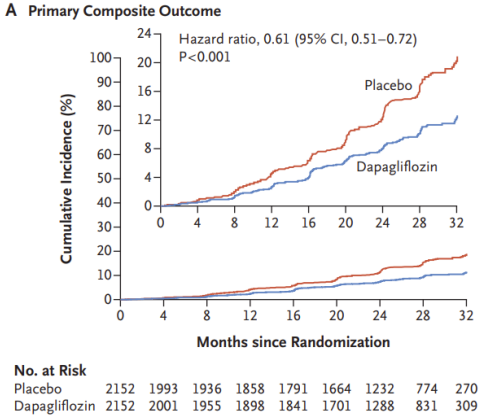


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

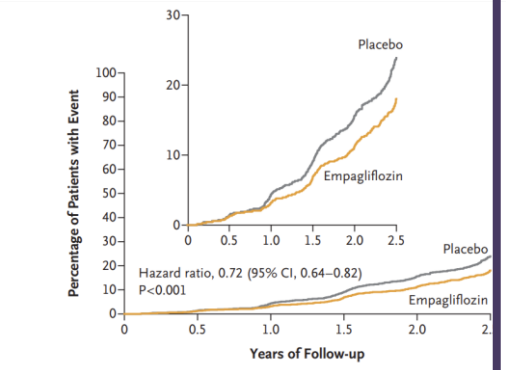



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

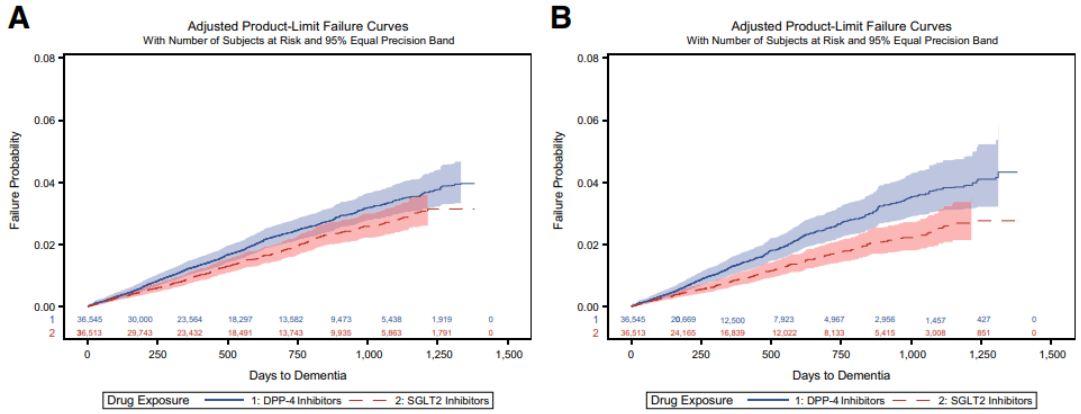



Diabetes Care Volume 46, February 2023 297

# Association of Sodium–Glucose Cotransporter 2 Inhibitors With Time to Dementia: A Population-Based Cohort Study

Diabetes Care 2023;46:297–304 | https://doi.org/10.2337/dc22-1705

Che-Yuan Wu,[1,2] Carina Iskander,[3] Christa Wang,[3] Lisa Y. Xiong,[1,2] Baiju R. Shah,[3,4] Jodi D. Edwards,[5,6,7] Moira K. Kapral,[3,8,9] Nathan Herrmann,[10,11] Krista L. Lanctôt,[1,2,10,11,12,13] Mario Masellis,[2,14] Richard H. Swartz,[2,3,14] Hugo Cogo-Moreira,[2,15] Bradley J. MacIntosh,[2,16,17] Jennifer S. Rabin,[2,14,18,19] Sandra E. Black,[2,13,14] Refik Saskin,[3] and Walter Swardfager[1,2,12]

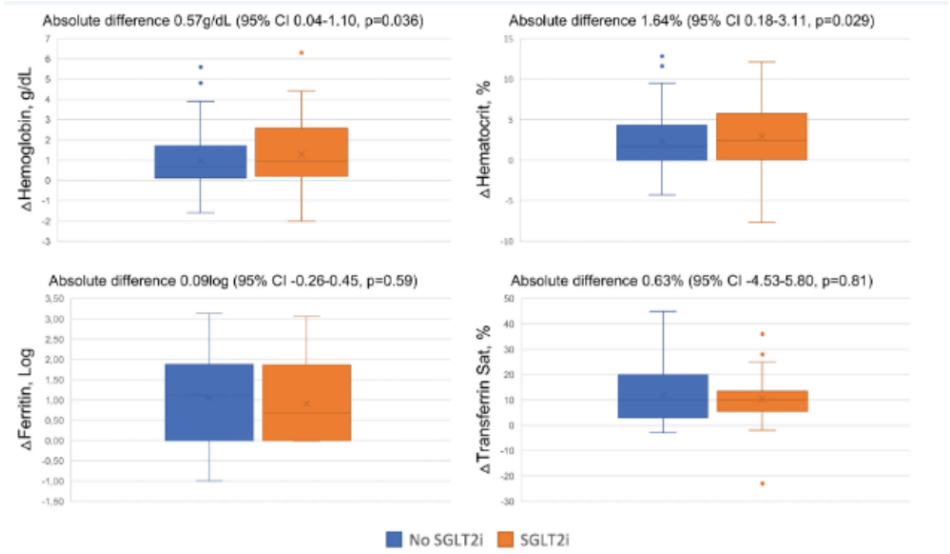


ESC European Society of Cardiology
European Journal of Heart Failure (2023) 25, 2191–2198
doi:10.1002/ejhf.2992

RESEARCH ARTICLE

# Erythropoietic response after intravenous iron in patients with heart failure and reduced ejection fraction with and without background treatment with sodium–glucose cotransporter 2 inhibitors

Pedro Marques[1,2,3]*, Paula Matias[1], Milton Packer[4,5], Joana T. Vieira[1], Francisco Vasques-Nóvoa[1,2], Abhinav Sharma[6], Thomas A. Mavrakanas[3], Fernando Friões[1,2,7], and João Pedro Ferreira[2,8]*




ESC European Society of Cardiology
European Journal of Heart Failure (2024) 26, 952–959
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RESEARCH ARTICLE

# Empagliflozin and risk of lower respiratory tract infection in heart failure with mildly reduced and preserved ejection fraction: An EMPEROR-Preserved analysis

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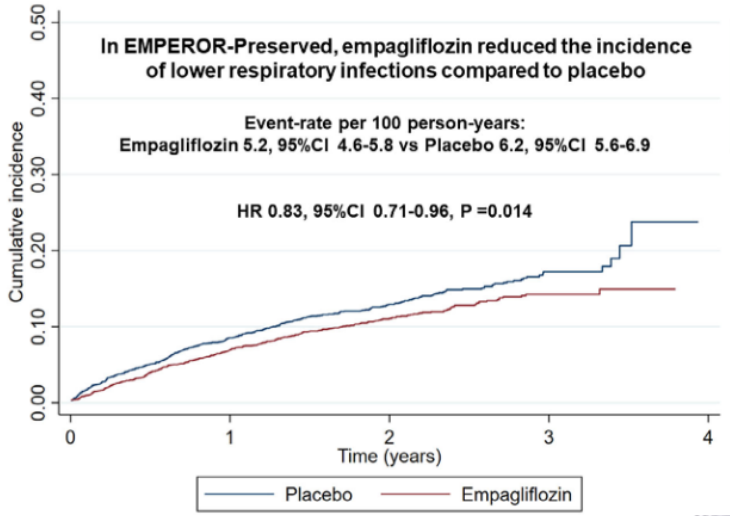


**Possible mechanisms by which empagliflozin reduced the incidence of lower respiratory tract infections:**

- General improvement of health status
- Reduction of systemic inflammation
- Reduction of lung congestion
- Reduction of oxidative stress
- Improvement of host defense mechanisms

# Conclusões

- Fármacos seguros e com evidência robusta de beneficio prognóstico **independentemente da categoria de FE**, subgrupo clínico ou terapêutica de *background*

- Mecanismos de ação provavelmente relacionados com a ativação de vias de sinalização associadas à restrição calórica e indução do fluxo autofágico (efeito sistémico)