SGLT2 Inhibitors in Heart Failure

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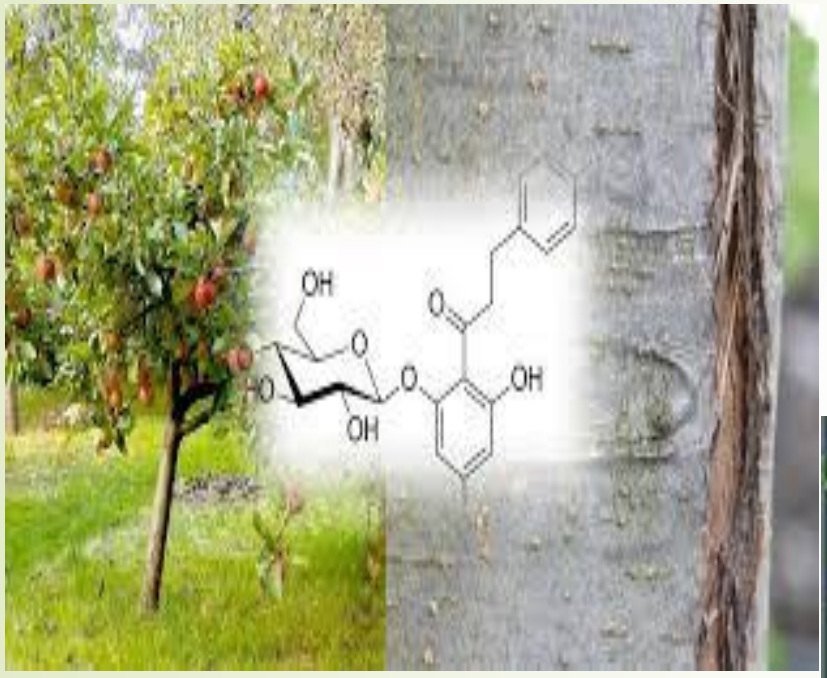
Rajaie Cardiovascular Medical and Research Center

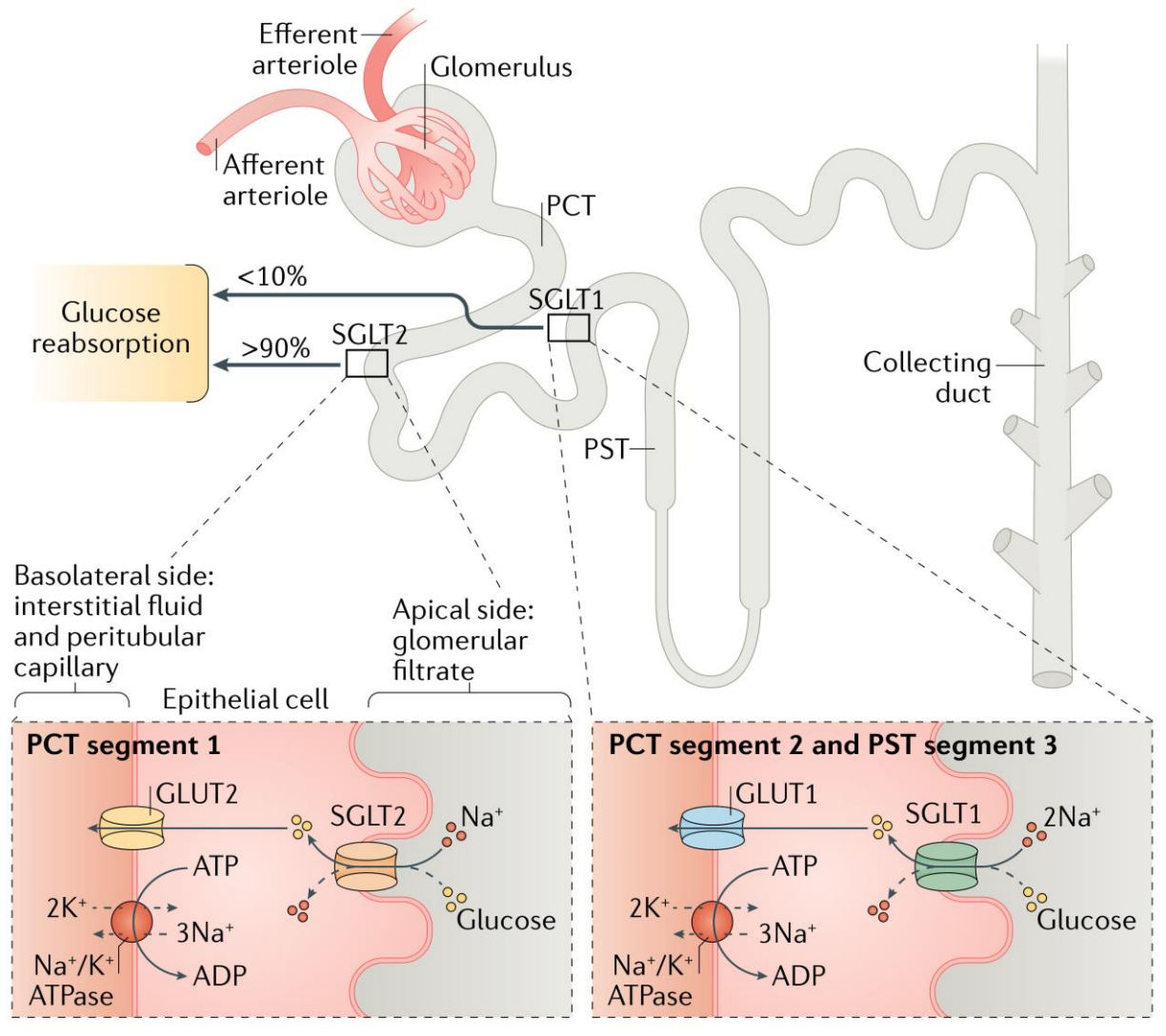
An apple a day keeps the doctor away…..



History of SGLT2 Inhibitors

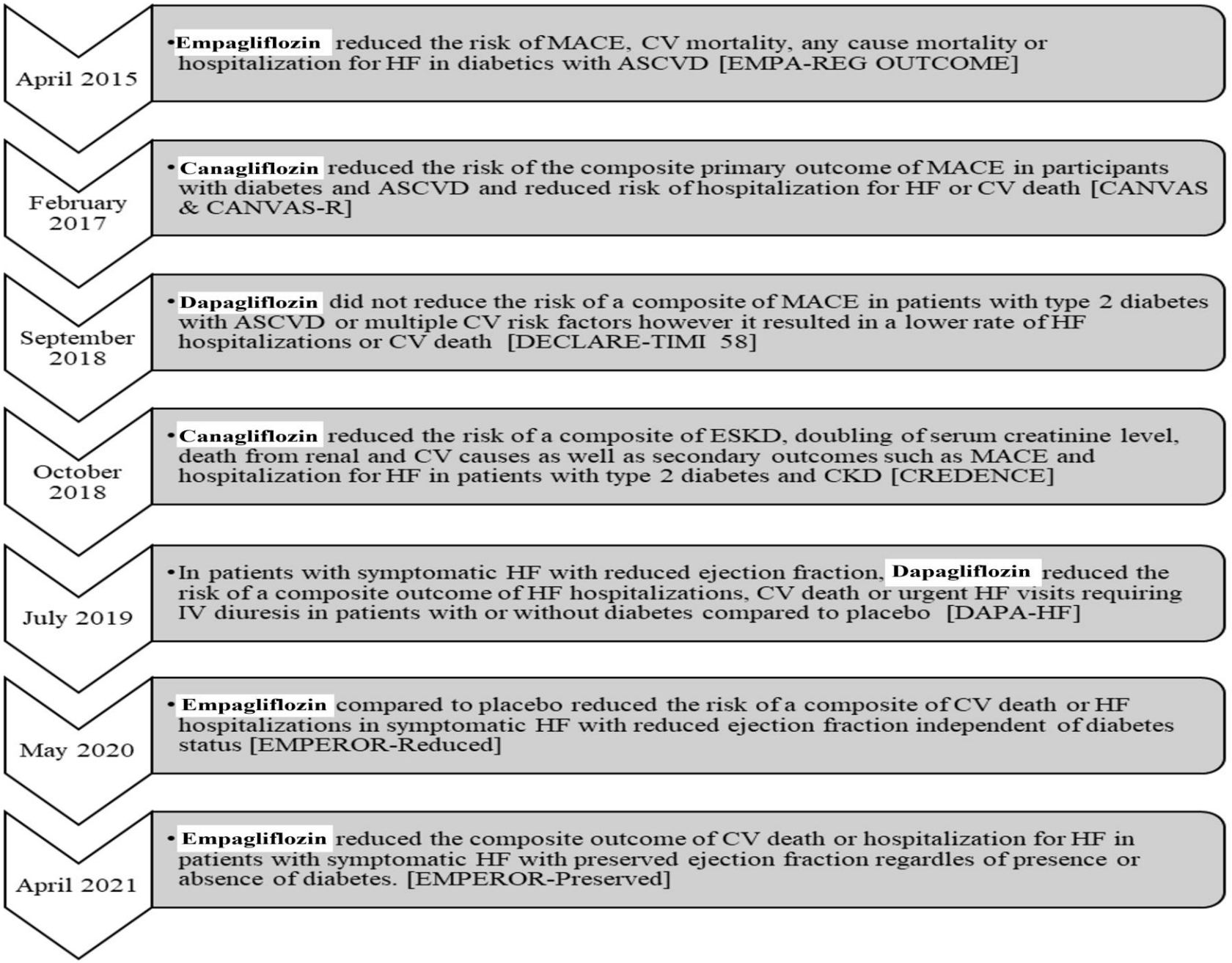
- 1835: discovery of Phlorizin(isolated from apple tree bark)
- 1886:glucosuria with phlorizin in dogs
- 1899:glucosuria with phlorizin in humans
- 1992: Cloning of gene for SGLT2
- 1999:Hypothesis of SGLT2 inhibition as a diabetes treatment
- 2008:Discovery of first selective Sglt2 inhibitor
- 2009:First human study with SGLT2 inhibitor

Mechanism of Action

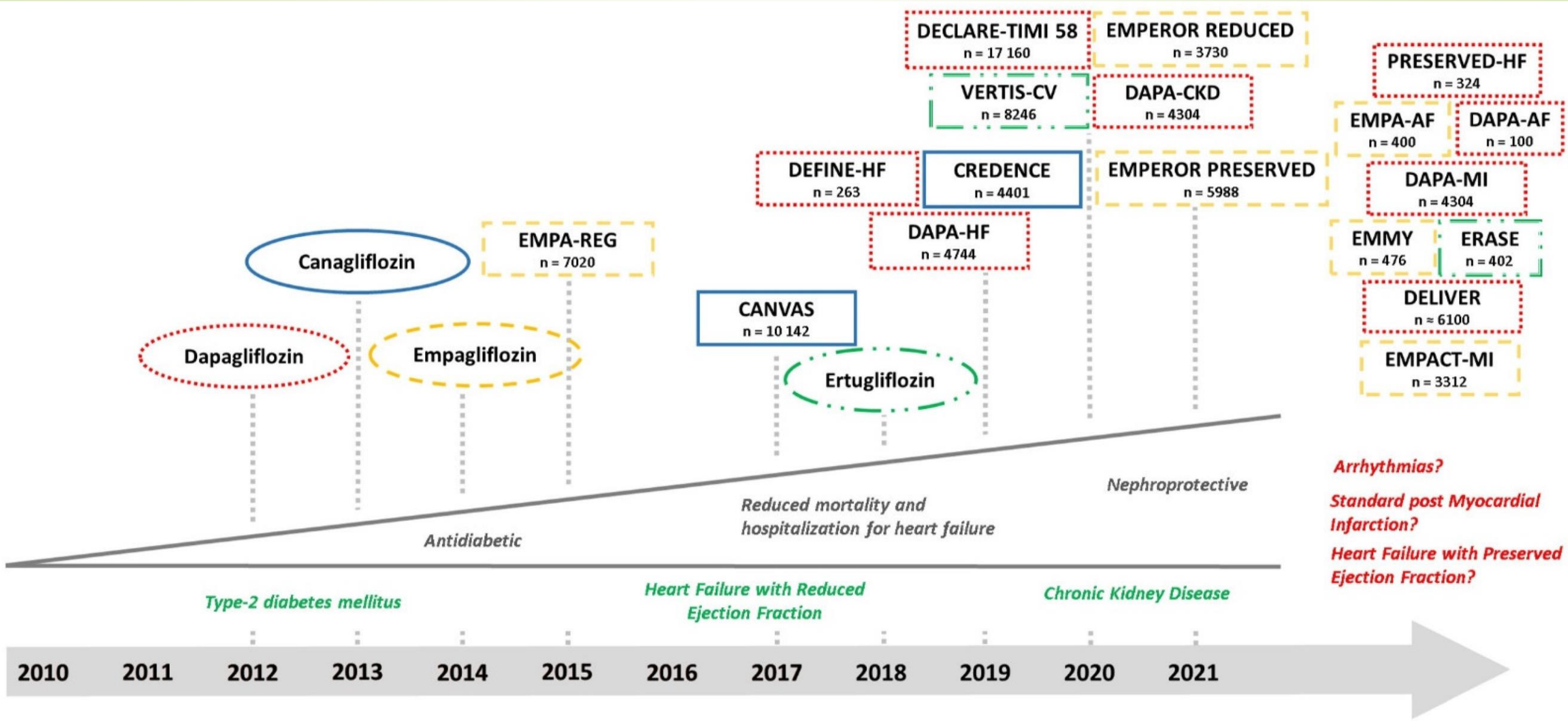


Inhibit proximal glucose reabsorption :

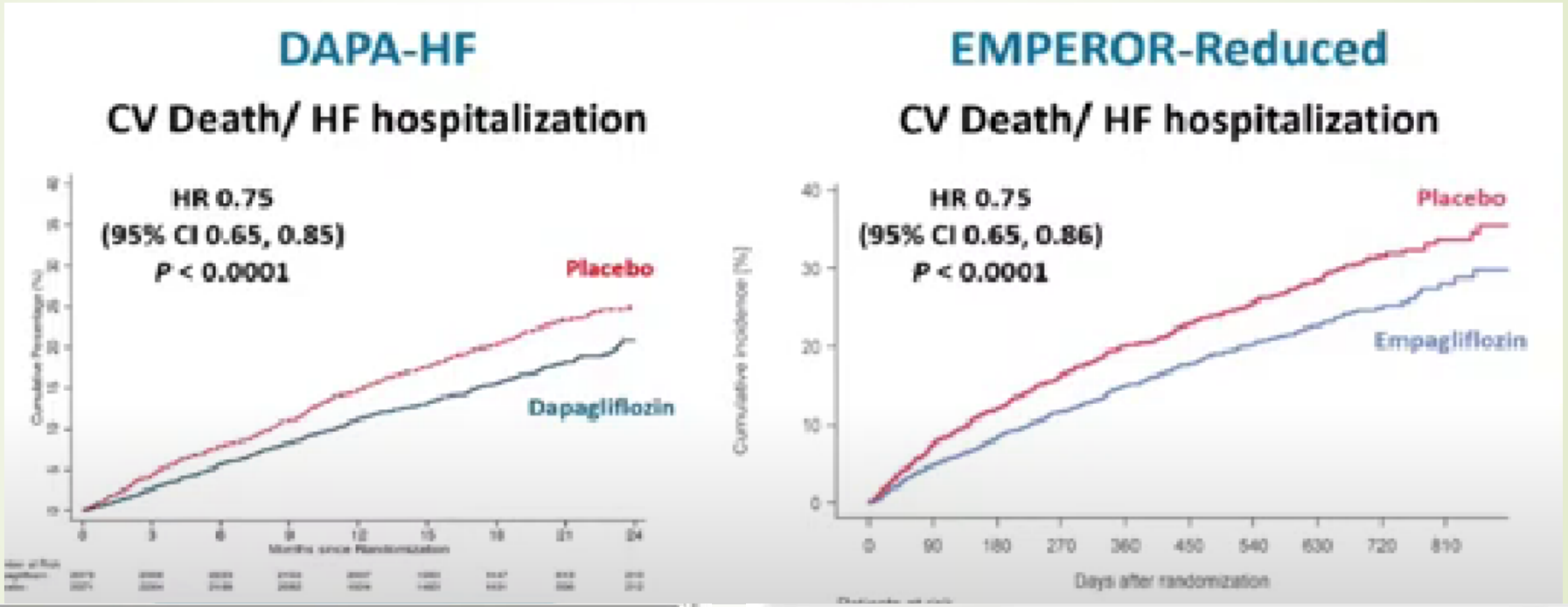
- **Glucosuria**
- **Diuresis**
- **Natriuresis**
- **BP reduction**
- **Weight reduction**

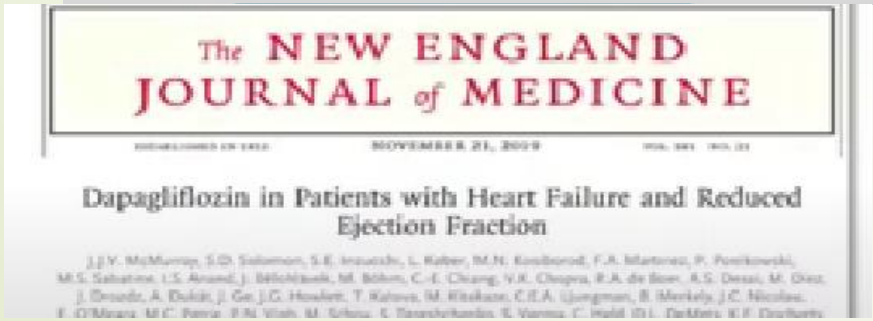

April 2015
•Empagliflozin reduced the risk of MACE, CV mortality, any cause mortality or hospitalization for HF in diabetics with ASCVD [EMPA-REG OUTCOME]
February 2017
•Canagliflozin reduced the risk of the composite primary outcome of MACE in participants with diabetes and ASCVD and reduced risk of hospitalization for HF or CV death [CANVAS & CANVAS-R]
September 2018
•Dapagliflozin did not reduce the risk of a composite of MACE in patients with type 2 diabetes with ASCVD or multiple CV risk factors however it resulted in a lower rate of HF hospitalizations or CV death [DECLARE-TIMI 58]
October 2018
•Canagliflozin reduced the risk of a composite of ESKD, doubling of serum creatinine level, death from renal and CV causes as well as secondary outcomes such as MACE and hospitalization for HF in patients with type 2 diabetes and CKD [CREDENCE]
July 2019
•In patients with symptomatic HF with reduced ejection fraction, Dapagliflozin reduced the risk of a composite outcome of HF hospitalizations, CV death or urgent HF visits requiring IV diuresis in patients with or without diabetes compared to placebo [DAPA-HF]
May 2020
•Empagliflozin compared to placebo reduced the risk of a composite of CV death or HF hospitalizations in symptomatic HF with reduced ejection fraction independent of diabetes status [EMPEROR-Reduced]
April 2021
•Empagliflozin reduced the composite outcome of CV death or hospitalization for HF in patients with symptomatic HF with preserved ejection fraction regardles of presence or absence of diabetes. [EMPEROR-Preserved]

SGLT2i trials



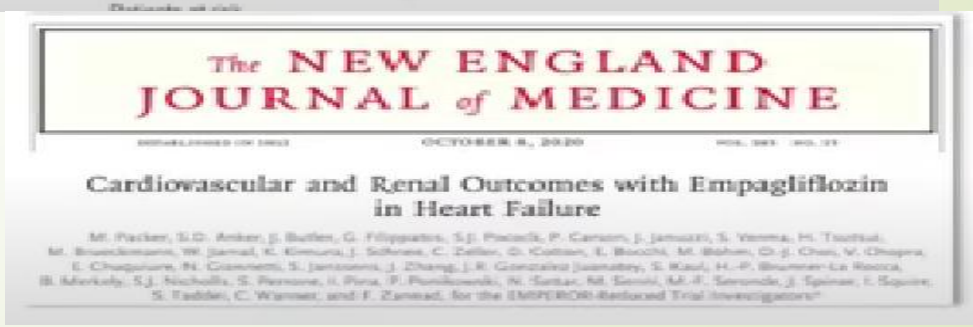
SGLT2i in Outpatients with HFrEF (with or without DM2)




The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 21, 2019

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction


The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 8, 2020

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

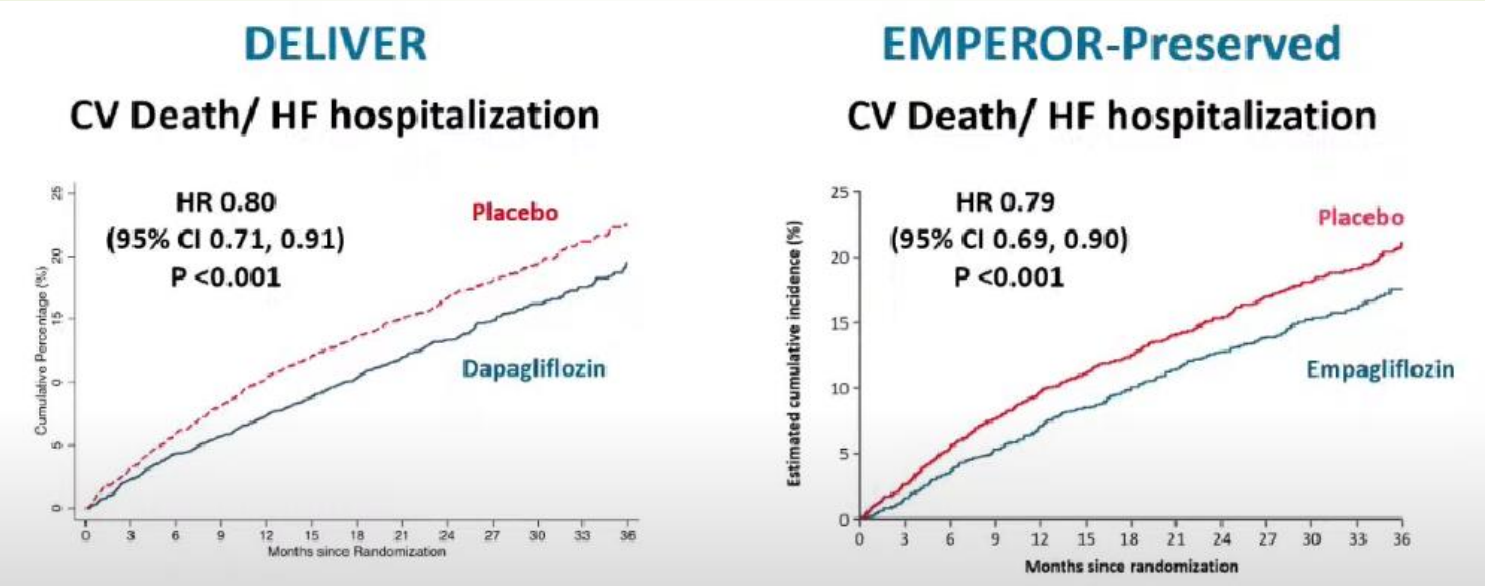
DAPA-HF and EMPEROR-Reduce Massage:

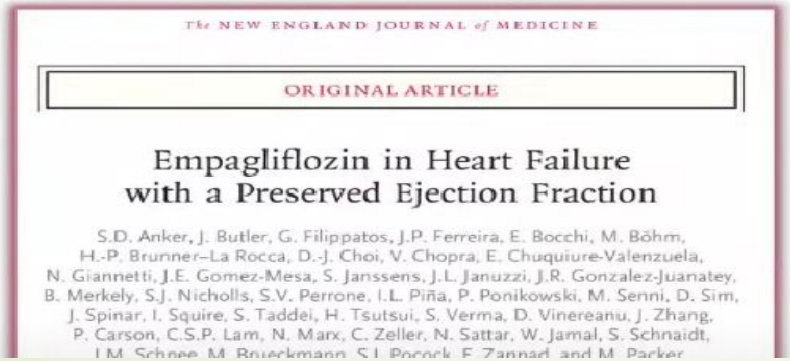
In Both Diabetic and Nondiabetic patients

SGLT2i when added to conventional therapy of Heart failure can

- ✓ Reduce risk of CV death and HF hospitalization
- ✓ Improve symptoms
- ✓ Slow decline in kidney function

SGLT2i in Outpatients with HFpEF (with or without DM2)




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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, I.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

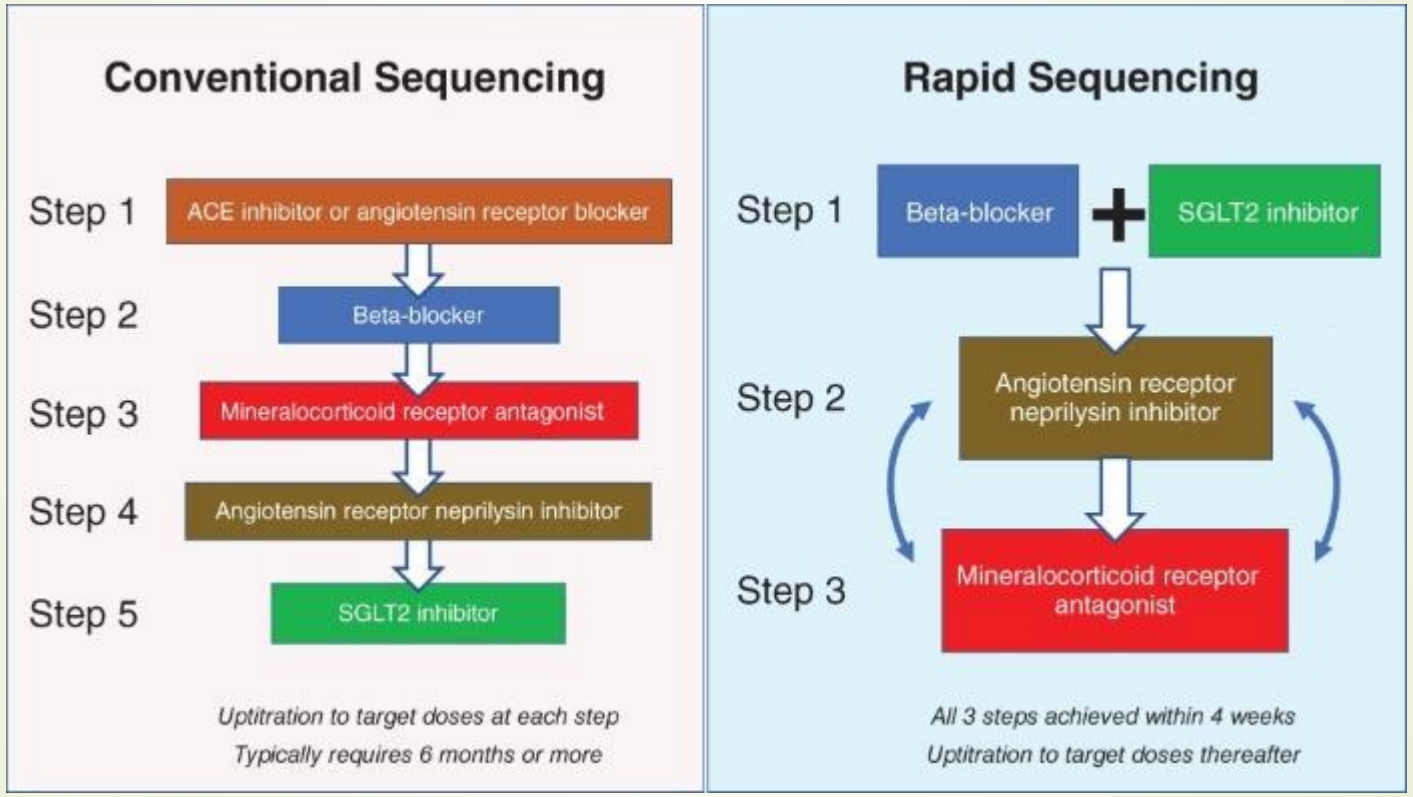
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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

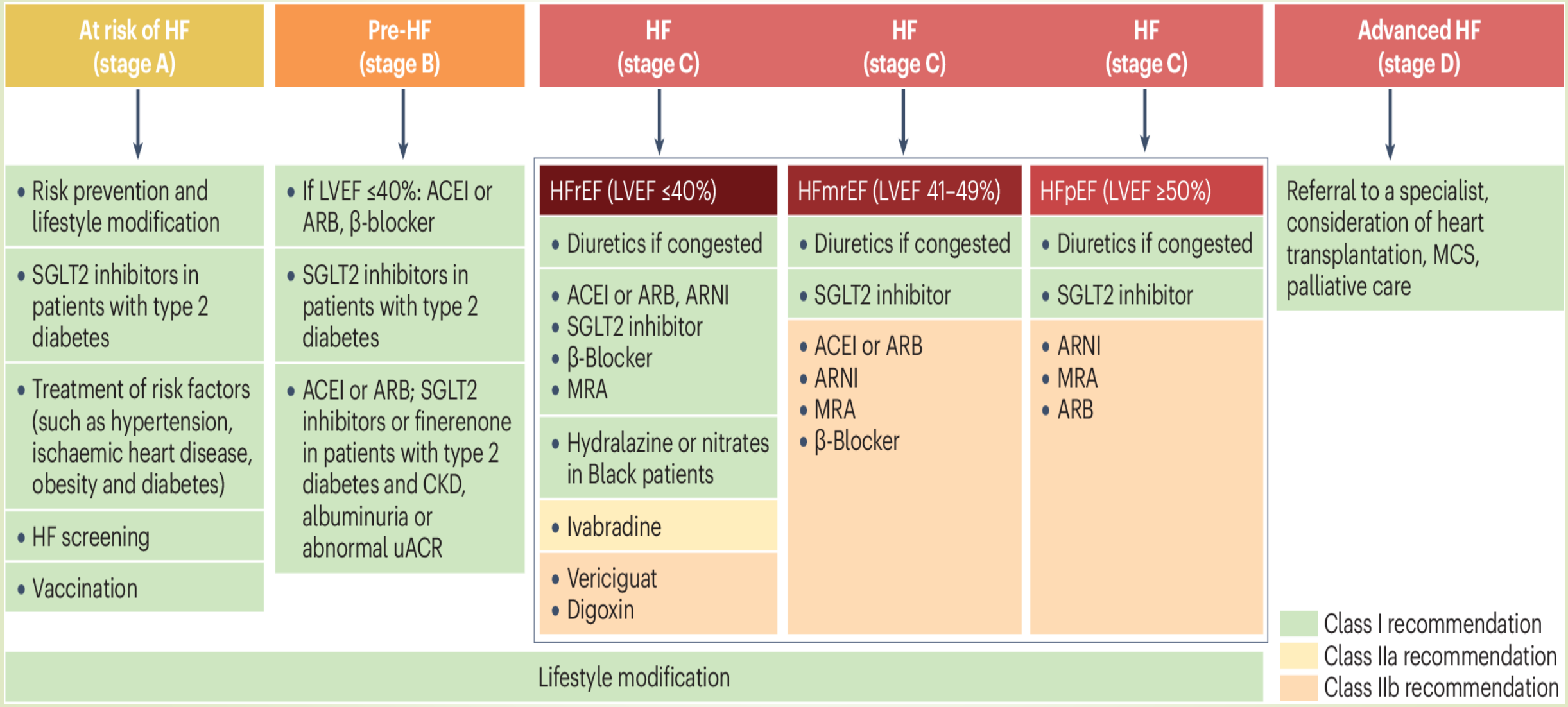
Sodium-Glucose Cotransporter 2 Inhibitors

Recommendation for SGLT2i Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
1	**A**	**1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.**
Value Statement: **Intermediate Value** **(A)**		**2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.**

SGLTRi : A new Era in Heart Failure Treatment



Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heart Fail. 2021 Jun;23(6):882-894


At risk of HF (stage A)
Pre-HF (stage B)
HF (stage C)
HF (stage C)
HF (stage C)
Advanced HF (stage D)
• Risk prevention and lifestyle modification
• SGLT2 inhibitors in patients with type 2 diabetes
• Treatment of risk factors (such as hypertension, ischaemic heart disease, obesity and diabetes)
• HF screening
• Vaccination
• If LVEF ≤40%: ACEI or ARB, β-blocker
• SGLT2 inhibitors in patients with type 2 diabetes
• ACEI or ARB; SGLT2 inhibitors or finerenone in patients with type 2 diabetes and CKD, albuminuria or abnormal uACR
HFrEF (LVEF ≤40%)
• Diuretics if congested
• ACEI or ARB, ARNI
• SGLT2 inhibitor
• β-Blocker
• MRA
• Hydralazine or nitrates in Black patients
• Ivabradine
• Vericiguat
• Digoxin
HFmrEF (LVEF 41–49%)
• Diuretics if congested
• SGLT2 inhibitor
• ACEI or ARB
• ARNI
• MRA
• β-Blocker
HFpEF (LVEF ≥50%)
• Diuretics if congested
• SGLT2 inhibitor
• ARNI
• MRA
• ARB
Referral to a specialist, consideration of heart transplantation, MCS, palliative care
Lifestyle modification
Class I recommendation
Class IIa recommendation
Class IIb recommendation

Other SGLT2i Effects in HFrEF

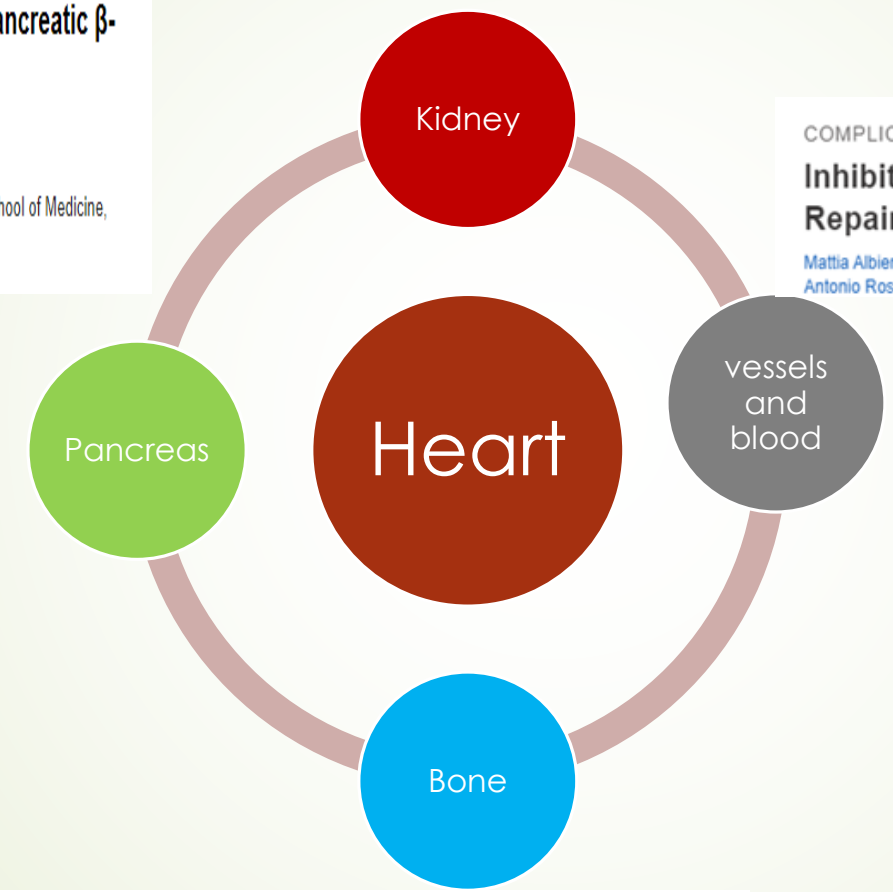
- Cardiac remodeling
- Reduce NT-ProBNP
- Reduce ventricular Arrhythmias
- Reduce Risk of Hyperkalemia
- Reduce Risk of Hyponatremia
- Reduce uric acid
- Correction of Anemia

SGLT2i Organ Protection Effects

Effects of Sodium-Glucose Co-Transporter-2 Inhibitors on Pancreatic β-Cell Mass and Function

by Akinobu Nakamura

Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan



COMPLICATIONS | APRIL 26 2021

Inhibition of SGLT2 Rescues Bone Marrow Cell Traffic for Vascular Repair: Role of Glucose Control and Ketogenesis FREE

Mattia Albiero; Serena Tedesco; Francesco Ivan Amendolagine; Marianna D'Anna; Ludovica Migliozzi; Gaia Zuccolotto; Antonio Rosato; Roberta Cappellari; Angelo Avogaro; Gian Paolo Fadini

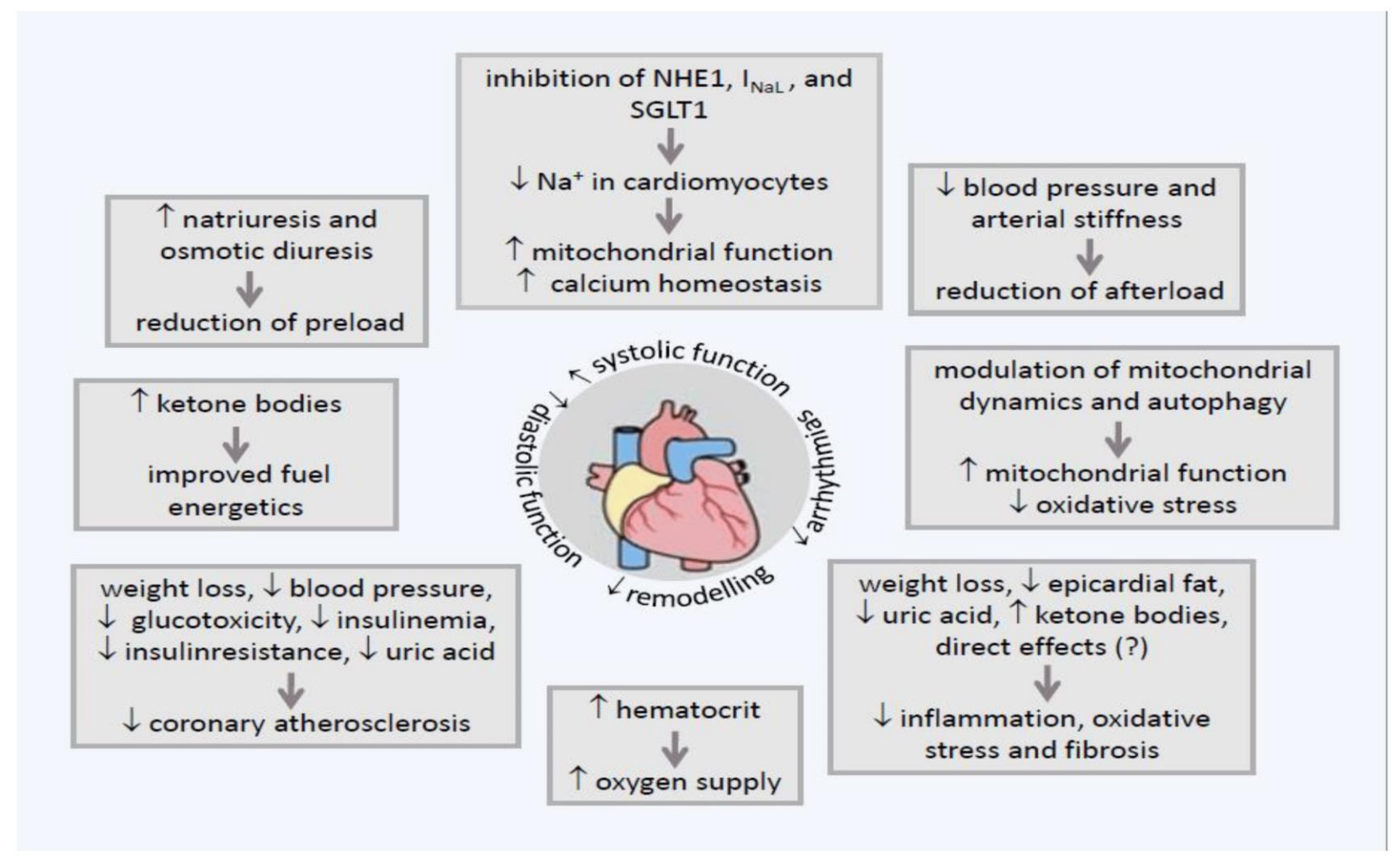
Front Endocrinol (Lausanne). 2022; 13: 918350.
Published online 2022 Jul 7. doi: 10.3389/fendo.2022.918350

PMCID: PMC9302585
PMID: 35872985

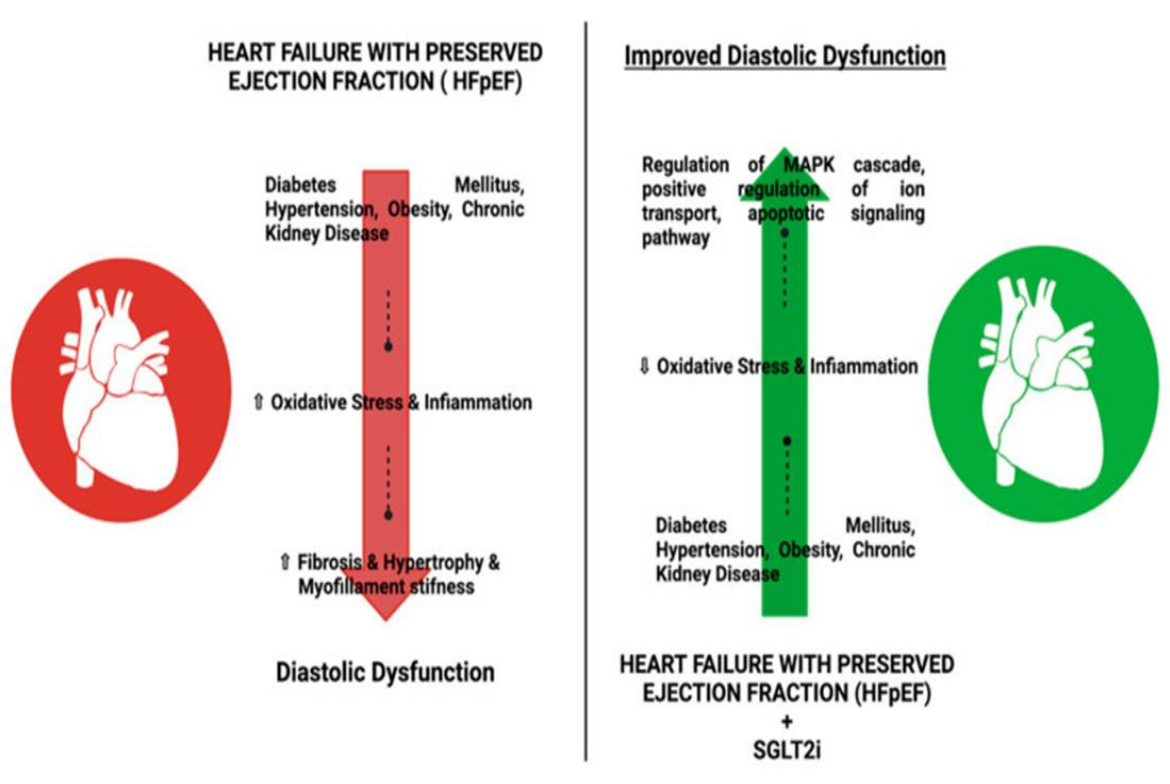
The Extraglycemic Effect of SGLT-2is on Mineral and Bone Metabolism and Bone Fracture

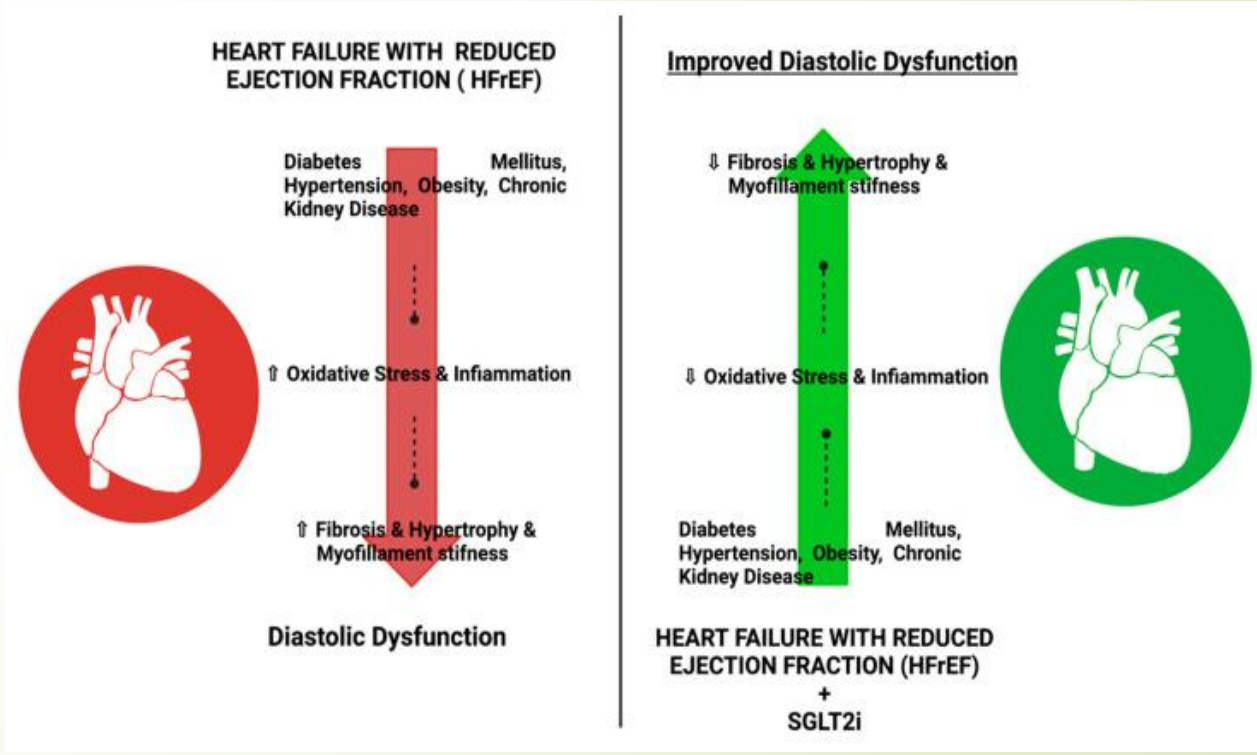
Bingzi Dong, [1 · †] Ruolin Lv, [1 · †] Jun Wang, [1] Lin Che, [2] Zhongchao Wang, [1] Zhouyang Huai, [3] Yangang Wang,✉ [1 · *] and Lili Xu✉ [1 · *]

Hypothesized SGLT2i Mechanisms in heart Failure Improvement



SGLT2i for HFrEF and HFpEF Diabetics and Non Diabetics





SGLT2 Inhibitors Practical Issues

How quickly do they work?

When they can be start ?Can Be started for inpatients or Patients with Stable chronic HF?

Are they safe (in all subgroups)?

How Quickly SGLT2i Works?

October 3, 2022

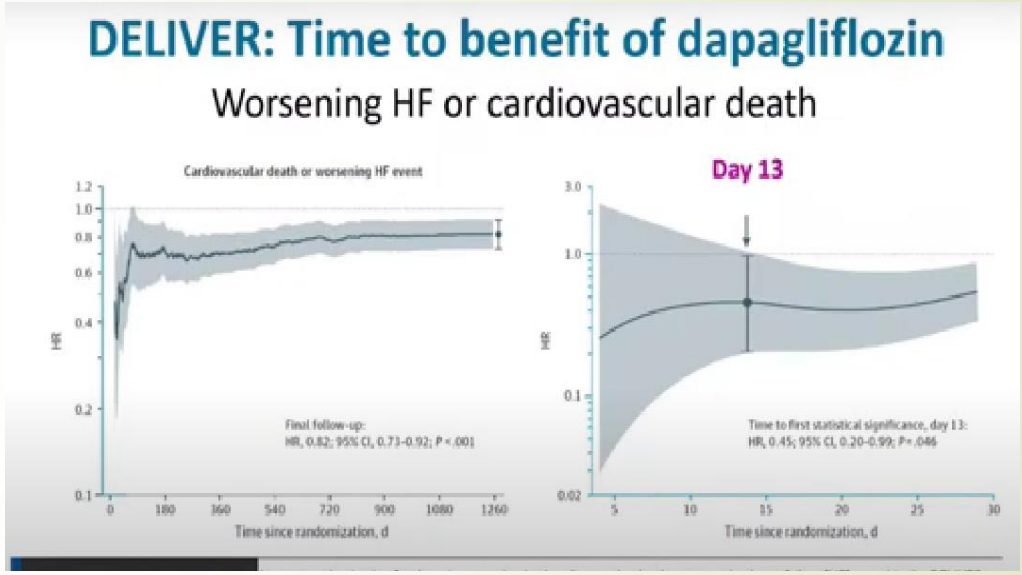
Time to Clinical Benefit of Dapagliflozin in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction

A Prespecified Secondary Analysis of the DELIVER Randomized Clinical Trial

Muthiah Vaduganathan, MD, MPH[1]; Brian L. Claggett, PhD[1]; Pardeep Jhund, MD, PhD[2]; et al

≫ Author Affiliations | Article Information

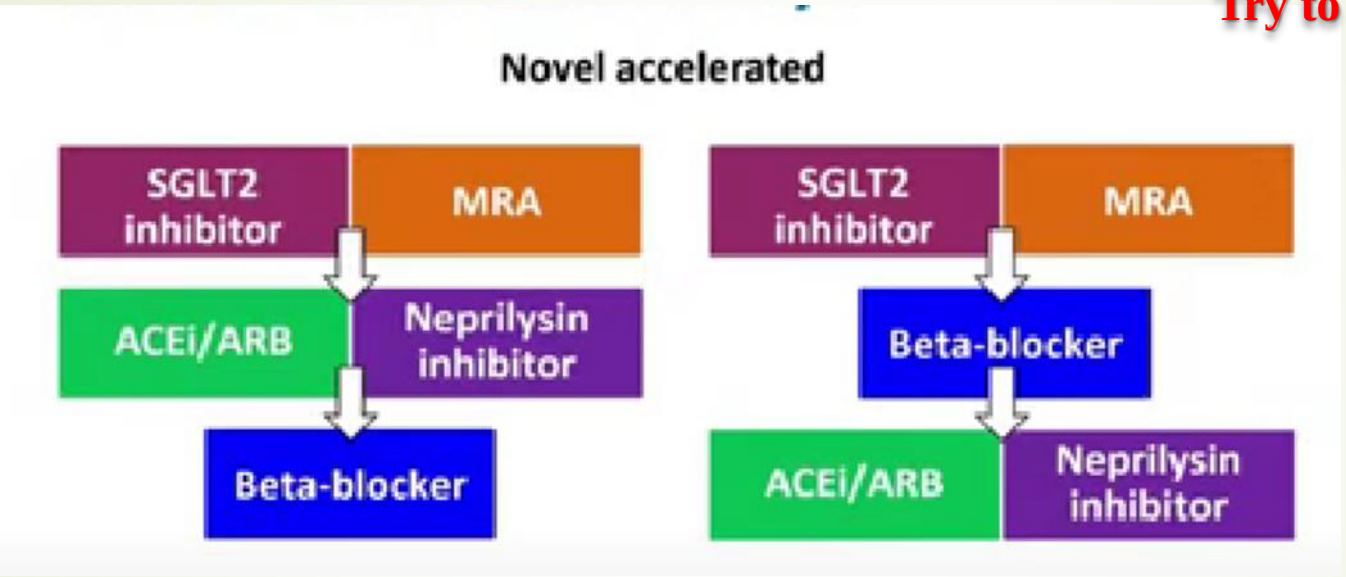
JAMA Cardiol. 2022;7(12):1259-1263. doi:10.1001/jamacardio.2022.3750



Conclusions and Relevance In the DELIVER trial, dapagliflozin led to early and sustained reductions in clinical events in patients with HF with mildly reduced or preserved ejection fraction with statistically significant reductions observed within 2 weeks of treatment initiation.

When SGLT2i can be start?

Try to get 4 treatment in 4 weeks



As a Lifesaving Treatment should started early

> Circulation. 2023 Apr 4;147(14):1067-1078. doi: 10.1161/CIRCULATIONAHA.122.062918. Epub 2023 Mar 6.

Patient Characteristics, Outcomes, and Effects of Dapagliflozin According to the Duration of Heart Failure: A Prespecified Analysis of the DELIVER Trial

Toru Kondo [#1,2], Karola S Jering [#3], C Jan Willem Borleffs [4], Rudolf A de Boer [5], Brian L Claggett [3], Akshay S Desai [3], Dan Dobreanu [6], Silvio E Inzucchi [7], Adrian F Hernandez [8], Stefan P Janssens [9], Pardeep S Jhund [1], Mikhail N Kosiborod [10], Carolyn S P Lam [11], Anna Maria Langkilde [12], Felipe A Martinez [13], Magnus Petersson [12], Pham Nguyen Vinh [14],

SGLT2i in chronic HF?

Conclusions: Patients with longer-duration HF were older, had more comorbidities and symptoms, and had higher rates of worsening HF and death. The benefits of dapagliflozin were consistent across HF duration. Even patients with long-standing HF and generally mild symptoms are not stable, and it is not too late for such patients to benefit from a sodium-glucose cotransporter 2 inhibitor.

Patient Characteristics, Clinical Outcomes, and Effect of Dapagliflozin in Relation to Duration of Heart Failure: Is It Ever Too Late to Start a New Therapy?

Su E. Yeoh, MBChB,[1] Pooja Dewan, MBBS,[1] Pardeep S. Jhund, MBChB, MSc, PhD,[1] Silvio E. Inzucchi, MD,[2] Lars Køber, MD, DMSc,[3] Mikhail N. Kosiborod, MD,[4] Felipe A. Martinez, MD,[5] Piotr Ponikowski, MD, PhD,[6] Marc S. Sabatine, MD, MPH,[7] Scott D. Solomon, MD,[8] Olof Bengtsson, Ph. Lic.,[9] Mikaela Sjöstrand, MD, PhD,[9] Anna Maria Langkilde, MD, PhD,[9] and John JV McMurray, MD[✉1], on behalf of the DAPA-HF Investigators and Committees

Conclusions

Longer-duration HF patients were older, had more comorbidity and symptoms, and higher rates worsening HF and death. The benefits of dapagliflozin were consistent across HF duration.

SGLT2i in Hospitalized Patients

EMPULSE Trial

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Adriaan A. Voors, Christiane E. Angermann, John R. Teerlink, Sean P. Collins, Mikhail Kosiborod, Jan Biegus, João Pedro Ferreira, Michael E. Nassif, Mitchell A. Psotka, Jasper Tromp, C. Jan Willem Borleffs, Changsheng Ma, Joseph Comin-Colet, Michael Fu, Stefan P. Janssens, Robert G. Kiss, Robert J. Mentz, Yasushi Sakata, Henrik Schirmer, Morten Schou, P. Christian Schulze, Lenka Spinarova, Maurizio Volterrani, Jerzy K. Wranicz, ... Piotr Ponikowski + Show authors

Initiation of empagliflozin in patients hospitalized for acute heart failure is well tolerated and results in. significant clinical benefit in the 90 days after starting treatment

SOLOIST Trial

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

Authors: Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., P. Gabriel Steg, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., +12, for the SOLOIST-WHF Trial Investigators* Author Info & Affiliations

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits.

Are SGLT2i safe Frail and Old Patients?

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Efficacy and Safety of Dapagliflozin According to Frailty in Patients With Heart Failure: A Prespecified Analysis of the DELIVER Trial

Jawad H. Butt, Pardeep S. Jhund, Jan Belohlávek, Rudolf A. de Boer, Chern-En Chiang, Akshai S. Desai, Jarosław Drożdż, Adrian F. Hernandez, Silvio E. Inzucchi, Tzvetana Katova, Masafumi Kitakaze, Mikhail N. Kosiborod, Carolyn S.P. Lam, Anna Maria Langkilde, Daniel Lindholm, Erasmus Bachus, Felipe Martinez, Béla Merkely, Magnus Petersson, ... See all authors

Originally published 27 Aug 2022 | https://doi.org/10.1161/CIRCULATIONAHA.122.061754 | Circulation. 2022;146:1210–1224

Other version(s) of this article

In DELIVER, frailty was common and associated with worse outcomes. The benefit of dapagliflozin was consistent across the range of frailty studied. The improvement in health-related quality of life with dapagliflozin occurred early and was greater in patients with a higher level of frailty.

SGLT2i Are Safe in patients on Many Different Drugs

Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Polypharmacy Status

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Original Research

Alexander Peikert, Parag Goyal, Muthiah Vaduganathan, Brian L. Claggett, Ian J. Kulac, Zi Michael Miao, Orly Vardeny, Mikhail N. Kosiborod, Akshay S. Desai, Pardeep S. Jhund, Carolyn S.P. Lam, Silvio E. Inzucchi, ... SEE ALL AUTHORS

J Am Coll Cardiol HF. 2023 Oct, 11 (10) 1380–1393

Adverse effects

EMPEROR-Reduced: Safety

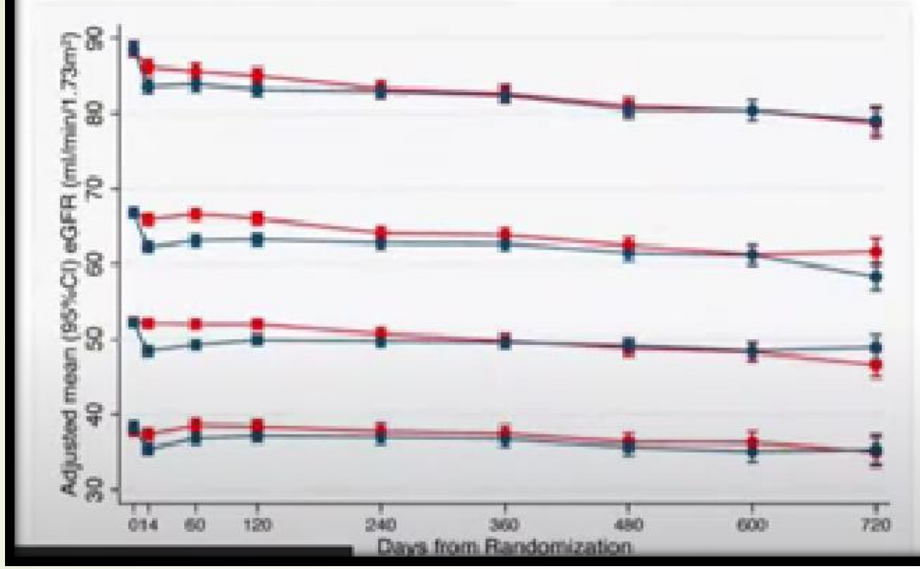
	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
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	13 (0.7)	10 (0.5)

DAPA-HF[19]	Dapagliflozin	Placebo	*P* value
Discontinuation caused by adverse event	4.7%	4.9%	0.79
Volume depletion	7.5%	6.8%	0.40
Renal adverse event	6.5%	7.2%	0.36
Amputation	0.5%	0.5%	1.00
Major hypoglycemia	0.2%	0.2%	NA
Diabetic ketoacidosis	0.1%	0	NA
Fournier's gangrene	0	<0.1%	NA
EMPEROR-Reduced[27]	**Empagliflozin**	**Placebo**	***P* value**
Hypotension	9.4%	8.7%	NA
Volume depletion	10.6%	9.9%	NA
Hypoglycemic events[a]	0.7%	0.6%	NA
Ketoacidosis	0	0	NA
Urinary tract infections	4.9%	4.5%	NA
Complicated urinary tract infections	1.0%	0.8%	NA
Genital infections	1.7%	0.6%	NA
Complicated genital infections	0.3%	0.3%	NA
Events leading to lower-limb amputation	0.7%	0.5%	NA

Abbreviation: NA, not available.
[a]In patients without type 2 diabetes mellitus.

DAPA-HF: Mean eGFR over time according to baseline eGFR category and randomised treatment assignment (both dapagliflozin and placebo groups shown)

eGFR categories: >75, <75- ≥60-, <60- ≥45, <45, and ml/min/1.73 m²



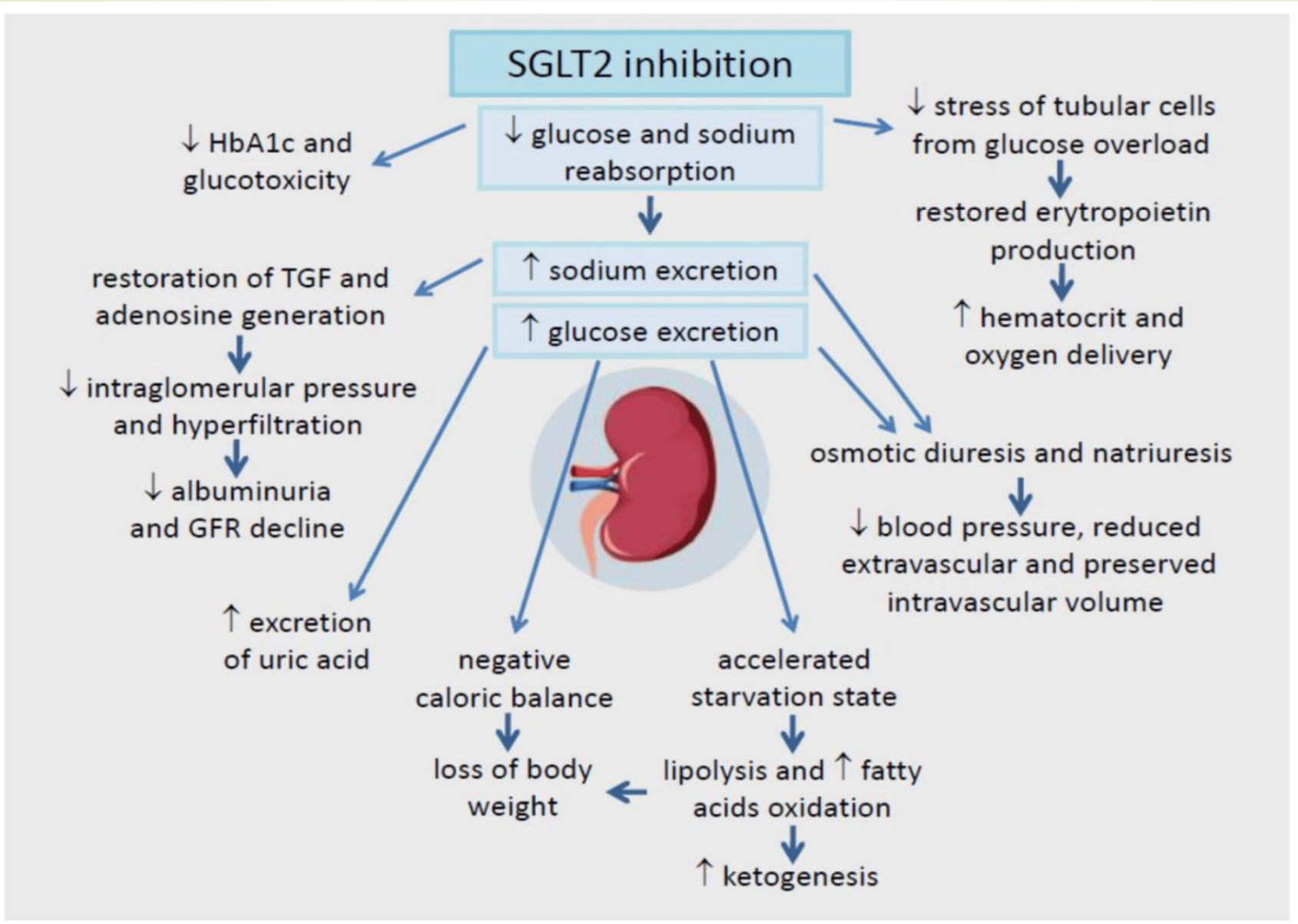
At 14 days:
The proportions of patients randomized to dapagliflozin with a >10%, >20% and >30% decline in eGFR were: 38.2%, 12.6%, and 3.4%, respectively; for placebo they were 21.0%, 6.4% and 1.3%, respectively.

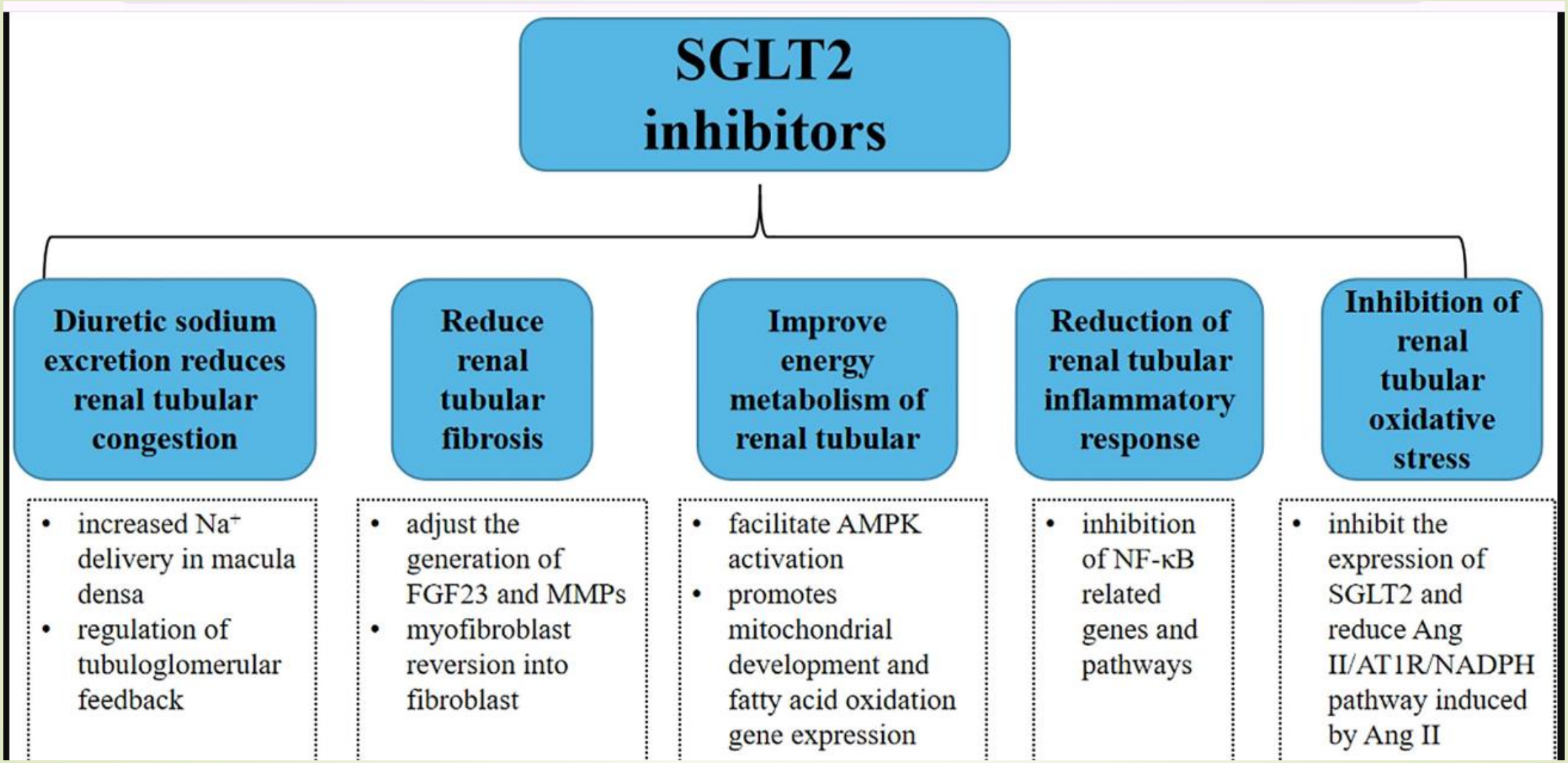
The number of patients with an eGFR decrease on dapagliflozin to <20 ml/min was 5 (0.22%)

eGFR Change Is More in Higher Initial eGFR and usually temporary

Early dip in GFR associated with better outcome

SGLT2i and Kidney




SGLT2 inhibitors
Diuretic sodium excretion reduces renal tubular congestion
• increased Na^+ delivery in macula densa
• regulation of tubuloglomerular feedback
Reduce renal tubular fibrosis
• adjust the generation of FGF23 and MMPs
• myofibroblast reversion into fibroblast
Improve energy metabolism of renal tubular
• facilitate AMPK activation
• promotes mitochondrial development and fatty acid oxidation gene expression
Reduction of renal tubular inflammatory response
• inhibition of NF-κB related genes and pathways
Inhibition of renal tubular oxidative stress
• inhibit the expression of SGLT2 and reduce Ang II/AT1R/NADPH pathway induced by Ang II

SGLT2 Inhibitors for CKD

Diabetic kidney disease	• Type 2 diabetes mellitus	• eGFR ≥25 ml/min per 1.73 m^2 • UACR 200–5000 mg/g[b]
Nondiabetic kidney disease	• Etiology of kidney disease: ischemic nephropathy, IgA nephropathy, FSGS, chronic pyelonephritis, chronic interstitial nephritis • No immunosuppression in prior 6 mo	• eGFR ≥ 25 ml/min per 1.73 m^2 • UACR 200–5000 mg/g[b]

SGLT2i have emerged as a key therapy to prevent progression of CKD in patients with albuminuria with or without diabetes including patients with IgA nephropathy, FSGS, and heart failure.

Conclusion

- SGLT2i therapy substantially mitigate cardiorenal morbidity in patients with CKD or HFrEF, regardless of the presence of T2DM and severity of CKD or HF.

- SGLT2i therapy is safe and well tolerated

SGLT2 Inhibitor

One Size Fits ALL?