

Insufficienza cardiaca: the revolution

HFpEF: dalla fisiopatologia alle evidenze cliniche del trattamento con SGLT2i

Prof. Nodari Savina



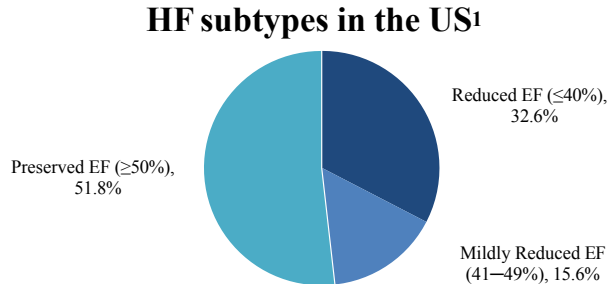
**Università
di Brescia**

Dipartimento Specialità Medico-Chirurgiche
Scienze Radiologiche e Sanità Pubblica



HFpEF is the most common form of HF worldwide

HFpEF accounts
for **~50%**
of HF cases¹



Prevalence of HFpEF vs HFrEF²



by **~1%**
annually

Gap expected to widen due to²:



- Aging population
- >70% of HF patients older than 65 years have HFpEF



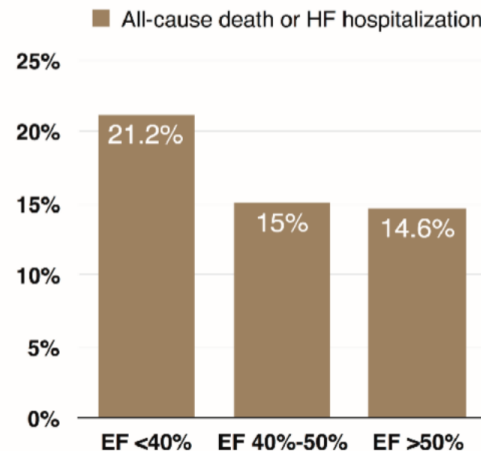
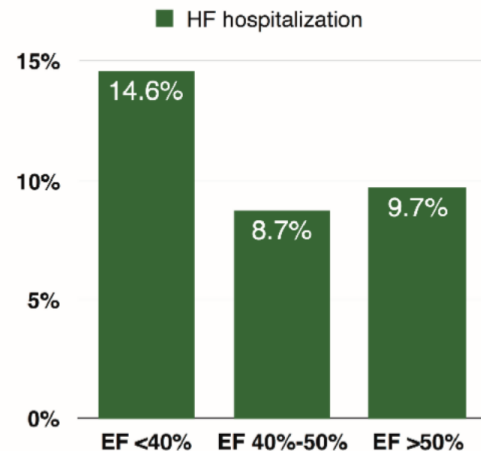
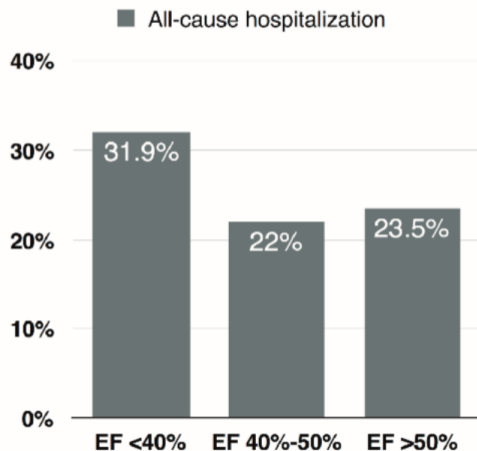
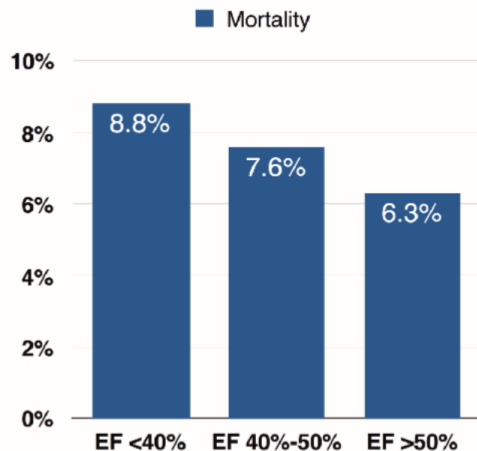
- Increasing prevalence of conditions associated with the development of HFpEF (e.g., obesity, insulin resistance, T2D)

EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes; US, United States

1. Gurwitz JH et al. *Am J Med* 2013;126:393–400; 2. Borlaug BA. *Nat Rev Cardiol* 2020;7:559–573

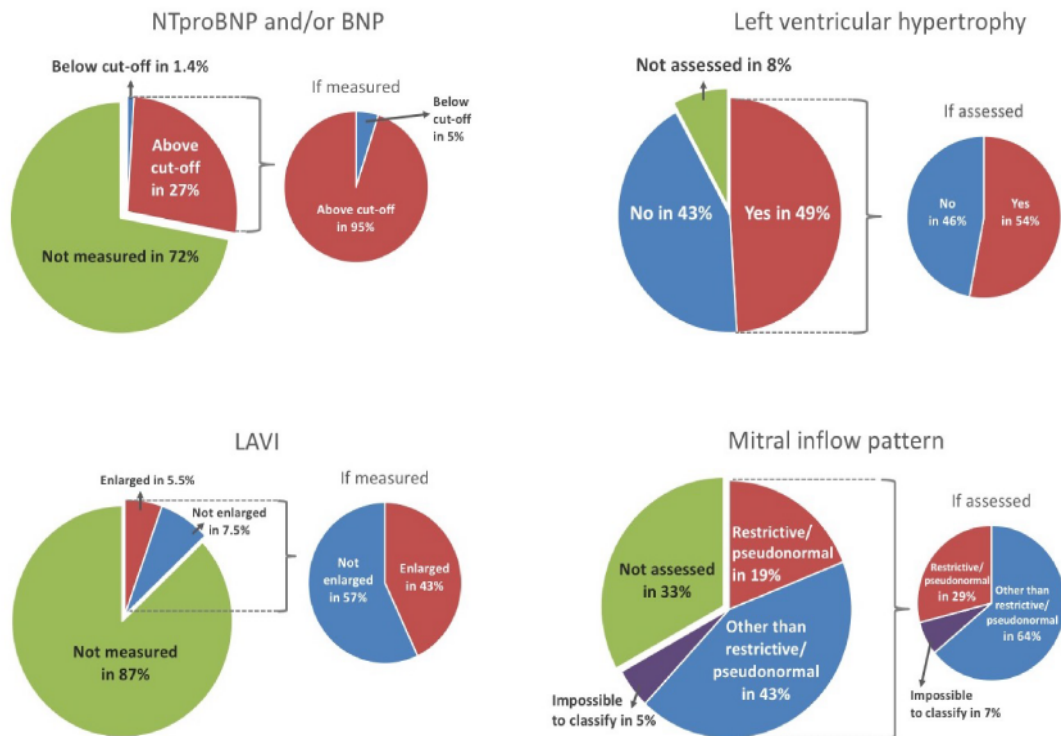


Outcomes at 1 year in outpatients with heart failure in the ESC Heart Failure Long-Term Registry

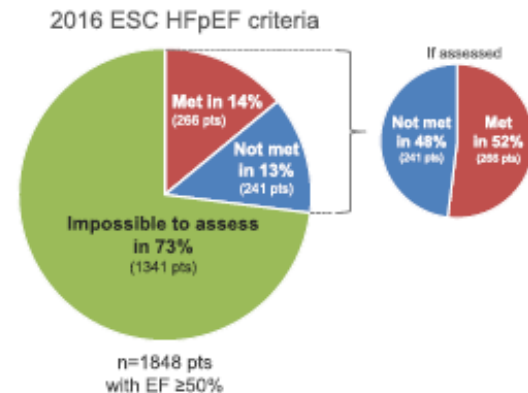


Is heart failure misdiagnosed in hospitalized patients with preserved ejection fraction?
From the European Society of Cardiology - Heart Failure Association EURObservational Research Programme Heart Failure Long-Term Registry

A



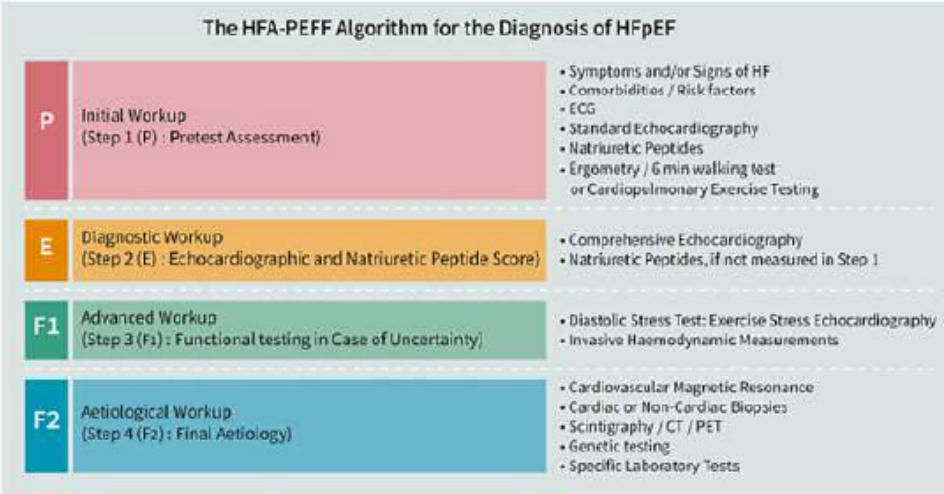
B



Different Diagnostic Algorithm

	Clinical Variable	Values	Points
H ₂	Heavy	Body mass index > 30 kg/m ²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
H ₂ FPEF score			Sum (0-9)
Total Points			
Probability of HFpEF			

Reddy M. et Al., *Circulation*, 2018



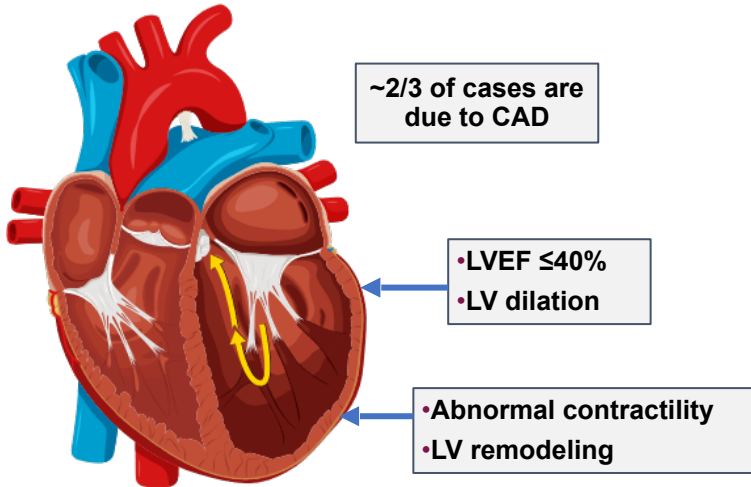
	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m ² or LVMI ≥ 149/122 g/m ² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m ² or LVMI > 115/95 g/m ² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml
Major Criteria: 2 points		≥ 5 points: HFpEF		
Minor Criteria: 1 point		2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements		

Pieske B. et Al., *European Heart Journal*, 2019

Differences in HF Pathophysiology

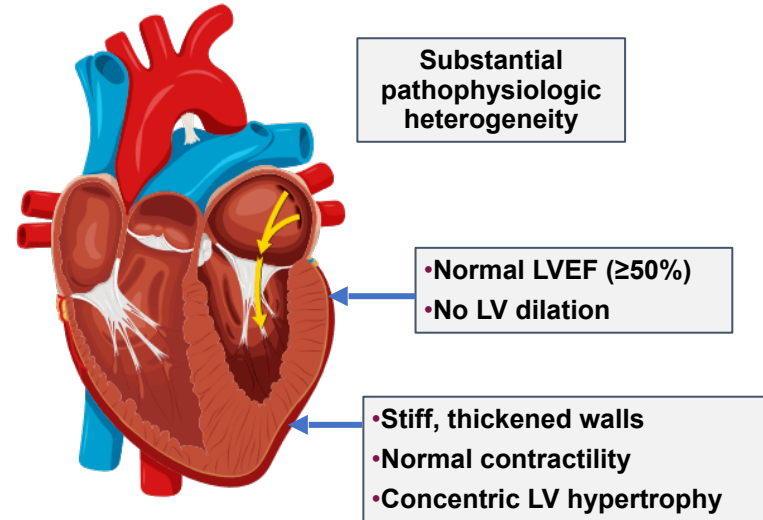
HFrEF

LV contraction is reduced resulting in inadequate cardiac output.

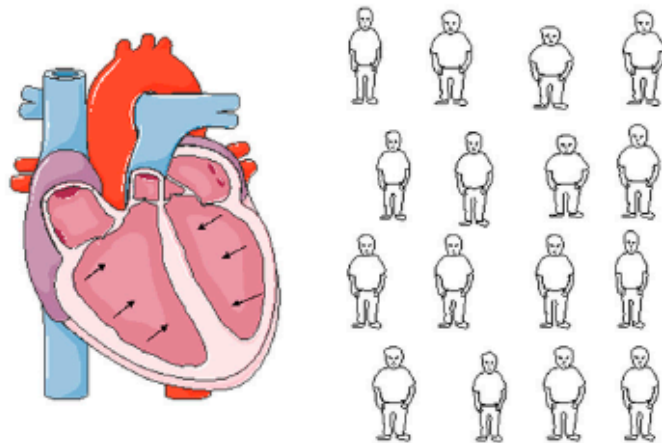


HFpEF

LV filling is reduced so that, even though LVEF is normal, cardiac output is reduced.



HFrEF



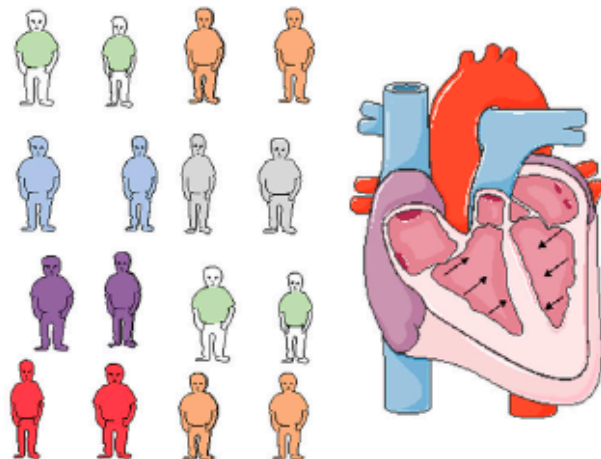
Homogeneous response to treatment

Several pharmacological and non-pharmacological interventions with established benefit on CV mortality and HF hospitalizations

«One size fits all approach»

Progress in Cardiovascular Diseases 63 (2020) 570–584

HFpEF



Heterogeneous population

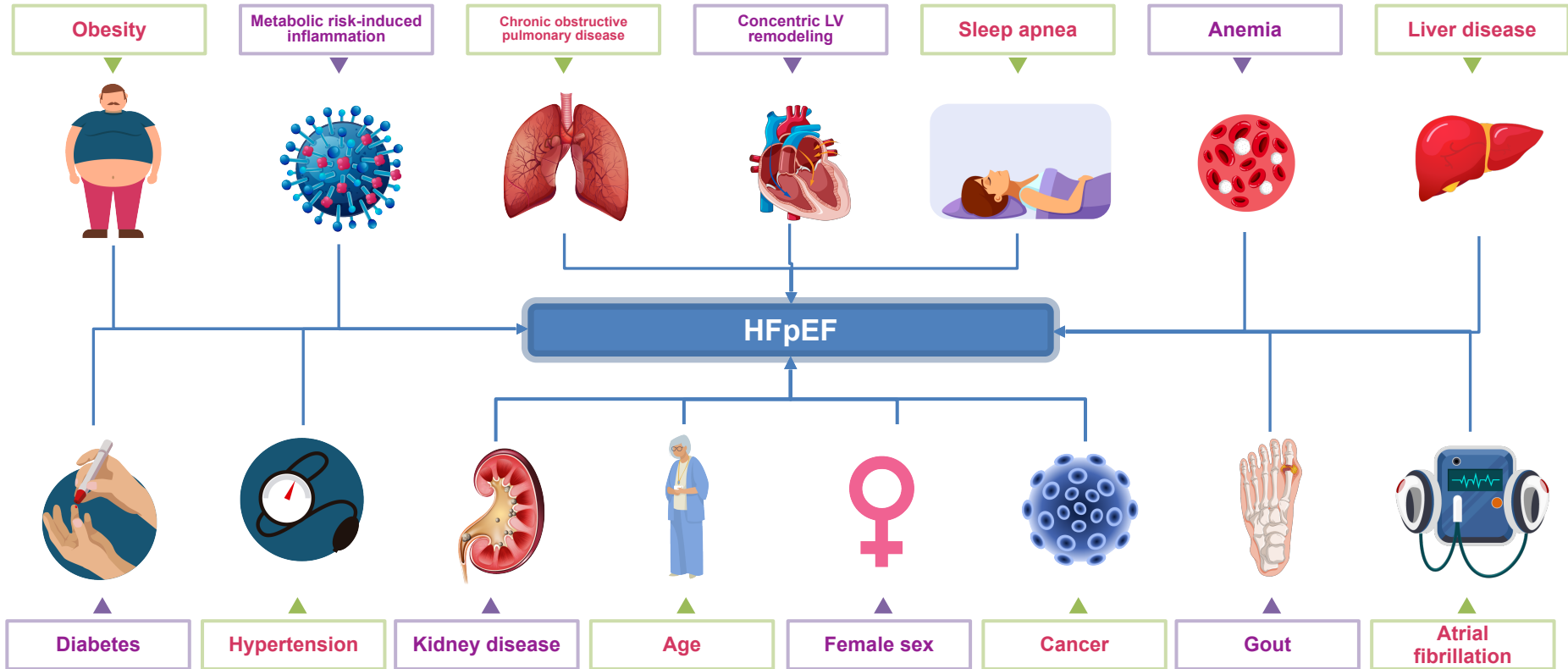
No effective treatments on CV mortality

Benefit of decongestion and MRA (trend with Candesartan and ARNI) on HF hospitalizations
Benefit of lifestyle interventions on symptoms and QoL

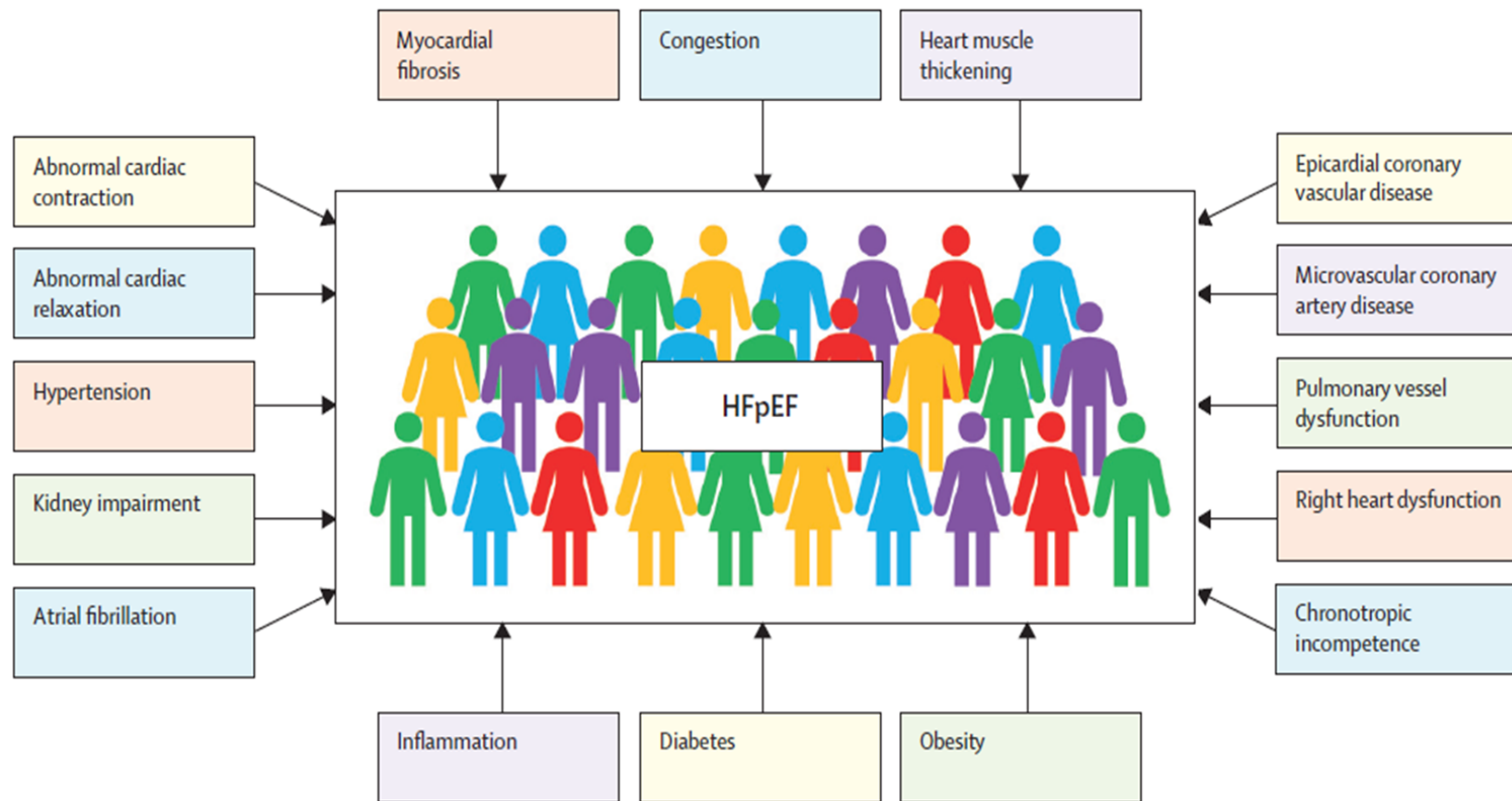
«Phenotype-specific treatment»

HFpEF has many comorbidities and risk factors

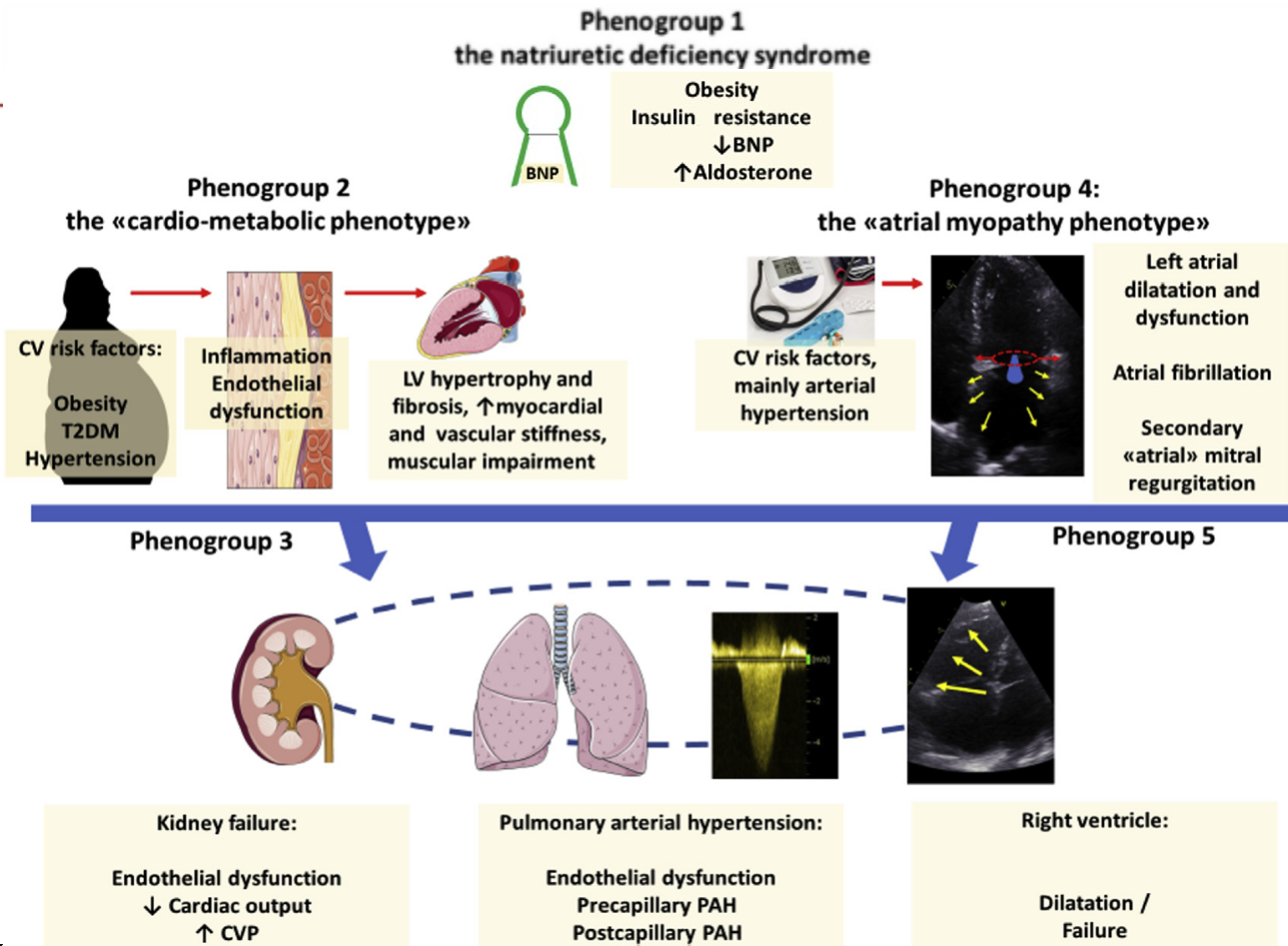
Risk factors and comorbidities involved in the development of HFpEF



HFpEF

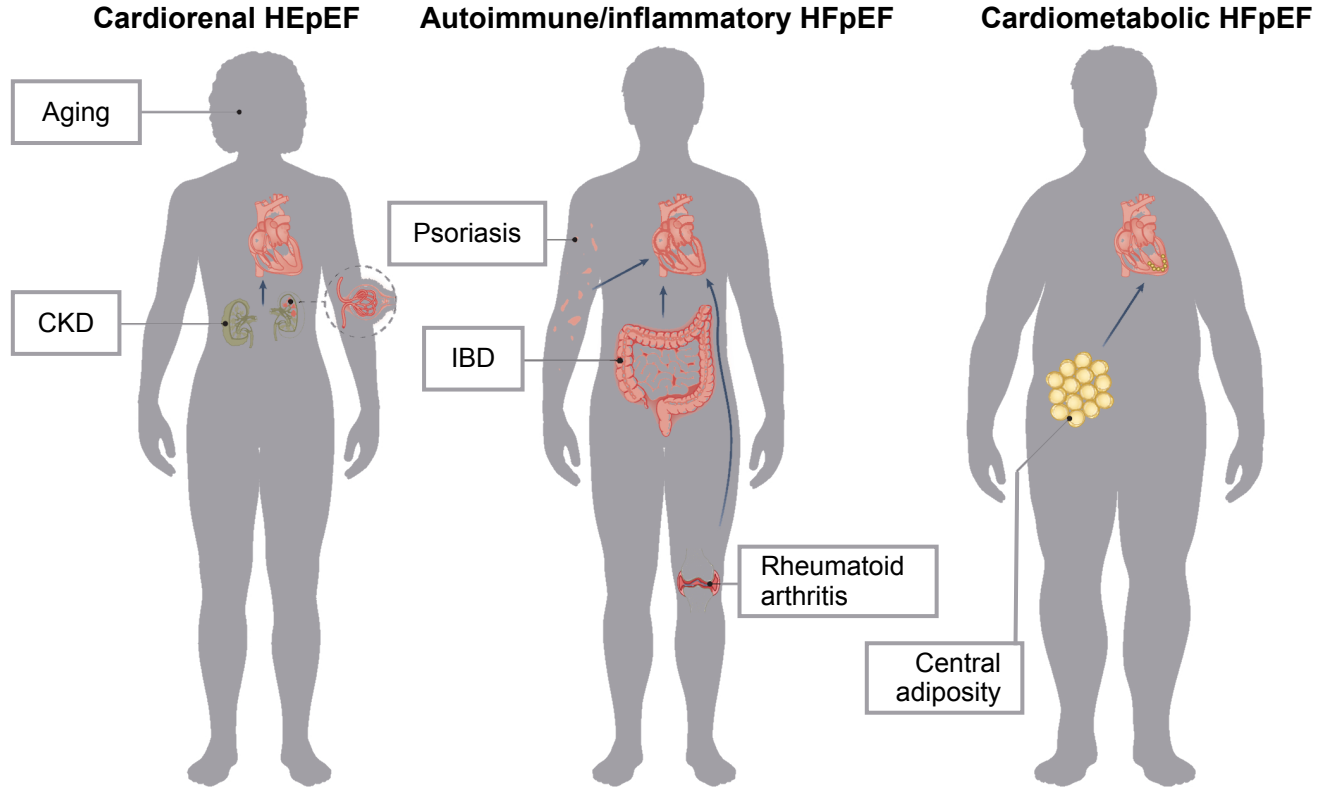


Main HFpEF clusters identified across different studies



BNP, B-type natriuretic peptide; CV, cardiovascular; CVP, central venous pressure; LV, left ventricular; PAH, pulmonary artery hypertension Galli E et al. *Heart Failure Clin* 17 2021;499–518

Fenotipi più comuni di HFpEF



CKD, chronic kidney disease; IBD, inflammatory bowel disease

Picture adapted from Schiattarella, G.G., Alcaide, P., Condorelli, G. et al. Immunometabolic mechanisms of heart failure with preserved ejection fraction. *Nat Cardiovasc Res* 1, 211–222 (2022)

HFpEF Is a Systemic Syndrome

Comorbidities induce systemic inflammation

Obesity



Hypertension



Type 2 Diabetes



Renal Insufficiency



Multi-organ involvement leads to diverse phenotypes HFpEF

Myocardial remodeling



Pulmonary hypertension



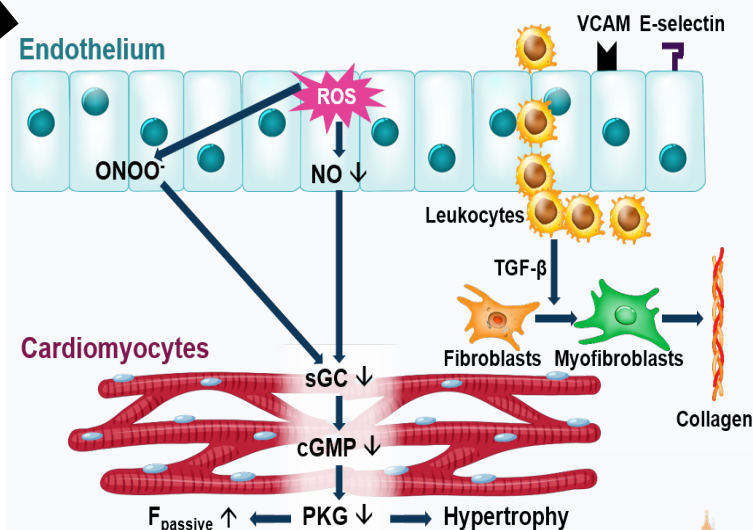
Renal sodium retention



Deficient skeletal muscle O₂ extraction during exercise



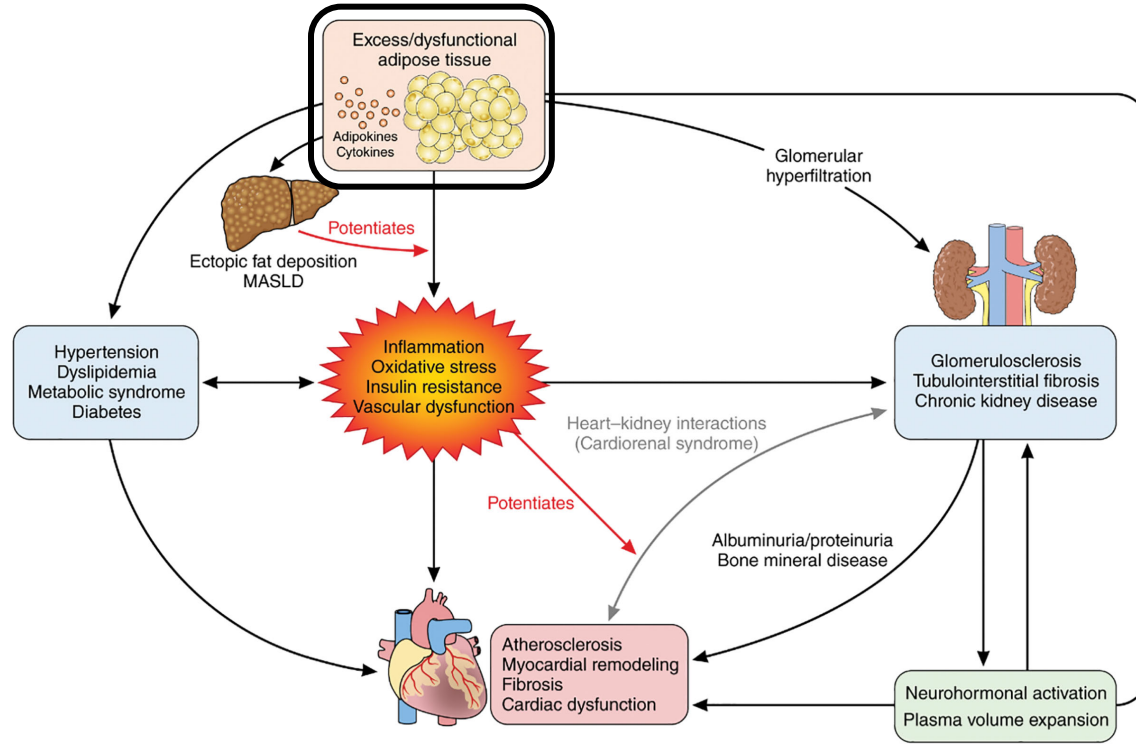
Endothelium-Cardiomyocyte Signaling



cGMP = cyclic guanosine monophosphate; F_{passive} = passive force; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; NO = nitric oxide; O₂ = oxygen; ONOO⁻ = peroxynitrite; PKG = protein kinase G; ROS = reactive oxygen species; sGC = soluble guanylate cyclase; TGF-β = transforming growth factor β; VCAM = vascular cell adhesion molecule.

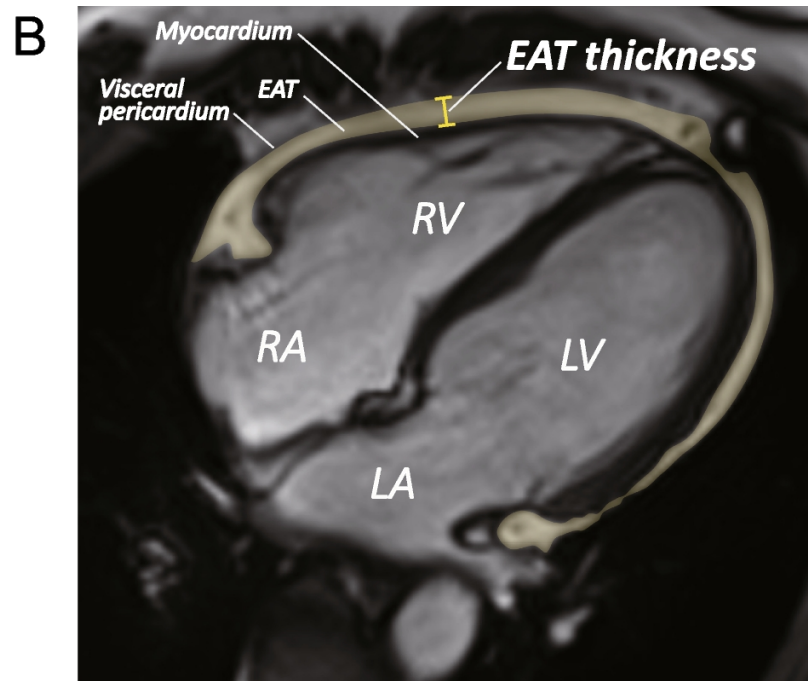
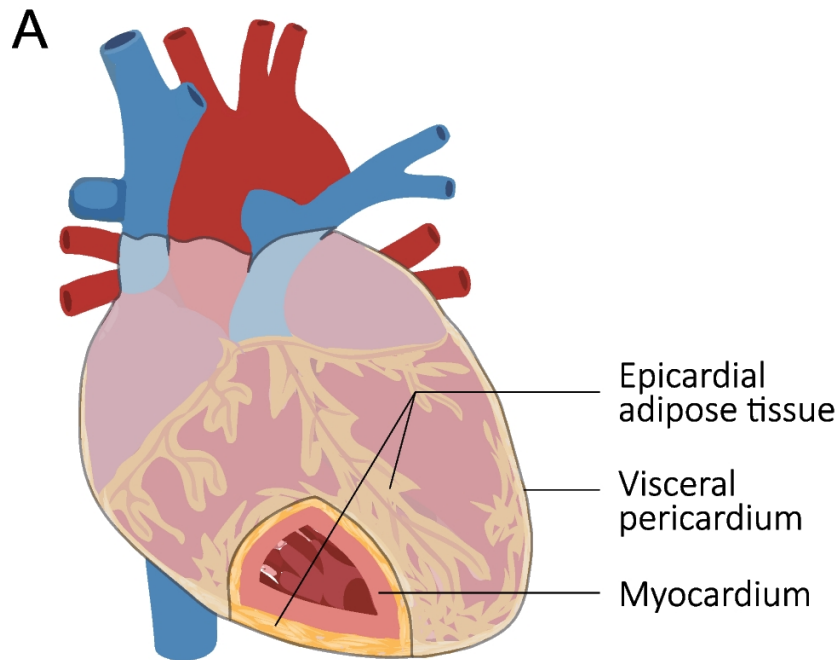
Adapted from Shah SJ et al. *Circulation*. 2016;134:73-90.

Pathophysiology of the Cardiovascular-Kidney-Metabolic (CKM) syndrome: A Scientific Statement From the American Heart Association



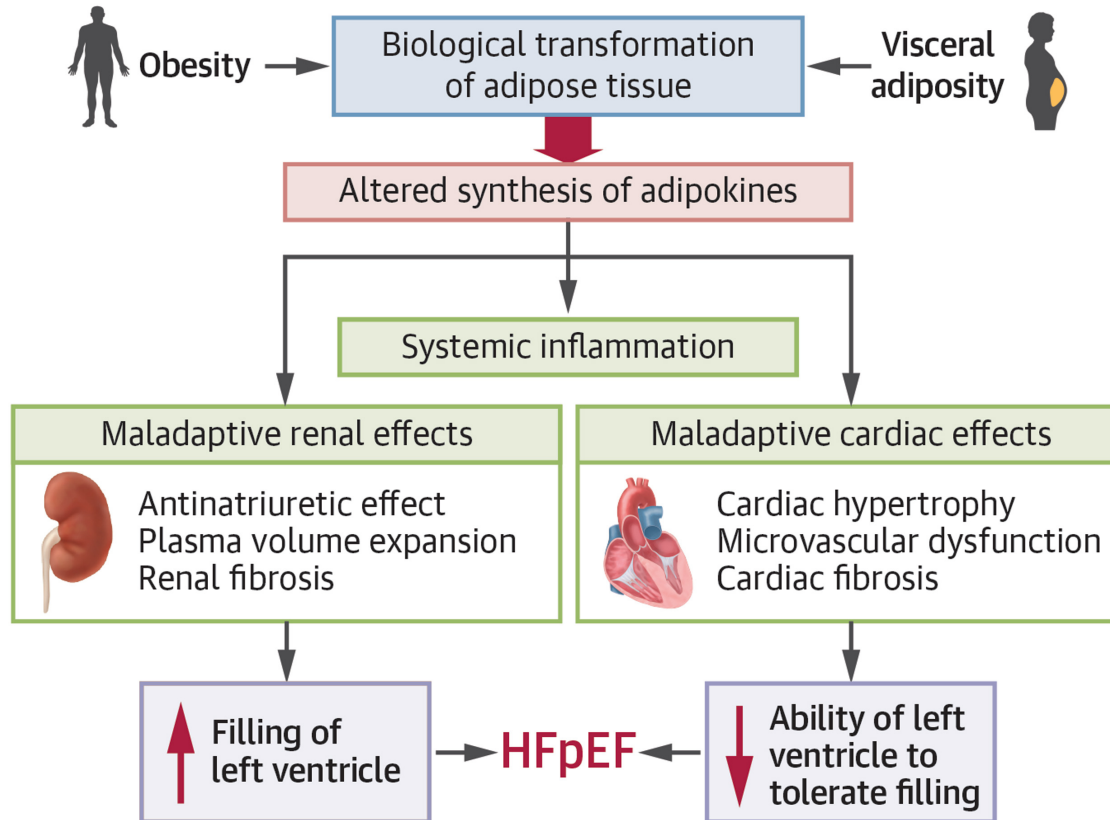
Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Després JP, Ho JE, Joseph JJ, Kernan WN, Khera A, Kosiborod MN, Lekavich CL, Lewis EF, Lo KB, Ozkan B, Palaniappan LP, Patel SS, Pencina MJ, Powell-Wiley TM, Sperling LS, Virani SS, Wright JT, Rajgopal Singh R, Elkind MSV, Rangaswami J; American Heart Association. . *Circulation*. 2023 Nov 14;148(20):1636-1664.

Localization and measurement of epicardial adipose tissue (EAT)

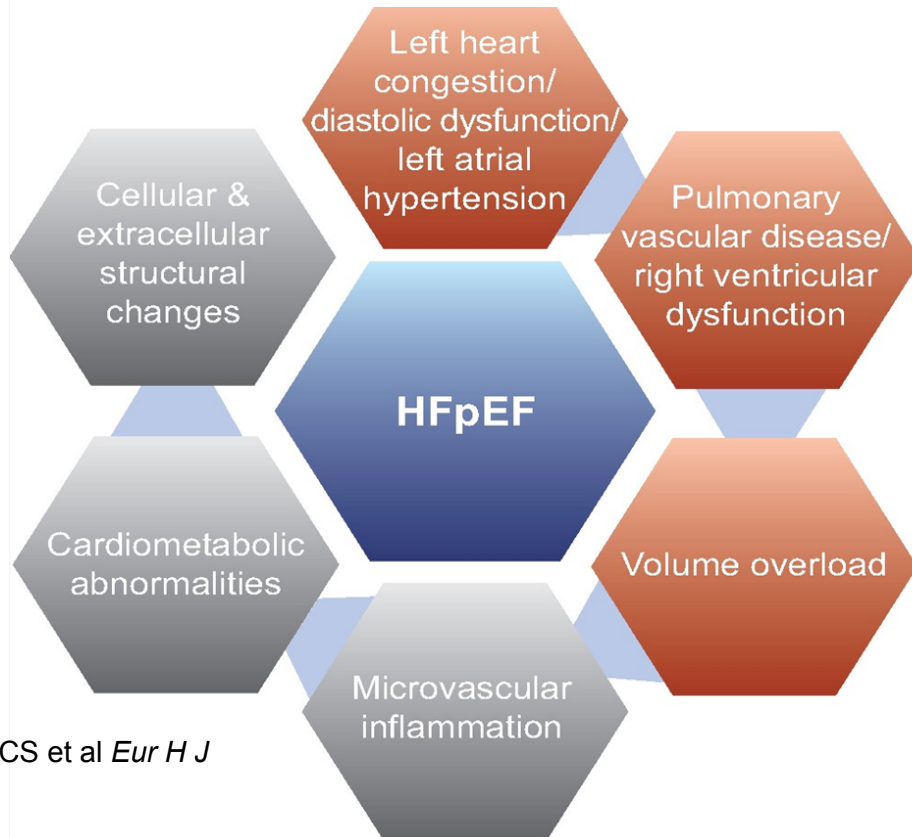


Choy M, Huang Y, Peng Y, Liang W, He X, Chen C, Li J, Zhu W, Wei FF, Dong Y, Liu C, Wu Y. Association between epicardial adipose tissue and incident heart failure mediating by alteration of natriuretic peptide and myocardial strain. BMC Med. 2023 Mar 29;21(1):117. doi: 10.1186/s12916-023-02836-4. PMID: 36978080; PMCID: PMC10053458.

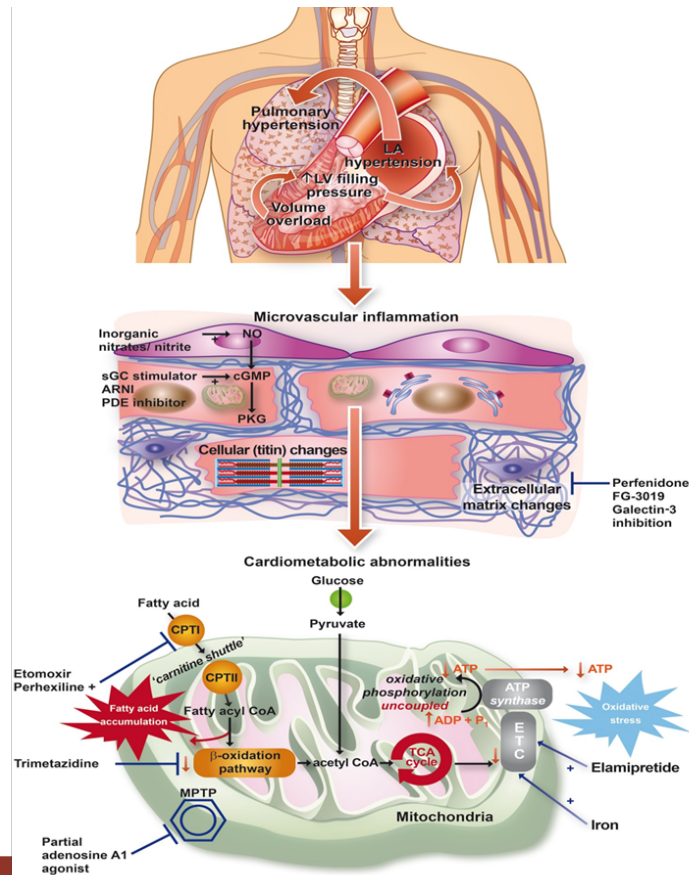
The Adipokine Hypothesis of HFpEF



Heart failure with preserved ejection fraction: from mechanisms to therapies



Lam CS et al *Eur H J*
2018

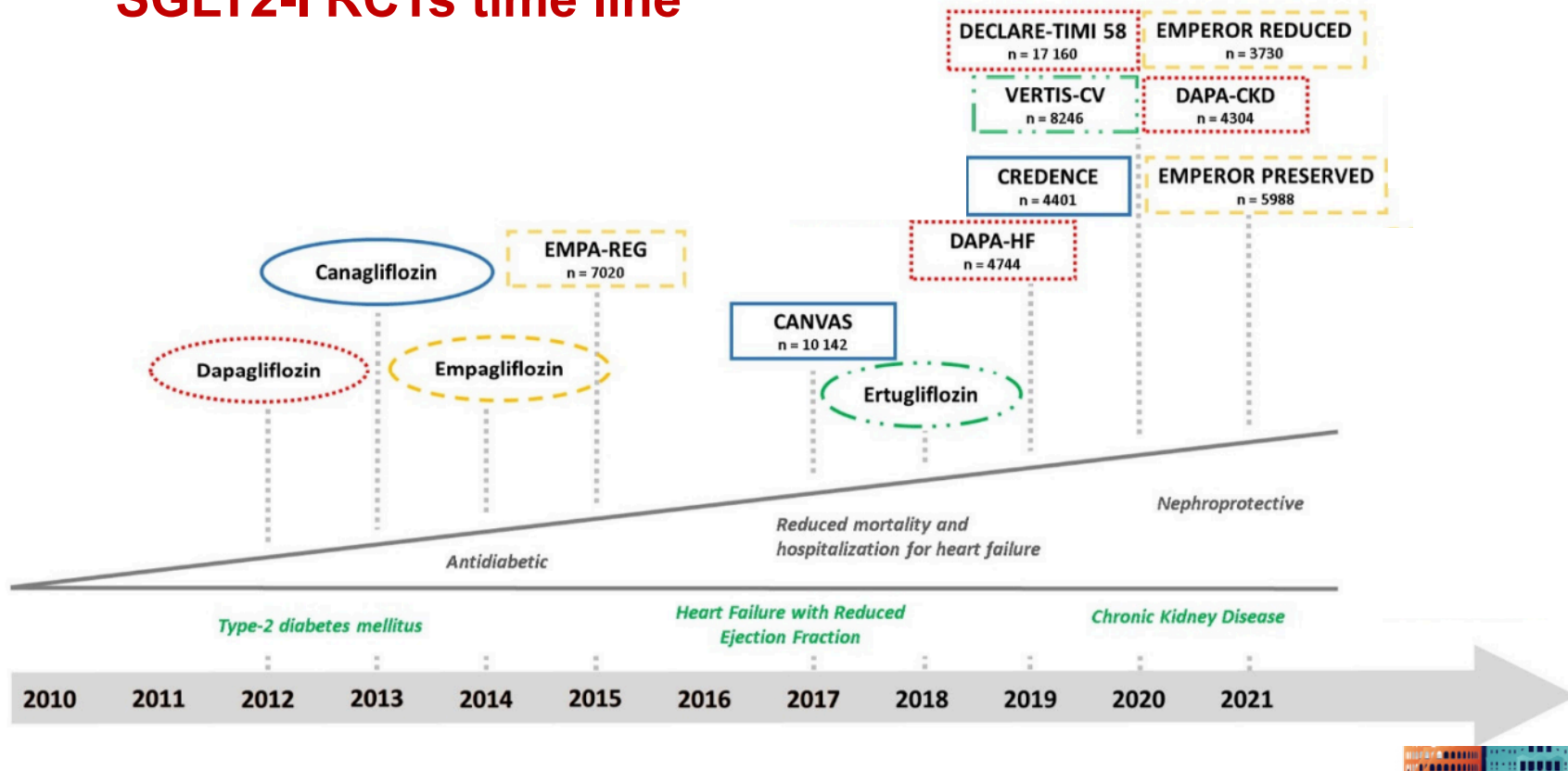


Sodium Glucose Cotransporter 2 Inhibitors

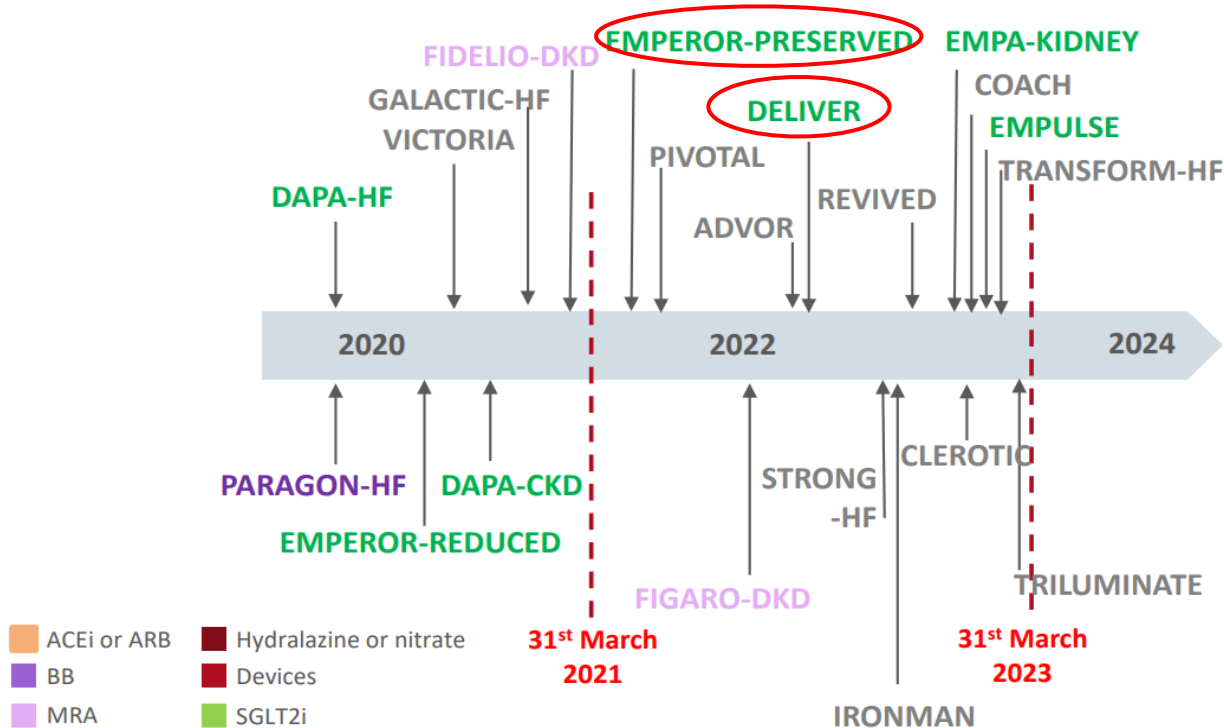
- Phlorizin, mixed SGLT1-2 and inhibitor discovered 150 yrs ago
- First tested in 1930s, found to cause glucosuria and lower BG
- Not used in humans due to lack of selectivity and poor absorption
- Clinical development eventually led to selective SGLT2i
- Dapagliflozin first approved for T2D in EU (2011), canagliflozin in the US (2013)



SGLT2-I RCTs time line



Amazing progress in heart failure



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. Chuquiere-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*

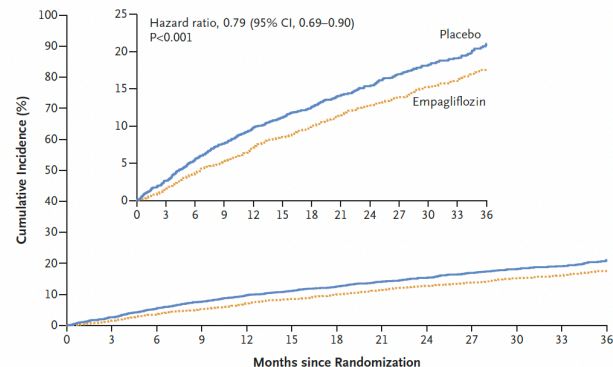
The NEW ENGLAND JOURNAL of MEDICINE

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. Drozd, J.C. Fang, M.A. Alcocer-Gamba, W. Al Hakeeb, 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. Thierier, 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*

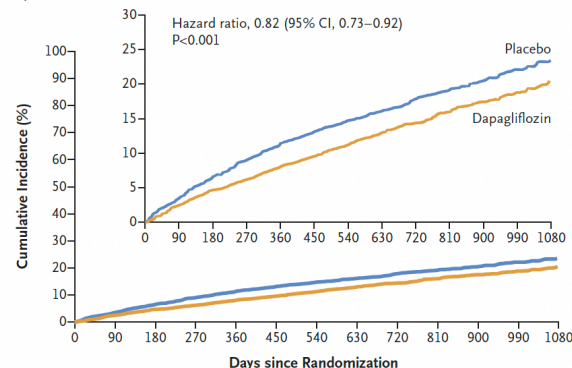
CV death or HF hospitalization



No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

A Primary Outcome

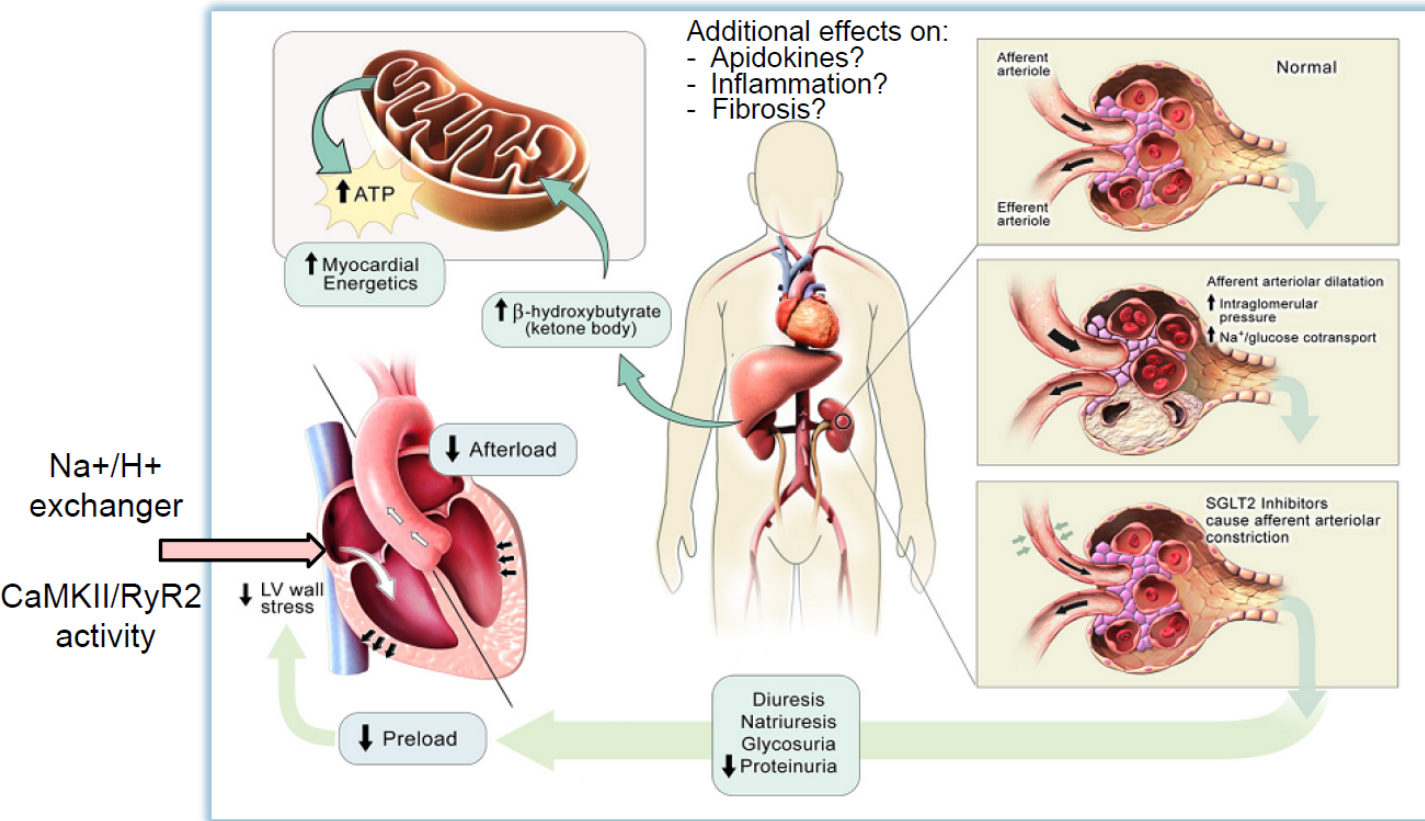


No. at Risk

Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389



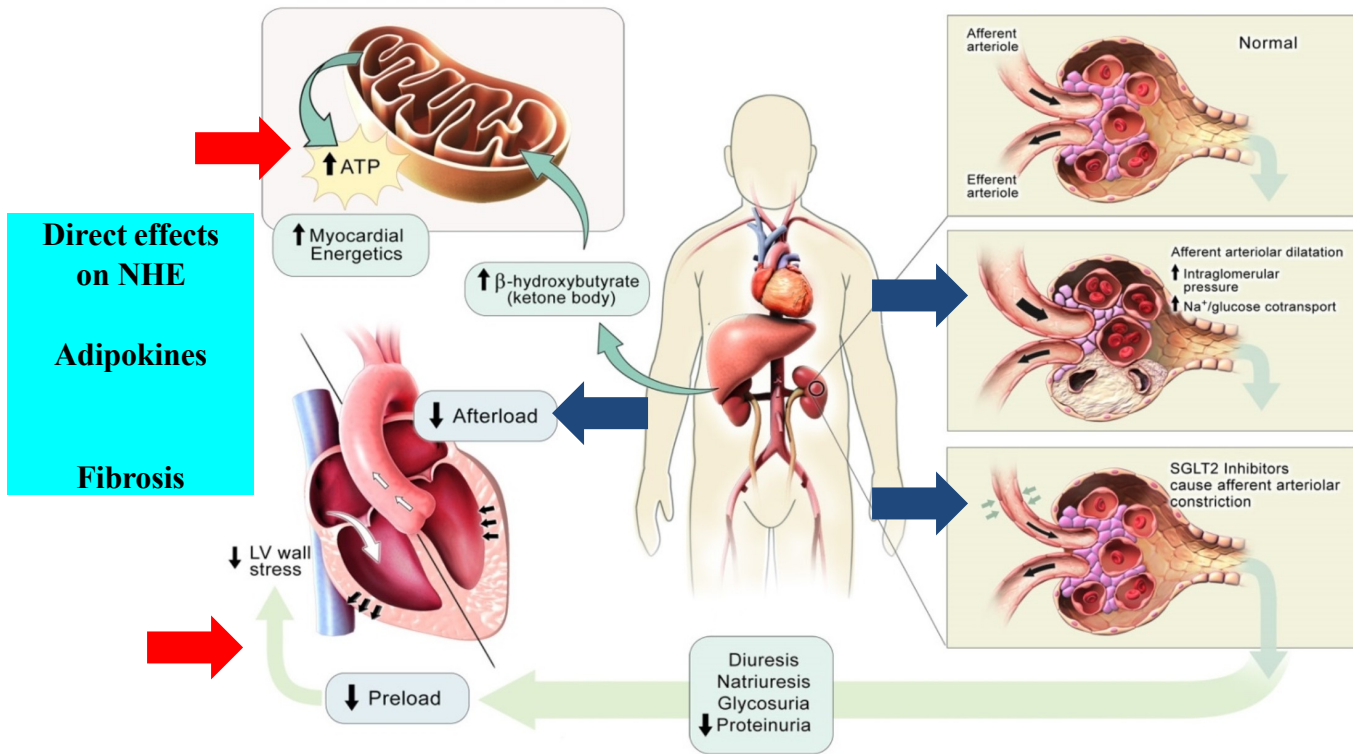
SGLT2 inhibitors: How do they work?



Adapted from
Verma, McMurray
& Cherney JAMA
Cardiol. 2017;
2:939-940



SGLT2 Inhibition and Mechanisms in HFpEF

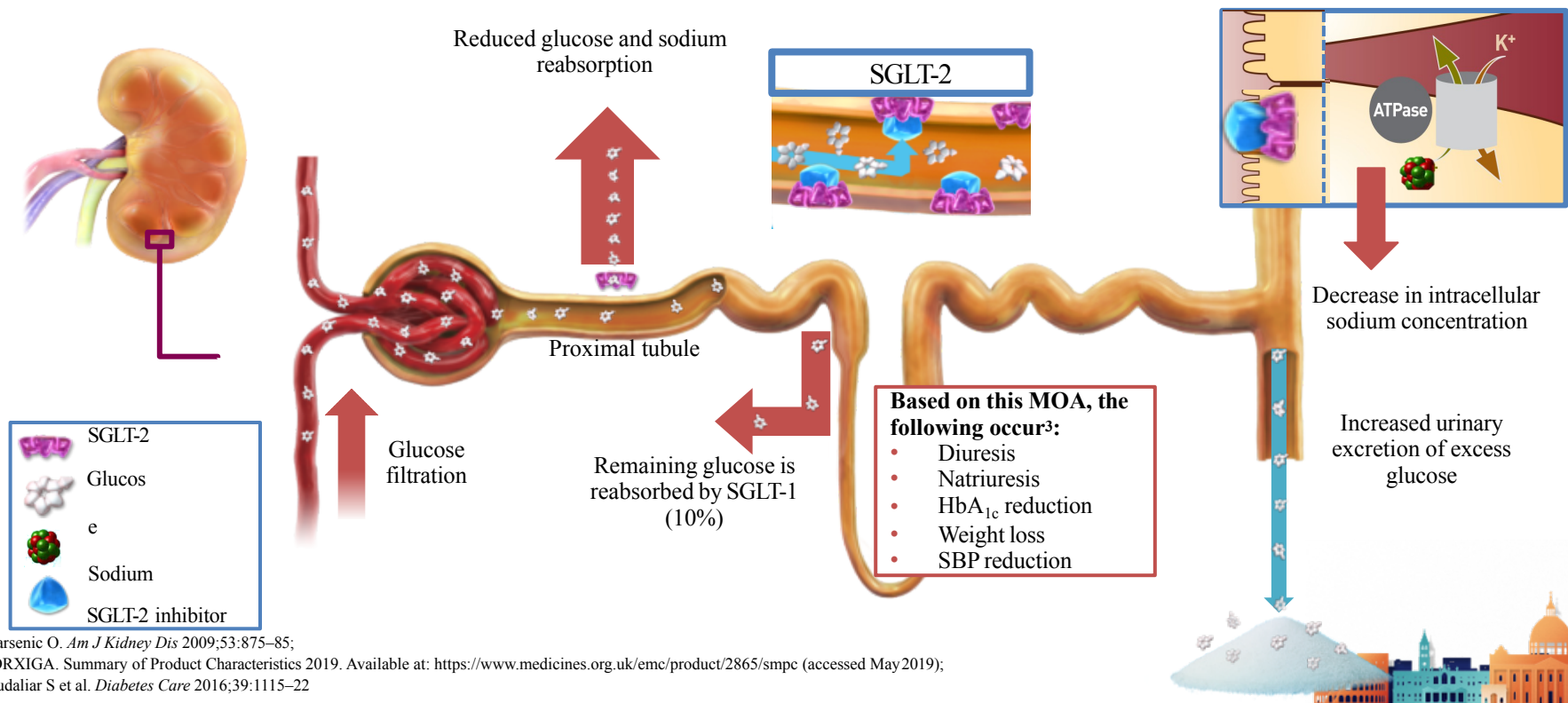


- Improved hemodynamics
 - Diuresis
 - Natriuresis
 - Afterload reduction
 - Lower PA pressure
- LV remodeling
- Myocardial energetics and metabolomics
- Nephroprotection

NHE, Sodium-hydrogen exchange; TGF, Transforming growth factor
Modified from Verma S, McMurray JJV, Cherney D. JAMA Cardiol 2017;2:939



SGLT-2 Inhibitors Block SGLT-2 and Reduce Glucose and Na⁺ Reabsorption¹⁻³

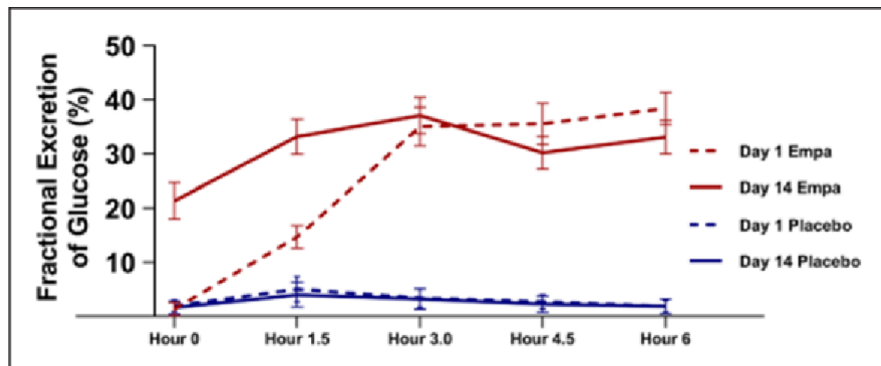


1. Marsenic O. *Am J Kidney Dis* 2009;53:875–85;

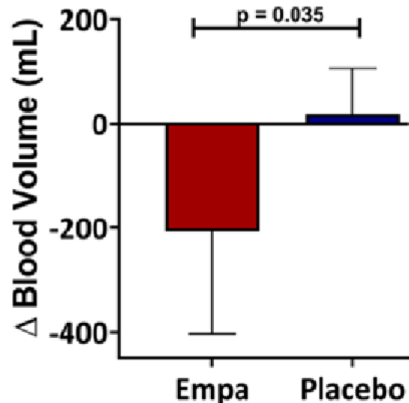
2. FORXIGA. Summary of Product Characteristics 2019. Available at: <https://www.medicines.org.uk/emc/product/2865/smpc> (accessed May 2019);

3. Mudaliar S et al. *Diabetes Care* 2016;39:1115–22

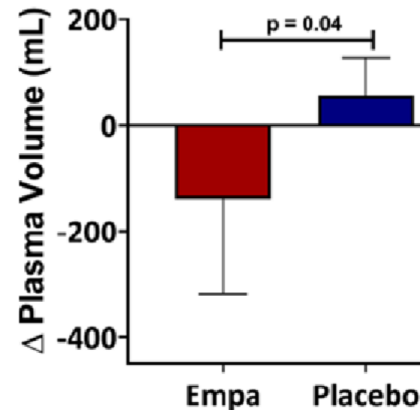
SGLT2 Inhibition and Diuretic Effects



A Change in Blood Volume at 14 Days



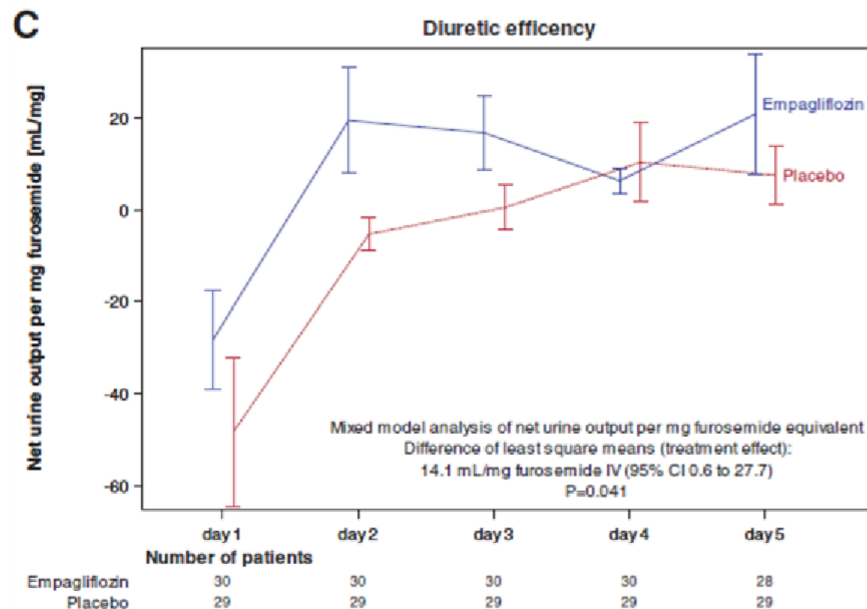
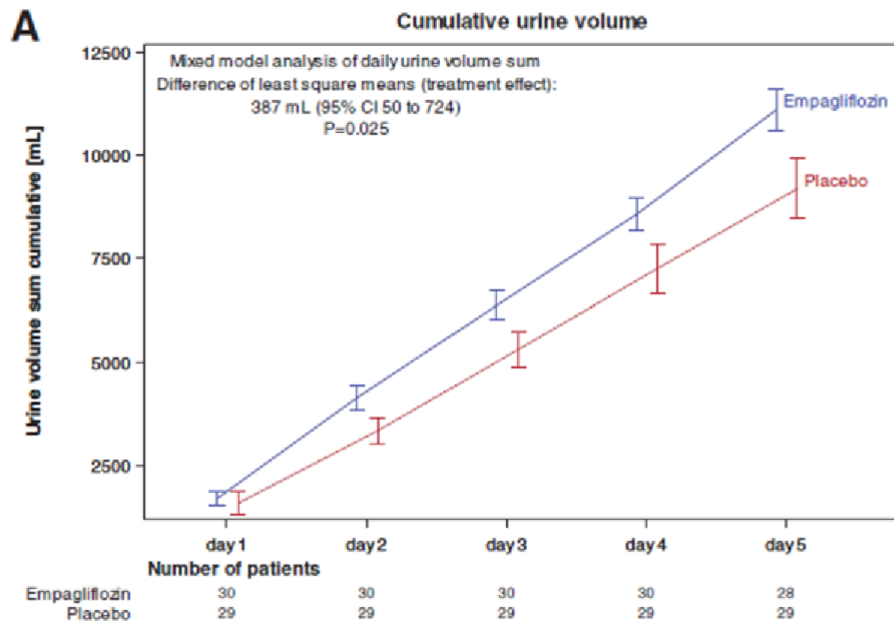
B Change in Plasma Volume at 14 Days



Testani et al, Circulation 2020



Effects on Urine Volume in Acute HF

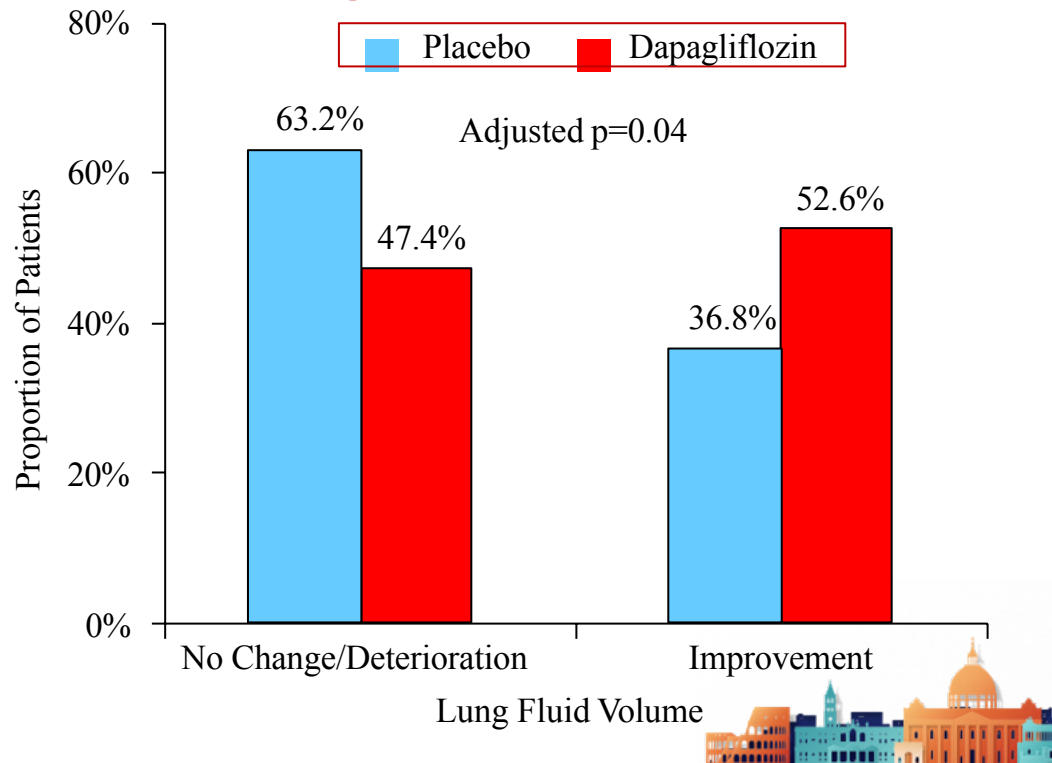


Schulze et al, Circulation 2022



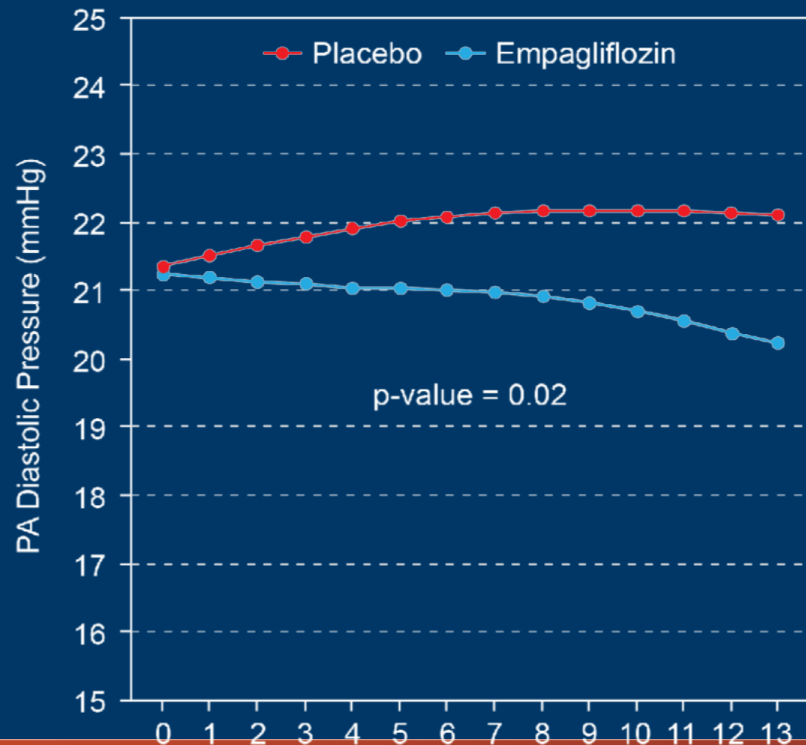
Proportion of Patients Who Experienced Improvement versus No Change/Deterioration in Lung Fluid Volume

- No significant difference in mean adjusted LFV at 12 weeks with dapagliflozin vs. placebo (34% vs. 35%, $p = 0.3$)
- Significantly fewer dapagliflozin-treated patients experienced no change/ deterioration in LFV – and a greater proportion of dapagliflozin-treated patients had an improvement in LFV

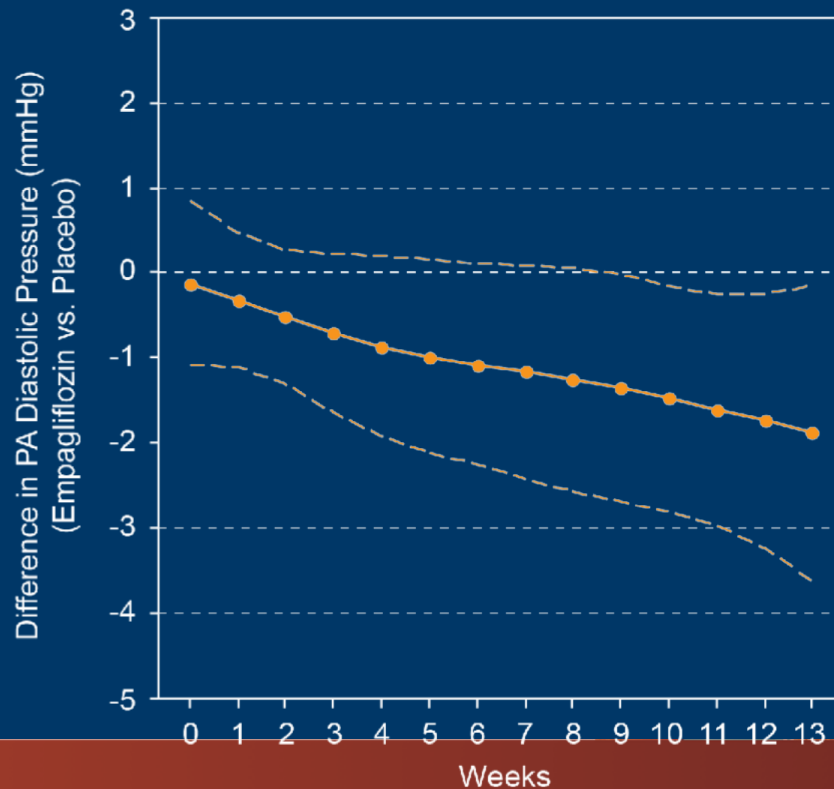


PA Diastolic Pressure

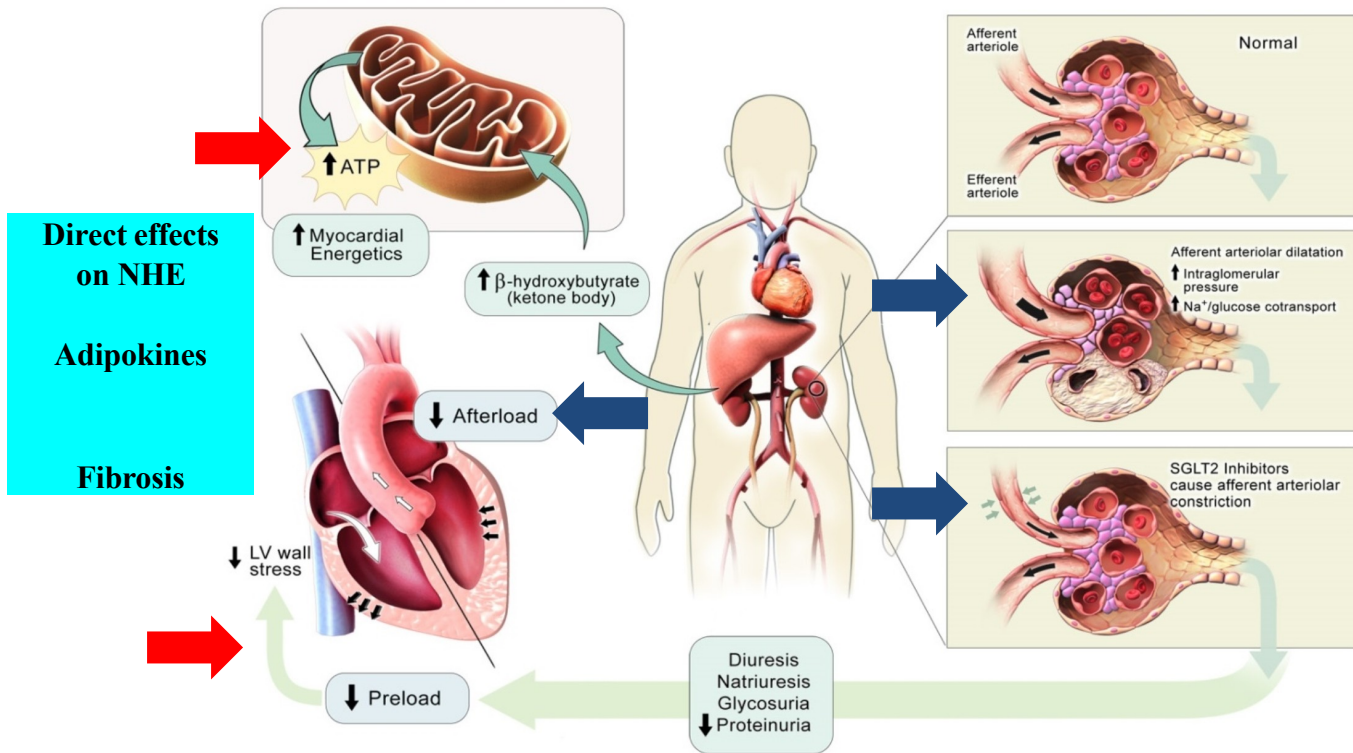
A. Effects of Empagliflozin vs. Placebo on Pulmonary Artery Diastolic Pressure



B. Difference in Pulmonary Artery Diastolic Pressure between Empagliflozin and Placebo over Time



SGLT2 Inhibition and Mechanisms in HFpEF

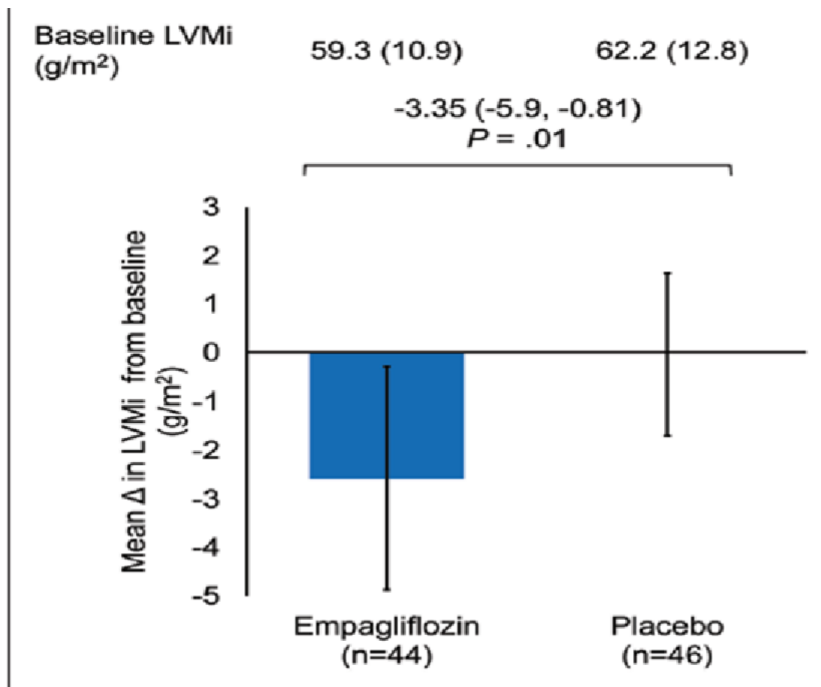


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NHE, Sodium-hydrogen exchange; TGF, Transforming growth factor
Modified from Verma S, McMurray JJV, Cherney D. JAMA Cardiol 2017;2:939



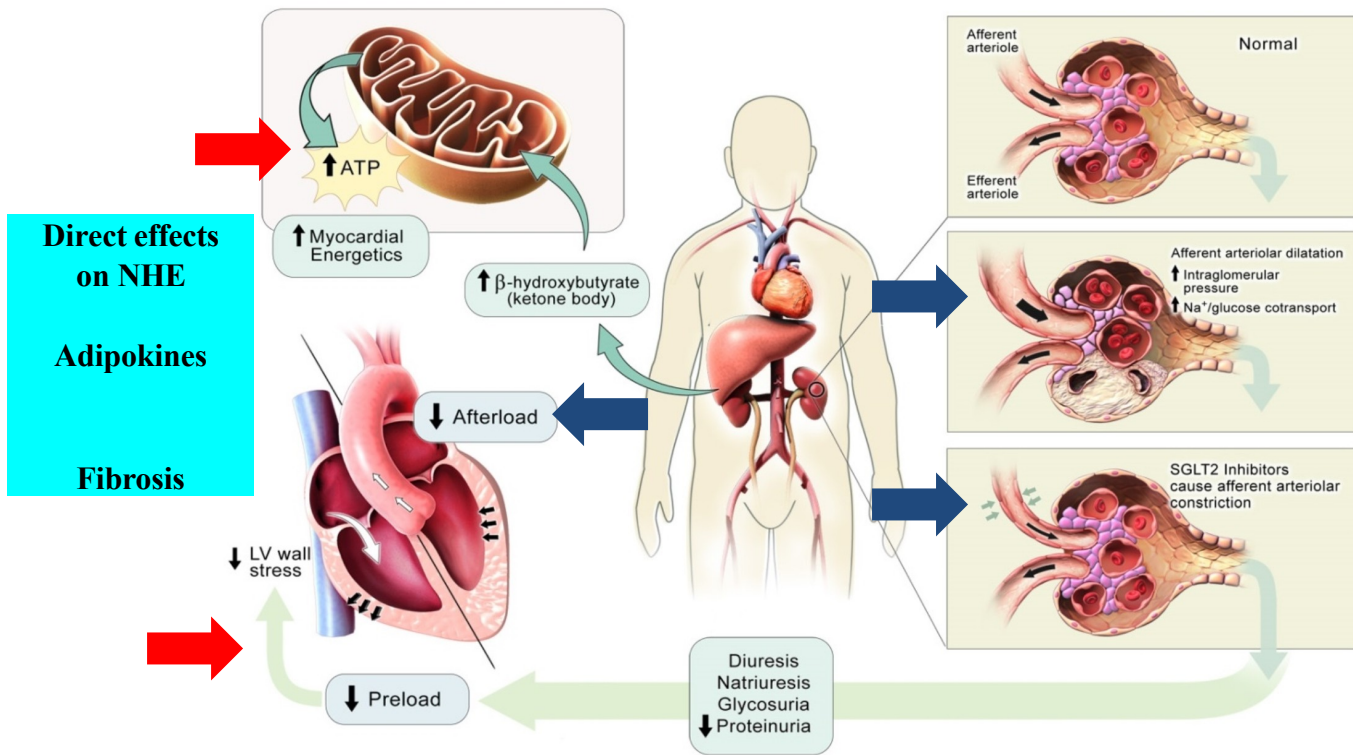
SGLT2 Inhibition and LV Remodeling



Verma S et al Circulation 2019



SGLT2 Inhibition and Mechanisms in HFpEF

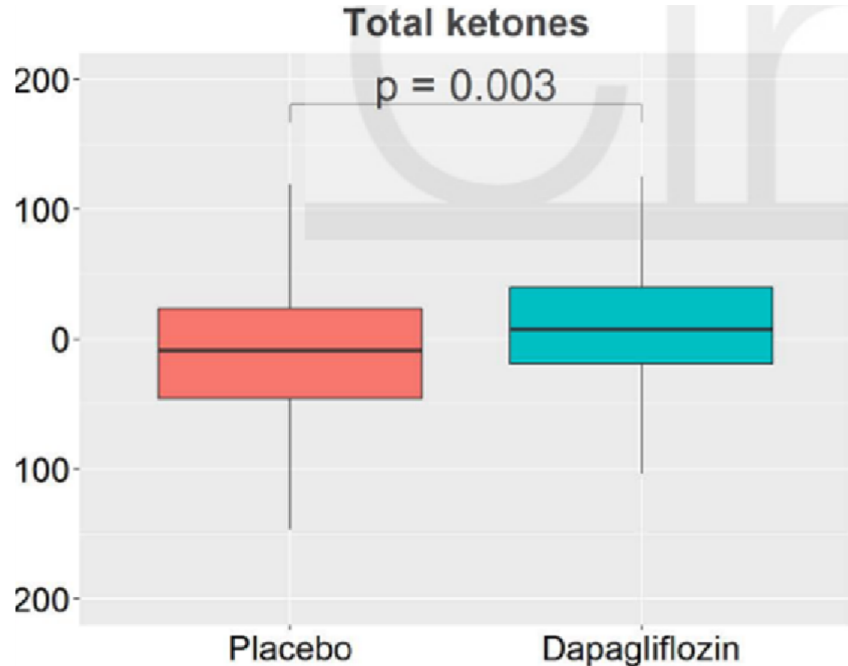
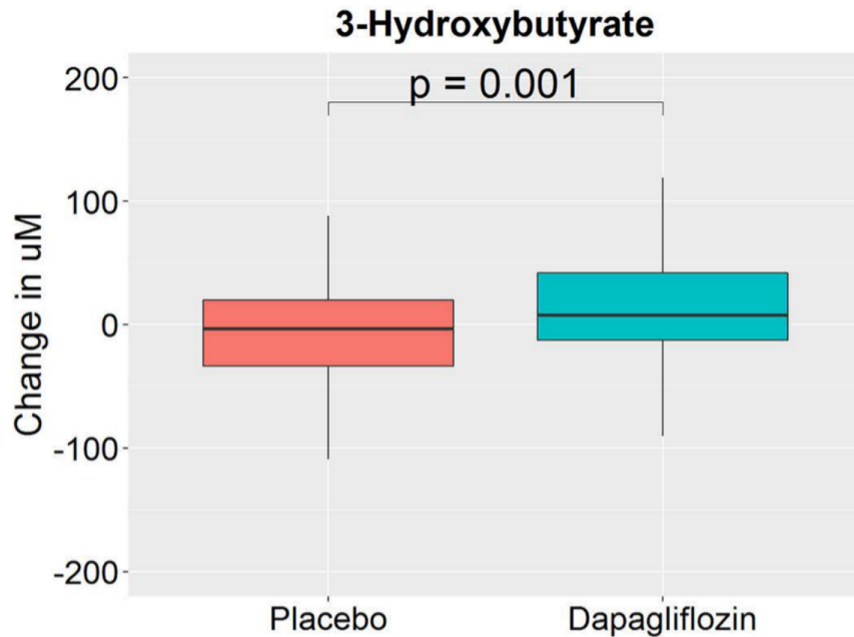


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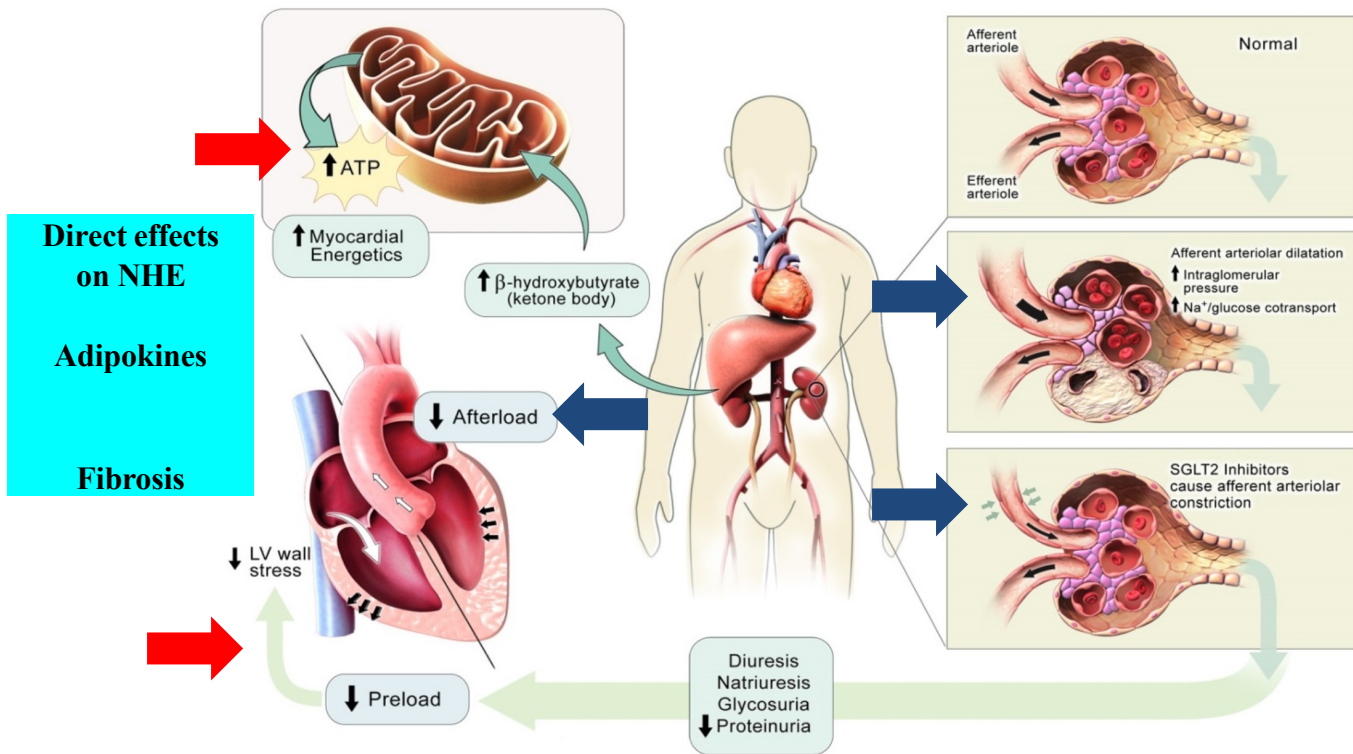
SGLT2 Inhibition and Metabolomics in HF



Selvaraj S et al Circulation 2022



SGLT2 Inhibition and Mechanisms in HFpEF



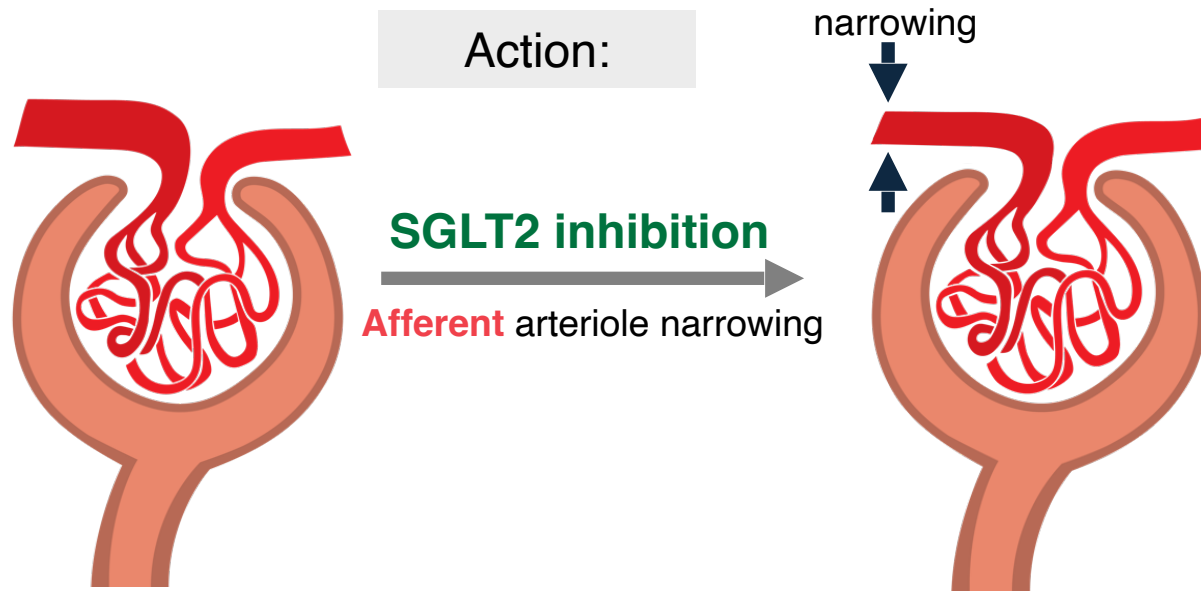
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Modified from Verma S, McMurray JJV, Cherney D. JAMA Cardiol 2017;2:939



SGLT2i exert a hemodynamic effect within the kidney

- By restoring the **Tubulo-Glomerular Feedback** (TGF), empagliflozin increases the afferent arteriole tone, thereby lowering glomerular hypertension^{1,2}



Clinical implications:

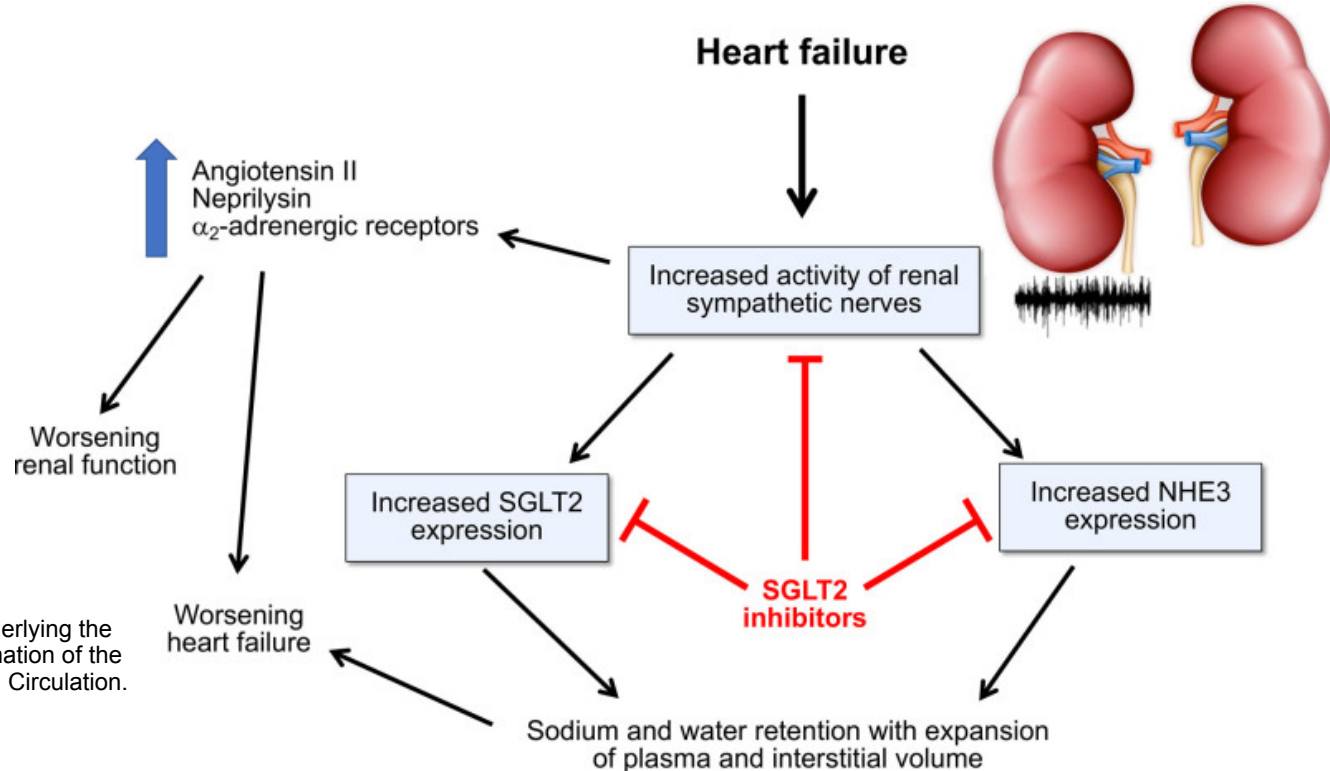
- Glomerular pressure decreases
- Early clinical marker:
 - Initial dip in GFR
 - Reduction of albuminuria

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.

1. Adapted from: Cherney D et al. Circulation 2014;129:587

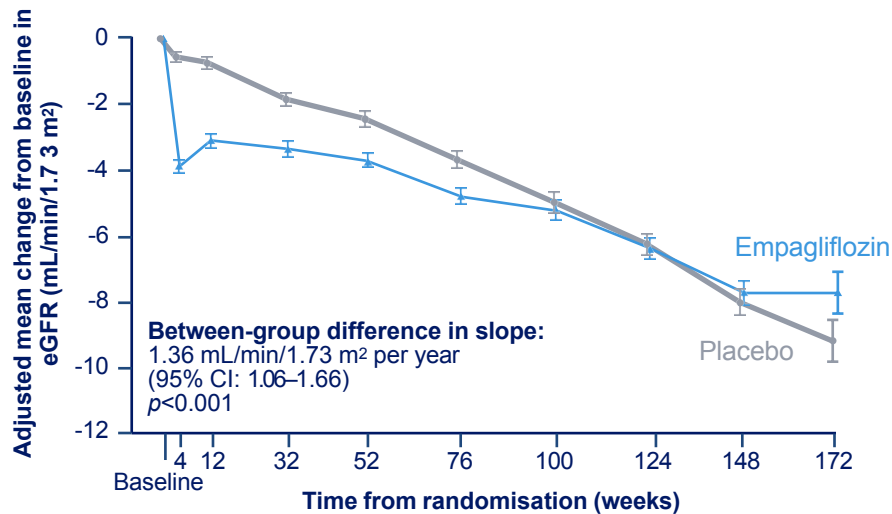
2. Skrtic M et al. Diabetologia 2014;57:2599

Proposed framework by which SGLT2 inhibitors might exert cardioprotective and nephroprotective effects by acting to mute renal sympathetic nerve activity and promote natriuresis and osmotic diuresis.



Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis. *Circulation*. 2022 Nov;146(18):1383-1405. doi: 10.1161/CIRCULATIONAHA.122.061732

Rate of decline in eGFR in EMPEROR-PRESERVED



The mean slope change in eGFR per year was:

-2.62 mL/min/1.73 m² on placebo

-1.25 mL/min/1.73 m² on empagliflozin

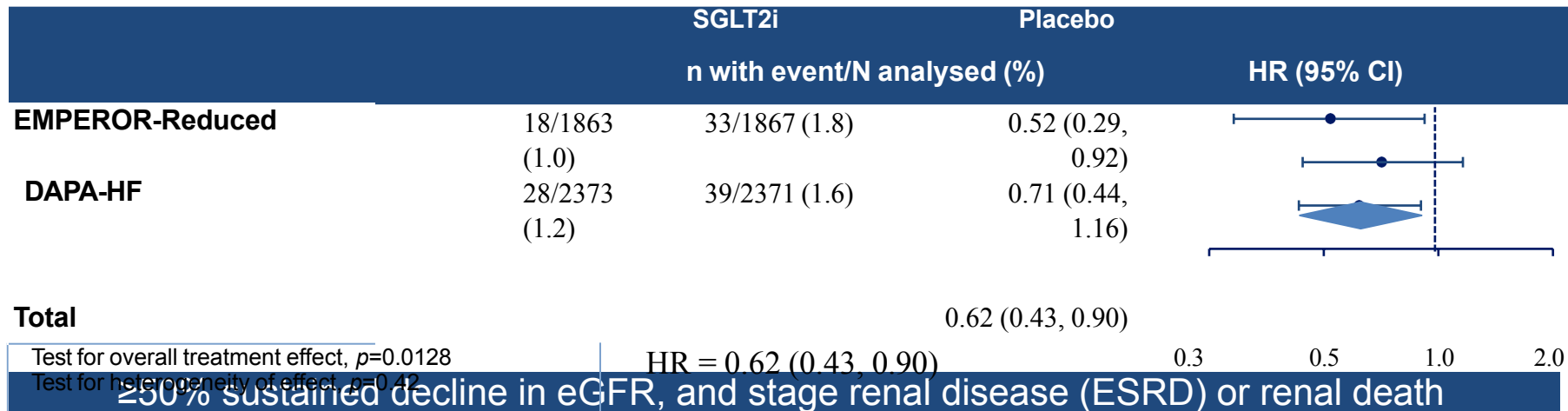
$p < 0.001$

No. with data at visit

Placebo	2911	2887	2759	2488	2333	1996	1443	1014	637	209
Empagliflozin	2925	2893	2785	2521	2343	1970	1431	1039	620	212



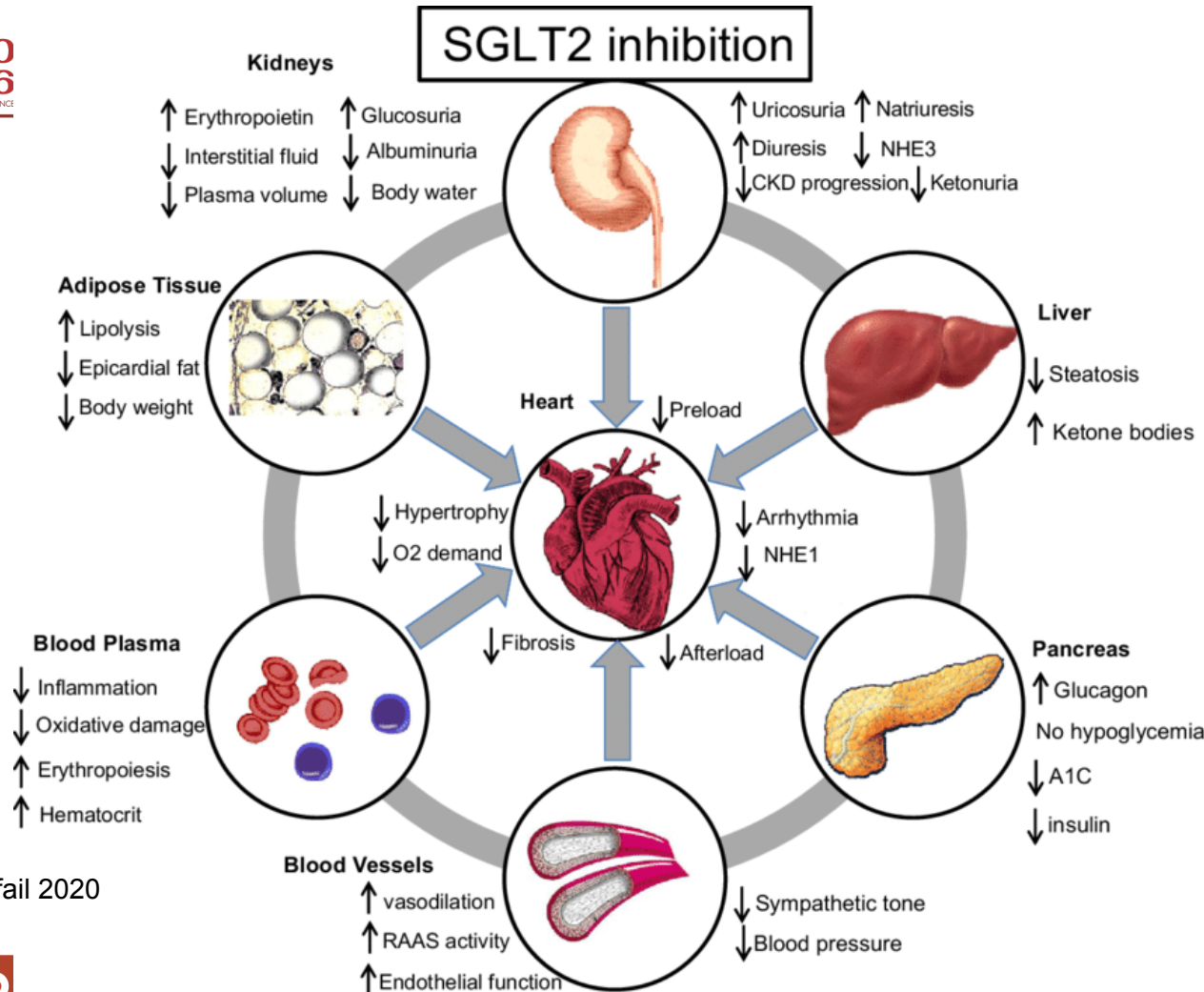
First Kidney Composite



CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, heart failure hospitalization; HR, hazard ratio; SGLT2i, sodium glucose like co-transporter 2 inhibitor Zannad F et al. Lancet, 2020, [https://doi.org/10.1016/S0140-6736\(20\)31824-9](https://doi.org/10.1016/S0140-6736(20)31824-9)



SGLT2i



Butler J et al Eur J Heart fail 2020



Stefan D. A
Hans-Peter B

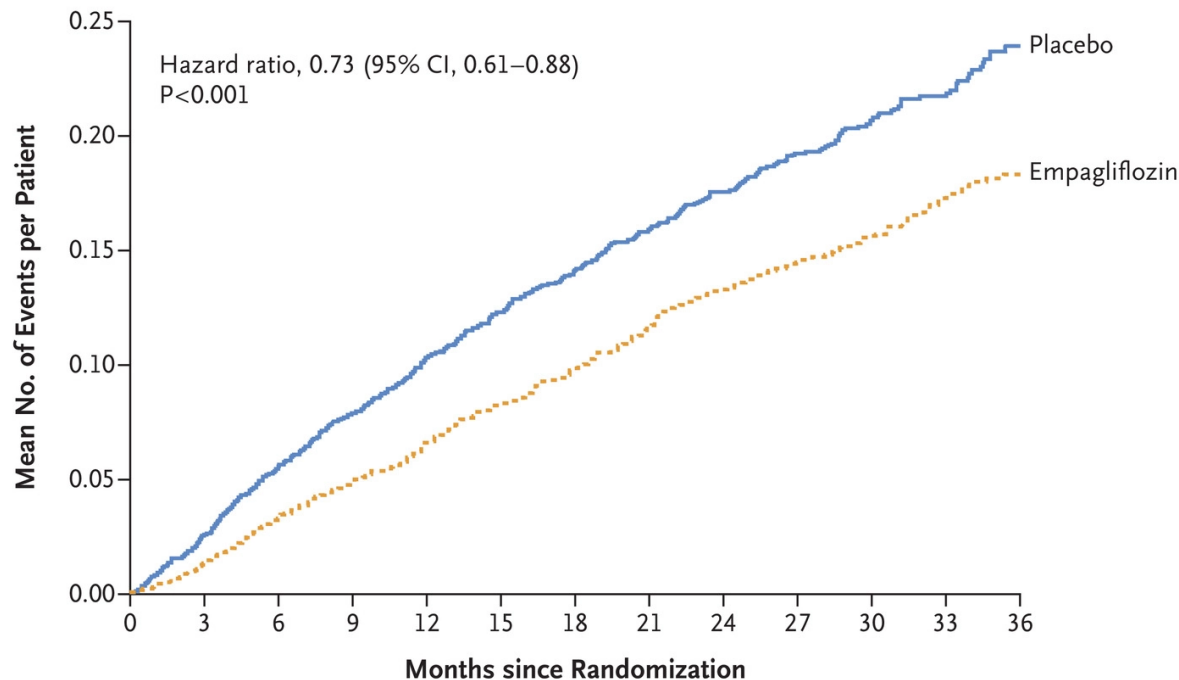
BACKGROUND

Sodium–glucose co-
transporter 2 inhibitors
with heart failure and
preserved ejection

METHODS

In this double-blind
study, patients with
ejection fraction of
usual therapy. The
failure.

Figure 1.
The esti
the same



No. at Risk

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Figure 3. **Hospitalizations for Heart Failure.**

The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

s (13.8%) in the
tio, 0.79; 95%
r risk of
appeared
heart failure was
541 with
urinary tract

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. Dobresanu, 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. Thierier, 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*

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

METHODS

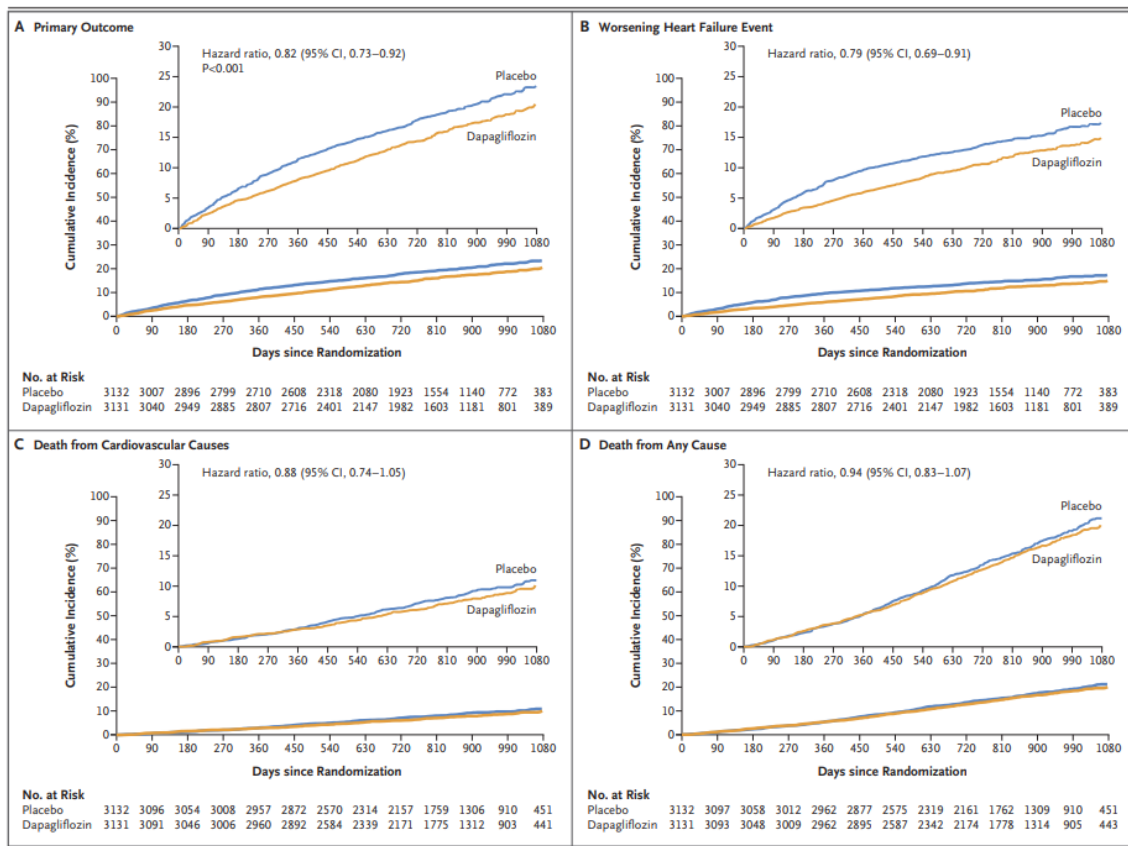
We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

RESULTS

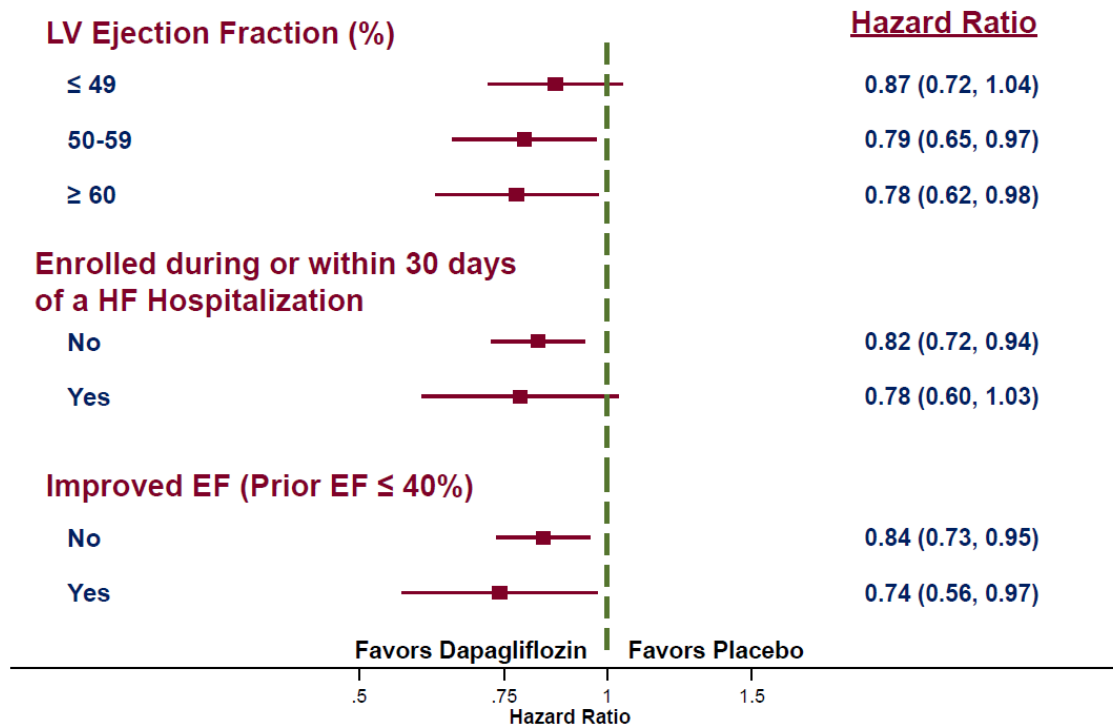
Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; $P < 0.001$). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)



Primary Endpoint in Prespecified Subgroups



Body mass index and cardiorenal outcomes in EMPEROR-Preserved: Principal findings and meta-analysis with the DELIVER trial

Question: Does BMI modify the benefit of empagliflozin in HFpEF in EMPEROR-Preserved?

BMI (kg/m²) Wt Δ (kg)

<25	-0.59
25 to <30	-1.48
30 to <35	-1.54
35 to <40	-0.87
≥40	-2.67

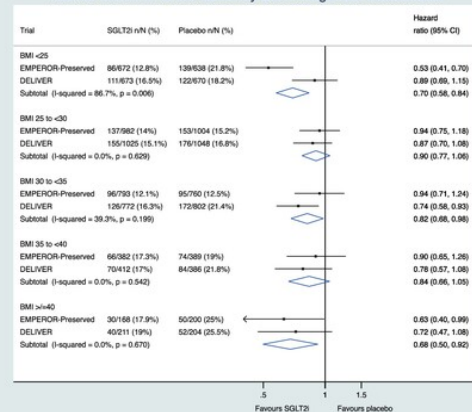
No BMI interactions with:

1° end-point	(p=0.19)
Total HHF	(p=0.19)
CV Death	(p=0.20)
eGFR slope	(p=0.85)

+ Trend towards greater KCCQ-CSS benefit at higher BMIs

Meta-analysis + DELIVER ; P=0.25 for interaction

Risk of first HHF or CV death by BMI categories: fixed effects

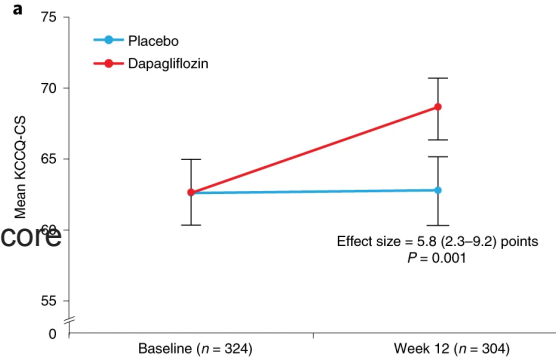


Conclusion: SGLT2i treatment yields benefit in patients with HFpEF regardless of baseline BMI

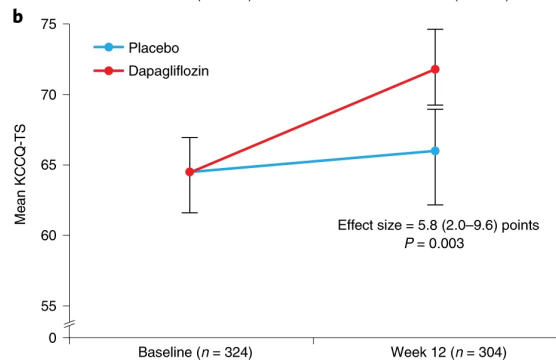
Sattar N, Butler J, Lee MMY, Harrington J, Sharma A, Zannad F, Filippatos G, Verma S, Januzzi JL, Ferreira JP, Pocock SJ, Pfarr E, Ofstad AP, Brueckmann M, Packer M, Anker SD. Eur J Heart Fail. 2024 Apr;26(4):900-909.

KCCQ Clinical Summary Score

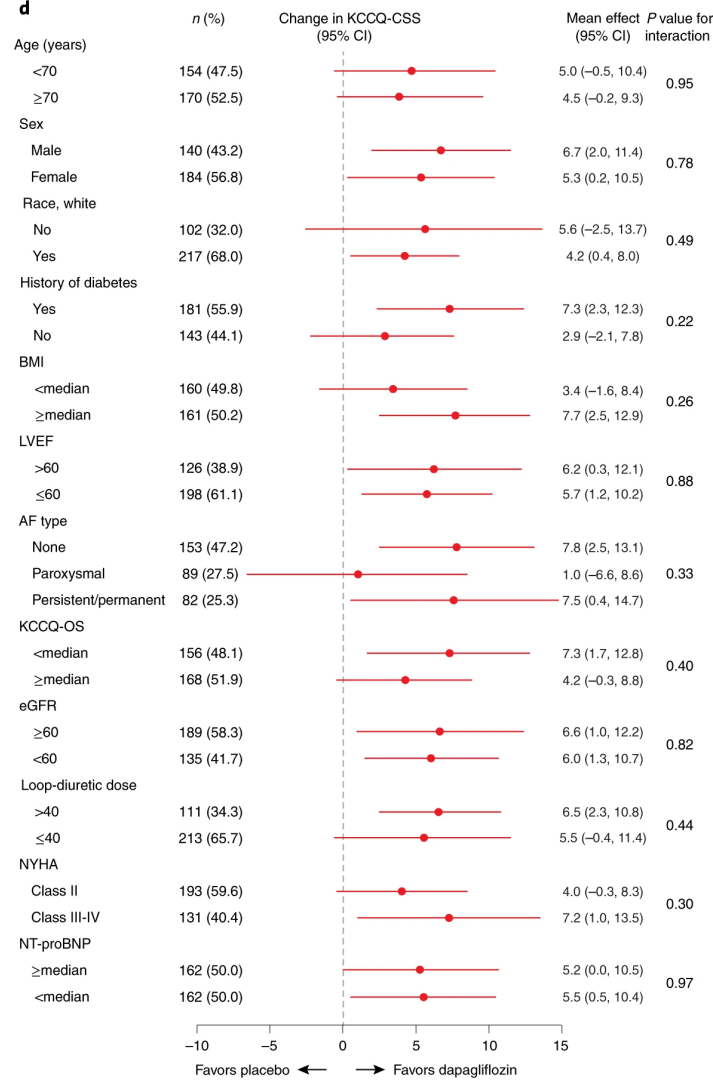
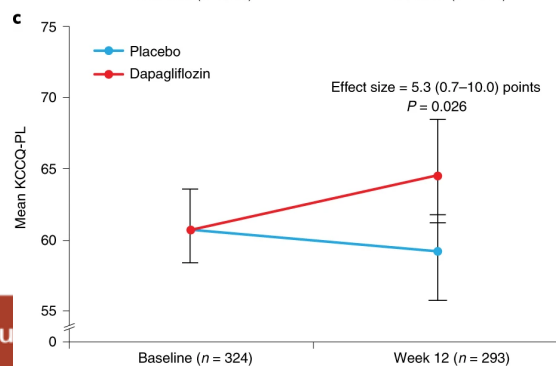
KCCQ Clinical Summary Score (KCCQ-CS)



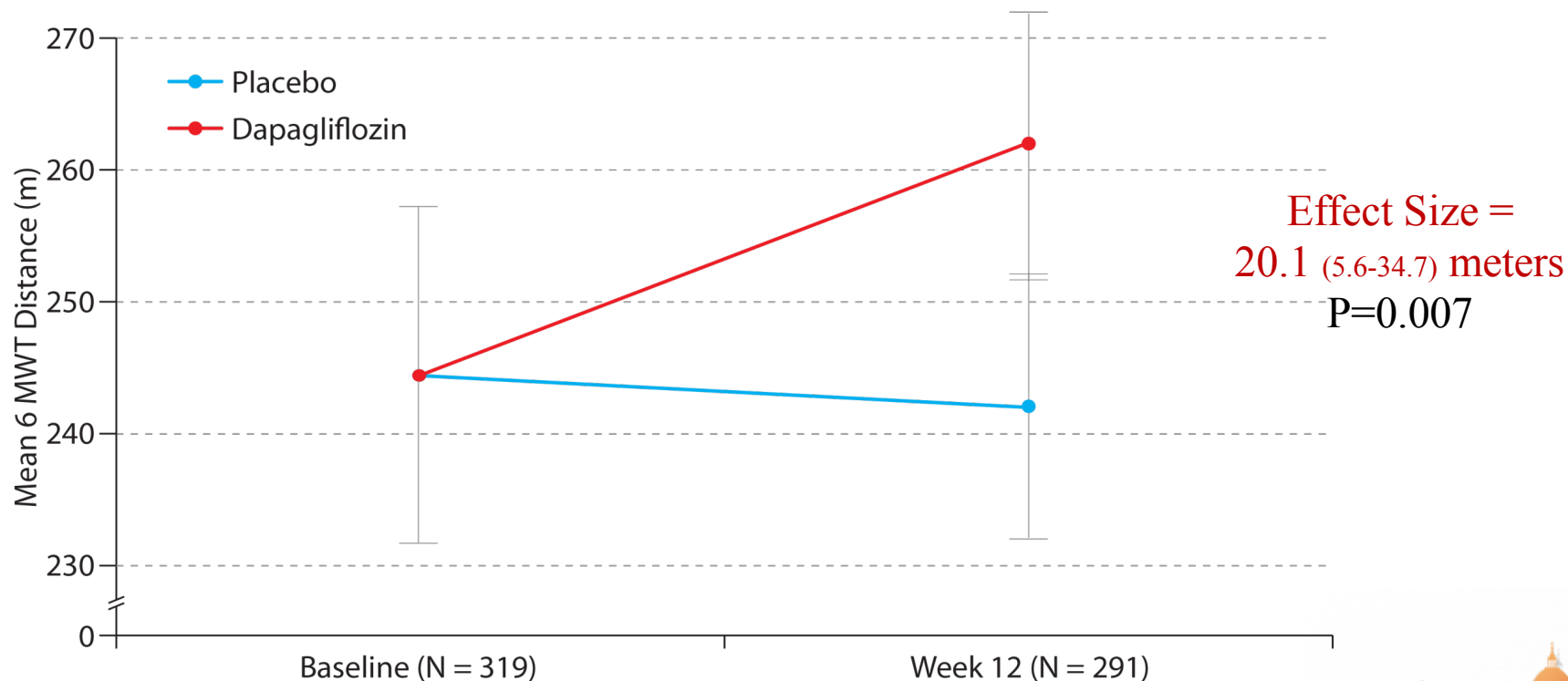
KCCQ Total Symptom Score (KCCQ-TS)



KCCQ Physical Limitations Score (KCCQ-PL)



6 Minute Walk Test



Nassif et al Nature Medicine 2021

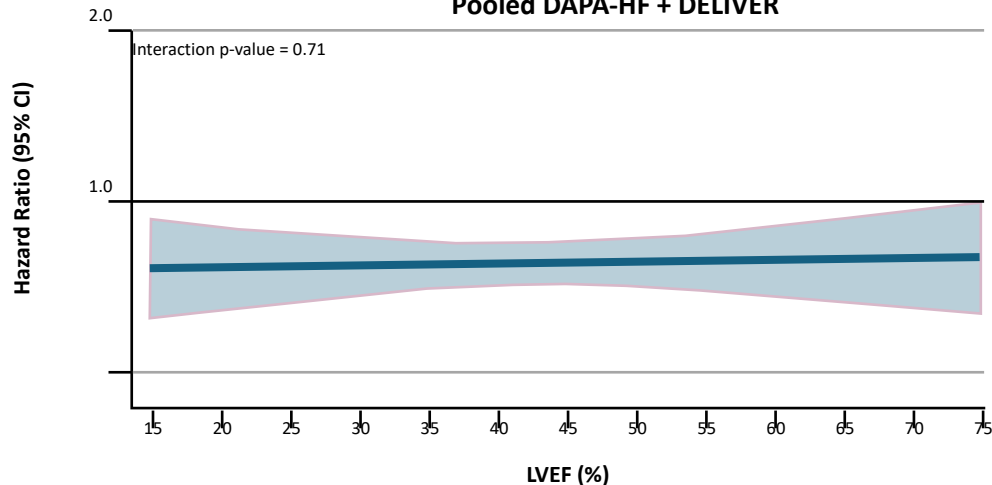


Benefit of SGLT2i is Consistent, With no Attenuation, Across LVEF^{1,2}

Dapagliflozin

CV Death or hHF^a

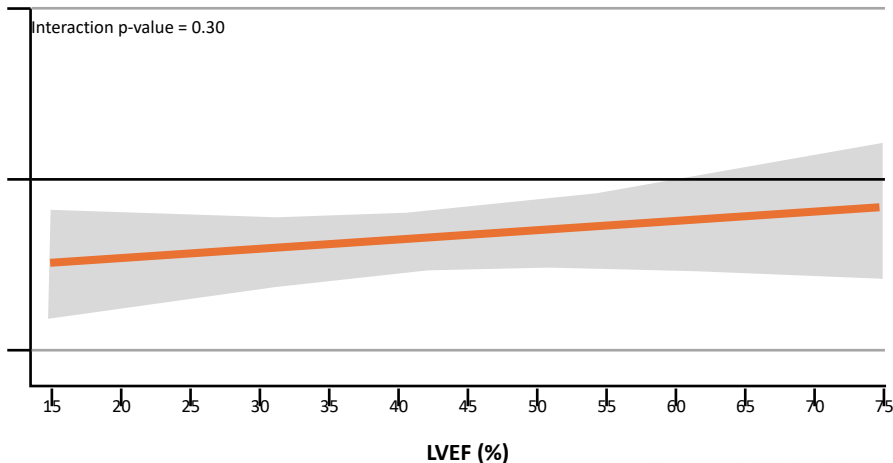
Pooled DAPA-HF + DELIVER



Empagliflozin

CV Death or hHF

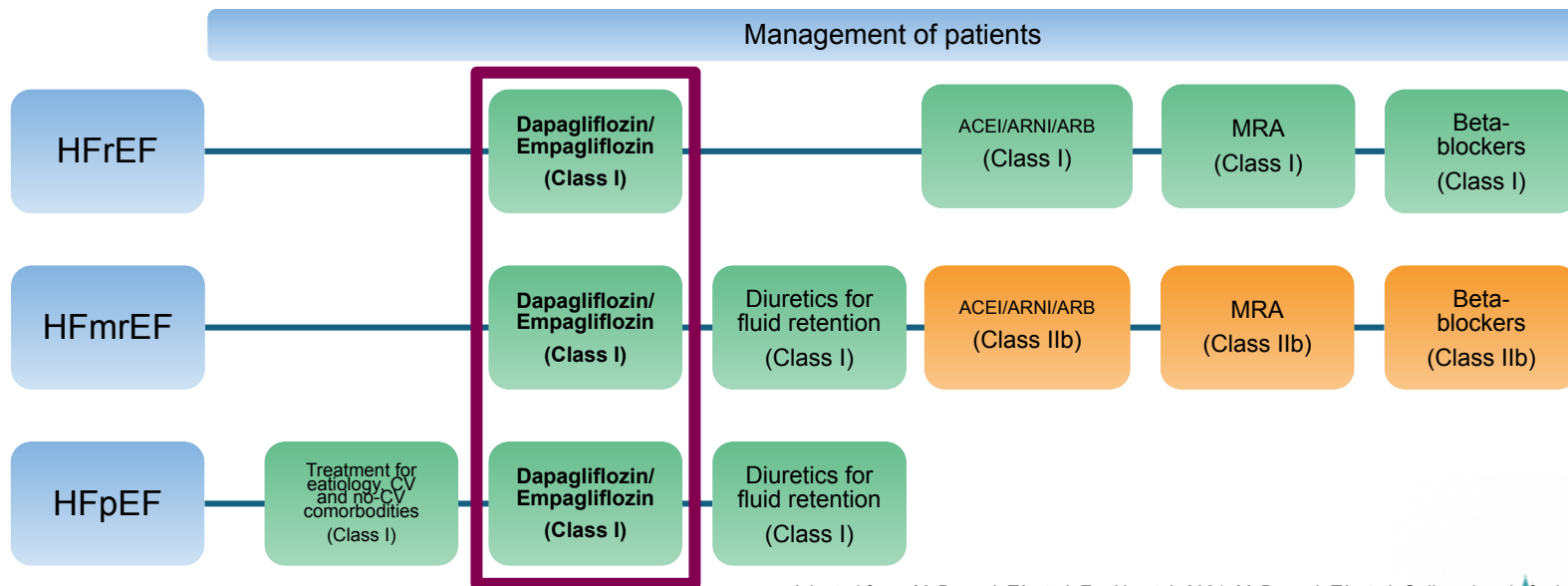
Pooled EMLPEROR REDUCED + PRESERVED



- ^aData utilizing linear modelling to ensure consistency across trials; ^bAll data is in comparison to placebo, except for ARNI which is in comparison to enalapril or valsartan.
- 1. Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; 2. In House Data, AstraZeneca.



ESC Heart Failure Guidelines focus update 2023: SGLT2i across the LVEF spectrum

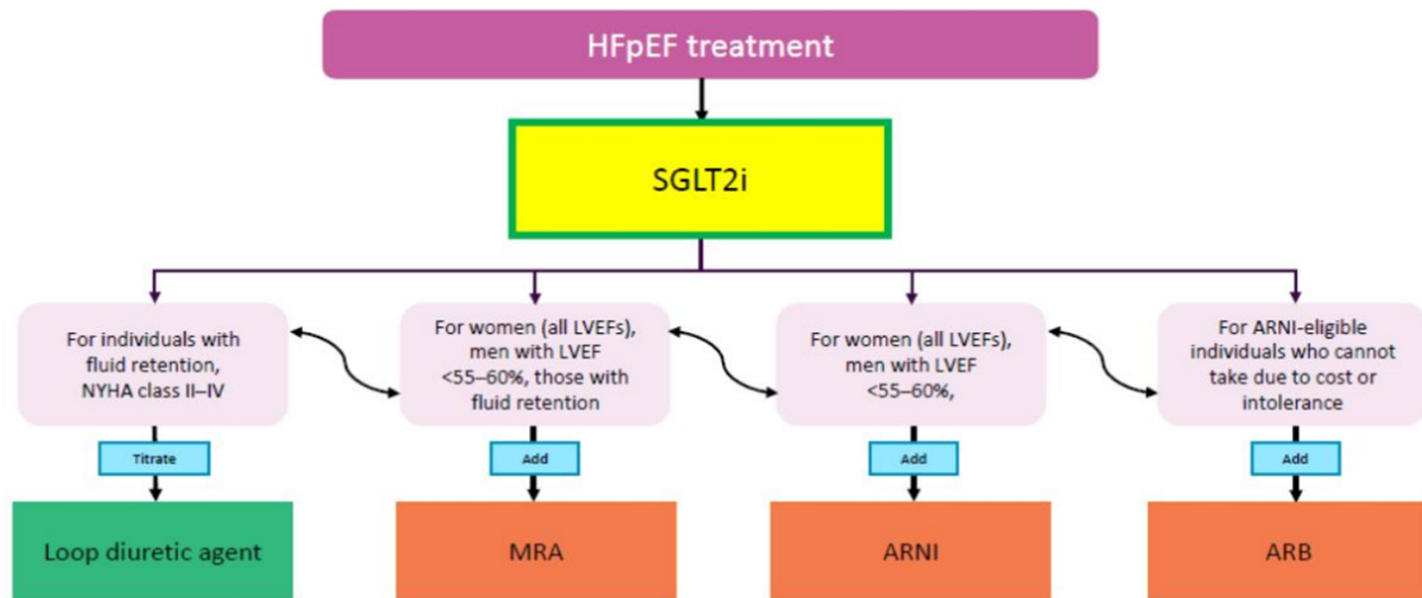


Adapted from: McDonagh TA et al. Eur Heart J. 2021; McDonagh TA et al. Online ahead of print. Eur Heart J. 2023.





2023 ACC Expert Consensus: Treatment algorithm for guideline-directed medical therapy in HFpEF



ACC, American College of Cardiology; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor
Kittleson MM et al. JACC 2023;81:1076-1126



Conclusions

- HFpEF now represents majority of HF in the community
 - High risk for clinical events, high burden of symptoms, physical limitations, and poor quality of life
- Heterogeneous disease with multiple phenotypes
- Great need for efficacious and safe therapies that address most of the underlying mechanisms
- SGLT2i provide effective decongestion, with favorable effects on LV remodeling and energetics and provide nephroprotection
- These translate to significant clinical benefits and positions the class well to become foundational therapy in HFpEF



Grazie per l'attenzione

Prof. Nodari Savina



**Università
di Brescia**

Dipartimento Specialità Medico-Chirurgiche
Scienze Radiologiche e Sanità Pubblica

