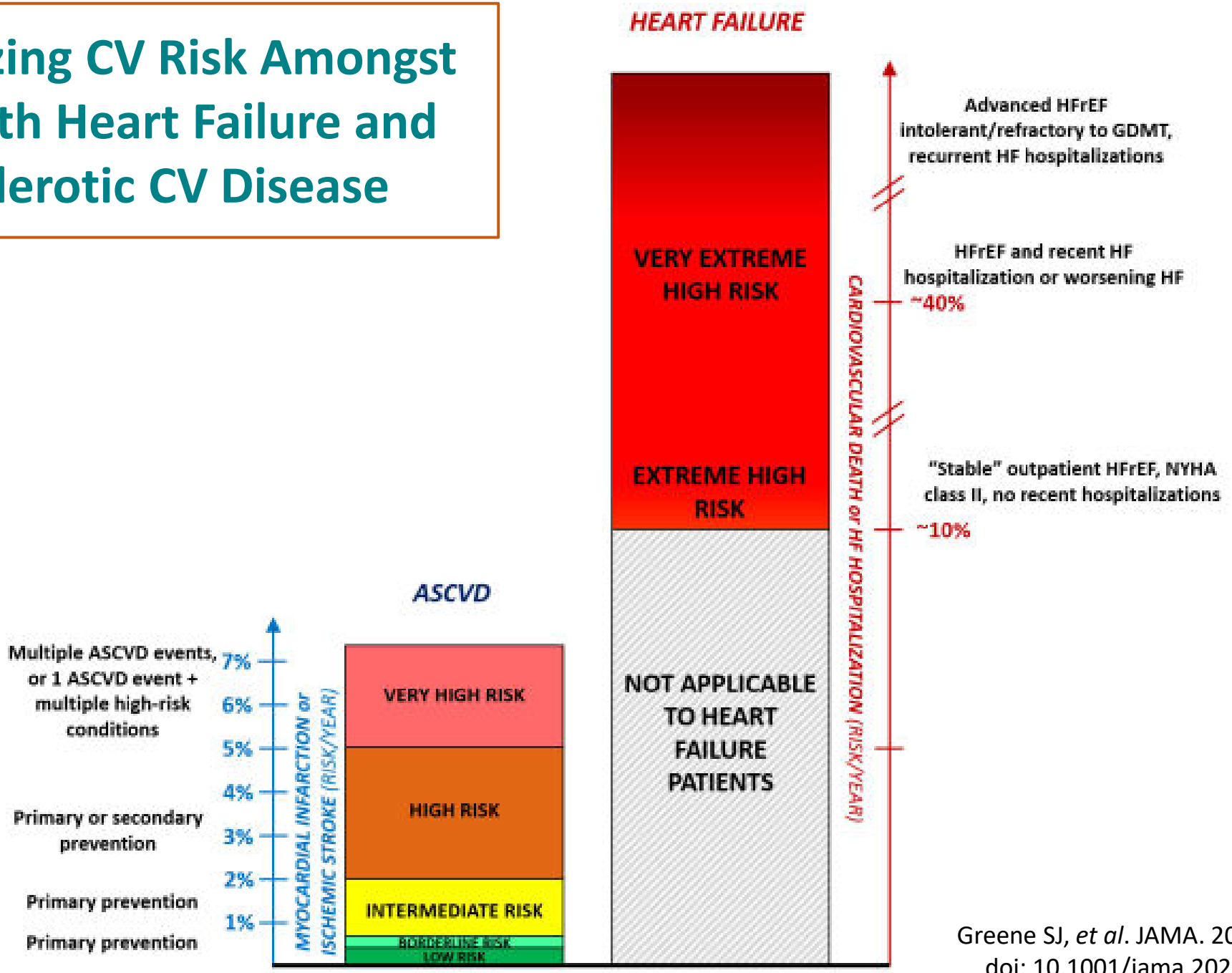
Approach to Heart Failure:Clinic to Cathlab

Dr Subhash Chandra

Chairman,Cardiology,

BLK MAX Hosp,N Delhi

Contextualizing CV Risk Amongst Patients with Heart Failure and Atherosclerotic CV Disease



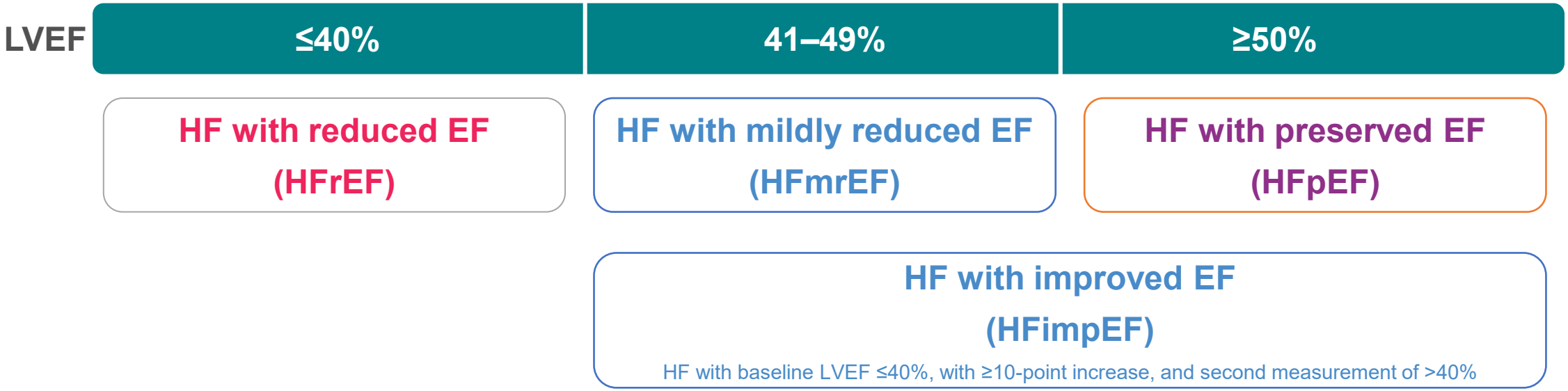
Greene SJ, *et al*. JAMA. 2021 Nov 15. doi: 10.1001/jama.2021.20739.

Consensus Statement

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association



Joint Position Paper. EJHF. 2021; doi:10.1002/ejhf.2115

Patient Characteristics in HFpEF and HFrEF Phenotypes

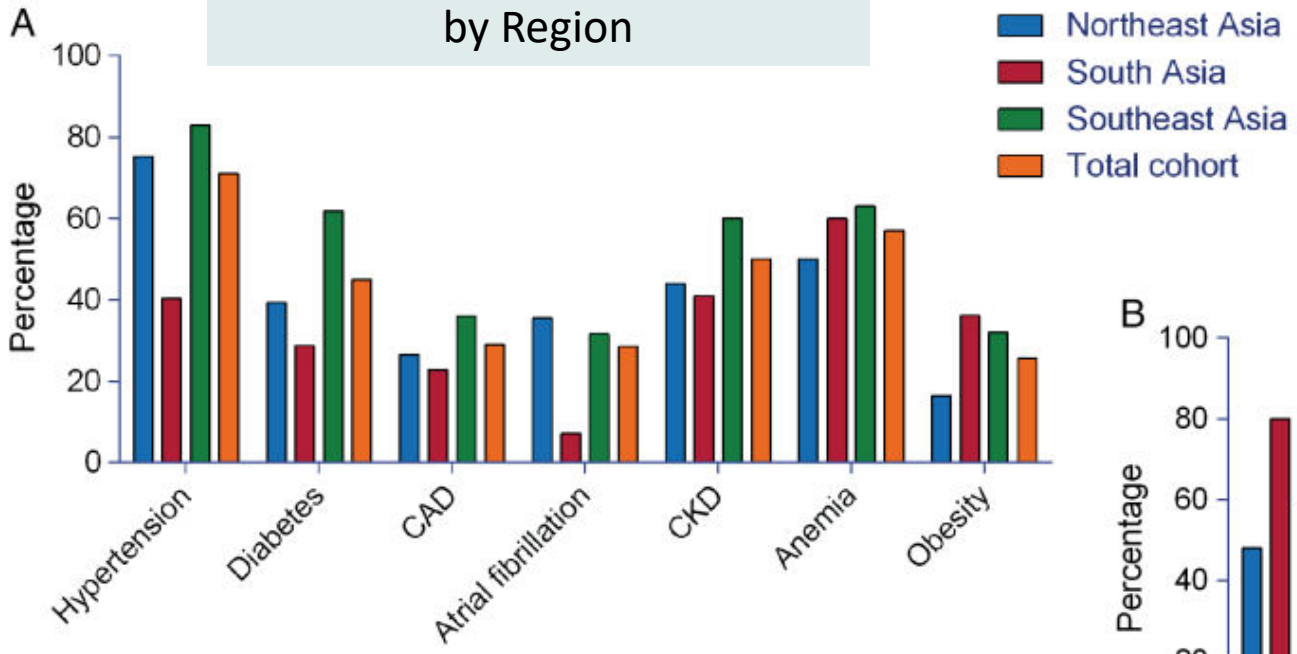
Characteristics	HFpEF	HFrEF
Age	Older	Youger
Gender	Females > males	Males > females
Hypertension	+++	++
Diabetes	+++	++
CAD or previous MI	+/++	+++
Renal failure	++	+
Obesity	++	+
Atrial fibrillation	++	+
Chronic lung disease	++	–

CAD, coronary artery disease; MI, myocardial infarction.

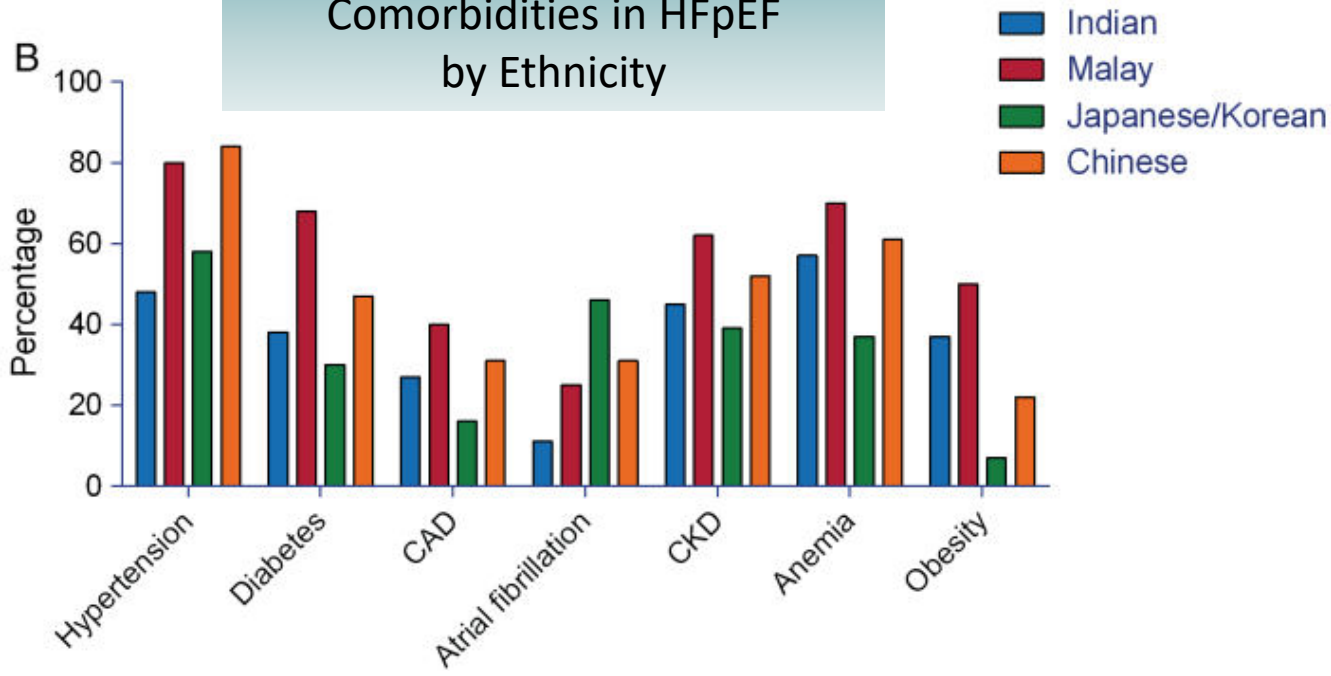
Heart Failure with Preserved Ejection Fraction in Asia (ASIAN HF)

Hypertension is the Commonest Risk-factor in HFpEF

Comorbidities in HFpEF
by Region

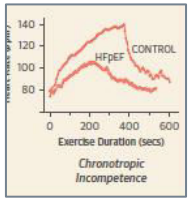


Comorbidities in HFpEF
by Ethnicity

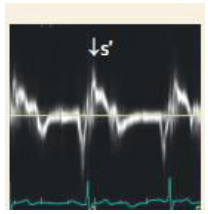


Asian HF Investigators. European Journal of Heart Failure. 2019; 21: 23-36.

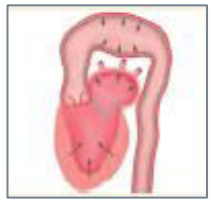
Cardiac Pathophysiology in HFpEF



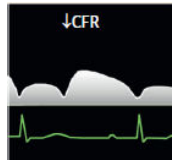
Chronotropic incompetence



LV systolic dysfunction



Vascular stiffening



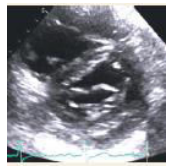
Coronary microvascular dysfunction

Diastolic dysfunction

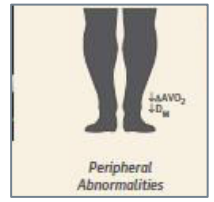
Impaired relaxation

Increased passive stiffness

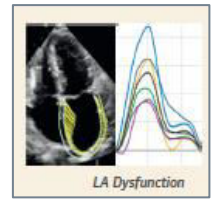
Pericardial restrain



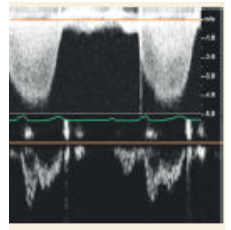
Peripheral abnormalities



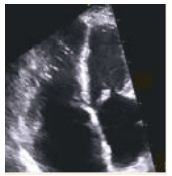
LA dysfunction



Pulmonary hypertension



RV dysfunction



Adapted: Obokata M *et al. JACC Cardiovasc Imaging.* 2020;13:245.

Decoding empagliflozin's molecular mechanism of action in heart failure with preserved ejection fraction using artificial intelligence

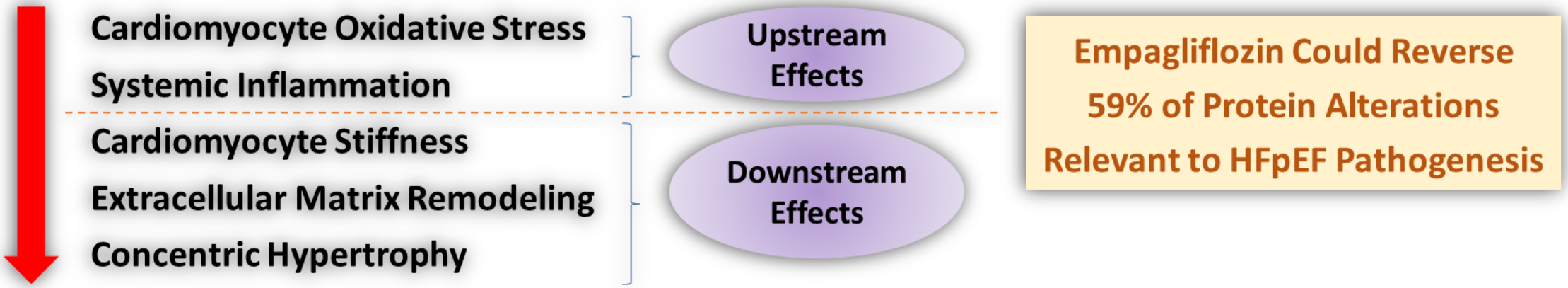
Evaluation of action of empagliflozin, on pathophysiological alterations in HFpEF

Analysis based on deep-learning with artificial intelligence-based algorithm

Findings also further validated in patients with HFpEF, with empagliflozin use over 12 months

NHE-1 inhibition: Prominent role, by **Modulation of Cardiomyocyte Oxidative Stress**

Most Probable Cascade Mechanism of Empagliflozin in HFpEF, with 94% Accuracy



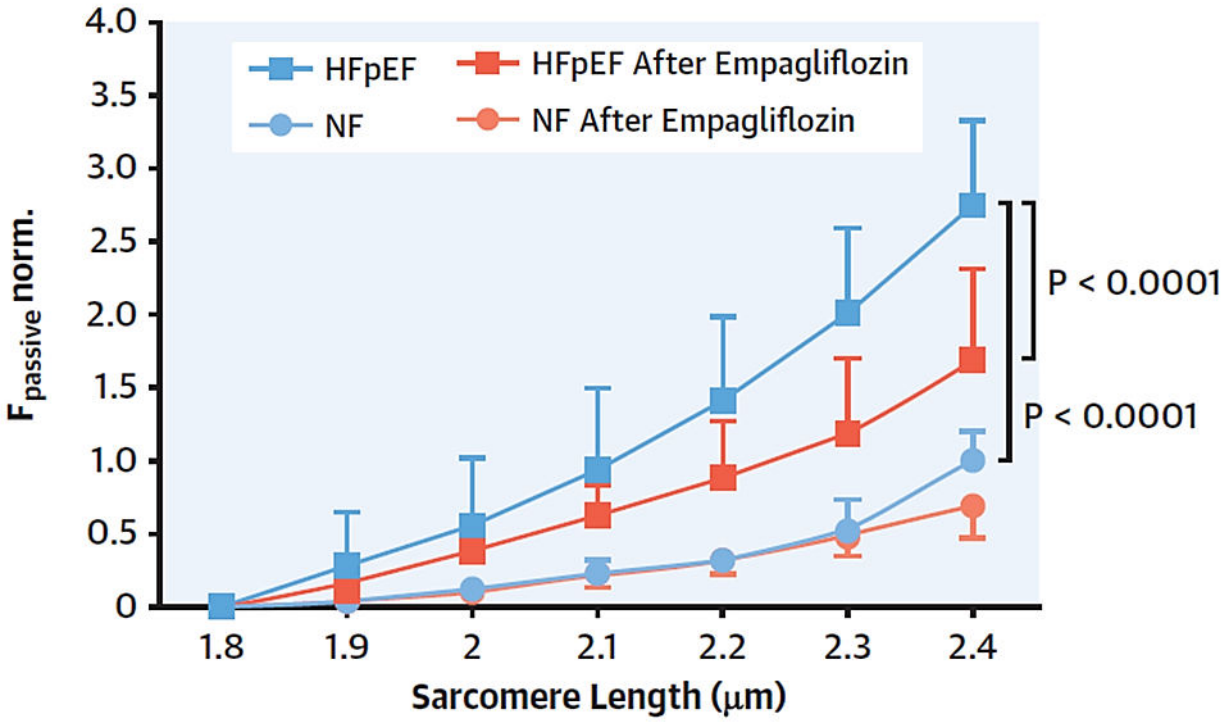
Empagliflozin mediated inhibition of Cardiac Na^+ H^+ Exchanger (NHE-1), as well as of SGLT-2 and NHE-3, had relevant effects for HFpEF

Bayes-Genis A et al. Sci Rep. 2021 Jun 8;11(1):12025.

Empagliflozin directly improves diastolic function in human heart failure

Cardiomyocytes Isolated from Patients with HFpEF, and from Healthy Donors

Empagliflozin Improved Diastolic Stiffness, and Diastolic Function, in Human Cardiomyocytes



Empagliflozin directly enhances phosphorylation of myofilament proteins, including:

- ✓ Titin
- ✓ Myosin binding protein C
- ✓ Troponin I

These effects reduce diastolic dysfunction, in cardiomyocytes isolated from human HFpEF

Cardiomyocytes from Patients with HFpEF and Non-failing (NF) Myocardium:
Normalized Passive Stiffness (F) measured at various sarcomere lengths, from 1.8 to 2.4 mm of cardiomyocytes, pre- and post- empagliflozin.

Adapted: Pabel S et al. Eur J Heart Fail. 2018 Dec;20(12):1690-700.

Natriuretic Peptides (NP) Use in Clinical Practice Guiding Principles (HFA-ESC)

- NP testing should always be used in conjunction with all other clinical information
- For patients with dyspnoea, NP testing has a very high accuracy in discriminating HF, from other causes of dyspnoea
- NP testing has high prognostic accuracy for risk of events, in patients with stable HF
- In patients with CV risk factors, screening with NP testing may help allow targeted measures to prevent development of HF
- NP cannot identify underlying cause of HF, and must be used with cardiac imaging
- BNP and NT-proBNP have comparable diagnostic and prognostic accuracy

Adapted: HFA-ESC. Eur J Heart Fail. 2019 Jun;21(6):715-31.

Echocardiography for HFpEF

Greater Number of Abnormalities Indicate Higher Likelihood (ESC)

Diagnosis of LV Diastolic Dysfunction or Raised LV Filling Pressure:

1. **Left Ventricular Mass Index**: ≥95 g/m^2 (Female), ≥115 g/m^2 (Male)
2. **Relative Wall Thickness**: >0.42

Supportive parameters;
Their absence does not exclude possible HFpEF

3. **Left Atrial Volume Index**: >34 mL/m^2 (sinus rhythm) or >40 mL/m^2 (atrial fibrillation), in absence of valve-disease, suggests chronically raised LV filling pressure
4. **E/e' Ratio at Rest**: >9

E/e' >9 has 78% sensitivity, but 59% specificity for HFpEF;
E/e' >13 has 46% sensitivity, but 86% specificity for HFpEF

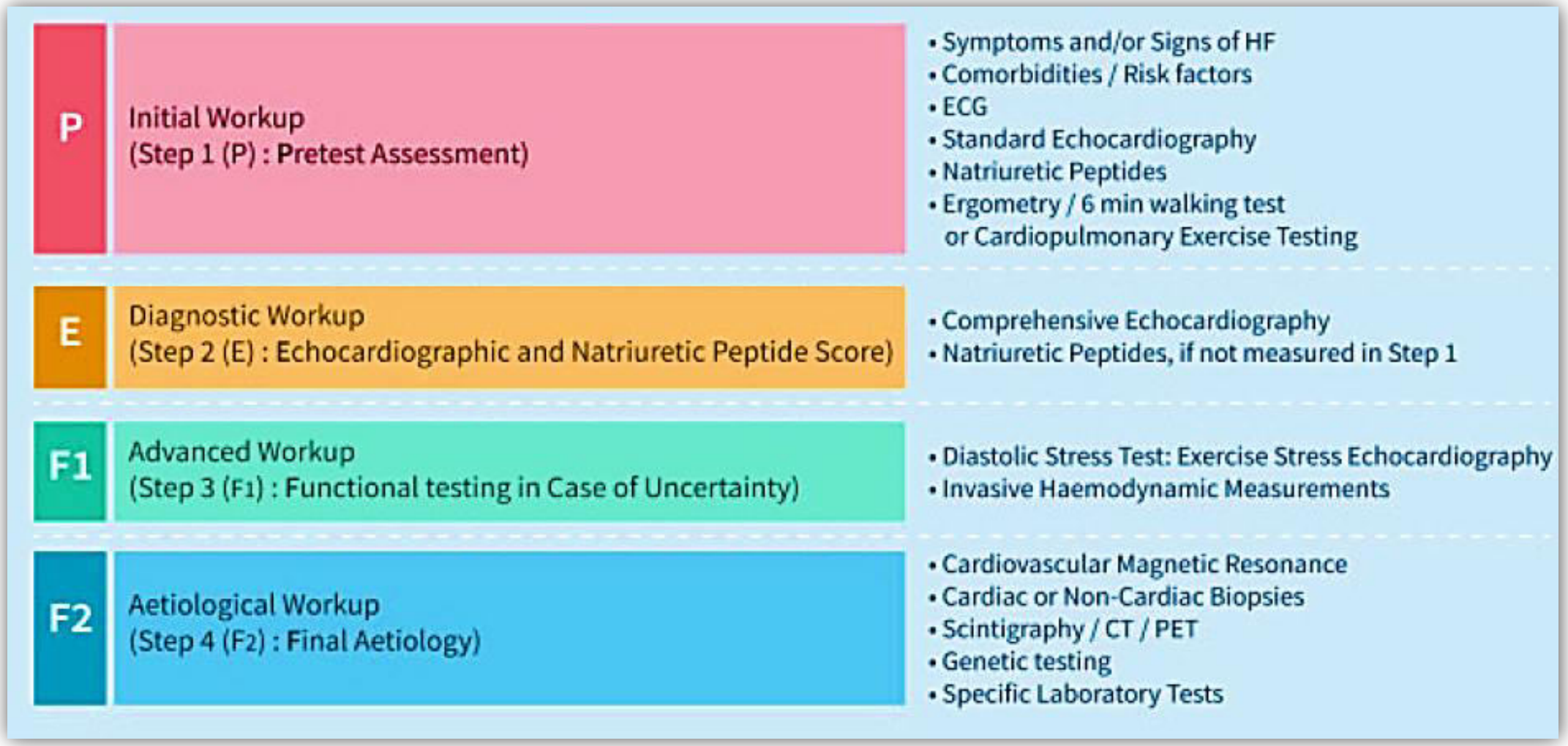
5. **Tricuspid Regurgitation Velocity at Rest**: >2.8 m/s
6. **Pulmonary Artery Systolic Pressure**: >35 mmHg

May have high specificity for diagnosis of HFpEF

Adapted: European Society of Cardiology, 2021

Diagnosis of Heart Failure with Preserved Ejection Fraction

PEFF Algorithm: Recommendation from HFA-ESC (2019)



Pieske B et al. Eur Heart J. 2019 Oct 21;40(40):3297-317.

Echocardiography and Natriuretic Peptide Score

Step 2 of PEFF Algorithm

	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/m² or LVMI ≥ 149/122 g/m² (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

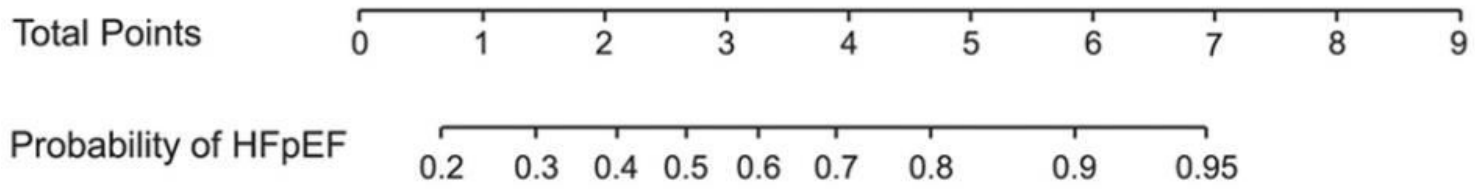
Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Pieske B et al. Eur Heart J. 2019 Oct 21;40(40):3297-317.

Tool for Diagnosis of Heart Failure with Preserved Ejection Fraction:

H2FPEF Score

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index >30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or persistent	3
P	**P**ulmonary hypertension	Doppler echocardiographic estimated right ventricular systolic pressure >35 mmHg	1
E	**E**lder	Age >60 years	1
F	**F**illing pressure	Doppler echocardiographic E/e' > 9	1
	H_2FPEF Score		**Sum (0-9)**



Adapted: Reddy Y et al. *Circulation.* 2018; 138: 861-70.

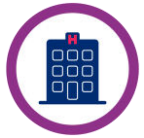
Empagliflozin Represents First Therapy with Conclusively Proven Benefits, In Patients with HFpEF, Regardless of T2DM

Trial	Treatment Arms	Primary endpoint	Results (HR and 95% CI)	Risk Reduction	P-value
EMPEROR-Preserved (2021)	**Empagliflozin vs placebo**	**HHF + CV death**	**0.79 (0.69-0.90)**	**-21%**	**0.0003**
CHARM-Preserved (2003)	Candesartan vs placebo	HHF + CV death	0.86 (0.74-1.00)	-14%	0.05
I-PRESERVE (2008)	Irbesartan vs placebo	Hospitalisation for CV cause + all-cause mortality	0.95 (0.86-1.05)	-5%	0.35
PEP-CHF (2006)	Perindopril vs placebo	All-cause mortality + HHF	0.92 (0.70-1.21)	-8%	0.55
DIG-PEF (2006)	Digoxin vs placebo	HHF + HF mortality	0.82 (0.63-1.07)	-18%	0.136
TOPCAT (2014)	Spironolactone vs placebo	HHF + CV death + aborted cardiac arrest	0.89 (0.77-1.04)	-11%	0.14
PARAGON-HF (2019)	Sacubitril/valsartan vs valsartan	CV death + total HHF	0.87 (0.75-1.01)	-13%	0.06
DELIVER (2022)	**Dapagliflozin vs placebo**	**Time to first CV death + worsening HF event**	**0.82 (0.73 to 0.92)**	**-18%**	**<0.001**

Adapted: Anker SD et al. N Engl J Med. 2021 Oct 14;385(16):1451-61. Yusuf S et al. Lancet. 2003;362:777. Massie BM et al. N Engl J Med. 2008;359:2456. Cleland JG et al. Eur Heart J. 2006;27:2338. Ahmed A et al. Circulation. 2006;114:397. Pitt B et al. N Engl J Med 2014;370:1383. Solomon SD et al. N Engl J Med. 2019;381:1609. Solomon SD et al. Eur J Heart Fail 2021;23(7):1217-25.

EMPEROR-Preserved Study

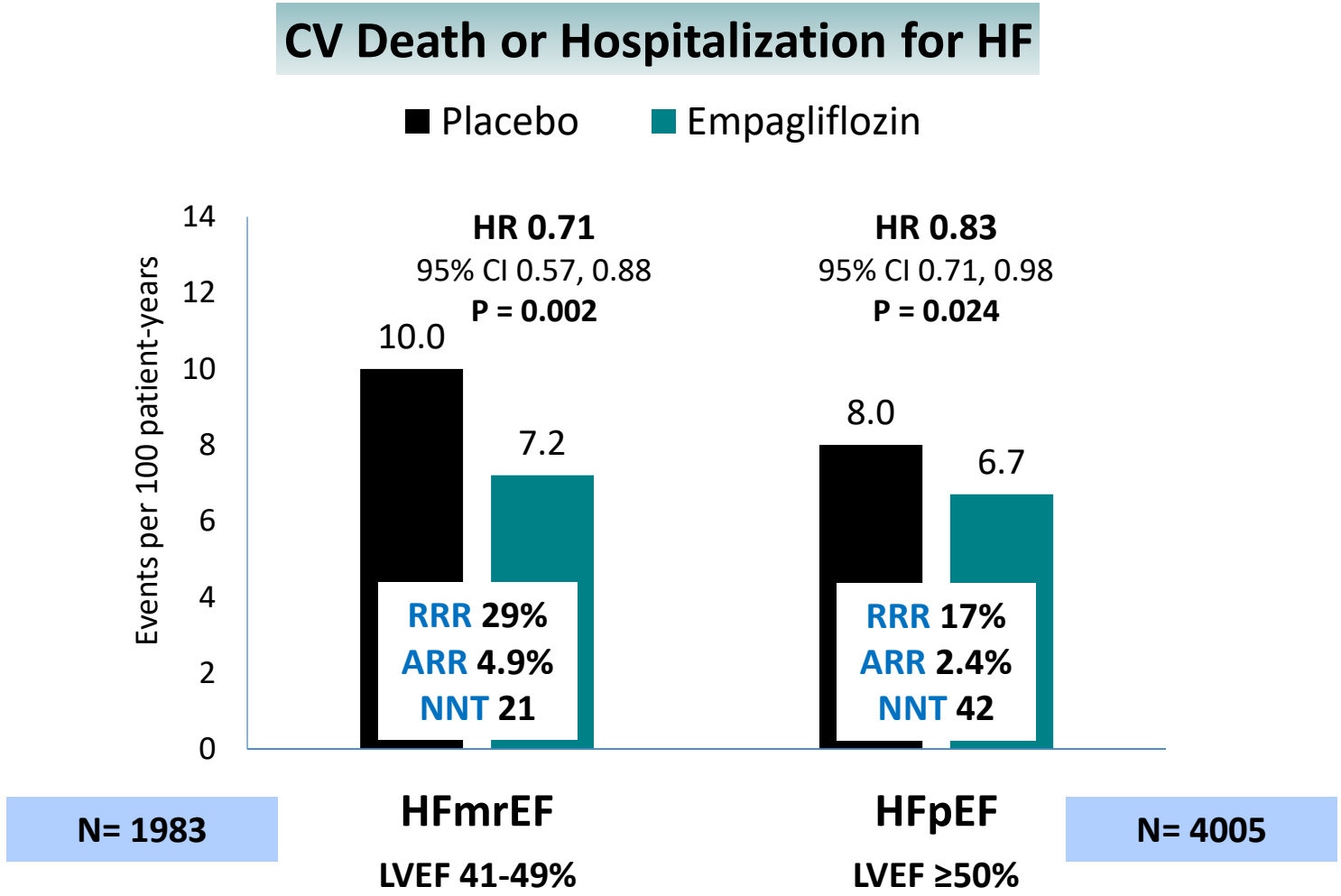
- Phase-III Randomized, Double-blind, Placebo-Controlled Trial in Adult Patients having LVEF >40%, with Empagliflozin 10 mg OD compared to placebo (on top of standard of care)
- With or without Type-2 Diabetes, and with eGFR ≥20 mL/min/1.73m^2
- 5988 patients, median follow-up= 26.2 months (event-driven)

 **CV Death or Heart-Failure Hospitalisation** (Primary endpoint)	**21%** Relative Risk-reduction **3.3%** Absolute Risk Reduction NNT of **31 over 26-months**	**HR 0.79** **(95% CI 0.69, 0.90)** ***p*<0.001**
 **First and Recurrent Heart-Failure Hospitalisations** (Key secondary endpoint)	**27%** Relative Risk-reduction	**HR 0.73** **(95% CI 0.61, 0.88)** ***p*<0.001**
 **eGFR slope** (Key secondary endpoint)	Stabilization of decline in eGFR, improved kidney outcomes	**Slope difference per year** **1.36 ml/min/1.73 m^2** ***p*<0.001**

Anker S et al. N Engl J Med. 2021 Aug 27. doi: 10.1056/NEJMoa2107038

Empagliflozin Shows Consistent Efficacy in HFmrEF and HFpEF

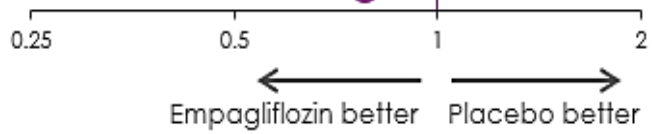
(EMPEROR-Preserved)



Adapted: Anker S. Presented at AHA Scientific Sessions, Nov 2021.

Consistent Benefits in CV Death or HHF Risk-Reduction with Empagliflozin by Baseline Sex, T2DM, CKD, and A-Fib/AF (EMPEROR-Preserved)

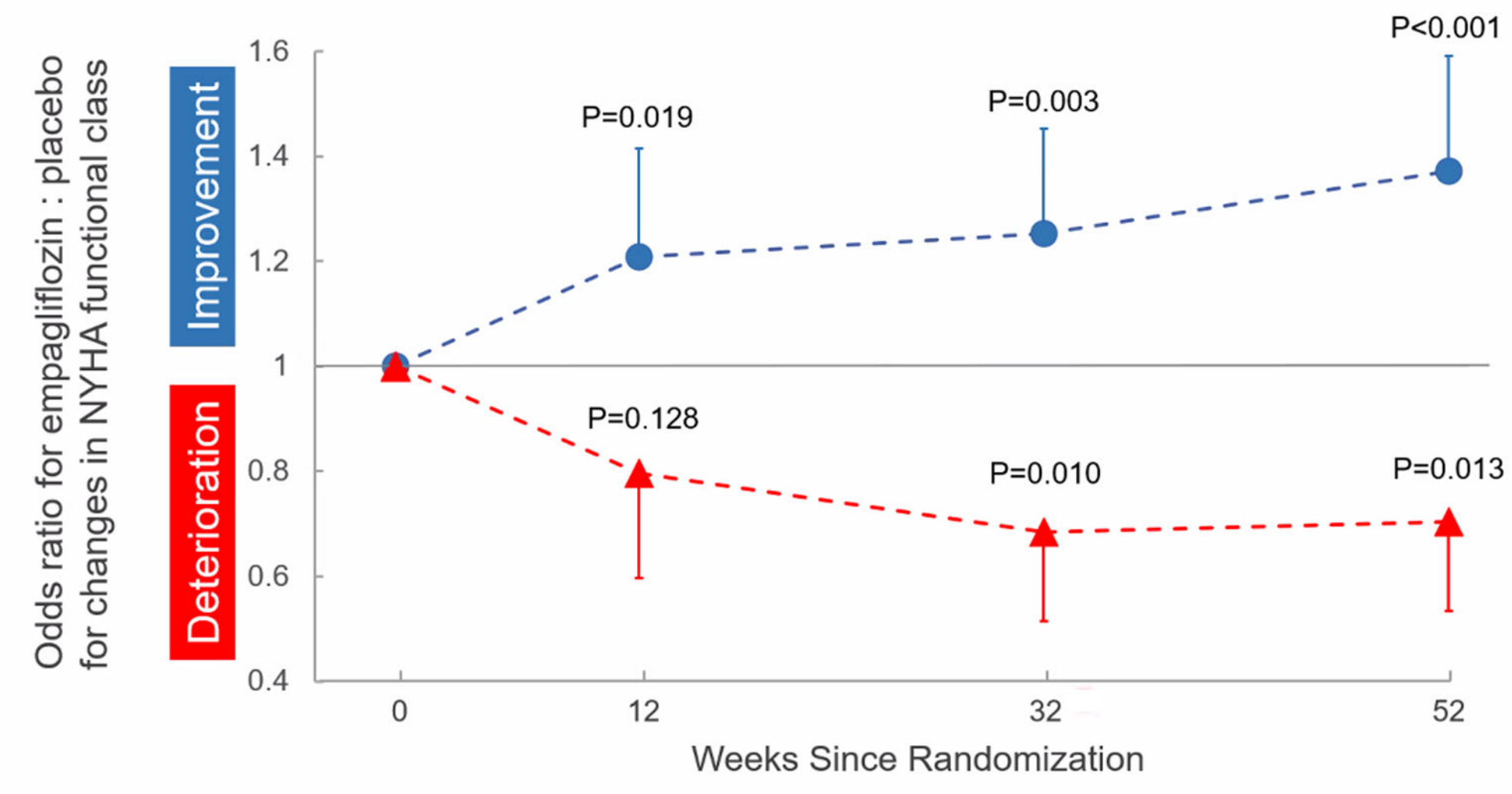
	Empagliflozin	Placebo	HR (95% CI)	P value interaction
	n with event/N analysed			
Overall	415/2997	511/2991	0.79 (0.69, 0.90)	
Sex				0.5360
Male	253/1659	297/1653	0.81 (0.69, 0.96)	
Female	162/1338	214/1338	0.75 (0.61, 0.92)	
Baseline diabetes status				0.9224
Diabetes	239/1466	291/1472	0.79 (0.67, 0.94)	
No diabetes	176/1531	220/1519	0.78 (0.64, 0.95)	
Baseline eGFR (CKD-EPI)				0.7673
≥60 mL/min/1.73 m²	152/1493	189/1505	0.81 (0.65, 1.00)	
<60 mL/min/1.73 m²	263/1504	321/1484	0.78 (0.66, 0.91)	
History of AF or atrial flutter				0.9588
No	170/1417	219/1427	0.78 (0.64, 0.95)	
Yes	244/1576	292/1559	0.78 (0.66, 0.93)	



Adapted: Anker S *et al.* N Engl J Med. 2021 Aug 27. doi: 10.1056/NEJMoa2107038.

Early and Significant Improvement in NYHA Class from Week 12 onwards

(Emperor-Preserved)



Butler J et al. Eur J Heart Fail. 2022; doi:10.1002/ejhf.2420.

No Unexpected Safety Outcomes with Empagliflozin vs. Placebo in EMPEROR Preserved Study

	Empagliflozin, n (%) (n = 2996)	Placebo, n (%) (n = 2989)
Patients with any adverse event	2574 (85.9)	2585 (86.5)
Patients with any serious adverse event	1436 (47.9)	1543 (51.6)
Selected AEs of interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension*	197 (6.6)	156 (5.2)
Acute renal failure	363 (12.1)	384 (12.8)
Ketoacidosis†	4 (0.1)	5 (0.2)
Hypoglycaemic events‡	73 (2.4)	78 (2.6)
In patients with diabetes mellitus	63 (4.3)	66 (4.5)
In patients without diabetes mellitus	10 (0.7)	12 (0.8)
Urinary tract infections	297 (9.9)	243 (8.1)
Complicated urinary tract infections	57 (1.9)	45 (1.5)
Genital infections	67 (2.2)	22 (0.7)
Complicated genital infections	8 (0.3)	8 (0.3)
Bone fractures	134 (4.5)	126 (4.2)
Events leading to lower limb amputation*	16 (0.5)	23 (0.8)

Shown are adverse events (AEs) up to 7 days following discontinuation of study medication, but lower limb amputations were shown up to the end of the trial. *Investigator-defined events. †All events occurred in patients with diabetes mellitus at baseline. ‡Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or that required assistance. Anker S *et al.* N Engl J Med. 2021 Aug 27. doi: 10.1056/NEJMoa2107038.

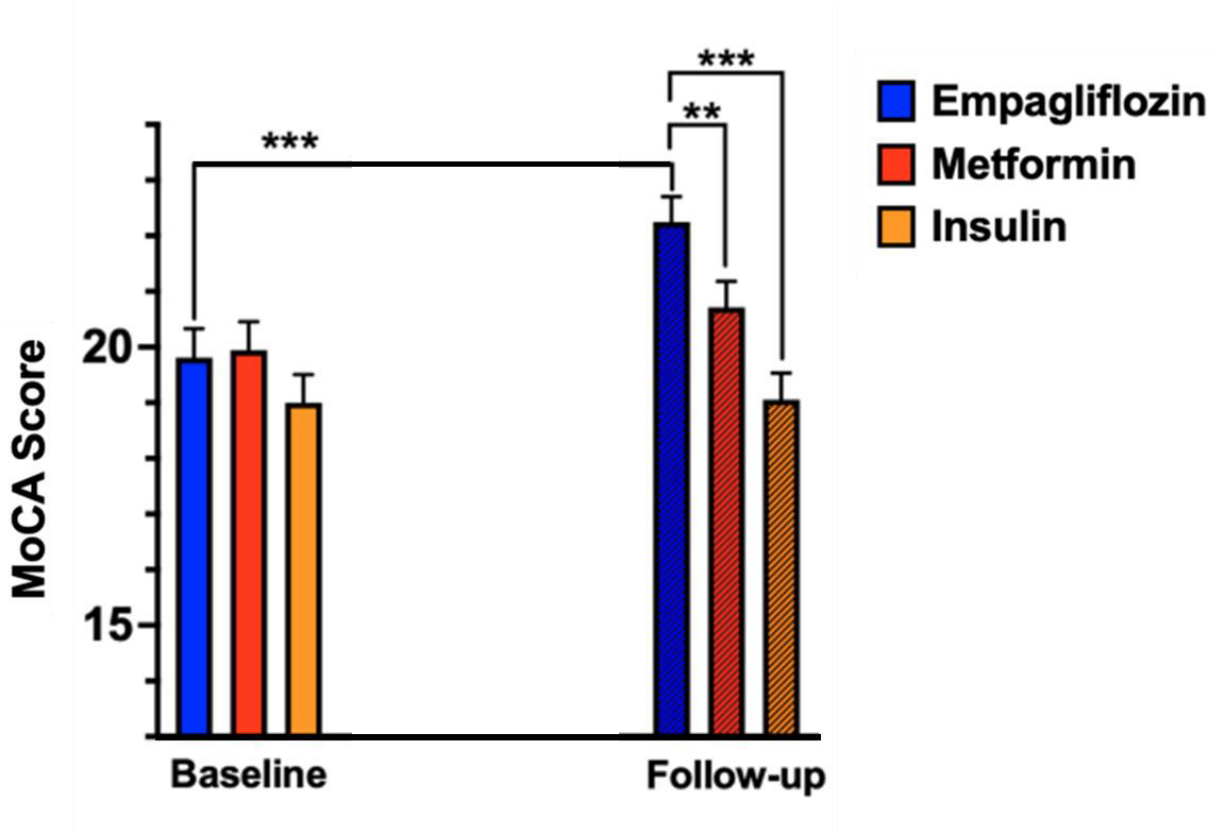
No Additional Safety Concerns in Elderly patients of HFpEF Empagliflozin compared to Placebo (EMPEROR Preserved)

Category of AEs, (%)	75–79 years		≥80 years		*p*-value for trend
	Empagliflozin (n= 662)	Placebo (n= 613)	Empagliflozin (n= 619)	Placebo (n= 679)	
Any AE	87.5	89.4	89.3	88.1	0.39
AE leading to discontinuation	21.3	20.4	22.8	22.1	0.73
Serious AE	50.8	55.0	53.2	58.8	0.37
Hypotension	12.1	9.6	11.8	11.5	0.28
Acute renal failure	11.9	11.7	14.1	13.8	0.31
Confirmed hypoglycaemic event	2.3	3.0	2.7	2.7	0.78
Urinary tract infection	9.8	7.2	14.2	11.5	0.87
Genital infection	3.6	0.8	1.1	0.4	0.56
Symptomatic hypotension	7.6	5.5	7.3	7.1	0.38

Adapted: Böhm M, et al. J Am Coll Cardiol 2022;80(1):1-18.

Empagliflozin Use May Improve Cognitive Impairment in Frail Older Patients with HFpEF and T2D

Empagliflozin use associated with 3.6-fold higher odds of amelioration in cognitive impairment (P <0.05)



Observational study in 161 frail older (>65 years) patients of T2D and HFpEF, followed for 1-month

Effect of empagliflozin, metformin, or insulin, on cognitive function

Montreal Cognitive Assessment (MoCA) scores performed at baseline and 1-month:

- Empagliflozin: 19.80 ± 3.77 vs. 22.25 ± 3.27 (P <0.001)
- Metformin: 19.95 ± 3.81 vs. 20.71 ± 3.56 (P = 0.26)
- Insulin: 19.00 ± 3.71 vs. 19.1 ± 3.56 (P = 0.81)

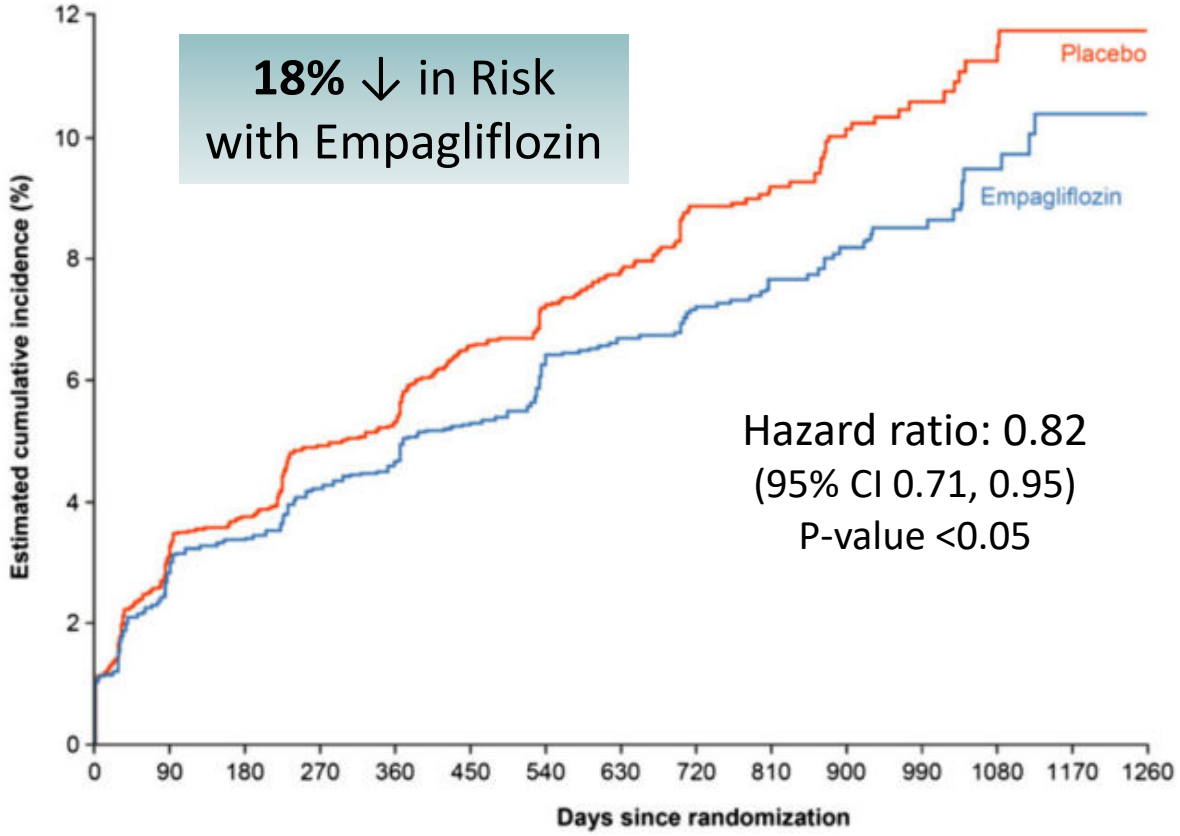
Data are Mean ± Standard deviation
**p-value < 0.01
***p-value <0.001

Mone P et al. Diabetes Care. 2022; 45: 1247-51.

Empagliflozin and Serum Potassium in Heart Failure: Analysis from EMPEROR-Pooled

Hyperkalaemia or Initiation of Potassium Binders with Empagliflozin vs. Placebo

Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved Studies in 9,583 Patients with HF



Empagliflozin reduced hyperkalaemia rates regardless of the definition used:

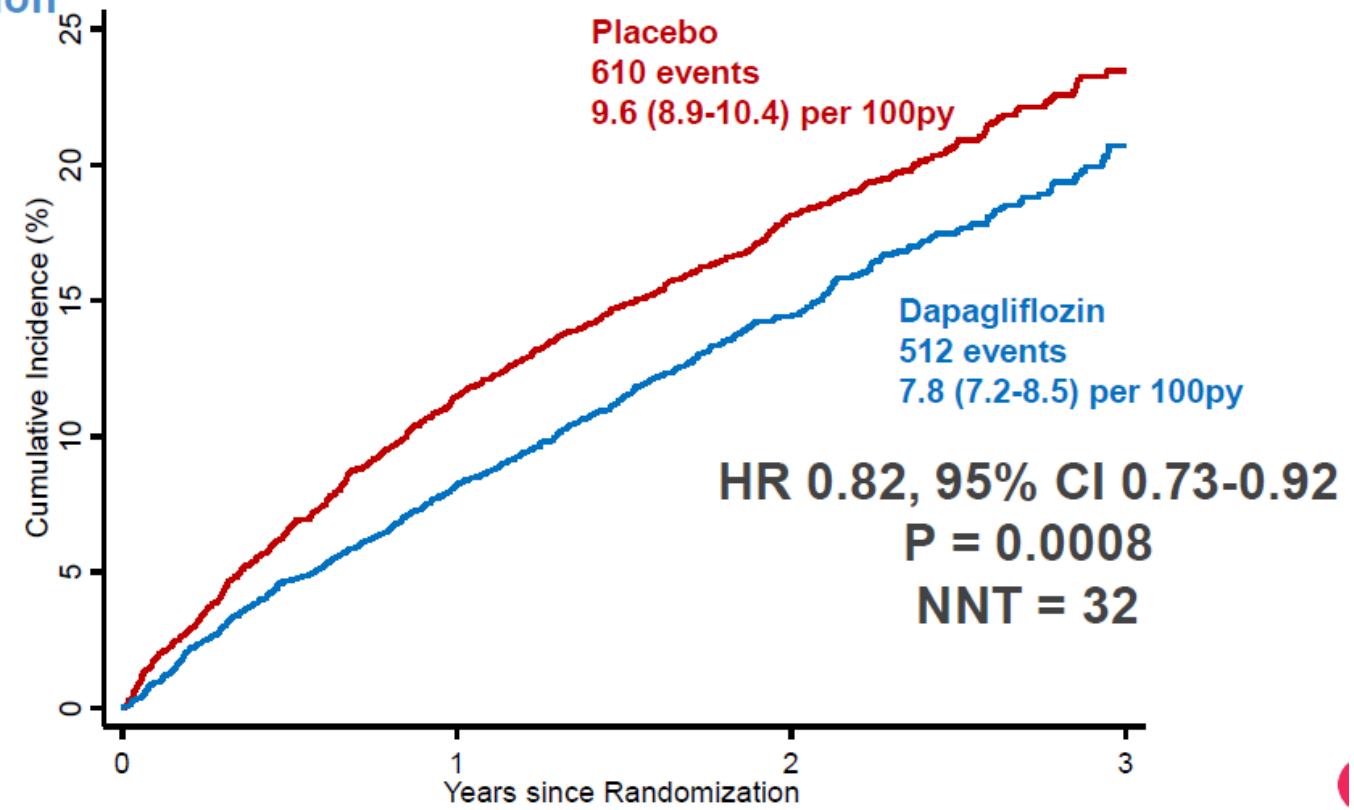
- Serum potassium >5.5 mmol/l: 8.6% vs. 9.9%, HR 0.85, 95% CI 0.74-0.97, P = 0.017;
- Serum potassium >6.0 mmol/l: 1.9% vs. 2.9%, HR 0.62, 95% CI 0.48-0.81, P < 0.001.

Hypokalaemia (investigator-reported or serum potassium <3.0 mmol/l) did not significantly ↑ with empagliflozin

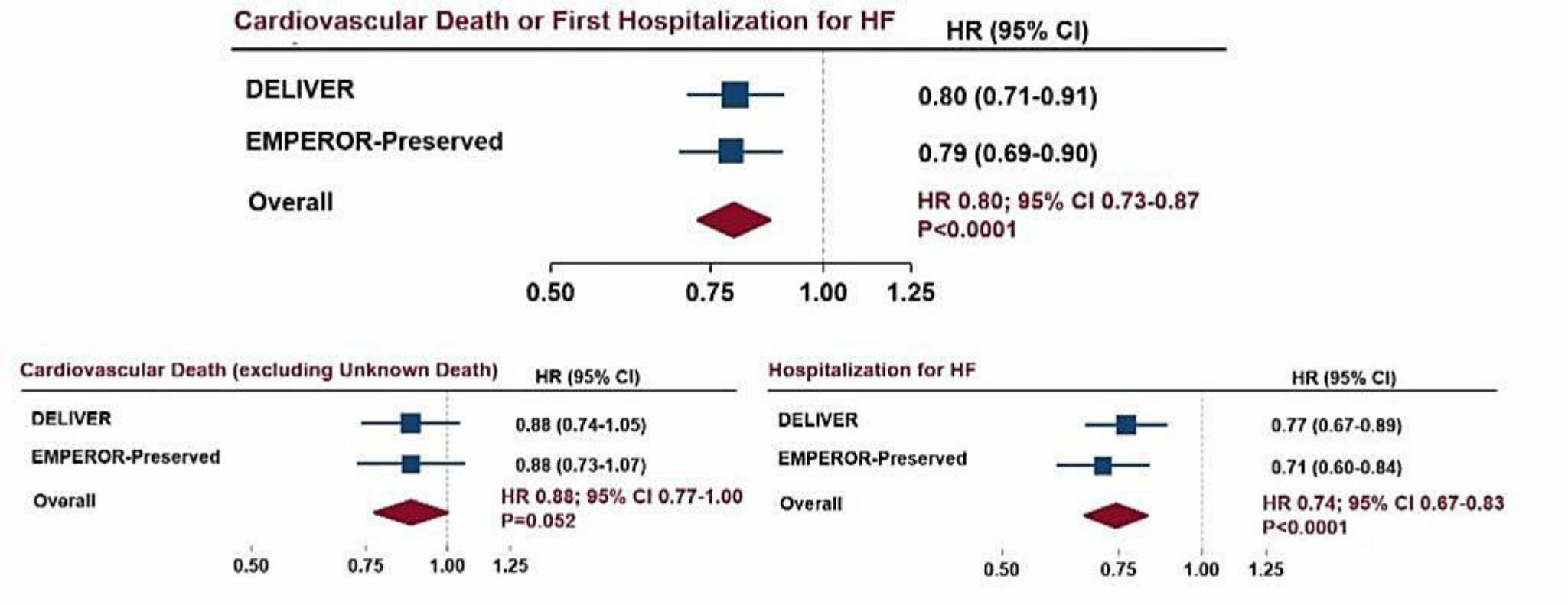
Ferreira JP et al. Eur Heart J. 2022 Jun 10;ehac306. doi: 10.1093/eurheartj/ehac306.

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
The DELIVER Trial

Primary Endpoint: CV Death or Worsening HF
Full Population

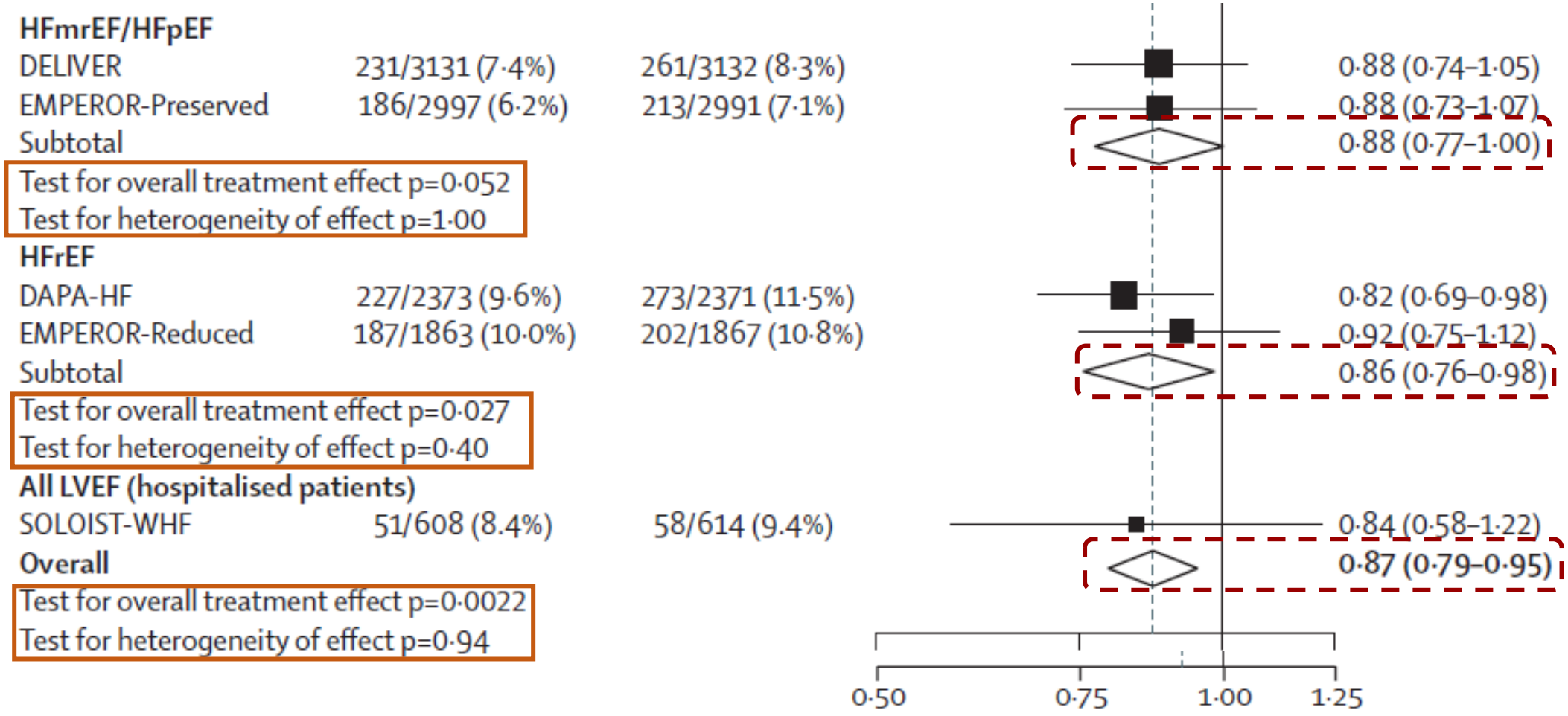


DELIVER and EMPEROR-Preserved Meta-Analysis:
↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components



$P_{heterogeneity} > 0.10$ for all endpoints

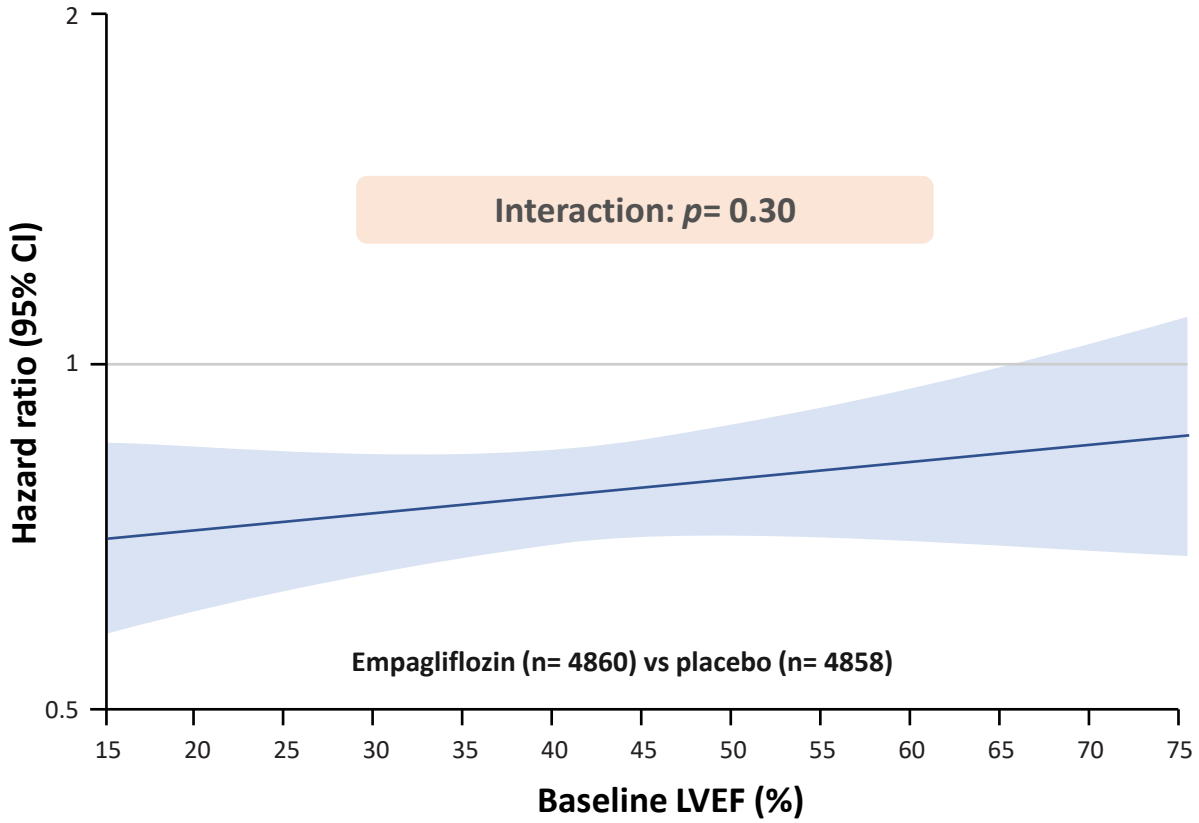
In Statistically Robust Meta-analysis of Studies in HF, SGLT2-i Consistently Reduced Risk of CV Death



Vaduganathan M et al. The Lancet. 2022 Aug 27. https://doi.org/10.1016/S0140-6736(22)01429-5

EMPEROR-Pooled: LVEF did not impact the effect of Empagliflozin on CV death or first HHF

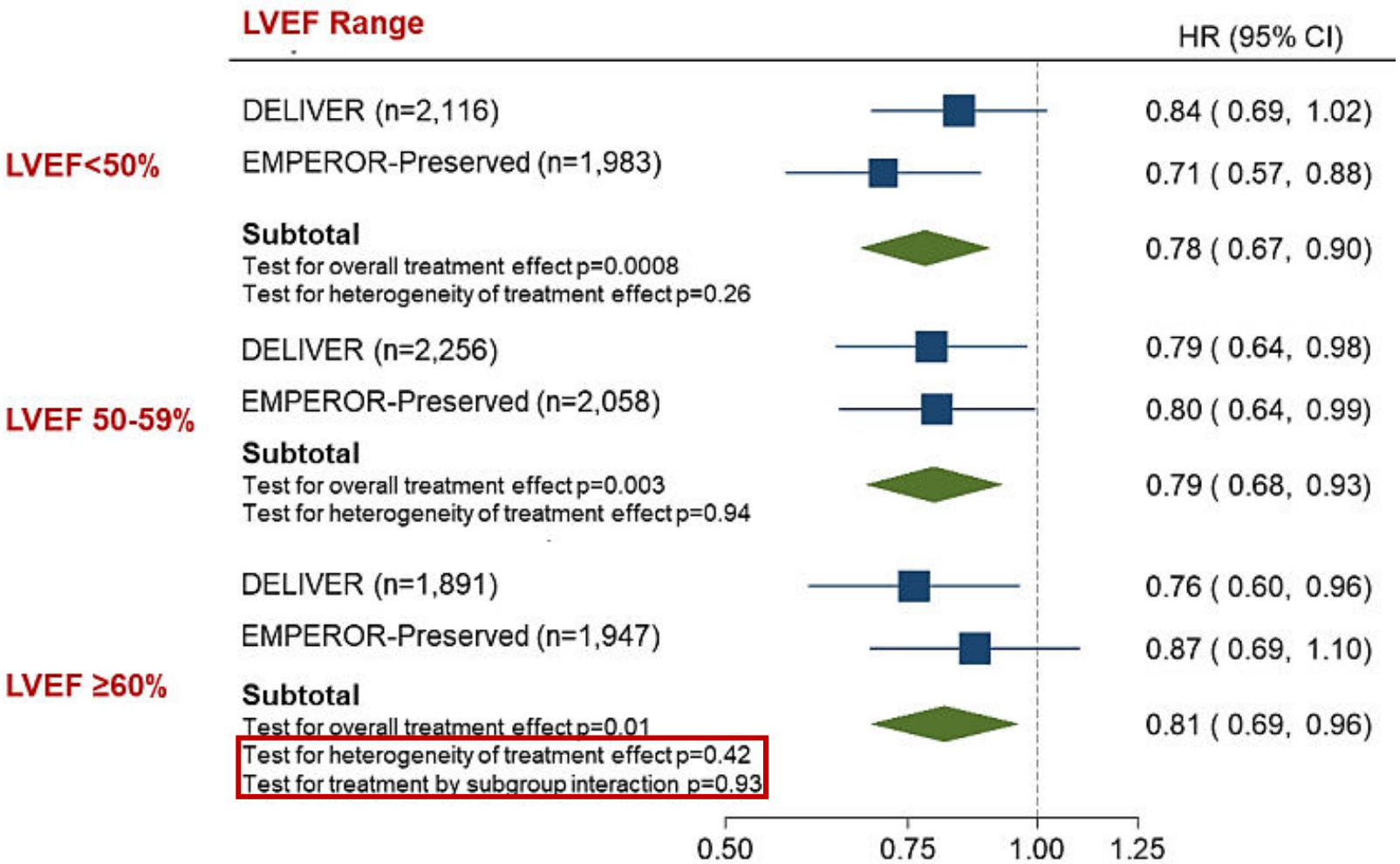
Primary composite endpoint: Time to first event of adjudicated CV death or HHF



Ejection fraction analysed as a continuous variable based on the assumption that the relationship is linear. Shaded areas represent the 95% CI.

Butler J, et al. Eur Heart J 2022;43(5):416-26

DELIVER and EMPEROR-Preserved Meta-Analysis: Consistent Reductions in Primary Endpoint across LVEF Range, including among LVEF ≥60%



Vaduganathan M et al. The Lancet. 2022 Aug 27. https://doi.org/10.1016/S0140-6736(22)01429-5

Empagliflozin is Approved in India and Globally for Treatment of Heart Failure Across the Spectrum of LV Ejection Fraction

Empagliflozin is indicated:

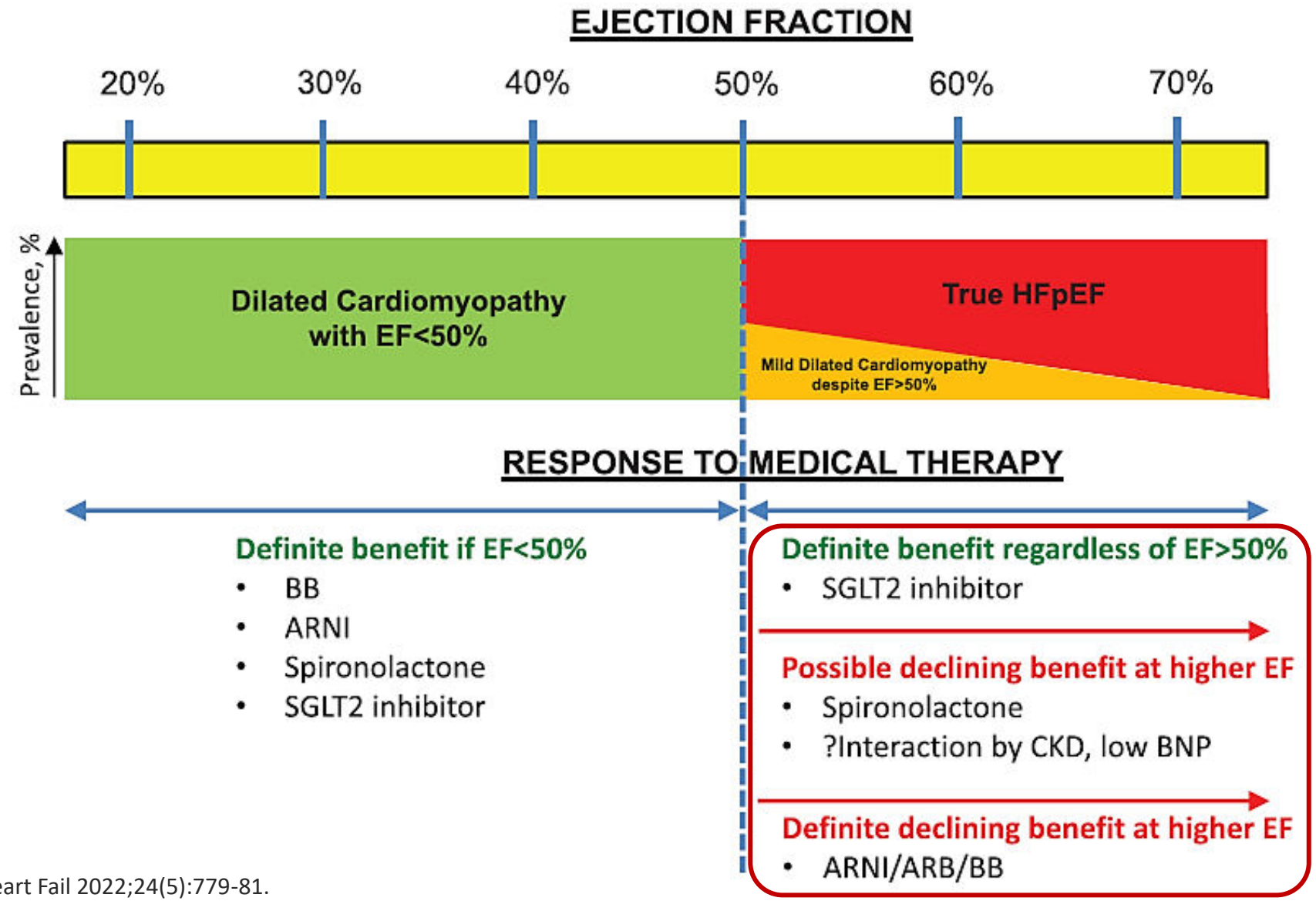
1. To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
2. To reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease.
3. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

SGLT2-i use must be avoided in hemodynamically unstable state; Counsel for maintaining good perineal hygiene;

Avoid use in acute severe medical/ surgical illness (Sick-Day Rule), in severe renal impairment, in type-1 diabetes

Jardiance prescribing information, version May 2022. Boehringer Ingelheim India Pvt Ltd.; Butler J, et al. Eur Heart J 2022;43(5):416-26

Using Ejection Fraction to guide Medical Therapy in HF



Reddy YNV. Eur J Heart Fail 2022;24(5):779-81.

2022 AHA/ACC/HFSA Guideline Recommendations

Patients with Heart Failure and Preserved Ejection Fraction

Recommendations for HF With Preserved Ejection Fraction*
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity (1-3).
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (4).
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (5-7).
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (8,9).
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (10,11).
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective (12,13).

*See Section 7.2, "Diuretics and Decongestion Strategies in Patients with HF," and Section 10.2, "Management of Atrial Fibrillation (AF) in HF" for recommendations for use of diuretics and management of AF in HF.

COR: Category of Recommendation; LOE: Level of Evidence

Braunwald's Corner

Heart failure with preserved ejection fraction: a stepchild no more!

Eugene Braunwald *

"On 27 August 2021 at the European Society of Cardiology meeting, Anker et al. presented the EMPEROR-Preserved trial, in which empagliflozin was compared to placebo in 5988 patients with HFpEF. The primary endpoint, a composite of cardiovascular death and hospitalization for heart failure was reduced significantly by 21%.

It would appear that finally the 'dam has been broken' and that HFpEF is no longer a stepchild!"

Braunwald E. Eur Heart J 2021;42(38):3900-1.

Role of Device Therapy in HF

- AICD: LVEF 35%,DCM,Isch.CMP
- CRT-D:LVEF 35%,LBBB QRS 130,RBBB QRS 150,Pacing dependence
- LA decompressive devices
- LVAD

Thank You