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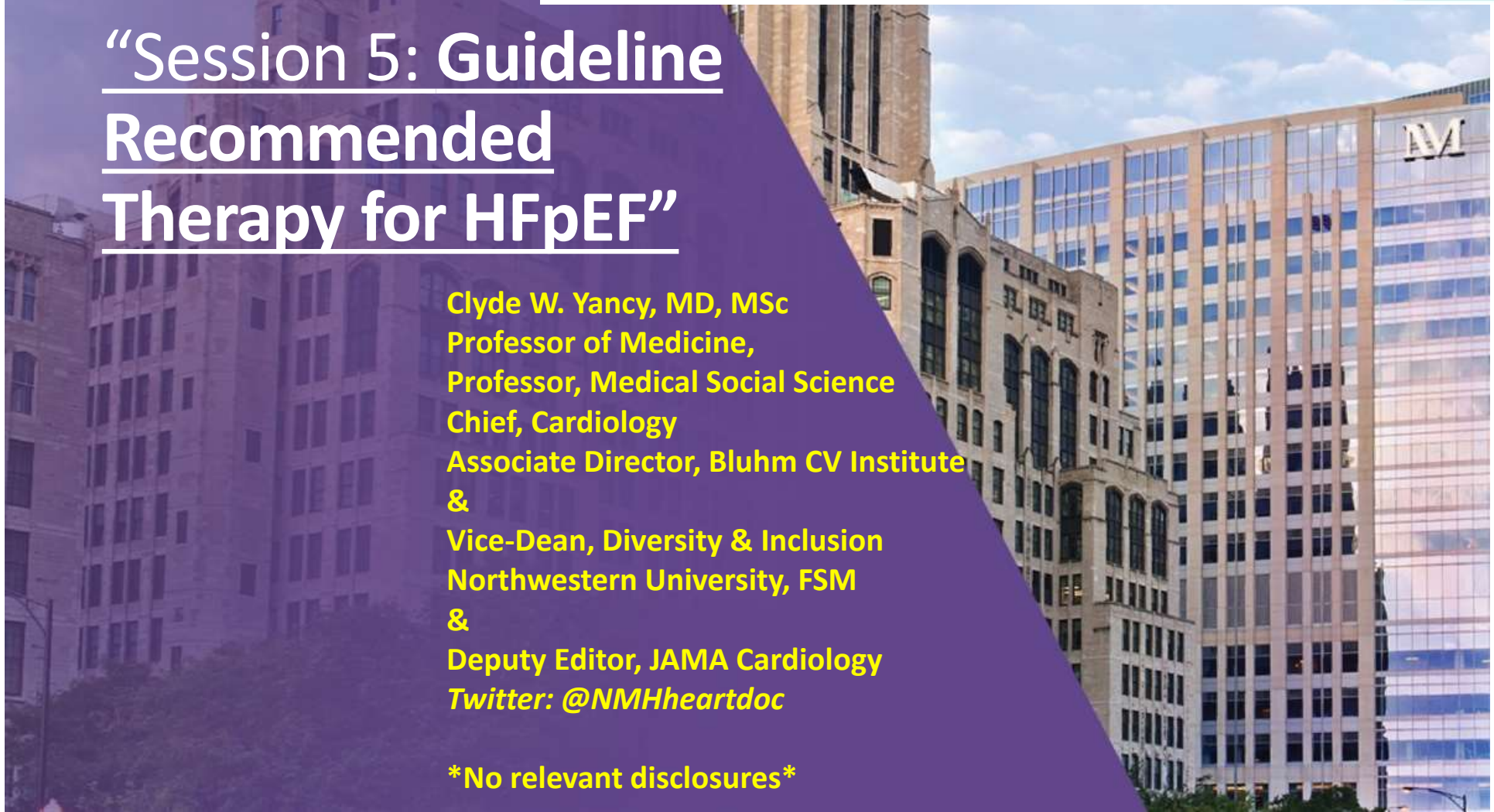
Cardiovascular Symposium India

"Session 5: **Guideline Recommended Therapy for HFpEF"**



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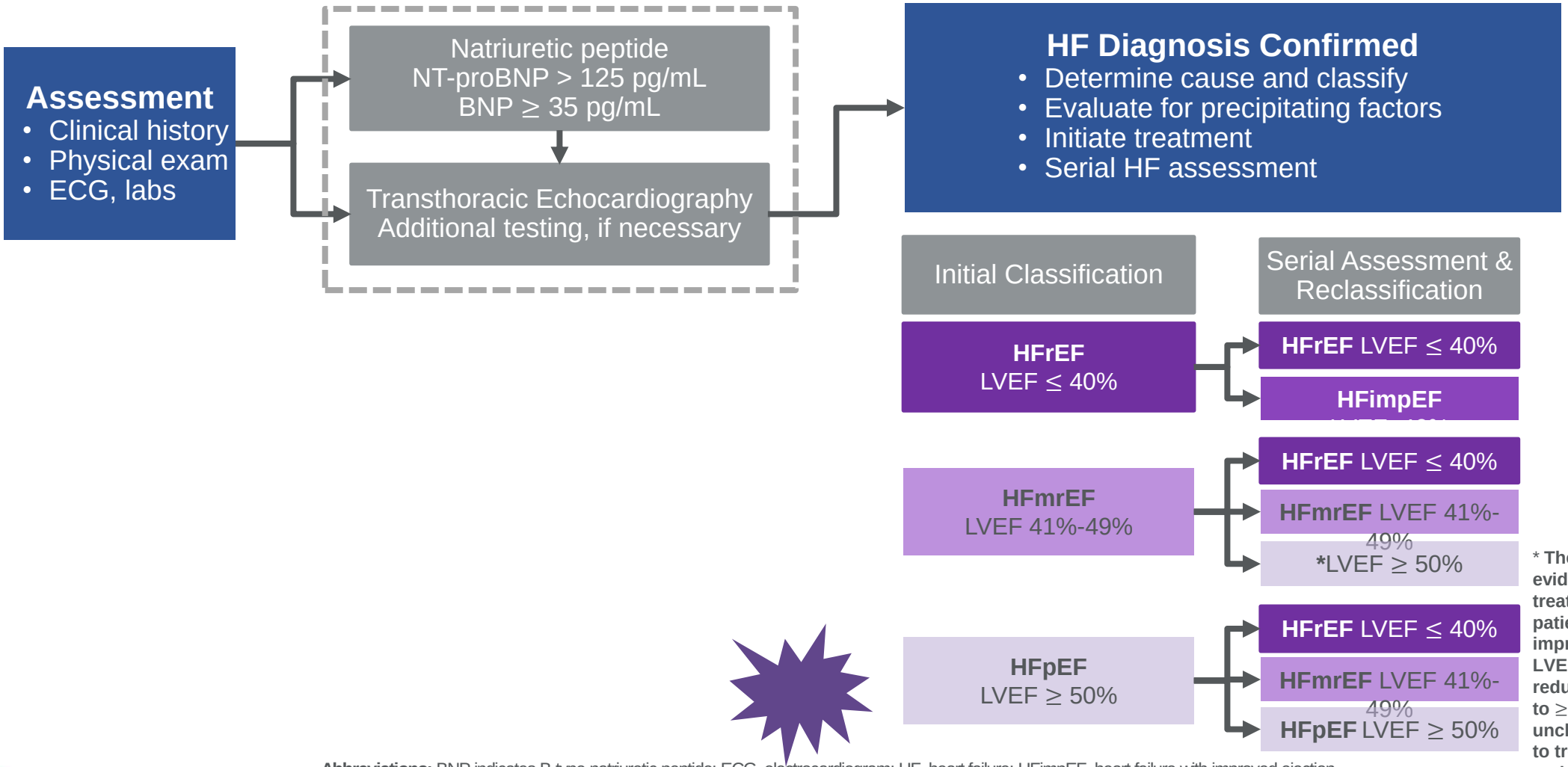
No relevant disclosures

Diagnostic Algorithm for HF and LVEF Based on HF Classification



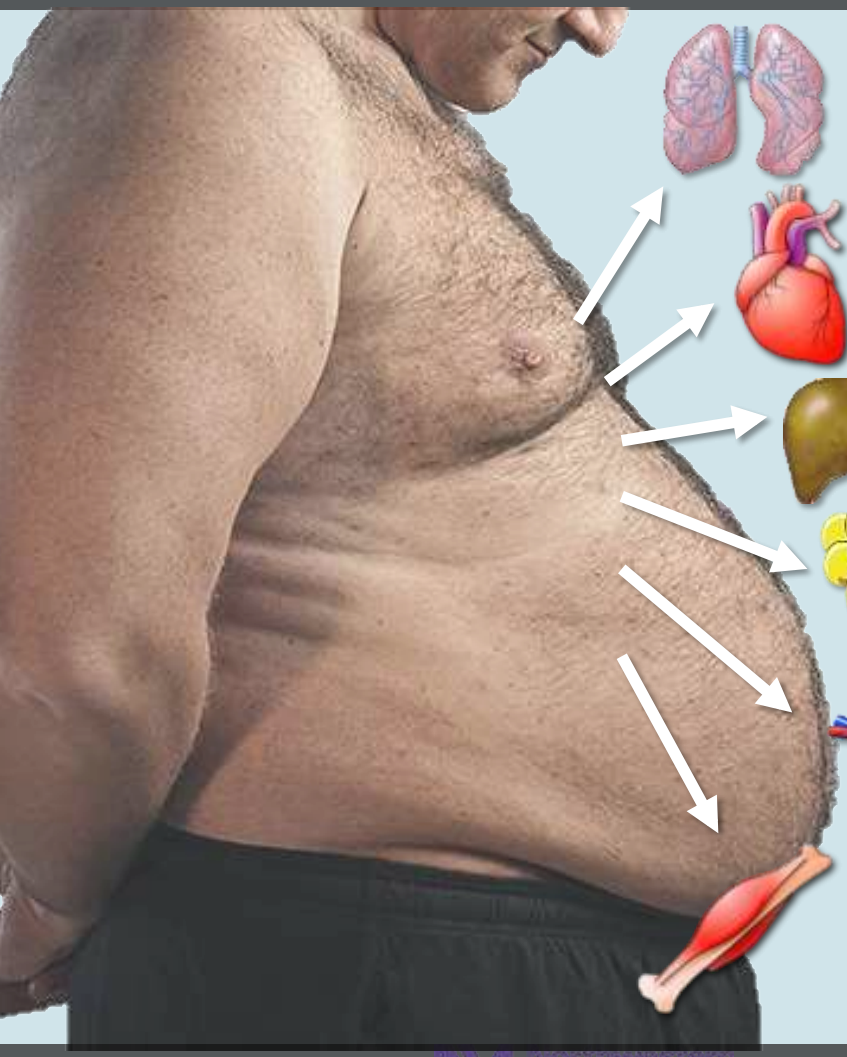
* There is limited evidence to guide treatment for patients who improve their LVEF from mildly reduced (41-49%) to ≥50%. It is unclear whether to treat these patients as HFpEF or HFmrEF.

Abbreviations: BNP indicates B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B type natriuretic peptide.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

American Heart Association.

HFpEF; a heterogenous condition



Lung
Chest wall restriction, reduced vital capacity, impaired ventilation and diffusion
Obstructive sleep apnea
Pulmonary hypertension

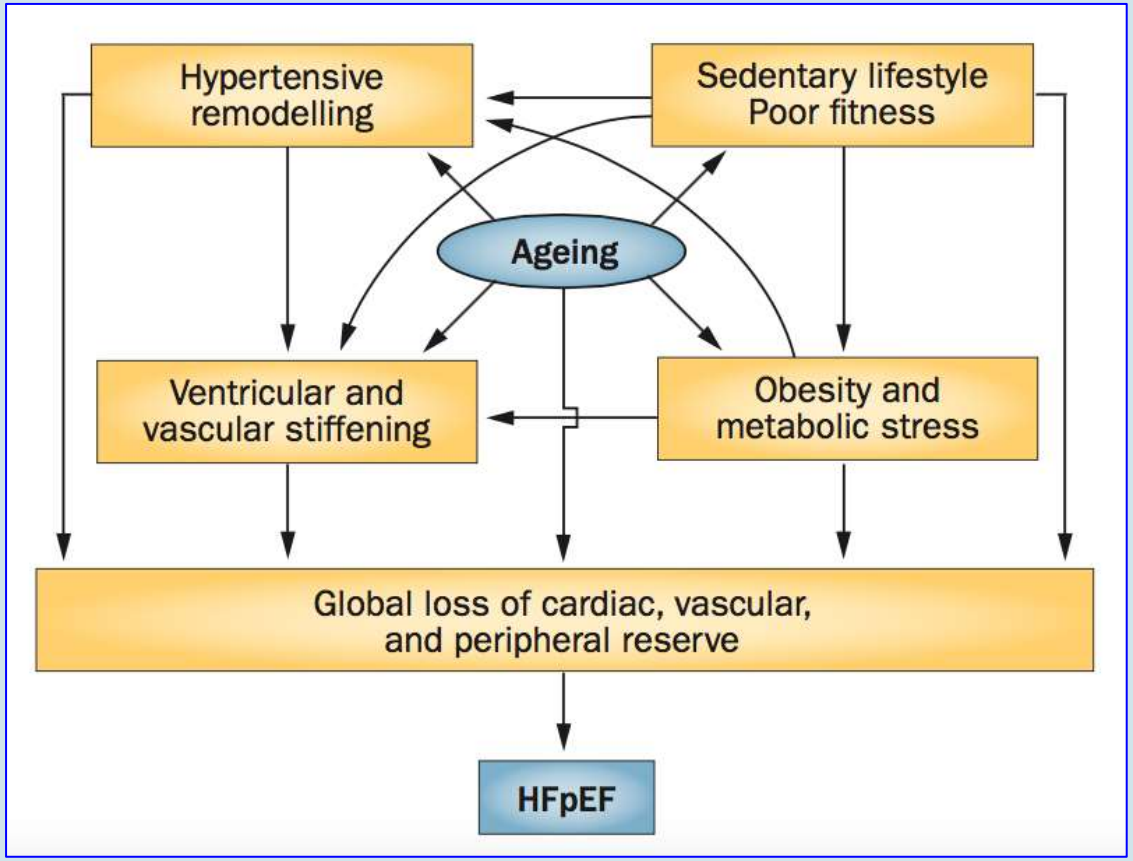
Heart
Direct and indirect myocardial lipotoxicity
Worsened cardiac mechanics
Diastolic dysfunction; increased filling pressures/ volume overload, increased afterload

Liver
Non-alcoholic fatty liver disease
Promotes generalized inflammatory state

Visceral adiposity
Inflammatory cytokines
Adverse neurohormones
Increased BNP clearance

Kidney
Direct toxic effects of perinephric fat
Glomerulomegaly with glomerular dysfunction

Skeletal muscle
Increased adipose infiltration
Impaired perfusion
Decreased diffusive O_2 transport
Mitochondrial dysfunction



Kitzman D, Shah SJ. *JACC* 2016; Borlaug B. *Nat Rev Cardiol* 2014

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What about guideline recommendations for HFpEF and/or HFmrEF?

2017 ACC/AHA/HFSA Guidelines: *treatment of HFpEF*

7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations

Recommendations for Stage C HF*p*EF			
COR	**LOE**	**Recommendations**	**Comment/Rationale**
I	B	**Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity (164, 165).**	2013 recommendation remains current.
I	C	**Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.**	2013 recommendation remains current.
IIa	C	**Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.**	2013 recommendation remains current.
IIa	C	**Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.**	2013 recommendation remains current (Section 9.1 in the 2013 HF guideline).
IIa	C	**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.**	2013 recommendation remains current.
IIb	B-R	**In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83, 166, 167).**	NEW: Current recommendation reflects new RCT data.
See Online Data Supplement C.			


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New Heart Failure Guidelines; ESC, 2021

GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC

Theresa A McDonagh ✉, Marco Metra ✉, Marianna Adamo, Roy S Gardner, Andreas Baumbach, Michael Böhm, Haran Burri, Javed Butler, Jelena Čelutkienė, Ovidiu Chioncel ... Show more

Author Notes

European Heart Journal, ehab368, https://doi.org/10.1093/eurheartj/ehab368

Published: 27 August 2021

Recommendations for treatment of chronic HF	
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb
HFmrEF	
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
HFpEF	
Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities are recommended in patients with HFpEF (see relevant sections of this document).	I

New (ESC) Guideline Directed Management for HFmrEF & HFpEF

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HFpEF; new hope?

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

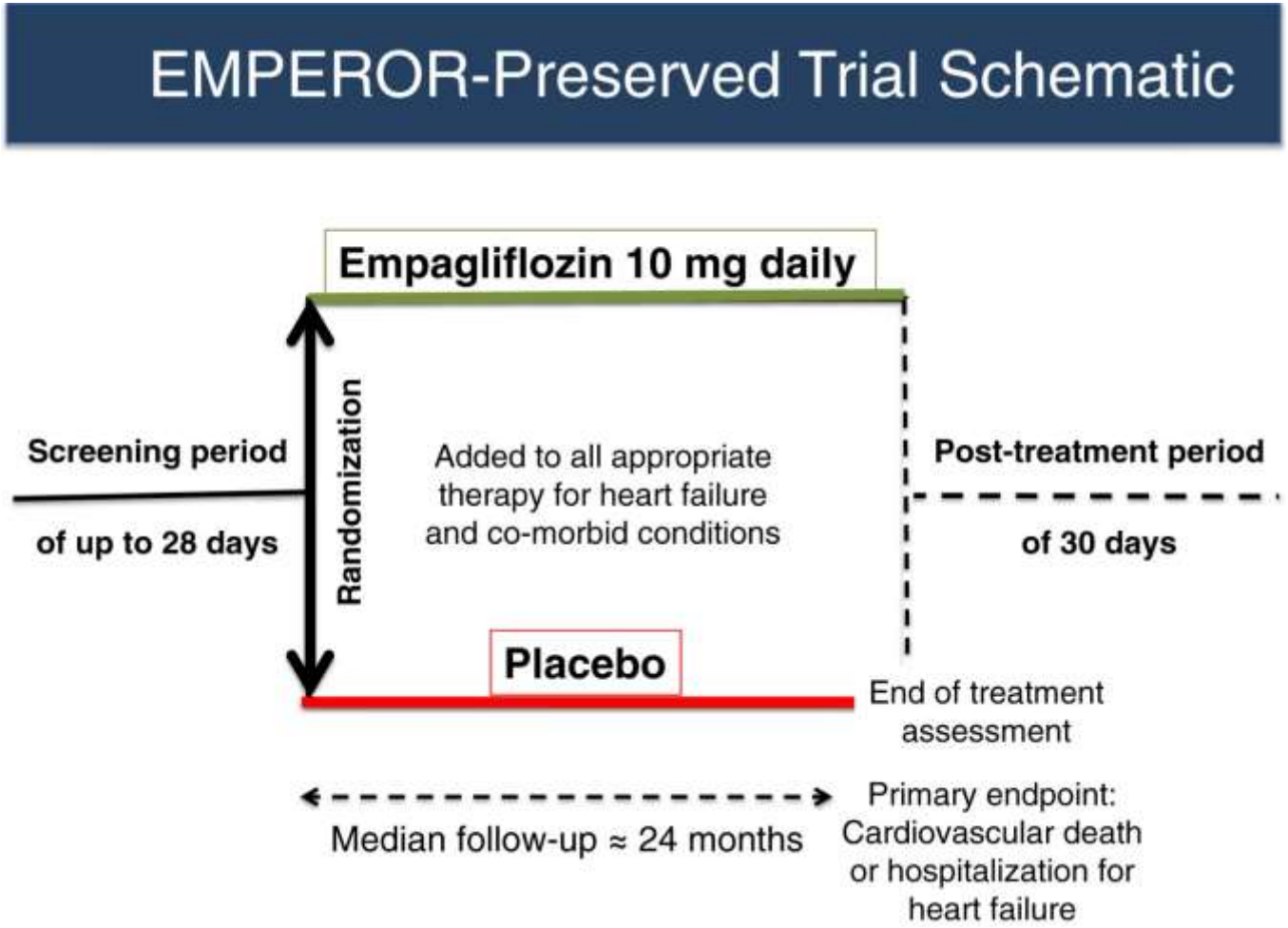
Eugene Braunwald ✉

European Heart Journal, Volume 42, Issue 38, 7 October 2021, Pages 3900–3901,
https://doi.org/10.1093/eurheartj/ehab601
Published: 27 September 2021

The three great cardiovascular physiologists of the 19th and 20th centuries— Otto Frank (Munich), Ernest Starling (London), and Carl Wiggers (Cleveland)—paid little attention to diastole and treated it as a stepchild. It was assumed that heart failure was caused by impaired systolic function. I embraced that mindset in my efforts in the early 1960s to translate the physiologists' experimental findings to patients, by describing two clinical techniques for assessing systolic function—the left ventricle's systolic dp/dt and its ejection fraction.

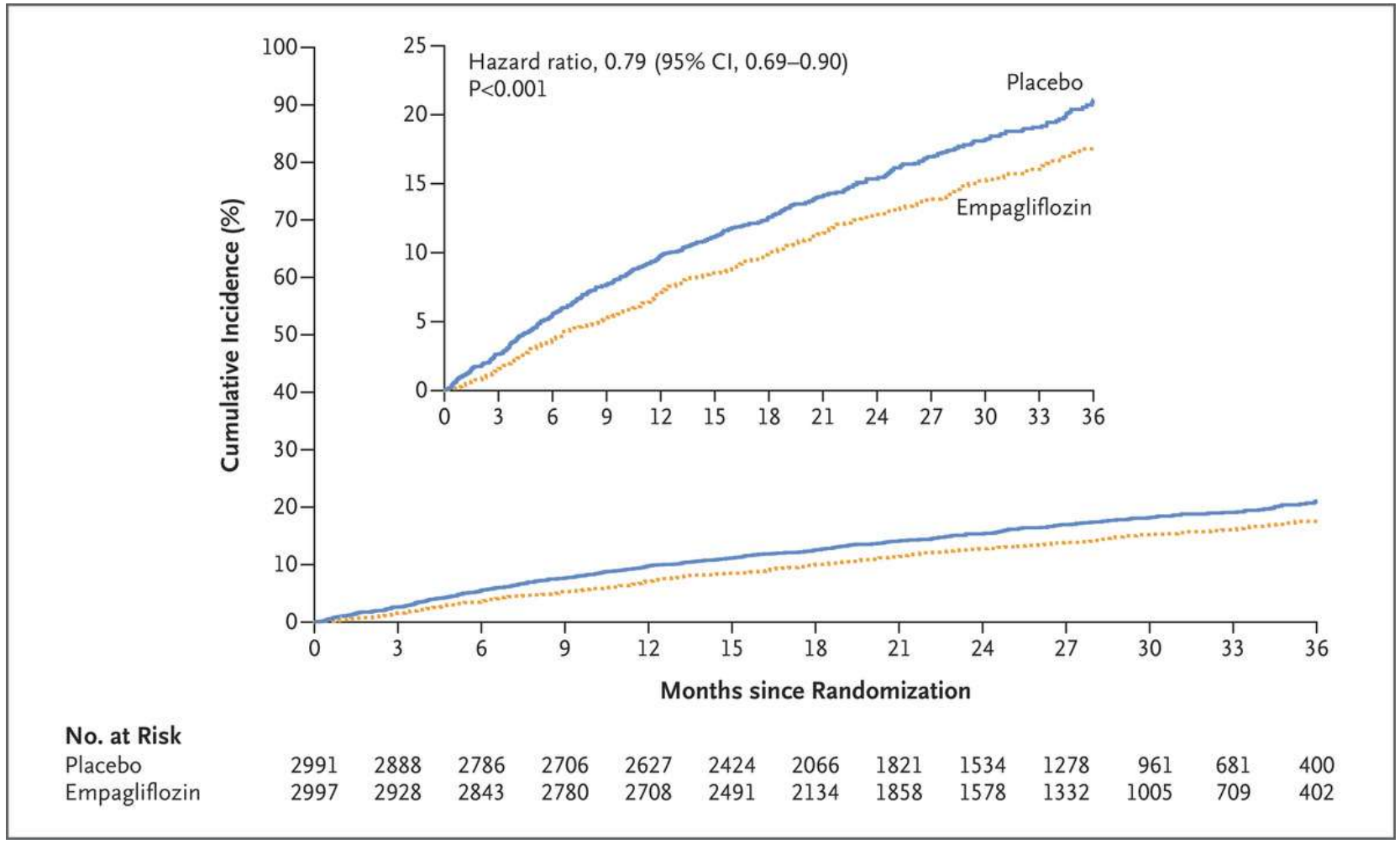
On 27 August 2021 at the European Society of Cardiology meeting, Anker et al. presented the EMPEROR-Preserved trial, in which empagliflozin was compared to placebo in 5988 patients with HFpEF. The primary endpoint, a composite of cardiovascular death and hospitalization for heart failure was reduced significantly by 21%.15 It would appear that finally the 'dam has been broken' and that HFpEF is no longer a stepchild!

Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial



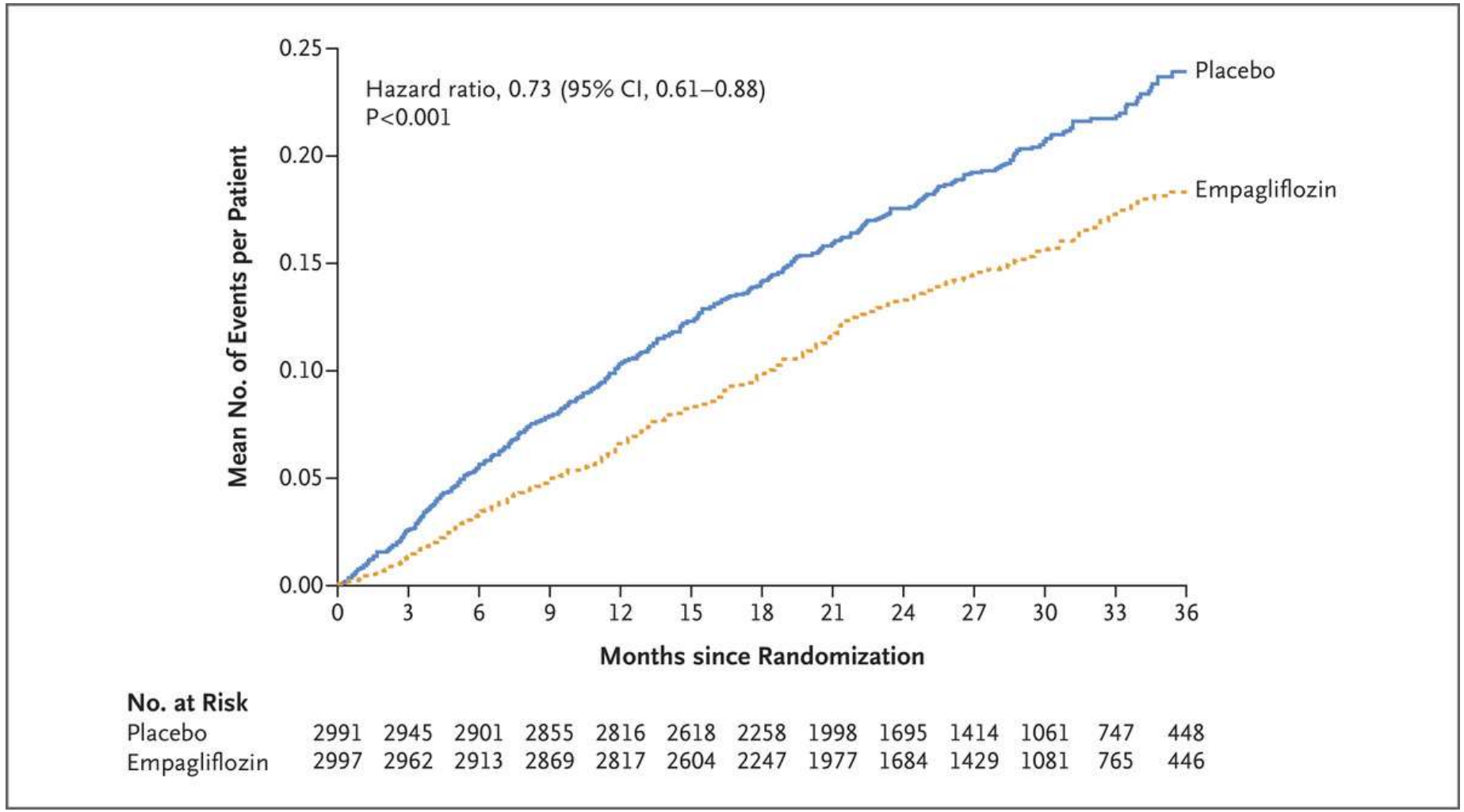
European Journal of Heart Failure, Volume: 21, Issue: 10, Pages: 1279-1287, First published: 16 September 2019, DOI: (10.1002/ejhf.1596)

Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.



SD Anker et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

Hospitalizations for Heart Failure.



Engl J Med 2021. DOI: 10.1056/NEJMoa2107038

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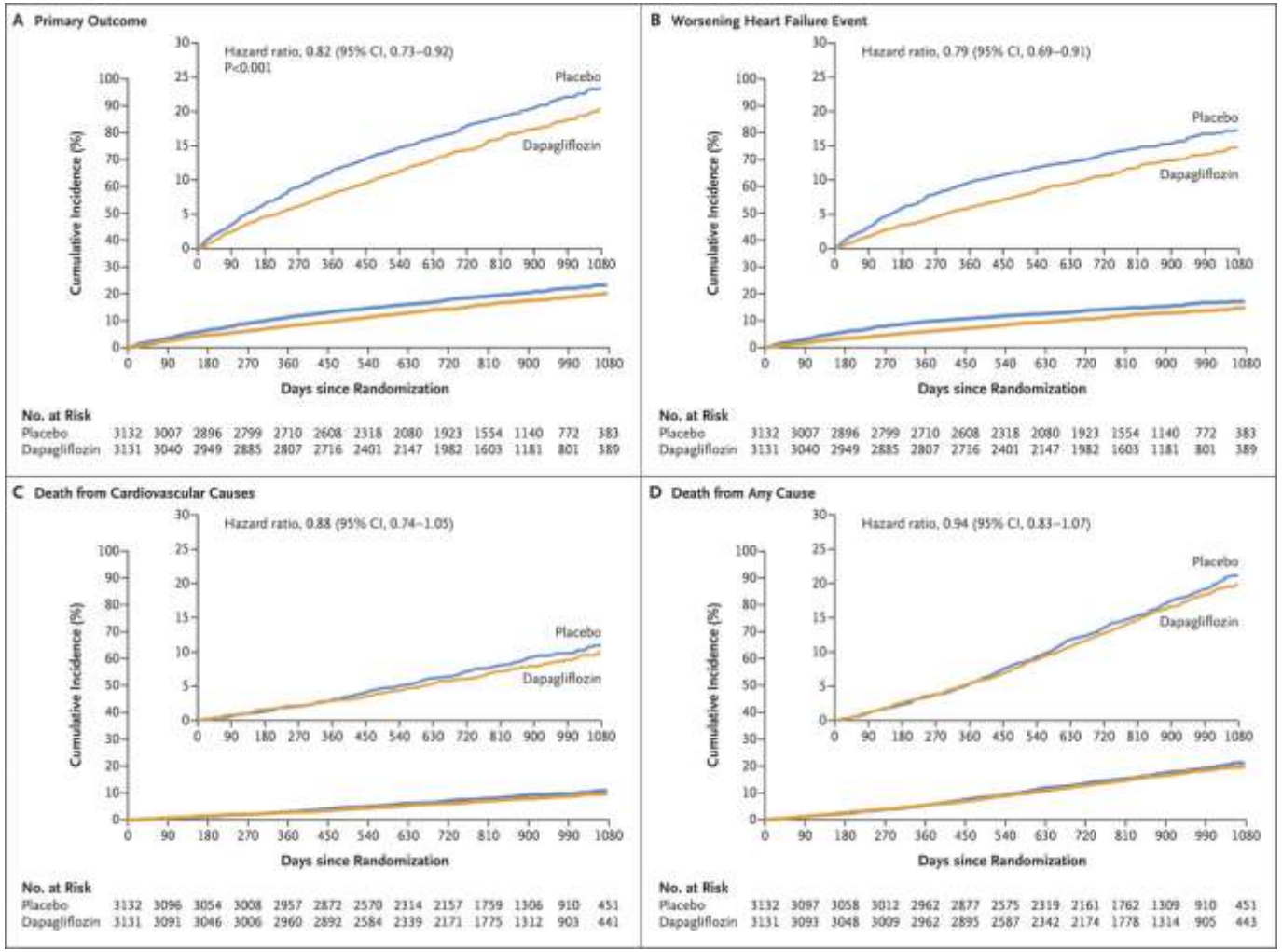
ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Brian Claggett, Ph.D., Rudolf A. de Boer, M.D., David DeMets, Ph.D., Adrian F. Hernandez, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., Carolyn S.P. Lam, M.D., Felipe Martinez, M.D., Sanjiv J. Shah, M.D., Akshay S. Desai, M.D., et al., for the DELIVER Trial Committees and Investigators*

DELIVER: Efficacy Outcomes in the Overall Population.



Solomon et al. N Engl J Med 2022;387:1089-1098.

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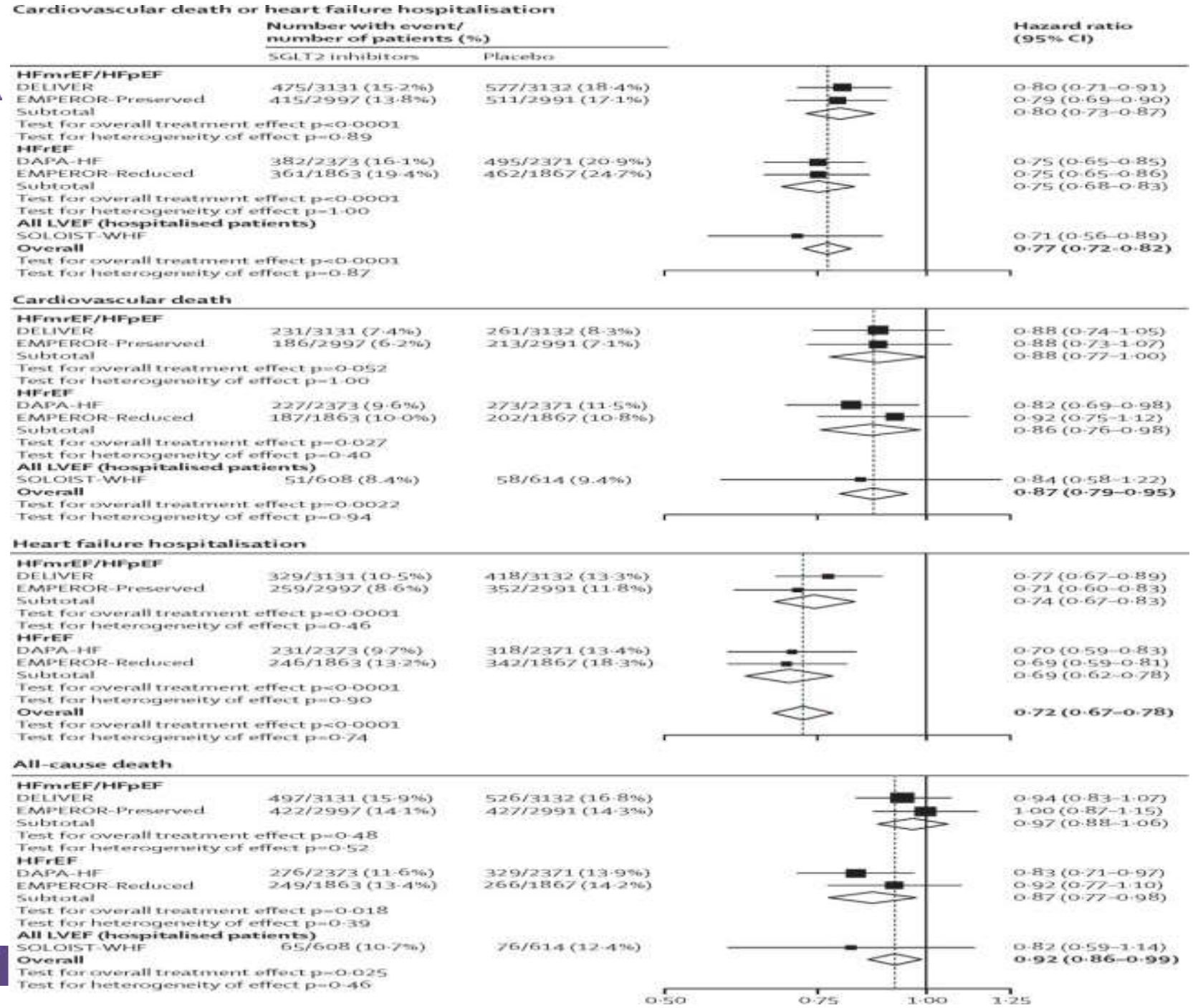
Cardiovascular death or heart failure hospitalisation
Number with event/ number of patients (%)
SGLT2 inhibitors
Placebo
Hazard ratio (95% CI)
HFmrEF/HFpEF
DELIVER 475/3131 (15·2%) 577/3132 (18·4%) 0·80 (0·71–0·91)
EMPEROR-Preserved 415/2997 (13·8%) 511/2991 (17·1%) 0·79 (0·69–0·90)
Subtotal 0·80 (0·73–0·87)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·89
HFrEF
DAPA-HF 382/2373 (16·1%) 495/2371 (20·9%) 0·75 (0·65–0·85)
EMPEROR-Reduced 361/1863 (19·4%) 462/1867 (24·7%) 0·75 (0·65–0·86)
Subtotal 0·75 (0·68–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=1·00
All LVEF (hospitalised patients)
SOLOIST-WHF 0·71 (0·56–0·89)
Overall 0·77 (0·72–0·82)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·87
Cardiovascular death
HFmrEF/HFpEF
DELIVER 231/3131 (7·4%) 261/3132 (8·3%) 0·88 (0·74–1·05)
EMPEROR-Preserved 186/2997 (6·2%) 213/2991 (7·1%) 0·88 (0·73–1·07)
Subtotal 0·88 (0·77–1·00)
Test for overall treatment effect p=0·052
Test for heterogeneity of effect p=1·00
HFrEF
DAPA-HF 227/2373 (9·6%) 273/2371 (11·5%) 0·82 (0·69–0·98)
EMPEROR-Reduced 187/1863 (10·0%) 202/1867 (10·8%) 0·92 (0·75–1·12)
Subtotal 0·86 (0·76–0·98)
Test for overall treatment effect p=0·027
Test for heterogeneity of effect p=0·40
All LVEF (hospitalised patients)
SOLOIST-WHF 51/608 (8·4%) 58/614 (9·4%) 0·84 (0·58–1·22)
Overall 0·87 (0·79–0·95)
Test for overall treatment effect p=0·0022
Test for heterogeneity of effect p=0·94
Heart failure hospitalisation
HFmrEF/HFpEF
DELIVER 329/3131 (10·5%) 418/3132 (13·3%) 0·77 (0·67–0·89)
EMPEROR-Preserved 259/2997 (8·6%) 352/2991 (11·8%) 0·71 (0·60–0·83)
Subtotal 0·74 (0·67–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·46
HFrEF
DAPA-HF 231/2373 (9·7%) 318/2371 (13·4%) 0·70 (0·59–0·83)
EMPEROR-Reduced 246/1863 (13·2%) 342/1867 (18·3%) 0·69 (0·59–0·81)
Subtotal 0·69 (0·62–0·78)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·90
Overall 0·72 (0·67–0·78)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·74
All-cause death
HFmrEF/HFpEF
DELIVER 497/3131 (15·9%) 526/3132 (16·8%) 0·94 (0·83–1·07)
EMPEROR-Preserved 422/2997 (14·1%) 427/2991 (14·3%) 1·00 (0·87–1·15)
Subtotal 0·97 (0·88–1·06)
Test for overall treatment effect p=0·48
Test for heterogeneity of effect p=0·52
HFrEF
DAPA-HF 276/2373 (11·6%) 329/2371 (13·9%) 0·83 (0·71–0·97)
EMPEROR-Reduced 249/1863 (13·4%) 266/1867 (14·2%) 0·92 (0·77–1·10)
Subtotal 0·87 (0·77–0·98)
Test for overall treatment effect p=0·018
Test for heterogeneity of effect p=0·39
All LVEF (hospitalised patients)
SOLOIST-WHF 65/608 (10·7%) 76/614 (12·4%) 0·82 (0·59–1·14)
Overall 0·92 (0·86–0·99)
Test for overall treatment effect p=0·025
Test for heterogeneity of effect p=0·46
0·50
0·75
1·00
1·25

From: **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**

JAMA Cardiol. Published online October 03, 2022. doi:10.1001/jamacardio.2022.3750

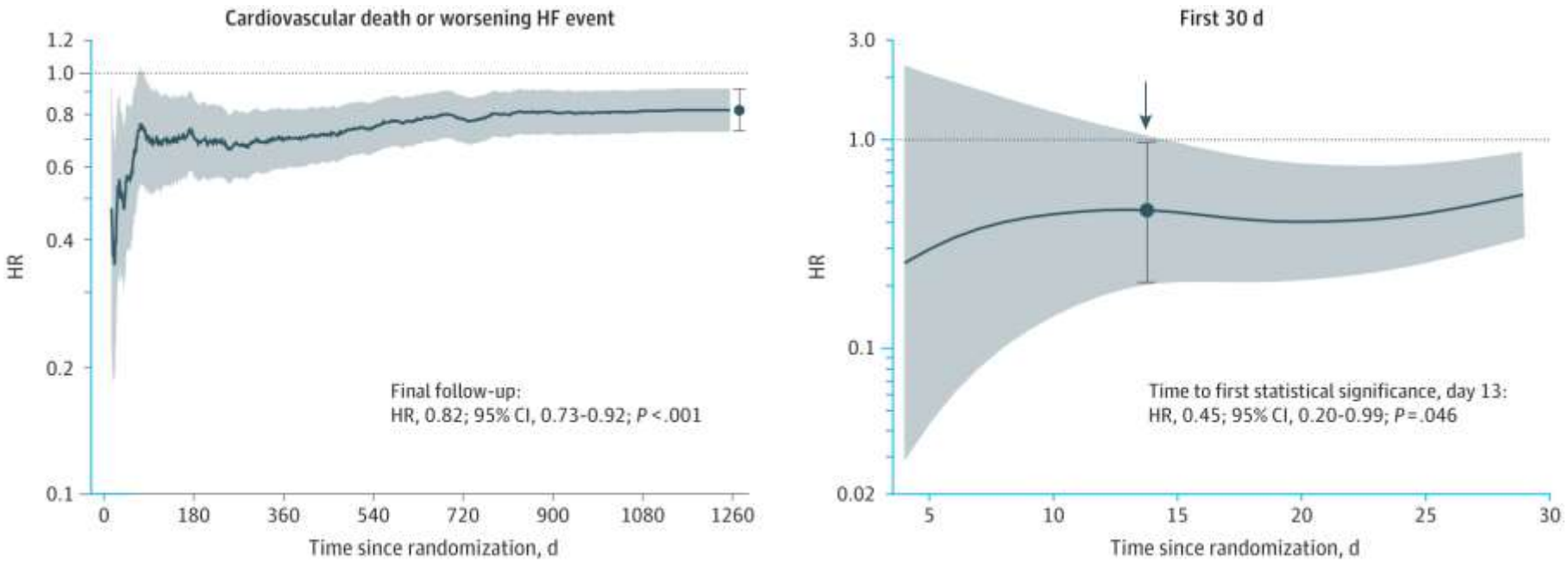

Figure Legend:

Time to Clinical Benefit for the Primary End Point in the DELIVER TrialHazard ratios (HRs) and 95% CIs by day postrandomization for the primary end point (cardiovascular death or worsening heart failure [HF] event) in the DELIVER trial, with a magnified view of the first 30 days postrandomization (smoothed by applying a locally weighted scatterplot smoothing procedure).

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New Heart Failure Guidelines AHA/ACC/HFSA, 2022

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Clinical Practice Guideline: J Am Coll Cardiol. Apr 01, 2022. Epublished DOI: 10.1016/j.jacc.2021.12.012

Recommendations for Patients at Risk of HF & Pre-HF

At Risk for HF (Stage A)

Primary Prevention

Patients with hypertension	Optimal control of BP (1)
Patients with Type 2 diabetes and CVD or high risk for CVD	SGLT2i (1)
Patients with CVD	Optimal management of CVD (1)
Patients with exposure to cardiotoxic agents	Multidisciplinary evaluation and management (1)
First-degree relatives of patients with genetic or inherited cardiomyopathies	Genetic screening and counselling (1)
Patients at risk for HF	Natriuretic peptide screening (2a)
Patients at risk for HF	Validated multivariable risk score (2a)

Pre-HF (Stage B)

Preventing the Syndrome

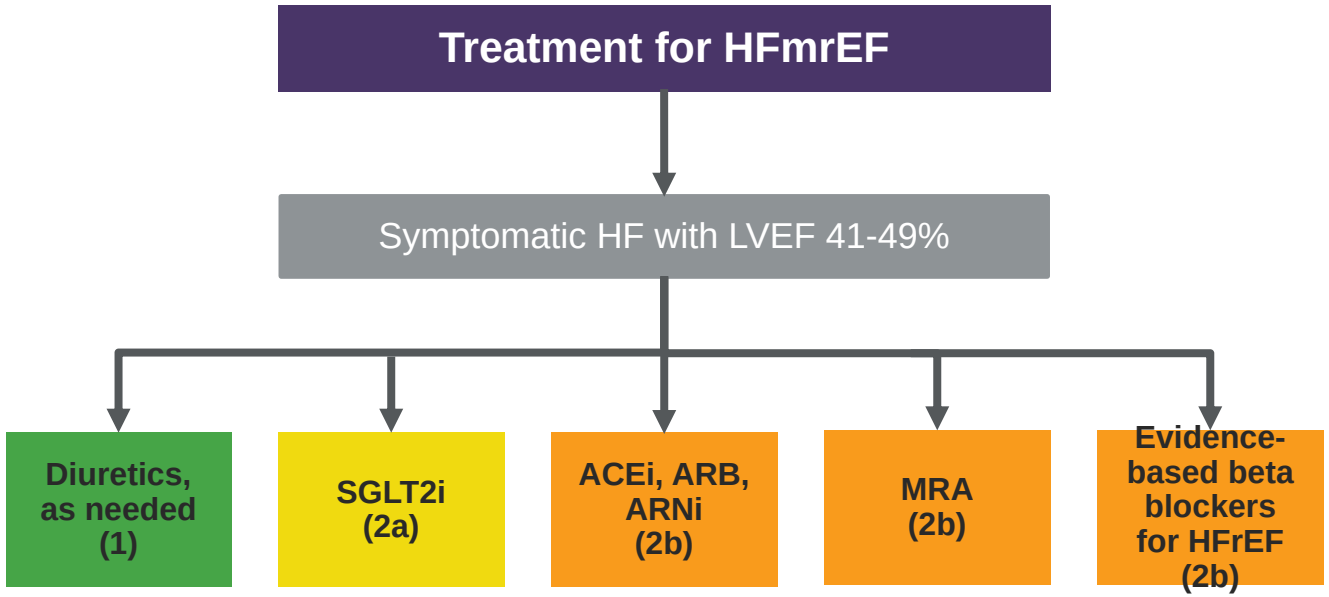
Patients with LVEF ≤ 40%	ACEi (1)
Patient with recent MI and LVEF ≤ 40 %	ARB if ACEi intolerant (1)
Patients with LVEF ≤ 40%	Beta blocker (1)
Patient with LVEF ≤ 30 %; >1 y survival; >40 d post MI	ICD (1)
Patients with nonischemic cardiomyopathy	Genetic counselling and testing (2a)

Continue Lifestyle modification and management strategies implemented in Stage A, through Stage B

Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

Recommendations for Patients with Mildly Reduced LVEF



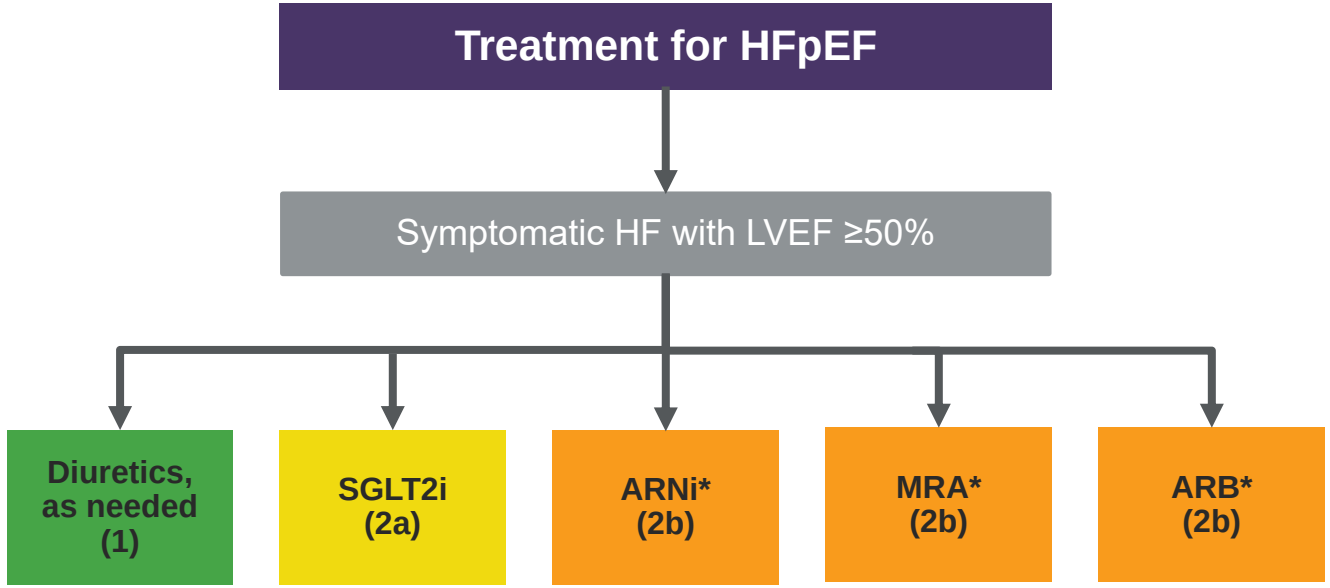
Patients With HFimpEF

COR	RECOMMENDATIONS
1	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (1)

Abbreviations: ARB indicates angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

Recommendations for Patients with Preserved LVEF



NOTE: *Greater benefit in patients with LVEF closer to 50%

Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium- glucose cotransporter 2 inhibitor.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

American Heart Association.

Diabetol Int. 2021 Jul; 12(3): 247–253.
Published online 2020 Oct 29. doi: 10.1007/s13340-020-00472-4
PMCID: PMC8172658
PMID: 34150432

Remogliflozin: the new low cost SGLT-2 inhibitor for type 2 diabetes mellitus

Shubham Atal,[✉1] Zeenat Fatima,[1] Sakshi Singh,[2] Sadasivam Balakrishnan,[1] and Rajnish Joshi[3]

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Abstract

Go to: ▸

SGLT-2 inhibitors have recently emerged as an important class of oral drugs for treatment of type 2 diabetes mellitus, especially in patients with cardiovascular or renal impairment, recommended in all recent treatment guidelines. They have additional advantages of weight and blood pressure reduction but also pose problems like genitourinary infections. These drugs generally have a high cost making affordability a major consideration in their prescription in developing countries like India. A new molecule remogliflozin has been approved in India in 2019 after a phase 3 trial proved its efficacy and safety in comparison to dapagliflozin. This drug has been priced substantially lower than other SGLT-2 inhibitors, and despite the disadvantage of twice daily administration, it potentially reduces treatment cost to less than half compared to other molecules of this class. With a good tolerability profile on the basis of available safety data till date, remogliflozin could be a useful alternative for providing SGLT-2 inhibitor therapy in a country like India where out of pocket expenses for drug acquisition matter significantly for the general population. However, long term safety and efficacy data especially on cardiovascular and renal outcomes are currently lacking for the drug.

Back to India…

Table 1: Cost comparison of different SGLT2 inhibitors of different brands

Name of the drug	Strength (in mg)	Brand number	Cost per 10 tablets (in rupees)
Canagliflozin	100mg	1	Rs.545
		2	Rs.549
		3	Rs.550
Dapagliflozin	10mg	1	Rs.521.42
		2	Rs.521.42
		3	Rs.573.5
Empagliflozin	10mg	1	Rs.470
		2	Rs.470
Remogliflozin	100mg	1	Rs.125

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Takeaways:

1. The predominant HF phenotype in India is likely HFpEF
2. SGLT2 inhibitors represent breakthrough therapy
3. Cost is a major consideration worldwide
4. Remogliflozin may be the answer in India, but *outcomes studies are needed*

Thank you!

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