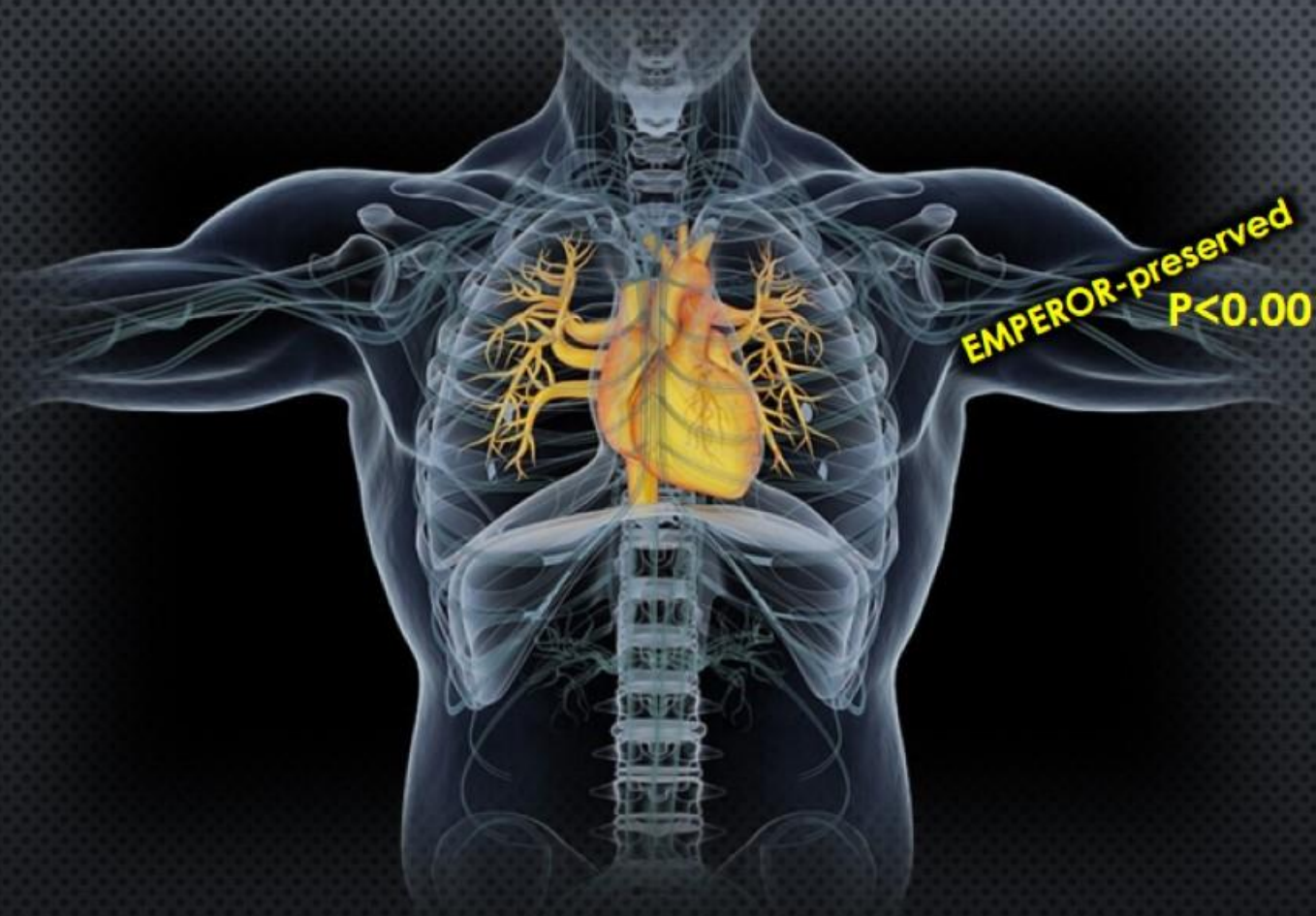
EMPEROR-preserved trial results



EMPEROR-preserved
P<0.001

HFrEF
- LVEF ≤40%

HFmrEF
- LVEF 41%–49%

HFpEF
- LVEF ≥50%

EMPEROR-reduced
P<0.001

Circulation. 2022;145:e895–e1032

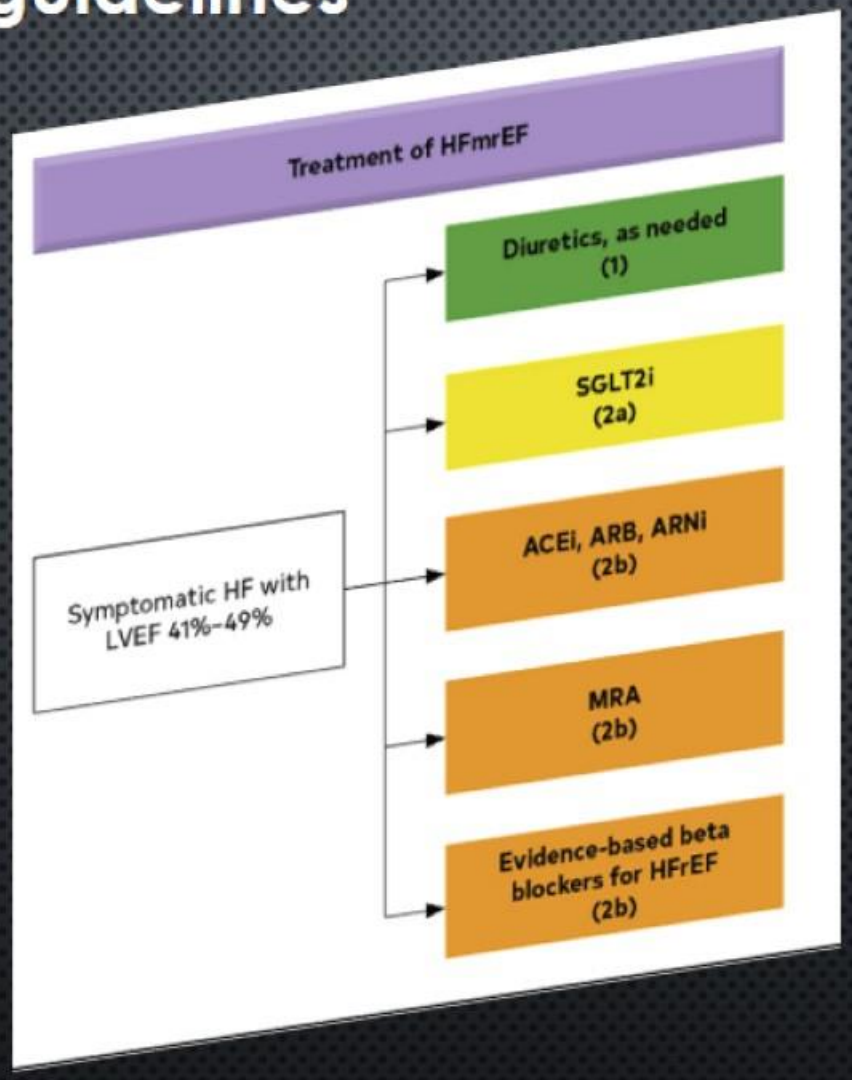
Empagliflozin FOR HEART FAILURE

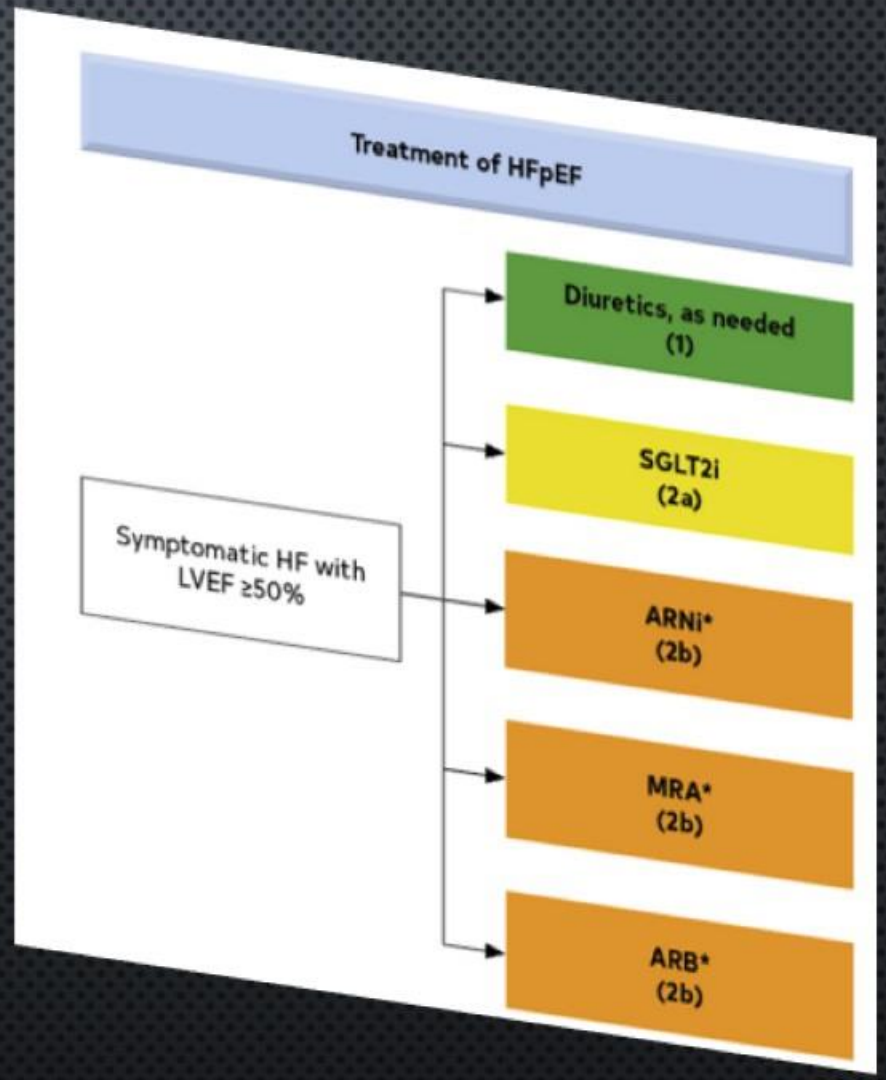
2022 Heart failure guidelines

Class 1 for HF ref <40%

- Beta blocker
- SGLT2i
- MRA
- ACEI/ARNI
- Diuretics prn

With of w/o diabetes





JACC VOL. 79, NO. 17, MAY 3, 2022:1757–1780

Adapted from JACC

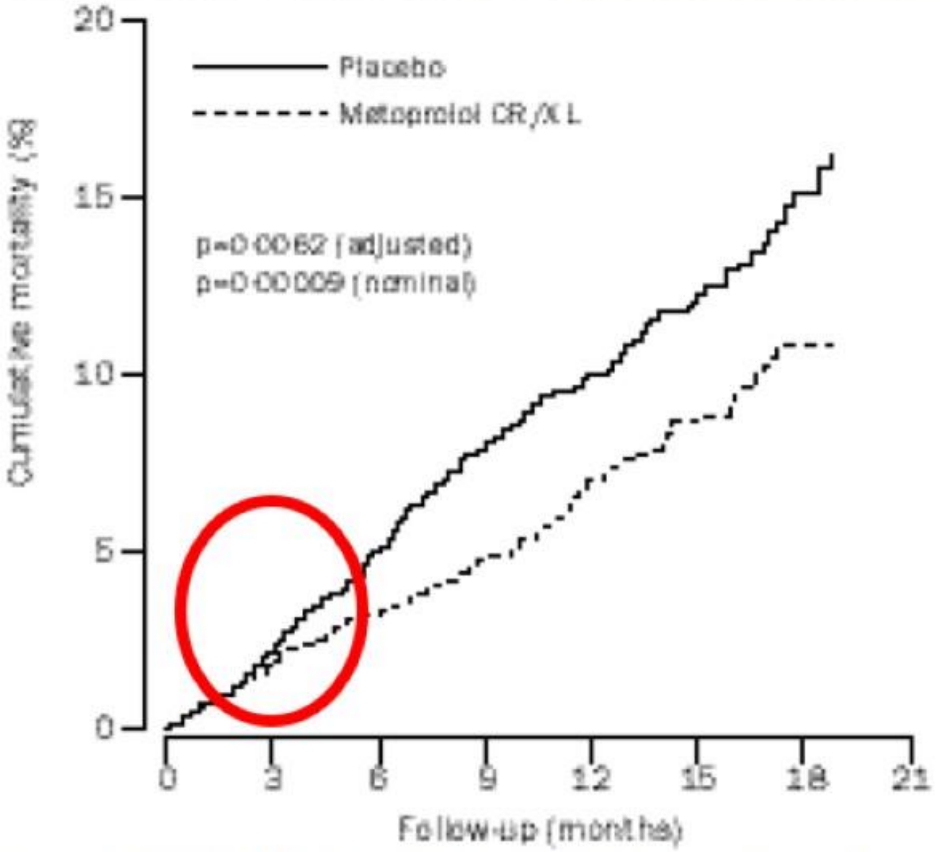


Figure 2: **Kaplan-Meier curves of cumulative percentage of total mortality**

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)

2 primary endpoints were all-cause mortality and all-cause mortality in combination with all-cause admission to hospital (time to first event).

*MERIT-HF Study Group**

Clinical		
Heart failure		
Ischaemic	1294 (65%)	1312 (66%)
Non-ischaemic	696 (35%)	689 (34%)
NYHA class		
II	811 (41%)	825 (41%)
III	1110 (56%)	1100 (55%)
IV	69 (3·4%)	76 (3·8%)
Previous myocardial infarction	950 (48%)	974 (49%)
Time since last myocardial infarction (years)*		
<1	151 (8%)	139 (7%)
1–5	341 (17%)	366 (18%)
≥5	457 (23%)	469 (23%)
Atrial fibrillation	324 (16%)	341 (17%)
Hypertension	871 (44%)	876 (44%)
Diabetes mellitus	495 (25%)	489 (24%)
Mean (SD) measurements		
Ejection fraction	0·28 (0·07)	0·28 (0·07)

The study was **stopped early** on the recommendation of the independent safety committee. Mean follow-up time was 1 year. All-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (**145** [7·2%, per patient-year of follow-up]) vs **217 deaths** [11·0 %], relative risk 0·66 [95% CI 0·53–0·81]; **p=0·00009** or adjusted for interim analyses p=0·0062).

jchf.guidelines.org.pdf

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

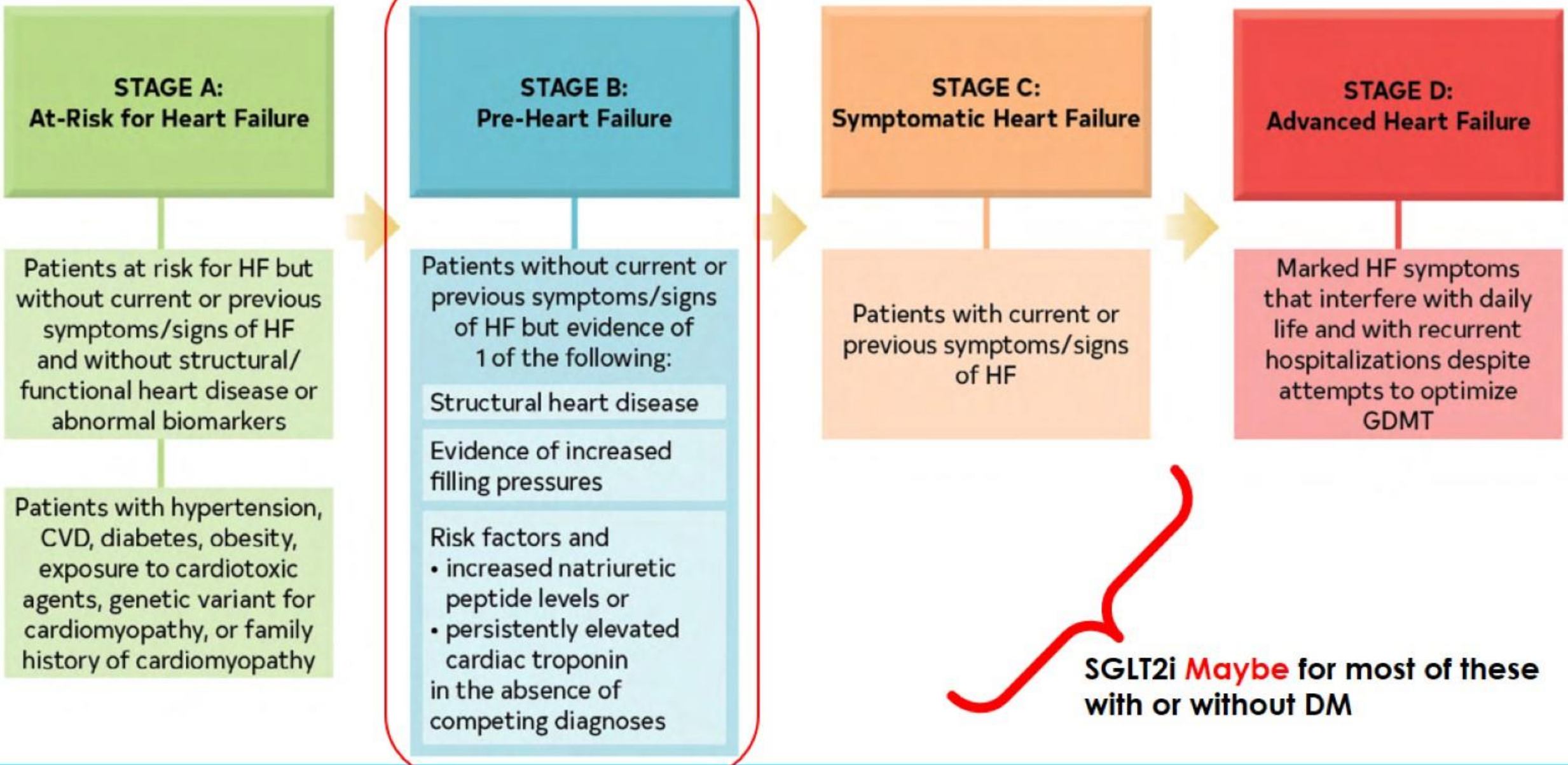
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Heart failure is a *complex clinical syndrome* with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood.

The writing committee recognizes that asymptomatic stages with structural heart disease or cardiomyopathies are not covered under the above definition as having HF.

Circulation. 2022;145:e895–e1032

Heart failure syndrome



Heart failure preserved EF

Double-blind trial, randomized

N=5988 patients with class II–IV heart failure and an ejection fraction >40%

Empagliflozin 10 mg/daily or placebo

Median of 26.2 months

All have standard of care

N Engl J Med 2021;385:1451-61

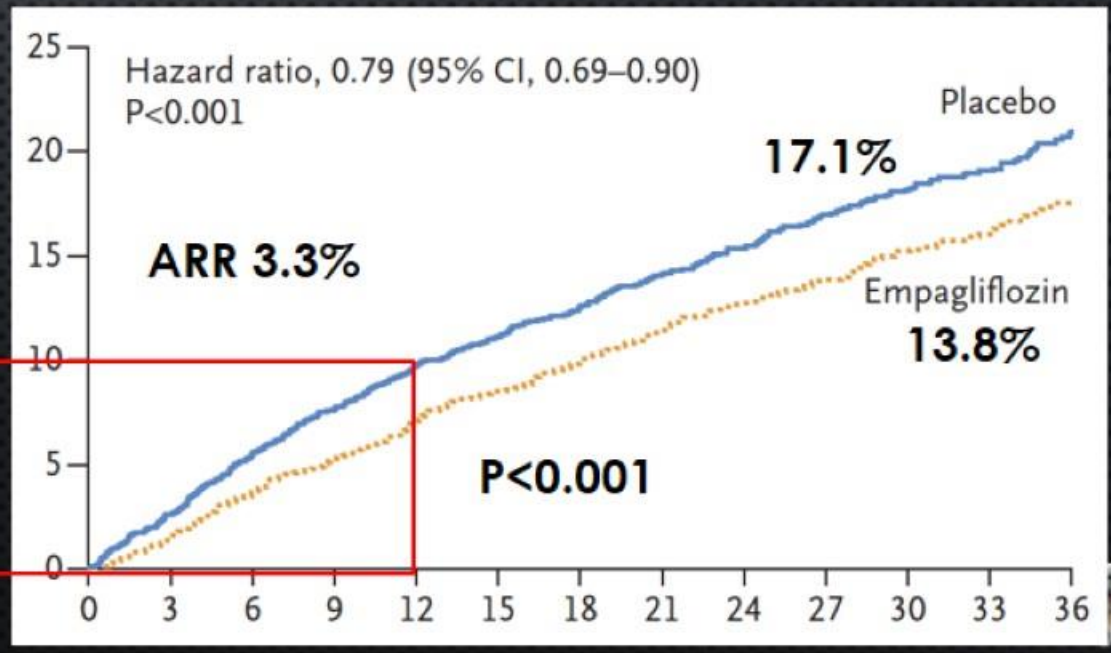
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

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

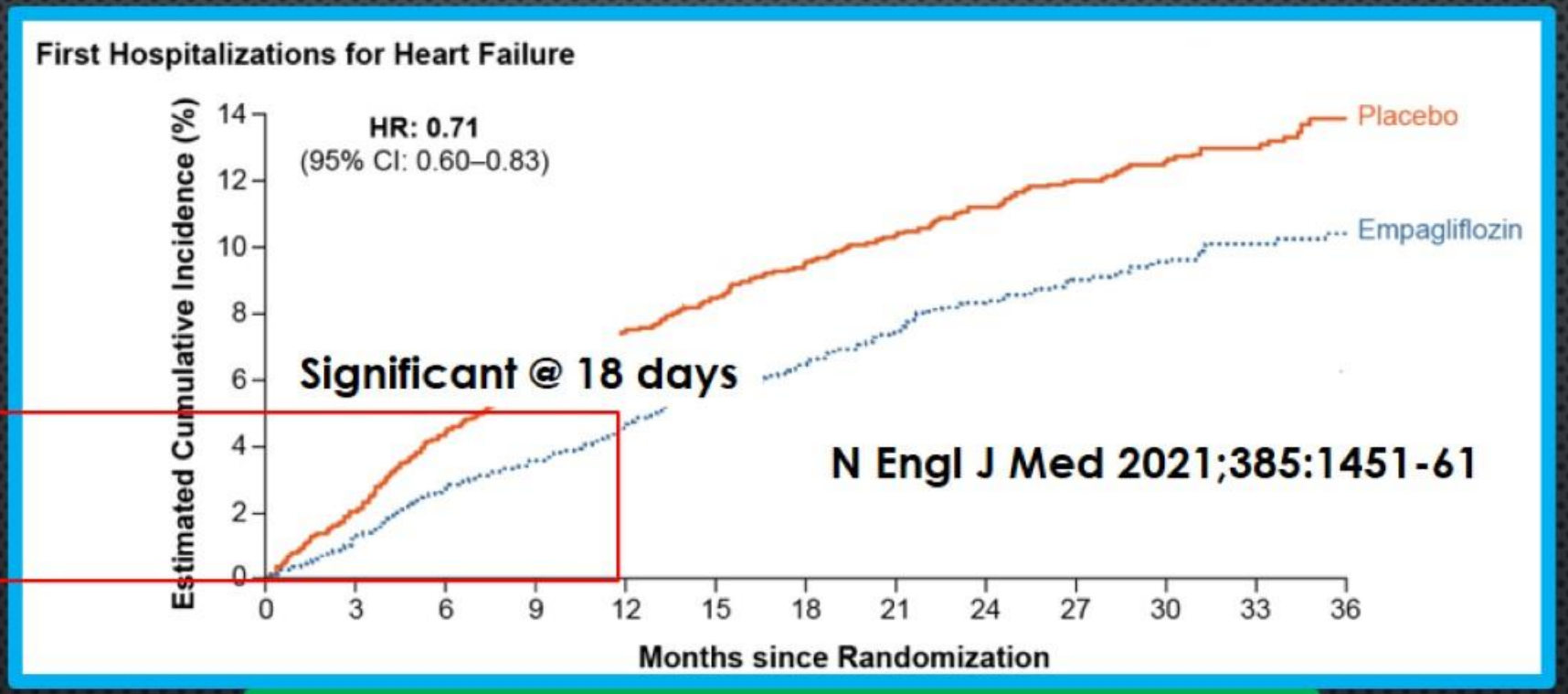
Primary outcome:
was a composite of **cardiovascular death** or **hospitalization for heart failure**

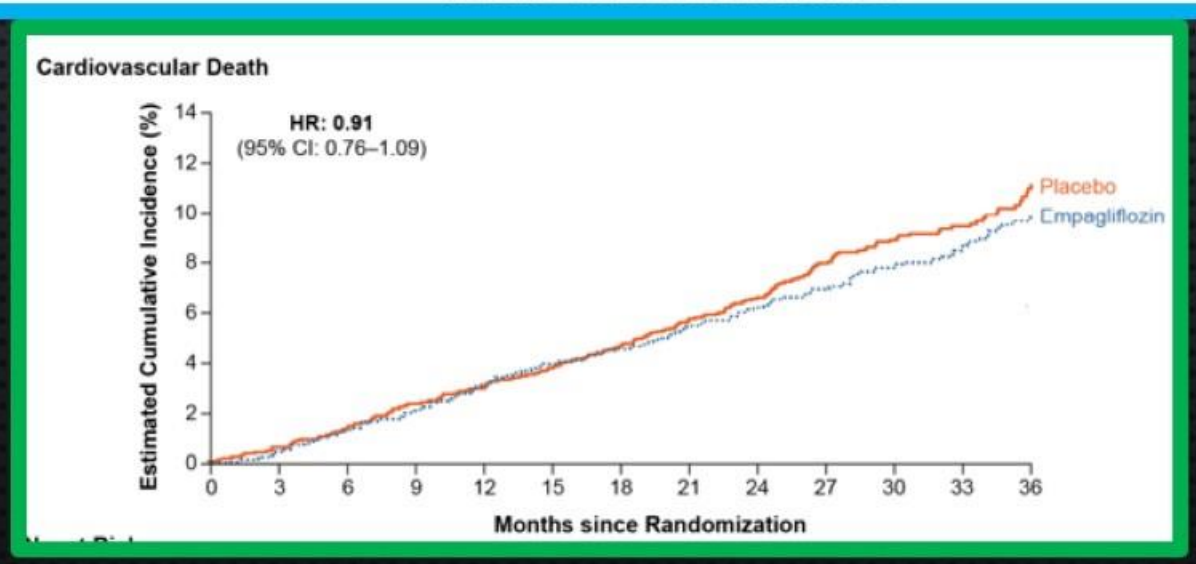


EMPEROR-Preserved

All received guideline directed medical therapy

Components of primary composite endpoint





EMPEROR-Preserved

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8

EMPEROR-Preserved

N Engl J Med 2021;385:1451-61

TABLE S2. CARDIOVASCULAR MEDICATIONS AT BASELINE

Type of medication — number (%)	**Empagliflozin** (n=2997)	**Placebo** (n=2991)
Inhibitor of renin-angiotensin system with or without neprilysin inhibitor	2428 (81.0)	2404 (80.4)
Sacubitril/valsartan	65 (2.2)	69 (2.3)
Mineralocorticoid receptor antagonist	1119 (37.3)	1125 (37.6)
Beta blocker	2598 (86.7)	2569 (85.9)
Digitalis glycosides	293 (9.8)	263 (8.8)
Aspirin	1240 (41.4)	1272 (42.5)
Statins	2042 (68.1)	2089 (69.8)

Inhibitors of the renin-angiotensin system include angiotensin converting-enzyme inhibitors and angiotensin receptor blockers.

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)

EMPEROR-Preserved

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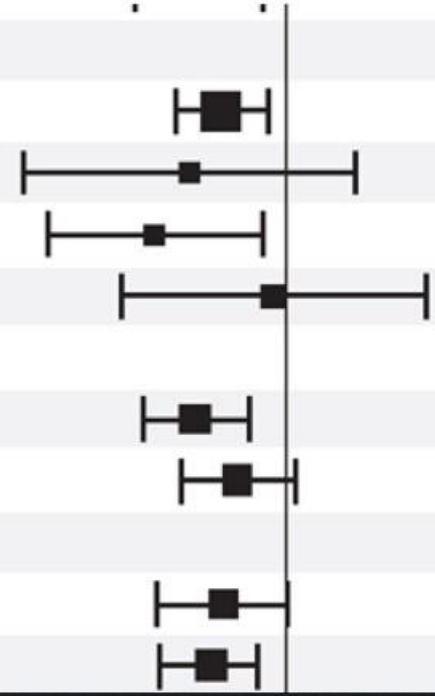
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Race			
White	310/2286	370/2256	0.81 (0.69–0.94)
Black	24/133	28/125	0.73 (0.42–1.25)
Asian	54/413	77/411	0.65 (0.46–0.92)
Other	27/164	36/198	0.95 (0.58–1.57)
BMI at baseline			
<30	223/1654	292/1642	0.74 (0.62–0.88)
≥30	192/1343	219/1349	0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline			
≥60 ml/min/1.73 m^2	152/1493	189/1505	0.81 (0.65–1.00)
<60 ml/min/1.73 m^2	263/1504	321/1484	0.78 (0.66–0.91)



EMPEROR-Preserved

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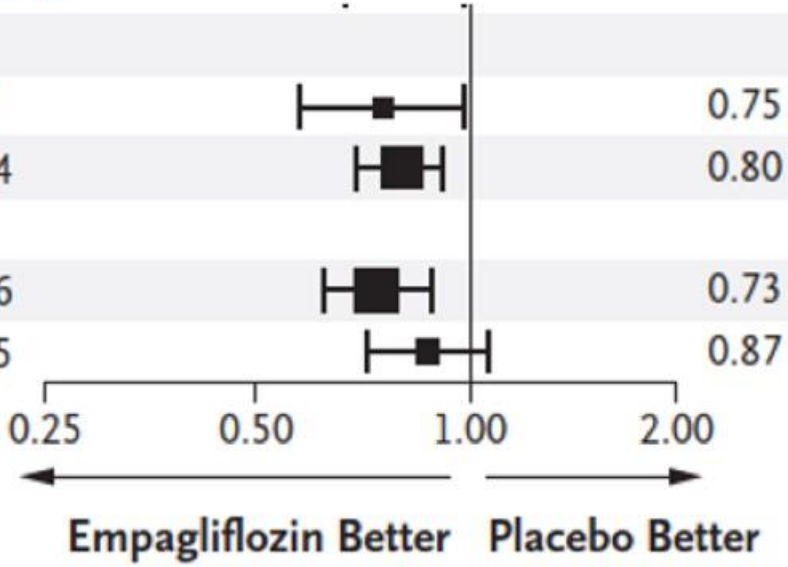
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
History of atrial fibrillation or atrial flutter			
No	170/1417	219/1427	0.78 (0.64–0.95)
Yes	244/1576	292/1559	0.78 (0.66–0.93)
Hospitalization for heart failure ≤12 mo			
No	258/2298	319/2321	0.81 (0.68–0.95)
Yes	157/699	192/670	0.73 (0.59–0.90)
NYHA class at baseline			
II	275/2435	361/2452	0.75 (0.64–0.87)
III or IV	140/562	150/539	0.86 (0.68–1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)			
<Median	126/1477	168/1508	0.76 (0.61–0.96)
≥Median	288/1516	341/1476	0.78 (0.67–0.91)

EMPEROR-Preserved

N Engl J Med 2021;385:1451-61

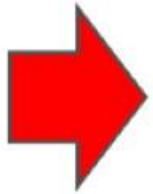
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Use of ACE-inhibitor, ARB, or ARNI at baseline			
No	90/569	121/587	0.75 (0.57–0.99)
Yes	325/2428	390/2404	0.80 (0.69–0.93)
Use of MRA at baseline			
No	233/1878	306/1866	0.73 (0.62–0.87)
Yes	182/1119	205/1125	0.87 (0.71–1.06)



EMPEROR-Preserved

N Engl J Med 2021;385:1451-61

	Empagliflozin (n=2997)	Placebo (n=2991)
	N (%)	N (%)
Death	422 (14.1)	427 (14.3)
Cardiovascular cause	219 (7.3)	244 (8.2)
Sudden cardiac death	99 (3.3)	114 (3.8)
Heart failure	40 (1.3)	51 (1.7)
Stroke	19 (0.6)	20 (0.7)
Acute myocardial infarction	5 (0.2)	5 (0.2)
Cardiovascular procedures	7 (0.2)	2 (0.1)
Cardiovascular hemorrhage	0	1 (<0.1)
Other cardiovascular causes	16 (0.5)	20 (0.7)
Undetermined cause of death	33 (1.1)	31 (1.0)



EMPEROR-Preserved

N Engl J Med 2021;385:1451-61

Selected adverse events of interest	EMPA	Placebo
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension[a]	197 (6.6)	156 (5.2)
Acute renal failure	363 (12.1)	384 (12.8)
Ketoacidosis[b]	4 (0.1)	5 (0.2)
Hepatic injury	115 (3.8)	155 (5.2)
Hypoglycemic events[c]	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[a]	16 (0.5)	23 (0.8)

Kidney disease and primary endpoints: works in both

EMPEROR-Preserved[1]

Adjudicated hHF or CV death	Empagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
All patients	415/2997	511/2991	0.79 (0.69-0.90)
No prevalent CKD	123/1378	165/1400	0.75 (0.60-0.95)
Prevalent CKD*	292/1615	344/1583	0.80 (0.69-0.94)

EMPEROR-Reduced[2]

Adjudicated hHF or CV death	Empagliflozin 10 mg	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
All patients	361/1863	462/1867	0.75 (0.65-0.86)
No CKD	142/879	187/867	0.72 (0.58-0.90)
Prevalent CKD*	219/981	273/997	0.78 (0.65-0.93)

Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction

MRA users and nonusers in the **EMPEROR-Preserved** (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved EF

5,988 patients were included
2,244 (37.5%) were using MRAs at baseline

Primary outcome: reduce first and recurrent HF hospitalizations

No significantly difference between **MRA** nonusers and MRA users

ORIGINAL INVESTIGATIONS

Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction

João Pedro Ferreira, MD, PhD,[a,b] Javed Butler, MD,[c] Faiez Zannad, MD, PhD,[b] Gerasimos Filippatos, MD, PhD,[d] Elke Schueler, Dipl Math,[e] Dominik Steubl, MD,[f,g] Cordula Zeller, Dipl Math,[h] James L. Januzzi, MD,[i,j,k] Stuart Pocock, PhD,[l] Milton Packer, MD,[m,n] Stefan D. Anker, MD, PhD[o]

ABSTRACT

BACKGROUND Mineralocorticoid receptor antagonists (MRAs) may be beneficial in reducing heart failure (HF) hospitalizations in patients with HF with preserved ejection fraction. The effect of sodium-glucose cotransporter 2 inhibitors in patients with HF with preserved ejection fraction according to MRA background therapy has not been reported.

OBJECTIVES The aim of this study was to examine the effect of empagliflozin in MRA users and nonusers in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial.

EMPEROR-Preserved

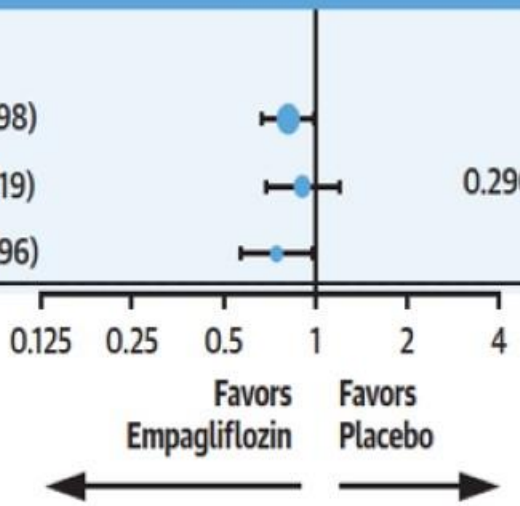
JACC 2022;79:1129

Empagliflozin reduced hyperkalemia

	No MRA					MRA					
	Placebo		Empagliflozin			Placebo		Empagliflozin			Interaction
	(n = 1,866)	IR	(n = 1,878)	IR	Treatment Effect	(n = 1,125)	IR	(n = 1,119)	IR	Treatment Effect	*P* Value
CV death or HF hospitalization	306 (16.4)	8.2	233 (12.4)	6.1	0.73 (0.62-0.87)	205 (18.2)	9.4	182 (16.3)	8.3	0.87 (0.71-1.06)	0.22
Total (first and recurrent) HF hospitalization	308		201		0.60 (0.47-0.77)	233		206		0.90 (0.68-1.19)	0.038
First HF hospitalization	208 (11.1)	5.6	131 (7.0)	3.4	0.60 (0.49-0.75)	144 (12.8)	6.6	128 (11.4)	5.8	0.86 (0.68-1.09)	0.032

P=NS

	Empagliflozin		Placebo				Interaction
	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	HR (95% CI)	HR (95% CI)	*P* Value
Initiation of potassium binders or investigator-defined hyperkalemia*							
Overall	195/2,986 (6.5)	3.61	235/2,980 (7.9)	4.41	0.81 (0.67-0.98)		
No MRA	101/1,870 (5.4)	2.94	107/1,857 (5.8)	3.21	0.90 (0.69-1.19)		0.2905
MRA	94/1,116 (8.4)	4.76	128/1,123 (11.4)	6.43	0.74 (0.56-0.96)		



EMPEROR-Preserved

JACC 2022;79:1129

Recommendations for Initial Laboratory and Electrocardiographic Testing

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	1. For patients presenting with HF, the specific cause of HF should be explored using additional laboratory testing for appropriate management.[1–8]
1	C-EO	2. For patients who are diagnosed with HF, laboratory evaluation should include complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone to optimize management.
1	C-EO	3. For all patients presenting with HF, a 12-lead ECG should be performed at the initial encounter to optimize management.

Circulation. 2022;145:e895–e1032

Recommendations for Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification

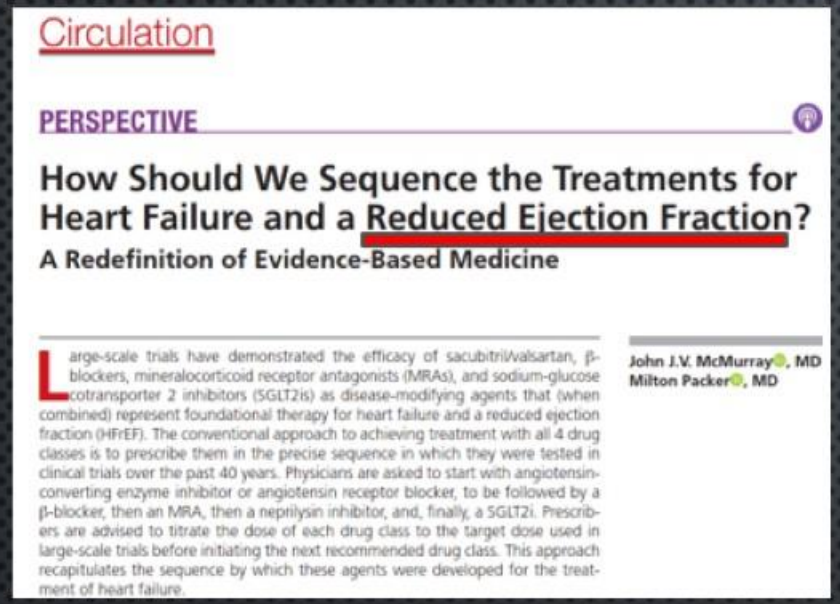
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients presenting with dyspnea, measurement of B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is useful to support a diagnosis or exclusion of HF.[1–12]
1	A	2. In patients with chronic HF, measurements of BNP or NT-proBNP levels are recommended for risk stratification.[11,13–29]
1	A	3. In patients hospitalized for HF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis.[11,13–19]

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.[1,2]
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[3,4]

New considerations in treatment of heart failure



Circulation

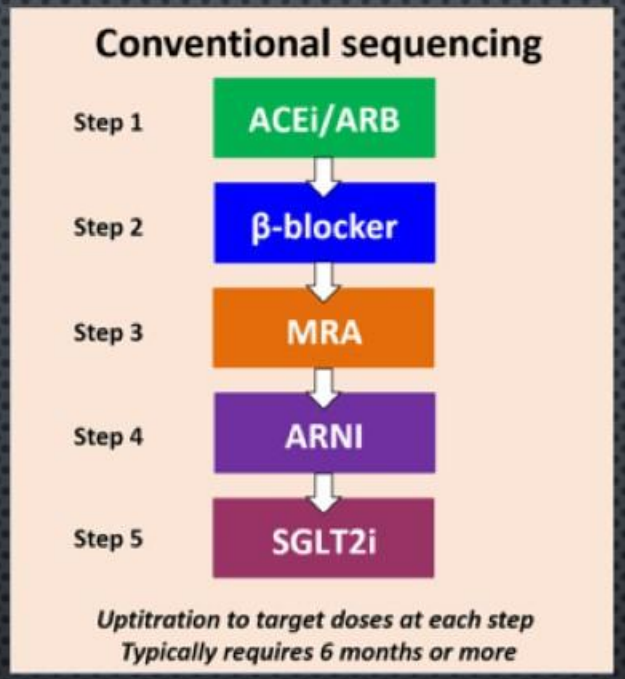
PERSPECTIVE

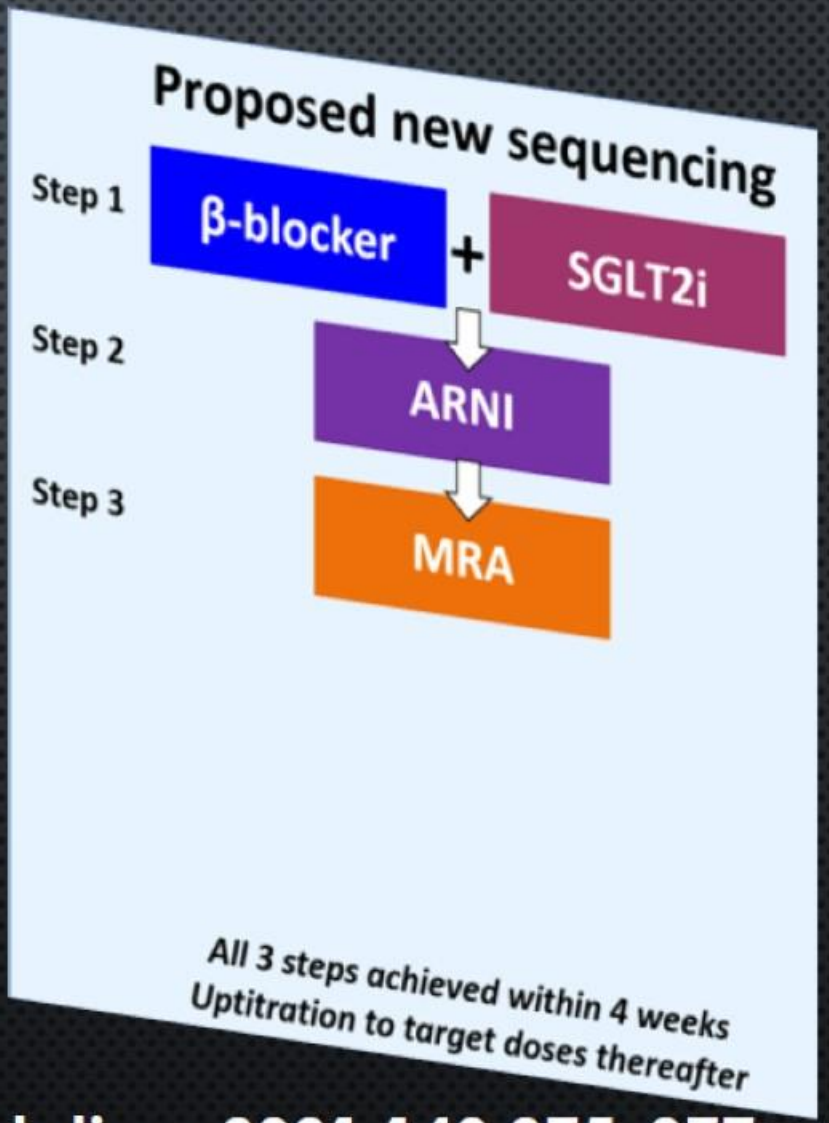
How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?

A Redefinition of Evidence-Based Medicine

John J.V. McMurray, MD
Milton Packer, MD

Large-scale trials have demonstrated the efficacy of sacubitril/valsartan, β-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is) as disease-modifying agents that (when combined) represent foundational therapy for heart failure and a reduced ejection fraction (HFrEF). The conventional approach to achieving treatment with all 4 drug classes is to prescribe them in the precise sequence in which they were tested in clinical trials over the past 40 years. Physicians are asked to start with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, to be followed by a β-blocker, then an MRA, then a neprilysin inhibitor, and, finally, a SGLT2i. Prescribers are advised to titrate the dose of each drug class to the target dose used in large-scale trials before initiating the next recommended drug class. This approach recapitulates the sequence by which these agents were developed for the treatment of heart failure.





β-Blockers: most effective drug class for the treatment of HFrEF, reduction of sudden death.

SGLT2is: reduce the risk of hospitalizations for heart failure, and may mitigate the short-term risk of worsening heart failure that may occur after a β-blocker is started

Circulation. 2021;143:875–877

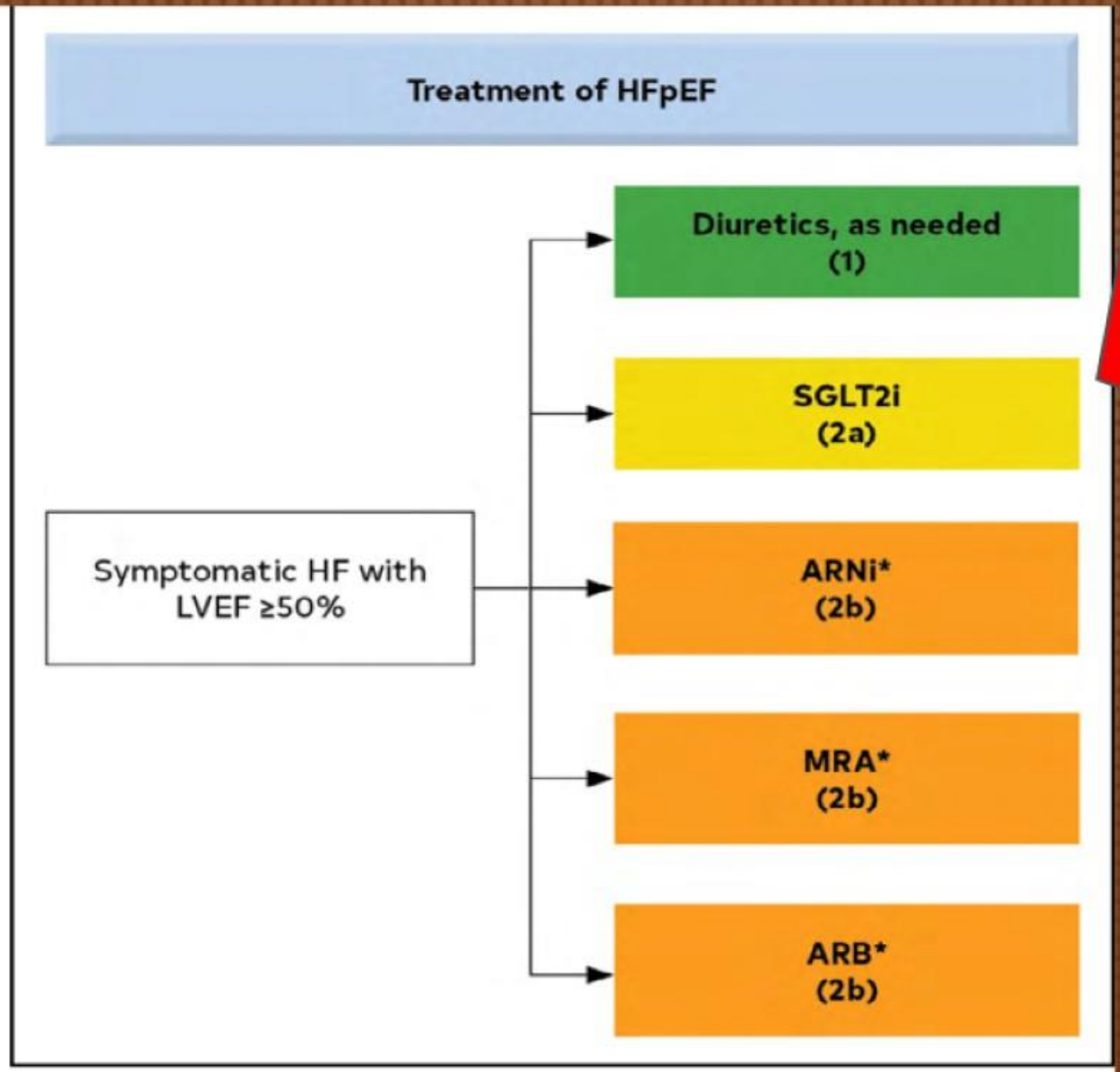


Figure 12. Recommendations for Patients With Preserved LVEF (≥50%).

Today, **the U.S. Food and Drug Administration approved Jardiance (empagliflozin) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults.**

Empagliflozin was originally approved by the FDA in 2014 as a supplement to diet and exercise to improve glucose control in adults with type 2 diabetes Feb 24, 2022

Randomly assigned 6263 patients with heart failure and LVEF > than 40% to receive 10 mg dapagliflozin

Primary outcome 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

Median of 2.3 years

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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=3131)	Placebo (N=3132)
Age — yr	71.8±9.6	71.5±9.5
Female sex — no. (%)	1364 (43.6)	1383 (44.2)
NYHA class — no. (%)‡		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean — %	54.0±8.6	54.3±8.9
Distribution — no. (%)		
≤49%	1067 (34.1)	1049 (33.5)
50–59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
Medical history — no. (%)		
Type 2 diabetes mellitus	1401 (44.7)	1405 (44.9)
Hypertension	2755 (88.0)	2798 (89.3)
Previous left ventricular ejection fraction ≤40%	572 (18.3)	579 (18.5)
Estimated GFR — ml/min/1.73 m^2	61±19	61±19

Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Variable	Dapagliflozin (N=3131)		Placebo (N=3132)		Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
	values	*events/ 100 patient-yr*	*values*	*events/ 100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths‡	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8§	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA
Death from any cause — no. (%)	497 (15.9)	7.2	526 (16.8)	7.6	0.94 (0.83–1.07)	NA

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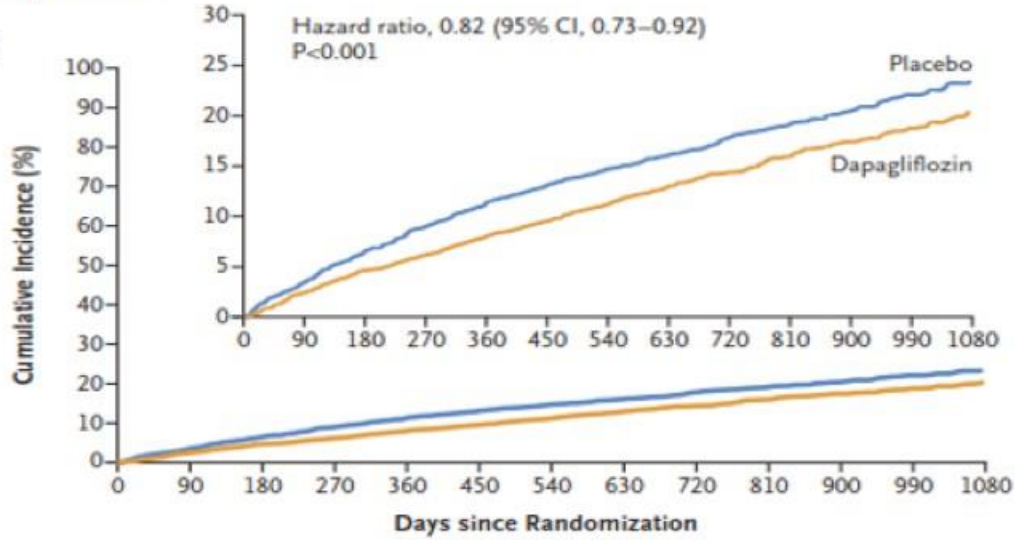
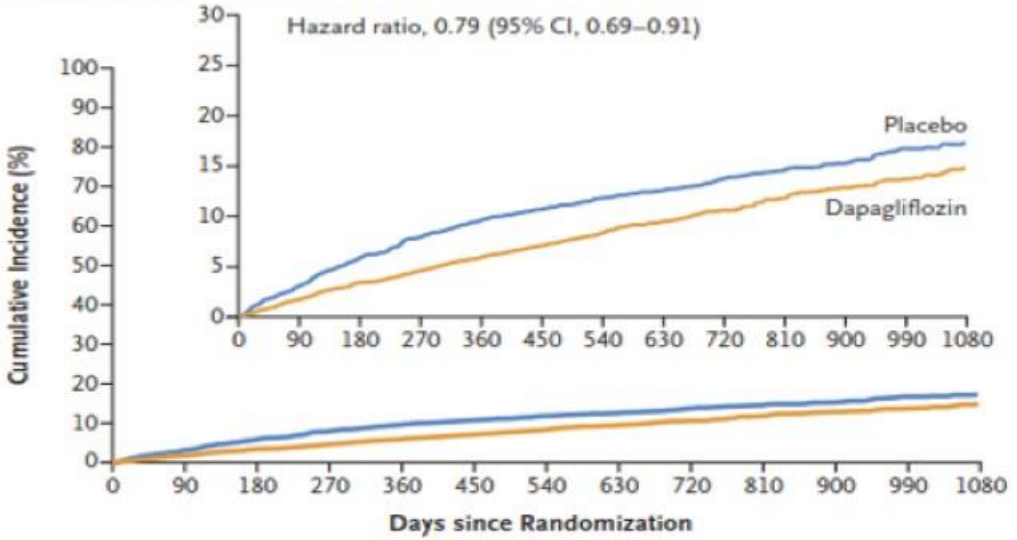
Primary Outcome



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

B Worsening Heart Failure Event



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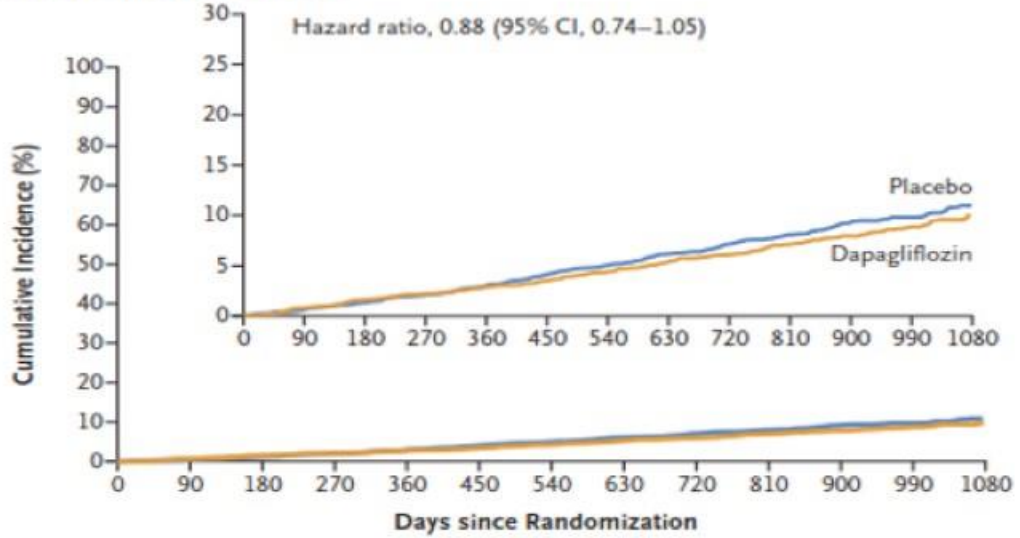
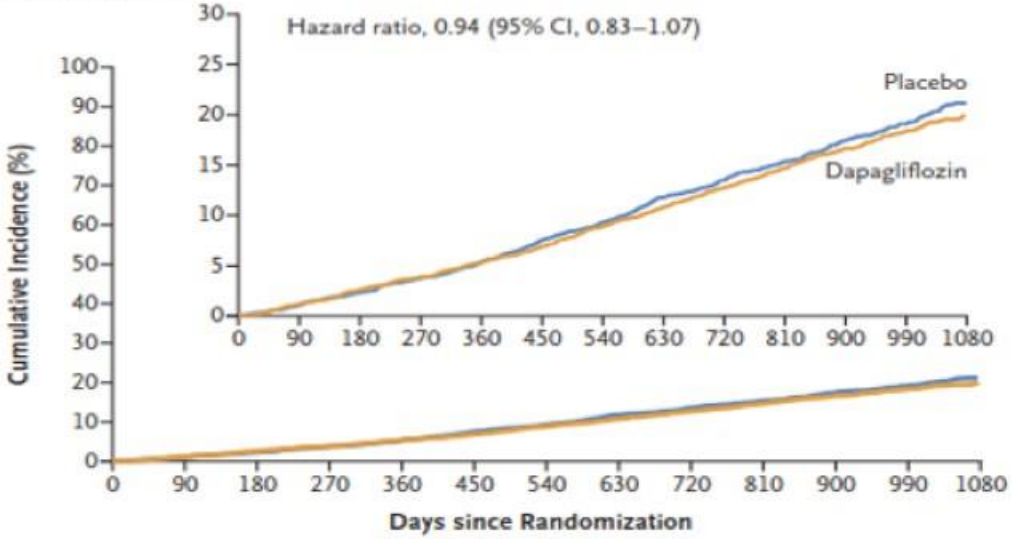
C Death from Cardiovascular Causes



No. at Risk													
Placebo	3132	3096	3054	3008	2957	2872	2570	2314	2157	1759	1306	910	451
Dapagliflozin	3131	3091	3046	3006	2960	2892	2584	2339	2171	1775	1312	903	441

D Death from Any Cause



No. at Risk													
Placebo	3132	3097	3058	3012	2962	2877	2575	2319	2161	1762	1309	910	451
Dapagliflozin	3131	3093	3048	3009	2962	2895	2587	2342	2174	1778	1314	905	443

Phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or more—or risk factors—see article

Mean body weight was 104.8 kg, the mean BMI was 38.0

72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of Tirzepatide once weekly

Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more

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Tirzepatide Once Weekly for the Treatment of Obesity

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ABSTRACT

BACKGROUND

Obesity is a chronic disease that results in substantial global morbidity and mortality. The efficacy and safety of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in people with obesity are not known.

METHODS

In this phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or more, or 27 or more and at least one weight-re-

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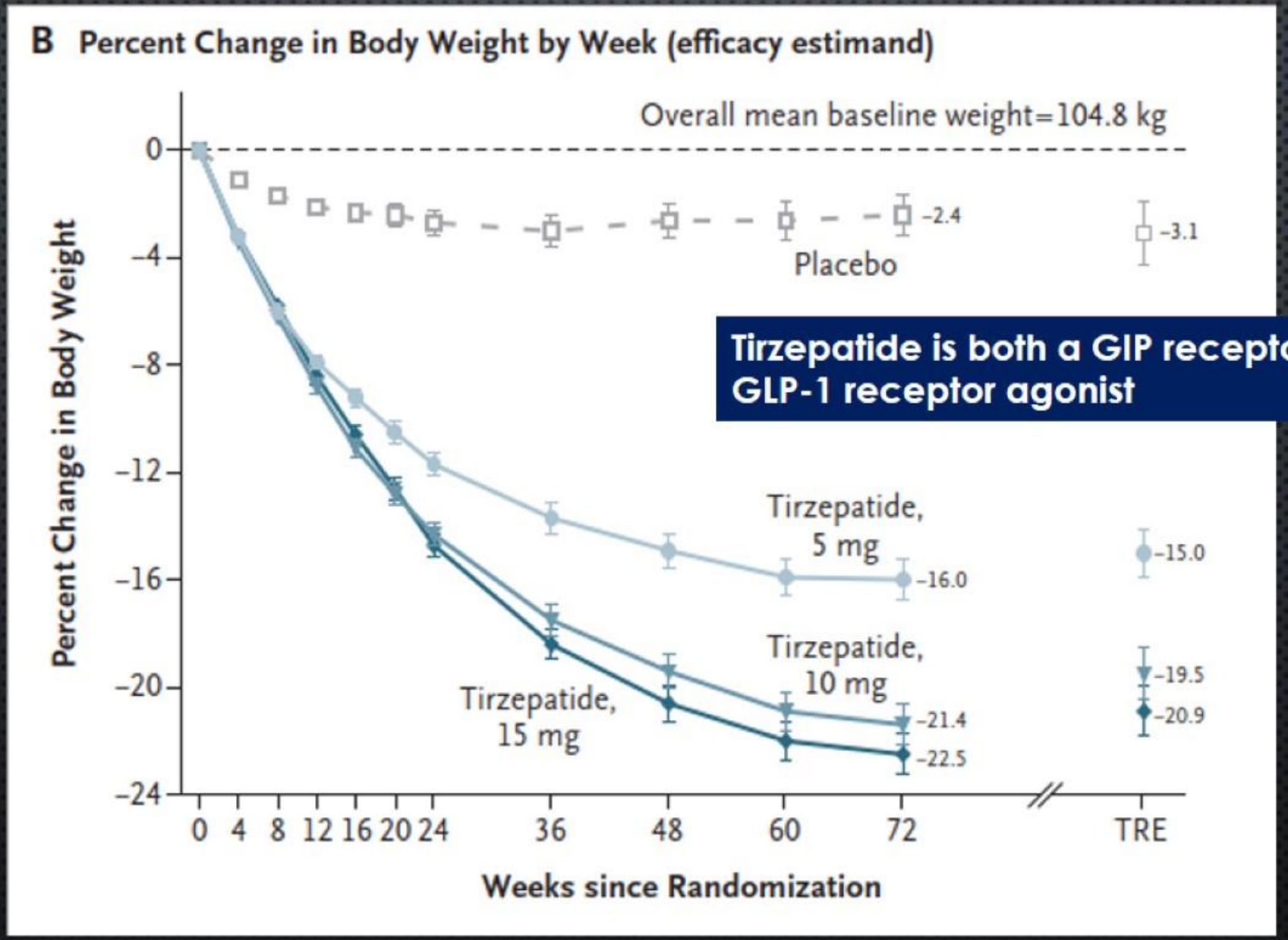

Tirzepatide is both a GIP receptor and GLP-1 receptor agonist

Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0

Comparative effectiveness of commonly used glucose-lowering medications, when added to metformin

Comparative effectiveness of four commonly used glucose-lowering medications, added to metformin, in achieving and maintaining a glycated hemoglobin level of less than 7.0% in participants with type 2 diabetes

Mean 5.0 years of follow-up in 5047 participants

ORIGINAL ARTICLE

Glycemia Reduction in Type 2 Diabetes — Microvascular and Cardiovascular Outcomes

The GRADE Study Research Group*

ABSTRACT

BACKGROUND

Data are lacking on the comparative effectiveness of commonly used glucose-lowering medications, when added to metformin, with respect to microvascular and cardiovascular disease outcomes in persons with type 2 diabetes.

METHODS

We assessed the comparative effectiveness of four commonly used glucose-lowering medications, added to metformin, in achieving and maintaining a glycated hemoglobin level of less than 7.0% in participants with type 2 diabetes. The randomly assigned therapies were insulin glargine U-100 (hereafter, glargine), glimepiride, liraglutide, and sitagliptin. Prespecified secondary outcomes with respect to microvascular and cardiovascular disease included hypertension and dyslipidemia, confirmed moderately or severely increased albuminuria or an esti-

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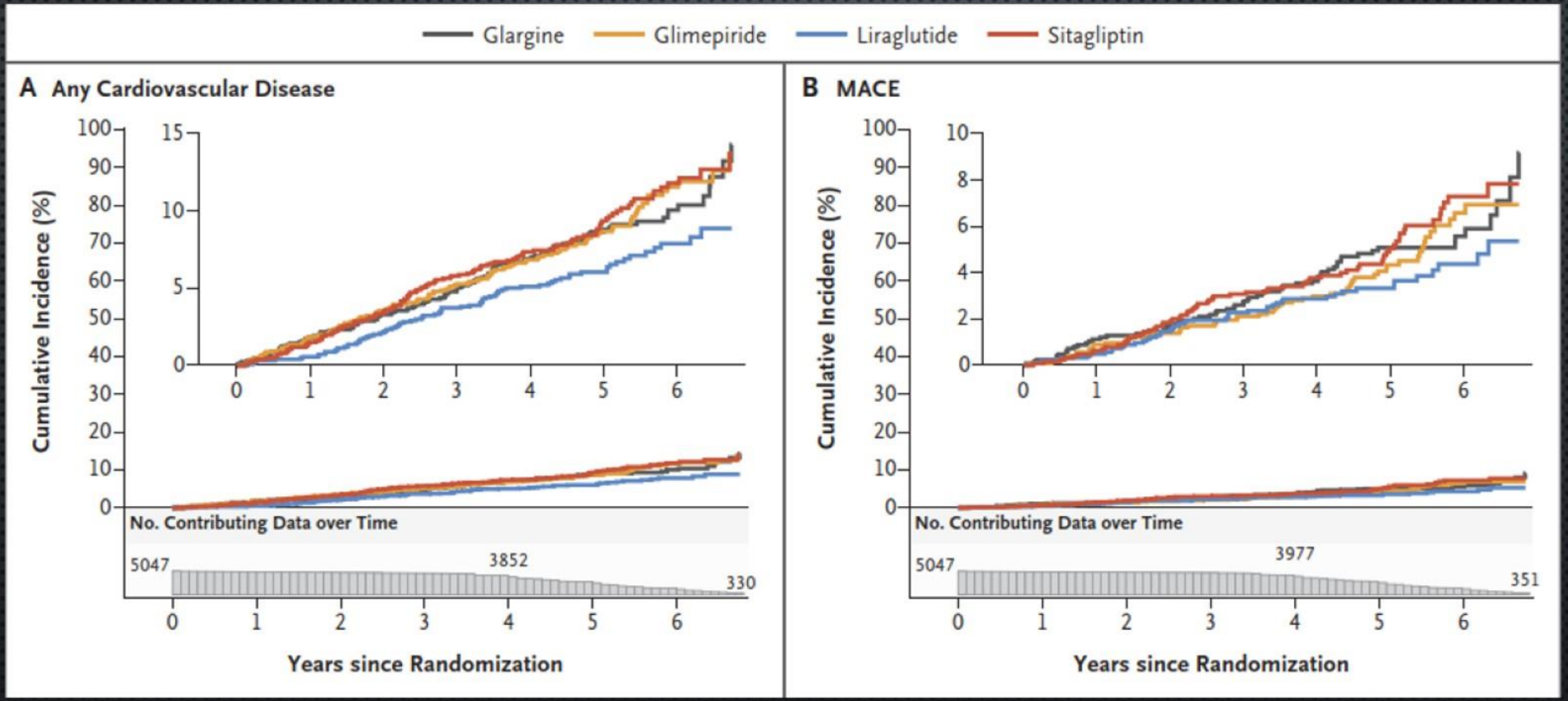
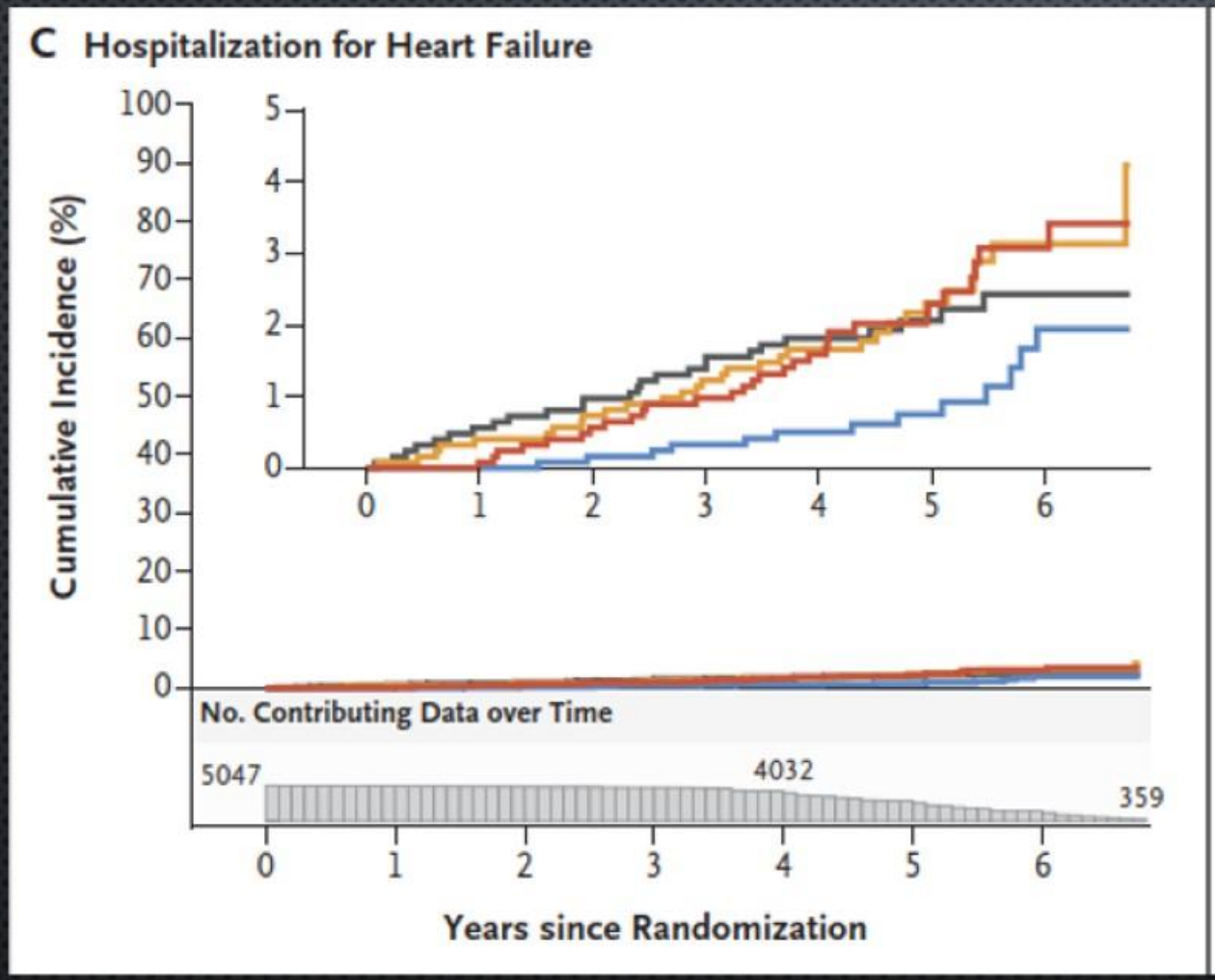
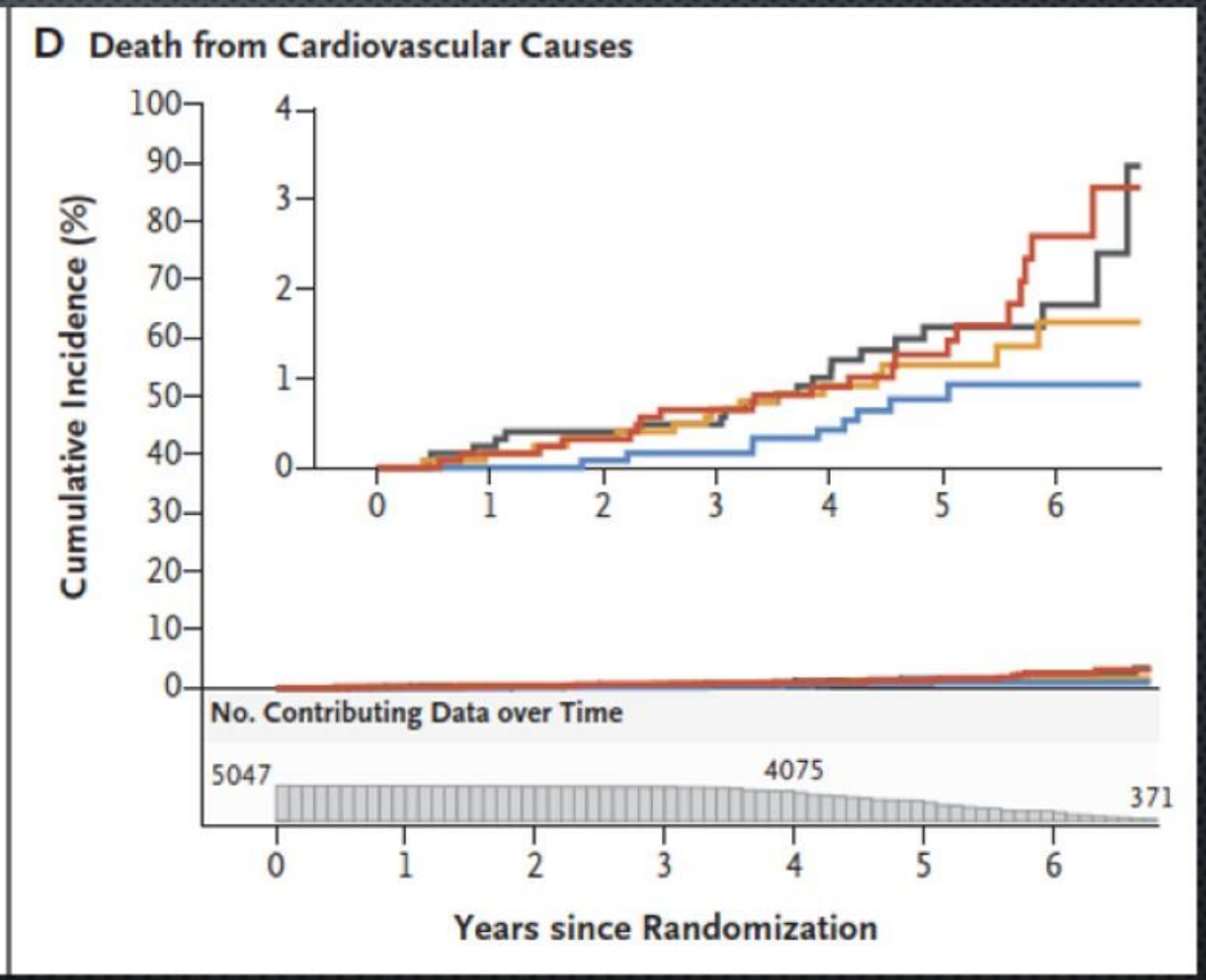
n engl j med 387;12 nejm.org September 22, 2022


Glargine
Glimepiride
Liraglutide
Sitagliptin
A Any Cardiovascular Disease
Cumulative Incidence (%)
No. Contributing Data over Time
5047
3852
330
Years since Randomization
B MACE
Cumulative Incidence (%)
No. Contributing Data over Time
5047
3977
351
Years since Randomization


C Hospitalization for Heart Failure
Cumulative Incidence (%)
No. Contributing Data over Time
5047
4032
359
Years since Randomization


D Death from Cardiovascular Causes
Cumulative Incidence (%)
No. Contributing Data over Time
5047
4075
371
Years since Randomization

E Death from Any Cause

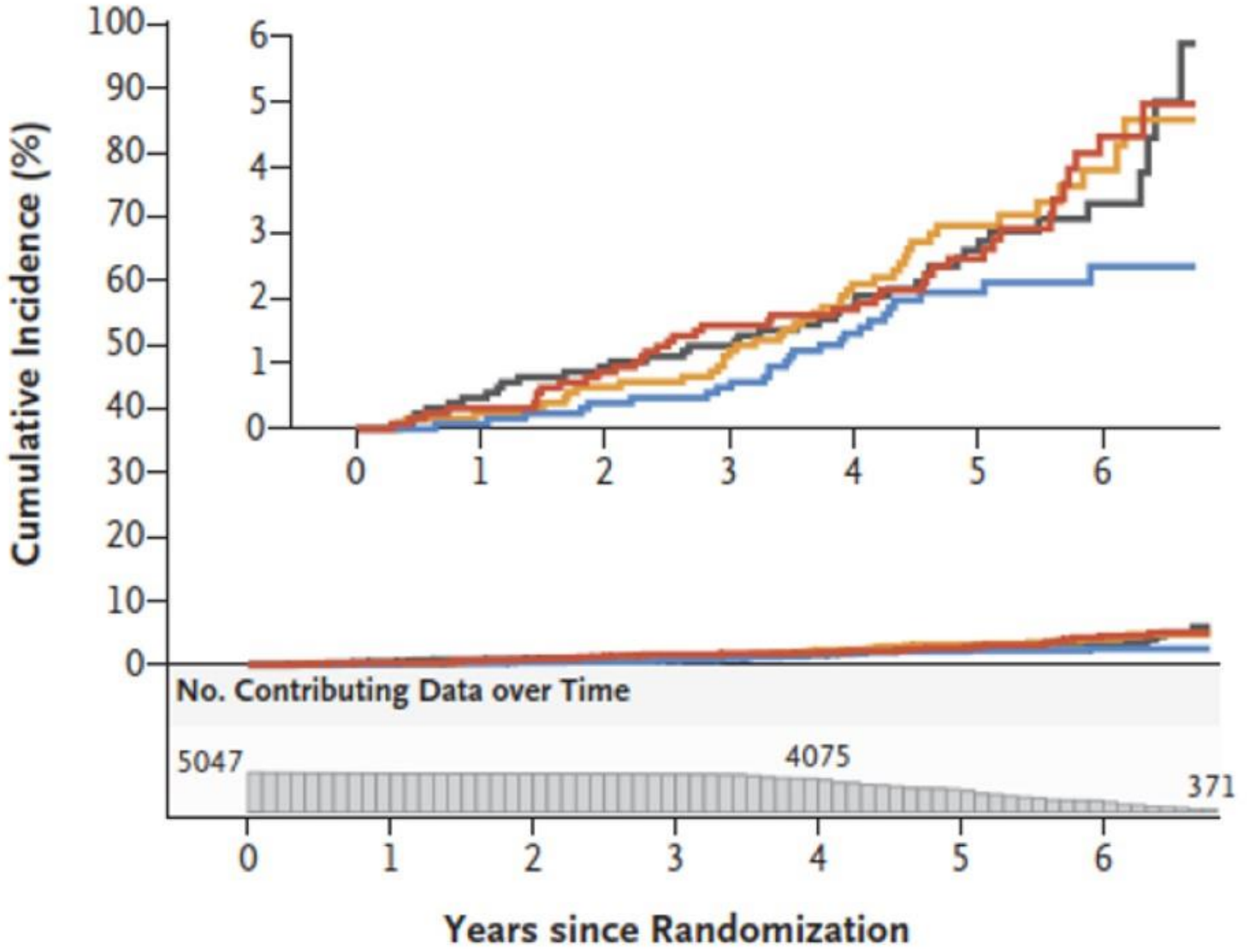


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Table 2. Cardiovascular and Mortality Outcomes in the Intention-to-Treat Analysis.*

Outcome	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)	Total (N=5047)
Any cardiovascular disease†					
No. of participants/no. at risk (%)	113/1257 (9.0)	115/1247 (9.2)	83/1251 (6.6)	121/1264 (9.6)	432/5019 (8.6)
Rate (95% CI)	1.87 (1.54–2.25)	1.92 (1.59–2.31)	1.36 (1.08–1.69)	2.00 (1.66–2.39)	1.79 (1.62–1.96)
Pairwise hazard ratio (95% CI)					
Glargine		0.97 (0.75–1.26)	1.37 (1.03–1.82)	0.93 (0.72–1.21)	
Glimepiride			1.41 (1.07–1.87)	0.96 (0.74–1.24)	
Liraglutide				0.68 (0.51–0.90)	
Sitagliptin					
Hazard ratio (95% CI) in one agent as compared with the others combined	1.07 (0.87–1.33)	1.12 (0.90–1.39)	0.71 (0.56–0.90)	1.18 (0.96–1.46)	

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Table 2. Cardiovascular and Mortality Outcomes in the Intention-to-Treat Analysis.*

Outcome	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)	Total (N=5047)
Hospitalization for heart failure					
No. of participants/no. at risk (%)	26/1257 (2.1)	30/1247 (2.4)	14/1251 (1.1)	30/1264 (2.4)	100/5019 (2.0)
Rate (95% CI)	0.42 (0.27–0.61)	0.48 (0.33–0.69)	0.22 (0.12–0.38)	0.48 (0.32–0.68)	0.40 (0.33–0.49)
Pairwise hazard ratio (95% CI)					
Glargine		0.86 (0.51–1.45)	1.85 (0.96–3.55)	0.87 (0.51–1.47)	
Glimepiride			2.16 (1.14–4.06)	1.01 (0.61–1.67)	
Liraglutide				0.47 (0.25–0.88)	
Sitagliptin					
Hazard ratio (95% CI) in one agent as compared with the others combined	1.11 (0.70–1.76)	1.36 (0.88–2.11)	0.49 (0.28–0.86)	1.35 (0.87–2.08)	

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Table 2. Cardiovascular and Mortality Outcomes in the Intention-to-Treat Analysis.*

Outcome	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)	Total (N=5047)
Death from cardiovascular causes					
No. of participants/no. at risk (%)	21/1257 (1.7)	16/1247 (1.3)	9/1251 (0.7)	21/1264 (1.7)	67/5019 (1.3)
Rate (95% CI)	0.33 (0.21–0.51)	0.26 (0.15–0.42)	0.14 (0.07–0.27)	0.33 (0.21–0.51)	0.27 (0.21–0.34)
Pairwise hazard ratio (95% CI)					
Glargine		1.29 (0.67–2.47)	2.30 (1.05–5.01)	1.00 (0.55–1.82)	
Glimepiride			1.78 (0.79–4.04)	0.77 (0.40–1.48)	
Liraglutide				0.43 (0.20–0.95)	
Sitagliptin					
Hazard ratio (95% CI) in one agent as compared with the others combined	1.43 (0.85–2.43)	1.02 (0.58–1.82)	0.47 (0.23–0.95)	1.44 (0.85–2.44)