Heart Failure Management Updates

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Disclosures

- None

Outline

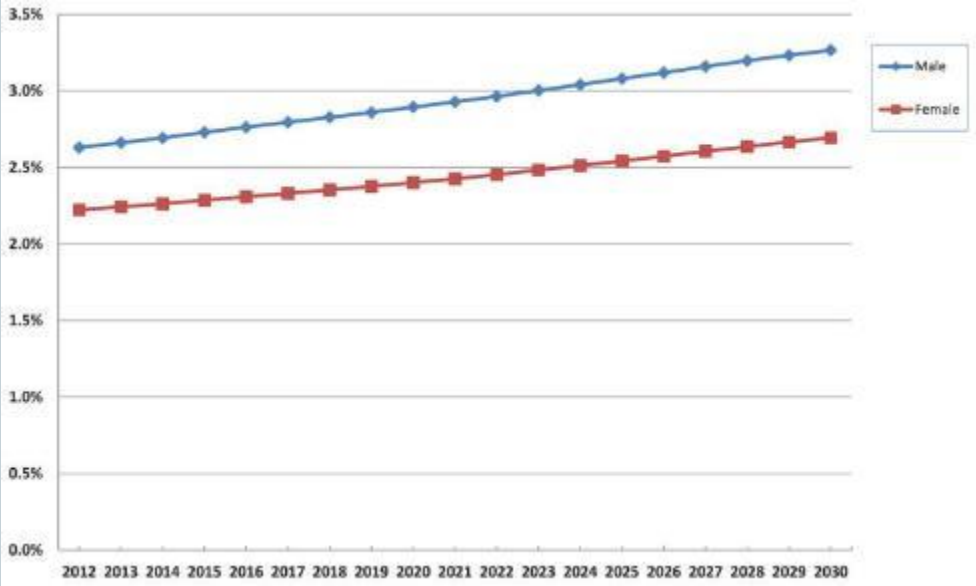
- Burden of Heart Failure
- Management of Heart Failure with Reduced Ejection Fraction (HFrEF): Updates
- Management of Heart Failure with Preserved Ejection Fraction (HFpEF): Updates
- Prevention of Heart Failure: Updates

Heart Failure Burden

Table 22-2. HF in the United States (Table view)

This table shows the prevalence, incidence, mortality, hospital discharges and cost related to heart failure in the United States. Where available, statistics are further divided by sex and race and ethnicity. The prevalence of heart failure in 2015 to 2018 was highest in non-Hispanic Black males.

Population group	Prevalence, 2015–2018, age ≥20 y	Incidence, 2014, age ≥55 y	Mortality, 2019, all ages*	Hospital discharges, 2018, all ages	Cost, 2012†
Both sexes	6 000 000 (2.1%) [95% CI, 1.8%–2.4%]	1 000 000	86 177	1 250 000	$30.7 billion



Tsao CW, et al. Heart Disease and Stroke Statistics-2022 Update. *Circulation*. 2022

Heidenreich PA, et al. Forecasting the impact of heart failure in the United States. *Circ Heart Fail*. 2013

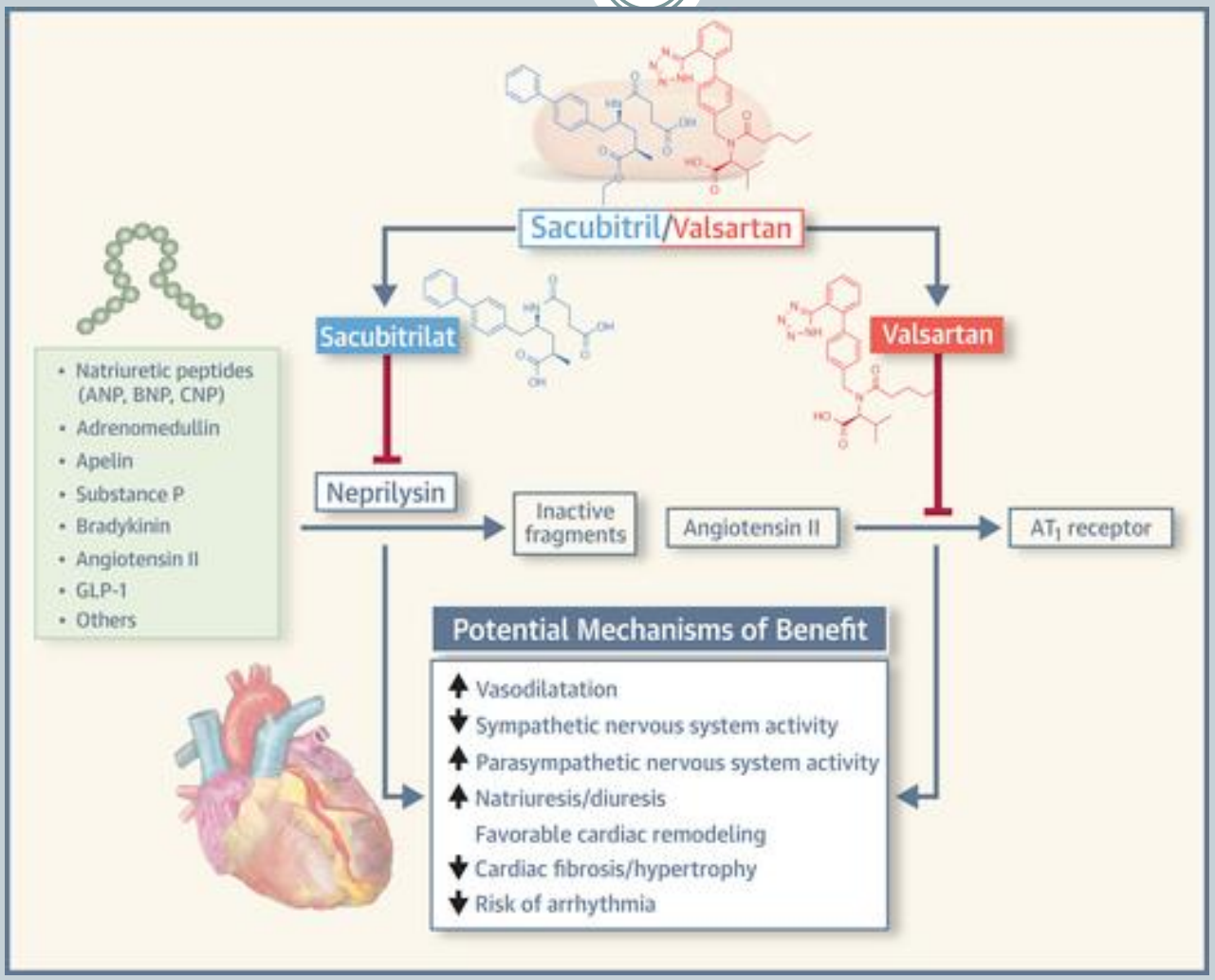
Management of HFrEF

Table 19. Recommendations for Pharmacological Therapy for Management of Stage C HF*r*EF

Recommendations	COR	LOE
Diuretics		
Diuretics are recommended in patients with HF*r*EF with fluid retention	I	C
ACE inhibitors		
ACE inhibitors are recommended for all patients with HF*r*EF	I	A
ARBs		
ARBs are recommended in patients with HF*r*EF who are ACE inhibitor intolerant	I	A
ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HF*r*EF	IIa	A
Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF on GDMT	IIb	A
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C
Beta blockers		
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A
Aldosterone receptor antagonists		
Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF ≤35%	I	A
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I	B
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B
Hydralazine and isosorbide dinitrate		
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF*r*EF on GDMT	I	A
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF*r*EF who cannot be given ACE inhibitors or ARBs	IIa	B
Digoxin		
Digoxin can be beneficial in patients with HF*r*EF	IIa	B

Yancy CW, et al.. 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2013

Angiotensin-Neprilysin Inhibitor -HFrEF



Docherty KF, et al. Sacubitril/Valsartan: Neprilysin Inhibition 5 Years After PARADIGM-HF. *JACC Heart Fail.* 2020

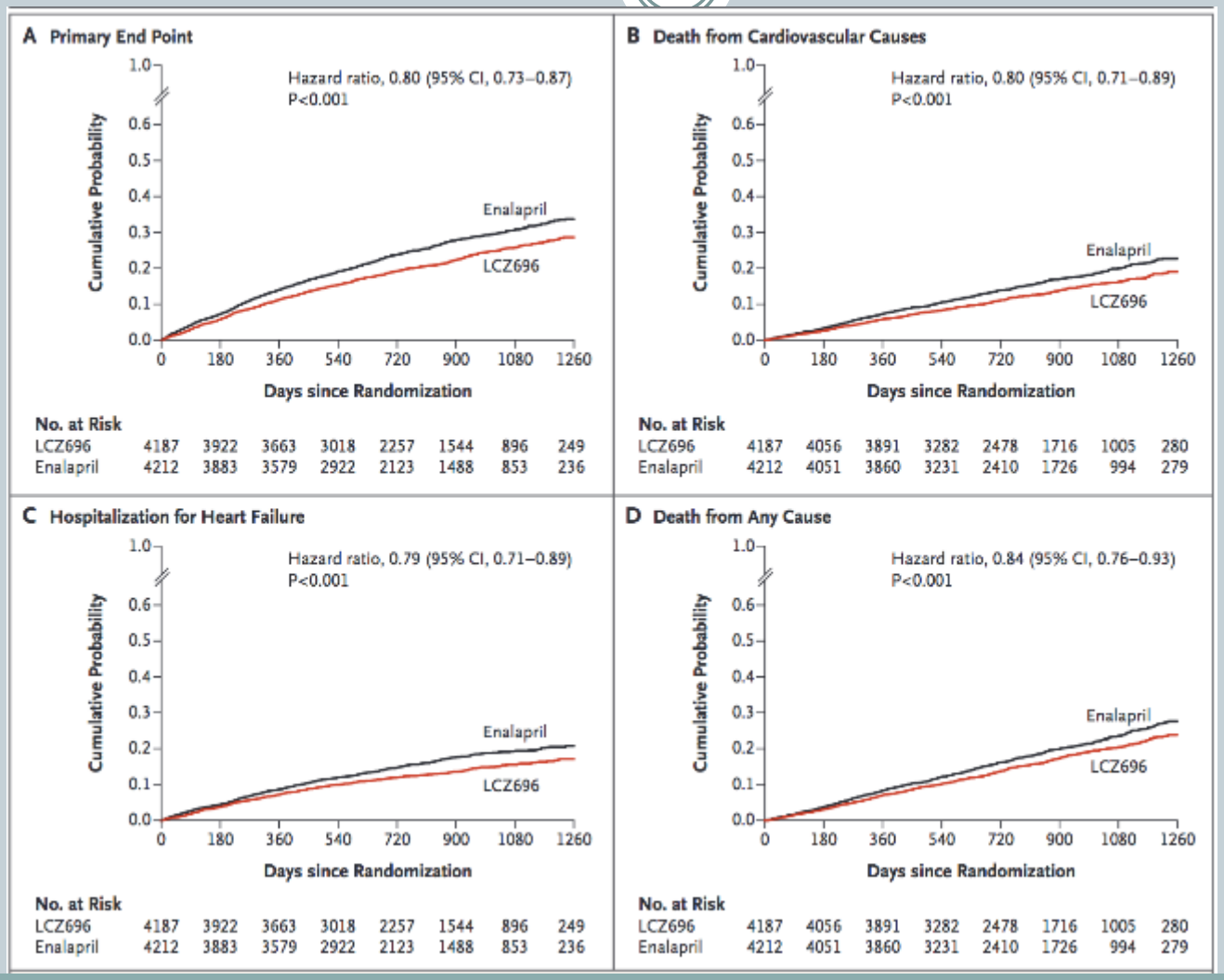
Angiotensin-Neprilysin Inhibitor -HFrEF

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian		
Other		
Region — no. (%)		
North America		
Latin America		
Western Europe and other‡		
Central Europe		
Asia–Pacific		
Systolic blood pressure — mm Hg		
Heart rate — beats/min		
Body-mass index§		
Serum creatinine — mg/dl		
Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)		
Left ventricular ejection fraction — %		
Median B-type natriuretic peptide (IQ		
Median N-terminal pro–B-type natriu — pg/ml		
NYHA functional class — no. (%)¶		
I		
II		
III		
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

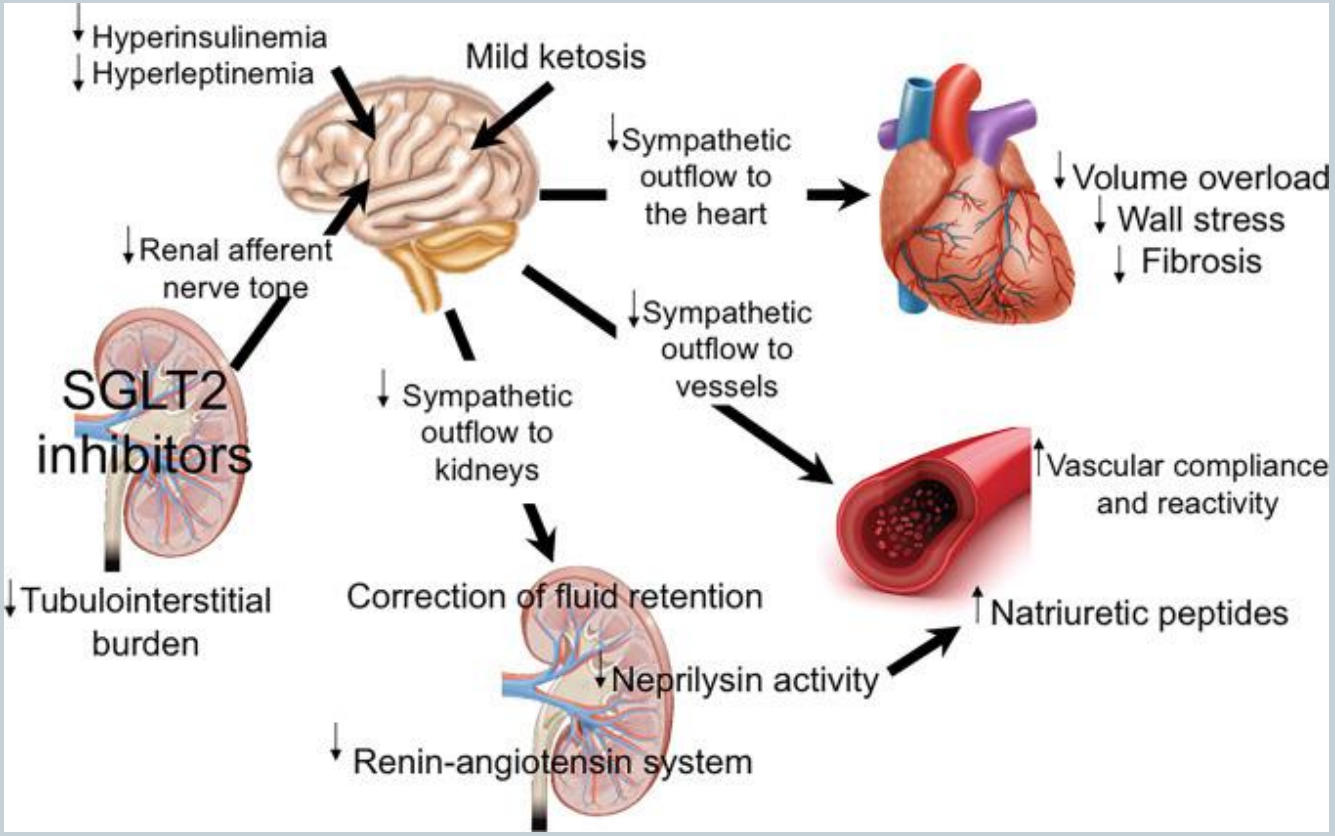
McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014

Angiotensin-Neprilysin Inhibitor -HFrEF



McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014

SGLT2i Proposed Mechanism



Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. *J Cardiol.* 2018

SGLT2i(Empagliflozin)- HFrEF

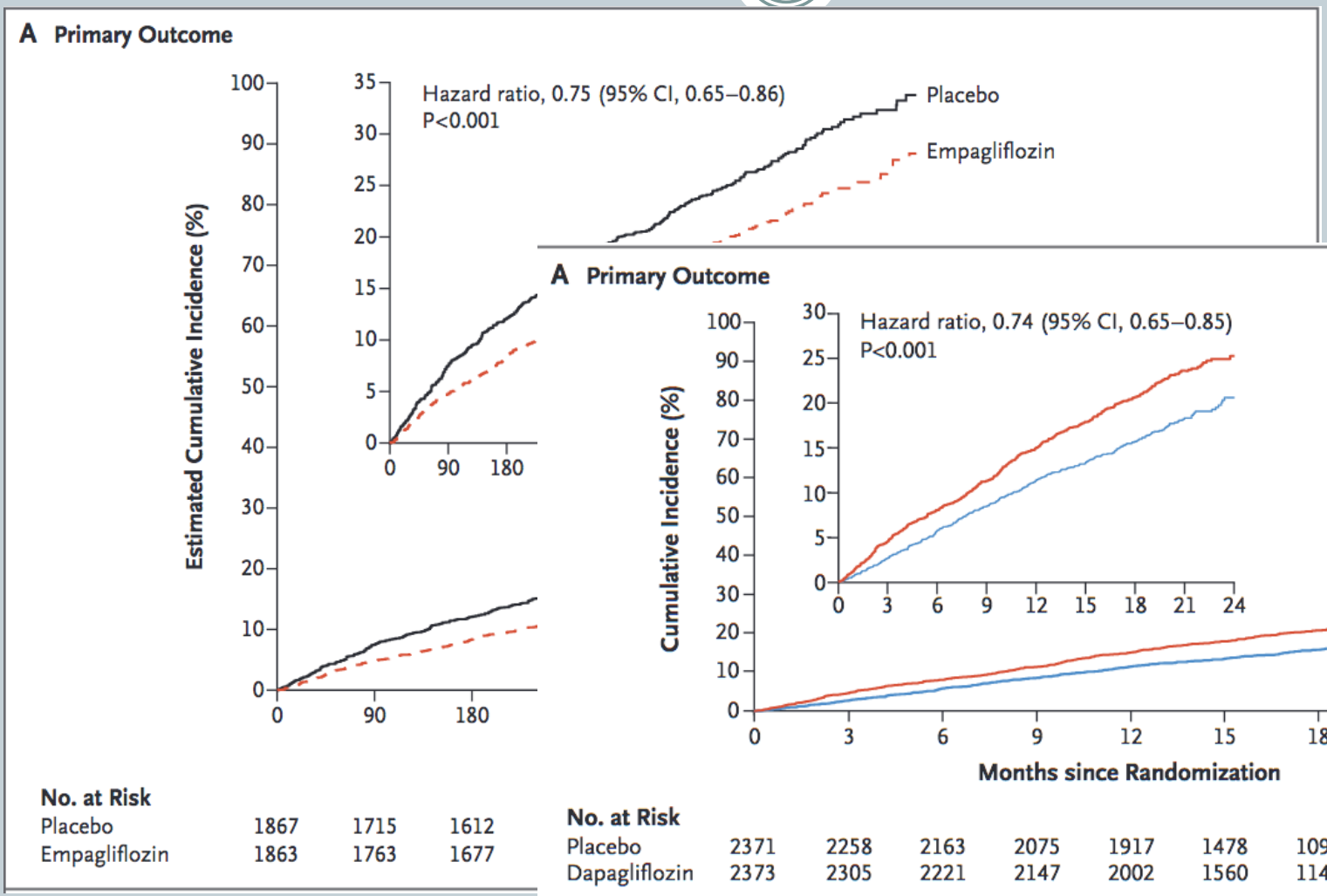
Table 1. Characteristics of the Patients at Baseline.*

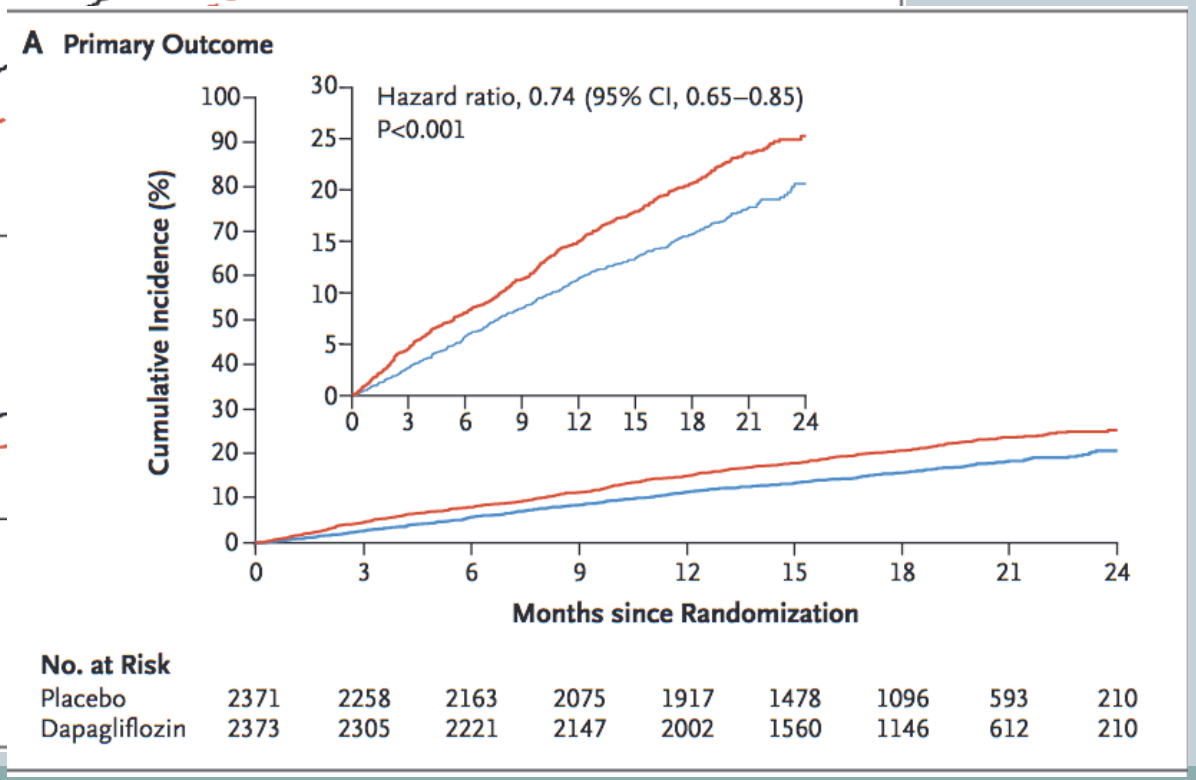
Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
Race — no. (%)†		
White	1325 (71.1)	1304 (69.8)
Black	123 (6.6)	134 (7.2)
Asian	337 (18.1)	335 (17.9)
Other or missing	78 (4.2)	94 (5.0)
Region — no. (%)		
North America		
Latin America		
Europe		
Asia		
Other		
NYHA functional class — no. (%)		
II		
III		
IV		
Body-mass index‡		
Heart rate — beats/min		
Systolic blood pressure — mm Hg		
Left ventricular ejection fraction		
Mean value		
Value of ≤30% — no. (%)		
NT-proBNP		
Median value (IQR) — pg/ml		
Value of ≥1000 pg/ml — no./total no. (%)		
Cause of heart failure — no. (%)		
Ischemic	983 (52.8)	946 (50.7)
Nonischemic	880 (47.2)	921 (49.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure in ≤12 mo	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

Packer M, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020

SGLT2i- HFrEF





Packer M, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020

McMurray JJV, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019

2022 HFrEF Guideline Recommendation

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality (1-5).
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible (6-13).
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality (1-5).
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).

Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

HFpEF Management: Previous

Table 21. Recommendations for Treatment of HF*p*EF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B[27,91]
Diuretics should be used for relief of symptoms due to volume overload.	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HF*p*EF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HF*p*EF	IIa	C
ARBs might be considered to decrease hospitalizations in HF*p*EF	IIb	B[589]
Nutritional supplementation is not recommended in HF*p*EF	III: No Benefit	C

Yancy CW, et al.. 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2013

HFpEF – Mineralocorticoid Antagonist (Spironolactone)

Table 1. Selected Baseline Characteristics of the Study Patients.*

Characteristic	Spironolactone (N=1722)	Placebo (N=1723)
Age — yr		
Median	68.7	68.7
Interquartile range	61.0–76.4	60.7–75.5
Age ≥75 yr — no. (%)	495 (28.7)	453 (26.3)
Female sex — no. (%)	888 (51.6)	887 (51.5)
White race — no. (%)†		
Left ventricular ejection fraction — %		
Median		
Interquartile range		
NYHA functional classification — no. (%)		
I		
II		
III		
IV		
Missing data		
Eligibility stratum		
Hospitalization in previous year with manage as major component — no. (%)		
Elevated natriuretic peptides in previous 60 d		
BNP — pg/ml		
Median		
Interquartile range		
NT-proBNP — pg/ml		
Median§		
Interquartile range	537–1634	627–2258
Current smoker — no. (%)	176 (10.2)	184 (10.7)

Table 1. (Continued.)

Characteristic	Spironolactone (N=1722)	Placebo (N=1723)
Serum creatinine — mg/dl‖		
Median	1.0	1.1
Interquartile range	0.9–1.2	0.9–1.2
Estimated GFR — ml/min/1.73 m²		
Median	65.3	65.5
Interquartile range	53.9–79.2	53.5–79.1
Hemoglobin — g/dl		
Median	13.2	13.3
Interquartile range	12.1–14.4	12.2–14.5
Region of enrollment — no. (%)		
Americas**	886 (51.5)	881 (51.1)
Russia and Georgia	836 (48.5)	842 (48.9)

Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014

HFpEF – Mineralocorticoid Antagonist (Spironolactone)

Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Prima						
Comp						
Death from causes						
Aborted ca						
Hospitaliza						

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).

Outcome	Americas (USA CAN ARG BRA) (N=1,767)			Eastern Europe (RUS GEO) (N=1,678)		
	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model
	Spironolactone (N = 886)	Placebo (N = 881)	HR(1 vs. 2), 95% CI, p-value	Spironolactone (N = 836)	Placebo (N = 842)	HR(1 vs. 2), 95% CI, p-value
Primary Outcome	242 (27.3%) 10.4 per 100 person-years	280 (31.8%) 12.6 per 100 person-years	0.82 (0.69-0.98) 0.026	78 (9.3%) 2.5 per 100 person-years	71 (8.4%) 2.3 per 100 person-years	1.10 (0.79-1.51) 0.576

Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014

SGLT2i(Empagliflozin) – HFpEF

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)
Race — no. (%)†		
White		
Black		
Asian		
Other or missing		
Geographic region — no.		
North America		
Latin America		
Europe		
Asia		
Other		
NYHA functional classific		
Class I		
Class II		
Class III		
Class IV		
Body-mass index‡		
Heart rate — beats per m		
Systolic blood pressure –		
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

Packer M, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020

SGLT2i(Empagliflozin) - HFpEF

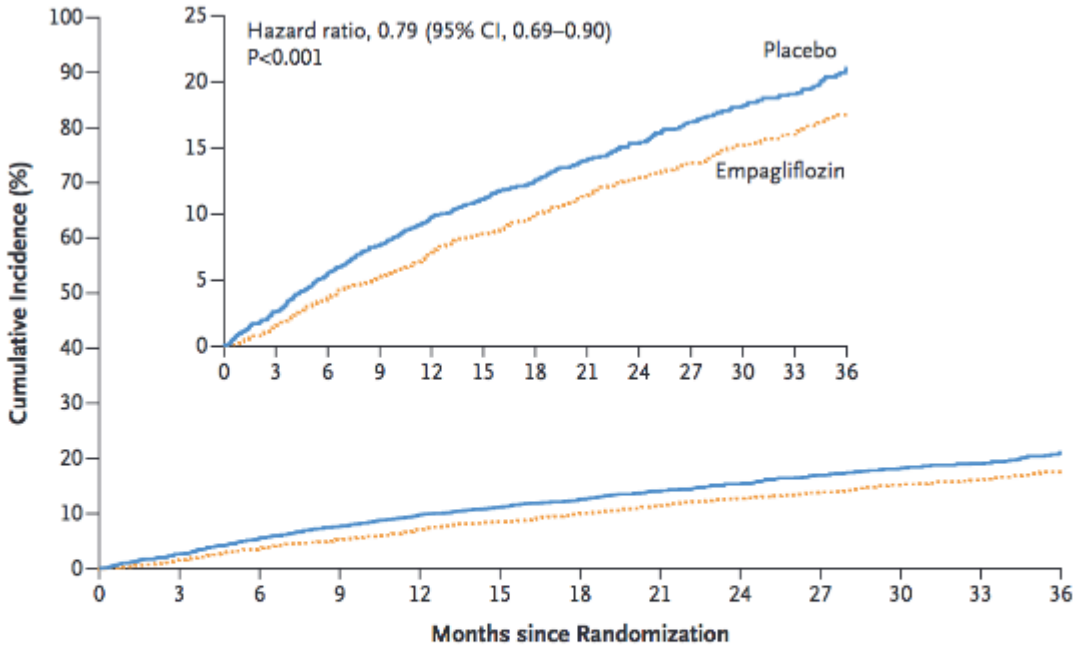


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.

The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

Packer M, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020

Angiotensin-Neprilysin Inhibitor –HFpEF(EF>45%)

Table 2. Primary and Secondary Outcomes.*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)

Solomon SD, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019

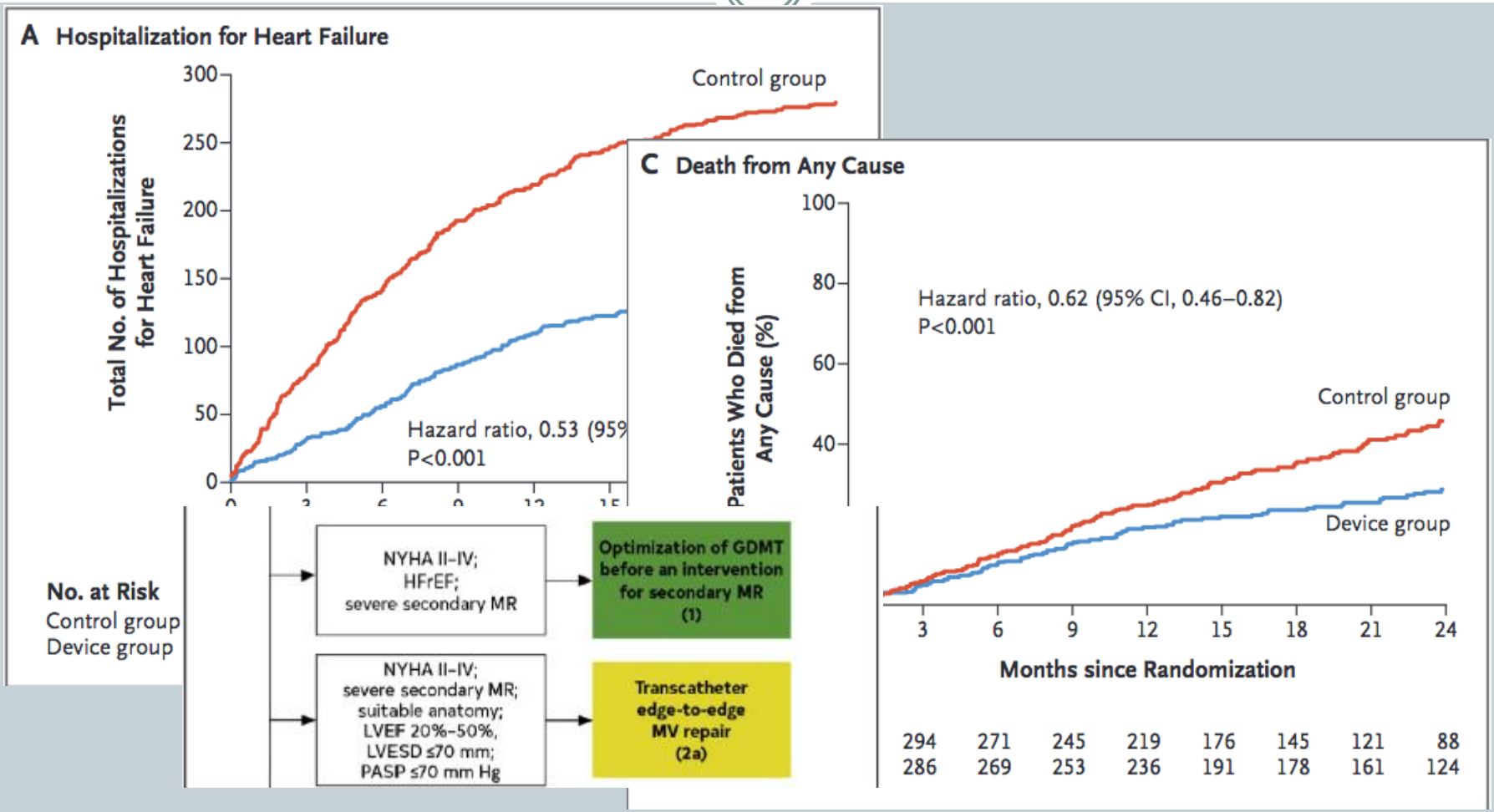
HFpEF Guideline Recommendations

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).

Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

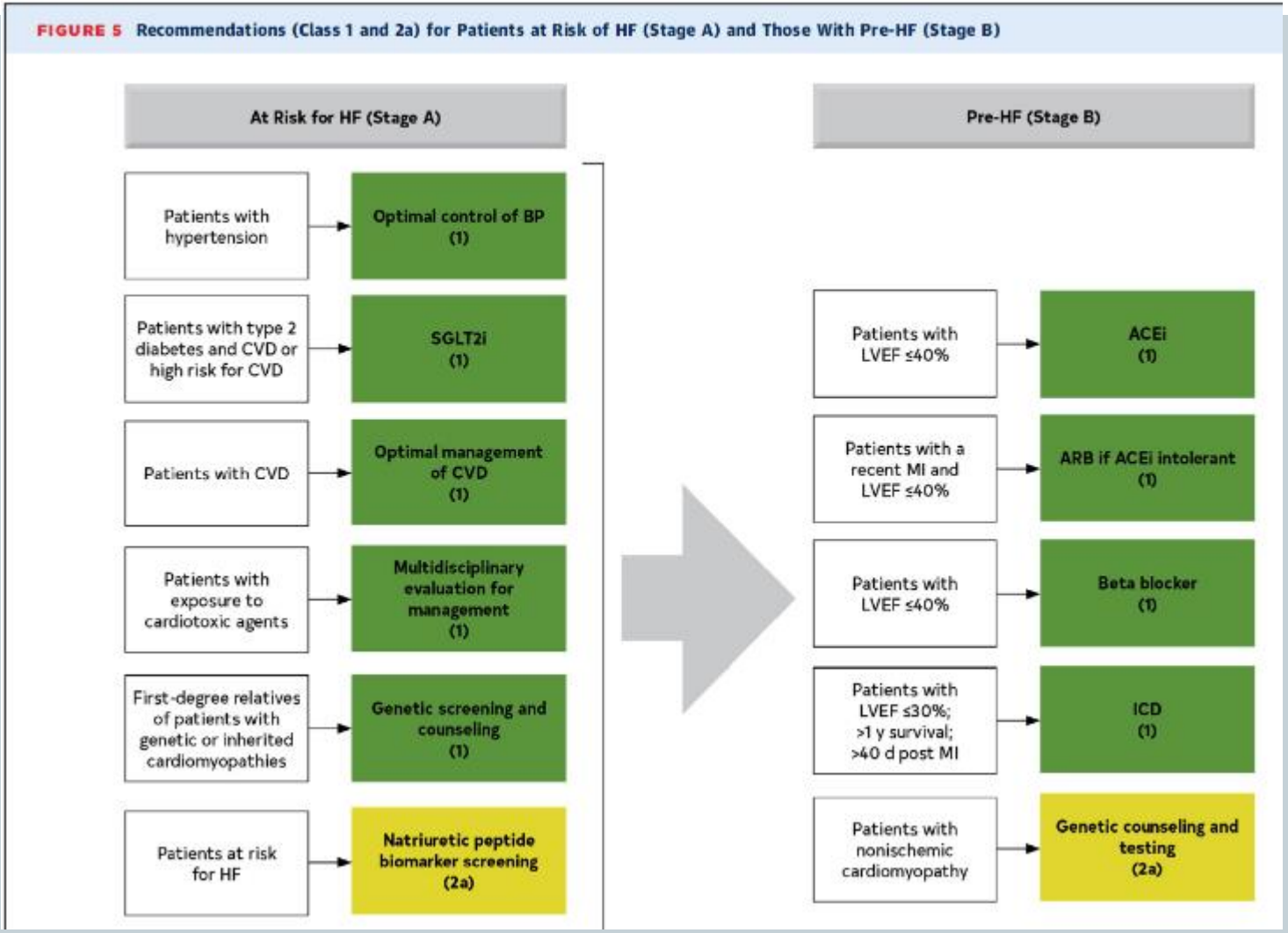
Transcatheter Mitral Valve Edge to Edge Repair (TEER)



Stone GW, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med*. 2018

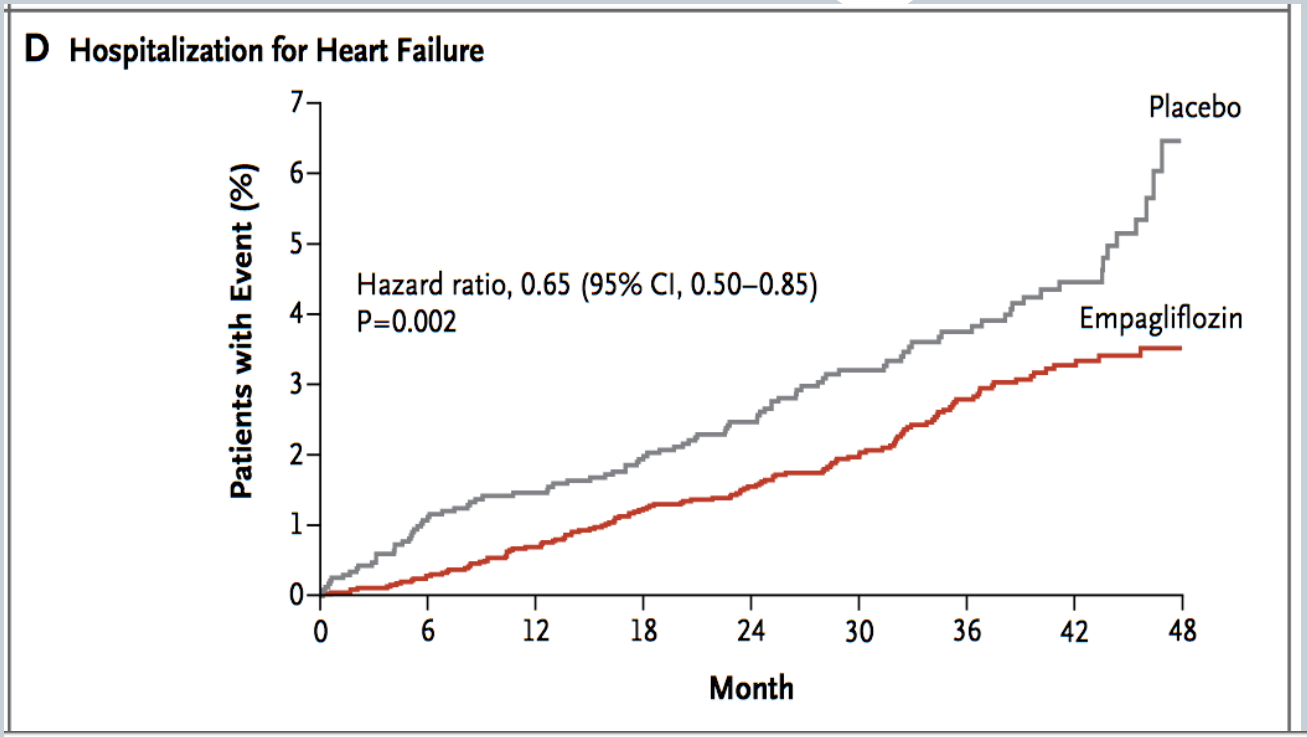
Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Heart Failure Prevention



Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

SGLT2i in DM: HF hospitalization



Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	

Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015

Wiviott SD, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019

Conclusion

- In HFrEF symptomatic patients, consider switching ACE inhibitors/ARB to ARNI, and starting SGLT2i
- In HFpEF patients, current standard therapy includes SGLT2i, and in select patients, consider ARNI
- Consider initiation of SGLT2i for heart failure prevention in patients with DM and CVD or high risk of CVD

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