

Treatment of Patients with Heart Failure with HFrEF and HFpEF

May 4, 2023

Barry Greenberg MD

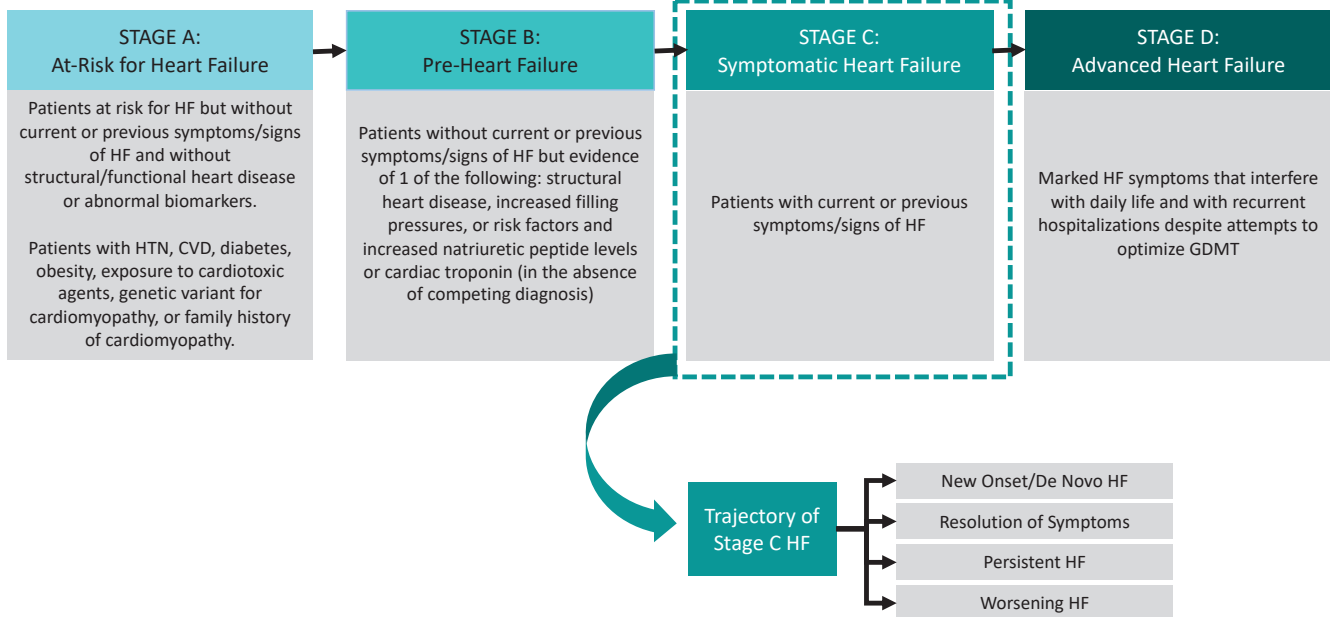
Distinguished Professor of Medicine

Director, Advanced Heart Failure Treatment Program

University of California, San Diego

UC San Diego
SCHOOL OF MEDICINE

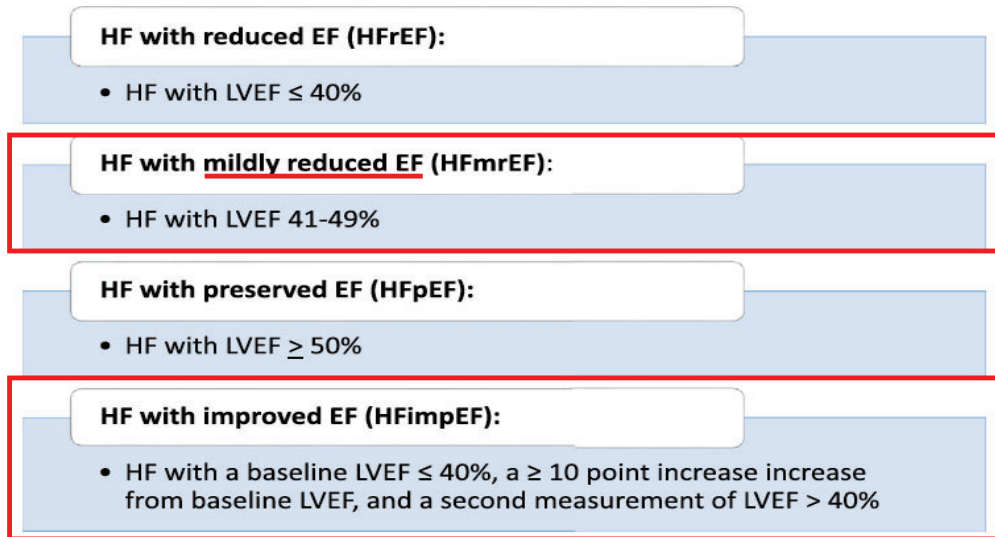
Stages of Heart Failure



Abbreviations: CVD indicates cardiovascular disease; GDMT, guideline-directed medical therapy; HF, heart failure; HTN, hypertension; and NYHA, New York Heart Association.

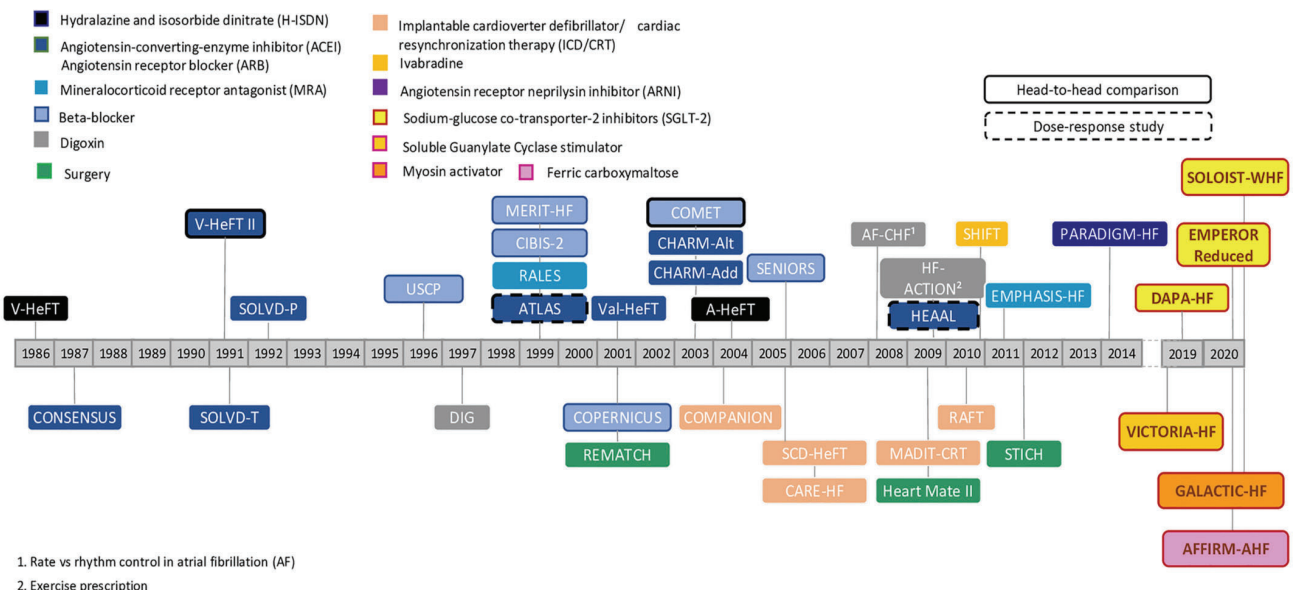


New Classification to HF According to LVEF



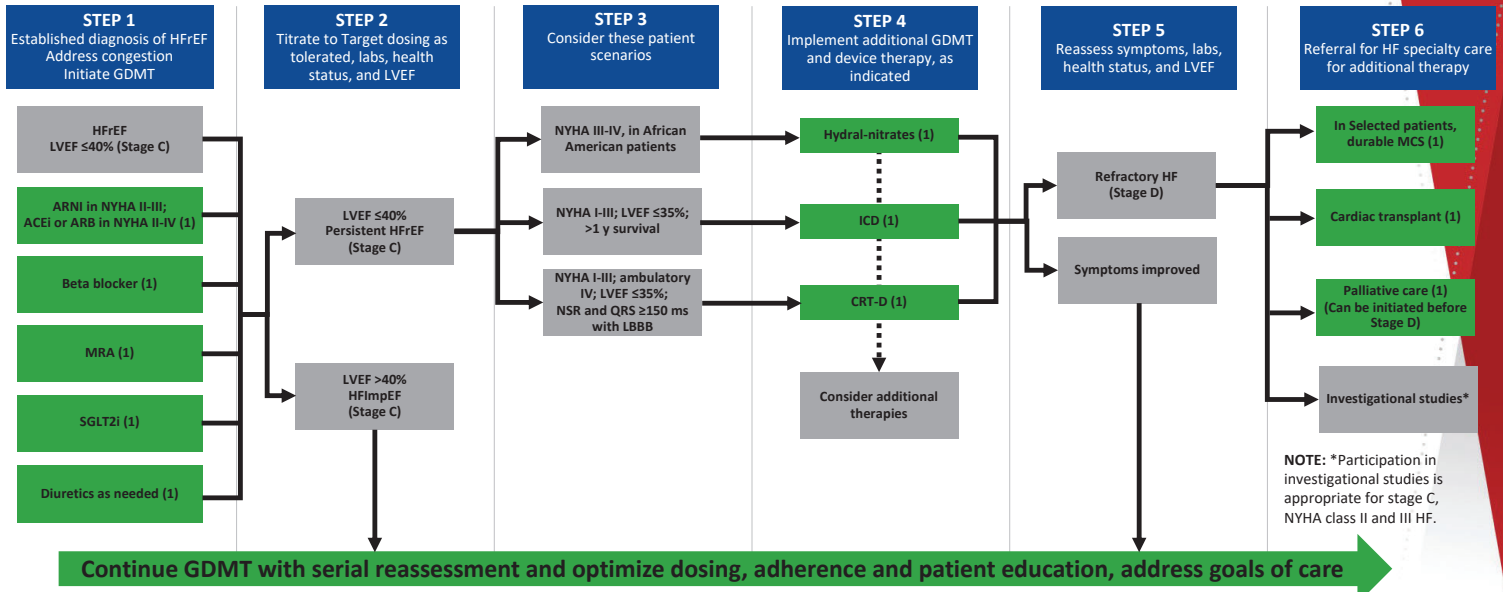
Bozkurt et al. Universal Definition and Classification of HF. J Cardiac Failure 2021

Heart Failure Trials 1986-2021





Treatment of HFrEF Stages C and D



Abbreviations: ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

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

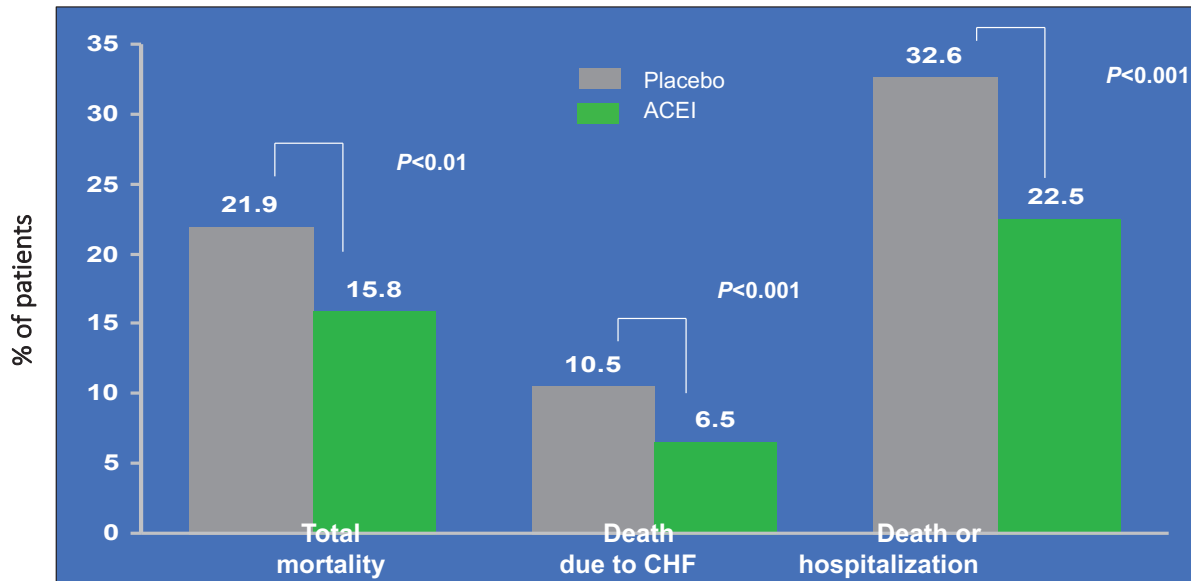


Foundational Drugs for Treating HFrEF (LVEF $\leq 40\%$)

	COR	LOE	Recommendations
RAAS Inhibitors (ARNIs preferred)	1	A	In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality
	1	A	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
	1	B - R	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
Beta blockers	1	A	In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality is recommended to reduce mortality and hospitalizations
MRAs	1	A	In patients with HFrEF and NYHA class II to IV symptoms, an MRA is recommended to reduce morbidity and mortality, if eGFR >30 mL/min/1.73 m ² and serum potassium is <5.0 mEq/L
SGLT2 Inhibitors	1	A	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

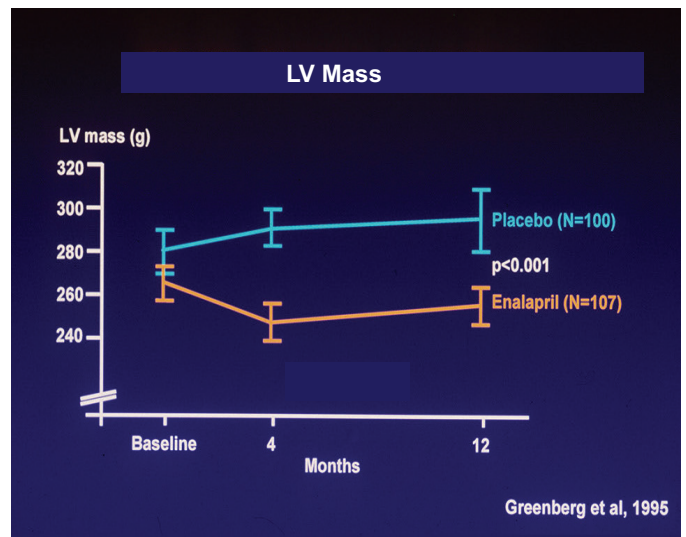
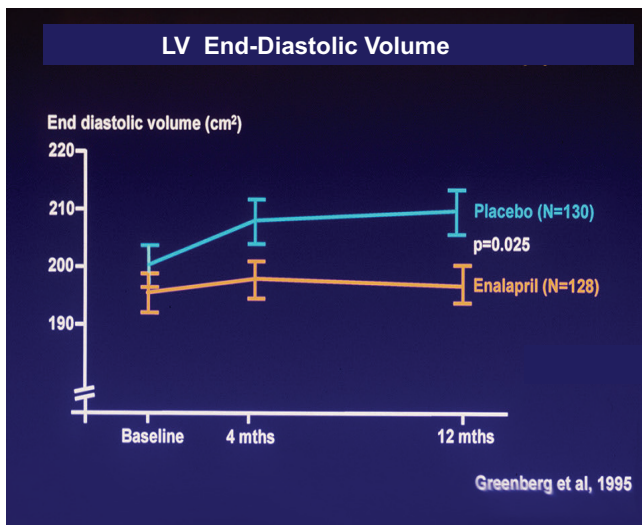
Improved Outcomes with ACEIs in HF

A Pooled Analysis of 32 Randomized Trials



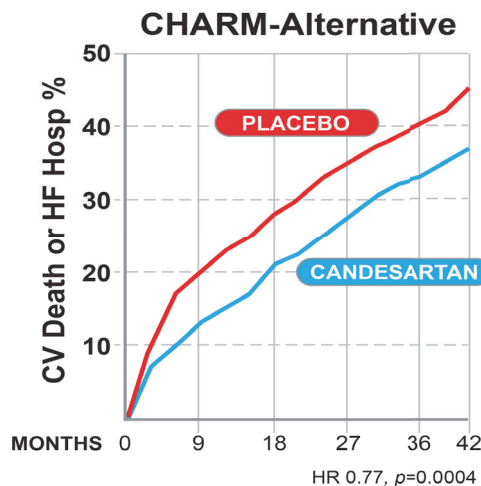
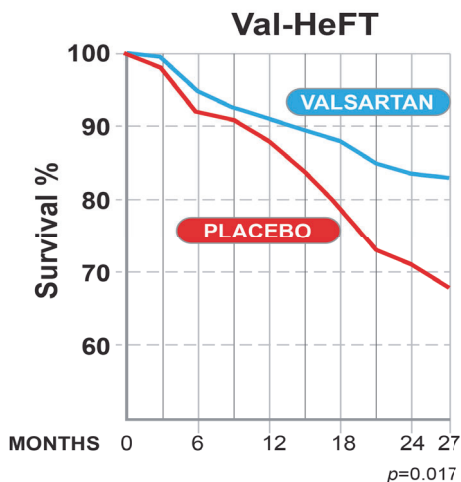
Garg et al. JAMA. 1995;273:1450.

ACEIs Inhibit LV Remodeling: SOLVD Echo Sub-study



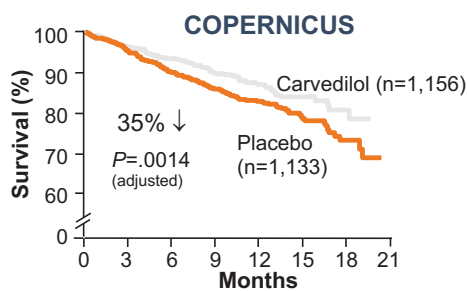
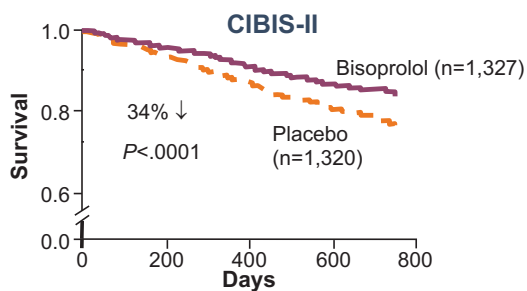
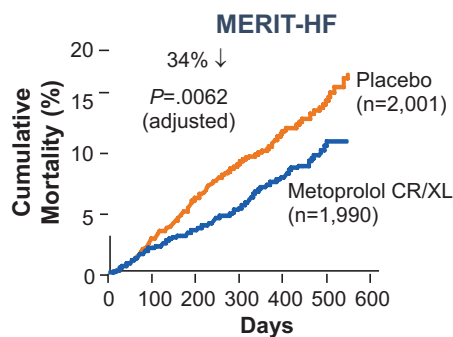
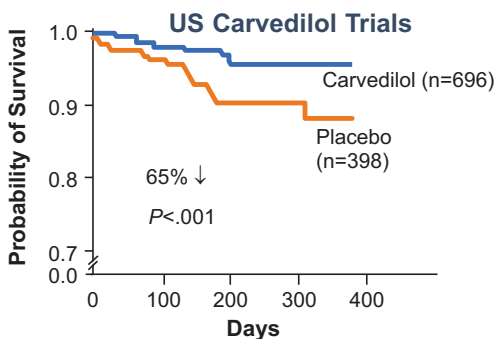
Greenberg B, et al. *Circulation*. 1995 May 15;91(10):2573-2581.

ARBs in ACEI Intolerant Patients



Maggioni AP et al. JACC 2002;40:1422-4.
Granger CB et al. Lancet 2003;362:772-6.

Mortality Further Reduced by ~35% When β -Blockade Is Added to ACEI



Packer M et al. *N Engl J Med.* 1996;334:1349-1355. MERIT-HF Study Group. *Lancet.* 1999;253:2001-2007. CIBIS-II Investigators. *Lancet.* 1999;353:9-13. Packer M et al. *N Engl J Med.* 2001;344:1651-1658.

Trials With Aldosterone Antagonist

Primary Endpoint: All-Cause Mortality

Trial	Placebo	Aldosterone Antagonist	Hazard Ratio	Log-rank P Value
EPHESUS Post-MI	554/3,319	478/3,313	.85 (.75, .96)	.008
RALES Advanced HF	386/841	284/822	.70 (.60, .82)	<.001
EMPHASIS Milder HF	356/1373	249/1364	.76 (.62, .93)	.008

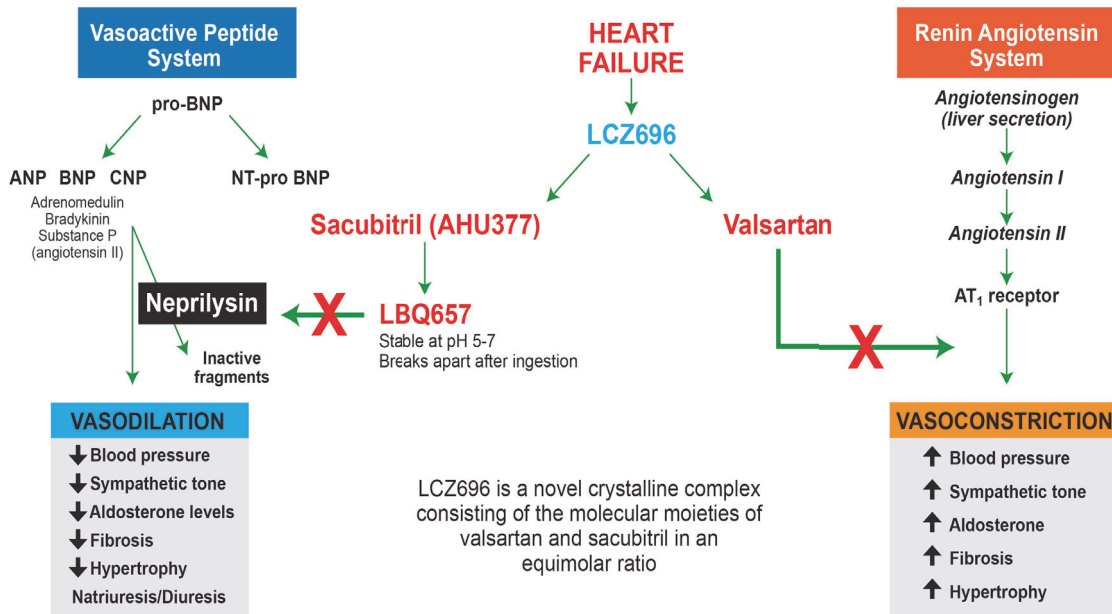
Pitt B. *N Engl J Med.* 2003;348:1309-1321.

Pitt B. *N Engl J Med.* 1999;341:709-717.

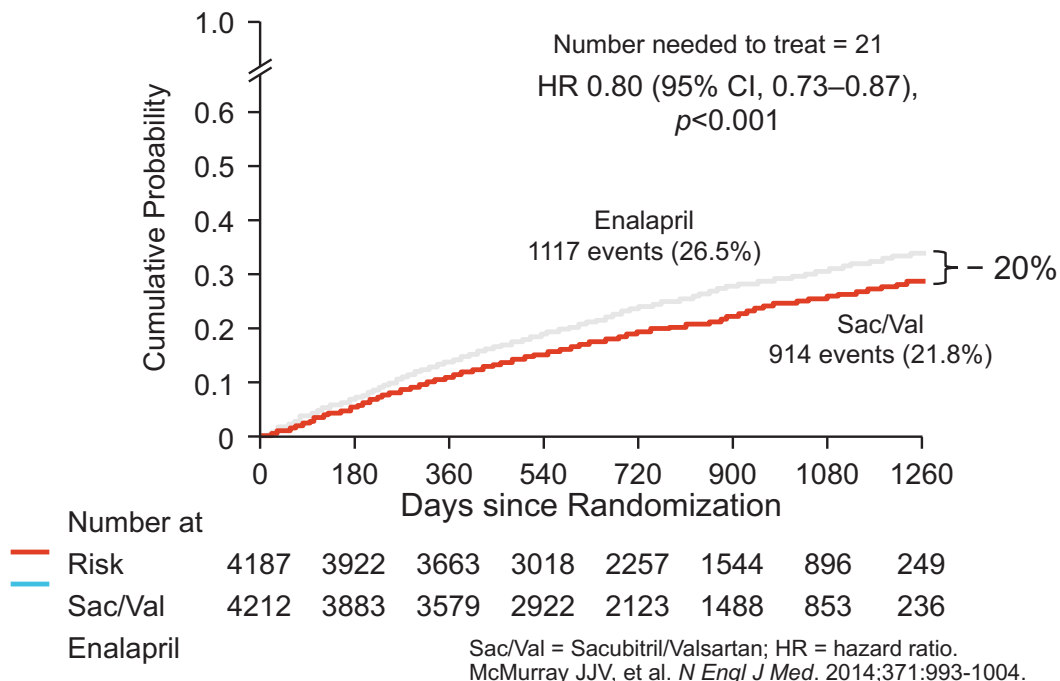
Zannad F et al. *N Engl J Med.* 2011;364:11-21

Recent Advances – ARNIs and SGLT2 Inhibitors

Sacubitril/Valsartan Mechanism of Action



PARADIGM-HF: Primary Endpoint of CV Death or HF Hospitalization



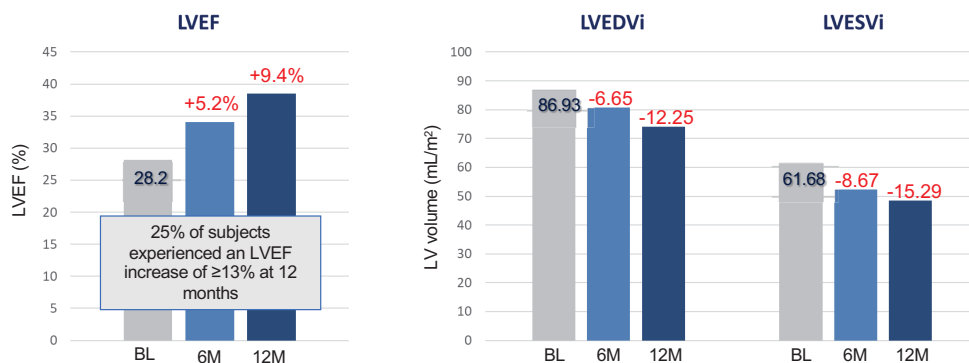
PARADIGM-HF: Effect of Sac/Val vs. Enalapril on the Primary Endpoint and Its Components

	Sac/Val (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	p- Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73–0.87)	<0.001
All-cause mortality	711 (17.0%)	835 19.8%	0.84 (0.76–0.93)	<0.001
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71–0.89)	<0.001
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71–0.89)	<0.001

McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.

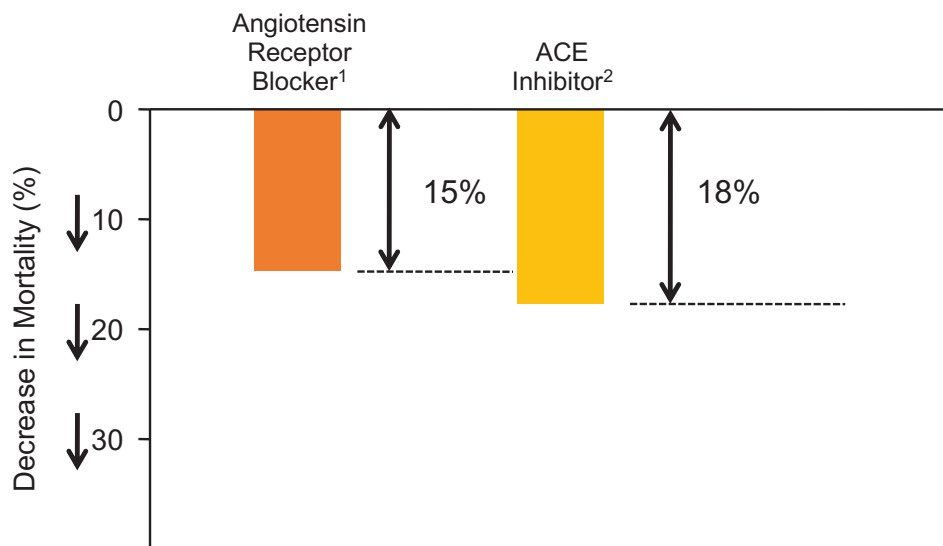
PROVE-HF Reverse Cardiac Remodeling with ARNI in HFrEF

Baseline to 12 months: all P <.001



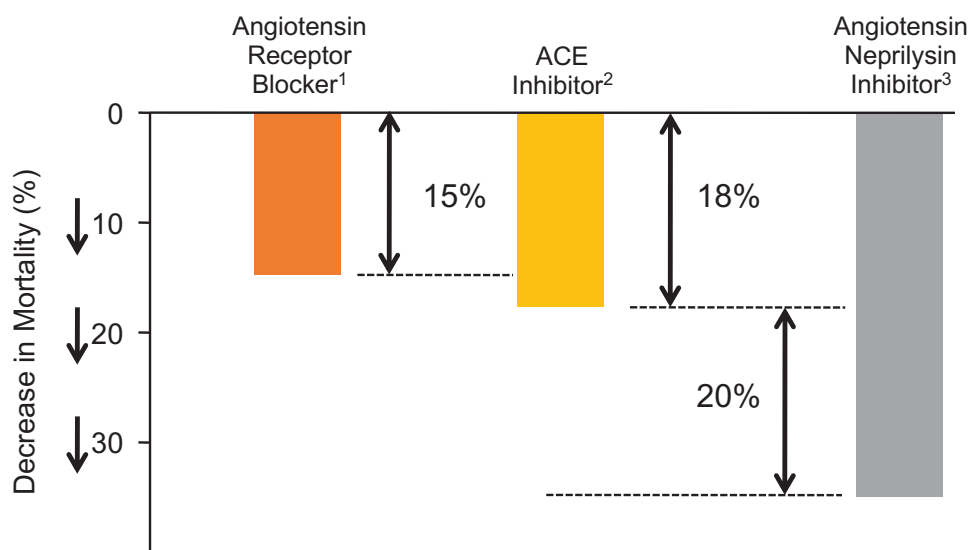
BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index

Effects of ACEIs and ARBs on Survival in HF Patients



1. Granger CB, et al. *Lancet*. 2003;362:772-776. 2. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302.

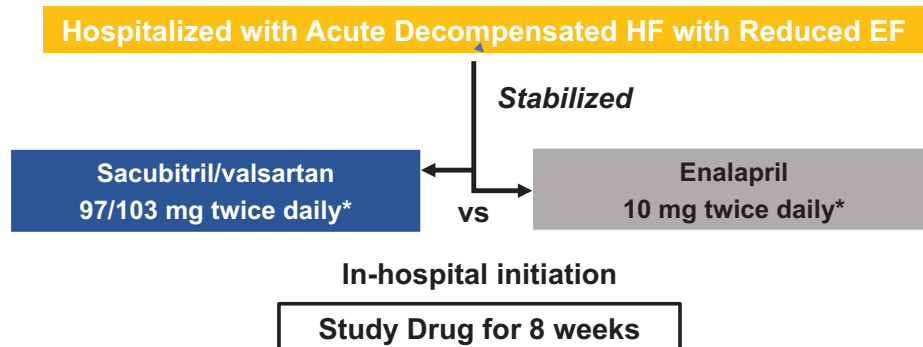
Comparison of ARNIs to ACEIs and ARBs



1. Granger CB, et al. *Lancet*. 2003;362:772-776. 2. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302. 3. McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

PIONEER-HF

Study Design



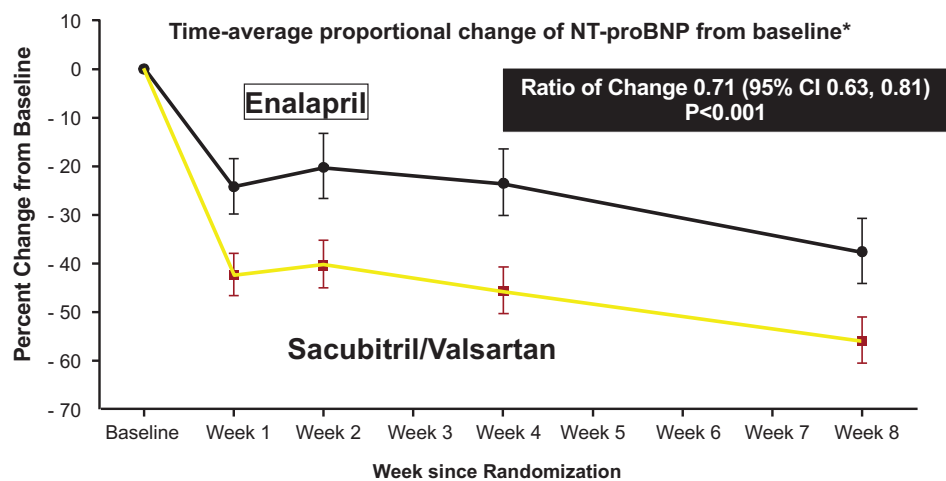
- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

*Target Dose
HF, Heart Failure. EF, Ejection Fraction

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.

PIONEER-HF

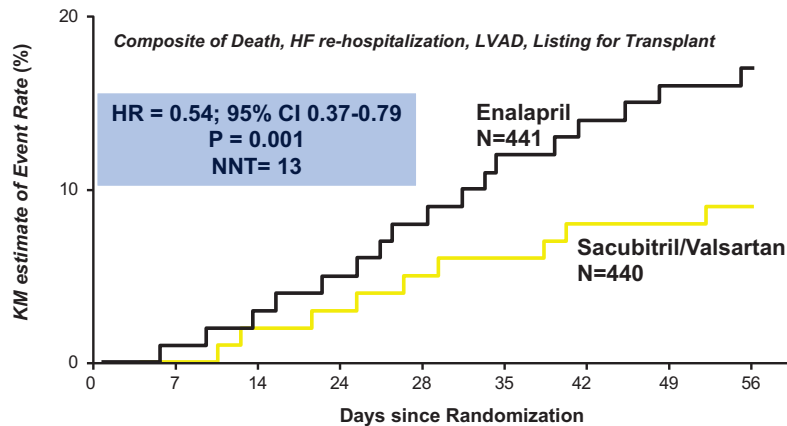
Primary Endpoint



Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.

PIONEER-HF

Serious Clinical Composite Endpoint

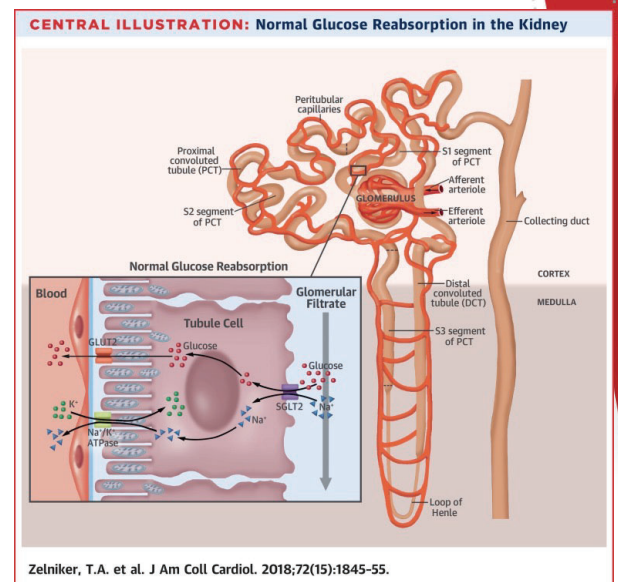


- Serious Clinical Composite endpoints were driven by a reduction in death and HF re-hospitalizations

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.

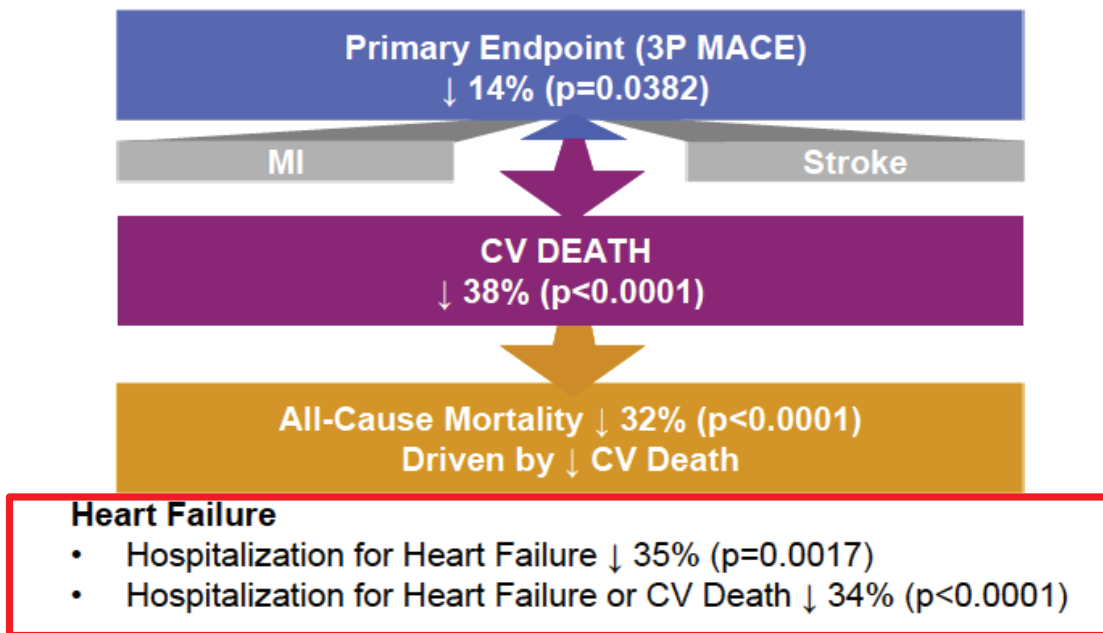
SGLT2 Inhibitors

- Virtually all glucose filtered by the kidney is reclaimed in the proximal tubule.¹ Sodium glucose cotransporter 2 (SGLT2) is responsible for 90% of this reabsorption.
- Selective inhibitors of SGLT2 have been developed.²
- By reducing renal glucose reabsorption, SGLT2 inhibitors increase urinary glucose excretion.³
- In patients with type 2 DM, SGLT2 inhibitors lead to:⁴
 - Significant reductions in HbA1c
 - Weight loss
 - Reductions in BP *without* increases in heart rate

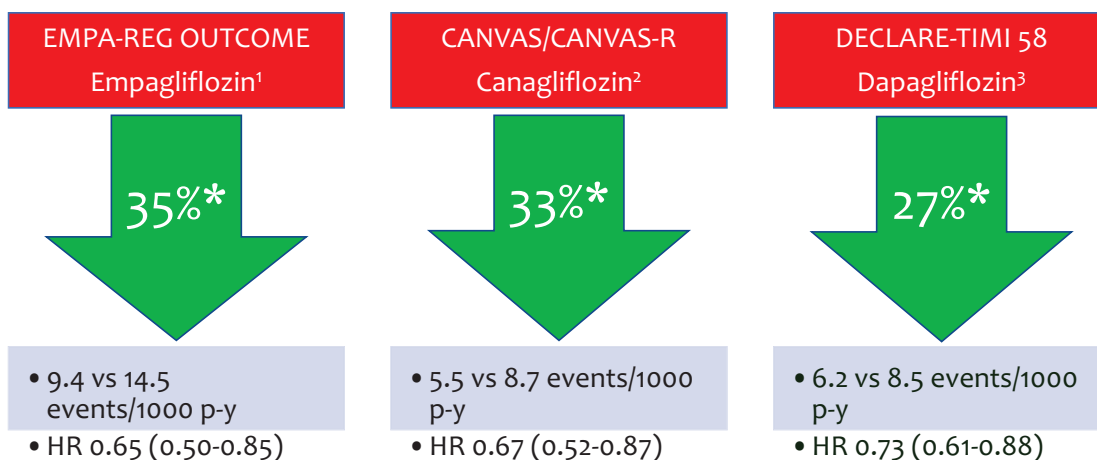


EMPA-REG OUTCOME Trial - 2015

EMPA-REG OUTCOME Trial: Key Results



Hospitalization for HF in Patients with T2DM Treated with SGLT2i

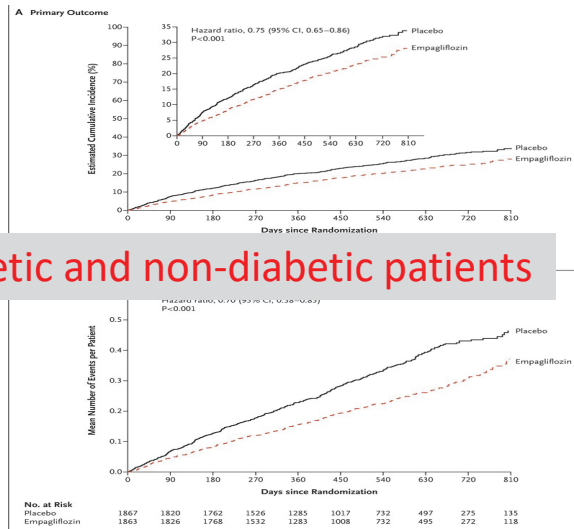
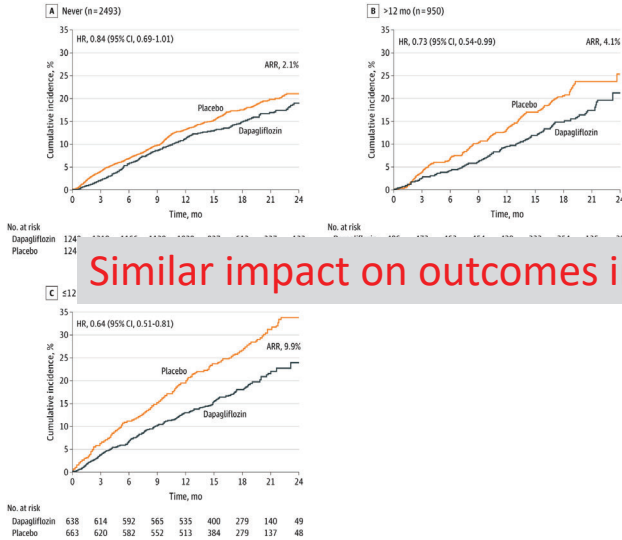


* P < .05; p-y, patient-years; NR, not reported. Not currently indicated by the US FDA for reducing hospitalization in patients with HF.
 1. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-2128; 2. Neal B, et al. *N Engl J Med.* 2017;377(7):644-657;
 3. Wiviott SD, *N Engl J Med.* 2019;380(4):347-357.

SGLT2 Inhibitors Improve Outcomes in HFrEF

EMPOWER-Reduced

DAPA-HF

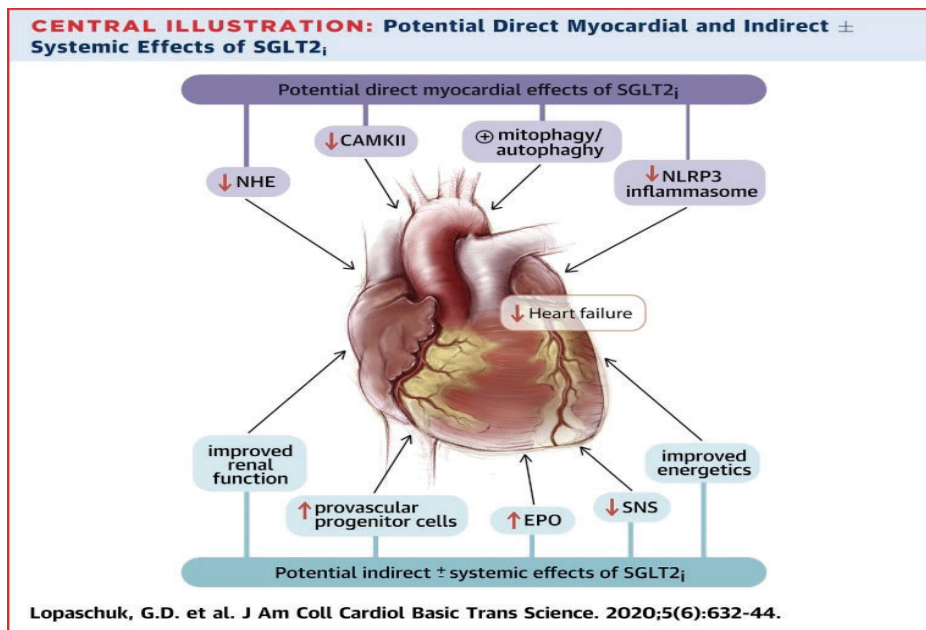


Similar impact on outcomes in diabetic and non-diabetic patients

JAMA Cardiol. 2021;6(5):499-507

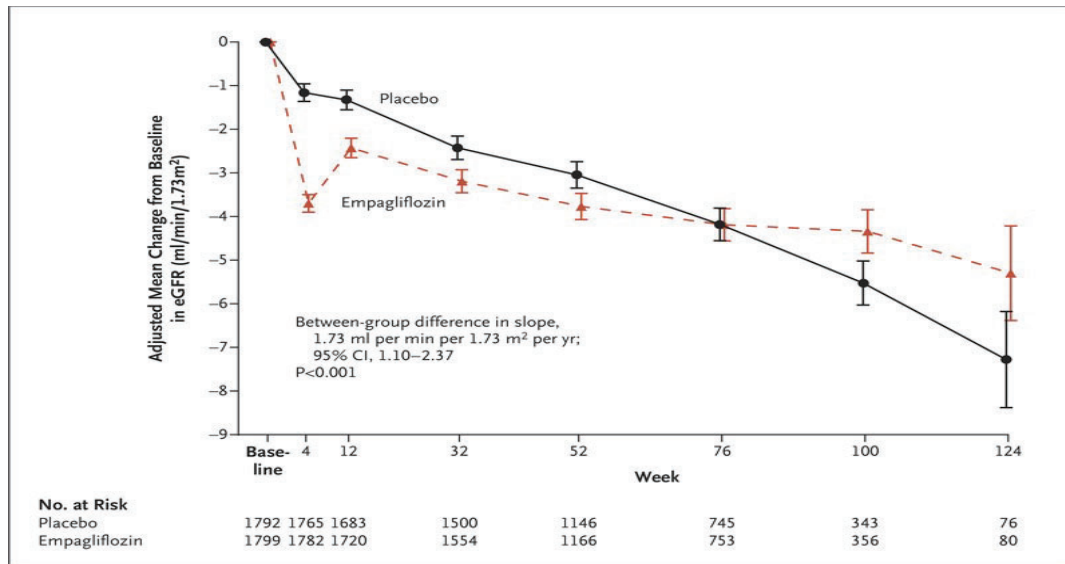
Packer M et al, NEJM. 2020

Potential Mechanism of Action of SGLT2 Inhibitors



Lopaschuk GB et al. JACC Basic Transl Sci. 2020 Jun; 5(6): 632-644

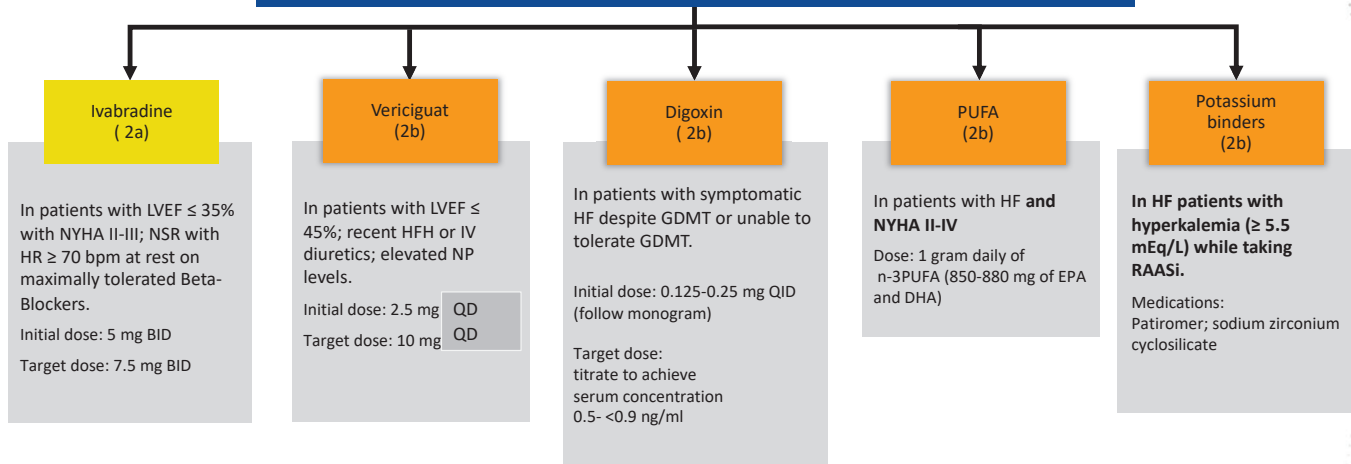
Effect of SGLT2i on Renal Function



Packer M et al, NEJM. 2020

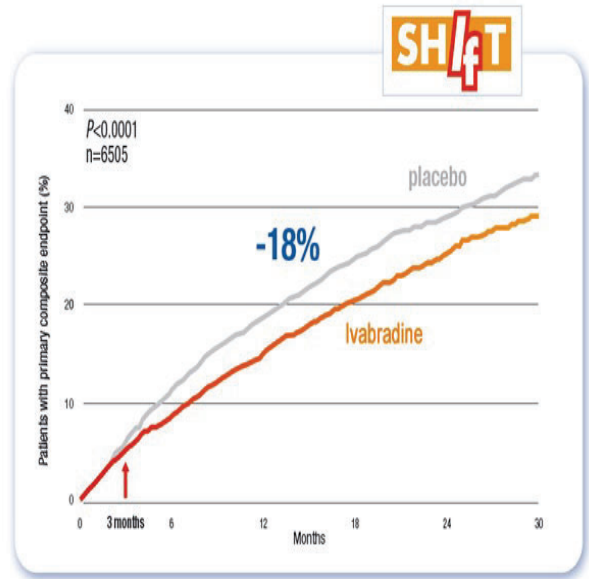
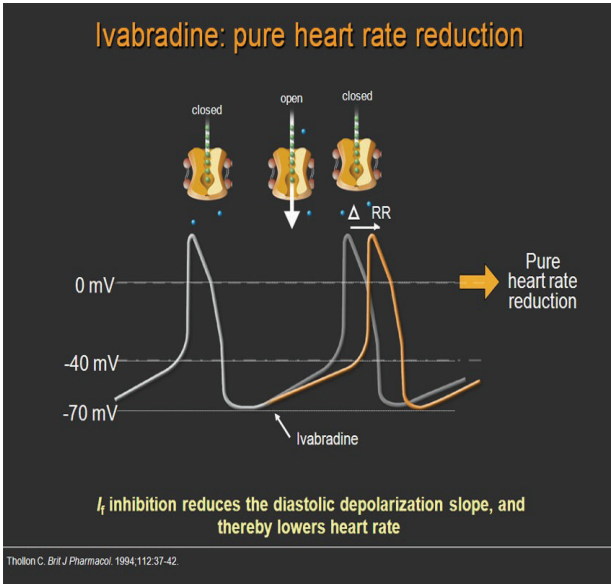
Additional Medical Therapies after GDMT Optimization

Additional medical therapies after optimizing GDMT



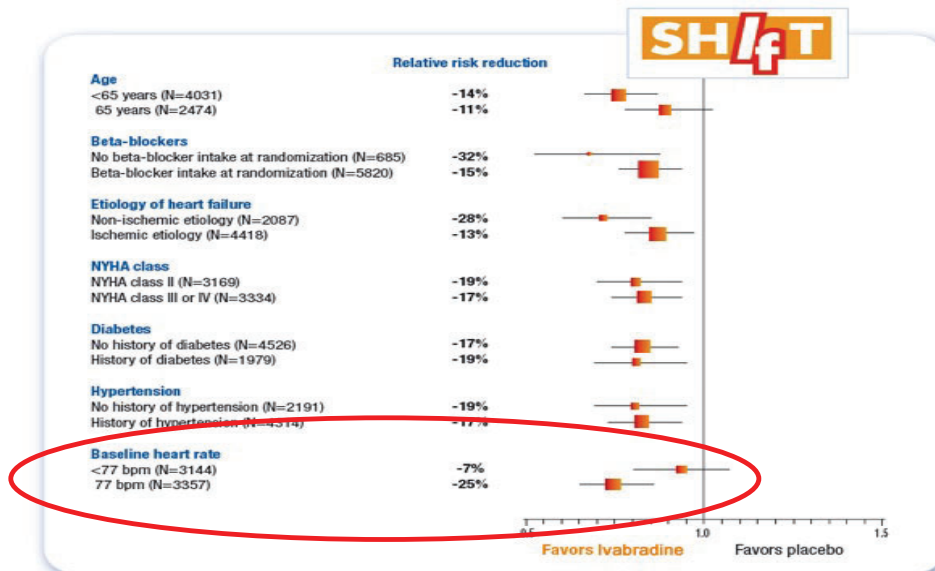
Abbreviations: DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; IV, intravenous; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NSR, normal sinus rhythm; NYHA, New York Heart Association; PUFA, polyunsaturated fatty acid; and RAASi, renin-angiotensin-aldosterone system inhibitors.

Ivabradine Effects on Combined CV Mortality and HF Hospitalization



Swedberg K, et al. *Lancet.* 2010 Sep 11;376(9744):875-85.

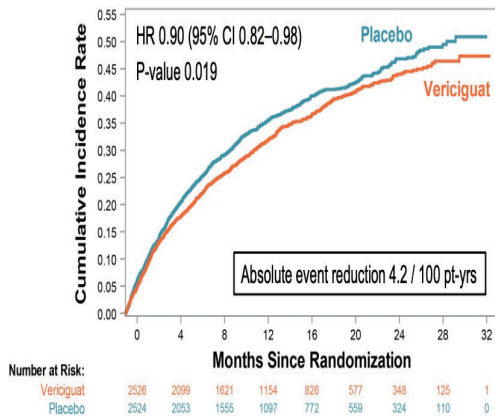
SHIFT: Subgroup Analysis



Swedberg K, et al. *Lancet.* 2010 Sep 11;376(9744):875-85.

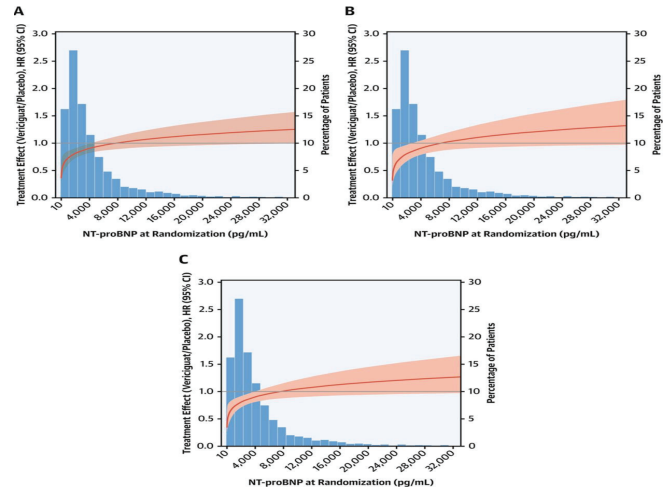
Vericiguat in Patients with HFrEF: VICTORIA-HF

Primary Composite Endpoint: CV Death or First HF Hospitalization



Armstrong PW et al. *N Engl J Med.* 2020;382(20):1883-1893.

Vericiguat Appears to be More Beneficial at NT-proBNP Levels <4,000 pg/ml

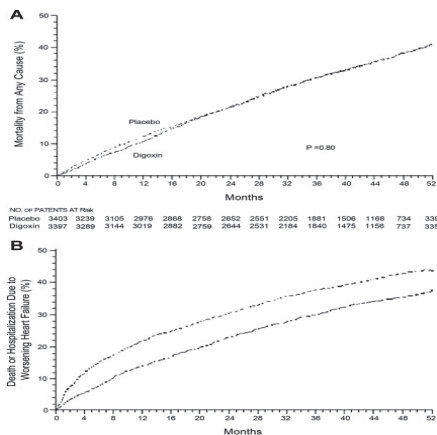


Justin A. Ezekowitz et al. *J Am Coll Cardiol HF* 2020;j.jchf.2020.08.008

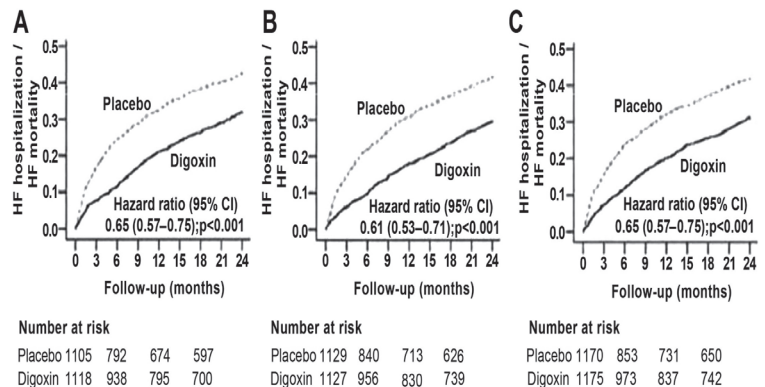
Digoxin



Results of the DIG Trial



Digoxin in Patients with Worsening HF

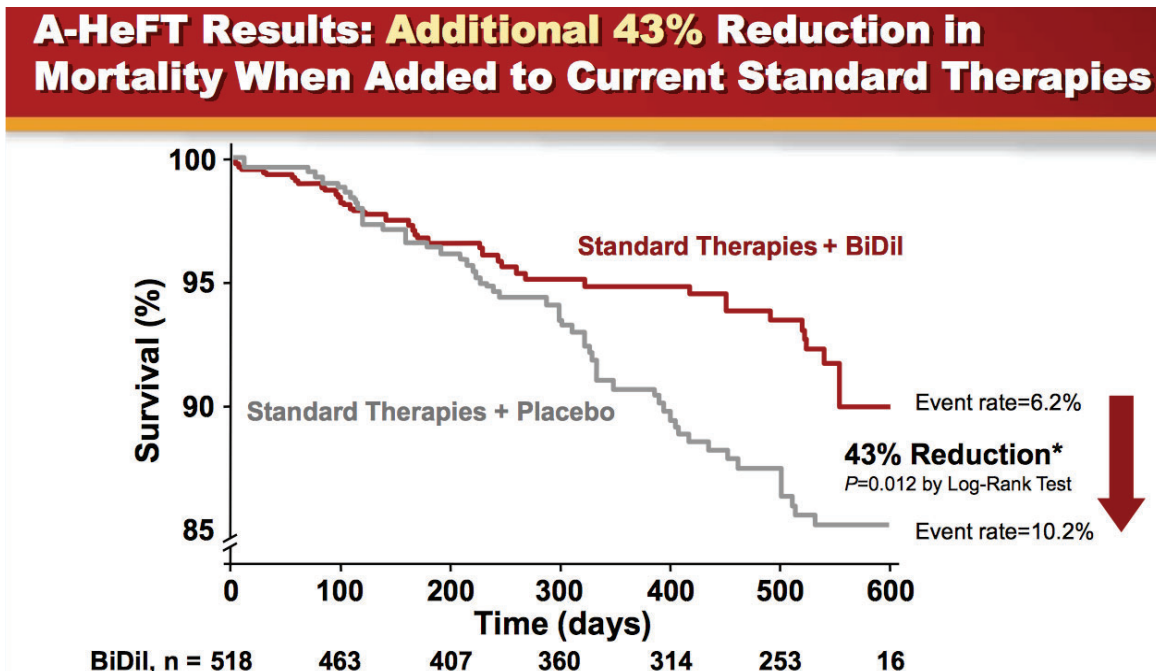


All-Cause Mortality and Incidence of Death or Hospitalization for Worsening HF in the DIG Trial (A) All-cause mortality; (B) incidence of death or hospitalization due to worsening HF. DIG = Digitalis Investigation Group; HF = heart failure.

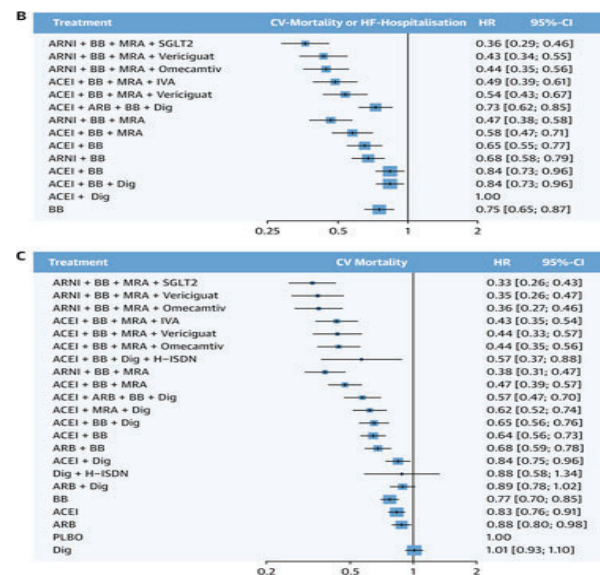
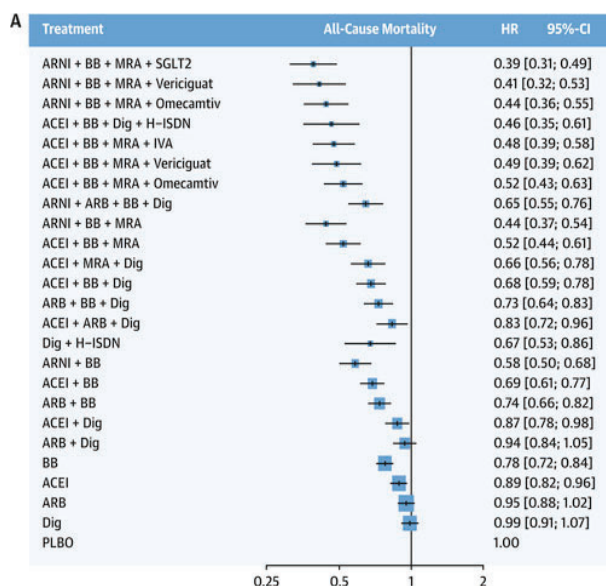
Ambrosy et al. *J Am Coll Cardiol* 2014, 63, 1823-32

Gheorghiadu et al. *Eur J Heart Failure* (2013); 15:551-9

A-HeFT: Effect of Hydralazine/Nitrate on Mortality



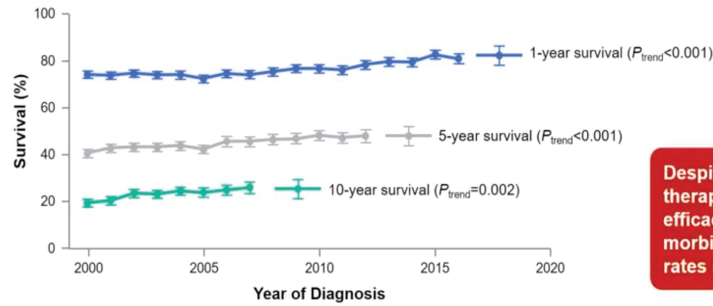
Aggregate Improvement in Outcomes with GDMT



Impact of Current Therapy on Mortality in Patients with HF

Mortality Among Patients Diagnosed with HF is High

Survival Rates for People With New Onset HF by Year of Diagnosis



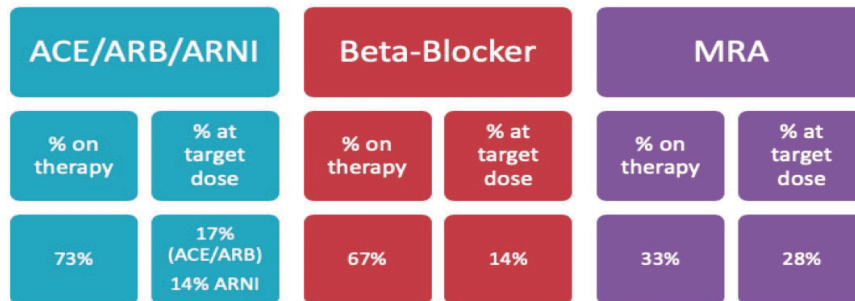
Despite the availability of therapies with established efficacy in HFrEF, morbidity and mortality rates remain high²

Primary care data in the United Kingdom for 55,959 patients aged 45 years and older with a new diagnosis of HF and 278,679 age- and sex-matched controls.

1. Taylor CJ et al. *BMJ*. 2019;364:l223. doi:10.1136/bmj.l223; 2. Yancy CW et al. *J Am Coll Cardiol*. 2018;71(2):201-230.

Use and Dosing of GDMT for HFrEF: CHAMP HF Registry

CHAMP-HF Results



J Am Coll Cardiol, 2018;72(4):351-366.

3,518 HFrEF patients without contraindications or intolerance to GDMT from 150 primary care and cardiology practices 2016-2018

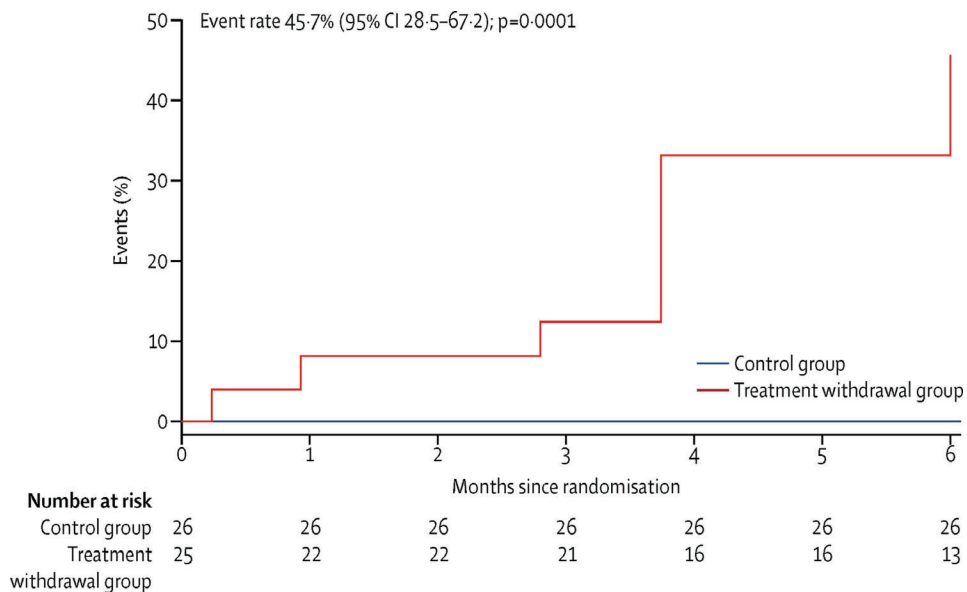
Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.

Greene S, Fonarow GC et al *JACC* 2019;72:351.-6.

Recommendations for Treating HFimpEF

COR	LOE	Recommendations
1	B - R	In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular dysfunction, even in patients who may become asymptomatic

Effect of Discontinuing GDMT in Patients with HFrecEF in TRED-HF



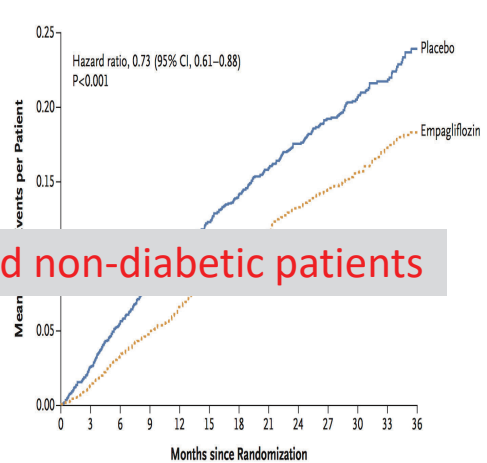
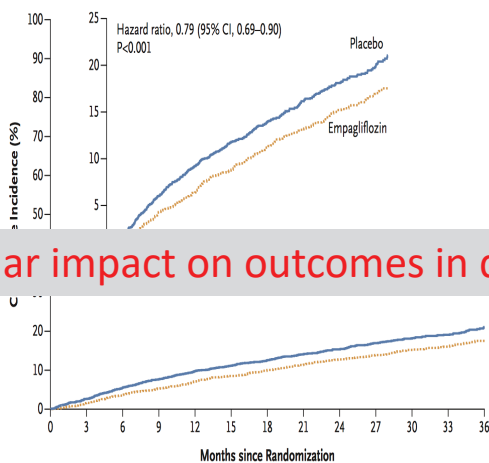
New Recommendations for Treating HFpEF

COR	LOE	Recommendations
2a	B - R	In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality
2b	B - R	In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, <u>particularly among patients with LVEF on the lower end of this spectrum</u>
2b	B - R	In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, <u>particularly among patients with LVEF on the lower end of this spectrum</u>

SGLT2 Inhibitors: Results of EMPORER-Preserved

Primary Endpoint: CV mortality/HF hospitalization

HF hospitalization

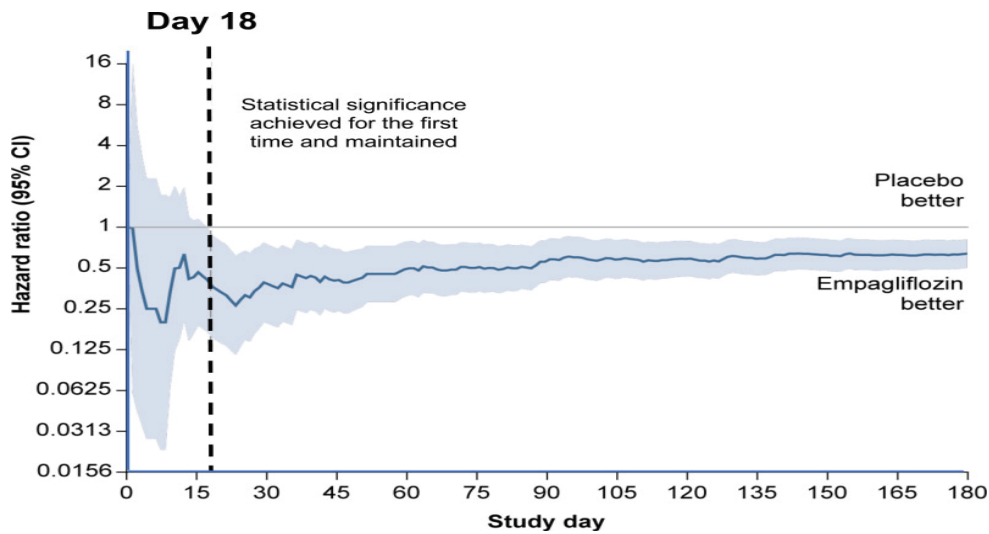


Similar impact on outcomes in diabetic and non-diabetic patients

No. at Risk	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

No. at Risk	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Time to First Event in EMPORER-Preserved



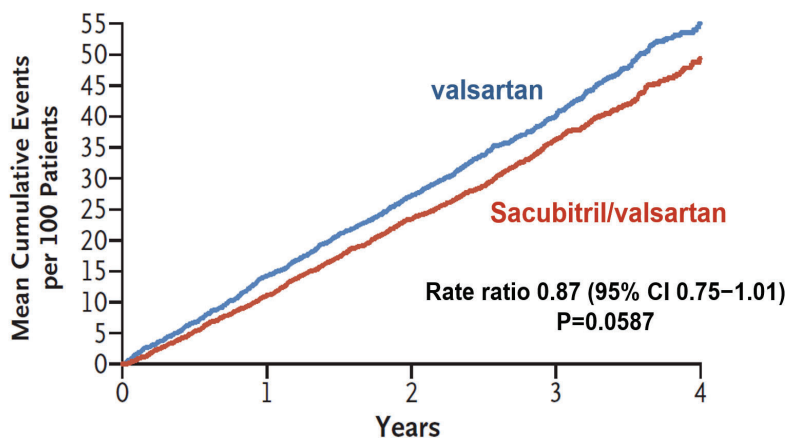
Packer M et al., Circulation. 2021 Oct 19; 144(16): 1284–1294

PARAGON-HF: Effects of an ARNI in HFpEF

PARAGON-HF: Primary composite outcome

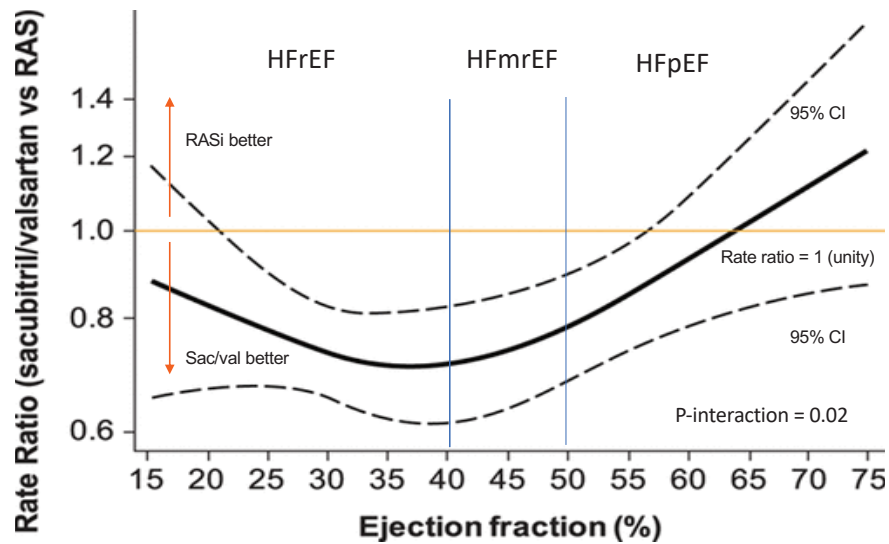
CV death and total (first and recurrent) HF hospitalizations

Primary Endpoint of CV
Death and Total HF
Hospitalizations



Solomon SD et al. NEJM 2020;381:1609-1620

Sacubitril-Valsartan Improves Outcomes Across the Spectrum of LVEF



Solomon S et al, Circulation 2020 Feb 4;141(5):352-361

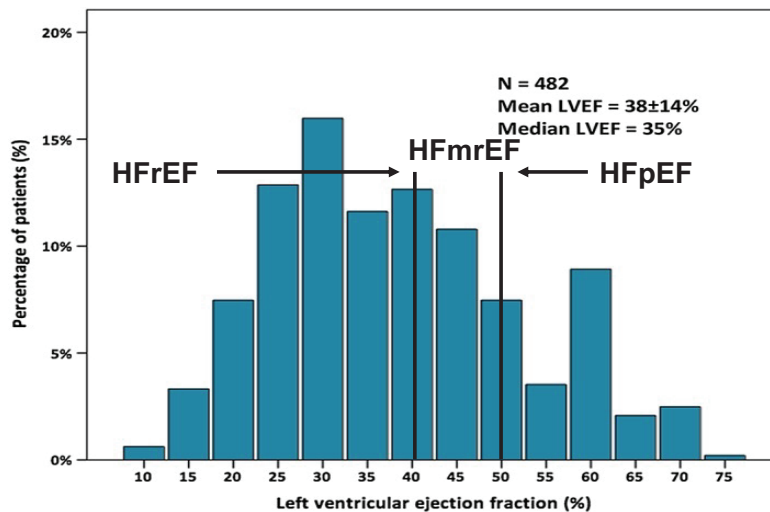
Improvement in NYHA Functional Class and KCCQ CSS with Sacubitril/Valsartan

	Sac/Val	Valsartan	Effect Size (95% CI)	P-value (2-sided)
NYHA class favorable change at 8 months – n	2316	2302		
Improved	15.0%	12.6%	OR, 1.45 (1.13 – 1.86)	0.004
Unchanged	76.3%	77.9%		
Worsened*	8.7%	9.6%		
KCCQ clinical summary score at 8 months – n	2250	2226		
LSM of change from baseline (SE)	-1.5 (0.4)	-2.5 (0.4)	Difference, 1.0 (0.0 – 2.1)	0.051
≥5 point Improvement	33.0%	29.6%		0.019
≥5 point Deterioration	33.5%	34.5%		0.467

February 21, 2021 US FDA Update

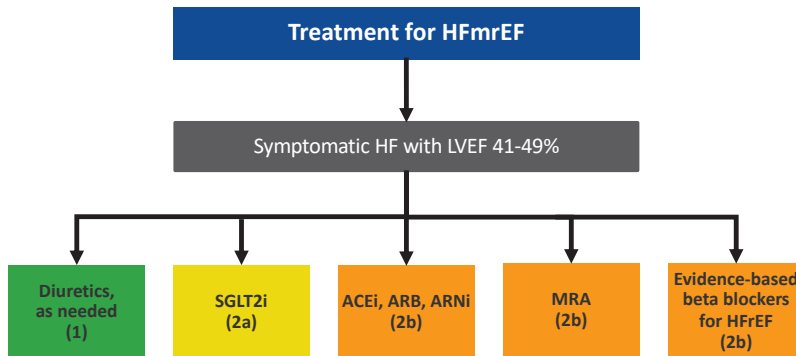
- Administration (FDA) has approved the following expanded indication for Entresto® (sacubitril/valsartan): to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure.
- Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.¹
- The label also states LVEF is a variable measure and clinical judgment should be used in deciding whom to treat.¹

Distribution of EF in HF Patients





Recommendations for Patients with HFmrEF (LVEF 40-49%)



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.

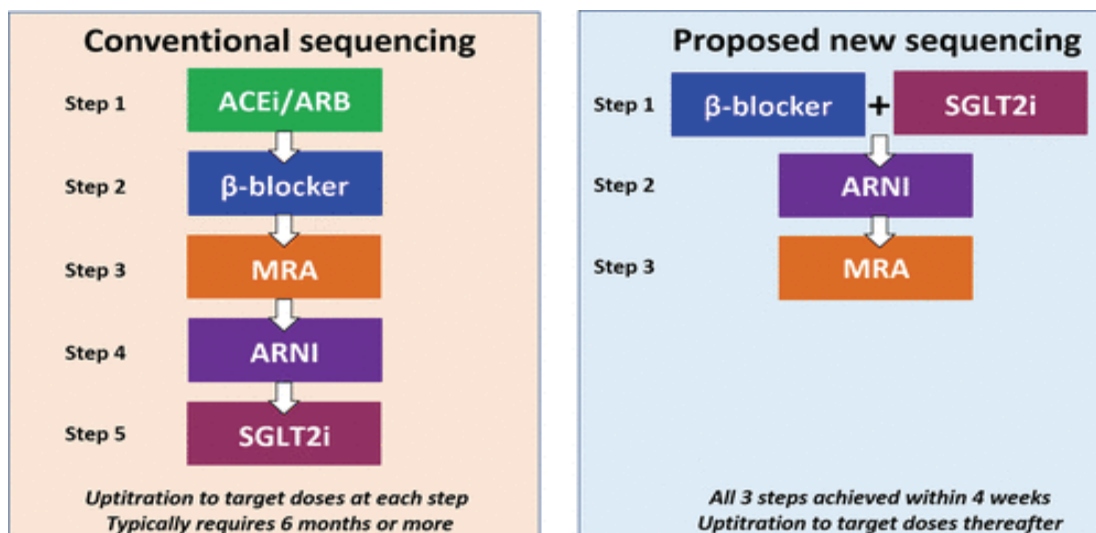
Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

New Recommendations for Treating HFmrEF (LVEF 40 – 49%)

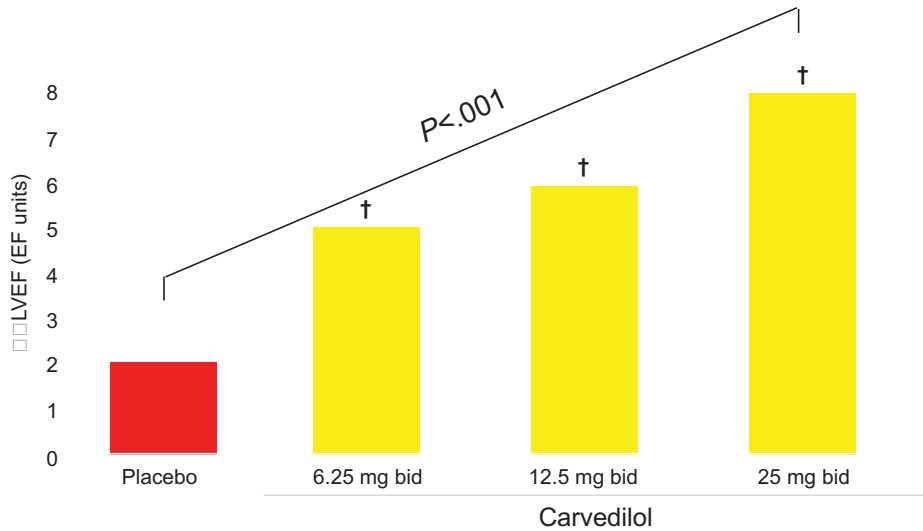
COR	LOE	Recommendations
2a	B - R	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality
2b	B - NR	Among patients with current or previous symptomatic HFmrEF, use of evidence-based beta blockers for HFrEF, ARNi, ACEi, or ARB, and MRAs may be considered, to reduce the risk of HF hospitalization and cardiovascular mortality, <u>particularly among patients with LVEF on the lower end of this spectrum</u>

Implementation of GDMT

Sequencing GDMT for Patients with Heart Failure



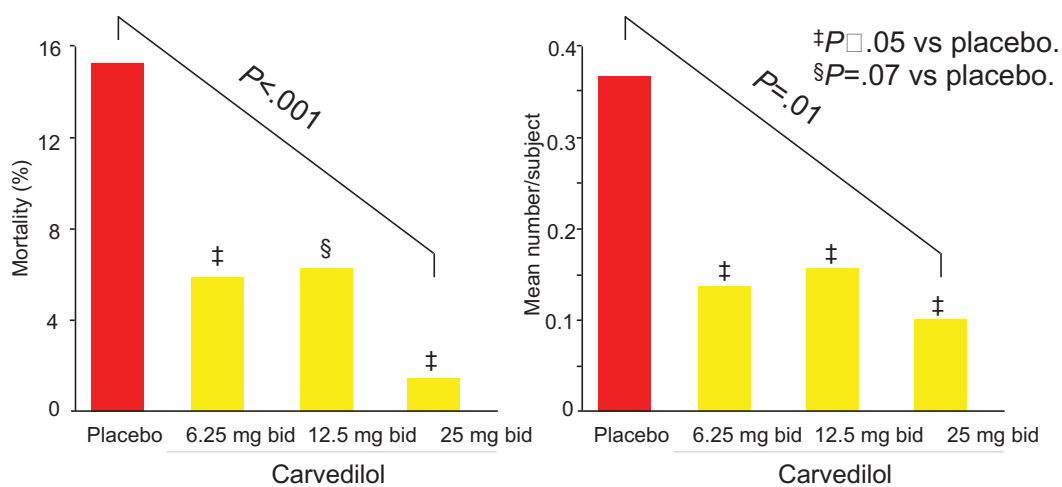
Effect of Carvedilol on Left Ventricular Ejection Fraction



Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n=261).
 †Multicenter Oral Carvedilol Heart Failure Assessment.

Adapted from Bristow MR., et al. *Circulation*. 1996;94:2807–2816.

Carvedilol Dose-Response Trial (MOCHA*): Effect on Mortality and Morbidity

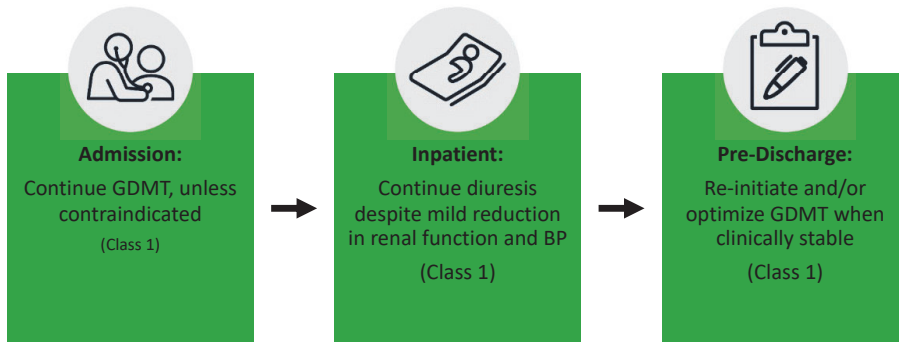


Adapted from Bristow MR., et al. *Circulation*. 1996;94:2807–2816.



GDMT During Hospitalization

Oral GDMT should be continued and optimized on admission, as doing so is associated with lower post-discharge death and readmission.



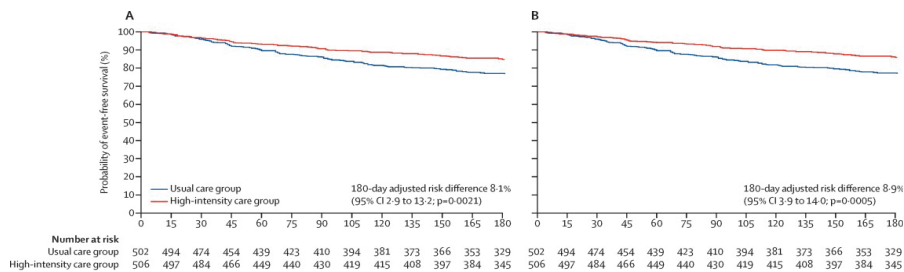
Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitor; AV, atrioventricular; BP, blood pressure; GDMT, guideline-directed medical therapy; and VTE, venous thromboembolism.



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

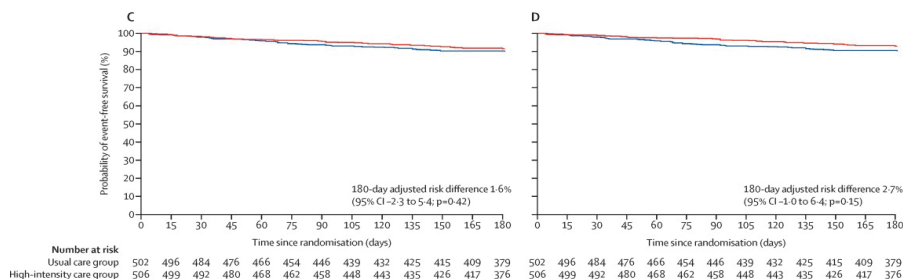
STRONG-HF: Improved Outcomes in the High-Intensity Care Group

HF readmission and all-cause mortality



HF readmission and all-cause mortality (excl. COVID-19 deaths)

All-cause mortality



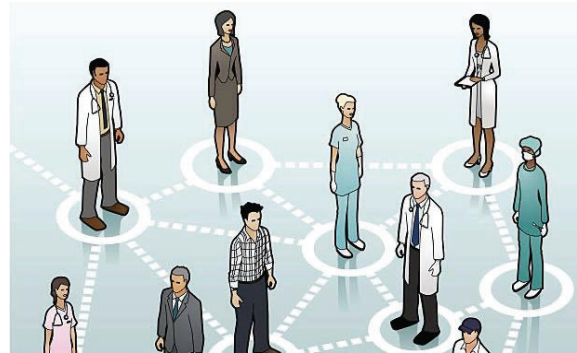
All-cause mortality (excl. COVID-deaths)



Recommendations for Disparities and Vulnerable Populations



COR	RECOMMENDATIONS
1	In vulnerable patient populations at risk for health disparities, HF risk assessments and multidisciplinary management strategies should target both known risks for CVD and social determinants of health, as a means toward elimination of disparate HF outcomes.



COR	RECOMMENDATIONS
1	Evidence of health disparities should be monitored and addressed at the clinical practice and the health care system levels.



Abbreviations: CVD indicates cardiovascular disease; and HF, heart failure.

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

Treating Chronic Heart Failure – Key Points

- Current guidelines identify therapies that can improve outcomes in a broad spectrum of patients with heart failure.
- Growing evidence that many of the available agents are effective regardless of left ventricular ejection fraction.
- The fact that beneficial effects can be observed early after starting treatment with drugs such as SGLT2 inhibitors should encourage early initiation.
- The failure to initiate and up-titrate effective heart failure therapies represents a missed opportunity to improve patient outcomes.

Thank you!

