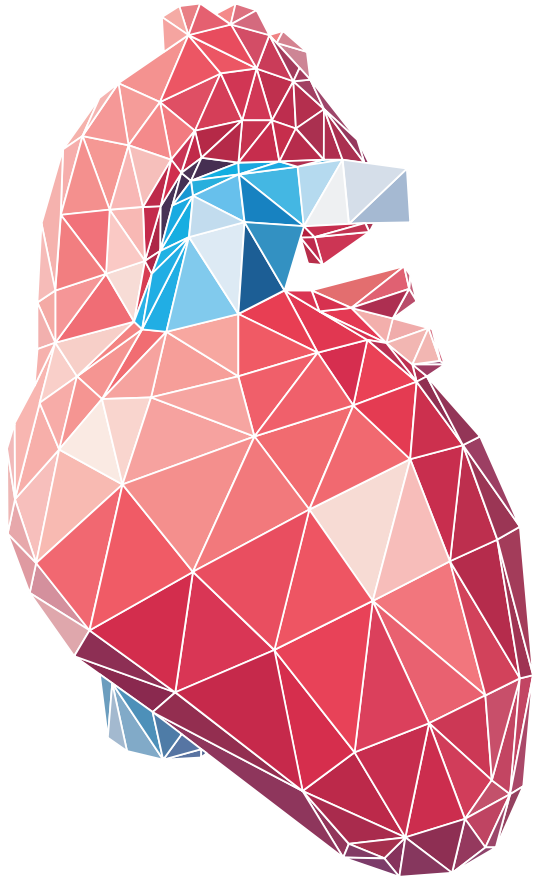


Heart Failure Overview

Classification of HF by LVEF

Type of HF according to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	• Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	• LVEF 41%–49% • Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	• LVEF ≥50% • Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

EF, ejection fraction; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. Circulationr4

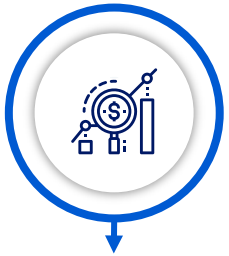
Burden of heart failure

HF continues to be a major cause of morbidity and mortality worldwide with a lifetime risk at age 40 years of ~20%[1]
Based on data from NHANES 2017 to 2020, ≈6.7 million Americans ≥20 years of age had HF[2]

Hospitalizations[2]

Hospitalizations for HF increased from 1,060,540 to 1,270,360 between 2008 to 2018

HFrEF (283,193 to 679,815)
HFpEF (189,260 to 495,095)



Medical Costs[2]

HF-associated medical costs between 2014 to 2020, were $24,383 per patient

The total cost of HF is projected to rise to $69.8 billion by 2030 (~127%)

Population Burden[2]

Expected to increase by 46% from 2012 to >8 million in 2030

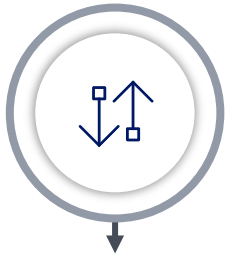
Diagnosis[2]

In 2019, there were 1,297,000 principal diagnosis hospital discharges for HF

Mortality[2]

In 2020, ~1 in 8 deaths in the US was HF associated

HF mortality increased by 48.6% compared to 2010



Incidence[3]

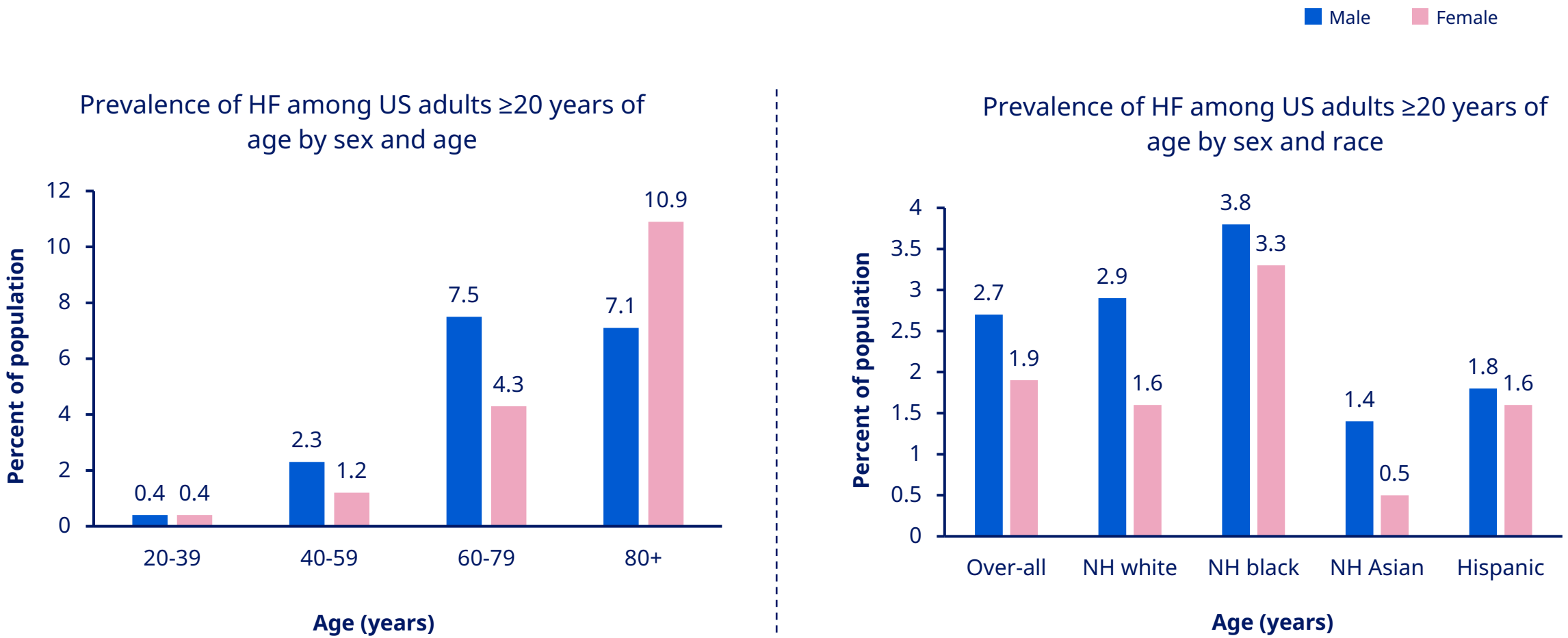
HFpEF is increasing at ~10% every 10 years relative to HFrEF

At present, >70% of patients with heart failure aged >65 years have a preserved ejection fraction

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NHANES, National Health and Nutrition Examination Survey

1. Kittleson MM et al. J Am Coll Cardiol. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393; 2. Tsao CW et al. Circulation. 2023;147:e93-e621; 3. Borlaug BA. Nat Rev Cardiol 2020;17:559–573

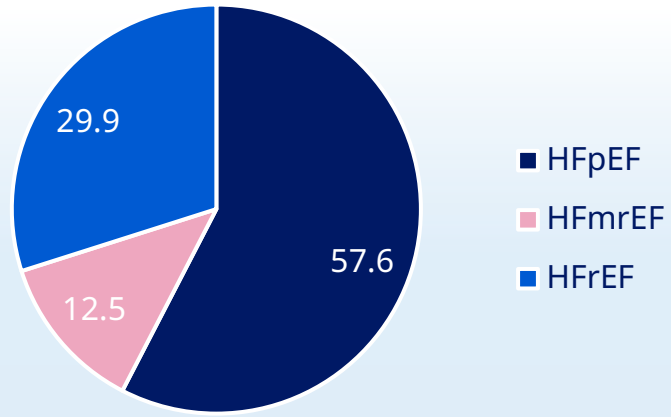
Prevalence of HF (NHANES, 2017–2020)



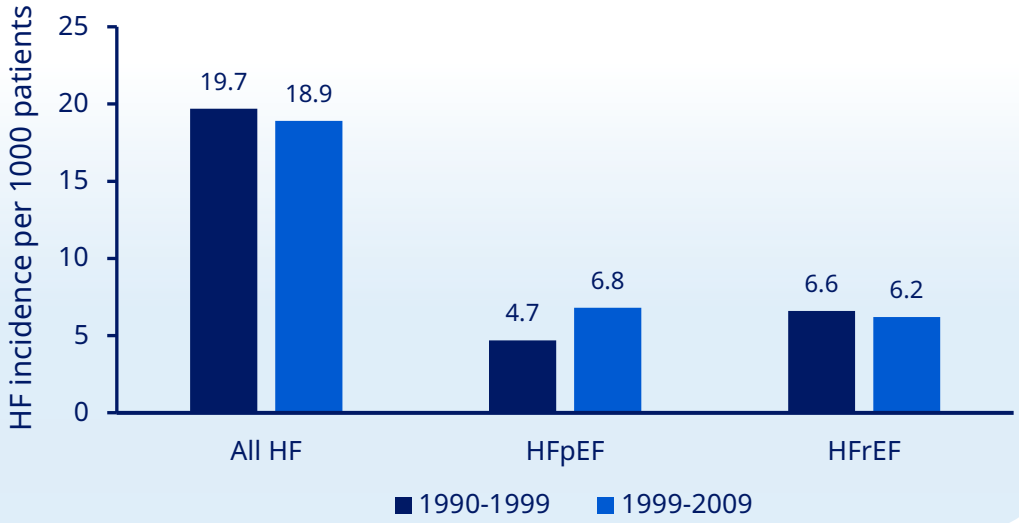
HF, heart failure; NHANES, National Health and Nutrition Examination Survey
Tsao CW et al. Circulation. 2023;147:e93-e621

Increasing prevalence of HFpEF

HF subtypes in the US[1]



HFrEF incidence declined across decades whereas HFpEF increased[2]



Prevalence of HFpEF vs HFrEF[3]

Increases by 10% every 10 years

Gap expected to widen due to[3]

- Ageing population
- Increasing prevalence of conditions associated with the development of HFpEF (e.g., obesity, hypertension, T2D)

EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes

1. Kumar V et al. J Card Fail. 2023;29(2):124-134; 2. Tsao CW et al. JACC Heart Fail. 2018;6(8):678-685; 3. Borlaug BA. Nat Rev Cardiol 2020;7:559–573

Heart Failure-Related Disparities Have Been Identified in Black Populations

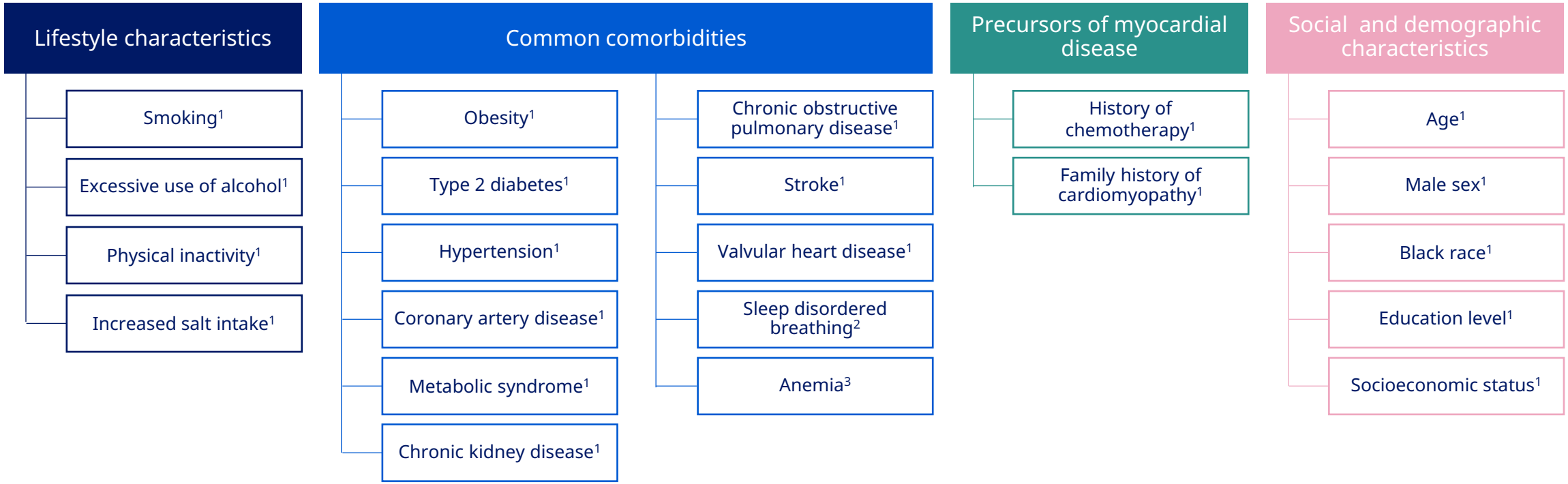
Heart failure

Systemic racism	Socio-behavioral factors	Structural factors	Multimorbidity	CV risk factors	Emerging risk factors
• Discrimination • Chronic stress • Access to care • Care delivery • Use of GDMT and advanced therapies	• Self efficacy • Health literacy • Childhood experiences • Family structure • Social isolation	• Food insecurity • Food deserts • Neighborhood safety and walkability • Poverty • Housing • Underemployment	• Asthma • Cancer • Musculoskeletal diseases • Mental illness	• Obesity • Type 2 diabetes • Sedentary lifestyle • Smoking • Hyperlipidemia	• ATTR cardiomyopathy • HCM genetic profile • Genetic contributors to heart failure manifestations

Organization | Community | Interpersonal | Individual | Public policy

CV, cardiovascular; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; ATTR, transthyretin amyloid.
Roger VL. Circ Res. 2021;128:1421-1434.

Risk Factors For Heart Failure



**Most important comorbidities for predicting risk of heart failure in existing risk models.*

1. Yang H et al. Open Heart. 2015;2:e000222; 2. Cowie MR and Gallagher AM. JACC: Heart Failure 2017;5:715–723; 3. Felker GM et al. J Am Coll Cardiol. 2004;44:959–966

Risk factors and comorbidities involved with HFpEF, HFmrEF and/or HFrEF

Phenotype, risk of cause-specific outcomes[1]

	HFrEF	HFmrEF	HFpEF
Phenotype			
Age	↑	↑↑	↑↑↑
Atrial fibrillation	↑	↑↑	↑↑↑
Chronic kidney disease	↑↑	↑↑	↑↑↑
Female	↓↓	↓	↑
Hypertension	↑	↑↑	↑↑↑
Ischemic heart disease	↑↑↑	↑↑↑	↑
Natriuretic peptide levels	↑↑↑	↑	↑
Prognosis			
CV risk	↑↑↑	↑	↑
Non-CV risk	↑	↑	↑↑

HFpEF and HFrEF share many risk factors, but some comorbidities differ[2]

HFrEF is often preceded by acute or chronic loss of cardiomyocytes due to

- Ischemia
- Genetic mutation
- Myocarditis
- Valvular disease

HFpEF is preceded by chronic comorbidities, such as

- Hypertension
- T2DM
- Obesity
- Renal insufficiency

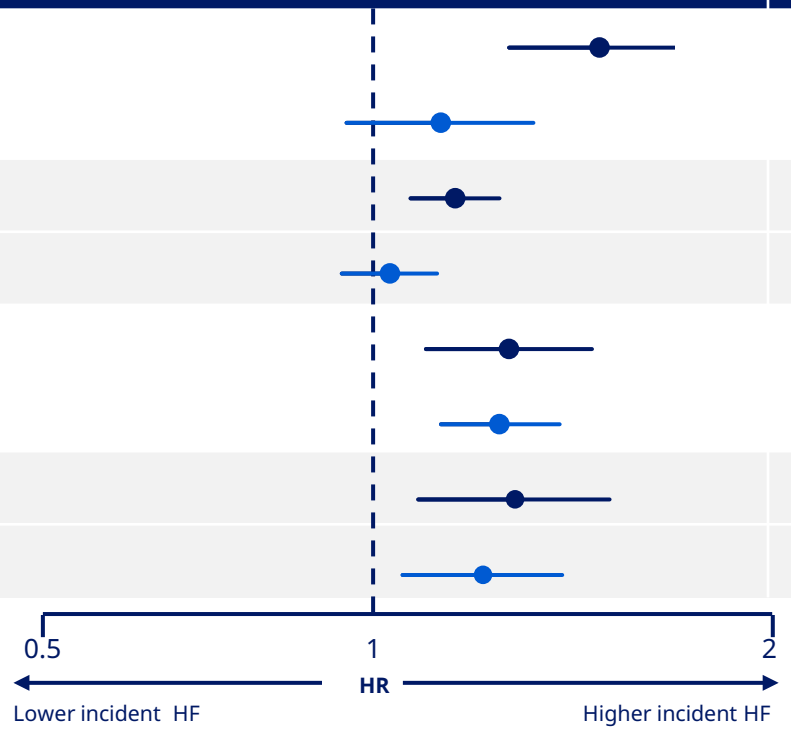
Patients with HFpEF

- are more likely to be older and with a two-fold predominance of females
- have a higher prevalence of non-cardiac comorbidities and higher incidence of hospitalization for comorbidity-related illness

↑ and ↓ denote higher or more common and lower or less common, respectively,
CV, cardiovascular disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus
1. Savarese G et al. Nat Rev Cardiol 2022;19:100–116; 2. Simmonds SJ et al. Cells 2020;9:242

BMI association with HF subtypes

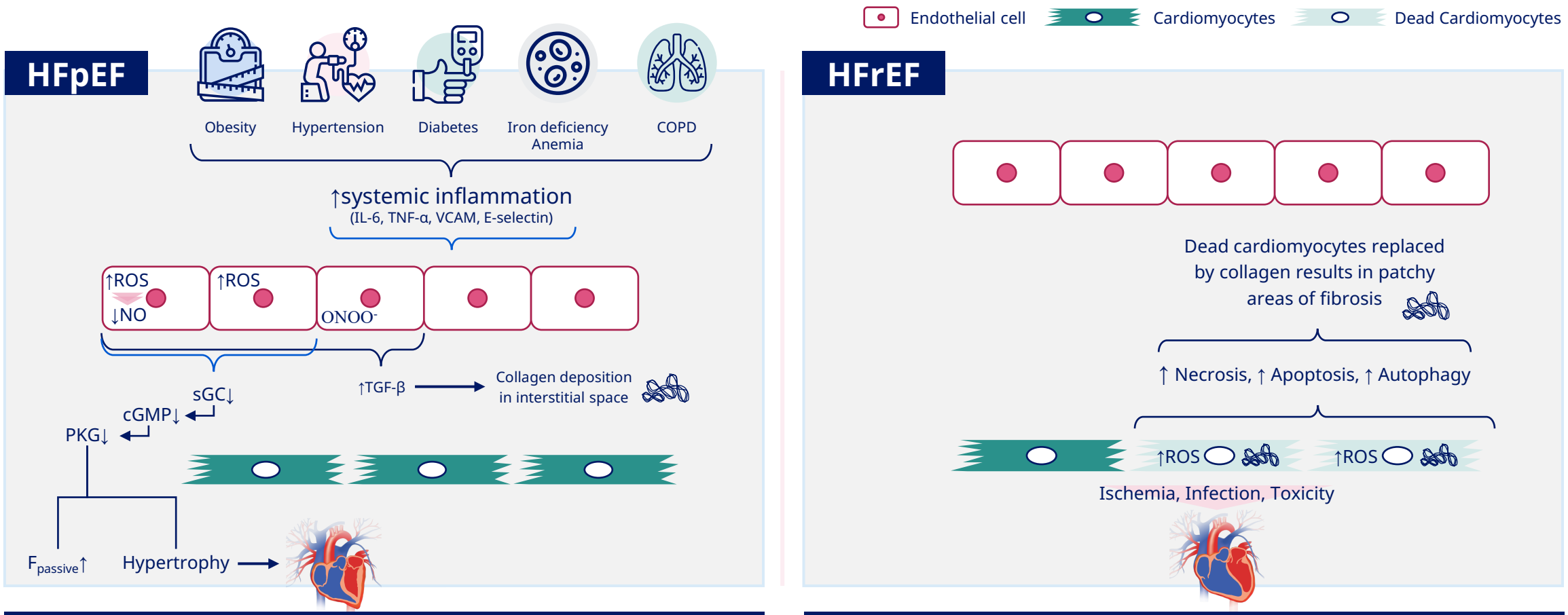
Cohort	Mean BMI (SD) kg/m^2	Outcome	HR (95% CI)	P-value
FHS	27.9 (5.1)	Incident HFpEF	1.69 (1.37 - 2.08)	<0.0001
		Incident HFrEF	1.17 (0.94 - 1.45)	0.17
CHS	26.7 (4.7)	Incident HFpEF	1.21 (1.09 - 1.34)	0.001
		Incident HFrEF	1.04 (0.93 - 1.16)	0.52
PREVEND	26.1 (4.2)	Incident HFpEF	1.37 (1.13 - 1.66)	0.002
		Incident HFrEF	1.34 (1.17 - 1.54)	<0.0001
MESA	28.3 (5.5)	Incident HFpEF	1.39 (1.11 - 1.73)	0.004
		Incident HFrEF	1.29 (1.07 - 1.55)	0.008



Greater BMI portended higher risk of HFpEF compared with HFrEF in community-based cohort studies

BMI, body mass index; CI, confidence interval; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; HF, heart failure; HR, hazard ratio; HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction; MESA, Multi-Ethnic Study of Atherosclerosis; PREVEND, Prevention of Renal and Vascular End stage Disease
Savji N et al. JACC Heart Fail. 2018;6(8):701-709- Supplementary

Myocardial dysfunction and remodeling in HFpEF and HFrEF



Concentric hypertrophy, increased LV relative wall thickness

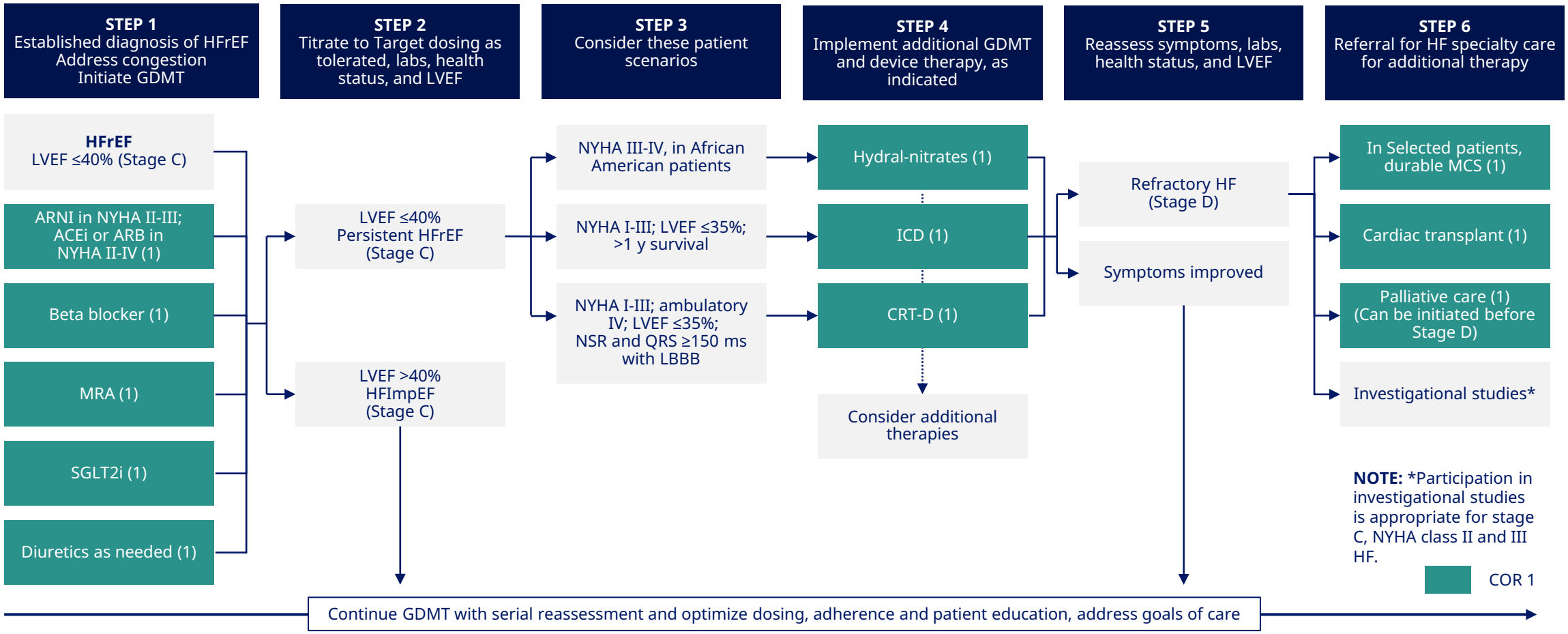
Progressive loss of cardiomyocytes, LV dilation and eccentric LV remodeling

cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; IL-6, interleukin-6; LV, left ventricular; NO, nitric oxide; ONOO-, peroxynitrite; PKG, protein kinase G; TGF-β, transforming growth factor; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; VCAM, vascular cell adhesion molecule

Paulus W et al. J Am Coll Cardiol. 2013;62:263–71

Treatment of HFrEF Stages C and D

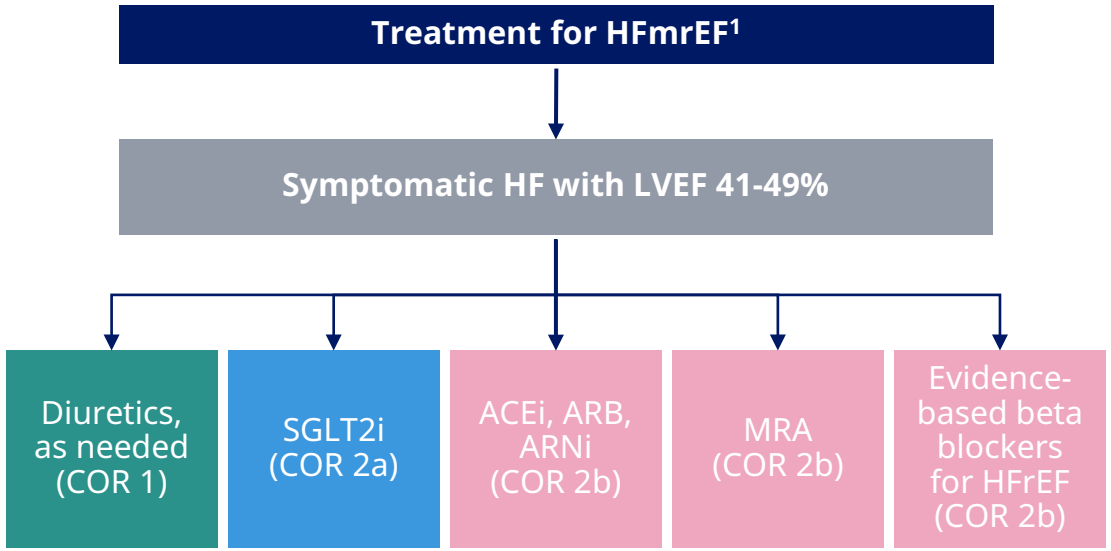
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

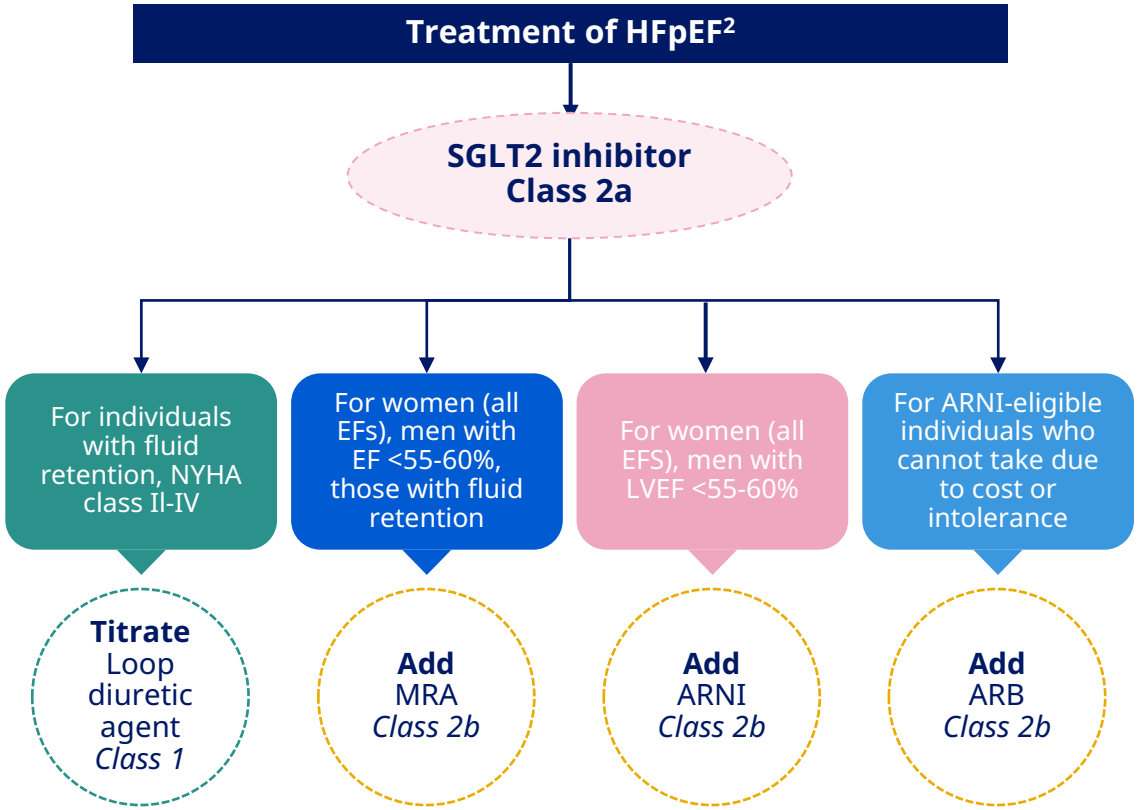


ACC, American College of Cardiology; ACEi indicates angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; COR, class of recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFSA, Heart Failure Society of America; 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.

Recommendations for Patients with Mildly Reduced LVEF or preserved LVEF





In patients with HFimpEF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic (COR 1)

ACEi, Angiotensin-converting enzyme inhibitors; ARB indicates angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; COR, class of recommendation; EF, ejection fraction; MRA, mineralocorticoid antagonist; 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; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor

1. Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. Circulation; 2. Kittleson MM et al. J Am Coll Cardiol. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393

Key Unmet need in HF

Sub type	Existing Therapy	Unmet need
HFpEF 	• Dapagliflozin and Empagliflozin have proven benefit for CV mortality and HHF[1] • MRAs significantly improve measures of diastolic function in individuals with HFpEF[1] • Exercise and weight loss are recommended to target the pathophysiology and contributing comorbidities[1] • Sacubitril/valsartan is approved for use in HFpEF. ARB may be used when an ARNI is contraindicated[1]	• Heterogenous disorder with focus on management of comorbidities[1] • Increasing prevalence and substantial morbidity and mortality[3] • >70% of HF patients older than 65 years have HFpEF[3] • Increasing prevalence of conditions associated with the development of HFpEF (e.g., obesity, T2D)[3] • Treatment options are currently limited[3]
HFrEF 	• Inhibition of the renin-angiotensin system is recommended to reduce morbidity and mortality for patients with HFrEF, and ARNi, ACEi, or ARB are recommended as first-line therapy[2] • Other recommended therapies include beta blockers, SGLT2i and loop diuretics (as needed)[2]	• Mortality rates continue to remain high (~75%) • Few patients with HFrEF are treated with recommended doses of evidence-based therapies[4] • The proportion of patients receiving guideline-recommended doses of ACE inhibitors and β-blockers is as low as 22% and 12% respectively[4]

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; MRA, mineralocorticoid receptor antagonists; QoL, quality of life; T2D, type 2 diabetes

1. Kittleson MM et al. J Am Coll Cardiol. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393; 2. Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. Circulation;3. Borlaug BA. Nat Rev Cardiol 2020;7:559–573; 4. Lam CSP et al. J Am Heart Assoc. 2019;8:e013389.

Products approved for management of HF*

Product	Indication
Sacubitril/valsartan brand name: Entresto[1]	• To reduce the risk of CV death and HHF in adult patients with chronic HF (Benefits are most clearly evident in patients with LVEF below normal) • For the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older • ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.
Dapagliflozin Brand name: Farxiga[2]	• To reduce the risk of sustained eGFR decline, ESKD, CV death, and HHF in adults with CKD at risk of progression • To reduce the risk of CV death, HHF, and urgent HF visit in adults with HF • To reduce the risk of HHF in adults with T2D and either established CV disease or multiple CV risk factors • As an adjunct to diet and exercise to improve glycemic control in adults with T2D
Empagliflozin Brand name: Jardiance[3]	• To reduce the risk of CV death and HHF in adults with HF • To reduce the risk of sustained decline in eGFR, ESKD, CV death, and hospitalization in adults with CKD at risk of progression • To reduce the risk of CV death in adults with T2D and established CVD • As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with T2D
Sotagliflozin Brand name: Inpefa[4]	• To reduce the risk of CV death, HHF, and urgent heart failure visit in adults with heart failure or T2D, CKD, and other CV risk factors
Vericiguat Brand name: Verquvo[5]	• To reduce the risk of CV death and HF hospitalization following a HHF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%

**As of February 2024*
CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; T2D, type 2 diabetes
1. Entresto. label (fda.gov); 2. Farxiga. label (fda.gov); 3. Jardiance. label (fda.gov); 4. Inpefa. label (fda.gov); 5. Verquvo. label (fda.gov)