

Heart Failure Overview



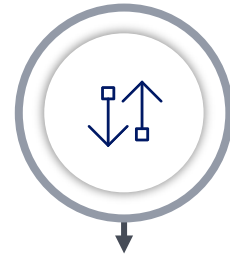
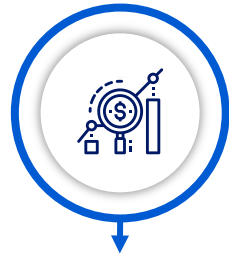
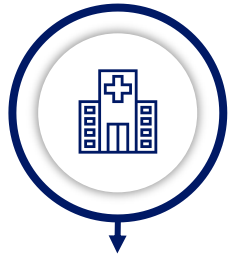
Classification of HF by LVEF

Type of HF according to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF \leq 40%
HFimpEF (HF with improved EF)	<ul style="list-style-type: none"> • Previous LVEF \leq40% and a follow-up measurement of LVEF $>$40%
HFmrEF (HF with mildly reduced EF)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • LVEF \geq50% • Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)



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 HF²



Hospitalizations ²	Medical Costs ²	Population Burden ²	Diagnosis ²	Mortality ²	Incidence ³
Hospitalizations for HF increased from 1,060,540 to 1,270,360 between 2008 to 2018 HF _r EF (283,193 to 679,815) HF _p EF (189,260 to 495,095)	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%)	Expected to increase by 46% from 2012 to >8 million in 2030	In 2019, there were 1,297,000 principal diagnosis hospital discharges for HF	In 2020, ~1 in 8 deaths in the US was HF associated HF mortality increased by 48.6% compared to 2010	HF _p EF is increasing at ~10% every 10 years relative to HF _r EF At present, >70% of patients with heart failure aged >65 years have a preserved ejection fraction

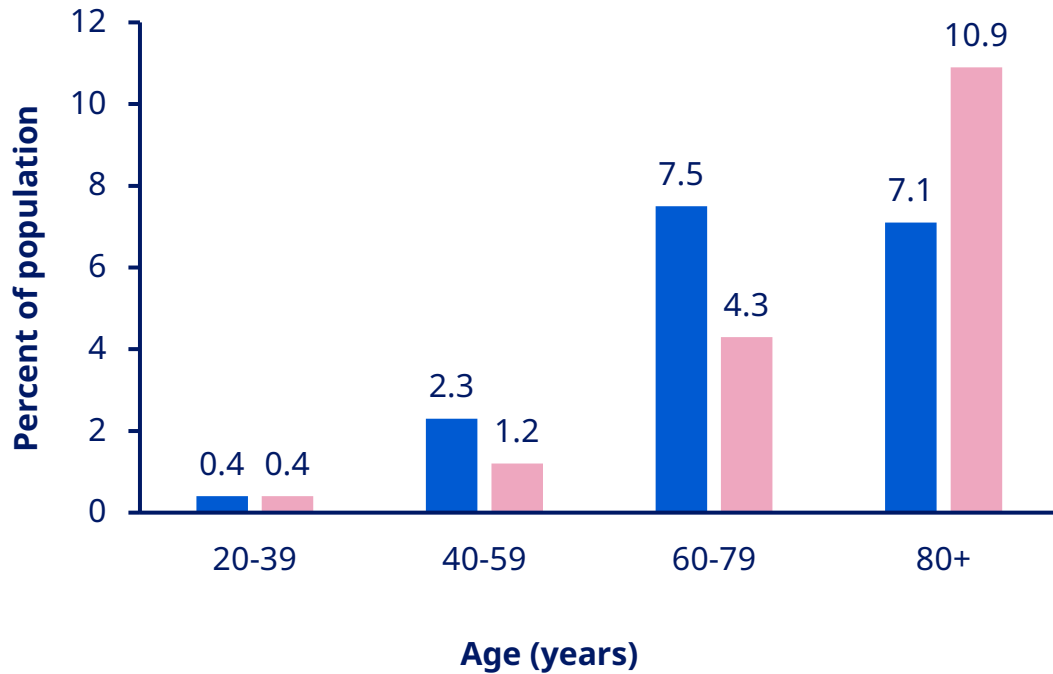


HF, heart failure; HF_rEF, heart failure with reduced ejection fraction; HF_pEF, heart failure with preserved ejection fraction; NHANES, National Health and Nutrition Examination Survey
 1. Kittleson MM et al. J Am Coll Cardiol. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393; 2. Tsao CW et al. Circulation. 2023;147:e93-e621; 3. Borlaug BA. Nat Rev Cardiol 2020;17:559-573

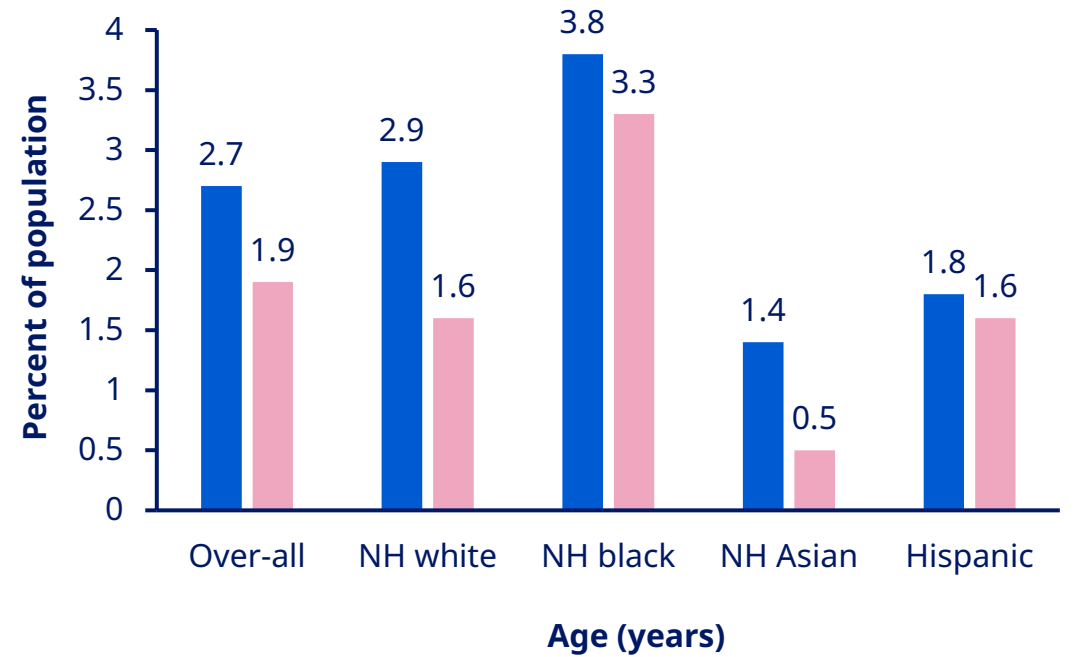
Prevalence of HF (NHANES, 2017–2020)

Male Female

Prevalence of HF among US adults ≥20 years of age by sex and age



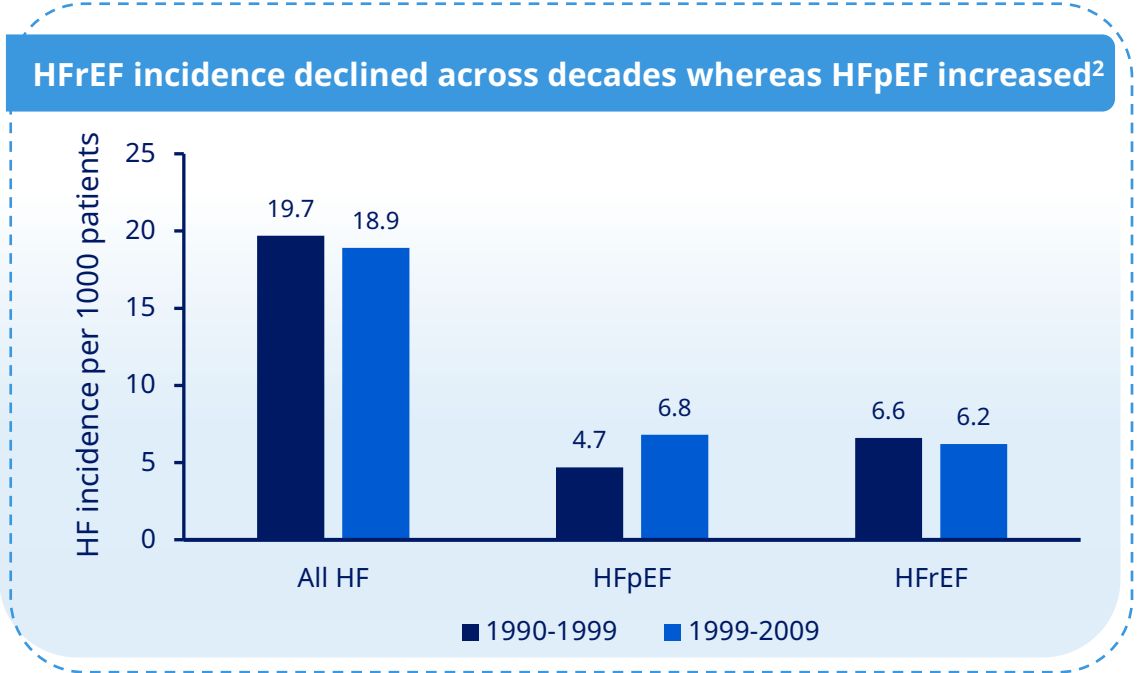
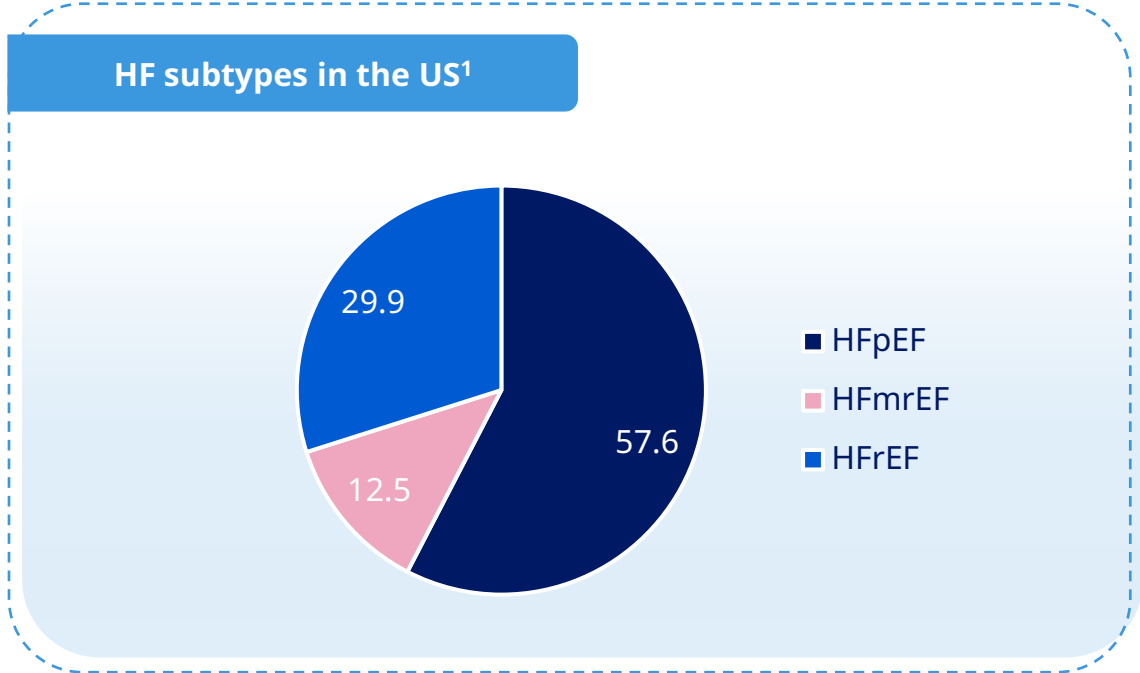
Prevalence of HF among US adults ≥20 years of age by sex and race



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



Increasing prevalence of HFpEF



Prevalence of HFpEF vs HFrfEF³
Increases by 10% every 10 years

Gap expected to widen due to³

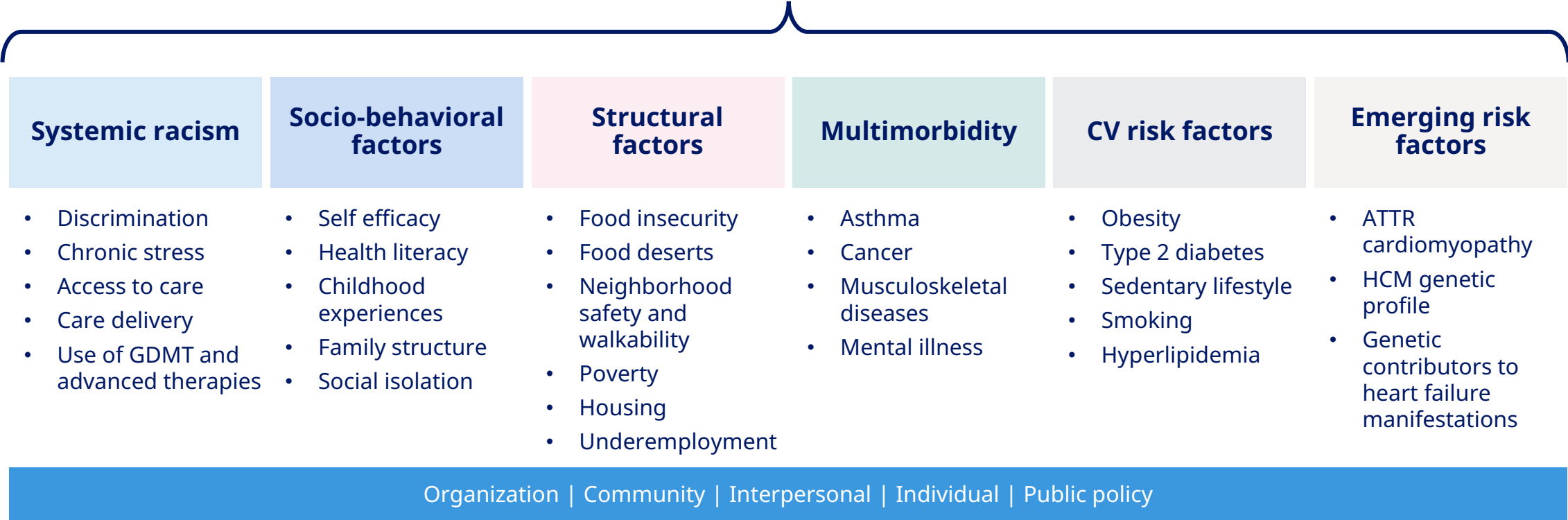
- Ageing population
- Increasing prevalence of conditions associated with the development of HFpEF (e.g., obesity, hypertension, T2D)



EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrfEF, 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

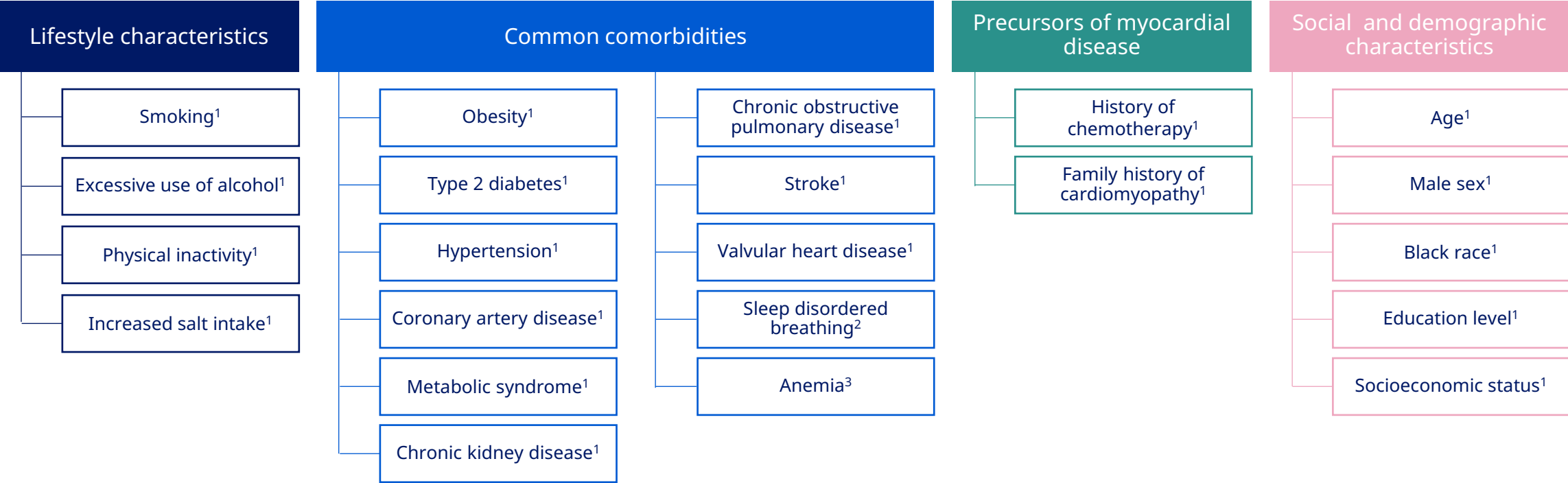
Heart failure



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 outcomes¹

	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 differ²

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

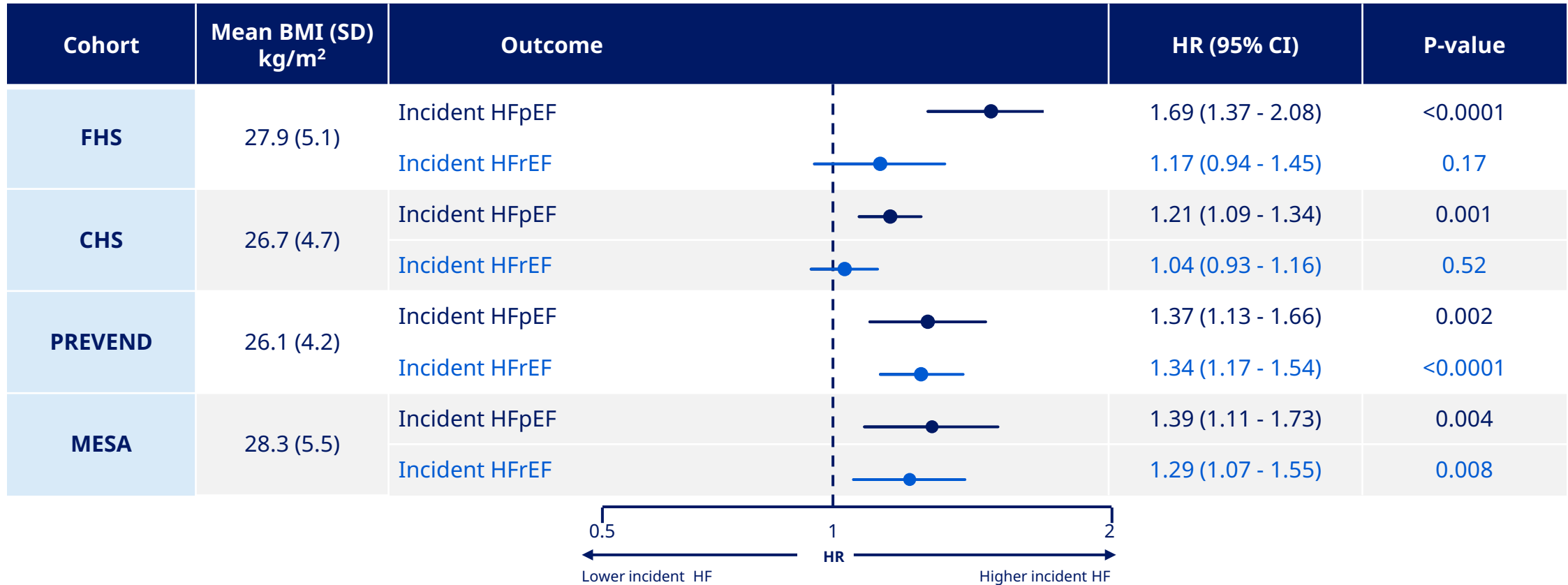
- are more likely to be older and with a two-fold predominance of females
- have a higher prevalence of non-cardiac comorbidities and higher incidence of hospitalization for comorbidity-related illness



↑ 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

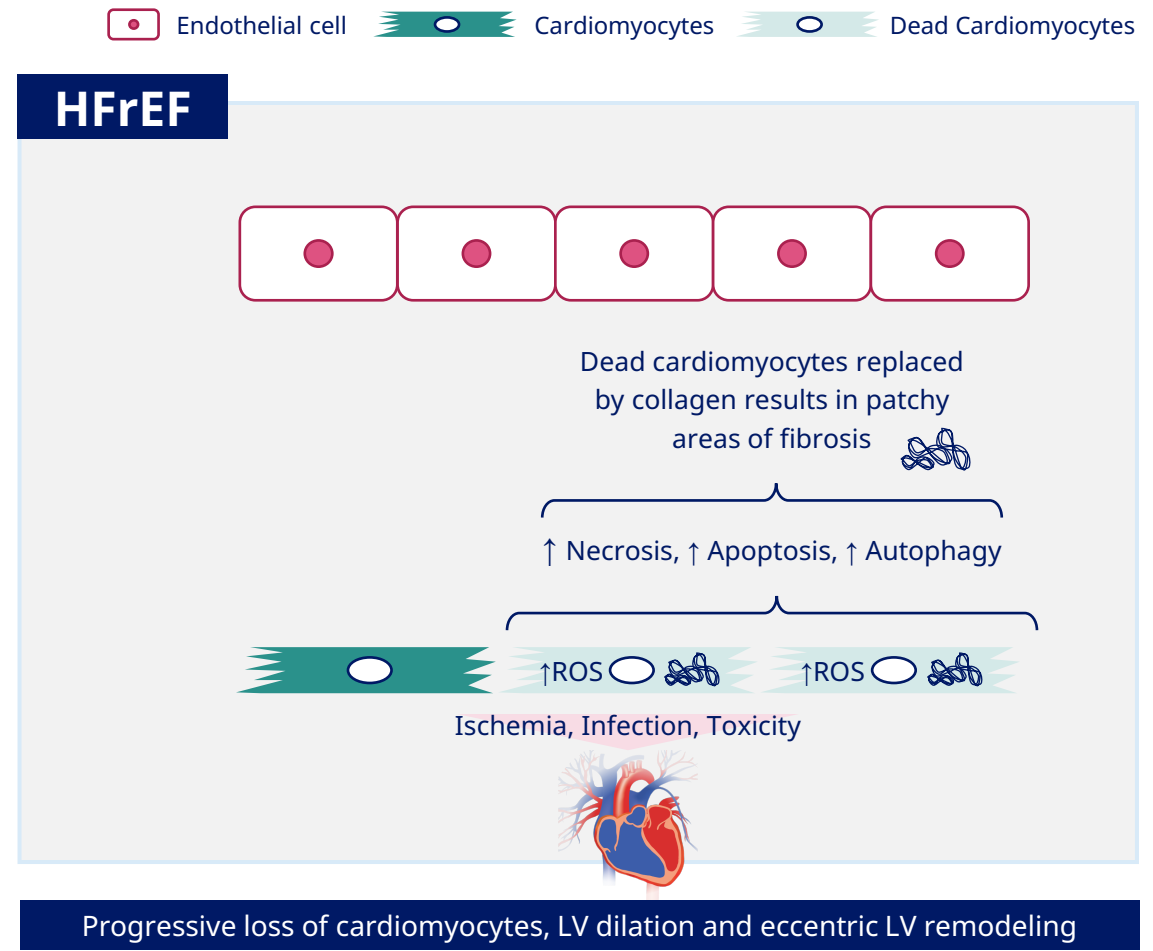
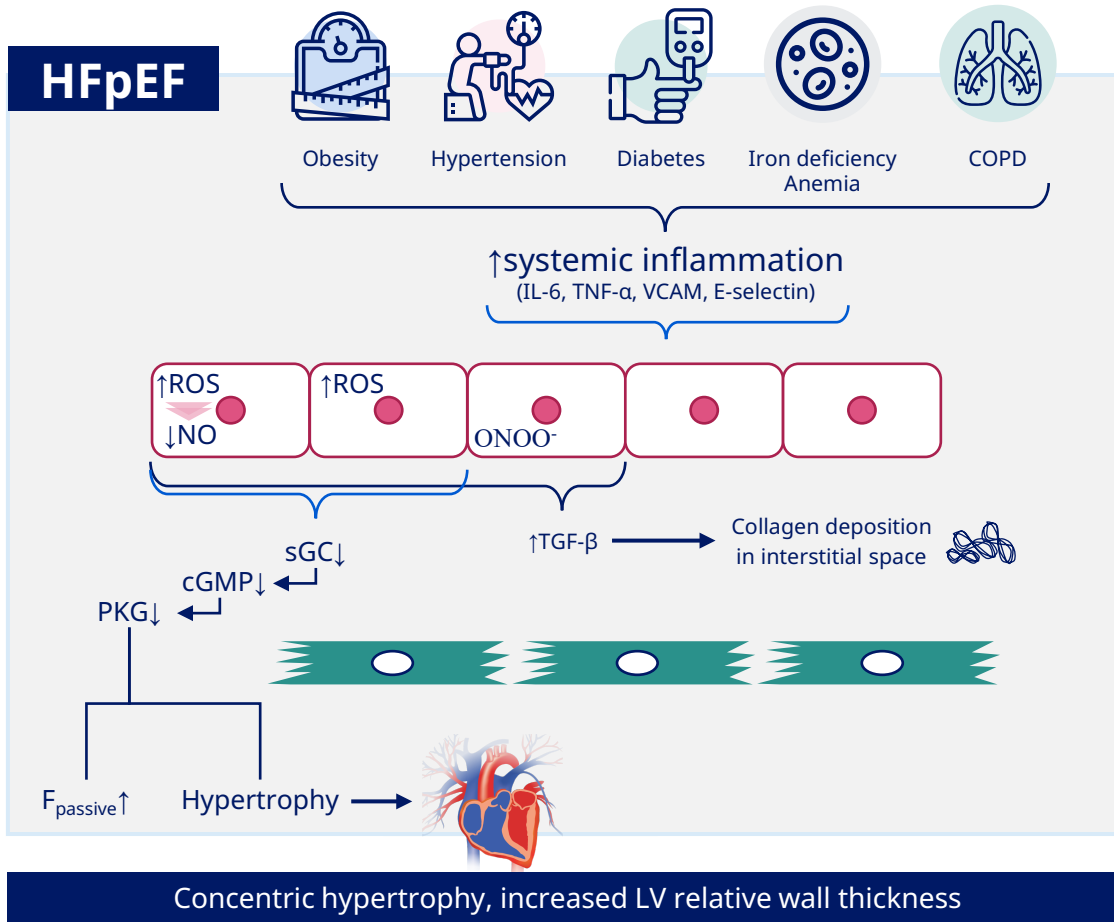


Greater BMI portended higher risk of HFpEF compared with HFrEF in community-based cohort studies

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

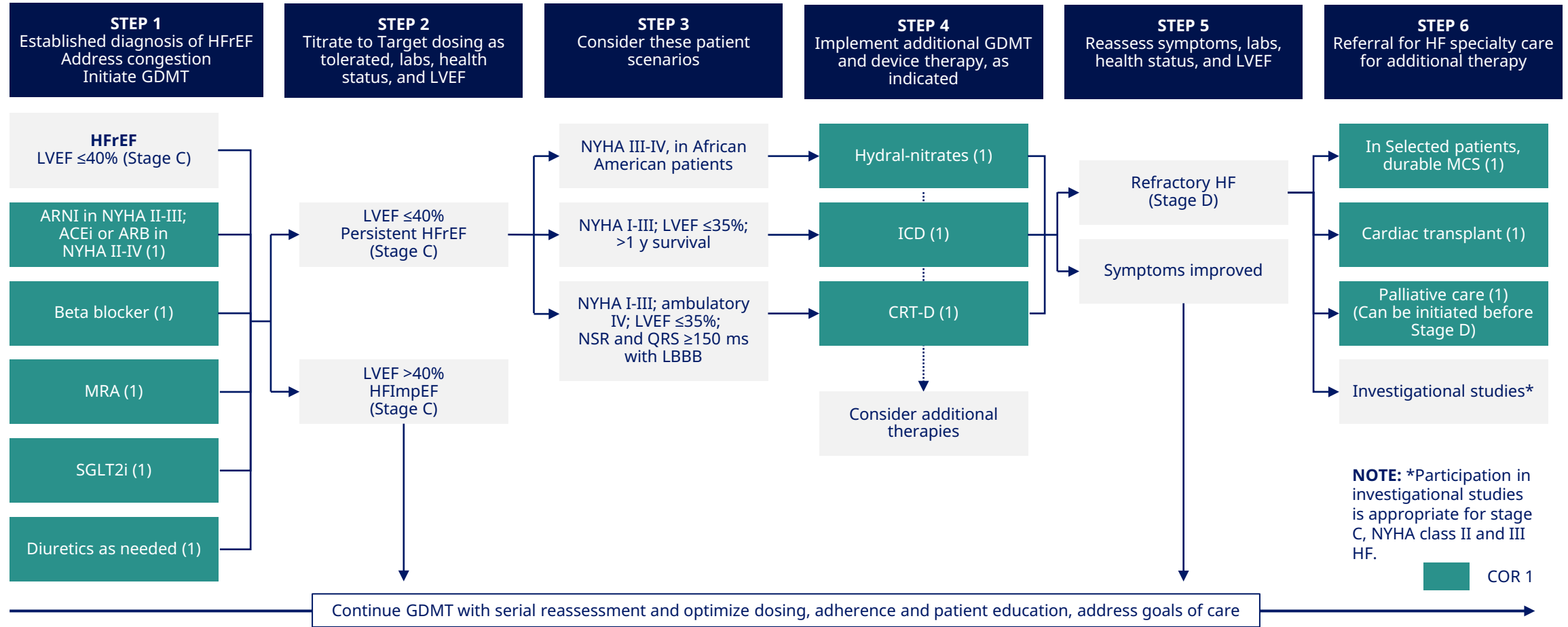


cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; IL-6, interleukin-6; LV, left ventricular; NO, nitric oxide; ONOO⁻, peroxynitrite; PKG, protein kinase G; TGF-β, transforming 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

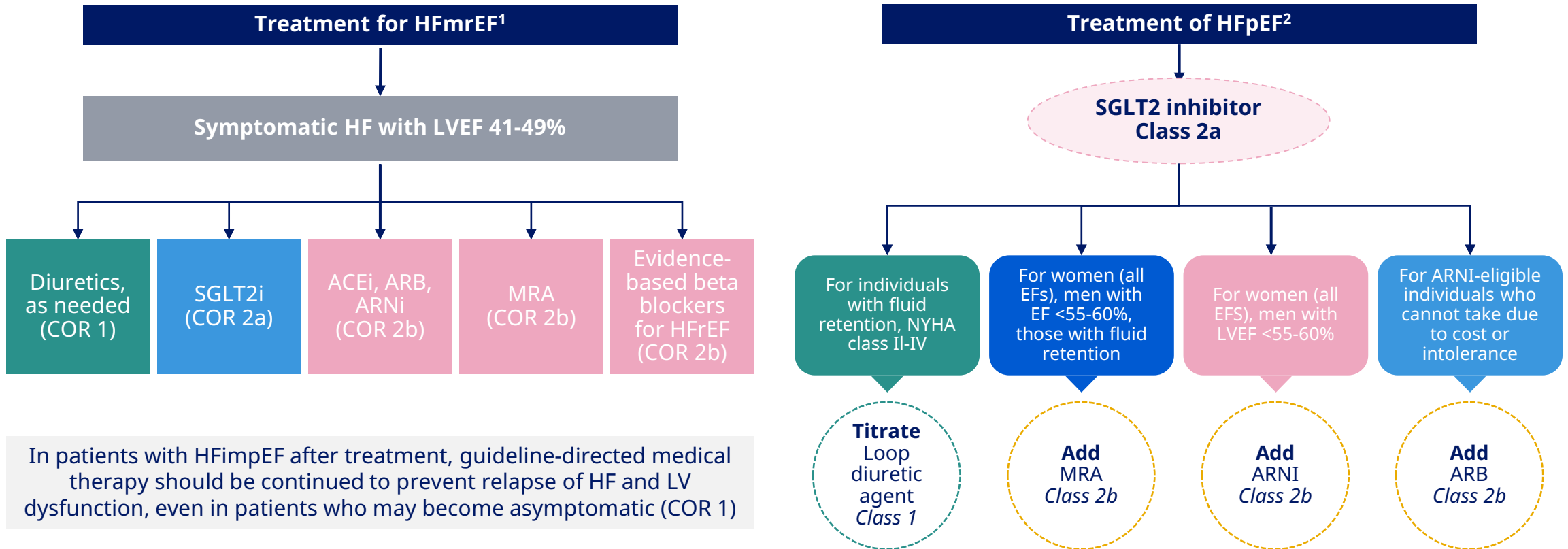


ACC, American College of Cardiology; ACEi indicates angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; COR, class of recommendation; GDMT, guideline-directed 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



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; 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

HFpEF



Existing Therapy

- Dapagliflozin and Empagliflozin have proven benefit for CV mortality and HHF¹
- MRAs significantly improve measures of diastolic function in individuals with HFpEF¹
- Exercise and weight loss are recommended to target the pathophysiology and contributing comorbidities¹
- Sacubitril/valsartan is approved for use in HFpEF. ARB may be used when an ARNI is contraindicated¹

Unmet need

- Heterogenous disorder with focus on management of comorbidities¹
- Increasing prevalence and substantial morbidity and mortality³
- >70% of HF patients older than 65 years have HFpEF³
- Increasing prevalence of conditions associated with the development of HFpEF (e.g., obesity, T2D)³
- Treatment options are currently limited³

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 therapy²
- 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 therapies⁴
- The proportion of patients receiving guideline-recommended doses of ACE inhibitors and β -blockers is as low as 22% and 12% respectively⁴

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: Entresto¹	<ul style="list-style-type: none"> 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: Farxiga²	<ul style="list-style-type: none"> 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: Jardiance³	<ul style="list-style-type: none"> 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: Inpefa⁴	<ul style="list-style-type: none"> 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: Verquvo⁵	<ul style="list-style-type: none"> 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 \(fda.gov\)](https://www.fda.gov/label); 2. Farxiga. [label \(fda.gov\)](https://www.fda.gov/label); 3. Jardiance. [label \(fda.gov\)](https://www.fda.gov/label); 4. Inpefa. [label \(fda.gov\)](https://www.fda.gov/label); 5. Verquvo. [label \(fda.gov\)](https://www.fda.gov/label)

