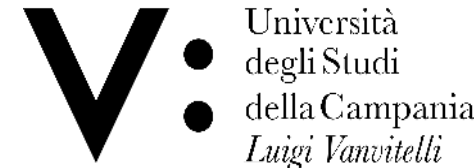


Scompenso Cardiaco Cronico: epidemiologia e opzioni di trattamento

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Definition of Heart Failure (HF)



Definition

The heart is unable to pump an adequate amount of blood with enough pressure and volume to meet the metabolic needs of the body

Clinical: HF is a **clinical syndrome** characterized by typical symptoms and signs caused by a structural and/or functional cardiac abnormality which leads to a reduced cardiac output and/or elevated intracardiac pressure at rest or during stress.

Heart Failure is a growing public health problem, with high morbidity and mortality

BURDEN

HF affects
~64 million
people
worldwide¹



Over **50%** of patients
with HF have **HFpEF**²

HOSPITALIZATION



HF is the **number one cause of hospitalization** in people >65 years^{2,a}



hHF is **projected to rise by ~50%** over the next 25 years³

MORTALITY



The 5-year mortality rate for patients with HF is **~50%**⁴

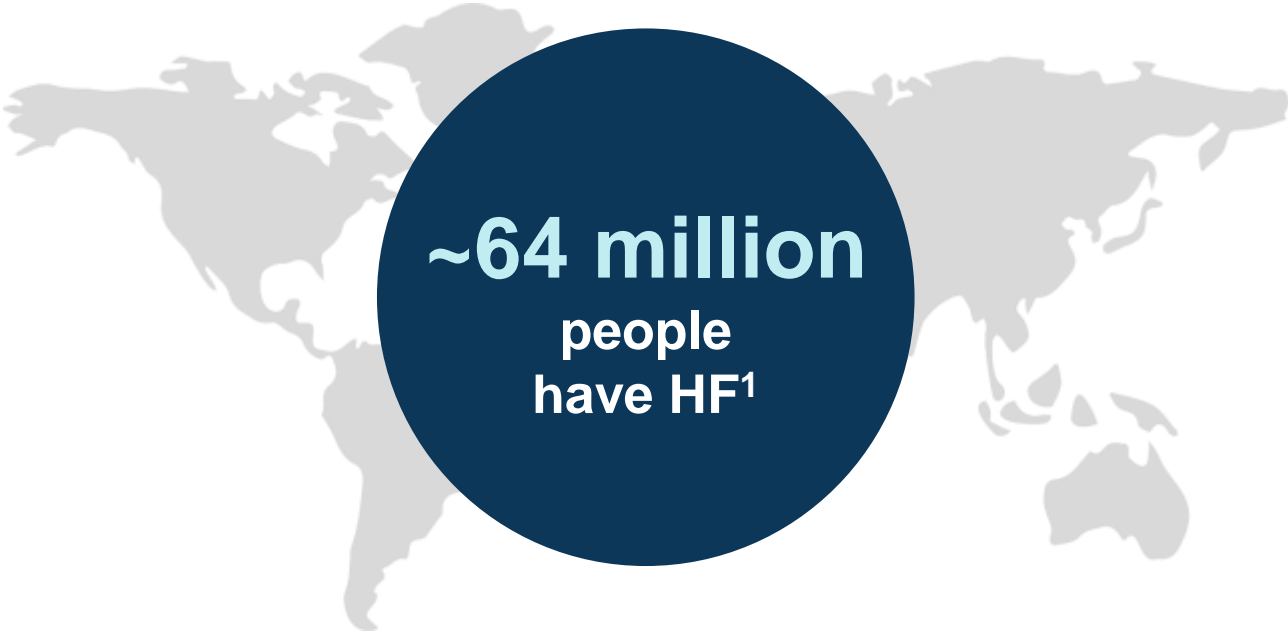


Mortality significantly increases after each HF readmission⁵

^aIn developed countries.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2018;392(10159):1789-1858; 2. Cowie MR et al. ESC Heart Fail. 2014;1(2):110-145; 3. Groenewegen A et al. Eur J Heart Fail. 2020;22(8):1342-1356; 55; 4. Jones NR et al. Eur J Heart Fail. 2019;21(11):1306-1325; 5. Setoguchi S et al. Am Heart J. 2007;154(2):260-266;

Heart Failure is a major public health problem worldwide



~64 million
people
have HF¹



Projected **~24% rise in cases** between 2012 and 2030²



5-year **mortality rate ~50%**³



HF **mortality risk is similar** to some of the common cancers in both men and women⁴



Economic burden **~350 billion US dollars**²



Over 50% of patients with HF have **HFpEF**⁵

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; US = United States.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2018;392:1789-1858; 2. Lippi G et al. *AME Med J*. 2020;5:15; 3. Jones NR et al. *Eur J Heart Fail*. 2019;21:1306-1325; 4. Mamas AM et al. *Eur J Heart Fail*. 2017;19:1095-1104; 5. Omote K et al. *Annu Rev Med*. 2022;73:321-337.



US Data

Heart Failure is a major public health problem in Italy



Over 850,000 people suffer from HF and its prevalence doubles with every decade of age (10% in people over 65y of age)^{1,5}



HF costs are estimated to be ~11,000€/pt/year (76% of costs are hospitalization-related) representing 2.4% of total national healthcare spending^{2,3}

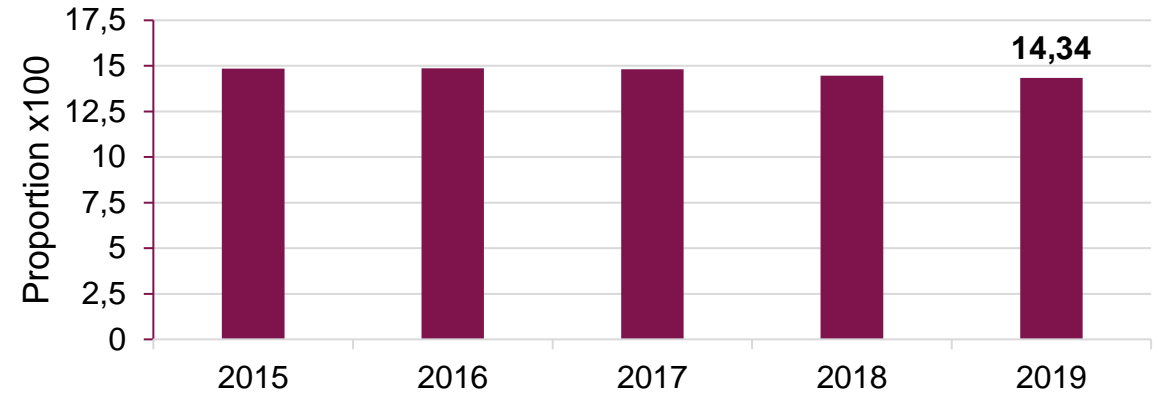


~200,000 hospitalization/year, of which 76.2% are for congestive HF^a

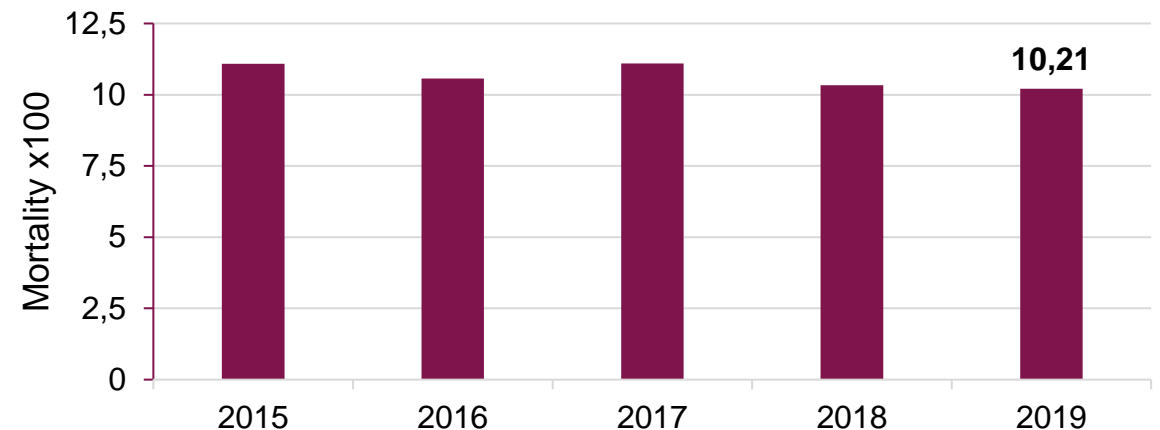


~14% of patients are readmitted and ~10% of patients die within 30 days after an hHF⁴

Congestive HF: hospital readmission 30 days after hospitalization



Congestive HF: mortality 30 days after hospitalization



^a congestive HF requiring IV diuretics therapy

HF = heart failure; hHF = hospitalization for HF; HF = heart failure; HFpEF = heart failure with preserved ejection fraction

1. <https://www.salute.gov.it>; 2. Maggioni AP et al, *Eur. J. Heart Fail.* 2016; 3 Heart failure policy and practice in Europe: Italy <https://www.hfpolicynetwork.org/resources/#D123>; 4. PNE data 2021, 2019 data reported; 5. Norhammar A, Bodegard J, Vanderheyden M, et al Prevalence, outcomes and costs of a contemporary, multinational population with heart failure *Heart Published Online First: 13 February 2023.* doi: 10.1136/heartjnl-2022-321702.

Diagnostic Criteria for HF Categories

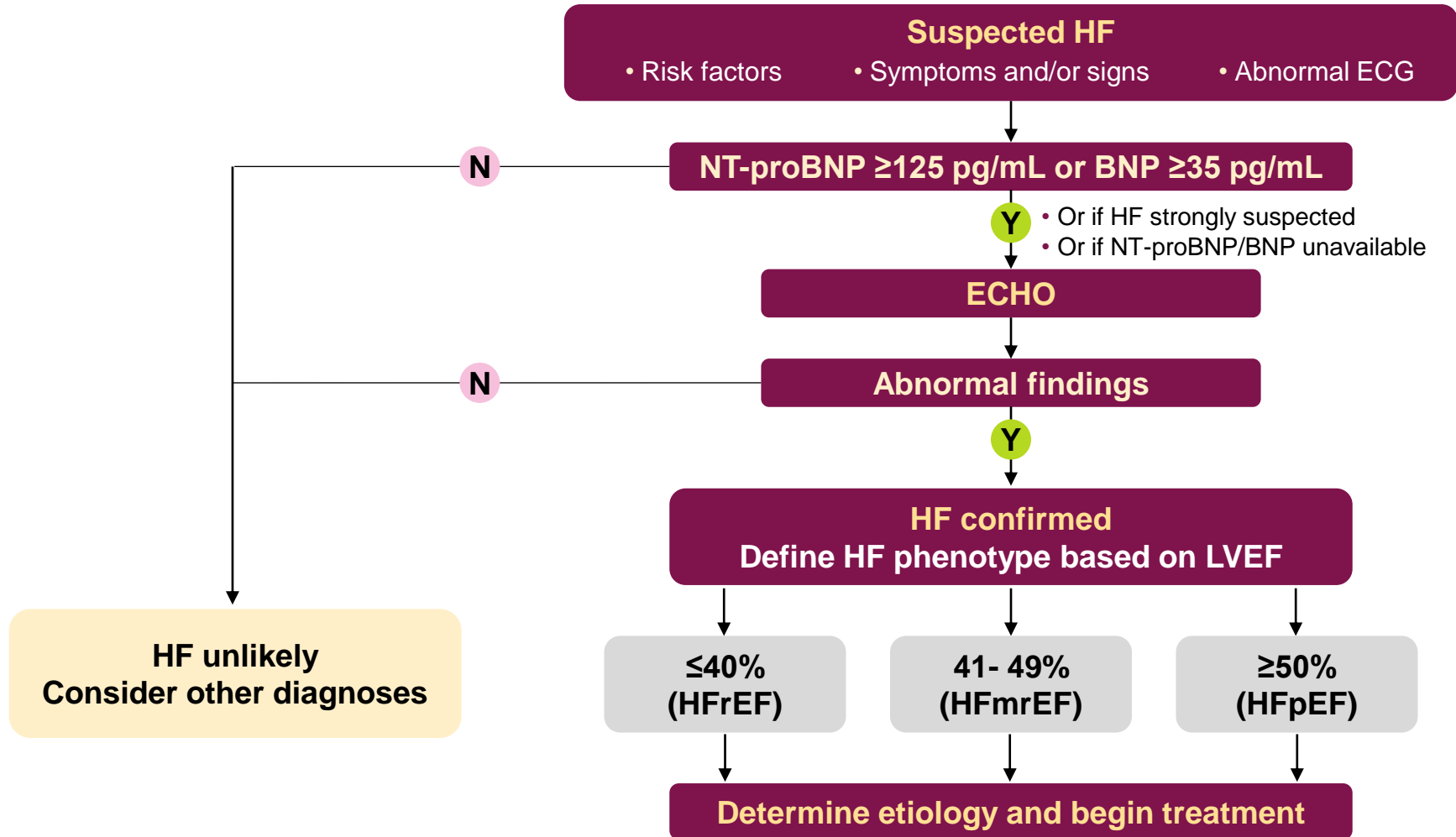
HF Category	Criteria	
	ESC ¹	AHA/ACC/HFSA ²
HFrEF	<ul style="list-style-type: none"> LVEF ≤40% 	<ul style="list-style-type: none"> LVEF ≤40%
HFmrEF	<ul style="list-style-type: none"> LVEF 41-49%^a 	<ul style="list-style-type: none"> LVEF 41-49% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF	<ul style="list-style-type: none"> LVEF ≥50% Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides^b 	<ul style="list-style-type: none"> LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFimpEF	<ul style="list-style-type: none"> NA 	<ul style="list-style-type: none"> Previous LVEF ≤40% and a follow-up measurement of LVEF >40%

^aThe presence of other evidence of structural heart disease (e.g. increased LA size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis of HFmrEF more likely; ^bThe greater the number of abnormalities present, the higher the likelihood of HFpEF.

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; 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; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; NA = not applicable.

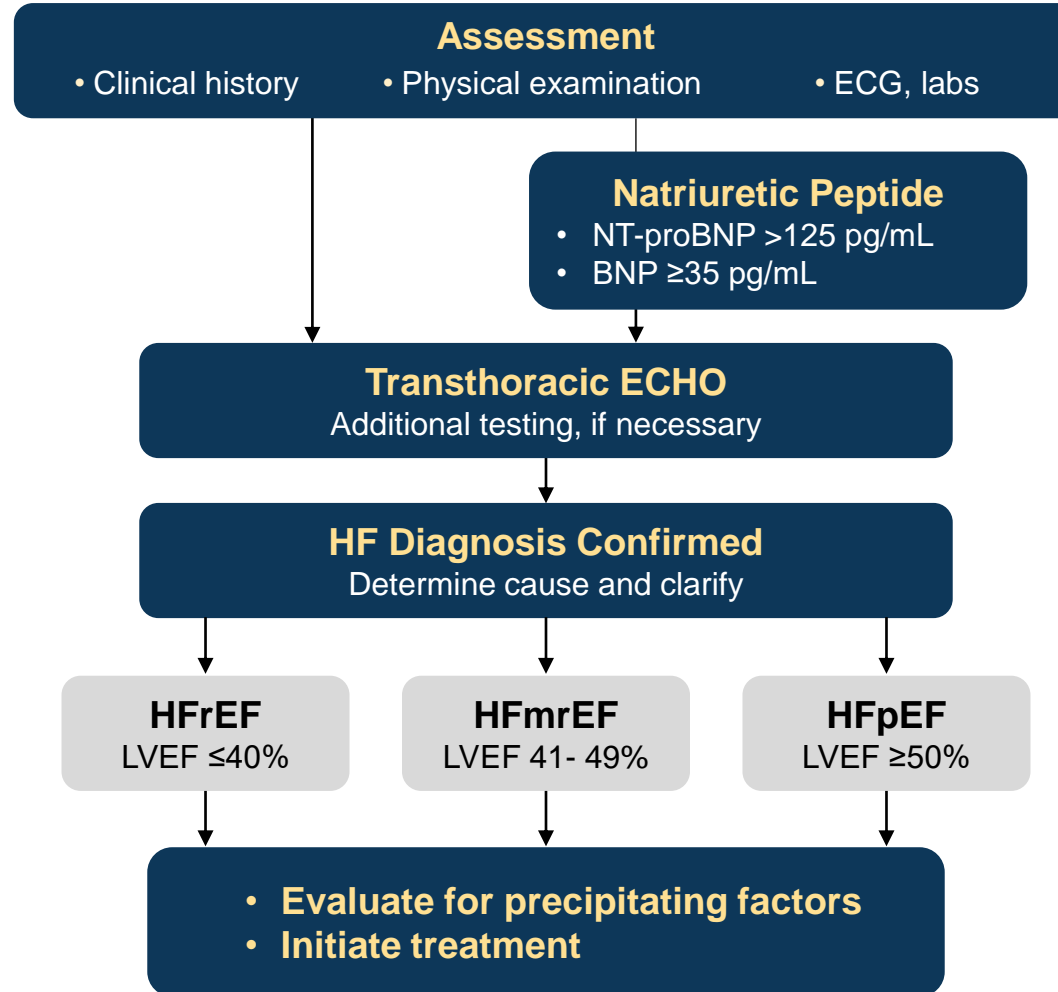
1. McDonagh TA et al. *Eur Heart J.* 2021;42(36):3599-3726; 2. Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

ESC Diagnostic Algorithm for HF



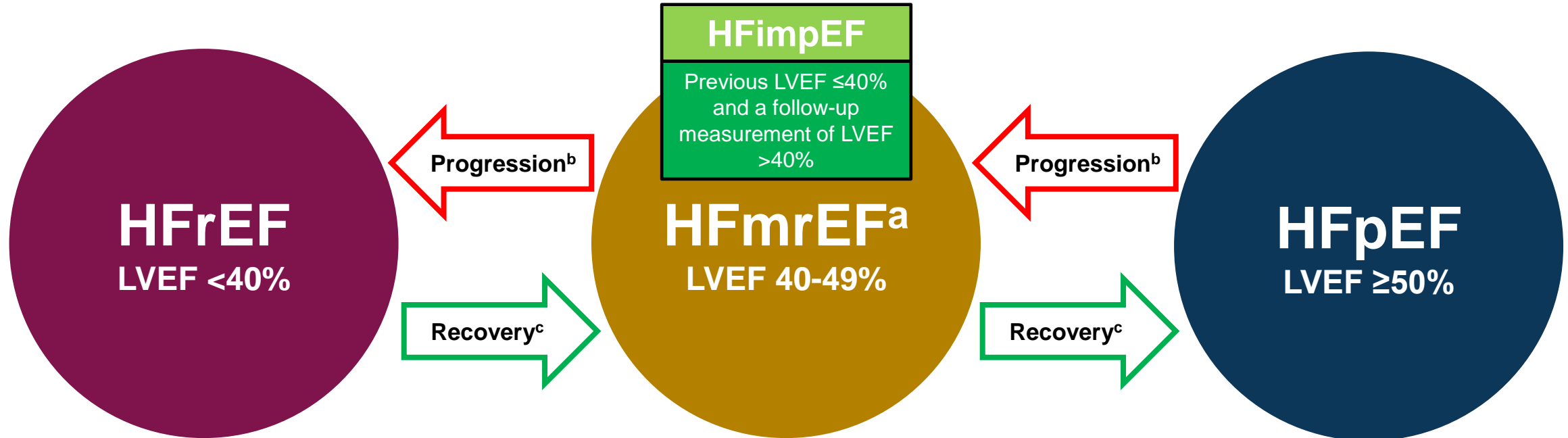
BNP = B-type natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiography; ESC = European Society of Cardiology; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

AHA/ACC/HFSA Diagnostic Algorithm for HF



ACC = American College of Cardiology; AHA = American Heart Association; BNP = B-type natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiography; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Changes in LVEF Occur Over Time and Are Associated With Specific Patient Characteristics



Factors associated with progression^b:

Diabetes, ischemic heart disease, lack of specialized HF follow-up, higher NT-proBNP levels

Factors associated with recovery^c:

Younger age, female, lower HF severity, shorter HF duration, fewer comorbidities

Data from patients with ≥2 EF measurements in the SwedeHF study (N=4942) between May 2000 and December 2012.

^aReference uses the term HF with midrange EF (EF 40-49%) for this group; ^bEF decrease; ^cEF increase.

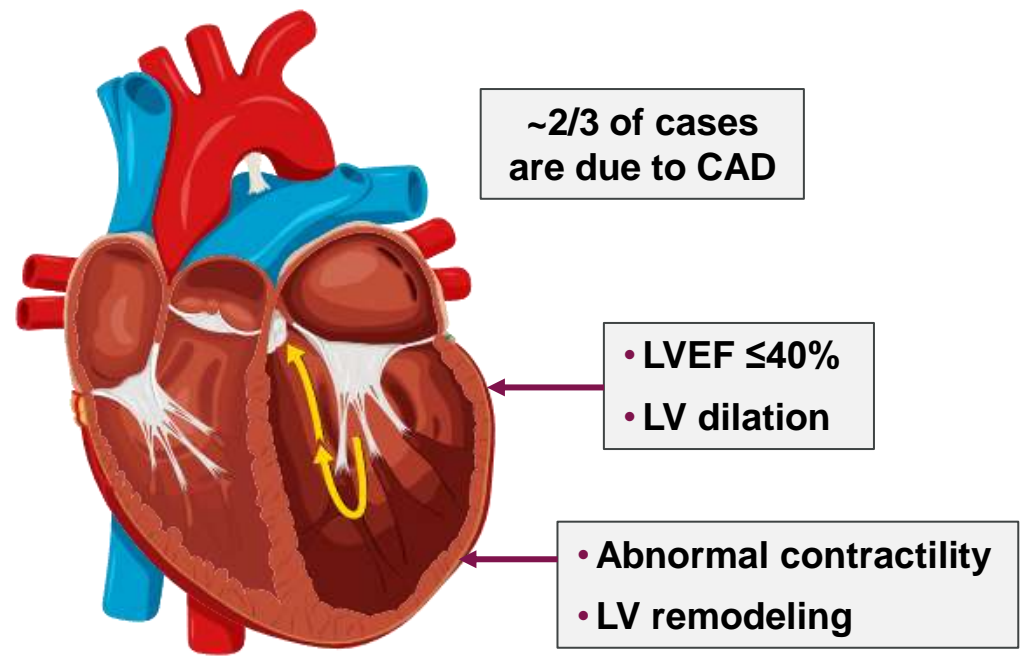
EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Savarese G et al. *JACC Heart Fail.* 2019;7:306-317.

Differences in HF Pathophysiology¹⁻³

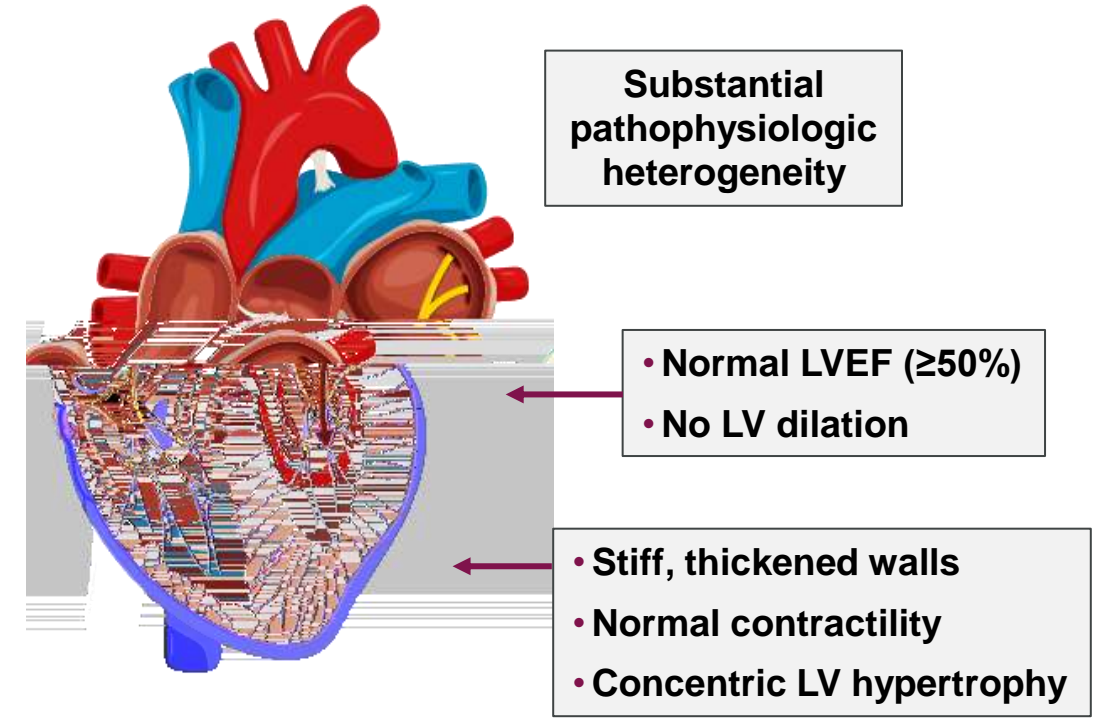
HFrEF

LV contraction is reduced resulting in inadequate cardiac output.



HFpEF

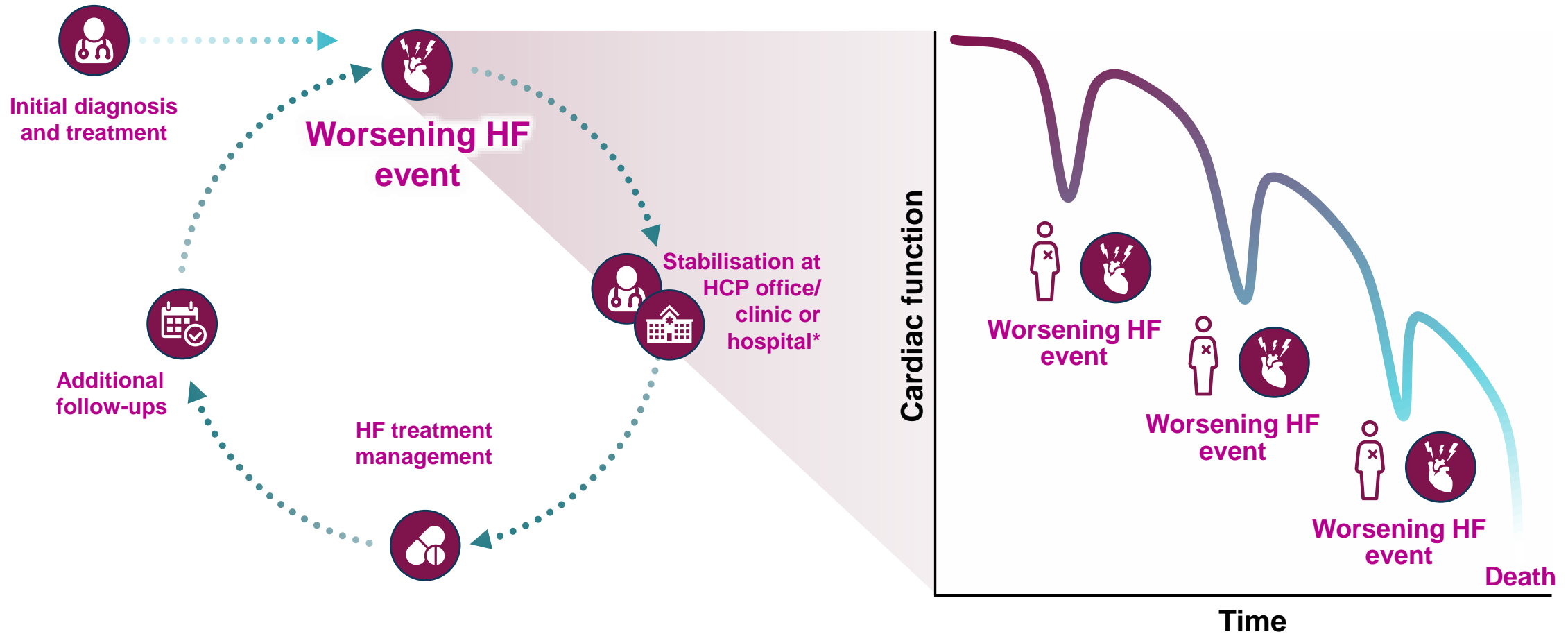
LV filling is reduced so that, even though LVEF is normal, cardiac output is reduced.



CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction.

1. Bloom MW et al. *Nat Rev Dis Primers*. 2017;3:17058; 2. Borlaug BA. *Nat Rev Cardiol*. 2014;11:507-515; 3. Redfield MM. *N Engl J Med*. 2016;375:1868-1877.

HF is a progressive condition: patients with HF are caught in a vicious cycle and progressively worsen over time



Adapted from Gheorghiade et al. *Am J Cardiol.* 2005 and Cowie et al. *ESC Heart Fail.* 2014.

*Adjustment of and potential addition to current therapy.

HCP, healthcare professional; HF heart failure.

1. Gheorghiade M et al. *Am J Cardiol.* 2005;96:11G–17G; 2. Cowie MR et al. *ESC Heart Fail.* 2014;1:110–145.

Despite poor prognosis, there is a lack of urgency for early identification and initiation of GDMT



Over 40% have HF symptoms up to 5 years prior to diagnosis¹



~75% are diagnosed with HF following an unplanned hHF^{1,2,a}



Over 30% mortality rate 1 year after hHF^{2,b}

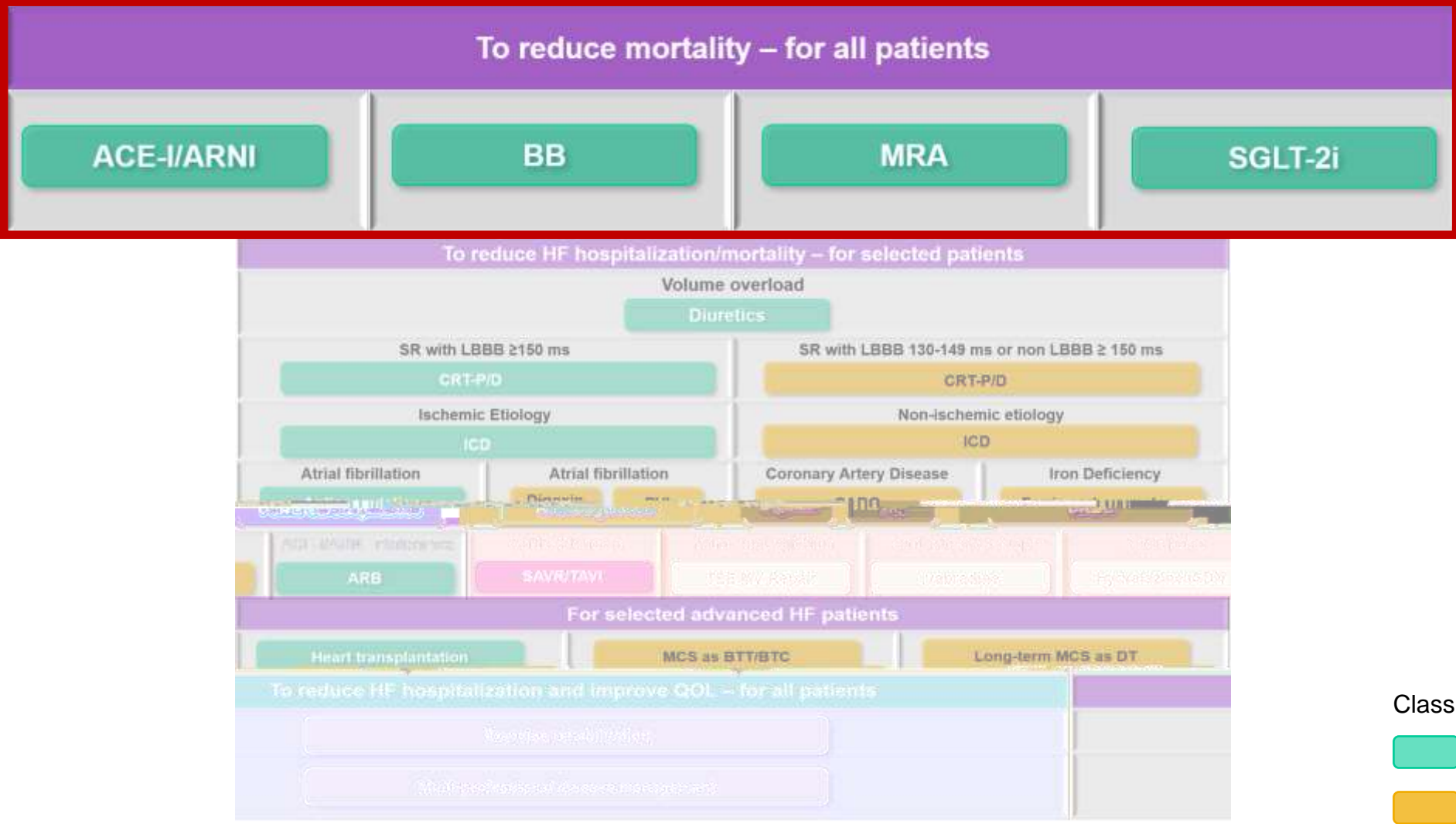


GDMT for HF is **suboptimal** for the majority of patients³

^aBased on data from 2010-2013¹ and 2017²; ^bBased on patients diagnosed with HF during hHF from 2012-2015.

1. Bottle A et al. *Heart*. 2018;104(7):600-605; 2. Lawson CA et al. Article and supplementary appendix. *Lancet Public Health*. 2019;4(8):e406-e420; 3. Ghazi L et al. *J Am Coll Cardiol*. 2022;79(22):2203-2213.

ESC 2021 Heart Failure Guidelines: Class Ia Recommendation for SGLT-2i in All Patients with HFrEF



Class of Recommendation
■ Class I
■ Class IIa

ESC 2021 Heart Failure Guidelines: SGLT2i is Recommended in Patients with HFrEF to Reduce the Risk of HF Hospitalization and Mortality

Recommendations	Class ^a	Level ^b
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

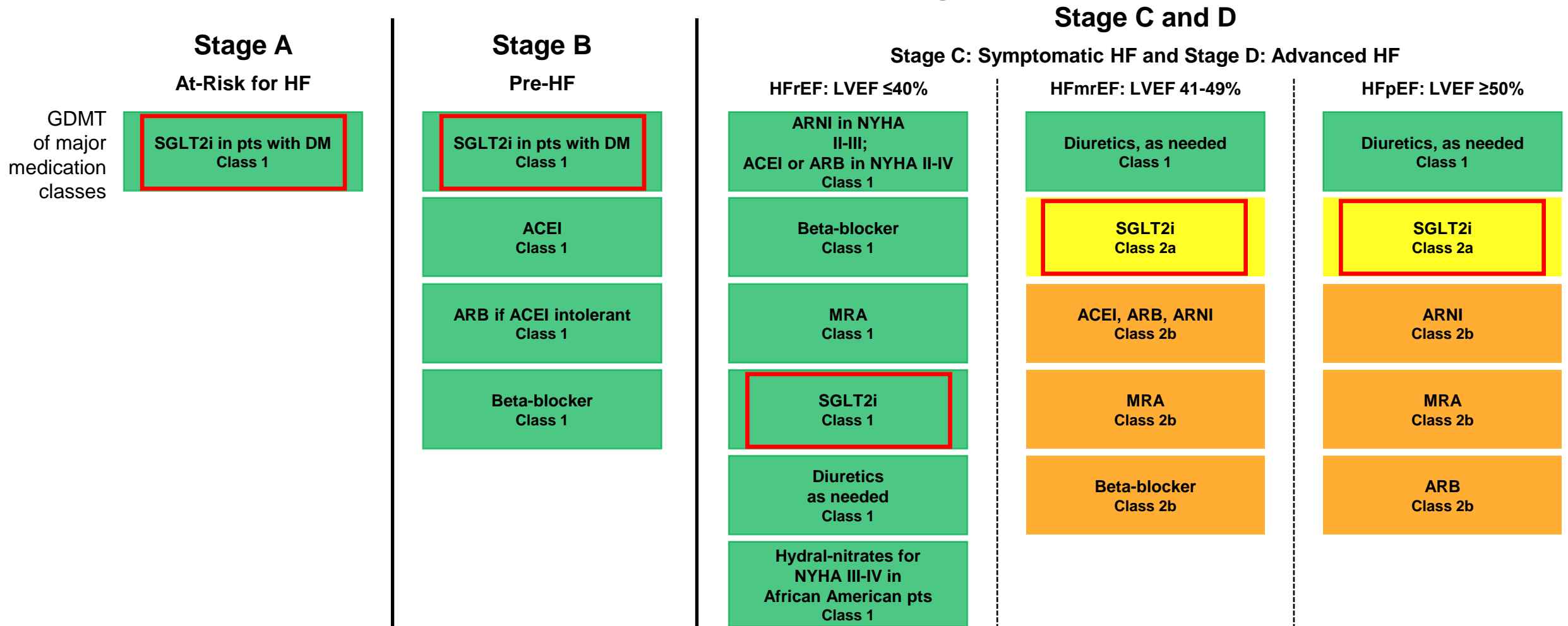
^aClass of recommendation; ^bLevel of evidence.

ACEI = angiotensin-converting enzyme inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

2022 AHA/ACC/HFSA HF Guidelines: SGLT2i Are Now Recommended Across All Stages and Types of HF

GDMT Across HF Stages

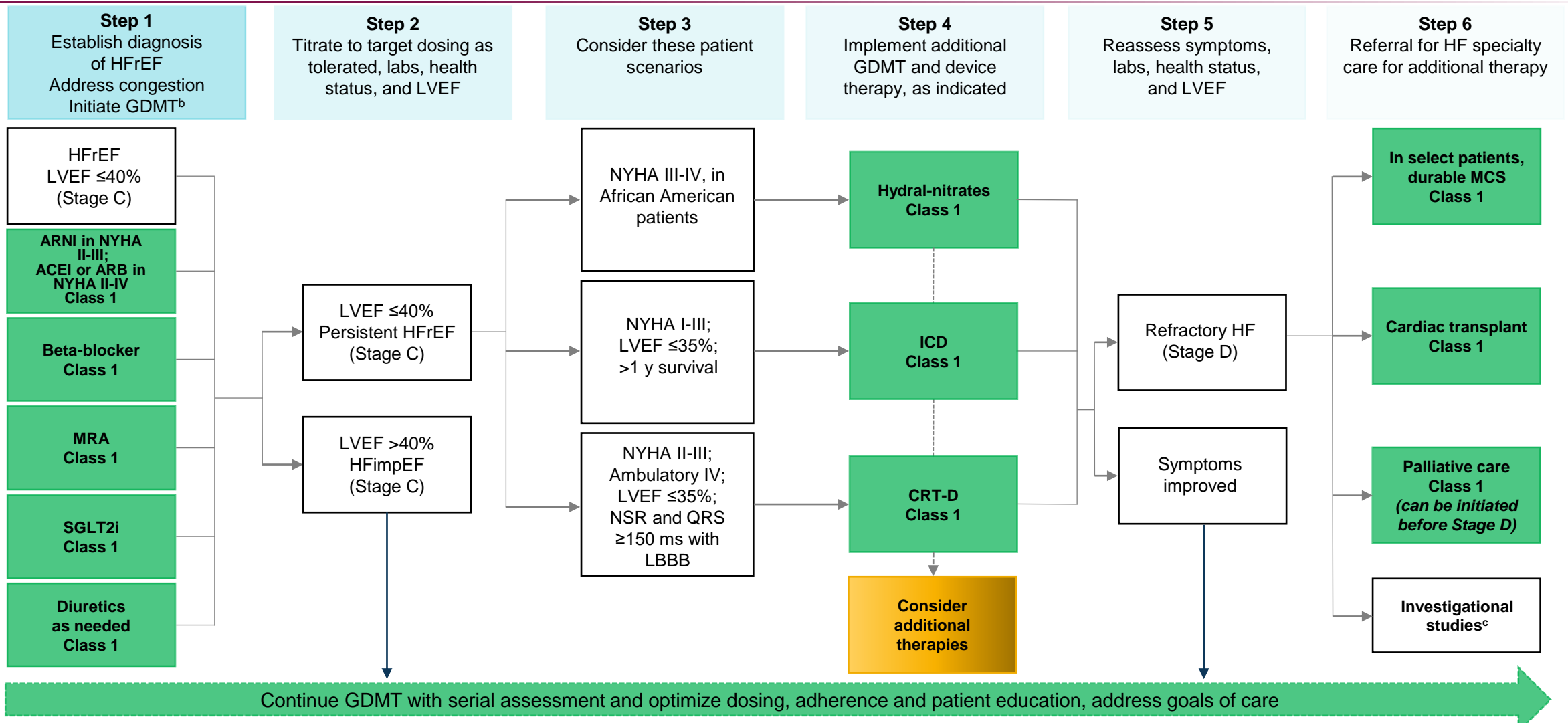


ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; ADA = American Diabetes Association; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; Hydral-nitrates: hydralazine and isosorbide dinitrate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Adapted from JACC. Guidelines and clinical documents. Management of heart failure guideline hub. Central illustration. JACC website.

Ad esclusivo uso del Medical Affairs.

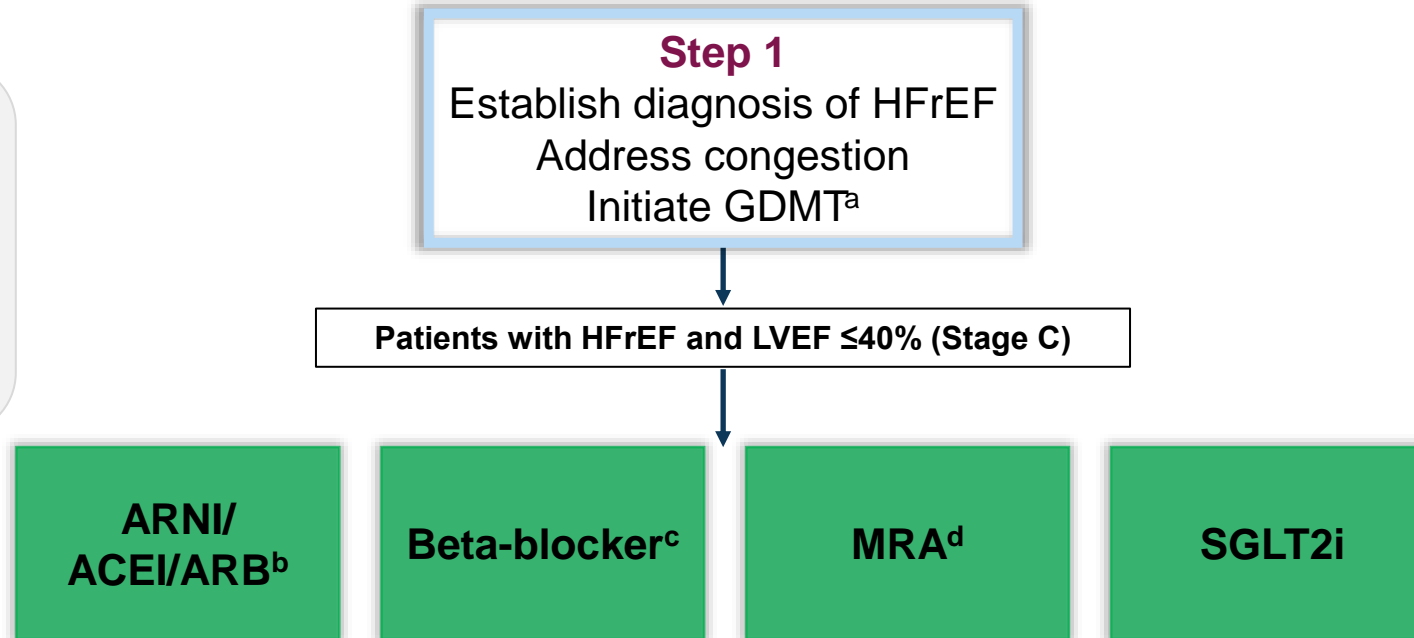
2022 AHA/ACC/HFSA HF Guidelines: Treatment of HFrEF^a



^aStages C and D; ^bStep 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication or need to follow the order of trial publication. Medication doses should be increased to target as tolerated; ^cParticipation in investigational studies as appropriate for stage C, NYHA class II and III HF.

2022 AHA/ACC/HFSA HF Guideline: SGLT2i Recommended as a Class 1A for HFrEF

Step 1 therapies may be started simultaneously or without specific medication sequence and should not be delayed



COR	LOE	Recommendation for SGLT2i
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.

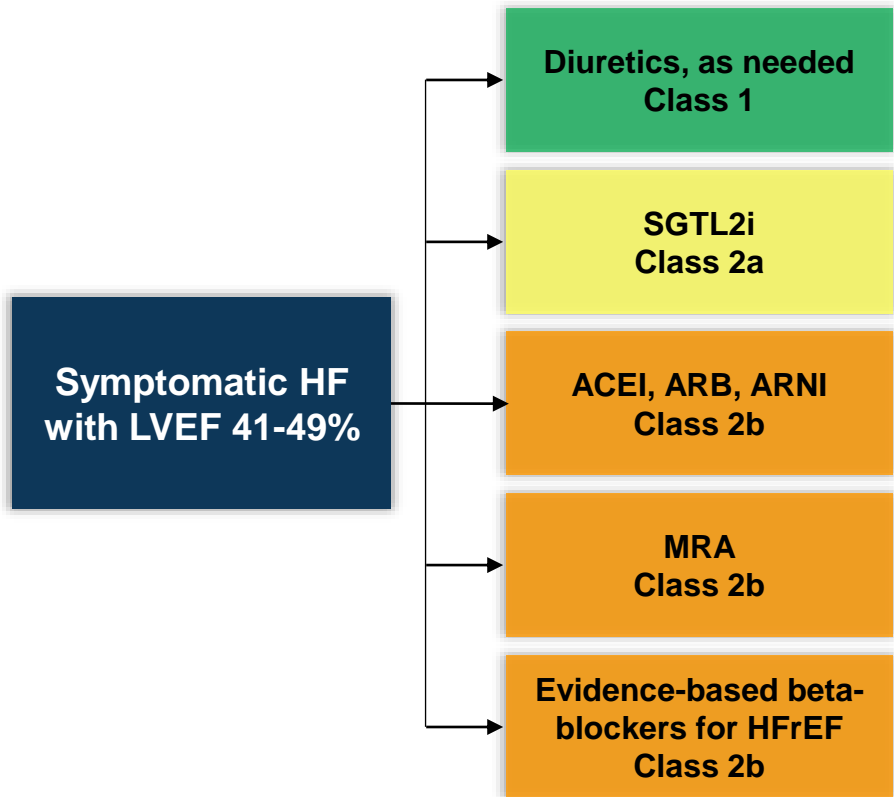
^aDiuretics are also recommended as needed in patients with fluid retention; ^bARNI is recommended as de novo or to replace ACEI or ARB in patients with NYHA class II-III. In patients with NYHA class II-IV, ACEI, or ARB when intolerant to ACEI due to cough or angioedema, is recommended when ARNI use is not feasible; ^cOne of the 3 beta blockers proven to reduce mortality; ^deGFR >30 mL/min/1.73m² and potassium <5.0 mEq/L.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; COR = class of recommendation; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LOE = level of evidence; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Adapted from Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

2022 AHA/ACC/HFSA HF Guidelines: SGLT2i are Now Recommended in the Treatment of HFmrEF (LVEF 41-49%)

Treatment of HFmrEF

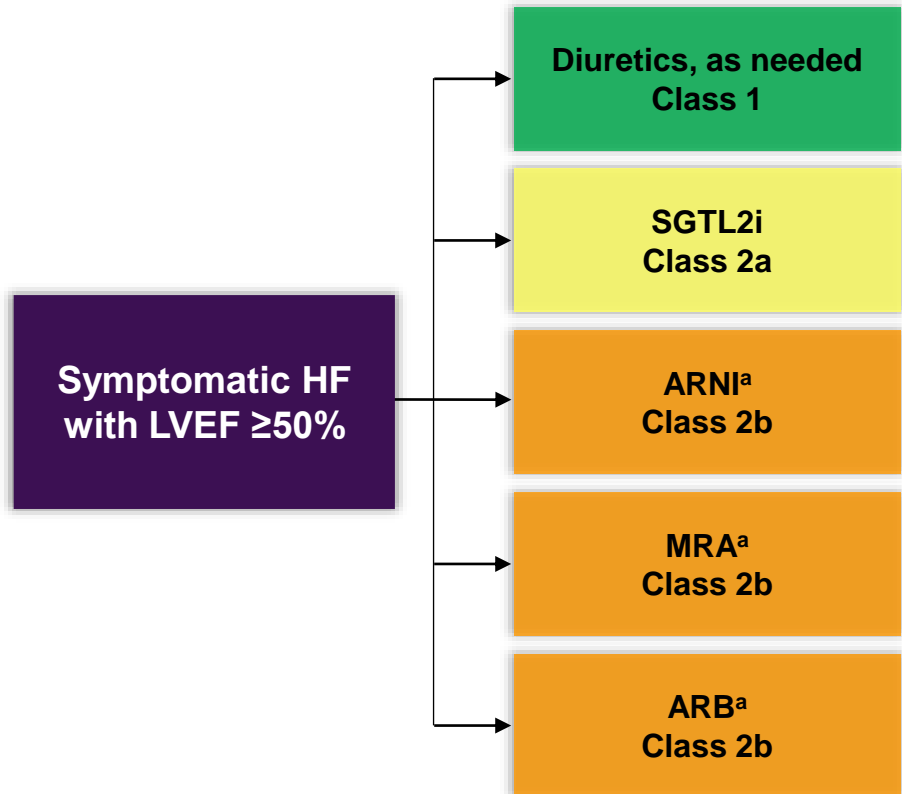


COR	LOE	Recommendations for HFmrEF
2a	B-R	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalization and cardiovascular mortality.
2b	B-NR	Among patients with current or previous symptomatic HFmrEF (LVEF, 41-49%), use of evidence-based beta blockers for HFrEF, ARNI, ACEI, or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor, AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; COR = class of recommendation; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LOE = level of evidence; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NR = nonrandomized; R = randomized; SGLT2i = sodium glucose cotransporter 2 inhibitor.

2022 AHA/ACC/HFSA HF Guidelines: SGLT2i are Now Recommended in the Treatment of HFpEF (LVEF ≥50%)

Treatment of HFpEF



COR	LOE	Select ^b Recommendations for HFpEF
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, particularly among patients with LVEF on the lower end of this spectrum.
2b	B-R	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.
2b	B-R	In selected patients with HFpEF, ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.

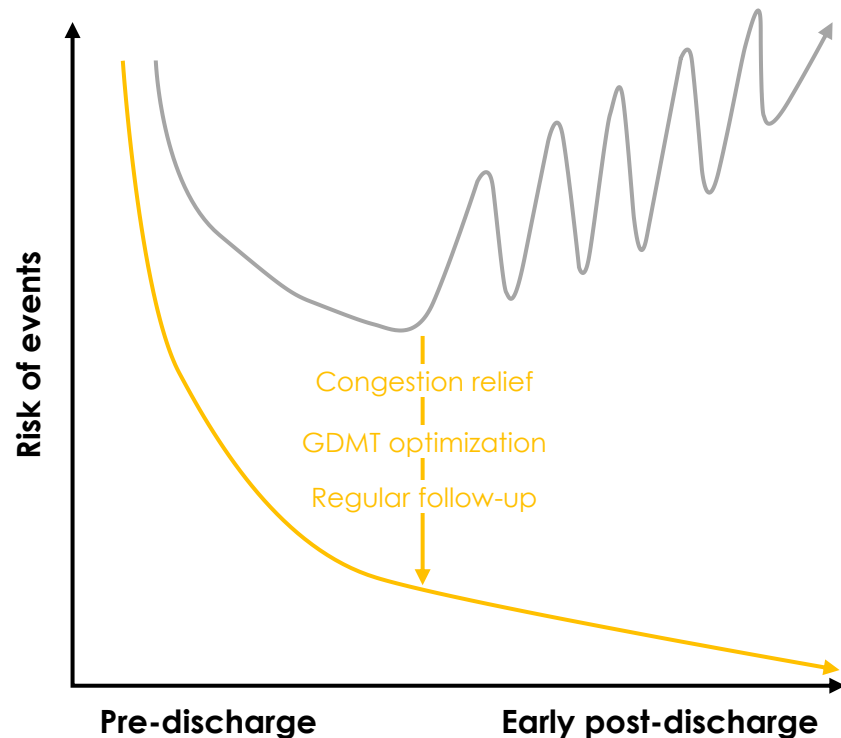
^aGreater benefit in patients with LVEF closer to 50%; ^bOther recommendations: titrate medication to reach blood pressure targets according to published clinical practice guidelines in patients with HTN to prevent morbidity (COR 1; LOE C-LD); management of AF can be useful to improve symptoms (COR 2a; LOE C-EO); routine use of nitrates or PDE-5 inhibitors to increase activity or QOL is ineffective (Class 3; LOE B-R).

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; COR = class of recommendation; EO = expert opinion; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFSA = Heart Failure Society of America; HTN = hypertension; LOE = level of evidence; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NR = nonrandomized; R = randomized; PDE-5 = phosphodiesterase-5; QOL = quality of life; SGLT2i = sodium glucose cotransporter 2 inhibitor.

Adapted from Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

Initiation of GDMT pre-discharge is critical to improve short- and long-term outcomes¹

Determinants of better outcome after discharge¹



- Treatment established pre-discharge tends to remain unchanged¹
- If treatment is suboptimal, it is likely to remain suboptimal¹
- Discharging eligible patients without medication:
>75% chance GDMT will not be initiated within the next year²

GDMT, guideline-directed medical therapy.

Clinical inertia has a major role in the lack of prescription of GDMT and should be overcome by proper implementation of current guidelines¹⁻³



Physician-related factors:^{2,3}

Non-prescription of GDMT
Not reaching target doses of GDMT
Risk treatment paradox



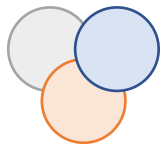
Patient-related factors:^{2,3}

Old age/frailty
Comorbidities
Poor adherence to medications
Lack of public awareness of HF



System-related factors:^{*2}

Fragmented, isolated care (compared with multidisciplinary systems)
Poor patient follow-up
Absence/erosion of doctor-patient relationship
Outdated/absence of protocols/pathways

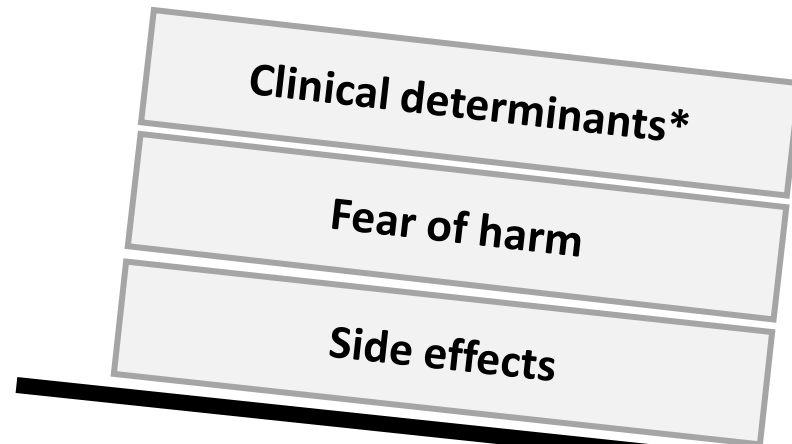


Delays in novel GDMT initiation are shown to be more pronounced in high-risk patients with comorbidities such as kidney disease and/or diabetes⁴

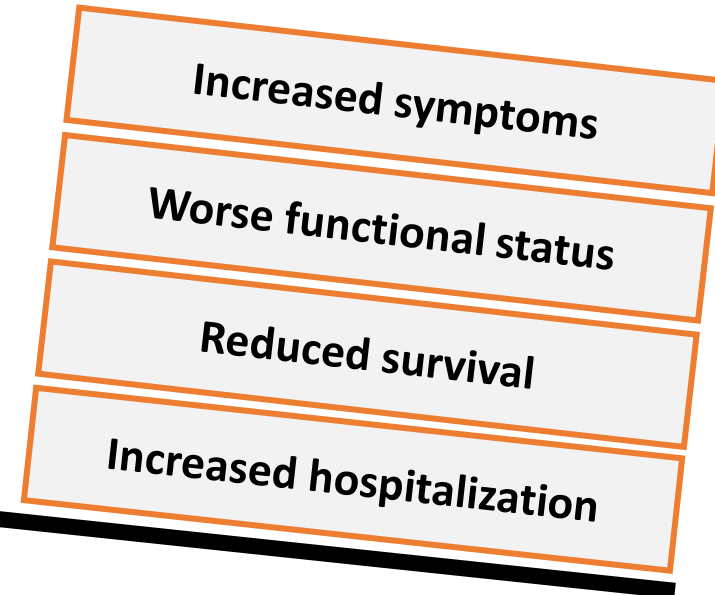
*Considerations regarding costs/reimbursement will not be covered in this session but are a significant barrier in many countries.
GDMT, guideline-directed medical therapy; HF, heart failure.

Why are hospitalized patients with HF still not being treated according to guidelines?¹

Risks of commission^{1,2}



Risks of omission²



In-hospital initiation of medication could be applied to improve GDMT use^{3,4}

*Low blood pressure, renal failure, hyperkalaemia. GDMT, guideline-directed medical therapy; HF, heart failure; QoL, quality of life.

Vericiguat is recommended for the comprehensive medical treatment of patients with worsening HF¹



ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Reference: 1. McDonagh TA *et al.* *Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

Vericiguat is specifically recommended for worsening HF in ESC 2021 guidelines

Recommendations	Class	Level
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA Class II–IV who have had worsening HF despite treatment with an ACEi (or ARNi), a beta blocker and an MRA to reduce the risk of CV mortality or HFH	IIb	B

Vericiguat was included in the guidelines before EU approval

Worsening HF is referred to in the guidelines for the **first time**, and vericiguat is **specifically recommended** for this patient group

Vericiguat is listed among the **disease-modifying drugs** due to the VICTORIA results

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFH, heart failure hospitalization; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Reference: 1. McDonagh TA *et al.* *Eur Heart J* 2021; <https://doi.org/10.1093/eurheartj/ehab368>.

6.3 Devices under evaluation

Cardiac contractility modulation (CCM) has been evaluated in patients with NYHA class III–IV HF, with an LVEF $\geq 25\%$ to $\leq 45\%$ and QRS duration ≤ 130 ms, and was associated with a small improvement in exercise tolerance and QOL.^{241,242}

Technologies that involve modification of the activity of the autonomic nervous system, e.g. baroreflex activation therapy,^{243,244} have also been shown to offer a modest improvement in effort capacity and QOL. However, currently, the evidence is considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization for these and a variety of other implantable electrical therapeutic technologies (see also Gaps in Evidence in section 16).



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